Falling down the cascade: the gaps in care delivery for people living with chronic hepatitis B in Australia

By
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University of Melbourne, Parkville, Australia
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Abstract

In Australia, an estimated 239,000 people were living with chronic hepatitis B (CHB) in 2016. Most of the affected community were born overseas and acquired their infection early in life, in countries with high and intermediate prevalence of hepatitis B. The mortality attributable to CHB is from both liver cancer (hepatocellular carcinoma) and cirrhosis. Hepatocellular carcinoma has poor five-year survival, increasing incidence globally, and was projected to become the sixth most common cause of cancer death in Australia in 2016. The first “Global Hepatitis Health Sector Strategy” was signed in 2016 by all the member states of the World Health Assembly including Australia, with the aim of eliminating viral hepatitis, including hepatitis B, as a public health concern by 2030.

The five studies presented in this thesis use the cascade of care framework to approach different aspects of the health system response to chronic hepatitis B in Australia. The studies have used different data sources and methodologies to measure the cascade and explore factors associated with the delivery of care.

The first study presents an analysis of national data from 2012. It proposed, for the first time, a cascade of care for chronic hepatitis B in Australia that included a novel “enrolled in care” indicator. The second study presents findings from a multicentre retrospective study of adherence to antiviral therapy for chronic hepatitis B from 2010-2013. The study measured the proportion of people adherent to treatment in tertiary settings and analysed the demographic and health system factors associated with poor adherence. The third study analysed the association of a pharmacy-based adherence measure (the medication possession ratio) with viral outcomes using a time-to-event analysis for favourable and unfavourable viral outcomes. The fourth study presents findings from a retrospective analysis of primary care data in a community health centre that received external support from a tertiary service to improve the delivery of guideline-based care for chronic hepatitis B, including surveillance for hepatocellular carcinoma. This study evaluated four and a half years of data focusing on hepatocellular carcinoma surveillance participation and adherence. The fifth study presents findings from a qualitative study: semi-structured interviews of African-Australians living with chronic hepatitis B. This study explored
participants’ understanding of health risks associated with hepatitis B, including their perceptions of their risk of developing hepatocellular carcinoma.

Findings from this thesis have shown that few people living with chronic hepatitis B in Australia were enrolled in care. It provided the first multicentre estimates of the adherence of people on antiviral therapy for chronic hepatitis B in our health system (using medication possession ratio as the measure of adherence) and that factors associated with poor adherence were younger age and poor continuity of clinician.

In a further study, the association between medication possession ratio and unfavourable viral outcomes was demonstrated for the first time. This analysis found that there was no true cut-off point or threshold to define adherence and the risk of poor outcomes. Rather, there was an increasing hazard ratio for unfavourable events with decreasing medication possession ratio. The findings also include results from a study that demonstrated hepatocellular carcinoma surveillance in a tertiary-supported general practice – with both participation and adherence to six-monthly scans with supported recall and reminder systems – is hard to achieve.

Finally, the fifth study presented as part of this thesis found that African-Australians living with chronic hepatitis B perceived and experienced significant risks to social and emotional wellbeing from the shock of diagnosis, fear of infectiousness, and discrimination from telling others about their illness, as well as physical or liver-related problems.

The results from this thesis have informed the development of the current Australian cascade of care for chronic hepatitis B and provided insights into the challenges of delivering health services to people living with chronic hepatitis B. These findings have led to recommendations for further development of the cascade at a national and regional level, and the need for further research and evaluation of the health system response to chronic hepatitis B.

The work presented demonstrates that Australia has failed to meet the targets of the 2014-2017 National Strategy and needs to rapidly improve essential elements of the cascade,
including increasing the proportion diagnosed and enrolled in care, to reach the targets of elimination of chronic hepatitis B as a public health concern by 2030.
Declaration

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at University of Melbourne or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others with whom I have worked is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged. The thesis is fewer than 100,000 words in length exclusive of tables, bibliographies and appendices.

Nicole Lisa Allard
Preface

The work of this thesis was carried out in collaboration with others and tables are presented relevant to each published paper or work to acknowledge the nature and proportion of the contribution of others, and in general terms the portions of the work that the candidate claims as original. The contributions of all persons involved in any multi-authored publications included in the thesis and all sources of funding are acknowledged.

No work arising from this thesis was submitted for other qualifications or carried out prior to enrolment in the degree. Editorial assistance was provided in preparation of the published papers contained in this thesis by the publishing journal after the paper had been through the peer review process. Peer reviewers were selected by the journals and were anonymous, but are presumed to be knowledgeable in the academic discipline of the relevant submitted publication.
<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>The cascade of care for Australians living with chronic hepatitis B: measuring access to diagnosis, management and treatment.</th>
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<td><strong>Funding</strong></td>
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<td><strong>Authors in order</strong></td>
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<td>Nicole Allard</td>
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<td>Jennifer MacLachlan</td>
<td>contributed to the design of the study, the acquisition and analysis of the data, and revision and approval of the final article.</td>
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<td>Title</td>
<td>Factors associated with poor adherence to antiviral treatment for hepatitis B.</td>
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</tbody>
</table>
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<td>Nicole Allard</td>
<td>contributed to the original concept design and coordination of the study, including organising the ethics and governance applications at the two sites the acquisition, cleaning and analysis of the data, and wrote the article.</td>
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<td>contributed to data acquisition, and revision and approval of the final article.</td>
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<td>Emily Wheeler</td>
<td>contributed to data acquisition, and revision and approval of the final article.</td>
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<td>contributed to design, and revision and approval of the final article.</td>
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<td>contributed to the revision and approval of the final article.</td>
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<td>contributed to the concept and design of the study and revision of the article.</td>
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<td><strong>Title</strong></td>
<td>Viral outcomes and adherence in chronic hepatitis B: the association of medication possession ratio (MPR) and viral outcomes</td>
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<td>The co-authors have reviewed the paper prior to submission and their comments have been incorporated into the work, which is presented in Chapter 4.</td>
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## Acronyms

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<td>AASLD</td>
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<td>APASL</td>
<td>Asia-Pacific Association for the Study of Liver Disease</td>
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<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
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<td>ALT</td>
<td>alanine aminotransferase</td>
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<td>anti-HBe</td>
<td>antibody to hepatitis B e antigen</td>
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<tr>
<td>anti-HBs</td>
<td>antibody to hepatitis B surface antigen</td>
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<tr>
<td>ASHM</td>
<td>Australasian Society for HIV medicine</td>
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<td>BBV</td>
<td>blood-borne virus</td>
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<td>CHB</td>
<td>chronic hepatitis B</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>EASL</td>
<td>European Society for the Liver</td>
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<td>GP(s)</td>
<td>General Practitioner(s)</td>
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<td>HBeAg</td>
<td>hepatitis B e antigen</td>
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<td>HBlG</td>
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<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
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<td>HBV</td>
<td>hepatitis B virus</td>
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<td>HBV DNA</td>
<td>hepatitis B virus DNA or viral load</td>
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<td>HCC</td>
<td>hepatocellular carcinoma</td>
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<td>HCV</td>
<td>hepatitis C virus</td>
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<td>HDV</td>
<td>hepatitis D virus</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>IHBS</td>
<td>Integrated hepatitis B service</td>
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<td>IQR</td>
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<td>LMIC</td>
<td>low- and middle-income countries</td>
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<td>NNDDSS</td>
<td>National Notifiable Diseases Surveillance System</td>
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<td>NICE</td>
<td>National Institute of Health and Care Excellence</td>
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<td>NT</td>
<td>Northern Territory</td>
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<td>MBS</td>
<td>Medicare benefits schedule</td>
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<td>MPR</td>
<td>Medication possession ratio</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>Section 100 – Highly Specialised Drugs Program</td>
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<td>VBT</td>
<td>Viral breakthrough</td>
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<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
List of tables

Table 1: Summary of adherence studies grouped on type of adherence measure used .................................................................45
Table 2: Hepatocellular surveillance recommendations from countries and professional bodies ...........................................................................49
Table 3: Viral events/patterns and classification in to outcome categories primary analysis ..................................................................................78
Table 4: Viral events/patterns and classification in to outcome categories secondary analysis ...........................................................................78
Table 5: Patient characteristics in viral outcomes analysis ..............................................................................................................80

List of figures

Figure 1: The cascade of care as proposed by WHO in 2016. .................................................................20
Figure 2: 2011 care cascade for CHB in the USA by Cohen et al. .............................................................35
Figure 3: 2011 Spectrum of care analysis for HIV in the USA from Gardner et al. ........36
Figure 4: Time-to-event analyses showing proportions of patients over time who experience the unfavourable event when threshold MPR = 0.80.................................86
Figure 5: Time-to-event analyses showing proportions of patients over time who experience the unfavourable event at MPR when threshold MPR = 0.90 ........86
Figure 6: Time-to-event analyses showing proportions of patients over time who experience the unfavourable event when threshold MPR= 0.95.........................87
Figure 7: The cascade of care for people living with CHB 2013-2016 .........................137
# Table of Contents

Abstract ................................................................................................................................. 2
Preface ................................................................................................................................. 6
Acknowledgements ................................................................................................................ 12
Publications arising from this thesis ................................................................................ 13
Acronyms ............................................................................................................................. 14
List of tables ......................................................................................................................... 15
List of figures ....................................................................................................................... 15

## Chapter 1: Introduction .................................................................................................... 18
  1.1 Introduction .................................................................................................................. 18
      1.1.1 Chronic hepatitis B global epidemiology and global strategic response .......... 18
      1.1.2 The cascade of care in a global context ......................................................... 19
      1.1.3 Chronic hepatitis B in Australia, epidemiology and strategic responses ........ 20
      1.1.4. Australian clinical recommendations and access to care ......................... 21
      1.1.5 The cascade of care in Australia ................................................................. 22
      1.1.6 Programs to improve CHB care in Australia ............................................... 22
      1.1.7 Summary ....................................................................................................... 23
  1.2 Theoretical framework ................................................................................................. 24
  1.3 Gaps in the research relating to the cascade of care ................................................ 24
  1.4 Questions addressed by this thesis ........................................................................... 26
  1.5 Aims of the projects ................................................................................................... 26
  1.6 Overview of studies and methodological approaches .............................................. 27
  1.7 Thesis plan .................................................................................................................. 29

## Chapter 2: Literature review .......................................................................................... 32
  2.1 Cascades of care .......................................................................................................... 32
      2.1.1. Introduction to cascades of care ................................................................. 32
      2.1.2 Challenges in the CHB cascade ................................................................. 33
      2.1.3 Australian National Strategies for CHB and reporting of indicators ........... 33
      2.1.4 Cascades of care prior to 2013 ................................................................. 34
      2.1.5 Considering the data sources for the cascade of care for CHB ................. 36
      2.1.6 Summary of literature on cascades ......................................................... 38
  2.2 Adherence to antiviral therapy ................................................................................... 38
      2.2.1 Introduction to adherence and its place in the cascade ............................... 38
      2.2.2 Antiviral treatment access in Australia ....................................................... 40
      2.2.3 Adherence measures ..................................................................................... 40
      2.2.4 Estimating adherence .................................................................................... 41
      2.2.5 Factors associated with poor adherence in CHB ....................................... 42
      2.2.6 Defining poor adherence and associated viral outcomes ......................... 43
      2.2.7 Summary of adherence literature and research implications ...................... 44
  2.3 HCC surveillance in people living with CHB ............................................................. 46
      2.3.1 Introduction to HCC in CHB and HCC surveillance and the cascade of care 46
      2.3.2 HCC surveillance recommendations ............................................................ 47
      2.3.3 The mortality benefit and harms of HCC surveillance ............................... 50
      2.3.4 Participation and adherence to HCC surveillance ....................................... 51
      2.3.5 Interventions to systematise or improve HCC surveillance ....................... 52
      2.3.6 Summary of HCC surveillance literature and research implications .......... 53
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4</td>
<td>Knowledge and perceptions of health risks in people living with CHB</td>
<td>54</td>
</tr>
<tr>
<td>2.4.1</td>
<td>Introduction and how knowledge impacts on care delivery</td>
<td>54</td>
</tr>
<tr>
<td>2.4.2</td>
<td>Knowledge of health risks in people living with CHB</td>
<td>56</td>
</tr>
<tr>
<td>2.4.3</td>
<td>Summary of how people with CHB understand health risks</td>
<td>57</td>
</tr>
<tr>
<td>3.1</td>
<td>The cascade of care for CHB</td>
<td>59</td>
</tr>
<tr>
<td>3.2</td>
<td>Paper 1: The cascade of care for Australians living with chronic hepatitis B: measuring access to diagnosis, management and treatment</td>
<td>61</td>
</tr>
<tr>
<td>4.1</td>
<td>Adherence to antiviral therapy</td>
<td>67</td>
</tr>
<tr>
<td>4.2</td>
<td>Paper 2: Factors associated with poor adherence to antiviral treatment for hepatitis B</td>
<td>68</td>
</tr>
<tr>
<td>4.3</td>
<td>Viral outcomes in CHB and association with the medication possession ratio</td>
<td>75</td>
</tr>
<tr>
<td>4.3.1</td>
<td>Introduction</td>
<td>75</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Aims</td>
<td>76</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Methods</td>
<td>76</td>
</tr>
<tr>
<td>4.3.4</td>
<td>Results</td>
<td>79</td>
</tr>
<tr>
<td>4.3.5</td>
<td>Discussion</td>
<td>87</td>
</tr>
<tr>
<td>4.3.6</td>
<td>Conclusion</td>
<td>89</td>
</tr>
<tr>
<td>5.1</td>
<td>HCC surveillance in a community setting</td>
<td>90</td>
</tr>
<tr>
<td>5.2</td>
<td>Paper 3: The challenge of liver cancer surveillance in general practice: Do recall and reminder systems hold the answer?</td>
<td>92</td>
</tr>
<tr>
<td>6.1</td>
<td>How health risks are understood by African Australians living with CHB</td>
<td>99</td>
</tr>
<tr>
<td>6.2</td>
<td>Paper 4: Knowing and telling: How African- Australians living with chronic hepatitis B understand HCC risk and surveillance</td>
<td>100</td>
</tr>
<tr>
<td>7.1</td>
<td>Discussion of findings, recommendations and conclusion</td>
<td>123</td>
</tr>
<tr>
<td>7.2</td>
<td>Overall findings and discussion</td>
<td>123</td>
</tr>
<tr>
<td>7.3</td>
<td>Limitations</td>
<td>127</td>
</tr>
<tr>
<td>7.4</td>
<td>Translation of research</td>
<td>130</td>
</tr>
<tr>
<td>7.5</td>
<td>Recommendations</td>
<td>130</td>
</tr>
<tr>
<td>8.1</td>
<td>Conclusion</td>
<td>137</td>
</tr>
<tr>
<td>Appendices</td>
<td>Presentations during course of candidature</td>
<td>156</td>
</tr>
<tr>
<td>Appendix A</td>
<td>Other publications contributed to during course of candidature</td>
<td>158</td>
</tr>
<tr>
<td>Appendix C</td>
<td>Committees and community involvement during candidature</td>
<td>160</td>
</tr>
</tbody>
</table>
Chapter 1: Introduction

1.1 Introduction

1.1.1 Chronic hepatitis B global epidemiology and global strategic response

The global burden of chronic hepatitis B (CHB) related mortality and morbidity continues to increase, with an estimated 237 million people living with CHB and 636,000 deaths attributed to cirrhosis and liver cancer in 2015 (1-3). The increasing burden of liver-related deaths has occurred despite the availability of a vaccine to prevent new infections and effective antiviral therapies that can prevent disease progression and cancer (4-6).

Hepatitis B virus (HBV) is a blood-borne virus (BBV) that is transmitted vertically at the time of birth, horizontally in childhood from cuts scratches and biting, and in adult life, sexually and through unscreened blood products, unsafe procedures and the sharing of injecting equipment(7). Globally, most transmission of HBV occurs due to vertical and early horizontal exposure in high and intermediate prevalence countries (8). CHB is a dynamic infection that over decades can cause liver injury as the result of the body’s immune response to the virus (9). CHB also can cause hepatocellular cancer (HCC) and is the second most significant carcinogen worldwide after tobacco (10). Untreated, the risk of death due to CHB is estimated to be 15-25% (11).

Mortality and morbidity from HCC and cirrhosis secondary to CHB infection can be prevented (1).

Primary prevention of the sequelae of CHB is possible with vaccination at birth (1), with the addition of immunoglobulin to children born to CHB positive mothers and antiviral therapy in the third trimester to reduce vertical transmission risk and vaccination of at-risk adults (12). Secondary prevention is possible by the regular monitoring of people living with CHB and the use of antiviral therapy to suppress viral replication and reduce the risk of progression to cirrhosis or HCC in people who are identified with ongoing liver injury (6, 13). Finally, the tertiary prevention of HCC-related mortality is possible with HCC surveillance and the early identification of
cancers that can be treated, with the aim of increasing survival and the potential for cure (14).

International leadership in the control and/or elimination of CHB as a public health concern has been slow when compared to other communicable diseases, including tuberculosis, malaria and human immunodeficiency virus (HIV). These diseases have, for several decades, been the focus of guidance and strategies from World Health Organisation (WHO) and funding mechanisms such as the Global Fund to support responses in low and middle income countries (LMIC). Globally in HBV control, there has been significant progress in the last decade with the implementation of primary prevention programs and increasing global coverage of triple dose HBV and birth dose vaccination programs: now estimated to be 84% and 39% respectively (15). However, significant challenges still remain both in increasing vaccination coverage and reducing transmission from unsafe healthcare practices, including blood transfusion and injection safety (15).

The momentum has been building in the last 3 years to respond to viral hepatitis globally as a significant health problem. In 2016, the World Health Assembly (WHA) – the governing body of WHO – endorsed the first Global Health Sector Strategy for Viral Hepatitis 2016-2021 (1). This led to the first Global Hepatitis Report in 2017 (15). WHO has also released accompanying clinical guideline manuals for care of people with CHB in 2015 (14) and a monitoring and evaluation framework for country programs in 2016 (1, 16). The aims of the global strategy are to halt transmission and ensure access to care, with a goal of elimination of viral hepatitis, both B and C, as a public health concern by 2030 (1).

1.1.2 The cascade of care in a global context
The monitoring and evaluation framework released by WHO includes a proposed structure for a cascade or continuum of care to evaluate delivery of programs, which has been adopted in the global report (16). The recommended cascade incorporates ten core indicators (see Figure 1) with an additional twenty seven indicators to measure health system response to hepatitis B, including the delivery of prevention
activities and care to people already chronically infected (16). The inclusion of a cascade of care analysis is recommended to all member countries to monitor progression towards the 2030 goal of elimination, and assist the targeting of resources and equity of care delivery within health systems (16). In the first global report, the cascade for CHB estimated only nine percent of people living with CHB in the world were diagnosed. Less than one percent were on antiviral therapy (15). The access to care for people with CHB is currently cost prohibitive in some of the most populous LMIC countries. An improvement in the global cascade will require the scaling up of diagnosis, treatment availability and laboratory capacity (1).

Figure 1: The cascade of care as proposed by WHO in 2016.

1.1.3 Chronic hepatitis B in Australia, epidemiology and strategic responses

In Australia, an estimated 239,000 people were living with CHB in 2016 (17). The majority of people with CHB in Australia were born overseas in endemic areas or are Aboriginal and Torres Strait Islander people (18). HCC also disproportionately affects these communities (18-20) and is increasing faster than any other cause of cancer deaths (19, 21). Liver cancer was projected to be the sixth most common cause of cancer death in Australia in 2016 (note: cancer statistics for 2016 are still projections based on complete data from previous years) and has poor five-year survival which, unlike most other cancers, has not improved in the last decade (22).
In Australia, unlike near neighbours in the Asia-Pacific region, vertical transmission is not a major contributor to increasing prevalence in the last three decades. The increasing numbers of people living with CHB in Australia is due to migration from high and intermediate prevalence countries, especially from East and South East Asia (17, 18).

HBV vaccination has been promoted to priority populations since the 1980s. It became part of the universal infant program, National immunisation Program Schedule, in May 2000 (23). The coverage of the three dose schedule vaccine for infants is estimated to be 95% (17) but the coverage of birth dose is unknown, as it has not been routinely collected in states and territories. Australia’s HBV vaccination program has mainly reduced the incidence of acute HBV infections, preventing horizontal transmission rather than lowering prevalence due to ongoing migration from high and intermediate prevalence countries.

The strategic direction for hepatitis B in Australia has, like the global strategic direction, been slower than in other blood-borne viruses. The first National Hepatitis B Strategy was developed in 2010 and highlighted the issues of under-diagnosis, low levels of care, gaps in knowledge in the primary care workforce, and poor uptake of effective antiviral therapy. The first strategy contained goals but no targets and several indicators that had no mechanism for reporting (24). The Second National Strategy for Hepatitis B (2014-2017) introduced targets with a simplified framework of indicators (25) including a target of increasing the proportion of the people on antiviral treatment to 15%. As we reach the end of this second strategic reporting period, the objectives, goals and targets of the planned third national strategy are undergoing a review process.

1.1.4. Australian clinical recommendations and access to care
The Australian recommendations for care of people with CHB includes at least yearly measurement of viral load, regular assessment of liver function, and six-monthly HCC surveillance for those at increased risk of HCC (26). The access to clinical services and
monitoring in primary and tertiary care settings is covered under the Medicare Benefits Schedule (MBS) and subsidised antiviral therapy is available on the Pharmaceutical Benefits Scheme (PBS) for patients that meet the clinical criteria (27).

The initiation of antiviral therapy was restricted to specialist physicians until 2015 and therefore prescribing and dispensing had occurred mostly in hospital settings. In the last five years, initiatives have aimed at upskilling the primary care workforce. The goal has been to increase monitoring and treatment for people with CHB by general practitioners (GPs) or primary care settings, rather than specialised hospital services. In 2015, changes to prescribing regulations allowed accredited GPs who had completed advanced training to initiate, and community pharmacies to dispense, antiviral therapy for CHB, for script written in either hospital or the community by any type of provider (27).

1.1.5 The cascade of care in Australia
At the commencement of this doctorate, there was no measurement of the cascade of care for CHB in Australia. The cascade has been used since the initial study was published in 2014 (early release online) to monitor the national, regional and local health system responses and to advocate for resource allocation. The main challenge in our context continues to be the large proportion undiagnosed and the proportion of those diagnosed enrolled in care which has not changed markedly since 2012 (28). A more detailed discussion of the Australian cascade of care is contained in Chapters 2, 3 and 7.

1.1.6 Programs to improve CHB care in Australia
There have been various regional approaches to increase diagnosis and care of people living with CHB. Some examples include regional programs in South Western Sydney, New South Wales (B positive), a service from Royal Darwin Hospital in the Northern Territory (NT) and the Integrated Hepatitis B service (IHBS) at Melbourne Health in Victoria.
The B positive program evaluated cost effectiveness (29) and had a limited centralised registry to enhance care, including surveillance based at the New South Wales Cancer Council (30). The program targeted local GPs in an area of higher CHB prevalence to enrol patients in the program with parallel increase in education. Funding, which was part of a research grant, ceased for the B positive program/ pilot in 2016 and there was not further time or expansion from the local or federal government. In the Northern Territory, specialised hospital services have been working to improve care delivery to Aboriginal people in remote communities by providing support to primary care clinics and specialist outreach services, and developing and testing a local language resource about CHB in partnership with the community (31). This initiative has ongoing research and jurisdiction finding to expand the success of the initial piloted communities until 2023. In Victoria between 2012 and 2016, the Victorian State Government funded the IHBS to assist general practices with CHB care and refer people with CHB to community care from Royal Melbourne Hospital. The service worked with practices to improve care and treatment and to offer patients alternatives to tertiary care but did not have funding extended past the initial pilot.

The impact of the programs targeting areas is difficult to quantify. For example, the South West Sydney area targeted by the B positive project has the highest uptake of antiviral therapy in the country (17). That is likely in part due to the sustained effort of the B positive program, but other factors such as the interest of the local medical community, health promotion programs, education of health professionals and knowledge in the community may also contribute to high levels of testing, monitoring and treatment uptake. In the NT, monitoring for CHB has increased but numbers on treatment remain low and stable, possibly reflecting the geographical and logistical challenges of delivering antiviral medication to remote communities, as well as competing health needs in the community.

1.1.7 Summary

CHB is a chronic disease that requires delivery of services over many decades to prevent morbidity and mortality. A coordinated health system response partnering with people, including culturally and linguistically diverse communities, Aboriginal and
Torres Strait Islander people and other affected groups, is required to reach a goal of elimination by 2030 (1). Understanding the cascade of care can inform policy and programs to improve healthcare delivery, prevent transmission and improve outcomes for people living with CHB.

1.2 Theoretical framework

The work presented in this thesis has addressed gaps along the care continuum by examining elements of the cascade of care and developing methodological approaches to estimate those elements in the affected population. The studies presented used the conceptual framework of a “cascade of care analysis”, which draws from a range of relevant data sources to evaluate the health system response to a disease, to both inform the questions generated and methods used to address those questions.

This literature review investigates the complexity of the cascade of care in CHB and considers the utility, accessibility and generalisability of data from national, tertiary and primary care sources in Australia and overseas to understand how to measure and investigate the factors that influence the cascade.

1.3 Gaps in the research relating to the cascade of care

The work included in this thesis addressed gaps in the research relating to how people were accessing care in the Australian health system. Using the cascade and particularly the framework of previously developed HIV cascades, it evaluated healthcare delivery, the epidemiology of CHB in Australia, and the natural history of CHB to understand the steps in the cascade and how these could be measured.

Many areas of the CHB cascade have not been well studied, either in Australia or overseas. The initial focus of study in Chapter 3 is on the broad question of how a cascade could be constructed, which data sources could be used, and how it could be repeated at intervals to measure progress at a national level.
In Australia, CHB affects Indigenous people and there are important gaps in the research addressing the cascade of care for Aboriginal and Torres Strait Islander people, including the percentage accessing care and the accessibility of services and treatment. This was not a specific focus of the work, but is an important area of future research to ensure equity in CHB care delivery, especially given the burden of CHB in Aboriginal and Torres Strait Islander people.

Chapter 4 examines the issue of medication adherence, viral suppression and antiviral therapy as part of quality of care delivery in the cascade. Adherence to antiviral therapy is important to suppress viral replication, to reduce the risks associated with a higher viral load (32, 33) and to prevent the development of resistance to the treatment. Very little was known about adherence in the Australian health system or the proportion receiving antiviral therapy who were virally suppressed, which is now a WHO-recommended core indicator in the care cascade (16).

The work presented in Chapter 5 from a community health centre uses a small and specific population and looks at primary care challenges delivering HCC surveillance. The inclusion of a primary health example represents an important part of the cascade, where improvement is needed both in terms of HCC surveillance and of CHB care delivery in general practice. The national strategy recommends that service delivery needs to shift away from specialised services, but there is limited understanding about what is feasible and this model’s limitations. There was also little information about HCC surveillance in any setting in Australia (34).

Many different communities are affected by CHB in Australia, who have different experiences of education, migration and health service access overseas and who are now resident and require care in the Australian health system. The many diverse groups affected are likely to have specific cultural understanding and interpretation of what it means to have CHB. In Chapter 6, a study is presented on how African-Australians understand health risk relating to CHB. African-Australians are at greater risk of cancer at a younger age and recommended to start six-monthly HCC
surveillance at aged 20, two to three decades before other groups based on region of birth recommendations.

There are many gaps in our understanding of how other communities understand their health risks and their experience of stigma and discrimination, for example, those born in South East Asian countries and the Pacific Islands who are affected by CHB. Further research and partnership with communities aiming to understand CHB in different cultural contexts and to understand the impact of stigma is required.

Gaps identified

I. The absence of a cascade of care for CHB in Australia
II. No estimates of the proportion on treatment who are virally suppressed or adherent to treatment.
III. Limited research previously in Australia on the factors associated with adherence to antiviral therapy.
IV. Limited studies on quality improvement in either tertiary or primary care.
V. No qualitative studies on understanding HCC surveillance, especially for African Australians.

1.4 Questions addressed by this thesis.

1. What should a cascade of care look like for CHB in Australia?
2. How can a measure of viral suppression and/or adherence be incorporated into the cascade and what should be the definition of adherence?
3. What are the factors associated with poor adherence to antiviral therapy?
4. What are the challenges of HCC surveillance participation and optimal delivery in primary care?
5. What is the perspective of African-Australians with CHB and how do they perceive their risk of HCC?

1.5 Aims of the projects
The studies undertaken as part of this thesis sought to use available data sources to address the knowledge gaps in the care cascade and to explore the factors associated with poor care provision in different settings. The projects aim:

I. To develop a cascade of care for CHB that includes a care-related indicator.

II. To estimate the proportion who are virally suppressed and to develop a definition of adherence from pharmacy-based adherence measures that can be used in the cascade

III. To look at factors associated with adherence to antiviral therapy.

IV. To evaluate the impact of system support to enhance HCC surveillance in a community setting.

V. To understand how African-Australians living with CHB understand their risk of liver cancer and other health problems, and challenges they face in accessing the health system.

1.6 Overview of studies and methodological approaches

Study 1: Development of an Australian cascade of care
Question: What should a cascade of care look like for CHB in Australia?

Methodology
A literature review was conducted of current cascades of care in Australia in other BBVs, international cascades for both CHB and HIV and two national hepatitis B strategy documents and indicator frameworks. A further examination of the relevant national data sources from the PBS and MBS was undertaken, along with discussion with data custodians to understand the inputs, limitations, reporting timeframes and the reliability of these publically available data sources. Finally, the new care indicator and construction of a cascade of care was proposed.

Study 2: Adherence in a multicentre hospital study.
Questions
What percentage of people receiving antiviral therapy of CHB are adherent to their therapy?
What are the viral outcomes for people, in a real-world setting, receiving antiviral therapy for CHB?
What are the factors associated with adherence in CHB?
How should adherence be defined from a pharmacy-based adherence measure?

Methods
A retrospective study of data collected between 2010 and 2013 from four public hospitals in Victoria, using pharmacy dispensing, demographic and pathology data matched by hospital identification number. The adherence measure used was the medication possession ratio (MPR). The initial study calculated the proportion adherent to therapy and factors associated with adherence to oral antiviral therapy using multivariate logistic regression.

The second study from these data analysed the viral outcomes in participants who had been under treatment for 3 months or greater and had two or more viral loads in the hospital pathology service. It used Anderson Gill time-to-event analysis to define hazard ratios for different values of MPR that have previously been used to define poor adherence and explored the performance of different cut-off points and their association with viral outcomes.

Study 3: HCC surveillance in a community setting
Questions
How is the frequency of and participation in regular hepatocellular carcinoma surveillance affected by enhancing recall and reminder systems in the community?

Methods
A retrospective analysis of four and a half years of clinical data from a community health centre, during a period when an external service assisted the clinic to improve the management of chronic hepatitis B, including HCC surveillance. The data was
analysed in STATA with chi-squared tests for difference of proportions to determine factors associated with good adherence to HCC surveillance.

Study 4
What is the perspective of African-Australians living with CHB on how they perceive their risk of HCC and how might that influence participation in HCC surveillance?

Methods
Qualitative methods were used to investigate the beliefs and motivation that might influence understanding, perceptions of risk and health behaviour of African-Australians living with CHB. Semi-structured interviews were conducted to explore the individuals’ experience of diagnosis, care received in the health system, and their knowledge and understanding of health risks from CHB, including HCC. Participants were recruited using purposive sampling, based on gender, country of birth, age and educational background, from a hospital and three community health clinics in Victoria in 2016. Recruitment continued until data saturation occurred and no new themes were identified.

Demographic and background information was collected including age, country of birth, year of arrival in Australia, year of diagnosis, the context of diagnosis, religion and educational background. Data analysis drew on a grounded theory approach supported by NVIVO 11.21. The coding framework adopted a constant comparative technique. Regular meetings during the coding period developed consensus on the themes identified in the data.

1.7 Thesis plan

This thesis is divided into relevant sections as parts of the cascade of care of care were approached during the period of candidature. It contains a literature review (Chapter 2), four papers and one unpublished study that form the results section (Chapters 3-6)
and a final chapter summarising overall findings, and discussing limitations, strengths and the implications of the findings for policy and further research.

The literature review (Chapter 2) expands on the content contained in the published papers. It includes a more detailed review of the cascade of care for CHB in Australia and overseas, findings relevant to factors associated with poor adherence to antiviral therapy and HCC surveillance, and studies about knowledge of health risks in people living with CHB.

The results section (Chapters 3-6) includes the three published papers, one accepted paper and one unpublished study. Chapter 3 presents the findings from the study of data sources to construct the first cascade of care for CHB in Australia (Paper 1: *The cascade of care for people living with Chronic Hepatitis B: measuring access to diagnosis management and treatment*).

Chapter 4 presents the work on adherence. First, a multicentre study on factors associated with adherence (Paper 2: *Factors associated with poor adherence to antiviral treatment for hepatitis B*) and the second part of this chapter presents an analysis of viral outcomes and medication possession ratio (MPR).

In Chapter 5, the findings from a retrospective study focused on HCC surveillance and what was achieved with systems support in a community setting. (Paper 3: *The challenge of liver cancer surveillance in General practice: do recall and reminder systems hold the answer?*)

Finally, in Chapter 6, a qualitative study recruited African-Australians living with CHB to understand how health risks from CHB are understood (Paper 4: *Knowing and telling: How African-Australians living with chronic hepatitis B understand HCC risk and surveillance*).

This thesis is not only structured to examine different elements of how we can measure and understand the influences on the cascade of care in Australia, but also to
progress from large ecological data sets to individual care trajectories. The initial cascade study looked at national publically available data sources (Chapter 3). The second and third looked at a multicentre hospital study with 1026 participants and a further analysis of 632 participants in the study of viral outcomes and the association with MPR (Chapter 4), then a clinical cohort in a single site in the community with 67 participants (Chapter 5) and finally, a qualitative study with analysis of data from 19 participants (Chapter 6).

Each data source contributes to a different aspect of the cascade of care: how it can be measured; the factors that influence the care delivery; and how the individual experience within the health system needs to be considered in the delivery of services. The findings from this thesis highlight the overall health system performance, the challenges of care delivery in tertiary and primary care, and the challenges faced by people living with CHB.
Chapter 2: Literature review

The literature review for this thesis is divided into the sections of the cascade as they were approached during the period of candidature. It contains relevant literature to the end of 2017. At the policy level in Australia and overseas, the measurement of a cascade of care for CHB has become part of monitoring frameworks nationally (28, 35) and is now recommended for all countries by the World Health Organisation (WHO) (16). To assist the reader of this section, a date relevant to the submission of the paper, presented in later chapters, is included to act as a guide to the literature relevant to the context in which the study was performed.

2.1 Cascades of care

This section is relevant to the study presented in Chapter 3, Paper 1: *The cascade of care for Australians living with chronic hepatitis B: measuring access to diagnosis, management and treatment*, published in June 2015.

2.1.1. Introduction to cascades of care

Cascades of care or care continuums are a measurement of a health system’s response to a disease. They usually approach a single disease and provide a framework for evaluating a public health response (36). They are widely used in HIV programmes overseas and provide a tool for presenting epidemiological data and linking programme indicators to population-based outcomes (37) and are now recommended in the evaluation of country responses to CHB (16). Cascade analysis can be used in evaluation of country targets to highlight disparities in healthcare delivery and provide a tool for advocacy for the allocation of resources to clinical services, public health programmes and community organisations (16) (37, 38).

Data sources for cascades of care are context-specific and are representative of the structure of the health system in which they are placed, as well as the availability of the data within that system (16). The accuracy and detail is dependent on the both the data source and the way it is approximated to the context of the public health disease
in the cascade. The literature reviewed in this section includes a review of the Australian national strategies for CHB, discussion on the challenges within a cascade of care for CHB and a review of cascades overseas in CHB and HIV.

2.1.2 Challenges in the CHB cascade

CHB differs from many other communicable diseases of public health importance because treatment is only required in an estimated 15-25% of people affected (9, 39, 40). The estimates of the proportion requiring treatment are based on natural history studies, mathematical modelling, and single centre studies that vary in their ability to be generalised to the Australian context (41-43). The measurement of the proportion of people with CHB on treatment, recommended as an indicator, does not therefore measure the proportion who enrolled and are retained in care (16). Measuring the proportion of people on treatment who achieve viral suppression is a measure of continuity of care, as well as access and adherence to antiviral therapy, but also does not capture the people not on treatment and not being monitored (33).

2.1.3 Australian National Strategies for CHB and reporting of indicators

Prior to 2010, there was no comprehensive national strategic approach to CHB in Australia. Strategic direction had lagged 20 years behind HIV and nearly a decade behind Hepatitis C (44). The First National Hepatitis B strategy covered the years 2010-2013 and set three goals, seven indicators and no targets.


1. To reduce the transmission of hepatitis B
2. To reduce the morbidity and mortality caused by hepatitis B
3. To minimise the personal and social impact of hepatitis B

The indicators related to a proposed cascade of care and part of the first National Hepatitis B Strategy were: the number diagnosed; the proportion diagnosed; the specific indicator-related measurement of the delivery and quality of chronic disease
care; the proportion on treatment; the proportion with a late diagnosis prior to HCC notification; and the proportion participating in HCC surveillance (24).

The Annual Surveillance Report of HIV, viral hepatitis, sexually transmitted infections (STI) (hereafter referred to as the annual surveillance report) and the BBV/STI surveillance and monitoring plan have reported on the national indicators for the national strategies. For the indicators related to care of people with CHB, there was no proposed reporting mechanism or data source and no structure proposed relating to a cascade of care. Annual surveillance reports during the first strategic period (2010-2011) reported the number of acute and unspecified cases of Hepatitis B by jurisdiction and prevalence estimates (45-47) but did not provide estimates on the proportion diagnosed, or on linkage to, engagement in or retention in care-related indicators (45-47) as recommended in a cascade of care.

In the Second National Hepatitis B strategy released in 2014, the goals remain unchanged, the number of indicators were reduced (25) and 2017 targets were introduced: 80% of all people with CHB diagnosed and 15% on antiviral treatment by the end of 2017 (25). The proportion on treatment was the only indicator relating to care provision for people already diagnosed with CHB retained in the new indicator framework. In the strategy, a recommendation in the surveillance and monitoring section referred to the importance of measuring monitoring and care for people not on treatment as “critical” and it was suggested that a care-related indicator such as HBV DNA be considered (25). The proportion diagnosed and the proportion on treatment was first reported in 2015 in the annual surveillance reports, as was the first cascade for care for CHB (35). Reporting on the cascade is now part of the surveillance and monitoring plan and annual surveillance reporting (28, 35). The third national strategy is currently being written for the next strategic period.

2.1.4 Cascades of care prior to 2013
The only cascade of care in CHB prior to 2013 was published in the USA in 2011 (Figure 2) and produced wide-ranging estimates for people living with CHB and, as a result, also wide-ranging estimates for both the proportion diagnosed and number entering care
The data sources in this study varied, as in all cascades and, for diagnosis and number entering care, used proportions from small studies that were not focused on measuring these outcomes in the population. The estimates of the proportion requiring treatment applied a relatively high proportion requiring treatment (25%) (43). The treatment data was sourced from drug company prescribing data and provided the most certain of all the estimates (43).

In summary, while the first USA cascade had a large degree of uncertainty of the estimates when applied to the whole USA population, it provided a framework to consider the creation of an Australian cascade.

*Figure 2: 2011 care cascade for CHB in the USA by Cohen et al.*

Linkage to care for people living with HIV has been an ongoing focus of the global upscaling of highly active antiretroviral treatment. Definitions of care continuums that have included estimates of the proportion enrolled in ongoing care and health outcomes in priority populations have appeared in the literature since the mid-2000s, but mainly focused on cohorts in care (48, 49). As the focus moved from discovery of
effective treatments to treatment access for whole populations, cascade analysis emerged as a tool to summarise health system performance, evaluate access and highlight disparities in care delivery. In 2011, an HIV cascade was developed in the USA by Gardner et al. (see Figure 3) which defined stages of care and took a whole health system approach, while acknowledging assumptions and data limitations (50). The methodology was later adopted in WHO and USA surveillance reporting (37, 51) and in Australia a cascade of care for HIV was included in surveillance reports in 2014 (52). The clear relationship between adherence and viral suppression and mortality and morbidity was established in HIV. Viral suppression is now recommended to be reported rather than adherence, as was in the original cascades (50).

Figure 3: 2011 Spectrum of care analysis for HIV in the USA from Gardner et al.
and apply it to the population living in Australia (54). The census method has been validated in an Australian context using antenatal data (55) and used to generate area-specific estimates of disease burden by Medicare Local and then Primary Health Network (17, 54). The proportion diagnosed has previously been estimated using a mathematical model which utilises National Notifiable Disease Surveillance System (NNDSS) data to derive the estimate from the number ever diagnosed over those who have ever had the disease (18).

The next step in the cascade was to consider linkage to care. In Australia for HIV, this is defined as receiving follow-up testing within three months after the initial diagnosis, with these data available from a large cohort study (52). The same cohort in the HIV cascade has also been used to estimate people adherent to treatment and the number who are virally suppressed. In CHB, however, there is no similar cohort in Australia and no estimates of enrolment of care with estimates of viral suppression from small single centre studies (56, 57).

All people living with CHB should receive regular monitoring (24) with at least yearly viral load and liver function tests. The number of MBS items reimbursed for individual tests are publically available by jurisdiction (58, 59). While assessment of liver function and HBV viral load or HBV DNA are recommended for the monitoring of disease activity in CHB to inform treatment decisions (60) there is no specific MBS item number for liver function tests. Rather, they are listed under general biochemical tests that can include other measurements, for example of renal function, that are being done for health problems other than CHB (58, 59). The HBV DNA item number, which is CHB-specific, has two MBS item numbers: one for monitoring when not on treatment (item 69482 reimbursed yearly) and one for monitoring on antiviral treatment (item 69483 which can be reimbursed up to 4 times a year) (59). In considering the cascade of care for HIV, HIV viral load was used as a proxy for linked to care, but in the context of CHB in Australia, item 69482 HBV DNA was a measurable marker of receiving care when not on treatment. The number of people on antiviral treatment for CHB in the Australian health system, with almost universal access to subsidised treatment on the PBS, can be estimated from publically available data.
2.1.6 Summary of literature on cascades

The measurement of cascade of care indicators is an important part of monitoring the performance and the progress of the delivery of healthcare to people living with CHB. There was no proposed structure of a cascade of care prior to 2013 and no clear reporting framework for an “enrolled in care” related indicator. After the review of National Strategy indicators, a comparison with cascade literature in the USA in both CHB and HIV – and considering the disease-specific challenges of CHB and data sources – a cascade of care was developed to include novel and relevant ways to measure healthcare access.

Cascade analysis in CHB is now recommended by WHO and has been incorporated into Australian annual surveillance reports (61-63). The first global cascade of care was published in 2017 (15).

2.2 Adherence to antiviral therapy

This section of the literature review is relevant to Chapter 4. This chapter includes Paper 2: Factors associated with poor adherence to antiviral treatment for hepatitis B (published June 2016) and an unpublished study on viral outcomes and the association of medication possession ratio (MPR).

2.2.1 Introduction to adherence and its place in the cascade

In 2016, the Global Health Sector Strategy on Viral Hepatitis set global treatment targets (1). The targets included the proportion of patients with chronic HBV infection on treatment, and in whom HBV DNA is suppressed, as a core indicator in the monitoring and evaluation framework of the recommended cascade of care (1, 16). The first global hepatitis report in 2017 estimated the proportion virally suppressed on treatment (using a small single centre study) highlighted the need for both further research and better data sources (15, 64).
First line CHB therapies are effective at suppressing HBV DNA (65, 66). Maximising adherence in chronic disease delivery is important to achieve goals of treatment which include the reduction of the risk of HCC and cirrhosis and preventing the development of resistance (16, 51). Current oral therapies are single tablet daily dosing, which is advantageous when promoting adherence (67, 68). However, CHB treatment is often started when a person with CHB is asymptomatic and may not result in any discernible health advantage from regular medication-taking, which has been shown in other chronic conditions to negatively impact adherence (69). Viral breakthrough (VBT) (greater than 1 log_{10} increase in HBV DNA) has been shown to be more likely in individuals with poor adherence (57, 70-72).

Health system performance, including factors such as the ease of access to clinical services, affordability and consistency of supply, can influence the proportion of the treated population who are adherent (69) and are specific to the health system in which treatment is delivered (73). Other causes of, or factors related to, poor adherence encompass environmental, disease and individual factors that are often poorly understood by treating clinicians (73). Periods of poor adherence may result from temporary or more long-term disengagement from care due to competing social, economic or health-related pressures (69).

There are few large real world studies estimating the proportion of people on CHB treatment who are adherent or achieve viral suppression. Previous cascades of care, including the global cascade, have estimated the proportion from small cohorts that are limited in their generalisability (43, 63).

In Australia, an estimate of the number of people taking treatment who are virally suppressed or adherent to therapy, as recommended by WHO, has not yet been incorporated as an indicator into strategy frameworks or into surveillance reports as part of the cascade of care at a national or jurisdictional level (state and territories) (1, 16).
2.2.2 Antiviral treatment access in Australia

In Australia, there is access to subsidised antiviral therapy for all Medicare eligible people with CHB who meet PBS clinical criteria. Treatment is subsidised if there is cirrhosis with a detectable viral load or, in the absence of cirrhosis, an elevated ALT level and an HBV DNA level > 20,000 IU/ML if HBeAg positive, or >2000 IU/ML if HBeAg negative. Antiviral treatment is also recommended for people who are immunosuppressed, and for pregnant women with a HBV DNA > 10,000,000 IU/ML to reduce the risk of perinatal transmission, but treatment is not subsidised by the PBS for these indications. The initiation of antiviral therapy was restricted to specialist physicians until 2015, when the prescribing criteria were changed to include GPs who have S100 prescribing authority. During the time period of the data collected for the adherence studies included in this thesis (2010-2013) most people were prescribed and dispensed antivirals in tertiary settings (74, 75).

2.2.3 Adherence measures

Adherence can be measured by self-report, physician report, measurement of drug levels (dependent on assay availability), direct measurement with memory cap bottles, and indirectly through pharmacy data (73). In CHB, all measures have been used to measure adherence across the body of published literature (see Table 1) but there has been a lack of consistency in definitions of adherence (70).

A drug assay is not currently routinely available for either of the two main oral therapies, entecavir and tenofovir. This method has only been used in assessing adherence to adefovir (76) an antiviral therapy no longer recommended for use due to its low barrier to the development of resistance (77). A study in Holland used memory cap bottles in 100 consecutive CHB patients to measure adherence. However, this method for estimating adherence in a population outside a trial is limited, as use of a specific device is likely to introduce an observational bias (78).

Multiple HBV adherence questionnaires have been developed and different methods applied across studies of self or clinician reported adherence (56, 57, 72, 79-81). The methods for measuring adherence have included any mention of poor adherence
recorded in the patient record by the clinician (72, 82), a single assessment of adherence (57, 80), prospective evaluation over a time period with multiple assessments using a standardised tool (83) or simultaneous assessment of both self and clinician report (56). Both self and clinician report can introduce social desirability bias. Specifically using any mention of adherence in clinical notes in a retrospective study when evaluating viral outcomes is likely to lead to bias, as clinicians are more likely to enquire and record a comment about adherence if an increase in HBV DNA is observed during patient care (72, 82). A study that used combined clinician and patient self-report showed that physicians overestimated adherence when compared to patients’ own reports (56).

Pharmacy adherence measures (PAMS) estimate medication in hand during an observed treatment period. PAMS can be easily calculated from pharmacy records and are less likely to have bias inherent in self-assessment or physician estimates of adherence. They measure the maximal possible adherence during a time period, as people can be dispensed medication yet remain poorly adherent (84).

Different PAMS methods include pill counts (the count of medication used on return visit to the pharmacy), pill pick up (a dichotomous measure of visits to refill prescriptions rather than tablets) and medication possession ratio (64, 71, 85, 86). Medication possession ratio (MPR) is a measure commonly used in HIV literature and has been correlated with viral outcomes, morbidity and mortality (84). MPR can, like other measures of adherence, over- or underestimate recent adherence due to stockpiling, loss of or not taking dispensed medication. Like other PAMS, it is measure of the best possible adherence during a time-period. MPR, as it is based on measurement of pharmacy data, misses primary non-adherence or people who never fill the first script, which can be up to one third of scripts written in other chronic diseases (87).

2.2.4 Estimating adherence
A limited number of studies have measured adherence of people taking antiviral therapy for CHB (57, 70, 78, 81) and only two in LMIC (81, 83). Estimation of poor
adherence has varied widely between 10-65% (70) of people on treatment using the different methods and over variable observation periods, from a single assessment of self-reported adherence (56, 57, 80) up to four years of clinical records (82). Different health systems and structures where cost, access or availability of medication varies may impact adherence within that system and limit the generalisability of the findings of adherence studies to other settings (67, 73, 88).

In studies using PAMS, estimates of poor adherence have varied: 45% in a large USA health insurance data set over 12 months (85); 35% in a randomised controlled trial assessing 105 participants over 24 months (86); 20% in a Spanish study (64); and 7% in a clinical cohort in Japan that did not follow up all patients, so may have underestimated the proportion adherent. The studies using PAMS as the measure of adherence have used different definitions to define poor adherence (see Table 1).

In Australia, there have been two studies of adherence utilising self-report +/- physician report as the adherence measure (56, 57). One was published after the initial paper included as part of this thesis was submitted (57). Both studies recruited in different hospital sites in Sydney. The first study comprised 80 participants (self and clinician reported adherence using a standardised assessment tool) and in the second, 211 participants were surveyed and asked adherence in the previous month. Both studies, using different definitions, found poor adherence in 35% of patients surveyed (56, 57). No Australian estimate of adherence for CHB and antiviral therapy has used PAMS.

2.2.5 Factors associated with poor adherence in CHB

The factors associated with poor adherence in published studies have included younger age of patients (76, 78, 79, 85), treatment with lamivudine (85) and recent initiation of therapy (85). Other factors variably associated with lower adherence on univariate analysis have included female sex, lower income (79), male sex (81) and positive HBV e antigen (HBeAg) (76).
In Australian studies, factors associated with poor adherence have included younger age of patients, language discordance between patient and clinician, and poor adherence to other medication (56, 57).

2.2.6 Defining poor adherence and associated viral outcomes

For published studies using PAMs, the threshold used for poor adherence has varied from 90-95% of prescribed medication dispensed for the observed period (64, 71, 85, 86). These thresholds have been based on a largely arbitrary assignment of a value to define adherence (85, 89) rather than a definition based on viral outcomes. VBT, defined as $>1 \times \log_{10}$ rise in HBV DNA, in two studies of adherence to entecavir showed a trend towards being associated with the chosen cut-off points, but were insufficiently powered to demonstrate significance (64, 71). A summary of adherence studies, method and adherence definitions appears in Table 1.

Previous studies have demonstrated a relationship between reported adherence and VBT (70-72, 76, 78, 79) but until recently there has not been a definition of adherence based on viral outcomes. A recent study showed VBT in the previous 12 months was associated with self-reporting “greater than one missed dose” in the last month (57). In this study, there was not a clear dose relationship or increased risk of VBT with a greater number of missed doses reported. The absence of a dose response relationship with the report of increased number of missed doses is probably due to social desirability bias: the patient not wanting to report higher number of missed doses (84). The authors concluded that greater than one missed dose per month represented approximately 93% of medication taken and therefore supported the <90% threshold previously used for poor adherence. While this study provides a very useful guide to clinicians about the assessment of adherence using a routine clinical question and the association with adherence and VBT, the validity of the translation of a self-reported method to a percentage definition of medication taken to define adherence is unclear.

The largest published study of the relationship between adherence to antiviral therapy and viral outcomes in CHB was a multicentre study from the USA that used a
retrospective review of clinical notes, in which any physician documentation of suboptimal adherence was used as a definition of non-adherence (72). Virological breakthrough occurred in up to ten percent of 557 participants at 24 months, with poor adherence ranging from nine to sixteen percent and higher in patients taking tenofovir. The retrospective nature of the data collected and the method to define poor adherence in the study likely introduces bias, as clinicians not under prospective study conditions in routine clinical practice would be more likely to ask about adherence if VBT was observed (72).

2.2.7 Summary of adherence literature and research implications
There is relative lack of research relating to adherence and virological outcomes in people receiving antiviral treatment for CHB. Understanding the factors associated with adherence in people undergoing treatment for CHB in Australia is important to understand the quality of antiviral treatment delivery and to prevent poor outcomes. The estimation of the proportion of people treated with antiviral therapy CHB who are adherent and have viral suppression are a central element of the cascade of care. Adherence is associated with viral outcomes in CHB but the relationship between PAMS or MPR values (90-95%) that have been used to define poor adherence in previous studies has not been established. In Australia, current estimates on the proportion of people who are virally suppressed comes from a single centre study of 211 participants (57). Measuring adherence, viral suppression and the factors associated with poor adherence can be used to inform the cascade of care and report on a key indicator, as is now recommended for all countries by WHO (16).
Table 1: Summary of adherence studies grouped on type of adherence measure used

<table>
<thead>
<tr>
<th>Study type</th>
<th>Author and year</th>
<th>(n)</th>
<th>Country</th>
<th>Method of assessing adherence</th>
<th>Period observed</th>
<th>Definition of non-adherence</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self and physician report</td>
<td>Chotiyaputta 2011&lt;sup&gt;79&lt;/sup&gt;</td>
<td>111</td>
<td>USA</td>
<td>Self-report</td>
<td>12 month</td>
<td>&lt;100%</td>
<td>LAM, TBV, TDF, ETV, ADV</td>
</tr>
<tr>
<td></td>
<td>Sogni 2011&lt;sup&gt;80&lt;/sup&gt;</td>
<td>190</td>
<td>France</td>
<td>Questionnaire</td>
<td>Single survey</td>
<td>&lt;100 (perfect)</td>
<td>LAM, TBV, TDF, ETV, ADV</td>
</tr>
<tr>
<td></td>
<td>Ha 2011&lt;sup&gt;82&lt;/sup&gt;</td>
<td>189</td>
<td>USA</td>
<td>Physician report</td>
<td>4 years</td>
<td>any report in notes</td>
<td>ETV, ADF</td>
</tr>
<tr>
<td></td>
<td>Giong 2012&lt;sup&gt;83&lt;/sup&gt;</td>
<td>80</td>
<td>Australia</td>
<td>Self and physician report</td>
<td>VAS survey</td>
<td>&lt;10 VAS scale</td>
<td>LAM, TDF, ETV, ADV</td>
</tr>
<tr>
<td></td>
<td>Peng 2015&lt;sup&gt;81&lt;/sup&gt;</td>
<td>211</td>
<td>China</td>
<td>PAM and self-report</td>
<td>12 months</td>
<td>Self-reported</td>
<td>LAM, TBV, ETV, ADV</td>
</tr>
<tr>
<td></td>
<td>Abreu 2016&lt;sup&gt;84&lt;/sup&gt;</td>
<td>183</td>
<td>Brazil</td>
<td>Self-report</td>
<td>CEAT HBV survey</td>
<td>CEAT HBV scale &lt;80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sheppard-Law 2016&lt;sup&gt;57&lt;/sup&gt;</td>
<td>281</td>
<td>Australia</td>
<td>Self-report</td>
<td>survey</td>
<td>Missed doses/ month</td>
<td>ETV, TDF</td>
</tr>
<tr>
<td></td>
<td>Ha 2016&lt;sup&gt;72&lt;/sup&gt;</td>
<td>557</td>
<td>USA</td>
<td>Self and physician report</td>
<td>24 months</td>
<td>any report in notes</td>
<td>ETV, TDF</td>
</tr>
<tr>
<td>Direct</td>
<td>Hilleret 2011&lt;sup&gt;76&lt;/sup&gt;</td>
<td>47</td>
<td>France</td>
<td>ADV level</td>
<td>36</td>
<td>Any undetectable ADV level</td>
<td>ADV or ADV+ LAM</td>
</tr>
<tr>
<td></td>
<td>Van Vlerken 2015&lt;sup&gt;78&lt;/sup&gt;</td>
<td>100</td>
<td>Netherlands</td>
<td>memory cap bottle</td>
<td>16</td>
<td>&lt;80%</td>
<td>ETV</td>
</tr>
<tr>
<td>Studies using PAMS</td>
<td>Chotiyaputta 2010&lt;sup&gt;83&lt;/sup&gt;</td>
<td>11,100</td>
<td>USA</td>
<td>PAM* (MPR)</td>
<td>12mths</td>
<td>&lt;90%</td>
<td>LAM, ETV, TDF, ADV</td>
</tr>
<tr>
<td></td>
<td>Berg 2010&lt;sup&gt;86&lt;/sup&gt;</td>
<td>105</td>
<td>Germany</td>
<td>PAM (Pill count)</td>
<td>24</td>
<td>&lt;94%</td>
<td>TDF, TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>Kamezaki 2013&lt;sup&gt;71&lt;/sup&gt;</td>
<td>203</td>
<td>Japan</td>
<td>PAM</td>
<td>26mths</td>
<td>&lt;90%</td>
<td>ETV</td>
</tr>
<tr>
<td></td>
<td>Romero Diaz-Moroto 2015&lt;sup&gt;84&lt;/sup&gt;</td>
<td>85</td>
<td>Spain</td>
<td>PAM</td>
<td>12</td>
<td>&lt;95%</td>
<td>ETV</td>
</tr>
</tbody>
</table>

PAM=Pharmacy adherence measure, MPR medication possession ratio CEAT HBV = assessment of adherence questionnaire for HBV, VAS= visual analogue scale, Drugs: ADV= adefovir, LAM= lamivudine, ETV= entecavir, TDF=tenofovir, TBV=telbivudine, FTC= Emtricitabine,
2.3 HCC surveillance in people living with CHB

This section presents the literature relevant to the study presented in Chapter 6 as Paper 3: The challenge of liver cancer surveillance in general practice: Do recall and reminder systems hold the answer? (published in November 2017).

2.3.1 Introduction to HCC in CHB and HCC surveillance and the cascade of care

There are regional differences in proportion of HCC attributable to CHB (2, 90, 91). The risk of the development of HCC in an individual living with CHB is increased in the presence of co-factors, including: cirrhosis, increasing age, certain HBV genotype or subgenotypes (especially A1 and C), male gender, coinfection with hepatitis C, D or HIV, other causes of liver disease including alcohol-related injury and non-alcoholic steatohepatitis (NASH) and environmental factors such as the ingestion of aflatoxins (92). While the development of HCC is more likely when cirrhosis is present, HCC has been reported to occur in the absence of cirrhosis in 10-40% of all HCC (93). Increasing HBV viral load is also independently associated with increased risk of both HCC and cirrhosis in a dose relationship response above 2000 IU/ml (9, 94, 95). Antiviral therapy has been shown to reduce the risk of HCC and can reverse cirrhosis and fibrosis (6).

HBV Genotypes and subgenotypes have different risk profiles for the development of HCC. The geographic distribution of different genotypes informs recommendations for surveillance by region of birth and age (see Table 2.2). In Asia, genotype C is associated with a higher risk of HCC than genotype B (96, 97) and in the Sub-Saharan African region, individuals with genotype A (subgenotype A1) have an increased risk of development of HCC than those with other genotypes (98). Studies in Southern Africa have also shown that the median age for HCC related to subgenotype A1 were 6.5 years earlier than other genotypes in the region (99). In Australia, many HBV genotypes are present in the affected population due to the history of migration from Europe, Asia, South America and Africa. Aboriginal and Torres Strait Islander people from the Northern Territory have a unique genotype C4 variant (100) and have three to six times the risk of developing HCC from all aetiologies. In the last two decades, an
increasing incidence of HCC has been observed in jurisdictions that adequately report Indigenous status (20, 101-103).

HCC surveillance is part of standard care delivery in CHB and the proportion eligible for surveillance receiving it was an indicator in the first National strategy document (24). It was not included in the second national strategy (25) as there was no available reporting mechanism, because both the MBS item number for ultrasounds could represent scans for other purposes and the number of people requiring HCC surveillance was unknown. In other contexts, for example in measuring the cascade of care for HIV, periodic surveys or clinical cohort data can be used to examine an aspect of care delivery. No such cohorts exist for CHB in Australia and so the number of people eligible for and the proportion receiving HCC surveillance is currently not measured.

2.3.2 HCC surveillance recommendations
The standard of care for liver cancer surveillance is 6-monthly ultrasounds with or without alfa-fetoprotein (AFP) (26, 39, 104-106). Liver ultrasounds have a sensitivity estimated 58%- 89% and specificity greater than 90%, with better performance when skilled operators are used (107). AFP has poor sensitivity and specificity, is not cost-effective and has limited added value when compared with ultrasound alone, but is still recommended by many guidelines (108) (see Table 2). In some remote settings, where access to radiology services is poor, it has been used to identify those who would benefit from ultrasound (109). Surveillance has been estimated to be cost-effective when the annual incidence of HCC exceeds 0.2% per annum (110). Other techniques for HCC surveillance, including biochemical tests and other imaging, have not been either validated or evaluated in terms of cost effectiveness and are not widely used.

The recommended 6 month interval of surveillance is based on natural history – the average tumour doubling time of six to eight months (107) – and randomised trials that showed no increased survival benefit from shorter time periods (111) but it is
unclear whether the threshold interval in population-wide screening will deliver a mortality benefit.

HCC surveillance has been recommended by professional bodies and country guidelines (see Table 2). HCC surveillance in a population is affected by the feasibility and cost of regular ultrasounds, the availability of treatment for surveillance detected tumours, and the structure of the health system (112). In Asia, use of risk assessment tools is recommended by the Asian Pacific Association for the Study of the Liver (APASL) (see Table 2) but these tools have not been validated outside South East Asia and are not currently recommended for use in Australia (113, 114). A predictive tool has also been developed in Europe for Caucasian patients on treatment to help identify patients who would benefit from surveillance (115). Current research into other markers in blood and urine could be utilised in HCC surveillance and may, with further development, be superior to the performance of AFP as a screening test, but none are currently recommended for routine use (106).

In Australia, recommendations for who should be enrolled in surveillance follow the American Association for the Study of Liver Disease (AASLD) guidelines updated in 2011 with a modification to include surveillance recommendations for Indigenous Australians (103, 116). The age and region recommendations are based on different strengths or grades of evidence (104-106). There are no recommendations that account for the decrease in risk of HCC when on antiviral treatment (106).

The weakest grade of evidence in the current guidelines is the recommendation for surveillance of men and women with CHB born in African countries or who are of African background from the age of 20 years (39, 104, 105). This recommendation is based on prevalence of the A1 sub genotype in Africa and small case control studies from South Africa (98, 99). A recent retrospective study in the USA showed that HCC was uncommon in African Americans without cirrhosis and cancers did not occur under the age of 40 years (93). The authors of the study suggested a change to the AASLD recommendation for HCC surveillance in African Americans from 20 to 30 years. However, the population differences in Australia and limitations of the study need to
be considered: the number of HCC in African Americans living with CHB were low; the data came from a veteran database so was almost exclusively male; and as all African American participants were born in America, the authors suggested that acquisition of the virus in adult life was likely (93). Most African-Australians in contrast were born overseas and acquired CHB early in life. WHO has also recognised that there is poor knowledge about CHB in the African region and that further research needs to be undertaken to understand the natural history of HCC to further inform strategies, including HCC surveillance in these affected populations (1).

*Table 2: Hepatocellular surveillance recommendations from countries and professional bodies*

<table>
<thead>
<tr>
<th>Source</th>
<th>HCC surveillance recommendations</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Region of origin</td>
<td>General</td>
</tr>
<tr>
<td>WHO</td>
<td>Not specified</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family history</td>
</tr>
<tr>
<td>EASL</td>
<td>Not specified</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family history</td>
</tr>
<tr>
<td>NICE</td>
<td>Not specified</td>
<td>Metavir Stage &gt;F2 or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20,000 IU/MI AND &gt; 40 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AND Family history</td>
</tr>
<tr>
<td>APASL</td>
<td>Not specified</td>
<td>Utilise risk scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dependant on cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>effectiveness in country</td>
</tr>
<tr>
<td>AASLD</td>
<td>Asian male &gt;40 y</td>
<td>Region and age criteria</td>
</tr>
<tr>
<td></td>
<td>Asian woman &gt;50 y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>African &gt;20 y</td>
<td>Family history</td>
</tr>
<tr>
<td>Australia</td>
<td>Asian male &gt;40 y</td>
<td>Region and age criteria</td>
</tr>
<tr>
<td></td>
<td>Asian woman &gt;50 y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>African &gt;20 y</td>
<td>Family history</td>
</tr>
<tr>
<td></td>
<td>ATSI &gt;50 y</td>
<td></td>
</tr>
</tbody>
</table>

2.3.3 The mortality benefit and harms of HCC surveillance

HCC surveillance aims to detect cancer early, at a stage amenable to curative treatments, and prevent HCC-related mortality (116). HCC often presents at a late stage and has a very poor five-year survival (118). Small tumours can be treated successfully with local resection and chemo embolisation techniques or liver transplantation, while larger or metastatic tumours are only suitable only for palliation (105, 106).

The evidence for reduction in mortality with HCC surveillance in CHB is not without controversy (110). Recent systematic reviews that have included HCC of mixed aetiology, hepatitis C infection and other causes of liver injury as well as CHB, draw different conclusions about the mortality benefits and the strength of evidence for HCC surveillance (119-121). Reported mortality benefits in surveillance-detected HCC have not always accounted for lead-time bias, the length of time between the detection of HCC from a surveillance test and its usual presentation, and the effect of variable surveillance intervals (120, 122).

Two large randomised control trials in China compared HCC surveillance versus no surveillance in participants with CHB (60, 123). One study found a reduction in HCC-related mortality in the intervention arm of the study, which used ultrasound and AFP. After 2 years of nearly 40% (60) however, there were issues with the study, including poor participation in the intervention arm, poor follow-up in the control arm, clustering effects of recruitment, and issues with the blinding technique used, which may have influenced the findings (119). A second study in China used a patient-randomised design stratified by township. It showed no clear mortality benefit with six-monthly AFP followed by ultrasound referral for high AFP values. There were also methodological issues in this study, with low participation in the intervention arm, sampling technique and analysis (108, 123). The study found fewer later-stage HCC in the intervention arm but no over effect on survival or HCC-related mortality. Randomised trials have also been used to compare mortality benefit of ultrasound surveillance intervals with no survival benefit seen in three- versus six-month intervals (124) or four- versus twelve-month intervals (111).
The observational studies and meta-analysis of studies assessing the mortality benefit from HCC surveillance have usually included participants with risk of HCC from mixed aetiology (92, 120). A recent systematic review focused on HCC surveillance, and cirrhosis from different causes showed evidence of a survival benefit (120). This analysis included studies that used different methodologies, surveillance intervals (six months to two years) and definitions of participation, which complicated the interpretation of the observed reduction in HCC-related mortality (120). A systematic review of HCC surveillance in all chronic liver disease also found evidence gaps and concluded that there were uncertainties about the mortality benefit of HCC surveillance (119). In the development of the WHO care and treatment guidelines for CHB the evidence for or against mortality benefits of surveillance analysis only included studies where CHB was the predominant aetiology (14). Overall a significant difference in five-year survival was observed in surveillance (31.4%) versus no surveillance (23.3%) with surveillance detecting smaller tumours that were more likely to fit current criteria for potentially curative treatments but drew on the studies in China that has methodological flaws (14). The outcomes from HCC surveillance programs or population-based registries have also been reported from Japan, Korea and New Zealand and these programs have shown mortality reduction and improved five-year survival in the population compared with prior to the program (125-127).

Harms associated with surveillance have been poorly documented (119, 128). A recent study that examined harms related to HCC surveillance for cirrhosis, CHB and HCV in the USA showed that false positives from ultrasounds resulted in harm, most frequently characterised as unnecessary radiation exposure due to follow-up scans (128).

2.3.4 Participation and adherence to HCC surveillance
Participation or adherence to population-based six-monthly HCC surveillance with ultrasound has been shown to be difficult to achieve, with findings from a range of different healthcare settings and countries showing proportions of eligible patients that are receiving surveillance are between 1.7-33% (122, 125, 127, 129). Participation
and adherence has been shown to be poor in both people with cirrhosis and in countries where national programs have been adopted to promote HCC surveillance and reduce liver-cancer-related mortality (62, 122, 125, 129). A recent systematic review of nine studies in the USA estimated pooled surveillance coverage in 17,286 eligible patients with cirrhosis of mixed aetiology, to be only 18% (120). Studies in the USA that are specific to HCC surveillance for CHB have found poor adherence and participation rates. Annual scanning was only carried out in 14% of 537 with cirrhosis, a high risk group for HCC (62); optimal adherence to six-monthly surveillance, following the criteria recommended by the AASLD guidelines (Table 2), occurred in 6.7% among 4576 non-cirrhotic patients (129); and 23% of 1329 people with CHB were receiving HCC surveillance (130). In Korea, a study of 604 people with CHB found that only 39% had ever attended screening and only 12.3% had attended in the last six months (131). Factors associated with improved HCC surveillance overseas have included older age (131), frequency of clinic visits (tertiary or primary care), specialist service involvement, and higher socio-economic status (122, 129). Definitions of participation and optimal adherence to surveillance are not consistent across the literature and vary from ever having an ultrasound, to semi-annual and biannual ultrasound (119, 120).

In Australia, the number of people requiring HCC surveillance and the rates of participation in HCC surveillance are unknown, but given the cascade estimates it is reasonable to assume that overall HCC participation in the eligible population is low (28). Small local studies in Australia suggest that only a quarter to a third of people who should receive surveillance do, even with enhanced reminder services and dedicated nursing staff (34, 132). HCC surveillance uptake requires clinicians to be enrolling appropriate patients in surveillance, ordering the tests at appropriate intervals, and patients then attending for their ultrasounds (63).

2.3.5 Interventions to systematise or improve HCC surveillance

While poor participation and inadequate HCC surveillance is well documented, few interventions aimed at improving surveillance have been reported (133). The possible targets for interventions include increasing the ordering of tests by clinicians, health
systems improvement to increase access or affordability to tests, and patient education to improve knowledge and participation (134, 135) (34). In Korea and Japan, countries with HCC as one of the top five causes of cancer deaths, national programs for liver cancer include both screening for viral hepatitis and a systematic approach to HCC surveillance (125). In Korea, a survey from 2010-2011 showed an increase in participation in HCC surveillance (defined as “an ultrasound in the last 2 years”) compared with a similar survey conducted in 2001 after introduction of a national cancer screening program that included people with CHB over 40 years of age in 2003 (131). Radiology-service-generated reminders in the United Kingdom (136) and mailed outreach reminders, which included systems navigation in the USA, were shown to be effective in improving HCC surveillance rates in people with cirrhosis (137).

In Australia, a nurse-led clinic set up to increase the adherence of cirrhosis patients to surveillance protocols achieved adherence 72% to HCC surveillance, defined as “within the last 7 months” (138). The B positive program in New South Wales enrolled CHB patients in a registry and supported GPs to provide guideline-based care, including HCC surveillance. There were difficulties with slow enrolment initially and the funding was discontinued in 2016 (30, 41). A tertiary hospital study in South Australia improved participation in HCC surveillance, of six-monthly scans over a 2 year period, from zero to 64% over a five-year period, by improving clinician education, recall systems and a focus on patient education in the form of written information (34).

Experience from other cancer surveillance programs, specifically breast and cervical, have shown that involvement of or embedding programs in the primary care setting can have a positive impact on participation in cancer screening, and tools, patient knowledge and development of decision aids can increase knowledge and participation in screening decisions (139, 140).

2.3.6 Summary of HCC surveillance literature and research implications
HCC participation has been demonstrated to be poor in various settings and is likely to be poor in Australia given the current cascade of care. Adherence and participation to HCC surveillance do not have consistent definitions across the literature. There have
been approaches to improving mortality from HCC by establishment of national HCC surveillance programs in Korea and Japan, and a registry in New Zealand for people with CHB. Very few interventions have been trialled to systematically improve participation and adherence to HCC surveillance. In Australia, the B positive project and the IHBS worked with general practices to improve care, including HCC surveillance, but are no longer funded.

There are many challenges of ensuring adequate HCC surveillance for people with CHB. In Australia, HCC surveillance is mainly required by people from culturally and linguistically diverse communities and Aboriginal and Torres Strait groups who already have lower participation in established cancer screening programs (bowel, breast and cervical) due to multiple factors (141).

2.4 Knowledge and perceptions of health risks in people living with CHB

This section presents the literature relevant to the study presented in Chapter 7 as Paper 4: Knowing and telling: How African- Australians living with chronic hepatitis B understand HCC risk and surveillance, which was accepted for publication in November 2017.

2.4.1 Introduction and how knowledge impacts on care delivery

How people perceive risk to their health can impact their wellbeing, health choices and participation in healthcare. The health risks for people with CHB include physical or predominantly liver-related consequences of CHB, HCC and cirrhosis, but also the social and psychological impact of living with a chronic viral infection. Knowledge about health risks can influence the decision to be tested, attend appointments and adhere to suggested monitoring and prescribed treatment. The Chronic Disease Model developed by Wagner et al proposed that while health systems improvement and redesign was an important part of improving delivery of chronic disease care, good health outcomes are dependent on the person living with the disease and the community in which that person lives being adequately informed so that the individual can interact with the health system to self-manage their own illness (142-144).
Understanding the risks in chronic hepatitis B is complicated, for both non-specialist clinicians and people with CHB. The natural history of CHB includes long periods of quiescence where monitoring is required to identify changes in viral replication and the immune response, but antiviral treatment is not indicated. Poor knowledge of CHB in the primary care workforce has been shown to be an issue in Australia and is a barrier to testing and appropriate referral (145-147). Improving the knowledge in the this workforce and in communities most affected by CHB were key objectives of the national hepatitis B strategies (24, 25)

Poor knowledge about CHB in the community can result in the experience of stigma and/or discrimination by people with CHB and create a barrier to care (148-150). Stigma, both experienced as societal discrimination and internalised, is not unique to BBVs and occurs in many chronic conditions, including those affecting mental health. However, in chronic infections there is also a perceived threat of potential infectiousness to others, both by the affected person and by others in their community (150, 151). The experience of stigma can create barriers to accessing healthcare and be a direct cause of social and emotional ill health (148, 151) affecting quality of life (149). Examples of the broader impacts of living with a chronic viral infection are well documented in HIV. Interventions have been trialled to reduce its effects, but in CHB, stigma-related research has been limited (150, 151).

The measurement of the proportion of people experiencing discrimination is included in the 27 additional indicators recommended in the Monitoring and Evaluation for Viral Hepatitis B and C report by WHO (16). The suggested measurement is the “number of people living with viral hepatitis who experienced discriminatory attitudes or actions towards them within the past 12 months” (16). While measurement of recent experience of stigma tracks changes over time or with progress in the whole of society’s attitude towards the disease, for an individual the experience of stigma, recent or distant, may affect health and health-seeking behaviour (152-154).
Studies investigating how health risks in CHB are understood can be classified into three main areas: knowledge in health workers delivering care or involved in testing (145-147); in communities with higher prevalence of CHB, particularly in the context of understanding liver cancer and the impact on testing or screening for CHB (155-158); and in people living with CHB. The review of the literature in this section focuses on studies in people living with CHB conducted both overseas and in Australia and includes knowledge and attitude surveys as well as qualitative studies analysing the impacts of living with CHB.

2.4.2 Knowledge of health risks in people living with CHB

Studies regarding CHB knowledge in people living with CHB have been most commonly conducted in Asian populations (148, 151) both in their country of origin (151, 154, 159-162) and in the USA (153, 154). Studies with locally developed survey tools have assessed different domains of knowledge that have included but not focused on an understanding of health risks or how to mitigate those risks (151, 154, 159-162). The most commonly assessed domain across the studies was knowledge of transmission (153, 154, 160, 163, 164). The assessment of a persons’ knowledge of liver-related health risks associated with CHB was often a closed question that included the words “liver cancer” or “damage” (153, 154, 160, 163). Knowledge was assessed to be poor in people living with CHB across all studies and in all contexts, with misconceptions about transmission, especially associated with the sharing of food, the shame of having an infection and a perceived risk of social consequences of experiencing or being vulnerable to stigma impacting social inclusion and psychological health (151, 154, 159-162). Fear of cancer and the transmission of CHB to loved ones were concerns impacting health and resulting in behaviour modification (153, 154, 163). The factors associated with better knowledge in surveys included higher educational attainment and increased time since diagnosis (160, 163).

Qualitative studies from Iran (162, 165), China (161), Malaysia (166) and Korea (159) have explored the impacts of CHB in people’s lives. Findings from these studies include that stigma affects psychological wellbeing, either through the experience of direct
discrimination or through internalised stigma (161, 162). This is in part due to a fear of infectiousness to others that results in behaviour modification, including self-exclusion (159, 162). Diagnosis is often a negative experience that is followed by a period of adjustment and acceptance, which is reduced by the knowledge that other family members are affected (161, 166). The fear of future ill health or death, the inevitability of liver problems, uncertainty and a lack of knowledge or access to treatment options affect psychological wellbeing (161). Poor knowledge was a result of inadequate information being communicated from professionals to people with CHB and common misconceptions of CHB (161, 166).

Ten studies were identified in Australia looking at knowledge of people living with CHB or containing findings on the health impacts perceived or experienced by people living with CHB. This included knowledge-focused questionnaires (149, 164, 167-169), five studies using interviews either with individuals or focus groups (31, 152, 170, 171) and one study using a mixed methods approach (172). Recruitment of participants in the studies was mainly in hospital settings. The majority of participants were Asian (152, 167, 168, 170, 172), with two in the community setting with Aboriginal or Torres Strait Islanders (31, 169), and all but two studies (31, 167) required English language proficiency. A small number of patients from African countries were recruited in two studies (167, 168). There was an emphasis on knowledge about transmission across the surveys (132, 164, 167-169, 172). Other domains included understanding of testing (172), the impact of diagnosis (171), epidemiology (168), what information was conveyed in the consultations (167) and barriers to services access (152, 167, 172). Questions on health risks or effects of diagnosis were included in two surveys and focused on liver-related outcomes (167, 168). No Australian study was designed to assess the perceived or experienced health risks of people living with CHB, although the experience of stigma, discrimination and risk of disclosure emerged as themes in semi-structured interviews (171, 172).

2.4.3 Summary of how people with CHB understand health risks
While knowledge of the health risks associated with a chronic disease is an important component of successful chronic care delivery, few published studies have aimed to
assess how these risks are understood. The knowledge of health risks, specifically liver-related illness, have been included in surveys, but these surveys do not explore in depth the impact of CHB on daily life. No study in Australia has focused on how people diagnosed with CHB or how African- Australians understand their health risks, or understand monitoring and HCC surveillance. While those born in the African region have increased risk of HCC at a younger age and are recommended to start HCC surveillance earlier than all other groups, they have only been included in Australian other-knowledge surveys in small numbers (168, 172).

Understanding risk is an important component of health literacy. It is vital to making health decisions and regular health-seeking behaviour. There is a gap in the current literature about how people living with CHB, including African-Australians, perceive and experience risks to their physical, social and emotional wellbeing, and how they understand the purpose of tests, including HCC surveillance, which is recommended to prevent HCC-related mortality.
Chapter 3: The cascade of care for CHB

3.1 About this chapter

The study presented in this chapter, published in 2015, was the first Australian cascade of care for CHB.

Australians living with CHB can access healthcare services using the universal healthcare system (Medicare) which includes testing Medicare benefits schedule (MBS) and antiviral treatment, pharmaceutical benefits schedule (PBS). Billing data is collected for all services performed on the MBS and PBS and aggregate data is publically available (173). CHB is a notifiable disease in Australia, with practitioner and laboratories required to report to jurisdictional health departments that in turn report to the National Notifiable Disease Surveillance System (NNDSS) (174). This study used a combination of sources to estimate the cascade: diagnosis estimates from the NNDSS; a model that had previously been developed to estimate the number of people living with CHB; and publically available data from the MBS and PBS to estimate the number enrolled in care.

The hypothesis was that using appropriate data sources, the number of people living with CHB, the proportion diagnosed, and the proportion of people in care with or without treatment could be estimated and combined to present a cascade of care. Also, constructing a cascade using this methodology would allow measurement at regular intervals to understand the trends in care delivery. The cascade analysis presented in the paper was conducted in 2013 and estimated the cascade for 2012.

The deterministic model utilised in this study was first developed in 2009 (53) and was used to generate population estimates and the proportion diagnosed with updated data from the NNDSS for 2012. The proportion diagnosed used the number ever diagnosed from the NNDSS and the population ever estimated to be living with CHB from the model. Publically available data of number of HBV DNA yearly tests and
people prescribed antiviral therapy for CHB from MBS and PBS were combined to estimate the number of people in care for 2012 and for the years 2008-2012.

Paper included in this chapter:

*The cascade of care for Australians living with chronic hepatitis B: measuring access to diagnosis, management and treatment.*

Allard NL, MacLachlan JH, Cowie BC

3.2 Paper 1: The cascade of care for Australians living with chronic hepatitis B: measuring access to diagnosis, management and treatment.
The cascade of care for Australians living with chronic hepatitis B: measuring access to diagnosis, management and treatment

Nicole L. Allard, Jennifer H. MacLachlan, Benjamin C. Cowie

Chronic hepatitis B (CHB) is a leading cause of mortality worldwide, resulting in an estimated 786,000 deaths from liver cancer and liver failure in 2010. In Australia, it has been estimated that about 218,000 people (1.02% population prevalence) were living with CHB in 2011, predominantly people born overseas in endemic areas and Aboriginal and Torres Strait Islander people. Liver cancer also disproportionately affects these communities and is the ninth most common cause of cancer mortality in Australia, increasing faster than any other cause of cancer deaths.

Chronic hepatitis B is a dynamic disease that changes over time, dependent on the immune response of the individual. The virus is a carcinogen and the viral load of an infected individual is a strong independent risk factor for both liver cancer and cirrhosis.

All people living with CHB should be regularly monitored, with assessment of liver function and hepatitis B virus (HBV) viral load recommended at least annually to monitor disease activity and inform treatment decisions. Viral load testing is funded through the Medicare Benefits Schedule (MBS) four times a year for patients receiving antiviral therapy and once a year for people with CHB who are not receiving therapy. In addition, 6-monthly liver cancer surveillance with ultrasound and alpha-fetoprotein (AFP) in patients at increased risk of liver cancer has been demonstrated to improve survival by detecting small tumours that are potentially amenable to curative therapies.

Appropriate treatment of CHB has been shown to reduce the risk of cancer by up to 75% and to be a cost-effective cancer prevention intervention in the Australian context. Current first-line therapies are potent, well-tolerated and have high barriers to development of resistance, but require prolonged (usually indefinite) treatment. Antiviral therapy is available on the Pharmaceutical Benefits Scheme (PBS) in Australia for patients who meet specific treatment criteria; however, prescription initiation is restricted to specialists, occurring mostly in hospital settings. Although it is estimated that, without treatment, 15–25% of people living with CHB will die as a result of the infection and its complications, not all patients will require antiviral treatment. Evidence of ongoing liver damage with persistently raised alanine transaminase (ALT) over a 3-6 month period and/or evidence of cirrhosis are indicators for initiation of therapy. Past modelling of cost effectiveness of antiviral treatment has used 15% as a lower end estimate of the population proportion that would benefit from treatment, and this is the treatment target in Australia’s Second National Hepatitis B Strategy 2014–2017.

Abstract

Objective: To estimate the level of access to diagnosis, management and treatment for people living with chronic hepatitis B (CHB) in Australia, and to identify the gaps in clinical care for people living with CHB.

Methods: Analysis of publicly available population level data including infectious disease notifications, Medicare and Pharmaceutical Benefits Scheme utilisation data, census-based estimates of CHB prevalence and burden, and mathematical modelling.

Results: In 2012, of the estimated 218,567 Australians living with CHB, 57% had been diagnosed, 17,367 people (8%) received recommended HBV DNA viral load testing (without treatment) and 10,987 (5%) received antiviral therapy.

Conclusions: This analysis reveals substantial gaps in the cascade of care for CHB in Australia, most notably in diagnosis (with 43% undiagnosed) and in recommended yearly monitoring (87% not in care). The number receiving therapy represents only one-third of those estimated to require treatment to prevent progressive liver disease and liver cancer.

Implications: These findings demonstrate that the majority of those affected are not receiving guideline-based care; highlight the need for improvements in opportunistic screening, engagement in care, and access to therapy; and provide a method to assess the impact of public health and clinical interventions in response to CHB over time.

Key words: hepatitis B, liver cancer, health systems, epidemiology, cascade of care

Article References

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In Australia, it is not known what proportion of people living with CHB are being appropriately monitored or receiving antiviral therapy. This study’s aim was to provide a measure of access to treatment and care for people living with CHB, by combining available epidemiological information on estimated numbers of people living with CHB with national surveillance, prescribing and testing data. For CHB in Australia, understanding the gaps in care provision and examining the evidence regarding why these gaps exist can guide efforts to address this emerging population health priority.21,22

A way of conceptualising these gaps is through a ‘cascade’ or ‘care continuum’ analysis, which aims to define population burden and engagement in a spectrum of clinical care from diagnosis to treatment. These analyses use measures specific to each disease and context and provide a method of evaluating health service responses to affected populations.21,22 Similar ‘cascade of care’ analyses have been undertaken in the United States for CHB and hepatitis C23,24 and in Australia for HIV.24

Methods

This cascade of care analysis uses data from different sources to establish the number of people living with CHB, the number diagnosed and the number receiving care (defined as annual viral load monitoring or treatment with antiviral therapy).

The number of Australians living with CHB has been estimated using 2011 Census-based estimates of the number of people within identified priority populations, combined with Australian and international estimates of CHB prevalence for these communities and the rest of the population. The resulting estimates were validated using mathematical modelling (for methodological details see MacLachlan et al.22)

The proportion of people living with CHB who have been diagnosed was estimated using model-derived estimates of the total number of people who have ever had CHB in Australia as the denominator, and the cumulative number of notifications of hepatitis B from 1971 to 2012 as the numerator. Mortality is not included in this aspect of the analysis, and therefore the proportion derived represents those ever having lived with CHB who have ever been diagnosed. Notifications of unspecified (chronic) hepatitis B from 1971 to 1991 were sourced from a review of the National Notifiable Diseases Surveillance System (NNDSS),22 and from 1992 to 2012 from current reports of the NNDSS (www.health.gov.au/cda/source/cda-index.cfm). These notifications data are presented in Table 1 according to state and territory for the period 1998–2012.

Separate MBS items are used by Medicare for HBV DNA viral load testing once-yearly for patients who are not receiving antiviral treatment and four times a year for those receiving treatment. The number of patients with an MBS rebate for an annual viral load test was used as a proxy of the numbers enrolled in care but not receiving treatment and was obtained from online Medicare reporting (www.medicareaustralia.gov.au/statistics/mbs_item.shtml).

Estimates of number of people receiving treatment were based on expenditure information from the Highly Specialised Drug (HSD) Program by state and territory, cross-referenced with patient-level PBS data requested directly from Medicare and further verified with supply information from pharmaceutical companies. Estimates of the number of individual patients receiving therapy are extrapolated based on the cost per script, which assumes that each patient received a full year of therapy.

The total number of people living with CHB potentially receiving guideline-based care was defined as the sum of those receiving annual viral load testing and those receiving treatment. Estimates of the proportion of people not in care were compared by state and territory, with significance of differences assessed using two-sample tests of proportions.

Results

From 1971 (when national notifications of hepatitis B infection first commenced) until 2012, a cumulative total of 154,703 notifications of CHB were made to the NNDSS. The modelled estimate for the total number of people who had lived with CHB not accounting for mortality over the time period simulated (from 1951 until end of 2012) was 271,137. This leads to an estimate of 57% of people who had lived with CHB over the period having ever been diagnosed and notified to the NNDSS. Numbers available for cumulative notifications for the period 1998–2012 by state and territory appear in Table 1.

As previously published in this journal, an estimated 218,567 Australians were living with CHB in 2011.21 This was the population total used to estimate percentages of those enrolled in care.

According to Medicare statistics, in 2012 there were 17,367 yearly HBV viral load tests billed to the MBS for individual patients, and 10,987 individuals received therapy funded by the PBS. Considered together, this represents 28,354 individuals who may be receiving care in accordance with guidelines, or 13% of the total number living with CHB, including 5% receiving antiviral treatment (see Figure 1).

Figure 1: Estimates of the cascade of care for people living with CHB in Australia.

218,567 Living with Chronic Hepatitis B infection

Diagnosed (57%) Undiagnosed (43%)

28,354 (13%) receiving yearly HBV DNA or treatment

Not in care 190,213 (87%)

10,987 (5%) on treatment

21,788 not receiving treatment of 15% of total (32,785) estimated to need treatment
These estimates are presented according to state and territory in Table 1, including the proportion of people living with CHB who are not receiving guideline-based care as defined. The proportion of individuals not receiving care in 2012 was significantly lower in NSW (82%) and Victoria (83%) than the national average of 87% (p<0.001 for both comparisons). Jurisdictions with a higher proportion of people not in care were Queensland, Western Australia, South Australia and Tasmania (94–98%).

Nationally, the number of HBV viral load tests conducted increased from 5,168 in 2008 to 17,367 in 2012, with around 3,000 additional tests occurring per year (Figure 2). The number of individuals receiving antiviral treatment has also increased, from an estimated 9,641 in 2011 to 10,987 in 2012 (14% increase).

**Discussion**

This is the first attempt to describe the cascade of care for people living with CHB in Australia at the population level. The predominant gaps in the cascade of care are failure to diagnose and failure to deliver guideline-based care to people living with CHB.

Based on this analysis, only one-third of people living with CHB who require antiviral therapy are actually receiving it; therefore, about 22,000 people in Australia who would benefit from treatment remain at increased risk of adverse outcomes, including liver cancer. Annual HBV viral load testing is performed on a small proportion of people living with CHB and disparities in access across states and territories are also apparent, with estimates of engagement (evidence of treatment or annual viral load testing) ranging from 2% to 18% of people living with CHB. While no doubt multifactorial, the causes for this disparity are likely to include different predominant populations affected by CHB across jurisdictions² and variable proportions of those living with CHB residing outside of capital cities.²⁵

The annual increase in the number of HBV viral load tests performed from 2008 to 2012 suggests an increasing trend of care delivery to people with CHB. However, the growth rate in testing over the time period did not keep pace with the number of notifications of CHB, which was more than 6,300 new notifications per year over the same time period.

The recently released Second National Hepatitis B Strategy 2014–2017 has listed as priority actions, increasing access to treatment and improving access to appropriate management for people living with CHB.²⁶ The gaps in population-based epidemiological data are recognised and there are new national targets for hepatitis B care delivery, including a 15% target for treatment and 80% target for diagnosis.²⁷ There is, however, no indicator or target included for people living with CHB not receiving treatment. Annual HBV viral load is a measurable proxy for care provision, specific to the CHB for the affected population that is similar to indicators used for other blood borne viruses.

In Australia, CHB predominantly affects communities that face broader healthcare inequities including decreased access to health services, experience stigma and discrimination, poorer health literacy and reduced ability to negotiate the health system.²⁷-²⁹ In addition to barriers for those affected by CHB, gaps in clinician awareness regarding appropriate testing and management of CHB, especially in primary care, have also been identified.³⁰-³² Barriers identified by general practitioners include stigma, poor community knowledge associated with the disease, restrictions on antiviral prescribing, competing health priorities, time pressures and lack of support for contact tracing of diagnosed individuals.³¹-³³ While systematic population screening occurs in women during antenatal care, women, their children and family members are often not followed up appropriately during pregnancy or following delivery.³⁴-³⁶

**Table 1: Proportion of people not in care (defined as not receiving treatment or yearly HBV viral load) by state and territory using 2011 Census derived estimates, PBS and MBS data.**

<table>
<thead>
<tr>
<th>State/Territory</th>
<th>Number of yearly viral load tests, 2012</th>
<th>Number of people receiving antiviral treatment, 2012 (percentage of census-based estimates on treatment)</th>
<th>Census based estimates of people living with CHB, 2011</th>
<th>Total notifications for unspecified (chronic) hepatitis B, 1998-2012</th>
<th>Proportion of people with CHB not in care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Capital Territory</td>
<td>265</td>
<td>152 (42%)</td>
<td>3,603</td>
<td>1,101</td>
<td>88%</td>
</tr>
<tr>
<td>New South Wales</td>
<td>7,782</td>
<td>5,844 (76%)</td>
<td>77,076</td>
<td>42,455</td>
<td>82%</td>
</tr>
<tr>
<td>Northern Territory</td>
<td>336</td>
<td>72 (2.0%)</td>
<td>3,556</td>
<td>1,527</td>
<td>89%</td>
</tr>
<tr>
<td>Queensland</td>
<td>1,412</td>
<td>941 (2.5%)</td>
<td>37,427</td>
<td>12,736</td>
<td>94%</td>
</tr>
<tr>
<td>South Australia</td>
<td>141</td>
<td>419 (2.9%)</td>
<td>14,442</td>
<td>5,350</td>
<td>96%</td>
</tr>
<tr>
<td>Tasmania</td>
<td>47</td>
<td>31 (0.9%)</td>
<td>3,513</td>
<td>628</td>
<td>98%</td>
</tr>
<tr>
<td>Victoria</td>
<td>6,856</td>
<td>2,079 (32%)</td>
<td>56,836</td>
<td>26,496</td>
<td>83%</td>
</tr>
<tr>
<td>Western Australia</td>
<td>528</td>
<td>549 (2.5%)</td>
<td>22,055</td>
<td>8,065</td>
<td>95%</td>
</tr>
<tr>
<td>Australia</td>
<td>17,367</td>
<td>10,987 (5.0%)</td>
<td>218,567</td>
<td>98,358</td>
<td>87%</td>
</tr>
</tbody>
</table>

*Total includes 19 people with CHB whose state was recorded as ‘other territory’.

The proportion of individuals receiving antiviral treatment is similar to indicators used for other blood borne viruses. In Australia, CHB predominantly affects communities that face broader healthcare inequities including decreased access to health services, experience stigma and discrimination, poorer health literacy and reduced ability to negotiate the health system.²⁷-²⁹ In addition to barriers for those affected by CHB, gaps in clinician awareness regarding appropriate testing and management of CHB, especially in primary care, have also been identified.³⁰-³² Barriers identified by general practitioners include stigma, poor community knowledge associated with the disease, restrictions on antiviral prescribing, competing health priorities, time pressures and lack of support for contact tracing of diagnosed individuals.³¹-³³ While systematic population screening occurs in women during antenatal care, women, their children and family members are often not followed up appropriately during pregnancy or following delivery.³⁴-³⁶

**Figure 2: Annual HBV viral load tests (item 69482) claimed on the MBS in Australia, 2008–2012.**

0 4,000 8,000 12,000 16,000 20,000 2008 2010 2012 Number of annual HBV viral load tests Year of test

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Limitations of this analysis are specific to each data source and step in the cascade. Census-based estimates of the number of people living with CHB rely on the accuracy of seroprevalence data. Although the majority are derived from local antenatal seroprevalence, where this is not available, it was assumed that CHB prevalence in migrants reflects that in their country of origin. Given the generally lower CHB prevalence in females than males, and the propensity for undercounting in census data, the number of Australians living with CHB is likely to be underestimated.

Notifications data miss diagnoses made overseas or local diagnoses that were not notified. For some jurisdictions, data are incomplete or missing during earlier time periods, for example, Northern Territory before 2005, South Australia 1991–95 and Victoria 1991–96, and their inclusion would increase the proportion of people estimated to be diagnosed. The methodology to derive the proportion diagnosed was for the entire period 1971–2012, with the resulting estimate applied to those currently living with CHB; differences in testing patterns over time would affect the accuracy of this approach. The net effect is likely to be an underestimation of the proportion diagnosed. Importantly, the proportion diagnosed from notifications data does not necessarily represent individuals being adequately informed about their health status.

Care provided to Medicare-ineligible patients will not be reflected in the MBS/PBS data used; however, given the relatively low numbers of people receiving ongoing care for CHB outside Medicare, this is unlikely to have a substantial impact on the final estimates of numbers in care. MBS data could include incorrect coding of a HBV viral load test for a patient on treatment or retesting of an individual in the same year. Given that receiving a yearly HBV viral load is only one component of the provision of comprehensive guideline-based ongoing care for an individual with CHB, using annual HBV viral load as a proxy of guideline-based care will overestimate the number of people enrolled in effective care. It is however clear that the overall numbers enrolled in care are low.

The estimate of numbers on treatment from the HSD data are limited by the assumptions that each person receives a full year of medication, without combination therapy, and that all prescribing of tenofovir outside of co-formulation with other antiretrovirals is for treating CHB, rather than HIV. The impact of these assumptions is likely to result in an overestimation of numbers on antiviral treatment for CHB.

Liver cancer surveillance is also an important part of care for people with CHB and recommendations for screening are based on the presence of cirrhosis, age and place of birth, and family history of liver cancer. Summary population data for 6-monthly ultrasounds and alpha-feto-protein specific to liver cancer surveillance for CHB are not available and MBS data would have to be linked to notifications to be able to calculate the proportion being regularly screened.

The use of population level data in this analysis is a key strength, removing the biases inherent in community or clinical cohorts in estimating engagement in care and uptake of treatment. Cohorts are inherently comprised of people who are aware of their diagnosis and enrolled in care. They provide useful data regarding the challenges of clinical care and quality of care provision, but do not account for those individuals who have not been engaged in a service. Community-based estimates of the proportion of people living with chronic hepatitis B who are aware of their diagnosis do include those who are not enrolled in care; however, they may still be limited by recall and selection biases relating to participant recruitment. The estimates of monitoring and treatment derived here are for the population at a national and jurisdictional level. The use of routinely collected public domain data allows for regular assessment of these key indicators at a population level, allowing for the monitoring of improvements in the response to CHB in Australia.

Conclusion

Ensuring access to testing, treatment and care for people living with CHB is a national health priority. This novel analysis demonstrates that nearly half of all Australians living with CHB have not yet been diagnosed, and the majority remain at risk of complications, as they are not receiving guideline-based care. This must urgently be addressed in the health system and at the community level or the burden of liver disease and liver cancer due to CHB will continue to rise.

Acknowledgements

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References


Chapter 4: Adherence to antiviral therapy

4.1 About this chapter
This chapter presents the findings from two studies that addressed adherence to oral antiviral therapy within the Australian health system. The first examined the factors associated with adherence in a retrospective multicentre study from four public hospitals during 2010-2013 and analysed the demographic and health system factors associated with adherence and is presented as a published paper.

The second study examined viral outcomes in the same multicentre cohort to establish the percentage who were virally suppressed or achieved viral suppression during the treatment period and the relationship of viral outcomes adherence as measured by medication possession ratio (MPR). This work is presented as the second part of the adherence chapter.

The hypothesis was that, as the percentage of the population adherent to antiviral therapy and the viral outcomes in Australia were unknown, a multicentre hospital pharmacy and pathology data set could be used to calculate these aspects of the cascade. Also as the relationship between the values of MPR and viral outcomes had not been established internationally an analysis could evaluate the utility of MPR values previously used to define adherence and the association with viral outcomes in a real-world data set.

Paper included in this chapter:

Factors associated with poor adherence to antiviral treatment for hepatitis B.
Allard N, Dev A, Dwyer J, Srivatsa G, Thompson A, Cowie B
4.2 Paper 2: Factors associated with poor adherence to antiviral treatment for hepatitis B.
Factors associated with poor adherence to antiviral treatment for hepatitis B

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Summary
Antiviral therapy for hepatitis B is effective and reduces the risk of progression to cirrhosis and liver cancer but is often required for an indefinite duration. Treatment adherence is important to prevent the development of resistance and optimize outcomes. Pharmacy adherence measures can be used to assess treatment adherence, with the medication possession ratio being less susceptible to bias than physician- or self-reported adherence. The aim of this study was to measure adherence in public hospital outpatients over a 3-year period and to examine factors associated with non-adherence. A retrospective study of pharmacy records of patients dispensed antiviral therapy for hepatitis B from four major hospitals in Melbourne between 2010 and 2013. Hospital record numbers were linked with and de-identified demographic information including age, sex, Indigenous status, country of birth, interpreter requirement, spoken language and postcode of residence. The medication possession ratio was the outcome measure with poor adherence defined <.90. Univariate logistic regression and multivariate logistic regression were performed to examine associations with non-adherence. Records of 1026 patients were included in the analysis. Twenty per cent of all participants met the definition of poor adherence. Significant factors affecting adherence included age <35 years (P=.002), hospital site and treatment by multiple doctors within shorter time periods. This is the largest study examining detailed factors associated with adherence to hepatitis B treatment. Understanding poor adherence in clinical settings, and the factors associated with lower adherence, is important to inform efforts towards promoting treatment adherence for hepatitis B.

KEYWORDS
adherence, antiviral therapy, hepatitis B

INTRODUCTION

The global burden of hepatitis B-related mortality continues to increase, with an estimated 617 000 deaths attributed to cirrhosis and liver cancer due to chronic hepatitis B virus infection in 2013.1,2

Antiviral therapy for chronic hepatitis B (CHB) is effective and reduces the risk of developing cirrhosis and liver cancer.2 Currently available therapies consist of either a defined course of pegylated interferon or long-term suppression of viral replication with oral antiviral medications.3,4 The need to increase access to treatments to respond to the needs of people living with viral hepatitis is apparent.6

In the management of chronic diseases, adherence to therapy is associated with improved outcomes.2,7 Suboptimal adherence to antiviral therapy in the treatment of CHB can also lead to the development of antiviral resistance and/or viral breakthrough,2 contributing to liver cirrhosis10 and liver cancer.
A limited number of studies using a variety of methods to calculate adherence to antiviral therapy for CHB have been published. The largest multivariate analysis from the United States using pharmacy claims data reported that younger age (<45), receipt of lamivudine and recent initiation of therapy were associated with poorer adherence to antiviral therapy but had limited demographic detail. In a number of smaller studies on univariate analysis, youth has been consistently associated with nonadherence. Other factors variably associated with lower adherence have included female sex, lower income, male sex, e antigen positivity, recent initiation of therapy and language discordance between clinician and patient.

Reasons for nonadherence encompass environmental, health system, disease and individual factors. Single, daily dosing of oral medication that has a good safety and side effect profile in CHB promotes adherence. However, CHB is usually asymptomatic and individuals may not perceive the benefit of medication taking. Communicating the need for adherence is complex in a condition spanning decades, with treatment only recommended for a minority of patients with active viral replication and ongoing liver injury or established cirrhosis.

Pharmacy-based adherence measures (PAMS) can be calculated from available data and are less prone to bias than physician or patient reports. In HIV treatment, PAMS have been correlated with virological outcomes, both failure and development of resistance, and mortality. In CHB, the available studies correlating measure of adherence including PAMS with virological data have been small and definition of good adherence has varied from 80% to 95% of doses taken.

Patients receive free hospital outpatient consultations under the national health insurance system (Medicare) with an interpreter if required. Antiviral medication is dispensed at the hospital pharmacy with a single copayment (between $5 and $30 USD) per 60 tablets or approximately 2 months of supply with some limited dispensing occurring in community pharmacies. In Australia, the majority of 10,000 prescriptions annually are from public hospital specialists.

The aims of this study were to describe the characteristics of the population receiving antiviral therapy, to estimate the adherence in public hospital patients receiving a single antiviral medication for the treatment of CHB using PAMS and to understand the factors that are associated with poor adherence.

2 METHODS

A retrospective analysis of pharmacy records for patients dispensed oral antiviral therapy for CHB from four large metropolitan public hospitals from July 2010 to June 2013 was conducted. Patients were excluded if aged <18 years, total treatment duration was less than 30 days, less than 3 pharmacy visits were recorded, or if on combination therapy. De-identified demographic information including age, sex, Indigenous status (identifying as Aboriginal and/or Torres Strait Islander), country of birth, requirement for an interpreter, spoken language and postcode of residence were retrieved from patient management software systems and matched with the pharmacy data using hospital record number. Socio-economic status was calculated using Socio-economic Indexes for Areas (SEIFA) based on postcode of residence and distance to hospital calculated by a web-based tool (http://www.distancecalculator.net) using straight-line distance between the hospital and the postcode of residence.

The medication possession ratio (MPR) was the outcome measure of adherence. Poor adherence was defined as an MPR of less than 0.9. This cut-off was used in the largest study of adherence to date “arbitrarily” and shown in a small cohort to be correlated with virological breakthrough on entecavir but not lamivudine. Where patients failed to collect medications 90 days after the last prescription period had finished, they were classified as lost to follow-up and additional days were discounted from the total number in the time period.

As the number of clinic visits, as distinct from pharmacy visits, was not available, consistency of care or how frequently a person saw different doctors was measured by assessing the average time period each doctor prescribed medication for a particular individual.

Data were analysed in STATA 13. Linear regression was used to explore associations between continuous variables and the MPR. Multivariate logistic regression was conducted with a backwards stepwise approach using a P value of .1 for inclusion in the final model.

\[
\text{MPR} = \frac{\text{Number of pills dispensed}}{\text{Number of days in time period} - \text{days lost to follow-up period}}
\]

This study was performed according to the World Medical Association Declaration of Helsinki http://www.wma.net/e/policy/b3.htm and was approved by the four participating hospitals ethics committees.

3 RESULTS

Pharmacy records were obtained for 1504 patients across the four participating hospitals. A total of 1026 patients were included in the final analysis after excluding those on combination therapy (241), attending for less than three visits (220), aged <18 years or on treatment for less than 30 days. This represents 1921 person-years of antiviral treatment for CHB. Information about the demographics of the study population is shown in Table 1.

Ninety per cent of people on treatment were born overseas, coming from 64 different countries. Most patients were born in Asia (73.5%); people born in Vietnam and China represented 33.3% and 13% or the total, respectively. There were 39 discrete language categories recorded with three categories representing more than one language group.

Poor adherence to antiviral therapy (MPR<0.90) was observed in 20% of pharmacy records. Thirteen per cent of patients had a period of loss to follow-up of 3 months or more during the 3-year period.

The majority of patients were receiving treatment with entecavir 0.5 mg (57%) or tenofovir (29%). Prescribing patterns varied in terms of length of treatment, number of drugs dispensed on each visit to the pharmacy and average duration of treatment prescribing by individual doctors involved in care of an individual patient (see Table 2). Half of the patients experienced a change in treating doctor on average every
Table 1: Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Median age</th>
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<tbody>
<tr>
<td>Total</td>
<td>1026</td>
</tr>
<tr>
<td>Gender</td>
<td>n (%)</td>
</tr>
<tr>
<td>Male</td>
<td>695 (67.7)</td>
</tr>
<tr>
<td>Female</td>
<td>331 (32.3)</td>
</tr>
<tr>
<td>Region of Birth</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>103 (10)</td>
</tr>
<tr>
<td>Asia</td>
<td>755 (73.5)</td>
</tr>
<tr>
<td>Africa</td>
<td>48 (4.7)</td>
</tr>
<tr>
<td>Europe</td>
<td>84 (8.2)</td>
</tr>
<tr>
<td>Other Oceania*</td>
<td>15 (8.2)</td>
</tr>
<tr>
<td>Aboriginal or Torres Strait Islander</td>
<td>n (1014)</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>1010</td>
</tr>
<tr>
<td>Interpreter required</td>
<td>n (1019)</td>
</tr>
<tr>
<td>Yes</td>
<td>348 (33.8)</td>
</tr>
<tr>
<td>No</td>
<td>671 (66.2)</td>
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*Includes NZ and pacific.

Table 2: Prescribing details

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<tr>
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<th>Median</th>
<th>Interquartile range</th>
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<tr>
<td>Pharmacy visits</td>
<td>11</td>
<td>(6–16)</td>
</tr>
<tr>
<td>Number of days of treatment</td>
<td>826</td>
<td>(326–1025)</td>
</tr>
<tr>
<td>Average duration of treatment prescribed per doctor</td>
<td>185</td>
<td>(139–308)</td>
</tr>
<tr>
<td>Medication dispensed average per visit</td>
<td>60</td>
<td>(47.5–87)</td>
</tr>
<tr>
<td>Number of doctors</td>
<td>3</td>
<td>(1–12)</td>
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<tr>
<td>Medication prescribed</td>
<td>n (%)</td>
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</tr>
<tr>
<td>Entecavir (0.5 mg)</td>
<td>991 (57.6)</td>
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</tr>
<tr>
<td>Entecavir (1.0 mg)</td>
<td>39 (3.8)</td>
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</tr>
<tr>
<td>Tenofovir (300 mg)</td>
<td>275 (28.8)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (100 mg)</td>
<td>98 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Adefovir (10 mg)</td>
<td>24 (2.3)</td>
<td></td>
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4 | DISCUSSION

This is the largest study of adherence of oral antiviral therapy for CHB in Australia and contributes to our understanding of factors that are associated with nonadherence to antiviral therapy for CHB. The study population represents approximately 10% of all people receiving antiviral treatment for CHB in Australia during the study period and presents the most detailed demographic and background information currently available for public hospital patients accessing care for hepatitis B. Poor adherence (defined by a MPR <0.90 in this study) in 1 of 5 patients is consistent with previous studies that ranged from 6% to 45% and lower than noncommunicable diseases.

Consistency of clinician should be considered in outpatient settings to reduce nonadherence. Mutual trust and communication has been reported in other studies across different chronic diseases including HIV treatment as a factor promoting more consistent medication taking and better chronic disease management. In a small study of people receiving care for CHB in a public hospital in Melbourne, seeing the same doctor was associated with higher hepatitis B knowledge. While hospitals accommodate trainees and staffing changes occur regularly, seeking to maximize the consistency of clinical care delivery may be an important strategy to support better adherence and optimizing care for individuals.

Young people are more at risk of being nonadherent to antiviral therapy for CHB as is the case for other chronic conditions. Recognition of the challenges faced by a younger person regularly taking medication at a time in their lives when they feel well is important. Health risks may seem remote, they are busy with work and family commitments, and regular attendance at central tertiary institutions may prove difficult. Reinforcement of adherence at each consultation, providing more flexible and convenient care arrangements, reminder systems and working with the individual to maximize medication adherence should be a routine part of clinical practice.

The variation in amount of medication prescribed and duration prescribed for did not impact on adherence; however, it has cost implications for hospitals and the patients. While the most common period of treatment supplied per occasion was 2 months, there was variation from 1 to 6 months of supply at one visit or 2–12 pharmacy visits per year. Individual clinicians make assessments in the hospitals to either increase supply or conversely increase contact and have closer oversight. There is evidence that regular contact helps adherence; however, convenience of care is also important. A patient perspective of what is optimal should be included in the development of further recommendations of the quantity of medication supplied per visit. Other initiatives including community pharmacy dispensing and community prescribing can both reduce the costs associated with care (including loss of working hours and loss of income for the person receiving long-term medication) and reduce pressure on pharmacies in tertiary hospitals.

 Aboriginal and Torres Strait Islander status was well reported, but few patients from the four hospitals identified as being Indigenous Australians (0.3%). No analysis of adherence was possible according to indigenous status due to these low numbers; however, the under-representation of Aboriginal and Torres Strait Islander people who are estimated to represent 2% of people living with CHB in Victoria (and 10% nationally) raises a wider concern of health inequity with low access to treatment in the hospital setting for this priority population. Language discordance has previously been associated...
with nonadherence to CHB antiviral therapy, but in this study in hospital clinics with access to adequate interpreting services no effect on adherence was observed. The diversity of the population receiving antiviral treatment for CHB who speak more than 38 different languages and are from more than 60 countries of birth is challenging in the development of programmes and materials to promote adherence. Development and testing of universal tools to explain risk and support individuals to understand medication taking should be considered in future health promotion funding.

The strength of this study is the examination of prescribing data from multiple hospitals, together with background demographic and health service data. It is limited by the ability of pharmacy data to measure adherence in a population. MPR reports maximum adherence and overestimates the “true” adherence or actual tablet taking. The reasons for nonadherence are complex and other patient-related factors are better addressed in direct patient surveys, and qualitative studies are not included in the hospital data.

Patient and doctor factors not recorded in routine data may explain differences seen between hospitals and require further study. The percentage of nonadherent participants is likely to be underestimated by the inclusion of only those records that had more than two pharmacy visits. There are multiple explanations for attendance for only one or two occasions, including loss to follow-up early in treatment, planned discontinuation of therapy, transfer of care to other settings, shorter therapy duration indication (e.g. during pregnancy to prevent mother to child transmission, or during a short period of immunosuppressive therapy to avert reactivation) or the onset of toxicity or adverse outcomes, among other possibilities.

People receiving treatment in major public hospitals are not necessarily representative of the population requiring treatment, as they have successfully negotiated the complexities of both the primary and

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### TABLE 3  Multivariate analysis of factors associated with poor adherence

<table>
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<th>Variable</th>
<th>Univariate</th>
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<th></th>
<th></th>
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<td></td>
<td>OR</td>
<td>P value</td>
<td>CI</td>
<td>aOR</td>
<td>P value</td>
<td>CI</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;35 years</td>
<td>826</td>
<td>-</td>
<td>-</td>
<td>1.63</td>
<td>.012</td>
<td>(1.11-2.40)</td>
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<tr>
<td>≤35 years</td>
<td>200</td>
<td>1.78</td>
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<td>(1.25-2.54)</td>
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<tr>
<td>Interpreter required</td>
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<tr>
<td>No</td>
<td>671</td>
<td>-</td>
<td>-</td>
<td>0.99</td>
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<td>(0.72-1.37)</td>
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<tr>
<td>2</td>
<td>206</td>
<td>1.02</td>
<td>.931</td>
<td>(0.65-1.59)</td>
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<tr>
<td>3</td>
<td>134</td>
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<td>.844</td>
<td>(0.63-1.75)</td>
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<tr>
<td>4</td>
<td>241</td>
<td>0.89</td>
<td>.598</td>
<td>(0.58-1.38)</td>
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<tr>
<td>5</td>
<td>152</td>
<td>1.19</td>
<td>.470</td>
<td>(0.74-1.92)</td>
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<tr>
<td>Least disadvantaged</td>
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<td>241</td>
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<td>.470</td>
<td>(0.74-1.92)</td>
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<td><strong>Distance to hospital</strong></td>
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<tr>
<td>&lt;5 Km</td>
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<td>5–10 km</td>
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<td>10–15 km</td>
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<td>(0.67-1.67)</td>
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<td>&gt;15 km</td>
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<td>.944</td>
<td>(0.65-1.56)</td>
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<tr>
<td>A</td>
<td>395</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>B</td>
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<td>2.04</td>
<td>.001</td>
<td>(1.34-3.09)</td>
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<tr>
<td>C</td>
<td>245</td>
<td>1.49</td>
<td>.053</td>
<td>(0.99-2.23)</td>
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<tr>
<td>D</td>
<td>196</td>
<td>1.27</td>
<td>.296</td>
<td>(0.81-1.98)</td>
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<tr>
<td><strong>Average number tablets dispensed per pharmacy visit</strong></td>
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<tr>
<td>60 tablets or less</td>
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<tr>
<td>Greater than 60</td>
<td>486</td>
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<td>(0.40-0.75)</td>
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<tr>
<td><strong>Average time period treated per doctor seen</strong></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;3 months</td>
<td>116</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>3–6 months</td>
<td>390</td>
<td>0.25</td>
<td>.&lt;.001</td>
<td>(0.16-0.38)</td>
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<tr>
<td>6–12 months</td>
<td>311</td>
<td>0.13</td>
<td>.&lt;.001</td>
<td>(0.07-0.21)</td>
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<tr>
<td>&gt;12 months</td>
<td>209</td>
<td>0.12</td>
<td>.&lt;.001</td>
<td>(0.06-0.20)</td>
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<tr>
<td><strong>Socio-economic Indexes for Areas (SEIFA).</strong></td>
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<table>
<thead>
<tr>
<th>Poor adherence MPR &lt;0.90</th>
<th>Adherent MPR &gt;0.90</th>
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<tbody>
<tr>
<td>52.59%</td>
<td>21.54%</td>
</tr>
<tr>
<td>12.54%</td>
<td>11.48%</td>
</tr>
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**FIGURE 1** Percentage of poorly adherent patients by average period of time treated by each doctor.
tertiary healthcare systems, and de facto assessment of risk of nonadherence plays a part in a clinician deciding to initiate long-term antiviral therapy, so caution must be taken when generalizing the findings of this study outside public hospital outpatient settings. Assessment of relative socio-economic disadvantage is limited in this study with stratification by postcode acting as a proxy for the socio-economic status of individuals. Assessment of education attainment is not recorded on hospital records and is likely to be important to consider when assessing risk for nonadherence in an individual, when combined with cultural differences in health literacy and health beliefs. 8,20

People living with CHB and on treatment in Australia are from a highly diverse range of backgrounds and speak numerous primary languages. Conveying clear messages, using interpreters, providing extra support and flexible care arrangements for younger people and building patient and clinician trust through consistency in treating doctors can improve adherence result in improved outcomes. 7,8 Adherence is a dynamic process and needs to be addressed regularly in a non-judgmental way working with individuals towards improved health. 6

One in 5 patients in this study did not take their hepatitis B therapy regularly and require further supportive care. Interventions piloted in other chronic diseases including involvement of pharmacists, family members and nurses, health messaging on mobile phones and other technology-based interventions to improve adherence could be incorporated in the management of CHB but will need to be evaluated in this population for both acceptability and efficacy.

Community dispensing and prescribing have recently been approved to decrease barriers to receiving antiviral therapy for people living with CHB in Australia. 25 As more people receive antiviral therapy, success will be measured not just by increasing numbers of people on treatment, but by the quality of care received and adverse outcomes averted in the population. Quality care will include support for individuals having difficulty adhering to regular medications that will prevent cancer and halt progressive liver disease. A measure of adherence is an important part of the “cascade of care” and should be assessed across the system and in each individual as is the case for other chronic viral infections as an essential metric of the quality of care delivered.

The main findings of this study are that age and consistency of care impacted on adherence while other factors including cultural background did not. It quantifies the adherence in this population and highlights the diverse cultural and linguistic backgrounds of people receiving care in the public health system and the need to address poor adherence in each individual.

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AUTHOR CONTRIBUTION

NA contributed to study preparation and development of the ideas, conception of the manuscript, data analysis and drafting of the manuscript. BC contributed to conception of the manuscript, supervision and review of draft. JD contributed to data collection and study conception and reviewing of the manuscript. AD, AT and GS contributed to reviewing of the paper and facilitated data collection at the sites.

ABBREVIATIONS

CHB, chronic hepatitis B; MPR, medication possession ratio; PAMS, pharmacy-based adherence measures; SEIFA, socio-economic Indexes for Areas.

REFERENCES


4.3 Viral outcomes in CHB and association with the medication possession ratio.

4.3.1 Introduction

An estimate of the number of people taking treatment who are virally suppressed or adherent to therapy has not yet been incorporated into the cascade of care at a national or jurisdictional level in Australia (25, 74). In CHB, while MPR has been used to define poor adherence, using values below 0.90, 0.94 and 0.95, these values have been arbitrarily chosen without clear reference to viral outcomes, including suppression becoming undetectable and/or mortality and morbidity (70, 85) (refer to Table 1 in Chapter 2). A small Spanish study (85 patients) analysed viral outcomes and MPR using below 0.95 to define poor adherence, but was insufficiently powered to clearly show this value was a threshold for adherence based on viral outcomes. Prior to 2015, the vast majority of prescriptions for antiviral therapy in CHB in Australia were from hospital specialists and dispensed from hospital pharmacies (17). Hospital pharmacies made a transition from jurisdictional (state and territory) government-facilitated reimbursement to national or PBS reimbursement of S100 antiviral medications in 2010-2012.

In the original HIV cascade from the USA (50), on which indicators were considered for the Australian CHB cascade and prior to guidance from WHO, the estimated population adherent to treatment/viral load undetectable was measured as the final step in the care continuum (see Figure 3). The HIV cascade of care has now shifted to the estimated proportion on treatment who are viral suppressed rather than adherent. This is now also one of the ten core current indicators in the WHO framework for the CHB cascade of care (16) (see Figure 1). In Australia as elsewhere, adequate viral suppression for those on therapy is important to improving outcomes, but is also dependent on adherence to the therapy. Antiviral therapies for CHB are highly effective and have a low barrier to resistance. The long term (five years and plus) cumulative virological response (suppression to undetectable viral loads) for entecavir and tenofovir is 95-99% (106). Viral suppression is the eventual expected outcome of
therapy, but for people who initiate treatment a consistent decline, with a $> 1 \times \log_{10}$ in HBV DNA in the initial 6 months, indicates a favourable treatment response (106).

The data in this study was from four hospitals located in Melbourne. The study included as a paper in this chapter used records of 1026 individuals to analyse the factors associated with adherence. During the years 2010-2013, the pathology systems changed at two hospitals: one changed computer systems and shortened the period that pathology data was available by 11 months; another started to use a private provider, which limited the pathology data available to July 2010 to November 2011 from that site. It was also the practice of one hospital to use some external private providers to collect HBV DNA. Participants were only included in this analysis if two or more HBV DNA were recorded in the hospital pathology system during the time on treatment. Therefore, only a subset of participants included in the initial factors related to adherence analysis were all included in this second analysis. The analysis of viral outcomes was done second to the original study, due to the time taken to acquire the data set.

4.3.2 Aims
The aims of this sub-study were to evaluate virological outcomes in an Australian multicentre setting, to determine the proportion of patients with adequate viral suppression and/or favourable outcomes on antiviral treatment, and to establish the association between MPR and the viral outcomes in patients receiving long-term oral antiviral therapy for CHB.

4.3.3 Methods
This study was a retrospective analysis of patient records of individuals dispensed antiviral therapy for CHB from four tertiary referral hospitals in Melbourne, Australia between 2010-2013. Pharmacy, demographic and pathology data were linked using hospital record number.
Participants were included if they were prescribed oral antiviral monotherapy with > 3 months on treatment and ≥ 2 HBV DNA viral load tests recorded in the hospital pathology service during the period they were observed on treatment.

Viral events were initially classified into unfavourable or favourable clinical outcomes, as presented in the Table 3. Viral breakthrough (VBT) was defined as a rise of greater than 1x log$_{10}$ (39, 106). Rises of less than 1x log$_{10}$ were classified in two ways in the primary analysis. The pattern seen in clinical practice of transient rises in viral load (one-time value rises above detectable and less than 150 IU/ml) or blips were analysed as a separate outcome and classified as favourable in main analysis. Other rises less than 1x log$_{10}$ were classified as unfavourable.

A sensitivity analysis for unfavourable outcomes – using a second definition with unfavourable outcomes as viral breakthrough and failure to become undetectable after 2 years – is presented in Table 4.

The MPR values were calculated from records of medication dispensed from the first pharmacy visit to the date immediately after, or at the same time as, the viral event was observed, as pharmacy pick-up dates did not always align with the date of pathology tests. For those who were fully suppressed throughout the time period, the MPR was calculated for the whole observed period. Participants could have more than one event recorded, with separate calculations made of cumulative MPR from initial dispensing date to prior to each event.
Table 3: Viral events/patterns and classification in to outcome categories primary analysis.

<table>
<thead>
<tr>
<th>Unfavourable viral outcomes</th>
<th>Favourable viral outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1x \log_{10}$ rise in HBV DNA level from nadir (viral breakthrough)</td>
<td>Fully suppressed (remaining HBV DNA undetectable for study period)</td>
</tr>
<tr>
<td>Detectable HBV DNA after 2 years on treatment</td>
<td>Becoming undetectable with no further rise</td>
</tr>
<tr>
<td>$&lt;1x \log_{10}$ rises HBV DNA not transient rises*</td>
<td>Falling HBV DNA with $&gt; 1x \log_{10}$ reduction and treatment $&lt; 2$ years</td>
</tr>
<tr>
<td>* transient rise = a single transient rise to HBV DNA level $&lt; 150$ IU/ML with return to</td>
<td></td>
</tr>
<tr>
<td>undetectable at next test</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Viral events/patterns and classification in to outcome categories secondary analysis.

<table>
<thead>
<tr>
<th>Unfavourable viral outcomes</th>
<th>Favourable viral outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1x \log_{10}$ rise from nadir, viral breakthrough</td>
<td>Fully suppressed (undetectable HBV DNA for observed period)</td>
</tr>
<tr>
<td>Detectable HBV DNA after 2 years</td>
<td>Becoming undetectable with no further rise</td>
</tr>
<tr>
<td></td>
<td>Falling HBV DNA with $&gt; 1 \log$ reduction and treatment $&lt; 2$ years</td>
</tr>
<tr>
<td>$&lt;1x \log_{10}$ rise in HBV DNA</td>
<td></td>
</tr>
</tbody>
</table>

The categorical variables were summarised using frequency and percentage. Continuous variables were summarised using mean and standard deviation (SD) or median and inter-quartile range (IQR) for parametric or non-parametric data, as appropriate. As the individual patients were permitted to contribute multiple unfavourable outcomes across the observation period, an Andersen-Gill time-to-multiple-event model was used to examine associations between MPR and the study outcomes. Hazard proportionality was assessed via analysis of scaled Schoenfeld residuals. All multivariable models were assessed for interactions between explanatory variables.
MPR was analysed with Youden analyses as a continuous variable to ascertain a possible cut point to define poor adherence. Further analyses of previously used categorical values of MPR to identify performance of those values of MPR in discriminating the outcome variables (0.80, 0.90, 0.95, 1.0 and the addition of oversupply defined as 1.05) was performed with receiver operating characteristic (ROC) sensitivity, specificity, and positive and negative predictive values (PPV, NPV). For all analyses, p<0.05 was considered significant. All analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria).

Data collection cleaning was performed in excel and preliminary analysis was performed in STATA. Assistance with further analysis performed in R was provided by a statistician whose contribution is acknowledged in the preface of the thesis.

4.3.4 Results
Six hundred and forty two (642) participant records were included in the final analysis, representing 1234 patient-years of antiviral treatment. Three hundred and eighty-four (384) of 1026 patients were excluded for insufficient data (<2 viral loads recorded in the hospital pathology services during the period on treatment).

The median time on treatment during the study period was 27.5 months (IQR 13.5 - 32.9) and the median number of viral loads performed was four (IQR 3-6). The median age was 46.6 years (IQR 37.0- 56.0) and 68% of participants were male (see Table 5). Most (91.7%) patients on antiviral medication were born overseas, with 77% of the total born in Asia (see Table 5). In total, 550 patients (85.7%) were on first-line oral antiviral therapies (either entecavir 0.5mg or tenofovir 300mg). The remainder were on other regimes: entecavir 1mg, adefovir 10mg, lamivudine 100mg.
Table 5: Patient characteristics in viral outcomes analysis

<table>
<thead>
<tr>
<th>Gender</th>
<th>Median age (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>441 (68.69%)</td>
</tr>
<tr>
<td>Female</td>
<td>201 (31.31)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region of birth</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>496 (77.26)</td>
<td>46.00 (31.00-55.09)</td>
</tr>
<tr>
<td>Europe</td>
<td>49 (7.63)</td>
<td>61.00 (53.00-68.39)</td>
</tr>
<tr>
<td>Australia</td>
<td>45 (7.01)</td>
<td>44.00 (31.00-55.60)</td>
</tr>
<tr>
<td>Africa</td>
<td>34 (5.30)</td>
<td>40.76 (33.52-47.34)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (1.56)</td>
<td>45.00 (53.00-59.39)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>8 (1.25)</td>
<td></td>
</tr>
</tbody>
</table>

An adequate response to antiviral therapy was achieved in 80.8%, either fully suppressed (undetectable throughout the observed period) or achieved undetectable HBV DNA after less than two years on treatment, with no further rises in viral load observed. Rises in HBV DNA $<1 \times 10^{10}$ IU/mL were observed in 97 (15.1%) with 56.7% of these events a single value less than 150 IU/mL (blip), then a return to undetectable and the remainder other rises $<1 \times 10^9$. Forty participants had two events recorded during the observed treatment period. Analysis of difference of proportions of favourable and unfavourable outcomes by entecavir vs. tenofovir ($p=0.30$) and first line recommended therapy (entecavir 0.5mg and tenofovir) vs. older drugs with a significant resistance profile (adefovir and lamivudine) showed no difference ($p=0.38$). The details of events and outcomes recorded by drug appear in Table 5. Decreasing MPR was associated with a greater hazard ratio for $<1 \times 10^9$ rises (0.008) but not transient rises or blips (0.093).
Of the participants with viral outcomes recorded, 346 (50%) had an MPR of <1.0 or less medication than days treated, 197 (28.9%) MPR of < 0.95 and 137 (20%) <0.90. (Note: these figures include individuals with more than one outcome recorded).
Table 6: Viral outcomes by drug and category

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Individuals n (%)</th>
<th>2 events</th>
<th>Fully suppressed</th>
<th>Became undetectable</th>
<th>Transient rises</th>
<th>Falling HBV DNA treated &lt;2yr</th>
<th>Total favourable outcomes</th>
<th>Viral break through ≥ 1 log₁₀ rise</th>
<th>&lt;1 log₁₀ rise</th>
<th>Detectable HBV DNA &gt; 2 years</th>
<th>Total unfavourable outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>642</td>
<td>40</td>
<td>340 (48.85)</td>
<td>179 (26.25)</td>
<td>55 (8.06)</td>
<td>47 (6.89)</td>
<td>621 (91.06)</td>
<td>17 (2.49)</td>
<td>42 (6.54)</td>
<td>2 (&lt;0.01%)</td>
<td>61 (9.44)</td>
</tr>
<tr>
<td>First line therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entecavir 0.5mg</td>
<td>407 (63.40)</td>
<td>22</td>
<td>216 (50.35)</td>
<td>118 (27.21)</td>
<td>35 (8.16)</td>
<td>27 (3.96)</td>
<td>396 (92.31)</td>
<td>8 (1.86)</td>
<td>24 (5.90)</td>
<td>1 (&lt;0.01%)</td>
<td>33 (7.69)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>143 (22.27)</td>
<td>11</td>
<td>61 (39.61)</td>
<td>48 (31.17)</td>
<td>10 (6.49)</td>
<td>19 (2.79)</td>
<td>138 (89.61)</td>
<td>6 (3.90)</td>
<td>9 (6.29)</td>
<td>1 (&lt;0.01%)</td>
<td>16 (10.39)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entecavir 1mg</td>
<td>29 (4.52)</td>
<td>1</td>
<td>16 (53.33)</td>
<td>3 (10.00)</td>
<td>6 (20.00)</td>
<td>1 (3.33)</td>
<td>26 (86.67)</td>
<td>2 (6.67)</td>
<td>2 (6.90)</td>
<td>0 (0.00)</td>
<td>4 (13.33)</td>
</tr>
<tr>
<td>Older drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>53 (8.26)</td>
<td>4</td>
<td>40 (70.18)</td>
<td>8 (14.04)</td>
<td>4 (7.02)</td>
<td>0 (0.00)</td>
<td>52 (91.23)</td>
<td>1 (1.75)</td>
<td>4 (7.54)</td>
<td>0 (0.00)</td>
<td>5 (8.77)</td>
</tr>
<tr>
<td>Adefovir</td>
<td>10 (1.56)</td>
<td>2</td>
<td>7 (58.33)</td>
<td>2 (20.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>9 (75.00)</td>
<td>0 (0.00)</td>
<td>3 (25.00)</td>
<td>0 (0.00)</td>
<td>3 (25.00)</td>
</tr>
</tbody>
</table>
The empirical cut-point or the Youden analysis identified an MPR value of 0.98, with sensitivity and specificity of 41% and area under ROC 0.41.

The time-to-event analysis found a significant association between MPR and viral outcomes, with an increased hazard of unfavourable events at lower MPR values (see Table 6 primary analysis). While there was a risk reduction of 79% for unfavourable outcomes with an MPR ≥ 0.90 relative to an MPR < 0.90, a value that was previously used to define adherence in 3 studies (71, 85) (p<0.001), it was not a clear cut-off for unfavourable outcomes. The time-to-event analyses curves for MPR values 0.80, 0.90 and 0.95, presented in Figures 4-6.

Table 7: Hazard ratios for MPR values and interpretation of risk reduction of unfavourable events using the primary analysis definitions controlling for receipt of adefovir or lamivudine.

<table>
<thead>
<tr>
<th>MPR</th>
<th>Hazard ratio (95% CI) p-value</th>
<th>Interpretation of risk reduction of unfavourable events</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.80</td>
<td>0.214 (0.12 – 0.37) &lt;0.001</td>
<td>79%</td>
</tr>
<tr>
<td>≥0.90</td>
<td>0.292 (0.17- 0.50) &lt;0.001</td>
<td>71%</td>
</tr>
<tr>
<td>≥0.95</td>
<td>0.334 (0.20 - 0.57) &lt; 0.001</td>
<td>67%</td>
</tr>
<tr>
<td>≥1.00</td>
<td>0.398 (0.22 - 0.73) 0.003</td>
<td>61%</td>
</tr>
<tr>
<td>≥1.05</td>
<td>0.600 (0.29 - 1.44) 0.287</td>
<td>No association</td>
</tr>
</tbody>
</table>

An example of interpretation of the results for an MPR value ≥ 0.80 is that there was a reduced risk of unfavourable events with a hazard ration of 0.214 or a 79% risk reduction in unfavourable events relative to <0.80. Oversupply defined as MPR ≥1.05 was not associated with a significant risk reduction of unfavourable events.

Further analyses of the MPR values using the secondary analysis definitions (Table 4) are presented in Table 7. This analysis used a definition of unfavourable outcomes as viral failure and detectable viral load at 2 years. It is presented in Table 8.
Table 8: Hazard ratios for MPR values and interpretation of risk reduction of unfavourable events using the secondary analysis definitions controlling for receipt of adefovir or lamivudine.

<table>
<thead>
<tr>
<th>MPR</th>
<th>Hazard ratio (95% CI) p-value</th>
<th>Interpretation of risk reduction of unfavourable events</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.80</td>
<td>0.08 (0.03 – 0.21) &lt;0.001</td>
<td>92%</td>
</tr>
<tr>
<td>≥0.90</td>
<td>0.11 (0.04, 0.30) &lt;0.001</td>
<td>89%</td>
</tr>
<tr>
<td>≥0.95</td>
<td>0.16 (0.05, 0.45) 0.001</td>
<td>84%</td>
</tr>
<tr>
<td>≥1.00</td>
<td>0.26 (0.07, 0.91) 0.034</td>
<td>74%</td>
</tr>
<tr>
<td>≥1.05</td>
<td>0.31 (0.04, 2.33) 0.254</td>
<td>No association</td>
</tr>
</tbody>
</table>

A further analysis of the MPR values and association with unfavourable outcomes as defined in the primary analysis is presented in Table 9. The table presents sensitivity, specificity, positive predictive value and area under the receiver operating characteristic (ROC) curve.
Table 9: Further analyses of medication possession ratio (MPR) and performance of MPR values as a test to predict unfavourable viral outcomes using primary analysis definition.

<table>
<thead>
<tr>
<th>MPR</th>
<th>Outcomes &lt; MPR</th>
<th>Unfav. outcomes &lt; MPR</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
<th>ROC* area (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>97</td>
<td>21</td>
<td>65.6 (52.3-77.3)</td>
<td>12.2 (9.8-15.1)</td>
<td>6.8 (4.9-9.2)</td>
<td>78.4 (68.8-86.1)</td>
<td>0.389 (0.33-0.45)</td>
</tr>
<tr>
<td>0.90</td>
<td>137</td>
<td>24</td>
<td>60.7 (47.3-72.9)</td>
<td>18.2 (15.2-21.5)</td>
<td>6.8 (4.9-9.2)</td>
<td>82.5 (75.1-88.4)</td>
<td>0.394 (0.33-0.46)</td>
</tr>
<tr>
<td>0.95</td>
<td>197</td>
<td>31</td>
<td>49.2 (36.1-36.1)</td>
<td>26.7 (23.3-30.4)</td>
<td>6.2 (4.2-8.7)</td>
<td>84.3 (78.4-89.1)</td>
<td>0.380 (0.31-0.45)</td>
</tr>
<tr>
<td>1.00</td>
<td>346</td>
<td>44</td>
<td>27.9 (17.1-40.8)</td>
<td>48.6 (44.6-52.6)</td>
<td>5.1 (3.0-8.0)</td>
<td>87.3 (83.3-90.6)</td>
<td>0.383 (0.32-0.44)</td>
</tr>
</tbody>
</table>

* The average of sensitivity and specificity for the binary MPR cut-point being tested

PPV = positive predictive value, NPV = negative predictive value, ROC = receiver operating characteristic curve, CI = confidence interval, MPR = Medication possession ratio
Figure 4: Time-to-event analyses showing proportions of patients over time who experience the unfavourable event when threshold MPR = 0.80

Figure 5: Time-to-event analyses showing proportions of patients over time who experience the unfavourable event at MPR when threshold MPR = 0.90
4.3.5 Discussion

This is the largest study examining the association between adherence as defined by MPR and virological outcomes in antiviral treatment for CHB (57, 70, 76, 82). Lower MPR values were associated with unfavourable viral outcomes in people taking antiviral medication for CHB with an increased risk of VBT. Approximately 80% of patients achieved suppression or were fully virally suppressed during the study period, which is consistent with previous smaller studies in Australia and overseas (57, 72, 175).

Values used for defining poor adherence have been largely arbitrary and have ranged from 80% to 95% (70, 71, 78, 79, 86, 89), with small studies that examined viral outcomes with a proposed cut-off of less than 90% (71) or 95% (64). This study found that the previous use of thresholds such as 0.90 is supported by evidence of a greater risk of unfavourable outcomes, but these thresholds are not absolute cut-off points to define adherence based on viral outcomes.
In Australia, a recent study of 211 patients showed that self-reported patient adherence is associated with viral outcomes, but there was no clear increase in relative risk with increased doses reported as having been missed (57). This absence of a dose response relationship is likely due to recall issues or social desirability bias inherent in this type of measure – the patient being less willing to report a greater number of missed doses to their clinician. Self-report, in a clinical context, has the advantage of a simple question to assess adherence, however, by using an objective pharmacy-based measure, MPR, or combining adherence measures in clinical practice, it is possible to better assess the risk of unfavourable viral outcomes and advise patients how to mitigate that risk.

A small number of patients in this study remained on earlier, less effective therapies, despite universal access to newer antiviral therapy, as is also observed in national prescribing data for Australia (176). Participants on lamivudine – a drug no longer recommended (106) – did not have an increased number of unfavourable outcomes, despite the lower barrier to resistance observed with these agents. This may in part be due to small numbers and decisions made by the clinician to keep a person on an older antiviral agent because they have achieved and maintained good virological suppression.

This study is limited through its use of retrospective clinical data that are heterogeneous: the number of pharmacy visits, amount of drug dispensed at each visit and number of viral loads performed over the time period varied. Calculation of MPR accounts for medication picked up from a pharmacy but does not equate to actual pill-taking (84). Oral antiviral therapy for the treatment of CHB was almost exclusively dispensed via the hospital system during the time period, so it is unlikely that MPR was underestimated. However, it is possible that viral load testing might have been performed elsewhere and therefore viral events missed. The analysis was performed using real word data (data not collected in clinical trial settings) with different types of medication that may have different efficacies when evaluating viral suppression. Host immunological changes causing viral suppression, or the development of antiviral resistance while on medication, could have influenced findings of undetectable viral load or viral breakthrough over and above medication adherence.
No measure of patient adherence is without limitations (84). MPR calculated over any time period masks variations in adherence; for example, a period of stockpiling followed by a period of poor adherence, losing medication or conversely, a period of poor adherence followed by regular medication-taking. This study was not designed to detect the association with MPR and adverse patient outcomes, including mortality, as has been previously described in HIV therapy. This kind of study in CHB would be a difficult prospect due to the differing natural history of HBV and HIV, with a much longer time to attributable mortality off-treatment in a smaller percentage of people with the infection.

Improving the outcomes for people receiving treatment for CHB must include a regular assessment of adherence and a focus on clinicians supporting patients to understand the importance of good adherence to antiviral therapy. Adherence interventions have been rarely trialled in CHB. There is a need to explore further barriers faced by individuals and then design and implement appropriate interventions to assist the 1 in every 5 patients in our health system who have poor adherence (89).

4.3.6 Conclusion

This study demonstrated that MPR is a useful measure to assess risk of poor viral outcomes and that the previously used 90% threshold for “good adherence” is supported by the risk of unfavourable events, but the dose response relationship must be considered in risk reduction.
Chapter 5: HCC surveillance in a community setting

5.1 About this chapter
Adherence to HCC surveillance is difficult to achieve, in part due to frequency and the need for responsive recall systems to facilitate attendance at appointments. Currently, estimating the proportion of people receiving optimal HCC surveillance is not part of the Australian cascade, although this was included as an indicator in the first National strategy and is an important part of CHB care and prevention of HCC-related mortality.

This chapter presents the findings from four and a half years of clinical data from a community health clinic that was trying to improve care for patients with CHB. During this time, the Integrated Hepatitis B Service (IHBS), an external service from Melbourne Health, provided a specialist nurse practitioner who worked across eight clinics to improve recall systems, liaise with hospital specialists, contact patients lost to follow-up, and provide education to general practitioners about recommended care and testing.

The IHBS program operated from 2012-2016 as the only primary-healthcare-focused CHB program in Victoria. The Department of Health and Human Services commissioned an external evaluation as part of a review of nursing hepatitis services. The review was not made public and funding ceased, resulting in the service being discontinued at the end of 2016. The review findings are presented in this thesis, particularly focusing on HCC surveillance to highlight issues in care delivery at the community level. The small numbers and the nature of the clinic population – young and mainly born in the African region – does not make this generalisable to other clinical services. However, the challenge to maintain monitoring, including HCC surveillance over long periods when treatment is usually not required, is common to all services providing care to people with CHB.

Paper included in this chapter:

The challenge of liver cancer surveillance in general practice: Do recall and reminder systems hold the answer?
5.2 Paper 3: The challenge of liver cancer surveillance in general practice: Do recall and reminder systems hold the answer?
The challenge of liver cancer surveillance in general practice: Do recall and reminder systems hold the answer?

Nicole Allard, Tracey Cabrie, Emily Wheeler, Jacqui Richmond, Jennifer MacLachlan, Jon Emery, John Furler, Benjamin Cowie

Background and objective
Hepatocellular carcinoma (HCC) surveillance reduces mortality in at-risk people living with chronic hepatitis B (CHB), but is difficult to achieve in practice. The objective of this study was to measure participation and adherence to liver cancer HCC surveillance in eligible patients in a community health centre, following support from the Integrated Hepatitis B Service (IHBS).

Method
A retrospective analysis of the medical records of patients with CHB who met the indications for HCC surveillance over a 4.5-year period of IHBS involvement was conducted. Data collected included the date of ultrasound examinations and HBV DNA viral load tests.

Results
Sixty-seven patients underwent HCC surveillance, representing 213 person years. The participation rate was 75%. Adherence to surveillance was considered good in 18 (27%) patients, suboptimal in 29 (43%) patients and poor in 20 (30%) patients. A greater proportion of patients were receiving HCC surveillance at the final audit (56%) than at baseline (10%; \( P < 0.001 \)).

Discussion
It is difficult to achieve optimal adherence to HCC surveillance, even with additional support.

Chronic hepatitis B (CHB) affects an estimated 239,000 Australians. The majority of those affected were born overseas in high-prevalence or intermediate-prevalence countries. \(^1\) CHB can lead to liver cancer – specifically, hepatocellular carcinoma (HCC) – and important added risk factors include the presence of cirrhosis, age, region of birth, male gender, co-infection with hepatitis C, D or human immunodeficiency virus (HIV), and other active liver disease (eg alcohol-related injury, non-alcoholic steatohepatitis). \(^2\)

Liver cancer is the fastest-increasing cause of cancer mortality in Australia. \(^3\) It is one of the few cancers with no improvement in five-year survival since 2009, and is projected to become the sixth most common cause of cancer mortality in Australia. \(^4\) Poor outcomes of liver cancer are occurring in an era when most other cancers (eg bowel, breast, cervical) are associated with improving survival because of a combination of early detection and improved treatment approaches. \(^2\)

Reducing mortality from HCC due to CHB can be achieved with improvements in primary, secondary and tertiary prevention measures by preventing both new infections and the sequelae of existing infections. \(^6\) Prevention of HCC in people who are already living with CHB can be achieved through regular monitoring and commencement of antiviral therapy, when appropriate. Antiviral treatment is associated with a reversal of cirrhosis and a reduction of HCC risk by up to 75%. \(^6\) Tertiary prevention of the consequences of CHB is achieved by HCC surveillance, with early detection of tumours that are amenable to curative therapy contributing to reduced mortality.

In Australia, the number of patients requiring and participating in HCC surveillance is unknown. Significant gaps exist in the care cascade, which suggests that participation is likely to be poor. Forty per cent of people living with CHB remain undiagnosed and 80% are not receiving regular care. \(^7\) Late diagnosis of CHB prior to HCC or cirrhosis diagnosis occurs in an estimated one-third of people. \(^8\)
Guidelines recommend HCC surveillance with liver ultrasonography, with or without alpha-fetoprotein measurement, every six months. Liver ultrasonography has a sensitivity of 58–89% and specificity >90% for the detection of HCC. In Australia, recommendations on who should be enrolled in surveillance is in accordance with the American Association for the Study of Liver Disease (AASLD) guidelines, with a modification to include specific surveillance recommendations for Aboriginal and Torres Strait Islander peoples. The recommendations for HCC surveillance in people living with CHB are listed in Box 1.

Box 1. Current Australian recommendations for HCC surveillance for people living with CHB

- All people with cirrhosis
- Those with a first-degree family history of HCC
- Asian men aged >40 years, and Asian women aged >50 years
- African people aged >20 years
- Aboriginal or Torres Strait Islander people aged >50 years

General practice management of CHB is essential for improving enrolment in chronic disease care, including successful participation in HCC surveillance, and is cost-effective. However, HCC surveillance is difficult to implement in practice. Reported mortality benefits vary for surveillance-detected HCC, but the optimal interval of surveillance is not clear. Harms associated with HCC surveillance, including the psychological impact and false-positive results, have not been well reported. A recent study reported that physical harm may occur in one-quarter of people in whom a lesion is identified; in most cases, harm was characterised as unnecessary imaging after a false-positive test. Optimal HCC surveillance requires clinicians to enrol appropriate patients, and for patients to attend for the scheduled ultrasonography. Factors associated with improved HCC surveillance include frequency of clinic visits (ie tertiary or primary care), specialist service involvement and higher socioeconomic status. In recognition of the need to support CHB care in general practice, the Integrated Hepatitis B Service (IHBS) was funded in Victoria from 2012 to 2016 to support general practices and link them with specialist units. The community health centre in this study is in western Melbourne, an area of high CHB prevalence, and servicing a large multicultural community. It became a partner of the IHBS after general practitioners (GPs) identified improving CHB management (including HCC surveillance) as a priority in their practice. IHBS nurses assisted the clinic by: conducting baseline audits; advising GPs on guidelines-based care; contacting patients lost to follow-up; strengthening standard recall and reminder systems by posting radiology and pathology requests, and regular review and phone calls to individuals failing to attend appointments. Return visits by the nurses were conducted every four months to follow up if patients had attended. The service used qualified interpreters on request. The aim of this study was to describe adherence to HCC surveillance and monitoring in a general practice that received external support to improve CHB management, including HCC surveillance.

Methods

We retrospectively analysed the impact of systems support on HCC surveillance over the period of IHBS involvement. At baseline of the IHBS involvement an audit of CHB patients in the practice was conducted and data, including HCC surveillance eligibility, demographics, most recent ultrasound and HBV DNA, were recorded. Included in the group who received surveillance and were followed up by the IHBS were people who were contactable and agreed to have their care delivered by the practice. Eligibility for HCC surveillance was determined by current Australian recommendations. Final data collection 4.5 years after the initial audit included the date of all ultrasound examinations and HBV DNA viral load test results in the clinical record over the study period; a binary variable if the clinician ordered tests at least yearly; number of booked appointments not attended; and if pregnancy, significant illness or reasons for any periods of non-attendance occurred. New patients were included in the final audit with time under observation from first visit to the clinic. Participants who became eligible because of age during the study period were included from January of the year of eligibility. Consistency of care was measured from the last 10 visits prior to the end of the observation period as the proportion seen by a single provider.

Participation in HCC surveillance was defined as two consecutive ultrasound scans and at least one scan every two years. The optimal interval for surveillance is based on tumour doubling time, which is estimated to be six to eight months, and currently there is no clear international definition. In this study, adherence to HCC surveillance recommendations was classified as poor (average <1 scan every 14 months), suboptimal (average ≥1 but <2 scans every 14 months and good (average ≥2 ultrasound every seven months). For each patient, the months to the last ultrasound from the first and second audit dates were calculated as a measure of improvement in surveillance because of increased focus on surveillance and IHBS involvement.

Data were collected in Microsoft Excel and analysed using Stata 11. Chi-squared and Fishers exact tests were used for difference of proportions. The study received human research ethics committee approval (Melbourne Health QA2013111).

Results

The baseline audit identified 80 patients who met the criteria for HCC surveillance; 37 were not enrolled in regular review.
because they received care elsewhere, were not contactable or declined follow-up (Figure 1). Sixty-seven patients received HCC surveillance in the community during the study period, representing 213 person years of follow-up. The number eligible for HCC surveillance in the clinic increased from 43 to 63 individuals and the proportion of patients being managed in hospital changed from 25% to 15% ($P = 0.055$).

The median age of patients undergoing surveillance was 37.6 years (interquartile range [IQR]: 28.6–50.2); 43 (64%) were born in a country in the sub-Saharan African region; and five (8%) had been diagnosed with cirrhosis. The overall participation rate was 75%; 13% underwent surveillance less frequently than every two years; and eight (12%) participants had no ultrasound examinations over the study period despite tests being ordered by the clinician at least yearly, with postal and telephone reminders. Clinicians ordered ultrasonography at least every 12 months for 60 (90%) patients. Failure to attend appointments occurred for 51 (76%) patients, with half of all patients having more than five missed appointments over the 4.5-year period. Characteristics associated with adherence categories are shown in Table 1.

A greater proportion of patients received an ultrasound examination in the seven months prior to the final audit, compared with the baseline audit (56% versus 10%; $P<0.001$). Four patients ceased surveillance at the clinic as three had transferred their care and one became HBsAg-negative and did not require further surveillance. One-quarter (17 participants) of patients who did not attend care had reasons recorded in their patient records, which included travel overseas, pregnancy and other significant health issues. Three potentially suspicious lesions that required further investigation were identified over the study period, but no liver cancers were identified. Thirty-four (51%) participants had a maximal interval between screening tests of >14 months during the observation period. As any measure of adherence missed variation over time, a visual representation of adherence showing individual-level data over the observed period is shown in Figure 2.

**Discussion**

Delivering guideline-based HCC surveillance in general practice presents substantial challenges. In the supported setting described in this study, participation in HCC surveillance was higher than in other clinical cohorts, and participation improved over the study period. However, optimal adherence to recommended surveillance intervals was only achieved in a quarter of patients. This is despite external clinician support, provider consistency (70% of clinic visits with single provider in two-thirds of patients), regular ordering of tests, and regular reminder letters and telephone contact. Patients were more likely to adhere to optimal surveillance intervals if they were on antiviral treatment, more recently diagnosed and having regular viral load tests.

While participants’ adherence was defined in this analysis as the number of ultrasound examinations over the study period, the patterns of adherence varied among individuals and over time. In this cohort, patients who were lost to follow-up for a period could re-engage, reflecting real-world data. Other factors.
such as pregnancy, travel and other significant illness, also affected adherence to surveillance. Half of the patients who had regular viral load tests had suboptimal or poor interval surveillance. This suggests that barriers to testing with ultrasonography may differ from barriers for blood tests, which were available at the clinic and did not require a separate booking or further attendance.

Limitations of this study include the size and specific clinic population. Individuals might have received care from other clinics, where other practitioners may also have order ultrasonography for surveillance. The impact of this would be to underestimate surveillance frequency. The findings are also unlikely to be generalisable to other community-based settings, particularly given that the clinic was staffed by GPs with an interest in hepatitis B (and refugee health), and received support from an external expert tertiary service. The study period was characterised by the partnership between IHBS and clinic, but this study does not seek to formally evaluate the program; rather, it describes the impact of systems support on HCC surveillance.

This study shows that intensive and supported systems improvement, while likely to improve HCC surveillance frequency, does not completely address complex issues involved in long-term, frequent cancer surveillance of people who (for the vast majority) have no symptoms related to their condition, and many of whom (particularly those born in Africa) are young. Family, employment, accommodation, other health priorities, health literacy, and other factors may all interfere with the ability to book and attend regular ultrasonography appointments in addition to clinic appointments and onsite pathology tests.

Optimal adherence to liver cancer surveillance is difficult to achieve. In Australia, this surveillance is not supported by external registries, media campaigns or appropriate educational material to promote surveillance among affected communities where people may have low health literacy. CHB care (including HCC surveillance) is a current national strategic direction, and needs to occur in general practice and tertiary centres to reach the many people eligible and not receiving care. Participation in more established cancer-screening programs (i.e. bowel, breast, cervical) is lower in overseas-born Australians because of reduced healthcare access, lower health literacy, and other cultural perceptions and understanding of cancer and cancer prevention. There are few studies of the barriers to, and knowledge of, HCC surveillance in affected communities. Overseas experience recall systems have had mixed success in improving adherence.

There are many outstanding questions in HCC surveillance, including the effects of variability in the quality of scans, expertise of reporting radiologists and different surveillance intervals, and at what time interval suboptimal surveillance frequency confers a mortality benefit. These outstanding questions are complicated by a lack of consistency in definitions of adherence and reporting of outcomes. There is policy discussion about the value of additional systems, including registries to enhance HCC surveillance. In New Zealand, Korea and Japan, reduction in mortality for HCC has been observed in population-based registries.

In conclusion, this study has demonstrated the challenges in enhancing

### Table 1. Characteristics by adherence to ultrasound surveillance and P value for difference of proportions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 67)</th>
<th>Good adherence (n = 16)</th>
<th>Suboptimal adherence (n = 29)</th>
<th>Poor adherence (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex male (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;35 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for surveillance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>57 (85.1)</td>
<td>12 (21.1)</td>
<td>26 (45.6)</td>
<td>13 (33.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Family history</td>
<td>5 (7.5)</td>
<td>4 (80.0)</td>
<td>1 (20.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>On treatment</td>
<td>16 (24.6)</td>
<td>8 (50.0)</td>
<td>7 (43.7)</td>
<td>1 (6.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Provider consistent*</td>
<td>41 (61.2)</td>
<td>13 (31.7)</td>
<td>20 (48.8)</td>
<td>8 (19.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Managed &lt;2 years</td>
<td>14 (20.9)</td>
<td>9 (64.3)</td>
<td>2 (14.3)</td>
<td>3 (21.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Viral load:every 14 months</td>
<td>39 (58.2)</td>
<td>16 (41.0)</td>
<td>19 (48.7)</td>
<td>4 (10.3)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Provider consistent – same clinician for more than seven of 10 visits
HCC surveillance in general practice. Future interventions will require an understanding of the target population and barriers they face to achieving optimal surveillance, including knowledge and risk perception. Systems improvement alone is unlikely to achieve good adherence to current guidelines for HCC surveillance.

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References
Chapter 6: How health risks are understood by African Australians living with CHB.

6.1 About this chapter

This chapter presents the work from a qualitative study undertaken in 2016. The preliminary analysis of the data from the community clinic in 2015 found that HCC surveillance participation was poor despite reasonable systems, assistance from the Integrated Hepatitis B Service, and interested clinicians who were aware both of liver cancer risk in the population and the recommendations for surveillance.

The clinic served an area that included many people born in the African region who had been screened and diagnosed with CHB as part of the refugee health program in the mid-2000s. The initial hypothesis was that poor understanding of liver cancer risk was affecting participation in HCC surveillance. There was no literature relevant to people born in the African region living with CHB and their understanding of health risks from CHB in Australia or overseas.

While the initial hypothesis was focused on the understanding of liver cancer risk, the methodology used semi-structured interviews (see Appendix A) that included health system experiences from diagnosis and an understanding of the illness narrative. Early in the analysis process, themes emerged about the breadth of health impacts of CHB, especially the social and emotional impacts of diagnosis and living with a chronic infection.

Paper included in this chapter:
Knowing and telling: How African- Australians living with chronic hepatitis B understand HCC risk and surveillance
Allard N, Emery J, Cowie B, Furler J.
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Keywords: Liver cancer, diagnosis, disclosure, stigma

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Abstract

African-Australians have a high prevalence of chronic hepatitis B (CHB) and an increased risk of liver cancer (hepatocellular carcinoma, HCC) at a younger age than other affected groups living with CHB. The prevention of HCC-related mortality is possible with timely diagnosis of CHB, regular monitoring, including liver cancer surveillance, and appropriate treatment with antiviral therapy. Currently, little is known about how African-Australians living with CHB understand their condition, their risk of liver cancer, and the need for regular monitoring. We conducted 19 semi-structured interviews with African-Australians who have CHB. The interviews explored the participants’ knowledge of CHB, their perceptions of future health risks, and experiences and understanding of healthcare. The three major themes identified in the analysis were the risks to physical health, including liver cancer, risks to social and emotional wellbeing from diagnosis and disclosure, and the fear and worry associated with being infectious. The understanding of risk and mitigation of that risk was framed by their understanding of health and ageing, as well as participants’ educational background and faith. Our findings show the importance of engagement with the broader social and emotional impacts of CHB by clinicians and services and can assist in developing interventions to increase participation in healthcare, including liver cancer surveillance.
What is known about the topic?

Currently, little is known about African-Australians’ understandings of the risks of chronic hepatitis B (CHB)-related liver cancer and need for ongoing patient monitoring.

What does this paper add?

African-Australians living with CHB understand their risk not only in terms of physical health and liver cancer, but also as risk to social and emotional wellbeing from diagnosis and disclosure, and the fear and worry associated with being infectious. This broader understanding needs to inform health and support services for this community.
Introduction

In Australia, chronic hepatitis B (CHB) disproportionately affects people who were born overseas in high prevalence countries, including those from sub-Saharan Africa (MacLachlan et al. 2013). In 2015, an estimated 10,000 African-Australians were living with CHB, or 4.3% of the 239,000 people estimated to be affected in Australia (MacLachlan et al. 2017). In people from sub-Saharan Africa, primary liver cancer or hepatocellular carcinoma (HCC) related to CHB is over four times more likely and occurs at a younger age (Kramvis and Kew 2005). HCC surveillance is recommended every 6 months from the age of twenty for men and women born in Africa who are living with CHB, compared to commencing from the age of 40 for other groups (Terrault et al. 2015).

Most migration from African countries to Australia has occurred in the last 20 years (Australian Bureau of Statistics 2012). Most African-Australians have come from low income countries and include people from diverse cultural, ethnic and religious backgrounds. Many arrived as refugees after experiencing disruption to education and health services due to persecution and conflict in their country of origin (Human Rights and Equal Opportunity Commission 2009).

Liver cancer was the sixth most common cause of cancer death in Australia in 2016 and has a poor five-year survival, which, unlike most other cancers, has not improved in the last decade (Brown et al. 2017). Reducing the risk of death from HCC requires timely diagnosis, prevention through appropriate antiviral therapy (Terrault et al. 2015) and surveillance, which aims to detect cancer early at a stage amenable to curative treatments (Bruix and Sherman 2011).

Optimal HCC surveillance, which includes six-monthly liver ultrasounds +/- a blood test for alpha-fetoprotein, is difficult to achieve in practice, with low participation rates observed overall, and lower rates in primary care compared with specialist settings (Singal et al. 2012). In Australia, the number of people requiring HCC surveillance and the rates of participation in HCC surveillance are unknown. Small local studies in Australia and overseas suggest that only between a quarter and a third of people who should
receive surveillance do, even with enhanced reminder services and dedicated nursing staff (Kennedy et al. 2013).

How can HCC surveillance implementation be improved? Health system factors – including cost, convenience, cultural appropriateness of services, and health provider recommendations for testing – contribute to adherence in healthcare, but it is important to consider other barriers to participation, including patient knowledge and their competing priorities (Sabaté 2003). Patient understanding is influenced in part by the way health providers convey health and risk information, which in turn affects their ability to participate actively in healthcare decisions (Stacey et al. 2017).

Currently, little is known about how people from the African region living in Australia understand CHB and associated health risks. Surveys of Australians with CHB have identified gaps in knowledge but have not explored in-depth patient understanding of HCC risk or understanding of surveillance, and have included few people from African countries (Preston-Thomas et al. 2013; Dahl et al. 2014; Hajarizadeh et al. 2015; Richmond et al. 2017).

The aim of this study was to explore how surveillance and risks associated with CHB are experienced and understood by African-Australians living with CHB. The results will inform future strategies to promote increased engagement with clinical services and prevent HCC in African-Australians affected by CHB.

Methods

We used qualitative methods to investigate the beliefs and motivations that might influence understanding, perceptions of risk and health behaviour. The study is reported according to the consolidated criteria for reporting qualitative research (COREQ) checklist (Tong et al. 2007) (Appendix 2).

African-Australians living with CHB were recruited using purposive sampling based on gender, country of birth, age and educational background from a hospital and three
community health clinics in Victoria in 2016. An onsite qualified interpreter was used, if required, from the Telephone Interpreting Service (TIS) (https://www.tisnational.gov.au/). Recruitment continued until data saturation occurred and no new themes were identified. Participants were reimbursed with a $25 gift voucher.

The interviews were conducted by a single female interviewer (NA), a general practitioner experienced in using interpreters and trained in qualitative research techniques, who was not involved in the participants’ care and was introduced as a researcher. Interviews took place at the clinical sites or at the participants’ home. Demographic and background information was collected, including age, country of birth, year of arrival in Australia, current year, the context of diagnosis, educational background and religion. Interviews ranged from 45 to 90 minutes in length and were informed by an interview guide that was developed by the research team and modified during the interview process (See Appendix B).

All audio files were de-identified, assigned a pseudonym and transcribed by the researcher (NA). The responses of participants using an interpreter were transcribed using the translation made by the qualified interpreter, translated at the time of the interview.

Analysis

Data analysis drew on a grounded theory approach (Strauss and Corbin 1990) supported by NVIVO 11.21. The coding framework adopted a constant comparative technique. Regular meetings between two authors (JF, NA) developed consensus on the themes identified in the data.

Ethics

The study was approved by the Melbourne Health Ethics Committee HREC Reference Number: HREC/15/MH/327 and received site(s) specific approval by cohealth. If any
issues were identified that were important to the clinical care of an individual participant, they were referred to their treating clinician. The researcher also addressed any questions and knowledge gaps at the end of the interview using some standard information leaflets and resources.

Results

Nineteen participants aged 18-64 years – eight men and eleven women – were interviewed. Four of the participants required interpreters, nine were from hospital clinics, and ten from community sites. All participants had arrived in Australia after 1995 and were from a variety of faith backgrounds and countries. (see Participant Table 1). Educational background ranged from no formal education to postgraduate study. Participant Table 1 also includes data on the number of years since the diagnosis of Hepatitis B and the setting in which each participant was diagnosed.

Major themes

We identified three major themes in how participants conceptualised CHB to be a risk to their health and wellbeing: risks to physical health (the risk of liver cancer, liver failure and death); risks to social and emotional wellbeing experienced from diagnosis and disclosure; and the fear and worry associated with being infectious or transmitting the infection, especially to their family.

While the understanding of risks fell into these three themes, cutting across each of these domains was the way that faith, culture, education, age, other physical health problems and social stressors framed these risks. Knowledge of health risks came from a variety of sources, including the indirect and direct experiences of risks associated with CHB and health information from other sources (see Figure 1).
Risks to physical health: liver problems

When asked directly about the risks to their future health from CHB, participants, as expected, reported liver problems including liver cancer. Risk of liver cancer was often overestimated, either as “big” or, when percentage terms were used, as being up to 50%, especially by those participants who knew someone who had died from liver cancer in their family or community. For example, the risk of cancer and death is explained by Fahiimo, a 54-year-old woman with no formal education, who describes how she sees her risk of cancer and how she has been informed about cancer risk by her experiences in her family and community:

“I think a big chance. I think a big chance [...] because I know my aunties was die of hepatitis B, was the cancer of the liver, and aunty same and uncle was same and I know in Melbourne at least 3 people that died ... We know we know this one (liver cancer) is very dangerous...” (Fahiimo)

In contrast, liver damage and cirrhosis were not as clearly reported as a health risk. However, the liver was understood to be an important and large organ essential to life that, if damaged, could result in failure, death and/or cancer. As explained by Akong, a 25-year-old woman with primary school education:

“...the hepatitis B can damage your liver in the future... and if they damage your liver and no transplant you will died for it. Because if there is no liver, there is not life.” (Akong)

For younger participants, liver problems, including cancer, were seen to be associated with ageing. As explained by Abdel, primary school educated, aged 32 years:

“when I get older and have less energy...that is when I think it (hepatitis B) is going to be more dangerous...” (Abdel)
The relationship between having regular scanning as a part of HCC surveillance and therefore reducing your risk of liver cancer death was generally not acknowledged by the participants. Scans were understood to be looking at liver health rather than early cancer detection. Grace, a 32-year-old, tertiary-educated woman whose brother had died from CHB-related HCC, when asked if she understood the reason for regular scans, said:

“No, not really. When I see my specialist usually I get told that everything is fine, the liver...the scan is OK, everything is going OK, that's all but what I know is it is checking to liver or something liver or things.”

This apparent discrepancy in what people reported they understood about liver cancer risk and what they understood about HCC surveillance was consistent across different ages and levels of educational attainment. The exceptions to this were the participants who had previously had a liver lesion, identified themselves, and understood that the scans were looking for a potential cancer.

**Risks of disclosure: being told, telling and not telling.**

The second theme that was identified was the risk to social and emotional wellbeing from both diagnosis of hepatitis and disclosure. Diagnosis was often a devastating event that was complicated by no or low level of prior knowledge of CHB, confusion with prior knowledge about HIV/AIDS, and the timing of the diagnosis during a period of major change, such as a first pregnancy, shortly prior to migration, or soon after arrival in Australia (see Participant Table 1). An adverse reaction to the diagnosis seemed less likely if there were family or friends to whom the person could safely disclose their status. An example of low levels of knowledge and a lack of information at the time of diagnosis was explained by Grace, diagnosed in Uganda pre-departure to Australia:

“...because the information they gave to me, you're positive hep B. And I'm like HIV is AIDS, nothing else, this is what I know. And then when I arrived to Australia I was questioning myself, What is hep B? What is hep B?” (Grace)
People came to accept their condition over time as they acquired knowledge and gained support from others, especially family and health professionals. Older participants spoke of how their acceptance had been assisted by coming to understand that CHB was a common problem in their family or community. In contrast, some younger participants had never knowingly met other people with CHB and seemed to have ‘self-stigmatised’, not telling anyone about their diagnosis.

Negotiating intimate relationships was another important aspect of the risk of disclosure. Immediate disclosure occurred when people were told of their diagnosis in the presence of other family members, often a spouse. While some participants found comfort in having another person present to support them, negative consequences also occurred. Women identified disclosure to their partner as a risk to their relationship, as their fidelity could be questioned by their partner. Gebremariam, a 29-year-old man, who was told of the diagnosis with his new wife present, reported that after the diagnosis and disclosure, his marriage broke down

“I only came to know about hepatitis B when I arrived to Australia and what it was. But when the doctor told me that I have hepatitis B it affected me a lot...it broke it...impacting me in my life.” (Gebremariam)

Disclosure could also result in the experience of wider societal stigma and discrimination outside the immediate family. This varied in severity and depended on the setting, but included such things as social exclusion by community members and negative experiences in healthcare, employment and educational settings. This broader societal discrimination was a threat to health and resulted in risks to personal safety, financial security, housing, educational and migration opportunities. An example of discrimination in a pre-school is described by Ahoc, a 38-year-old woman with no schooling, when talking about her son who also had CHB:

“The doctor...they called to the childcare and they said this boy you got to be careful because he got hepatitis B and they reject my son to go to the kindergarten...”
Interviewer: “Did he end up going to another kindergarten?”

Ahoc: “No my son didn’t go to the kindergarten because they reject for the kindergarten.” (Ahoc)

The direct experience of institutional-based discrimination in an education, healthcare or workplace setting was not understood as an infringement of human rights. For example, no participant had sought support from consumer organisations or legal advice. Rather, the experience of discrimination had given them insight into negative personal impacts of disclosure and societal stigma related to CHB.

Indirect experiences of stigma and discrimination that informed understanding were not always directly related to CHB, but rather were based on stories about how the community reacted to people with other health problems, especially HIV infection. The influence of culture and community attitudes to illness and the perceived risk of social exclusion was a present and future health risk to social and emotional wellbeing.

The process of disclosure or telling others was a complex negotiation. It involved weighing up the potential consequences of social exclusion from stigma and discrimination, the potential for social isolation resulting from self-stigmatisation, and a perceived responsibility to inform and protect others, including health professionals and family members.

**Risk to others: being infectious and concern about passing the infection to others.**

Concern about passing CHB to others, especially family members, and worry about being infectious was the third theme we identified. The burden of potentially being infectious to others encumbered the individual with an obligation to inform healthcare professionals, guests and family members about their status, which risked negative
reactions associated with disclosure. As explained by Yosef, a 44-year-old tertiary-educated man:

“...you will take all the precautionary measures but you are not supposed to freak out other people. You know, so it (the Hepatitis B) does really jump out and not do this or that to them.”

There was also an emotional burden associated with the responsibility to protect others, especially children. Women were particularly worried about passing on the infection at birth. As explained by Akong, a 25-year-old Sudanese woman with four children:

“...the thing that worry me...I don’t want to pass it to my kids. I want it to stay with me because I don’t want my kid to be worried about this.” (Akong)

The understanding of preventing transmission to others involved things such as the modification of behaviour in the home with family, especially being cautious of blood spills and hiding personal grooming equipment from guests and children. Vaccination was understood to be protective but knowing family members had been vaccinated did not stop the modification of behaviour. The risk of infectiousness and of transmission was usually emphasised by health professionals involved in the care of participants, as explained by this short but telling statement from Nia, an 18-year-old university student:

“...Don’t share toothbrushes...they said that a lot.” (Nia)

**Framing and contextualising risk**

Perception of liver health risks changed with age and indirect or direct experiences of ill health or complications. Regular medical care and healthy lifestyle choices were seen as important to risk mitigation. Risks of liver-related ill health and cancer were understood to increase with age. The key ages were reported as the forties or fifties when the immune system was thought to be weaker.
Faith also framed understanding of health risks in participants from both Muslim and Christian backgrounds. Cancer and death were seen as predetermined by God. However, fatalism and religious belief did not necessarily preclude active health choices. In fact, at times faith could be seen as encouraging adherence to lifestyle modification and the advice of doctors. An example of this is expressed by Amina, a 49-year-old Eritrean of Orthodox Christian faith:

“...our religion is let us know to protect ourselves, through exercise, through...good food, but if you are going to die this is left for God.”

The Australian healthcare system and care received by doctors, either in general practice or the hospital, was reported as important in keeping well and was highly valued. Frequent changing of doctors, especially in the context of hospital clinics, was seen by participants to risk the quality of their care. Participants reported no specific cost barriers to accessing regular tests and doctors, although for those in paid employment, getting time off for attendance at radiology appointments was an issue.

Discussion

African-Australians living with CHB perceive and experience health risks associated with CHB that are not only physical but include threats to social and emotional wellbeing and identity. Social and emotional health are threatened especially during the year or two after diagnosis, and then on an ongoing basis due to disclosure risks and the worry of being infectious, or becoming unwell and how this might affect loved ones. In this study, liver cancer risk was generally overestimated and the purpose of surveillance and the importance of primary prevention seemed not well understood.

A strength of our study is that it is the first to explore perception of health risks, including risk of HCC, in African-Australians living with CHB. This study took the views of people from five different countries and a variety of faith and cultural backgrounds. The findings are supported by other studies looking at fears of people with CHB (Carabez et al. 2014) and the experience of diagnosis (Richmond et al. 2017). The study is limited by only
interviewing people who are already engaged in healthcare and is likely to overstate the knowledge of CHB, liver cancer and HCC surveillance when compared with people not in regular care. The gender of the interviewer and her background as a GP might also have influenced the data collected. Our study does not represent the full diversity of all African-Australians. As the data was transcribed from the interpreters’ words, rather than direct translations, it is possible the knowledge or perception of risks were misrepresented.

Chronic disease care requires participation and partnership from healthcare systems, providers, and community to encourage informed and “activated” patients, as described by the “chronic care model” (Bodenheimer et al. 2002a, 2002b). Currently in Australia, in the context of CHB, we are failing to create this environment, as indicated by low levels of community knowledge about this important condition (Wallace et al. 2008; Wallace et al. 2011a; Wallace et al. 2011b; Adamson and Murphy 2015; Sievert et al. 2017). Neither is “patient activation” encouraged or supported by the experience of, or perceived risk of, stigma and discrimination. The burden of worry associated with being infectious has previously been described (Richmond et al. 2017; Sievert et al. 2017) and needs to be addressed through clear communication and promotion of vaccination, so people can be reassured that friends, family and loved ones, especially children, are protected.

It is important to assist clinicians to accurately communicate risk of liver cancer, and help patients understand the reasons for HCC surveillance and vaccination to prevent cancer-related mortality. Risk communication is complicated in healthcare settings (Paling 2003) and risk language has to be clear and consistent (Edwards et al. 2002). There is evidence that use of decision aids can increase participation in cancer screening activities (Stacey et al. 2017). Developing a decision aid in HCC surveillance could assist health practitioners convey messages about HCC, increase patient understanding, and allay unnecessary cancer worry for people living with CHB. This is an important area for further research.

The findings from this research suggest areas where healthcare system changes could improve the experiences of African-Australians living with CHB. Health promotion messages need to broaden beyond liver health and transmission risks and encompass
education on rights and breaking down of stigma. Mobilising faith communities could be an important area to explore to assist promoting health messages. The isolating experiences of diagnosis need to be addressed as a health risk. Messages about transmission need to emphasise the importance of screening for family and household members and primary prevention through vaccination, so people can better negotiate the emotional and social risks associated with infectiousness and disclosure.

**Conclusion**

Chronic hepatitis B poses a risk to social, emotional and physical wellbeing for those affected. The risk of HCC, the purpose of surveillance, and importance of vaccination for close contacts appeared not well understood in African Australians in our study. There is a need for clinicians to better communicate risks and provide support for the social and emotional impacts of CHB. However, because the target audience is broad, resources will need to address the educational, cultural and ethnic differences and diversity in the affected community.

**Conflicts of interest**

The authors have no conflicts of interest to declare.


Strauss, AL, Corbin, JM (1990) 'Basics of qualitative research : grounded theory procedures and techniques.' (Sage Publications: Newbury Park, Calif.)


Figure 1: Knowledge acquisition and how risks to health are framed.
Table 1: Characteristics of participants, with assigned pseudonym and age and years since diagnosis at time the interview was conducted 2016

<table>
<thead>
<tr>
<th>No.</th>
<th>Pseudonym</th>
<th>Gender</th>
<th>Age (years*)</th>
<th>Country of Birth</th>
<th>Education</th>
<th>Interpreter required</th>
<th>Year arrived</th>
<th>Years since diagnosis</th>
<th>Context of diagnosis</th>
<th>Religion</th>
<th>Treatment</th>
<th>Family history of liver complications</th>
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<tr>
<td>1</td>
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<td>no</td>
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<td>Christian</td>
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<td>yes (liver cancer)</td>
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<tr>
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<td>32</td>
<td>Sudan</td>
<td>English Classes</td>
<td>no</td>
<td>2006</td>
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<td>Muslim</td>
<td>no</td>
<td>no</td>
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<tr>
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<td>Tertiary</td>
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<td>3</td>
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<td>Christian</td>
<td>no</td>
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<td>18</td>
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<td>Muslim</td>
<td>no</td>
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<td>South Sudan</td>
<td>English Classes</td>
<td>no</td>
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<td>Christian</td>
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<td>Ahoc</td>
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<td>English Classes</td>
<td>no</td>
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<td>Christian</td>
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<td>no</td>
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<td>Tertiary</td>
<td>no</td>
<td>2004</td>
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<td>2009</td>
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<td>Eritrea</td>
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<td>1999</td>
<td>15</td>
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<td>Muslim</td>
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<td>Christian</td>
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<td>no</td>
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<td>Christian</td>
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<td>no</td>
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<td>9</td>
<td>GP initiated</td>
<td>Muslim</td>
<td>yes</td>
<td>yes (liver cancer)</td>
</tr>
</tbody>
</table>
Tell me about your experience of hepatitis B.

Probe: Let the interviewee explain their illness narrative, including experiences from prior to diagnosis through to present time.
How did they feel about having hepatitis B?
At diagnosis? Now? How has that changed over time?

Tell me about your experiences of medical services for your hepatitis B.

Who has looked after you with your hepatitis B?

Prompts: How did that go?
Have you ever had a break from medical services for a while?
Tell me about that.
Which person/s have helped you to understand Hepatitis B?
Have you ever experienced disrespectful behaviour from health people about hepatitis B?

Tell me about how you see hepatitis B affecting your health in the future.

Tell me about what might happen.
Tell me about what you think might be you chance of that happening to you.
How does religion help you understand this?
Probe: How has this been explained to you?

Prompt: Have you been told about the risk of liver cancer?
What do you think are the chances you will get liver cancer in the next 10 years?
How would you explain this risk to someone else?

Tell me about how you feel about having regular blood tests or scans.

Probe: Tell me about how it is to have testing done (ask about scans and blood tests).
What do you think those tests are for?

What would you like to understand about Hepatitis B?

Probe: What information has helped you understand hepatitis B? Who has helped you to understand hepatitis B?
How would you like to receive this information? What would you like to understand about what might happen in the future?

Reporting against COREQ: 32-item checklist for qualitative studies.
Domain 1: Research team and reflexivity

Personal Characteristics
1. Interviewer/facilitator: Nicole Allard
2. Credentials: MBBS, MPH, PhD candidate
3. Occupation: General practitioner and PhD candidate
4. Gender: Female
5. Experience and training: Completed a qualitative training course; fifteen years' experience working in refugee health.

Relationship with participants
6. Relationship established: no prior relationship with participants except one participant who she had met in community-related events, however was recruited from a site.
7. Participant knowledge of the interviewer: the researcher was introduced as a PhD candidate from the University of Melbourne
8. Interviewer characteristics: The Interviewer has worked as a clinician delivering chronic hepatitis B care in a general practice setting, where the patient group includes many born in the African region, and has an interest in HCC surveillance participation and improving health systems and access.

Domain 2: STUDY DESIGN

Theoretical framework
9. Methodological orientation: grounded theory

Participant selection
10. Sampling: consecutive clinic attendee and purposive sampling.
11. Method of approach: asked by the clinician delivering care with plain language statement and then referred to the researcher in person or by telephone for further explanation and arranging an interview time
12. Sample size: 19
13. Non-participation: Eight (8) recorded refusals after referral to the researcher for further discussion. Other refusals directly to the clinicians (there were multiple sites and recruiting clinicians) were not recorded.
14. Setting of data collection: Data was collected at the clinic site or at the participants’ home.
15. Presence of non-participants: at five interviews done with women in their home, children were present.
16. Description of sample: description of the 19 participants appears in Participant Table 1.

Data collection
17. Interview guide: interview guide was used and altered after initial three interviews.
18. Repeat interviews: no repeat interviews occurred; four were sent transcripts of their interviews for comments.
19. Audio/visual recording: audio recording was performed for all but one interview that was transcribed simultaneously.
20. Field notes: Field notes were made by the researcher at the end of each interview.
21. Duration: The interviews were 45-90 minutes.
22. Data saturation: Data saturation was discussed at regular meetings with the supervisor as the data was coded.
23. Transcripts returned: Four were returned for comment, although none were received.

Domain 3: analysis and findings

Data analysis
24. Number of data coders: One coder and one supervisor discussing codes and emerging themes.
25. Description of the coding tree;
26. Derivation of themes: Themes were derived from the data.
27. Software: NVIVO 11.2
28. Participant checking: none to date planned.
29. Quotations presented and identified: Yes.
30. Data and findings consistent: The supervisor checked a selected number of transcripts to provide feedback and check emerging themes.
31. Clarity of major themes: as presented, three major themes/findings.
32. Clarity of minor themes: as presented
Chapter 7: Discussion of findings, recommendations and conclusion

7.1 Overall findings and discussion

This thesis combines four publications and one unpublished manuscript reporting the outcomes of five studies. Combined, these studies explore the measurement of the current cascade of care, how further indicators could be incorporated to improve the care cascade, and the reasons for gaps in the current health system response to people living with CHB in Australia.

The work presented in this thesis explores different data sources and methodologies relevant to the Australian context and examines factors associated with care enrolment in people living with CHB, using both quantitative and qualitative methodology. This body of work created the first cascade of care for CHB in Australia, measured adherence and viral suppression in a multicentre cohort, identified factors associated with poor adherence to antiviral treatment, explored the challenges of liver cancer surveillance in the community in an enhanced service, and explored how African-Australians understand their health risks associated with living with CHB. These five studies have important implications for both clinical practice and health policy.

In development of a cascade of care for CHB, a novel indicator was created using MBS and PBS data to estimate the number of people living with CHB in 2012 who are enrolled in care in Australia. It found that overall only thirteen percent of the estimated affected population were enrolled in care and that there were important disparities across jurisdictions with enrolment in care ranging from two to eighteen percent. Other significant gaps in the cascade in 2012 included that nearly half of the estimated population living with CHB remain undiagnosed (45) and that low numbers of people are receiving antiviral treatment. The cascade used publically available data and can be reproduced annually. The indicators that were included in this study are now recommended by WHO in the framework to evaluate and monitor population responses to CHB (16).
Two studies are presented, examining factors associated with adherence to antiviral therapy and the association with viral outcomes with adherence from a multicentre retrospective study, which utilised a pharmacy adherence measure, MPR. The first study found that twenty percent of the people receiving antiviral therapy in public hospitals are poorly adherent (defined as MPR < 0.90) to antiviral treatment, which is consistent with the findings of previous studies in Australia and overseas (56, 57, 64, 71, 72, 76, 78-82, 85). Treatment was being delivered to a very culturally diverse group, with thirty-nine spoken languages represented in the group of participants. Few Aboriginal or Torres Strait Islander people were receiving treatment in the hospital system from 2010-2013, suggesting inequity for Indigenous Australians in the current cascade of care which urgently needs to be addressed.

Poor adherence was associated with younger age (< 35 years) and frequent changes in hospital doctor (more common at one of the four hospital sites). The finding of the association with youth in our health system is consistent with other studies of CHB antiviral adherence (57, 79, 85) and of adherence in chronic disease in general (69) but the association with provider continuity in CHB was a novel finding. Provider consistency has previously been associated with knowledge about CHB in people living with CHB (167). In other studies of adherence in other chronic diseases, the importance of the patient-provider relationship, in terms of both longevity and trust, has been shown to have a positive impact on adherence (69). This finding contributes to our understanding of factors in our health system that can be readily modified to improve adherence in the delivery of antiviral therapy and potentially other aspects of care.

The second study, which is the largest study to date in Australia or overseas to explore the association between MPR values (<1.00, <0.95, <0.90 and <0.80) and viral outcomes, found that while previously used definitions of poor adherence using MPR are supported by the risk of unfavourable viral outcomes, there is not a true threshold; rather, an increased hazard of poor outcomes with decreasing MPR value. This finding can be used in future studies of adherence to provide a rationale for using MPR as a
measure and can be applied to the cascade in conjunction with predicted response rates of antiviral therapy, if a measurement of pharmacy-based adherence is more practical than viral suppression in the treated population. This is relevant especially in LMIC where measurement of viral loads may be constrained by cost.

MPR is a useful and objective measure of adherence that can be calculated from pharmacy records and, in a clinical environment, can be used by clinicians as a tool either alone or in combination with self-reported assessment of adherence to identify risks of VBT and target advice to their patients.

This study also provided the first multicentre estimate of viral suppression in the Australian cascade of care for people with CHB receiving antiviral therapy. This finding was supported by another recent single centre study of 211 participants (57). In the absence of a larger study or data set for analysis, this provides the current best estimate of viral suppression in the cascade from a sample representing approximately six percent of people on treatment in Australia in 2012.

The thesis also presented the findings from the first study to examine the impact of systems support to improve HCC surveillance in general practice. The study found that, while participation increased from a low baseline prior to the external service involvement in the practice, it remains difficult to achieve optimal adherence to liver cancer surveillance, even when recall and reminder systems are implemented and there is focused follow-up with specialist nurses in an engaged practice that has identified management of CHB as a priority. Previous studies of CHB in community settings in Australia showed poor adherence to guidelines (132), challenges in care delivery, and poor knowledge in general practice (145-147, 170) but none have examined HCC surveillance and the limits of health system improvement that involved recall remainder and support of specialised nurses. The finding that it is hard to achieve the recommended frequency of HCC surveillance intervals is consistent with experience of systems improvement both in Australia in a tertiary setting (34), in a nurse-led clinic for people with advanced liver disease (138), and overseas (137).
Participation in other cancer programs with state- or national-based registries, breast, bowel and cervical cancer, is lower in people from culturally diverse backgrounds and Aboriginal and Torres Strait Islander people due to various reasons that include communication barriers, knowledge, health literacy, fatalistic views about cancer, and poorer healthcare access (177). Interventions to improve early cancer detection have had mixed success. Community-based education can increase awareness but does not necessarily increase participation. Individual messages have been shown to be preferable to posted material and a letter from trusted health services more likely to be successful than general population-based health promotion messages (177, 178). In the future, increasing the proportion of those people living with CHB who are eligible for HCC surveillance and who receive optimal HCC surveillance will require improvement across many areas in the health system. Areas for improvement include increasing the number diagnosed and enrolled in care; the development of adequate culturally responsive messages to the target population and their communities increasing understanding of HCC surveillance; and involvement of trusted health services or providers, including general practitioners, in delivery of regular interval HCC surveillance (178). The difficulty of delivery frequent scans underscores the importance of novel methods of surveillance under development that do not require ultrasound.

The final part of this thesis presented the first qualitative study focused on how people living with CHB understand health risks, including liver cancer associated with CHB, and the first study looking specifically at the experience of African-Australians living with CHB. The study found that African-Australians living with CHB experience and perceive many challenges and risks to their health beyond physical or liver-related health problems. Their social and emotional wellbeing is affected by diagnosis with a chronic infection, the ongoing risks, stigma and discrimination associated with disclosure, and the fear of being infectious to others, especially loved ones. The risk of HCC was overestimated by the interviewed African-Australians and HCC surveillance was poorly understood. This lack of understanding about the reason for the tests in people who were engaged in care could contribute to the ability of the individual to prioritise
attending scans and has implications when understanding the reasons for poor participation in and adherence to six-monthly HCC surveillance.

7.2 Limitations

Various limitations exist in the approach and methodology of the studies included in this thesis in part relating to a changing policy environment. In the development of a cascade of care for CHB, indicators were informed by data that was both available and reproducible for measurement of progress in the number enrolled in care over time. The main limitation is that this indicator estimates the number of people in care in that year, and while it can be used over time to evaluate ecological trends, conclusions cannot be drawn about whether the same individuals are being tested or treated in each subsequent year. It was also not possible to estimate the number of people enrolled in a timely manner after diagnosis using this data, as there was no linkage of yearly tests to diagnoses. This is an indicator currently recommended in the WHO monitoring and evaluation framework and not measured by the Australian cascade (16). The PBS data captures treatment for most but not all people living with CHB in Australia. The PBS data does not record treatment for recommended indications such as pregnancy and immunosuppression, which are not subsidised or for people who are not eligible for Medicare reimbursement, and therefore slightly underestimates of the numbers on treatment. The population and proportion diagnosed estimates incorporated into the cascade are derived from a deterministic mathematical model. The population estimates have been also supported by census-based estimates of the population burden of CHB (17, 18, 54) but estimates of the diagnosed proportion are limited by the assumptions of the model (18).

The data source of the current care indicator of the cascade allows for geographical breakdown of numbers and comparison of care delivery by area, but breakdown by other important demographic details, particularly by Aboriginal and Torres Strait Islander status, is not included in the proposed cascade. Equity in care delivery is important to measure, aligns with national strategic goals (25, 179) and is recommended by the WHO monitoring and evaluation framework (16).
The adherence study was conducted in four public hospitals using data from 2010-2013, a period in which most antiviral medicines were dispensed in this setting. The policy environment has evolved and from mid-2015, community prescribing and dispensing became possible which limits the generalisability of the findings. While community prescription by trained S100 general practitioners is still limited, community dispensing is increasing and therefore people prescribed antiviral therapy are no longer required to go to hospital pharmacies to fill their prescriptions this increase access is currently under evaluation for benefits and potential risks. This has changed both access and convenience, which may impact adherence in those receiving antiviral therapy for CHB, and therefore the generalisability of the findings in this study to the current context.

In examining factors associated with adherence, the study used socio-economic index for areas (SEIFA) as a measure of socioeconomic status. SEIFA is an estimate only of a population’s socioeconomic status and does not account for variations of wealth within postcodes. The factors that impact adherence are multifaceted and the study was limited by demographic information available in the hospital record and specifically by the fact information is not collected on educational status and health literacy, which can impact adherence (69). The impact of the hospital site on adherence may be due to staff rations or physical barriers like parking not measured.

The study of viral outcomes and the association with MPR were limited by the pathology data available from the hospitals. Some events may have been missed in individuals whose HBV DNA viral load was performed at other pathology providers. It is also possible that people with fewer measurements of viral load could be more likely to be poorly adherent to medication and therefore unfavourable outcomes missed, even if they were exclusively receiving testing at the hospital. The limitations are due to the “real world” nature of the data set, where the number of appointments for those in care, the prescribing habits of clinicians, the frequency of ordering of HBV DNA tests, and attendance for those tests can vary.
The study of HCC surveillance performed in the community included a period of intervention, but did not seek to formally evaluate the intervention, and has retrospectively analysed the data. The generalisability of the findings is also limited by the size, the specific population in the community site, the focus of the IHBS involvement, and the high level of interest of the general practitioners involved at the site, but demonstrates what can be achieved in a system approximating near-to-best practice.

The qualitative study focused on semi-structured interviews with African-Australians, but in Australia, people born in the African region living in Australia represents a diverse group from different educational, cultural, ethnic, and religious backgrounds that do not necessarily have a common identity. Further research is required to capture the diversity of that experience and how it might affect the perceptions of the health risks associated with CHB. African-Australians represent approximately five percent of people living with CHB in Australia and are recommended to commence HCC surveillance at a younger age (20 years) than affected groups from other regions due to the increased risk of HCC. Therefore, the experience of liver cancer and perceptions of risk in the African-Australian community may not be shared with other people from other regions. The participants were recruited from primary and tertiary care and most had known about their CHB for many years. African-Australians not in care may have a different perception, particularly of risk of HCC and liver problems.

The cascade of care has been measured annually since 2012 and only small changes in the proportion diagnosed and on treatment have been observed over this period (see Figure 7). The estimated population living with CHB has increased as migrants from high and intermediate prevalence countries have arrived and, based on both the model derived and 2016 census-based estimates, is now just over 239,000. Notification data is essentially stable, with approximately 7000 new diagnoses annually. Treatment numbers have increased but only proportionally to the increasing affected population. The result is that the proportion of people with CHB receiving treatment or an annual HBV DNA viral load has increased by a few percentage points. The lack of improvement in the cascade of care for CHB is in part explained by the
performance of various parts of the health system and the challenges experienced by people living with CHB, as explored by the work presented in this thesis.

7.3 Translation of research

The cascade of care proposed by this thesis was adopted in the National surveillance reports in 2015, with annual MBS and PBS data available since 2012 (28, 35). Similar methodology has been adopted in the National Viral Hepatitis Mapping Project annual reports that have examined care provision, first by Medicare Local (ML) and then more recently by Primary Health Care Network (PHN) with census-based estimates replacing the estimates of population used in the national cascade (17, 176, 180). The cascade of care is part of national surveillance. As part of the current consultation for new national strategies for 2018-2021, potential new indicators are being discussed. The cascade has been incorporated into training material for primary care and been utilised as an advocacy tool by hepatitis organisations for greater funding and health system responses to CHB.

7.4 Recommendations

Multiple recommendations for policy, clinical care and further research can be made from the findings of this thesis, relevant to improving the reporting and outcomes of the care cascade for people living with CHB.

Recommendation 1: The care indicator combining people on treatment and not on treatment but receiving regular monitoring – now used in the reporting of a national cascade – is considered as one of the indicators in the new national strategy currently under development.

Rationale:

- The current National Strategy document contains a treatment but not a care indicator for people living with CHB.
• Treatment is only currently recommended for people with cirrhosis or active liver damage, so currently the national strategy is not setting targets for, or addressing in the indicator framework, care delivery to people not on treatment.
• All people living with CHB are recommended to have at least yearly monitoring.
• Measuring the proportion of people enrolled in care is recommended by the current WHO monitoring and evaluation framework.
• The cascade developed (Chapter 3) proposed a novel and measurable indicator of care provision that can also be used in comparisons between jurisdictions to ensure equity of access and used to allocate resources.

Recommendation 2: That the cascade of care is developed further to measure equity of care delivery, particularly to Aboriginal and Torres Strait Islander people.

Rationale
• The current cascade does not address inequity in care delivery by Indigenous status (Chapter 4).
• Equity in care delivery is a part of national strategic goals.
• Few Aboriginal and Torres Strait Islander people were on treatment in Victorian public hospitals in 2010-2013 (Chapter 5).
• Development of the cascade of care in specific populations can identify gaps and needs for service improvement, funding, and community consultation.

Recommendation 3: That the cascade of care is further developed to include the effectiveness of the delivery of antiviral treatment by incorporating measurement of viral suppression or adherence in the population on treatment. Furthermore, that MPR could be used as a proxy for viral suppression, as viral outcomes have been shown to be strongly associated with MPR values.

Rationale:
• Data sources for viral outcomes in CHB come from multiple private and public hospital laboratories that report results to clinicians.

• There is no large representative clinical cohort currently in Australia for people living with CHB, unlike HIV and now HCV, where viral outcomes can be evaluated outside single sites.

• Linked Medicare data could be used to calculate adherence, using MPR, in the population on antiviral treatment, and by applying predicted viral outcomes (Chapter 4) to calculate and estimate viral suppression.

• Measurement of viral outcomes in people on treatment is currently recommended by the WHO monitoring and evaluation framework.

Recommendation 4: Continuity of clinician should be prioritised in public outpatient settings to improve adherence to antiviral therapy.

Rationale:

• Hospitals have training and staffing requirements that often result in changes of clinicians, which affect patient care, communication and the building of trust.

• It is important to regularly assess adherence in people receiving antiviral therapy.

• Poor adherence to antiviral therapy is associated with frequent change in provider (Chapter 4).

• Where possible in the health system, continuity of doctor should be prioritised or consistent nursing support should be considered to counteract frequent changes that affect adherence.

Recommendation 5: Initiatives should be developed to educate clinicians that younger people have a higher risk of poor adherence. They should regularly assess adherence in this group, understand barriers that individuals face, and advise patient strategies to improve adherence.
• Younger people (<35 years of age) are at great risk of poor adherence (Chapter 4).
• Adherence needs to be regularly assessed in a non-judgemental atmosphere by clinicians.
• Strategies to assist with daily pill-taking, convenience of picking up medicine, and steps to take if medication is lost or scripts misplaced, to ensure continuity of supply.

Recommendation 6: Further research is required into how adherence and participation in HCC surveillance can be improved, including improving knowledge, understanding barriers to getting regular ultrasounds, and further development of new markers for point-of-care testing.

Rationale:
• HCC surveillance presents a challenge of both its frequency and the need to book and attend another appointment with another provider (Chapter 5). The impact of health systems improvement is limited.
• HCC surveillance is potentially even more difficult in rural and remote settings where access to ultrasounds is limited.
• Current development of point-of-care testing (either portable ultrasounds or other tests) could improve HCC surveillance participation, detection of HCC, and outcomes for people diagnosed with HCC.

Recommendation 7: That a plain language risk communication and/or decision-making tool is developed to explain the purpose of HCC surveillance and that it is trialled in communities affected by CHB.

• African-Australians in care had a poor understanding of HCC surveillance (Chapter 6) and adherence and participation is hard to achieve (Chapter 5).
• Communication of risk in cancer screening or surveillance is complicated and needs to involve the patient in understanding the risks, benefits and harms, or undergoing regular testing to inform and empower them to make decisions.
• Currently, there is no tool in Australia that communicates the risk of HCC and the purpose of surveillance to people with CHB.

Recommendation 8: People with CHB need improved support from clinicians and community to prevent adverse impacts on their emotional, social and physical wellbeing, especially after diagnosis.

Rationale:
• The impact of diagnosis can be devastating, resulting in physical, social and emotional health issues that include social isolation, financial disadvantage, depression and anxiety (Chapter 6).
• The negative impact of diagnosis and living with CHB is reduced by support from family and friends who are living with CHB (Chapter 6).
• Further research and program initiatives need to target new interventions to improve the lived experience for people living with CHB.
• Clinicians need to ensure that there is follow-up and time to answer the questions, give advice and offer support to people newly diagnosed with CHB, as health providers are a valued source of health information.

Recommendation 9: That further research and work into stigma and discrimination experienced by people living with CHB needs to include initiatives and evaluation of the impact of those initiatives to inform communities, decrease self-stigmatisation, and include a rights-based framework in which to inform people living with CHB.

Rationale:
• Disclosure is an ongoing threat to social and emotional wellbeing for people living with CHB (Chapter 6).
• Clinicians need to provide up-to-date information on rights and inform people with CHB that in most settings, it is not necessary to disclose status, due to universal precautions and protection of the general population by vaccination.
• Programs need to be implemented in parallel with education of communities and healthcare professionals to reduce the risk of people experiencing stigma in those settings.

Recommendation 10: That in delivering information on the risks of transmission by health promotion or clinical staff to people living with CHB, messages are modified/changed to contain a stronger emphasis on the protection for family members through vaccination and checking their immunity, so people living with CHB are not taking unnecessary precautions around the home and are freed from the worry associated with being infectious.

Rationale:
• Unnecessary precautions and worry associated with being infectious affect the lives of people living with CHB (Chapter 6).
• An effective vaccine is available to all household members, so household transmission should not be a concern for people living with CHB.
• Fear of infectiousness or of transmission to others is likely to cause modification of behaviour, social isolation, and harm to social and emotional wellbeing.
• We should shift to a “vaccinate and protect” message as the primary health promotion strategy around transmission and educate people with CHB that they are not a risk to wider society.
Recommendation 11: Further resources are required to fund policy improvement, programs and research to improve the cascade of care for people living with CHB in Australia.

Rationale:

- The proportion diagnosed, in care and on treatment, has not changed significantly in the last 3 years of the 2nd National Hepatitis B Strategy or since 2012 and remains low (Chapter 3).
- Funding for community education, screening, and education of the primary care workforce has not been sufficient to increase the proportion diagnosed or enrolled in care.
- There are proven interventions to improve testing and care enrolment in at-risk populations and diagnosed with CHB (181).
- Australia is a signatory to the Global health sector strategy on Viral Hepatitis, which aims to eliminate hepatitis as a public health concern by 2030.
- The current trend of change observed in the cascade will not see Australia meeting the targets of 90% diagnosed and 65% reduction in mortality for people living with CHB in Australia by 2030.
- Further research based on interventions and understanding community perceptions is needed to improve diagnosis and enrolment in care to meet targets and to improve adherence and community engagement to prevent poor outcomes.
7.5 Conclusion

In conclusion, the work included in this thesis has contributed to a greater understanding of the challenges faced by people living with CHB accessing care in the Australian health system, by looking at the structure of the cascade of care and factors associated with care. The outputs from this thesis are particularly relevant in the current policy context, as the new National Hepatitis B Strategy is being written for Hepatitis B and as national, state and territory jurisdictions consider their responses to reach the goal of elimination by 2030.

The Australian health system response has failed to meet any of the targets of the 2014-2017 strategic reporting period and only small increments of change in the cascade have been observed (see Figure 7). In the next decade, focus needs to shift from measurement to implementation and evaluation of new programs that improve the access to healthcare and the lived experience of people with CHB.

Figure 7: The cascade of care for people living with CHB 2013-2016

(reproduced with permission from National Hepatitis B Mapping report)
There is increasing understanding that in the future there will be broader treatment eligibility, greater than 15%, to prevent sequelae in the population and a need to invest more heavily in reaching undiagnosed if there is to be a cure available. It is unlikely, if current trends continue, that Australia will meet the current global targets for elimination of CHB as a public health concern by 2030. Further investment in the health system response is required to improve access to diagnosis care and treatment, which would enable Australia to achieve elimination targets. The population with CHB in Australia is continuing to increase and resource allocation needs to meet this challenge. It is important the response improves not just the metrics of the cascade, but also the quality of life of people living with CHB by addressing social, emotional and physical wellbeing.

Australia as a high-income country, with universal access to healthcare services encompassing primary and tertiary care, has the chance to lead an effective response to hepatitis B, but must improve the cascade of care in the next strategic period or risk continuing to fail to meet the needs of Australians affected by CHB.
Chapter 8: References


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Appendices

Appendix A: Presentations during course of candidature

**Oral presentations**
Challenges in primary care delivering viral hepatitis related care: Keynote 11 August 2017 – Australasian Viral Hepatitis Elimination Conference Cairns August 2017


Viral outcomes in patients with Chronic Hepatitis B and correlation with Pharmacy adherence measures – Australasian viral hepatitis conference, Gold Coast September 2016

Workshop: The role of the GP in hepatitis B: you can prevent liver cancer – GP15 Melbourne 21-23 September 2015

The cascade of care for people living with chronic hepatitis B: access to treatment and monitoring in Australia – 9th Viral hepatitis conference, Alice Springs September 2014, Symposia session.

Hepatitis B: changing demographics in Australia engagement in care and coverage of treatment Invited speaker, Australasian Hepatology Association Summit, Adelaide June 2014

**Poster presentations**


Appendix B: Other publications contributed to during course of candidature

Peer-reviewed journals


Chapters in books or resources


Editorial contributions


Educational material magazines or supplements (not peer reviewed)


CHECK program April 2016 and April 2014; case studies for GP education.
Interviewed for Good Practice magazine.
Appendix C: Committees and community involvement during candidature

- Board Member Hepatitis Victoria from 2014 and current Vice President.
- RACGP representative Departmental advisory committee for blood-borne viruses (DACBBV) Victorian Department for Health and Human Services (2014 to present).
- RACGP representative Hepatitis C elimination working group (from 2016 to present).
- GP Hepatitis B Clinical Advisor for Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (March 2016 to present).
- Organising committee Viral Hepatitis Elimination Conference (Cairns August 2017).
- Organising committee First World Indigenous People’s Viral Hepatitis Conference (Alice Springs 2014).
- Member of ASHM committee for the review of the National Hepatitis B testing policy 2016.
- Member Victorian Hepatitis B Alliance (VHBA) (from 2013 to present).
- Convenor Victorian hepatitis B primary care interest group (from 2015 to present).
- Member RACGP Special interest group for refugee health (from 2015 to present).
- Member of WHO (WPRO) team conducting a rapid assessment of viral hepatitis health sector response in Cambodia in partnership with the Cambodian Ministry of Health (October 2017)