Hepatitis B in Australia’s Northern Territory: Understanding the true story

by

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Declaration

I hereby declare that the work included in this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Abstract

Chronic Hepatitis B (chronic HBV infection) affects 350 million people globally and causes significant morbidity and mortality in the form of cirrhosis and liver cancer. The overall prevalence of chronic HBV infection in Australia is around 1%; however Indigenous Australians are disproportionately affected. In the Northern Territory (NT) exact prevalence rates in Indigenous communities are not known but have been estimated to be between 2.4-14%. Universal vaccination commencing at birth has been in place in the NT since 1990 and effective antiviral treatments are available, however only 2.4% of those living with chronic HBV infection are receiving treatment for it. Low health literacy is one of the multiple barriers preventing access to care particularly in a cross-cultural context.

Following the literature reviews in section A, this thesis covers three major areas of work that have formed my PhD studies (sections B, C and D).

In section B, I present a detailed description of the sero-epidemiology of hepatitis B in the NT based on 20 years of Territory-wide laboratory data. Overall HBsAg prevalence is 3.40%, increasing to 6.08% for Indigenous Australians.

In section C, I present the CHARM (Characterising hepatitis B in northern Australia through molecular epidemiology) cohort. This study identified the unique and universal hepatitis B subgenotype in Indigenous Australians in the NT to be C4. Full genome sequencing has identified C4 to be a recombinant virus with molecular markers associated with rapid progression to cirrhosis and liver cancer.

Section D reports a qualitative participatory action research study looking at hepatitis B-specific health literacy and the provision of patient information. The results of this study have informed and enabled production of a bilingual (English and Yolŋu matha) electronic application to
provide information for Indigenous people about hepatitis B. The ‘Hep B Story’ app is freely available through the Apple app store and the Google play app store.
Plain language summary of this thesis

Hepatitis B is a virus that affects the liver and is also found circulating in an infected individual’s blood. It is most commonly transmitted from one person to another vertically from mother to child, through sexual contact or through direct blood contact. It can either cause acute infection that the body fights and clears itself or chronic infection where the virus persists in the blood for more than six months. Whether or not an individual will progress to chronic infection is inversely proportional to the age at which the virus is acquired. Therefore if you acquire your virus at the time of birth you have at least a 90% chance of having chronic infection, whereas if you acquire your hepatitis B in your mid-20s it is more than 90% likely you will clear it yourself.

Worldwide, around 240 million people have chronic infection with hepatitis B, and about 20% of those chronically infected will progress to cirrhosis and liver failure or liver cancer as a consequence of their hepatitis B. Hepatitis B is thought to be responsible for 80% of liver cancers worldwide and around 700,000 deaths per year. In Australia, hepatitis B affects 1% of the population, however it has been suggested that the people of the Northern Territory have much higher prevalence levels. A vaccine to prevent hepatitis B has been given to all babies born in the NT since 1990 and funded treatments are available for people living with chronic infection. More recently it has been established that not all hepatitis B across the world is exactly the same. Different types (called genotypes) of hepatitis B have been described from different areas of the world and named A-J, with multiple numbered sub-types e.g. A1/B2.

This thesis describes three main areas of work that I have conducted over the last three to four years which aim to provide high-quality evidence to improve the overall understanding and provision of care to people living with chronic hepatitis B in the NT. The three areas covered are:

1. Establishing exactly how big a problem hepatitis B is in the people of the NT;
2. Finding out which specific types of hepatitis B are found in the Indigenous people of the NT; and
3. Establishing what people in one remote community understand about hepatitis B.

Section A introduces the overall aims and questions I have tried to answer and provides a summary of the understanding of the three main areas from the worldwide published literature.

Section B reviews a large dataset of all the hepatitis B-related tests that have been carried out in the NT over the last 20 years. The results of this review tell us how many people are chronically infected with hepatitis B, how many have had past infections and how many have never been exposed to hepatitis B and would benefit from vaccination. This data establishes that, compared to the rest of Australia, there are high levels of hepatitis B in the NT. Overall, 3.4% of the NT population is infected. This figure climbs to 6.1% of the Indigenous population and drops to 1.6% in the non-Indigenous population. It also shows that numbers of people infected have been falling over time; however this fall in numbers started before 1990, when the vaccine was introduced for all babies, so other factors must be contributing.

Section C describes a study called CHARM, which stands for Characterising hepatitis B in the Northern Territory through molecular epidemiology. CHARM was set up to establish what types of hepatitis B are found in the NT. It has found some very interesting results: of 128 individuals who have taken part in the study, 84 had enough hepatitis B viruses in their blood to tell what type they were infected with, and all these individuals had the same type of hepatitis B. This type, called C4, is an unusual one and has only been described twice before, in two Indigenous Australians from Queensland.

This result is not what we were expecting, so we changed our plan a little and went on to look at this virus and the people infected with it in much more detail. We found it has its origins from two different types of hepatitis B. Part of the C4 structure is like other C types, while part is like type J. This means that the C4 virus is slightly different to the virus used to make the hepatitis B vaccine. Although we know the vaccine works to some degree, because of the falling numbers of chronic hepatitis B infection, over time it might mean it is less effective than in other places. We
need to look into this further. We also found that this appears to be a particularly aggressive form of hepatitis B and may cause liver failure more quickly than other viruses. We suggest this means we should consider earlier treatment for people with C4 hepatitis B.

Section D describes a qualitative study based on talking to people in one specific Indigenous community in the NT about what they understood about hepatitis B. We spoke to people living with chronic hepatitis B, general community members and health workers at the clinic, about their experiences. We also asked them what kind of information they would like to have about hepatitis B and how we could best make that available to them. They gave us much useful information that we used with ongoing input from the community to inform the production of an electronic application (‘app’). The app called the ‘Hep B Story’ is interactive and talks in both English and Yolnu matha – the local Indigenous language. The app can be downloaded and users can see what they think about it. It is freely available from the Apple app store, the Google play store or from the following link http://www.menzies.edu.au/hepbstory/.
Dedication

This thesis is dedicated to my ‘support team’ consisting of my husband Richard, my two beautiful children Matthew and Hannah, and my parents Margaret and David.
Acknowledgements

In the spirit of respect, I would first like to acknowledge the people and the Elders of the Aboriginal and Torres Strait Islander Nations who are the Traditional Owners of the land and seas of Australia.

Without the help of a great number of people the work described in this thesis would never have started and would certainly never have been completed.

The first people on this list are my family, my ‘support team’ as they have come to be known over the latter part of my PhD candidature. They have loved and supported me and most importantly provided endless childcare for my beautiful children Matthew and Hannah. Mum, Dad and Richard – this thesis would not exist without your unbelievable commitment to me, and for that I am truly blessed. To Hannah and Matthew – thank you for still greeting me with the same gorgeous enthusiasm even when I have been at work all day at the weekend again!

Dr Josh Davis is a PhD scholar’s dream supervisor and I am so thankful that I had the good fortune of meeting him in Darwin. I couldn’t help but become infected by his passion for high-quality research on viral hepatitis and for all things Territorian. I have honestly never met anyone who is so true to their word and who I respect greatly and equally in both a clinical and research arena – thank you, thank you, thank you Josh.

Professor Nick Anstey – thank you for supporting me whenever and with whatever has been needed throughout my whole candidature; it has been much valued and appreciated. Also at Menzies, Dr Vanessa Johnston – thank you for introducing me to qualitative research and guiding and advising me so well in this area in which I was a novice. Associate Professor Steve Tong – your calm considered opinion has been greatly valued again and again and again – thank you.
Menzies staff who are not part of my supervisory panel but who have been key in making this work happen include Paula Binks for her outstanding project management and organisation skills, Katie McGuire and Catharine Kent for their meticulous data entry and double checking, and Mark Chatfield, Steve Buchanan and Federica Barzi for Stata, database and general statistics advice.

I have been amazingly privileged to work with and get to know Professor Stephen Locarnini and his team at VIDRL, all of whom are inspirational scientists who welcomed me warmly to Melbourne and enabled me to learn so much about their work. Stephen, Lilly Yuen, Scott Bowden, Roz Edwards, Nadia Warner, Renae Walsh, Tina Sozzi, Kathy Jackson and Peter Revill – thank you so much for allowing me into your world. An extra special thank you to Margaret Littlejohn for being an amazing mentor, taking all those random calls from Darwin when she wasn’t even at work, answering all my questions and most of all for not giving away that I was pregnant when she realised that not long after I had realised it myself!

Also at the Peter Doherty Institute, Associate Professor Ben Cowie has been incredibly supportive from afar throughout my candidature and has provided invaluable help, enthusiasm and good advice whenever asked. I am extremely grateful to him for that.

Steve Guthridge, Shu Li, Lilly Li and Alan Cao from Health Gains planning – thank you so much for your invaluable advice and assistance with the data linkage aspect of my epidemiology project and for being so patient with my multiple requests to repeat things.

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I would like to acknowledge, thank and pay my deep admiration and respect to Sarah Bora Bukulatjpi, who has humbled and continually amazed me with her dedication and inspirational attitude to her work as an Aboriginal health practitioner. You have taught me so much and I will not forget your wise words. I would also like to thank Sherrie Novley as well as all the individuals living with chronic hepatitis B, and community members and health professionals who took part in the interviews which informed the development of the electronic app. You taught me so much about really listening to people and never forgetting the importance of a person’s first language.

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Last, but by no means least, I would like to thank the National Health and Medical Research Council and Sidney Myer Trust for providing me with the funding to be able to carry out this work.
Peer reviewed publications arising from this work


Manuscripts planned for submission or submitted to peer reviewed journals


3. Yeun L, Littlejohn M, Davies J, Davis J, Tong S, Locarnini S. The phylogeography of hepatitis B sub-genotype C4: are we closer to determining the true origins of the Australian antigen? Planned for submission.

Abstracts published and/or presented at national or international meetings


Oral presentations at national or international meetings


7. **Invited speaker Davies J** The NT Hep B Story in 2013. Northern Territory Centre for Disease Control Annual Conference, September 2013, Darwin, NT, Australia.


Declaration of the author’s contribution

This thesis is my own work and was written under the supervision of Dr Joshua Davis. All the chapters that are not multi-author published papers were written by me. All the multi-author published papers where I am first author (except Chapter 8) were originally drafted and predominantly written by me. Chapter 8, where I am second author, was originally drafted by Margaret Littlejohn (first author) with significant input from me. All the statistical analyses were performed predominantly by me. The qualitative analyses were performed by me and Sarah Bukulatjpi, with guidance from Vanessa Johnston, in the context of a participatory action research project where multiple cycles of evaluation and consultation with the community involved occurred.

The sero-epidemiology study reported in Chapter 5 was planned and designed by Joshua Davis and me. Data collection was co-ordinated by me with significant input from Associate Professor Rob Baird, Dr Geoff Higgins and Dr Mile Beaman, each representing their laboratory service. Data linkage was carried out by Shu Li and her team at the Health Gains Planning section of the NT Health Department. Data management and statistical analysis was carried out by me with help and advice from John Condon, Josh Davis and Steven Tong.

The original CHARM study was initiated by Joshua Davis and Steven Tong in 2009. In 2010, I initially joined as a doctor recruiting patients and increasingly became more involved in the ongoing development, design and adaptation of the CHARM study and now cohort. I have remained involved in recruiting patients as have all the medical doctors and specialist nurses involved in the Royal Darwin Hospital Liver Clinic and the Alice Springs Infectious Diseases doctors. I have managed all the data, carried out all statistical analyses and written all papers resulting from this study so far, with the exception of Chapter 8, where I am second author. The laboratory work, consisting of initially genotyping then full genome sequencing and recombination analysis for the CHARM study, has been carried out by staff at the Victorian...
Infectious Disease Laboratory in Melbourne, with whom we have been and are working very closely, in particular Margaret Littlejohn, Lilly Yuen, Ben Cowie and Stephen Locarnini.

The participatory action research project described in Chapters 10 and 11 was planned and designed by me in response to a request from, and in conjunction with, Sarah Bukulatjpi and the staff of the community health centre. Vanessa Johnston provided senior advisory input into the methodology and analysis techniques. All analyses were originally carried out by me with input from Sarah Bukulatjpi. All papers were written predominantly by me. The software development and coding of the app were carried out by Luci Caldwell and Krupa Patel at Dreamedia, Darwin.
List of Abbreviations

AASLD – The American Association for the Study of Liver Disease

ALT – Alanine aminotransferase

APASL – The Asia-Pacific Association for the Study of the Liver

Anti-HBc – Antibodies to hepatitis B core antigen

Anti-HBe – Antibodies to hepatitis B e antigen

Anti-HBs – Antibodies to hepatitis B surface antigen

CALD – Culturally and Linguistically Diverse

CDC – Centre for Disease Control

CHARM – Characterising hepatitis B in northern Australia through molecular epidemiology

Chronic HBV infection – Chronic hepatitis B virus infection

EASL – The European Association for the Study of Liver

GAVI – Global Alliance for Vaccines and Immunisation

GESA – Gastroenterological Society of Australia

HBeAg – Hepatitis B e antigen

HBIG – Hepatitis B immunoglobulin

HBsAg – Hepatitis B surface antigen

HBV – Hepatitis B virus

MSM – Men who have sex with men
# Contents

## Section A - Introduction and literature reviews

- Chapter 1 - Background, context, scope and aims of the thesis ........................................ 3
  1.1 Background .................................................................................................................. 5
  1.2 Context ........................................................................................................................ 6
  1.3 Scope and structure of thesis ....................................................................................... 6
  1.4 Aims and hypotheses ................................................................................................. 8
  1.5 References .................................................................................................................. 10

- Chapter 2 - The epidemiology of chronic hepatitis B ........................................................ 11
  2.1 Overview and clinical aspects of chronic hepatitis B infection .................................... 13
  2.2 Worldwide epidemiology ............................................................................................ 22
  2.3 Australian epidemiology .............................................................................................. 28
  2.4 Northern Territory epidemiology ................................................................................ 34
  2.5 Conclusions ................................................................................................................. 42
  2.6 References .................................................................................................................. 43

- Chapter 3 - Molecular epidemiology of hepatitis B ........................................................ 49
  3.1 Hepatitis B the virus .................................................................................................... 51
  3.2 Worldwide molecular epidemiology .......................................................................... 56
  3.3 Molecular epidemiology of HBV in Australia .............................................................. 65
  3.4 Molecular epidemiology of HBV in Indigenous Australians ........................................ 67
  3.5 The clinical implications of HBV genotype ................................................................. 68
  3.6 Conclusions ................................................................................................................. 74
  3.7 References .................................................................................................................. 75

- Chapter 4 - Health literacy ............................................................................................. 83
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>What are the barriers to accessing care?</td>
<td>85</td>
</tr>
<tr>
<td>4.2</td>
<td>Health literacy</td>
<td>87</td>
</tr>
<tr>
<td>4.3</td>
<td>Cross cultural communication</td>
<td>102</td>
</tr>
<tr>
<td>4.4</td>
<td>Existing hepatitis B educational resources</td>
<td>104</td>
</tr>
<tr>
<td>4.5</td>
<td>Participatory action research in developing health education resources</td>
<td>108</td>
</tr>
<tr>
<td>4.6</td>
<td>Conclusions</td>
<td>110</td>
</tr>
<tr>
<td>4.7</td>
<td>References</td>
<td>112</td>
</tr>
</tbody>
</table>

**Section B – The epidemiology of hepatitis B in the Northern Territory** | 119 |

Chapter 5 - The sero-epidemiology of HBV in Australia’s Northern Territory based on 20 years of Territory-wide testing data | 121 |

5.1 Preamble | 123 |
5.2 Abstract | 125 |
5.3 Introduction | 127 |
5.4 Methods | 128 |
5.5 Results | 134 |
5.6 Discussion | 144 |
5.7 References | 150 |

Chapter 6 - The prevalence of co-infection with either hepatitis C, hepatitis D or HIV in an Indigenous cohort with chronic hepatitis B in the Northern Territory | 153 |

6.1 Preamble | 155 |
6.2 Abstract | 156 |
6.3 Introduction | 157 |
6.4 Methods | 157 |
6.5 Results | 158 |
6.6 Discussion | 160 |
Section D - Hepatitis B specific health literacy in the context of NT remote Indigenous communities: understanding it and establishing culturally appropriate ways to improve it ..........................................................................................................................211

Chapter 10 - The hepatitis B related knowledge, perceptions and experiences of remote dwelling Indigenous Australians and their health care providers ..........................................213
10.1 Preamble ..................................................................................................................................................215
10.2 “Only your blood can tell the story” – a qualitative research study using semi-structured interviews to explore the hepatitis B- related knowledge, perceptions and experiences of remote-dwelling Indigenous Australians and their health care providers in northern Australia - manuscript as published in BMC Public Health .................................................................................................217
10.3 Implications and questions arising from this paper ........................................................................219

Chapter 11 - Development of a culturally appropriate education tool for hepatitis B ...221
11.1 Preamble ..................................................................................................................................................223
11.2 Towards shared understandings: Development of a culturally appropriate bilingual electronic app about hepatitis B for Indigenous Australians - manuscript as published in The Journal of Medical Internet Research Research Protocols ..................................................................................225
11.3 Implications and questions arising from this paper ........................................................................227

Section E – Conclusions and future directions .........................................................................................229

Chapter 12 - Conclusions and future directions .........................................................................................231
12.1 Introduction ..........................................................................................................................................233
12.2 Conclusions ...........................................................................................................................................233
12.3 Future directions ......................................................................................................................................236
12.4 Summary statement ...............................................................................................................................239
Section F - Appendices ................................................................................................................. 241

Appendix 1 - Sensitivity analyses from Chapter 5 ........................................................................ 243
Appendix 2 - CHARM clinical record form .................................................................................. 245
Appendix 3 - CHARM cohort study clinical record form .............................................................. 247
Appendix 4 - Davies et al. Hepatitis D is rare or non-existent in hepatitis B virus infected Indigenous Australians in the Northern Territory manuscript as published in Australian and New Zealand Journal of Public Health ................................................................................................................. 249
Appendix 5 - Screen shots from electronic application - Yolŋu matha ........................................ 251
Appendix 6 - Screen shots from electronic application – English ................................................ 253
Appendix 7 - Electronic application evaluation questionnaire ..................................................... 255
Table of Tables

Table 2.1: Risk of progression to chronic HBV infection with respect to age at exposure to HBV [4] .......................................................................................................................................................... 15

Table 2.2: The phases of chronic hepatitis B infection as described by EASL [7], AASLD [8], APASL [4], ASHM [9] and GESA [8] ...................................................................................................................................................... 16

Table 2.3: Comparison of International and Australian recommendations for when treatment should be considered ................................................................................................................................................................. 18

Table 2.4: Percentage of countries within each WHO region where first-line drugs for chronic HBV infection are available on the essentials medicines list or via a government subsidised program [9] ........................................................................................................................................................................ 19

Table 2.5: Worldwide estimates for the number of people living with chronic HBV infection taken from Ott et al. [18] ...................................................................................................................................................... 23

Table 2.6: Meta-analysis data to estimate the prevalence of chronic HBV infection in Indigenous adults/pregnant women in Australia before and after universal vaccination. Data from Graham et al. [53] ...................................................................................................................................................... 34

Table 2.7: Summary of the HBsAg positive rates in NT primary school students and teachers in 1989 adapted and expanded from Gardner et al. [59] ...................................................................................................................................................... 37

Table 2.8: Summary of all peer-reviewed literature reporting HBV prevalence for the NT ......... 41

Table 3.1: Common polymerase mutations leading to antiviral drug resistance ....................... 56

Table 3.2: Summary of geographical distribution of genotypes and sub-genotypes using most recent reclassifications (current Jan 2015). Compiled using [20-22, 30, 33, 35, 43, 48, 55, 56, 59, 64, 69] ...................................................................................................................................................... 64

Table 3.3: Hepatitis B genotypes of recent immigrants to Sydney with relation to their ethnicity as reported by McIntosh et al. [71] ...................................................................................................................................................... 65

Table 3.4: Location, viral load and genotype of 18 samples from the Torres Strait Islanders (unpublished with permission VIDRL) [73] ...................................................................................................................................................... 67
Table 4.1: Summary of assessment tools used to measure health literacy .................................. 91
Table 5.1: Summary of demographics and HBsAg, anti-HBs and anti-HBc positive results broken down by Indigenous status and sex ............................................................................................. 137
Table 5.2: Unadjusted and adjusted odds ratios with 95% confidence intervals for factors associated with an increased or decreased risk of being HBsAg positive .................................................. 139
Table 5.3: Comparison of HBsAg, anti-HBs and anti-HBc prevalence over time and between Indigenous and non-Indigenous people among those referred for HBV testing in the NT ........ 140
Table 9.1: Baseline demographics and clinical details at study entry and the latest time point recorded for 128 sub-genotype C4 chronic HBV infection patients ......................................................... 194
Table 9.2: Detailed information regarding treatment naive patients who transitioned into a different phase during follow up ........................................................................................................... 199
Table 9.3: Detailed information regarding patients who transitioned into a different phase during follow up and have received or are receiving antiviral treatment .................................................. 200
Table of Figures

Figure 2.1: Worldwide prevalence estimates as described by Ott et al [18] ......................... 24

Figure 3.1: The structure of a hepatitis B virion and a sub-viral particle and the replicative cycle
of hepatitis B virus within a hepatocyte. Taken and adapted from Glebe with permission [1],
detailed explanation below. ........................................................................................................... 51

Figure 3.2: Schematic representation of the hepatitis B viral genome with the four open reading
frames outlined, the location of the key promoter areas and the pregenomic and three sub-
genomic RNA strands produced during replication labelled....................................................... 53

Figure 3.3: Schematic representation of the three types of S protein: small, middle and large with
the region relating to the ‘a determinant’ marked ......................................................................... 54

Figure 3.4 Map of the worldwide distribution of hepatitis B virus genotypes and sub-genotypes
using [1-9]. ...................................................................................................................................... 59

Figure 4.1: The Paasche-Orlow & Wolf model [68] ................................................................... 99

Figure 4.2: The hepatitis B Story ................................................................................................ 106

Figure 4.3: The Hepatitis B Bear educational resource ................................................................. 107

Figure 4.4: The participatory action research cycle ................................................................. 108

Figure 5.1: Flow diagram detailing sources of testing data and production of dataset including
only the latest set of results for each individual with all the duplicate tests and individuals
removed ....................................................................................................................................... 133

Figure 5.2: Bar chart showing the percentage of the total NT population tested for any HBV
marker between 2007 and 2011 by age group at time of testing .............................................. 134

Figure 5.3 Age* distribution of individuals who had blood collected for any HBV marker between
2007 and 2011 in the NT compared to the age distribution of the total population of the NT as
per ABS census data 2011. *Age at time blood was collected. Red is Indigenous people, blue is
non-Indigenous people ................................................................................................................. 135
Figure 5.4: Pie chart showing the usual residence of all individuals (A) and HBsAg positive individuals (B) ............................................................................................................................... 136

Figure 5.5: Age distribution of HBeAg positive individuals at the time their last eAg sample was collected for non-Indigenous and Indigenous individuals ....................................................... 138

Figure 5.6: Graphs showing the prevalence (with 95% CI) of HBsAg (A), anti-HBs (B) and anti-HBc (C) by birth cohort for the whole study population and Indigenous and non-Indigenous groups ........................................................................................................................................ 141

Figure 5.7: Scatter plots with 95% CI and line of best fit showing the prevalence of HBsAg (A), anti-HBs (B) and anti0HBc (C) for individuals born since 1980 with markers for overall, Indigenous and non-Indigenous groups ........................................................................................................................................ 142

Figure 6.1: Percentage of study patients residing in each geographical region of the Northern Territory ........................................................................................................................................... 159

Figure 6.2: Bar chart showing the percentage of people negative and those not tested for hepatitis C (HCV), hepatitis D (HDV) and HIV antibodies........................................................................................................ 160

Figure 9.1: Box showing recommended minimum follow up for Indigenous CHB patients by the Royal Darwin Hospital Liver Clinic........................................................................................................ 192

Figure 9.2: Bar chart showing phase of disease at study entry detailed by age group .............. 195

Figure 9.3 Scatter graph showing ALT at study entry and final follow up point for each individual with respect to phase of disease at study entry. Solid lines at 19, 30 and 54 represent the normal ALT cut off for women with CHB, men with CHB and the standard laboratory respectively. Each blue dot represents the result of one female individual, each red dot represents the result of one male individual. (2 very high ALT levels 1462 and 1000 not shown, both in the immune escape phase). SN=study number..................................................................................................................................... 196

Figure 9.4: Bar Chart showing the number of patients who would have their phase of disease changed if the higher laboratory based normal for ALT is used.................................................. 197
Figure 9.5: Bar chart showing the percentage of individuals with chronic HBV infection who have ever received treatment (128), who were receiving treatment at study entry (n=128) and final time point (n=128) and the percentage of cirrhotic chronic HBV infection patients receiving treatment at study entry (n=15) and final time point (n=24) ...................................................... 198

Figure 9.6: Bar chart showing the percentage of cirrhotic and non-cirrhotic individuals in each disease phase at entry to the study and at the most recent follow-up point.............................. 198

Figure 9.7: Percentage of individuals with follow-up blood and imaging tests as per recommended time intervals for blood tests and one or more results for imaging presented by disease phase at entry to the study ................................................................. 201
Section A - Introduction and literature reviews
Chapter 1 - Background, context, scope and aims of the thesis
1.1 Background

The hepatitis B virus (HBV) has infected one-third of the world’s population at some point in their life, with more than 240 million people chronically infected [2, 3]. Chronic hepatitis B (chronic HBV infection) is responsible for significant worldwide morbidity and mortality in the form of liver cirrhosis and liver cancer. The Indigenous population of the Northern Territory of Australia is reported to have a high prevalence of chronic HBV infection with published estimates over the last 40 years ranging from 2.4-13.3%, however robust contemporary estimates are not available.

In the era of full genome sequencing, hepatitis B virus has been divided into 10 different genotypes (A–J) and many sub-genotypes [5]. There is increasing evidence from the worldwide literature that different genotypes behave in different ways, particularly with respect to the natural history of disease and the risk of progression to cirrhosis and hepatocellular carcinoma [6]. The molecular epidemiology of HBV in Indigenous Australians is unknown.

The first Australian National Strategy for Hepatitis B was launched in 2010 [7] with the goal of reducing the transmission of, and morbidity and mortality caused by, hepatitis B and to minimise the personal and social impact of hepatitis B. In order to begin to address this strategy, both epidemiological and molecular virological information about chronic HBV infection in the Indigenous population of the NT is needed. Alone, however, this will not be enough to achieve the strategy’s goal; attention needs to be focused on removing some of the multiple barriers to accessing chronic HBV infection care that exist. Health literacy defined by the WHO as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health” [8] is recognised as one of the potential barriers to people accessing care for chronic HBV infection. Hepatitis B-specific health literacy is much broader than hepatitis B-related knowledge although knowledge is one important component. There is no published information about the level of
hepatitis B-related knowledge in Indigenous people in the NT and no culturally appropriate educational tools about hepatitis B for Indigenous people.

1.2 Context

The Northern Territory of Australia is a sparsely populated (211,944 individuals – 2011 Census data [1]) and vast expanse (more than 1 million square kilometres) of land spanning tropical and subtropical areas of northern and central Australia. It has the highest percentage of Indigenous Australians of all the states and territories of Australia, with 26.8% of the population identifying as Aboriginal and Torres Strait Islander peoples. The majority of the Indigenous population live in more than 100 small remote or very remote communities. The majority of Indigenous people in the NT do not speak English as their first language and often it is a fourth or fifth language. Health beliefs and worldviews vary significantly across the many different language groups in the NT and are often significantly different to the biomedical or Western worldview of health and medicine.

1.3 Scope and structure of thesis

The overarching aim of this thesis to provide high quality evidence to inform improvements in the understanding of, and provision of care to, people with chronic hepatitis B in the Northern Territory of Australia. Three broad areas are covered: the epidemiology of chronic HBV infection, the molecular epidemiology of HBV, and hepatitis B-specific health literacy. Taken together this different but complementary information provides a solid evidence base on which to build an effective response to the National Hepatitis B strategy moving towards optimising the management of chronic HBV infection in the NT.

Section A (Chapters 1 to 4) includes three separate literature reviews. The first focuses on the epidemiology of chronic HBV infection across the world, in Australia and in the NT. Chapter 3 is a contemporary review of the rapidly expanding knowledge with respect to the molecular epidemiology of HBV and the clinical importance of genotype in terms of treatment, morbidity
and mortality. The concept of health literacy, measuring health literacy, barriers to accessing care for chronic HBV infection, cross-cultural communication and our current knowledge of patient’s understanding of chronic HBV infection both internationally and in Australia are discussed in Chapter 4.

Section B (Chapters 5 and 6) focuses on the epidemiology of HBV in the NT and reports the results of a large dataset containing 20 years of Territory-wide testing data providing up-to-date estimates of HBV prevalence. Section C (Chapters 7 to 9) is concerned with the CHARM study (Characterising hepatitis B in northern Australia through molecular epidemiology). The results of the original cross-sectional study, virological information from subsequent full genome sequencing of HBV, and the first four years of the ongoing cohort study it has evolved into are reported. Section D (Chapters 10 and 11) describes the process and results of a qualitative study, used to inform the development of a culturally appropriate educational tool about hepatitis B. This is followed by a detailed description of the process of development of the tool and the final product.

In summary, Section B defines the magnitude of the hepatitis B problem in the NT, Section C focuses on improving our understanding of the genotype of the HBV virus we are dealing with and Section D provides a tool to enable us to communicate effectively with our patients, develop shared understandings and hopefully break down barriers to care.

Chapters 7, 8, 10 and 11 are presented as published papers with no alteration from the published format. Chapters 5 and 9 are submitted for publication and although reformatted for this thesis are unchanged in content. References are listed at the end of each chapter for consistency.
1.4 Aims and hypotheses

1.4.1 The epidemiology of hepatitis B virus in the Northern Territory of Australia

**Aims**

To obtain detailed (including anti-HB-c and anti-HBs as well as HBsAg), accurate, up-to-date estimates of HBV sero-prevalence in the Northern Territory; and

To evaluate the change in HBV sero-prevalence with respect to birth cohort with particular reference to pre- and post- the introduction of universal HBV vaccination at birth.

**Hypotheses**

The prevalence of hepatitis B in the NT is higher than in the rest of Australia and still remains high;

The prevalence of hepatitis B has fallen in those born after the implementation of universal HBV vaccine at birth in 1990; and

The hepatitis B sero-prevalence in antenatal women is not representative of the population as a whole.

1.4.2 The molecular epidemiology of hepatitis B virus in the Northern Territory

**Original Aim**

To establish the genotypes of hepatitis B circulating in the NT.

**Original hypothesis**

There will be a mix of genotypes B and C circulating in the NT.

**Updated aims**

To describe the molecular virology of the unique C4 sub-genotype through full genome sequencing and phylogenetic analysis; and
To establish a cohort of individuals with C4 chronic HBV infection and follow them up longitudinally to learn as much as possible about the natural history of C4 disease.

**Updated hypotheses**

Sub-genotype C4 HBV is the exclusive genotype in the Indigenous population of the NT;
Sub-genotype C4 HBV has molecular markers consistent with an aggressive disease phenotype;
There are virological reasons as to why the current genotype A-based HBV vaccine may be suboptimal in the setting of C4 HBV; and
The natural history of C4 chronic HBV infection is different from other genotypes.

**1.4.3 Hepatitis B specific health literacy in the context of NT remote Indigenous communities: understanding it and establishing culturally appropriate ways to improve it**

**Aims**

To enable a participatory action research project aimed at understanding the knowledge, perceptions and experiences of remote Indigenous adults relating to HBV;
To use the evidence base created above to inform the development of a culturally appropriate educational tool for Indigenous patients living with chronic HBV infection; and
To produce an interactive, mobile, culturally appropriate educational tool about HBV.

**Hypotheses**

Biomedical knowledge about chronic HBV infection is low in Indigenous communities;
Low levels of HBV knowledge impact on and contribute to low levels of hepatitis B-specific health literacy;
Developing a culturally appropriate educational tool about HBV using an evidence base produced from Indigenous community members will increase its ability to improve HBV-related knowledge; and

Increased HBV knowledge will enable improvements in HBV specific health literacy and remove barriers to accessing appropriate care.

1.5 References


Chapter 2 - The epidemiology of chronic hepatitis B
2.1 Overview and clinical aspects of chronic hepatitis B infection

In this chapter I will initially provide some definitions and an overview of the clinical aspects of chronic hepatitis B infection (chronic HBV infection) as well as approaches to prevention and control. I will then discuss the epidemiology of chronic HBV infection from a worldwide, Australian and then Northern Territory (NT) perspective.

2.1.1 Definitions

Chronic Hepatitis B virus (HBV) infection – evidence of HBV infection (i.e. HBsAg positive) for more than 6 months.

Chronic Hepatitis B (CHB) – chronic necroinflammatory disease of the liver caused by persistent infection with HBV.

Occult Hepatitis B – an individual who is HBsAg negative but has detectable hepatitis B virus (HBV) DNA in their blood.

World Health Organisation (WHO) levels of prevalence – High chronic HBV infection prevalence > 8%, intermediate 2-8%, low <2% prevalence in the general population [2].

National and Northern Territory Centre for Disease Control (CDC) notifiable disease definitions for hepatitis B for the purposes of the notifiable disease register:

**Newly acquired (National and NT)** - a confirmed case requires the following laboratory definitive evidence:

Detection of hepatitis B surface antigen (HBsAg) in a patient shown to be negative within the last 24 months;

OR
Detection of HBsAg and IgM to hepatitis B core antigen, in the absence of prior evidence of hepatitis B virus infection;

OR

Detection of hepatitis B virus by nucleic acid testing, and IgM to hepatitis B core antigen, in the absence of prior evidence of hepatitis B virus infection.

Unspecified (National and NT) - a confirmed case requires the following laboratory definitive evidence AND that the case does not meet the criteria for a newly acquired case:

Detection of hepatitis B surface antigen (HBsAg), or hepatitis B virus by nucleic acid testing, in a patient with no prior evidence of hepatitis B virus infection [3].

Chronic (NT only) - a confirmed case requires the following laboratory definitive evidence AND that the case does not meet either the newly acquired or unspecified definitions:

Detection of hepatitis B surface antigen (HBsAg), or hepatitis B virus by nucleic acid testing, in a patient with prior evidence of hepatitis B virus infection more than six months ago [4].

2.1.2 Transmission

The hepatitis B virus is highly infectious; it can remain viable outside the human body for at least seven days and is contained in all bodily fluids to varying degrees [5]. The highest concentrations are in the blood and it is exposure to blood containing high levels of HBV DNA which poses the greatest risk of transmission. This can be during the process of birth, from accidental blood contact during everyday activities, through needle exposure or sexual contact. The reason a detailed understanding of transmission is crucial for discussing chronic HBV infection epidemiology is that the risk of an individual progressing to chronic HBV infection as defined above is significantly different depending on the age at which an individual is infected with the
hepatitis B virus (Table 2.1) [6]. This means that transmission patterns also vary depending on
the background prevalence of chronic HBV infection in a country, region or household. In high
prevalence countries, mother to child and early childhood horizontal transmission predominate,
whereas in low prevalence settings, sexual exposure and unsafe needle use account for the
majority of new HBV acquisitions.

Table 2.1: Risk of progression to chronic HBV infection with respect to age at exposure to HBV
[4]

<table>
<thead>
<tr>
<th>Age at exposure to hepatitis B virus</th>
<th>Chance of developing chronic infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal</td>
<td>90</td>
</tr>
<tr>
<td>Infancy – 2 years</td>
<td>50</td>
</tr>
<tr>
<td>Infancy – 5 years</td>
<td>25-30</td>
</tr>
<tr>
<td>Over 5 years</td>
<td>5-7</td>
</tr>
</tbody>
</table>

2.1.3 Phases of chronic disease

Although our understanding of the natural history of chronic HBV infection has increased
significantly over the last 10 years, particularly with the ability to measure HBV DNA levels and
the use of increasingly sophisticated serological assays, many questions remain unanswered.

Exactly why the natural history of chronic HBV infection is so variable, age dependent and
seemingly complex is still not clearly understood. HBV replication is not considered to be directly
cytopathic and it is understood that liver injury, viral control and serological status are a
consequence of complex virus-host interplays. More detailed virology, and the potential impact
of different hepatitis B genotypes, will be explored in more detail in Chapter 3 of this thesis. This
lack of clarity of the molecular pathogenesis of hepatitis B contributes to a lack of consistency
over time and geographical location regarding the understanding and nomenclature of the
different phases of chronic disease.
Table 2.2: The phases of chronic hepatitis B infection as described by EASL [7], AASLD [8], APASL [4], ASHM [9] and GESA [8]

<table>
<thead>
<tr>
<th>GESA ASHM</th>
<th>Immune tolerant</th>
<th>Immune clearance</th>
<th>Immune control</th>
<th>Immune escape</th>
<th>Resolved infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL</td>
<td>immune tolerant</td>
<td>immune reactive</td>
<td>inactive HBV carrier state</td>
<td>HBeAg negative chronic HBV infection</td>
<td>HBsAg negative</td>
</tr>
<tr>
<td>AASLD</td>
<td>immune tolerance</td>
<td>HBeAg positive chronic HBV infection</td>
<td>inactive carrier state</td>
<td>HBeAg negative chronic HBV infection</td>
<td>Recovery</td>
</tr>
<tr>
<td>APASL</td>
<td>immune tolerant</td>
<td>immune clearance</td>
<td>Low replicative phase</td>
<td>Relapse/variant form of immune clearance/ HBeAg negative hepatitis</td>
<td>HBsAg sero-clearance – state closest to cure</td>
</tr>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&gt;20,000</td>
<td>&gt;20,000</td>
<td>&lt;2000</td>
<td>&gt;2000</td>
<td>undetectable</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Serum ALT</td>
<td>normal</td>
<td>Persistently or intermittently abnormal</td>
<td>normal</td>
<td>Persistently or intermittently abnormal</td>
<td>normal</td>
</tr>
<tr>
<td>Liver histology</td>
<td>Normal or mild hepatitis</td>
<td>Moderate to severe hepatitis +/- cirrhosis</td>
<td>Normal or mild hepatitis +/- cirrhosis</td>
<td>Moderate-severe hepatitis +/- cirrhosis</td>
<td>No active hepatitis</td>
</tr>
</tbody>
</table>

Contemporary understandings as defined by the main bodies that produce international guidelines: The European Association for the Study of Liver (EASL), The American Association for
the study of Liver Disease (AASLD) and The Asia-Pacific Association for the Study of the Liver (APASL) are compared to the Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine and the Gastroenterological Society of Australia (GESA) guidelines in Table 2.2. During this thesis I will use the terms immune tolerant, immune clearance, immune control and immune escape to refer to the 4 phases of chronic HBV infection (definitions below).

In the immune tolerant phase an individual has a high viral load and is HBV e antigen (HBeAg) positive, but alanine transaminase (ALT) levels are normal, with minimal or no inflammation occurring within the liver. In the setting where chronic HBV infection is acquired perinatally or in early childhood, the immune tolerant phase tends to last until early adulthood (although this does vary by genotype – see Chapter 3).

The immune clearance phase is characterised by a decrease in HBV DNA levels and an increase in ALT and histological inflammation. Individuals can progress quickly to immune control, remain in this phase for many months or years allowing significant liver damage to occur, or proceed directly to the immune escape phase. It is during this process the eAg is lost and eAb becomes detectable; the process of ‘e sero-conversion’. It is generally agreed that if this phase persists for more than six months, treatment should be considered.

Immune control is a phase characterised by minimal viral replication (HBV DNA viral loads less than 2000 IU/mL) and resulting low levels of hepatic inflammation. As a consequence, the risk of progressive disease is very low. However, any damage already incurred from immune clearance will still be present, hence people in immune control can have advanced fibrosis or cirrhosis and may still need treatment, although most will not.

Immune escape represents a relapse of active disease with increasing HBV DNA levels to more than 2000 IU/mL, fluctuating ALT levels and active hepatitis on histology, however eAb remains
positive. Recognition of this phase of chronic HBV infection, like immune clearance, should trigger consideration of treatment.

Resolution of chronic HBV infection occurs when an individual develops antibodies to the surface antigen – hence, anti-HBs – and HBsAg becomes undetectable. Although classed as resolved infection, as with the previous phases it is still possible to regress, particularly if an individual becomes immunosuppressed either through illness or secondary to medication. The other scenario that can occur is ‘occult hepatitis B’ where there is HBV DNA detectable but HBsAg is negative, however this is relatively rare.

Table 2.3: Comparison of International and Australian recommendations for when treatment should be considered

<table>
<thead>
<tr>
<th>Guideline</th>
<th>HBeAg positive</th>
<th>HBeAg negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA IU/ml</td>
<td>ALT</td>
</tr>
<tr>
<td>APASL 2015 [8, 10]</td>
<td>&gt;20,000</td>
<td>&gt;2 ULN</td>
</tr>
<tr>
<td></td>
<td>All cirrhots if HBV&gt;2000IU/ml</td>
<td>All cirrhots if HBV&gt;2000IU/ml</td>
</tr>
<tr>
<td>AASLD 2009 [6]</td>
<td>&gt;20,000</td>
<td>&gt;1-2x ULN</td>
</tr>
<tr>
<td>EASL 2012* [9]</td>
<td>&gt;2000</td>
<td>&gt;ULN</td>
</tr>
<tr>
<td>GESA 2010 [11]</td>
<td>&gt;20,000</td>
<td>&gt;1-2xULN</td>
</tr>
</tbody>
</table>

*Patients who fulfil the above criteria for HBV DNA and severity of liver disease, treatment may be initiated even if ALT normal
The terminology varies across the three main international and the Australian guidelines, however there is (in the most recent guideline updates) general consensus on what can be expected to happen in each phase, those who should definitely be treated and the three first-line agents to treat with. Table 2.3 provides a comparison of the different guideline recommendations with respect to treatment.

2.1.4 Treatment

First-line agents as agreed by EASL, AASLD and APASL are: pegylated interferon as a finite course and either entecavir or tenofovir as long-term nucleos(t)ide analogue antiviral agents. Other agents available include lamivudine, adefovir, telbivudine and emtricitabine (all nucleos(t)ide analogues) as well as non-pegylated interferon, however problems with development of resistance (for the nucleos(t)ides) and lack of efficacy make them second-line agents. Unfortunately the three first-line agents are not available in many countries (particularly resource-poor settings) and, when treatment does occur, use of second-line agents worldwide is common. Please see Table 2.4 for details of this by WHO regions as described in the recent WHO global policy report on hepatitis control [12].

Table 2.4: Percentage of countries within each WHO region where first-line drugs for chronic HBV infection are available on the essentials medicines list or via a government subsidised program [9]

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Peg-interferon</th>
<th>Entecavir</th>
<th>Tenofovir*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>25</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>Americas</td>
<td>33</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>41</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>European</td>
<td>61</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>South East Asia</td>
<td>36</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

* Although listed as available in many countries it is only available for people living with HIV, not chronic HBV infection.
2.1.5 Prevention

The availability of a vaccine to prevent chronic HBV infection and increasing access to this vaccination has resulted in major changes to the worldwide epidemiology of chronic HBV infection as detailed in Section 2.2.

The first vaccine was developed by Blumberg and colleagues shortly after identification of the ‘Australia antigen’ in the late 1960s [13]. It was a purified blood product containing surface antigen proteins initially collected from men who have sex with men (MSM) and people who inject drugs (PWID), as they were recognised to be at high risk of having HBV infection. The first clinical trial assessing the vaccine’s efficacy was published in 1980. This double blinded, randomised control trial used two doses of the serum-derived vaccine versus placebo given to 1,083 MSM in New York. Of those given the vaccine, 96% had a confirmed antibody response and there was a significant decrease in the acquisition of hepatitis B over the next 18 months of follow up in the vaccine group (1.4 v 18% P<0.0001) [14].

A small study in the Netherlands in 1979 showed giving hepatitis B immune globulin (HBIG) to babies of mothers living with chronic hepatitis B within 48 hours of birth, and then six monthly, was protective against HBV infection [15]. However there were some theoretical concerns about the possibility that HBV vaccination at such an early age might induce tolerance to HBV antigens and actually increase a baby’s chances of becoming chronically infected. Wong et al. explored this in a double blind randomised control trial published in The Lancet in 1984 disputing these concerns and confirming the effectiveness of providing a birth dose of vaccine together with HBIG, followed by vaccination at one, two and six months of age, in preventing mother to child transmission of HBV infection [16]. This serum-derived vaccine was available for use from 1983 onwards.
In 1986 Emini et al. described the synthesis and purification of HBsAg produced in genetically engineered *Saccharomyces cerevisiae* cells [1]. This method led to the development of the recombinant DNA vaccine currently in use, which has been available in Australia since 1987. Although there are some concerns in the NT about sub-optimal vaccine efficacy specifically in Indigenous Australians (discussed in detail in Chapter 3) it is generally regarded as a safe and efficacious vaccine in the majority of individuals [1]. The 1992 World Health Assembly recommended worldwide vaccination against hepatitis B [17].

Other important measures to reduce transmission on a population level are securing a safe blood supply and sterile healthcare equipment, identifying and treating people living with chronic HBV infection, providing vaccination for high-risk group adults and household contacts in addition to universal infant vaccination programs, and promoting safe sexual practices and enabling people to access clean injecting equipment.

The differential risk of progressing to chronic HBV infection based on age means that the introduction of universal childhood vaccination impacts on the routes of transmission differently in high prevalence countries moving more transmission to adulthood. As the risk of chronic HBV infection when HBV is acquired in adulthood is much lower this in itself will be reflected in a dramatic reduction in chronic HBV infection.

2.1.6 The worldwide control strategy

In 2010 the 63rd World Health Assembly adopted a resolution proposed by the World Hepatitis Alliance calling for a comprehensive prevention and control strategy for viral hepatitis. This led to the development of the Global Hepatitis Program at WHO, which has developed a Strategic Framework which includes 4 axes: raising awareness, promoting partnerships and resourcing; evidence-based policy and data for action; prevention of transmission including universal hepatitis B immunisation and; screening, care and treatment [18]. At the end of 2012, 183
countries had introduced HBV vaccination into their routine childhood vaccination schedules with only 12 (all low prevalence) countries still adopting a targeted approach to vaccination.

GAVI (Global Alliance for Vaccines and Immunisation), an international public-private partnership, has been supporting hepatitis B vaccine since 2001 for some of the world’s poorest countries [19]. Different regions of the world have introduced HBV vaccination at different times, in varying schedules and at varying cost to the individual being vaccinated. Coupled with the complex natural history of HBV, this means detailed contemporary estimates of chronic HBV infection prevalence are difficult to determine but are crucial to guide evidence-based policy on an international, national and local level.

2.2 Worldwide epidemiology

Over 240 million people in the world have chronic HBV infection, with approximately 2 billion or 30% of the world’s population having been infected at some time [19, 20]. Two recent systematic reviews, and one review [19] of global epidemiology, have provided detailed up-to-date estimates of global chronic HBV infection prevalence.

Ott et al. [11] reviewed the English language literature from 1980 until 2007 for all countries, identifying 6,064 citations detailing hepatitis B prevalence. This was reduced to 1,233 based on the abstract and 396 once the full text had been reviewed and eligibility criteria applied. One criterion applied was that data were required to be reasonably representative of the general population rather than from high-risk groups such as PWID or MSM. Only one country (USA) had a primary national data source available for use – the National Health and Nutrition Examination Survey. Age, sex and country specific HBsAg sero-prevalence data were extracted from each study and prevalence of HBsAg was modelled for 21 regions of the world. As well as overall prevalence for 1990 and 2005, (Table 2.5) age, sex and region specific HBsAg sero-prevalence rates were reported with a general decrease in prevalence between the two time points.
Table 2.5: Worldwide estimates for the number of people living with chronic HBV infection taken from Ott et al. [18]

<table>
<thead>
<tr>
<th>Year</th>
<th>Males</th>
<th>Females</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Persons HBsAg positive</td>
<td>Prevalence %</td>
<td>Persons HBsAg positive</td>
</tr>
<tr>
<td>1990</td>
<td>118 million</td>
<td>4.4</td>
<td>105 million</td>
</tr>
<tr>
<td>2005</td>
<td>127 million</td>
<td>3.9</td>
<td>113 million</td>
</tr>
</tbody>
</table>

These are the estimates of sero-prevalence used by WHO in the recent global report on the prevention and control of viral hepatitis [20]. The authors do, however, caution that using data from systematic reviews and modelling can overestimate prevalence for high-income regions and underestimate for low-income regions, as well as not reflecting the heterogeneity within low-prevalence countries in particular. This is notable when looking at the Australian prevalence estimate which is 2-4% (Figure 2.1) for adults and children, an overestimate for overall general population prevalence. Western sub-Saharan African countries had the highest sero-prevalence rates in the world, up to 12% in the age group up to 19 years in 1990 (having fallen to 10% by 2005). South-East Asia and parts of Latin America showed significant drops in sero-prevalence rates for children, from 4-5% in 1990 to 1.5% in 2005, attributed to vaccination programs.

Merrill and Hunter [22] searched all published English and non-English language studies between 1990 and July 2009, identifying 3,698 papers in total discussing hepatitis B prevalence. Following abstract review this number was reduced to 708 and then 568 once all exclusion criteria were applied; 99 of these 568 were in languages other than English, and overall 21,838,249 individuals were represented. The worldwide median prevalence estimate for chronic HBV infection in the general population from this study was 4.3%, which equates to 313 million infected individuals, with no significant global trend reported over the 10 year period 1990-2009. This review is limited by the quality of the studies available, the majority being cross-sectional in design, and
the lack of information in the majority about vaccination status and policy at the time of the study. Goldstein et al. [23] used mathematical modelling using existing data sources and knowledge of the natural history of hepatitis B and the efficacy of vaccination as an alternative way of estimating chronic HBV infection prevalence, disease burden and assessing the impact of vaccination. A model was developed to calculate age-specific risk of acquiring HBV infection, Figure 2.1: Worldwide prevalence estimates as described by Ott et al [18]

Map 1. Map for children.

hepatitis B and progression to chronic HBV infection. This model estimated that 580,000 deaths were attributable to chronic HBV infection in the year 2000. It estimated that without vaccination, in the surviving year 2000 birth cohort, 64.8 million more people would become infected and 1.4 million would die from HBV-related disease worldwide. Prior to universal vaccination, chronic HBV infection estimates were calculated for 15 country groups ranging from 11.83% for countries such as Cambodia, China, Taiwan and Vietnam to 1.1% for Australia, New Zealand and Japan and 0.38% for most of western Europe.

2.2.1 Impact of vaccination in specific countries

A number of countries report significant reductions in chronic HBV infection prevalence as they transition into an era where universal vaccination has been implemented for over a whole generation.

China undertook a national chronic HBV infection sero-survey using multi-stage random sampling in 2006, including 82,078 individuals. This is 14 years after the inclusion of hepatitis B vaccination into the Chinese national childhood immunisation schedule; however vaccination only became free at the point of delivery in 2005. Despite this, overall sero-prevalence has dropped from 10% in 1992 to 7.2% in 2006 and in the under 5 years age group is now only 1.0%, equating to a 90% decrease [24].

The Gambian Hepatitis Intervention Study commenced in 1986 and randomly allocated 125,000 infants to vaccination or not. This was replaced by a nationwide immunisation program for all infants in 1990. A cross-sectional survey in 2007-8 located and tested 2,670 individuals who were part of the GHIS; unfortunately only 753 (28%) could be linked back to the original vaccination records. Based on these 753 individuals, HBsAg prevalence was 12.4% in those not vaccinated and 0.5% in those vaccinated. Interestingly in those fully vaccinated, 27% were positive for anti-HBc, indicating resolved infection, compared to 56% in the never vaccinated
group [25]. In a separate arm to this study, 4,613 children born since universal vaccination were also retested, with an overall prevalence of chronic HBV infection of 0.5%.

The Taiwanese national hepatitis B immunisation programme commenced in 1984 for children born to high-risk mothers only. It was then extended to all newborns in 1986 with catch-up programs for preschool and primary school children until 1990. The program consists of four doses of vaccine and a dose of HBIG to babies of mothers who are HBeAg positive at the time of birth. Prior to this program, more than 90% of the general population of Taiwan under the age of 40 years had been infected with hepatitis B and 15-20% had chronic HBV infection [26]. Fifteen years after the program began, chronic HBV infection rates in children under the age of 15 years had fallen to 0.7% [27]. The recent report detailing 30-year outcomes shows significant decreases (more than 90% reductions) in mortality from infant fulminant hepatitis, chronic liver disease and hepatocellular carcinoma [28].

### 2.2.2 Migrants as a high-risk group

High-income, low-prevalence regions such as North America, Western Europe and Australia often have significant migrant populations which originate from highly endemic regions of the world. Rossi et al. [29] conducted a systematic review looking at the worldwide sero-prevalence of chronic HBV infection and immunity in immigrants and refugees. This review includes 110 studies, 90% of which were carried out in the setting of asymptomatic screening, representing 209,822 migrants from all regions of the world. This work estimates there are 3.5 million immigrants and refugees (95%CI 2.8-4.5) living in receiving countries with chronic HBV infection. The proportion of all migrants with chronic HBV infection ranged from 3.7-9.7% in different host countries, with the highest number residing in the USA, Canada, Germany, Italy, the United Kingdom and Australia in that order. Higher rates were found in refugees as opposed to migrants and more than half of all individuals included were non-immune to hepatitis B, and hence would benefit from vaccination. Pooled sero-prevalence estimates of chronic HBV infection in migrants...
from different world regions mirrored the prevalence of chronic HBV infection in their regions of origin, highlighting them as an important risk group in low-prevalence countries.

2.2.3 Indigenous populations as a high-risk group

Indigenous populations worldwide are disproportionately affected by chronic HBV infection, in particular in the Amazon Basin region [30], the circumpolar Artic region [31], Taiwan [32], Russia [33], Africa [34] and New Zealand [35]. The details with respect to Australian Indigenous people will be discussed in Section 2.3. Recently the Inaugural World Indigenous Peoples’ Conference on Viral Hepatitis was held in Alice Springs, Northern Territory, Australia (14-16 September 2014). There was representation from numerous areas of the world where chronic HBV infection in Indigenous populations is being highlighted and starting to be addressed as an urgent and preventable public health issue. The Amazon basin, North America and the circumpolar region, Taiwan, Russia, South-East Asia and Australian Indigenous populations were some of the many areas of the world included in the proceedings. The Anwernekenhe (which means belongs to us in the Arrerente language) consensus statement was produced as a result of the meeting urging nation-states and their governments to make special provision in health and funding policies for equitable access to prevention, testing, treatment and management of viral hepatitis in Indigenous peoples. While this was the first conference to focus on viral hepatitis in Indigenous populations, over 30 years on from the availability of hepatitis B vaccine there are numerous long-standing programmes tackling viral hepatitis within Indigenous populations. Alaskan Native people in the mid-1970s had an overall prevalence of HBsAg positivity of greater than 6% and up to 20% in some areas [36]. In 1984 a comprehensive HBV control program was initiated including universal infant immunisation as well as population-wide (all Alaskan native people) screening and immunisation where appropriate [37]. Twenty-five years later, acute hepatitis B and hepatocellular carcinoma have been eliminated in Alaskan Native children, with no cases of
acute hepatitis B since 1992 [38]. Similar decreases are anticipated in the Canadian Aboriginal population and Greenland Inuit in time [39].

2.2.5 PWID as a high risk group

PWID are another high risk group of individuals worldwide. A recent systematic review estimates that of the 16 million people (range 11-21) worldwide who inject drugs 1.2 million (range 0.3-2.7) have chronic HBV infection and 2.3 million (range 2.3-9.7) have evidence of past infection [40]. This is based on the review of 190 sources reporting HBsAg rates and 186 reporting anti-HBc prevalence across 59 and 43 countries respectively.

2.3 Australian epidemiology

Australia as a whole is classified by WHO as a low prevalence country for chronic HBV infection, however there are pockets of higher prevalence in certain high-risk groups such as Indigenous Australians, migrants from highly endemic countries, PWID and MSM. In 1952, HBV was notifiable in Victoria, then described as ‘homologous serum jaundice’ which later transitioned into the label ‘serum hepatitis’ and then hepatitis B [41]. Since 1971, hepatitis B has been part of the National Notifiable Diseases Surveillance System in Australia, with annual reports collating data from all states and territories to include all cases notified. Universal vaccination for all infants including a birth dose, plus HBIG administered to all babies born to mothers who have chronic HBV infection, was implemented across Australia in 2000 [42].

2.3.1 The Australian control strategy

Universal blood donor screening was introduced by the Australian Red Cross in 1971 [43] then targeted vaccination of “high risk” infants (those born to HBsAg positive mothers) and individuals followed in 1988 [43]. Universal antenatal screening was formally recommended in the 1990 Australian College of Obstetrics and Gynaecology guidelines [44] and universal birth
dose and childhood vaccination for hepatitis B was introduced Australia wide in the year 2000. Around 2009 some units across Australia (including Royal Darwin Hospital in the NT in 2010) commenced the provision of antiviral therapy (initially lamivudine and then tenofovir) in the last trimester of pregnancy for HBsAg positive mother with a high viral load (> 10 million IU/ml).

The first Australian National Hepatitis B Strategy was launched in 2010 [45] with the aim of “reducing the transmission of and morbidity and mortality caused by hepatitis B and to minimise the personal and social impact of hepatitis B.”

This has been followed by the second national strategy [46] launched in 2014 with much more specific aims and tangible targets to achieve by 2017, namely:

1. Achieve HBV childhood vaccination coverage of 95%;
2. Increase hepatitis B vaccination coverage of priority populations;
3. Increase to 80% the proportion of all people living with chronic HBV infection who are diagnosed; and
4. Increase to 15% the proportion of all people living with chronic HBV infection who are receiving antiviral treatment.

In order to achieve these targets it is essential to have accurate data regarding the epidemiology of chronic HBV infection in the population. A number of methods can be used to develop these data on a national level including: sero-surveys (the historical gold standard); using existing routinely collected data in various ways such as data linkage or risk group estimations; and mathematically modelling, either generic or specific.

In 2012 supported by the major advocacy and healthcare organisations in Australia and New Zealand the Auckland Statement was launched at the 8th Australasian Viral Hepatitis conference in Auckland. The targets for hepatitis B included in this statement were:
1. To apply consistent approaches to funding hepatitis B vaccinations for those at greatest risk;
2. To ensure at least 80% of people living with hepatitis B or hepatitis C are diagnosed;
3. To guarantee that 10% of people living with hepatitis B receive antiviral treatment.

2.3.2 National sero-surveys

Three national sero-surveys have been conducted; however at the time of writing only two of these have been reported in the published literature. Both were convenience samples accessing sera collected for other diagnostic tests. The first survey [47] accessed serum collected between 1996 and 1999 from 3,336 individuals aged between 1 and 59 years. Equal numbers of males and females were included and samples were stratified by age and tested for anti-HBs (n=3336), anti-HBc (n=2476), and in all those that were anti-HBc positive, HBsAg testing was attempted (55 of 81). Unfortunately, due to the nature of the study sample, 26 of the 81 samples that tested positive for anti-HBc had insufficient sample available to complete all required testing and hence determine an HBsAg result. A sensitivity analysis was therefore conducted to produce a minimum (assuming all missing were negative) and adjusted (coding missing results proportionally to the other HBsAg results) prevalence estimate. Prevalence estimates were calculated separately for each age stratum and then age groups were weighted based on the 1998 Australia age profile. Minimum estimates of chronic HBV infection were 91,500 (0.49%) with an adjusted estimate of 163,000 (0.87%). The second sero-survey [11] accessed sera collected in 2002 (n=2762 for anti-HBs, n=1009 for anti-HBc) with the same methodology except in this case only two of the 61 anti-HBc positive samples could not be tested for HBsAg. Minimum prevalence estimates assuming those two to be negative were 0.7% (95% CI 0.6-0.7) and maximum estimates assuming the missing values were positive were 0.8% (95%CI 0.8-0.9). The third sero-survey accessed sera collected in 2007-2008 and was reported in the WHO global
policy report on the prevention and control of viral hepatitis [46] as having been carried out, but no published results are currently available.

Although sero-surveys are seen as the gold standard methodology for reporting prevalence of infectious diseases there are a number of problems with these data when looking for accurate estimates of chronic HBV infection to guide national policy and plan intervention strategies. Even when using convenience samples, published results are not available in a timely fashion with at least a five year time lag between collection of sera and publication of these studies. Bias may be a factor as these are all individuals who have presented to healthcare facilities in order to have blood taken for an unspecified reason and in both sero-surveys samples were not tested in proportion to the age distribution of the population, and those under 1 and over 60 were not represented at all. In Australia, as in many other low prevalence countries, chronic HBV infection is unequally distributed within the population with certain groups such as Indigenous Australians, migrants from highly endemic countries, PWID and MSM carrying a greater percentage of the burden. In particular, migrants from high and intermediate prevalence countries in Asia have been estimated to account for approximately half of the people with chronic HBV infection in Australia [48]. Indigenous Australians represented 2.6% of the population in the 2011 Census [49] but account for 9.3% of those affected by chronic HBV infection [50].

A further sero-survey was undertaken specifically covering the state of Victoria (95.7% of samples from Victorian postcodes) with serum from 1995, 2000 and 2005 included [51-53]. Although this was also a sample of convenience taken from stored serum archived at the Victorian Infectious Diseases Reference Laboratory, a number of measures were undertaken to attempt to reduce any potential selection bias. Any samples from patients ever referred for testing for HBV, hepatitis C or HIV previously were excluded, and proportionate numbers of each sex and age group were included. Of the 3,212 samples tested, HBsAg prevalence was 1.1%
overall (95% CI: 0.8-1.6). Standardised chronic HBV infection prevalence estimates for Melbourne were slightly higher at 1.4%. It was suggested this may be due to Melbourne having proportionally (compared to the rest of Australia) more residents who are born overseas in intermediate prevalence countries.

2.3.3 Alternative estimates

To examine alternative methods of producing contemporary and timely estimates of chronic HBV infection prevalence and to attempt to ensure priority populations were better identified, a national mapping project was undertaken with detailed results published in 2013 and 2015. This project used estimates of chronic HBV infection in the whole population and identified groups (people born overseas, Indigenous Australians, PWID, MSM, and non-Indigenous people born in Australia) derived from review of published literature and the 2011 Australian Census. With respect to people born overseas, country of birth was taken from the Census data and estimates of chronic HBV infection prevalence in country of birth were derived from published literature estimates. The chronic HBV infection prevalence for Indigenous Australians was taken from the systematic review discussed below [39] with population numbers from the 2011 Census. The denominator for PWID was obtained from the Australian Institute of Health and Welfare National Drug Strategy Household Survey 2010 and chronic HBV infection prevalence from the Nelson et al. [55] global systematic review. Estimates of numbers of MSM and chronic HBV infection prevalence in this group were taken from the available published literature. In addition to this risk group method, a deterministic, dynamic mathematical model of hepatitis B in the Australian population from 1951 onwards was created, separate age strata were modelled and the model was parameterised using a wide range of data sources. The deterministic mathematical model was constructed several years earlier as part of the senior author’s PhD thesis (Cowie [53]). This was used to validate the results of the risk group-based methodology. Model derived estimates were then compared with annual hepatitis B surveillance notifications.
to estimate the proportion of people living with chronic HBV infection who have not been diagnosed.

The risk-based methodology estimated there to be 218,000 people living in Australia with chronic HBV infection (1.02%) with the majority (56.1%) having being born overseas, predominantly in the Asia/Pacific region. Of those born in Australia, Indigenous Australians make up 9.3%, PWID 5.7% and MSM 4.4%. The Northern Territory has the highest overall prevalence of all states and territories at 1.68%. The model-based methodology produced an estimate of 204,000 (0.91%) and suggested that 44% of those living with chronic HBV infection had not been diagnosed or notified. The second mapping report provides further details about current levels of diagnosis, monitoring and treatment, vaccination and treatment outcomes such as hepatocellular carcinoma utilising national datasets. The cascade of care presented in this report estimates 43% of those living with chronic HBV infection to be undiagnosed, 87% to be in no appropriate care for their chronic HBV infection and only 5% (2.4% in the NT) to be receiving treatment [56].

2.3.4 Indigenous Australians

In 2013 Graham et al. [57-65] published a review of chronic HBV infection prevalence among Indigenous Australians looking specifically at studies carried out before and after the year 2000 so as to try to establish the impact of the implementation of universal vaccination. Twenty-two studies were included, nine of which were conducted in the NT and will be discussed in more detail in the next section. Looking at the two time periods, 10 studies were pre-2000 and 12 post, nine were cross-sectional in design, seven clinical audits, three serological surveys on convenience samples and two retrospective analyses of midwifery data, with one longitudinal study [51]. Meta-analysis was carried out for the sub-groups of adults and pregnant women. Pre-2000 chronic HBV infection prevalence varied between 3.6% and 26% with 6 of the 10 studies reporting rates greater than 8% or high prevalence as per WHO criteria. Post-2000 studies
prevalence results ranged from 0.8% to 12%. Meta-analysis data are presented in Table 2.6. These results are encouraging in that prevalence rates are falling, but concerning in that the disparity between Indigenous and non-Indigenous individuals is persisting. The Indigenous population sample size of the majority of included studies was small, many were clinical audits and the majority were carried out in remote and regional settings so may not be transferrable to the urban Indigenous population.

Table 2.6: Meta-analysis data to estimate the prevalence of chronic HBV infection in Indigenous adults/pregnant women in Australia before and after universal vaccination. Data from Graham et al. [53]

<table>
<thead>
<tr>
<th></th>
<th>Pooled HBsAg prevalence in adults/pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (95% CI)</td>
</tr>
<tr>
<td>Pre-2000</td>
<td>6.47% (4.56-8.39)</td>
</tr>
<tr>
<td>Post-2000</td>
<td>2.25% (1.26-3.23)</td>
</tr>
</tbody>
</table>

2.4 Northern Territory epidemiology

The ASHM hepatitis B mapping project estimated the Northern Territory ‘Medicare Local’ (Primary care group) to have the highest overall hepatitis B prevalence in Australia at 1.68% or 3,555 individuals. This project estimated 59% of those living with chronic HBV infection to be Indigenous Australians and 22% to have been born overseas [53]. In the second mapping report the NT has a notification rate for chronic HBV infection of 90.4/100,000 people, which is the highest in Australia at three times the national average. The NT has the highest documented rate of testing for HBV viral loads at 204 tests per 100,000 people but this still only equates to 15% of those affected receiving regular monitoring. Only 2.4% of those living with chronic HBV infection in the NT are estimated to be receiving antiviral therapy [3]. Together these reports highlight the magnitude of the challenges facing the NT with respect to chronic HBV infection.
2.4.1 The Northern Territory setting

It is postulated but not proven that the major route of HBV transmission in the NT Indigenous population is vertical – mother to child around the time of birth, however there is no solid data to confirm this and the contribution of early horizontal transmission has not been extensively explored. The Northern Territory (NT) has a small overall population of 211,000 spread over a large geographical area of more than a million square kilometres. Thirty percent of the population are Indigenous Australians and 30% of this group live in very remote settings. There is also a significant migrant population, in particular from the countries just north of the NT in South-East Asia where chronic HBV infection prevalence is historically high by WHO definitions.

The Northern Territory was the first jurisdiction in Australia to introduce universal hepatitis B vaccination. It was introduced for all Indigenous babies born in the NT from 1988 and then for all babies from 1990, 10 years before it became Australia-wide policy [73]. Until the year 2000 the NT schedule included a birth dose followed by two further doses in the first six months of life, with HBIG given to the infants of all HBsAg positive mothers. Since 2000 the schedule has included four doses of vaccine (at birth, 2, 4 and 6 months). A catch-up program was conducted in 1998 in NT schools for all children aged 6-16 years of age (those born between 1982 and 1992) who had not been vaccinated at birth. Hepatitis B has been a notifiable disease in the NT since 1992 however only acute cases were recorded until 2006. From 2006 onwards all cases have been notifiable and classified as newly acquired, chronic or unspecified (see definitions in 2.1.1). The NT Centre for Disease Control (CDC) holds this information in a central database. Annual figures for acute and unspecified HBV notifications are reported annually to the National Surveillance program.
2.4.2 Historical data

Barrett (1972) first reported higher prevalence rates for HBsAg in Indigenous patients in northern Australia in 1972 [74]. Stored sera from 891 Indigenous Australian patients from northern Queensland, the Torres Strait and the NT showed a sero-prevalence of 8.1% in adults and 3.4% in children. Barrett then obtained further sera taken between 1968 and 1974 from 1,301 Indigenous Australians representing 16 centres across the NT [62]. The samples were tested for HBsAg, serotype and Anti-HBs. This study also included Aboriginal patients from Queensland (892), Torres Strait Islanders (58) and Australian Caucasians from Brisbane (234).

Prevalence of HBsAg positivity was 8.5% in the NT Aboriginal patients compared to 2.7% in the Queensland Aboriginal patients. The age distribution between the two groups was also different, with the NT patients having much higher sero-prevalence in the youngest age groups compared to Queensland. All but one of the Aboriginal samples was serotype ay in contrast to the Torres Strait Islander samples which were ad (this is discussed further in Chapter 3). It was also observed that family clustering of HBsAg positive cases was apparent. The author had some concern regarding the accuracy of the serological tests used and felt that if anything the results were a minimum estimate.

In 1992 Gardner et al. [79] conducted a prospective cross sectional sero-survey of school children and staff in 24 selected primary schools across the NT. Some 1,115 students 9-17 years of age gave consent to be in the study and had finger-prick blood samples taken for HBsAg and Anti-HBs, while 209 staff also had serological testing performed. All study participants completed a brief questionnaire including demographics and ethnic background, and HBsAg positive samples were also tested for HBV DNA. A summary of the results is presented in Table 2.7. Not only were high prevalence rates of current and past HBV infection reported for Aboriginal school children but markers of past infection were higher for both staff and students from otherwise low prevalence backgrounds.
Table 2.7: Summary of the HBsAg positive rates in NT primary school students and teachers in 1989 adapted and expanded from Gardner et al. [59]

<table>
<thead>
<tr>
<th>Background</th>
<th>Study group</th>
<th>Region</th>
<th>HBsAg Positive (%)</th>
<th>Anti-HBs Positive (%)</th>
<th>HBsAg/Ab Positive (%)</th>
<th>All sero-markers negative (%)</th>
<th>Past or present HBV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Students</td>
<td>Urban</td>
<td>2 (0.3)</td>
<td>74 (13.5)</td>
<td>0</td>
<td>474 (86)</td>
<td>13.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rural</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (100)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Staff</td>
<td></td>
<td>3 (1.6)</td>
<td>20 (11.1)</td>
<td>0</td>
<td>157 (87.2)</td>
<td>12.8%</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>Students</td>
<td>Urban</td>
<td>2 (1.2)</td>
<td>32 (19.4)</td>
<td>0</td>
<td>131 (79.4)</td>
<td>20.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rural</td>
<td>22 (8.0)</td>
<td>138 (50.4)</td>
<td>12 (4.4)</td>
<td>102 (37.2)</td>
<td>62.8%</td>
</tr>
<tr>
<td></td>
<td>Staff</td>
<td></td>
<td>0</td>
<td>9 (37.5)</td>
<td>0</td>
<td>15 (62.5)</td>
<td>37.5%</td>
</tr>
<tr>
<td>Other</td>
<td>Students</td>
<td>Urban</td>
<td>1 (0.9)</td>
<td>33 (30.6)</td>
<td>1 (0.9)</td>
<td>73 (67.6)</td>
<td>32.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rural</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Staff</td>
<td></td>
<td>0</td>
<td>2 (40)</td>
<td>0</td>
<td>3 (60)</td>
<td>40%</td>
</tr>
</tbody>
</table>

A small (n=161) sero-survey was undertaken in the NT alongside the first Australian national sero-survey using blood collected between 1996 and 1999 [66]. The age of participants ranged from 1-84 years and all samples were tested for Anti-HBs and Anti-HBc; if positive for Anti-HBc they were tested for HBsAg. The indigenous status of participants included in the sample was not known. Overall sero-prevalence of HBsAg positivity was 0.8 (95% CI: 0-1-1.7), very similar to the Australia-wide results. Anti-HBs prevalence was much higher at 41% (95% CI: 30.1-51.2) in the NT, as was Anti-HBc prevalence at 28% (95% CI: 16.4-39.3%). The former represents earlier introduction of universal HBV vaccination, although the latter suggests that despite universal vaccination, rates of previous HBV infection are still high in the NT (this will be discussed further in Chapter 2.3).

2.4.3 Antenatal data

Antenatal data recorded routinely in the NT has been explored extensively by several research groups over the last 10 years. This has been possible and useful due to the universal screening of women in pregnancy, early inclusion of hepatitis B vaccine into the NT childhood immunisation
schedule, the NT midwives’ data collection system and the NT immunisation database. An audit of all births at Royal Darwin Hospital (1515) during 2003 was undertaken to check HBV screening rates, HBIG delivery to infants and vaccination rates of infants born to HBsAg positive mothers. With a screening uptake of 94.3%, chronic HBV infection prevalence was 2.27% (95% CI: 1.58-3.23) overall, 4.07% (95% CI: 2.63-6.20) in Indigenous women and 1.16% (95% CI: 0.59-2.20) in non-Indigenous women. HBIG was received within 12 hours for all cases and immunisation was completed in 93.3% of cases by 9 months [68]. This study was then complemented by equivalent data from Alice Springs Hospital for the year 2005 [67] producing similar prevalence estimates with a chronic HBV infection prevalence among Indigenous women of 3.2% (95% CI:1.8-5.5); that for non-Indigenous women was 0.6% (95% CI: 0.01-2.2). The data were then aggregated to give a more powerful overall estimate of chronic HBV infection in antenatal women for the NT of 3.7% in Indigenous and 0.98% in non-Indigenous women [76].

Wood et al. [76] assessed all women giving birth over the period 01 July 2002 to 30 June 2004 identified from the NT midwives’ data collection system. Their records were linked using the hospital record number to the NT Government pathology service electronic results system (Labtrack) to obtain any HBsAg results in the nine-month period before they gave birth. Chronic HBV infection sero-prevalence rates were then calculated by age group, location of delivery and indigenous status. The 15-40 year old female population prevalence was calculated by weighting the age-specific prevalence estimates using the age distribution of the NT female population in mid-2002 taken from Australian Bureau of Statistics data. Overall, 3.1 % were positive for HBsAg (95% CI: 1.9-4.3), for Indigenous women 5.5% (3.4-7.7) and non-Indigenous women 0.8 %(-0.2-1.7) [80].

Most recently Liu et al. [24, 26] performed a data linkage study reviewing mothers birthing in NT public hospitals between 2005 and 2010. The NT perinatal register (containing all births) was linked to the CDC NT Notifiable Diseases System database (containing all HBV diagnoses).
ecological study design was then used to compare prevalence rates for mothers who were born before and after the implementation of universal vaccination in the NT (1990). Women born overseas or not usually resident in the NT were excluded (2,024), leaving 10,797 for analysis, Australian Indigenous mothers accounted for 52.6% of these birthing mothers. Overall, 138 women (1.3%) of the 10,797 included linked to a positive HBsAg test result. Indigenous women had a significantly higher prevalence than non-Indigenous women (2.4% versus 0.04% \( P<0.001 \)). When looking at Indigenous women over time those born in the pre-vaccine era had a prevalence of 2.8% compared to 0.8% in the post-vaccine era. Women living in remote (1.3%) or very remote regions (3.1%) had higher prevalence rates than outer regional residents (0.6%).

This study demonstrates falling rates of chronic HBV infection in Indigenous mothers in the NT, however the sero-prevalence rate of 0.8% in those who should have been fully immunised is still higher than has been reported elsewhere. Only HBsAg is reported in the notifiable disease reports so this study was not able to capture individuals who have resolved HBV infection. It is also important to note that all mothers who were born overseas were excluded from this study to enable a true assessment of the vaccine program for people born in the NT. It is important therefore to acknowledge that this study does not report on overall prevalence of chronic HBV infection in the NT.

2.4.5 Recent data

An audit of a convenience sample of 112 Indigenous patients in a remote East Arnhem community, who had undergone an adult health check including hepatitis B serology in 2008, was undertaken by Carroll et al. [71]. Unfortunately complete HBV serology was only available for 26 (23%) of these patients. Evidence of past infection as evidenced by positive Anti-HBc was documented in 43 of 68 (63%) and chronic HBV infection (defined as two or more HBsAg positive results more than six months apart) was documented in 9/76 or 12% (95% CI: 6-21). Of 21
patients with a documented vaccination history 3 were Anti-HBc positive, indicating past
infection despite vaccination.

A small prospective serological survey published in 2010 [1] identified and obtained blood for
HBV serology from 37 adolescents who had been fully vaccinated as children. Eleven (30%)
showed evidence of past hepatitis B infection and 4 (11%) had active infection as evidenced by
HBsAg positivity.

There is a lack of recent NT-wide data detailing chronic HBV infection sero-prevalence. What is
concerning from the data available is the persistently high rates of HBsAg positivity in Indigenous
individuals, especially in the context of 27 years of universal vaccination. This was the baseline
on which we planned the epidemiological study described in Chapter 8.
Table 2.8: Summary of all peer-reviewed literature reporting HBV prevalence for the NT

<table>
<thead>
<tr>
<th>Author and year published</th>
<th>Study population</th>
<th>Study period</th>
<th>Study design</th>
<th>Indigenous status</th>
<th>Sample size</th>
<th>HBsAg prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett 1972</td>
<td>Children Adults</td>
<td>1968</td>
<td>Sero-survey</td>
<td>Indigenous</td>
<td>114</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>5.0</td>
</tr>
<tr>
<td>Gardner 1992</td>
<td>School children</td>
<td>1989</td>
<td>Cross sectional school survey</td>
<td>Low risk</td>
<td>556</td>
<td>0.36</td>
</tr>
<tr>
<td>Teachers</td>
<td>Low risk</td>
<td></td>
<td></td>
<td>Indigenous</td>
<td>439</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td>109</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Teachers</td>
<td></td>
<td></td>
<td></td>
<td>209</td>
<td>1.4</td>
</tr>
<tr>
<td>Wood 2005</td>
<td>General age 1-84 years</td>
<td>1996-1999</td>
<td>Sero-survey</td>
<td>Unknown</td>
<td>161</td>
<td>0.8</td>
</tr>
<tr>
<td>Romanes 2006</td>
<td>Pregnant women</td>
<td>2003</td>
<td>Retrospective audit</td>
<td>All</td>
<td>1402</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indigenous</td>
<td>540</td>
<td>4.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-Indigenous</td>
<td>862</td>
<td>1.16</td>
</tr>
<tr>
<td>Schultz 2007</td>
<td>Pregnant women</td>
<td>2005</td>
<td>Retrospective audit</td>
<td>All</td>
<td>792</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Indigenous</td>
<td>433</td>
<td>3.2</td>
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<td></td>
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<td></td>
<td>Non-Indigenous</td>
<td>359</td>
<td>0.6</td>
</tr>
<tr>
<td>Schultz 2008</td>
<td>Pregnant women</td>
<td>2003 &amp; 2005</td>
<td>Combination of above 2 audits</td>
<td>All</td>
<td>2194</td>
<td>2.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indigenous</td>
<td>973</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-Indigenous</td>
<td>1221</td>
<td>0.9</td>
</tr>
<tr>
<td>Wood 2008</td>
<td>Pregnant women</td>
<td>2002-2004</td>
<td>Retrospective data linkage</td>
<td>All</td>
<td>1061</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indigenous</td>
<td>534</td>
<td>4.1</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-Indigenous</td>
<td>527</td>
<td>1.2</td>
</tr>
<tr>
<td>Carroll 2010</td>
<td>Adults</td>
<td>2008</td>
<td>Retrospective clinical audit</td>
<td>Indigenous</td>
<td>76</td>
<td>12</td>
</tr>
<tr>
<td>Dent 2010</td>
<td>Adolescents</td>
<td>2005</td>
<td>Prospective cross sectional survey</td>
<td>Indigenous</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>Liu 2012</td>
<td>Pregnant women</td>
<td>2005-2010</td>
<td>Data linkage</td>
<td>All</td>
<td>10797</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indigenous</td>
<td>5678</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-Indigenous Australian born</td>
<td>5119</td>
<td>0.04</td>
</tr>
</tbody>
</table>
2.5 Conclusions

Chronic HBV infection is a vaccine preventable, treatable, chronic infection with a global distribution. The worldwide, national and local epidemiology is currently changing for multiple reasons including vaccination, population movements, increasing treatment availability and an increasing advocacy agenda. Chronic HBV infection epidemiology is very variable even across different regions and population groups within the same country.

Traditional sero-surveys are still important and provide reliable information about true chronic HBV infection prevalence, however they are time consuming and expensive. Mathematical modelling and innovative methods using existing data sources appear to provide accurate estimates and can be updated in a timely fashion. In this dynamic landscape it is increasingly crucial for timely epidemiological data to be available to governments and healthcare providers. This can then enable tailored implementation of the most appropriate and effective strategies to prevent new acquisitions and reduce morbidity and mortality for those already living with chronic HBV infection.

The majority of the data presented for the NT is either historical in context or specific to certain groups such as antenatal women or specific geographical locations. There are no detailed and up-to-date NT specific prevalence data on which to base and plan public health strategy and work towards reaching the targets laid out in the Second National Hepatitis B Strategy.
2.6 References

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Chapter 3 - Molecular epidemiology of hepatitis B
3.1 Hepatitis B the virus

3.1.1 Lifecycle

Hepatitis B, a member of the Hepadnaviridae family, is a small (3,200 base pairs) enveloped partially double stranded DNA virus.

Figure 3.1: The structure of a hepatitis B virion and a sub-viral particle and the replicative cycle of hepatitis B virus within a hepatocyte. Taken and adapted from Glebe with permission [1], detailed explanation below.

Figure 3.1 shows the structure of a hepatitis B virion (A) made up of a central nucleocapsid core with relaxed circular DNA and the polymerase protein surrounded by core proteins. The envelope is made up of small, middle and large surface proteins which contain the ‘antigenic loop region’ important for binding. Sub-viral particles (B) are composed of small, middle and large surface proteins only and do not contain viral DNA. They can be filamentous or spherical.
and are present in the serum of individuals living with chronic HBV infection in concentrations that are 1,000 to 10,000 times greater than that of HBV virions.

It has only been discovered in the past three years that HBV binds (1) via the pre S1 region of the large surface envelope protein to the sodium taurocholate co-transporting polypeptide (NTCP), and entry can be blocked by silencing this receptor [2]. Endocytosis of the virion then occurs and the released nucleocapsid is transported to the nucleus (2). Once inside the nucleus the HBV DNA is released and converted into covalently closed circular (ccc) DNA (3) complexed with histone and non-histone cellular proteins (4). From this episomal cccDNA one pregenomic (larger than the full genome) and two sub genomic (smaller than the full genome) messenger RNAs are produced (5). The sub genomic mRNAs undergo translation at the endoplasmic reticulum to form the three surface (S) proteins small, middle and large (6). Some of these surface proteins are formed into sub-viral particles and secreted out of the cell and some are directed to envelope mature nucleocapsids (13). Meanwhile, viral replication occurs through translation of the pregenomic mRNA to produce core proteins and polymerase; these along with pregenomic RNA are assembled into immature core particles within the cytoplasm of the hepatocyte (9) and (10). The pregenomic mRNA also produces soluble and secreted e antigen (15). Inside the immature nucleocapsid, reverse transcription occurs and the mature nucleocapsid (11) is either transported to the nucleus to maintain the cccDNA pool (12) or enveloped with surface proteins and secreted through multivesicular particles (14). A fourth smaller mRNA (not shown) is produced from the cccDNA and once translated produces the HBV X protein.

3.1.2. Genome

The 3.2kb genome of the hepatitis B virus has four overlapping open reading frames: S, Pol, Core and X. (Figure 3.2).
The polymerase gene [nucleotides ~ 2307 – 1623 (when the EcoR1 site = 1)] encodes the viral polymerase including the terminal protein, reverse transcriptase and RNase H, all of which are crucial for viral replication as detailed above. The surface gene (nucleotides ~ 2848-835) encodes the large, middle and small surface proteins formed from the subunits S, preS1 and preS2 (Figure 3.3). These are the surface envelope proteins of the HBV virus and as shown in figure 3.1 are important for viral hepatocyte binding and cell entry [1]. The overlapping nature of the open reading frames mean that mutations in one reading frame can affect others; this is particularly true for the S gene which completely overlaps with Pol [3]. The ‘a determinant’ or major antigenic determinant is located between amino acid (aa) positions ~ 99-161 in the S domain [4], it has a (hypothetical) complex, three-dimensional structure due to multiple disulphide bridges.
between cysteine residues [1]. This is the area targeted by vaccine-induced and naturally produced surface antibodies [5, 6].

**Figure 3.3: Schematic representation of the three types of S protein: small, middle and large with the region relating to the ‘a determinant’ marked**

![Diagram of S protein types with marked region]

The precore/core gene (nucleotides ~ 1814-2452) encodes for the structural core protein and also allows synthesis and processing of a non-structural form of the core protein, e antigen. The e antigen plays a prominent, although not completely understood, role in the HBV-host immune system interaction [7]. It is thought to act as an immune regulator inducing T cell tolerance (particularly affecting Th1 cells) and consequently ineffective T cell lysis of infected hepatocytes [7]. In the contest of perinatal infection this may predispose to chronic infection [8] and its presence is associated clinically with very high HBV viral loads (see 2.1.3 for further details). The X gene (nucleotides ~ 1390-1840) encodes the X protein. The function of the X protein is not completely understood but it is hypothesised to be central in modulating the epigenetic regulation of cccDNA and hence influencing HBV replication [9]. There is also accumulating evidence to support a role for the X protein in promoting hepatocarcinogenesis by interrupting the apoptotic process of liver cells and DNA repair mechanisms [10].
3.1.3 Mutations of significance

The exact mutation rate of HBV is disputed, but as viral reverse transcriptases lack a proof reading function they are error prone. HBV viral loads and turnover rates can be very high (estimated de novo HBV production rates of $10^{11}$ virions per day [11]); in combination this means that HBV populations within an individual are a mixture of a large number of quasi-species.

As the ‘a determinant’ of the envelope protein lies within the S gene, mutations in this area can render a virus capable of infecting fully vaccinated individuals, as this is the region that the vaccine induced neutralising Anti-HBs binds to. As the binding of HBsAg to anti-HBs is also the basis of the serology diagnostic test, the ability to diagnose chronic HBV infection can also be affected by mutations in this region. The most frequently described mutation in the S gene is sG145R, first described in an Italian infant in 1990 [12]. This is generally referred to as a ‘vaccine escape mutant’ although other specific mutations (sP120P/T) have been shown to produce the same HBV phenotype [13, 14].

As HBeAg is produced through translation of the core gene, pre-core and basal core promoter mutations in particular can influence its production. The most common of these is G1896A, creating a stop codon which prohibits production of HBeAg. Another effect of G1896A is to stabilise a stem loop in the pregenomic RNA, enhancing viral replication [15] and hence providing a survival advantage for this mutation.

The double mutation A1762T and G1764A in the basal core promoter region down regulates HBeAg production and leads to an increase in viral replication [16].

Mutations in the polymerase gene can lead to drug resistance as the commonly used HBV antivirals are nucleos(t)ide reverse transcriptase inhibitors. Table 3.1 lists the common mutations associated with drug resistance with respect to HBV drugs.
<table>
<thead>
<tr>
<th>Mutation</th>
<th>Drug</th>
<th>M204V/I/S YMDD locus</th>
<th>A181T/V</th>
<th>N236T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tenofovir*</td>
<td>Sensitive</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Entecavir*</td>
<td>Intermediate</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td></td>
<td>Adefovir</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>Telbivudine</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td></td>
<td>Lamivudine</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>

Information taken from [17] * Entecavir resistance requires a combination of mutations to be present namely L180M + M204V/I +/- I169T +/- T184S/A/I/L/G/C/M +/- S202C/G/I +/- M250I/V. # No definite Tenofovir associated resistance mutations have been described.

3.2 Worldwide molecular epidemiology

3.2.1 Definitions

Genotypes and sub-genotypes

Currently there are nine different genotypes (A-I) and one ‘putative genotype’ (J) of the HBV described. Over time, since the first description of genotypes A-D in 1988 [18], there have been multiple slightly differing definitions of what molecular characteristics constitute the definition of a separate genotype. Recently numerous groups [19-21] have called for clarity, suggesting a move towards an international consensus regulated by the International Committee on Taxonomy of Viruses (ICTV) and consistency is emerging in the published reclassification of various sub-genotypes. The most recent minimum criteria for proposing a new genotype proposed by Kramvis [22] include:

1. the need for a number of complete genome sequences (when only one exists it should be designated a putative genotype until others become available);
2. as many sequences as possible (utilising public databases) should be used for comparison to ensure robust analysis;
3. sequences selected for comparison should not have insertions or deletions (indels) or be recombinants of defined genotypes to prevent artificial increases in the nucleotide divergence;
4. new strains should be checked for recombination between known genotypes/sub-genotypes;
5. recent literature should be consulted in order to obtain up-to-date information (to avoid contemporaneous allocation of a new genotype/sub-genotype); and
6. a nucleotide divergence of at least 7.5% (this figure was previously quoted as 8%).

In order to define a sub-genotype the most recent recommendations suggest in addition to 1-5 above:

- a nucleotide divergence of between approximately 4 and 7.5%, monophyletic clustering and good bootstrap support (from the phylogenetic analysis – see definition below); OR
- if nucleotide divergence is <4% distinct geographical separation and/or different serological subtypes, monophyletic clustering and good bootstrap support.

**Serotypes**

Prior to the widespread availability of full genome sequencing and genotype allocation, hepatitis B virus was divided into nine different major serotypes based on the antigenic determinants of HBsAg: ayw1, ayw2, ayw3, ayw4, ayr, adw2, adw4, adrq+, adrq-. The a part of the ‘a determinant’ is common to all HBV. HBsAg, The d/y is determined by position 122 and the w/r by the amino acid at position 160. As described above, due to the ability of variants in this region to cause morphological changes in the antigen binding site, different serotypes can potentially have different abilities to bind surface antibodies [6].
Phylogenetics

Phylogeny is the study of evolutionary relationships between groups of organisms. In the case of HBV, it involves comparing the DNA sequence of different HBV viruses at the nucleotide level with each other to look for differences and similarities in order to make quantitative estimates about how related to each other specific viruses are. The results of these analyses are presented as ‘trees’ where the branches are the edges and the internal nodes represent the most recent common ancestor of that group of viruses. Trees classify various HBV viruses into groups, as all branches arising from one node are part of the same group (derived from the last common ancestor) and are termed ‘monophyletic’ [23].

3.2.2 Geographical distribution of genotypes and sub-genotypes

The majority of HBV genotypes and sub-genotypes have distinct geographically defined distributions (Figure 3.4 and Table 3.2). Within this geography there is also a tendency for the genotype and particularly sub-genotype distribution to be influenced by ethnic background and country of origin of the individual. There are also increasingly well described associations between historical migration patterns both forced and voluntary, and genotype distributions. One example of this is the origin of HBV sub-genotype A1 in Africa and dispersal along 9th to 19th century trade and slave routes to North America and Asia [24].
Figure 3.4 Map of the worldwide distribution of hepatitis B virus genotypes and sub-genotypes using [1-9].
Genotype A was initially described in 1988 [18], and 10 years later the first sub-genotype of A was named A’ [25]. Genotypes Aa (Africa) and Ae (Europe) were then described based on geography [26] and subsequently named A1 and A2. A1 is most common in sub-Saharan Africa and south Asia whilst A2 is found in Europe and North America. A3 was reported in 2005 from Cameroon and two individuals originating from the Gambia who were living in Sweden [27, 28]. Later Olinger et al. [29] named a sub-genotype from Mali “tentative A4” and A5 from Nigerian patients; both these sub-genotypes were based on small numbers of samples that were mostly partial rather than full genome sequences. In the most recent literature, tentative A4 and A5 are reclassified with the original A3 as quasi-sub-genotype A3 [20, 22, 30]. A6 (which has now been renamed A4) is based on HBV from a group of Belgian patients who were of African origin, originally from Congo and Rwanda [31]. Tentative A7 described by Hubschen et al. [32] based on samples from Cameroon has also been included in the quasi A3 group based on further analysis using all available strains of A to compare with, not just a few representative strains [30].

Pourkarim et al. [33] define “quasi sub-genotype” as a lineage which, during full analysis taking into account “all circulating strains” of the same genotype and sub-genotypes, does not fit the criteria of the “sub-genotypes” but clusters together with good boot strap support in a phylogenetic tree distinct from all other sub-genotypes. It is suggested by Pourkarim that “quasi sub-genotypes” are probably the result of years of inter-host evolution of HBV in a well-defined geographical location and that geography may be important in this evolving classification system.

Genotype B HBV, also initially described in 1988 [18], was divided into Bj (Japan) and Ba (Asia) by Sugauchi et al. [34] based on the geographical distribution of the isolates. It was acknowledged at this time that Bj viruses were not recombinant viruses whereas there was evidence to support the Ba group being comprised of B/C recombinant viruses. Bj was subsequently renamed B1 and Ba B2; the same group also described B3 from Indonesia and B4 from Vietnam and France (one
isolate) [35]. Two groups simultaneously described B5 from patients in the Philippines [36, 37], and in 2007 B6 was isolated from Arctic indigenous populations [38]. Multiple new sub-genotypes were identified in quick succession from Indonesia (B7-B9) [39-41], as well as viruses from two individuals from Yunnan province in China also being named B6 [42]. Contemporary reclassification of genotype B has created a quasi B3 group that includes the original B3, B5, B7-9 and the B6 group from China. The Arctic indigenous B6 has been renamed B5 [22, 43].

Genotype C has the greatest number of sub-genotypes currently (C1-C16) and is proposed to be the oldest of all genotypes [44]. Its distribution is widespread across the Asia-Pacific region with C1 and C2 originally described in 2004 from patients in East Asia and China respectively [35, 45]. C3 predominates in Micronesia and Polynesia [35] and C4 prior to our study had only been identified from two individuals, both Indigenous Australians [46]. There has been a multitude of different C sub-genotypes described from Indonesia C6 [47], C8 - C16 [48]. There have also been multiple occasions where different C sub-genotypes have both been reported simultaneously from different regions and duplicate names given (C6 Indonesia and the Philippines – now named C7 [49], C11 in Indonesia – renamed C11 and C12 [50, 51]). Despite the identification of recombinant viruses in a recent re-analysis of over 1,200 genotype C full genome sequences, Shi et al. [48] found that the majority of sub-genotype C classifications were true sub-genotypes based on current criteria (C1, 3, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16). This analysis informed a reclassification of genotype C which proposes a quasi sub-genotype C2 incorporating C2, C14 and several previously undefined sequences. Although C4 (C and unknown), CD1 (C/D) and CD2(C/D) were identified as recombinant viruses, and the criteria for sub-genotype classification advise to be cautious of designating recombinant viruses as a sub-genotype, there are no guidelines as to how to report them and so their status was maintained. Shi [20] and Kramvis [22] have both recently published contemporary reviews of genotype and sub-genotype
Until 2006 Genotype D had sub-genotypes 1-4 [35]; it is the most diffusely distributed genotype, with D3 being documented in Europe, North America and Southern Africa. D1 is predominantly found in the Mediterranean region and D2 across Europe and Asia. D4 has been identified in Indigenous populations in Micronesia, Papua New Guinea and north eastern Australia, as well as a distinct ethnic group in the Arctic region – the Arctic Denes. D5 has only been found in India [52]; D6 was reported from Papua, Indonesia [47], D7 from Tunisia [53] and D8 from Niger [54]. Recent reclassification based on 304 full genome sequences obtained from public databases has condensed the sub-genotypes of D down to 6 [55] (Table 3.2).

Genotype E, originally described in 1994, has no sub-genotypes and has been reported from West and Central Africa [56].

Genotype F is found predominantly in the Amerindian population of South and Central America with the exception of the Alaskan native F1 isolates [57]. It was split into four ‘clusters’ initially based on partial genomes [58] and then the four sub-genotypes (F1-F4) were clarified based on the availability of a larger number of strains including full genome sequences [59].

Genotype G, formally identified in the year 2000 [60], has only been isolated in adults and has no particular defined geographical distribution with cases from the USA, Mexico and numerous countries in Europe. It seems to require co-infection with another hepatitis B genotype (normally A) in order to produce chronic infection as it is unable to produce HBeAg due to stop codons at positions 2 and 28 of the precore region [61]. A potential association with HIV and sexual transmission in the context of men who have sex with men has been postulated [62].
Genotype H was first described from two Nicaraguan patients and one Californian in 2002 [63]. The Nicaraguan patients’ viruses had previously been classified as ‘cluster III’ of genotype F using partial genome sequencing, but with full genome analysis and the inclusion of the third closely related strain met the criteria for a new genotype. Genotype H has since been predominantly described in Mexicans both in the native and Mestizo (Mestizo is the name given to people with mixed ancestry resulting from admixture between Spaniards, Amerindians and Africans from the 16\textsuperscript{th} century onwards) populations suggesting its presence prior to the arrival of Caucasians to the Americas [64].

Genotype I was proposed in 2008 based on the analysis of four strains of HBV from Vietnamese patients [65], however it was not until further full genome sequences, including those from Laos [66], India [67] and China [68], were analysed that the criteria [19] for a new genotype were felt to be met. It has already been spilt into two sub-genotypes I1 and I2 [66].

Genotype J was described from a Japanese patient who spent several years in Borneo during the Second World War and later presented with HBV-related hepatocellular carcinoma; his virus underwent full genome sequencing. When compared with 1,440 strains retrieved from Genbank 10.9 to 15.7%, sequence divergence was documented and a possible new genotype J proposed [69]. To date no other genotype J sequences have been identified, hence it is referred to as a ‘putative’ genotype.
Table 3.2: Summary of geographical distribution of genotypes and sub-genotypes using most recent reclassifications (current Jan 2015). Compiled using [20-22, 30, 33, 35, 43, 48, 55, 56, 59, 64, 69]

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Sub-genotype most recent classification (previous classifications)</th>
<th>Geographical distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A1 (A’ Aa)</td>
<td>Sub-Saharan Africa, South Asia</td>
</tr>
<tr>
<td></td>
<td>A2 (Ae)</td>
<td>Northern Europe, North America</td>
</tr>
<tr>
<td></td>
<td>Quasi A3 (A3 tentative A4 A5)</td>
<td>Western Africa</td>
</tr>
<tr>
<td></td>
<td>A4 (A6)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>B1 (Bj)</td>
<td>Japan</td>
</tr>
<tr>
<td></td>
<td>B2 (Ba)</td>
<td>Taiwan, China, Vietnam</td>
</tr>
<tr>
<td></td>
<td>Quasi B3 (B3 B5 B7-9)</td>
<td>Indonesia, Philippines, China</td>
</tr>
<tr>
<td></td>
<td>B4</td>
<td>Vietnam, France, Cambodia</td>
</tr>
<tr>
<td></td>
<td>B5 (B6)</td>
<td>Alaska, Northern Canada, Greenland</td>
</tr>
<tr>
<td>C</td>
<td>C1 (Ce)</td>
<td>Taiwan, Japan, Korea, east Asia, China</td>
</tr>
<tr>
<td></td>
<td>Quasi C2 (C2, C14, previously unclassified in Genbank)(Cs)</td>
<td>China, Thailand, Laos, Vietnam, Indonesia</td>
</tr>
<tr>
<td></td>
<td>C3</td>
<td>Micronesia, Polynesia</td>
</tr>
<tr>
<td></td>
<td>C4</td>
<td>Indigenous Australians – 2 isolates North Queensland</td>
</tr>
<tr>
<td></td>
<td>C5</td>
<td>Philippines, Vietnam</td>
</tr>
<tr>
<td></td>
<td>C6</td>
<td>Indonesia</td>
</tr>
<tr>
<td></td>
<td>C7</td>
<td>Philippines</td>
</tr>
<tr>
<td></td>
<td>C8-16</td>
<td>Indonesia</td>
</tr>
<tr>
<td>D</td>
<td>D1</td>
<td>Africa, Europe, Mediterranean basin, India</td>
</tr>
<tr>
<td></td>
<td>D2</td>
<td>Europe, Asia</td>
</tr>
<tr>
<td></td>
<td>D3 (D6)</td>
<td>Europe, North America, South Africa, Papua New Guinea</td>
</tr>
<tr>
<td></td>
<td>D4</td>
<td>Micronesia, Papua New Guinea, Artic Denes, North eastern Indigenous Australians</td>
</tr>
<tr>
<td></td>
<td>D5</td>
<td>India</td>
</tr>
<tr>
<td></td>
<td>D6 (D7)</td>
<td>Morocco, Algeria, Tunisia</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>West and central Africa</td>
</tr>
<tr>
<td>F</td>
<td>F1</td>
<td>Central America, Argentina, Alaska</td>
</tr>
<tr>
<td></td>
<td>F2</td>
<td>Nicaragua, Venezuela, Brazil, Columbia</td>
</tr>
<tr>
<td></td>
<td>F3</td>
<td>Venezuela, Columbia</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>Argentina</td>
</tr>
<tr>
<td>G</td>
<td></td>
<td>France, Germany, USA, Mexico, UK, Italy</td>
</tr>
<tr>
<td>H</td>
<td></td>
<td>Nicaragua, Mexico, USA</td>
</tr>
<tr>
<td>I</td>
<td>I1</td>
<td>Laos, Vietnam, China</td>
</tr>
<tr>
<td></td>
<td>I2</td>
<td>Laos, India, Vietnam</td>
</tr>
<tr>
<td>J</td>
<td>Putative</td>
<td>Japan (Borneo)</td>
</tr>
<tr>
<td>Recombinant viruses named as such</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD1</td>
<td>Tibet - China, Mongolia</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>Tibet – China, Belgium</td>
</tr>
<tr>
<td></td>
<td>D/E (D8)</td>
<td>Niger</td>
</tr>
</tbody>
</table>
3.3 Molecular epidemiology of HBV in Australia

In 1998, McIntosh et al. [70] described the molecular epidemiology of hepatitis B in 33 new immigrant families living in Sydney. All families had a child identified as being HBsAg positive (n=22) or Anti-HBc positive (n=11) as part of a separate school survey [71]. Families were from Vietnam, Cambodia, Thailand, Laos, the Philippines, Tonga and Lebanon as well as a New Zealand Maori and two Indigenous Australian families. All family members had blood taken for hepatitis B serology, liver function tests, antigenic subtyping and HBV DNA analysis. Genotypes were assigned based on the criteria at the time described by Norder et al. [4]. Results are presented in Table 3.3 below.

Table 3.3: Hepatitis B genotypes of recent immigrants to Sydney with relation to their ethnicity as reported by McIntosh et al. [71]

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Genotype</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnamese</td>
<td>B</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>4</td>
</tr>
<tr>
<td>Vietnamese/Cambodian</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1</td>
</tr>
<tr>
<td>Cambodian</td>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>6</td>
</tr>
<tr>
<td>Cambodian/Thai</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>Thai</td>
<td>C</td>
<td>1</td>
</tr>
<tr>
<td>Laotian</td>
<td>C</td>
<td>7</td>
</tr>
<tr>
<td>Phillipino</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>Maori New Zealanders</td>
<td>D</td>
<td>1</td>
</tr>
<tr>
<td>Tongan</td>
<td>C</td>
<td>1</td>
</tr>
<tr>
<td>Lebanese</td>
<td>D</td>
<td>1</td>
</tr>
<tr>
<td>Australian Indigenous</td>
<td>D</td>
<td>2</td>
</tr>
</tbody>
</table>

The genotype distribution clearly clustered within families and reflected the country of origin of the family. There is no information about where in Australia the Indigenous families included came from. The Indigenous people were both female aged 11, HBeAg positive and serotype ayw2.
In 2001 Sugauchi et al. [46] reported full genome sequence analysis of HBV from five Indigenous Australian individuals from Queensland. The five study isolates were compared to 48 full genome sequences from human HBV genotypes A-G and six full genome sequences from non-human primates obtained from public DNA databases (Genbank/European Molecular Biology Laboratory (EMBL)/DNA Data Bank of Japan (DDBJ)).

The five Australian strains were found to represent genotype D (n=3) and a novel variant genotype C not previously reported. This was the first time sub-genotype C4 was reported in the world literature. Mean nucleotide difference over the full genome for the novel variant C from other Cs was 6.7% (range 5.9-7.4%), with bootstrap values of 100%, and both were serotype ayw. No other C sub-genotype reported to date is serotype ayw. When analysed using the small S gene the two novel variant C samples, later designated C4 by Norder et al. [35], formed a novel genotype that was distinctly separate from genotype C in the phylogenetic tree (now known to be the first identification of sub-genotype C4). These two individuals were born in the north Queensland towns of Cherbourg and Murgon (6.5km apart) and on the approximate latitude of the lower border of the Northern Territory. One of these individuals had liver cancer at the time his blood was taken.

The three genotype D sequences were found by phylogenetic analysis to be most closely related to a strain from a healthy blood donor from Papua New Guinea.

Unpublished work from an MBBS honours thesis [72] in partnership with the Victorian Infectious Diseases Reference Laboratory (VIDRL) has documented HBV genotypes from 18 individuals from the Torres Strait Island region of Australia. Samples were collected in the Torres Strait, transported to VIDRL where HBV DNA was extracted and amplified using standard methods. Consensus sequences were constructed using SeqScape (ABI Prism, Applied Biosystems, Foster City, CA). Genotypes were identified using SeqHepB as previously described [73]. Phylogenetic
analysis was undertaken using 84 reference strains from Genbank (genotypes A-H) using BioEdit [74]. Neighbour-joining trees were constructed and evaluated by bootstrap re-sampling with 1,000 replicates. Genotypes C1 and C3 were identified (Table 3.4).

Table 3.4: Location, viral load and genotype of 18 samples from the Torres Strait Islanders (unpublished with permission VIDRL) [73]

<table>
<thead>
<tr>
<th>Island of sample collection</th>
<th>Viral load IU/ml</th>
<th>genotype/sub-genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamaga</td>
<td>12,000,000</td>
<td>C1</td>
</tr>
<tr>
<td>Bamaga</td>
<td>245,000,000</td>
<td>C1</td>
</tr>
<tr>
<td>Bamaga</td>
<td>22,682,500</td>
<td>C1</td>
</tr>
<tr>
<td>Bamaga</td>
<td>237,275,000</td>
<td>C1</td>
</tr>
<tr>
<td>Bamaga</td>
<td>299</td>
<td>C1</td>
</tr>
<tr>
<td>Darnley Island</td>
<td>75,550,000</td>
<td>C1</td>
</tr>
<tr>
<td>Darnley Island</td>
<td>46,400,000</td>
<td>C1</td>
</tr>
<tr>
<td>Murray Island</td>
<td>982</td>
<td>C1</td>
</tr>
<tr>
<td>Murray Island</td>
<td>203</td>
<td>C1</td>
</tr>
<tr>
<td>Murray Island</td>
<td>1,968</td>
<td>C1</td>
</tr>
<tr>
<td>Murray Island</td>
<td>68,625,000</td>
<td>C1</td>
</tr>
<tr>
<td>Murray Island</td>
<td>220</td>
<td>C1</td>
</tr>
<tr>
<td>Thursday Island</td>
<td>28,300</td>
<td>C1</td>
</tr>
<tr>
<td>Saibai Island</td>
<td>32,000,000</td>
<td>C3</td>
</tr>
<tr>
<td>Saibai Island</td>
<td>54,225,000</td>
<td>C3</td>
</tr>
<tr>
<td>Thursday Island</td>
<td>456</td>
<td>C1</td>
</tr>
<tr>
<td>Thursday Island</td>
<td>202</td>
<td>C1</td>
</tr>
<tr>
<td>Thursday Island</td>
<td>1,704</td>
<td>C1</td>
</tr>
</tbody>
</table>

3.4 Molecular epidemiology of HBV in Indigenous Australians

The only hepatitis B genotypes from Indigenous Australians published before the commencement of our study were the two ‘novel variant C’ and three genotype D4 samples from Queensland [46] and the two genotype D samples from individuals living in Sydney [70] (birth location unknown). Interestingly, in 1976 Barrett described the HBV serotypes of Indigenous Australians living in the NT and Queensland as ay (113/134) α (20/134) and ad (1/134) [75].
3.5 The clinical implications of HBV genotype

There is accumulating evidence that HBV genotype has a significant impact on the natural history of chronic HBV infection, including the rate of progression to liver cirrhosis and the development of hepatocellular carcinoma (HCC). There are also data to support a difference in the response to interferon therapy dependant on genotype; however at this time there is no evidence to suggest genotype alters responses to oral antiviral therapy.

The geographical distribution of HBV genotypes means that there is a peculiar bias in the literature with regards to studies examining the impact of genotype on clinical outcomes. The majority of studies compare the Asian genotypes B with C or the European genotypes A with D; there are few studies comparing other combinations of genotypes.

3.5.1 Genotype and natural history of chronic HBV infection

The most extensive literature in this area is with respect to genotype B versus C, the majority of which comes from Asia where these genotypes predominate. In a cohort study of 272 Taiwanese adults with chronic HBV infection, those with genotype C were more likely to be HBeAg positive at recruitment. Over five years of follow up, patients with genotype C HBV were significantly more likely to have multiple flares of hepatitis without achieving HBeAg seroconversion than genotype B patients [76]. Two other retrospective liver clinic-based studies [77, 78] in Taiwan and Hong Kong also reported significantly delayed HBeAg seroconversion in genotype C as opposed to genotype B chronic HBV infection. The Taiwanese study included 146 HBeAg positive adult patients followed for a mean duration of 52 months. Genotype C patients were significantly older at inclusion (mean age 37 vs 29 years P<0.001) and had a significantly lower rate of eAg seroconversion (27 vs 47%, P<0.025) than genotype B patients [77]. In the Hong Kong study, including 332 ethnically Chinese patients with a mean follow up of 48 months,
spontaneous HBeAg seroconversion occurred approximately one decade earlier in genotype B compared to genotype C patients.

As part of a prospective longitudinal study, 206 asymptomatic Taiwanese adults with HBeAg positive chronic HBV infection identified during blood donation, were followed up every 3-6 months for an average of 10.8 years (range 3-20) [79]. The occurrence of spontaneous HBeAg seroconversion was significantly higher in genotype B than genotype C patients (72 vs 48%, P=0.003). Reactivation of chronic HBV infection (defined by increased ALT and reappearance of HBV DNA) was significantly more likely in genotype C patients (P=0.04) and on multivariate analysis, reactivation and genotype C were independent factors predictive of cirrhosis.

In a prospective community-based study following 1,536 Alaskan natives with chronic HBV infection, the genotype was identified in 1,158. The following pattern of genotype distribution was seen: A (n=150), B (n=44), C (n=74), D (n=656), F (n=233). These individuals have been followed six monthly for a median of 20.5 years. Genotype C patients were significantly more likely to be HBeAg positive on initial and final samples and time to HBeAg clearance was longer (P<0.001 for both). Age at which 50% of people cleared HBeAg was less than 20 years for genotypes A, B, D and F and 47.8 years for genotype C (P<0.001) [80]. There is also evidence to suggest that genotype B5 (previously B6), which is unique to the circumpolar Arctic region, has a particularly benign course. HBeAg seroconversion occurs early, viral loads are low and cirrhosis and HCC has not been documented [38, 57].

In a cross-sectional prospective study based in Hong Kong, 1,106 treatment-naive chronic HBV infection patients with genotypes B (49%) and C (51%) were assessed for liver fibrosis using transient elastography (Fibroscan®). Patients with genotype C had no or mild fibrosis less often (42% vs 55% P< 0.0001) and advanced fibrosis more often (25% vs 19% P=0.015) [81].
In summary there is evidence that individuals with genotype C chronic HBV infection have a significantly longer duration of eAg positivity, more episodes of reactivation and increased rates of significant fibrosis and cirrhosis than genotype B patients (strongest evidence) and genotype A and D patients. With respect to genotype F, the age of HBeAg seroconversion is later for genotype C but rates of reactivation are similar. This pattern of delayed eAg seroconversion means that female patients with genotype C disease are more likely to be eAg positive with a high viral load during their childbearing years. This means vertical transmission is much more likely to occur and so further contributes to maintaining chronic HBV infection in a population group.

With respect to the other genotypes there is one prospective study following 258 Spanish patients with genotypes A, D and F for a mean duration of 94 months. Sustained remission after HBeAg clearance was higher in genotype A than D (55% vs 32%, P<0.01) and death from liver disease was more frequent in genotype F than A or D.

3.5.2 Genotype and hepatocellular carcinoma

HBV genotype C has been repeatedly reported to be independently associated with an increased risk of hepatocellular carcinoma (HCC) in comparison to genotype B [82-85]. In a prospective cohort study 4,841 Taiwanese men were followed up 6 monthly for an average of 12 years. Both high viral load (highest quintile vs lowest) and genotype C (versus genotype B) HBV were independently associated with an increased risk of HCC with adjusted odds ratios of 7.26 (95% CI 3.54-14.89) and 5.11 (95% CI 3.20-8.18) respectively [84]. The REVEAL-HBV study group reported consistent findings with respect to genotype C versus B from their prospective community-based cohort study [85]. With respect to 2,762 Taiwanese adults with a total of 33,847 person years of follow up, HCC incidence rates per 100,000 person years were 306 (95%CI 237-388) for individuals with genotype B HBV compared to 786 (95% CI 627-973) for those with genotype C. This equates to a hazard ratio of 1.76 for HCC for genotype C chronic HBV infection. This study
also reported a hazard ratio of 1.73 for developing HCC with the presence of the basal core promoter region mutation A1762T/G1764A versus wild type [85]. Chan et al. studied a prospective cohort of 1,006 chronic HBV infection patients in Hong Kong with a median follow up time of 7.7 years during which 8.8% developed HCC. Genotype C and having a viral load in the highest stratum (log HBV DNA > 6.5 copies/ml) were significantly associated with development of HCC. Interestingly, within the genotype C group those with sub-genotype Ce/C1 (versus Cs/C2) had the highest risk, with a hazard ratio of 2.75 (95%CI 1.66-4.56 P<0.0001) compared to genotype B [83].

There is some evidence to support earlier (particularly in those < 35 years of age) development of HCC in chronic HBV infection patients with genotype B virus as well as an increase in HCC in genotype B HBV patients without cirrhosis [86, 87]. Evidence is also emerging with respect to differences in the characteristics of HCC at presentation [88] and also the risk of tumour recurrence [89] dependent on genotype, although whether this has any impact on mortality is not yet clear.

Livingston et al. [90] report a high incidence and early presentation of HCC in genotype F chronic HBV infection patients in their cohort of 1,536 Alaskan natives. The median age at HCC diagnosis was 22.5 years compared to 60 years for other genotypes (A, C, D). Of 52 HCC patients, 68% had genotype F HBV compared to 18% of those without HCC (P<0.001). In this study there was no significant association between basal core promoter or precore mutations and HCC in genotype F HBV.

Genotype A1 which is the predominant HBV sub-genotype in eastern and southern Africa, is associated with a statistically significantly increase in the risk of HCC, relative risk 4.5 (95% CI 1.86-10.90), when compared to genotypes D and E in a southern African setting [91]. This study also reported the mean age of HCC diagnosis to be 6.5 years younger than non-A genotypes (D
and E). Interestingly, despite this high incidence of HCC at a younger age, the natural history of sub-genotype A1 is to become eAg negative earlier and to have a significantly lower viral load when compared to other genotypes [92]. This is in complete contrast to what we know about genotype C and suggests there may be a molecular mechanism for the increased tendency to carcinogenesis. This further highlights the importance of genotype dependent differences in the course and consequences of chronic HBV infection.

The relationship between specific mutations in HBV and HCC development has not yet been clearly defined. A recent meta-analysis reviewed 43 studies looking at the association of HBV mutations and risk of HCC. It reported statistically significant summary odds ratios of HCC for any PreS mutation (3.77), C1653T in EnhII (2.76), T1753V (2.35) and the double mutation A1762T/G1764A in the BCP region (3.79). They did not find an association between the precore mutations G1896A and C1858T regardless of HBeAg status and genotype [93].

3.5.3 Genotype and treatment responses

Current evidence has not shown any significant difference in response to oral antiviral therapy with respect to HBV genotype [94]. However there is evidence that genotype is an important consideration in the decision to commence interferon therapy [94, 95]. This evidence is summarised in this section.

The most convincing evidence exists with respect to HBeAg positive chronic HBV infection. Janssen et al. carried out a randomised double-blinded multicentre (42 in Europe, East Asia and North America) controlled trial in HBeAg positive chronic HBV infection patients. There were 307 patients randomised to receive 52 weeks of Pegylated Interferon alfa (PegIFN) 2b plus lamivudine or placebo, with a primary outcome measure of HBeAg loss at end of treatment and 24 weeks post treatment. There was no difference between the groups in achieving the primary outcome (36% v 35%), however response did vary by HBV genotype: A (47%), B (44%), C (28%).
and D (25%). In multivariate analysis this was statistically significant when A was compared to D but not when B was compared to C [96]. A significant difference in HBsAg loss was also reported with respect to genotype from an ancillary study based on the same trial cohort. The gradient of A>B>C>D was demonstrated with A versus D again reaching statistical significance [97]. Longer term follow up of this group (mean 3.0+/− 0.8 years) confirmed persistence of HBeAg negativity in 81% of all patients who achieved this outcome at 24 weeks post therapy. Again, genotype A patients achieved significantly higher rates of both HBeAg and HBsAg negativity compared to other genotypes (B, C, D) [98]. A further multicentre randomised open-label study based in China (only including genotypes B and C) reported genotype B and younger age to be significant predictors of response (HBeAg loss) to both pegylated and standard interferon therapy in HBeAg positive chronic HBV infection patients [99]. However Lau et al., when comparing pegylated interferon, lamivudine and the combination of the two in HBeAg positive patients, in a multicentre randomised partially blinded controlled trial, showed no significant difference in outcome with respect to genotype [100].

In a clinic-based retrospective study of HBeAg negative chronic HBV infection patients given standard interferon therapy for 48 weeks, sustained response (HBV DNA levels undetectable and normal ALT) was measured at 6 months post treatment. Genotype A chronic HBV infection patients achieved a significantly higher rate of sustained response compared to genotype D patients (49% vs 26%; P<0.005) [101]. A prospective randomised partially double-blinded controlled trial in HBeAg negative patients, comparing PegIFN alone and in combination with lamivudine suggested better virological responses in genotype C patients [102]. However in long-term follow up (three years post PegIFN treatment completion) no difference in HBsAg loss was found according to genotype [103].
The only study specifically looking at response to antiviral therapy in genotypes E-H suggests, based on small numbers, that genotypes E, F and H appear to be sensitive to interferon [104] but further prospective study is needed.

3.6 Conclusions

Our knowledge with respect to the molecular epidemiology of HBV is rapidly expanding. Genotype and sub-genotype classification is evolving and being constantly refined in parallel with the rapidly increasing number of variants of HBV being identified.

Clear differences in natural history, transmission, HCC development and treatment responses based on genotype are emerging. These are not yet fully explained, and the delineation of the exact role of genotype in these areas is complicated by the distinct geographical distribution seen. This makes comparisons of multiple genotypes not only logistically challenging but also means that deciphering the role of ethnicity is an added complexity.

Despite this, it is imperative that we continue to advance our understanding of the molecular epidemiology of HBV and its impact on clinical outcomes. This will enable us to move towards individualised tailored approaches to HBV control and clinical management.
3.7 References


79. Chu C-M, Liaw Y-F: 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(3):411-417.


Chapter 4 - Health literacy
4.1 What are the barriers to accessing care?

The barriers to people accessing care for chronic HBV infection are multifactorial and vary depending on population group and geographical region. There are, however, a number of areas that are consistently reported across all groups. These include low levels of chronic HBV infection knowledge; systems access issues, ineffective communication (particularly language and cultural differences) and the often asymptomatic nature of chronic hepatitis B.

4.1.1 Internationally

There is a lack of robust qualitative data specifically addressing this issue internationally. A review summarising all published data on barriers to care and treatment of hepatitis in Europe found only six studies specifically addressing hepatitis B [1]. Only two of these, both cross sectional in design, commented on barriers to care. Two factors were reported as making a statistically significant contribution to an individual not receiving antiviral therapy. These were being an immigrant [2], and being female [3]. In Latin America [4] lack of symptoms, delay in diagnosis, lack of chronic HBV infection knowledge, and access to antivirals are all felt to be important barriers to hepatitis B care based on expert opinion. In Singapore a qualitative study based on semi-structured focus groups with chronic HBV infection patients reported low levels of chronic HBV infection knowledge leading to indifferent or inappropriate health-seeking behaviours [5]. In the USA, English language proficiency, lack of health insurance, non-citizenship and different worldviews on health and negative perceptions of Western medicine are highlighted as barriers to care for Asian Americans [6]. Chinese Canadians cited time, inconvenience and lack of English proficiency as their major barriers to accessing care in a questionnaire-based study [7].
4.1.2 Australia

In Australia, a national hepatitis B needs assessment undertaken in 2007 highlighted the need for better data to guide a consistent co-ordinated public policy and also a need to engage with affected communities [8]. A qualitative study based on semi-structured interviews and focus groups with people living with chronic HBV infection in Australia also found low levels of chronic HBV infection knowledge. Participants also reported experiencing a lack of confidence in the professional knowledge of service providers with respect to chronic HBV infection. This study went on to identify the need for culturally appropriate resources and improved education for all about chronic HBV infection [9]. Among Indigenous Australians, a recent situational analysis [10] [11] in the Torres Strait region again identified variable levels of chronic HBV infection knowledge across all healthcare providers and amongst people living with chronic HBV infection. Pertinent issues to address to facilitate improvements in chronic HBV infection management were cited as the absence of a system based approach, competing health priorities, the silent nature of the disease and the lack of culturally and linguistically appropriate resources. Preston-Thomas et al., [12] in a questionnaire-based survey also conducted in the Torres Strait, similarly identified low levels of knowledge about chronic HBV infection, both in healthcare providers and Indigenous Australian patients with chronic HBV infection, again highlighting the lack of culturally appropriate resources available to facilitate improved understanding.

Hepatitis B knowledge was recently assessed in a viral hepatitis clinic outpatient setting at a tertiary referral hospital in Victoria. A hepatitis B knowledge-based questionnaire developed by the research team was used as the assessment tool. Fifty-five adult patients attending follow up for their chronic HBV infection completed the knowledge assessment; 93% of these individuals were born outside Australia and interpreters were used in 17%. Misconceptions regarding modes of transmission, with 53% and 58% respectively reporting possible transmission via kissing and mosquito bites, as well as lack of knowledge of risks of cirrhosis (11% aware) and
hepatocellular carcinoma (18% aware) were reported. This study group may not be representative of the wider general Australian population living with chronic HBV infection as over half had completed tertiary education and all were already diagnosed and engaged in care with more than half already on antiviral treatment [13]. In the context of this demographic and a tertiary hospital setting it is likely this is an overestimate of hepatitis B-specific knowledge compared to the general population of people living with chronic HBV infection.

When looked at in turn, all the potential barriers to care identified both nationally and internationally are encompassed within the most holistic definitions of health literacy. The next section of this chapter will explore the evolving literature with respect to health literacy, viewing it as a multidimensional construct. It would be logical then to hypothesise that improving health literacy should remove barriers to care, hence enabling improved access to diagnosis and appropriate management for individuals living with chronic HBV infection.

### 4.2 Health literacy

#### 4.2.1 Definitions and concepts

The World Health Organisation defines health literacy as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health” [14]. This is one of 17 distinct definitions of the term ‘health literacy’ reported in a recent systematic review [15] on the subject and is broader than many in the literature [16-18]. However, this particular definition still assumes a biomedical understanding and a Western worldview of health. It is increasingly appreciated that health literacy is a multi-dimensional concept, with a multitude of contributing factors. There are a wide range of individual capacities contributing to health literacy, such as listening, speaking, writing and reading skills, referred to as basic, fundamental [19] or functional [20] health literacy. But the concept of health literacy also incorporates a broader ability to
process, evaluate and act on information and knowledge, which Nutbeam labels “interactive health literacy” [20]. Combining functional and interactive health literacy with information regarding social and economic determinants of health allows the development of “critical health literacy” typified by the process of advocacy, autonomy and empowerment in the health arena.[20].

In a recent attempt to develop a consensus on core principles to underpin health literacy curricula, ‘The Calgary Charter on health literacy’ was produced with an updated definition:

“Health literacy allows the public and personnel working in all health-related contexts to find, understand, evaluate, communicate, and use information. Health literacy is the use of a wide range of skills that improve the ability of people to act on information in order to live healthier lives. These skills include reading, writing, listening, speaking, numeracy, and critical analysis, as well as communication and interaction skills.”

Two specific factors, culture and worldview, are increasingly acknowledged as important antecedents contributing to health literacy [19, 21-23]. There are a myriad of different definitions of culture; when referring to culture in this thesis I am using the broad definition of the culture of a society as “… the totality of its shared beliefs, norms, values, rituals, language, history, knowledge and social character” [24]. Worldview derived from the German term ‘Weltanschauung’, which literally translated means views of the world, and was defined by Freud as “an intellectual construction which solves all the problems of our existence uniformly on the basis of one overriding hypothesis”. In this thesis worldview is defined as “the fundamental cognitive, affective, and evaluative presuppositions a group of people make about the nature of things, and which they use to order their lives [25]”.

When referring to health literacy in this thesis I am using a broad, holistic interpretation of this multidimensional construct which is respectful of culture and worldview.
**4.2.2 Measures of health literacy**

There are multiple diverse instruments available to measure health literacy, with one recent review describing 51 in total [26], but this is an area in evolution and currently there is no single available tool that comprehensively and holistically measures health literacy.

Tools can be divided into three broad categories: those that assess health literacy in general (Table 4.1), disease or condition specific, and population or language specific. Earlier tools with which there is the most experience such as the REALM (Rapid Estimate of Adult Literacy in Medicine) [27] and TOFHLA (Test of Functional Health Literacy for Adults) [28], are narrow in their assessment, which is limited to the functional health literacy of an individual. Multiple variations of the REALM and TOFHLA have been developed: short form, short version, revised version and teen version, Spanish version and dental health version, mostly with the aim of making the tool easier and quicker to administer or more appropriate to a particular setting.

Variations of the concept of REALM such as the Medical Achievement Reading Test (MART) [29] and more latterly Medical Term Recognition Test (METER) [30] exist (Table 4.1) but do not add any breath to the assessment process. The NVS (Newest Vital Sign) [31] does involve some evaluation and application of health information, so going beyond just functional health literacy, however its construct validity compared to the TOFHLA is low and its low specificity means it is prone to overestimating rates of inadequate health literacy [32].

In the mid-2000s there was a move to identify and validate self-reported screening questions as a measure of health literacy, the aim being to establish a quick and easy screen that could be carried out in a clinical setting and correlated adequately with scores on TOFHLA and REALM. Williams et al., when using the TOFHLA as the assessment tool to measure health literacy in two groups of public hospital patients in the USA, also asked each individual three screening questions about reading ability. They concluded the self-reported answers did not predict accurately those with low functional health literacy as measured by the TOFHLA [33]. In 2004
Chew et al. assessed 16 candidate screening questions with Likert type responses 1-5 and identified three that correlated well with inadequate health literacy as described by the S-TOHFLA [34]. The setting for this study was a Veterans’ Administration clinic in the USA; this is referred to as the Set of Brief Screening Questions (SBSQ). Wallace et al. evaluated these same three questions again in a different USA-based primary-care population and used the REALM as the reference standard rather than S-TOFHLA [35]. They concluded that one question: “How confident are you filling out medical forms by yourself?” was accurate in detecting limited health literacy.

Morris et al. used a modified version of one of Chew et al.’s three questions: “How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?” in a primary care diabetic population [36]. This is referred to as the Single Item Literacy Scale (SILS) and had an NPV of 0.9 and a PPV of 0.4 compared to the S-TOFHLA.

The USA, Canada and Australia have all made use of proxy measures of health literacy from more general adult literacy population surveys to calculate population-wide estimates of the prevalence of low health literacy. The National Assessment of Adult Literacy, Health Activities Literacy Scale and Australian Literacy and Life Skills Survey are all briefly described in Table 4.1.
Table 4.1: Summary of assessment tools used to measure health literacy

<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Brief description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Estimate of Adult Literacy in Medicine (REALM)</strong> [27] – multiple versions exist.</td>
<td>125 medical word recognition and pronunciation test.</td>
<td>Quick and easy to administer, no test of understanding.</td>
</tr>
<tr>
<td><strong>Test of Functional Health Literacy for Adults (TOFHLA)</strong> [28] – multiple versions exist.</td>
<td>2 timed sections: 50 item cloze style reading comprehension test of health related content; 17 item numeracy skills assessment in a health context.</td>
<td>Takes 22 minutes to complete, available in English, Spanish, German, French and Italian.</td>
</tr>
<tr>
<td><strong>Medical Achievement Reading Test (MART)</strong> [29] – similar to REALM</td>
<td>Medical word recognition and pronunciation test, 42 words. Small type and glossy cover creating plausible excuses for non-recognition of words, hence less intimidating</td>
<td>Quick and easy to administer, no test of understanding, lack of content and criterion validity.</td>
</tr>
<tr>
<td><strong>Newest Vital Sign (NVS)</strong> [31]</td>
<td>Six questions about a nutrition label from an ice cream container.</td>
<td>Quick (3-5mins), available in English and Spanish, more sensitive than specific.</td>
</tr>
<tr>
<td><strong>Australian Literacy and Life Skills Survey (ALLS)</strong> [37]</td>
<td>Survey of knowledge and skills across four areas: prose literacy, document literacy, numeracy and problem solving.</td>
<td>Proxy measure of health literacy on a population level.</td>
</tr>
<tr>
<td><strong>National Assessment of Adult Literacy (NAAL)</strong> [26]</td>
<td>USA based population survey included 28 items to measure health literacy</td>
<td></td>
</tr>
<tr>
<td><strong>Health Activities Literacy Scale (HALS)</strong> [26]</td>
<td>USA based population survey used 191 health related items taken from other adult literacy surveys</td>
<td></td>
</tr>
<tr>
<td><strong>Set of brief screening questions (SBSQ)</strong> [34]</td>
<td>3 questions with 5 item Likert type scale responses</td>
<td>Self-reported, compared to S-TOFHLA</td>
</tr>
<tr>
<td><strong>Single item Literacy Scale (SILS)</strong> [36]</td>
<td>1 of above questions identified as being as accurate</td>
<td>Self-reported compared to S-TOFHLA</td>
</tr>
<tr>
<td><strong>Health Literacy management Scale (HeLMS)</strong> [38]</td>
<td>Self-reported survey questions covers 8 domains with 29 items</td>
<td>Based on well-defined conceptual framework, robust development.</td>
</tr>
<tr>
<td><strong>Health Literacy Questionnaire (HLQ)</strong> [39]</td>
<td>Self-reported survey questions developed from HeLMS. 44 items, 9 different scales items</td>
<td>Broad definition of health literacy assessed.</td>
</tr>
<tr>
<td><strong>The Swiss Health Literacy Scale (HLS-CH)</strong> [40]</td>
<td>Self-reported survey questions 127 questions on 30 competencies for health</td>
<td>Translated into German, French and Italian. Assesses multiple domains of health literacy.</td>
</tr>
<tr>
<td><strong>All Aspects of Health Literacy Scale (AAHLS)</strong> [41]</td>
<td>4 functional, 3 communicative, 4 critical and 3 empowerment based items. Self-reported survey questions</td>
<td>Based on Nutbeam’s definitions of functional, interactive and critical, assessing all domains</td>
</tr>
<tr>
<td><strong>European Health Literacy Survey Questionnaire (HLS-EU-Q)</strong> [42]</td>
<td>Self-reported survey based with 47 items covering 3 domains healthcare, disease prevention &amp; health promotion</td>
<td>Comprehensive, conceptual based measure of multiple dimensions of health literacy. Available in multiple languages</td>
</tr>
</tbody>
</table>
Following the Calgary Charter on health literacy [43] and two large (1,600 participants) USA-led international (at least six other countries involved) discussion forums, there was a call to action to enable the development of more holistic measures of health literacy based on an explicit definition with the aim of testing an underpinning theory of health literacy [44]. The appreciation that not just the individual but also the provider and health systems need to be assessed and that comparison across contexts including culture, life course, population group and research setting should be possible was highlighted.

This process is still ongoing, however a new generation of health literacy assessment tools are appearing based on well-defined conceptual frameworks, detailing robust development processes, comprehensively addressing multiple dimensions of the complex social construct that is ‘health literacy’ in its broadest form. Some of these: The Health Literacy Management Scale [38], Health Literacy Questionnaire [39], the Swiss Health Literacy Scale [40], All Aspects of Health Literacy scale [41] and the European Health Literacy Survey Questionnaire [42] are described in Table 4.1.

None of these scales have been used in the context of Indigenous Australians and although several have been translated into other languages (none into any Aboriginal languages) all approach health with a Western biomedical viewpoint. There is no explicit consideration of any alternative worldview of health or specific cultural contexts within the published details of these tools. There are no published, validated tools to measure hepatitis B specific health literacy currently available.

4.2.3 Health literacy in Australia

In 1993 as part of the Australian Government’s response to the WHO strategy ‘Health for all by the year 2000’, Nutbeam et al. published ‘Goals and Targets for Australia’s health in the year 2000 and beyond [45]’. This report identified health literacy as one of the four main areas to
focus on in order to improve health and reduce health inequalities for all Australians. The first national assessment of health literacy, based on data collected as part of the 2006 Adult Literacy and Life Skills Survey (ALLS), was published by the Australian Bureau of Statistics in 2008 [37]. The ALLS surveyed 8,988 individuals aged between 15 and 74 with respect to the following four domains: prose literacy, document literacy, numeracy, and problem solving. Health literacy was classed as a fifth domain with a score calculated as a by-product of the aforementioned domains using specific questions related to health issues. A level for health literacy between 1 and 5 was assigned to each individual; a level of 3 or higher was defined as “the minimum required for individuals to meet the complex demands of everyday life and work in the emerging knowledge based economy”. Only 43% of Australian’s achieved this minimum level overall. There were no major differences across states and territories; however the NT did have the lowest overall level at 37%. Increased levels of health literacy were associated with increased levels of education of the individual and of their parents, being employed, and being between 15 and 39 years of age. Lower levels were associated with migrant status and in particular being born in a mainly non-English speaking country. There is no specific breakdown with respect to Indigenous Australians in this report.

‘A healthier future for all Australians’ is the final report of the National Health and Hospitals Reform Commission published by the Australian Government Department of Health and Ageing in 2009 [46]. This again highlights building health literacy as a key strategy in strengthening consumer engagement and voice, which is documented as one of five levers of reform, to support the development of an agile and self improving health system. It is suggested that this could be achieved in part by including health literacy as a core element of the national curriculum for schools.

Barber et al. [47] report that up to a quarter of Australians have sub-optimal health literacy depending on which tool is used for measurement. This study interviewed 310 individuals in
Victoria and measured their health literacy using REALM, TOFHLA and NVS finding that between 6.8% (TOFHLA) and 25.9% (NVS) of those interviewed had less than adequate functional health literacy. The lack of correlation between the three tools used reiterates the problems of the reproducible measurement of even functional health literacy with existing tools. Unfortunately this study is likely to represent an underestimate of those with less than adequate health literacy due to a low response rate (19%) and the self-selection into the study group of those with higher incomes and better levels of education than the general Victorian population.

Using the NVS to assess functional health literacy of the South Australian population, Adams et al. [48] obtained 2,824 survey responses (61.2% participation rate) and showed 45% were either at risk of or had a high likelihood of inadequate functional health literacy. Being in one of these two groups was associated with increasing age and markers of socioeconomic disadvantage however, interestingly, of those reporting an income of over $100,000 or a bachelor degree, 20% were still found to have less than adequate functional health literacy. Inadequate functional health literacy was more prevalent amongst those with significant chronic conditions such as diabetes, heart disease and stroke.

4.2.4 Health literacy in Indigenous Australians

Christie et al. [49] have used qualitative methods to explore views of health literacy in the particular cultural context of remote Indigenous communities in the NT, as well as carrying out a scoping study looking at ways to improve health literacy in this region. These authors suggest that “effective health literacy is largely to do with effective communication”. Based on research, they argue that building on an individual’s existing knowledge using a culturally appropriate approach (i.e., a relevant respectful partnership which is mindful of language, worldview, existing knowledge and beliefs) to achieve a shared understanding of the issue at hand is more beneficial than attempts by health practitioners to simply ‘transfer’ biomedical knowledge to
their patients. Culturally appropriate resources, in particular visual and multimedia resources, to aid this process were identified in their scoping study as lacking [50].

Zarcadoolas et al. [51] define health literacy as “the evolving skills and competencies needed to find, comprehend, evaluate and use health information and concepts and make educated choices, reduce health risks, and improve quality of life”. Vass et al. [52] have examined the impact of Indigenous Australians’ (specifically the Yolŋu people of East Arnhem Land) language and worldview on health literacy using this definition under the four domains: fundamental, scientific, community and cultural health literacy. They discuss the impact of language and worldview on fundamental health literacy, acknowledging its significant impact and proposing that it is possible to overcome this through oral education in people’s first language. They emphasise the need for careful consideration of contextual rather than literal translation of medical words. When discussing the impact of worldview on scientific health literacy the fact that the indigenous worldview does not include the concept of a microscopic world, and that circulation and digestion are also not understood to exist in the biomedical sense, are highlighted. With respect to the community domain, the lack of understanding of Western healthcare systems, their policies, procedures and expectations make navigating a healthcare journey and seeking out information even more challenging. When discussing cultural health literacy it is pointed out that the Yolŋu cultural understanding of health is better explained as a comprehensive entity of well-being linked with land, law and relationships, not just the individual. While acknowledging that words and worldviews vary across different indigenous nations, Vass et al. suggest that the principles of working in depth in language and through the indigenous worldview are likely to be relevant to other indigenous groups, particularly where English is a second language and the worldview of health is not a biomedical one.

Senior and Chenhall [53] present an ethnographic perspective of health behaviour and beliefs in an Arnhem Land Indigenous community. They describe how people often hold fatalistic beliefs
with respect to engagement with their own health, as viewed through biomedical frameworks, but concurrently engage with a range of pragmatic responses to health problems such as engaging with traditional healers and over-the-counter Western medicines. That belief in the inevitability of and observed experience of the normalisation of ill health creates a barrier to responsibility. This lack of control over an individual’s health destiny is reinforced by a historical context of dispossession and inequality and a cultural context that places emphasis on the role of sorcery in sickness and death.

Ireland et al. [54], again through a descriptive ethnographic study, present evidence of low levels of knowledge with respect to biomedical constructs related to sexual health in a remote Indigenous community in the NT. Markedly different understandings of anatomy, physiology and causation of disease are discussed which present significant opportunity for misunderstanding, mistrust and ineffective communication if delivering sexual health education via a biomedical model.

### 4.2.5 Links between low health literacy and poor health outcomes

Low levels of health literacy have been shown to be associated with poor health outcomes in two systemic reviews addressing this issue. The first, published in 2004 [55], included 44 studies, and the second, published in 2011 [56] (an update by some of the same authors), included 96 studies. All included studies in both the above reviews were graded as good or fair quality by explicit criteria. In the majority of these studies health literacy has been measured using either REALM or a version of the TOFHLA and so essentially is referring to fundamental health literacy. The vast majority of this work has been carried out in a US-based setting within a biomedical worldview of health.

Baker and colleagues have looked in detail at a cohort of 3,260 elderly (>65 years old) Medicare enrollees in a managed care organisation in four US cities. In this setting they found increased
rates of hospital admissions [57] and ED visits [58] but not out-patient visits [59] in those with inadequate health literacy as measured by the S-TOFHLA. Mortality was significantly increased in those with inadequate health literacy with an adjusted hazard ratio of 1.52 (95% CI 1.26-1.83) for all-cause mortality [60].

In the setting of heart failure Peterson et al. also found an association between low health literacy as measured by the SBSQ and all-cause mortality with an adjusted hazard ratio of 1.97 (95%CI 1.3-2.97) P<0.001 [61]. Using a brief four item screening questionnaire to assess health literacy, Bostock et al. report an adjusted hazard ratio of 1.4 for all-cause mortality in those with low health literacy. This longitudinal study followed 7,857 people over the age of 52 years in the UK for an average of 5.3 years of follow up [62].

There is moderate evidence from multiple studies to support the association between low health literacy and reduced knowledge of various chronic diseases [56]. The impact of health literacy on type 2 diabetes, in the context of elderly Americans has been extensively reviewed. The evidence for poorer diabetic specific knowledge is clear cut, however the independent association between low health literacy and clinical outcomes such as HbA1c is inconsistent and less convincing [63].

There are no studies specifically looking at measures of health literacy and its relationship to health outcomes in the specific context of chronic HBV infection. There has been some work looking at the impact of health literacy on the health of HIV-infected individuals. Although most of these studies are again based in the USA and use the REALM or TOFHLA as the measure of health literacy, low health literacy has been associated with lower HIV-related knowledge and reduced adherence to antiviral medications [64]. Adequate HIV specific health literacy, defined as a patient knowing their CD4 count and HIV viral load, more than doubled the odds of attending >75% of follow up appointments. A reported good relationship with their provider was
also associated with significantly higher CD4 counts and greater odds of viral suppression [65].

Despite the geographical distribution and global impact of HIV there has to date been little published literature with regard to adaptation of health literacy measures to other cultural contexts [64] to allow further exploration of these questions outside the USA and Europe.

Both in the general context of low health literacy and the HIV specific context there has been some evidence to suggest that health literacy may be a mediating factor on the relationship between race/ethnicity and poor health outcomes [56]. This concept has not been formally explored in the context of Indigenous Australians.

Paasche-Orlow & Wolf [22] have proposed a model of the pathways that exist between low levels of health literacy and poor health outcomes (Figure 4.1). This is a component-cause model, which suggests that an individual’s level of health literacy influences three critical components of healthcare: access and utilisation, provider-patient interactions, and self-care, which in turn impact on health outcomes (e.g. someone with poor health literacy about hepatitis B may present later and have a poorer outcome from their hepatocellular carcinoma due to their lack of knowledge of a screening program aimed at early diagnosis). It also emphasises the importance not only of individual factors but system, provider and extrinsic factors that contribute to each area. An example of this would be the lack of appropriate health education resources to assist the healthcare provider in effectively communicating the importance of attending hepatocellular carcinoma screening to a patient with low health literacy.

4.2.6 Improving health literacy

Improving fundamental health literacy has been shown to have positive effects on patients’ knowledge, experience and use of health services [66]. It is less clear whether it independently improves health outcomes. Despite previous and ongoing research into the contributing factors to health literacy and its effect on health outcomes, there is a lack of conclusive evidence with
regard to the types of interventions that are most effective at improving health literacy [67]. This question is especially hard to definitively assess when there is no universally agreed definition of health literacy or measurement tool that satisfactorily measures all aspects of this multidimensional social construct.

**Figure 4.1: The Paasche-Orlow & Wolf model [68]**

There is now increasing experience with the use of innovative, interactive, internet, mobile phone and tablet-based resources to improve health literacy in some settings [68, 69]. Evidence supporting the use of alternative format resources to increase knowledge is available and has also suggested positive impacts on self efficacy and health behaviour [70].
In the context of HIV, Ownby et al. [71] have developed a computer-delivered, touch screen, hour-long multimedia interactive education tool. Based on the conceptual framework of the information-motivation-behaviour skills model, its aim was to increase adherence to HIV medication through improving HIV specific health literacy. Health literacy was measured using the TOFHLA and medication adherence using the Medication Events Monitoring System (MEMS; Aardex Group Ltd, Sion, Switzerland). Adherence was significantly improved after the intervention in those with baseline adherence <95% even after adjusting for baseline health literacy and cognitive function.

In the context of Indigenous Australia, a number of disease specific interventions aimed at improving health literacy are in development or underway, however none have completed or published definitive results to date. Several groups have produced applications (apps) in the area of mental health [72] but robust evaluation of their value is still awaited. In northern Australia, Christie’s research group has proposed a tablet-based, easily transportable, touch pad body resource, which does not contain any embedded health messages, but rather focuses on aspects of a healthy body. Their vision is that this could be used as the foundation for a further discussion about the impact of chronic diseases on the body and how treatments act to return the body to a healthy state [49]. However, this resource has not been produced as yet.

An international multi-centre interventional trial protocol has recently been published looking at cardiovascular disease medication health literacy among Indigenous peoples in Australia, New Zealand and Canada[73]. Following a development phase involving qualitative work (not described in detail) significant gaps in patient’s cardiovascular disease knowledge were identified. Subsequently an intervention including health worker delivered education sessions, a tailored information booklet and interactive tablet application was developed in conjunction with the involved communities. The main aim of the study is to assess cardiovascular disease
specific health literacy, pre and post intervention. The assessment tool used for measurement has been developed by the research team with specific details not available.

In the context of dental health literacy, a cluster randomised trial is underway in South Australia examining the impact of a tailored intervention on health literacy in Indigenous adults [74]. This trial builds on extensive qualitative work carried out with this community exploring knowledge, perceptions and informing the intervention and assessment protocols. One example of how the community engagement has changed the protocol of this trial is that the health literacy assessment tool was changed from the REALD-30 – the REALM for Dentistry – to the HeLM due to the feeling that the HeLM was more culturally appropriate.

A group in Victoria has commenced the ‘Ophelia process’ (Optimising Health Literacy) and published a study protocol detailing the process [75]. The aim of this project, which is based across eight health and community care organisations, is to develop and assess a systematic process, which then produces a framework. The framework details various intervention options tailored to specific communities health literacy needs. The process is outcomes orientated and focuses on two key questions: “What are the health literacy strengths and weaknesses of clients at participating sites?” and “How do sites interpret and respond to these in order to achieve positive health and equity outcomes for their clients?”. The process will utilise the HLQ as the health literacy assessment tool.

Once these planned interventions are completed we will have much-needed information about the use of the newer health literacy measurement tools (HeLM & HLQ) in an Australian Indigenous context. These results will also start to build an evidence base as to the success of the various interventions on health outcomes in this setting.
4.3 Cross cultural communication

Effective communication is not only central to improving health literacy [76], it is a crucial element in achieving culturally safe healthcare, which in essence can be defined as “Shared respect, shared meaning, shared knowledge and experience of learning together” [77].

4.3.1. Culturally and linguistically diverse communities

Wilson et al. [78], through a large telephone survey, looked at the effect of limited English proficiency on medical comprehension in the presence and absence of language concordant physicians. It was concluded that although access to a language concordant physician mitigated the increased risk of misunderstanding it did not completely eliminate it. This suggests that the communication problem is often more than simply the language itself. Limited English proficiency and linguistic isolation (no one > age 14 years within the household who can speak English) combined with cultural belief systems and attitudes towards care are barriers to hepatitis B care highlighted for Asian Americans. It is suggested that these can be partially overcome with interpreters but that cultural sensitivity training in conjunction with addressing the language barriers is vital [6]. There are likely to be many similarities in migrant populations living in countries where the language of healthcare is not their first language.

As the majority of Australians living with chronic HBV infection were born overseas and significant proportions speak little or no English, the importance of the availability of hepatitis B specific resources in the commonest languages (Chinese, Vietnamese and Korean) has been highlighted [79]. However qualitative exploration of oral health literacy in Chinese mothers in south-western Sydney highlighted that direct translation is not the whole solution. “English leaflets are not for me” again revealed the importance of appropriate cultural interpretation and contextual translation to ensure your message is received in the way intended [80].
It remains an area of contention whether implementing cultural competency training for healthcare professionals directly improves patient outcomes. The most recent systematic review on the subject suggests that although research is limited, the trend is towards a benefit, and the lack of a conclusive answer is most likely due to the paucity of high-quality studies [81].

4.3.2 Communication in an Indigenous context

In the context of the NT Indigenous population, English is usually a second (or even third or fourth) language; therefore, achieving effective cross cultural or ‘culturally safe’ communication can be challenging, as has been extensively documented in healthcare settings over the last decade [82-84]. Miscommunication between health providers and patients has been reported to be pervasive, however using interpreters and translators is perceived to be only part of the solution [82]. Different worldviews and knowledge systems that exist among Indigenous Australians, including alternative concepts of physiology, pathology and disease causation, also contribute [53, 54]. An often misinformed assumption by health providers of shared understandings [82], along with the absence of opportunities and resources to construct a body of shared understanding, perpetuate this miscommunication. More recently, research suggesting that some Indigenous patients believe that healthcare workers deliberately withhold information from them highlights the extreme lack of trust that can develop as a consequence of ineffective communication [83].

Although no work has been done specifically looking at educational tools for people living with chronic HBV infection in this context, a dementia awareness resource has been piloted in three Aboriginal languages in the NT. The resource produced by Alzheimer’s Australia Northern Territory consisted of a 16 minute DVD, ‘Looking out for Dementia’, in English, Warlpiri, Kriol and Djambarrpuuyngu (a dialect of Yolŋu matha). The qualitative evaluation consisted of an Indigenous advisory group, Indigenous researcher involvement throughout, five focus groups, five semi-structured interviews with healthcare professionals and direct observation of the
resource being implemented. Not only was the availability of the information in local languages important for comprehension but it was also reported to validate respect for culture, facilitate understanding and engagement, be sincerely appreciated by strengthening good will, and help to develop health vocabularies [85]. Although the use of the resource was felt to lead to more positive behaviours in those caring for individuals with dementia there was no objective outcome measure of health literacy or specific behavioural change outcomes within the evaluation.

Although cross-cultural communication, cultural competency, cultural safety and training to improve these facets clearly overlaps with and contributes to health literacy, they are often compartmentalised and treated separately when discussed in peer reviewed literature. Low health literacy and challenging cross-cultural communication often occur concurrently, both contribute to disparities in healthcare and there is evidence that improving them individually leads to improvements in health outcomes. It would therefore seem logical to attempt to address them in unison rather than as separate entities. Lie et al. have presented a conceptual framework to do this with the hope of shifting the focus towards collaborative health literacy and cultural competence education to reduce health disparities. [86]

4.4 Existing hepatitis B educational resources

Although many hepatitis B educational resources exist, some of which are discussed in more detail below, none developed for use in the clinical setting are tailored to any Australian Indigenous people’s language or worldview.

The Australian Indigenous Healthinfo net, a website run by a level II research centre within Edith Cowan University in Western Australia (WA), collates and makes readily accessible resources aimed at or felt to be of use to Indigenous Australians [87]. They have 62 educational resources under the heading ‘Hepatitis’ however only four of them focus solely on hepatitis B. An
additional 12 deal with combinations of hepatitis A, B, C and HIV in a sexual health format. One leaflet developed by the Queensland Association for Health Communities is in Creole but all other written information is in English.

The Aboriginal Resource Development Services (ARDS) is an Indigenous organisation that has worked in the Arnhem Land region of the Northern Territory for 40 years with a specific focus on capacity building and adult education. They have built up a whole series of resources available to purchase and educational programs looking at germ theory, infectious diseases and antibiotics with an Indigenous worldview. More recently they have developed a series of radio broadcasts about hepatitis and the liver in general as part of their sexual health project [88]. The programs are in Yolŋu matha and have been broadcast on Yolŋu radio and are available to listen to through their website free of charge. Yolŋu radio is broadcast across six remote communities and 30 homelands in North East Arnhem Land and Darwin.

The ‘hepatitis B Story’ is a plain English language resource developed and launched in November 2013 by Gabrielle Bennett in conjunction with St Vincent’s Hospital, Melbourne and the Inner North West Melbourne Medicare Local [89]. It is predominantly aimed at people from culturally and linguistically diverse backgrounds and / or those with low health literacy. It is general in its approach and presents information clearly and succinctly using a biomedical worldview (Figure 4.2). It also suggests and describes the ‘teach back’ strategy as a useful tool to use when communicating with patients with low health literacy. There are currently no published data available with regard to the details of the development process or formal evaluation.
The ‘Hepatitis B Bear’ developed by Dr Miriam Levy and her team at Liverpool Hospital in south-west Sydney was launched in 2012 as a flip chart and a series of YouTube videos. This resource uses the analogy of a bear renaming the phases of hepatitis B as silent, damage, control, escape and clear (Figure 4.3). Limited details with regard to its development and results of a community evaluation with small numbers of patients were presented as a poster at the 65th Annual Meeting of the American Association for the Study of Liver Diseases in Boston in November 2014 [90]. Initial interest, opinion and evaluation have been overwhelmingly positive. The target of the resource is culturally and linguistically diverse communities in an urban setting.

The Australian Society for HIV medicine also produces a hepatitis B educational resource for patients newly diagnosed with hepatitis B in 13 different languages and Hepatitis Australia produces a similar style leaflet in four languages: English, Chinese, Vietnamese and Arabic.
Figure 4.3: The Hepatitis B Bear educational resource
4.5 Participatory action research in developing health education resources

4.5.1 What is participatory action research?

Participatory action research (PAR) is a framework or approach to undertaking qualitative research that establishes structures for full and equal participation in the research by the community involved. It was founded in the work of Kurt Lewin [91] and is often used interchangeably with the terms ‘action research’, ‘community-based research’ and ‘community-based participatory research’. It can be best described as a cyclical process of reflection, evaluation and action, where respect for and involvement of the community in all aspects of the research process is an integral part of the methodology (Figure 4.4). It is particularly suited to exploring and understanding human experiences of a particular situation, under which people are experiencing disparities in health, the idea being that by involving those experiencing the disparity, the issues can be seen from their perspective and through reflection, evaluation and ultimately action, a solution can be developed and the disparity ameliorated. This in turn empowers the involved community and acts as a driver for social change.

Figure 4.4: The participatory action research cycle
4.5.2 PAR in Indigenous communities

PAR is increasingly recognised as valuable in Indigenous health research both internationally [92, 93] and in Australia [94-96]. It has the potential to reduce the negative effects and experiences that Australian Indigenous people have with respect to historical experiences of research, top-down hierarchal approaches and culturally inappropriate study designs. It attempts to look at a situation from numerous viewpoints to holistically appreciate the issues, sitting more comfortably with the Australian Indigenous view of health as the wider concept of well-being, than more traditional research methods. It also has research translation and dissemination as an integral component of the methodology and the potential through participation to create ownership and sustainability of developed solutions. However, it has recently been pointed out by Rhodes et al. [93] that we may be making some assumptions as to the benefits of PAR. He suggests that researchers may often spend a lot of time dedicated to partnership development and less rigorous attention to evaluation of whether the developed intervention has impacted on health outcomes. It is imperative that we are mindful of this to enable PAR projects to fulfil their potential and for Indigenous people to gain the most benefit.

4.5.3 PAR in the development of health education resources.

A number of studies report successful outcomes of PAR projects in the context of developing health resources in Indigenous communities [97, 98].

A PAR project was undertaken with the Aboriginal Community Controlled Health Service in WA to develop a response to the hugely disparate diabetes-related amputation rates between Aboriginal and non-Aboriginal people [98]. A number of existing diabetic foot care resources were discussed at six focus groups. Participants were unequivocal in their preference for real pictures of foot problems as opposed to cartoons and preferred to develop their own messages “Look after your feet” in pictures and words being their preference. As well as leading to
recommendations and specifications regarding which resource should be rolled out across WA, the project had the unintended consequences of the local Aboriginal health training college incorporating diabetes foot care training into their student training programs.

Also in the context of diabetes, the Family Education Diabetes Series (FEDS) is a community-based participatory research project based in an American Indian community in the Mid-West of the USA [97]. The developed intervention is a six month program of bi-weekly social/education meetings where patients, their families, healthcare providers and local elders partake in health measurements, share a meal and discuss and explore individual educational needs. To measure impact on outcomes, participants were then followed through an entire program and reviewed at three and six months post completion. Participants showed statistically significant improvements in BP, glycaemic control and weight loss. The FEDS program continues to date.

4.6 Conclusions

Barriers to care for hepatitis B are multifactorial but appear to centre on factors which contribute to health literacy when using a holistic definition of this multidimensional construct. The limited data available suggests hepatitis B specific knowledge in Australians living with chronic HBV infection and their healthcare providers is low and there is a lack of culturally appropriate education tools to facilitate intervention in this area.

Health literacy research is in evolution and although multiple measurement tools exist, most have been developed in a Western setting with no specific consideration of culture and different worldviews of health. Acknowledging this, when measured using either specific tools or qualitative methods, the prevalence of low health literacy appears to be significant, both in the general Australian population and among Indigenous Australians.
Being mindful of the problems of measurement there is evidence to suggest links between poor health outcomes and low health literacy and some positive trends between improvements in health literacy and better health outcomes. Communication, specifically in a cross-cultural environment which is often concurrently one of low health literacy, can be challenging and clearly significantly contributes to attempts to improve health literacy.

There is a perceived and documented lack of culturally appropriate education resources specifically for Indigenous Australians about hepatitis B. It is likely in this cultural context, where English is not the first language, worldviews of health are different and health literacy in a biomedical sense is low, that qualitative methodology using a PAR framework will be most useful in exploring hepatitis B specific health literacy.
4.7 References


47. Barber M, Staples M, Osborne R, Clerehan R, Elder C, Buchbinder R: Up to a quarter of the Australian population may have suboptimal health literacy depending upon the measurement tool: results from a population-based survey. *Health Promot Int* 2009, 24(3):252 - 261.


Section B – The epidemiology of hepatitis B in the Northern Territory
Chapter 5 - The sero-epidemiology of HBV in Australia’s Northern Territory based on 20 years of Territory-wide testing data
5.1 Preamble

The first National Hepatitis B strategy [1] published in 2010 listed Indigenous Australians as a priority group and called for action to reduce the morbidity and mortality associated with HBV.

As detailed in Chapter 2 of this thesis, the epidemiological data on which to base an appropriate efficient and sustainable response to this call in the NT was not available in 2011 when this study was conceived.

In 2012 Liu et al. [2] published a data linkage study based on NT antenatal women showing a significant decrease in chronic HBV infection prevalence in Indigenous birthing mothers, which was very encouraging. There were some concerns about the generalizability of a women-only study to the total population and it was based on HBsAg records only so did not provide any information about anti-HBc or anti-HBs prevalence. Also, due to an understandable desire to assess the effectiveness of the NT childhood vaccination program, all mothers born overseas were excluded from the study meaning the information provided about non-Indigenous people with chronic HBV infection in the NT was limited.

Also in 2012 the NT Centre for Disease Control, with which we have worked closely, produced a summary report of all HBV notifications provided to them between 1990 and 2011, (2005-2011 for non-acute cases) [3]. This confirmed suspicion regarding higher NT prevalence levels compared to Australia-wide, particularly in the Indigenous population (2.2%) but also suggested a significant 10-fold reduction in rates of infection in the post-vaccination era. There was no information regarding anti-HBs or anti-HBc available.

During the planning phase of this study numerous people told me on numerous occasions that they would advise me against a data linkage type project as part of a PhD due to difficulties with timelines. I carried on regardless; however as it transpires they were very wise. This was also not a standard ‘data linkage’ project where clear separation of those doing the linkage and analysis is strictly maintained, as we required identifiable data to enable linkage of our data with the NT.
client master index to obtain Indigenous status and we needed to make this process as safe as possible. Consequently the process of obtaining ethical and data custodian approvals, and obtaining and managing the data extracts in a way which minimised access and maintained sound methodology while enabling optimal use of available data was long, slow and challenging. I am therefore very excited to present the cross-sectional data analysis in this chapter and can now confidently say that the challenging process of making this data set exist was worthwhile.
5.2 Abstract

Background
Chronic hepatitis B (chronic HBV infection) is endemic in the Northern Territory (NT) of Australia where universal newborn and infant vaccination was introduced for all children in 1990. Prevalence estimates range from 0.8% to 13.3% but are based on small studies or taken from specific populations such as antenatal women. There are no contemporary population-wide HBsAg sero-prevalence data available.

Methods
We created a large dataset containing the results of all hepatitis B diagnostic tests including: HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe and HBV DNA obtained from NT residents during the time period 1991-2011 (329,426 testing episodes). These data were linked with the NT client master index database to obtain Indigenous status and the most recent test results for each individual were extracted as a cross-sectional database including 88,112 unique individuals.

Results
Based on all tests carried out from 2007-2011 inclusive (35,633 individuals), the prevalence of chronic HBV infection was 3.40% (95%CI 3.19-3.61). The prevalence was higher in Indigenous Australians (6.08% [95% CI 5.65%-6.53%]) than non-Indigenous people (1.56% [1.38%-1.76%]), P<0.0001. Males were more likely to have chronic HBV infection than females (OR 1.53, 95% CI 1.42-1.66, P<0.0001), and those living in remote areas were more likely than non-remote dwelling people (OR 1.84 95%CI 1.62-2.10).

Analysis by birth cohort showed a steady fall in HBsAg prevalence over time starting well before the introduction of universal vaccination. Whilst the HBsAg sero-prevalence by birth cohort continued to decline after the introduction of universal vaccination overall and for Indigenous individuals, it was at a slower rate (0.09% per year pre-1990 versus 0.009% per year post-1990.
and 0.23% per year pre-1990 versus 0.17% per year post-1990 respectively) and it increased for non-Indigenous individuals (0.0005% reduction versus a 0.16% increase per year).

**Conclusions**

Chronic HBV infection rates are still high in the NT. Indigenous Australians and men are disproportionately affected. HBsAg prevalence has fallen significantly over time; however data since 1990 are currently inadequate to confidently assess the true impact of the NT childhood vaccination programme. A recent trend showing increasing HBsAg prevalence in non-Indigenous individuals needs further exploration but is likely to be attributable in part to increased migration from HBV endemic populations.
5.3 Introduction

Chronic hepatitis B is common in the Northern Territory (NT), however estimates of prevalence to date have been based either on small population specific studies (specific communities [4-7] or antenatal women [8, 9]) or Australia-wide mapping studies (ASHM mapping project [10, 11]), which used mathematical models to estimate sero-prevalence based on the ethnicity in a region and previously published prevalence estimates within each ethnic group. Studies from specific remote communities have estimated the prevalence to be between 2-12% even in the post-universal vaccination era [4-6]. The NT introduced universal childhood hepatitis B vaccination for all Indigenous children in 1988 and for all children in 1990 with a school based catch-up program for those aged 6-16 years in 1998-9 (born from 1982-1992). An ecological study using NT Centre for Disease Control notification data and midwifery registers has shown a decrease in chronic HBV infection prevalence since the introduction of universal vaccination but still documented substantial disparity between Indigenous and non-Indigenous women [2]. The Australia-wide Hepatitis B Mapping Project estimated that the NT has the highest prevalence of chronic HBV infection of any jurisdiction in the country at 1.68% overall, that 59% of those with chronic HBV infection in the NT are Indigenous Australians and only 2.4% are receiving antiviral therapy [10].

The Second National Hepatitis B Strategy [12], launched in 2014, estimates that 45% of individuals in Australia with chronic HBV infection are unaware of their diagnosis and identified Indigenous Australians as a priority group for testing [13]. Specific targets are set out including increasing the proportion of people living with chronic HBV infection that have been diagnosed to 80% and improving the percentage of those on antiviral treatment to 15%, as well as increasing the vaccination coverage of priority populations. In order to move towards achieving these targets it is crucial to develop detailed epidemiological estimates of not only the overall prevalence of chronic HBV infection but also indicators of access to testing and the proportion of the population who are immune to infection.
A number of factors make this information particularly important to guide effective and sustainable public health interventions in the NT. The Indigenous Australians of the NT have been recently identified to be universally infected with a particular sub-genotype of hepatitis B C4, which has molecular markers of an aggressive phenotype and a different serotype to the currently used vaccine [14, 15]. The logistics of delivering optimal care for chronic HBV infection including hepatocellular carcinoma screening in the NT are particularly challenging as over 100 remote communities are spread over an area greater than 1 million square kilometres. Thirty percent of the population are Indigenous Australians and 30% of this group live in very remote settings.

The gold standard study design for obtaining the prevalence of hepatitis B would be a sero-survey including either an entire population or a truly random sample of a population. However, community consultation with NT Indigenous Australians suggested that it is preferable to make the best use of all existing data sources prior to asking people to give extra blood samples. Since most data about sero-epidemiology of HBV in the NT are based on small community samples or antenatal testing, there are important knowledge gaps about the epidemiology of HBV in males, older people and children.

This study aimed to use the results of all existing hepatitis B serology results from NT residents taken over 20 years (1991-2011 inclusive) to provide a contemporary estimate of chronic HBV infection prevalence in the NT. It also aimed to investigate geographical distribution, Indigenous status and age group. We also evaluated the prevalence and patterns of anti-HBs and anti-HBc, representing resolved hepatitis B infection and protective immunity against hepatitis B.

5.4 Methods

This study was a retrospective analysis of all available hepatitis B laboratory results including: HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe and HBV DNA viral loads carried out in the Northern
Territory (NT) between 1991 and December 2011. The primary aim was to obtain an estimate of HBsAg prevalence for the NT overall as well as by Indigenous status. Secondary aims were to establish the prevalence of anti-HBs positivity, anti-HBc positivity, levels of anti-HBe, HBeAg and HBV DNA testing and to evaluate all HBV markers by birth cohort with reference to key dates in the introduction of universal vaccination in the NT.

Ethical approval was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC-2012-1745) and the Central Australian Human Research Ethics Committee (HREC-14-244).

We defined chronic HBV infection as everyone with a documented HBsAg positive result. We analysed three subsets of the data: the whole dataset, data from 2007-2011 and data from 2007-2011, with only absolutely confirmed cases (defined as HBsAg positive on at least two occasions at least six months apart within our database) of chronic HBV infection. This was done to establish if there were large difference in the results obtained by each method as each has advantages and disadvantages and also to establish the likely level of underestimation of chronic HBV infection using the formal definition of chronic HBV infection needing two documented tests greater than six months apart.

We defined remote residence as living outside the urban Darwin (postcodes 0800-0821, 0829-0832), Katherine (0850-0851) or Alice Springs (0870-0871) areas.

**Raw data sources**

It has been previously documented that 97.9% of all hepatitis B notifications in the NT come from one of the following three pathology providers: Northern Territory Government Pathology Service (NTGPS), Western Diagnostic Pathology (WDP) or SA Pathology (SAPath), formally the Institute of Medical and Veterinary Science (IMVS) [3]. We therefore approached these laboratories for a data extract for the tests results for 1991–2011. Demographic details including birth date, gender, and community of usual residence were also obtained. An individual’s unique
hospital record number (HRN), used to access all public health services in the NT, was only available on a small percentage of the laboratory data extracts. It was therefore necessary for us to obtain surname and forename for each individual in order to perform the data linkage as described below. Identifying details were then removed and analysis was carried out on de-identified data.

The received data were processed into a uniform format and amalgamated to create a master dataset (details of this process provided in Appendix 1A) where each line of data was given a unique study identification number and represented a single testing episode on a specific day (this could include more than one test result, e.g. HBsAg and anti-HBs done on the same blood draw). It was recognised that individuals may have had multiple tests both over time and at different locations and hence have results from multiple providers.

Data linkage

The NT Department of Health (DoH) maintains a data warehouse containing the client master index (CMI), a resource that contains personal identifying information of all residents accessing NT public (government funded) health services. For each individual the name, date of birth, sex, usual place of residence, Indigenous status and HRN is contained in the CMI. Audits of the CMI have documented a high degree of accuracy [16] and this index has been used in previous data linkage projects [2]. We amalgamated the laboratory records from the three pathology providers, stripped the hepatitis B results, and provided the remaining individual identification details for linkage to the CMI by the DoH Health Gains Planning Unit. Deterministic matching based on 11 combinations of the variables forename, surname, date of birth and address was used to obtain Indigenous status for each individual and assign unique person identifiers. Between 5 and 50% of the data matched on each of the 11 levels was manually checked for accuracy and corrected as necessary until acceptable accuracy was obtained (Appendix 1B).

Returned linked data contained Indigenous status and a unique encoded version of the HRN for
each unique study identification number (the unique ID number allocated prior to the data linkage which represents an individual testing episode) to enable us to identify the individual person as well as the testing episode. Data was therefore de-identified prior to linkage back to the hepatitis B results information.

**Data set for analysis**

To enable a cross-sectional analysis the linked results above were reviewed and merged back to the testing results using the unique study identification number. The data set was then organised to include the most recent available result for each of the following tests: HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe and HBV viral load, for each individual for whom Indigenous status was available. This cross-sectional dataset included 88,175 individuals for analysis (Figure 5.1).

As the total dataset was collected over a 20-year period, in order to minimise the impact of biasing factors such as death, loss of HBsAg, and movement out of the NT over that time period, a sensitivity analysis was undertaken to determine the most accurate dataset to use for the main analysis (Appendix 1C). The three datasets considered were: the whole dataset spanning 1991-2011 including 88,189 individuals, the last five years (2007-2011) including 35,633 individuals, and the last five years with only 100% confirmed cases of chronic HBV infection included (inclusion criteria being two confirmed HBsAg positive test results in our database separated by greater than six months duration) which included 35,287 individuals. The results in this paper describe the analysis of the second option above, a cross-sectional sample of the whole dataset including only the latest test result from each individual who had a blood sample taken for any hepatitis B marker between 01 January 2007 and 31 December 2011 and who was still active within the government system (i.e. to the knowledge of the DoH CMI they were alive at the time of analysis).
Data were managed and analysed in STATA (Statacorp, College Station, Texas) version 13. In descriptive analysis, measures of central tendency and dispersion used were median, interquartile range (IQR) for non-normally distributed data and mean, standard deviation (SD) if data were normally distributed. Proportions within categorical groups were calculated with the denominator as the total number of individuals who had a result available for that variable and presented with binomial confidence intervals. Chi squared tests were used to assess differences between categorical groups and two-way tests of proportions for differences within and across categories. Logistic regression was used to produce odds ratios for dichotomous dependent variables such as HBsAg; post estimation diagnostics included classification statistics and the Pearson Goodness of Fit test. Interrupted time series analysis using regression with Newey West standard errors was used to analyse HBsAg prevalence before and after the implementation of universal vaccination in the NT. The Cumby-Huizinga general test for auto-correlation was applied to the time series analysis to determine the appropriate lag to account for auto-correlation [17].
Figure 5.1: Flow diagram detailing sources of testing data and production of dataset including only the latest set of results for each individual with all the duplicate tests and individuals removed.

- **NT Government Pathology service**
  - 92,589 testing episodes
  - Jan 1998-July 2012

- **Western Diagnostic Pathology Service**
  - 226,336 testing episodes
  - Dec 1991-July 2012

- **SA Pathology**
  - 28,062 testing episodes
  - Jan 1998-Jan 2012

346,987 lines of data

Those with no identifying details removed

329,426 testing episodes

Linked to client master index to obtain Indigenous status

247,196 results returned

- 194,321 unique testing episodes
- 91,227 unique individuals – dropped if
  - Indigenous status unknown

**88,175 individuals for analysis**
5.5 Results

The study describes the most recent hepatitis B serology results for 35,633 individuals, 14,025 of whom identified as Indigenous Australians, who had blood collected in the Northern Territory of Australia over the five-year time period 2007-2011 inclusive. Using 2011 Census data for population numbers this accounts for 17% of the total NT population and 25% of the NT Indigenous population. The percentage of individuals tested detailed by age group is shown in Figure 5.2.

The majority (82.1%) of individuals tested were between the ages of 20 and 59 years at the time their blood was collected (Figure 5.3). The median age of participants was 32 years (IQR 25-44) and of those tested, 57.8% (95% CI 57.3-58.3) were female and 39.4% (95% CI 38.9-39.9) were Indigenous Australians. Both Indigenous Australian males (32.0 v 37.6 years) and females (29.6 v 31.2 years) were younger at the time of testing than non-Indigenous individuals.

Figure 5.2: Bar chart showing the percentage of the total NT population tested for any HBV marker between 2007 and 2011 by age group at time of testing
Figure 5.3 Age* distribution of individuals who had blood collected for any HBV marker between 2007 and 2011 in the NT compared to the age distribution of the total population of the NT as per ABS census data 2011. *Age at time blood was collected. Red is Indigenous people, blue is non-Indigenous people.
Overall, 33.3% (95% CI 32.8-33.9) had a remote usual place of residence at the time of testing, (Figure 5.4). Indigenous Australians were more likely to live remotely (51.1% v 18.3% P<0.0001) and less likely to live in Darwin city (44.3% v 9.5% P<0.0001).

Overall 980 individuals were found to be HBsAg positive, which equates to a prevalence of 3.40% (95% CI 3.19-3.61) of those who had an available result (n=28,853) among those people referred for HBV testing in the NT. For Indigenous Australians this increased to 6.08% (95% CI 5.65-6.53) compared to 1.56% (95% CI 1.38-1.76) for non-Indigenous Australians (P<0.0001) (Table 5.1).

Both non-Indigenous [OR 1.37 (95%CI 1.21-1.55)] and Indigenous [OR 1.93 (95%CI 1.66-2.24)] males had greater odds of being HBsAg positive than women (Table 5.2).

Figure 5.4: Pie chart showing the usual residence of all individuals (A) and HBsAg positive individuals (B)
More Indigenous 60.7% (95% CI 59.7-61.6) than non-Indigenous Australians 55.4% (95% CI 54.4-56.3) had documented evidence of immunity, defined as Anti-HBs >10IU/ml, P<0.001. Anti-HBc positivity representing past infection with HBV was present in 25.2% (95% CI 24.7-25.8) of people overall but 38.3% (95% CI 37.4-39.1) of Indigenous Australians versus 11.7% (95% CI 11.1-12.3) of non-Indigenous Australians (P<0.0001) Table 5.1. In those individuals who had results available for all three HBV markers, HBsAg, anti-HBs and anti-HBc, isolated anti-HBc positivity was significantly more common in Indigenous Australians at 11.0% (95% CI 10.3-11.6) versus 3.8% (95% CI 3.3-4.2) P<0.0001.

Table 5.1: Summary of demographics and HBsAg, anti-HBs and anti-HBc positive results broken down by Indigenous status and sex

<table>
<thead>
<tr>
<th>2007-2011 inclusive</th>
<th>Overall N=35,633</th>
<th>Indigenous n=14,025 (39%)</th>
<th>Non-Indigenous n=21,608 (61%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age in years at sample date (IQR)</strong></td>
<td>32.4 (24.5-43.7)</td>
<td>30.8 (21.5-43.3)</td>
<td>33.2 (26.3-44.0)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Female % (95% CI)</strong></td>
<td>57.8 (57.3-58.3)</td>
<td>53.7 (52.8-54.5)</td>
<td>60.5 (59.9-61.2)</td>
</tr>
<tr>
<td><strong>HBsAg positive % (95% CI)</strong></td>
<td>3.40 (3.19-3.61)</td>
<td>6.08 (5.65-6.53)</td>
<td>1.56 (1.38-1.76)</td>
</tr>
<tr>
<td><strong>HBsAg positive men % (95% CI)</strong></td>
<td>4.99 (4.59-5.40)</td>
<td>8.27 (7.53-9.05)</td>
<td>2.22 (1.86-2.62)</td>
</tr>
<tr>
<td><strong>HBsAg positive women % (95% CI)</strong></td>
<td>2.35 (2.13-2.59)</td>
<td>4.31 (3.83-4.84)</td>
<td>1.18 (0.99-1.40)</td>
</tr>
<tr>
<td><strong>Anti-HBs &gt;10IU/ml % (95% CI)</strong></td>
<td>58.0 (57.3-58.7)</td>
<td>60.7 (59.7-61.6)</td>
<td>55.4 (54.4-56.3)</td>
</tr>
<tr>
<td><strong>Anti-HBc positive % (95% CI)</strong></td>
<td>25.2 (24.7-25.8)</td>
<td>38.3 (37.4-39.1)</td>
<td>11.7 (11.1-12.3)</td>
</tr>
</tbody>
</table>

Only 43.1% of individuals (95%CI 42.5-43.6) had results available for all three HBV diagnostic markers HBsAg, anti-HBc and anti-HBs. Indigenous Australians were significantly more likely to
have all three markers available 60.9% (95% CI 60.1-61.7) versus 31.5% (95% CI 30.1-32.1)
P<0.001.

With respect to HBeAg, 891 (90.9% 95% CI 88.9-92.6), of the 980 individuals with a positive
HBsAg had an HBeAg result available, 18.2% (95% CI 15.7-20.1) of them being positive. For anti-
HBe, 888 (99.7% 95% CI 99.0-99.9) had an anti-HBe result available with 75.9% (95% CI 72.9-
78.7) being positive. Fifty-five HBsAg positive individuals were negative for both HBeAg and Anti-
HBe (7.6% 95% CI 5.7-9.7) and two positive for both markers (1.2% 95% CI 0.1-4.4). There was a
current HBV DNA result available for 222 of the 980 HBsAg positive individuals (22.7% 95%CI
20.1-25.4).

Figure 5.5: Age distribution of HBeAg positive individuals at the time their last eAg sample
was collected for non-Indigenous and Indigenous individuals

Males, Indigenous Australians and those who live remotely were shown by logistical regression
to have increased odds of being HBsAg positive (Table 5.2).
Table 5.2: Unadjusted and adjusted odds ratios with 95% confidence intervals for factors associated with an increased or decreased risk of being HBsAg positive

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>OR of being HBsAg positive</th>
<th>OR adjusted for other tabulated variables</th>
<th>P value for the adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous Australia</td>
<td>4.08 (3.54-4.71)</td>
<td>3.81 (3.29-4.44)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.53 (1.42-1.66)</td>
<td>1.56 (1.44-1.70)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Living remotely</td>
<td>1.93 (1.78-2.10)</td>
<td>1.21 (1.05-1.39)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

Birth cohort analysis

Only 9.7% (95% CI 9.4-10.0) of those tested for any HBV marker between 2007 and 2011 were born in the universal vaccine era (post-August 1990). Overall HBsAg prevalence was 1.89% (95% CI 1.39-2.51) in this group. In Indigenous people prevalence was lower than non-Indigenous people (1.77 versus 2.15) and has decreased significantly over time (Table 5.3). In the non-Indigenous group the prevalence has actually increased in the universal vaccine era, although the total numbers tested in this group is small (791); we have no information with respect to the ethnic background of the non-Indigenous people.

Anti-HBc prevalence has fallen by birth cohort over time from very high levels of over 50% in those before the 1980s to a point where Indigenous and non-Indigenous groups now have a similar prevalence (Figure 5.4A). Anti-HBs prevalence levels have steadily increased over time for those born between 1935 and 1985 and then dropped for a period before increasing again for those born post-2000 (Figure 5.4B). When examined in more detail (Figure 5.5B), even though the confidence intervals are wide it does appear that a reduction in anti-HBs positivity has occurred especially among Indigenous individuals. The confidence intervals for all three markers, HBsAg, anti-HBs and anti-HBc, become much wider in the more recent birth cohorts (Figure 5.5) especially for the non-Indigenous group. This is most likely due to low numbers being tested in these more recent birth cohorts.
Interrupted time series analysis examining HBsAg prevalence overall and for Indigenous and non-Indigenous individuals is detailed in Figure 5.6. It shows that, for Indigenous people, there was no change in the rate of decrease in sero-prevalence over time after, compared to before, the universal vaccine era. Specifically, in the Indigenous group HBsAg prevalence was decreasing at a rate of 0.23% per year (95% CI -0.26 to -0.19 P<0.0001) prior to the implementation of HBV universal vaccination, and this trend in reduction continued unchanged for those born after universal vaccination at a rate of 0.17% per year (95% CI -0.23 to -0.10 P = 0.0017). However in the non-Indigenous group there is actually an increase in HBsAg prevalence post 1990; the possible reasons for this are discussed in detail below but are most likely to be attributable to increased migration from HBV-endemic populations.

Table 5.3: Comparison of HBsAg, anti-HBs and anti-HBc prevalence over time and between Indigenous and non-Indigenous people among those referred for HBV testing in the NT

<table>
<thead>
<tr>
<th>Time period</th>
<th>HBsAg % (95%CI)</th>
<th>Anti-HBs % (95%CI)</th>
<th>Anti-HBc % (95%CI)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 1982*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4.02 (3.74-4.31)</td>
<td>57.5 (56.7-58.4)</td>
<td>30.1 (29.4-30.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Indigenous</td>
<td>8.03 (7.40-8.70)</td>
<td>62.4 (61.1-63.6)</td>
<td>48.8 (47.6-50.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>1.76 (1.54-2.01)</td>
<td>53.5 (52.4-54.7)</td>
<td>13.9 (13.2-14.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>1982-1990*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.31 (1.98-2.68)</td>
<td>63.0 (61.6-64.3)</td>
<td>18.7 (17.7-19.7)</td>
<td>0.56 (0.48-0.67)</td>
</tr>
<tr>
<td>Indigenous</td>
<td>4.20 (3.53-4.95)</td>
<td>63.8 (61.9-65.6)</td>
<td>29.9 (28.3-31.6)</td>
<td>0.50 (0.41-0.61)</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>0.86 (0.60-1.19)</td>
<td>62.1 (60.1-64.0)</td>
<td>5.7 (4.9-6.7)</td>
<td>0.48 (0.34-0.69)</td>
</tr>
<tr>
<td>Post 1990*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.89 (1.39-2.51)</td>
<td>48.5 (46.3-50.7)</td>
<td>10.9 (9.7-12.2)</td>
<td>0.46 (0.34-0.62)</td>
</tr>
<tr>
<td>Indigenous</td>
<td>1.77 (1.20-2.52)</td>
<td>47.0 (44.3-49.7)</td>
<td>11.6 (10.2-13.2)</td>
<td>0.21 (0.14-0.30)</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>2.15 (1.26-3.42)</td>
<td>51.6 (47.6-55.5)</td>
<td>9.0 (7.0-11.3)</td>
<td>1.22 (0.74-2.01)</td>
</tr>
</tbody>
</table>

*No one born prior to 1982 would have had access to a childhood vaccination program in the NT. *Routine vaccination at birth for all Indigenous babies was introduced in 1988 and for all babies in 1990. A school-based catch-up program ran in 1998 for 6-16 year olds (those born between 1982 and 1992). *All these individuals, if born or attended school in the NT, should have had access to a vaccination program.
Figure 5.6: Graphs showing the prevalence (with 95% CI) of HBsAg (A), anti-HBs (B) and anti-HBc (C) by birth cohort for the whole study population and Indigenous and non-Indigenous groups.
Figure 5.7: Scatter plots with 95% CI and line of best fit showing the prevalence of HBsAg (A), anti-HBs (B) and anti-HBc (C) for individuals born since 1980 with markers for overall, Indigenous and non-Indigenous groups.
Figure 5.8: Interrupted time series analysis looking at HBsAg prevalence trends for (A) Indigenous, (B) non-Indigenous and (C) total population pre and post 1990.
5.6 Discussion

This cross-sectional analysis of a large NT-wide hepatitis B serology dataset documents a high contemporary prevalence of HBsAg positivity at 3.4% among people referred for HBV testing in the Northern Territory of Australia. There is a significantly higher prevalence in Indigenous Australians (6.08%) compared to their non-Indigenous counterparts (1.56%) and also in men (4.99%) compared to women (2.35%). These overall figures are higher than other recent Australian estimates of chronic HBV infection prevalence. The most recent Australian serosurvey documents an Australia-wide chronic HBV infection prevalence of 0.8% [18] and the National Australian Hepatitis B Mapping Project, which used existing general population and high-risk group prevalence estimates of chronic HBV infection alongside census data to estimate an Australia-wide chronic HBV infection prevalence of 1.02% and an NT prevalence of 1.68% [10, 11]. A meta-analysis looking at chronic HBV infection prevalence in Indigenous Australians reported chronic HBV infection prevalence in the post-2000 studies to be 3.96% for Indigenous adults and pregnant women [19].

It is encouraging that we also document a significant reduction in HBsAg prevalence over time in Indigenous individuals to the extent that in the most recent birth cohort (2000 onwards) the Indigenous prevalence (0.88%) is lower than the non-Indigenous prevalence (3.95%) among those referred for HBV testing. It is, however, interesting that when looking at a formal interrupted time series analysis the prevalence of HBsAg was falling among those referred for HBV testing prior to the introduction of universal vaccination and the rate of decline was not significantly different in the post-intervention period (Figure 5.8A). In non-Indigenous individuals the prevalence has actually increased post-1990 among those referred for HBV testing (Figure 5.8B). For the non-Indigenous group it is likely that this increase represents individuals who were not born in the NT and likely migrated from high prevalence countries. The lack of country of birth data for the non-Indigenous people limits the ability to explore the reasons for changes
within this group in any great detail. Evidence from the Hepatitis B mapping project would suggest that at least half the NT non-Indigenous chronic HBV infection group were born overseas, with the Philippines, China, Vietnam, Greece and Papua New Guinea being the top five countries of birth [11]. Australian Bureau of statistics data show that although the number of people reporting their country of birth to be overseas dropped from 20.4% of the NT population in 1996 to 18.9% of the population in 2011, the number of people reporting a country of birth in high prevalence hepatitis B countries increased. The absolute number of people in the NT from the Philippines, Thailand and Cambodia doubled during this period, while those born in China, Myanmar and India more than tripled [20]. We know from international data that migrants born overseas and now living in high-income, overall low chronic HBV infection prevalence countries such as Australia retain a chronic HBV infection prevalence that mirrors that of their birth country [21]. There is also evidence that approximately half the migrant individuals living in high-income countries such as the USA, UK, Canada and Australia are non-immune to HBV and would benefit from vaccination [21]. Obviously the universal childhood vaccination program will have no impact in this group and alternative screening and vaccination strategies need to be considered.

With respect to the Indigenous group, a data linkage study looked at the HBV prevalence in birthing mothers in the NT before and after the introduction of universal vaccination, with HBV prevalence in Indigenous women shown to fall from 3.5% in the pre-vaccine era (taken as before 1982 so as to include the catch up program) to 0.8% in those born after 1989 [2]. Equivalent figures from our data are approximately double these estimates, with a pre-1982 birth cohort chronic HBV infection prevalence in Indigenous men and women of 8.03% compared to 1.77% for those born post-1990. This is concurrent with Indigenous men having an OR of chronic HBV infection of 1.93 compared to Indigenous women. This disparity in HBsAg prevalence between men and women has also been documented in other high-chronic HBV infection regions of the world [22, 23] and cautions against using antenatal data as the only tool for assessing changes in
chronic HBV infection prevalence over time. The Liu study [2], as well as documenting the significant decrease in prevalence pre- and post- introduction of universal vaccination, also suggests that chronic HBV infection prevalence was falling albeit at a slower rate (reduction per year 0.08%) prior to 1982. The exact reasons for this are not completely clear. In the NT Indigenous population the exclusive HBV genotype identified to date is C4 [14] and genotype C HBV-infected individuals undergo HBeAg sero-conversion at least a decade later than other genotypes [24]. We do not know the mix of C and non-C genotypes in the NT non-Indigenous population. Women of childbearing age with exclusively genotype C HBV have very high viral loads at the time they give birth, hence facilitating vertical transmission. It is therefore possible that changes in birthing practices over time, moving from community births with traditional midwives to predominantly hospital births (from the mid-1970s) where caesarean section was more likely to occur, may have contributed to this decline [25]. Traditional practices involved female elders supporting birthing women in sacred ‘borning camps’ situated away from the main settlement in a process guided by rites and rituals [26]. It could also be postulated that cultural practices in general and specifically ‘men’s business’ (such as traditional circumcision, scarification and bloodletting) have changed over time to potentially include less blood exposures and perhaps are not as widespread as they were in the 1940s, 50s and 60s [27] [28, 29]. Other published literature [30] has shown a fall in HBsAg prevalence among urban dwelling Aboriginal Australians which was attributed to urbanization and improved living conditions, it is possible that this is also contributing in our setting.

We have previously described the molecular virology of HBV sub-genotype C4 in detail [15], showing that it is a recombinant virus (with the recombed section of HBV genotype J being over the area of the a determinant which is crucial for antigen antibody binding) with a different serotype to the vaccine strain (ayw3 as opposed to adw2); this is a virological reason as to why the current vaccine used in the NT may not be as effective in this population as it is where no serological mismatch exists.
We do however caution against over-interpretation of the most recent data due to the relatively small number of tests carried out overall in the most recent birth cohorts (1990 onwards). Our data clearly identify an urgent need for active and systematic studies looking at HBsAg, anti-HBs and anti-HBc prevalence in children and adults born after 1990 to enable a comprehensive analysis of the effectiveness of universal vaccination as an intervention.

We report the first detailed prevalence data for the NT and for Indigenous Australians regarding anti-HBs and anti-HBc, documenting very high anti-HBc prevalence in Indigenous Australians: an overall prevalence of 38% increasing to over 50% in those born prior to 1950. These levels of anti-HBc positivity are very similar to those reported from China prior to the introduction of their HBV vaccination program [31]. We also report a steady decrease in anti-HBc positivity over time in both Indigenous and non-Indigenous Australians, which also predates the introduction of universal vaccination. Anti-HBs positivity slowly increased until around the time of the introduction of universal vaccination, where there appears to be a real drop for a period (Figure 5.7) followed by a more recent return to levels of 88.9%. This, in the context of such high rates of anti-HBc positivity, could be explained by a switch over in that time period from very high slow-weaning titres secondary to natural immunity, to lower titres due to vaccine-induced immunity. A substantial reduction in exposure and associated reduction in anti-HBs boosting as a result may also be contributing. Again the most recent birth cohorts are limited by the smaller number of individuals in these groups being tested, and attendant wide confidence intervals around point estimates (Figure 5.7A).

Chronic HBV infection has been notifiable in the NT since 2005; a summary report [3] of all notified cases between 2005 and 2011 showed an Indigenous prevalence of 6.4 times the non-Indigenous prevalence, a male to female ratio of 1.44:1 and a decreasing prevalence prior to the introduction of universal vaccination, which are all consistent with our findings. The geographical spread and pattern of chronic HBV infection cases was also similar to our data,
which is reassuring for the accuracy of the notification system and supports the accuracy of our data.

We will have slightly over-estimated chronic HBV infection prevalence as we have assumed all HBsAg positive individuals have chronic HBV infection when we know that some will, in fact, represent acute HBV. We feel that this is a reasonable assumption based on the fact that in the period 2007-2011 there were only 27 acute HBV notifications in the NT (NT Centre for Disease Control data). When we looked at repeat testing over time for these 27 individuals, 9 have now been confirmed to be chronic HBV infection, for 7 no repeat testing could be found and 11 had confirmed acute HBV. When conducting our sensitivity analysis, using the most conservative criteria of only including those individuals who had definitely had two confirmed HBsAg positive tests separated in time by six months or more, we would have removed 346 HBsAg positive people from the included dataset which would have clearly produced an underestimate of prevalence. These 346 people would have been removed as they have only ever had one HBsAg test done, negating our ability to determine the chronicity and also clearly highlighting significant deficits in the appropriate follow up of HBsAg individuals in this setting. Hence the degree of overestimation of chronic HBV infection in this study is likely to be negligible, in the order of a relative increase of 5%.

Our dataset is retrospective and this means there will be a level of bias introduced due to the non-systematic way in which people are tested for hepatitis B those in higher risk groups are more likely to be tested, hence potentially overestimating the sero-prevalence of chronic HBV infection. However, much of the HBV testing for adults in the NT is routine rather than risk-based, including antenatal testing, the routine adult health check and routine sexual health checks. Our dataset clearly lacks numbers in the very old and very young age groups, particularly for those born since the introduction of universal birth-dose vaccination in 1990. It is likely that
this testing/referral bias will be most evident in these younger groups where there are small numbers and fewer reasons for routine rather than risk-based HBV testing.

Our findings have implications not only for the planning and delivery of a sustainable strategy to combat chronic HBV infection in the NT, but more widely for the pitfalls of prevalence data from specific population groups such as antenatal women when there is such a marked difference in prevalence between the sexes and in older versus younger age groups. While our data do support the assertion that the HBV vaccination is leading to a decreased HBV prevalence, they also suggest that the vaccine is only one of several factors responsible for the falling prevalence of chronic HBV infection in the NT. The need for detailed sero-surveys, including the very young and the very old, is highlighted to confirm whether the universal HBV vaccination program is indeed effective in the NT.
5.7 References


Chapter 6 - The prevalence of co-infection with either hepatitis C, hepatitis D or HIV in an Indigenous cohort with chronic hepatitis B in the Northern Territory
6.1 Preamble

We have reported a high prevalence of hepatitis B surface antigen positivity (6.08%) in those Indigenous people who have been tested for hepatitis B in the NT between 2007 and 2011 (Chapter 5). It is well recognised that co-infection with one or more additional blood-borne viruses can cause faster progression of liver disease. Hepatitis B, Hepatitis C, Hepatitis D and HIV are all notifiable diseases in the NT. However there is no systematic recording of those co-infected with more than one of these viruses. The CHARM study described in detail in section C is now a cohort study including 128 individuals infected with chronic hepatitis B and includes information about each individual’s hepatitis D, hepatitis C and HIV serostatus at baseline. I have analysed this data as a first step towards providing estimates of the prevalence of co-infection in the setting of Indigenous Australian communities in the NT.
6.2 Abstract

Introduction
Co-infection of hepatitis B infected patients with either hepatitis C, hepatitis D or HIV infection is not uncommon in regions of the world where chronic HBV infection is endemic. There is evidence that progression to cirrhosis and rates of hepatocellular carcinoma are increased in the presence of co-infection. In the Northern Territory Indigenous Australian population, HBsAg sero-prevalence is high; however there is little available information about the prevalence of co-infection.

Methods
We established the hepatitis C, D and HIV serostatus of Indigenous Australians with chronic HBV infection who were already enrolled in the CHARM study (described in section C). This was done either by review of existing available results or by testing of the blood sample taken at entry into the CHARM study. The aim of this sub-study is to report the prevalence of these three blood-borne viruses in this group of Indigenous Australians with chronic HBV infection.

Results
Of 128 individuals included in the analysis, 103, 73 and 106 had test results available for hepatitis C, hepatitis D and HIV antibody testing respectively. Individuals included in the study had a mean age of 38 years, 51% were male and a wide range of different regions of the NT were represented. All tests (100%) carried out for these three blood-borne viruses were negative.

Conclusions
In the setting of NT Indigenous communities, although chronic HBV infection is endemic, co-infection with any of hepatitis C, hepatitis D or HIV is rare or non-existent.
6.3 Introduction

Worldwide, 240 million, 170 million and 34 million people are infected with hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) respectively [1]. All three of these viruses can be spread by blood-borne transmission routes and consequently co-infections with two or more of these viruses are common in chronic HBV infection endemic areas. Of HIV positive individuals, approximately 10% [2] are estimated to be chronically infected with HBV, and liver-related mortality is over 17 times higher in these co-infected individuals than HBV mono-infection[3]. The prevalence of HBV/HCV co-infection varies widely between regions and there is a lack of large-scale population studies assessing this issue [4]. In Egypt, where HCV prevalence is high, the prevalence of dual infection with HBV/HCV is reported to be 0.7% [5] whereas a large USA-based study showed HBV infection in 5.8% of those with HCV [6]. Rates of progression to cirrhosis [7] and hepatocellular carcinoma [8] are increased in those with HBV/HCV co-infection. Hepatitis D, which requires an individual to be infected with HBV, infects 18 million people in the world with significant regional variation in prevalence [9].

Current Gastroenterological Society of Australia Chronic Hepatitis B Guidelines [10] recommend baseline testing for HCV and HIV in all individuals with chronic HBV infection and testing for HDV in all those from higher risk countries. The Pacific islands, Mediterranean, parts of South America and Africa are listed in the definition of ‘higher risk countries’. In the Northern Territory notification data for 2012 show 36 new cases of HIV, 237 new cases of hepatitis C and 0 new cases of hepatitis D infection [11] were notified to the NT Centre for Disease Control. There are no published data about prevalence of co-infection in the NT population or in Indigenous Australians with chronic HBV infection.

6.4 Methods

A detailed description of the CHARM cohort study follows in Chapters 7, 8 and 9. In brief, individuals enrolled into the CHARM study were all Indigenous Australians born in the Northern
Territory and had chronic HBV infection. As part of the clinical and demographic information collected for their inclusion in the CHARM study they had their HCV, HDV and HIV status established. The results with respect to HDV co-infection for the first 55 patients have been published as a letter to the editor [12] (Appendix 4). This chapter presents the results of all three blood-borne virus tests as a first step to establishing if co-infection of hepatitis B is a problem in this setting.

6.5 Results

The demographic and HBV infection details of the 128 individuals who have now been enrolled in the CHARM study are presented in Table 6.1.

Table 6.1: Demographics and baseline HBV markers of all patients

<table>
<thead>
<tr>
<th>N=128</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>38.4 years (29.5-49.0)</td>
</tr>
<tr>
<td>Male</td>
<td>65 (51%)</td>
</tr>
<tr>
<td>Indigenous status</td>
<td>128 (100%) Indigenous Australians</td>
</tr>
<tr>
<td>BMI median (IQR)</td>
<td>23 (20-26)</td>
</tr>
<tr>
<td>IDU history</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27 (21%)</td>
</tr>
<tr>
<td>eAg status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>45 (35%)</td>
</tr>
<tr>
<td>Negative</td>
<td>83 (65%)</td>
</tr>
<tr>
<td>Equivocal</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>eAb status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>76 (60%)</td>
</tr>
<tr>
<td>Negative</td>
<td>50 (39%)</td>
</tr>
<tr>
<td>Equivocal</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>HBV DNA viral load (IU/ml) median (IQR)</td>
<td>1006 (65-1.6x10^7)</td>
</tr>
<tr>
<td>Evidence of cirrhosis</td>
<td>15 (12%)</td>
</tr>
</tbody>
</table>

Patients were recruited from across the Northern Territory. The distribution of patients’ main location of residence is presented in Figure 6.1.
Hepatitis C antibody tests were available for 103 of 128 patients and all (100%) were negative. No hepatitis C RNA testing was performed. This leads to an estimate of HCV/HBV co-infection of 0% (one-sided 97.5% confidence interval 0 to 3.5%).

Hepatitis D antibody tests were available for 73 of 128 patients and all (100%) were negative. A random selection of 13 of these samples was further tested for HDV RNA and all were negative. This leads to an estimate of HDV/HBV co-infection of 0% (one-sided 97.5% confidence interval 0 to 4.9%).

106 of 128 patients had an HIV antibody result available and all (100%) were negative (Figure 6.2). This leads to an estimate of HIV/HBV co-infection of 0% (one-sided 97.5% confidence interval 0 to 3.4%).
6.6 Discussion

Our data shows that co-infection with either HCV, HDV or HIV is non-existent in our group of 128 Indigenous Australians with chronic hepatitis B infection.

This, in conjunction with the notification data from the NT (showing only 1 reported case of HDV over the last 10 years in a non-Indigenous individual), suggests HDV is rare or non-existent in Indigenous Australians in the NT chronically infected with HBV. We have previously published a letter to the editor reporting the first 55 patients HDV results from this cohort of 128 patients. On the basis of this we recommended that it was not necessary to routinely screen Indigenous Australians in the NT with chronic HBV infection for HDV [12]. This recommendation has since been incorporated into the NT Hepatitis B Vaccination and Public Health Guidelines [13]. These more recent data add further weight to this recommendation. It is also relevant to note that the number of people being tested for HDV reduced in the second half of this study and this may have been influenced by this updated recommendation.
With respect to HCV and HIV it is encouraging that there is no co-infection with these viruses in the study population. Both HCV and HIV are known to increase the rate of progression to cirrhosis and risk of HCC in chronic HBV infection patients. We would, however, still advocate for HCV and HIV screening in all chronic HBV infection patients in the NT. Although entecavir is not used for treatment of HIV infection it has been shown in the setting of HBV HIV co-infection to have anti-HIV activity when given as monotherapy. In a multi-centre study looking at the viral characteristics of HIV and HBV in 17 patients given entecavir monotherapy, 13 of 17 patients demonstrated a reduction in their HIV viral load and the M184V resistance mutation emerged in 6 of 17 patients [14]. Tenofovir is a critical part of the most commonly used HIV antiretroviral treatment regimens, which have traditionally included at least three drugs to avoid the development of resistance [15]. It is therefore still critical to be sure that an individual with chronic HBV infection does not have HIV before commencing therapy as the harmful consequences of either tenofovir or entecavir monotherapy in the setting of an undiagnosed co-infection would be significant.

The rate per 100,000 individuals of new diagnoses of HCV infections for non-Indigenous Australians in 2011 was 40 compared to 142 for Indigenous Australians. In the NT these rates were 84 and 95 for Indigenous and non-Indigenous individuals respectively [16]. Once identified, hepatitis C can increasingly be successfully treated, however if not recognised there is good evidence that liver-related morbidity and mortality is increased [17].

This information, taken together, supports the continued screening of all Indigenous chronic HBV infection patients in the NT for HCV and HIV despite the lack of any documented co-infection in this cohort.

The likely explanation for our findings is that the at-risk age groups and routes of transmission differ in the NT for these three viruses. HBV is thought to be transmitted by mother to child transmission, or possibly early horizontal childhood transmission in the NT. On the other hand,
the predominant route of transmission of HCV in Australia as whole is intravenous drug use [11]. Anecdotally, intravenous drug use is rare among remote dwelling Indigenous Australians and in our cohort of 128, when directly asked, no one reported a history of IDU (Table 6.1). The predominant route of HIV transmission in Australia is sexual transmission in men who have sex with men. Although the NT has some of the highest incidence rates of sexually transmissible infections of any Australian state, chronic hepatitis B infection is rarely acquired by the sexual route (because over 95% of adults clear HBV virus spontaneously following infection). Hence our data support our assumptions about the predominant routes of transmission of these three viruses in the NT.

Limitations of this study include the lack of complete screening for each of the three blood-borne viruses even in this prospective study setting and the relatively small number of individuals included in the study.

Future work should include advocating for more systematic and complete screening for HCV and HIV in chronic HBV infection patients in the NT. It is however interesting that in this chronic HBV infection cohort taken from a high prevalence setting there is no evidence of any co-infection. This warrants consideration of potential HBV virological and host genetic factors which may be contributing to this situation.
6.7 References


Section C – The molecular epidemiology of hepatitis B in the Northern Territory
Chapter 7 - The CHARM study (Characterising Hepatitis B in northern Australia through Molecular epidemiology)
7.1 Preamble

The molecular epidemiology of hepatitis B in the Northern Territory was unknown at the start of this study. It was hypothesised that it would be a mix of genotypes B and C due to the geographical proximity of the NT to South East Asia. The plan was to include all individuals who had hepatitis B and were born in the NT, lived the first five years of their life in the NT and likely acquired their hepatitis B either via mother to child or early horizontal transmission.
7.2 The molecular epidemiology of hepatitis B in the Indigenous people of northern Australia
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7.3 Implications and questions arising from this paper

It is unexpected and unusual to find only one genotype of HBV spread across such a large geographical area.

The serotype mismatch between C4 HBV (ayw3) and the currently used vaccine adw2 is a virological reason as to why the HBV vaccine based on genotype A may not be as efficacious in our setting where the exclusive sub-genotype in the Indigenous population is C4. This requires further investigation both from a virological and an epidemiological point of view.

Multiple molecular markers previously reported to be consistent with an increased rate of cirrhosis and HCC have been shown to be frequently present in our C4 samples. We need to go on now to determine in more detail the extent and frequency of these polymorphisms.
Chapter 8 - The molecular virology of hepatitis B virus sub-genotype C4 in northern Australian Indigenous populations
8.1 Preamble

The surprising and intriguing results of the CHARM study described in Chapter 7 led us to extend our plans for the virological studies being carried out in conjunction with VIDRL. We agreed to move from simply establishing the genotype of each individual’s virus to performing full genome sequencing whenever there was sufficient virus to do so. This also enabled more detailed phylogenetic analysis and geographical comparisons of viruses as well as recombination analysis and mutation analysis to be performed.
8.2 Molecular virology of hepatitis B virus sub-genotype C4 in northern Australian Indigenous populations
Item removed due to copyright restrictions.
8.3 Implications and questions arising from this paper

The phylogenetic analysis showing geographical clustering of C4 viruses according to where an individual was born, where their mother was born (generally the same place) and where they lived for the first five years of their lives (again generally the same place), is very interesting from the point of view of the evolutionary history of the HBV. This warrants further investigation and more detailed phylogenetic analysis potentially using tools such as BEAST analysis – currently in progress.

The conformation of the multiple polymorphisms consistent with an aggressive molecular genotype warrants further investigation with a clinical cohort study to determine if this does translate into an aggressive phenotype of chronic HBV infection.
Chapter 9 - Towards genotype specific care for chronic hepatitis B: learning from the clinical follow up of a cohort of Indigenous Australians with the unique hepatitis B sub-genotype C4
9.1 Preamble

The initial criteria for the CHARM study did not restrict recruitment to Indigenous Australians. However as the study progressed it became apparent that we had not come across any non-Indigenous Australians who met the other inclusion criteria namely: over 18 years, have chronic HBV infection, born and lived for the first five years of their life in the NT and likely to have acquired their HBV in early life. It also became apparent that we were not finding the mix of genotype Bs and Cs that we had expected to find but that everyone had the same genotype as described in Chapters 7 and 8, the natural history of which was unclear since it had never been found in any other population. The decision was therefore made to make an ethics amendment to enrol only Indigenous people and, more importantly, to convert the original cross-sectional study to a longitudinal cohort study to try to learn as much as possible about this unique sub-genotype of HBV C4. This chapter details that process and reports the results of the first four years of follow up of this cohort.
9.2 Abstract

Background

There is increasing evidence to suggest that, amongst those with chronic HBV infection, the natural history and rate of progression to cirrhosis and hepatocellular carcinoma is influenced by hepatitis B virus genotype. This chapter aims to describe the establishment of a cohort of Indigenous Australians with sub-genotype C4 chronic hepatitis B and establish what we can learn from the first four years of clinical follow up.

Methods

Indigenous Australians from the Northern Territory of Australia who were already recruited into the CHARM study (a cross-sectional study which established sub-genotype C4 to be the exclusive genotype present in this group) were followed up over time from initial inclusion into the study. Clinical and laboratory information collected as part of their routine clinical care was gathered retrospectively. Phases of disease were assigned as per the Australian GESA guidelines, and cirrhosis was defined as either a fibroscan > 12kPa or at least one marker of cirrhosis present on both ultrasound and basic blood tests. We also compared the monitoring these patients received against that recommended by the Royal Darwin Hospital Liver Clinic.

Results

Of 128 patients followed over a median of 27 months, 27 (21%) individuals transitioned from one disease phase to another, 7 (5%) lost e antigen and 3 seroconverted to surface antigen (2%). In this relatively young cohort (median age 38 years), 34 (27%) had cirrhosis by the end of the follow up period with the majority of these being in the immune control phase of disease.

Clinical follow up did not meet recommended guidelines for any of the parameters measured, however treatment rates increased over the study period, from 7% at the beginning of the follow up period to 18% of the cohort receiving antiviral treatment at the end of follow up.
Conclusions

In this cohort of hepatitis B sub-genotype C4 patients we report an aggressive and dynamic clinical phenotype. High rates of cirrhosis at a young age are documented and appear to occur in the early phases of disease, suggesting that a lower threshold for treatment should be considered. In the context of remote Indigenous Australia, clinical follow up is less than optimal; however treatment rates are improving over time.
9.3 Introduction

The worldwide literature increasingly supports the importance of hepatitis B virus (HBV) genotype with respect to the natural history of chronic hepatitis B (chronic HBV infection) [1, 2], as well as the risk of cirrhosis [3, 4] and hepatocellular carcinoma (HCC) [5, 6]. Genotype C HBV, which predominates in South East Asia [7], has been shown to have a higher risk of progression to cirrhosis [4], longer duration of eAg positivity [8, 9] and higher rates of HCC [10] compared with genotype B. Some genotypes such as B5 (previously classified as B6) found in Alaskan natives have shown a much more benign course [11, 12]. There is no current evidence to support any significant difference in response to nucleotide/nucleoside antiviral therapy on the basis of HBV genotype [13], however there is evidence to support genotype C HBV being less responsive to interferon therapy than genotypes A and B [14].

The Indigenous population of the Northern Territory of Australia has a high prevalence of chronic HBV infection of approximately 6% (Chapter 9) which is exclusively sub-genotype C4 [15]. HBV sub-genotype C4 has only ever been identified in Indigenous Australians and has molecular markers consistent with rapid progression to cirrhosis and increased risk of HCC [16]. The natural history of HBV genotype C4 is currently unknown.

The second Australian National Hepatitis B strategy [17], launched in 2014, sets out specific targets, with the aim of reducing further transmission of HBV and improving the management of those who already have chronic HBV infection in order to decrease associated morbidity and mortality. These targets include increasing HBV vaccine coverage of priority populations (Indigenous Australians identified as a priority population), increasing to 80% the proportion of people living with chronic HBV infection who are diagnosed, and increasing to 15% the proportion of people living with chronic HBV infection who are receiving antiviral treatment. One of the main outcomes of chronic HBV infection that treatment aims to prevent is HCC. Recent evidence shows an age-adjusted annual incidence of HCC of 22.7/100,000 for Indigenous
Australians in the NT [18] which is similar to the high population-wide rate in China. The recommendations made from this recent paper [18], which have been incorporated into the main NT primary care reference manual (CARPA) [19], are for HCC screening with ultrasound and alpha fetoprotein for all Indigenous chronic HBV infection patients who are over the age of 50 in addition to the standard recommendation for all those with cirrhosis to receive screening.

We have expanded our original study Characterising Hepatitis B in Northern Australia Through Molecular Epidemiology (CHARM) [15], set up to determine the genotypes of HBV in the NT, to establish a long-term prospective cohort of Indigenous Australians in the NT with C4 HBV. The aim of this paper is to describe the process of establishing the cohort and review the first four years of available data collected in a real world setting to inform delivery of the NT response to this sub-genotype of chronic HBV infection, which is unique to Indigenous Australians.

**9.4 Methods**

This cohort of Indigenous chronic HBV infection patients originated as a cross-sectional study to determine the genotypes of HBV present in the Northern Territory of Australia, which has been described in detail elsewhere [15]. Patients were recruited between June 2010 and August 2014 through the Royal Darwin Hospital Liver Clinic Service, which is based in Darwin but has regular outreach clinics to multiple remote communities across the NT, spread over an area of over 1 million km$^2$. Following informed consent, demographic, clinical and laboratory information was collected from chronic HBV infection patients during the course of their routine clinical care. Blood for HBV viral load, genotype and full genome sequencing (viral load dependent) were obtained and processed at the Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne.
When it became apparent that the exclusive and unique genotype present in this population was sub-genotype C4, further ethical approval was sought to convert this study into a prospective cohort study. At the time of enrolment into the study, baseline information about location of birth and early life, mother’s birth location, risk factors for viral hepatitis, treatment and current liver disease was collected. The results of routine blood tests for full blood count, electrolytes, renal function, liver function, coagulation profile, hepatitis C virus, hepatitis D virus and human immunodeficiency virus were recorded. Cirrhosis was considered to be present if either a fibroscan (when an NT-based machine became available in late 2012) had been carried out with a result of greater than 12Kpa or there was at least one abnormality present on both ultrasound and blood tests. For ultrasound this could include splenomegaly, enlarged portal vein diameter, reverse flow in the portal vein, or enlarged caudate lobe of the liver. Blood abnormalities considered significant included international normalized ratio > 1.3, platelet count < 150 x 10^9/L, albumin < 35g/dL, or serum bilirubin > 17Umol/L. At the time of recruitment into the study a management plan based on the stage of chronic HBV infection and the severity of concurrent liver disease was documented. Patients were then returned to standard clinical follow up via their treating medical or primary care team. In August 2014, when the decision was made to follow up these individuals in the long term, further clinical and laboratory data were collected retrospectively from the patient’s medical records. This information included all repeat episodes of the clinical and laboratory parameters collected at the initial recruitment visit and in addition body mass index, alpha fetoprotein, hepascore, fibroscan, gastroscopy and treatment details were collected. Moving forward, this information will be collected prospectively and individual patients will be contacted to attend at the appropriate time for follow up. Clinical review and repeat blood tests were looked for at six monthly intervals from the date of recruitment. Review and test results were included in the analysis if they occurred within a two-month window either side of the allocated six monthly review date. Figure 9.1 details the minimum follow up for Indigenous chronic HBV infection patients in the Northern Territory, which should be adapted to
be more frequent if needed, based on results. This is the policy of the Royal Darwin Hospital Liver Clinic, and is based on the Gastroenterological Society of Australia guidelines [20] and the CARPA guidelines [19]. The age cut off for screening Indigenous Australians is 50 years based on local data [18], for non-Indigenous individuals in our liver clinic we use the most up to date AASLD guidelines which would include Asian males > 40 years, Asian females > 50 years and African males > 20 years in addition to those included in Figure 9.1.

Each patient was allocated a disease phase (immune tolerance, clearance, control, escape or resolved infection) at the date of enrolment and at the last point of follow up. With respect to alanine transaminase (ALT) levels normal was defined as <30 U/L for men and <19U/L for women [21]. Definitions used were: immune tolerance patients must be HBsAg positive, HBeAg positive, normal ALT; immune clearance patients must be HBsAg positive, HBeAg positive, abnormal ALT; immune control patients must be HBsAg positive, HBeAg negative, HBV viral load<2000 IU/ml, normal ALT(or alternative explanation for raised ALT) ; immune escape patients must be HBsAg positive, HBeAg negative, HBV viral load>2000 IU/ml; resolved infection patients must be HBsAg negative with HBV viral load not detected, having previously been HBsAg positive. If both eAg and eAb were negative or either one was equivocal or there was any concern, the individual case was reviewed manually and assigned a phase using all available longitudinal information.
All need baseline ultrasound and fibroscan

- Immune tolerance and control
  - 12 monthly liver function tests and HBV viral load
- Immune clearance and escape
  - 6 monthly liver function tests and HBV viral load
- Over 50 years of age and all with cirrhosis or FH of HCC
  - 6 monthly ultrasound and alpha fetoprotein

Ethical approval was obtained from the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research (HREC-09/105).

Data were entered into a purpose-built web-based database and analysed using STATA version 12 (Statacorp, College Station, TX, USA). Results are presented as mean +/- standard deviation for normally distributed parameters and median +/- inter quartile range for non-normally distributed parameters.

All patients recruited into the CHARM study who had confirmed chronic HBV infection were included in this longitudinal cohort, including those who did not have a sufficient viral load for genotyping. Since 100% of genotyped patients had C4 genotype, we made the assumption that all patients in the CHARM longitudinal cohort were infected with genotype C4.
9.5 Results

Between June 2010 and August 2014, 128 patients were recruited from 32 different remote communities in six different regions of the NT. Of these, 84 had sufficient detectable HBV DNA to enable genotyping and 100% were sub-genotype C4. Full genome sequence analysis was obtained from 55 HBV viruses representing 43% of all samples. Chronic HBV infection sub-genotype C4 patients were followed up for a median of 27 months (IQR 12-42, range 6-48), equal to a total of 286 person years of follow up. A patient was considered to enter the cohort and follow up to begin from the date of enrolment into the CHARM study. Hence, although the maximum follow up is four years, there is a range of follow up durations from 67 days to 1,538 days.

Baseline demographics and clinical parameters at study entry and the latest time point recorded are detailed in Table 9.1.

Figure 9.2 shows disease phase at study entry by age group. Over the reviewed time period, seven individuals changed their HBeAg status from positive to negative (6) and equivocal (1). Six of these individuals developed anti-HBe. Median age at HBeAg seroconversion was 33 years and individual ages at time of clearance were 27, 28, 32, 33, 35, 37 and 53 years.

Three individuals aged 28, 40 and 65 years cleared HBsAg during the follow up period. It is of note that the 28 year old may have had acute HBV as this individual was anti-HBc IgM positive, however anti-HBe was also positive, raising the possibility of chronic HBV infection with an acute flare that then resolved.

Twenty-seven individual (21.1% 95% CI 14.4-29.2) patients changed their phase of disease over the period of follow up; this includes 14 patients who have received or are receiving antiviral treatment. Details of all 27 patients are in Table 9.2.
Table 9.1: Baseline demographics and clinical details at study entry and the latest time point recorded for 128 sub-genotype C4 chronic HBV infection patients

<table>
<thead>
<tr>
<th>N=128</th>
<th>Study Entry</th>
<th>Latest time-point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (IQR)</strong></td>
<td>38.4 years (29.5-49.0)</td>
<td>40.2 years (31.7-51.5)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>65 (51%)</td>
<td></td>
</tr>
<tr>
<td><strong>Indigenous status</strong></td>
<td>128 (100%) Indigenous Australians</td>
<td></td>
</tr>
<tr>
<td><strong>BMI median (IQR)</strong></td>
<td>23 (20-26)</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccine status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>95 (74%)</td>
<td></td>
</tr>
<tr>
<td><strong>1 dose received</strong></td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td><strong>2 doses received</strong></td>
<td>8 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fully vaccinated</strong></td>
<td>20 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>None</strong></td>
<td>88 (69%)</td>
<td>29 (23%)</td>
</tr>
<tr>
<td><strong>0-2 STD drinks per day</strong></td>
<td>16 (13%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td><strong>3-4 STD drinks per day</strong></td>
<td>2 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>&gt;4 STD drinks per day</strong></td>
<td>15 (12%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Binges &lt;4 STD drinks</strong></td>
<td>Not collected at baseline</td>
<td>0</td>
</tr>
<tr>
<td><strong>Binges&gt; 4STD drinks</strong></td>
<td>Not collected at baseline</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>6 (3%)</td>
<td>87 (68%)</td>
</tr>
<tr>
<td><strong>eAg status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td>45 (35%)</td>
<td>39 (30%)</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>83 (65%)</td>
<td>88 (69%)</td>
</tr>
<tr>
<td><strong>equivocal</strong></td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>eAb status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td>76 (60%)</td>
<td>79 (62%)</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>50 (39%)</td>
<td>44 (34%)</td>
</tr>
<tr>
<td><strong>equivocal</strong></td>
<td>1 (1%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td><strong>HBV DNA viral load (IU/ml) median (IQR)</strong></td>
<td>1006 (65-1.6x10^7)</td>
<td>270 (26-1084658)</td>
</tr>
<tr>
<td><strong>ALT U/L median(IQR)</strong></td>
<td>28 (19-42)</td>
<td>28 (19-41)</td>
</tr>
<tr>
<td><strong>ALT U/L % &gt; laboratory ULN (lower cut off)</strong></td>
<td>20 (56)</td>
<td>16 (60)</td>
</tr>
<tr>
<td><strong>Platelets (x 10^9/L) median (IQR)</strong></td>
<td>245 (203-290)</td>
<td>237 (188-296)</td>
</tr>
<tr>
<td><strong>Albumin (g/L) median (IQR)</strong></td>
<td>42 (38-45)</td>
<td>42 (39-44)</td>
</tr>
<tr>
<td><strong>Creatinine (µmol/L) median (IQR)</strong></td>
<td>71 (62-87)</td>
<td>72 (62-90)</td>
</tr>
<tr>
<td><strong>Evidence of cirrhosis</strong></td>
<td>15 (12%)</td>
<td>24 (19%)</td>
</tr>
<tr>
<td><strong>Evidence of cirrhosis excluding fibroscan results (available for 32 individuals)</strong></td>
<td>14 (11%)</td>
<td>21 (16%)</td>
</tr>
<tr>
<td><strong>Phase of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immune tolerance</strong></td>
<td>20 (16%)</td>
<td>15 (12%)</td>
</tr>
<tr>
<td><strong>Immune clearance</strong></td>
<td>26 (20%)</td>
<td>27 (21%)</td>
</tr>
<tr>
<td><strong>Immune control</strong></td>
<td>70 (55%)</td>
<td>78 (61%)</td>
</tr>
<tr>
<td><strong>Immune escape</strong></td>
<td>11 (8%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Resolved infection</strong></td>
<td>1 (1%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Currently receiving antiviral treatment</strong></td>
<td>Entecavir 8 (6%)</td>
<td>Entecavir 16 (13%)</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 1 (1%)</td>
<td>Tenofovir 7 (5%)</td>
</tr>
<tr>
<td><strong>Ever received antiviral therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>Death during follow up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Laboratory upper limit of normal is 54U/L, lower cut off is 19U/L for women and 30U/L for men. # Cause of death known for 3 individuals: breast cancer, parotid cancer and end stage renal disease.
The median ALT level both at study enrolment and final follow up was 28U/L which is well below the standard laboratory cut-off of 54U/L. Individual patient ALT levels are shown in Figure 9.3 by disease phase both at study entry and final follow-up date. This graph shows the large proportion of individuals who would be classed as being in a different phase if the higher level of ALT was used (Figure 9.4). This moves them from a phase where treatment is considered (immune clearance) into a phase where treatment is not considered (immune tolerance).
Figure 9.3 Scatter graph showing ALT at study entry and final follow up point for each individual with respect to phase of disease at study entry. Solid lines at 19, 30 and 54 represent the normal ALT cut off for women with CHB, men with CHB and the standard laboratory respectively. Each blue dot represents the result of one female individual, each red dot represents the result of one male individual. (2 very high ALT levels 1462 and 1000 not shown, both in the immune escape phase). SN=study number
In nine study patients, HBV treatment had already been commenced or was initiated at the enrolment visit. At the end of this period of follow up, 23 individuals were taking antiviral medication; no individual received interferon therapy (Table 9.1 and Figure 9.5). At the final time point of follow up 34 (27%), individuals overall showed evidence of cirrhosis and of these 14 were on treatment (Figure 9.5). The median age of those with cirrhosis was 38 years (IQR 29-49). The most common phase of disease to be in for cirrhotic patients both at entry to the study and at the latest follow up point was the immune control phase (Figure 9.6). This is important, as this is not a phase when treatment is generally considered a high priority.

There were no diagnoses of HCC during the short follow-up period and none of the deaths in the study period were due to a known HCC (cause of death was only available for three of seven deaths).
Figure 9.5: Bar chart showing the percentage of individuals with chronic HBV infection who have ever received treatment (128), who were receiving treatment at study entry (n=128) and final time point (n=128) and the percentage of cirrhotic chronic HBV infection patients receiving treatment at study entry (n=15) and final time point (n=24).

Figure 9.6: Bar chart showing the percentage of cirrhotic and non-cirrhotic individuals in each disease phase at entry to the study and at the most recent follow-up point.
Table 9.2: Detailed information regarding treatment naive patients who transitioned into a different phase during follow up

<table>
<thead>
<tr>
<th>SN</th>
<th>Entry phase</th>
<th>Final phase</th>
<th>Follow up (months)</th>
<th>HBV DNA (IU/ml)</th>
<th>ALT</th>
<th>Age (years)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>escape</td>
<td>Resolved infection</td>
<td>54</td>
<td>594 &lt;20</td>
<td>1462</td>
<td>36</td>
<td>f</td>
</tr>
<tr>
<td>3</td>
<td>clearance</td>
<td>control</td>
<td>48</td>
<td>1095580000 17</td>
<td>66</td>
<td>25</td>
<td>m</td>
</tr>
<tr>
<td>17</td>
<td>tolerance</td>
<td>clearance</td>
<td>48</td>
<td>2265260000 363495328</td>
<td>17</td>
<td>24</td>
<td>f</td>
</tr>
<tr>
<td>20</td>
<td>escape</td>
<td>control</td>
<td>42</td>
<td>9680 460</td>
<td>98</td>
<td>31</td>
<td>f</td>
</tr>
<tr>
<td>22</td>
<td>tolerance</td>
<td>clearance</td>
<td>42</td>
<td>13000000 14000000</td>
<td>12</td>
<td>27</td>
<td>f</td>
</tr>
<tr>
<td>39</td>
<td>tolerance</td>
<td>clearance</td>
<td>36</td>
<td>208296897 60307434</td>
<td>29</td>
<td>28</td>
<td>m</td>
</tr>
<tr>
<td>43</td>
<td>control</td>
<td>escape</td>
<td>42</td>
<td>415 4000</td>
<td>16</td>
<td>32</td>
<td>f</td>
</tr>
<tr>
<td>55</td>
<td>clearance</td>
<td>control</td>
<td>30</td>
<td>7729938 190</td>
<td>12</td>
<td>25</td>
<td>m</td>
</tr>
<tr>
<td>59</td>
<td>tolerance</td>
<td>clearance</td>
<td>36</td>
<td>85804738 42929731</td>
<td>27</td>
<td>20</td>
<td>m</td>
</tr>
<tr>
<td>69</td>
<td>control</td>
<td>Resolved infection</td>
<td>24</td>
<td>&lt;20 4000</td>
<td>31</td>
<td>64</td>
<td>f</td>
</tr>
<tr>
<td>75</td>
<td>clearance</td>
<td>control</td>
<td>18</td>
<td>10364 &lt;20</td>
<td>16</td>
<td>25</td>
<td>f</td>
</tr>
<tr>
<td>79</td>
<td>control</td>
<td>Resolved infection</td>
<td>24</td>
<td>&lt;15 38</td>
<td>64</td>
<td>f</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>tolerance</td>
<td>clearance</td>
<td>12</td>
<td>49000000</td>
<td>12</td>
<td>30</td>
<td>f</td>
</tr>
</tbody>
</table>
Table 9.3: Detailed information regarding patients who transitioned into a different phase during follow up and have received or are receiving antiviral treatment

<table>
<thead>
<tr>
<th>SN</th>
<th>Entry phase</th>
<th>Final phase</th>
<th>Follow up</th>
<th>HBV DNA (IU/ml)</th>
<th>ALT</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>clearance</td>
<td>treatment control</td>
<td>48 months</td>
<td>4222 &lt;20</td>
<td>68 &lt;20</td>
<td>53 f</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>clearance</td>
<td>treatment control</td>
<td>48 months</td>
<td>23971000 646</td>
<td>54 35</td>
<td>23 f</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>escape</td>
<td>treatment control</td>
<td>48 months</td>
<td>10044 &lt;20</td>
<td>21 37</td>
<td>37 m</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>clearance</td>
<td>treatment control</td>
<td>48 months</td>
<td>111495426 19000</td>
<td>46 &lt;20</td>
<td>19 f</td>
<td>Tenofovir</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>tolerance</td>
<td>clearance</td>
<td>42 months</td>
<td>140226779 51000000</td>
<td>16 28</td>
<td>20 f</td>
<td>Tenofovir antenatal</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>clearance</td>
<td>treatment control</td>
<td>36 months</td>
<td>85857783 60</td>
<td>33 23</td>
<td>27 m</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>tolerance</td>
<td>clearance</td>
<td>36 months</td>
<td>81347 11000</td>
<td>12 29</td>
<td>28 f</td>
<td>Tenofovir antenatal</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>clearance</td>
<td>treatment control</td>
<td>36 months</td>
<td>222108440 2902</td>
<td>44 35</td>
<td>30 m</td>
<td>Tenofovir</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>tolerance</td>
<td>clearance</td>
<td>30 months</td>
<td>131177600</td>
<td>15 60</td>
<td>25 f</td>
<td>Tenofovir</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>clearance</td>
<td>treatment control</td>
<td>24 months</td>
<td>56715 &lt;20</td>
<td>13 10</td>
<td>39 f</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>tolerance</td>
<td>escape</td>
<td>18 months</td>
<td>1200000 1084658</td>
<td>19 81</td>
<td>35 m</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>101</td>
<td>escape</td>
<td>treatment control</td>
<td>12 months</td>
<td>384000</td>
<td>67</td>
<td>42 m</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>clearance</td>
<td>treatment control</td>
<td>12 months</td>
<td>4729055 &lt;20</td>
<td>257 28</td>
<td>27 m</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>escape</td>
<td>treatment control</td>
<td>6 months</td>
<td>6150 &lt;20</td>
<td>81 205</td>
<td>58 m</td>
<td>Entecavir</td>
<td></td>
</tr>
</tbody>
</table>
All patients had some further follow up for their chronic HBV infection after enrolment into the study. Overall, 55% had regular liver function testing and 28% HBV viral load testing as dictated by their phase of disease at study entry. Liver ultrasound was carried out at some point during the follow-up period for 65% of patients and fibroscan for 25%. This information is detailed by disease phase below (Figure 9.7), showing that those in the immune control phase achieved the most complete follow up. No individuals fully achieved the HCC screening recommendations.

**Figure 9.7: Percentage of individuals with follow-up blood and imaging tests as per recommended time intervals for blood tests and one or more results for imaging presented by disease phase at entry to the study**

### 9.6 Discussion

This paper describes the clinical follow up over a median period of 27 months of the only cohort of HBV sub-genotype C4 patients described thus far. Using the most conservative definitions of phase of disease and ALT levels, over 20% of individuals transitioned into a different phase of disease over a relatively short period of follow up. This highlights the importance of viewing
chronic HBV infection as a dynamic disease that requires regular re-assessment to evaluate the need for treatment and not labelling people ‘inactive carriers’, which implies a benign static prognosis.

The average rate of seroconversion from HBeAg positive to anti HBe positive (including data from all genotypes) is said to be 8-12% per year [22] dropping to 5.92% per year in the REVEAL group which only included genotypes B & C [23]. We document an e seroconversion rate of 2-3% per year in our C4 patients, substantially lower than that in the literature for other genotypes. The age distribution of individuals in each phase of disease at study entry (Figure 9.2) is consistent with published evidence that genotype C in general is associated with a significantly older age of e seroconversion [24]. None of our patients who changed disease phase seroreverted to HBeAg positive, which is also thought to occur more commonly in genotype C disease. We may have missed this phenomenon due to the general policy in the NT not to re-test eAg status once an individual has become anti-HBe positive. Three individuals became anti-HBs positive hence ‘clearing’ their chronic HBV infection. This is a rate of around 1% per year which is in line with expected clearance rates of 1-2% per year but lower than the 2.26% documented in a large Taiwanese cohort (genotypes B&C) [25].

It is important to note that in this cohort, median ALT levels do not seem to be raised (median 28U/L) and using the standard local laboratory cut off of 54U/l a large number of patients would be misclassified (Figure 9.3). This is particularly important in terms of obtaining antiviral treatment through the Australian pharmaceutical benefits scheme (PBS), as abnormal ALT is one of the qualifying criteria (in non-cirrhotic patients). The lower, gender-specific ALT level cut offs were initially based on a group of Italian blood donors [21]; subsequently other larger studies from the USA and most recently China support these lower ‘normal’ values [26, 27]. These revised cut-off levels are also now accepted and recommended by the main HBV guideline bodies [28, 29]. A large study based in Hong Kong [30] compared histology from liver biopsy to
ALT levels in a group of 211 HBeAg positive chronic HBV infection patients and 108 anti-HBe positive individuals. This study concluded that ALT did not predict significant liver injury with 22.5% of HBeAg positive patients, with normal ALTs having F3 or greater fibrosis on biopsy. It is also prudent to remember that all our patients are Indigenous Australians and there is not a validated normal ALT range for Indigenous Australians.

We have previously documented that the majority of C4 HBV viruses which have had full genome sequence analysis (55 of 128) have mutations that have been previously associated with increased rates of cirrhosis and HCC [16]. Of this group of relatively young (median age 38.4 years) patients, 12% had evidence of cirrhosis at study entry and by the final point of follow up, markers of cirrhosis were documented in 19% of the group. One explanation could be that the availability of a fibroscan (from 2012 onwards) has enabled us to identify more cirrhosis in the second half of the study period. However of the 32 individuals, who had a fibroscan, six were consistent with cirrhosis and three also had results that met the non-fibroscan criteria for cirrhosis, so they would have been identified anyway. Hence if we remove the influence of the fibroscan results from the analysis we still have 11% at baseline and 16% at final follow-up point with both ultrasonographic and blood markers of cirrhosis. Chan et al. demonstrated genotype C patients to have higher levels of advanced fibrosis (25%) than genotype B HBV patients (19%) as demonstrated by fibroscan (>9kPa with normal ALT, >12kPa with elevated ALT) in their prospective study of 1106 chronic HBV infection patients (median age 45 years) [4]. The majority of cirrhotic individuals in our C4 cohort were in the immune control phase both at study entry and final follow up (Figure 9.6) but some are in the immune tolerance and immune clearance phase. This is at odds with standard thinking about the natural history of chronic HBV infection, which is that significant fibrosis and cirrhosis is uncommon in the early phases [22]. This could be interpreted to mean that the majority of liver damage in C4 chronic HBV infection is occurring in the earlier disease phases and persists even when HBV viral loads are low and ALT has normalised. It could also be representative of another cause for the cirrhosis, however in this
group alcohol intake at baseline was none for 69% of patients, and median BMI is 23, so it is unlikely that alcohol and non-alcoholic steato-hepatitis are playing a large role in this cohort. Kumar et al. [31] reviewed 1,387 patients with chronic HBV infection with over one year of follow up looking at those with either persistently normal (<40U/l), persistently elevated or intermittently elevated ALTs. They found that of those with persistently normal ALT levels, 40% of HBeAg positive patients and 13% of eAg negative patients had greater than grade 2 fibrosis on liver biopsy. However these patients were predominantly non C HBV genotypes. It is recommended [28] that all cirrhotic patients with any detectable viral load are commenced on antiviral treatment; this again highlights the importance of regular reassessment looking for changes in an individual’s situation that may mean they warrant treatment, irrelevant of their stage of chronic HBV infection disease.

The logistics of follow up in the context of remote NT are challenging, however even in this study setting the overall level of follow up when compared to guideline-based care is disappointing (Figure 9.7). Individuals in the immune control phase appear to be receiving the most complete care; it is not clear why this should be. The fact that follow up is less frequent in this stage (12 monthly versus 6 monthly), and the criteria for allocation into this phase are more consistent across the literature, may be contributing. It may be that these are the individuals who are already having an annual health check, as is recommended in the NT, and this would in part explain the discrepancy between LFTs and HBV DNA results being available as only the former would be included in the routine adult health check. Access to ultrasound is reasonable for a one-off baseline scan but very inadequate when looking at HCC screening. A positive finding is that the number of people receiving treatment in this remote setting has increased and is for this group of individuals above the 15% target recommended in the Second National Hepatitis B Strategy [17]. However, at the follow-up point, a further six should now be considered for treatment. Ku et al. compared specialists against primary care providers in how well they followed chronic HBV infection management guidelines in a USA setting. They found that
individuals reviewed by a specialist were significantly more likely to have a complete laboratory work up (defined as having HBeAg, ALT and HBV DNA available) than those reviewed in primary care (62% vs 33% P<0.001) [32]. Also in a USA setting, Sarkar et al. showed in a large (12,016 chronic HBV infection patients) retrospective review that only 40% of patients had a documented HBV DNA level an ALT result within the last 18 months [33].

We are recommending that everyone should have a Fibroscan and this is consistent with the most recent Australian Liver Association consensus guidelines [34] however we are aware there are a number of issues with this recommendation. There is still a reasonably large variation in the value of Fibroscan result that is accepted to indicate cirrhosis (ranging from 9.0 kPa to 13.1 kPa) and multiple factors that can potentially affect the result such as ALT level, fasting state and BMI. As such it is currently suggested that Fibroscan should be one of the multiple factors used to determine suitability for hepatitis B treatment and this should take place in specialist rather than primary care. There is only one Fibroscan machine for the whole of the NT (this is a portable machine which can be used in the remote setting), the majority of the Fibroscans in this cohort were carried out in the remote setting, the reliability of the device in this setting is assumed to be good but there is no published evidence to confirm this. In addition to this it is not currently funded by Medicare.

The main limitation of this study is that all follow-up data were collected retrospectively and hence were incomplete. This has led us to move to prospective follow-up data collection from this point forward. It has also given us the opportunity to make specific recommendations to the NT Hepatitis B Strategy to work towards improving chronic HBV infection management in the non-study setting. We have also included patients who were already on or have commenced treatment in the study as it would clearly be unethical not to commence treatment when it is warranted, although this will modify the natural history of the disease. In assigning a diagnosis of cirrhosis to patients we did not use the gold standard of liver biopsy so could potentially be
overestimating the number of patients with cirrhosis. We did not document any cases of HCC in
this cohort; we suggest that this is likely to be mostly a consequence of the short duration of
follow up to date.

In conclusion this study is the first to report clinical follow up of a cohort of individuals with sub-
genotype C4 chronic HBV infection. Our results support the molecular virological findings
previously reported suggesting that C4 has an aggressive phenotype with relatively high rates of
cirrhosis similar to other C genotypes. Our data also show that the majority of cirrhotic patients
are already cirrhotic by the immune control phase this means we urgently need a larger data set
with ongoing prospective follow up to confirm this finding. If confirmed it raises the question as
to whether earlier treatment would be warranted in this setting. We have demonstrated it is
possible to achieve the treatment targets set out in the Second National Hepatitis B strategy in a
remote setting, however there is also room for significant improvement in holistic follow up for
Indigenous chronic HBV infection patients in the NT.
9.7 References


Section D - Hepatitis B specific health literacy in the context of NT remote Indigenous communities: understanding it and establishing culturally appropriate ways to improve it
Chapter 10 - The hepatitis B related knowledge, perceptions and experiences of remote dwelling Indigenous Australians and their health care providers
10.1 Preamble

Through my clinical work at Royal Darwin Hospital and clinical outreach visits to multiple remote communities the difficulties in explaining HBV infection to Indigenous patients living with chronic HBV infection became increasingly apparent to me. Discussing this with Dr Josh Davis and Sarah Bukulatjpi, one of the Aboriginal Health Practitioners in one remote clinic, I was somewhat reassured that this wasn’t just because I was a white English female doctor but a somewhat common problem. Sarah suggested that we needed a culturally appropriate tool to help people understand; this was the beginning of the participatory action research project that is described in detail in this chapter. There is very little information published about knowledge and understandings of hepatitis B in the Indigenous population of Australia.
10.2 “Only your blood can tell the story” – a qualitative research study using semi-structured interviews to explore the hepatitis B-related knowledge, perceptions and experiences of remote-dwelling Indigenous Australians and their health care providers in northern Australia
“Only your blood can tell the story” – a qualitative research study using semi-structured interviews to explore the hepatitis B related knowledge, perceptions and experiences of remote dwelling Indigenous Australians and their health care providers in northern Australia

Jane Davies1*, Sarah Bukulatjpi2, Suresh Sharma3, Joshua Davis1 and Vanessa Johnston1

Abstract

Background: Hepatitis B is endemic in the Indigenous communities of the Northern Territory of Australia and significantly contributes to liver-related morbidity and mortality. It is recognised that low health literacy levels, different worldviews and English as a second language all contribute to the difficulties health workers often have in explaining biomedical health concepts, relevant to hepatitis B infection, to patients. The aim of this research project was to explore the knowledge, perceptions and experiences of remote dwelling Indigenous adults and their health care providers relating to hepatitis B infection with a view to using this as the evidence base to develop a culturally appropriate educational tool.

Methods: The impetus for this project came from health clinic staff at a remote community in Arnhem Land in the Northern Territory, in partnership with a visiting specialist liver clinic from the Royal Darwin Hospital. Participants were clinic patients with hepatitis B (n = 12), community members (n = 9) and key informants (n = 13); 25 were Indigenous individuals. A participatory action research project design was used with purposive sampling to identify participants. Semi-structured interviews were undertaken to explore: current understanding of hepatitis B, desire for knowledge, and perspectives on how people could acquire the information needed. All individuals were offered the use of an interpreter. The data were examined using deductive and inductive thematic analysis.

Results: Low levels of biomedical knowledge about Hepatitis B, negative perceptions of Hepatitis B, communication (particularly language) and culture were the major themes that emerged from the data. Accurate concepts grounded in Indigenous culture such as “only your blood can tell the story” were present but accompanied by a feeling of disempowerment due to perceived lack of “medical” understanding, and informed partnerships between caregiver and patient. Culturally appropriate discussions in a patient’s first language using visual aids were identified as vital to improving communication.

Conclusions: Having an educational tool in Indigenous patient’s first language is crucial in developing treatment partnerships for Indigenous patients with hepatitis B. Using a culturally appropriate worldview as the foundation for development should help to reduce disempowerment and improve health literacy.

Keywords: Hepatitis B, Health literacy, Culture, Portable electronic applications, Language, Indigenous population
**Background**

Significant health disparities exist between Indigenous and non-Indigenous Australians resulting in a 10–11 year average reduction in life expectancy for an Indigenous child born between 2005 and 2007 [1]. Liver disease is the third largest contributor (11%) to this gap in life expectancy with chronic hepatitis B (CHB) contributing significantly, in the form of liver cirrhosis and hepatocellular carcinoma (HCC).

CHB is endemic in the Indigenous communities of the Northern Territory (NT) of Australia with prevalence rates estimated to be between 0.8% [for children born in the universal vaccine era (1988 onwards)] and 14.2% (for adults born pre universal vaccination) [2–8], this is compared to 1% in Australia as a whole [9]. Despite the availability of effective, government subsidised treatments only an estimated 5% [10] of all people living with CHB in Australia are receiving appropriate management for their infection. This disparity in rates of Hepatitis B and low uptake of treatment is also seen in other Indigenous populations across the world [11,12].

The barriers to people accessing care for CHB are multifactorial but among Indigenous Australians, include gaps in knowledge, low health literacy and challenges in accessing the appropriate care [13]. Both a recent situational analysis [14] and a qualitative study [15] in the Torres Strait region of Australia identified low levels of knowledge about CHB both in health care providers and Indigenous Australian patients with CHB. Christie et al. [16] have explored views of health literacy in the particular cultural context of remote Indigenous communities in the NT, as well as carrying out a scoping study looking at ways to improve health literacy in this region. Christie (2010) suggests that “effective health literacy is largely to do with effective communication” (p.40). Based on their research, they argue that building on an individual’s existing knowledge using a culturally appropriate approach (i.e. a relevant respectful partnership which is mindful of language, worldview, existing knowledge and beliefs) to achieve a shared understanding of the issue at hand is more beneficial than attempts by health practitioners to simply ‘transfer’ biomedical knowledge to their patients [17]. Although many health promotion or information resources exist for hepatitis B [18], all the above [13–17] studies as well as the Australian National Hepatitis B strategy [19] highlight the lack of culturally appropriate resources, in particular visual and multimedia resources, available to facilitate shared understandings of Hepatitis B and strengthen health literacy.

In the context of the NT Indigenous population, English is usually a second (or even third or fourth) language; therefore, achieving effective cross cultural or “culturally safe” communication can be challenging, as has been extensively documented in health care settings over the last decade [20–22]. Miscommunication between health providers and patients has been reported to be pervasive, however using interpreters and translators is perceived to be only part of the solution [20]. Different worldviews and knowledge systems that exist among Indigenous Australians, including alternative concepts of physiology, pathology and disease causation also contribute [23]. An often misinformed assumption by health providers of shared understandings [20], along with the absence of opportunities and resources to construct a body of shared understanding perpetuate this miscommunication. Two specific factors, culture and worldview, are increasingly acknowledged as important antecedents contributing to health literacy [24–27]. There are a myriad of different definitions of culture; when referring to culture in this paper we use the broad definition of the culture of a society as “… the totality of its shared beliefs, norms, values, rituals, language, history, knowledge and social character” [28]. Participatory projects working with Indigenous communities in the design and development of health education resources have been successful in improving health literacy and participation in healthcare in other disease areas [29,30].

The aim of this research project was to explore the knowledge, perceptions and experiences of remote dwelling Indigenous adults and their health care providers relating to hepatitis B infection. We also aimed to gauge interest among Indigenous participants in further knowledge of this disease and gain perspectives on how and in what format people could best acquire the information they needed. This was the first stage of a wider participatory action research (PAR) project with the intention of using the results as the evidence base to inform development of a culturally appropriate Hepatitis B educational resource.

**Methods**

This project was undertaken in northern Australia between July 2012 and December 2013. It was based at the health clinic of a remote community in Arnhem Land, 521 km northeast of Darwin (the capital of the NT). This community has a population of 2,124 with an average age of 24 years; 89% are Indigenous Australians and only 9.5% of the population speak English as their first language. There is an average of 4.2 people per available bedroom and 78% of households are considered to be overcrowded. There are three general stores, a school, a library, a health clinic as well as a police station and a community church.

The overall project design was based on PAR principles; specifically, ongoing consultation, reflection and discussion with the community throughout each iterative cycle. JD (a female non-Indigenous researcher and clinician with
experience in working in a cross cultural environment) and SB (a female Indigenous researcher and health worker in the remote community) worked alongside each other in constructing the interview schedule, recruitment, data collection, analysis and interpretation. This paper reports the results of the first part of this project which was the first formal PAR cycle and provides the evidence base for the development of a culturally appropriate educational tool for hepatitis B, the second phase of the project (details not presented here). However prior to this project informal discussions regarding the issues facing the community with respect to the burden of disease produced by Hepatitis B, the lack of community understanding and the difficulties health workers have in explaining Hepatitis B to community members had been discussed within clinic meetings and with the visiting liver clinic service. The impetus for the project came from the community clinic. Their enthusiasm for the project led to the development of a collaborative research partnership between the community clinic, the Royal Darwin hospital liver clinic and Menzies School of Health Research and establishment of the formal PAR process.

Ethical approval for the study was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) as well as Miwatj Health Aboriginal Corporation (an Aboriginal-controlled health service representing communities across East Arnhem Land) and Charles Darwin University.

Semi-structured interviews were carried out with 3 groups of people; key informants (health clinic staff, community health educators, liver clinic staff - both urban and remote, – and doctors and nurses, Indigenous and non-Indigenous), Indigenous people living with CHB and Indigenous community members. Interviews explored the background of the individual, their hepatitis B knowledge, their experience of health communication/education about hepatitis B, available resources and their perspectives about potentially useful educational tools. All participants were shown two existing resources; an animation about the liver and its function (chosen as it was part of an electronic education package targeted at Indigenous Australians) and a flip chart, (developed in Victoria, Australia, intended for use in the clinic setting and aimed mainly at Asian individuals) about hepatitis B and asked to comment on them as a way of generating ideas/preferences for any future educational tool. Patient and community member interviewees were also asked from where they acquired their knowledge about HBV, what influenced their current understanding, and barriers to understanding (Table 1).

JD and SB recruited participants into the study and carried out the interviews; both had received specific training in interview techniques prior to the commencement of the project. All patients were given the option of an accredited interpreter in their first language if this was not English both for the process of obtaining written informed consent and the interview itself.

A mixture of purposive (non-probability sampling in which the researchers suggest who to approach to be included in the study based on them possessing certain characteristics [31]) and network (using existing participants to suggest other people to approach [32]) sampling was used to recruit individuals from a range of different backgrounds with a proportionate mix of gender, age and Hepatitis B status. The majority of participants were recruited through the community clinic and the hospital liver clinic; however some individuals were recruited through the social and professional networks of the research team.

Interviews were carried out in numerous settings ranging from the community clinic, our hospital clinic, our research institution, individuals’ homes and gardens, under trees and at an international conference (8th Australasian Viral Hepatitis Conference, Auckland, September 2012). Interviews were audio recorded and ranged in duration from 20 to 45 minutes. Information collected in Yolŋu matha was translated into English in real time by the accredited interpreter and meaning and understanding clarified by SB (bilingual researcher present at all interviews carried out in Yolŋu matha) as part of the recording. Transcription of the interviews was in English.

An audio diary of the real time experience and reflections on the interviews was kept by JD and SB and included in the data analysis. All participants were offered an AUD$30 electricity voucher in recognition of their time and effort in contributing to the study.

In the process of exploring patients’ and providers’ knowledge, experiences and perceptions of HBV, data emerged on the potential impact of low levels of health literacy on healthcare interactions and therefore future health outcomes as well as the pathways through which this may occur. As such, we have used Paasche-Orlow & Wolf’s model [25] Figure 1 of the pathways that exist between low levels of health literacy and poor health outcomes as an organising model for our data analysis.

Data analysis was carried out by JD and SB, with input from VJ and JS. It commenced with the first interview and was continuous throughout the project. Data immersion consisted of carrying out the interviews, reading the transcripts and listening to the audio recordings multiple times on multiple occasions dispersed over time. Sections of text were organised into codes based both on the categories covered in the interview schedules and also inductively as the text was digested and understood. Codes were also reflected upon with reference to the Paasche-Orlow & Wolf model in particular with regard to the similarities and differences in using this model in this particular cultural context (Yolŋu people) for this particular disease (Hepatitis B). Concurrently and inductively the codes were...
Table 1 Interview guides used for semi-structured interviews

<table>
<thead>
<tr>
<th>Key Informants</th>
<th>Hepatitis B patients and community members</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current role background demographics</strong></td>
<td>Role within family, community, work</td>
</tr>
<tr>
<td>experience with regard to;</td>
<td>Social situation, children, partner</td>
</tr>
<tr>
<td>viral hepatitis</td>
<td>Schooling – what age left</td>
</tr>
<tr>
<td>Indigenous health</td>
<td>Reason for clinic attendance today</td>
</tr>
<tr>
<td>within East Arnhem land</td>
<td>Hepatitis B status - when first knew about Hepatitis B status</td>
</tr>
<tr>
<td><strong>Hepatitis B knowledge</strong></td>
<td>What do you understand by the phrase Hepatitis B infection</td>
</tr>
<tr>
<td>own level of knowledge, where did this come from your perception of the general Indigenous populations knowledge</td>
<td>If no knowledge move directly to communication section</td>
</tr>
<tr>
<td>Indigenous patients knowledge</td>
<td>What do you think it is/does, does it concern you</td>
</tr>
<tr>
<td>what do you think are barriers to increased knowledge (e.g. language, cultural, knowledge systems, health beliefs)</td>
<td></td>
</tr>
<tr>
<td>do you think increased knowledge will make a difference to patient adherence/outcomes, why, why not</td>
<td>How do you think you get Hepatitis B</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Is it a problem for you or your family</td>
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<tr>
<td></td>
<td>How did you learn about Hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Whose opinion, story do you most trust, why, how did this person talk to you</td>
</tr>
<tr>
<td></td>
<td>What do you think about doctors/nurses/AHWs opinions/beliefs</td>
</tr>
<tr>
<td><strong>Communication</strong></td>
<td>What is your experience of talking to doctors/nurses/midwives / AHWs about your health in general/specifically Hepatitis B</td>
</tr>
<tr>
<td>Are you involved in; testing patients, explaining results, counselling regarding treatment options, follow up, screening protocols</td>
<td>How do you think this could be better</td>
</tr>
<tr>
<td></td>
<td>Do they use interpreters, how does this help you</td>
</tr>
<tr>
<td></td>
<td>Do they use pictures/flipcharts/other tools to help you understand</td>
</tr>
<tr>
<td></td>
<td>Which of these things do you prefer</td>
</tr>
<tr>
<td></td>
<td>Do they help, why</td>
</tr>
<tr>
<td></td>
<td>How would it help you if you understood more about your health/hepatitis B</td>
</tr>
<tr>
<td><strong>Available resources &amp; ideas for educational tool</strong></td>
<td>What kind of thing do you think would help you to understand better – flip chart/pictures/talking/electronic/tablet/phone based tool</td>
</tr>
<tr>
<td>Have you used any resources to help with communication/health education, if so details</td>
<td>Look at these resources, are any of them attractive to you, which do you like, what do they say to you</td>
</tr>
<tr>
<td>Do you use/need/have available interpreters</td>
<td>What are your thoughts about an ipad based resource</td>
</tr>
<tr>
<td>Do you have an idea of what kind or resources might help</td>
<td></td>
</tr>
<tr>
<td>Please look at this collection of resources/images and tell me what you think about them, would they be helpful in this context, how could we use them in this context</td>
<td>What things do you want to know about</td>
</tr>
<tr>
<td>How do you feel about an electronic/tablet based resource, how would you see that working, advantages vs disadvantages</td>
<td>What about pictures</td>
</tr>
<tr>
<td>Are there any resources you like from different situations</td>
<td>What about language</td>
</tr>
<tr>
<td>What format do you think will work (electronic, flipchart, other)</td>
<td>What about interaction</td>
</tr>
<tr>
<td>Any ideas about what should be included</td>
<td>Will it help, why, why not</td>
</tr>
<tr>
<td>What about language, images, interactive or not</td>
<td></td>
</tr>
</tbody>
</table>

Key informants = health clinic staff, community health educators, liver clinic staff both nurses and doctors, Community members and Hepatitis B patients = Indigenous people living in the remote community with and without Hepatitis B.
Paasche-Orlow & Wolf [25] have proposed the following model of the pathways that exist between low levels of health literacy and poor health outcomes. This is a component-cause model, which suggests that an individual’s level of health literacy influences three critical components of healthcare: access and utilisation, provider-patient interactions and self-care, which in turn impacts on health outcomes (e.g. someone with poor health literacy about Hepatitis B may present later and have a poorer outcome from their hepatocellular carcinoma due to their lack of knowledge of a screening programme aimed at early diagnosis). It also emphasises the importance of not just individual factors but system, provider and extrinsic factors that contribute to each area such as the lack of appropriate health education resources to assist the health care provider in effectively communicating the importance of attending hepatocellular carcinoma screening to a patient with low health literacy. This model emerged as a useful conceptual framework during preliminary data analysis and was to guide the remainder of the analysis.

Figure 1: Adapted version of Paasche-Orlow & Wolf’s model of the pathways linking health literacy and health outcomes [25].

organised into broader categories and themes. On multiple occasions clarification was sought regarding the cultural context of specific terms and ideas from SB. SB returned to individual participants to verbally clarify findings on a number of occasions however transcripts were not routinely returned to participants for checking. Data were organised and managed in NVivo 10 (QSR International Pty Ltd, Victoria, Australia).
JD, SB, SS & JSD are all clinical care providers as well as researchers and acutely aware of the ethical implications of this within this project particularly for those individuals interviewed who were Hepatitis B patients. Careful explanation of the fact that the research project and an individual’s clinical care are completely separate and mutually exclusive was undertaken with the Hepatitis B patient group in particular. Care was taken to conduct the interviews completely separately in both time and location from any clinical care so as to maintain this separation.

We adhered to the RATS guidelines in reporting this project.

Results

Thirty two semi-structured interviews were carried out between July and September 2012. Participants consisted of clinic patients with hepatitis B (11), other community members (9) and key informants (12). Twenty-four (75%) were Indigenous people. Median age of participants was 45 years (IQR 35–55) and 18 (56%) were female. Highest level of education attained was junior school for one individual (3%), secondary school for 23 (72%) and tertiary education for 8 (25%). All participants had the opportunity to use an interpreter (the principal Indigenous language spoken in the community). The remainder were carried out in English.

Knowledge about hepatitis B: “Only your blood can tell the true story”

There was a distinct lack of biomedical knowledge regarding CHB, especially in the people living with CHB group, and even among those who had been previously reviewed in the liver clinic and/or were currently on oral antiviral treatment for CHB. People living with CHB and community members generally acknowledged that they did not know or have any understanding of what hepatitis B was and were commonly unable to attempt any explanation on direct questioning.

However, when contextual translation was provided in Yolnu matha some understanding often emerged:

“Something like that person will get that virus inside the body. Sometimes he [the virus] will be gone and sometimes will stay there for bit long. That’s the story I know”.

“When I see people with hepatitis they have a yellowish thing - eye - you know just around the eye balls and that thing to me, it tells me that the person either have a hepatitis or kidney failure”.

Indigenous community member

The word “germ” and an understanding of germs being micro-organisms that required a microscope to visualise them was recurrently touched upon, with specific reference to previous education programmes and research projects carried out in the community both by The Aboriginal Resource Development Service (ARDS) in Darwin and Menzies School of Health Research. These experiences appeared to have led to an increased understanding of biomedical concepts around infectious diseases in general and were discussed in a positive light.

Despite this many misconceptions about hepatitis B from a biomedical perspective were identified, particularly around causation and transmission. In particular the ideas that CHB can be caused by smoking, lifestyle factors, diet and lack of exercise were frequently reported by community members:

“Maybe because I was washing myself too much in cold water it may have caused the sickness or me sleeping outside”.

“When you smoke you get the sickness in the lungs and in the liver”.

Indigenous Hepatitis B patient

This was also reflected in comments made by numerous people that before “western influences” CHB didn’t exist as a problem; it was a “new” sickness that people did not really know much about and could be prevented by reverting to a more traditional lifestyle.

Many people reported that their underlying beliefs about health and disease are based on traditional medicine including sorcery as causation of disease and traditional plant-based remedies as treatments. Although there were no bush medicines reported that can be used to specifically treat CHB, a remedy made from paper bark trees was described as being used and felt to be effective for liver sickness in general. The biomedical or “balanda” (white person) version of hepatitis B was very much seen as an alternative explanation; new information that didn’t exist in previous generations.

There was also some confusion surrounding Human Immunodeficiency Virus (HIV) and CHB. Some community members reported that the two diseases were one and the same sickness. This misunderstanding appeared to contribute significantly to the sense of stigma or shame around a diagnosis of CHB, and that it had to be kept a secret because of what it might reveal about sexual orientation or partner preference. As well as this, the opinion that an individual patient may be to blame in some way for acquiring CHB, which appeared to be centred on awareness that CHB could be sexually acquired, was recurrently voiced.

This lack of biomedical knowledge was not confined to the patient and community members. Some key informants,
both Indigenous and non-Indigenous, also acknowledged that they found it a difficult area to understand clearly themselves. Multiple health professionals reflected on the role of working in an endemic setting seeing a high volume of people living with CHB as necessary to achieve true competency in the management of CHB, stating that prior to this, their understanding was more superficial.

The topic of hepatitis B is part of the routine curriculum studies undertaken by Aboriginal health workers (AHW) and this appeared to be the origin of knowledge for this group, as similar concepts and responses were reported. The concepts of mother to child transmission, sexual acquisition and the infectiveness of blood and other body fluids were expressed by several AHWs; however they were less clear about the natural history of the disease, the interpretation or meaning of blood test results, and the potential for treatment or intervention.

**Perceptions of hepatitis B: “It's like a silent killer; I can drop dead anywhere so I take my tablets and pray”**

People living with CHB and community member perceptions about CHB tended to portray the disease in a negative light, describing it as a “scary sickness”, a “serious infection”, a “big sickness”. People living with CHB in particular described fear as a motivating factor for their actions and behaviours, which either pushed them to take their tablets to prevent imminent death or made them too afraid to attend the clinic, so acting as a barrier to receiving any care.

Within the key informant group there was recurrent reference to the many more urgent competing health priorities in remote communities, such as ischemic heart disease, diabetes and renal disease. CHB, owing to its long term, insidious or asymptomatic nature, in combination with the lack of appropriate resources, resulted in it being neglected and often not adequately addressed. Multiple logistical issues were also felt to contribute to an almost fatalistic view of what was achievable, such as: the remote and dispersed nature of the patient population; the difficulty accessing secondary care physicians and investigations, especially liver ultrasound; the turnover of health care professionals, and lack of continuity of care. In the context of these factors it was perceived that CHB is just too complex a problem to tackle. It was also noted that even where good quality educational resources are available for other diseases, they are rarely used in clinical practice. Instead, they sit on a shelf gathering dust or the technology to use them is either not there or does not work. It is not clear if this is because they are not useful, did not have community input into their development or have not been well implemented or evaluated.

"People (with Hepatitis B) tend to be asymptomatic for long periods in contrast to chronic diseases like ischemic heart disease, chronic airways disease, chronic kidney disease, diabetes, and day to day problems that people can identify as being directly linked to the condition so it tends to be way down the list of priorities".

**Non-Indigenous health worker**

"The system relies on people being involved for the long haul and yet there's not a single clinic where we were outlasted by the clinic or the nurse manager of the clinic or the GP where we were there for longer than anyone else in all of the East Arnhem Clinics".

**Non-Indigenous health worker**

"I think, I mean working in the top end I've seen a lot of really nice materials that have been developed educationally and flip books and things. In my experience they're rarely used".

**Non-Indigenous health worker**

Among non-Indigenous key informants there was a perception that it was not possible to translate certain key words such as 'liver' and 'kidney' accurately into Yolŋu matha and hence adequate explanations of hepatitis B were challenging to achieve even with a translator. An Indigenous community member working as a translator, however, said that this was not true.

"Most of the time by and large Yolŋu are hunter gather people. They can cut up a kangaroo, wallabies; they can identify those things [liver and kidney] pretty well, they can make that distinction. It is common knowledge to be able to identify them, there are clear words for them [liver and kidney] and they are different”.

**Indigenous community member**

**Experiences of living with Hepatitis B: towards a shared understanding**

Non-Indigenous individuals in the study (all key informants) tended to significantly overestimate the depth of shared understanding between themselves and Indigenous individuals when discussing CHB. When reviewing existing resources with the non-Indigenous health workers there was recognition that there were too many medical terms and a feeling that they were too detailed in content. However, the general concepts that were explained in these resources were felt to be appropriate. Indigenous participants also described an excess use of jargon but also reported that the concepts used were foreign and difficult to relate to.
He is saying he's been to the clinic, they have explained several times. Sometimes he doesn’t understand [what they are saying], especially the doctors.

Indigenous Hepatitis B patient

This lack of shared understanding was also touched upon when discussing the use of AHWs as translators in the context of clinic consultations about CHB. Although a few of the doctors with extensive experience of working in a remote community environment had good insight into the difficulties AHW may face in explaining biomedical concepts, there was a general feeling that having an AHW with them during a consultation to translate their biomedical explanation was adequate to achieve a shared understanding. In stark contrast to this, AHW participants reported finding this expectation overwhelming as they did not feel sufficiently equipped to be able to facilitate a satisfactory explanation due to their lack of understanding of what was being said.

If I don’t understand the message then how am I gonna convey it.

Indigenous health workers (key informants)

Multiple patients voiced the concern that they were asked to have many blood tests related to their diagnosis of CHB, without receiving adequate explanation of their purpose, and that there was a lack of follow up to receive and discuss the results. This lack of understanding and communication left them feeling worried, angry and frustrated and in several cases like the clinic staff were purposely hiding something from them, resulting in a lived experience of disempowerment and inferiority.

"I hold my temper at that time, when I don’t get my results back I feel like I need, I want to do something like smash windows or something here at the hospital".

"I figured there was something wrong with me when they kept on requesting more and more bloods from me".

"That’s one of the things. Sometimes doctors hide something to the patient and they don’t want to tell straight".

Indigenous Hepatitis B patients

The results described so far highlight factors which all contribute to the patient-provider aspect of the Paasche-Orlow & Wolf model (Figure 1). As well as clearly impacting on an individual’s Hepatitis B specific health literacy these factors appear to shape healthcare interactions, potentially representing a foundation step in the pathways that exist between low levels of health literacy and poor health outcomes in Indigenous Australians.

The importance of language in health education and healthcare interactions

Indigenous participants across all 3 groups overwhelmingly cited language as the single most important feature of any potential educational resource and also as the most significant barrier to achieving effective cross cultural communication.

“She’s saying, she doesn’t understand, it’s not much meaningful. The words are big words, the numbers are not good, and the words are not good. Should be in language”.

Indigenous Hepatitis B patient

On multiple occasions through the process of interviewing (at the request of individuals normally in the patient group), we used a trained interpreter to provide a brief clinic style explanation of CHB, and this appeared to be able to significantly increase an individual’s understanding of their illness.

It was however emphasised repeatedly that the translation process was not simply a case of turning the English into Yolnu matha and that multiple steps were needed; to ensure the individual translating has adequate understanding, to allow/enable contextual translation, to communicate the message via the interpreter in the appropriate language, to check understanding in language, to ask the interpreter to back translate the participant’s understanding and to clarify any miscommunication, as well as great care not to simplify the message too much such that the detail was lost. Indigenous participants perceived that the best path is to remove all medical jargon and acronyms and translate the simple English into Yolnu matha, using accurate but “culturally safe” concepts. The value and preference for visual aids, again of a culturally safe and accurate nature, was a predominant comment.

It became apparent over the duration of the project that there was a lack of shared understanding of the word “silent” between non-Indigenous key informants (health workers) and patients in the context of hepatitis B. Whereas the non-Indigenous health care professional may use the word ‘silent’ to describe the immune tolerance (early stage CHB when viral load is high but minimal liver damage is occurring) or immune control phase (later stage CHB following e antibody seroconversion where viral load is low and minimal liver damage is occurring) of hepatitis B, a Yolnu patient or AHW may interpret this to mean that the sickness is brought about by sorcery”, with
negative connotations of retribution or punishment. Although not held by all, this was a commonly held belief voiced amongst the Indigenous people interviewed.

The relationship between culture and communication in health education

Culturally important relationships between certain individuals, which health care providers may not be aware of, were seen as a barrier to effective communication. For example; a well-respected senior male elder in the community may feel uncomfortable with having a younger female interpreter in a medical consultation, as it would infer something negative about his knowledge of the subject or ability to understand the health care worker and so decline the assistance of an interpreter altogether. This can then result in the individual having an inadequate understanding of the information presented to them.

The importance of gender sensitivity, not only in a clinical scenario but also in any potential educational resource was touched on by individuals in all groups. The ability for people to speak honestly and in detail about hepatitis B was felt to be culturally difficult between individuals of different gender. Patients and community members felt this to be more important if the gender mismatch was between two Indigenous individuals and not as significant if the second individual was a non-Indigenous individual or a health care professional. However some non-Indigenous health care professionals felt that consultations between a health worker and patient of the same gender tended to result in improved cross cultural communication and improved rapport.

Motivation to understand more about hepatitis B: “we want to learn more about this sickness”

Despite a lack of biomedical knowledge, Indigenous participants passionately voiced a desire to understand more about hepatitis B. The importance of telling the full and true story was emphasised, in not missing out the details, but finding a culturally appropriate contextual translation to allow a shared understanding of the important information. Indigenous participants were enthusiastic about spreading this knowledge to all to whom it may be relevant in order to allow them to make choices about seeking management. Both Indigenous people living with CHB and community members perceived that the moral and ethical obligation was on “us”, the health care providers, the ones giving injections (vaccination) and taking blood tests to ensure patients were appropriately informed. This understanding was felt to be very powerful in facilitating autonomy and respect, as well as being vital to a respectful patient – health care professional relationship.

“She’s saying she wants to learn more about this hepatitis B so she can pass the story to her people, to her family. And to encourage them to come to the clinic and have a check-up.”

Indigenous Hepatitis B patient

A culturally appropriate education resource: what we need...

When discussing educational resources, non-Indigenous key informants reported that an analogy with hepatitis B using a local animal (e.g. a crocodile or snake) to represent how the virus can lie dormant in the liver and then suddenly attack resulting in serious health consequences would be culturally appropriate. By contrast, Indigenous participants generally preferred more medical imagery requesting to see a real human-like figure with a real liver, and a story based in a culturally appropriate setting. One participant remarked that the majority of local animals are hunted as food by community members, so it would be counterproductive to use them to explain a human sickness - people would then think they could get the disease from the animal.

A strong desire to understand the detail about Hepatitis B was recurrently expressed but the need for contextual translation done in a culturally appropriate way was stressed. In general, Indigenous participants reported a preference for an electronic format with an emphasis on interactive pictures and less text. If text is utilised, it was clear from participants that it must be in Yolu matha and spoken as well as written.

There was a recurrent specific request for a separate “women’s business” section to speak about the issues specifically related to pregnancy.

Figure 2 summarises the important aspects from the results which have been taken forward into the process of developing a culturally appropriate tool to aid in the development of effective treatment partnerships for Indigenous patients with CHB.

In light of our results we have adapted Paasche-Orlow & Wolf’s model Figure 3 to highlight how the relationships between health literacy and poor health outcomes may operate for Indigenous Australians with respect to hepatitis B.

Discussion

This study documents low levels of biomedical knowledge about hepatitis B which appear to be influenced by a multitude of factors including culture, gender, competing health priorities and a lack of shared understanding. Pessimistic almost fatalistic perceptions of the disease predominated across all groups of individuals interviewed. In terms of experiences the major theme identified was communication particularly the importance of having information available in an individual’s first language to aid
Figure 2 Key features of the results from the qualitative study that have formed the evidence base for the development of a culturally appropriate tool aid in the development of a shared understanding of the Hep B story with Yolŋu people.
in effective cross cultural communication. Indigenous individual's repeatedly expressed a desire for increased knowledge and insight into the ability of this knowledge to reduce disempowerment and improve Hepatitis B specific health literacy. Ideas as to how to best enable this to happen included using visual aids, electronic formats, simple language and the absolute requirement for information to be available in Yolnu matha.

Knowledge and beliefs are important patient factors in the patient-provider interaction component of Paasche-Orlow & Wolf's model linking low levels of health literacy and poor health outcomes. A lack of biomedical knowledge about hepatitis B was identified in Indigenous individuals across all groups interviewed. This is consistent with data from Indigenous individuals in the Torres Strait [15] as well as non-Indigenous Australians from culturally and linguistically diverse backgrounds [13].

Lack of knowledge and erroneous beliefs about hepatitis B, as well as contributing to low levels of health literacy, may lead to a reduced ability or willingness to participate in decision making about management plans. This in turn may influence adherence with the plan and subsequent necessary self-care activities. Multiple factors affecting the provider side of the patient-provider interaction were also identified. Communication skills to allow shared understandings to be developed as well as insight into how best to achieve this are crucial in our context, where there are multiple competing priorities; however lack of these skills is identified in our results as an ongoing barrier to achieving shared understandings. In the context of Australian Indigenous peoples where English is not the first language and culture and worldview are very different we would suggest that the patient-provider interaction not only significantly contributes to health literacy but is a
pre-requisite to allowing access & utilisation of care and self-care to occur and so ultimately influencing health outcomes (Figure 3).

As well as the patient-provider factors described above, extrinsic factors such as support technologies, health education and resources are identified as key factors to allow optimisation of self-care. The wider project that this research is part of was initiated due to a lack of culturally appropriate resources about CHB for use in clinical practice. Our data identified a real desire for more knowledge and understanding around CHB for all in the community to motivate and empower people living with CHB and community members, which in turn should increase self-management in relation to CHB. Our results identify a clear ambition by community members and people living with CHB towards ‘critical health literacy’ as defined by Nutbeam et al. [33] as the tertiary level of health literacy encompassing not only communication of information and development of personal skills but also personal and community empowerment.

There is now increasing experience with the use of innovative, interactive, internet, mobile phone and tablet-based resources to improve health literacy in other settings [34,35]. In the context of Indigenous Australia, several groups have produced apps in the area of mental health [36] but robust evaluation of their value is still awaited. In northern Australia, Christie’s research group has proposed a tablet-based, easily transportable, touch pad body resource, which does not contain any embedded health messages, but rather focuses on aspects of a healthy body. Their vision is that this could be used as the foundation for a further discussion about the impact of chronic diseases on the body and how treatments act to return the body to a healthy state [16]. The evidence derived from this project that will be taken forward to phase 2 of the PAR process and used to guide the development of a culturally appropriate educational tool about Hepatitis B is summarised in Figure 2.

Effective communication is not only central to improving health literacy [37], it is a crucial element in achieving culturally safe healthcare, which in essence can be defined as “shared respect, shared meaning, shared knowledge and experience of learning together” [38]. More recently, research suggesting that some Indigenous patients believe that health care workers deliberately withhold information from them highlights the extreme lack of trust that can develop as a consequence of ineffective communication [21]. As communication transcends all aspects of health literacy, hence “culturally safe communication” at both a system and individual level is clearly integral to its improvement. Culturally safe communication has also been suggested as being important in reducing ethnic and racial disparities in healthcare [39]. Specifically in the Australian Aboriginal context, involvement of the local community in developing and implementing health education programmes, so they are culturally safe, has been shown to directly influence their effectiveness [29,30,40] and attention to worldview and language are argued to be integral to achieving improvements in health education [41]. It is therefore disappointing that more than a decade after the publication of Cass et al’s [20] paper documenting the pervasive nature of miscommunication between Indigenous people and their health care professionals, our results show the major barrier to achieving critical health literacy is still poor cross-cultural communication. Consistent with the view of Vass et al. [41] who suggest “the health literacy of Indigenous Australians can be improved by promoting the oral use of the peoples’ first language in the health sphere” Indigenous participants anticipate they will better understand and be able to process and act on information given to them in their own language.

Our results also provide further insight into the complexity of achieving effective and culturally safe communication in this setting, when, for example, the lack of a shared understanding of one word – “silent” – which is used so commonly in clinical practice with hepatitis B patients can lead to such significant misunderstanding. We have also highlighted the potential for miscommunication to be perpetuated in health settings when communities are not adequately consulted about health education and health promotion resources. The well-meaning but mistaken beliefs among non-Indigenous key informants in this study about the appropriateness of using animal analogies when discussing how hepatitis B affects the liver or the mistaken belief that the lack of a direct translation of a word prohibits meaningful translation of key messages, are two examples from our data.

The negative perceptions and fear of hepatitis B as a disease may originate from the low levels of health literacy documented and contribute to stigma and potential non-disclosure of diagnosis as well as having implications for individual clinical care and the success of public health interventions. This pessimism may be confounded by the lack of shared understanding and different health beliefs about causation in the context of provider-patient interactions. Additionally, the non-Indigenous key informants in this study perceived that there are multiple logistical barriers and competing priorities to providing effective and appropriate long term care for people living with CHB and felt overwhelmed by the task. This negativity is likely to adversely influence an individual’s access and utilisation of care and so contribute to the relationships between limited health literacy with inequitable health outcomes as per Paasche-Orlow & Wolf’s model.

Our study is limited by the fact it only included one community and because of multiple previous education and research projects in this community in the discipline
of infectious disease, it is likely that this community has higher health literacy that most regarding infectious disease. Specifically, Cultural practices, traditions and world view may be totally different to other Australian Indigenous peoples; however, our findings about the importance of communications and shared understandings are likely to transcend region and apply to all Indigenous Australians. This view is supported by the similarities between our findings, and those of Preston-Thomas et al., who investigated HBV knowledge in a completely different group of Indigenous Australians – Torres Strait Islanders. Although not directly translatable to other cultures, it is likely that the modified factors highlighted in Figure 3 will be of greater importance to those people living with CHB from culturally and linguistically diverse backgrounds, particularly if they are receiving care in a country where the language of health care is not their own first language.

Although low levels of biomedical knowledge about CHB are clearly a significant barrier and an important influence on health literacy our findings resonate more clearly with Christie et al’s [16] definition of health literacy. In this context, what is really critical to improving health literacy is developing a shared understanding between patients and providers, which hinges on effective communication. If we can use the insight we have gained from this study and work with the people who provided it to develop an educational tool grounded in their culture, in their first language and make it easily accessible, that would be a first step to improving health literacy about CHB. Qualitative research using a participatory approach holds promise of breaking cross-cultural barriers in health communication and health care. We acknowledge that there will also need to be appropriate implementation and evaluation of the resulting resource to ensure its success.

Conclusions

Biomedical knowledge about Hepatitis B is low in this Indigenous community in the Northern Territory, experiences and perceptions about CHB are in general negative and at times nihilistic. However there is a strong desire for increased knowledge and evidence of increased understandings with contextual translation of information. Patient provider interactions leading to the development of shared understandings between Indigenous people living with CHB and the health care professionals looking after them are the foundation for improving health literacy and so health care outcomes related to CHB. Language and using a culturally appropriate worldview are crucially important in developing an educational resource to aid in developing treatment partnerships for Indigenous patients with CHB. Maintaining a participatory approach to development should help to reduce disempowerment and overcome some of the barriers to its implementation and success.

Endnote

*SORCERY as a cause of disease is a commonly held belief in Indigenous communities in Arnhem Land particularly where a death is sudden, unexplained or happens to someone who is seen outwardly as healthy. It can be a form of retribution or punishment but is not always viewed in this way.

Abbreviations

ARDS: Aboriginal Resource Development Service; CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; PAR: Participatory Action Research; NT: Northern Territory.

Competing interests

JD & JSD have received an unrestricted educational grant from Gilead Sciences to finance all aspects of this project with the exception of their time which is supported by the NHMRC (PhD scholarship to JD), early career fellowship to JSD) and Sidney Myer funds (top up scholarship to JID).

Authors’ contributions

JD & JS designed the study with input from VJ, SS & JSD. JD & JB carried out the interviews and analysed the data. JD wrote the first draft of the paper with input from SB and critical reviewing by VJ, SS and JSD. All authors read and approved the final manuscript.

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10.3 Implications and questions arising from this paper

The results of this paper have formed the evidence base for the development of the electronic app described in detail in Chapter 11.

The most striking implication from this work is the need for more attention to be paid to the use of interpreters and to ensuring that there is the time and space within health care to allow shared understandings and trusting relationships to develop. Unless we can effectively communicate with our patients and achieve these shared understandings we cannot translate our increasing knowledge of C4 HBV into improvements in care for Indigenous people.
Chapter 11 - Development of a culturally appropriate education tool for hepatitis B
11.1 Preamble

Once the analysis of the first PAR cycle was complete we commenced development of the electronic application described in detail in this chapter. We were very lucky to work on this project with Dreamedia, a Darwin-based communications and media company, which carried out the software development.
11.2 Towards shared understandings: development of a culturally appropriate bilingual electronic app about hepatitis B for Indigenous Australians
Development of a Culturally Appropriate Bilingual Electronic App About Hepatitis B for Indigenous Australians: Towards Shared Understandings

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Abstract

Background: Hepatitis B is endemic in Indigenous communities in Northern Australia; however, there is a lack of culturally appropriate educational tools. Health care workers and educators in this setting have voiced a desire for visual, interactive tools in local languages. Mobile phones are increasingly used and available in remote Indigenous communities. In this context, we identified the need for a tablet-based health education app about hepatitis B, developed in partnership with an Australian remote Indigenous community.

Objective: To develop a culturally appropriate bilingual app about hepatitis B for Indigenous Australians in Arnhem Land using a participatory action research (PAR) framework.

Methods: This project was a partnership between the Menzies School of Health Research, Miwatj Aboriginal Health Corporation, Royal Darwin Hospital Liver Clinic, and Dreamedia Darwin. We have previously published a qualitative study that identified major knowledge gaps about hepatitis B in this community, and suggested that a tablet-based app would be an appropriate and popular tool to improve this knowledge. The process of developing the app was based on PAR principles, particularly ongoing consultation, evaluation, and discussion with the community throughout each iterative cycle. Stages included development of the storyboard, the translation process (forward translation and backtranslation), prelaunch community review, launch and initial community evaluation, and finally, wider launch and evaluation at a viral hepatitis conference.

Results: We produced an app called “Hep B Story” for use with iPad, iPhone, Android tablets, and mobile phones or personal computers. The app is culturally appropriate, audiovisual, interactive, and users can choose either English or Yolŋu Matha (the most common language in East Arnhem Land) as their preferred language. The initial evaluation demonstrated a statistically significant improvement in Hep B-related knowledge for 2 of 3 questions (P=0.01 and 0.02, respectively) and overwhelmingly positive opinion regarding acceptability and ease of use (median rating of 5, on a 5-point Likert-type scale when users were asked if they would recommend the app to others).
Conclusions: We describe the process of development of a bilingual hepatitis B-specific app for Indigenous Australians, using a PAR framework. The approach was found to be successful with positive evaluations.

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KEYWORDS
culture; development; health literacy; hepatitis B; indigenous population; language; portable electronic apps

Introduction

Overview

Chronic hepatitis B (CHB) is endemic in the Indigenous communities of the Northern Territory (NT) of Australia with prevalence rates estimated to be between 3% and 14.2% [1-7], compared with 1% in Australia as a whole [8]. Despite the availability of effective, government subsidized treatments, only 25% of all individuals living with CHB in Australia are estimated to be receiving guideline-based care, with only 5% receiving antiviral therapy [9]. This disparity in rates of hepatitis B and low uptake of treatment is also seen in other Indigenous populations across the world [10,11].

The barriers to Indigenous Australians accessing care for CHB are multifactorial but mainly include the following: gaps in knowledge, low health literacy, ineffective cross-cultural communication, and logistical challenges in accessing the appropriate care. The challenges of effective cross-cultural communication in the context of remote Indigenous communities of the NT have been documented extensively [12-15] with miscommunication said to be pervasive and language translation felt to be only part of the problem. Although many health promotion or information resources exist for hepatitis B [16], the Australian National Hepatitis B strategy [17] and a number of other studies [18-22] specifically highlight the lack of culturally appropriate resources available to facilitate shared understandings of hepatitis B for Indigenous Australians.

We have previously described the results of a qualitative study exploring the knowledge, perceptions, and experiences of remote dwelling Indigenous adults and their health care providers relating to hepatitis B infection [23]. User preferences from this study included the preference for an electronic format with a predominance of pictures; sufficient medical details; human-like figures, not animal analogies; to be in Yolŋu Matha (local Indigenous language) as well as in English; to be interactive; and to use a culturally appropriate world view; building on existing knowledge to facilitate shared understandings. An unrelated scoping study [21] that examined ways to improve and support health education and language interpreting in Aboriginal communities in East Arnhem Land (NT) concluded that user-friendly, interactive, tactile, and aesthetically appropriate resources were most successful at facilitating communication. Involvement of the community in the development of resources in a “bottom-up fashion” was also highlighted as crucial to their eventual success. Multimedia resources were felt to be the most useful with a “touch pad body electronic device” being proposed as a tool to facilitate communication around health issues [24].

In Australia, 64.6% of the population owns a mobile phone [25] with the ability to download electronic apps. There has been an explosion in the development and use of apps with 46 billion downloads worldwide in 2012. This figure is estimated to exceed 200 billion/year by 2017 [26], at which time it is predicted that 50% of mobile phone users will have downloaded a health-related app. The potential to harness this technology as a means to improve health literacy, communication, and treatment uptake is yet to be fully realized. Only recently have published articles started to emerge with respect to the evidence base used to develop health-related apps and any subsequent evaluation of their utility and impact [27,28]. Further, only limited literature exists in this field and it raises concerns regarding the accuracy of information [29,30], alignment of advice with evidence-based guidelines [31], and lack of input from users/patients into product design and evaluation of effectiveness [32]. The data with regard to apps specifically targeted at Indigenous or culturally and linguistically diverse groups are even sparser. We are aware of the development of a number of mental health apps and a rheumatic heart disease app (Menzies School of Health Research, Darwin, Australia) specifically for Indigenous Australians but not of any published literature with respect to the development process of health apps for Indigenous populations.

Participatory Action Research Methodology

Participatory action research (PAR), a cyclical process of reflection, evaluation, and action, where respect for and involvement of the community in all aspects of the research process is an integral part of the methodology, is increasingly recognized as valuable in Indigenous health research [33-35]. There are a number of studies reporting successful outcomes of PAR projects in the context of developing health resources in Indigenous communities [36,37]. This paper aims to describe the process of the development and report the results of the initial evaluation of a culturally appropriate bilingual app about hepatitis B as part of a PAR project.

Methods

Overview

This project was undertaken in northern Australia between September 2012 and October 2014. It was based at the health clinic of a remote community in Arnhem Land, 521 km northeast of Darwin (the capital city of Australia’s NT). This community has a population of 2124 with an average age of 24 years, of which 88.98% (1890) are Indigenous Australians and only 9.5% (202) of the population speak English as their first language. On average, there are 4.2 people for each available bedroom and 83.19% (1767) of people live in households considered to
be overcrowded. The community has 3 general stores, a school, a library, a police station, and a community church.

Herein we report the results of the second phase of this PAR project. Phase 1 (previously reported in detail [23]) was a qualitative study consisting of semistructured interviews carried out with 3 groups of people, namely, key informants (health clinic staff, community health educators, and liver clinic staff from both urban and remote areas, including doctors and nurses from both Indigenous and nonindigenous groups), Indigenous people living with CHB, and Indigenous community members. Interviews explored the following: background of the individuals, their hepatitis B knowledge, their experience of health communication/education about hepatitis B, available resources, and their perspectives about potentially useful educational tools. The results of phase 1 of the study then formed the evidence base for the development of the bilingual app (phase 2). The original impetus for the project came from the staff of the community clinic. Their enthusiasm for the project led to the development of a collaborative research partnership between the Miwatj Health Aboriginal Corporation Community Clinic (an Aboriginal-controlled health service representing communities across East Arnhem Land), the Royal Darwin Hospital Liver Clinic, and the Menzies School of Health Research.

Ethical approval for the study was obtained from the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research as well as Miwatj Health Aboriginal Corporation. Figure 1 details the timelines for the development process.

**Figure 1.** Major stages and timelines for the development of the Hep B Story electronic app. Curved arrows represent time points where episodes of community consultation occurred.

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**Development of the Storyboard**

Using the specifications and concepts derived from phase 1 of the PAR process (Figure 2), the project team, which included JD, SB, JSD, LC, SS, and VJ, developed an initial storyboard detailing important ideas, images, and themes to be included in the education tool (Figure 3).

This was then developed by Dreamedia, a Darwin-based graphic design and software company, into an initial screen-by-screen storyboard. Subsequently detailed screen-by-screen scripts were developed by the project team, initially in simple English. These preliminary versions of the app were presented back to the community to facilitate and enable evaluation by clinic staff and liver clinic patients. Appropriate modifications were made according to community input. There were in excess of 20 iterations of the storyboard over the period from February 2013 to July 2014.
Figure 2. Main concepts and ideas taken from phase 1 [23] of the participatory action research (PAR) process to provide the initial evidence base for the culturally appropriate hepatitis B electronic app. The PAR cycle shows the principle stages involved in a PAR project.

- Local language: The necessity for any educational tool to be in a local Indigenous language "Yolgu matha".
- Visual and interactive: Culturally appropriate and respectful images using real people rather than animal analogies. There was an emphasis on interactive pictures and text.
- To tell the full "true story": People wanted enough detail to be provided but with appropriate contextual translation, rather than complex concepts to be made so simple that meaning was lost.
- Accessible: To be available to as many people as possible so easy to use, in an electronic format so available through any smart phone, tablet, computer and to have audio as well as text.
- Cultural respect: Consideration for culturally appropriate gender representation and a separate women’s section to discuss issues around mother to child transmission.

Figure 3. Screen-by-screen examples of the development process showing first and last versions.
Translation Process

The specific language that the app is translated into is “Djambarrpuyngu,” a member of the “Yolŋu Matha” group of Australian Indigenous languages used by Yolŋu people in Northeast Arnhem Land. The term “Yolŋu Matha” will be used in this paper to refer to the language from this point forward as this is the term used in the app in line with community wishes.

Two experienced interpreters from the local community were identified, one allocated to do the forward translation (ie, English to Yolŋu Matha) and one to undertake the backtranslation (ie, Yolŋu Matha back to English, so as to check the accuracy of the translation) according to the World Health Organization guidelines [38]. Both interpreters had previously translated health education materials and participated in a pretranslation hepatitis B education session to enable familiarization with the material. Conceptual equivalence (aiming for shared understanding of a word or phrase rather than a word-for-word literal translation) was discussed and encouraged wherever appropriate. Backtranslation was undertaken independently by the second of the interpreters, then the English checked, and clarified by JD (English-speaking doctor with experience in a cross-cultural environment) and SB (bilingual Aboriginal Health Worker), again with emphasis on conceptual and cultural equivalence rather than linguistic equivalence. The final Yolŋu Matha translation was reviewed again by SB. Voice-overs were recorded at Dreamedia studios in both English and Yolŋu Matha.

Prelaunch Community Review

Functional prototype versions of the electronic app were produced on 4 occasions by Dreamedia and presented to the community for review. Discussion and input from clinic staff (both Indigenous and nonindigenous) and Indigenous liver clinic patients were sought on each occasion. Changes were then incorporated into the next version of the app and the process was repeated until unanimous approval was achieved.

Launch and Initial Community Evaluation

In July 2014, a launch event was organized in the community, which involved presentation of the app by JD and SB, and an invitation to take part in the initial evaluation process. The evaluation questionnaires had sections to be completed before and after exploring the app. People were guided through the questionnaire process in real time by a bilingual research assistant who translated the questions and answers into Yolŋu Matha where needed or requested.

Viral Hepatitis Conference Launch and Initial Evaluation

The inaugural Indigenous Peoples’ Conference on Viral Hepatitis in Alice Springs, NT (September 2014) was chosen as an appropriate place to launch the app to the wider sector. The app was presented as part of an exhibit where individuals could explore the app in their own time. We invited all conference delegates to help evaluate the app using the aforementioned questionnaire.

Evaluation Questionnaire Analysis

Data were entered into Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) and analyzed using Stata version 13 (StataCorp, College Station, TX, USA). Overall preapp and postapp knowledge scores were created by calculating a total score out of 6 (based on the number of correct responses to Q1 and Q4) and presented as percentages. Quantitative continuous variables were presented as mean ± standard deviation for normally distributed parameters and median ± interquartile range (IQR) for non-normally distributed parameters. Bivariate analyses were performed using Student t test, paired Student t test for preapp and postapp knowledge comparisons, Fisher exact test for comparisons with any cell value less than 5, and Mann-Whitney test for nonparametric data.

Likert-type items (Q2 and Q3) were treated as ordinal data, presented as median values with frequencies, and associations between groups were calculated using Kendall Tau-b [39]. For each Likert type, item 1 equates to “strongly agree,” 2 “agree,” 3 “neutral,” 4 “disagree,” and 5 “strongly disagree.” For positive statements, allocated scores were the inverse of the assigned number to enable higher scores to reflect more positive responses.

Results

Main Findings

The app we produced is called “Hep B Story” and is available as a free download for Apple devices through the Apple App Store, for Android devices through the Google Play Store, and as a Web-based app through the Menzies School of Health Research website. The app’s title screen allows the user to choose the language as either English or Yolŋu Matha and they can navigate from the beginning to the end through the entire app (except for the “women’s business” section), or choose to go to the “chapter select” screen to skip to a specific section or enter the women’s business section. There are 7 “chapters” as detailed in Figure 4, some of which contain animations. The treatment section includes a game, which involves dragging tablets into a man’s mouth each day. If you do not get him to take the medicine consistently enough, his hepatitis B virus becomes resistant to the tablets and his liver becomes diseased. Each screen has an audio button, which will play the voice-over in English or Yolŋu Matha and the text is also displayed on the screen in the preferred language.
Development of the Storyboard

As with the text, the images for each screen were discussed in detail over several iterations. Particular emphasis was placed on getting an appropriate balance of gender representation throughout the app, as well as a desire for the individual on the front screen to be gender neutral. Initially, the title screen figure had brown skin, but after community review it was felt that this may imply that all people with hepatitis B have brown skin, and therefore, the color was changed to blue to be ethnically neutral.

The cultural appropriateness of an image to represent sexual transmission was the subject of much discussion. This mode of transmission was, however, downplayed at the community’s request for reasons of stigma and also as the main route of transmission in this population is thought to be mother-to-child transmission during parturition.

The screen representing liver function initially had visual representations of various liver functions (eg, fruit to represent its role in helping to process food). On consultation with the community, this was felt to be a culturally inappropriate use of lateral thinking and was described as a decoy and confusing. People preferred to remove all the pictures and just have the words over the liver images as in the final version (Figure 3).

A separate women’s business section was a recurrent request. It was important to community members that this was not something that you would “stumble upon” while looking through the app and it had to be separate, warranting an active decision to visit this section. “Women’s business” is the commonly used local term for health and other matters specific to women, such as pregnancy.

Translation Process

The script was translated taking into account context and cultural appropriateness. The Yolŋu Matha version was much longer than the English version (10 pages of text as opposed to 5). There were a number of reasons for this: Yolŋu Matha is a more verbose storytelling language; there is not a direct translation for many terms, for example, “Hep B” in the backtranslation was “those invisible germs that are the sickness in your blood called Hep B.” For clarity, this phrase was then used on each occasion Hep B was mentioned, and therefore increased the number of words. The text was translated meticulously by a senior male Yolŋu elderly person with great attention to detail, contextualization of the text, and cultural appropriateness. For example, the sentence talking about how one of the liver’s functions is to produce clotting factors in the translated version says “it is like a factory that makes good oil, it will help the blood to clot and fight sickness.” A senior female elderly person backtranslated this again with the same attention to detail. Issues raised following the backtranslation were literal interpretation of concepts, the difficulty when there are many words for one thing, and the importance of choosing the most appropriate one for the specific context needed.

Prelaunch Community Review

One of the key requests from phase 1 of this study was for a visual tool; however, an app prototype without the full text appearing alongside the audio was not well received. The community consensus was to have the full text there so that people could either listen or read depending on their preference. A request was made to add kava drinking (a drink made from the extract of the root Piper methysticum with sedative and anesthetic properties, which is commonly used as a recreational drug in parts of Arnhem Land) to the screen about the dangers of the combination of alcohol and hepatitis B for the liver. An image of a family with several members infected was also suggested to be included on the screen talking about epidemiology.
Launch and Initial Community Evaluation

The launch in the community was met with excitement and pride at seeing an electronic app in Yolŋu Matha. The evaluation questionnaire was completed by 16 people, median age 34 years (IQR 30-59), with 12 (75%) being women. Results are presented in Tables 1 and 2.

Viral Hepatitis Conference Launch and Initial Evaluation

The launch and 3-day exhibit at the Viral Hepatitis Conference in Alice Springs, NT (September 2014) were also met with a positive response. The questionnaire was completed by 56 people, median age 45 years (IQR 36-54), with 50 (89%) being women. Results are presented in Tables 1 and 2.

Table 1. Demographics of participants and results of the opinion-based component of the evaluation questionnaire.

<table>
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<tr>
<th>Demographics of groups</th>
<th>Community launch group (N=16)</th>
<th>Conference delegate group (N=56)</th>
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</thead>
<tbody>
<tr>
<td>Age in years median (interquartile range)</td>
<td>34 (30-59)</td>
<td>45 (36-54)</td>
<td>.34</td>
</tr>
<tr>
<td>Indigenous status (%)</td>
<td>94 (15/16)</td>
<td>21 (12/56)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>75 (12/16)</td>
<td>89 (50/56)</td>
<td>.20</td>
</tr>
<tr>
<td>Self-rated hepatitis B knowledge (% who strongly agree or agree)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never heard of hepatitis B</td>
<td>50 (8/16)</td>
<td>4 (2/56)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>I knew a lot about hepatitis B</td>
<td>31 (5/16)</td>
<td>66 (37/56)</td>
<td>.02</td>
</tr>
<tr>
<td>Postapp opinion using the 5-point Likert scale Median score, % giving that answer (n/N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I found the app easy to use (for Q3a)</td>
<td>5, 67 (10/15)</td>
<td>5, 80 (44/55)</td>
<td>.29</td>
</tr>
<tr>
<td>Easy to understand (for Q3b)</td>
<td>5, 67 (10/15)</td>
<td>5, 75 (41/55)</td>
<td>.43</td>
</tr>
<tr>
<td>Contained enough information for my needs (for Q3c)</td>
<td>5, 47 (7/15)</td>
<td>5, 67 (37/55)</td>
<td>.42</td>
</tr>
<tr>
<td>Contained too much information for my needs (for Q3d)</td>
<td>2, 50 (6/12)</td>
<td>4, 17 (9/54)</td>
<td>.005</td>
</tr>
<tr>
<td>I would recommend the app to my family and friends (for Q3f)</td>
<td>5, 69 (9/13)</td>
<td>5, 67 (36/54)</td>
<td>.72</td>
</tr>
<tr>
<td>Use the app again myself (for Q3g)</td>
<td>5, 64 (9/14)</td>
<td>5, 55 (29/53)</td>
<td>.56</td>
</tr>
</tbody>
</table>

<sup>a</sup>P values are comparisons between the community launch group and the conference delegate group.

<sup>b</sup>“Self-rated hepatitis B knowledge” and “Postapp opinion” constituted the results of opinion-based questions.
Table 2. Results of the knowledge-based component of the evaluation questionnaire.

<table>
<thead>
<tr>
<th>Knowledge-based questions</th>
<th>Community launch group (n=16)</th>
<th></th>
<th>Conference delegate group (n=56)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preapp</td>
<td>Postapp</td>
<td>$P$ value$^b$</td>
<td>Preapp</td>
</tr>
<tr>
<td>Can you name 3 ways by which hepatitis B can be passed from one person to another?</td>
<td>33 (16-50)</td>
<td>58 (39-77)</td>
<td>.01</td>
<td>100 (100-100)</td>
</tr>
<tr>
<td>If you have hepatitis B what is the best way to tell if the virus is causing damage to your liver?</td>
<td>25 (1-49)</td>
<td>38 (11-64)</td>
<td>.16</td>
<td>92 (85-99)</td>
</tr>
<tr>
<td>If you have hepatitis B what can you do to help your liver to stay healthy (name 2 things)?</td>
<td>47 (29-65)</td>
<td>50 (28-72)</td>
<td>.58</td>
<td>84 (76-93)</td>
</tr>
</tbody>
</table>

$^a$Values are presented as mean score % (95% CI).

$^bP$ value for paired t test comparing preapp versus postapp knowledge scores.

Evaluation Questionnaire Results

Overall, 72 individuals completed the evaluation questionnaire of whom 62 (86%) were women and 27 (38%) were Indigenous Australians, with a median age of 44 years (IQR 34-54). There was a good representation of individuals from most parts of Australia with only Tasmania and Australian Capital Territory not being represented. With regard to preapp and postapp knowledge assessment, there was a statistically significant increase in the first knowledge-based question in the community launch group ($P=.01$) and in the final one in the conference delegate group ($P=.02$, Table 2).

Participants’ opinions of the app after use were generally positive, with 5 of the 6 questions on this achieving a median rating of 5 on the 5-point Likert-type scale. The free text comments were overwhelmingly positive with multiple references to ease of use, culturally appropriate graphics, and the importance of being able to both read and listen in Yolŋu Matha. Multiple requests were made for the app to be translated into other languages. A recurrent criticism was made referencing the lack of inclusivity with regard to gender and sexually diverse communities by the wider key informant group.

Discussion

Principal Findings

We describe in detail the process of development of the “Hep B Story” app, a culturally appropriate educational resource about CHB, through a community partnership using a PAR framework. “Hep B Story” is the first app to be produced in Djambarrpuynyu, a member of the Yolŋu Matha group of Australian Indigenous languages spoken widely in the North East Arnhem Land in Australia’s NT. The continuous iterative cycle of consultation, evaluation, and adaptation has led to the production of a tool that the community was proud of and excited about. Initial evaluations from both the community and a wider group of key stakeholders have been overwhelmingly positive.

The production of apps and literature concerning their development are rapidly increasing; however, for the vast majority of health-related apps, there is currently no standardized development or regulatory process for assessment of their quality or effectiveness [27]. There are few published descriptions of the process of health app development and it is often difficult to ascertain, when considering using or recommending an app, who exactly has produced the content and if end users have been involved in the process. Recent reviews of apps for specific disease areas have highlighted concerns regarding factual accuracy, lack of end user involvement, and the effectiveness of apps to add value to standard health care practice [28]. A Cochrane review [31] looking specifically at apps facilitating the self-management of asthma (>100 apps available) concluded that the current evidence base (only 2 studies included) is not sufficient to advise clinical practitioners, policy makers, or the general public regarding app effectiveness. A number of reviews on dermatology apps directed toward skin cancer screening have reported wide ranges of sensitivity and specificity for the diagnosis of melanoma [30,40], with one reporting that 88.2% of biopsy-proven melanoma was classified by the app as “medium risk” and individuals were thus advised to “monitor only” [41]. A trial protocol has been published for an evaluation of the effectiveness of a suicide-prevention app in Indigenous Australian youth (currently recruiting); however, no details are currently available as to how the app was developed [42]. Recently, regulations have been introduced by both the United States Food and Drug Administration and the European Union for “medical device” apps (those intended as an accessory to a regulated medical device or those that transform a mobile platform into a regulated medical device, such as an app intended to diagnose cardiac arrhythmias). These regulations do not currently apply to health information or education apps [43]. A number of app clearinghouse websites are now available...
with varying levels of review and accreditation of health-related apps [27].

In the context of Indigenous health, community partnerships and the use of PAR methodologies have been shown to help break down barriers to communication [34,36], and understandably people respond to information in their own language more positively than that in a second language. Our experience highlights the importance of meticulous translation, backtranslation, and the attention to detail needed to ensure that the messages you are giving are both linguistically and contextually correct and will be understood in the way intended. There is great potential for harm if this process is not robust. This was highlighted in phase 1 of the PAR process when during the process of the interviews it appeared that there was a lack of shared understanding of the word “silent” between nonindigenous health workers and Indigenous patients in the context of hepatitis B. The health workers used this to describe the asymptomatic nature of hepatitis B noted at times, whereas the patients understood this to mean that the sickness is brought about by sorcery [23].

We also highlight the great value that can be gained from repeated reviews of and conversations about a product throughout the development process, particularly having a real prototype version of the app to comment on. This allowed multiple changes and additions to the visual appearance and aesthetics of the app such as the color of the person and the images on the liver function screen, which would have been difficult to tease out from verbal-only communication. It also provides multiple opportunities to open up communication facilitating collective agreement making and allowing “bottom-up” changes to occur, which have been highlighted as crucial to change in the context of remote Indigenous communities [24].

Initial evaluations of the Hep B Story app were overwhelmingly positive, with all but 1 question (question 3d) assessing user’s opinions achieving a median rating of 5 on a 5-point Likert-type scale. Question 3d was a negative statement compared with all the others, which were positive and it may be that this was confusing or difficult to translate as the lowest score for this question came from the community evaluation. This needs further clarification and exploration before the design of any subsequent evaluation. It will also be important to consider why the numbers of people completing the questionnaire in the community launch group were much lower than the conference delegate group. It may be that due to different cultural and communication protocols, as a questionnaire-based evaluation is not the optimal methodology to use in this setting. There was a significant increase in knowledge after use of the app for questions 1a in the community launch group (P=0.01) and 1c in the conference delegate group (P=0.02). Although the mean score increased from 25% to 38% in the community launch group for knowledge question 1b, this was not statistically significant (P=0.16), and it is possible that this would reach significance with a larger sample size. It is also important to acknowledge the persistence of low levels of knowledge in the community launch group even after exploring the app and pertinent to critically examine whether this is likely to be a problem with the app itself or the way the questions were asked and the methodology used in this initial evaluation. Culturally appropriate measurement of the impact of interventions aimed at improving health knowledge is problematic, with a tendency to attempt to quantify “knowledge” without having any validated tools to achieve this in an Indigenous setting. There are a number of studies in progress in an Australian Indigenous setting using adapted versions of validated health literacy measurement tools such as the Health Literacy Management Scale and Health Literacy Questionnaire, which will hopefully provide much needed information in this area [44-46]. Christie and Verran [24] have suggested that, in the context of East Arnhem Land, low health literacy is not so much a knowledge problem but a need for allowing shared understandings to develop, and our work from the first phase of this PAR project would generally concur with this [23]. It is, therefore, worthwhile considering the cultural appropriateness of any kind of “knowledge measurement” within our further evaluation. It is important that a larger more formal evaluation of this app does take place to confirm and add more detail regarding the impact on knowledge and ultimately behavior change; however, it may be that an interview-based evaluation methodology is more appropriate. Because of the nature of the PAR process, it would be difficult to objectively evaluate this app’s effectiveness and acceptability in a community that has already been so involved in its development. We are therefore planning a separate evaluation in a different location where Yolŋu Matha is spoken and hepatitis B is common.

Even in a community where there has been significant engagement, involvement, and interest in the hepatitis B project, levels of knowledge around CHB were low with 50% (8/16) of people having never heard of it. This is consistent with the work done in the Torres Strait region of Australia [19,22], which reported a lack of awareness and/or knowledge of CHB and the measures to reduce its health impact both at the patient and at the health care provider level. The free text comments from the conference delegate group with respect to gender and sexually diverse communities highlighted the conflicts that can arise in PAR projects. Obtaining the right balance between cultural appropriateness and community wishes versus inclusivity of potentially underrepresented groups in this context can be challenging.

Limitations to extensive engagement and involvement of end users in the process of app development include the length of time needed to undertake this process robustly, particularly in communities where English is not the first language, and worldviews of health are very different. This is especially relevant to digital technologies where the pace of change is so fast. As an intended consequence of the methods used to produce the app, it is very specifically tailored to the culture and needs of Yolŋu people; therefore, its translatability to other groups is always going to require further consultation and adaptation. Although this process can be streamlined when the framework and technical coding for the app are available, it is still a significant undertaking. Another obvious issue is that not everyone has access to a mobile phone or tablet device. As such, we felt it crucial to also have the app available through an
Internet site that can be accessed from nonportable computers such as those in health care facilities.

The potential for adaptation to other languages is important in the context of hepatitis B, which disproportionately affects Indigenous people both in Australia and across the world. There is also great potential to personalize and incorporate clinical tools into the app such as tracking of blood test results, triggers for follow-up, medication reminders, and even self-assessment tools. One example would be adapting the “number connection test,” which is a widely used method for detecting the reduced spatial awareness and coordination present in hepatic encephalopathy. This currently consists of a timed test connecting numbered dots on a sheet of paper, which could be adapted into a game-style version and included in the app. The section about alcohol and kava could incorporate harm-reduction strategies, monitoring of consumption, and abstinence encouragement tools.

Conclusions

Health-related apps have a huge potential to contribute and impact positively on health care; however, there is also substantial risk of harm in the absence of an evidence base to guide standards, regulation, and development. This is particularly true for populations where health beliefs and worldview are different and English is not the first language. These are the very populations that are most affected by CHB.

We described using a PAR framework with both end users and key informants providing their inputs into the content and development of a hepatitis B-specific app. Although this process was time consuming, the approach was very successful, with a majority of participants providing positive responses. The long-term effectiveness with respect to improving patient’s health literacy leading to behavior change and increased treatment uptake will be evaluated over time.

Acknowledgments

We thank the translation and Yolŋu Matha voice-over team, Maratja Dhamarrandji and Dorothy Gapany; the English voice-over team, Tristan Etherington and Christine Mills; the design and development team, Chris Torralba, Krupa Patel, Aoife Dowling, and Alice Plate as well as all study participants and local health clinic staff who all so generously gave their thoughts and time to contribute to this study. This study was also supported in part by a National Health and Medical Research Council project grant (Grant No GNT 1060811).

Conflicts of Interest

JD and JSD have received an unrestricted educational grant from Gilead Sciences to finance this project with the exception of their time, which is supported by the National Health and Medical Research Council (PhD scholarship to JD, early career fellowship to JSD) and Sidney Myer funds (top-up scholarship to JD).

References


Abbreviations

CHB: chronic hepatitis B
IQR: interquartile range
NT: Northern Territory
PAR: participatory action research

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doi:10.2196/resprot.4216
PMID:
11.3 Implications and questions arising from this paper

The initial evaluation of this product although generally positive highlighted that a questionnaire-based evaluation may be not the most culturally appropriate way of evaluating this product. It was always our intention to carry out a formal evaluation of this product in a different community that hadn’t been integrally involved in its development but where Yolŋu matha is still understood. It is important that we think carefully about the most appropriate methodology for this evaluation in light of the results of this paper.

If the formal evaluation is positive then it raises the need to adapt both visually and language wise this product to enable as many people as possible to have access to culturally appropriate hepatitis B specific information in their own first language as possible.
Section E – Conclusions and future directions
Chapter 12 - Conclusions and future directions
12.1 Introduction

In this chapter I will review in turn each of the key hypotheses that have been addressed in this thesis. This work has established some important new information about hepatitis B which is crucial to and already feeding into policy in the NT aiming to improve care for people living with chronic HBV infection. It has, however, also raised many more questions to be answered about this intriguing virus. I have presented the true story as we understand it to date but there are several more chapters yet to be written before the story of the Australian antigen is complete.

12.2 Conclusions

12.2.1 What is the prevalence of hepatitis B in the Northern Territory?

It has been estimated by both small community-based studies, larger studies based on antenatal women and a nationwide mapping project that the NT has a high prevalence of chronic HBV infection. We have confirmed this showing an overall prevalence of 3.4%, increasing to 6.1% in Indigenous Australians and falling to 1.6% in non-Indigenous people. These figures are based on a dataset including 35,633 individuals who had blood for hepatitis B markers taken between 2007 and 2011 as part of their routine clinical care. There is a significant gender difference in prevalence, with men having an odds ratio of having chronic HBV infection of 1.53 compared to women. These figures are crucial to planning an effective and sustainable response to the National Hepatitis B Strategy.

12.2.2 Has the prevalence of hepatitis B fallen in those born after the implementation of universal HBV vaccine at birth in 1990?

HBsAg prevalence has fallen significantly over time particularly in Indigenous Australians. Prevalence peaked at just below 15% for those born in the 1940s and 1950s to 1.7% for those born post-1990, which is very encouraging. However what is intriguing and not fully explained is the fact that prevalence was falling steadily in Indigenous Australians with a trend of 0.23%
reduction per year well before the hepatitis B vaccine had even been formulated. This requires further clarification and exploration.

12.2.3 What are the genotypes of hepatitis B circulating in the Northern Territory?
Although the Australia antigen now known as HBsAg was first discovered in the blood of an Australian Aboriginal man, until the CHARM study little was known about the genotypes of HBV in Indigenous Australians. We have identified a unique and so far universal sub-genotype of HBV C4 in the Indigenous population of the NT. Of the 128 people recruited to date, 84 had sufficient virus to allow genotyping and all were sub-genotype C4. This finding in itself was unexpected and has raised many further questions, some of which are answered below; the remainder are part of ongoing or planned work.

12.2.4 What do we know about the molecular virology of hepatitis B sub-genotype C4
In conjunction with VIDRL we have extended the original genotyping to full genome sequencing where possible, recombination analysis and phylogenetic studies. These analyses have established that C4 is a true sub-genotype with less than 8% but greater than 4% difference in its DNA structure to other HBV viruses. It is a recombinant virus including a HBV C backbone with the region of the ‘a determinant’ of C4 being identical to that of genotype J virus between amino acid positions 57 and 176. One consequence of this recombination is that the serotype of C4 HBV is ayw3. This is different to all other C genotypes and the current HBV vaccine, which is based on genotype A HBV and is serotype adw2. This vaccine mismatch could potentially reduce the efficacy of HBV vaccination in the setting of C4 HBV and requires further exploration.

The phylogenetic analysis using the full genome sequences of C4 HBV in relation to the geography of where the individual infected with that virus was born and spent the first five years of their life is fascinating. Along with the genotype J recombination, there is a very high level of clustering into distinct geographical regions across the NT. This suggests an introduction of this
sub-genotype into Australia via Asia with the arrival of the first humans, and subsequently sustained transmission at a community level, which again requires further exploration.

12.2.5 What do we know about the natural history of C4 chronic hepatitis B

In the genome of the C4 virus we have documented numerous molecular markers which in the literature are recognised as being associated with increased risk of progression to cirrhosis and HCC. The analysis of the first four years of our now established CHARM cohort study is consistent with this, showing markers of cirrhosis in 19% of patients in the study with a relatively young median age of 38 years. No HCC has been documented as yet in this group of 128 individuals which is encouraging, but may mostly be a reflection of the short duration of follow up to date. The CHARM cohort study also suggests that in the logistically challenging setting of remote NT there is room for improvement in adhering to recommended follow-up guidelines. These data are being fed into local and Territory wide service development plans. It is however encouraging that treatment is being received by 18% of this cohort which is above the proportion recommended in the Second National Hepatitis B Strategy.

12.2.6 What are the knowledge, perceptions and experiences of Indigenous people in the remote Northern Territory?

It is difficult for a community to advocate for better care for a chronic disease if many people are not aware of its existence or the consequences of chronic infection. Our data show levels of biomedical knowledge about hepatitis B in one remote community to be low and perceptions around hepatitis B and communication with medical personnel to be negative. However when we were able to delve deeper using people’s first language to communicate, accurate concepts grounded in culture such as “only your blood can tell the true story” emerged. The importance of enhancing cross-cultural communication, predominantly by using effective interpreters and health information contextually translated into people’s first language, cannot be highlighted strongly enough.
Paasche-Orlow & Wolf’s model of the pathways linking health literacy and health outcomes suggests that the provider-patient interaction is a key contributing factor to health literacy. Our experience in the setting of remote Indigenous Australia where English is not the first language, and culture and worldview are very different, is that this interaction is a pre-requisite to allowing access and utilisation of care and self-care to occur. It is likely that this will also translate to other settings when people from linguistically and culturally diverse backgrounds are receiving care for chronic HBV infection and the language of health care is not their own first language.

12.2.7 What does a culturally appropriate educational tool about hepatitis B for Indigenous people look like?

It is electronic and interactive with a preference for images. It must tell the true story and it must be in local language – Yolŋu matha. Please see appendices for screen shots or download for yourself from the Apple app store, the Google play app store or use online via the Menzies website http://www.menzies.edu.au/hepbstory/.

Initial evaluations have been overwhelmingly positive and revealed a significant improvement in Hep B-related knowledge. However a formal, culturally appropriate evaluation needs to be carried out to truly establish the impact of this resource on improving hep B-specific health literacy.

12.3 Future directions

There are many more questions and important follow on studies that need to be carried out to build on the work described in this thesis. Many recommendations have been made, I am acutely aware that many more could be reasonably made based on the data presented, however to prevent this list being overwhelming I have summarised the most urgent of these below:

1) HBV sub-genotype C4 has molecular markers associated with increased risk of progression to cirrhosis and hepatocellular carcinoma – is this actually seen in infected people?
a) Chapter 9 describing the early CHARM cohort and retrospective review of hepatocellular carcinoma rates suggest it does; and

b) Further prospective work is needed to confirm this including long-term follow up and continued recruitment into the CHARM cohort, expanding the study to include routine Fibroscan and setting up a structured surveillance programme for HCC.

2) If HBV C4 does lead to accelerated fibrosis/cirrhosis and higher rates of HCC should this influence clinical management?

a) Would there be any value in having a lower threshold for commencing antiviral treatment (e.g. during the immune tolerance phase); and

b) Do we need a multi-centre prospective randomised control trial of individualised genotype specific HBV treatment?

3) HBV sub-genotype C4 has a serotype mismatch with the current vaccine. Does this translate into decreased vaccine efficacy?

a) More detailed virological studies are ongoing in conjunction with VIDRL including mapping the anti-HBs neutralisation domain of HBV C4 and in vitro infection studies; and

b) Prospective comprehensive sero-surveys which include a better representation of people born since 1990, who have received HBV vaccination as part of the universal childhood vaccination program are needed.

i) We have just received ethical approval to carry out a community-wide modified sero-survey in one specific remote community in the NT. This will include children down to the age of one year and adults in all age groups, including the over 60s group, those who are under-represented in the sero-epidemiology presented in Chapter 5. It will also include a comparison of the sensitivity and specificity of a rapid point of care and saliva-based diagnostic tests in the remote community setting; and

ii) We are also planning a prospective study called BAMBI (Babies and mothers with hepatitis B infection). Using HBV immunoglobulin registers we will identify 200
women with chronic HBV infection who have given birth since 1990 and approach them and their children to be tested for HBV serology and HBV viral loads as well as clinical information and vaccination histories. This will allow us to establish rates of vaccine failure in this group.

4) If decreased vaccine efficacy is confirmed - It will then be important to ask the question - is the current NT vaccination schedule and the currently used genotype A-based vaccine optimal in the setting of C4?
   a) What are the clinical consequences?
   b) Should a different vaccine schedule or vaccine product be used?

5) HBV sub-genotype C4 is the exclusive genotype in all Indigenous people we have tested in the NT. How far has it spread geographically?
   a) We plan to expand the CHARM study to include the northern area of Western Australia and Queensland to try to establish the answer to this question; and
   b) What about Timor Leste, Indonesia and Malaysia, our closest northern neighbours?

6) The ‘Hep B Story’ app appears to have a positive impact on hepatitis B-specific health literacy.
   a) A culturally appropriate formal evaluation needs to be undertaken to support the initial evaluation findings presented in Chapter 11; and
   b) If favourable results are established, attention focused on adapting it in both content and language to be available to as wide an audience as possible.
      i) We have already had interest from those working with speakers of other central and northern Australian languages such as Warlpiri and Kriol; and
      ii) We have also had interest from speakers of several non-Indigenous languages
   c) If favourable the concepts and general findings from this work should be presented to a wider audience and used to inform the development of resources for a range of disorders, not just hepatitis B.
7) The logistics of liver cancer screening in the NT contest are challenging – is there another way to do this in a remote setting?

a) In collaboration with Imperial College London we are setting up a pilot study in the NT to explore the possibility of using a novel urine metabolite screening test as an alternative to ultrasound and alpha fetoprotein.

12.4 Summary statement

The prevalence of hepatitis B in the NT is high, particularly in the Indigenous population, but thankfully HBV prevalence is falling over time. Biomedical knowledge about chronic HBV infection is low but the potential to build shared understandings with culturally appropriate educational resources in people’s first language is now an exciting reality. The Indigenous population has a unique sub-genotype of HBV C4, a recombinant virus which appears to have an aggressive phenotype. There is a serological mismatch between C4 HBV and the HBV vaccine serotype which raises a possible virological explanation for possible decreased efficacy of the current vaccine. We still have a great deal to learn about HBV C4 but the work presented in this thesis suggests we need to be moving towards clinical and public health management which is tailored to the genotype of the HBV virus as well as to the individual affected.
Nhä nhunu dhu malathun yalalañumirriyndja

Appendix 1 - Sensitivity analyses from Chapter 5
Appendix 1A

<table>
<thead>
<tr>
<th>NTGPS</th>
<th>Westerns</th>
<th>SAPathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• separate text file in notebook for each year and each result</td>
<td>• one notebook text file</td>
<td>• 2 excel spreadsheets</td>
</tr>
<tr>
<td>• 1998-2012</td>
<td>• 1991-2012</td>
<td>both include unique Patient ID number</td>
</tr>
<tr>
<td>• Total 75 files</td>
<td>• 226,336 lines of data</td>
<td>• 1=Patient data 18,112 lines of data</td>
</tr>
<tr>
<td>• Data order:</td>
<td>• Data order: HBsAg, HBsAb, HBeAg, HBeAb, HBVDNA, Patient</td>
<td>• Data order: Patient ID, Surname,</td>
</tr>
<tr>
<td>name,surname,</td>
<td>surname, Patient given name, Patient</td>
<td>forename, dob, sex, Address2,</td>
</tr>
<tr>
<td>HRN#, labnumber,</td>
<td>birthdate, HRN, WDP lab number, Date</td>
<td>Address1, postcode</td>
</tr>
<tr>
<td>dob, collection</td>
<td>of Service, Patient address, Patient city,</td>
<td>• 2=results 28,062 lines of data</td>
</tr>
<tr>
<td>date, result,</td>
<td>Patient state, Poscode, Patient sex</td>
<td>• Data order: request number, collection</td>
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<tr>
<td>sex, doctor, patient location</td>
<td></td>
<td>date, patient ID, sag, cab, sab, eag, eab, dna</td>
</tr>
<tr>
<td>• 92,589 lines of data once all files amalgamated in STATA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Three separate STATA data files created (Figure 5.1)

Appended together to create one dataset – 346,987 lines of data

Variables harmonised

Master data set including all information -- processed as per figure 5.1
## Appendix 1B

<table>
<thead>
<tr>
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<td>2</td>
<td>Surname, name, dob</td>
<td>156318</td>
</tr>
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<td>3</td>
<td>Surname, name, dob (surname and name-reverse)</td>
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<td>Surname, name (without middle name), dob</td>
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<tr>
<td>5</td>
<td>Surname, name (without middle name), dob (reverse)</td>
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<td>6</td>
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<td>First 2 letters in surname and first 2 letters in name, dob, (reverse)</td>
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<td>Surname, name, dob±2 days</td>
<td>1366</td>
</tr>
<tr>
<td>9</td>
<td>Surname, name, dob±2 days, (reverse)</td>
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</tr>
<tr>
<td>10</td>
<td>Surname, name, dob (1 letter different in dob)</td>
<td>3435</td>
</tr>
<tr>
<td>11</td>
<td>Surname, DOB, Address</td>
<td>5067</td>
</tr>
</tbody>
</table>

### Notes:

1. Reverse in the above table refers to the surname and name in reverse order.
2. 5% data were manually check Level 1-5, 8,10-11, small % wrong hospital record numbers corrected.
3. 50% data for level 11 manually checked.
Appendix 1C

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Indigenous</th>
<th>Non-Indigenous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age in years at sample date (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>31.8 (24.6-41.9)</td>
<td>30.1 (21.5-41.6)</td>
<td>32.5 (26.1-42.2)</td>
</tr>
<tr>
<td>2007-2011</td>
<td>32.4 (24.5-43.7)</td>
<td>30.8 (21.5-43.3)</td>
<td>33.2 (26.3-44.0)</td>
</tr>
<tr>
<td>2007-2011 CHB only</td>
<td>32.4 (24.5-43.6)</td>
<td>30.6 (21.5-43.0)</td>
<td>33.2 (26.3-44.0)</td>
</tr>
<tr>
<td><strong>Sex Female % (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>58.3 (58.0-58.7)</td>
<td>55.4 (54.9-56.0)</td>
<td>59.9 (59.5-60.3)</td>
</tr>
<tr>
<td>2007-2011</td>
<td>57.8 (57.3-58.3)</td>
<td>53.7 (52.8-54.5)</td>
<td>60.5 (59.9-61.2)</td>
</tr>
<tr>
<td>2007-2011 CHB only</td>
<td>58.0 (57.5-58.5)</td>
<td>54.0 (53.1-54.8)</td>
<td>60.6 (59.9-61.3)</td>
</tr>
<tr>
<td><strong>HBsAg positive % (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>3.38 (3.25-3.52)</td>
<td>6.47 (6.17-6.78)</td>
<td>1.58 (1.46-1.70)</td>
</tr>
<tr>
<td>2007-2011</td>
<td>3.4 (3.19-3.61)</td>
<td>6.08 (5.65-6.53)</td>
<td>1.56 (1.38-1.76)</td>
</tr>
<tr>
<td>2007-2011 CHB only</td>
<td>2.22 (2.06-2.40)</td>
<td>4.43 (4.25-5.05)</td>
<td>0.72 (0.60-0.86)</td>
</tr>
<tr>
<td><strong>Anti-HBs &gt;10IU/ml % (95%CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>61.4 (60.1-61.8)</td>
<td>62.5 (61.9-63.2)</td>
<td>60.3 (59.7-61.0)</td>
</tr>
<tr>
<td>2007-2011</td>
<td>58.0 (57.3-58.7)</td>
<td>60.7 (59.7-61.6)</td>
<td>55.4 (54.4-56.3)</td>
</tr>
<tr>
<td>2007-2011 CHB only</td>
<td>58.5 (57.8-59.1)</td>
<td>61.4 (60.4-62.3)</td>
<td>55.8 (54.8-56.7)</td>
</tr>
<tr>
<td><strong>Anti-HBc positive % (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>27.0 (26.6-27.3)</td>
<td>42.5 (41.9-43.2)</td>
<td>12.7 (12.3-13.1)</td>
</tr>
<tr>
<td>2007-2011</td>
<td>25.2 (24.7-25.8)</td>
<td>38.3 (37.4-39.1)</td>
<td>11.7 (11.1-12.3)</td>
</tr>
<tr>
<td>2007-2011 CHB only</td>
<td>24.2 (23.6-24.7)</td>
<td>37.3 (36.4-38.2)</td>
<td>10.6 (10.1-11.2)</td>
</tr>
</tbody>
</table>

Table A5.1 Summary of median age, sex distribution, HBsAg, anti-HBs and anti-HBc data from each of the three analyses conducted as part of the sensitivity analysis.

Whole group = 88,175 individuals, 35% (30,464) Indigenous, 65% (57,711) non-Indigenous

2007-2011 = 35,633 individuals, 39% (14,025) Indigenous, 61% (21,608) non-Indigenous

2007-2011 CHB only = 35,287 individuals, 39% (13,823) Indigenous, 61% (21,464) non-Indigenous
Figure A1.1 Pie charts showing usual residence of HBsAg positive individuals: A=whole group, B=2007-2011, C=2007-2011 CHB only.
### Table A1.2
Summary of HBsAg prevalence by sex with odds ratios for each of the three groups included in the sensitivity analysis.

<table>
<thead>
<tr>
<th>HBsAg positive prevalence</th>
<th>Male % (95%CI)</th>
<th>Female % (95%CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole group</strong> n=88,175</td>
<td>5.01 (4.76-5.27)</td>
<td>2.32 (2.18-2.47)</td>
<td>0.50 (0.46-0.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>2007-2011 N=35,633</strong></td>
<td>4.99 (4.59-5.40)</td>
<td>2.35 (2.13-2.59)</td>
<td>0.49 (0.43-0.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>2007-2011 CHB</strong></td>
<td>3.22 (2.90-3.56)</td>
<td>1.58 (1.40-1.78)</td>
<td>0.51 (0.43-0.59)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Table A1.3
Summary of results in the pre and post vaccine era for the whole group analysis.

<table>
<thead>
<tr>
<th></th>
<th>Indigenous</th>
<th></th>
<th>Non-Indigenous</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre 1990 % (95%CI)</td>
<td>Post 1990 % (95%CI)</td>
<td>Pre 1990 % (95%CI)</td>
<td>Post 1990 % (95%CI)</td>
</tr>
<tr>
<td>HBsAg</td>
<td>6.89 (6.57-7.21)</td>
<td>1.81 (1.30-2.47)</td>
<td>1.55 (1.43-1.67)</td>
<td>2.73 (1.84-3.90)</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>63.6 (62.9-64.3)</td>
<td>49.9 (47.5-52.4)</td>
<td>60.6 (60.0-61.3)</td>
<td>52.4 (48.9-55.8)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>45.4 (44.7-46.1)</td>
<td>12.1 (10.8-13.6)</td>
<td>12.7 (12.3-13.1)</td>
<td>12.3 (10.2-14.5)</td>
</tr>
</tbody>
</table>
### Table A1.4 Summary of results in the pre and post vaccine era for 2007-2011 group

<table>
<thead>
<tr>
<th></th>
<th>Indigenous</th>
<th></th>
<th>Non-Indigenous</th>
<th></th>
<th>Overall</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
</tr>
<tr>
<td>HBsAg</td>
<td>6.73</td>
<td>1.81</td>
<td>1.52</td>
<td>2.49</td>
<td>3.51</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td>(6.25-7.23)</td>
<td>(1.21-2.61)</td>
<td>(1.34-1.72)</td>
<td>(1.45-3.95)</td>
<td>(3.29-3.74)</td>
<td>(1.47-2.69)</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>62.6</td>
<td>46.4</td>
<td>55.6</td>
<td>51.2</td>
<td>58.9</td>
<td>47.9</td>
</tr>
<tr>
<td></td>
<td>(61.6-63.6)</td>
<td>(43.6-49.2)</td>
<td>(54.7-56.6)</td>
<td>(47.1-55.4)</td>
<td>(58.2-59.6)</td>
<td>(45.6-50.3)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>42.5</td>
<td>11.3</td>
<td>11.8</td>
<td>9.6</td>
<td>26.8</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>(41.6-43.5)</td>
<td>(9.7-12.8)</td>
<td>(11.2-12.4)</td>
<td>(7.3-11.9)</td>
<td>(26.2-27.4)</td>
<td>(9.5-12.1)</td>
</tr>
</tbody>
</table>

### Table A1.5 Summary of results in the pre and post vaccine era for 2007-2011 CHB only group

<table>
<thead>
<tr>
<th></th>
<th>Indigenous</th>
<th></th>
<th>Non-Indigenous</th>
<th></th>
<th>Overall</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
</tr>
<tr>
<td>HBsAg</td>
<td>5.00</td>
<td>0.72</td>
<td>0.74</td>
<td>0.30</td>
<td>0.1860</td>
<td>2.36</td>
</tr>
<tr>
<td></td>
<td>(4.58-5.45)</td>
<td>(0.34-1.28)</td>
<td>(0.62-0.89)</td>
<td>(0.04-1.08)</td>
<td>(2.18-2.55)</td>
<td>(0.32-1.01)</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>63.4</td>
<td>46.8</td>
<td>56.0</td>
<td>52.1</td>
<td>59.5</td>
<td>48.5</td>
</tr>
<tr>
<td></td>
<td>(62.3-64.4)</td>
<td>(44.0-49.7)</td>
<td>(55.0-56.9)</td>
<td>(47.8-56.3)</td>
<td>(58.7-60.2)</td>
<td>(46.1-50.9)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>41.5</td>
<td>10.5</td>
<td>10.8</td>
<td>7.6</td>
<td>25.7</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>(44.7-46.1)</td>
<td>(10.8-13.6)</td>
<td>(10.2-11.4)</td>
<td>(5.6-10.0)</td>
<td>(25.1-26.3)</td>
<td>(8.5-11.0)</td>
</tr>
</tbody>
</table>

Table A1.4 Summary of results in the pre and post vaccine era for 2007-2011 group

Table A1.5 Summary of results in the pre and post vaccine era for 2007-2011 CHB only group
Figure A1.2 Graphs showing HBsAg, anti-HBs and anti-HBc prevalence patterns by birth cohort using the whole group dataset.
Figure A1.3 Graphs showing HBsAg, anti-HBs and anti-HBc prevalence patterns by birth cohort using the 2007-2011 CHB only dataset.
Sensitivity analysis

Figure A1.4 Graphs showing the birth cohort analysis for each of the three datasets used in the sensitivity analysis for HBsAg, anti-HBs and anti-HBc.
Appendix 2 - CHARM clinical record form
CHARM – Characterising Hepatitis B in northern Australia through Molecular epidemiology Case Report Form v.2

Demographics

First name: ___________________________  HRN:  __________
Last name: ___________________________  DOB:  ________
Gender:  
0=female, 1=male
Ethnicity:  
0=Caucasian, 1=Aboriginal, 2=Torres Strait Islander, 3=Pacific Islander, 4=other

Investigator details

Investigator initials: ___________________________
Current date:  
Current location:  

Inclusion criteria  (0=no, 1=yes)

HBsAg +ve  
Age ≥ 18  
First 5 years of life in Top End  
Likely perinatal / early horizontal acquisition

Study discussed with patient:  
Information sheet provided:  
Consent granted:  

Residential details  (if unknown, write unknown)

Place of birth:  
Main residence in 1st 5 yrs of life:  
Mother’s place of birth:  

All inclusion criteria must be positive to proceed

All these procedures must be completed to proceed

Complete details on reverse side.

Study number:  

For Josh or Steve to allocate
### CHARM – Characterising Hepatitis B in northern Australia through Molecular epidemiology
#### Case Report Form v.2

**Risk factors**

<table>
<thead>
<tr>
<th>Alcohol use:</th>
<th>0 = none, 1 = 0-2, 2 = 3-4, 3 = &gt;4, 9 = unknown, units is std drinks/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVDU:</td>
<td>0 = none, 1 = past, 2 = current, 9 = unknown</td>
</tr>
<tr>
<td>Diabetes:</td>
<td>0 = no, 1 = yes</td>
</tr>
</tbody>
</table>

**Treatment**

| Past HBV treatment: | 0 = none, 1 = lamivudine, 2 = adefovir, 3 = tenofovir, 4 = tenofovir, 5 = interferon, 9 = unknown. Enter up to 3 treatments. |
| Current HBV Rx:     |                                                                         |

**Investigations**

Serologies and ultrasound within past 12 months. Apart from HIV/HCV/ultrasound/biopsy, all other investigations should be ordered if not available. If any investigation is pending or has been ordered, write "R" or "W" (if ordered through RDH or Westerns respectively) next to box and leave box blank.

For serology 0 = negative, 1 = positive, 2 = equivocal, 3 = not done.

<table>
<thead>
<tr>
<th>eAg</th>
<th>HCV Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eAb</th>
<th>HIV Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBV DNA VL (IU/ml)</th>
<th>HDV Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>ALT</th>
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<table>
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<tr>
<th>Bilirubin</th>
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<table>
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<table>
<thead>
<tr>
<th>Platelets</th>
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<tbody>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = none, 1 = mild/suppressed on medication, 2 = severe/refractory</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = none, 1 = grade 1 (sleep disturbance, impaired concentration), 2 = grade 2 (drowsiness, disorientation), 3 = grade 3 (confusion, confusion, amnesia)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biopsy (most recent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheuer score (0, 1, 2, 3, 4) if done, 8 = done, but result unknown, 9 = not done</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated date if done:</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = not done, 1 = normal, 2 = increased echogenicity, no portal HT, 3 = portal HT</td>
</tr>
</tbody>
</table>

**Additional comments:**


Appendix 3 - CHARM cohort study clinical record form
CHARM – Characterising Hepatitis B in northern Australia through Molecular epidemiology
Case Report Form review

<table>
<thead>
<tr>
<th>Study number</th>
<th>HRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>First name</td>
<td>DOB</td>
</tr>
<tr>
<td>Last name</td>
<td>Vaccination status</td>
</tr>
<tr>
<td>Genotype</td>
<td>BMI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Baseline</th>
<th>+6M</th>
<th>+12M (1Y)</th>
<th>+18M</th>
<th>+24M (2Y)</th>
<th>+30M</th>
<th>+36M (3Y)</th>
<th>+42M</th>
<th>+48M (4Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
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<td>Alcohol use</td>
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</tr>
<tr>
<td>Clinical</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Known Cirrhosis</td>
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<td></td>
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</tr>
<tr>
<td>Ascites</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>For all blood tests: 0=negative; 1=Positive; 0=Not done or missing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eAg</td>
<td></td>
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<tr>
<td>eAb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV VL (log 10 IU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (umol/L)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>ALP (U/L)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If found, please return to Steven Tong or Jane Davies at the Menzies School of Health Research. Telephone 08 8988 8196.

CODES: 0=no, 1=yes, 9=unknown.
ALCOHOL: 0=none, 1=0-2, 2=3-4, 3=>4 std drinks/day, 4=binges<4, 5= binges>4 std drinks, 8=unknown.
ASCITES: 0=none, 1=mild/suppressed on medication, 2=severe/refractory.
ULTRASOUND: 0=not done, 1=normal, 2=increased echogenicity, no portal HT, 3=portal HT.
GASTROSCOPY: 0=not done, 1=normal, 2=oes varices, 3=gastric varices, 4=other.
If found, please return to Steven Tong or Jane Davies at the Menzies School of Health Research. Telephone 08 8988 8196.

**CODES**: 0=no, 1=yes, 9=unknown. **ALCOHOL**: 0=none, 1=0-2, 2=3-4, 3=>4 std drinks/day, 4=binges<4, 5= binges>4 std drinks, 8=unknown. **ASCITES**: 0=none, 1=mild/suppressed on medication, 2=severe/refractory.

**ULTRASOUND**: 0=not done, 1=normal, 2=increased echogenicity, no portal HT, 3=portal HT. **GASTROSCOPY**: 0=not done, 1=normal, 2=oes varices, 3=gastric varices, 4=other

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**PAST AND PRESENT TREATMENT**

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**COMMENTS**
Appendix 4 - Davies et al. Hepatitis D is rare or non-existent in hepatitis B virus infected Indigenous Australians in the Northern Territory as published in Australian and New Zealand Journal of Public Health
Item removed due to copyright restrictions.
Appendix 5 - Screen shots from electronic application - Yolŋu matha
Nurruyirryun ga dhäwu

Dhuwali rerri Hep B marr’yun ga dhiyal NT-ny


Wiripu melany dhâwu gunga’yunamirr, marnji–wurrupanamirr.
Dhuwal Hep B rerri


Walu ngupan bitjian bili gułan gurrupanmiri. Ga nuni ngayi yołtuw nuni ngayi ga nyatham dhuwali remi Hep B, ga nuni nhanju dhu mangu' wandirr nhakun birkamirimry, bala nhakun dhu nathamar wimpunyino yon yułtuw gułan, nuniyini nhaku mañga bili gurrupanmiry nuniyini rerri Hep B—n. Ga maññyurdu dhu bitjian nuni ngayi dhu birkamirimry maku butpinmiry wakalañur, wo mañ manarur, nuna balar mañga mangu' wuñuphurra bala yan gurrupanmiry remin nuniyini. Yaku nhuma dhu gurrupanmiri nuni nhuma dhu gow-djaalawalatiningi, nha mañ walkunhammiri ga chang'yuñmiri wo wimpuny nhuma dhu ga cha-wumbyasingi nuni yuñur yaka ngayi dhu nuniwuljëndhi nhuma gurrupanmiri nuniyini remi Hep B.

Dhuwali remi Hep B watal dhu ga gurrupanmiri nuni yuñujinka djiqàjëndi yuñur, nuni watal dhu dhañypanmiri ga bañqi nuni bili yan djiqënd. Bayhi warmy ngayi dhu dhuwali remi Hep—ny ga yöra djanwanyi nabcñupuny yon yułtuw mangu'ñurudja. Yurr nuni ngayi dhu gułanggurumy yuñur dhañthun, nhinany ngayi dhu ga nuniyini remini walañ yari, 1 week yan bala yumna ngayi dhu dhinggamany.


Gurrupanmirri yan nhuma dhu dhuwali remi Hep B, dhuwalatjaryi galja—nyatham birlanmirry gommi, nuni ngayi wanganyndja nhmu lunumirimry remmir, nyatham ngayi ga dhuwali remi yaku Hep B. Dirramur dhu gurrupan Mysukal wo Mysukal dhu gurrupan Dirramur.
Nhaltjan ga biğila djäma

GULAI'D GA RURRWUYUN
GUDGA'YAN GA NHATHA GA BUJDUKUM
GUNGA'M NHUNANY GA RERRIKTHUNADJUR
GUDGA'YUN GA MAŊGU'-WANDINYADJUR

Nhunu gulan' / mangun’ yan dhawumirrnydja

Gulanç djakap biyak bili, yaka moŋu


Ga ḋuli Ḉayi ga dharrawany ḋorra Hep B nhokal gulanŋur ga nhuruŋu biŋilaŋy ga yaka djaima manymakkum, nheny dhu Ḉunhi yan māram bulu djakap ge mirrjin. Mak nhe dhu ga dhakay ŋamany nhuruŋu rumbalnydja manymak, yurr nhuruŋu mangun yuwałktja ḋawumirr nha nhe remirim wo yaka.
Dhamwa yol'nuwul' mala ḋunhi walal ga ḋayatham dhuwal ga ḋerri yaku Hep B. Marraŋalndja walal ḋunhi remny ṭathil yan ḋunhi walal yuṭa yan yol'nu, bald walal gan ḋunhi ḋayathaŋal weyin'umirra dhungarra ḋupara. Wirpuwurnalndja yol'nuwal mala ḋunhiyi buwak mowiri buyara marr Jurkun ga yaka ḋayi ga mirthir remkmadam nhakun ḋorra ḋayi ga ḋunhiyi ḋerri. Mak ḋayi dhu ga ḋorrany weyin'umirr dhungarra ḋupan, yurr wirpuny mak ḋayi dhu ḋunhiyi ḋerri run'yuna yakurrjur bald yan ḋayi dhu midikuma ḋunu bi'dilany' bawalamirriynha walty. Nheny dhu gunganhamirr nhunapinya nhe.
Mirritjin / djakdjin märram gulmaram ḋunjhiyi rerriny'

Nhā nhuŋu dhu malŋθun yalalaŋnumirriynjdja


Select Chapter
Ņalapalmirr mala

Nanitji

Biḍilaṇur ganydjarr-ḍumurr rerri nhakun ga märtyuna dhiyaṇyuny bala

Yaka dhu ga bukmakthuny märram mirrîtjin


Biḍila midikumanawuy

Marŋgithi nhaltjan nhe dhu ga märram nhunu mirritjin mala


Gurrupul mirritjin dhiyak yolŋuw
Marŋithi nhaltjan nhe dhu ga märram nuŋu mirriţjin mala

YALŊGI

MÄRR GĂNGGA

dÄL
Marngithi nhaltjan nhe dhu ga märam nhuŋu mirritjin mala

Give the man his medicine by dragging the tablet over his mouth
Give the man his medicine by dragging the tablet over his mouth
Give the man his medicine by dragging the tablet over his mouth
Marŋithi nhaltjan nhe dhu ga märram nhuŋu mirritjin mala

Give the man his medicine by dragging the tablet over his mouth
Marŋgithi nhaltjan nhe dhu ga märam nhuŋu mirritjin mala

Give the man his medicine by dragging the tablet over his mouth
Marngithi nhaltjan dhe dhu ga marram nhandu mirriyin mala

Give the man his medicine by dragging the tablet over his mouth
Give the man his medicine by dragging the tablet over his mouth
Marŋithi nhaltjan nhe dhu ga märram nhuŋu mirritjin mala

Give the man his medicine by dragging the tablet over his mouth
Results

Yo manymak mirithirr djaga nhuŋu dhiyak yolŋuw ŋunha nhanŋu bidilany manykthinan

Bulu bulyurr / wutthurr giniŋgaarr
Bukmak dhäwu bigilawuyu rerri


Nhe dhu ga mārram djakap nhunû gulangû ga miritjín nhe dhu ga mārram, bitjan bili, mār nhunû dhu ga bigila ga djama manymakkum. Ga mārray nhunû miritjín biyak bili.

Yothumirr miyalk

Dhukarr mirritjingu ga djakapgu

Walal dhu malqamram nyumukupiny/qoyjur qunhiyi buwayak mewiri qunhiyi Hep B-w, qunirali yothumirriwal miyalkal, qunhiyiny nhakan manymak mirithirr walu ga norra qunhiyi yothuwal waljakunharaw walal dhu marragjirthu gulungarm ram qunhiyi reeri Hep B nhanukal yothuwal mirritjingu racial dhu yothuwal yeku marram reeri. Ga bai racial dhu qunhiyi yothu dhawal-guyara, bala yan dhu marram marrma djakcin, ga bulu durinbele marrma(2) ralindi dhu djulkthun, ga bulu qunirji dambumirriw (4) ralindi dhu djulkthun ga bulu yalala qumirniy 6 ralindi dhu djulkthun, racial dhu marram djakcin.

Ga raciali ne ga mirithirmydja garrwanvjdja namba nyatham buwayak mewiri Hep B nhokal gulaqur ndiwal, nhokal yothuynjdja dhu marram bumaknhla djakcin malany qunhi ga lakaram dhuwali garrwanj. Ga nhama racial dhu marragjirthu nhuruwuy nha, ga wuana nhanukal, marr racial dhu ga marram mirritj malany tablet, bensur 28 weeknr balanyamirriy qunhi racial yothumirriyin. Dhiairuniy dhu mirritjintju yupmaram qunhiyi buwayak mewiri malany nhokal gulaqur, yan bili walu nhuru racial dhu yothu dhawal-guyara. Dhiairuniyina ga manuljir lekaram qunhi manymaknhla nhuru racial noorra nhokalajaw yothuwal yaii yakaq marram qunhiyi reeri Hep B. Yakan racial dhu qandiy guurrupan nhuru yothuwal qunhiyi reeri Hep B.
**Yothuw mirritjin ga djaktjin**

Duli nhuru buwayakta mewim nyoyur namba ga nhokai yothuy ga marram bukmak djaktjin malany, nyunhiiny mayali nhakun nyunkiyo remiwi dha---gurrupanarraw mirthirirr nyumukuniny.

Ga njuli nhuru gamwamydja Hep B buwayak mewim nhokai gulaqur, ga marram nhie njuli ga mirritjin bejuru 7 najindi njunhi nhie njuli yothunimiyirr ga nhokai yothuniny-dja njuli ga marram bukmakum djaktjin malany, nyunhiiny mayali nhakun dha---gurrupanarraw nhokalaraw yothuninjaja njunhiyi Hep B--ny rem mirthirra nyumukuninyhna.

Ga mirthirr nyai dhuwali manyamak mirthirr ga njururu nhuru yothuw, nyai dhu ga marram djakap gulaqgu nhanjuwuw balanyamirriy dhu njuruyiriwun, njunhi nyai yothu dhungarra wanyangi marr, marr nyai dhu yaka marram Hep B re.rr.
Appendix 6 - Screen shots from electronic application – English
Hepatitis B or Hep B for short (the yellow dots in the picture) is a virus that causes Hep B infection. Virus is a medical word meaning a tiny invisible germ that needs to live inside a person or animal to stay alive.

Hep B uses a person's liver as its home and their blood as transport to get around the body and to move to new places. In humans the liver is on the right side of the body just below the ribs. It is connected to blood vessels or pipes that move blood around the body. You have Hep B infection if the virus is living in your liver and can be found in your blood.
Hep B is common in the Northern Territory, about one person out of every 10 has it. Often a few people in one family will have Hep B and most commonly they will have got it when they were very young.
The Story Fishing

One common way to get Hep B infection is if blood from someone who already has it gets into your body. In the story below the little girl who already has Hep B is fishing with her friend, she accidentally cuts her finger on the hook and her blood drops onto an open sore on the little boy’s leg, giving him Hep B. It can be this easy to pass Hep B from one person to another.

If you are young when you get Hep B it is most likely it will stay in your body and cause infection. If you are an adult when it passes to you it might stay but there is a chance your body will fight it and win by removing it from your body.
The Story

Other ways to get Hep B

Mother to child transmission
Hep B can pass from a mum to her baby when the baby is still inside or at the time she gives birth. In the past this was the commonest way to get Hep B in the NT, now there are lots of things we can do to stop this happening.

Day to day blood contact
Any time when blood from a person with Hep B touches your blood it is possible for the infection to pass from them to you. This might happen in a footy game or a fight where there is a break in the skin. It does NOT happen with normal contact such as shaking hands, kissing and hugging or sharing plates and cups.

Needle contact
The Hep B in one person’s blood can pass to another person through sharing needles or if you stab yourself with a used needle. Although Hep B needs to live in a person to survive for a long time it can stay alive for about a week outside the body.

Razors
If you share a razor with someone who has Hep B they could pass it on to you. Even a very small amount of blood on a razor can have a lot of Hep B in it. It can stay alive for about a week outside the body, it can then pass into your body through any tiny cut to your skin when shaving with a shared razor.

Sexual transmission
Another way for adults to get Hep B is through having sex, the man can pass it to the woman or the woman can pass it to the man.
What your liver does
Liver Function

Cleans the blood
Helps digest food
Protects you from infection
Helps to stop bleeding

Your liver is on the right side of your body just below your ribs. It does a lot of important jobs for your body. You can’t survive for long without a working liver. It helps to clean your blood by removing unwanted or harmful substances. It helps break up your food and enable your body to use it well. It is like a factory that makes special chemicals to help the blood to clot and to fight off infection.
Hep B can be living in you for a long time without causing any symptoms or sickness but it can still be causing damage to your liver. The only way to know if you have Hep B infection is to do a special test on your blood to look for the virus. This can tell you how much virus is in your blood.
Only your blood can tell the story Regular Checks

It is really important to have regular blood tests to see how much virus is in your blood and to see if your liver is working well. If there is a lot of Hep B in your blood or your liver is not working well you might need further tests or medicine. You might still feel well, only your blood can tell the true story.
Only your blood can tell the story Sleeping disease

Most people who have Hep B infection got it when they were young so have been living with it for many years. In some people the virus is there but only in small amounts and it is not causing any damage or sickness it is sleeping. It might stay sleeping for many years but it might also wake up and start to cause damage to your liver at any time.
You can be protected
Immunisation

All children born in the NT since 1990 should have been immunised to protect them from Hep B. This is a course of 3 or 4 Hep B needles to protect them from the infection. If you were born before 1990 or you are not sure if you have had the needle you can have a blood test to find out. If you do not have Hep B and are not already protected the clinic can arrange for you to have the immunisation.
Children with Hep B normally feel well and continue to grow normally even though the virus is living in their liver. They often have high levels of virus in their blood meaning it is easy to pass on to other people from day to day blood contact. You cannot tell that someone has Hep B unless you do a blood test.
What happens over time
Adults

As people with Hep B become adults most of them continue to feel well. The virus continues to live in their liver but the levels of virus in their blood often come down to a lower level. As people get older some develop a sickness because of damage to the liver from the Hep B. If they are having regular blood tests the damage to the liver can be detected early before it gets too bad.
What happens over time

Alcohol

Alcohol (or grog) and kava can also damage the liver. If you already have Hepatitis B living in the liver and you then drink too much grog, it means you have two things hurting the liver. This can mean the damage to your liver happens much quicker and is more severe.
What happens over time
Liver cancer is more common

If you have Hep B for a long time your chance of getting a cancer of the liver is higher than if you don’t have Hep B. This is why when you reach the age of 50 your doctor will ask you to have blood tests and ultrasound scans of the liver every 6 months. If a liver cancer is growing in your liver and it is found before it gets too big there are good treatments for it. If it is very big when it is found it is hard to treat.
Treatment
Not everyone needs treatment

Your regular blood tests will show how much virus is in your blood and how well your liver is working. When the virus level is low and your liver tests are normal you don’t need any medicine. We say that the virus is sleeping.

The virus can wake up at any time so it is important we keep doing the regular blood tests. If the Hep B virus level is high and your liver tests are abnormal you may be offered medicine. The medicine is normally a tablet that you have to take every day. Even if you need treatment you may still feel well but you still need to take the tablet every day. This will keep your liver working well and stop the Hep B from causing any more damage.
Treatment
Damaged liver

If you don’t get medicine for your Hep B when you need it the virus will slowly cause more and more damage to your liver. Eventually the liver becomes all bumpy and small this is called cirrhosis. When your liver is like this it can’t work properly. You will start to feel sick. The white bit of your eyes might go yellow called jaundice. You might vomit up blood or pass blood when you go to the toilet. You might see your tummy swell up with fluid. You might become forgetful or confused.
Treatment
How to take your tablets

If you need medicine it is important that you take it every day. If you miss some tablets the virus uses the time when there is no medicine in your body to change. If this happens lots of times the tablets won’t work any more. When this happens we call the virus resistant to the medicine.

Give the man his medicine by dragging the tablet over his mouth
Treatment
How to take your tablets

CHOOSE GAME DIFFICULTY

EASY

MEDIUM

HARD
Treatment
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth
Treatment
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth.
Treatment
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth
Treatment
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth
Treatment
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth
Treatment
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth
TREATMENT
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth
Treatment
How to take your tablets

Give the man his medicine by dragging the tablet over his mouth
Results

Well done, you have kept this person's liver healthy.

Play Again?
Treatment

Important messages

If you don't let your blood tell the story the Hep B can cause damage to the liver. If you need treatment and you only take it sometimes the Hep B can become resistant and the medicine won't work any more. If your liver is so damaged that it stops doing its job you will become very sick.

You can keep your liver strong by having regular blood tests, not drinking grog and taking medicine if you need it. Remember only your blood can tell the true story of how much virus is there and how well your liver is working. Even if you need medicine you might still feel normal.
Women’s Business
Pregnant Women

When women who have Hepatitis B become pregnant it is important to see how much virus is in their blood by having a special blood test. Some will have a high level of Hep B and some will have a low level, the only way to know is to have the blood test.
Women’s Business
Treatment Paths

If you have a low level of virus in your blood it is important your baby is protected as soon as they are born to stop the Hep B passing on to them. They need to have 2 needles as soon as they are born and then one at 2 months, 4 months and 6 months.

If you have a high level of virus in your blood your baby should have all the needles as described above. You also need to talk to a doctor about having a tablet medicine from week 28 of your pregnancy. This medicine brings the virus level in your blood down by the time you have your baby. This means you are much less likely to pass the Hep B onto your baby.
Women’s Business
Importance of treatment for baby

If your virus level is low and your baby has all the needles the chance of you passing Hep B to them is very low.

If your virus level is high and you take medicine from about 7 months of pregnancy and your baby has all the needles the chance of you passing Hep B to your baby is very low. It is important for your baby to have a blood test at the age of one year to make sure they don’t have Hep B.
Acknowledgements

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Maratja Dhamarrandji
Dorothy Gapany
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Appendix 7 - Electronic application evaluation questionnaire
### Evaluation of the “Hep B story” app Alice Springs

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Q1. Pre app

Can you name 3 ways Hep B can be passed from one person to another

If you have Hep B what is the best way to tell if the virus is causing damage to your liver

If you have Hep B what can you do to help your liver to stay healthy (name 2 things)

Q2. Pre app

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Q3. Post app

I found the app……..  

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<td>0</td>
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</tr>
<tr>
<td>C. Contained enough information for my needs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D. Contained too much information for my needs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E. Improved my understanding of Hep B</td>
<td>0</td>
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</tbody>
</table>

I Would........

F. Recommend the app to my family and friends  

<table>
<thead>
<tr>
<th></th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. Use the app again myself</td>
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</table>

Q4. Post app

Can you name 3 ways Hep B can be passed from one person to another

If you have Hep B what is the best way to tell if the virus is causing damage to your liver

If you have Hep B what can you do to help your liver to stay healthy (name 2 things)

The best thing about the app is...........  

If I could change the app I would prefer...............