Novel approaches to an improved understanding
of the epidemiology and control
of hepatitis B virus infection in Australia

Benjamin Campbell Cowie
MBBS GradDipClinEpi FRACP

Submitted in total fulfilment of the requirements of the degree
of Doctor of Philosophy

March 2009

Department of Medicine (Royal Melbourne Hospital / Western Hospital)
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne
Abstract

Background
The most recent estimate for the number of Australians living with chronic hepatitis B virus (HBV) infection is 150,000, with over one million ever having been infected. One in four people with chronic infection will die as a result.

Worldwide, the burden of chronic HBV infection is great. As many as 400 million people are chronically infected, and the World Health Organisation estimates that as a result HBV infection is the tenth leading cause of death.

Aim
The aim of the research presented in this thesis is to improve the accuracy and relevance of our understanding of the epidemiology and control of HBV infection in Australia, through the development of new methodological approaches to the collection and analysis of relevant epidemiological data.

Methods
Three novel approaches were adopted. First, a serosurvey of a randomised, age-structured convenience sample of over 3200 specimens was performed spanning the period from 1995 to 2005 to estimate the prevalence of markers of infection with, and immunity to HBV. Secondly, a comparative analysis of the serosurvey results with national surveillance notifications since 1971 and migration records since 1945 was undertaken. Finally, a complex deterministic mathematical model of HBV infection in Australia was constructed simulating the entire population between 1951 and 2050.

Results
The serosurvey indicates that chronic infection with HBV is more common in the Victorian population than existing national serosurvey estimates suggest, and the coverage of immunisation programs (particularly of adolescents) is far from universal. Significant geographic, age, and gender disparities in the prevalence of chronic HBV infection were identified in the serosurvey, which appear in part to relate to historical migration patterns and which could be used to develop a targeted and effective public health response.
The comparative analysis of the serosurvey results with notifications and migration data demonstrates coherence of these disparate sources of information, and suggest that knowledge of migration patterns can lead to robust predictions of future notifications. The novel regression model developed implies that at least 50,000 people with chronic HBV infection are undiagnosed.

The mathematical model of HBV infection in the Australian population is unique in many respects, and has been validated against external data to provide reassurance regarding the accuracy of the simulated outcomes. Some of these outcomes include an estimated 160,000 Australians living with chronic HBV infection in 2009, increasing by several thousand people every year, and that less than 5 per cent of chronic infections entering the population are able to be addressed by domestic vaccination or other prevention programs.

**Conclusion**

The new insights into the epidemiology of HBV infection in Australia provided by the approaches described all suggest a large and increasing burden of chronic HBV infection. New approaches are needed to provide essential policy outcomes to assist and empower Australians living with chronic HBV infection. If this does not occur, the economic and human costs to our community are likely to become great.
Declaration

This is to certify that

i. the thesis comprises only my original work towards the PhD except where indicated,

ii. due acknowledgment has been made in the text to all other material used,

iii. the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Dr Benjamin Campbell Cowie
Acknowledgments

There are a number of people without whose support and assistance this thesis would never have been realised. First, I wish to acknowledge my supervisors; A/Professor Heath Kelly, Professor Graham Brown, A/Professor Margaret Hellard, and Professor Sharon Lewin. I greatly appreciate their collective and individual guidance, understanding and support. I would also like to thank other colleagues who were instrumental in the realisation of this research. The staff in the Epidemiology Unit and Serology Laboratory at the Victorian Infectious Diseases Reference Laboratory (VIDRL) gave valuable support and advice. In particular, Theo Karapanagiotidis and Adam Enriquez trained me in the serological techniques used, and performed a proportion of the testing for the serosurvey.

Principal financial support for this research was received from the Epidemiology Unit, VIDRL. The Centre for Clinical Research Excellence in Infectious Diseases (CCREID) provided support for attending a mathematical modelling course at the London School of Hygiene and Tropical Medicine in 2006. The Communicable Disease Prevention and Control Unit, Department of Human Services Victoria kindly made available commissioned data from the Australian Bureau of Statistics. Abbott Diagnostics provided the serology kits for the serosurvey at a reduced cost. I received postgraduate scholarships to pursue this research from the CCREID and the National Health and Medical Research Council; without these, this research could not have been undertaken.

I acknowledge the inspiration of the patients living with hepatitis B infection it has been my privilege to provide care for in recent years. Many have told of generations of family members dying of probable complications of hepatitis B; it is my hope that in some small way, this thesis contributes to a policy environment that can avert such outcomes in the future.

Our family and friends have been continually supportive and encouraging. My family has been unwavering in their assistance and support over the duration of this research, during which time we have been joined by our two beautiful children Anders and Helena. In helping raise our children and supporting us over the last four years, my parents Adel and Ross, my sister Tiffany, and many other family members and friends have been selfless and giving and I will always be grateful for this very tangible and most important assistance. However the primary credit for how wonderfully our children are growing up, and the person on whom the last four years of my work and study has impacted the most, is my wife Carreen. Without your support through it all, this thesis would never have existed.
Table of contents

Preamble ....................................................................................................... 1
Title ................................................................................................................ 1
Aim .................................................................................................................. 1
Research Questions .......................................................................................... 1
Hypothesis ....................................................................................................... 2
Thesis outline .................................................................................................. 2

1 The epidemiology of HBV infection in Australia and characteristics of the public health response ....................................................... 4
   1.1 Background ............................................................................................ 4
   1.2 Methods .................................................................................................. 7
   1.3 The epidemiology of HBV infection in Australia ...................................... 8
      1.3.1 Acute HBV infection ....................................................................... 8
      1.3.2 Chronic HBV infection .................................................................. 12
         1.3.2.1 Low prevalence populations .................................................. 12
            1.3.2.1.1 First time blood donors .................................................... 12
            1.3.2.1.2 Antenatal screening of non-Indigenous Australian-born women .. 13
         1.3.2.2 High prevalence populations .................................................. 13
            1.3.2.2.1 Migrants born in HBV endemic areas .................................. 13
            1.3.2.2.2 Indigenous Australians ...................................................... 18
            1.3.2.2.3 Injecting drug users ............................................................ 21
            1.3.2.2.4 Men who have sex with men ............................................... 22
            1.3.2.2.5 People serving custodial sentences ..................................... 23
            1.3.2.2.6 High prevalence populations – conclusion ......................... 24
      1.3.2.3 National HBV serosurveys 1996–99 and 2002 .................................. 24
   1.4 Elements of the Australian public health response to HBV .................... 27
      1.4.1 Securing the blood supply and reducing health care associated transmission ................................................................. 27
      1.4.2 Vaccination ..................................................................................... 28
         1.4.2.1 History of vaccine development and introduction ....................... 28
         1.4.2.2 Low prevalence countries ......................................................... 30
            1.4.2.2.1 Selective vaccination .......................................................... 30
            1.4.2.2.2 Universal vaccination .......................................................... 32
         1.4.2.3 High prevalence countries .......................................................... 34
         1.4.2.4 Cost effectiveness ....................................................................... 36
      1.4.3 Antiviral treatment as a means of preventing transmission ............... 40
   1.5 Conclusion ............................................................................................. 43
## 2 Hepatitis B virology and natural history ................................................. 44
  2.1 HBV structure, replication strategy and life cycle ........................................ 44
  2.2 Genotypes .................................................................................................... 47
    2.2.1 Geographic distribution of HBV genotypes, phylogenetic analysis, co-infection and recombination ................................................................. 47
    2.2.2 Clinical significance of HBV genotypes .................................................. 53
  2.3 Mutations of clinical relevance .................................................................... 56
  2.4 Use of sequencing for transmission analysis .............................................. 60
  2.5 Clinical virology .......................................................................................... 61
    2.5.1 HBV serology .......................................................................................... 61
    2.5.2 Natural history of HBV infection .............................................................. 63
      2.5.2.1 Phases of infection ............................................................................. 63
      2.5.2.2 Morbidity and mortality ................................................................. 64
      2.5.2.3 Treatment to modify the natural history of HBV ............................ 65
  2.6 Conclusion .................................................................................................... 65

## 3 The Victorian Hepatitis B Serosurvey 1995 – 2005 .............................. 67
  3.1 Introduction .................................................................................................... 67
  3.2 Aim .............................................................................................................. 67
  3.3 Methods ........................................................................................................ 67
    3.3.1 Sample size calculation .......................................................................... 67
    3.3.2 Sample selection program ...................................................................... 69
    3.3.3 Sample retrieval, information handling and testing .................................. 70
    3.3.4 Serosurvey data handling and statistical analysis .................................... 72
    3.3.5 Assessment of representativeness ......................................................... 73
    3.3.6 Ethical approval ..................................................................................... 74
    3.3.7 Management of failed HBsAg test run, 28 March 2007 ......................... 74
  3.4 Results .......................................................................................................... 74
    3.4.1 Estimates of HBV infection ..................................................................... 75
    3.4.2 Estimates of immunisation ...................................................................... 79
    3.4.3 Assessment of representativeness ......................................................... 80
  3.5 Discussion ....................................................................................................... 83

## 4 Parsimonious regression modelling of migration and HBV notifications in Australia ................................................................. 89
  4.1 Review of seroprevalence data and evidence for HBsAg trends .............. 89
  4.2 Methods – data comparison ................................................................. 90
    4.2.1 Victorian Hepatitis B Serosurvey 1995 - 2005 .................................... 90
    4.2.2 National Notifiable Diseases Surveillance System reporting .................. 90
    4.2.3 Migration data .....
4.2.4 Derivation of time lags .................................................................................................................. 91
4.2.5 Construction of simple linear regression model .............................................................................. 92
4.3 Results .............................................................................................................................................. 92
  4.3.1 Data comparison – Serosurvey, NNDSS and migration ................................................................. 92
    4.3.1.1 Incorporation of time lag ................................................................................................................. 94
  4.3.2 Parsimonious regression model ........................................................................................................ 95
    4.3.2.1 Confirmation of optimal lag period ................................................................................................. 96
    4.3.2.2 Results of simple regression model ............................................................................................... 98
    4.3.2.3 Validation of regression assumptions ......................................................................................... 100
    4.3.2.4 Using the regression model for prediction ..................................................................................... 106
4.4 Discussion .......................................................................................................................................... 108

5 Construction of a mathematical model of HBV in Australia ............... 114
  5.1 Background ......................................................................................................................................... 114
    5.1.1 General principles in modelling of infectious diseases .................................................................. 114
    5.1.2 Applications of mathematical modelling ....................................................................................... 114
    5.1.3 Strengths / weaknesses .................................................................................................................. 116
  5.2 Modelling of HBV infection ................................................................................................................. 117
    5.2.1 International models ....................................................................................................................... 117
    5.2.2 Australian model .......................................................................................................................... 118
  5.3 Types of mathematical model considered ......................................................................................... 119
  5.4 Model construction ............................................................................................................................. 121
    5.4.1 Software used / coding .................................................................................................................... 121
    5.4.2 Conceptual model structure ............................................................................................................. 121
      5.4.2.1 Rationale for age structure ........................................................................................................ 124
      5.4.2.2 Rationale for including migration .......................................................................................... 127
    5.4.3 Parameterisation ............................................................................................................................ 127
      5.4.3.1 Background population variables .............................................................................................. 128
        5.4.3.1.1 Derivation of background age-specific mortality rates ....................................................... 129
        5.4.3.1.2 Projection of mortality rates from 2005 to 2051 .................................................................. 131
      5.4.3.2 Migration variables .................................................................................................................. 134
        5.4.3.2.1 Migration to Australia 1951–2005 and projections to 2051 .................................................. 134
        5.4.3.2.2 Migrant age distribution .................................................................................................. 134
        5.4.3.2.3 Migrant HBV infection status ......................................................................................... 135
    5.4.3.3 HBV parameters .......................................................................................................................... 136
    5.4.4 Parameter sensitivity analyses ..................................................................................................... 138
    5.4.5 Modelling of immunisation .......................................................................................................... 141
    5.4.6 Assumptions, generalisations and exclusions .............................................................................. 143
    5.4.7 Equations ....................................................................................................................................... 145
    5.4.8 Static versus dynamic force of infection .................................................................................... 145
      5.4.8.1 Sensitivity of dynamic model to WAIFW matrix ........................................................................ 151
    5.4.9 Equilibrium starting conditions .................................................................................................. 155
6 Outcomes of a deterministic compartmental mathematical model of HBV in Australia ................................................................. 160

6.1 Model outcomes...................................................................... 160
  6.1.1 Acute infections ................................................................. 160
  6.1.2 Chronic infections .............................................................. 164
  6.1.3 Mortality attributable to HBV infection .............................. 170
  6.1.4 Impact of immunisation ....................................................... 174
    6.1.4.1 Acute infections .......................................................... 175
    6.1.4.2 Chronic infections ....................................................... 177
    6.1.4.3 Mortality ................................................................. 179
  6.1.5 Comparison between static and dynamic models ............... 181
    6.1.5.1 Acute infections .......................................................... 181
    6.1.5.2 Chronic infections ....................................................... 182
    6.1.5.3 Mortality ................................................................. 183
    6.1.5.4 Impact of immunisation ............................................... 183
  6.2 Validating the model against external data ......................... 186
    6.2.1 National Notifiable Diseases Surveillance System ............. 186
      6.2.1.1 Acute infections ....................................................... 186
      6.2.1.2 Chronic infections .................................................... 189
    6.2.2 Seroprevalence surveys .................................................. 191
      6.2.2.1 Victorian Hepatitis B Serosurvey 1995-2005 ................ 191
      6.2.2.2 National Serosurveys 1996-99 and 2002 ..................... 194
    6.2.3 Mortality data ............................................................. 196
  6.3 Model limitations and weaknesses ....................................... 197
  6.4 Summary ............................................................................ 197
    6.4.1 Model structure and assumptions best fitting external data 197
    6.4.2 Critical outcomes of optimised model ............................. 198
  6.5 Concepts for model extension and applications .................... 199
  6.6 Conclusion .......................................................................... 200

7 Conclusion .................................................................................. 203

7.1 Summary ................................................................................. 203
  7.1.1 The epidemiology of HBV infection in Australia and characteristics of the public health response ........................................ 203
  7.1.2 Hepatitis B virology and natural history .............................. 203
7.1.3 The Victorian Hepatitis B Serosurvey 1995 – 2005........................................ 204
7.1.4 Parsimonious regression modelling of migration and HBV notifications in Australia.......................................................................................................................... 205
7.1.5 Outcomes of the complex mathematical model of HBV in Australia....... 205
7.2 Recommendations for action........................................................................ 206
  7.2.1 Augment the public health response to notifications of chronic HBV infection.......................................................................................................................... 208
  7.2.2 Implement community-based HBV screening programs.............................. 210
  7.2.3 Encourage appropriate opportunistic screening with adequate follow up for all patients................................................................. 213
  7.2.4 Provide vaccination for those most at risk...................................................... 214
  7.2.5 Expand access to HBV treatment................................................................. 216
  7.2.6 Health care provider education...................................................................... 218
  7.2.7 Community education and empowerment...................................................... 220
  7.2.8 Provide Australian financial support for birth dose vaccination programs in high prevalence countries................................................................. 221
  7.2.9 Urgent creation and implementation of a comprehensive National Hepatitis B Strategy.......................................................................................................................... 224
  7.3 Addressing the research questions................................................................. 225
  7.4 Closing statement............................................................................................ 228

Bibliography ........................................................................................................ 230

Appendices
1 Serosurvey failed HBsAg test run resolution ..................................................... 244
2 Equations for the deterministic model of HBV infection in Australia .............. 253
3 Articles published in peer-reviewed journals related to PhD research .............. 261
4 Published chapters in monographs related to PhD research ............................ 267
5 Other publications .............................................................................................. 279
6 Presentations of PhD research at national conferences .................................... 284
7 Other presentations related to PhD research ..................................................... 285
8 Participation in committees related to PhD research ........................................ 287
9 Awards related to PhD research ........................................................................ 288
10 Human Research Ethics Committee approval ............................................... 289
List of Tables and Figures

Table 1.1 – Existing and revised (additional) CDC recommendations for routine testing for chronic HBV infection ................................................................. 6
Figure 1.1 – NNDSS notifications of acute and unspecified HBV infection 1994 – 2006 ... 10
Figure 1.2 – Notification rate for incident HBV infections in Australia by age-group and gender, 2006 ........................................................................................................ 10
Table 1.2 – Average, minimum and maximum proportion of annual cases of incident HBV infection notified in Victoria from 1995-2005 to whom the listed risk factors apply ........... 11
Figure 1.3 - Global HBsAg prevalence .............................................................................................. 15
Table 1.3 – Results of large serosurvey of Sydney schoolchildren 1990-91 .......................... 16
Table 1.4 – Studies of the prevalence of HBsAg and other markers of HBV infection in Indigenous Australians ................................................................. 20
Table 1.5 – Studies of the prevalence of HBsAg and other markers of HBV infection in injecting drug users ......................................................................................... 21
Table 1.6 – Studies of the prevalence of HBsAg and other markers of HBV infection in people serving custodial sentences ............................................................ 23
Table 1.7 – HBV serology results from the first (1996-99) and second (2002) national serosurveys ................................................................................................. 26
Table 1.8 – Proportion of infants of HBeAg-positive mothers with detectable HBsAg at 6 months of age by intervention, with corresponding Protective Efficacy Rate .......... 29
Figure 1.4 – Notification rate of incident HBV in Australia by age group, 1995 to 2006 .... 33
Figure 1.5 – Countries supported by GAVI to introduce infant hepatitis B vaccination as at November 2007 ...................................................................................... 35
Table 1.9 – Advised vaccination strategies against HBV according to prevalence of chronic infection ........................................................................................................ 38

Figure 2.1 – A schematic representation of the HBV genome, with corresponding transcripts and translated protein products ................................................................. 45
Figure 2.2 – A diagrammatic representation of the life cycle of HBV ........................................ 47
Table 2.1 – Worldwide distribution of HBV genotypes ................................................................ 48
Figure 2.3 – Global distribution of HBV genotypes .................................................................... 50
Figure 2.4 – Unrooted phylogenetic dendrogram of 630 HBV S gene sequences .................... 52
Table 2.2 – Typical interpretations of patterns of HBV serology results .................................... 62
Figure 2.5 – Phases of HBV infection with typically associated HBV DNA and ALT levels and HBeAg/anti-HBe status ................................................................. 63

Table 3.1 – Sample size calculations for the Victorian Hepatitis B Serosurvey 1995 – 2005 .............................................................................................................. 68
Table 3.2 – Schematic representation of sample data handling sheets used ................................ 71
Table 3.3 – Serological profiles used to define HBV status codes ............................................ 73
Table 3.4 – Complete serosurvey results by test year and age group ...................................... 76
Table 3.5 – HBV status by location for Victorian samples with complete postcode available .............................................................................................................. 77
Figure 3.1 – Proportion of people born overseas by SSD within Melbourne superimposed with the percentage of samples for each SSD that were HBsAg positive .............................. 78
Table 3.6 – Sample status codes by test year ........................................................................ 78
Table 3.7 - HBV status by test year for age groups included in NIP universal vaccination programs and also for all samples ................................................................. 79
Figure 3.2 – age distribution of all samples in the serosurvey compared with the average age distribution of the Victorian population from 1995, 2000 and 2005 ......................................... 81
Figure 3.3 – age distribution of serosurvey samples compared with the age distribution of the Victorian population in (a) 1995 (b) 2000 and (c) 2005 .......................................................... 81
Figure 3.4 – Geographic distribution by Victorian statistical division of (a) Victorian population in 2000 and (b) serosurvey samples with percentage of population/samples from Melbourne and non-metropolitan Victoria shown ........................................................................ 82
Figure 3.5 – Geographic distribution by Melburnian statistical subdivision of (a) population of Melbourne in 2006 and (b) serosurvey samples ........................................................................ 82
Table 3.8 - Sample and standardised prevalence estimates by gender, age group, and geographic regions within Victoria and Melbourne .............................................................. 83
Table 3.9 – Victorian serosurvey results for 2000 compared with results of Sydney endoscopy cohort 1999-2001 serology results ........................................................................... 85

Figure 4.1 – Number of samples in the serosurvey from each 5-year birth cohort, 1901 – 2005 ........................................................................................................................................... 90
Figure 4.2 – HBsAg prevalence in serosurvey samples by 5-year birth cohort .................... 92
Figure 4.3 – Migration to Australia by source country seroprevalence, 1945 – 2005 .......... 93
Figure 4.4 – Estimated HBsAg positive migrant (EHPM) arrivals in Australia by 5-year period, 1945 – 2005 ........................................................................................................... 93
Figure 4.5 – Comparison of HBsAg prevalence in serosurvey by birth years, EHPM entering Australia, and national notifications of unspecified (chronic) HBV infection without incorporation of time lag .......................................................... 94
Figure 4.6 - Comparison of HBsAg prevalence in serosurvey by birth years, EHPM entering Australia, and notifications of unspecified (chronic) HBV infection incorporating time lags .............................................................................................................................................. 95
Figure 4.7 – Scatter plot of national chronic HBV infection notifications against EHPM ten years prior, with derived birth years shown .............................................................. 96
Table 4.1 – Number of national HBV infection notifications and EHPM, 1976 – 2005 ...... 97
Table 4.2 – Characteristics of linear regression models incorporating a range of estimated lag periods between migration and notification .......................................................... 97
Figure 4.8 – Linear regression models of notifications against EHPM with 95% confidence intervals (CI). (a) No lag (b) 5 year lag (c) 10 year lag (d) 15 year lag ........................................ 98
Figure 4.9 - Linear regression model of NNDSS notifications against HBsAg positive migrant estimates 10 years prior with 95% CI ........................................................................... 99
Figure 4.10 – Comparison of the linear regression model shown in figure 4.9 with a complex, locally weighted regression function ................................................................. 100
Figure 4.11 – Plot of residuals (difference between actual notifications and those predicted by the regression model) across fitted values for EHPM from the regression in figure 4.9. 101
Figure 4.12 – Normal plot of standardised residuals from the regression model in figure 4.9 ................................................................. 102
Figure 4.13 – Plot of leverage of observations on the fitted line against the square of standardised residuals for the regression model presented in figure 4.9 ........................................... 103
Figure 4.14 – Regression model presented in figure 4.9 with individual observations marked with derived birthyear .......................................................................................................... 104
Table 4.3 – Comparison of regression model including all observations with the model excluding the four most influential observations ........................................................................ 105
Figure 4.15 – Visual representation of the regression models compared in table 4.3 .......... 105
Table 4.4 – Annual EHPM arriving 1996-2006 with projected notifications to 2016 ...... 106
Figure 4.16 – Use of the regression model to predict values for notifications based on values of EHPM with 95% confidence intervals for individual forecasts shown ............................................ 107
Figure 4.17 – Annual EHPM and notifications incorporating 10 year lag, with prediction of notifications to 2016 with 95% prediction interval ........................................................................... 108
Figure 4.18 – Locally weighted nonparametric multiple regression of actual notifications and predicted notifications against derived birth year ........................................................................... 109

Table 5.1 – Mathematical models of HBV infection identified in the literature and used for parameterisation of the model described in this thesis ................................................. 117-118
Figure 5.1 – Schematic representation of modelled transition between HBV infection states ........................................................................... 122
Figure 5.2 – Simplified flowchart of the structure of the mathematical model of HBV infection constructed ................................................................................................. 123
Figure 5.3 – Sub-models for assessment of (a) cumulative cases and (b) cumulative deaths ........................................................................................................................................... 125
Figure 5.4 – Notification rate for incident HBV infections in Australia by age group and gender, 2006 ........................................................................................................................................... 126
Table 5.2 – Population parameter estimates used in the parameterisation of the model and their sources .............................................................................................................. 127-128
Figure 5.5 – Annual mortality rate by age group, Australia, 1951 to 2004; plus linear trend of mortality rate in 45+ age group with forward projection ............................................. 131
Figure 5.6 – Annual mortality rate by age group, Australia, 1951 to 2004 plus projections to 2050 ............................................................................................................................................. 133
Figure 5.7 – Projected annual deaths, Australia, 2005 - 2050 under different 45+ age group mortality assumptions compared with ABS series B projections ............................................. 133
Figure 5.8 – Age distribution of all migrants to Victoria, 1975 – 2006 ......................................................................................................... 134
Table 5.3 – Estimated HBV infection status of migrants by source country HBsAg prevalence ................................................................................................................. 135
Table 5.4 – Changing percentage of migrants settling in Australia by source country HBsAg prevalence, 1945 – 2005, plus estimated percentage of all migrants with chronic infection ......................................................................................................................... 136
Table 5.5 – Estimates for HBV parameters used in the model by age group, plus individual estimates from sources used .......................................................................................... 136-138
Table 5.6 – Range of force of infection (FoI) and migration projections used in the model for sensitivity analysis ................................................................................................................ 139
Figure 5.9 – Proportion of total FoI acting on susceptible contacts by age group of infectious contact under different WAIFW structures; (a) WAIFW 1 assuming homogeneous mixing, (b) WAIFW 2 with increased within-age group mixing and (c) WAIFW 3 with completely heterogeneous mixing based on age group categories ........................................ 147
Table 5.7 – FoI contributed by each individual infectious unit by age group acting on susceptibles in each age group under the three WAIFW contact matrix assumptions ......... 149
Figure 5.10 – Dynamic (a) base FoI and (b) high FoI acting on each age group over time. Assumes base migration and no immunisation .............................................................. 150
Figure 5.11 – Number of people with acute HBV Infection by WAIFW matrix used in high dynamic FoI model over time for people aged (a) 0-4 years (b) 5-14 years (c) 15-44 years and (d) over 45 years ................................................................................................................... 152
Figure 5.12 – Age distribution of the Australian population in the model (base migration assumption), 1951 – 2050 ........................................................................................................... 153
Figure 5.13 – Age distribution of people with chronic HBV infection in the high static FoI model (base migration), 1951 – 2050 ...................................................................................... 153
Figure 5.14 – (a) Number of people with acute HBV infection and (b) cumulative acute HBV infections by WAIFW over time in high dynamic FoI model, base migration, no immunisation ........................................................................................................................ 154
Table 5.8 – Initial HBV status of the simulated Australian population by age group in 1951 ............................................................................................................................................ 155
Figure 5.15 – Slider window for the HBV model showing sliders to control proportion of susceptible members of different age groups vaccinated annually, a ‘vaccine toggle’ with binary values of 0 or 1, and two sliders to allow sensitivity analysis by multiplying the FoI and migration projection assumptions .......................................................................................... 157
Figure 5.16 – Comparison between the modelled population of Australia and ABS records and projections, 1951 – 2050 ............................................................................................... 158
Figure 5.17 – Comparison between the modelled population of Australia and ABS records and projections for 1951 – 2050 for people aged (a) 0-4 (b) 5-14 (c) 15-44 and (d) 45 plus ........................................................................................................................................... 158

Figure 6.1 – Number of people with acute HBV infection by FoI over time. Static FoI model, base migration assumption .............................................................. 161
Figure 6.2 – Number of people with acute HBV infection by migration over time. Static FoI, base FoI assumption .......................................................................................................................... 161
Figure 6.3 – Number of people with acute HBV infection by migration assumption over time. Dynamic FoI model (WAIFW 1), base FoI assumption ............................................ 162
Figure 6.4 – Number of people with acute HBV infection by age-group over time. Static FoI, base FoI and migration assumptions .............................................................................................................. 163
Figure 6.5 – Cumulative number of acute HBV infections by FoI over time. Static FoI, base migration assumption .......................................................................................................................... 164
Figure 6.6 – Cumulative number of acute HBV infections by migration over time. Static FoI, base FoI assumption .......................................................................................................................... 164
Figure 6.7 – Number of people with chronic HBV infection by FoI over time. Static FoI, base migration assumption ................................................................................................... 165
Figure 6.8 – Number of people with chronic HBV infection by migration over time. Static FoI, base FoI assumption ..................................................................................................... 166
Figure 6.9 – Number of people with chronic HBV infection by age-group over time. Static FoI, base FoI and migration assumptions ............................................................................. 166
Figure 6.10 – Annual domestic chronic HBV infections and annual entry of migrants with chronic infection over time. Static FoI, base FoI and migration assumptions ..................... 167
Figure 6.11 – Proportion of chronic HBV infections which are domestically acquired over time. Static FoI, high FoI and base migration assumption ........................................... 167
Table 6.1 – Median and 5th - 95th percentile range of proportion of chronic HBV infections acquired domestically by FoI assumption from 1951 – 2050 assuming base migration .... 168
Figure 6.12 – HBsAg prevalence by FoI over time. Static FoI, base migration assumption ............................................................................................................................................ 169
Figure 6.13 – HBsAg prevalence by migration over time. Static FoI, base FoI assumption............................................................................................................................................ 169
Figure 6.14 – HBsAg prevalence by age group over time. Static FoI, base FoI and migration assumptions .......................................................................................................................... 170
Figure 6.15 – Deaths in people with acute and chronic HBV infection by FoI over time. Static FoI, base migration assumption ..................................................................................................... 171
Figure 6.16 – Deaths in people with acute and chronic HBV infection by migration over time. Static FoI, base FoI assumption ..................................................................................................... 172
Figure 6.17 – Cumulative deaths in acute and chronic HBV infection over time. Static FoI, high FoI and base migration assumptions .......................................................................................... 172
Figure 6.18 – HBV mortality ratio over time. Dynamic FoI model, high FoI and base migration assumptions .......................................................................................................................... 174
Figure 6.19 – Impact of immunisation on the number of people with acute HBV infection over time. Static FoI, intermediate FoI and base migration assumptions ........................................ 175
Figure 6.20 – Impact of immunisation on the cumulative number of acute HBV infections over time. Static FoI, intermediate FoI and base migration assumptions ........................................... 176
Figure 6.21 – Impact of immunisation on (a) cumulative number of domestically acquired chronic HBV infections and (b) the number of people with chronic HBV infection over time. Static FoI, intermediate FoI and base migration assumptions ........................................... 177
Figure 6.22 – Impact of immunisation on the HBsAg prevalence over time. Static FoI, intermediate FoI and base migration assumptions .......................................................... 178
Figure 6.23 – Impact of immunisation on (a) annual deaths in acute HBV infection and (b) number of cumulative deaths in acute HBV infection over time. Static FoI, intermediate FoI and base migration assumptions ........................................... 179
Figure 6.24 – Impact of immunisation on annual deaths in people with chronic HBV infection and cumulative deaths in people with chronic HBV infection over time. Static FoI, intermediate FoI and base migration assumptions ........................................... 180
Figure 6.25 – Number of people with acute HBV infection and cumulative number of acute HBV infections over time. Static versus dynamic FoI model, high FoI and base migration assumptions .......................................................... 182
Figure 6.26 – Cumulative domestically acquired chronic HBV infections and total number of people with chronic HBV infection over time. Static versus dynamic FoI model, high FoI and base migration assumptions ................................................................. 183

Figure 6.27 – Annual and cumulative deaths in (a) acute and (b) chronic HBV infection over time. Static versus dynamic FoI model, high FoI and base migration assumptions ........ 184

Figure 6.28 – Impact of immunisation on the number of people with acute HBV infection over time. Static versus dynamic FoI model, high FoI and base migration assumptions .... 185

Figure 6.29 – Comparison of the number of people with acute HBV infection by FoI with acute notifications to NNDSS and doubled notifications over time. Static versus dynamic FoI model, base migration assumption ................................................................. 187

Figure 6.30 – Comparison of acute HBV infections under a range of vaccination uptake values (1-10%) for adults aged 15-44 with actual notification data (NNDSS x10). Dynamic high FoI model, base migration assumption, vaccination according to expanded NIP parameters other than in 15-44 age group ................................................................. 188

Figure 6.31 – Comparison of people with chronic HBV infection (alive, deceased, and the sum of both) compared with the cumulative number of notifications to the NNDSS since 1971. Also shown is the resultant estimate of the proportion of all people with chronic HBV who have been diagnosed and notified. Dynamic high FoI model, base migration assumption, vaccination according to expanded NIP parameters ................................................................. 190

Table 6.2 – Comparison of results from Victorian serosurvey with outcomes of high dynamic FoI model with base migration assumption incorporating expanded NIP .................. 192

Table 6.3 – Comparison of vaccinated proportion of 15 – 44 year age group in the Victorian serosurvey with outcomes of high dynamic FoI model using base migration assumption and expanded NIP ........................................................................................................ 193

Table 6.4 – Comparison of results from National serosurveys with outcomes of high dynamic FoI model with base migration assumption incorporating expanded NIP .................. 195

Table 6.5 – Select outcomes of the high dynamic FoI model (base migration, expanded NIP assumptions) for 2010, 2020 and 2050 ........................................................................... 198

Table A1.1 – HBsAg run 28/03/07 – results by OD range ........................................................... 244

Table A1.2 - HBsAg run 28/03/07: Sample ID, OD, Result and anti-HBs status by OD group ........................................................................................................ 246-248

Table A1.3 – Worksheet replica for manual HBsAg EIA assay 29/03/07 ........................................ 248

Table A1.4 – Characteristics of samples selected for manual HBsAg EIA assay 29/03/07 ........................................................................................................ 249

Table A1.5 – Results of second manual HBsAg EIA assay 29/03/07 compared to initial automated HBsAg EIA assay 28/03/07 ........................................................................... 251
### List of abbreviations used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>ACIR</td>
<td>Australian Childhood Immunisation Register</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Antibody to hepatitis B core antigen</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Antibody to hepatitis B e antigen</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Antibody to hepatitis B surface antigen</td>
</tr>
<tr>
<td>CALD</td>
<td>Culturally and linguistically diverse</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control (United States)</td>
</tr>
<tr>
<td>CHB</td>
<td>Chronic hepatitis B</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals (95% limits used throughout this thesis)</td>
</tr>
<tr>
<td>DHS</td>
<td>Department of Human Services (Victoria)</td>
</tr>
<tr>
<td>EIA</td>
<td>Enzyme immunoassay</td>
</tr>
<tr>
<td>EHPM</td>
<td>Estimated HBsAg Positive Migrant(s)</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>FoI</td>
<td>Force of infection</td>
</tr>
<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunisation</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Hepatitis B e antigen</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>IDU</td>
<td>Injection Drug Use/r</td>
</tr>
<tr>
<td>NIP</td>
<td>National Immunisation Program</td>
</tr>
<tr>
<td>NNDSS</td>
<td>National Notifiable Diseases Surveillance System</td>
</tr>
<tr>
<td>OD</td>
<td>Optical density</td>
</tr>
<tr>
<td>OWR</td>
<td>Out (of reader) Working Range (relating to OD reading)</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>$r^2$</td>
<td>Coefficient of determination</td>
</tr>
<tr>
<td>S100</td>
<td>Section 100 – Highly Specialised Drugs Program, Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>VIDRL</td>
<td>Victorian Infectious Diseases Reference Laboratory</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Preamble

Title

Novel approaches to an improved understanding of the epidemiology and control of hepatitis B virus infection in Australia.

Aim

To improve the accuracy and relevance of our understanding of the epidemiology and control of hepatitis B virus (HBV) infection in Australia through the development of new methodological approaches to the collection and analysis of relevant epidemiological data.

Research Questions

• What is the current understanding of the burden of HBV infection in Australia?
• What are the population, individual and viral factors which influence the outcome of HBV infection?
• How can a serological survey of a convenience sample be made more representative of the general population, and how can this representativeness be assessed? Can a serosurvey conducted in this manner improve our estimates of the population prevalence of chronic HBV infection, and of immunisation coverage?
• How can existing demographic data be used to extend our understanding of HBV epidemiology in Australia?
• Can mathematical modelling be used to establish estimates of the burden of HBV infection in Australia over time, and how can the accuracy and reliability of such models be tested?
• Finally, following synthesis of the findings of this doctoral research, can priorities for public health policy be identified that could address the increasing burden of chronic HBV infection?
Hypothesis

Well designed mathematical models of HBV infection, parameterised with contemporary local data, will improve our understanding of the epidemiology of HBV in Australia, with a view to suggesting further public health strategies to mitigate the impact of this infection on those living with chronic infection, and on the health care system as a whole.

Thesis outline

This doctoral thesis commences with a comprehensive critical review of the published literature on the epidemiology of HBV in Australia. Specific focus is given to the differences in epidemiology underlying acute and chronic HBV infection and a discussion of groups in the Australian community with high prevalence of chronic HBV. This leads to a critical analysis of the public health response to HBV, nationally and internationally.

Chapter 2 examines the virology and natural history of HBV infection, which is fundamental to an understanding, not only of the burden of HBV infection, but also of the ability of the virus to escape from the control strategies raised in chapter 1 – vaccination and antiviral treatment – with implications for sustaining effective interventions on the level of both the individual and the community. The chapter also explores aspects of clinical virology, an understanding of which underpins data presented in subsequent chapters, including the complexities of HBV serology and natural history across the various phases of infection.

Chapter 3 describes the design, performance and analysis of the largest single serosurvey for markers of infection with HBV in Australia. The serosurvey, employing a novel technique to reduce bias, was used to establish robust estimates of HBV prevalence and vaccine uptake in the community. These data are essential for developing a better understanding of the epidemiology of HBV in the general population as discussed in chapter 1, and were also used for the development and validation of analytical tools in subsequent chapters.

Chapter 4 compares the results of the serosurvey with data on migration and surveillance notifications in the public domain, and presents the development and application of a novel statistical approach for analysing the relationship between these data sources.
Chapters 5 and 6 of this thesis present the construction and outcomes of a complex mathematical model of HBV infection in Australia from 1951 to 2050, incorporating the effects of migration and vaccination. Using this model the evolution of the burden of HBV in Australia is described, along with the impact of existing immunisation programs. Further inference, including the proportion of chronic infections notified, the relative contributions of infections acquired locally and overseas to the burden of chronic HBV in Australia, and mortality attributable to HBV are presented.

The final chapter, after summarising and synthesising the new information developed in this doctoral research, presents recommendations for action, particularly on how to address the increasing, and from the public health perspective largely unaddressed, burden of chronic HBV infection in Australia.
1 The epidemiology of HBV infection in Australia and characteristics of the public health response

1.1 Background

In 1984, Professor Ian Gust of Fairfield Hospital in Melbourne estimated that there were 144,000 Australians living with chronic hepatitis B virus (HBV) infection (1). By 1996 his estimate was 250,000 (2). Worldwide over 2 billion humans have been infected with this virus, 350-400 million of whom are now estimated to be chronically infected with HBV (3-6). Approximately 25% of these carriers, most of them infected at birth or in early childhood, will develop serious liver disease such as cirrhosis or hepatocellular carcinoma (4) and as a result, HBV infection is the tenth leading cause of death worldwide (7).

In 1996, Kaldor et al (8) published an epidemiological review of the incidence of HBV infection in Australia. By examining national surveillance data in addition to published studies, the number of incident HBV infections in adults was estimated at 1,110 in 1993, with 100 progressing to chronic carriage. The number of incident infections actually notified to State and Territory health departments in 1993 was 278 (9). This review highlighted gaps in information on HBV epidemiology and vaccine coverage at the time, and called for standardised case definitions, improved follow-up and investigation of new cases, the performance of repeated serological surveys for prevalence and incidence of HBV infection, and monitoring of immunisation status.

Much has changed since these recommendations were made. The most notable alteration to the public health response to HBV has been the incorporation of vaccination against HBV in the National Immunisation Program (NIP) for infants since May 2000, with catch up vaccination for 12-13 year old adolescents since 1998-99 (10). Two national serological surveys of samples of convenience have included HBV amongst the infections tested for (11, 12), and a large record linkage study from NSW has examined the mortality burden of chronic HBV and hepatitis C virus (HCV) infection (13). Reports of the burden of chronic HBV infection in hospital cohorts have been published (14-17), as have community-based investigations of high-prevalence populations including Indigenous Australians (18) and migrants (19-21). The rising incidence of hepatocellular carcinoma (HCC) due to chronic viral hepatitis, particularly HBV, has been documented in Indigenous Australians (22) and
migrants (23, 24); HCC has the most rapidly rising incidence of any internal cancer in a recent NSW report, with median survival after diagnosis amongst the shortest of all cancers (24).

It is perhaps surprising that such research progress has been made given the virtual absence of a national policy approach to HBV (24-26). Limited examples of national interventions include steps to secure the blood supply through routine donor screening for HBsAg in the early 1970s and the inclusion of hepatitis B vaccine in the NIP.

Unlike our response to HCV and the human immunodeficiency virus (HIV), there is still no national strategy to coordinate a broad based public health approach to the increasing burden of chronic HBV infection in Australia. Other than for Indigenous Australians, the impact of universal childhood hepatitis B vaccination on the numbers of people with chronic infection in this country is open to question, as most Australians with chronic HBV infection are migrants who acquired infection in their country of birth early in childhood (11). This question is explored further in chapter 6.

In September 2008 the Centers for Disease Control and Prevention (CDC) in the United States published revised recommendations for the identification and management of people living with chronic HBV infection, in the context of epidemiologic similarities to the Australian context - a significant and expanding burden of disease associated primarily with migration of people from endemic areas (27). A fundamental component of these recommendations was the expansion of routine testing to include many more people at risk for chronic HBV infection than was previously the case (table 1.1).

The impact would be profound if these recommendations were implemented in Australia; approximately three million of us would be candidates for routine screening under the birth-country HBsAg prevalence criterion alone. This is because more than 25% of Australians were born overseas, the majority in countries with intermediate (2 - 8%) or high (>8%) HBsAg prevalence (7, 28, 29). In the Australian context it would be imperative to include Indigenous people, given the higher prevalence of chronic HBV in Indigenous Australians (11).
<table>
<thead>
<tr>
<th>Existing recommendations</th>
<th>New recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>People born in regions of high HBsAg prevalence (&gt;8%)</td>
<td>People born in regions of intermediate and high HBsAg prevalence (&gt;2%)</td>
</tr>
<tr>
<td>Blood and tissue donors</td>
<td>People not vaccinated as infants whose parents were born in regions with high HBsAg prevalence</td>
</tr>
<tr>
<td>Haemodialysis patients</td>
<td>Injection-drug users</td>
</tr>
<tr>
<td>All pregnant women</td>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>Infants born to HBsAg positive mothers</td>
<td>Patients needing immunosuppressive therapy e.g. chemotherapy or for autoimmune diseases or following transplantation</td>
</tr>
<tr>
<td>Household, needle-sharing, or sexual contacts of HBsAg positive people</td>
<td>People with elevated ALT or AST for unknown reasons</td>
</tr>
<tr>
<td>Sources of blood/body fluid for exposures that might require PEP</td>
<td>People living with HIV/AIDS</td>
</tr>
</tbody>
</table>

Table 1.1 – Existing and revised (additional) CDC recommendations for routine testing for chronic HBV infection (27).

There are increasing calls for change in both public policy and clinical management relating to chronic HBV infection in this country. In 2008 a new monograph of clinical guidelines was jointly produced by the Cancer Council NSW and the Australasian Society for HIV Medicine entitled B Positive - all you wanted to know about hepatitis B: a guide for primary care providers (30). The same year a report entitled the National Hepatitis B Needs Assessment was produced by the Australian Research Centre in Sex, Health and Society of La Trobe University (26). Both documents describe the failure of Australia’s public health response to chronic HBV infection, with one quarter of the most recent estimate of 160,000 Australians chronically infected (12) expected to die as a result of cirrhosis and/or HCC (7).

In recent years there has been a rapid expansion of treatment options for people with chronic infection, with five of the seven agents currently approved for the treatment of chronic HBV infection by the Therapeutic Goods Administration only becoming available in the last five years:
• Interferon α-2a/b - 1997
• Lamivudine - 1999
• Adefovir - 2004
• Pegylated interferon α-2a - 2005
• Entecavir - 2006
• Telbivudine - 2006
• Tenofovir - 2009

With more effective therapies now available, the ability to beneficially modify the natural history of chronic HBV infection, and also to reduce further transmission has been significantly advanced (30, 31). Enrolment in regular monitoring to assess disease activity and for HCC screening where appropriate (32) is also most important, with randomised controlled trial evidence supporting previous observational data that HCC surveillance significantly reduces cancer mortality (33).

These opportunities to intervene to maintain the health of people living with chronic HBV infection, in addition to the longstanding availability of a safe and effective vaccine to prevent infection in the first instance for those at risk, mandate that a better understanding of the epidemiology of HBV in our community be developed as a necessary element of any comprehensive national response. It is the objective of this chapter to examine and synthesize the available information from a variety of sources to describe estimates of the burden of acute and chronic HBV infection in this country, to provide both a rationale for and context behind the research agenda that is presented in this thesis.

1.2 Methods

A systematic literature search was conducted in January 2006 using MEDLINE (via both PubMed / National Library of Medicine and Ovid hosts) 1966-2006, EMBASE 1980-2006, Web of Science (Science Citation Index Expanded and Social Sciences Citation Index) 1966-2006 and the Australasian Medical Index (Meditext). No language restrictions were applied. The search terms used included the following terms, both as medical subject headings (MeSH) and in text search wherever possible:
In addition, an automatic search request using the same criteria was generated using the National Center for Biotechnology Information ‘My NCBI What’s New’ service at the NLM (http://www.ncbi.nlm.nih.gov/sites/myncbi/about/). As a result, notifications of new research indexed on MEDLINE each month identified using this search strategy was received by e-mail from February 2006.

The title (and when available, abstract) of the papers identified were then examined for relevance – the main reason for exclusion being when the original term ‘Australia antigen’ was used for hepatitis B surface antigen in articles which were not relevant to the epidemiology of hepatitis B in Australia. Reference lists of identified studies were examined to identify further relevant studies not discovered in the initial literature search, as were the bibliographies of pertinent textbooks.

Notifiable disease surveillance reports from those states and territories in Australia publishing this information were obtained, in addition to the annual reports of the National Notifiable Diseases Surveillance System (NNDSS) back to commencement of surveillance for HBV in 1971 (34).

1.3 The epidemiology of HBV infection in Australia

1.3.1 Acute HBV infection

Much of the information available on acute HBV infection comes from notifiable diseases surveillance programs. The states and territories in Australia forward data on a nationally agreed set of communicable diseases to the Commonwealth Department of Health and Ageing to allow national communicable disease surveillance (35). Although changes in case definitions and reporting patterns by the various authorities have impacted on this
information, the data described here are from the most current reports available for the years shown. The current surveillance case definitions, adopted by the Communicable Diseases Network Australia in July 2002 (36) are;

- **Newly acquired** (‘incident’ or ‘acute’) hepatitis B:
  - The presence of hepatitis B surface antigen (HBsAg) in a patient shown to be negative in the preceding 24 months, or
  - Detection of HBsAg and IgM to hepatitis B core antigen (HBcAg), in the absence of prior evidence of HBV infection, or
  - Detection of HBV DNA and IgM to HBcAg, in the absence of prior evidence of HBV infection.

- **Unspecified** (generally equated with ‘chronic’) hepatitis B:
  - The presence of HBsAg, together with
  - The presence of IgG (but no IgM) antibodies to HBcAg; and
  - No clinical illness consistent with acute viral hepatitis.

Figure 1.1 shows notifications to the NNDSS of acute and unspecified HBV infection from 1994 to 2006, the most recent full year of data available. A significant upward trend observed in notifications of both incident and unspecified HBV infections was observed through the 1990s, peaking in 2000-2001 (35, 37-40). In 2002 the surveillance data showed the first drop in notified unspecified infections since 1996, a trend which continued until 2005, with acute notifications also falling notably. These temporal trends are explored in detail in chapter 4. The total unspecified notifications for the 13 years represent 0.43% of the 2001 Australian population (41).

The age distribution of incident HBV infections in Australia is reflective of patterns of infection in a low prevalence population (2, 5, 7), with the majority of new infections occurring in late adolescence and early to middle adulthood. The impact of the universal adolescent catch-up vaccination program is reflected in reducing rates of infection amongst teenagers and young adults compared with the 1990s (40), especially among females in whom the peak incidence of infection was in 15-19 year olds prior to 2000. Males are more commonly notified with acute HBV than females, with a ratio between 1.5:1 and 2:1 over the last 15 years. This gender disparity is also the case for chronic HBV notifications but is less marked (40, 42, 43).
Figure 1.1 – NNDSS notifications of acute and unspecified HBV infection 1994 – 2006. Rates (italics) are per 100,000 population for the relevant year. (35, 37, 38, 44)

Figure 1.2 – Notification rate for incident HBV infections in Australia by age-group and gender, 2006. Taken from (40).
Risk factor information for incident HBV infections is currently reported by Victoria, South Australia, Tasmania, the Northern Territory and the Australian Capital Territory (40). Victoria has been reporting these data longest, and Victorian cases represent over 80% of those with risk factor information reported by NNDSS (44, 45).


These data demonstrate the predominant risk factors for acute infection in Victoria are the same as for other low prevalence populations, being injecting drug use (IDU) and unprotected sexual contact, predominantly heterosexual (7, 29, 46). These risk factors apply to the 5% or less of notified HBV infections that are incident (figure 1.1) (46, 47); the epidemiology of chronic HBV is considerably different.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Average annual proportion of cases</th>
<th>Minimum annual proportion of cases</th>
<th>Maximum annual proportion of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injecting drug use</td>
<td>45%</td>
<td>26%</td>
<td>61%</td>
</tr>
<tr>
<td>Unsafe sex</td>
<td>36%</td>
<td>23%</td>
<td>60%</td>
</tr>
<tr>
<td>Other including household contact</td>
<td>7%</td>
<td>1%</td>
<td>18%</td>
</tr>
<tr>
<td>None identified</td>
<td>16%</td>
<td>6%</td>
<td>24%</td>
</tr>
<tr>
<td>Unknown</td>
<td>7%</td>
<td>0%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Table 1.2 – Average, minimum and maximum proportion of annual cases of incident HBV infection notified in Victoria from 1995-2005 to whom the listed risk factors apply. From 2002 onwards, more than one risk factor could apply to each case (48).
1.3.2 Chronic HBV infection

Although surveillance case notifications provide vital information about trends in communicable disease incidence and prevalence and provide the opportunity for follow-up, investigation and contact tracing of persons notified (an opportunity wasted for cases of chronic HBV infection in Australia (27, 49)), it is recognised that a large proportion of people infected with HBV are not tested, let alone notified to health authorities (3, 8, 13, 50-54). Possible explanatory factors include the relative under-utilisation of existing health structures by some of the groups at highest risk of acquiring HBV, the typically long asymptomatic period prior to the onset of any clinical illness, and missed opportunities for screening those with identified risk factors for infection by their treating doctors (19, 27, 55).

To gain a better understanding of the true prevalence of chronic HBV infection in Australia, a number of studies have been undertaken testing for serological markers of infection with HBV. These will be discussed by category of risk group in which the study was conducted, followed by an analysis of the results of two national serosurveys of samples of convenience from laboratories around Australia from 1996 to 1999 (11) and in 2002 (12).

1.3.2.1 Low prevalence populations

1.3.2.1.1 First time blood donors

First time blood donor HBsAg prevalence in Australia has been reported in several papers published between 1983 and 2004 as being between 0.1 - 0.5% (8, 11, 21, 56, 57). Initial donors represent a group at lower risk than the general population for a number of possible reasons including volunteer bias, self-selection, cultural and linguistic reasons and more recently to the exclusion criteria used in screening questionnaires prior to donation which include specific risk factors for blood borne virus infection. Anti-HBs prevalence in the 1983 study was 5%, indicating previous infection in this pre-vaccine era (57).

Recent estimates from the Australian Red Cross Blood Service indicate that the process of education and selection of blood donors in the period 2000-2006 lead to a 6-12 fold reduction in the prevalence of HBsAg in first-time blood donors relative to that of the general community, reinforcing that this is a low-prevalence group of the population (58).
1.3.2.1.2 Antenatal screening of non-Indigenous Australian-born women

Studies of HBsAg prevalence in this relatively low-prevalence group have reported HBsAg prevalence ranging from 0.1% – 0.3% (8, 11), and are therefore comparable to the blood donor prevalence estimates.

1.3.2.2 High prevalence populations

1.3.2.2.1 Migrants born in HBV endemic areas

The burden of chronic HBV infection in high prevalence populations cannot be over-emphasised. Where HBsAg carriage exceeds 10%, HBV has been estimated to account for 3% of all deaths, a figure higher than pre-vaccine polio mortality (59). Approximately 90% of the world’s population (and greater than 10% of Australians) were born in countries with intermediate or high HBV endemicity (27, 28).

In 1996, in the proceedings of a roundtable meeting entitled ‘Progress towards the comprehensive control of hepatitis B’ (2), Professor Ian Gust stated that (other than for Indigenous Australians) rates of HBsAg carriage reflect those found in the country of birth of an individual’s parents or grandparents, being lowest (approximately 0.1%) in descendants of British migrants, 2-5% in migrants from the Mediterranean region and their children, and highest (5-15%) among migrants from South-East Asia and the Pacific Islands. His estimates had changed little in over a decade (60, 61).

Limited epidemiological information is available from surveillance registries of people notified with chronic HBV infection in Australia. The majority of such notifications are made only by the testing laboratory, not the treating doctor, with different regulatory requirements for doctors to notify such cases across Australian jurisdictions (40, 46).

Even when doctors do notify, the epidemiological information gleaned can be limited – for example, less than half of all Australian infectious disease notifications in 2006 documented Indigenous status (40). With regards to country of birth, the predominant determining risk factor for chronic HBV (and other diseases including tuberculosis, malaria, and enteric fever), this question was only added to notifiable infectious diseases reporting forms provided
to notifying doctors in Victoria in September 2008 (Health (Infectious Diseases) (Amendment) Regulations 2008 – Schedule 4).

It is therefore rare for surveillance information to address the epidemiology of chronic HBV. Even when expanded surveillance occurs, this is almost always directed towards incident HBV (46, 47, 62). An expanded HBV surveillance program conducted in inner-western Sydney in 2005 followed up all notifications with the dual purposes of improving detection of incident cases and gathering epidemiological information (46). Of the 295 notifications received, only three were acute. Country of birth information was obtained for just over half the notified cases, with 90% born outside Australia. East and South-East Asian countries (predominantly China and Vietnam) contributed over 80% of those born overseas. The information from this surveillance-based program, one of the few to address the epidemiology of chronic HBV infection, is supported and extended by a number of Australian studies.

Research from Australia and overseas suggests that the prevalence of chronic HBV infection in migrants resembles that of their country of birth (figure 1.3) (16, 17, 19, 20, 27, 29, 57, 63-66). With increased migration from these areas, HBV prevalence significantly increased in Australia in the second half of the 20th century (2, 23), predominantly driving the more than 60-fold increase in Australian notifications of HBV infection from 0.66 notifications per 100,000 population in 1971 (34) to 41.2 notifications per 100,000 in 2001 (44).

An early indication of this epidemiological shift came in a South Australian study of 709 South-East Asian refugees undergoing routine screening prior to receiving dental care in the early 1980s, which demonstrated that 19% were HBsAg positive, with two thirds having serological evidence of chronic or resolved HBV infection (57).

A significant proportion of Australian data on seroprevalence of markers of HBV infection by birth country has been derived from routine antenatal screening. Kaldor et al (8) reviewed seven such studies conducted between 1984 and 1990 of HBsAg in pregnant women from around Australia. The HBsAg prevalence estimates by country of birth ranged from:

- 3.7 - 4.7% in women born in Mediterranean countries
- 2.7 - 17% in Pacific Islander women
- 5.3 - 15% in women born in South-East Asia.
These three groups accounted for 10% of deliveries in 1993, and together with births to Indigenous Australian mothers, accounted for 90% of the estimated 1082 infants annually who would acquire chronic HBV infection if not treated at birth (8).

From July 1991 to June 1992, 336 infants were notified to the Department of Human Services in Victoria as being born to HBsAg positive mothers. Of these women, 62.7% were born in South-East or East Asia, and only 6% were born in Australia (63). This report suggested that the HBsAg prevalence across all women giving birth in Victoria that year was 0.52%. More recent antenatal screening data in the central Sydney area from 1996-1999 were presented in 2004 (11). HBsAg prevalence over the period was 1.5%, with highest rates in women born in South-East Asia (5.4%), North-East Asia (4.9%) and Pacific islands (3.7%). The antenatal screening results for pregnant women throughout New South Wales from 1998-2000 revealed that HBsAg prevalence was 0.82%.

A large (n=2883) community-based study of 11-12 year old children in Sydney in 1990-91 (21) stratified children into low, medium and high risk for HBV infection according to ethnicity, place of birth, and parents’ place of birth. The risk factors used, and results of
serologic testing, are shown in table 1.3. The study, carefully designed to look for evidence of horizontal transmission amongst the students, could find no such evidence. Only 17% of the children with chronic HBV were born in Australia, with most of those infected having been born in Asia; 97% of all high risk children were Asian or Pacific Islanders.

Two surveys conducted in the Laotian and Cambodian communities in Melbourne in 1998 and 2002 respectively supported the antenatal screening findings of higher seroprevalence in migrants from South-East Asia, with 9% of Laotian and 8% of Cambodian participants HBsAg positive (19). Approximately 80% of these chronically HBV infected people were previously unaware of the diagnosis, and many had ongoing contact with their regular general practitioners without apparently having been offered HBV screening, a failure in secondary prevention care that is not peculiar to the Australian migrant experience (55) nor to the primary care setting (15).

A significant increase in the proportion of humanitarian and refugee entrants to Australia coming from Africa was seen in the early years of this decade (64). Although there is significant heterogeneity in HBsAg prevalence across the continent, Sub-Saharan Africa is considered a high-prevalence area (figure 1.3). In community based studies from Melbourne (64) and Perth (65) published in 2006, HBsAg prevalence in migrants from all areas of Africa was 8% and 6.5% respectively.

<table>
<thead>
<tr>
<th>Definition (see figure 1.3 for birth country HBsAg prevalence)</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child and both parents born in Australia or other low prevalence country</td>
<td>1347</td>
<td>602</td>
<td>731</td>
</tr>
<tr>
<td>Child and/or either parent born in intermediate prevalence area</td>
<td>93.1%</td>
<td>89.9%</td>
<td>59.8%</td>
</tr>
<tr>
<td>Proportion immunised</td>
<td>6.7%</td>
<td>8.4%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Proportion ever infected</td>
<td>0.2%</td>
<td>1.7%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Proportion chronically infected</td>
<td>0.07%*</td>
<td>0.34%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

Table 1.3 – Results of large serosurvey of Sydney schoolchildren 1990-91 (21).
*represents a single child who had lived in Papua New Guinea when aged 1-3 years.
The findings of these studies are reinforced by recent accounts from tertiary referral centres in Australian capitals. In a cohort of 2115 endoscopy patients in central Sydney surveyed (15), 2.1% were HBsAg positive and 11.6% had evidence of past or current HBV infection. Of patients born in Australia, 1.1% were HBsAg positive, compared with 3.5% of those born overseas. Of patients born in the Asia-Pacific region 30.4% had evidence of past or current HBV infection, compared with 18.9% of those born in the Mediterranean littoral, 10.9% of those born in other parts of the world outside Australia, and 6.1% of Australian-born patients. Critically, nearly one third of the patients with chronic HBV infection were unaware of this fact, 80% of whom were receiving care for other diseases in a large teaching hospital in the centre of the most populous city in Australia.

In a tertiary hospital in Melbourne, of 174 patients born in Sub-Saharan Africa seen in infectious diseases clinics between 2003 and 2006 who were tested for markers of HBV infection, two thirds had evidence of ever having been infected, and 22% of the total (38/174) were chronically infected (16). In a report on 703 patients with chronic HBV infection seen at another Melbourne hospital between 1996 and 2003 (14), 78% were migrants born in 65 different countries, with 65% of the total being of Asian ethnicity. Most common countries of birth of migrants in this cohort were Vietnam (37% of total cohort), China (17%), Greece (7%) and Italy (3%).

A study of HCC at a third hospital in Melbourne compared the 77 cases diagnosed between 1975 and 1983 with the 113 cancers detected between 1995 and 2002 (66). The proportion of HCC diagnoses in people born in Asia and Africa both quadrupled between these periods, and the proportion of these cancers caused by HBV increased by a third. In the latter period, HBV was the cause of 2% of HCC in those born in Australia compared with 30% in those born overseas. A similar study from south-western Sydney of HCC patients diagnosed between 1993 and 2003 (60) revealed the number of Asian born patients doubled in the second half of the study period relative to the first half, with viral hepatitis (mostly HBV) being responsible for 91% of HCC amongst Asian patients. Median age of diagnosis for those with HBV was 58 years, with median survival less than six months (60).
Similar trends in HCC and other hepatitis-related mortality on a population (as opposed to hospital cohort) level have been reported extensively in NSW recently (13, 67). This is likely to be due to the observation that HCC has the fastest rising incidence of any cancer in NSW (24), an observation which also led to the Cancer Council NSW funding the development of a new HBV guide for primary care providers which was published in 2008 (30).

In 2007 Amin and colleagues reported that the proportion of diagnoses of HCC in NSW linked to HBV increased more than 70% between 1994-6 and 2000-2002, with more than two thirds of all HBV-linked HCC occurring in people born in Asia (67). Rate ratios for HCC of any cause among people born in China and Vietnam were 10 to 12 times those for people born in Australia. Median age of diagnosis of HBV related HCC was 58 years, with a median survival following diagnosis of just 15 months (67). These deaths are a fundamental determinant of the finding in a related linkage study published in the Lancet in 2006 which demonstrated that NSW residents notified with chronic HBV have a standardised mortality ratio of 1.4 relative to uninfected individuals (13).

On the basis of these and other Australian studies it has been commented that a large proportion of people chronically infected with HBV entered the country relatively recently (2) and that 50% of HBsAg seropositive people in Australia have emigrated from South-East (33.3%) and North-East (16.2%) Asia (11). Furthermore, the steady increase in the number of Australians chronically infected with HBV is already resulting in rising attributable mortality. An analysis of the nexus between HBV epidemiology and migration in Australia is the subject of chapter 4 of this thesis, with further insight into this relationship (and projected mortality as a result) developed through the outcomes of mathematical modelling presented in chapter 6.

1.3.2.2.2 Indigenous Australians

Since the Nobel Prize-winning discovery of HBsAg (formerly ‘Australia antigen’) in the serum of (amongst others) 12 out of a sample of 208 Indigenous Australians from Western Australia by Dr Baruch Blumberg and colleagues over forty years ago (68, 69), a high prevalence of markers of HBV infection has been noted in Indigenous communities. Wide variation in markers of past infection, and in the rate of chronic carriage of HBsAg, has been
described, with higher rates being reported in rural and remote areas than in urban centres (11, 70).

Not only in the high prevalence of infection, but also in the modes of acquisition, age distribution of infection, rate of progression to chronic carriage and disease, and outcomes of chronic infection, many Indigenous communities have a burden of disease more akin to developing nations than to other Australians born in Australia (17, 22, 59, 71).

A number of different studies have been conducted into the prevalence of markers of infection with HBV, including HBsAg carriage, and hepatitis B surface antibody (anti-HBs) and core antibody (anti-HBc) seroprevalence, in the last two decades. The results of some of these are summarised in table 1.4. The range of carriage of HBsAg ranges from less than 3% (and as low as 0.5%) amongst urban Indigenous women on antenatal screening to over 25% in remote areas of South Australia and Queensland. The corresponding seroprevalence of markers of prior HBV infection ranges from as low as 10% in adolescents in NSW in 2008 to over 90% in remote communities.

On the basis of some of these published studies and other data, O’Sullivan et al estimated the prevalence of HBsAg to be 2% in urban Indigenous Australians and 8% in those living in rural areas when formulating national estimates to generate a risk group-based comparison to their serosurvey data (11). Indigenous Australians, constituting 2% of the total population, were estimated to represent 16% of Australians chronically infected with HBV.

In 2008, Einsiedel and colleagues published an account of racial disparities in infection related mortality at Alice Springs Hospital (17). Of all Indigenous deaths in hospital from 2000-2005, 2.9% were caused by end stage liver disease in people with chronic HBV infection, compared with none in non-Indigenous patients. This figure is equivalent to the population mortality attributable to HBV infection in high prevalence countries of Africa and Asia (59).
<table>
<thead>
<tr>
<th>Study</th>
<th>Population of Indigenous Australians</th>
<th>%HBsAg +</th>
<th>Other markers of infection with HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumberg 1965</td>
<td>Serum from Western Australia (WA) sent to Blumberg in Philadelphia (n=208)</td>
<td>6%</td>
<td>NB for these studies the use of original, less sensitive detection methods would have resulted in artificially low estimates when compared with more recent studies (57, 72)</td>
</tr>
<tr>
<td>Barrett 1976</td>
<td>Communities in the Northern Territory (NT) and Queensland (Qld). Collected between 1961 and 1974 (n=2193)</td>
<td>NT: 8.5% Qld: 2.7%</td>
<td></td>
</tr>
<tr>
<td>Burrell 1983</td>
<td>People aged over 10 years from desert communities in South Australia (n=327)</td>
<td>26%</td>
<td>92% positive for markers of HBV</td>
</tr>
<tr>
<td>Britton 1985</td>
<td>Pregnant women in Sydney (n=67)</td>
<td>9%</td>
<td>53.8% positive for any markers of HBV</td>
</tr>
<tr>
<td>Holman 1987</td>
<td>Residents in WA aged over 12 years (n=1150)</td>
<td>7.9% (up to 22% in a desert community)</td>
<td>52.4% positive for any HBV markers – from 25% in SW of WA to 85% in remote desert community</td>
</tr>
<tr>
<td>Moore 1987</td>
<td>Pregnant women in non-metropolitan WA (n=816)</td>
<td>3.6%</td>
<td></td>
</tr>
<tr>
<td>Campbell 1989</td>
<td>Residents of a town in north-western NSW (n=375)</td>
<td>19%</td>
<td>72% positive for markers of HBV</td>
</tr>
<tr>
<td>Gill 1990</td>
<td>High school students in the Kimberly, WA (n=277)</td>
<td>6.1%</td>
<td>28.2% positive for markers of HBV</td>
</tr>
<tr>
<td>Campbell 1991</td>
<td>Children in rural New South Wales (NSW) (n=297)</td>
<td>14%</td>
<td>69% positive for any HBV markers</td>
</tr>
<tr>
<td>Gardner 1992</td>
<td>Primary school children in NT (n=439)</td>
<td>8.2% (14.8% in a rural school)</td>
<td>46.9% positive for HBsAg or anti-HBs</td>
</tr>
<tr>
<td>Butler 1997</td>
<td>Male prisoners in Sydney (n=41)</td>
<td>12%</td>
<td>29% anti-HBc +</td>
</tr>
<tr>
<td>Malcolm 2000</td>
<td>Incompletely vaccinated teenagers from a community in north Qld (n=108)</td>
<td>26%</td>
<td>94% anti-HBc +</td>
</tr>
<tr>
<td>O’Sullivan 2004</td>
<td>Pregnant women in central Sydney 1996-1999 (n=266)</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Panaretto 2006</td>
<td>Pregnant women in Townsville, Qld (n=419)</td>
<td>0.5%</td>
<td>One (0.24%) case of acute HBV detected</td>
</tr>
<tr>
<td>Wood 2008</td>
<td>Pregnant women in NT (n=522)</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td>van der Poorten 2008</td>
<td>Indigenous adolescent offenders, NSW (n=179)</td>
<td>3.4%</td>
<td>9.6% anti-HBc +</td>
</tr>
</tbody>
</table>

Table 1.4 – Studies of the prevalence of HBsAg and other markers of HBV infection in Indigenous Australians (8, 11, 18, 57, 68, 70, 72-79).
### 1.3.2.3 Injecting drug users

As described, approximately 50% of incident HBV infections notified currently are linked to IDU in Victoria (11). This is in keeping with patterns of transmission in low prevalence populations worldwide, where most infections are acquired in early adult life through unsafe IDU, and sexual activity (2, 8, 11, 51, 73).

A summary of studies in IDUs is presented in table 1.5. These show a prevalence of Anti-HBc of 42-47%, approximately 5 times the background prevalence in the general population (11). HBsAg prevalence was much lower, at 1.6-3.0%, with the exception of the early study by Gust which demonstrated an HBsAg prevalence of nearly 9%. Other than this study, the relatively low rate of HBsAg carriage despite a relatively high proportion of the population testing positive to Anti-HBc is a common serologic pattern in low prevalence populations where the majority of incident infections occur later in life and are more likely to resolve without progression to chronicity.

<table>
<thead>
<tr>
<th>Study (published)</th>
<th>Population</th>
<th>%HBsAg +</th>
<th>Other markers of infection with HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gust 1982</td>
<td>Victoria (n=633)</td>
<td>8.9%</td>
<td></td>
</tr>
<tr>
<td>Anderson 1994</td>
<td>Sydney Sexual Health Centre, 1991 (n=153)</td>
<td>2.9%</td>
<td>42% anti-HBc+</td>
</tr>
<tr>
<td>Crofts 1994</td>
<td>Victoria – peer and community outreach, 1990-91 (n=315)</td>
<td>1.6% (males 2.1%, females 0.8%)</td>
<td>47%</td>
</tr>
<tr>
<td>Crofts 1997</td>
<td>Victoria – peer outreach, 1990-95 (n=626)</td>
<td>45.2% anti-HBc+ at baseline. Incidence of new HBV infection was 1.8 per 100 person-years</td>
<td></td>
</tr>
<tr>
<td>Bradshaw 2005</td>
<td>Melbourne – street outreach, 1999-2002 (n=314)</td>
<td>3% (Indigenous: 7%, S.E. Asian: 14%)</td>
<td>33% (Indigenous: 44%, S.E. Asian: 50%)</td>
</tr>
</tbody>
</table>

**Table 1.5** – Studies of the prevalence of HBsAg and other markers of HBV infection in injecting drug users (8, 11, 74-76).
1.3.2.4 Men who have sex with men

High rates of HBV infection have been reported in men who have sex with men (MSM), particularly in those men who have multiple partners (8, 11, 51, 61). The risk of HBV infection also increases in heterosexuals as the lifetime number of partners increases (52) and higher rates are seen amongst heterosexual attendees at sexual health clinics (61). Furthermore, whereas rates of HBV infection dropped through the late 1980s and 1990s in MSM, probably as a result of safer sexual practices in the context of the HIV epidemic (61), the same cannot be said of heterosexual transmission, as demonstrated in the Victorian risk factor analysis presented previously.

In 1983, a survey of 496 MSM attending a general practice in Melbourne (77) demonstrated 46.8% had markers of prior HBV infection, 3% had chronic HBV, and two additional participants were found to have acute HBV at the time of assessment. Markers of prior infection rose steadily with time since initiation of homosexual contact, from 19% in the men who had been having sex with men for two years or less, to 58% in men whose duration of homosexual activity was greater than 20 years. The same year, a sample of 163 active members of a ‘gay’ club in Adelaide demonstrated 37% had serological markers of HBV infection, with 5.5% having chronic HBV (57).

In a study performed by Anderson et al through the Sydney Sexual Health Centre published in 1994, patients identified as MSM had a prevalence of HBsAg of 3.3%, and of anti-HBc of 38.2% (78). In common with IDU, the relatively low rate of progression to chronicity relates to a later age at infection.

An evolving concern is that of people co-infected with HIV and chronic viral hepatitis. In the Australian HIV observational database with over 2000 participants, 77% have been tested for HBsAg to date and 6.3% have been found to be positive. Furthermore, markers of past or present HBV infection can be detected in over 50% of MSM with HIV (79). Not only is HBV infection more common in HIV infected MSM but HIV infected people have a higher likelihood of progressing to chronic HBV and have an accelerated course of liver disease and progression to cirrhosis than HIV negative patients (80, 81). This is an area of much ongoing study, particularly with respect to effective combination antiviral regimens active against both viruses.
1.3.2.2.5 People serving custodial sentences

The high prevalence of blood borne viruses in prison populations has been ascribed chiefly to the association between incarceration and IDU (82-85), although other high risk behaviours are also noted, including tattooing with inadequately disinfected equipment and unprotected sexual contact (82, 84, 85). Between one and two thirds of Australian prison entrants have been reported to have a history of IDU, and one third of IDUs have a history of imprisonment (84). Furthermore, Indigenous Australians are disproportionately represented in prisons relative to their proportion in the general population (83-87).

The findings of several studies that have assessed the prevalence of infection with blood borne viruses in Australian prisoners are summarised in table 1.6.

<table>
<thead>
<tr>
<th>Study (published)</th>
<th>Population</th>
<th>%HBsAg +</th>
<th>Other markers of infection with HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crofts 1995</td>
<td>Victorian prisoners, 1991-92 (n=3627)</td>
<td>2.5%</td>
<td>33% anti-HBc+ Incidence of new HBV infection was 12.6 per 100 person-years – 50% suffered acute icteric illness</td>
</tr>
<tr>
<td>Butler 1997</td>
<td>Male prisoners in Sydney, 1994 (n=408)</td>
<td>3.2% (12.2% in Indigenous inmates)</td>
<td>31% anti-HBc+</td>
</tr>
<tr>
<td>Thompson 1998</td>
<td>Juvenile offenders, Melbourne (n=83)</td>
<td></td>
<td>6.1–8.5% anti-HBc+</td>
</tr>
<tr>
<td>Butler 1999</td>
<td>NSW prisoners, 1996 (n=789)</td>
<td></td>
<td>35% anti-HBc+ (54% in Indigenous inmates)</td>
</tr>
<tr>
<td>Butler 2008</td>
<td>Juveniles (age 14-21) in detention in NSW, 2003 (n=200)</td>
<td>4% (of whom 37.5% co-infected with HCV)</td>
<td>11% anti-HBc+</td>
</tr>
<tr>
<td>van der Poorten 2008</td>
<td>Non-Indigenous adolescent offenders, NSW (n=530)</td>
<td>1.1%</td>
<td>5.2% anti-HBc+</td>
</tr>
</tbody>
</table>

Table 1.6 - Studies of the prevalence of HBsAg and other markers of HBV infection in people serving custodial sentences (82-84, 86-88).
1.3.2.6 High prevalence populations – conclusion

It is therefore apparent that there are well defined groups within the Australian community who have a substantially higher prevalence of chronic HBV infection than the general population. In particular, migrants from high prevalence countries represent the largest population of people with chronic HBV infection living in Australia, followed by Indigenous Australians (11, 57). This is related to the fact that, unlike other high prevalence populations, Australians in these two groups are mostly infected at birth or in early childhood, with correspondingly much higher rates of progression to chronic disease.

The important question that studies dedicated to investigating HBV infection in certain sections of the community cannot readily answer is: what is the prevalence of HBV in the Australian population as a whole? As a result, estimates have been derived using blood donor and antenatal screening seroprevalence results (particularly of Australian-born, non-Indigenous women) to represent the general community’s disease burden. As discussed in 1.3.2.1, this is likely to lead to under-estimation of the prevalence of HBsAg in the general population.

The only way to address this issue is to undertake more representative serologic testing of the population as a whole, as recommended by Kaldor and colleagues in 1996 (8). It was eight years before such a serosurvey for markers of HBV infection in Australia was reported (11).

1.3.2.3 National HBV serosurveys 1996-99 and 2002

The national serosurveys conducted between the years 1996-99 and in 2002 used samples of convenience from people aged between 1 and 59 years, derived from residual serum remaining after routine diagnostic testing collected from a number of laboratories throughout Australia (11, 12). Sera were obtained from States and Territories proportional to their population size, with equal numbers of males and females, and the sera were stratified according to age. The samples were initially tested for anti-HBs and anti-HBc, with all anti-HBc positive samples then tested for the presence of HBsAg.

The serum samples used in these studies were tested for serological markers of a range of different infections at different times (89), resulting in the consumption of significant
volumes of serum, and repeated freeze-thaw cycles and handling of the samples (11). This lead to significant difficulties in analysing the HBV results for the first national serosurvey, as of the 81 anti-HBc positive samples, nearly one third (n=26) had indeterminate HBsAg status, either through insufficient serum left to perform the test (n=7) or weak positive results believed to be due to contamination (n=19) with insufficient specimen left to perform further testing (11). To reflect the resultant uncertainty, the authors conducted a sensitivity analysis, coding all these indeterminate results as negative (minimum estimate) or by assigning HBsAg status proportional to the HBsAg results for the 56 anti-HBc positive sera adequately tested (adjusted estimate). These calculations resulted in population-based estimates of chronic HBV infection in Australia of 91,500 people (0.49% of Australian population, 95% CI 0.13-0.85%) for the minimum estimate and 163,500 people (0.87% of Australian population, 95% CI 0.39-1.35%) for the adjusted estimate.

The range of the sensitivity analysis used in this paper has led to the very widely used estimate of “90,000 to 160,000” people with chronic HBV living in Australia (24-26, 30). It is important to realise that this range does not include the 95% confidence intervals for either the minimum or the adjusted estimates – doing so would result in a range of approximately 25,000 – 250,000 people chronically infected with HBV. Furthermore, the use of this earlier estimate appears to so far be unaffected by the publication of the second national serosurvey in 2007 based on serum samples collected in 2002 (12). In the latter serosurvey, far fewer samples were affected by the volume and contamination problems encountered in the first study, with a correspondingly much lower sensitivity to uncertainty.

In the report of the first serosurvey, the authors compared the minimum estimate for HBsAg (0.49%) with the risk-factor based estimate reported in the same paper (0.47%) and the HBsAg prevalence in the large (n=40,000) NHANES III cross-sectional seroprevalence survey in the USA (0.42%) (52). However as discussed in the paper, the risk-factor based approach used a population prevalence outside identified risk groups of 0.1% based on first-time blood donor data which are unlikely to be representative of the general population. This was reinforced when the HBsAg prevalence in the 2002 serosurvey was closer to the adjusted estimate of the initial study (0.7/0.8%) (12). The results of the two national serosurveys are presented in table 1.7.
<table>
<thead>
<tr>
<th></th>
<th>First national serosurvey 1996-99 (11)</th>
<th>Second national serosurvey 2002 (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=</td>
<td>% positive</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>3336</td>
<td>28.7</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>2476</td>
<td>6.9</td>
</tr>
<tr>
<td>HBsAg (min.)</td>
<td>55</td>
<td>0.5</td>
</tr>
<tr>
<td>HBsAg (adj.)</td>
<td>55</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table 1.7 – HBV serology results from the first (1996-99) and second (2002) national serosurveys.

A limitation of the design of these serosurveys (which is shared by the Victorian serosurvey presented in chapter 3) is that samples of convenience following diagnostic testing were used, introducing a selection bias which is not possible to quantify. This is discussed in more detail in chapter 3 (3.5). Unlike the Victorian serosurvey, no data were available for people aged 60 years or over, and samples from people previously tested for viral hepatitis were not excluded, potentially increasing selection bias. Samples were also not tested in proportion to the age distribution of the population; instead summary estimates derived by weighting individual age-group strata, leading to greater uncertainty around estimates for relatively under-sampled ages (such as those aged between 30 and 60 in the first serosurvey, and those age 10-19 and over 30 in the second serosurvey, in both cases particularly for anti-HBc and HBsAg testing).

It is evident from table 1.7 that the second serosurvey results for HBsAg prevalence have much narrower confidence intervals, and are closer to the adjusted estimate from the prior study. Based on this, it would seem that no longer should the 90,000 to 160,000 estimate for HBsAg prevalence in Australia be used – especially as this does not include the confidence intervals around these estimates. Rather, the burden of chronic HBV in Australia as of 2002 would be approximately 150,000 people, with the range of confidence being 120,000 to 180,000. The national serosurveys will be discussed later in this thesis – in chapter 3 for comparison with the results of the Victorian serosurvey, and again in chapter 6 when being used to help validate the outcomes of a mathematical model of HBV in Australia.
1.4 Elements of the Australian public health response to HBV

1.4.1 Securing the blood supply and reducing health care associated transmission

Within four years of the initial discovery of the Australia antigen, the association with hepatitis (and in particular, post-transfusion hepatitis) had been made and the initial attempts to screen donor blood and exclude units testing positive were in place at Philadelphia General Hospital, where Baruch Blumberg was an attending physician (69). Although debate continued regarding the reliability of the tests and the proportion of post-transfusion hepatitis that could be averted, by the early-mid 1970s testing was compulsory in the USA (6) and in other countries including Australia, leading to a profound reduction in this previously very common complication. This process was accelerated in the American context from 1969 by law suits brought by patients acquiring hepatitis against blood banks (and hospitals and treating doctors) for failing to test donor units (69). In 1986 the USA introduced screening for anti-HBc to augment the protection against transfusion mediated infection (6).

In the Australian blood-banking system between 2000 and 2006, detection of HBsAg in donor units constitutes 41% of all blood borne viruses isolated (58), with 605 cases identified in 6.3 million donations. Of those identified with chronic HBV infection interviewed, the probable risk factors identified were country of birth for 20%, and parental ethnicity in 51%.

Another critical area where health-care associated HBV caused outbreaks with significant morbidity and mortality was in haemodialysis units. Screening of dialysis patients with the use of separate machines and then whole units for those infected, and improvements in sterilization, were also initiated in Philadelphia by an associate of Blumberg and helped control such outbreaks until the vaccine was developed (69).

Protection against HBV infection in health care workers (HCWs) has involved both vaccination (as discussed subsequently, HCWs represent one of the successes of the selective vaccination program), but also the implementation of universal blood and body fluid precautions that were promoted by the CDC in response to the HIV epidemic in 1985 (90). These recommendations and the infection control procedures that have built on them, have not only protected HCWs but also their patients from health-care associated HBV infection (61).
1.4.2 Vaccination

1.4.2.1 History of vaccine development and introduction

The first hepatitis B vaccine, derived from purified HBsAg from the serum of people with chronic infection, was invented by Blumberg and colleagues within a few years of the initial discovery of Australia antigen in 1965 (69). The patent was filed in 1969, issued in 1972, and further development was licensed to Merck in 1975. A clinical trial of the vaccine was conducted in MSM in New York City in 1978-79 with a high degree of protection demonstrated (91). This study, published in 1980, also showed a significant reduction in incidence within 75 days, suggesting that the vaccine might be effective as a post-exposure intervention. Within two years the serum-derived HBsAg vaccine was approved by the Food and Drug Administration in the USA, and became available in most developed countries including Australia soon afterwards.

Initial NHMRC guidelines were established in 1983, at a time when the high cost of the vaccine limited widespread use (61). It was considered that the most effective role for the vaccine would be to offer it to groups considered to be at highest risk of infection, such as HCWs, residents of institutions for people with intellectual disabilities, IDU, MSM, and household contacts of known carriers. Similar approaches were instituted in other industrialised countries (61).

In the mid 1980s a novel hepatitis B vaccine was developed, derived from HBsAg expressed in yeast cells (Saccharomyces cerevisiae) containing plasmids into which the HBV S-gene had been inserted (92). This vaccine, free of the concerns (and practical difficulties) of using vaccine derived from the serum of people with chronic HBV infection, was available in Australia from 1987 (10). The vaccine is safe and highly effective, eliciting durable (93, 94) immunity (reflected in an anti-HBs titre >10 IU/L (10)) in 95% of vaccinated children and young adults, with falling response rates to primary vaccination in older adults (95). Other factors associated with poorer vaccine response include immunodeficiency and chronic disease (including renal failure, particularly for patients receiving haemodialysis, and chronic liver disease) (10, 95). Patients in these groups are also recommended to receive booster doses when their anti-HBs level falls below 10 IU/L, unlike those without these risk factors in whom booster vaccination is unnecessary (10, 93).
The highest risk of developing chronic HBV infection occurs following neonatal infection, with a 90% chance of progression to chronicity (96). Epidemiological studies in Asia and Africa in the 1970s demonstrated that the majority of infants vertically infected were exposed during or after birth, rather than in utero (69). This fact, together with the early clinical trial evidence that post-exposure prophylaxis with vaccination might be feasible (91), led to the hypothesis that infant vaccination against HBV could prevent vertical transmission with the attendant high likelihood of chronic infection. This was supported by reports of a protective effect of administering hepatitis B immunoglobulin (HBIG – prepared from the serum of blood donors with high levels of anti-HBs) to neonates born to HBV infected mothers (97).

Four years after the publication of the initial clinical trial of hepatitis B vaccine, a placebo-controlled, randomised controlled trial of vaccination both with and without the administration of HBIG conducted in infants born to highly replicative (HBeAg positive, see 2.5.2.1) mothers in Hong Kong was reported in the Lancet (97).

The hypothesis that neonatal vaccination could reduce vertical transmission was comprehensively supported by this trial, with the best protective efficacy observed in those babies receiving both active and passive vaccination (table 1.8). Both vaccination alone, and vaccination plus HBIG, resulted in significant reductions in the proportion of infants HBsAg positive at 6 months (p<0.0001), with incremental protective efficacy for those receiving HBIG as well as vaccine.

<table>
<thead>
<tr>
<th></th>
<th>Group I n = 36</th>
<th>Group II n = 35</th>
<th>Group III n = 35</th>
<th>Group IV n = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>0, 1, 2 &amp; 6 months</td>
<td>0, 1, 2 &amp; 6 months</td>
<td>0, 1, 2 &amp; 6 months</td>
<td>Placebo</td>
</tr>
<tr>
<td>HBIG</td>
<td>Monthly 0 – 6 months</td>
<td>Birth only</td>
<td>-</td>
<td>Placebo</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>2.9%</td>
<td>6.8%</td>
<td>21%</td>
<td>73.2%</td>
</tr>
<tr>
<td>PER</td>
<td>96.0%</td>
<td>90.7%</td>
<td>71.3%</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1.8 – Proportion of infants of HBeAg-positive mothers with detectable HBsAg at 6 months of age by intervention, with corresponding Protective Efficacy Rate (PER: (attack rate in placebo group – attack rate in treatment group)*100/attack rate in placebo group). From (97).
In response to this study and other evidence of efficacy, serum-based vaccine for infants at high risk (initially only those born to HBsAg positive mothers) became available from 1983 (98), followed by recombinant vaccine in 1987 (10).

### 1.4.2.2 Low prevalence countries

#### 1.4.2.2.1 Selective vaccination

In Australia, as in most industrialised countries in the decade following the introduction of hepatitis B vaccine, a selective vaccination program was developed, utilising a variety of funding sources and eligibility criteria, based on targeting those in the population (infants and otherwise) at particular risk of infection. By the early 1990s however it became apparent that selective vaccination strategies had failed to have a significant impact on the incidence of HBV infection or the size of the pool of people living with chronic infection (51, 53, 61, 73). It has been suggested that this is because persons at increased risk are often not identified as such until after exposure to this higher risk has commenced, by which time infection may already have occurred (51, 61). The failure of selective vaccination of high-risk groups is not confined to Australia, but rather has been observed in many well resourced low prevalence countries (99).

Due to the high likelihood of progression to chronic infection in exposed infants, failure of selective vaccination programs in this group is of particular concern. An early report of a large inner Sydney maternity service revealed that of 1429 neonates identified as being at high risk of HBV infection between 1987 and 1988, nearly 20% were lost to follow up without completing the full course of vaccination (98). Of even greater concern was that the proportion of children born to HBsAg positive mothers not being fully vaccinated was no better at 17%. In Adelaide in 1991-1992, a prospective study of five hospitals demonstrated that of the parents of 110 eligible high risk infants, only 67 responded to the questionnaire, and of these only 70.1% of babies had completed vaccination against HBV (100).

In Victoria in 1992-1993, a survey of Maternal and Child Health Centres reported on 3611 of 5744 infants identified as high risk of HBV due to maternal birthplace or ethnicity, representing 8.8 per cent of all Victorian births (101). No hepatitis B vaccination was received by 12.8% of these infants, and 36% were either incompletely vaccinated or records
were unavailable. One year prior, of 336 infants born to known HBsAg positive mothers in Victoria, only 57.4% were documented to have been completely immunised against HBV (63).

Evidence for the failure of the selective vaccination outside the context of averting vertical transmission to neonates is also widespread. Of high risk patients without a history of HBV infection attending the Sydney Sexual Health Centre in 1991 (78), only 27.6% of MSM, 27.9% of local female sex workers, and 7.1% of IDU reported previous vaccination against HBV. More recent data from an IDU outreach study in Melbourne show that only 26% of those tested were vaccinated against HBV (76). Prisoners are also a poorly vaccinated group, with reports of vaccination coverage ranging from less than 10% (82, 84) to 20-25% (83, 88).

For Indigenous Australian children and teenagers, some studies indicate protective immunity or complete vaccination history in only 44 – 54% of targeted recipients (18, 102). As described by Malcolm and colleagues, over 90% of incompletely vaccinated teenagers in an Indigenous community in North Queensland had been infected with HBV and 26% were chronically infected (18). More encouragingly, a 1998 study by Hanna et al (103) on the HBV vaccination status of Indigenous children in far North Queensland reported that approximately 80% of children were fully vaccinated, although there is still a significant gap in vaccination status between Indigenous and non-Indigenous Australian children.

Only 19% of high risk children in the large school-based study by Burgess and colleagues in 1990-91 (21) had been vaccinated; a greater proportion (21%) had been infected, one third of whom had chronic HBV infection. Four years later, only 31% to 68% of Vietnamese children in South-Western Sydney were fully vaccinated (104). In community surveys of immigrants from South-East Asia living in Melbourne in 1998 and 2002, only 16.5% of participants had serological evidence of vaccination against HBV despite being a recognised high-risk group and having been in Australia for a median of 12-14 years (19). These surveys also identified the problems of language barriers, poor knowledge about hepatitis and unrecognised infection with obvious implications for capacity for control of transmission.
1.4.2.2 Universal vaccination

Examples of failure of selective vaccination strategies such as those described here led to the 1991 recommendation by the WHO that all countries integrate HBV vaccination into their national immunisation schedule by 1997 (51, 53, 61, 105). In contrast to selective immunisation programs, universal infant vaccination in both low and high prevalence countries has proven effective at reducing the burden of HBV infection. The United States, a low prevalence country with groups at higher risk not dissimilar to the pattern of infection in Australia, introduced universal infant vaccination in 1991, resulting in an 80% fall in notifications of acute HBV infection in children, with notified new cases of HBV reducing by more than 75% overall between 1987 and 1998 (106). Similar trends were noted in Italy, an intermediate prevalence country, following the implementation of universal infant and adolescent vaccination in 1991 (7).

In June 1996, with 75 countries having incorporated HBV vaccination into their schedule (105), the NHMRC issued recommendations for universal HBV vaccination for Australian infants and adolescents (8, 10). At the time of this change in policy, all States and Territories had policies resembling the former NHMRC guidelines, except the Northern Territory where universal infant vaccination had been funded since 1990 (8, 35) – although with less than uniform uptake, at least initially (107).

By 1998 over 100 countries worldwide had adopted universal infant and/or adolescent immunisation (51), which commenced in Australia in May 2000 (10). By this time, it was estimated that a billion doses of vaccine had been administered worldwide (69). Data from the Australian Childhood Immunisation Register suggests that since the inclusion of hepatitis B vaccine in the National Immunisation Program approximately 95% of infants born in Australia receive HBV vaccination (35, 108).

Since the effect of the universal infant vaccination program in Australia would not be evident for some 15 years after commencement (11, 51, 106), it was augmented by a catch-up program for adolescents aged 10-13 from 1998 (10). This program provides an uncertain but far from complete level of coverage. Estimates from school based studies have suggested uptake of the order of 70% amongst schools and students returning surveys (109-111). However in the 2002 national serosurvey, anti-HBs prevalence amongst 12-17 year olds (all
of whom would have been eligible for the program) was only 45.5% - and even in States where established school-based programs existed, the prevalence was only 56.6% (12). The proportion of samples from adolescents in the eligible age groups in the Victorian serosurvey with anti-HBs was very similar, being between 55 and 60% in both 2000 and 2005 (chapter 3 – tables 3.9 and 3.12 and section 3.4.2).

Despite the suboptimal coverage achieved by the adolescent catch-up program, the significant reduction in notifications of acute HBV infections since 2001 can partly be attributed to this intervention. In 2000-2006, acute HBV infections in Australia dropped by 69% in people aged 15-19, and 52% in those aged 20-29, in contrast to little or no change in other age groups (figure 1.4) (40). The relative contribution of adolescent vaccination and the influence of other factors applying predominantly to acquisition during adolescence and early adulthood, such as an apparent ‘heroin drought’ between 2002 and 2004 (112), cannot be determined with certainty.

![Figure 1.4](image)

**Figure 1.4** – Notification rate of incident HBV in Australia by age group, 1995 to 2006, showing the particular reduction in the 15-19 year age group from 2000 onward. Taken from the Annual report of the NNDSS, 2006 (40).
Although the coverage of universal infant vaccination appears high (108), other groups such as children migrating from regions without hepatitis B vaccination remain at risk. This reinforces the importance of improving the coverage of the universal catch-up program for adolescents, and for ongoing efforts to improve vaccination delivery to high risk groups (11, 51, 61, 105, 106).

1.4.2.3 High prevalence countries

Hepatitis B vaccine (both serum-derived and recombinant formulations) was initially very expensive, limiting uptake even in developed economies (61). The earliest implementation of a comprehensive and universal vaccination program in a high prevalence country occurred in Taiwan on 1st July 1984 (69). This program has resulted in a reduction in HBsAg carriage in children under 15 years from 9.8% in 1984 to 0.7% in 1999, with a corresponding 75% drop in hepatocellular carcinoma in these children also observed (7, 106).

The 90% reduction in HBsAg prevalence in children achieved in this program is a testament to the greatest promise of the vaccine; converting high HBV prevalence populations (with the associated burden of morbidity and mortality) to low prevalence populations over the course of three to four generations if 90% or greater infant vaccination coverage can be maintained (113, 114).

The major barrier to realising this promise is vaccine cost. Costs have dropped remarkably in the last two decades, as despite the relatively high technology production requirements for recombinant vaccine, the ability to produce large quantities of vaccine along with economies of scale has reduced the price per dose of monovalent recombinant vaccine to national health authorities from the UNICEF Supply Division to between 20 and 30 US cents (115) – approximately one third the cost of a dose of yellow fever vaccine, and one sixth that of measles/mumps/rubella vaccine. This represents a drop in price per dose to UNICEF of nearly 90% between 1996 and 2005, driven by rising global demand attracting increasing numbers of manufacturers, thereby generating greater competition for supply contracts (116).

A critical contribution to the delivery of affordable hepatitis B vaccine to intermediate and high prevalence countries with less developed economies has been the GAVI Alliance (http://www.gavialliance.org – the Global Alliance for Vaccines and Immunisation). In the
period between 2000 and 2007, the GAVI Alliance supported hepatitis B vaccination programs expanded to cover 67 eligible countries with an annual GDP per capita of less than SUS$1000, vaccinating 192 million children (116) (figure 1.5). In 18 of these countries (including Indonesia and China), support has been given for the introduction of a birth dose which is essential for the prevention of vertical transmission (97). Hepatitis B vaccine, one of three original GAVI vaccines, remains the most popular offered by the alliance (116).

An example of a country assisted to implement hepatitis B vaccination by GAVI is China, where an estimated 50% of all HBV-related deaths worldwide occur (116). As a result, the proportion of children receiving three doses of vaccine rose from 72% in 2000 to 84% in 2005 (115). The proportion of children receiving the critical birth dose of vaccine rose from 29% in 1997 to 82% in 2005 (116). In 2005, the Chinese government declared that hepatitis B vaccine (along with all WHO Expanded Programme on Immunisation (EPI) vaccines) would be provided free to all children, eliminating administrative charges (116). This decision is likely to significantly improve coverage, especially in poorer Western provinces of China which have previously reported much poorer results than wealthier, more urbanised Eastern coastal areas (117). As a result, China is on track to reduce the future global burden of deaths due to HBV infection by as much as one half over the next few generations (114, 116, 117).

![Figure 1.5](image-url)  
*Figure 1.5 – Countries supported by GAVI to introduce infant hepatitis B vaccination as at November 2007 (green). From (116).*
The majority of the world’s population chronically infected with HBV lives within the Western Pacific WHO Region, of which both China and Australia are members. As of 2006, 22 of the 23 Regional member states with high HBV prevalence had incorporated a birth dose of hepatitis B vaccine into their schedule, with an estimated birth dose coverage for infants in these countries of 75% (118). This is an amazing achievement over the space of one decade, but further efforts are needed. This is particularly true in Africa where only 1% of infants born in high prevalence countries receive the birth dose (118). A mathematical model of the global burden of HBV published in 2005 estimated that routine infant vaccination against hepatitis B, including a birth dose, would prevent >80% of global HBV-related deaths (114).

1.4.2.4 Cost effectiveness

Although universal infant vaccination against HBV has been demonstrated to be effective at reducing the incidence of HBV infection in both high and low prevalence countries, assessment of the cost effectiveness of such programs is essential. The two are by no means synonymous; a program which delivers important public health objectives may not be cost effective, and conversely a highly cost effective intervention may not provide desired outcomes, especially if implementation is incomplete (selective hepatitis B vaccination of high risk individuals being a good example).

Mathematical modelling of HBV transmission was undertaken in the United Kingdom (UK) to address this matter (119, 120). The stimulus for this research was the recommendation of the WHO in 1991 that all countries incorporate universal vaccination against HBV in their infant vaccination schedules (61), a recommendation which was (and remains) contrary to that of the UK Department of Health, along with those of several other North-Western European low HBV prevalence countries. The authors of these papers point out that, in addition to the WHO, vaccine manufacturers were also keen promoters of the universal policy (119). This is also apparent in the Australian medical literature (53, 61, 121).

In the UK model only sexual and vertical transmission of HBV was considered – no transmission due to IDU was simulated – and the impact of migration on HBV prevalence was not considered (119, 120). The analysis demonstrated that universal infant vaccination was not a cost effective intervention for the UK (119, 120). Similar research was conducted in the Netherlands a few years later for the same reason, to assess the cost effectiveness of
universal vaccination in the light of the WHO recommendations (122). This also included construction of a model based on the UK research described (120), but extended to include migration (122). The conclusion was the same, and the Netherlands also has not introduced universal vaccination.

The lack of cost effectiveness found in these studies contrasts with the findings of analyses using Markov models in the USA and Australia (53, 123), the Australian study essentially being an adaptation of the American analysis to local conditions and costs. The Australian group calculated that the additional cost per life year gained over the selective vaccination approach was $11,862, and concluded that this, being low compared with many other health care interventions, represented a worthwhile investment of public funds (53). This analysis is to my knowledge the only published mathematical model of the epidemiology of HBV infection in Australia, and is analysed in detail in chapter 5. Both the American and Australian cost effectiveness analyses, which found universal vaccination to be cost effective, used very high probabilities of infection which favours universal vaccination. Neither considered the effect of migration.

In the final analysis of these four studies, it should perhaps be unsurprising that those funded by national health authorities in well resourced low prevalence countries conclude universal infant hepatitis B vaccination is not cost effective (120, 122), whereas those funded by vaccine manufacturers operating in the same countries find universal infant hepatitis B vaccination is cost effective (53, 123).

Beyond the examples presented, a large number of methodologically disparate cost effectiveness studies have been published in the scientific literature in the last two decades. These have often lacked clarity, transparency, and demonstrate significant heterogeneity in both assumptions and outcomes (124). A systematic review of all 90 original economic analyses of hepatitis B vaccination identified up to the year of publication in 1994 found that, due to uncertain or unclear methodology in many of the studies, few came to valid conclusions (125). As a result, the authors of the review held that no conclusions about the efficiency of hepatitis B vaccination programs could be drawn based on the evidence available at the time (124, 125).
Another systematic review was published in 2001, assessing cost effectiveness analyses published following the previous review and up to the year 2000 (126). This comprehensive review, by Philippe Beutels of the University of Antwerp (funded by an unrestricted grant from vaccine manufacturers), assessed cost effectiveness of universal vaccination according to HBV prevalence in the population. In addition to the prevalence categories presented in figure 1.3, low prevalence countries were further divided into very low (population HBsAg prevalence <0.5% - Scandinavia, the United Kingdom, and Ireland) and low (HBsAg prevalence 0.5-2% - all other low prevalence countries, including Australia, North America, and most Western European countries) (126). This study found that the accuracy of models had improved since the publication of the earlier review, but that considerable improvements in transparency and comparability between models were still required. The review concluded that universal infant vaccination programs is justifiable on the basis of economic evaluation, and furthermore is cost saving to society (but not to the health care sector) in all HBV prevalence categories except the very low prevalence countries, where selective vaccination was favoured (provided coverage in risk groups was sufficiently high) (126). The results of this study were adapted into tabular form in a review article (7), a further modification of which is presented in table 1.9.

<table>
<thead>
<tr>
<th>HBV prevalence</th>
<th>Strategy advised based on economic analyses</th>
<th>Cost saving to society?</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Universal neonatal vaccination</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Universal neonatal, infant or adolescent vaccination (dependent on local economic, logistical and epidemiological conditions)</td>
<td>Yes</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>Selective vaccination (provided coverage in risk groups sufficiently high)</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

Table 1.9 – Advised vaccination strategies against HBV according to prevalence of chronic infection. Adapted from (7) being an adaptation of (126).
It would therefore appear that universal vaccination of infants in Australia is a cost effective intervention for society. However with greater than 25% of Australia’s population having been born overseas (28) and migration (predominantly from HBV endemic areas, see 5.4.3.2.3) projected to represent the same proportion of Australia’s natural increase over the next 40 years (127), reliance on universal vaccination of infants born here will not be sufficient. Lack of coverage in people born overseas is particularly problematic as susceptible migrants from high prevalence countries remain at high risk of HBV infection following settlement in a low-prevalence country (128-132), largely due to a higher likelihood of household or other contact with people living with chronic HBV infection (133). Universal infant vaccination will therefore not replace appropriately targeted selective vaccination strategies in Australia, and the coverage of selective vaccination will need to be improved from the levels presented in 1.4.2.2.1 for those most at risk.

A final point in favour of universal infant vaccination relates to increases in the prevalence of chronic HBV infection through migration, as has occurred in Australia, particularly over the last 60 years (chapter 4). In a theoretical population model of HBV transmission published in Nature Medicine in 2001 (113), the authors explored the positive feedback mechanism which defines HBV epidemiology – namely, that the higher the prevalence of chronic infection, the lower the average age at acquisition, with a correspondingly higher likelihood of progression to chronic infection, leading to higher numbers of people chronically infected in the population thus completing the feedback loop. This mechanism results in highly non-linear phenomena in HBV prevalence, and demonstrates ‘catastrophic behaviour’ – small changes in underlying conditions result in rapid and large shifts in endemicity between stable low and high HBV prevalence equilibrium conditions (113).

The theoretical model provides an explanation for the observed heterogeneity of HBV prevalence worldwide (figure 1.3), but also suggests that relatively minor changes to the prevalence of chronic HBV infection in a community (for example through migration) can result in dramatic and self-perpetuating shifts to a high prevalence equilibrium state. Thus a shift in community HBsAg prevalence from 0.2% to the threshold value of around 0.7% (holding all other factors constant) will result in transition to an HBV endemic state, with population HBsAg prevalence reaching 2% after 50 years and stabilising at around 5% prevalence of chronic HBV infection (113). Below this threshold, the low endemic state persists. Recent serosurvey data (12) and the results of the complex model of HBV infection
presented in chapter 6 suggest Australia reached this 0.7% HBsAg prevalence threshold around the year 2000.

For the catastrophic behaviour presented in the model to occur, a large proportion of the low endemicity population must be susceptible to HBV infection. As the authors note, removal of this potential through broad-based immunisation will be an effective safeguard against endemic transition (113). It is an interesting juxtaposition in the Australian context that at the very time that available data suggest that population prevalence of chronic HBV infection reached the threshold for transition to endemicity, universal vaccination programs for infants and adolescents were introduced.

1.4.3 Antiviral treatment as a means of preventing transmission

Vaccination cannot address the burden of HBV disease in individuals already chronically infected. The fact that these individuals are the source of the majority of incident infections (in low and high prevalence countries alike) (27, 113, 133-135) means that an adequate public health response to incident HBV infections must reduce opportunities for transmission from those chronically infected to those who are susceptible.

One way of doing this, vaccination of contacts and people at risk of being in contact with people who are chronically infected, has been presented, and more efforts must be taken in this regard as discussed in 1.4.2.2.1 and 1.4.2.4. In an American study of people diagnosed with chronic HBV infection, only 55% of doctors interviewed advised vaccination of contacts, and less than 20% of household and sexual contacts had actually commenced vaccination, despite being at high risk of infection (135).

The other approach is antiviral treatment of those chronically infected. This achieves the dual benefit of reducing complications and premature mortality, and also reducing infectiousness through suppression of viral replication (49). The armorial motto of the former Fairfield Infectious Diseases Hospital in Melbourne proclaimed *Unius cura salus omnium*, ‘The health of all through the care of one’. In this respect infectious diseases are unique in the fields of epidemiology and public health.
Encouraging appropriate treatment of chronic infections to avert further transmission is a paradigm that is well established in the responsibilities of health departments worldwide. For example, the imperative to promptly treat pulmonary tuberculosis in order to reduce the number of secondary (and further) cases is well recognised and prioritised by communicable disease divisions. Another example is the assistance provided to people living with HIV/AIDS and their health care providers to encourage engagement with treatment services. One of the reasons for this is that treatment with highly active antiretroviral therapy (HAART) is able to reduce viral replication to undetectable levels in most patients.

A number of mathematical models of HIV transmission (set in both high income, low prevalence and low income, high prevalence populations) have estimated that the epidemic could contract markedly (136, 137) or even be eliminated (138) through widespread use of HAART. The reduction in infectivity that can be achieved through effective treatment is such that it led to the recent controversial statement by the Swiss National AIDS Commission that a patient receiving HAART with undetectable replication cannot transmit HIV through unprotected sexual contact (139), a finding which has been challenged by the WHO and UNAIDS, amongst others.

For these reasons, following notification of either pulmonary tuberculosis of HIV infection, public health authorities take a leading role, to the extent of contact tracing, making appointments with health care providers, through to case management where required. Such is not the case for chronic HBV infection (49), although the CDC has recently recommended that such approaches be implemented (27).

The natural history of chronic HBV infection will result in a large pool of infectious individuals remaining decades after the implementation of universal vaccination, even were no further migration from endemic regions to add to this reservoir. It has been recognised since long before effective treatment for chronic HBV infection was available that therapy able to reduce or eliminate the infectiousness of those chronically infected would greatly enhance the prospects for a rapid reduction in the prevalence of HBV in the population (98, 113, 140).

Whereas numerous mathematical models of HBV treatment exist (predominantly for the purpose of assessing cost effectiveness) (133, 141-143), none assess the role of treatment in
the reduction of infectiousness and therefore transmission of HBV in either low or high prevalence populations. Even in a cost effectiveness study published in 2007 addressing screening, treatment and ring vaccination of contacts of people with chronic infection, no account was taken of the impact of treatment on reducing secondary infections, unlike the approach adopted with vaccination (133).

The one mathematical model of HBV transmission that addresses the question of the impact of treatment on population prevalence is the catastrophic dynamics model of Medley and colleagues (113) discussed in 1.4.2.4. The authors suggest that reduction of the impact of those chronically infected through effective treatment could result in rapid control of the incidence of new infections because of the non-linear effect of such an intervention - reducing the force of infection in the population increases average age at infection, resulting in less probability of progression to chronicity, further reducing the force of infection.

Thus by interrupting the positive feedback mechanism which defines HBV epidemiology, treatment of those with chronic infection is suggested to be a very valuable tool in the public health response to HBV, one that could make local elimination and, with time, global eradication of HBV a viable goal – in a far shorter time scale than by relying on vaccination alone (113). The viability will ultimately be determined by the ability of high prevalence countries of Asia and Africa to access highly effective treatments, with affordability being a critical factor.

Finally, there are data supportive of the prevention of HBV transmission with antiviral treatment. Standard treatment with vaccine and HBIG (see 1.4.2.1 and table 1.8) of infants born to women with highly replicative HBV infection (HBeAg positive with a plasma HBV DNA viral load above 100 million copies/mL – immune tolerance, see 2.5.2.1) is less effective than is usually the case (144, 145). Previous studies have indicated that maternal treatment with lamivudine could further reduce the chance of transmission (146-149). A randomised controlled trial conducted in China supported this hypothesis (150), although significant loss to follow up in the placebo arm complicated analysis (80). Despite this fact, and in the light of previous evidence, the principle of using antiviral treatment as a means of preventing transmission of HBV has been demonstrated in this context.
1.5 Conclusion

The global epidemiology of HBV infection is complex, with heterogeneous patterns of incident and prevalent infection in different populations. This complexity arises through the self-sustaining patterns of low and high prevalence in different regions, and is further enhanced by the large migrant movements of the last century, particularly from high to low HBV prevalence countries. This is particularly the case for Australia, with changing patterns of migration over a relatively short period (chapter 4). Furthermore, the total migrant component of the Australian population is large, with high HBV prevalence areas predominant in migrant intake over the last two decades. In addition, the only Australians not to have migrated recently are also a high HBV prevalence population, with a burden of resultant mortality akin to that of high prevalence developing countries (17).

Despite the increasing burden of chronic HBV infection in Australia, the public health response has so far revolved around universal infant vaccination. This strategy cannot address the large majority of chronic HBV infections in Australia that were acquired overseas prior to migration. Expansion of selective vaccination to include those at highest risk is who remain susceptible is still required. Opportunistic screening of those at risk of chronic infection such as migrants from endemic areas and Indigenous people, and improving access to treatment for these groups, are critical elements of an adequate public health response to HBV that are yet to be addressed.
2 Hepatitis B virology and natural history

2.1 HBV structure, replication strategy and life cycle

Five years after the discovery of HBsAg by Blumberg and associates (68, 69), Dane described both complete HBV virions and subviral HBsAg particles in the serum of patients infected with HBV (151, 152). Although research into natural history and epidemiology of HBV infection proceeded rapidly (69), early virological research was hampered by the narrow host range of HBV (humans and primates), and the lack of an efficient tissue culture system (152, 153). It was with the advent of molecular virology that much deeper investigation became possible. HBV was molecularly cloned from the serum of patients in 1979 and the complete DNA sequence determined (154), leading to an explosion of research into the molecular biology of HBV, the fruits of which include the safe and highly effective recombinant HBsAg-based vaccine which became available in the mid 1980s (92).

HBV was the first member to be discovered of a new family of viruses, now designated Hepadnaviridae (for hepatotropic DNA viruses) (154). It is the smallest human DNA virus discovered, with a genome of approximately 3200 base pairs (155, 156) in a partially double-stranded relaxed circular DNA structure (152). This genome is covalently bound to the viral DNA polymerase and contained within an icosahedral nucleocapsid (155) which itself is contained within a viral envelope consisting of virally encoded HBsAg proteins of different sizes, and host-derived lipid components (157).

The compact genome comprises four partially overlapping open reading frames (ORFs) with no non-coding regions in the genome – all regulatory signals also encode protein sequences (152). The four ORFs encode the polymerase protein (Pol gene), HBcAg and HBeAg (C gene), the large, major and small HBsAg proteins (S gene) and the HBx protein (X gene) (158). The Pol gene covers some 80% of the viral genome and overlaps the S gene (159). A schematic of the HBV genome and its products is reproduced in figure 2.1.

The replication strategy of the Hepadnaviridae is unique among animal DNA viruses in that an RNA intermediate is used via a reverse transcription step (152). Outside Hepadnaviridae, this strategy is used only by the cauliflower mosaic virus.
Figure 2.1 – A schematic representation of the HBV genome, with corresponding transcripts and translated protein products. Taken from (154).

Following binding of the HBV envelope to an as yet unidentified cellular receptor (154, 160) and transport into the cytoplasm of the hepatocyte, the viral nucleocapsids are transported to the cell nucleus where they are uncoated (160). Once introduced into the host nucleus, the relaxed circular double-stranded DNA is transformed into a covalently closed circular DNA (cccDNA) template (viral mini-chromosome) from which four major RNA transcripts are generated (155, 160) under the influence of respective promoters regulating the expression of these transcripts, being the basal core promoter (BCP or Cp), the large surface antigen (Pre-S1 or S1p) promoter, the major surface antigen (S or S2p) promoter, and the X gene promoter (Xp) (154, 160). These transcripts are 3.5-, 2.4-, 2.1- and 0.7-kb in length, respectively.

The cccDNA template is a very stable, long-lived molecule which appears not to be directly affected by antiviral therapy (161), although impaired replenishment of cccDNA through inhibition of intracellular recycling may lead to reduced numbers of infected hepatocytes over...
time. Reactivation of replication from cccDNA is thought to be the primary vehicle of recurrence of active hepatitis in patients who have stopped antiviral therapy or who have become immunocompromised (153).

The RNA transcripts are translated to produce the viral proteins, with HBcAg (nucleocapsid protein) and its secreted form HBeAg, and the polymerase all deriving from the two forms of 3.5kb RNA, the envelope proteins (HBsAg) from the 2.4- and 2.1-kb RNA, and the HBx protein (a transcriptional activator of many promoters with numerous and incompletely defined actions on the host cell) from the 0.7-kb RNA. The 3.5kb, greater than genomic length RNA (termed pregenomic or pgRNA) also provides the template for reverse transcription of the HBV genome (154, 160, 162).

HBV genome replication commences with the packaging of the pregenomic RNA template with the polymerase/reverse transcriptase molecule bound to its own pgRNA transcript into subviral particles. Within the nucleocapsid core reverse transcription then occurs (154, 160) commencing with generation of the (-) strand DNA followed by the (+) strand, the synthesis of which is halted prior to completion leading to the characteristic partially double-stranded DNA structure of HBV virions.

The now matured core particles are then either

i. enveloped by budding into the endoplasmic reticulum, where the surface antigen encoding mRNAs have been translated (154), and released from the cell by exocytosis; or

ii. recycled to the nucleus in a process of auto-infection to reform cccDNA and initiate another cycle of replication (154).

In stably infected hepatocytes, the nucleus may contain between 30 – 50 cccDNA molecules (153). In addition to these viral mini-chromosomes, the viral DNA can become integrated into the host genome through recombination events; this process may have a causative role in the development of HCC (153, 163). A diagrammatic representation of the HBV life cycle is presented in figure 2.2.
Figure 2.2 – A diagrammatic representation of the life cycle of HBV from attachment through formation of cccDNA, transcription, translation, creation of new HBV virions, and ultimately exocytosis or return to the nucleus to reform cccDNA (ICP, intracellular conversion pathway). Taken from (164).

2.2 Genotypes

2.2.1 Geographic distribution of HBV genotypes, phylogenetic analysis, co-infection and recombination

From the early 1970s genetic variability in HBV was recognised and described by means of antigenically defined subtype determinants, subsequently found to specified by different amino acids at specific positions in the S protein, together with the main antigenic determinant \( a \) (152, 159). In 1988 Okamoto (165) and colleagues compared 18 different HBV genome sequences and found they could be classified into four groups (A through D) based on an inter-group divergence in nucleotide sequence of 8% or greater, which has subsequently become the degree of differentiation used to define HBV genotypes (158-160, 166). The former serologically determined subtypes of HBV failed to discriminate between the sequenced genotypes, indicating that the antigen-based subtypes of envelope polypeptide did not reflect true genotypic variation of HBV (165).
Since the Okamoto study four further genotypes have been defined, for a total of eight HBV genotypes designated A through H. Multiple subgenotypes (with between 4 and 8% intergroup nucleotide difference) have also been described (159, 166). As was observed using subtype classification (152) notable geographic clustering of HBV genotypes has been well described and continues to evolve (table 2.1) (152, 159, 167, 168). The distribution of these genotypes through the human population worldwide has led to much speculation as to the length of time HBV has been co-evolving with humans (161, 169), and illuminates patterns of human migration and contacts between peoples dating from remote human pre-history (155, 159, 166, 168).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Distribution and notes</th>
</tr>
</thead>
</table>
| A        | Northern and Western Europe  
           North America  
           Central and South Africa  
           Hong Kong, Philippines, South and East Africa |
| B        | China, Taiwan, South East Asia and Japan |
| C        | China, Korea, South East Asia, Japan, Taiwan  
           Pacific islands  
           Indigenous Australians |
| D        | Widest distribution  
           Highest prevalence in belt from Mediterranean littoral to India  
           West and South Africa  
           Asia Pacific  
           Indigenous Australians |
| E        | Sub-Saharan Africa and Madagascar  
           Probable ancient human HBV progenitor genotype (161) |
| F        | Indigenous populations of Central and South America and Alaska  
           Most divergent genotype: ‘original genotype of the New World’ (152)  
           Also isolated in Polynesia – support for Kon-tiki hypothesis? (159, 168) |
| G        | To date only isolated in Western Europe and North America. |
| H        | American Indians in central America, also in Mexico and California  
           Phylogenetic offshoot of genotype F |

Table 2.1 – Worldwide distribution of HBV genotypes. References: (14, 20, 151, 154, 155, 158, 160, 165, 167, 169-172)
A picture of various genotypic regions of the world is apparent (figure 2.3). However HBV genotypic information also reflects contacts between peoples harbouring distinct genotypes. Genotype A strains have been recovered from Asian and African populations with significant contact with Europeans and North Americans such as Hong Kong and the Philippines (20, 152). Indeed in countries with waves of immigration overtime, genotypes are reflective of these movements – such as in South Africa, where genotype A has been introduced from Britain and the Netherlands, and D from Southern Europe and India (152), and the USA, where a large cross-sectional survey showed a strong statistical correlation between ethnicity and HBV genotype (170). HBV genotype A was prevalent among white and black patients whereas genotypes B and C were most common in Asian patients. The predominant genotype among patients born in the USA, Europe, the Far East and South East Asia were A, D, C and B respectively. There is evidence that with continuing migration from Asia to North America, and given the high prevalence of chronic HBV infection in this population, that genotype C is becoming the most common genotype of chronic HBV infections in North America overall (171).

Another clear example of successive waves of migrants contributing to HBV genotypic diversity in an immigrant nation is Australia, where genotypes A through D are present in the general population with contribution of genotype A from Britain and Northern Europe, followed by migration from Southern Europe and more recently the Middle East and the Indian subcontinent bringing genotype D, and significant migration from East and South-East Asia and the Pacific contributing genotypes B and C (14, 20, 152). Reflecting the epidemiological differences between acute and chronic HBV infections in Australia and other low prevalence countries discussed in chapter 1, based on limited available data acute HBV infection in this country is disproportionately caused by genotypes D and A, whereas genotypes B and C are responsible for most chronic HBV infections currently, indicating childhood acquisition in Asia with subsequent migration (1.3.2.2.1) (11, 14, 20, 166, 172).

This contrasting genotypic predominance in acute and chronic infections was illustrated by two recent studies from Melbourne. Bell and associates at St Vincent’s Hospital in Melbourne reported in 2005 on a large cohort of patients chronically infected with HBV (14). Of the 703 patients, 82% were born overseas, 65% in Asia and 14% from the Mediterranean littoral. In a subset of 103 patients whose viral genomes were sequenced, the proportions
Figure 2.3 – Global distribution of HBV genotypes. Numbers indicated the number of isolates genotyped in each country. The size of the pie charts is for visual clarity only. Taken from (166).

were 8% genotype A, 29% B, 41% C and 22% D. In contrast, unpublished data from the Victorian Infectious Diseases Reference Laboratory (172) shows of 43 acute HBV notifications to the Victorian Department of Human Services in the 6 months to March 2003, the 34 with HBV DNA isolated and able to be sequenced had a different genotypic breakdown; 21.2% genotype A, 21.2% B, 12.1% C and 47% D.

The situation is different in the Indigenous Australian population where chronic infection with genotypes C and D predominate (20, 166, 173). Despite the fact that Indigenous Australians were among the first people in whom HBsAg was isolated (68, 69) it was not until 2001 that a Japanese/Australian collaboration first sequenced the complete HBV genome from Indigenous people, namely five patients with chronic HBV from various areas of Queensland (173). Three of the HBV strains were identified as genotype D, most closely related phylogenetically to isolates from PNG, according to the authors supporting the theory of human migration from South East Asia to the then conjoined Australian/Papua landmass.
with a common ancestral human population bearing a common ancestral HBV strain. The other 2 isolates were classified as a novel, divergent subgenotype of genotype C, most closely resembling New Caledonian and Polynesian strains, raising the possibility of prehistoric contact between Indigenous Australian and Polynesian populations (173).

Phylogenetic analysis of HBV strains worldwide has been applied to the question of human migration by many groups in the last two decades. The popular view supported by comparative analysis of human and simian HBV strains, is that the virus first infected humans in the Old World. The high prevalence in Amazon Indians, and the large degree of divergence of the Indigenous American HBV genotypes, suggests that it is a virus that has long been associated with humanity (161). Viral features that may have helped sustain HBV in the human population so long include the modes of transmission, high communicability, and long asymptomatic infectious period (161). Another factor underlying the widespread endemicity of HBV infection is that, with a median age of attributable mortality well beyond the life expectancy of humans for virtually our entire history on an evolutionary timescale, HBV infection would have exerted minimal selection pressure on prehistoric humans.

Analysis of human and simian HBV strains reveals 3 branches; one for Old World primates, a second for the ‘Old World’ human HBV genotypes A-E and G, and a third to the most divergent, ‘New World’ human HBV genotypes F and H and the New World Woolly Monkey HBV (152, 159, 166) (figure 2.4). The fact that human genotypes A-E and G are phylogenetically closer to old world simian HBV strains than to human genotypes F and H has been taken to suggest that a single HBV transmission event of a common ancestor of genotype A-E and simian HBV occurred in the Old World after separation of the branch that led to genotypes F and H and WMHBV (152, 166). These theories are controversial and the subject of ongoing debate.

A further degree of complexity in HBV genetics arises from the issues of co-infection with different genotypes and subsequent recombination events. Mixed genotype infections and recombinations of HBV genotypes are not rare clinically (156). Co-infection with different genotypes, presumably through the simultaneous transmission of several genotypes or sequential infections with different genotypes (152), has been reported in children and adults in regions where several genotypes circulate, and such co-infections have been detected in up to 5% of serum samples in large studies (166).
With increasing co-infection comes increasing potential for recombination events. The time at which recombination occurs in HBV replication is unknown (166). Recalling the replication strategy of HBV, with a single pgRNA molecule contained within a nucleocapsid core being transcribed into a single partially dsDNA genome, the probability of template shift would seem to be very low (152, 166). It is more likely the recombination occurs in the nucleus where genomic segments can be exchanged between cccDNA molecules from different co-infecting genotypes (166).

Genomic recombination can lead to large evolutionary jumps and may provide a mechanism of variation within the individual infected patient and within a population between different
genotypes that co-circulate in the same area. A/D recombinants are found in Africa and India, and B/C recombinants in Asia. In Tibet, with a very high prevalence of chronic HBV, a recombinant genotype C/D strain is common (152, 159, 166).

Two major B subgenotypes as described by Norder et al (159), B1 (Bj - Japan) and B2 (Ba - Asia) circulate in different parts of East Asia along with genotype C. B2 is now thought to be a recombination of genotypes B and C (174). It has been proposed that some differences in HCC incidence between Japanese and Taiwanese patients with genotype B infections is related to this recombination (156, 175). This is discussed further in the next section which explores clinical correlates of infection with different HBV genotypes.

2.2.2 Clinical significance of HBV genotypes

Besides the insight given into the evolutionary history of HBV and the molecular epidemiology of HBV infection worldwide, evidence continues to emerge that the particular genotype and even subgenotype of HBV infecting an individual may have an impact on the natural history of their infection (152, 155, 156, 159, 167, 170, 174, 176, 177) and on the response of the infection to antiviral treatment (152, 155, 156, 167, 174, 176, 178).

Much of the information on the clinical significance of HBV genotypes has been based on studies of patients with chronic HBV infection in Asia, and is therefore restricted by and large to comparisons between genotype B and C infections (167, 176). Conversely when studies in Europe and North America are undertaken the comparison is often made between genotypes A and D. This makes comparisons of outcomes of infection across the range of HBV genotypes difficult.

Although the number of studies exploring this question is large, and many of the findings somewhat controversial as discordant results are sometimes found in any given population, a summary of their findings is presented below.

Natural history of infection

- Consensus built from a number of studies suggests that infection with genotypes C and D is associated with a higher HBeAg + rate, more active liver disease, faster progression to cirrhosis and HCC than is infection with genotypes A and B (152, 155, 156, 159, 167, 170, 174, 176). Longitudinal studies in Asia have also shown that
patients with genotype B infection show spontaneous HBeAg seroconversion earlier and more commonly, are less likely to experience hepatitis flares, and more likely to remain in remission following HBeAg seroconversion than patients with genotype C infection (167, 174, 176).

- Most investigations of the incidence of HCC by genotype suggest genotype C infections are more frequently associated with development of HCC, and with disease onset at a younger age, than are infections with genotype B (152, 167, 174).

- However, one study from Taiwan (175) showed that genotype B was more common in young patients with HCC, in contrast to research from Japan. All of these genotype B infections belonged to subgenotype B2 (Ba) (167), the recombinant B/C strain which is different from the B1 subgenotype in Japan (Bj) (159) leading to suggestions that this is the reason for the discrepant results (156, 176).

- In a Spanish study (179) of 258 patients, HBeAg seroconversion rates were similar in genotype A and D infections, but sustained remission was more common in genotype A, as was HBsAg clearance. The outcomes of death and need for transplantation were comparable. Genotype F was associated with significantly higher mortality than genotypes A and D but the number of genotype F infections was small (19).

- With respect to outcome of acute infection, studies in Japan (180) and Switzerland (181) have shown significant differences in the HBV genotype amongst acute infections and those chronically infected (disproportionately high B vs. C and D vs. A genotypes in acute infection, respectively). Whereas it is possible that this reflects a difference in progression to chronic infection (155, 159, 176), an alternate interpretation is that a shift in predominant HBV genotype has occurred with time due to immigration or mode of transmission and therefore age at acquisition (152, 167), as is the case in Australia (11, 14, 20, 166, 172).

- Norder and associates (159) speculated on the genotypic differences in mode of acquisition of HBV infection. In endemic countries, either vertical (China, South East Asia, Pacific – genotypes B and C) or early horizontal transmission (Africa – genotypes A, D and E) predominates. They considered that the difference may lie in the longer HBeAg + replicative phase in genotype B and C infections (174) leads to a higher proportion of viraemic pregnant women, versus the possibly higher viral load in A, D and perhaps E infections (176) contributing to horizontal spread between children.
Treatment outcomes

- Genotype C is more resistant to treatment with standard interferon than genotype B and genotype D appears more resistant than genotype A (152, 155, 156, 167, 174, 176, 178).
- A recent multinational trial of 266 patients treated with pegylated interferon with or without lamivudine revealed significant differences in treatment outcome by genotype (178, 182). HBeAg loss occurred in 47% of genotype A infections, 44% of B, 28% of C and 25% of genotype D infections (p=0.01). HBV genotype was an independent predictor of response on multivariate analysis. HBsAg seroconversion occurred significantly more often in genotype A (13%) compared with D (2%).
- A similar discrepancy in outcomes between genotype B and C infections was seen in a trial of another pegylated IFN preparation with a 6 month treatment duration (183), but this difference was not significant when treatment was given for 12 months (184) which is the current treatment duration recommendation in Australia (30).
- No correlation between genotype and response to nucleoside/nucleotide analogue therapy has been demonstrated (171, 176). There are few studies addressing this issue, with most examining lamivudine having small sample sizes and significant heterogeneity in treatment protocols (155). Some studies have shown a greater likelihood of sustained response following treatment cessation in genotype B but in other studies this has not been observed (167).
- Zollner and colleagues reported lamivudine resistant mutants emerge more rapidly in genotype A than D in a small group of 26 German patients (159, 167, 185) but the difference disappears after a year of therapy (156, 176) and the effect of differential concordance cannot be discounted with such a small sample.
- A recent study evaluated the influence of HBV genotype on response to entecavir (186) with no difference noted.

In many of these studies there is a potentially large impact of confounding factors which may be associated both with the infecting genotype and the clinical outcome of HBV infection and create the appearance of an association where none exists. Examples include the geographic area, ethnicity, access to treatment, age at infection, mode of acquisition, stage of disease at presentation or study inclusion, alcohol and aflatoxin exposure, treatment concordance, and
so on (152, 167). This is especially true of cross-sectional studies where no assessment of temporal relationship and causality can be made.

However there is growing evidence that HBV genotype can influence disease outcomes and response to therapy, at least as far as interferon is concerned. Further research is needed to confirm these observations to determine if HBV genotyping should be included in the evaluation of patients with chronic HBV infection with treatment tailored accordingly, as is currently the case with other chronic viral infections such as HCV and HIV (174).

The ideal study of the influence of genotype on clinical outcome would involve a prospective cohort study of an otherwise balanced cohort of children infected early in life with different HBV genotypes with long-term follow up to assess their progress (152, 155, 176). Such a study does not seem likely ever to occur.

### 2.3 Mutations of clinical relevance

The interplay between different unique aspects of HBV replication discussed earlier determines the frequency of viral mutations. Reverse transcriptase, with the lack of any proofreading function, introduces mutations at a relatively high rate (155, 158, 162). However the multiple gene overlaps occurring in the laconic genome mean that a mutation in any given gene potentially incurs corresponding mutation in another. This can have functional consequences for both genes, which acts to reduce the development of genetic variability (152, 153, 158, 159). The presence of distinct genotypes notwithstanding, the HBV genome is not highly variable despite distributions in human populations worldwide, exemplified by maximal divergences of approximately 15% identified in the S gene (161).

The result of these countervailing influences is an average mutation (nucleotide substitution) rate for HBV estimated at between $1.4 - 4.2 \times 10^{-5}$ substitutions per site per year, higher than that of other DNA viruses but slightly lower than retroviruses and significantly lower than RNA viruses (152, 155, 156, 161, 166, 169, 174). However, with the high viral loads achieved during chronic infection (millions or billions of copies of virus in every millilitre of blood during immune tolerance, see 2.5.2.1), and the persistent infection often lasting decades, many HBV variants (quasi-species) may co-exist in a host at any given time with multiple mutations (155, 166, 174). It has been estimated that up to $10^{10}$ transcription errors
occur in a patient’s virus particles per day (153) and with a minimum viral turnover estimated at $10^{11}$ virions per day, it is possible that every possible mutation occurs at every position in the HBV genome in a patient every day (158, 161).

Some of these mutations may be selected for by pressures within the host environment, such as immune responses and antiviral therapy, and thus persist and offer the virus a survival advantage (155, 158, 162, 166). Indeed it would appear that given the mutational rate described, prior to any antiviral exposure, a population of HBV variants exists within a patient that already harbour drug resistance mutations (161). Analogous to the situation discovered with HIV, effective treatment of chronic HBV infection may require combination therapy to permit activity of at least one of the component antiviral agents against random mutant strains resistant to another of the components of the combination (161).

Two of the best characterised mutations of clinical relevance are those associated with HBeAg negative chronic HBV infection, namely the precore and basal core promoter mutations, which are selected in response to host immune pressure.

The precore mutation at nucleotide position 1896 results in the generation of a translational stop codon in the precore gene. The molecular confirmation of the HBV DNA at this point is a highly conserved stem loop structure (epsilon, $\epsilon$) which is critical for reverse transcription and encapsidation (152, 160-162). In this stem, the G1896 base pairs with the nucleotide at position 1858. In genotypes A and F this nucleotide is a C, but in genotypes B, D, E, G and some C a T is situated at 1858 (152, 155, 160-162). Thus in the latter the G1896A is selected for because it stabilizes the $\epsilon$ stem/loop, thereby generating a stop codon and blocking production of precore protein (HBeAg) potentially leading to chronic HBeAg-negative hepatitis. Conversely in genotype A and F infections, G1896A is not selected for because there is already a stable G-C pairing existent, resulting in well described genotypic differences in the frequency of precore and CP mutations (160-162, 167, 174, 176, 177).

The function of HBeAg is incompletely understood. HBeAg has been shown to have a role as an immune toleragen, or as a target of immune response, in chronically infected hosts but it also slows HBV replication through an inhibition of pgRNA encapsidation (160, 174, 176).
Thus the G1896A mediated abolition of HBeAg production is thought to enhance replication in addition to evading immune clearance (160, 174, 176).

The basal core promoter group of mutations most commonly occur at nucleotide positions 1762 and 1764. These mutations result in a reduction in precore and core mRNA transcription (162) and can be found in isolation, or in conjunction with precore mutations, largely dependent on the HBV genotype (162), but in general they are more often observed in genotype A infections which are constrained from developing the precore mutation in response to immune pressure by the C at nucleotide 1858. Mutations such as A1762T plus G1764A results in a decrease in (but not absence of) HBeAg generation and, with the removal of the inhibitory effect on replication of this protein, an increase in viral load (155, 160).

Whereas some studies have suggested that precore and basal core promoter mutations are associated with fulminant hepatitis, more severe liver disease, and HCC, these variants have also been detected in inactive carriers and patients with mild disease (20, 152, 155, 157, 174, 187). More recent information, including from the large cross-sectional survey of 694 patients in the USA discussed elsewhere, show a correlation between BCP mutants and cirrhosis and hepatic decompensation (156, 174, 176, 177) and HCC (156, 188).

Another point of clinical relevance is that patients infected with precore and/or BCP mutants may respond less well to conventional interferon than patients with wild-type HBV (155, 161, 174, 187), perhaps related to the difference in available immunodominant epitopes, the host immune response, and the immunomodulatory mode of action of interferon. Given the association of these mutations with particular HBV genotypes (167, 174, 177), determining whether these mutations mediate this difference in treatment effect or are confounders of the genotype/treatment outcome association is not certain.

A critical site for immune pressure induced mutation is the S gene, encoding the HBsAg proteins which induce the major immune response providing protective immunity (162, 174) and which are expressed in hepatitis B vaccine. The ‘a’ determinant of the exposed hydrophilic region of HBsAg from residues 99-200 is the immunodominant epitope (158), and mutations in this region have been observed following vaccination and also passive immunisation with HBIG (20, 158-160, 162, 166, 174, 189). The best described mutation is
sG145R which has been associated with vaccine failure (158, 160, 162, 174) although a wide range of others have been described. Mutations in the ‘a’ determinant of HBsAg, in addition to conferring immune escape, may lead to difficulty of detection of infection by conventional EIA-based diagnostic tests (158, 189) which methodologically rely on HBsAg – anti-HBs interaction.

Another question regarding vaccine escape is whether there is a difference in incidence of vaccine escape between genotypes. There are some studies which suggest serotypes may influence vaccine efficacy (176), and Norder and associates question whether current genotype A derived vaccines are optimal in areas with divergent prevailing genotypes such as genotype E in West Africa, where vaccine failure is more common (159).

A different selection pressure acting on HBV is the use of antiviral medications such as nucleoside and nucleotide analogues, which select for mutations in the target HBV Pol (162, 174). The prototypic example is the YMDD mutation induced by lamivudine therapy which develops over a few years in the majority of patients undergoing treatment (159, 160, 162) and which confers a major reduction in sensitivity to the drug. Adefovir resistance occurs less frequently, and is mediated by different mutations at nucleotide positions 181, 214-15 and 236-238 (160, 162, 174). Resistance to entecavir appears to be even less common and most, but not all causative mutations have been associated with prior lamivudine resistance (160, 174). Examples are Pol mutations such as rtS184G, rtS202I and rtM250V (162). A further concern given the overlapping nature of the S and Pol sequences is the selection through antiviral pressure of possible vaccine escape mutants that, furthermore, may be difficult to detect by conventional serologic means (158, 189).

Although antiviral resistant mutant strains of HBV may lack replicative fitness, other mutations can compensate for this deficit (174). An example is the precore G1896A mutation which can compensate for deficient replication in lamivudine resistant strains (162). Other compensatory mutations in the Pol gene can also reduce HBsAg reactivity in diagnostic tests (158).

The consequences of mutations in the X gene, like the function of the HBx product itself, are poorly understood (160). Mutations in this region have been reported to be associated with
the development of HCC although this is not certain (160, 174). An association between X gene mutations and fulminant hepatitis has also been suggested (152).

### 2.4 Use of sequencing for transmission analysis

In 2.2 phylogenetic analysis of the HBV genome was discussed in relation to investigating the co-evolution of HBV with humans over millennia. However molecular characterisation of HBV genomic relatedness over much shorter time frames has been used successfully to investigate and confirm routes of transmission or sources of suspected outbreaks in a number of settings (20, 166). These have included examples as diverse as infections in patients traced to a contaminated bone marrow storage tank (190), to a large number of mysterious silent HBV infections in a Japanese gridiron team (191). In the nosocomial setting numerous examples include numerous haemodialysis centre outbreaks (see 1.4.1), cardiac transplant recipients, and the fatal infection of two Japanese paediatricians by an infected infant (152).

Often, the S gene or pre-S plus S genes are used rather than analysing the entire genome as S gene differences have been demonstrated in most circumstances to successfully differentiate between genotypes and subgenotypes of HBV (152, 159, 166). However, there is increasing evidence that the S gene is too highly conserved to accurately define recent transmission patterns (20, 192, 193), leading to suggestions that more variable regions (or full genomic analysis) should be used for this purpose (194-196) (see appendix 3, A3.1 and A3.2).

In an Australian study of migrant families who had recently settled in New South Wales, separate sequencing of PCR products of both the S and distal-X precore regions of 58 DNA positive serum samples was performed (20). When relatedness between the strains was assessed by sequence comparison, clear separation of strains from different countries was observed, with tighter clustering of strains from families within these groups. Almost identical grouping of strains was observed by separate analysis of the S gene and distal-X precore regions, although it was found that the hypervariable distal-X region provided better discrimination between family groups and may be a particularly useful tool for tracing transmission.

The epidemiological power of these techniques can be profound. In the Australian study, when divergent strains within a family were detected, the authors suggested that further
information obtained from participants indicated that the infection was likely to have derived from separate sources (20). The study also detected 15 non-synonymous mutations in the distal-X precore region including 2 precore mutants, and 5 non-synonymous mutations in the S-gene, including a ‘classical’ Thr/Ala 126 vaccine escape mutant in a 14 year old boy vaccinated 6 months previously without serology having been performed.

In the setting of an apparent outbreak of acute HBV in Victoria in 2001-2002 (62), phylogenetic analysis of viral isolates from the 34 patients who were viraemic out of 43 notified acute HBV infections between September 2002 and March 2003 was undertaken at the Victorian Infectious Diseases Reference Laboratory (172) (unpublished data). Sequencing of the Pol gene identified several mutations in the acute HBV infections including 7 ‘a’ determinant mutations that have been associated with vaccine escape, and most interestingly, transmission of lamivudine resistance mutations rtM204V and rtL180M to a naïve patient.

Phylogenetic analysis of the Pol sequences was also undertaken, with 5 potential clusters of patients identified in this fashion. However when the sequences in these clusters were compared with control samples from chronically HBV infected patients, corresponding sequences were identified. The investigators felt that these were therefore common isolates with no evidence of transmission from a single source.

An alternative hypothesis is that the region sequenced, having significant S gene overlap, is too highly conserved to allow appropriate discrimination between related isolates as discussed above (see Appendix 3, A3.1 and A3.2). Sequencing of more variable genetic regions of the viral isolates for phylogenetic analysis would allow this hypothesis to be tested (research which is soon to commence). A similar, larger study from the Netherlands recently added support for this alternative interpretation, with the S region statistically significantly less variable than the C region on sequence analysis of 131 acute HBV isolates (194).

2.5 Clinical virology

2.5.1 HBV serology

Since the initial discovery of HBV by serological means over forty years ago (68) this methodology has remained the cornerstone of diagnosis of HBV infection and assessment of immunity through either vaccination or natural infection. However the pattern of serologic
parameters required for assessment of HBV status is considered complex by many clinicians (26, 30) and misinterpretation is common (26).

A systematic approach to the interpretation of HBV serology is therefore important. The pattern of HBV serologic results and their typical interpretation derived from publications from the CDC (29) appears in table 2.2.

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>anti-HBc</th>
<th>anti-HBs</th>
<th>susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>negative</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>positive</td>
<td>resolved HBV infection</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>negative</td>
<td>vaccinated</td>
</tr>
<tr>
<td>HBsAg</td>
<td>anti-HBc</td>
<td>IgM anti-HBc *</td>
<td>acute HBV infection *</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>positive</td>
<td>positive (↑ titre)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>anti-HBc</td>
<td>IgM anti-HBc *</td>
<td>chronic HBV infection *</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>positive</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>anti-HBc</td>
<td>anti-HBs</td>
<td>various possibilities</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>negative</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.2** – Typical interpretations of patterns of HBV serology results. Possibilities for the last row (isolated anti-HBc positivity) include distant past infection with anti-HBs titre having fallen below the assay detection limit, recovery from recent acute HBV infection, a false positive result, and ‘occult’ HBV – chronic infection in the absence of detectable HBsAg. *anti-HBc IgM can sometimes be detected at a low titre in patients experiencing a flare of chronic HBV infection. Adapted from (29).
2.5.2 Natural history of HBV infection

2.5.2.1 Phases of infection

A graphical representation of the phases of HBV infection that a person infected in childhood passes through are depicted in figure 2.5, which also shows the typical serum HBV DNA and alanine aminotransferase (ALT) levels and HBeAg/anti-HBe results associated with each phase. An elevated ALT is indicative of necroinflammatory activity in the liver, whereas high HBV DNA levels and HBeAg positivity reflect high levels of HBV replication.

The interplay between viral replication and host immune response varies across the phases of HBV infection and determines the level of ongoing liver damage and the likelihood of developing cirrhosis and/or HCC. Minimal hepatocyte necroinflammatory activity occurs during the immune tolerance phase as the mediator of this injury, the host immune response, is not invoked during this phase which on average lasts until the fourth decade of life for those infected at birth (197). Similarly, little ongoing damage occurs during immune control, HBV replication is suppressed to low levels resulting in minimal infection of naive hepatocytes and corresponding negligible immune mediated hepatocyte destruction.

Figure 2.5 – Phases of HBV infection with typically associated HBV DNA and ALT levels and HBeAg/anti-HBe status.
Patients in these two phases of HBV infection were previously described as ‘healthy carriers’ due to the lack of evidence of progressive liver damage. However increasing recognition of the role of transition between these phases with corresponding liver damage, and of the independent role of high levels of viral replication on disease outcome (198), has led to strong arguments against the concept of the healthy carrier (199).

In contrast, people living with chronic HBV infection in either the immune clearance or immune escape phases experience ongoing immune-mediated destruction of infected hepatocytes. If this necroinflammatory activity is not suppressed by either effective immune control or the use of anti-HBV therapy (2.5.2.3), fibrotic changes in the liver progress with increasing likelihood of developing cirrhosis and HCC over time (32).

2.5.2.2 Morbidity and mortality

Due to the variable degree of liver damage dependent on phase of infection, the greatest burden of morbidity and mortality occurs in patients who have had ongoing necroinflammatory activity for many years, with resultant cirrhosis. This is why the incidence of liver-related mortality in people with chronic HBV reported in the large NSW linkage study increased exponentially after the age of 40 years (13).

Annual incidence of progression to cirrhosis varies from 2-5% in HBeAg positive patients, and 8-10% in those with HBeAg-negative chronic HBV (200) reflecting the progressive nature of liver damage in the immune escape phase of HBV.

Progression to decompensated cirrhosis occurs in approximately 3% of patients annually, with a higher rate in the presence of high levels of viral replication (198, 200). People with cirrhosis are also much more likely to develop HCC (24, 32), with annual incidence of 5-10% in those infected at birth. This risk also increases with increasing levels of viral replication (198).

Most people with chronic HBV infection ultimately attain, and retain immune control of their infection and suffer no long term sequelae. However a significant proportion of people experience ongoing liver disease, resulting in death due to decompensated cirrhosis or HCC. The proportion of those chronically infected with HBV who die as a result is estimated at
around 25% (6, 7, 13, 25, 31, 56, 61, 201-203) (see 6.2.3). As a result, in populations at particular risk for chronic infection – such as people born in endemic areas, or Indigenous Australians – HBV is responsible for approximately 3% of all mortality (17, 59).

2.5.2.3 Treatment to modify the natural history of HBV

Recent recognition of the biological gradient in the relationship between HBV DNA viral load and progression to cirrhosis (and decompensation) or HCC has led to the increasing focus given to high HBV DNA levels as an indication for therapy, with maximal suppression of replication as the primary goal (198, 200, 204). This contrasts somewhat with the existing approach (reflected in national and international guidelines) relying in most instances on elevated ALT levels as indication for therapy, with higher thresholds for HBV DNA viral load tolerated (31, 205, 206). Recently published Australian guidelines reflect this change in emphasis to a certain degree (30, 207).

The dose-response relationship between viral load and increased risk of progression to advanced liver disease has been used as a rationale for improving clinical outcomes through suppression of HBV replication with antiviral therapy. Although this inference is plausible, evidence for the ability to modify the natural history of HBV infection in this way remains limited (30, 198, 204, 208-210) and long-term follow up studies are urgently required to confirm this prospect (209, 210).

2.6 Conclusion

Understanding hepatitis B virology is fundamental to understanding the impact of this virus on individuals and on the community. Using these virological foundations, understanding of differences in epidemiology, natural history and treatment response related to genotype is possible. This is particularly important in the context of the changing genotypic predominance in Australia caused by migration from endemic areas, particularly the Asia-Pacific region. Furthermore, viral dynamics are essential to an understanding of pathogenesis, and treatment modalities and outcomes, and of viral mutations permitting escape from vaccine-derived immunity or viral suppression through antiviral treatment. Genomic
sequencing with phylogenetic analysis has also been applied to investigation of clusters of HBV infections to improve public health responses.

The ability to infer HBV infection or immunisation status from the pattern of serology results is an important foundation for seroprevalence studies of HBV infection and such inference is discussed further with respect to the Victorian Hepatitis B Serosurvey 1995-2005 in 3.3.4, and in relation to the results of other Australian HBV serosurveys in 6.2.2.2. In chapter 4, the time lag between a person with chronic HBV infection migrating to Australia and being notified to the National Notifiable Diseases Surveillance System is explored, and it is hypothesised that the reason the median age of notification is 35 years is related to the natural history of HBV infection, specifically the age of progression to immune clearance. In chapters 5 and 6, presenting the complex model of HBV infection in Australia, such parameters as likelihood of progression to chronicity, resolution of chronic infection, and mortality attributable to HBV at different ages could neither be understood nor properly applied without an understanding of the natural history of this infection.

This chapter has shown that this natural history is at all times determined by the interaction between viral replication and the host’s immune response. The long asymptomatic period prior to the onset of any illness, and the typically very high viral load for the first few decades of life (immune tolerance) increase the potential for transmission to susceptible contacts, but also afford the ability to diagnose and treat prior to both these unwanted outcomes of infection.
3 The Victorian Hepatitis B Serosurvey 1995 - 2005

3.1 Introduction

As presented in chapter 1, current estimates of the population prevalence of HBV infection in Australia are the product of a limited number of studies (8, 11, 12). This lack of data, of concern to those working in the field within Australia and internationally for years (8, 25-27, 131) must be addressed before a coordinated, appropriately focussed and funded national response to the expanding problem of chronic HBV infection can be undertaken (24-26, 30).

3.2 Aim

The Victorian Hepatitis B Serosurvey 1995-2005 was undertaken to investigate the prevalence of markers of infection with, and immunity to, HBV in an age-structured randomised sample of convenience drawn from archived residual serum following diagnostic testing. The serum samples were held at the Victorian Infectious Diseases Reference Laboratory (VIDRL), a state reference laboratory and public health virology research facility in Melbourne, Victoria. VIDRL is accredited by the National Association of Testing Authorities (NATA) and is host to a range of Victorian, Commonwealth and World Health Organisation services and collaborating centres.

The aim was to estimate the prevalence of chronic HBV infection in Victoria, to analyse secular trends in estimates of infection, and to assess the serological evidence of immunity following the introduction of universal vaccination against hepatitis B for infants and adolescents under the auspices of the National Immunisation Program (NIP) (10).

3.3 Methods

3.3.1 Sample size calculation

Sample size calculations for precision were performed to determine the number of samples required in each test year to afford adequate precision around the serologic marker with the lowest expected prevalence (HBsAg) such that the 95% confidence intervals not include zero. A minimum estimated HBsAg prevalence of 0.5% was derived from a recent Australian serosurvey (11). The sample size was determined in order that the estimates for each test year
would be sufficiently precise; by extension, the sample size for analyses across all test years would therefore be more than adequate, allowing for sub-group analysis by other explanatory variables such as age and region.

The minimum estimate for HBsAg in the reference study (11) was 0.5%, therefore the 95% two-sided confidence intervals (CI) would necessarily be no greater than 0.8% (0.4% each side). Using these CI an initial target of 1200 samples from each test year was determined. With this sample size, corresponding 95% CI for precision around anti-HBs and anti-HBc estimates derived from the same study were 28.7 +/- 2.6% and 6.9 +/- 1.4% in each test year. These calculations are shown in table 3.1.

\[
SE = \sqrt{p(1-p)} \quad \text{and} \quad n = \frac{p(1-p)}{(SE)^2}
\]

where
- \( SE \) = standard error
- \( p \) = proportion positive for serologic marker
- \((1-p) \) = proportion negative
- \( n \) = number of samples per test year

<table>
<thead>
<tr>
<th>Marker</th>
<th>SE Calculation</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg[min]</td>
<td>( \sqrt{0.005(1-0.005)} ) ( \frac{0.002036 \times 1.96}{\sqrt{1200}} )</td>
<td>0.5% ± 0.4% (0.1 – 0.9%)</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>( \sqrt{0.069(1-0.069)} ) ( \frac{0.00732 \times 1.96}{\sqrt{1200}} )</td>
<td>6.9% ± 1.4% (5.5 – 8.3%)</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>( \sqrt{0.287(1-0.287)} ) ( \frac{0.0131 \times 1.96}{\sqrt{1200}} )</td>
<td>28.7% ± 2.6% (26.1 – 31.3%)</td>
</tr>
</tbody>
</table>

Table 3.1 – Sample size calculations for the Victorian Hepatitis B Serosurvey 1995 – 2005.
3.3.2 Sample selection program

A well recognised weakness inherent in using samples of convenience drawn from residual serum following diagnostic testing is that such samples are liable to selection bias (211). It is probable that patients having diagnostic blood tests are not representative of the general population. They are more likely to have illness which requires diagnosis or monitoring; such illnesses include HBV infection and other diseases which are epidemiologically associated, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (80).

This is a potentially even greater concern given the samples of convenience in question had been referred for testing at an infectious diseases reference laboratory. In addition to samples referred for testing by private pathology companies (particularly for serological testing), VIDRL receives a range of samples from Victorian public hospitals and is also used as a primary pathology provider for the Melbourne Sexual Health Centre and a number of general practices with a high caseload of MSM. As such, a random selection of all serum samples would be expected to have a higher prevalence of markers of HBV infection than would a sample from private pathology companies, let alone the population in general.

In an attempt to mitigate this unquantifiable bias and construct a sample set more representative of the Victorian population, a unique software interface was developed in liaison with the developer of the existing pathology result database software at VIDRL (MediPATH, Last Resort Support, Cranbourne North, Victoria). This interface was designed to select samples for inclusion in the serosurvey from the stored serum archive at VIDRL according to the following step-wise process:

1. The program was provided with the range of available sample numbers for the years 1995, 2000 and 2005 held in -20°C storage at VIDRL. For samples from 1995 which had been subjected to ‘culling’ (disposal of 80% of all samples to allow storage of new samples), this involved going down to the freezers and manually cataloguing the remaining boxes and sample number ranges.

2. The program was also provided with the age and gender distribution of the Victorian population for these years (Australian Bureau of Statistics (ABS) data provided by Trevor Lauer, Communicable Disease Prevention and Control Unit, Public Health Branch, Department of Human Services Victoria).
3. The program interface allowed specification of sample types to be included (for the purposes of this study, specimen numbers of serum samples only were used, so excluding cerebrospinal fluid, faecal samples, swabs and other non-serum samples).
4. The total number of samples to be retrieved was set.
5. Any samples from a patient ever referred for serologic testing for HBV, HCV or HIV were excluded to reduce the bias referred to previously.
6. Remaining candidate sample numbers were then selected according to an automatic randomisation process in proportion to the age and gender distribution of the Victorian population for the appropriate test year until the target number of sample numbers was reached.

The sample selection procedure did not use available geographic information (postcode) in an attempt to generate a geographically representative sample set (as was the case for gender and age). This was for two reasons; first, a significant proportion of samples (approximately 20% of those used in this serosurvey) did not have adequate postcode data and, for the 1995 test year in particular, this would further have reduced the ultimate sample size. Second, adequate information on the Victorian population by postcode was unavailable. Instead, postcodes were subsequently individually linked to geographic statistical divisions within Victoria and then used in the analysis of the serosurvey results to assess both representativeness (3.3.5) and HBV status by statistical areas (3.3.4).

3.3.3 Sample retrieval, information handling and testing

Microsoft Office Excel spreadsheets (Microsoft Corporation, Redmond, Washington USA) were generated which contained the details of candidate samples selected in the method described for each test year with ten samples recorded per page (a representation of five such sample records appears in table 3.2). These lists contained sample information necessary information for retrieval and identity cross-checking (sample and patient ID numbers and patient surname) in addition to the demographic data to be retained following de-identification - postcode (where available), age at time of test, age group, and gender.
### Table 3.2 – schematic representation of sample data handling sheets used.

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Patient ID</th>
<th>Surname</th>
<th>PC</th>
<th>Age</th>
<th>Age group</th>
<th>Sex</th>
<th>Unique ID</th>
<th>sAb</th>
<th>cAb</th>
<th>sAg</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>95501111</td>
<td>711111</td>
<td>ANAME</td>
<td>3000</td>
<td>5.1111</td>
<td>5 to 9</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95502222</td>
<td>722222</td>
<td>BNAME</td>
<td>3100</td>
<td>12.2222</td>
<td>10 to 14</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95503333</td>
<td>733333</td>
<td>CNAME</td>
<td>3200</td>
<td>25.3333</td>
<td>25 to 29</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95504444</td>
<td>744444</td>
<td>DNAME</td>
<td>3300</td>
<td>32.4444</td>
<td>30 to 34</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95505555</td>
<td>755555</td>
<td>ENAME</td>
<td>3400</td>
<td>45.5555</td>
<td>45 to 49</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Candidate stored frozen serum samples were retrieved from secure -20°C storage rooms at VIDRL, thawed at either +4°C (for testing the following day) or room temperature (for same-day testing) and aliquots transferred into new specimen tubes in a serology laboratory ventilation cabinet. No samples were refrozen prior to testing for anti-HBs and anti-HBc once thawed to avert repeated freeze-thaw cycles which have been suspected as the cause of inaccuracies in other Australian serosurveys (11), however following testing and confirmation of a successful test run that met test controls and was free of obvious error, samples were frozen once again. Any samples that were not demonstrated to be anti-HBc negative were then retrieved and thawed once more to test for HBsAg (see below).

Unique eight-digit identification numbers were generated and printed on barcodes for the purposes of this study; 20060001- for 1995, 20062001- for 2000 and 20064001- for 2005. Each sample tube was labelled with one copy of the barcode prior to entering the laboratory. If a sample was missing or judged to be of insufficient volume to allow full testing at the time of retrieval, the candidate sample was struck from the master list at that juncture. This could also occur at the time of aliquotting in the serology laboratory if insufficient serum was observed following thawing. Missing or inadequate volume samples were replaced by age- and gender-matched samples wherever possible, using the same retrieval methodology.
Any sample with apparently sufficient serum to allow full testing was then included in the study. A matching barcode label to that for the tube receiving the serum aliquot was then applied to the appropriate section of the list (‘Unique ID’ column in table 3.2). Prior to testing, all identifying information other than for postcode, age at time of test, age group and gender was permanently delinked by physically removing this section of the printed lists (cutting along the dark grey column in table 3.2) and erasing those parts of the final spreadsheets stored on a password-protected section of the VIDRL network drive.

Aliquotted serum samples were stored at +4°C until 90 samples were ready for testing for anti-HBs and anti-HBc to enable the maximum number of samples per run (leaving space on the testing carousel for up to six control samples). For the majority of test runs, anti-HBs and anti-HBc were tested sequentially in the same run to once again maximise efficiency and reduce the length of time samples were left thawed.

All samples were tested for the presence of anti-HBs and anti-HBc by enzyme immunoassay (EIA) using validated commercial kits (Murex Biotech/Abbott Diagnostics Division, Temple Hill, Dartford UK). Any sample with a positive, borderline, indeterminate or otherwise unknown anti-HBc result was tested for HBsAg, again using commercial Murex Biotech/Abbott Diagnostics kits. The EIA reactions were performed using a Triturus EIA Analyzer (Grifols S.A., Barcelona Spain) owned by the Serology Unit, Division of Virology, VIDRL. A discounted purchase price for the commercial EIA kits used was negotiated with the manufacturer in support of this research project. The kits were purchased by the Division of Epidemiology, VIDRL.

### 3.3.4 Serosurvey data handling and statistical analysis

The resultant dataset included unique sample identifiers (permanently de-linked with respect to identifying information) with patient age, gender and postcode for each test year, plus results of EIA for anti-HBs, anti-HBc and where the latter was not determined to be negative, HBsAg. The pattern of serological markers for each individual sample enabled assignment of HBV infection status to each sample according to the scheme shown in table 3.3 (see 2.5.1 for the interpretation of HBV serology).
Table 3.3 – Serological profiles used to define HBV status codes

<table>
<thead>
<tr>
<th></th>
<th>Anti-HBs</th>
<th>Anti-HBc</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Immunised</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Infected</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Resolved</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Isolated anti-HBc</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td>where any parameter missing or indeterminate</td>
</tr>
</tbody>
</table>

Victorian postcodes were individually mapped to ABS divisions (212) to enable analysis by geographic area. Information on population characteristics by statistical division for the 2001 and 2006 Australian censuses was obtained from resources available on the ABS website (http://www.abs.gov.au/websitedbs/d3310114.nsf/home/Census+data). Vaccine coverage data was obtained from the Australian Childhood Immunisation Register (ACIR) reports (108, 213).

Statistical analysis was performed using Stata v8.2 and subsequently Stata v10.0 (StataCorp, College Station, Texas USA). 95% confidence intervals around seroprevalence estimates were calculated using the exact binomial method; p-values for differences in antibody prevalence were calculated by z test, and for differences in HBV status between groups were calculated by chi-square test.

### 3.3.5 Assessment of representativeness

Age and gender distributions of the sample were compared to ABS estimates for the Victorian population for the respective test years, and the geographic distribution of the sample postcodes was compared to the Victorian population by statistical divisions within Victoria and statistical subdivisions within the statistical division of Melbourne. Direct standardisation of seroprevalence estimates relative to the Victorian or Melburnian populations was performed for age group, gender and geographic area to assess for the impact of differences between the sample and the source population on prevalence estimates. This was done by applying sample seroprevalence results by each parameter in question (for example, anti-HBs by age group) to the source population structure for the same parameter, allowing assessment of how different the seroprevalence estimates would have been if the sample perfectly reflected the structure of the Victorian population by each parameter.
3.3.6 Ethical approval
Ethics approval for this serosurvey was obtained from the Melbourne Health Human Research Ethics Committee (HREC 2005.096).

3.3.7 Management of failed HBsAg test run, 28 March 2007

On the second run of HBsAg testing of anti-HBc positive samples, conducted on 28 March 2007, many low-level positive results were obtained. Of the entire run of 91 anti-HBc positive samples, 43 were positive, 60% of which gave low-level positive results. This is a much higher proportion of HBsAg positive samples than expected on epidemiologic grounds, and also than on the first HBsAg test run which was 13.4%. It is also a very large proportion of low-level positive samples.

Further evidence of testing error was obtained when the plate was read by a separate stand-alone plate reader in the Serology Laboratory. In the penultimate well of the tray, which was not used in the test run and therefore should have been empty, the reader gave an OD result of 0.291, indicating a positive result. This is categorical evidence of cross-well contamination of either sample or reagents leading to false positive results.

Details regarding the investigation of this run failure, and the steps taken to resolve the problem are described in detail in Appendix 1.

3.4 Results

Ultimately 3212 samples were included in the serosurvey – 926 from 1995, 1110 from 2000 and 1176 from 2005. Less than 1% of all samples tested gave inconclusive or incomplete results for any parameter, usually due to insufficient volume to complete testing. This compares favourably with other recent HBV serosurveys in Australia (11, 12).
3.4.1 Estimates of HBV infection

Complete results of the serosurvey by test year and age-group are presented in Table 3.4. Of all 3212 samples tested the prevalence (and 95% CI) for the parameters assayed was:

- **anti-HBs positive** = 30.3% (28.7-31.9)
- **anti-HBc positive** = 9.4% (8.4-10.5)
- **HBsAg positive** = 1.1% (0.8-1.6)

Analysis by a number of important descriptors including test year, age, gender, and geographic area of residence was undertaken. It is important to recognise that the sample size was not determined to adequately power such sub-analysis and that therefore negative statistical tests (that is, findings of no significant difference) in particular should be interpreted with this in mind.

A steady increase from 1995 to 2005 was observed in both anti-HBs (17.4% to 40.5%) and anti-HBc (6.5% to 11.3%) (p<0.001 for both comparisons). HBsAg prevalence peaked at 1.9% in 2000 and dropped significantly in 2005 to 0.6% (p=0.005).

Males were significantly more likely to have been infected with HBV than females. 11.1% of males (9.6-12.7) were anti-HBc positive compared to 7.5% of females (6.2-8.8) (p<0.001). Males were also more likely to be chronically infected, with 1.3% being HBsAg positive (0.8-1.9) compared to 0.9% (0.4-1.4) for females but this difference was not significant (p=0.24).

Across all test years, the mean prevalence of HBsAg in women of childbearing age (15-44 years) was 1.4% (0.7-2.5). For women in the peak childbearing age range of 20-39 years (accounting for over 90% of Australian births (214)) the mean prevalence was 1.6% (0.7-3.1), rising from 1.2% in 1995 to 1.8% in 2005 although this difference is not statistically significant (p=0.65). For the 309 samples from women in metropolitan Melbourne aged 20-39 HBsAg prevalence was 2.3% (0.9-4.6%) compared to 0% (0-4.3%) in the 84 non-Melburnian Victorian samples from women in this age group (p=0.16).
Table 3.4 – Complete serosurvey results by test year and age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. tested</th>
<th>% positive anti-HBs (95% CI)</th>
<th>% positive anti-HBc (95% CI)</th>
<th>% positive HBsAg (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 4</td>
<td>28</td>
<td>35.7 (18.6-55.9)</td>
<td>0 (0-12.3)</td>
<td>0 (0-12.3)</td>
</tr>
<tr>
<td>5 to 9</td>
<td>31</td>
<td>9.7 (2.0-25.8)</td>
<td>0 (0-11.6)</td>
<td>0 (0-11.2)</td>
</tr>
<tr>
<td>10 to 14</td>
<td>37</td>
<td>13.5 (4.5-25.8)</td>
<td>0 (0.9-5.5)</td>
<td>0 (0-5.0)</td>
</tr>
<tr>
<td>15 to 19</td>
<td>72</td>
<td>12.5 (5.9-22.4)</td>
<td>2 (0.9-7.6)</td>
<td>2 (0-2.8)</td>
</tr>
<tr>
<td>20 to 24</td>
<td>82</td>
<td>32.2 (22.6-43.1)</td>
<td>3.1 (0.7-9.7)</td>
<td>2 (0-6.2)</td>
</tr>
<tr>
<td>25 to 29</td>
<td>81</td>
<td>19.5 (7.9-29.5)</td>
<td>1.2 (0.7-6.6)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>30 to 34</td>
<td>83</td>
<td>25.3 (16.4-36.0)</td>
<td>1.2 (5.9-21)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>35 to 39</td>
<td>81</td>
<td>14.8 (7.9-24.4)</td>
<td>2.5 (1.4-12.2)</td>
<td>2 (0-6.2)</td>
</tr>
<tr>
<td>40 to 44</td>
<td>74</td>
<td>15.1 (7.8-25.4)</td>
<td>1.4 (0.7-5.3)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>45 to 49</td>
<td>73</td>
<td>17.8 (9.8-25.5)</td>
<td>1.6 (0.7-6.7)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>50 to 54</td>
<td>76</td>
<td>19.6 (10.2-32.4)</td>
<td>1.2 (0.7-6.7)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>55 to 59</td>
<td>45</td>
<td>11.1 (3.7-24.1)</td>
<td>2.2 (1.0-11.8)</td>
<td>2 (0-6.2)</td>
</tr>
<tr>
<td>60 to 64</td>
<td>48</td>
<td>14.6 (6.1-27.8)</td>
<td>1.4 (0.7-7.4)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>65 to 69</td>
<td>49</td>
<td>9.3 (2.6-22.1)</td>
<td>1.8 (1.6-8.7)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>70 to 74</td>
<td>38</td>
<td>13.2 (4.4-25.1)</td>
<td>0.9 (0-4.9)</td>
<td>0 (0-0.2)</td>
</tr>
<tr>
<td>75 to 79</td>
<td>22</td>
<td>4.3 (1.1-22.8)</td>
<td>1 (0.1-15.4)</td>
<td>1 (0-0.2)</td>
</tr>
<tr>
<td>80 and over</td>
<td>25</td>
<td>4 (0.1-20.4)</td>
<td>1 (0-13.7)</td>
<td>1 (0-0.2)</td>
</tr>
</tbody>
</table>

Missing (% total) 3 (0.32) 5 (0.54) 1 (0.11) 0 6 1 0 6 1 1 0 0.09 2 1 0.18 0.01 0.12 0.12

All ages 926 17.4 (15.0-20.0) 6.5 (5.0-8.3) 0.9 (0.4-1.7) 1110 30.2 (27.5-33.0) 9.8 (8.1-11.7) 1.9 (1.2-2.9) 1176 40.5 (37.7-43.4) 11.4 (9.5-13.2) 0.6 (0.2-1.2) 3212 30.3 (28.7-31.9) 9.4 (8.4-10.5) 1.1 (0.8-1.6)
HBV infection status by location for the 2598 Victorian samples with complete postcode information available is shown in Table 3.5. Although the proportion of susceptible samples from outside Melbourne was significantly higher (p<0.001), the vaccination rates were not different (22.6 vs. 23.9%, p=0.44). The proportion of samples from patients ever infected with HBV was higher in Melbourne than in the rest of Victoria (12% vs. 2.8%, p<0.001), as was the proportion of HBsAg positive samples (1.5% vs. 0.3%, p=0.013).

Marked diversity in anti-HBc and HBsAg prevalence across different areas of Melbourne was also observed. Figure 3.1 shows the proportion of residents born overseas in the 2006 Census (215) and the HBsAg prevalence of serosurvey samples by ABS statistical subdivisions (SSD) within Melbourne. A notable although by no means absolute association is observed. A striking example is that of the 56 samples from the Greater Dandenong SSD being the region with highest proportion of people born overseas (~56% on the 2006 census), 7.2% were HBsAg positive and 30.9% were anti-HBc positive.

Table 3.6 shows that the proportion of the samples from subjects susceptible to infection reduced from nearly 80% in 1995 to 55% in 2005 – largely explained by the increase in the immunised proportion from 13.6 to 33% over this period, but also by the significant increase in patients with natural immunity following HBV infection, rising from 6.5% in 1995 to 11.3% in 2005 (p<0.001 for all comparisons). The proportion of samples with isolated anti-HBc was 2.2%.

<table>
<thead>
<tr>
<th></th>
<th>Metropolitan Melbourne (n = 1944)</th>
<th>Non-metropolitan Victoria (n = 654)</th>
<th>p-value for comparison (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>63.4%</td>
<td>74.5%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Immunised</td>
<td>23.9%</td>
<td>22.6%</td>
<td>p = 0.44</td>
</tr>
<tr>
<td>Infected</td>
<td>1.5%</td>
<td>0.3%</td>
<td>p = 0.013</td>
</tr>
<tr>
<td>Resolved</td>
<td>7.6%</td>
<td>1.2%</td>
<td>Ever infected 12% vs 2.8% p &lt; 0.001</td>
</tr>
<tr>
<td>Isolated anti-HBc</td>
<td>2.4%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.2%</td>
<td>0.2%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.5 – HBV status by location for Victorian samples with complete postcode available.
Figure 3.1 – Proportion of people born overseas by SSD within Melbourne in the 2006 Census of Population and Housing (215) superimposed with the percentage of samples that were HBsAg positive in the serosurvey for each SSD.

<table>
<thead>
<tr>
<th></th>
<th>1995</th>
<th>2000</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>79.1%</td>
<td>66.6%</td>
<td>55.2%</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>13.6%</td>
<td>23.2%</td>
<td>33.0%</td>
</tr>
<tr>
<td>Infected</td>
<td>0.9%</td>
<td>1.9%</td>
<td>0.60%</td>
</tr>
<tr>
<td>Resolved</td>
<td>3.4%</td>
<td>6.7%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Isolated anti-HBc</td>
<td>1.9%</td>
<td>1.1%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Other</td>
<td>1.2%</td>
<td>0.6%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Table 3.6 – Sample status codes by test year.
3.4.2 Estimates of immunisation

Hepatitis B vaccine was incorporated into the NIP for adolescents in 1998 and infants in 2000 as discussed in chapter 1 (10, 108) in line with WHO recommendations since 1991 (61). These changes are reflected in significant increases in anti-HBs prevalence in the relevant age-groups. Table 3.4 demonstrates that anti-HBs prevalence in 0-4 year olds rose from 35.7% (18.6-55.9) in 1995 to 71.8% (59.9-81.9) in 2005 (p=0.001). For children aged 10-14, anti-HBs positivity rose from 13.5% (4.5-28.8) in 1995 to 57.7% (45.4-69.4) by 2000 (p<0.001).

The relative contribution of vaccination and resolved infection to estimates of population immunity can only be assessed by examining the complete serological profile of each sample. HBV infection status for the samples drawn from age-groups targeted by universal vaccination programs are shown by test year in Table 3.7. The proportion of 0-4 year olds that were susceptible to HBV infection fell from 64.3% in 1995 to 27.8% in 2005 (p<0.001). Although this is largely explained by an increase in the immunised proportion (anti-HBs positive only) from 35.7% to 66.7% over this time period (p<0.001), there was also one HBsAg positive 3 year-old in the 2000 test group, and one child with resolved infection in both 2000 and 2005.

<table>
<thead>
<tr>
<th></th>
<th>0–4 years old</th>
<th>10–14 years old</th>
<th>All samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>64.3%</td>
<td>51.6%</td>
<td>27.8%</td>
</tr>
<tr>
<td>Immunised</td>
<td>35.7%</td>
<td>45.3%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Infected</td>
<td>0%</td>
<td>1.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Resolved</td>
<td>0%</td>
<td>1.6%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Isolated anti-HBc</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
<td>0%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Table 3.7 - HBV status by test year for age groups included in NIP universal vaccination programs and also for all samples.
From 1995 to 2000 the proportion of 10-14 year olds susceptible to HBV infection fell significantly from 86.5% to 40.9% (p<0.001). The subsequent reduction to 39.5% in 2005 was not significant (p=0.81). Although again mostly due to immunisation with isolated anti-HBs positivity rising from 13.5 to 54.9% in 2000 (p<0.001), the immunised proportion dropped non-significantly in 2005 (p=0.32). Immunity due to resolved infection was unexpectedly high with 10% of samples anti-HBe positive in 2005, compared with 2.9% in 2000 (p=0.08) and none in 1995 (p=0.046). No samples in this age-group were HBsAg positive.

Most notified acute HBV infections in Australia occur in people between the ages of 20 and 45 years (44, 45). From 1995 to 2005, vaccination coverage increased from 18.4% to 36.1% in samples from people in this age group, with the proportion of samples coming from patients remaining susceptible to infection falling from 74.2% to 51.5% (p<0.001 for both comparisons).

3.4.3 Assessment of representativeness

The final sample of 3212 sera (89% of the target) closely followed the age, gender and geographic distribution of the Victorian population (216, 217) (figures 3.2-3.5). However, samples from children under 15 years of age particularly in 1995 were under-represented (figures 3.2 and 3.3). This problem is common in convenience sample serosurveys due to the relative infrequency of diagnostic blood testing in young children. The disproportionate deficit in 1995 samples occurred as all remaining samples in this age group were exhausted in the conduct of this serosurvey, preventing the retrieval of replacement samples for inadequate specimens as was possible for the latter two test years. Males were slightly over-represented, and although the proportion of samples from Melbourne versus non-metropolitan Victoria was almost identical to the population structure of the state (figure 3.4) there was a some disparity in sampling between statistical subdivisions within Melbourne (figure 3.5).

To assess the impact of these differences on population prevalence estimates, direct standardisation with weighting by age group, gender and region was undertaken relative to the composition of the source population as shown in table 3.8. The similarity between the sample and standardised prevalence estimates provides reassurance regarding the representativeness of the sample with respect to the parameters assessed.
Figure 3.2 – age distribution of all samples in the serosurvey (green) compared with the average age distribution of the Victorian population from 1995, 2000 and 2005 (blue).

Figure 3.3 – age distribution of serosurvey samples (purple) compared with the age distribution of the Victorian population in (a) 1995 (b) 2000 and (c) 2005. The deficit of samples from patients less than 15 years of age predominantly occurs for samples from 1995.
**Figure 3.4** – Geographic distribution by Victorian statistical division of (a) Victorian population in 2000 and (b) serosurvey samples with percentage of population/samples from Melbourne and non-metropolitan Victoria shown.

**Figure 3.5** – Geographic distribution by Melburnian statistical subdivision of (a) population of Melbourne in 2006 and (b) serosurvey samples.
Table 3.8 - Sample and standardised prevalence estimates by gender, age group, and geographic regions within Victoria and Melbourne

<table>
<thead>
<tr>
<th>Samples</th>
<th>Weighting by</th>
<th>Sample prevalence estimates</th>
<th>Standardised prevalence estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anti-HBs</td>
<td>Anti-HBc</td>
</tr>
<tr>
<td>All</td>
<td>Gender</td>
<td>30.3%</td>
<td>9.3%</td>
</tr>
<tr>
<td>1995</td>
<td>Age group</td>
<td>17.4%</td>
<td>6.5%</td>
</tr>
<tr>
<td>2000</td>
<td>Age group</td>
<td>30.2%</td>
<td>9.7%</td>
</tr>
<tr>
<td>2005</td>
<td>Age group</td>
<td>40.5%</td>
<td>11.2%</td>
</tr>
<tr>
<td>All</td>
<td>Age group</td>
<td>30.3%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Victoria</td>
<td>Statistical Division</td>
<td>30.1%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Melbourne</td>
<td>Statistical Subdivision</td>
<td>32.3%</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

3.5 Discussion

The prevalence estimates of 30.3% for anti-HBs, 9.4 for anti-HBc and 1.1% for HBsAg are all higher than the results from a previous national serosurvey of 2,476 sera gathered in 1996-1999 from 45 laboratories around Australia with corresponding estimates of 28.7%, 6.9% and 0.49/0.87% (11). A more recent national serosurvey of samples collected in 2002 estimated anti-HBs prevalence at 32.3%, but both anti-HBc and HBsAg were again lower than in our study at 6.1% and 0.7/0.8% (12). Of these differences, only the comparisons between anti-HBc prevalence between the Victorian and both national serosurveys (p<0.001 and p=0.001) and between the HBsAg prevalence in the Victorian serosurvey and that of the minimum estimate in the earlier serosurvey (p=0.014) achieve statistical significance at an α=0.05 level. Interestingly, a recent paper from the Centers for Disease Control in Atlanta also estimated the prevalence of HBsAg in Australia at 1.1% but anti-HBc at only 5.5% (114).
One explanation of the higher prevalence of markers of infection in this study is that it was based predominantly on Victorian samples (95.7% of samples with complete postcodes), whereas the other seroprevalence surveys were national (11, 12). Although the proportion of immigrant Victorians is similar to the rest of Australia, compared with the national average a lower proportion of Victorians born overseas come from low HBV prevalence countries (35.8% versus 47.2%), and a greater proportion from intermediate prevalence countries (39.1% versus 27.0%) (28, 218). The proportion of Victorian migrants born in high HBV prevalence regions is comparable with the Australian average (25.1% versus 25.8%). Another possible explanation is improvements in the sensitivity and detection thresholds of commercially available serological assays for markers of HBV infection.

The Victorian serosurvey results for 2000 closely resemble the outcomes of a study of endoscopy patients attending a central Sydney hospital between 1999 and 2001 (15) (table 3.9). Patients in the Sydney cohort, having an older median age (52.3 years), and attending for a procedure an indication for which is surveillance for or management of complications of cirrhosis, would perhaps be expected to have a higher prevalence of markers of current and past HBV infection. This was observed, but the difference was relatively small. The proportion of patients vaccinated was also similar. These similarities could indicate similar temporal trends at play in both cohorts; however another possibility is that the Victorian serosurvey participants, rather than being representative of the general community, were more similar to patients with chronic diseases under the care of tertiary services. This does not however explain the subsequent reduction in HBsAg prevalence in 2005.

The observation that HBsAg prevalence peaked in 2000 and dropped significantly in 2005 (p=0.005) may be related to imprecision arising from the relatively small number of HBsAg positive samples (n=36) in the serosurvey. However a similar peak in 2000-2001 with subsequent decline has been observed in unspecified (non-incident or chronic) HBV notifications to the National Notifiable Diseases Surveillance System (NNDSS) (44) (chapter 1, figure 1.1), suggesting the serosurvey may have detected an underlying trend also reflected in surveillance data. The most likely hypothesis is that the trend is real and that both data sources reflect changes in migration patterns into Australia over the last few decades. This hypothesis is explored in detail in chapter 4 of this thesis.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>66.6%</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>23.2%</td>
<td>20.3%</td>
</tr>
<tr>
<td>Current infection</td>
<td>1.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Past infection</td>
<td>8.8%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Table 3.9 – Victorian serosurvey results for 2000 compared with results of Sydney endoscopy cohort 1999-2001 serology results (15).

There were regional differences in markers of HBV infection, with 1.5% of the Melburnian samples positive for HBsAg, and with statistical subdivisions in Melbourne ranging from 0% to as high as 7.3% (2.0-17.6) carriage – the latter estimate being a prevalence close to that which defines highly endemic populations (see 1.1 and figure 1.3). However the relatively low sample size within the smaller geographic subdivisions means such estimates are subject to significant uncertainty (as demonstrated by the broad confidence interval shown above). Such regional variation was also observed in a HBV serosurvey conducted in 1996 in England and Wales (131, 211), with the hypothesized cause being variability in the proportion of people born overseas in different areas, as is also the case for the Victorian serosurvey (3.4.1 and figure 3.2).

The HBsAg prevalence estimates for women of child-bearing age (1.4% for the entire sample, rising to 2.3% for Melburnian women) are supported by previous antenatal screening studies. In 1984, Gilbert reported 1.8% HBsAg prevalence in antenatal testing of women at the Royal Women’s Hospital in Melbourne, with a prevalence of 0.5% in Australian-born women and 11% in women born in SE Asia (219). More recent antenatal data from Sydney, New South Wales give an overall prevalence of 1.5%, reaching 4.9-5.4% for women born in NE and SE Asia (11). Similar underlying epidemiology is suggested (but cannot be confirmed) in this serosurvey in that all Victorian women in this age group chronically infected with HBV lived in areas where more than 30% of the population were born overseas in the 2006 census (215).

The anti-HBs prevalence of 71.8% was less than expected in the 0-4 age group when tested in 2005 – and one three-year old was also anti-HBc positive, indicating immunity through resolved infection rather than vaccination. The anti-HBs estimate for 1 year-olds in the 2002 national serosurvey was substantially higher at 86% (12). These children should have been
included in the universal vaccination program for infants starting in 2000 if born in Australia, and any born outside Australia would be eligible for catch-up vaccination (220). The ACIR estimate for the proportion of children fully immunised against HBV by 12 months of age has been consistently 94-95% since vaccination commenced (108). With the expectation of seroconversion to anti-HBs of over 95% in this age group (221) anti-HBs positivity in this cohort should therefore be around 90%.

There are a number of possible explanations for this observation. Coverage or seroconversion, or both, may be overestimated. In the 2006 Australian Census, 8.5% of 0-4 year olds living in Victoria were born overseas, 54.5% from countries with intermediate or high HBV prevalence (7, 29, 218). If the source countries lacked universal hepatitis B vaccination, this would contribute a group of susceptibles not accounted for in the ACIR data (not being registered with Medicare by age 12 months). Conversely, those migrating from areas of high endemicity will be contributing to the pool of children with chronic or resolved HBV infection.

For the 10-14 year old group, the proportion immunised was 5% less in 2005 than in 2000, but this could be due to vaccination of children already previously infected who would not therefore be included in the ‘Immunised’ status group (isolated anti-HBs positivity). The estimates of 50-55% coverage amongst 10-14 year olds are comparable with the 2002 national serosurvey anti-HBs prevalence result for 12-17 year olds in states with established school-based vaccination programs, which was 56.6% (12).

The use of samples of convenience introduces a selection bias which is impossible to quantify without a comparator, such as large-scale random population sampling. Such studies are rare (52, 222) expensive (211, 223), and remain susceptible to bias (211, 223).

Previous research has demonstrated that seroprevalence estimates derived from samples drawn from the VIDRL archive are comparable to those determined by random cluster sampling (223). This validation of an existing sample archive appears to be unique and could be considered to strengthen the case that the prevalence estimates derived from this serosurvey are generalisable to the Victorian population. However this comparative study was an investigation of markers of vaccine-derived immunity in school-aged children. Exposure to universal vaccination, measured through antibody prevalence in school-aged
children, is less likely to be prone to selection bias than is evidence of past or present infection with, or immunisation against a virus with very heterogeneous epidemiology in a population with generally low prevalence containing sub-populations with a substantially higher burden of disease (as discussed in chapter 1).

A significant hurdle was encountered in conducting the serosurvey in the form of the failed automated HBsAg run (3.3.7 and Appendix 1). The resolution of this problem required extensive time, re-testing and analysis. This process was assisted by thorough contemporaneous record keeping and analysis of OD readings and anti-HBs results for the same samples. The solution of using the OD cut-off of 1.0 to assign final sample status was validated in 100% of samples able to be re-tested which affords greater certainty to the results derived in this fashion.

Despite excluding samples from people ever tested for HBV, HCV and HIV, the Victorian HBV serosurvey 1995-2005 demonstrated a higher burden of chronic HBV infection than previously thought, with 1.1% (0.8-1.6) of samples across the three test years positive for HBsAg. If this is representative of the seroprevalence in the population, it would equate to over 54,000 (approximate 95% CI 39,000–79,000) chronic infections in a Victorian population of 4.93 million people in 2006 (218). If the CDC estimate (114) is correct, and this prevalence can be extrapolated to the population of Australia (28), there are some 218,000 (95% CI 159,000-318,000) people with chronic HBV infection in Australia.

As mentioned previously, the estimate of 1.1% HBsAg prevalence is higher (not statistically significantly) than the most recent national serosurvey estimate of 0.7/0.8% (95% CI 0.6-0.7/0.8-0.9) (12) with possible explanations discussed previously. Furthermore, the HBsAg prevalence in the Victorian serosurvey varied widely across the ten year period which generates some caution about applying an averaged estimate to the population. An analysis to be presented in chapter 4 will explore the effect of recent secular migration trends which appear to be responsible for this significant short-term variability in the serosurvey results, trends which may be responsible for the higher than expected HBsAg prevalence in the sample. Furthermore, the results of the complex mathematical model of HBV epidemiology in Australia to be presented in chapter 6 will suggest that HBsAg prevalence in Australia is close to that of the national serosurvey.
Nonetheless, in the light of this serosurvey and the other recent large-scale convenience sample serosurvey conducted in Australia (12) it appears that our community has a higher burden of HBV infection than previously thought. The current study also suggests lower population immunity from recently introduced universal vaccination programs than other research has suggested. This research should be repeated in other States to explore any differences in the findings, and should also be repeated in Victoria in the future (for example in five years time) to permit further analysis of temporal trends in infection and vaccination.

Having generated robust local data in the serosurvey reported in this chapter, the subsequent development of tools to accurately assess the evolution of chronic HBV infection in Australia will be the subject of the rest of this thesis.
4 Parsimonious regression model of migration and HBV notifications in Australia

4.1 Review of seroprevalence data and evidence for HBsAg trends

In chapter 3 the results of the Victorian Hepatitis B Serosurvey 1995-2005 were presented. With HBsAg prevalence of 1.1% (0.8-1.6%) the serosurvey estimates suggest more than 54,000 Victorians are chronically infected with HBV (approximate 95% CI 39,000 - 79,000). This is higher than estimates from comparable recent Australian studies (11, 12). Significant differences in prevalence estimates in the Victorian serosurvey were observed according to birth year, test year, region of residence and gender.

The prevalence of HBsAg rose from 0.9% (0.4-1.7) in 1995 to 1.9% (1.2-2.9) in 2000 before falling significantly to 0.6% (0.2-1.2) in 2005 (p=0.005). This observation could be related to imprecision arising from the fact that there were only 36 HBsAg positive samples in the serosurvey. However a similar rise to a peak in 2000-2001 with subsequent decline was observed in unspecified (hereafter referred to as chronic) HBV infection notifications to the NNDSS (44), suggesting the serosurvey may have detected an underlying trend also reflected in national surveillance data (chapter 1, figure 1.1).

Analysis of serosurvey data by geographic region also revealed significant differences in the prevalence of HBV infection. Samples from Melbourne (2006 population 3.59 million), where 35% of residents are born overseas, had a HBsAg prevalence of 1.5% compared with 0.3% in samples from the rest of Victoria (2006 population 1.34 million) where people born overseas constitute only 16.7% of the population (table 3.5) (224). A similar association between the proportion of residents born overseas and the prevalence of HBsAg in the serosurvey samples was also apparent within Melbourne (figure 3.1) (215). Furthermore, the reason our serosurvey HBsAg prevalence estimate may be higher than comparable national estimates may be the relatively higher proportion of Victorians born in countries with intermediate HBV prevalence, and a correspondingly lower proportion born in low prevalence countries as discussed in 3.5.

The hypothesis that will be explored in this chapter is that the temporal and geographic trends in HBsAg prevalence estimates derive from changes in migration patterns into Australia in
recent decades. Evidence will be provided in support of this hypothesis, with demonstration of a parsimonious linear regression model capable of predicting chronic HBV infection notifications in Australia until 2016.

4.2 Methods – data comparison

4.2.1 Victorian Hepatitis B Serosurvey 1995 - 2005

To analyse secular trends in the prevalence of chronic HBV infection over time, five-year birth cohorts were constructed (1901-05, 1906-1910...2001-2005) and the HBsAg prevalence of all 3212 samples from the serosurvey was analysed by these cohorts. A histogram of the birth-year cohorts appears in figure 4.1

4.2.2 National Notifiable Diseases Surveillance System reporting


Figure 4.1 – Number of samples in the serosurvey from each 5-year birth cohort, 1901–2005.
The most recent number of notifications for a given year was used – for example, if numbers of notifications for 2001 appeared in the 2001 through 2005 annual reports, then the total used for this analysis would be that published in 2005. This is because reclassification of cases and differences between State and National surveillance systems in reconciling data can take some time (even years) to resolve and the most recent published estimates are more likely to represent stable consensus figures.

4.2.3 Migration data

Information for migration into Australia by source country was obtained in 5-year summary format from 1945 to 1975 (225) and by year from 1976-2005 (226). Source countries were categorised into low, intermediate and high HBsAg prevalence from existing estimates (7, 29, 122) (chapter 1, figure 1.3). The prevalence of chronic HBV infection in migrants was assumed not to differ from that of source populations (see 1.3.2.2.1) and was taken as 0.5% for low-prevalence (<2%) countries, 5% for intermediate prevalence (2-8%) countries and 10% for high-prevalence (>8%) countries, estimates which are consistent with those used in recent research in Australia and internationally (114, 122, 227). The same prevalence assumptions were applied to Census place of birth data to generate cross-sectional estimates of chronic HBV prevalence in Australia in 1996, 2001 and 2006 (226). By applying the source country prevalence to available migration data, numbers of estimated HBsAg positive migrants (EHPM) settling in Australia were derived.

4.2.4 Derivation of time lags

Point estimates of median time lag between birth, migration and notification were derived from the age distributions of migrants to Australia in 2000 and 2005 (226, 228) and of all migrants to Victoria between 1975 and 2006 (unpublished ABS data commissioned by the Communicable Disease Control Unit, Department of Human Services Victoria), and from age distributions of notifications of unspecified HBV infections in the years 2000 and 2005 from NNDSS annual reports (38, 45).
4.2.5 Construction of simple linear regression model

Univariate linear regression was performed in Stata v10.0 (StataCorp, College Station, Texas USA) to analyse the association between migration and notification, and to confirm the time lag between these variables that best fit the available annual data from 1976 onwards.

4.3 Results

4.3.1 Data comparison – Serosurvey, NNDSS and migration

Analysis of the serosurvey data by birth-year cohort revealed a bimodal distribution of HBsAg prevalence (figure 4.2). The first peak occurred in people born in the 1920s and 1930s, with a maximum HBsAg prevalence of 2% (0-4.3%). A second, broader peak occurred in those born in the 1950s – 1980s, with a peak HBsAg prevalence in the 1966-1970 birth cohort of 2.3% (0.5-4.2%).

The proportion of immigrants arriving in Australia from 1945 to 2005 from countries in the three HBV prevalence categories, plus those from ‘other’ countries (unknown or not stated in the data sources), is shown in figure 4.3. From these migration patterns the number of EHPM arriving in Australia by five year groupings were estimated using source country prevalence of chronic HBV infection derived as described in 4.2.3 (figure 4.4).

![HBsAg prevalence by birth-year group](image-url)

**Figure 4.2** – HBsAg prevalence in serosurvey samples by 5-year birth cohort.
Figure 4.3 – Migration to Australia by source country seroprevalence, 1945 – 2005

Figure 4.4 – EHPM arrivals in Australia by 5-year period, 1945 – 2005.

A comparison between HBsAg prevalence by birth cohort in the serosurvey, estimated HBsAg positive migrants entering Australia, and notifications of chronic HBV infection to the NNDSS without any time lag incorporated are shown in figure 4.5.
Figure 4.5 – Comparison of HBsAg prevalence in serosurvey by birth years (secondary Y axis in percent), EHPM entering Australia, and national notifications of unspecified (chronic) HBV infection (both on primary Y axis in number of people) without incorporation of time lag.

No association is immediately apparent between these data sources in figure 4.5, but this is to be anticipated: having these variables on the same time scale without incorporating time delays assumes that birth, infection with HBV, migration and notification to the national surveillance network all occur in the same five year period which is clearly implausible. In deriving the necessary time lags it is important to use robust data, and to test the fit of this derived time lag to the data being analysed.

4.3.1.1 Incorporation of time lag

The median time lags established according to the data sources cited in the methods were 25 years from birth to migration, and 35 years from birth to notification, for an estimated median lag from migration to notification of 10 years. The comparison in figure 4.5 with these time lags having been incorporated is demonstrated in figure 4.6.
Figure 4.6 - Comparison of HBsAg prevalence in serosurvey by birth years (per cent, secondary Y axis), EHPM entering Australia, and notifications of unspecified (chronic) HBV infection (number of people, primary Y axis) incorporating time lags as described in the text.

The association between seroprevalence by birth year group, estimates numbers of people with chronic HBV infection settling in Australia, and national surveillance notifications is now much more apparent. The bimodal birth-cohort distribution of HBsAg carriage in the serosurvey reflects the estimates for the number of HBsAg positive migrants entering Australia, the two peaks of which are driven largely by immigration after 1945 from intermediate prevalence countries in southern Europe and after 1975 from high prevalence regions of Asia (225). The earlier peak in chronic HBV infection prevalence occurs too early for the surveillance notification system to detect, however the later peak is reflected closely in notifications ten years later as shown in figure 4.6, with both of these variables depicted on the same y-axis scale.

4.3.2 Parsimonious regression model

The relationship between the number of EHPM and subsequent surveillance notifications displayed by 5-year time periods in figure 4.6 was further examined using annual data for migration between 1976 and 2005 as described. A scatter plot of notifications against EHPM incorporating the derived time lags is shown in figure 4.7.
Figure 4.7 – Scatter plot of national chronic HBV infection notifications against EHPM ten years prior, with derived birth years (migration -25 years or notification -35 years) shown. Data included in this chart covers migration from 1976 to 1995 and notifications from 1986 to 2005.

The relationship observed between EHPM and notifications for the 5-year time periods as demonstrated in figure 4.6 is apparent from the comparison of annual data shown in figure 4.7, and appears to be linear. This observation suggested the use of simple (univariate) linear regression modelling for the dual purpose of (i) confirming the lag period that best fitted the annual data and (ii) determination of the statistical significance of the association and inference of other useful information about the correlation.

4.3.2.1 Confirmation of optimal lag period

The available annual notifications and EHPM from 1976 appears in table 4.1. To assess the fit of the point estimate of a 10 year lag between migration and notification derived from external sources, separate linear regression models constructed with lags of 0, 5, 8-12 and 15 years were tested (table 4.2).
Table 4.1 – Number of national HBV infection notifications and EHPM, 1976 – 2005.

The annual data was demonstrated to be most compatible with the time lag of 10 years derived from external data sources as described above, with a highly significant p-value (p<0.001) and a high coefficient of determination (r²) of 0.75 (see below for discussion). This can also be demonstrated graphically as in figure 4.8 for a selection of modelled lag times.

Table 4.2 – characteristics of linear regression models incorporating a range of estimated lag periods between migration and notification, demonstrating the highest r² value and equal lowest p-value is obtained with a 10 year lag.
Figure 4.8 – Linear regression models of notifications against EHPM with 95% confidence intervals (CI) for the fitted regression lines shown (shaded area). (a) No lag (b) 5 year lag (c) 10 year lag (d) 15 year lag. The fit of the model to the data is seen to be best in (c).

4.3.2.2 Results of simple regression model

The Stata v10.0 output from the simple linear regression model of notifications on EHPM incorporating the 10 year lag between migration and notification is presented below.
This output contains the following information about the correlation:

- The p-value of the model is <0.0001
- The regression coefficient of notifications on EHPM is 1.04 (95%CI 0.74 – 1.34).
- The r² of the model is high at 0.75.
- The Y intercept of the fitted line is 149.

Discussion of these outcomes and the inferences that can be made about the relationship, including the significance of the gradient of the regression line and the Y intercept value, is presented in 4.4.

The regression model is depicted graphically in figure 4.9. The CI depicted are those derived from the standard error of the prediction, and show the confidence around the estimate for the mean notifications for a given number of EHPM ten years earlier. It can therefore be said with 95% confidence that the true regression line of notifications on EHPM lies within these bounds. These narrow CI are statistically related to the strong p-value of the regression. This is not the same as saying 95% of individual observations will lie within these margins; the CI for individual estimates are much wider (figure 4.16) as they must account for individual variability in observations (229).

Figure 4.9 - Linear regression model of NNDSS notifications against HBsAg positive migrant estimates 10 years prior with 95% CI.
4.3.2.3 Validation of regression assumptions

Three main assumptions underlie the use of regression modelling. These include that the relationship between the independent or predictor variable (X) and the dependent or outcome variable (Y) is linear, the variability of Y should be uniform across the range of X, and that the values of Y should have a normal distribution for each value of X (229). For this analysis, the independent variable X is EHPM and Y is annual notifications with unspecified (chronic) HBV infection.

Assessment of the linearity of the relationship is possible in the first instance by visual assessment of the regression line through the data points (figure 4.9). The high r² value of the model presented reassures that the linear relationship of Y on X explains much of the variability observed, with a very significant p-value for the linear association. Further visual assessment is possible by comparing the simple regression line with the results of a more complex, locally weighted regression of Y on X (figure 4.10).

![Figure 4.10 – Comparison of the linear regression model shown in figure 4.9 with a complex, locally weighted regression function (using ‘lowess’ command in Stata).](image)
This nonparametric ‘smoothing’ function demonstrates that the relationship is quite linear, although it appears there is a slight excess of negative residuals (the difference between the predicted Y value (the regression line) and the observed Y value) at the lower and higher values of X, and more positive residuals around the midpoint. This results in a ‘tugging’ of the locally weighted regression function below the simple regression line at either end, while it trends above the model in around the median values of X.

Construction of a plot of residuals against the fitted values from the regression model allows visual examination of whether the variability in notifications is constant across the range of EHPM (figure 4.11). In this plot the ‘cloud’ of data points appears relatively random and centred on the zero line (representing the fitted values), so the assumption that the variability in notifications is relatively constant across varying EHPM appears to be reasonable. There is some curvature to the line apparent however, as was previously demonstrated in the locally weighted nonparametric regression function. The same deviations are observed, with negative residuals at either extreme of X and positive residuals in the midrange of X.

![Figure 4.11](image.png)

**Figure 4.11** – Plot of residuals (difference between actual notifications and those predicted by the regression model) across fitted values for EHPM from the regression in figure 4.9.
Assessment of the assumption that Y is normally distributed at each X value can be undertaken by generating a normal plot of standardised residuals (with mean=0, standard deviation=1) with a diagonal line representing a normal distribution and lines representing 2 standard deviations either side of the mean (figure 4.12).

For the assumption of normality to be met, the standardised residuals should follow the diagonal, and 95% of the observations should fall within the area bounded by +/-2 standard deviations. The distribution of residuals appears normal in figure 4.12, and all standardised residuals lie within the range described by +/-2 standard deviations.

To confirm the appearance of normality from this graphical assessment with a statistical test, a Shapiro-Francia test for normality can be performed. The Stata output of this test when applied to the residual values from the regression of notifications on EHPM incorporating the 10 year time lag appears below.

```
.shapiro res
```

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs</th>
<th>W'</th>
<th>V'</th>
<th>z</th>
<th>Prob&gt;z</th>
</tr>
</thead>
<tbody>
<tr>
<td>res</td>
<td>20</td>
<td>0.96741</td>
<td>0.853</td>
<td>-0.283</td>
<td>0.61142</td>
</tr>
</tbody>
</table>

Figure 4.12 – Normal plot of standardised residuals from the regression model in figure 4.9.
The p-value for the test is 0.61, thus the null hypothesis of normality stands.

A further test of the influence of individual observations on the regression line can be conducted by plotting leverage (the influence of individual points on the gradient of the regression line) versus residuals (actually the square of the standardised residual) (figure 4.13). This provides evidence of the effect of influential points and outliers on the model.

The red lines in figure 4.13 represent the mean leverage (horizontal) and squared normalised residual (vertical). The observation representing the highest leverage (birth year 1951) has little influence on the gradient as it has a low residual value and lies close to the regression line; the same can be said for the point representing the highest residual value (birth year 1969) as it close to the mean of X and therefore has little influence on the slope of the fitted line. This analysis can be confirmed visually by examining the relationship of the observations mentioned to the fitted regression line in figure 4.14.

Figure 4.13 – Plot of leverage of observations on the fitted line against the square of standardised residuals for the regression model presented in figure 4.9.
Four of the twenty observations shown in figure 4.13 lie above the means of both residual values and leverage. These are the most influential points on the gradient of the regression line. However figure 4.14 demonstrates that the influence of these points acts in opposite directions on the gradient of the fitted line; birth years 1952 and 1953 act to increase the incline by ‘tugging’ the fitted line downward at low values of X, whereas birth years 1963 and 1964 have the opposite affect by depressing the line at high values of X. Furthermore, the influence of these points is mitigated by the two observations with highest leverage (birth years 1951 and 1966) which lie very close to the regression line (low residuals).

Finally, the influence of these points can be determined by fitting a regression model excluding these observations and assessing the impact on the regression coefficient (gradient of the fitted line) and the p-value, CI and $r^2$ of the model (table 4.3).

**Figure 4.14** – Regression model presented in figure 4.9 with individual observations marked with derived birth year. Also shown are the 95% CI for prediction of individual observations (as opposed to CI around the regression line as shown in figure 4.9).
<table>
<thead>
<tr>
<th>Observations used in regression model</th>
<th>Regression coefficient with 95% CI</th>
<th>p-value for association</th>
<th>Coefficient of determination ($r^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.04 (0.74-1.34)</td>
<td>&lt;0.001</td>
<td>0.75</td>
</tr>
<tr>
<td>Four most influential observations excluded</td>
<td>1.06 (0.71-1.40)</td>
<td>&lt;0.001</td>
<td>0.76</td>
</tr>
</tbody>
</table>

**Table 4.3** – Comparison of regression model including all observations with the model excluding the four most influential observations (1952, 1953, 1963 & 1964).

Table 4.3 demonstrates that the coefficient of the regression lines is very similar (1.06 versus 1.04 notifications for every EHPM), with CI very slightly wider in the regression excluding the four influential observations, indicating that the better fit of the regression line (indicated by the slightly increased $r^2$ value) is outweighed by the 20% loss of sample size. The p-values are identical. The similarity between these models is shown in figure 4.15. The gradients (regression coefficients) appear nearly identical with parallel fitted lines. The only observed difference (statistically insignificant) that the regression excluding the four influential points has a marginally greater Y intercept when X (EHPM) equals zero (371 versus 149).

![Figure 4.15](image-url) – Visual representation of the regression models compared in table 4.3. Blue line = original regression model, red line = model excluding the four most influential points.
The results of the analysis presented in this section indicate that the regression model of notifications on EHPM meets the assumptions underlying such analysis, and that no individual observations appear to have undue influence on the model. Having validated the regression in this way, further inference can be derived from the model, including predictions of future notifications using recent migration information for Australia.

4.3.2.4 Using the regression model for prediction

Using the regression model described, predictions of notifications for the values of EHPM from 1996 to 2005 were generated. The 95% prediction intervals were also generated. The confidence intervals depicted in figure 4.10 were for a mean value of Y for a given X, effectively representing the confidence interval for the fitted regression lines, not for individual observations. Understandably, the limits of confidence around estimates of a forecast individual point are wider, as they must reflect individual variability in Y as well as the variability of the mean of a group of observations.

Table 4.4 shows the EHPM per year for 1996 – 2006, with projected notifications and the 95% confidence intervals for the forecasts. These estimates are depicted graphically against the regression model in figure 4.16, with the existing observations used to generate the regression model presented previously (green) and the projections for 2006 – 2016 (orange).

<table>
<thead>
<tr>
<th>EHPM 1996 - 2006</th>
<th>Projected notifications 2006 - 2016</th>
<th>Lower 95% prediction limit</th>
<th>Upper 95% prediction limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>5624</td>
<td>5993</td>
<td>3771</td>
<td>8214</td>
</tr>
<tr>
<td>4717</td>
<td>5050</td>
<td>2847</td>
<td>7254</td>
</tr>
<tr>
<td>3989</td>
<td>4294</td>
<td>2081</td>
<td>6507</td>
</tr>
<tr>
<td>4368</td>
<td>4688</td>
<td>2482</td>
<td>6893</td>
</tr>
<tr>
<td>4683</td>
<td>5015</td>
<td>2812</td>
<td>7218</td>
</tr>
<tr>
<td>5665</td>
<td>6035</td>
<td>3812</td>
<td>8259</td>
</tr>
<tr>
<td>5016</td>
<td>5361</td>
<td>3155</td>
<td>7567</td>
</tr>
<tr>
<td>5258</td>
<td>5613</td>
<td>3402</td>
<td>7823</td>
</tr>
<tr>
<td>6134</td>
<td>6523</td>
<td>4277</td>
<td>8769</td>
</tr>
<tr>
<td>6759</td>
<td>7172</td>
<td>4882</td>
<td>9463</td>
</tr>
<tr>
<td>6719</td>
<td>7131</td>
<td>4844</td>
<td>9418</td>
</tr>
</tbody>
</table>

Table 4.4 – Annual EHPM arriving in Australia 1996-2006 with projected notifications to NNDSS from 2006-2016 (+95% CI) derived from the linear regression model.
Figure 4.16 – Use of the regression model to predict values for notifications based on values of EHPM with 95% confidence intervals for individual forecasts shown.

Naturally, all predicted notifications lie along the fitted line as this is how the predictions are being generated. The 95% CI for individual forecasts are again shown in this plot. Annual EHPM and notifications from the model incorporating the 10 year lag are presented in figure 4.17, with the extension of the model into predicted notifications to the year 2016 with 95% prediction interval.

Finally, the validity of the linear model used to make these predictions can be assessed by fitting locally weighted nonparametric multiple regression ‘smoothing’ functions to the data as was performed in 4.3.2.3 when validating the regression assumptions. Figure 4.18 shows the results of this multiple regression procedure, with derived birth year shown on the X axis and number of notifications on the Y axis. The proximity of the two functions for overlapping values of X reflects the strength of the linear model predictions.
4.4 Discussion

The Victorian HBV serosurvey 1995-2005 demonstrated a higher burden of chronic HBV infection than previously thought, with 1.1% (0.8-1.6) of the surveyed samples positive for HBsAg. Trends in HBsAg prevalence by both geographic region and test year suggest a strong influence of changes in migration patterns underlying the serosurvey results and national notification data.

Although it has long been recognised that migration from high HBV prevalence regions has a profound influence on the prevalence of HBV in Australia, specific annual trends in migration into Australia have not been invoked to explain the rapid rise in notifications of chronic HBV infection through the 1980s and 1990s (34, 38), nor indeed the subsequent decline observed in this decade.
Comparison of three disparate data sources – the Victorian serosurvey, annual notifications to the NNDSS and EHPM settling in Australia – shows that each reflects the same trends in HBV prevalence in this country, once the passage of time from birth to migration to notification is considered. From this analysis it can be estimated that 140,000 HBsAg positive people have migrated to Australia in the last 30 years.

Furthermore, estimates of Australian residents with chronic HBV infection born overseas can be derived by applying the source country HBsAg prevalence estimates used to derive EHPM as described in 4.2.3 to place of birth information from Australian Census data from 1996, 2001 and 2006 (226). These estimates rose from 240,000 in 1996 to 294,000 in 2006, the latter representing 1.4% of the Australian population. This is certainly an overestimate as it does not account for the significant excess mortality associated with chronic HBV infection (13) with the average HBsAg prevalence in this ‘at risk’ population expected to decline over
time. Notwithstanding this fact, it would appear that existing estimates of the prevalence of chronic HBV infection in the community (11, 12) are likely to be conservative.

Simple linear regression modelling confirmed the 10 year median lag period derived from external sources. This technique was also used to assess the strength of the association between EHPM and notified cases of unspecified HBV infection from the annual data for both available from 1976 onwards. The correlation was very strong, with the test of significance of the association returning a p-value of <0.001, indicating that the probability that the observed association between these variables arose by chance is less than 0.1%. The statistical strength of the correlation is notable considering that the number of observations used in the regression model with a 10 year lag was only 20.

Furthermore, the coefficient of determination ($r^2$) of the regression model was very high for an epidemiological study at 0.75, and is due to the clustering of observations close to the regression line (with correspondingly low residual values) (figure 4.9). This suggests that by estimating the number of EHPM in the method described it is possible to account for 75% of the variation in notifications 10 years later.

Why is the median time lag between migration and notification 10 years? A simple explanation on the social level is that migrants are, in general, poorly served by existing health care services (26, 30) and previous research has showed that many migrants from areas with highly prevalent chronic HBV infection have limited understanding of viral hepatitis (19, 26). Hence accessing health services for screening tests may not occur for many years after settlement (if at all). Evidence from Australia and overseas suggests that even when migrants from high prevalence countries do attend medical practitioners, opportunistic screening for HBV infection occurs infrequently (19, 55) even when specific recommendations to do so are contained in national guidelines (27).

However there is another explanation related to the natural history of HBV infection which may explain the consistency of this lag period. Evidence from a large Chinese study of people living with chronic HBV infection (197) demonstrated that the median age of HBeAg seroconversion (progression from immune tolerance to immune clearance/control, see 2.5.2.1) was 34.5 years. This process is associated with immune-mediated destruction of infected hepatocytes resulting in elevated hepatic transaminase levels in the serum and
sometimes significant symptoms. A person with risk factors for chronic HBV infection is more likely to be tested for this infection by their clinician when presenting with these features, which is perhaps why the median age for notifications with chronic HBV infection in both Victoria and throughout Australia is 35 years (see 4.2.4 and 4.3.11). The median age of HBsAg patients in the Victorian serosurvey was also 35, with an interquartile range from 27 to 43 years. With a persistent median age of migrants of around 25 years (which in turn is determined for the most part by specific governmental selection criteria), the 10 year time lag between migration and notification is constructed.

The regression coefficient (gradient of the fitted line) was 1.04, with 95% confidence intervals from 0.74 to 1.34. This can be interpreted that for every 100 EHPM settling in Australia, 104 cases of chronic HBV infection (95%CI 74 to 134) would be notified 10 years later. The Y intercept of the regression line (number of notifications if the number of EHPM 10 years earlier = 0) was 149. However the confidence intervals for this value were very broad (-1332 to 1629) and the p-value for rejecting the null hypothesis that the intercept is zero was non-significant. In linear regression analysis, the further an observation departs from the mean of the independent variable or X (here, HBsAg positive migrants with a mean of approximately 4700), the wider the confidence intervals around the estimate of the dependent variable Y. This was shown in figure 4.9 as the confidence intervals around the regression line are narrowest around the mean X value and curve away from the fitted line in each direction. In the case of the Y intercept which occurs at X=0, this is remote from the mean X value of 4700 and also from the nearest observation upon which the model is built which occurs at an X of approximately 1800.

The strength of the association between EHPM and notifications, and the high proportion (75%) of variability in notifications attributable to EHPM 10 years earlier, allows reasonably secure ten year projections of notifications of chronic HBV infection in Australia to be constructed from the regression model. The notifications forecast by the model oscillate between 4000 and 6000 until the middle of next decade before rising further. These projections assume the relationship between EHPM and notifications remains constant over the next decade. However if expanded post-arrival screening programs or other public health policies are introduced in relation to chronic HBV infection in Australia, the median 10-year ‘notification lag’ would drop. For example, the Sudanese-born population of Australia rose from approximately 5,200 in 2001 to 29,300 in 2006, with most entering under the
humanitarian migration program as refugees. As a high HBV prevalence country, over 8% of these migrants would be chronically infected with HBV – perhaps substantially above this proportion. Although referral bias must be assumed, of a cohort of 174 migrants from Sub-Saharan Africa between 2003 and 2006 seen in a tertiary hospital in Melbourne, 22% had chronic HBV infection (16). A community-based study of African refugees in Melbourne in 2005 revealed 8% were chronically infected with HBV (64).

Refugees, unlike other migrants to Australia, are targeted for post-arrival screening for infections including HBV and the effect of this on the model presented would be to markedly reduce migration-to-notification lag with a relative excess of notifications in the short term, and a compensatory reduction in the notifications 10 years after arrival expected from the model. Such an excess is seen for the notification years 2003-2005 (figures 4.18 and 4.19) and may result from increased case detection in refugees and humanitarian arrivals (230).

Increasing universal vaccination of infants was implemented across many high-prevalence countries late in the last century and through the course of this decade (6, 115), including some countries in the Asia-Pacific region which are a source of significant migrant intake for Australia (see 4.3.1). The impact of these programs is likely to become apparent in Australian surveillance notifications in the 2020s and beyond, as those migrants protected by vaccination at birth will reach the peak migration age at that time and notifications would start to drop once the 10 year lag period had passed. This subject is discussed further in relation to more complex models of the epidemiology of HBV infection in Australia in chapters 6 and 7 of this thesis.

There are a number of weaknesses in this analysis. Median ages for migration and notification were used to establish the time lags used in this analysis, rather than using complete age distributions. Migrants are assumed not to differ from other citizens of source countries in terms of HBsAg prevalence although it is worth noting that there is ample evidence that this assumption holds (19, 30). Point prevalence estimates for source countries by category of population HBV infection prevalence (0.5% for low, 5% for intermediate and 10% for high prevalence countries) have been used to summarise a range of HBsAg values but this is the usual practice in similar research (114, 122). As is observed in Australia, a number of countries have very different chronic HBV infection parameters within sections of the population and no attempt has been made to quantify differential migration from different
communities within source countries. Because a hypothesis about migration was being tested in this chapter, migration was the only explanatory variable in this linear regression model – despite this, 75% of the variation in notifications of chronic HBV infection over time could be accounted for. A more complex model may be able to account for more of the observed variation; this is the subject of the following two chapters.

These potential concerns notwithstanding, this analysis shows that disparate Australian data all suggest a large and expanding epidemic of chronic HBV infection. In addition to the thousands of Australians already known to be living with chronic HBV infection, inference from this linear model suggests more than 50,000 recently arrived HBsAg positive migrants have not yet been notified to the national surveillance system, with the vast majority of these Australians being undiagnosed and therefore unaware of the infection that will ultimately result in the death of one in four of them (7). The need for an upgraded public health response in the face of increasing numbers of people chronically infected with HBV is apparent.
5 Construction of a mathematical model of HBV in Australia

5.1 Background

5.1.1 General principles in modelling of infectious diseases

A mathematical model is at heart a simplified quantitative representation of a real world system. Although there exists a great diversity of model structures, related to the broad range of questions of interest to those designing the models, the essential common feature is an attempt to gain a better understanding of an often very complex process by reducing it to a simplified mathematical construct.

The first applications of mathematical modelling to understanding the epidemiology of infectious diseases were undertaken by British physicians William Hamer and Ronald Ross in the first two decades of the 20th Century. Hamer developed epidemic models of common childhood infections, whereas Ross studied malaria transmission (following his Nobel Prize-winning discovery of the life cycle of malaria parasites). The independent work of these modellers extended the research of their 19th Century compatriot and fellow physician, William Farr, who defined the mathematical principles underlying epidemic infections.

It has been stated that there are three primary qualities of mathematical models (231):

1. **Parsimony** – the model should have all essential elements, and no more
2. **Generality** – the model should be able to be extrapolated to the situation being simulated, and also analogous populations and situations
3. **Prediction** – the end result must include a tool with a predictive capacity

An attempt was made to incorporate these qualities in the mathematical model of HBV in Australia constructed for this thesis with each modification and iteration as described below.

5.1.2 Applications of mathematical modelling

Mathematical modelling can be a powerful tool to improve the understanding of the interactions between pathogen and host, both on an individual, small network and whole population level. The process of constructing a model, with the necessity for systematic gathering of data with which to parameterise the simulation, also highlights areas that require further basic epidemiologic data. Modelling can therefore assist in prioritising further
research. This role is further augmented during sensitivity analysis - if a given parameter when varied within a plausible range results in large differences in outcomes of interest, an area needing more research is thus identified if our understanding of the epidemiology of this disease is to advance.

It is only in the context of such a quantitative simulation that large numbers of alternative assumptions, perturbations and control strategies can be modelled to direct policy and further research. Also, mathematical models allow prediction of future outcomes within the necessary uncertainties underlying such a process.

Such possibilities have led to an increasing application of mathematical modelling techniques to a large number of infectious diseases, both endemic and emergent. As is the case with any formal research project, the first step in constructing a mathematical model must be to define the questions to be answered by the model as this will necessarily affect the design of the simulation in order that the answers can be found.

The questions to be answered by the Australian HBV model were;

1. Can a mathematical model improve our understanding of the burden of acute and chronic HBV infection in Australia?
2. What are the critical assumptions underlying such a model, and are data available to inform these?
3. Can such a model assess the long-term impact of universal infant and catch-up adolescent vaccination, being the primary control program for this disease in Australia?
4. What are the model predictions for the number of people infected with HBV both acutely and chronically over the next several decades, how many people are likely to die as a result, and how certain can we be of these predictions?
5. How can the model outputs be validated against existing data to provide reassurance that the model is simulating reality sufficiently accurately to be able to generalise the results?
6. Once the above questions have been answered, the final question to be answered is: What are the policy implications of the model outcomes, especially for predictions in the burden of HBV infection over the next few decades, and can the model suggest strategies to reduce this burden?
5.1.3 Strengths / weaknesses

Any simulation of a complex reality can only be as reliable as the data with which it is informed. Mathematical models are no exception, though it is at least possible to undertake sensitivity analyses around uncertain or critical information as described above.

A dictum attributed to Albert Einstein that readily applies to mathematical models is “Theories should be as simple as possible, but no simpler”. It is therefore important to include all the detail required to answer the research questions defined, and just as important to exclude unnecessary complexity. The balance between parsimony and realism is naturally a difficult one, with no absolute fulcrum, and must be re-defined with each simulated situation and population.

Mathematical models, unlike many research tools with which the epidemiology of infectious diseases can be investigated, allow prediction of future events, but as described above such predictions rest firmly on the quality of the data informing the model, and are naturally affected by increasing uncertainty the further the predictions are made from the present as unknown perturbations and population differences come into play. One way to assess the security of such predictions is to optimise the model over an extended period of time in the past for which epidemiologic data are available, to validate ‘predictions of the past’ against reality (or at least, our understanding of the situation in reality).

In creating the model of HBV presented in this thesis, an attempt was made to incorporate these strengths and account for the weaknesses. The data used has been derived from a wide range of disparate sources to reduce reliance on any single type or source of information (5.4.3), and sensitivity analysis was undertaken both for critical assumptions (5.4.4) and in terms of an essential structural element of the model (5.3 and 5.4.8). The compartmental model structure used (5.3 and 5.4.2) included only those elements deemed essential to answer the research questions, and complexities included were considered essential and the rationale for their inclusion explored and justified (5.4.2.1 and 5.4.2.2). Although the model predicts events more than 40 years into the future, these predictions were based on those produced by the Australian Bureau of Statistics (ABS) and incorporated sensitivity analysis around critical assumptions (5.4.3 and 5.4.4), and the model used a long ‘run in’ period of over 50 years for the purposes of validation against existing epidemiological estimates.
5.2 Modelling of HBV infection

5.2.1 International models

A number of mathematical models of HBV infection exist in the published literature, designed to answer a variety of questions and simulating HBV epidemiology in a variety of settings, including both low prevalence and high prevalence populations and sub-populations. Those analysed and incorporated in the parameterisation of the model for HBV in Australia are listed in table 5.1. For description of model type and force of infection (FoI), see 5.3.

<table>
<thead>
<tr>
<th>First author, year, and reference</th>
<th>Model type</th>
<th>FoI</th>
<th>Population +/- type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong 1995 (143)</td>
<td>Stochastic (Markov model)</td>
<td>None (all infected at baseline)</td>
<td>Patients with chronic HBV</td>
<td>Meta-analysis of clinical trials of interferon α-2b and treatment cost effectiveness analysis using a Markov model.</td>
</tr>
<tr>
<td>Williams 1996 (120)</td>
<td>Deterministic</td>
<td>Dynamic</td>
<td>Low prevalence</td>
<td>Models vertical and sexual transmission across a variety of sexual activity strata. Transmission due to IDU and impact of migration/ethnicity not assessed.</td>
</tr>
<tr>
<td>Fendrick 1999 (123)</td>
<td>Stochastic (Markov model)</td>
<td>Static</td>
<td>Low prevalence</td>
<td>Vaccine cost effectiveness analysis. A very high FoI is assumed in this and a related study (see 5.4.4).</td>
</tr>
<tr>
<td>Zhao 2000 (232)</td>
<td>Deterministic</td>
<td>Dynamic</td>
<td>High prevalence</td>
<td>Informed by very large epidemiological datasets from China.</td>
</tr>
<tr>
<td>Harris 2001 (53)</td>
<td>Stochastic (Markov model)</td>
<td>Static</td>
<td>Low prevalence</td>
<td>Vaccine cost effectiveness analysis for Australia (see 5.2.2) predominantly adapted from (123), including the high FoI (see 5.4.4)</td>
</tr>
<tr>
<td>Medley 2001 (113)</td>
<td>Deterministic</td>
<td>Dynamic</td>
<td>Theoretical populations – low and high prevalence</td>
<td>Theoretical model exploring catastrophic dynamics of HBV transmission based on population seroprevalence and perturbations thereof.</td>
</tr>
<tr>
<td>Kretzschmar 2002 (122)</td>
<td>Deterministic</td>
<td>Dynamic</td>
<td>Low prevalence</td>
<td>Extension of (120) modelling vertical and sexual transmission but also incorporating the effect of</td>
</tr>
<tr>
<td>Model Reference</td>
<td>Type</td>
<td>Population</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Goldstein 2005 (114)</td>
<td>Deterministic</td>
<td>Static</td>
<td>Global population</td>
<td>Model analysing the burden of chronic HBV and resultant mortality worldwide, and impact of vaccination.</td>
</tr>
<tr>
<td>Kanwal 2005 (142)</td>
<td>Stochastic (Markov model)</td>
<td>None (all infected at baseline)</td>
<td>Patients with chronic HBV</td>
<td>Cost effectiveness analysis for treatment alternatives for chronic HBV with abnormal ALT. No FoI as all infected at baseline.</td>
</tr>
<tr>
<td>Sutton 2006 (233)</td>
<td>Deterministic</td>
<td>Dynamic</td>
<td>High incidence sub-population</td>
<td>Model assessing the impact of prison-based vaccination on HBV transmission amongst IDUs in England and Wales.</td>
</tr>
<tr>
<td>Hutton 2007 (133)</td>
<td>Stochastic (Markov model)</td>
<td>Static</td>
<td>High prevalence sub-population</td>
<td>Cost effectiveness analysis of HBV screening and vaccination of Asians and Pacific Islanders in the USA.</td>
</tr>
<tr>
<td>Hu 2008 (234)</td>
<td>Stochastic (Markov model)</td>
<td>Static</td>
<td>High incidence sub-population</td>
<td>Cost effectiveness analysis of HBV screening and vaccination of IDUs.</td>
</tr>
</tbody>
</table>

Table 5.1 – Mathematical models of HBV infection identified in the literature and used for parameterisation of the model described in this thesis.

5.2.2 Australian model

Only one mathematical model of HBV infection in Australia has been published, which is that prepared by Harris et al and published in the Australian and New Zealand Journal of Public Health in 2001, in an article entitled “An economic evaluation of universal infant vaccination against hepatitis B virus using a combination vaccine (Hib-HepB): a decision analytic approach to cost effectiveness” (53).

This model, as is the case with all the Markov models presented in table 5.1, was conceived to provide an economic evaluation of a health care program – in this case, for inclusion of vaccination against HBV in the infant vaccination program. As is the case for all vaccination cost effectiveness studies presented, the Australian model uses a static FoI (see 5.3), and the resulting linear model therefore cannot incorporate herd immunity. It models the HBV-specific health outcomes of an Australian birth cohort of 260,000 infants over an 80 year
period using different vaccination strategies. As such, it does not incorporate the impact of migration on the burden of HBV in the population.

This study, funded in part by a vaccine producing company which also employed one of the authors, used transition probabilities drawn from two previous cost effectiveness analyses, especially that of Fendrick et al (123) in the USA, which was also sponsored by industry. These probabilities include a static FoI that is much higher than other estimates obtained from the literature (see table 5.5 and discussion in 5.4.4).

This FoI was derived from surveillance data from the USA in the mid-1980s, some 15 years prior to the publication of these models, and represent a period of time when acute HBV notifications in the USA were at an all-time high, and more than three times the number of notifications when the models were published (54, 235). Thus the numbers of acute infections anticipated, and therefore the impact of universal infant vaccination, are greater than if the FoI had been based on more recent data, either from the USA or from Australia.

5.3 Types of mathematical model considered

An essential criterion which categorises mathematical models is whether chance is incorporated into the transition between modelled states. A model where these transitions (for example, becoming infected) are governed by probability is termed a stochastic model, and is particularly appropriate where the role of chance is important to the outcomes of the model. A classic example is that of a small or isolated population, where after initial introduction an infection can either be extinguished or persist in the community - with very different outcomes based on the early role of chance. The probability of given modelled outcomes is derived by performing a large number of model ‘runs’ to generate a probability distribution of the range of outcomes of interest. One type of model that typically incorporates stochastic transitions is an individual model, with each member of the population handled separately and individual calculations determining the passage of individuals through modelled states.

In contrast, deterministic models generally categorise the population into relevant groups and model transition between categories or states (from which the term compartmental model is derived) using averaged rates across discrete time steps. This is typically achieved using difference or differential equations to describe time-dependent changes in the populations of
the states modelled. Deterministic models are appropriate where the role of chance in an individual transition event is not important to the eventual outcome of the model, such as when the numbers in each group or state is large.

Another important distinction between mathematical models is whether the force of infection (FoI) – the risk of a susceptible member of the population becoming infected per unit time – is static or constant over the run of the model, or dynamic, changing with the numbers of infectious individuals in the population over time.

A distinguishing feature of the epidemiology of infectious diseases is the very fact that they are infectious – every case is also a risk factor, depending on the mode of transmission of the infection in question. Traditional cost effectiveness analyses for prevention or treatment of infectious diseases, such as those using conventional Markov processes, retain a static FoI over the duration of the model. Thus,

\[
FoI = k \quad - \text{a simple constant value at all times.}
\]

This is a simplification which ignores the essential fact that with a greater number of infectious cases in the community, the FoI on susceptible individuals will rise, as a greater number of contacts capable of transmitting infection will be with infectious individuals as they assume a larger proportion of the total population. Such models, which are used for the majority of cost effectiveness analyses for vaccination programs, are therefore unable to assess the important consideration of herd immunity.

In contrast, dynamic models incorporate an increasing FoI with increasing numbers of infectious individuals in the population over time. Therefore,

\[
FoI = k'I \quad - \text{a value which is the product of a constant FoI per infectious individual and the number of infectious individuals in the population.}
\]

These can be more difficult to construct and require a range of assumptions which may have limited data to inform them.
Given the large population involved in the model constructed for this thesis (the entire population of Australia, running from approximately 8 million to 30 million people over a century), and perhaps more importantly the relatively large number of infected individuals in the population (rising from tens to hundreds of thousands of people over the simulated period) a deterministic model was deemed appropriate.

Due to the potential impact of increasing numbers of chronically infected individuals over time due to migration, and to the countervailing downward pressure on acute infections due to the implementation of national immunisation programs against HBV, it was felt necessary to model the FoI dynamically. However, as a form of sensitivity analysis and to explore the differences in the two classes of simulation, both static and dynamic FoI models were constructed and compared.

5.4 Model construction

5.4.1 Software used / coding

Data for inclusion in the model were handled in Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, Washington USA). The mathematical modelling program used was Berkeley Madonna version 8.3.14 (Berkeley Madonna Inc., Berkeley, California USA).

5.4.2 Conceptual model structure

A schematic representation of the HBV infection states used in this model is presented in figure 5.1. Each of the blue boxes represents an infection state (susceptible, immune (through vaccination), acute infection, chronic infection, cleared infection). The arrows represent the flow of individuals in the population between these compartments.

This diagram is obviously a simplification in that it does not represent many of the important processes that are required in such a population model, such as the age structure, flow between age groups, births, migration and deaths. A more complete representation of the model flowchart with these factors incorporated is presented in figure 5.2.
Figure 5.1 – Schematic representation of modelled transition between HBV infection states. Blue boxes represent these states, and arrows represent the flow of individuals defined by the natural history of HBV infection, with the white boxes defining the respective transitions.

In figure 5.2, arrows still depict the flow of people between the infection states as in figure 5.1 but now also represent ageing, births and migration entering the population and deaths leaving it. The spheres superimposed on the flows represent formulae defining the flows from the reservoirs according to the parameters and equations defining the modelled behaviour.

The four rows of reservoirs represent the four age groups into which the Australian population was divided for the purpose of the model: 0 to 4 years, 5 to 14 years, 15 to 44 years and 45 years and over. The rationale for these divisions is explained in 5.4.2.1.

The separate cylinders containing smaller cylinders represented at the bottom of figure 5.2 represent sub-models which were constructed to allow assessment of the cumulative number of acute and chronic infections, and the cumulative deaths in uninfected individuals as well as in those acutely and chronically infected with HBV, across the entire modelled time period. These sub-models are depicted in figure 5.3. The lighter coloured reservoirs depicted are ‘aliases’ of the respective HBV states in the primary model. In this way, identical flows of people are modelled as occurs in the primary model without then being removed from the destination state through ageing, mortality and so on, allowing the cumulative cases (or deaths) to be tallied without distorting the population structure of the primary model.
Figure 5.2 – Simplified flowchart of the structure of the mathematical model of HBV infection constructed. Flow across rows represents transition between infection states; downward flow between rows represents ageing between the four age groups (0-4, 5-14, 15-44 and 45+). The sub-models allowing assessment of cumulative cases and cumulative deaths appear at the bottom. This flowchart image is an output from Berkeley Madonna.
Births only enter the youngest age stratum. Migration is possible into all age strata, and all HBV states except acute infection due to the short duration of this state, modelled as thirteen weeks (see table 5.5 for derivation of model parameters). Ageing occurs from younger to older age strata across all HBV states, and mortality (both background and disease-specific in the case of acute and chronic HBV infections) also occurs from all reservoirs (births and migration are represented flowing from, and deaths flowing into, infinity $\infty$).

The start time, time increment (for integration of the differential equations) and run length of any mathematical model of infectious diseases must be chosen carefully to answer the questions of interest, but also to reflect the information available and temporal characteristics of the disease being modelled. For example, integration time steps must not be too long when compared with the incubation or time to resolution of the infection otherwise the simulation outcomes can be distorted. It is also preferable to model a period where input estimates can be drawn from external data to test and validate the model across the known time period.

Therefore it was decided to model HBV infection in Australia for the century from 1951 to 2050, with integration time steps (using the common fourth-order Runge-Kutta integration method in Berkeley Madonna) of six months which were demonstrated to be sufficiently short to avoid distortion of transition between reservoirs – further reductions in the integration time step did not appreciably alter any outcomes. Starting the model in 1951 not only allows for an extensive ‘run-in’ period during which the model outputs can be tested against existing data, but also captures the profound post-war (and subsequent) migration boom that is a fundamental demographic characteristic of the Australian population (225), not least for the proportion of migrants born in intermediate and high HBV prevalence regions (chapter 4).

5.4.2.1 Rationale for age structure

The epidemiology and natural history of HBV infection is fundamentally related to age. The FoI (risk of a susceptible person being infected with HBV) is determined by age (by virtue of age determining the exposures associated with transmission of infection), as is the likelihood of progression to chronicity once infected (see chapter 1). Finally, the outcomes of both acute and chronic infection are affected by the age of the host, with older persons more likely to
Figure 5.3 – Sub-models for assessment of (a) cumulative cases and (b) cumulative deaths. The lighter-coloured reservoirs are ‘aliases’ of reservoirs in the primary model. This flowchart image is an output from Berkeley Madonna.
have symptomatic acute infection, and more likely to develop complications of chronic infection such as cirrhosis and HCC (relating to the duration of the infection in those exposed at birth, and also to the natural history of HBV with different phases of infection) (chapter 2).

The typical age at infection in high prevalence countries is at birth or in early childhood. This results in a high probability of progression to chronicity, and in turn a significant number of girls infected in this way being chronically infected by the time they enter childbearing age. This feedback loop maintaining high prevalence has been well described in mathematical models of HBV endemic populations (113, 140, 232).

In low HBV prevalence populations such as Australia, the most common modes of transmission for incident infections are through sexual contact and IDU (40, 45). This is reflected in the age distribution of incident infections reported to the National Notifiable Diseases Surveillance System (NNDSS) in Australia (40) (figure 5.4).

Vaccination policy for HBV, as with other diseases, is based on immunising the population at risk prior to the period of risk of the infection in question. National universal immunisation programs against HBV in Australia (see chapter 1) are administered to two age groups; infants under the age of 12 months, and adolescents aged 12 – 13 years in the first year of secondary school (10).

![Figure 5.4 – Notification rate for incident HBV infections in Australia by age group and gender, 2006. Taken from (40).](image)
Age is also an important determinant of response to vaccination, with waning seroconversion rates following primary immunisation as age increases – from 95% in children and young adults, to 50% in those aged 60 years or greater (95).

For all these reasons, an age-stratified model of HBV infection was considered essential. It was decided that the four age groups mentioned (0 to 4 years, 5 to 14 years, 15 to 44 years and 45 years and over) would capture the necessary detail in differences amongst modelled parameters whilst not unnecessarily complicating the model age structure with too many strata. Similar stratification (including an oldest age group comprising all individuals over the age of between 40 and 50) is common to many published mathematical models of HBV infection (53, 120, 122, 123, 232). The differences in parameters across the age groups used are discussed in 5.4.3.

It should be noted at this point that no attempt was made to separately model HBV infection in the population according to sex. This generalisation must be justified, not least because of the disparity in risk of incident infection by gender as demonstrated in figure 5.4. This is discussed in 5.4.6.

5.4.2.2 Rationale for including migration

As has been previously explored throughout this thesis (chapters 1, 3 and 4), migration from intermediate and high HBV prevalence countries is the most important determinant of the burden of chronic HBV infection in Australia (11). This fact is common to all low-prevalence countries with significant numbers of residents born in high-prevalence areas (27, 122, 131) and is the reason migration into Australia into all age strata is included in the model developed for this thesis. Such an analysis in population HBV models is not universally adopted (53, 120, 122).

5.4.3 Parameterisation

All population mathematical models employ simplifications of population characteristics to streamline the design or running of the model. These can include ignoring the effect of ageing, ignoring migration, modelling a discrete birth cohort, ignoring background mortality, or setting the total deaths to equal births resulting in a static population size.
However it was decided that given the importance of age as a determinant of many aspects of HBV infection (see 5.4.2.1), age could not be ignored, and nor could migration (5.4.2.2).

Furthermore, in order to answer questions about the epidemiology of HBV infection across the entire country over time the population as whole was necessarily simulated. This necessitated obtaining a large number of parameter estimates, not only of HBV infection and disease progression variables, but for background population parameters, back to at least the start time of the model, the year 1951. This proved a significant challenge in some respects.

### 5.4.3.1 Background population variables

Population parameter estimates used in the model and the sources from which they were derived are presented in table 5.2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Years</th>
<th>Sources</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Births</strong></td>
<td>1951 – 2004</td>
<td>ABS 3105.0.65.001 Table 36: Births registered by sex, 1824 onwards</td>
<td></td>
</tr>
<tr>
<td><strong>Background mortality rates</strong></td>
<td>1951 – 2004</td>
<td>ABS 3105.0.65.001 Table 43. Births registered by sex, states and territories, 1824 onwards Table 47. Crude death rates by sex, states and territories, 1860 onwards Table 45. Standardised death rates, 1971 onwards Tables 52 &amp; 56. Probability of dying between exact age x and exact age x+1, females &amp; males (qx), 1881 onwards ABS 3302.0 Table 1.9 Deaths, Summary, 1996-2006</td>
<td>Age group standardised death annual mortality rates derived from average qx values of male and female life tables 52 and 56 according to the method described in 5.4.3.1.1. Remaining tables (43,45,47) used to verify calculated mortality and resultant annual deaths</td>
</tr>
</tbody>
</table>
Table 1. Projected population, Components of change and summary statistics—Australia Series B

<table>
<thead>
<tr>
<th>Period</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 – 2050</td>
<td>As above, plus ABS 3222.0 Table 1. Projected population, Components of change and summary statistics—Australia Series B</td>
<td>Estimates for 2005, 2006, 2011, 2016, 2021, 2026, 2031, 2036, 2041, 2046 and 2051 available. Linear trend interpolation performed in Excel for other years up to 2050. These estimates were used to verify calculated mortality derived in the method described in 5.4.3.1.1 and 5.4.3.1.2.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total migration (Net Overseas Migration)</th>
<th>1951 – 1974</th>
<th>Immigration: Federation to Century’s End, DIMA 2001</th>
<th>HBV status and age distribution of migrants derived according to methods described in 5.4.3.2.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1975 – 2004</td>
<td>ABS 3412.0</td>
<td>Series B estimates of numbers of migrants used as base case with series A and C used as high and low range assumptions for sensitivity analysis. See 5.4.3.2 for methods used to estimate HBV status and age distribution of migrants.</td>
</tr>
<tr>
<td></td>
<td>2005 - 2050</td>
<td>ABS 3222.0 Table 1. Projected population, Components of change and summary statistics—Australia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total population and age distribution</th>
<th>1951 – 2004</th>
<th>ABS 3105.0.65.001 Table 19. Population, age and sex, Australia, 1901 onwards</th>
<th>Total population and age group proportions for 1951 used for initial model conditions. Subsequent years used to validate model and calculate annual deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2005 – 2050</td>
<td>ABS 3222.0 Table B9. Population projections, By age and sex, Australia - Series B</td>
<td>Used to validate model outputs</td>
</tr>
</tbody>
</table>

Table 5.2 – Population parameter estimates used in the parameterisation of the model and their sources. Key: ABS 3105.0.65.001 Australian Historical Population Statistics, 2006 ABS 3222.0 Population Projections, Australia, 2004 to 2101 ABS 3302.0 Deaths, Australia, 2006 ABS 3412.0 Migration, Australia, 2005-06 Immigration: Federation to Century’s End, DIMA 2001 (225)

5.4.3.1.1 Derivation of age-specific mortality rates

Perhaps the most difficult task encountered in parameterising this model was in deriving background annual mortality rates for the designated age groups in the model. Direct data on the number of deaths by age group were not available to the start of the modelled time period and major difficulties were encountered when trying to adapt the available historical population statistics (236) to the question at hand.
The ultimate resolution of this parameterisation problem was undertaken according to the following steps:

1. Mortality rates \((qx)\) for males and females were obtained from the Australian Historical Population Statistics for 2006 (236) and rates for the sexes were averaged.

2. The sum of individual annual mortality rates for every age represented in the age group was obtained for the 0-4, 5-14 and 15-44 age groups, i.e. for the 0-4 age group

\[
\sum_{i=0}^{4} \mu_i
\]

where \(\mu_i\) is the annual mortality rate at age \(i\)

3. This sum of probabilities was divided by the number of years represented by the age group to give an average annual mortality rate for each of the three younger age groups. Again using the example of the 0-4 age group,

\[
\frac{\sum_{i=0}^{4} \mu_i}{5}
\]

4. This technique is only possible given the low and (relatively) uniform mortality rates within each age group. For example, between 1975-77 a 15 year-old female had a probability of dying of 0.00037 before her 16th birthday, compared with a 44 year-old female with a probability of death of 0.0024 ((236) - Table 52). Although appreciably larger, neither is dramatically different from the mean annual mortality rate for women aged 15 to 44 in that period of 0.00091. Contrast this to the difference between a 50 year old woman of the same era with a mortality rate of 0.00408 and a woman aged 90 years with a likelihood of dying within a year of 0.18027.

5. A conceptually straightforward resolution to this problem was found. Simply put, deaths in those aged over 45 must equal total deaths minus those in younger age groups. Therefore, the annual mortality rates in the younger groups were multiplied by the number of people in the age groups, with the resultant number of deaths subtracted from the total registered deaths for that year derived from ((236) - Table 43). This number of deaths was then divided by the population aged 45 plus to derive a summary mortality rate for the final age stratum.
For years not covered by the life tables’ qx functions, linear interpolation was performed in Microsoft Excel. Figure 5.5 shows the trend in the mortality rates derived as described above from 1951 to 2004. In addition, a linear trend line of mortality in those aged 45 and over is plotted with the equation depicted in the chart area. This linear function explains 88% of the variability in mortality rates in this age group as demonstrated by the coefficient of determination (r²). Although this is a simplification of a more complex trend (with minimal change in mortality until 1968 and a more rapid decline than the linear function thereafter), this parsimonious approach is justified by validation against ABS data, demonstrated in figure 5.7 and in more detail in 5.4.11.

5.4.3.1.2 Projection of mortality rates from 2005 to 2051

Estimated numbers of deaths according to the Series B predictions from the ABS (127) were available for the years 2005, 2006, 2011, 2016, 2021, 2026, 2031, 2036, 2041, 2046 and 2051. Linear trend interpolation was performed in Microsoft Excel for other years up to 2050. These estimates were used to verify calculated number of deaths based on mortality rates for the four age groups.

Figure 5.5 – Annual mortality rate by age group, Australia, 1951 to 2004; plus linear trend of mortality rate in 45+ age group with forward projection.
For the youngest three age groups, annual mortality was held static at the 2004 rates. This was done because the secular trends in these mortality rates had ‘flattened’ in recent decades (figure 5.5) and little further significant reduction is therefore likely to impact upon these rates. The same cannot be said for mortality in the 45+ age group also as shown in figure 5.5.

A further reduction in age-specific mortality is very likely to occur in sub-strata within this large age grouping. However a countervailing influence will be the increasing median age of persons within this large age group, resulting in an increase in mortality rates in the group over time.

Three alternate assumptions in the net balance between these trends were assessed relative to the ABS Series B death projections (127). These assumptions are illustrated graphically in figure 5.6, which also depicts the steady background mortality rates in the younger age groups after 2005.

- Assumption 1 – the decline in mortality continues in the linear trend described previously until a ‘threshold’ mortality rate of 0.01 is reached (in around 2037). This assumption holds that the increasing average age in the 45+ age group has minimal effect on the overall mortality rate.
- Assumption 2 – no decline in mortality after 2005. This assumption holds that any decrease in age-specific mortality is counterbalanced completely by the increasing average age in this group.
- Assumption 3 – the age specific mortality in the group continues to decline according to the linear trend for approximately 10 years, after which the reduction in mortality is balanced by increasing age and the mortality rate remains static for several years. Finally, the linear trend is reversed with increasing mortality to account for increasing average age across the group. This assumption was constructed following comparison of the projected deaths under the previous two assumptions with ABS Series B projections in an attempt to reduce the disparity.
Figure 5.6 – Annual mortality rate by age group, Australia, 1951 to 2004 plus projections to 2050. Different mortality assumptions for the 45+ age group are shown; refer to text for details.

Figure 5.7 displays the predicted number of deaths from 2005 to 2050 under the Series B projections from the ABS (127) along with the number of deaths under the three assumed mortality rate models for the 45+ age group described above.

Figure 5.7 – Projected annual deaths, Australia, 2005 - 2050 under different 45+ age group mortality assumptions (see text) compared with ABS series B projections.
The third mortality model assumption is demonstrated to best approximate the ABS projections, and was therefore the mortality rate used for the mathematical model. Naturally, if this age group was divided into smaller strata, then the reversal in mortality trend reduction would not be seen particularly in the younger substrata of this age group.

5.4.3.2 Migration variables

5.4.3.2.1 Migration to Australia 1951-2005 and projections to 2051

Numbers of migrants to Australia by country of birth were obtained from 1951-2005 as described in the previous chapter in 4.2.3 (225, 226). Projections of net overseas migration (NOM) were obtained from published ABS estimates (127). The mid-range projection for migration (Series B) was used as the base-case scenario, with high and low projections (series A and C respectively) used for sensitivity analysis around migration estimates.

5.4.3.2.2 Migrant age distribution

The age distribution of migrants to Australia over the entire modelled period was derived primarily from the age distribution of all 763,000 migrants to Victoria between 1975 and 2006 (commissioned ABS data obtained by the Communicable Disease Prevention and Control Branch, Victorian Department of Human Services) which is shown in figure 5.8.

Figure 5.8 – Age distribution of all migrants to Victoria, 1975 – 2006.
This information was compared to migrant age distribution estimates from an existing mathematical model incorporating migration into a low-prevalence country (122). The resultant age distributions were grouped into the age strata used in this model described in 5.4.2.1, so that 10% of migrants were modelled to be 0-4 years of age, 15% 5-14, 65% 15-44, and 10% over 45 years over the 100 year period modelled.

5.4.3.2.3 Migrant HBV infection status

As migrants remaining susceptible to HBV and those with prior resolved HBV infection were to be modelled in addition to those with chronic HBV, estimates of the proportions of the population of low, intermediate and high prevalence countries in these three states were derived from published data (7, 29, 114, 122, 227). The resultant estimates are shown in table 5.3.

In order to categorise the projected migrants from 2005 onwards into source country HBV prevalence, the country of birth of all migrants to Australia from 1985 to 2005 (225, 226) was assigned to HBV prevalence categories as described above. The reason why migration after 1985 was chosen to base future projections of migrant source region was that there was a fundamental shift in migrant HBV source region after this year as demonstrated in table 5.4.

This shift was largely due to the removal of the White Australia policy in the early-mid 1970s, in conjunction with an influx of refugees following the Vietnam War and other South-east Asian conflicts (225) and a progressive withdrawal of various forms of public subsidy of British migration to Australia (such as the assisted passage program) by both governments through the 1970s (225).

<table>
<thead>
<tr>
<th></th>
<th>Susceptible</th>
<th>Infected</th>
<th>Resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>94.5%</td>
<td>0.5%</td>
<td>5%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>60%</td>
<td>5%</td>
<td>35%</td>
</tr>
<tr>
<td>High</td>
<td>20%</td>
<td>10%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Table 5.3 – Estimated HBV infection status of migrants by source country HBsAg prevalence.
Table 5.4 – Changing percentage of migrants settling in Australia by source country HBsAg prevalence, 1945 – 2005, plus estimated percentage of all migrants with chronic infection.

After around 1985 the proportion of migrants born in low, intermediate and high prevalence regions stabilised and has remained relatively unchanged when compared to the previous 40 years (chapter 4, figure 4.3). Therefore the source country HBV prevalence proportions used for the projections from 2005 to 2051 are: low prevalence 35%, intermediate prevalence 25%, and high prevalence 40%.

5.4.3.3 HBV parameters

Estimates for HBV parameters were derived from a range of sources including existing mathematical models (113, 114, 120, 122, 140, 232, 233), cost-effectiveness analyses (53, 123, 133, 142, 143, 234), review articles (95, 96), and reports of international (131), Australian (38, 44) and Victorian surveillance programs (237-239). The summary estimates for these parameters are shown in table 5.5.
<table>
<thead>
<tr>
<th>Duration of acute infection (weeks)</th>
<th>All patients</th>
<th>13</th>
<th>13 (113, 140, 232, 233)</th>
<th>15 (120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infection mortality (proportion)</td>
<td>0-4 years</td>
<td>0.001</td>
<td>Derived from combined probabilities of fulminant infection and death in fulminant infection from: (53, 114, 123, 133, 234)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-14 years</td>
<td>0.0014</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-44 years</td>
<td>0.0035</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 plus years</td>
<td>0.0035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression to chronicity (proportion)</td>
<td>Neonate</td>
<td>0.5</td>
<td>0.85 (232)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.88 (123)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.885 (96, 120, 122)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.9 (53, 114, 133)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-4 years</td>
<td>0.07 – 0.9 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.08 – 0.9 (123)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1 – 0.85 (232)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3 (114)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.35 (96)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-14 years</td>
<td>0.06 (114)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06 – 0.8 (123)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.07 – 0.9 (53)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1 (232)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.16 (122)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2 (96)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-44 years</td>
<td>0.05 (122, 233, 234)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06 (114)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06 – 0.1 (53)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06 – 0.08 (123)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.075 (96)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1 (120, 232)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 plus years</td>
<td>0.03 (122)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.04 (53, 123)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.05 (96, 233, 234)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06 (114, 133)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1 (120, 232)</td>
<td></td>
</tr>
<tr>
<td>Chronic infection mortality (proportion dying /year)</td>
<td>0-4 years</td>
<td>0</td>
<td>Derived from combined probabilities (depending on study) of progression to active disease, cirrhosis, decompensated cirrhosis, HCC, liver transplant and death from: (53, 114, 123, 133, 142, 143, 232, 234)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-14 years</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-44 years</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 plus years</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution of chronic infection</td>
<td>0-4 years</td>
<td>0</td>
<td>0 (114)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.01 (143, 232)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 5.5 – Estimates for HBV parameters used in the model by age group, plus individual estimates from sources used (with references for the sources used appearing next to each estimate).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Proportion Clearing / Year</th>
<th>Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-14 years</td>
<td>0.005</td>
<td>0.015 (120)&lt;br&gt;0.018 (123)&lt;br&gt;0.02 (53)&lt;br&gt;0.025 (113, 140, 233)</td>
</tr>
<tr>
<td>15-44 years</td>
<td>0.01</td>
<td>0.005 (114)&lt;br&gt;0.01 (143, 232)&lt;br&gt;0.015 (120)&lt;br&gt;0.018 (123)&lt;br&gt;0.02 (53)&lt;br&gt;0.025 (113, 140, 233) 0.1 (234)</td>
</tr>
<tr>
<td>45+ years</td>
<td>0.025</td>
<td>0.005 (114)&lt;br&gt;0.01 (143)&lt;br&gt;0.015 (120)&lt;br&gt;0.018 (123)&lt;br&gt;0.02 (53)&lt;br&gt;0.025 (113, 140, 233)&lt;br&gt;0.05 (232)&lt;br&gt;0.1 (234)</td>
</tr>
<tr>
<td>Efficacy of Vaccination (Proportion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 years</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>5-14 years</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>15-44 years</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>45+ years</td>
<td>0.75</td>
<td></td>
</tr>
</tbody>
</table>

#### 5.4.4 Parameter sensitivity analyses

Sensitivity analyses for FoI and migration were constructed based on the range of estimates in source data as described in table 5.6. There were a number of reasons why these parameters were chosen for sensitivity analysis. Total numbers of acute and chronic HBV infections are highly sensitive to variations in FoI and migration estimates respectively. This is to be expected since the acute infections by definition occur within Australia and are therefore determined by the FoI acting on susceptible individuals in the model; moreover, most infections are in adults and therefore resolve without progression to chronic infection.
Parameter Group | Base estimate | Range of estimates for sensitivity analysis
--- | --- | ---
**Force of Infection (FoI)** (infections/million/year) | 0 - 4 years | 6 | 1x base = “base FoI”
| 5 - 14 years | 6 | 3x base = “intermediate FoI”
| 15 - 44 years | 80 | 5x base = “high FoI”
| 45 plus years | 20 | |
**Net Overseas Migration Australia, 2005 – 2050** (number of people) | 110,000 | 80,000 = “low migration”
| | | 110,000 = “base migration”
| | | 140,000 = “high migration”

Table 5.6 – Range of FoI and migration projections used in the model for sensitivity analysis

In contrast, the majority of chronic infections arise from infection in childhood which is far more common in countries with high HBV prevalence, explaining why migration is the fundamental determinant of the number of chronic infections.

Another reason for performing a sensitivity analysis for these parameters is because there is marked uncertainty in these parameter values, for quite different reasons.

It is very difficult to estimate the FoI for the general population. It is well recognised that notifiable diseases surveillance systems underestimate disease incidence, particularly for infections with a large proportion of asymptomatic cases (40, 54). What is more difficult is estimating the proportion of such infections that are notified. One attempt to answer this question for acute HBV infections involved the implementation of an active surveillance system for clinically diagnosed acute viral hepatitis in a county of Washington State, USA in the 1980s and comparison of the results to the conventional passive surveillance system (50).

This study determined that passive surveillance was missing one third of cases of acute HBV, but it is important to recognise two important facts: first, that the active surveillance relied on clinical cases of viral hepatitis diagnosed by clinicians and would therefore have missed asymptomatic, mild or non-specific infections; and secondly that even those people with apparent acute viral hepatitis who were unable to obtain medical care (in the absence of universal free health care in the USA, conceivably correlating with such economically marginalised groups as IDU and migrants, illegal or otherwise) would not be captured by the active surveillance program. The true proportion of incident HBV not captured by the passive surveillance system is therefore likely to be substantially greater than 33%.
The CDC Division of Viral Hepatitis publishes estimates of the disease burden from viral hepatitis in the USA (54). In these estimates surveillance notifications are considered to represent approximately one third of all acute clinical cases of HBV, and only 10% of all incident HBV infections. These estimates are derived from data on HBV seroprevalence obtained in the Third National Health and Nutrition Examination Survey (NHANES III) of 20,000 US residents between 1988 and 1994 (52). Specifically, a technique known as catalytic modelling was applied to the seroprevalence data to derive the estimated FoI acting on different age groups required to generate the observed seroprevalence curves (240).

A problem with using catalytic modelling is that migration of people infected in high prevalence countries distorts the seroprevalence estimates by age group; this is why catalytic modelling applied to the Victorian Hepatitis B Serosurvey 1995 – 2005 was unable to help inform estimates of FoI for the Australian HBV model constructed for this thesis and was ultimately abandoned. Over 18% of subjects included in the NHANES III HBV study were born outside the USA (52), and no mention is made in either the CDC’s HBV incidence estimates derived from the NHANES data using catalytic modelling (240) nor in their viral hepatitis disease burden document (54) of whether these migrants were excluded from the catalytic model. In the initial catalytic modelling paper there is a category for Asian/Pacific Islanders (240). Given that this description is not expressly defined to represent American-born descendants of this ethnic group (and also by the observation that the incidence rate calculated for this group from their anti-HBc prevalence is more than 11 times that of people classified as ‘whites’), it is safe to assume that migrants are incorporated in the CDC catalytic model. As a consequence, concerns should be held about the validity of both the incidence rate derived in this manner (240), and by association the assumption that the true incidence of acute HBV is 10 times surveillance notifications (54).

It is therefore certain that surveillance notifications underestimate actual incident HBV infections, by a most uncertain degree. Consequently, the range of FoI values adopted in this model for the purpose of sensitivity analysis (table 5.6) lie between twice the Australian notification rates for the relevant age group (‘baseline’, ‘base case’ or ‘low’ FoI) to between three (‘intermediate’) and five times (‘high’) this value, being six and ten times the notification rate respectively. It is also important to realise that these surveillance notification rates are affected by vaccination against HBV, resulting in a reduction in the estimated FoI derived from these data.
It is worth noting that the upper bound of the FoI in this sensitivity analysis for the 15-44 year age group remains only one fifth of that assumed in two of the source studies (53, 123) which were both economic analyses of combined hepatitis B / *Haemophilus influenzae* type B vaccination programs for infants funded in part by vaccine manufacturers. Their estimates for FoI in the 15-44 age range were therefore nearly 50 times the notification rate in the national and Victorian surveillance systems (38, 237). This was discussed in section 5.2.2.

For migration, unlike FoI, the uncertainty lies not in a lack of data for this parameter, as detailed records by birth country are available in the public domain, especially since 1975. Rather, the uncertainty arises in an attempt to project migration – both in absolute numbers, and in source country HBV prevalence – for the next 42 years. Any estimate must necessarily be very approximate, especially given the profound changes in migration to Australia over the last 58 years as described in 5.4.3.2.3. The range in the estimated total number of migrants was derived from ABS projections (127) as described in table 5.2 and the source country HBV prevalence derived from the proportions observed from 1985 to 2005 shown in table 5.4.

### 5.4.5 Modelling of immunisation

Immunisation from the year 1985 onwards is included in the model structure. Immunisation of susceptible individuals is modelled for all age strata, although immunisation of the youngest two age groups is restricted to coverage once they become eligible under the auspices of the National Immunisation Program (NIP). This is in the year 2000 for infants and from 1998 for the adolescent catch-up program (10) (chapter 1). For the purposes of the model, the adolescent catch-up program runs until 2012 when the first cohort of infant vaccinees reach the oldest eligible age for the catch-up program (14 years).

It should be noted that antenatal screening and subsequent interventions to prevent vertical transmission are not included in this model. However the derivation of FoI using surveillance system notifications occurred within a context of antenatal screening and intervention and therefore reflects these public health strategies; furthermore, the infant NIP incorporated in the model acts to prevent a significant amount of vertical transmission.
The way that vaccination was coded was to incorporate terms for vaccine availability, vaccine efficacy, the proportion of children vaccinated, and the existence or otherwise of a vaccination program at each given time point across the model. Each of these terms was specific for each age group.

For example, for the 0-4 age group, transition from susceptible to immunised is defined by the formula:

\[ \text{Sus}_0 \times \text{vacc}_\text{eff}_0 \times \text{vacc}_\text{prop}_0 \times \text{vacc}_\text{prog}_0 \times \text{vacc}_\text{avail} \]

With:

- \( \text{Sus}_0 \) representing all susceptible children in the age group at a given time
- \( \text{vacc}_\text{eff}_0 \) being the efficacy of vaccine in the age group (95% for these children)
- \( \text{vacc}_\text{prop}_0 \) being the proportion of susceptibles vaccinated
- \( \text{vacc}_\text{prog}_0 \) being an indicator variable to instruct the model in what year to commence the NIP, coded for this age group as:
  \[ \text{vacc}_\text{prog}_0 = \text{IF}(\text{TIME} \geq 2000) \Rightarrow 1 \text{ ELSE } 0 \]

Similarly, \( \text{vacc}_\text{avail} \) is a term to prevent vaccination being modelled prior to hepatitis B vaccine becoming available, set to 1985 for the purposes of this model. This is more important for vaccination of adults, for whom no NIP exists and vaccination earlier in the model occurs. The \( \text{vacc}_\text{avail} \) term is coded as:

\[ \text{vacc}_\text{avail} = (\text{IF}(\text{TIME} \geq 1985) \Rightarrow 1 \text{ ELSE } 0) \times \text{vacc}_\text{tog} \]
\[ \text{vacc}_\text{tog} = 1 \]

The \( \text{vacc}_\text{tog} \) variable was included to allow comparison of outcomes with and without vaccination in a single run using batch runs with \( \text{vacc}_\text{tog} \) taking values of either 0 (no vaccination) or 1 (with vaccination).

To enable a range of proportions of susceptibles covered by the immunisation program to be modelled dynamically with real-time assessment of the impact on outcomes of interest, the
‘Slider’ function of Berkeley Madonna was utilised (see 5.4.10.2). Once defined, this graphical interface allowed manipulation of the parameters with automatic re-compiling of the model with every change in the vaccinated proportion of the population across the age strata.

5.4.6 Assumptions, generalisations and exclusions

A number of simplifying assumptions necessarily underlie any mathematical model seeking to describe complex interactions of pathogenic microorganisms with large populations. Some of these are listed below.

- This model is deterministic and does not model individual risks, transmission probabilities, or smaller subpopulations (except for migrants, and these are not separately modelled once migration has occurred). Nor is gender, sexual orientation, or ethnicity including Indigenous status incorporated. Therefore transmission between individuals is by necessity a ‘summary’ of probabilities, including that for vertical transmission.

- The importance of sex in considering the epidemiology of HBV infection includes a significantly different risk of incident infection (see figure 5.4). Furthermore, there are other gender disparities in the epidemiology and natural history of HBV infection, including the fact that males are far more likely to develop complications of chronic HBV including cirrhosis, HCC and death (69). However many of the sources of data used to parameterise the model were not stratified by gender, and adding separate sex categories for all reservoirs and transitions in the model would have greatly added to the complexity of the model structure. This model is intended as a summary exploration of the entire population of Australia over a prolonged period, and therefore it was felt that significant loss of parsimony by incorporating sex differences (particularly as the data necessary to do so was often unavailable) was not justified.

- It is important to recognise that Indigenous Australians were not explicitly incorporated as a separate subpopulation in the model. As presented in chapter 1, Indigenous Australians have a very diverse, but generally much higher burden of chronic HBV infection than other Australians born in this country. Although Indigenous Australians constitute a relatively small proportion of the population (2.3% in the 2006 Census), they have been estimated to represent 16% of people
chronically infected with HBV in this country (11). While separate compartments representing this population were not included in the model, the parameters used in the construction of the model incorporated information from this subgroup.

- For the same reasons given for Indigenous Australians, sub-modelling of migrants and their children (to the first generation at least) could allow analysis of the dynamics of clustering of infection, and assessment of the impact of targeted intervention strategies. However, such subgroup analysis would add great complexity and require a number of assumptions (regarding intermarriage for example) for which data may be lacking. Thus mathematical modelling of HBV infection in Indigenous Australians, and in Australians born overseas and their children, may be more appropriately implemented in entirely separate, standalone models.

- Considering the 45 plus age group as a single stratum results in analysing a very heterogeneous group together, especially regarding mortality (both all-cause, and HBV specific) which required complex compensatory calculations (5.4.3.1.1).

- Another impact of the age group structures used was the incorporation of neonates into the 0-4 age group, with very different risks of progression to chronic HBV across this age stratum (shown in table 5.5) which necessitated using a summary progression risk across all these ages.

- No emigration is incorporated in the model, though in the ABS projections Net Overseas Migration (NOM) is used to ensure population balance. The source country prevalence estimates for 1985 – 2005 are applied to this NOM figure; no attempt to categorise emigrants by birth country (and therefore HBV prevalence) has been made.

- For this population model, immunisation simulated includes the NIP for infants and adolescents plus non-NIP vaccination of adults aged 15 - 44 years. No immunisation of children outside the NIP, or of adults over 45 years, is modelled.

- Immunisation of migrants in their source countries has not been included. This is likely to have an impact in twenty to thirty years as residents who were included in their countries’ infant immunisation programs will begin to reach the age of peak migration to Australia (6, 115). However, this impact may not be as profound or as immediate as hoped; in 2006, estimated coverage of the birth dose of hepatitis B vaccine in high HBV prevalence countries was estimated to be only 36% worldwide, although in the South-East Asian and Western Pacific WHO regions estimated coverage was higher, at 46% and 75% of high prevalence countries respectively.
Once again, further analysis including the impact of variable rates of infant vaccination in source countries is planned.

- To derive age group specific FoI, the same multiplier of surveillance notifications (x2 for base case, x10 for high case) was used for all age groups. It is however likely that the ratio of notified to actual infections is higher in older age groups, with symptomatic and icteric acute HBV more common as age increases (chapter 2). The result is that the FoI in younger age groups is probably lower than it should be relative to older age groups.

5.4.7 Equations

Appendix 2 presents the equations used to describe the initial conditions, the flows through the model compartments, the population, infection and vaccination parameters, and the derived summary variables for the static FoI model and sub-models.

5.4.8 Static versus dynamic force of infection

As described in 5.3, a dynamic FoI model was constructed in addition to the base model with static FoI described in Appendix 2. A critical component of modelling a dynamic FoI is to determine effective contacts capable of transmitting infection between groups within the model. Some models assume homogeneous mixing – that all groups (or individuals) in the population are equally capable of transmitting (or acquiring) infection from all others. This is often not a realistic assumption. For example, many infections (such as measles, rubella, and influenza) appear to have a higher FoI in children than in adults, related to age related mixing patterns (such as school clustering), but possibly also to biological differences in children and their response to infections (with increased susceptibility to developing chronic infection as for HBV, or more asymptomatic infection such as hepatitis A virus, or prolonged infectiousness such as for influenza).

Where there is evidence for heterogeneity in mixing leading to epidemiologic differences in the FoI (for example by age group, or number of sexual partners per unit time, or time since initiation of IDU), heterogeneous mixing can be incorporated to render the transmission probabilities more realistic. A ‘Who Acquired Infection From Whom’ (WAIFW) matrix is constructed to represent the differential probability of effective contact. There is often limited
(or no) actual data to inform such a matrix for the population in question, and assumptions are made on the basis of plausibility.

The base case WAIFW matrix for this model is represented in figure 5.9(a). The underlying assumption for this ‘base case’ matrix is that the probability of contact with an infectious member of the population from a given age group is relative to the proportion of all infectious persons in the population within that age group. This is a form of homogeneous mixing assumption in that contact capable of transmitting infection depends only on the age distribution of infectious individuals in the population, not on differential contact rates within or across age strata. This age distribution is derived from the numbers of acutely and chronically infected individuals in the population in the year 2000 – the rationale for using this year is explained below.

To assess the sensitivity of the model to this mixing assumption, two alternate WAIFW matrices were constructed. WAIFW 2 augments the proportion of effective contacts from within the same age group as the susceptible contact by halving the proportion of infectious contacts from other age groups compared to their proportion of the infectious individuals in the population (that is, half of the proportions in the base case WAIFW matrix) other than for susceptibles in the 0 – 4 age group, where the infectious age group augmented is the 15 – 44 stratum to account for vertical transmission (figure 5.9(b)). This within-age group increase in effective contacts reflects modes of transmission important for HBV such as sexual contact and IDU (see chapter 1). WAIFW 3 used for sensitivity assumes even more heterogeneity in infectious contacts in that all infections arise from contact within age strata, again excepting the youngest susceptible group where all infections arise from the 15 – 44 age group (figure 5.9(c)).

An additional complexity which arises in the dynamic modelling of chronic infections (including HBV, but also other infections such as HIV, HCV, Epstein Barr virus, herpes simplex and syphilis to name a few) is the relative infectiousness of an infected person during the acute phase of their infection, versus that during chronic infection (which is in itself a simplification of a complex natural history with variable infectiousness across the period of chronic infection, especially for HBV as discussed in chapter 2). For this model, the relative infectiousness of chronically infected hosts was 0.16 that of acutely infected individuals, a
Figure 5.9 – Proportion of total FoI acting on susceptible contacts by age group of infectious contact under different WAIFW structures; (a) WAIFW 1 assuming homogeneous mixing, (b) WAIFW 2 with increased within-age group mixing and (c) WAIFW 3 with completely heterogeneous mixing based on age group categories.
value applied in prior mathematical models (140, 233) which was originally developed from epidemiological data gathered in a high prevalence country.

Finally, the FoI for the dynamic model was derived for each age group in the following way:

1. The baseline FoI from the static model was used as the foundation of the dynamic FoI
2. This static baseline FoI, having been derived from information predominantly gathered in the last two decades, was applied for the year 2000 in the dynamic model
3. The number of [acutely infected + 0.16*[chronically infected]] individuals was calculated from the baseline static model estimates for the year 2000 to represent ‘infectious units’ in each age group
4. This number was used to derive the age distribution of infectious individuals in the population as described above
5. For each age stratum the total FoI acting on susceptibles in the year 2000 was multiplied by the proportion of the force of infection derived from infectious units in each age group (e.g. by the age distribution of all infectious units for the base case model), divided by the total number of infectious units in that age group to determine a FoI per infectious unit in each age stratum.
6. The FoI per infectious unit derived in this fashion was then applied to the model over the entire run period (1951-2050) to simulate a dynamic FoI depending on both the number of infectious units in each age group, and the FoI of these units acting upon susceptibles in each age group.

An example of this process for the 0 - 4 age group appears below.

For year = 2000

<table>
<thead>
<tr>
<th>Age 0 – 4</th>
<th>Age 5 – 14</th>
<th>Age 15 – 44</th>
<th>Age 45+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Chronic</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>1.82</td>
<td>2460</td>
<td>3.85</td>
<td>11404</td>
</tr>
<tr>
<td>143.69</td>
<td>76679</td>
<td>35.58</td>
<td>43880</td>
</tr>
</tbody>
</table>

Assuming infectiousness of chronically infected individual is 0.16 that of acutely infected

Composite infectious units per age group in year 2000 =

\[
\begin{align*}
\text{Age 0 – 4:} & \quad 1.82 + (0.16\times2460) = 395.42 \\
\text{Age 5 – 14:} & \quad 3.85 + (0.16\times11404) = 1828.34 \\
\text{Age 15 – 44:} & \quad 143.69 + (0.16\times76679) = 12413.26 \\
\text{Age 45+:} & \quad 35.58 + (0.16\times43880) = 7056.38
\end{align*}
\]
For base WAIFW risk is proportional to age distribution of infectious units (homogeneous mixing) therefore relative contribution is:

- Age 0 – 4: \(\frac{395.42}{21693.4} = 0.018228\)
- Age 5 – 14: \(\frac{1828.34}{21693.4} = 0.084281\)
- Age 15 – 44: \(\frac{12413.26}{21693.4} = 0.572214\)
- Age 45+: \(\frac{7056.38}{21693.4} = 0.325278\)

For age group 0 – 4:

- FoI (2000) = 0.000006
- Therefore FoI from 0 – 4 age group = 0.000006*0.018228 = 1.09368E-07
- And FoI per infectious unit in 0 – 4 age group = 1.09368E-07/395.42 = 2.76587E-10

These calculations result in a FoI per infectious unit which varies considerably between the WAIFW matrix structures as shown in table 5.7.

<table>
<thead>
<tr>
<th>WAIFW 1</th>
<th>From 0 - 4</th>
<th>From 5 - 14</th>
<th>From 15 - 44</th>
<th>From 45+</th>
</tr>
</thead>
<tbody>
<tr>
<td>On 0 – 4</td>
<td>2.7797E-10</td>
<td>2.7796E-10</td>
<td>2.7796E-10</td>
<td>2.7796E-10</td>
</tr>
<tr>
<td>On 5 -14</td>
<td>2.7797E-10</td>
<td>2.7796E-10</td>
<td>2.7796E-10</td>
<td>2.7796E-10</td>
</tr>
<tr>
<td>On 15 – 44</td>
<td>3.7062E-09</td>
<td>3.7061E-09</td>
<td>3.7061E-09</td>
<td>3.7061E-09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WAIFW 2</th>
<th>From 0 - 4</th>
<th>From 5 - 14</th>
<th>From 15 - 44</th>
<th>From 45+</th>
</tr>
</thead>
<tbody>
<tr>
<td>On 0 – 4</td>
<td>1.3827E-10</td>
<td>1.3840E-10</td>
<td>3.8084E-10</td>
<td>1.38695E-10</td>
</tr>
<tr>
<td>On 5 -14</td>
<td>1.3827E-10</td>
<td>1.7805E-09</td>
<td>1.3861E-10</td>
<td>1.38695E-10</td>
</tr>
<tr>
<td>On 15 – 44</td>
<td>1.8436E-09</td>
<td>1.8454E-09</td>
<td>5.0778E-09</td>
<td>1.84927E-09</td>
</tr>
<tr>
<td>On 45+</td>
<td>4.6090E-10</td>
<td>4.6134E-10</td>
<td>4.6202E-10</td>
<td>1.88362E-09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WAIFW 3</th>
<th>From 0 - 4</th>
<th>From 5 - 14</th>
<th>From 15 - 44</th>
<th>From 45+</th>
</tr>
</thead>
<tbody>
<tr>
<td>On 0 – 4</td>
<td>0</td>
<td>0</td>
<td>4.8444E-10</td>
<td>0</td>
</tr>
<tr>
<td>On 5 -14</td>
<td>0</td>
<td>3.2843E-09</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>On 15 – 44</td>
<td>0</td>
<td>0</td>
<td>6.4592E-09</td>
<td>0</td>
</tr>
<tr>
<td>On 45+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.8426E-09</td>
</tr>
</tbody>
</table>

Table 5.7 – FoI contributed by each individual infectious unit by age group acting on susceptibles in each age group under the three WAIFW contact matrix assumptions.
The resultant base-case dynamic FoI for each age group over the run time of the model is depicted in figure 5.10(a), with horizontal black bars indicating where the dynamic FoI crosses the static FoI estimate for each group. As expected, this occurs at the year 2000 in each case. The FoI estimates for the youngest two age groups are similar at all time points and therefore overlap. The FoI over time for the high FoI case is shown in figure 5.10(b). It is important to note that the dynamic FoI models were subjected to the same range of sensitivity analyses as the static models as described in 5.4.4.

Figure 5.10 – Dynamic (a) base FoI and (b) high FoI acting on each age group over time. Assumes base migration and no immunisation. FoI estimates over time are similar for the two youngest age groups and therefore overlap on these charts.
5.4.8.1 Sensitivity of dynamic model to WAIFW matrix

To assess the impact of the different WAIFW structures described in 5.4.8, all three were incorporated into separate dynamic models in Berkeley Madonna and the outputs compared. To maximise the impact of differences, all comparisons below use the high FoI assumption.

Firstly, acute infections in each age group are compared between the three WAIFW matrix structures (figure 5.11). A number of useful inferences can be made from these data. Firstly, the variation in the number of acute infections under the different contact matrices is far less for the 0 – 4 and 15 – 44 age groups. This is because under all WAIFW assumptions the majority (57%, 78% and 100%) of infectious contacts for both occur with the 15 – 44 age group (which has the highest number of infectious units at all times in the model). This is not the case for susceptibles in the other age strata where there is more variability in the proportion of contacts across the age strata.

Secondly, in all but the oldest age group, at the end of the modelled period in 2050 the number of acute infections is highest for WAIFW 1, intermediate for WAIFW 2 and lowest for WAIFW 3. This order is reversed in the 45+ age group. The explanation for this observation appears to lie in the fact that infectious contacts between age groups are greatest for WAIFW 1 and become less prominent in WAIFW 2 and irrelevant in WAIFW 3.

Therefore contact with those in the 45+ age group is lowest for the younger age groups, but highest in that 45+ age group in WAIFW 3 (as 100% of contacts arise within this age group). Why does contact with the oldest group determine the differences in acute infections? Figure 5.12 shows the age distribution of the whole population from 1951 to 2050.

With the ageing of the Australian population, the proportion in the 45+ age stratum increases at the expense of younger age groups over time. At around 2005, this age group outnumbered those aged 15 to 44 years for the first time in history; and at the end of the model in 2050 they are predicted to constitute nearly half of the entire population.
Figure 5.11 – Number of people with acute HBV Infection by WAIFW matrix used in high dynamic FoI model over time for people aged (a) 0-4 years (b) 5-14 years (c) 15-44 years and (d) over 45 years.
Although this underlying trend in the general population influences the differences in FoI across the matrix structures, this occurs through an increase in the relative proportion of infected persons in each age group, not the total population in each age group. The proportion of people with chronic HBV by age group in the static model (again using the high FoI case) is shown in figure 5.13.

**Figure 5.12** – Age distribution of the Australian population in the model (base migration assumption), 1951 - 2050.

**Figure 5.13** – Age distribution of people with chronic HBV infection in the high static FoI model (base migration), 1951 – 2050.
The increasing relative proportion of the population with chronic HBV in the 45+ age stratum is reflected in the differences in acute infections across the WAIFW structures. As shown, the change in these proportions predominantly occurs after 1995, which is reflected in figure 5.11 showing acute infections for each age group by WAIFW in that the divergence in acute infections for each WAIFW occur in the second half of the modelled period.

Despite these differences the total numbers of acute infections differ relatively little across the WAIFW structures, and the opposite impact on the youngest three strata compared with the 45+ group results in countervailing trends, reflected in a lack of difference between the outcomes of different matrix structures in total and cumulative acute infections across all age groups as shown in figure 5.14.

**Figure 5.14** – (a) Number of people with acute HBV infection and (b) cumulative acute HBV infections by WAIFW over time in high dynamic FoI model, base migration, no immunisation.
The similarity in these outcomes is demonstrated by superimposed outcome plots across the three WAIFW structures in the figure. The homogeneous mixing assumption therefore appears to adequately explain total incident HBV infections across age groups and is thus sufficient for exploring scenarios and developing predictions that are not specific to individual age groups.

5.4.9 Equilibrium starting conditions

As discussed in chapters 1 and 5, Australia is in general a low HBV prevalence country which has experienced significant settlement from intermediate and high prevalence regions since the end of World War II (225). Table 5.3 shows the estimated proportions of a low prevalence population that are susceptible to HBV, that are chronically infected and that have cleared HBV infection are 94.5%, 0.5% and 5% respectively. Also as discussed in chapter 1, in low prevalence countries infection with HBV typically occurs through sexual contact and IDU with peak infection rates in the teens into early-mid adulthood. This is also reflected in the much higher FoI acting on these ages as shown in table 5.5 and in figure 5.10.

The starting population (8.42 million) and age distribution for the model were drawn from ABS data ((236) - Table 19). The distribution of the population by HBV status was designed to reflect the epidemiology of HBV in a low prevalence country and is shown in table 5.8.

<table>
<thead>
<tr>
<th>HBV infection status</th>
<th>Susceptible</th>
<th>Chronic infection</th>
<th>Cleared infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 years</td>
<td>99.8%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>5-14 years</td>
<td>99.4%</td>
<td>0.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>15-44 years</td>
<td>94%</td>
<td>0.7%</td>
<td>5.3%</td>
</tr>
<tr>
<td>45+ years</td>
<td>94%</td>
<td>0.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>All ages</td>
<td>95.5%</td>
<td>0.5%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Table 5.8 – Initial HBV status of the simulated Australian population by age group in 1951.
It is important to recognise that outside any consideration of migration, Indigenous Australians are Australian-born individuals with high HBV prevalence (see 1.3.2.2.2). This group was not specifically incorporated in the model starting conditions given the relatively small proportion of indigenous Australians in the total population (see 5.5.6).

**5.4.10 Assessing the impact of perturbations**

A profound advantage of mathematical models in general is the ability to make changes in underlying variables to assess for the impact on model outcomes. This is no less the case in mathematical models of infectious diseases, where such changes can be desired for the purposes of sensitivity analysis around critical assumptions, or to consider the impact of other perturbations such as the introduction of vaccination. Two separate methods for incorporating such changes were used in the model presented.

**5.4.10.1 Batch runs**

Berkeley Madonna allows the batching of model runs with variation of a specified parameter between two chosen values (in either arithmetic or geometric sequence) with as many intermediate values also modelled as desired. Any model outputs of interest can then be assessed graphically or numerically as per usual. This function is particularly useful for sensitivity analysis and was used extensively for this purpose as shown throughout chapter 6.

**5.4.10.2 Sliders**

An introduction to the Slider interface in Berkeley Madonna was made in 5.4.5 in relation to modelling of immunisation. By defining which parameters are to be included in the Slider interface and specifying a range of values and the increments in which to vary these values, it is possible to recompile the model each time one of these parameters is varied and assess the impact of such variation immediately for any chosen model outputs. Another use for this function (and also for the Batch runs command above) is to define a ‘toggle’ which can take the values of 0 or 1. This binary value can then be used to examine the impact of a given factor on the model simulations – for example, HBV epidemiology with and without vaccination. The slider interface constructed for the model is shown in figure 5.15.
5.4.11 Testing the model – comparison to ABS projections

One of the advantages of basing estimated births and derived mortality rates from ABS data was that the model outputs in terms of population constituents could be validated against the detailed ABS population projections by age group (127). This allowed debugging of any coding errors that may otherwise have gone unrecognised, and to allow an assessment of the overall representativeness of the simulated Australian population from 1951 to 2050.

The value of this approach was highlighted when, despite careful balancing of births, deaths and migration figures undertaken as described in 5.4.3.1, an error in coding of the ageing process resulted in deviations from the expected population size and age distribution over time, deviations which indicated the presence of the coding error and suggested the nature of the error was in either ageing or mortality. Once the problem was recognised, a simple coding solution was implemented and the model population projections balanced almost exactly with ABS data for both the total population (figure 5.16) and age distributions of the population over the simulation period (figure 5.17). The high degree of concordance between the model population and age distribution over time with ABS records and projections not only reassures as to the functioning of the model transition processes, it suggests that the methods used to estimate background mortality rates are also highly accurate.
An example of the precision of the modelling procedure used is that the ‘kinks’ observed in the ABS data in the youngest two age groups around 1970 and again in the mid 1990s are also captured by the model. Interestingly, these kinks appear to be caused by the ‘echoes’ of the post-war baby boom, with the surge of population born during the boom having their children on average once they reach their 20s (circa 1970), and when their own children have children in turn (1990s).

**Figure 5.16** – Comparison between the modelled population of Australia and ABS records and projections, 1951 – 2050.

**Figure 5.17** – Comparison between the modelled population of Australia and ABS records and projections for 1951 – 2050 for people aged (a) 0-4 (b) 5-14 (c) 15-44 and (d) 45 plus.
5.5 Discussion

A deterministic compartmental model of HBV in Australia was chosen due to the large population size involved and significant population proportions in each group, minimising the effect of chance (stochasticity) on the outcomes of the model. The age structures were chosen to capture fundamental differences in the risk of infection, progression to chronicity if infected, mortality both all-cause and HBV-specific, and national vaccination programs and vaccine efficacy. The inclusion of migration in the model was considered essential given that this one factor is the predominant determinant of the number of Australians living with chronic HBV infections. Sensitivity analyses around FoI and migration were included due to the significant effect of variations in these values on acute and chronic infections respectively. Both static and dynamic FoI models were constructed to assess the differences in outcome using both these techniques; a comparison of these outcomes will be presented in chapter 6 of this thesis.

The close balance between ABS data and projections and the model output across period simulated demonstrates that the population data inputs including births, age-specific mortality rates, and migration by age group used for the model closely reflect the actual situation occurring in Australia over the last 50 years, and that predicted to be that case to the year 2050 by the foremost statistical and demographic body in the country. Validation of parameters related to HBV infection, derived as described in 5.5.3.3 from a wide range of sources, requires an analysis of model outputs and is described in the following chapter.
6 Outcomes of a deterministic compartmental mathematical model of HBV in Australia

The analysis of the model outcomes will focus initially on the static FoI model and compare the outcomes of the static model with those of the dynamic FoI model using the ‘base case’ WAIFW matrix (WAIFW 1) discussed in 5.4.8. The discussion will include acute HBV infections, chronic HBV infections, and deaths in those with acute and chronic HBV, followed by a discussion of the impact of immunisation on these outcomes. Sensitivity analysis around the FoI and migration assumptions will be undertaken for the reasons discussed in 5.4.4.

6.1 Model outcomes

6.1.1 Acute infections

The number of people with acute HBV infection (point prevalence of acute HBV infection) across the simulation period of the static model assuming no vaccination is shown in figure 6.1. As expected, the impact of variations in the FoI is considerable; by 2050 acute infections under the high-case assumption are nearly six times those in the base assumption. As the duration of an acute infection in the model is 13 weeks, total incident infections per year can be approximated by multiplying the point prevalence by four. Thus the difference between low and high FoI static models in annual acute infections in 2050 is approximately 4000.

The large increase in numbers seen in the first year of the simulation in some of the figures is an artefact of the starting values (see 5.4.9). No people occupy the acute infection reservoir at the start of the simulation, thus under the influence of the FoI there is a rapid increase until the correct balance is reached. Therefore the figures affected by this artefact are those modelling acute infection, or deaths due to acute infection. It is also more pronounced in the static as opposed to dynamic FoI model outputs as in the latter, the number of acute infections is a function of the number of infectious individuals in the population which increases over time.
In contrast to the impact of FoI assumptions, acute infections in the static model are minimally sensitive to migration estimates as shown in figure 6.2. The reason that incident infections diverge in this graph only after 2005 is that this is the period where migration is estimated; prior to 2005, actual migration data were used.
It is important to remember that the FoI in the static model is constant and not related to the number of infectious individuals in the population. This is why migration, being the source of the majority of chronically infected individuals in the population (as discussed in previous chapters of this thesis and further demonstrated in 6.1.2), has minimal impact on acute infections in the static model. The small difference in acute HBV infections simply reflects the absolute increase in the susceptible population under the higher migration assumptions.

Although a more comprehensive exploration of the differences between the static and dynamic FoI models is provided in 6.1.5, it is important to demonstrate this fundamental difference between static and dynamic FoI models. As previously discussed (5.3) an increase in the number of infectious individuals in the population (in this case through migration) leads to an increase in the chance of susceptible members of the population being infected. Figure 6.3 reveals the impact of migration on acute infections when a dynamic FoI is used, with all other factors held constant.

In the static model the difference in the point prevalence of people with acute HBV infection between the migration assumptions was less than 20 per year in 2050; in the dynamic model with no other parameter changes the difference is nearly 200 people with acute infection at the end of the model.

![Figure 6.3 – Number of people with acute HBV infection by migration assumption over time. Dynamic FoI model (WAIFW 1), base FoI assumption.](image)
The burden of HBV infection varies across different age groups, particularly in a generally low prevalence population where most acute infections occur through sexual transmission and IDU amongst adults, and where most chronic infections enter the population through migration (predominantly of adults). With respect to incident infections figure 6.4 shows the point prevalence of acute HBV infection in the static model by age group.

Another way of assessing the burden of acute infections across the period of the model is to assess the cumulative number of acute infections. This is made possible through the use of the ‘cumulative cases sub-model’ discussed in 5.4.2. The cumulative number of incident HBV infections under the different FoI estimates is presented in figure 6.5 and demonstrates that variations in the FoI have a profound impact on total cumulative acute infections.

Similar to the context of point prevalence of acute infections over time, a sensitivity analysis around migration estimates reveals minimal impact on the cumulative total of acute infections (figure 6.6); this is not the case in a dynamic FoI model for the reasons given above.

**Figure 6.4** – Number of people with acute HBV infection by age-group over time. Static FoI, base FoI and migration assumptions. Age groups 0-4 and 5-14 use primary Y axis, 15-44 and 45+ use secondary Y axis.
6.1.2 Chronic infections

In direct contrast to incident infections, chronic HBV infections depend largely on migration assumptions and are relatively insensitive to changes in the FoI. The majority of people with chronic HBV acquire the infection overseas prior to migrating with only a small minority having been infected domestically.
Figure 6.7 demonstrates the lack of impact on variations in FoI on the number of people living with chronic HBV infection in the population. In contrast, alterations to migration have a profound impact on the prevalence of chronic HBV infection (figure 6.8). As was the case in the previous section (except figure 6.3), the outcomes presented here are from the static FoI model.

Similarly to the case for acute HBV but for a different reason (migration of adults with chronic HBV rather than acute infections in adults), the burden of chronic HBV is also disproportionately large in the older age groups (figure 6.9).

A useful inference from the model is to assess the proportion of chronic infections entering through migration relative to those arising through domestic infection. It is well recognised that migration is responsible for most chronic infections (see 5.4.2.2) but using the model it is possible to quantify these proportions over the time period simulated.

![Figure 6.7](image)

**Figure 6.7** – Number of people with chronic HBV infection by FoI over time. Static FoI, base migration assumption.
Figure 6.8 – Number of people with chronic HBV infection by migration over time. Static FoI, base FoI assumption.

Figure 6.9 – Number of people with chronic HBV infection by age-group over time. Static FoI, base FoI and migration assumptions. Age groups 0-4 and 5-14 use primary Y axis, 15-44 and 45+ use secondary Y axis.

Figure 6.10 shows annual domestic chronic HBV infections versus annual entry of people with chronic HBV infection. Annual entry of migrants with chronic HBV levels out after 2005 due to the use of ABS projections for migrant entry after this date.
This analysis demonstrates that the vast majority of chronic HBV infections are imported. The proportion of all people entering the chronic HBV infection state through domestically acquired infection progressing to chronicity in any year is shown in figure 6.11. The static model is again used, but now the FoI is set the maximum level within the range for sensitivity analysis to maximise the contribution of domestic infections to the total.
As shown in figure 6.11, people with acute infections progressing to chronicity within Australia constitute only 3 to 9.5% of chronic infections entering the population across the period simulated even when using the maximum FoI.

Analysing the output from this simulation in Stata v10.0, the median proportion of infections acquired domestically for different FoI assumptions (keeping migration at the base level for all comparisons) and the spread of values across the period simulated (from the 5th to 95th percentile) is shown in table 6.1.

It is therefore apparent that at least 95% of chronic infections across the modelled period enter the population through migration, even when the FoI is set to the maximum level within the range determined for sensitivity analysis. This is comparable with estimates from the United Kingdom, with domestically acquired chronic HBV accounting for 3.9% of the annual incidence of chronic infections (131). This has clear implications for the ability of universal vaccination programs within Australia to make any impact on the burden of chronic HBV infection in this country, a topic discussed further in 6.1.4.

Another way of assessing the burden of chronic HBV is to examine the population HBsAg prevalence, which was coded in the model simply by dividing the number of people living with chronic HBV infection by the total population. Figure 6.12 presents the impact on HBsAg prevalence across the period of the simulation of differences in static FoI assumptions while holding migration at the base level.

<table>
<thead>
<tr>
<th>FoI assumption</th>
<th>Median percentage of chronic HBV infections domestically acquired</th>
<th>5th – 95th percentile range of proportions across simulation, 1950 to 2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base FoI</td>
<td>0.9%</td>
<td>0.6 – 1.2%</td>
</tr>
<tr>
<td>Intermediate FoI</td>
<td>2.7%</td>
<td>1.9 – 3.6%</td>
</tr>
<tr>
<td>High FoI</td>
<td>4.4%</td>
<td>3.1 – 5.8%</td>
</tr>
</tbody>
</table>

*Table 6.1 – Median and 5th - 95th percentile range of proportion of chronic HBV infections acquired domestically by FoI assumption from 1951 – 2050 assuming base migration.*
Minimal difference in the ultimate HBsAg prevalence is seen across FoI values in figure 6.12 (for example, in 2010 the HBsAg ranges from 0.73% to 0.76% between the base and high FoI cases), reflecting once again that domestic infections play little role in determining the burden of chronic HBV in the community. This is also demonstrated in figure 6.13 in the marked sensitivity of HBsAg projections to variations in migration estimates.
In the base case migration estimate, HBsAg prevalence remains roughly constant over time at 0.75%. In the low migration case HBsAg prevalence drops in a linear fashion to 0.6% by 2050, a level not seen since the 1980’s according to the model. In contrast, the high migration case results in a continual increase in HBsAg prevalence over time until it stabilises at around 0.86% from around 2035.

The prevalence of chronic HBV infection varies considerably between age groups, with the base FoI and base migration static model showing the highest prevalence in the 15 – 44 age group and the lowest in the 0 – 4 age group, being less than a fifth of that of the highest prevalence group (figure 6.14).

6.1.3 Mortality attributable to HBV infection

An important aspect of the model constructed is that it incorporates deaths associated with HBV infection and those due to background mortality. This allows an estimation of attributable mortality to be made. Figure 6.15 illustrates deaths in those with acute and chronic HBV infection by FoI in the static model.
Two essential features are evident; firstly that deaths in those chronically infected outnumber those in acute HBV by a factor of more than 200 to 1, and secondly that variations in FoI impact significantly on acute deaths but minimally on those in chronic HBV. The converse is true for variations in migration assumptions in the static model as shown in figure 6.16.

Another way of assessing deaths attributable to HBV is by looking at cumulative deaths over the entire period of the simulation in both acutely and chronically HBV infected individuals as shown in figure 6.17 for the static model with base migration, where FoI is set to the highest level in order to examine the scenario in which the number of deaths due to acute HBV infection is at a maximum.
Figure 6.16 – Deaths in people with acute (primary Y axis) and chronic HBV infection (secondary Y axis) by migration over time. Static FoI, base FoI assumption.

Figure 6.17 – Cumulative deaths in acute (primary Y axis) and chronic HBV infection (secondary Y axis) over time. Static FoI, high FoI and base migration assumptions.
Despite using the highest FoI setting, acute deaths number 700 over the 100 year run of the simulation, in marked contrast to 140,000 deaths in people with chronic HBV over the same time period.

In all of the mortality data presented so far it is important to realise that the deaths accounted are all deaths in those with acute and chronic HBV, not specifically those attributable to HBV infection. Whereas the majority of deaths in those with acute HBV will be attributable to the infection given the short period of this disease state (13 weeks) and low expected background mortality over this period, the same cannot be assumed for chronic HBV in which state people remain for decades on average until eventual clearance or death.

To assess the attributable mortality due to HBV at any time point during the model, a term called *HBV mortality ratio* was defined in Berkeley Madonna in the following way:

\[
\begin{align*}
\text{HBV mortality rate} &= \frac{\text{deaths in chronic HBV}}{\text{number chronically infected}} / \text{year} \\
\text{Uninfected mortality rate} &= \frac{\text{deaths in uninfected}}{\text{number uninfected}} / \text{year} \\
\text{HBV mortality ratio} &= \frac{\text{HBV mortality rate}}{\text{Uninfected mortality rate}}
\end{align*}
\]

This ratio of the death rate in those with chronic HBV to the death rate in uninfected members of the population is sensitive to the estimates of background and HBV-specific mortality rates entered into the model having been derived from multiple data sources as described in 5.4.3.1 and 5.4.3.3, but is also sensitive to the proportion of the population in each age group at a given time, and to changes in migration which affect the age distribution particularly of those with chronic HBV infection but to a lesser degree the population as a whole.

The median age of migrants is 25 years (see 5.2.4 and 5.3.1.1) and that of the Australian population as a whole is 37 years (241). Three quarters of migrants are younger than the Australian median age on arrival, resulting in a net reduction in median age through increased migration. This influence is in contrast to the prevailing demographic trend of increasing median age in the population. These social trends are thus reflected in the summary HBV mortality ratio which is shown in figure 6.18 (the high dynamic FoI model with base migration was used for this analysis).
Figure 6.18 – HBV mortality ratio over time. Dynamic FoI model, high FoI and base migration assumptions.

The median HBV mortality ratio over the period is 1.29, with a range from 1.13 to 1.35. This range is negatively skewed due to the decline in the mortality ratio observed from around 2020 onwards with increasing background mortality in the oldest age group (see 5.4.3.1.2). Further analysis of the implications of this ratio for estimating attributable chronic HBV mortality is presented in 6.2.3.

6.1.4 Impact of immunisation

The models were constructed to allow assessment of the effect of immunisation of any proportion of any age group over time (see 5.4.5). The limits imposed on vaccination include availability of vaccine after 1985, commencement of the National Immunisation Program (NIP) from 1998 for adolescents (in the model represented by the 5 – 14 age group), and from 2000 for infants (in the model, 0 – 4 age group). Existing data from the Australian Childhood Immunisation Register (ACIR) for infants indicates 90%-plus coverage with HBV vaccination (108, 115). Similar data are more difficult to find for adolescents, but results of both the serosurvey undertaken as part of this doctoral research (3.4.2 and 3.5) and also the 2002 national serosurvey (12) suggest coverage of around 60%.

Data for adult vaccination uptake outside the auspices of the NIP are even more difficult to obtain but certainly is far lower than the levels achieved through nationally funded programs. For the purposes of the following analyses, vaccination of 3% of eligible adults aged 15 – 44
per year from 1985 is assumed as this provides the best fit with NIDS notifications of acute HBV under the dynamic model as described in 6.2.1; this assumption is further tested against serosurvey data in 6.2.2. These levels of coverage (90% in the 0 – 4 group from 2000, 60% in the 5 – 14 group from 1998 to 2012, 3% in the 15 – 44 group from 1985, and none in the 45+ group) will subsequently be referred to as the ‘expanded NIP’. All the comparisons presented in this section use the static model with an intermediate FoI and base migration assumptions; differences in vaccination impact between the static and dynamic FoI models are presented in 6.1.5.4.

6.1.4.1 Acute infections

It is to be expected that vaccination of susceptibles against HBV will have the greatest impact on acute infections, and this is indeed the case as shown below. In the static model, cases of acute HBV start to fall as soon as vaccination becomes available in 1985, with a more rapid decline following the advent of universal childhood vaccination programs as shown in figure 6.19. As a result, people with acute HBV infection (point prevalence) are predicted to fall from over 700 in 2050 to less than 200 as a result of estimated current levels of immunisation.

![Figure 6.19](image_url) – Impact of immunisation on the number of people with acute HBV infection over time. Static FoI, intermediate FoI and base migration assumptions.
It is worth noting that this pattern of acute infections – specifically, the peak in 1985 with subsequent decline - was not reflected in surveillance notifications in Australia, where acute infections did not peak until 2000-2001 (figure 1.1). In 6.1.5.4 this prediction from the static FoI model is contrasted with that of the dynamic model, with a discussion of which better fits observed data.

The impact of the expanded NIP on acute HBV infections is seen clearly in figure 6.20, with the cumulative acute infections over the run time of the model falling by 85,000 or 40% of all acute infections over the 100 years modelled.

However to achieve this reduction in acute HBV cases, more than 18 million complete courses of vaccination (representing some 65 million doses of monovalent or polyvalent hepatitis B vaccine) would be required. Thus for every 1,000 people vaccinated, less than 5 acute HBV infections would be averted (1.3 for every 1,000 doses of vaccine administered).

Figure 6.20 – Impact of immunisation on the cumulative number of acute HBV infections over time. Static FoI, intermediate FoI and base migration assumptions.
6.1.4.2 Chronic infections

Domestically acquired chronic HBV infections are predicted to be significantly reduced through vaccination as demonstrated in figure 6.21(a). At the end of the modelled period, the cumulative number of domestically acquired chronic HBV infections drop by around 40% or 5550 cases under the influence of the expanded NIP – 1 case averted for every 3240 people completely vaccinated, using over 11700 doses of vaccine.

Figure 6.21 – Impact of immunisation on (a) cumulative number of domestically acquired chronic HBV infections and (b) the number of people with chronic HBV infection over time. Static FoI, intermediate FoI and base migration assumptions.
However as discussed in 6.1.2, domestically acquired chronic HBV represents less than 5% of all chronic infections entering the Australian population over the 100 years simulated in the model. Figure 6.21(b) demonstrates the lack of impact of the expanded NIP on the overall prevalence of chronic HBV infection in Australia in the 5 decades following the introduction of universal childhood vaccination. This is also reflected in the inability of the expanded NIP to affect the HBsAg prevalence in the community (figure 6.22). Projections from the model indicate that even were Australia to mobilise huge resources to vaccinate the whole population (including vaccinating 100% of children and adolescents under the NIP, and vaccinating 10% of all susceptible adults every year) then as of 2050 the prevalence of HBsAg in this country would fall only 0.02%, from 0.75% with no vaccination at all to 0.73%.

Vaccination as a public health strategy therefore cannot address the burden of chronic HBV in Australia. In contrast, infant vaccination programs in the high prevalence countries which are the source of a large amount of Australia’s migrant intake could significantly reduce the burden of HBV both in the source country, and subsequently in Australia once these birth cohorts contribute to migrant intake (7.2.8).

**Figure 6.22** – Impact of immunisation on the HBsAg prevalence over time. Static FoI, intermediate FoI and base migration assumptions.
6.1.4.3 Mortality

Death is an uncommon result of acute HBV infection, one that is more likely with increasing age of the host. As presented in 5.4.3.3, in the model deaths from acute HBV occur once for every thousand infections in young children, rising to 3.5 deaths per thousand adult infections. Figure 6.23 shows that the expanded NIP reduces deaths due to acute HBV from approximately 7 to 2.5 per year at 2050.

Figure 6.23 – Impact of immunisation on (a) annual deaths in acute HBV infection and (b) number of cumulative deaths in acute HBV infection over time. Static FoI, intermediate FoI and base migration assumptions.
Thus approximately 125 deaths are averted over the entire period of the simulation, representing one life saved for every 144,000 people vaccinated. If the FoI is set to the high assumption, 80,000 people must still be vaccinated to avert each death.

The maximal possible impact of the expanded NIP is seen using the dynamic model with both the FoI and migration set to the highest end of the range for sensitivity. Under these conditions, the cumulative deaths due to acute HBV falls from 945 with no immunisation to 524 under the expanded NIP, therefore requiring that 42,750 people receive 155,000 doses of hepatitis B vaccine to avert each death.

Although these inferences regarding deaths due to acute HBV suggest a large number needed to immunise to avert each death, an impact of the expanded NIP on deaths is nonetheless observed. Such is not the case for deaths due to chronic HBV as shown in figure 6.24, reflecting once again the inability of universal vaccination to make an appreciable impact on the public health burden of chronic HBV.

Figure 6.24 – Impact of immunisation on annual deaths in people with chronic HBV infection (primary Y axis) and cumulative deaths in people with chronic HBV infection (secondary Y axis) over time. Static FoI, intermediate FoI and base migration assumptions.
6.1.5 Comparison between static and dynamic models

In 5.3 the differences between static and dynamic FoI models were discussed. In 5.4.8 the construction of the contact (‘WAIFW’) matrix for the dynamic model was explained, and the relative insensitivity of the model to alternate contact matrix assumptions was demonstrated. For the dynamic model outputs presented throughout this chapter the initial matrix (WAIFW 1) assuming homogeneous mixing relative to the age distribution of the population acutely and chronically infected with HBV is used. For all the following comparisons, migration is at the base assumption, but FoI is set to the high case scenario to maximise the differences observed between the static and dynamic models.

6.1.5.1 Acute infections

The contrast in outcomes between the model incorporating a dynamic FoI with that using a static FoI will be most prominent for acute infections as the transition from susceptible to acutely infected is governed by this parameter. This contrast was discussed previously in 6.1.1.

Figure 6.25 shows that acute HBV infections are higher in the static model for the first half of the simulation and in the dynamic model for the latter half. This is because the static FoI remains constant regardless of the number of infectious people in the community.

In contrast, the dynamic FoI is sensitive to these changes and increases with the number of people in the population able to transmit HBV infection. The cumulative number of incident infections also differs, with the dynamic model predictions reaching parity with those of the static FoI model in around 2030. Following this point the cumulative total acute infections is higher under the dynamic FoI assumption, for a relative 18% difference at the end of the simulation in 2050.
6.1.5.2 Chronic infections

Figure 6.26 demonstrates differences in cumulative domestically acquired chronic HBV infections between the static and dynamic FoI models, which reflect the differences in cumulative acute infections presented in figure 6.25. This is because a proportion of these acute infections by necessity result in the chronic HBV infections that are domestically acquired. In contrast, the total prevalence of chronic infection at all times is as insensitive to whether the FoI is static or dynamic as it is to variations in the baseline FoI assumption (6.1.2) for the same reason; more than 95% of all chronic infections are acquired overseas.

6.1.5.3 Mortality

For the reasons presented above the differences between the static and dynamic HBV model with respect to deaths in people infected with HBV lie in the context of acute HBV only, with no differences seen in deaths in people living with chronic HBV (figure 6.27).
6.1.5.4 Impact of immunisation

The impact of immunisation programs on the epidemiology of an infectious disease in a population is an important area of difference between models utilising static or dynamic FoI processes. In static FoI models, the impact of immunisation is linear; protection is afforded only to those immunised, with no difference in the FoI acting on those remaining susceptible, and thus herd immunity cannot be simulated using such models. In contrast, a dynamic FoI model can reflect herd immunity. If an individual who would otherwise become infected is protected by vaccination, this individual’s contribution to the dynamic FoI acting on susceptible members of the population is removed.

For the following comparison the FoI remains at the high assumption to maximise differences observed, base migration is assumed, and the expanded NIP presented in 6.1.4 is used. Figure 6.28 shows the profound differences between static and dynamic models in the impact of the expanded NIP on acute HBV infections. In the static model, once the vaccination of a small proportion of adults per year starts in 1985 acute HBV infections drop immediately as discussed in 6.1.4.1 – the constant FoI is acting on a lower number of susceptible people in the age group with the highest FoI, 15 – 44 year olds. This reduction becomes more marked after the onset of universal childhood vaccination in 1998 & 2000.
In contrast, in the dynamic model acute HBV cases continue to increase from 1985 until around 2000 despite adult vaccination. This is because the reduction in acute cases through protection of those vaccinated \textit{plus} the removal of their contribution to the FoI acting on susceptibles is outweighed by the expanding numbers of people with chronic HBV infection entering through migration.

**Figure 6.27** – Annual (primary Y axes) and cumulative (secondary Y axes) deaths in (a) acute and (b) chronic HBV infection over time. Static versus dynamic FoI model, high FoI and base migration assumptions.
The models show that under the influence of migration, HBsAg prevalence in Australia rose nearly 20% between 1985 and 1990 from 0.57% to 0.67%, the fastest rate of increase over the 100 year period of the simulation. In the dynamic model it is not until the introduction of universal vaccination in 1998-2000 that immunisation overcomes the influence of increasing numbers of infectious individuals in the population, resulting in a decline in acute infections. Both models ultimately show an approximate 75% reduction in the number of people with acute HBV infection at 2050 due to the expanded NIP, with a point prevalence of 493 incident infections in the dynamic high FoI model versus 311 in the static high FoI model.

Thus there are profound differences between the model using a static FoI and that using a dynamic FoI with respect to acute HBV infections and associated mortality, and minimal differences with respect to chronic HBV and associated measures such as population HBsAg prevalence and chronic HBV mortality. The impact of vaccination on acute HBV is similar between the models at the end of the simulation, but the dynamics occurring early in the vaccination period are very different.

The reduction in the prevalence of chronic HBV in the population due to universal vaccination in the dynamic FoI model is 4.2%. This figure is determined by the proportion of chronic HBV that arises through domestic infection (see 6.1.2 and table 6.1). It is higher than...
the ‘best case’ relative reduction achievable in 6.1.4.2 because the FoI in this instance is
dynamic and at the high end of the sensitivity range, both of which act to maximise the
impact of vaccination. In the mathematical model of HBV infection in the Netherlands
constructed by Kretzschmar et al (122), using migrant HBV prevalence similar to the
Australian context, the reduction in chronic HBV infection prevalence 50 years after the
introduction of universal vaccination is very similar at 4.5%.

The dynamic FoI model has theoretical advantages in that a FoI responsive to the number of
infectious people in the population is more intuitive and epidemiologically plausible; but do
external data demonstrate that such a model more closely simulates reality to justify the
significant additional complexity required? This question is addressed in the following
section.

6.2 Validating the model against external data
   6.2.1 National Notifiable Diseases Surveillance System
      6.2.1.1 Acute infections

The modelled numbers of acute HBV infections can be validated using surveillance
notification data. It is important to realise that the model simulates and reports all infections,
not just those that are symptomatic, nor only those notified to the surveillance system. The
lack of certainty around the proportion of acute HBV infections that are notified to
surveillance systems was discussed in detail at 5.4.4.

Figure 6.29 is a complex chart which shows the number of people with acute HBV infection
from 1980 to 2010 comparing static and dynamic FoI models using base, intermediate and
high FoI assumptions. Also depicted are acute HBV infection notifications to the NNDSS
from 1993 to 2007 and two further curves representing twice and ten times the notified
number of cases. These 2x- and 10x-notifications curves are included to represent a range of
estimates of actual HBV infections accounting for both subclinical infections and failure to
test and/or notify symptomatic infections. As the number of cases notified would have been
affected by selective vaccination from the mid-1980s and then by the NIP program for
adolescents from 1998 and infants from 2000, the model outputs include such vaccination
(with parameters set as per the ‘expanded NIP’ definition in 6.1.4). Migration is held at the
base assumption for all model simulations shown.
Figure 6.29 – Comparison of the number of people with acute HBV infection by FoI with acute notifications to NNDSS (242) and 2x- and 10x-notifications (see text) over time. Static versus dynamic FoI model, base migration assumption.

It should be noted that the significant peak in acute HBV from 2001-2003 was related to an outbreak amongst IDU in Victoria (62), during which time the Victorian proportion of all acute HBV notifications in Australia rose to 45% from an average of 36% for the period 1993-2000 and 2004-2007 (242). It is in analysing data drawn from a relatively small number of infections over a short time period that the effects of stochasticity referred to in 5.3 become apparent.

Nonetheless important insights can be obtained from this graph. Firstly, as described in 6.1.5.4 the static model predicted acute infections would fall as soon as vaccination became available in 1985, whereas in the dynamic FoI model this did not occur until around 2000. Figure 6.29 shows that the trend observed in the dynamic model appears to more closely reflect notified incident HBV infections. Furthermore, the vaccination parameters assumed under the ‘expanded NIP’ discussed in 6.1.4 appear to fit the notification data, and the coverage of between 2% and 4% of susceptible adults from 1985 onwards generates a curve most closely resembling the trends in acute HBV notifications (figure 6.30), which is why the
Figure 6.30 – Comparison of acute HBV infections under a range of vaccination uptake values (1-10%) for adults aged 15-44 with actual notification data (NNDSS x10). Dynamic high FoI model, base migration assumption, vaccination according to expanded NIP parameters other than in 15-44 age group.

point estimate of 3% was applied (6.1.4). This assumption is further tested against seroprevalence data in 6.2.2.

Secondly, the intermediate and high FoI models appear to more accurately reflect the true numbers of acute HBV infections than the base case assumption. The base FoI models lie between the notifications and the 2x-notifications plots and are therefore almost certainly an underestimate of actual infections. Acute infections in the intermediate FoI models fall between the 2x-notifications and 10x-notifications plots, which although substantially below the CDC estimate for the true proportion of incident infections notified (54) may well represent reality given the CDC estimate may be too high (see 5.4.4).

However the high FoI model most closely approaches the CDC estimate of total incident cases relative to notifications, and furthermore has the advantage of maximising the impact of domestic infections and therefore vaccination programs. This is useful as a conservative
approach, given the findings previously presented of minimal effect of domestic vaccination against HBV infection. For these reasons of approximating both the trend and the number of estimated true incident infections, and conservatively maximising the impact of hepatitis B vaccination of the population, the model used in subsequent comparisons is the dynamic FoI model at the high end of the range used for sensitivity analysis.

### 6.2.1.2 Chronic infections

Annual notifications and cumulative notifications were obtained from NNDSS data going back to 1971 (4.2.2). The cumulative number of notifications was compared to the total number of people ever infected with chronic HBV. To do this, the total number of people living with chronic HBV plus the total number of people chronically infected who had died was added across the length of the modelled period. This is because notifications since 1971 will include a significant number of people who have died, from both attributable and all cause mortality (6.2.3).

Figure 6.31 shows these data, along with the derived proportion of all people (alive and dead) notified with chronic HBV infection since notifications commenced in 1971. The proportion is low, estimated at 56% in 2006; however it is increasing relatively rapidly. Over the last ten years, the proportion of people with chronic HBV that had been notified increased by 2.7% per year in an almost linear fashion, reflecting the apparently linear increase in the cumulative number of notifications.

The estimate of 56% of all people with chronic HBV having been notified is remarkably similar to the estimate of 60% presented in the NSW record linkage study report in the Lancet by Amin and colleagues in 2006 (13), which was based on an analysis of the first national serosurvey data and incidence and prevalence estimates from the 1990s (8, 11). The only other estimates of the proportion of people with chronic HBV diagnosed come from community based studies which reveal a very low level of prior awareness (such as only 20% in South-East Asian migrants in Melbourne (19)) to slightly higher but comparable levels in a hospital endoscopy cohort (69% of those testing positive previously aware; (15)).
Figure 6.31 – Comparison of people with chronic HBV infection (alive, deceased, and the sum of both) compared with the cumulative number of notifications to the NNDSS since 1971 (primary Y axis). Also shown is the resultant estimate of the proportion of all people with chronic HBV who have been diagnosed and notified (secondary Y axis). Dynamic high FoI model, base migration assumption, vaccination according to expanded NIP parameters.

The linearity of increase in cumulative notifications suggested that simple linear extrapolation may provide an estimate of the likely future patterns of cumulative notifications, and therefore also of the proportion of all people with chronic HBV notified into the future. Analysis of the cumulative number of notifications from 1987 to 2006 was conducted in Stata, demonstrating a mean increase in notifications of 5755 per year. Using this simple linear model, the proportion of total chronic HBV infections notified was predicted on the assumption that the linear relationship will hold into the reasonably proximate future.

This analysis predicts that the yearly increase in the proportion notified, currently 2.7% per year as described, will gradually fall to 1.5% per year by 2010, and 1.2% per year in 2020. As a result, the proportion of people living with chronic HBV that will have been notified is...
predicted to reach 70% in 2013, and 80% in 2021. It must be recalled from 4.3.2.4 and 4.4 that extending model projections further outside the range of the data on which the model is constructed (in this case, beyond the years 1987 to 2006) increases the uncertainty around such predictions. It is probable that the proportion notified will ultimately plateau to describe a sigmoid curve. The level at which this plateau will occur remains speculative, but will be determined by the notification lag for new migrants discussed in chapter 4, barring the implementation of comprehensive HBV screening for all newly arrived migrants.

6.2.2 Seroprevalence surveys

The dynamic high FoI model incorporating the expanded NIP vaccination assumptions, having been shown to best approximate NNDSS data for acute HBV infections, was subsequently tested against the results of several serosurveys. These included both the Victorian serosurvey undertaken as part of this doctoral research (chapter 3), and published national serosurveys. It should be noted that the static high FoI model was also tested in this way, with essentially identical results. This is not surprising given the underlying vaccination and migration assumptions are the same, leading to very similar outcomes for the proportions of the population remaining susceptible, having been vaccinated, and having chronic or resolved HBV infection.

6.2.2.1 Victorian Hepatitis B Serosurvey 1995-2005

Table 6.2 shows a comparison of the results of the serosurvey presented in chapter 3 against the model output. The susceptible and vaccinated proportions of the population are close across all years, with the comparative proportions being within 5% of each other on an absolute scale at all time points. This observation suggests that the vaccination assumptions underlying the ‘expanded NIP’ closely reflect the vaccination experience of the 3,212 patients who contributed serum to the serosurvey. It also indicates that the migration and FoI estimates are not greatly divergent from reality (otherwise the proportions of susceptible people in the population would be affected).
Whereas estimates of uptake of NIP funded vaccination for infants and to a lesser degree adolescents exist and have been used to inform the vaccination parameters used in this model, much less information exists for selective vaccination of adults. Most of these data are derived from studies of selective high-risk groups and cannot readily be extrapolated to the general population. The Victorian Hepatitis B Serosurvey data are able to assist with these estimates as shown in figure 6.32. These charts demonstrate the rising prevalence of vaccine-derived immunity over the 10 years covered by the serosurvey, most strikingly in the children targeted by the NIP, but also in older age groups.

![Vaccine-derived anti-HBs prevalence](image)

**Figure 6.32** – Prevalence of vaccine derived anti-HBs (anti-HBc negative samples) in Victorian serosurvey by age-group by test year.
The estimates of vaccine coverage in the 15-44 age group in the Victorian serosurvey were used to test the ‘expanded NIP’ assumption (6.1.4) of 3% susceptible adult annual vaccination after 1985 (fitted using notifications data as described in 6.2.1.1). The results of this comparison are presented in table 6.3. The concordance of these estimates provides validation of both datasets; the serosurvey shows the vaccination estimates used for the model resemble reality, and correspondingly the mathematical model lends support to the notion that, for vaccine uptake amongst those aged 15 – 44 years at least, the serosurvey is representative of the population of Australia (not just of Victoria).

These results confirm those of the comparison with NNDSS in 6.2.1 that the vaccination estimates used in the model appear to reflect actual vaccine uptake.

A similar nexus between the model and the serosurvey is not seen with people chronically infected with HBV. The explanation behind the significant variation in HBsAg prevalence across the three years of the serosurvey was discussed in chapter 3, and more thoroughly explained in chapter 4 as a function of migration 10 years prior. The model, not being subject to such influences as HBeAg seroconversion nor referral bias, ignores such trends and reports the simulated burden of people with chronic HBV, regardless of whether they have been tested and/or diagnosed or otherwise.

<table>
<thead>
<tr>
<th>Year</th>
<th>Serosurvey vaccine-derived anti-HBs prevalence (%)</th>
<th>95% C.I. for serosurvey estimate (exact binomial) (%)</th>
<th>Predicted vaccinated proportion from mathematical model using ‘expanded NIP’</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>18.7</td>
<td>15.1 – 22.6</td>
<td>17.8</td>
</tr>
<tr>
<td>2000</td>
<td>24.8</td>
<td>20.9 – 29.1</td>
<td>25.5</td>
</tr>
<tr>
<td>2005</td>
<td>43.5</td>
<td>38.8 – 48.4</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Table 6.3 – Comparison of vaccinated proportion of 15 – 44 year age group in the Victorian serosurvey with outcomes of high dynamic FoI model using base migration assumption and expanded NIP (see 6.1.4).
Finally, both the serosurvey and the model demonstrate a steady rise in the proportion of people with resolved HBV infection as would be expected from the migration data presented previously. However the magnitude of this trend was different, with a rise from 5.3% to 10.2% in the serosurvey compared with just 7.1% to 7.9% in the model. This may relate to uncontrolled bias in the convenience sample. It may also be because over 95% of known postcode samples in the serosurvey were residents of Victoria, where a higher proportion of people born overseas are from intermediate HBsAg countries than the average for Australia, with a correspondingly lower proportion from low prevalence countries (see 3.5).

6.2.2.2 National Serosurveys 1996-99 and 2002

Two national serosurveys have reported summary prevalence estimates of anti-HBs, anti-HBc and HBsAg (11, 12). However unlike the Victorian serosurvey individual sample HBV infection status was not reported (see table 3.3 for the serological patterns defining HBV status). To enable comparison with the model, the distribution of HBV infection status across these serosurveys was estimated from the prevalence estimates in the following way;

- **Susceptible**\( \quad I - ([\text{anti-HBs}] + [\text{HBsAg}] + [0.25* \text{anti-HBc}]) \)
- **Vaccinated**\( \quad [\text{Anti-HBs}] - 0.75*( [\text{Anti-HBc}] - [\text{HBsAg}] ) \)
- **Chronic infection**\( \quad [\text{HBsAg}] \)
- **Cleared infection**\( \quad [\text{Anti-HBc}] - [\text{HBsAg}] \)

Such categorisation is not precise, although an attempt has been made to account for the influence of isolated anti-HBc positive samples which in the Victorian serosurvey represented a quarter of all samples positive for antibodies to HBc antigen (chapter 3). This correction can be seen in the term to derive susceptibles which are defined as those lacking anti-HBs or HBsAg and also 25% of those who are anti-HBc positive (the isolated anti-HBc positive group who, lacking both HBsAg and anti-HBs, would otherwise have been incorrectly labelled as susceptible). A similar adjustment is made when estimating the vaccinated proportion. Those who are anti-HBs positive through natural infection are removed from the proportion vaccinated, but if consideration is not given to isolated anti-HBc positive individuals an erroneously low proportion of vaccinees in the population would result. Table 6.4 compares the results of these serosurveys with the output of the high dynamic FoI model; the first serosurvey, collected from 1996-99, is compared with the model outcomes for 1998.
The estimates for the proportions of the population that remain susceptible to infection and those that have been vaccinated are quite close for the second serosurvey. In contrast, the proportion of vaccinated samples in the first serosurvey is more than double the model vaccination estimate. To achieve this level of coverage through vaccination of 15 – 44 year olds, the model suggests it is necessary to vaccinate 7% of the susceptible population in this age group each year from 1985 to 1998. This would result in 33% of this age stratum being vaccinated by 2000 and 50% by 2005, well in excess of the prevalence of anti-HBs positive, anti-HBc negative samples seen across these ages in the Victorian serosurvey as described in 6.2.2.1.

The national serosurvey estimates do however closely parallel the model predictions for the prevalence of HBsAg in the community. In the first serosurvey, HBsAg prevalence was subject to significant uncertainty due to the exhaustion of available serum and possible contamination (11). The second serosurvey provided a more robust estimate of 0.7 or 0.8% prevalence, with the total range of confidence stretching from 0.6 to 0.9%. This estimate correlates strongly with the prediction of the model, unlike the results of the Victorian serosurvey. It is not certain why the Victorian serosurvey is more sensitive to the temporal factors underlying diagnosis and notification of HBV discussed in chapter 5 than are the national serosurveys. One possibility is the status of the Victorian Infectious Diseases Reference Laboratory as a public virology reference laboratory, whereas the numerous laboratories contributing to the national serosurvey would be expected to have quite different client bases and referral patterns.
The prevalence of anti-HBc dropped between the two national serosurveys. This is most unlikely to reflect a real fall in anti-HBc prevalence in the community for the reasons related to migration into Australia explored throughout this thesis. From the linear regression model presented in chapter 4 it can be estimated that some 34,000 people with chronic HBV infection settled in Australia during the period between 1996 and 2002 spanned by the national serosurveys. In the same period a further 240,000 people with anti-HBc due to resolved infection are estimated to have joined the Australian population through migration (5.4.3.2.1 and 5.4.3.2.3). Thus the trends in both the model and the Victorian serosurvey of a persistent increase in the anti-HBc positive proportion of the community are more likely to be accurate.

6.2.3 Mortality data

In 6.1.3 the HBV mortality ratio of those with chronic HBV relative to uninfected members of the population was reported as 1.29, with a range from 1.13 to 1.35 over the century simulated. It was noted that the range of values this ratio adopts over time is due to the sensitivity of this summary measure to the age distribution of the population and resulting raw death rate, and also to changes in migration affecting the age distribution of the population in general and those with chronic HBV in particular. If the impact of the ageing population is limited by analysing the HBV mortality ratio between 1951 and 2020, the median ratio only rises to 1.30, although the range contracts to between 1.22 and 1.35.

The HBV mortality ratio of 1.29 is consistent with existing data. In the large NSW record linkage study published by Amin and colleagues in the Lancet in 2006 (13), the standardised mortality ratio for those notified with HBV infection relative to the general community was 1.4 (95% C.I. 1.3 to 1.5).

In 6.1.3 it was noted that not all deaths in those with chronic HBV can be attributed to the infection. An estimate of the attributable fraction was derived from the HBV mortality ratio as follows:

\[
\text{Mortality ratio in those with chronic HBV relative to uninfected} = 1.29 : 1
\]

\[
\text{Therefore fraction of mortality attributable to HBV} = \frac{(1.29 - 1)}{1.29} = 0.225
\]
Therefore the average mortality in those with chronic HBV that is attributable to HBV is 0.225 or 22.5% of such deaths. This proportion is supported by existing estimates of adverse outcomes of chronic HBV (see 2.5.2.2), which have included risks of cirrhosis and liver cancer of 25% (7), mortality due to chronic liver disease and HCC of 25% (6, 56, 61, 201-203), advanced liver disease in 20-30% (25), and serious sequelae in 15-40% (31). Furthermore, adopting the methodology described above to establish attributable mortality in the NSW record linkage study results in an estimate of 28.6% (13).

Applying the 22.5% estimate for attributable mortality to deaths in those chronically infected in the high dynamic FoI base migration model, as of 2008 some 320 deaths per year can be attributed to chronic HBV infection. This increases to 550 attributable deaths annually by 2050. The cumulative number of deaths attributable to chronic HBV infection over the entire period of the simulation is approximately 30,700. In the absence of all vaccination, this estimate rises only 1.3% to 31,100. This again demonstrates the inability of the Australian vaccination program to impact on the burden of chronic HBV infection. In contrast, increasing migration to the higher ABS prediction increases attributable deaths by 7.5% to 33,000 over the period of the simulation.

6.3 Model limitations and weaknesses

Any mathematical simulation of reality can only be as accurate and complete as the data used in its construction, and only as robust as the assumptions underlying its processes. In many areas, especially deriving the FoI and estimating future migration, significant uncertainty exists which can only partly be addressed by sensitivity analysis. Uncertainty in parameters not subjected to sensitivity analysis also exists. A critical limitation of the model was that Indigenous Australians were not separately analysed as a higher prevalence sub-population. A more detailed discussion of assumptions and exclusions is presented in 5.4.6; ideas to extend the model and remove some of these limitations are presented in 6.5.

6.4 Summary

6.4.1 Model structure and assumptions best fitting external data

Although both the dynamic and static FoI models fitted mortality and seroprevalence data equally well, the dynamic model using a FoI at the high end of the range used for sensitivity
analysis most closely approximated national notifications data for acute HBV infection. In
addition to the assumption of 90% infant vaccination coverage derived from the ACIR (108),
the estimates of 60% adolescent coverage and 3% coverage of those aged 15 – 44 best fit the
notifications data and the Victorian serosurvey estimates.

6.4.2 Critical outcomes of optimised model

As a result of this validation against a variety of external data, critical inference from the high
dynamic FoI model using base migration and ‘expanded NIP’ assumptions is presented in
table 6.5. Consistent with recent national serosurvey data (12), and with the results presented
previously in chapters 3 and 4 of this thesis, the burden of chronic HBV infection is large and
rising. Although HBsAg prevalence is expected to remain stable over the next four decades,
the number of people living with chronic HBV will rise by 50,000 in this period. Deaths in
those with acute HBV will remain relatively constant; those attributable to chronic HBV,
already significant, will rise by more than 200 per year to 560 by 2050. Suggestions for
policy and programs derived from this model and findings from across the body of the thesis
are presented in 7.5.

<table>
<thead>
<tr>
<th>Year</th>
<th>2010</th>
<th>2020</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Australians living with chronic HBV</td>
<td>162,350</td>
<td>182,600</td>
<td>211,300</td>
</tr>
<tr>
<td>Proportion of people with chronic HBV diagnosed and notified</td>
<td>65%</td>
<td>75-80%</td>
<td>-</td>
</tr>
<tr>
<td>HBsAg prevalence of Australian population</td>
<td>0.75%</td>
<td>0.76%</td>
<td>0.74%</td>
</tr>
<tr>
<td>Annual acute HBV infections</td>
<td>615</td>
<td>550</td>
<td>500</td>
</tr>
<tr>
<td>Annual deaths due to acute HBV</td>
<td>5.7</td>
<td>5.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Annual deaths attributable to chronic HBV</td>
<td>325</td>
<td>365</td>
<td>560</td>
</tr>
<tr>
<td>Cumulative deaths attributable to chronic HBV from 01/01/2000</td>
<td>3,405</td>
<td>6,880</td>
<td>20,550</td>
</tr>
</tbody>
</table>

Table 6.5 – Select outcomes of the high dynamic FoI model (base migration, expanded NIP assumptions) for 2010, 2020 and 2050
6.5 Concepts for model extension and application

1. Construction of a sub-model for the analysis of the burden of HBV in Indigenous Australians to allow specific inference about this critically affected group.

2. The utility of constructing a sub-model for migrants and their children should also be explored, with assessment of the further insights possible relative to the significant increase in model complexity (5.4.6).

3. Separation of deaths due to chronic HBV into those due to decompensated cirrhosis, hepatocellular carcinoma (HCC) and other causes would allow modelling of interventions or other strategies (such as HCC screening programs) to reduce complications and mortality.

4. Narrower age strata for the model would permit more precise assessments of age-specific HBV-related and background mortality, and permit analysis such as life-years lost due to HBV mortality etc. This would be at the expense of a significant increase in model complexity.

5. A model using Victorian data for population age structure and country of birth, migration, births and age-specific mortality would allow more precise comparison with the Victorian Hepatitis B Serosurvey 1995 – 2005 than the Australian models presented in this chapter. Given the lack of accessible migration data by state in the resources used for the Australian model, this would require a modelled period to start in 1976. The Census conducted in that year would allow the initial population values for age structure and HBV status (from country of birth) to be modelled.

6. A critical extension of the model would be to incorporate appropriate treatment of people with chronic HBV. Much of the data to allow this extension was gathered in the process of parameterising the existing model. However increased complexity in the model structure (for instance, to differentiate people with chronic HBV who would benefit from treatment versus those who would not, discussed in chapter 2) would be required. A further difficulty is that virtually all existing data on treatment outcomes uses surrogate markers (such as suppression of HBV DNA, normalisation of ALT or HBeAg seroconversion) rather than hard endpoints such as mortality (209, 210). Any model predictions would therefore reflect this uncertainty.

7. Incorporation of vaccination programs in high HBV prevalence countries which are sources of migration to Australia would be an important extension to the model to assess the impact on estimates of the burden of chronic HBV here, and also to inform
an analysis of the effectiveness of Australian investment in overseas infant vaccination programs to reduce the prevalence of chronic HBV both in source countries and ultimately in Australia.

These suggestions for further extension of the model would be variably complicated to undertake and all add to the utility of the model in some way. However the last two considerations would perhaps contribute most to assessment of policy priorities for HBV infection in Australia, as both are aspects of the real-world situation not currently included in model even in general or summary format, and both are ready targets for the implementation of programs to control the burden of chronic HBV infection internationally.

6.6 Conclusion

The dynamic FoI model using a high FoI, base migration and assumed vaccination parameters as described was demonstrated to give results that are concordant with a range of established data. This model describes a significant and increasing burden of chronic HBV in our community, a burden which the existing lynchpin of the public health response to HBV – immunisation – is almost completely unable to address. The fact that this model estimates chronic HBV is currently responsible for the deaths of three times as many Australians as is HIV/AIDS (243, 244) speaks volumes about the inadequacy of the public health response to the first discovered and most ignored blood borne virus.

In 5.1.2, six questions to be addressed by the model were presented. In concluding the discussion of the results of the model, these questions must be answered.

1. *Can a mathematical model improve our understanding of the burden of acute and chronic HBV infection in Australia?*
   Yes, the results of the model have provided much information about acute and chronic HBV, the successes and limitations of vaccination, the relative contributions of domestic and imported chronic HBV, and projections of the burden of disease for decades to come, and estimates of attributable mortality.

2. *What are the critical assumptions underlying such a model, and are data available to inform these?*
Many assumptions were necessary, with two of the most critical being the FoI and migration estimates – which is why sensitivity analysis was conducted around these parameters with a range of data sources used to inform the range of such analysis. In addition, rather than assuming either a static or dynamic FoI was most appropriate, both were designed and implemented.

However, whereas robust high quality data is available for migration, the same is not true for FoI, and enhanced surveillance to compare notified with actual incident infections, and other techniques to collect better FoI data are identified by the model as being a priority for future research. Another area identified by the modelling analysis as requiring more data to improve the reliability of modelled outcomes is the current burden of complications of chronic infection in the Australian context, through procedures such as comprehensive data linkage to generate prospective chronic HBV registries. These and other matters related to the need for further research are presented in 7.2.1 and 7.2.9.

3. Can such a model assess the long-term impact of universal infant and catch-up adolescent vaccination, being the primary control program for this disease in Australia? Yes – this impact was assessed for acute and chronic infections and the mortality associated with each. Furthermore, estimates of the ‘number needed to vaccinate’ were presented for all these outcomes. The impact of interventions other than domestic vaccination could also be assessed by incorporating extensions to the model as presented in 6.5, allowing relative priority to be quantitatively assigned to some of the recommendations for action to follow in 7.2.

4. What are the model predictions for the number of people infected with HBV both acutely and chronically over the next several decades, how many people are likely to die as a result, and how certain can we be of these predictions? These predictions are presented extensively through this chapter, with summary estimates presented in table 6.5. With respect to certainty, this is covered in the answers to questions 2 and 5.

5. How can the model outputs be validated against existing data to provide reassurance that the model is simulating reality sufficiently accurately to be able to generalise the results?
Validation of the model against surveillance notifications, seroprevalence surveys both presented as part of this doctoral thesis and published by others, and mortality data was discussed in detail in 6.2 and indicated that the high dynamic Foi model with migration and vaccination assumptions as described corresponds to existing external data sources.

6. Once the above questions have been answered, the final question to be answered is: What are the policy implications of the model outcomes, especially for predictions in the burden of HBV infection over the next few decades, and can the model suggest strategies to reduce this burden?

Recommendations for action resulting from the model and from the findings presented throughout this thesis are discussed in 7.2.
7 Conclusion

The final chapter of this doctoral thesis will summarise and synthesise the findings of the preceding constituent chapters. Following this, recommendations for action derived from the results of this body of research will be presented. The research questions posed in the preamble to the thesis will then be addressed, following which the closing statements for this thesis will be given.

7.1 Summary

7.1.1 The epidemiology of HBV infection in Australia and characteristics of the public health response

1. The greatest burden of chronic HBV infection in Australia is experienced by migrants from high prevalence countries, and by Indigenous Australians.
2. The public health response has predominantly revolved around vaccination of susceptible members of the population, initially selectively and more recently with universal vaccination of infants and adolescents.
3. This strategy cannot address the vast majority of chronic HBV infections that are acquired overseas prior to migration.
4. Expansion of selective vaccination to include those at highest risk is still required.
5. The focus of Health Departments is on notifications of incident HBV infection. The approach to chronic infections is restricted to data recording, which does nothing to assist those affected or their primary care clinicians.
6. Opportunistic screening of those at risk of chronic infection, particularly migrants from endemic areas and Indigenous people, is needed urgently.
7. Also essential is improving access to appropriate education and treatment for these groups, both for their individual health, to avert future morbidity and mortality and associated health care costs, and to prevent transmission of infection to contacts.

7.1.2 Hepatitis B virology and natural history

1. HBV genotypes are highly associated with geographic region, and emerging evidence of differences in clinical and therapeutic outcomes suggests changes in predominant
genotypes causing infection in Australia may alter our understanding of these aspects of the management of chronic HBV infection.

2. An understanding of viral dynamics allows an appreciation of the capacity of HBV to escape selection pressures including vaccination and antiviral therapy through mutation. This will be critical to the detection of, and response to such mutations as the scaling up of both control methods occurs in the Australian population this century.

3. The natural history of HBV infection is complex, and is defined by the dynamic interaction between viral replication and the host immune response. The long asymptomatic period prior to the onset of illness, and the typically very high viral load for the first few decades of life increase the potential for transmission to susceptible contacts, but also affords the ability to diagnose and treat prior to both these unwanted outcomes of infection.

4. An understanding of the serological and clinical complexities of HBV infection is important to developing a rational approach to the burden of disease in the community. It was also essential for the various research components of this thesis. Education about these complexities is crucial to enhance the ability of Australian primary care practitioners who must be at the forefront of the next phase of Australia’s public health response (26, 30).

7.1.3 The Victorian Hepatitis B Serosurvey 1995 - 2005

1. The prevalence of chronic HBV infection in Victoria is higher than previously thought, and appears geographically and temporally related to historical migration patterns.

2. Differences in migrant settlement have also resulted in profound geographic heterogeneity in HBsAg prevalence, with 1.5% of Melburnian samples being HBsAg positive, five times the prevalence of non-Metropolitan Victorian samples. There is even more pronounced regional diversity within Melbourne, with prevalence ranging from 0% to nearly 8%.

3. HBsAg seroprevalence amongst Melburnian women of childbearing age was 2.3%. This high prevalence, together with the 90% chance of progression to chronicity for neonates infected, outlines the importance of universal maternal HBsAg screening with systematic and long-term follow up to ensure adequate management of mothers, babies and also screening of contacts. It also highlights the importance of the universal birth dose of
hepatitis B vaccine, for when the selective strategy fails as has repeatedly been shown to occur (1.4.2.2.1).

4. Assumptions regarding the universality of National Immunisation Program (NIP) coverage need to be revisited – especially for adolescent vaccination, which appears to cover only 50-55% of eligible adolescents, in keeping with results of the 2002 national serosurvey (12).

### 7.1.4 Parsimonious regression modelling of migration and HBV notifications in Australia

1. Between 4,000 and 8,000 people with chronic HBV infection migrate to Australia each year, for a total of 140,000 since 1975.
2. There is a median 10 year lag between migration and notification of chronic HBV infection, related to the age distribution of migrants and notified cases, the latter possibly being related to the average age at onset of immune clearance (2.5.2.1 and 4.4).
3. Construction of a simple linear regression model allowed confirmation of this lag, but also demonstrated the highly significant relationship between migration and notifications 10 years later, explaining 75% in variability of notifications annually.
4. The model predicts that the number of notifications in Australia will oscillate between 4,000 and 6,000 cases annually, for a total of nearly 49,000 notifications over the decade to 2016.
5. At least 50,000 people who have migrated to Australia recently have undiagnosed chronic HBV infection, with one quarter of these undiagnosed infections likely to result in death.
6. Vaccination programs in endemic countries (1.4.2.3) which constitute the place of birth of millions of Australians will not impact on the burden of chronic HBV in migrant Australians for at least another 20 years.

### 7.1.5 Outcomes of the complex mathematical model of HBV in Australia

1. The optimised model of chronic HBV infection in Australia used incorporated a dynamic force of infection at the high end of the range used for sensitivity analysis. The outcomes of this model were validated against external data including notifiable diseases surveillance, national serosurveys, and the Victorian Hepatitis B serosurvey (chapter 3).
2. The prevalence of chronic HBV infection in Australia is estimated to be 0.75%, with 160,000 people living with chronic HBV as of 2009. Amongst those aged 15-44 years, HBsAg prevalence is 1.1%.

3. 22.5% of these people - 36,000 Australians – will die of their infection if appropriate treatment is not received. Over 3,000 deaths due to chronic HBV have occurred in the last decade.

4. More than one third of those with chronic infection, in excess of 60,000 Australians, remain undiagnosed, although the proportion of all cases notified is increasing over time.

5. Less than 5% of chronic infections entering the population each year arise through domestic infection.

6. 99% of deaths attributable to HBV in 2009 will be due to chronic, rather than acute HBV.

7. The national immunisation program for infants and adolescents has reduced acute HBV infections and deaths due to acute HBV. The decrease in acute infections will continue, resulting in a 75% reduction in annual acute infections by 2050.

8. The impact of vaccination on deaths due to acute HBV is significant, with some 13 lives saved per year as of 2050. Total (acute and chronic) deaths averted through vaccination from 1985 to 2050 are estimated at around 800. The number of people needed to be fully immunised to avert each death to 2050 is approximately 23,000.

9. Despite the large numbers needed to vaccinate to avert acute infections, it is probable that the universal vaccination program is cost saving to society as a whole once non-health care associated costs are accounted (1.4.2.4).

10. The national immunisation program will have no effective impact on the number of people with chronic HBV infection, HBsAg prevalence or deaths due to chronic infection, all being predominantly determined by migration (see point 5. above), with the important exception of Indigenous Australians in whom effective infant vaccination campaigns have, and will continue, to address the burden of chronic HBV infection in this group.

11. However, the NIP (together with other programs such as maternal screening) may insulate Australia against the effects of the ‘positive feedback loop’ of increasing HBsAg prevalence in the community with subsequent transition to a state of HBV endemicity (1.4.2.4).

12. Estimated annual deaths attributable to chronic HBV infection in 2006 (n=313) are more than three times the number of recorded deaths with an underlying cause of all viral hepatitis - acute, chronic and unspecified (n=96) (243). This suggests the cause of death
records markedly underestimate deaths related to chronic infection with HBV and also HCV.

13. The model estimate for attributable HBV deaths is also greater than the number of deaths due to HIV/AIDS in 2006 (n=100) (243), a figure confirmed by other sources (244) and therefore unlikely to be as significantly under-estimated as that for viral hepatitis. In relative terms, the public health response to the burden of chronic HBV infection would appear to be grossly inadequate. This is reinforced by national estimates that greater than 60% of people living with HIV/AIDS are receiving specific antiviral therapy, compared with less than 2% of people living with chronic HBV infection (245).

7.2 Recommendations for action

In this section, nine inter-related recommendations for immediate action to address the increasing burden of chronic HBV infection in Australia will be outlined, along with the rationale for each derived from the findings presented throughout this thesis. In addition to external references, the rationale for these arguments will refer to the thesis chapters which provide evidence supporting each recommendation.

The recommendations are:

1. Augment the public health response to notifications of chronic HBV infection
2. Implement community-based HBV screening programs
3. Encourage appropriate opportunistic screening with adequate follow up for all patients
4. Provide vaccination for those most at risk
5. Expand access to HBV treatment
6. Health care provider education
7. Community education and empowerment
8. Provide Australian financial aid for birth dose inclusive vaccination programs in high prevalence countries
9. Urgent creation and implementation of a comprehensive National Hepatitis B Strategy
7.2.1 Augment the public health response to notifications of chronic HBV infection

**Rationale**

- In contrast to the approach taken with notifications of acute HBV infection, reports of unspecified (chronic) infection to Australian public health authorities are recorded, with no further action taken (ch.1). It would appear that the underlying assumption is that all patients notified will be appropriately counselled, managed and referred for treatment if necessary by the testing doctor. The validity of this assumption has never been tested in Australia, although a recent report suggests many patients are adequately counselled neither prior to nor following diagnosis of chronic HBV infection, are typically not given written information, and often receive vague or inaccurate advice regarding natural history or treatment options (26). Similar experiences were reported systematically in an audit of notified cases of chronic infection from the United States in 2001 (135).

- Chronic infections are responsible for 99% of all deaths attributable to the virus in Australia (ch.6), and most incident infections arise following transmission from a chronically infected person (ch.1.5) (1.4.3). These facts contrast strongly with the prevalent public health practice of following up all cases of acute HBV infection, but taking no action beyond keeping records of cases of unspecified or chronic HBV infection, which outnumber the former more than twenty-fold (ch.1).

- In September 2008, the Centers for Disease Control (CDC) in the United States published revised recommendations for the identification and public health management of people with chronic HBV infection (27). In addition to an expansion of routine screening guidelines (7.2.2), the CDC call for a change in the way public health authorities respond to notifications of chronic HBV infection – a disease which has only been nationally notifiable in the USA since 2005 (11). Significantly expanding the role of surveillance registries of notified cases of chronic infection is advised, with the ‘minimum’ approach being similar to that undertaken currently in Australia.

- The CDC recommendations advise building on this foundation in a tiered fashion, to develop chronic HBV infection registries into tools for public health intervention and clinical management. The expanded roles discussed include:
  - Facilitating and tracking the follow-up of notifications with chronic HBV infection
  - Assisting with notification of contacts and co-ordinating testing and vaccination as indicated
- Communication with or referral to health care providers
- Providing geographic and temporal estimates of the epidemiology of chronic HBV infection
- Linkage with cancer registries and mortality data to establish robust disease burden estimates

Such an expansion would obviously require significantly increased funding devoted to hepatitis programs, and the first three elements are more akin to the approach taken for HIV and tuberculosis notifications in the USA and also in Australia. Depending on the intensity of the expansion, the resources required could be considerable, not least when one considers annual notifications of non-incident HBV infection currently range between 6000 and 8000 in Australia (ch. 1), some three times the number for HIV and tuberculosis combined.

Recommendations

- All persons notified with chronic HBV infection should be sent information from the Health Department regarding their diagnosis, plain language explanations of natural history, infection prevention, and treatment options, and directions to further resources. A crucial aspect of such information will be to include directions on how to receive further information written in languages for predominantly affected culturally and linguistically diverse (CALD) communities.

- At a minimum, data on country of birth, languages spoken at home and potential household and sexual contacts should be collected for all notified cases in addition to the demographic data now recorded.

- Health Departments should track and, where necessary, facilitate follow up (including referral to public hepatitis services where required) for all notifications with chronic HBV infection.

- A particular priority area must be case management for all women diagnosed with chronic HBV infection on antenatal screening, to ensure adequate clinical follow up for mothers and infants, and to guarantee complete and timely vaccination of all infants born to chronically infected mothers to prevent vertical transmission.

- Health Departments should assist patients and their treating doctors in the process of contact notification. Health Departments should take primary responsibility for screening of contacts and vaccination where required, a process which has been shown to be
epidemiologically (246) and fiscally effective (133). Vaccination should be provided free for contacts.

- Ongoing assessment of temporal and geographic trends in surveillance notifications of chronic HBV infection, for the purpose of targeting community education, assessment of appropriateness of CALD resources in place and to ascertain priority areas where the gap between disease burden and available resources (clinical and otherwise) is widest or is diverging most rapidly. Time-series analysis of sub-regional notification data could also be used to assess the impact of public health programs promoting screening for affected communities.

- Data linkage research should connect surveillance notifications with liver cancer registries, mortality data, hospital separations datasets, antenatal screening programs and other relevant information repositories to urgently address the lack of disease burden data for this highly prevalent infection.

- All these recommendations must be undertaken within a cultural and linguistic framework appropriate to communities most affected by chronic HBV infection in Australia (see 7.2.7). An essential first step in this regard is to engage with these communities, their representatives and those with expertise in public health education and program delivery to them. These people should be involved in the conceptual and design phases of all programs to be implemented, not just consulted prior to roll-out of these interventions. This is a cornerstone of healthy public policy (247).

### 7.2.2 Implement community-based HBV screening programs

**Rationale**

- More than one third of Australians with chronic HBV infection have not been diagnosed, representing over 60,000 people (ch.1,4,6).

- One quarter of these people will die as a result of this illness (ch.1,2,6).

- This outcome can be modified with appropriate management including antiviral medication and screening for HCC (ch.2).

- Even when HBV infection is diagnosed, it is often too late for the patient. One quarter of all HBV-related deaths in a large record linkage study from New South Wales occurred within six months of notification, suggesting diagnosis was only made once the patient presented with end-stage liver disease such as HCC or decompensated cirrhosis (13).
• People cannot choose to engage with treatment services if they do not even know they are infected. Enabling people to take control of their own health is central to reducing health inequities and is a fundamental requirement for health promotion as enshrined in the Ottawa Charter (247).

• Failure to screen for HBV infection in people at high risk due to region of birth despite recurrent medical contact (in the community and in hospitals) spanning many years has been repeatedly demonstrated in the Australian and international contexts (ch.1) (15, 19, 55).

• HBV infection is one of the top 10 causes of death worldwide (7). Most of these deaths occur in the Asia-Pacific region. This region currently contributes two thirds of all migration to Australia, more than 40% of whom arrive from high prevalence areas (>8% HBsAg prevalence) where HBV is responsible for over 3% of all cause mortality (ch.1,4).

• Chronic HBV infection meets all the WHO criteria for screening for disease (248). It is an important health problem for the individual and the community (ch.1,6); suitable diagnostic tests are available (ch.2); there is a typically a long asymptomatic period of infection (ch.1,2); accepted treatments are available and they are more effective when started earlier in the course of the disease (ch.2); and the cost of diagnosis and treatment is economically balanced in relation to health care costs as a whole. Importantly, the WHO principles assert that screening should be a continuing process.

• Community-based HBV screening programs have been successfully implemented in contexts similar to Australia where there are high-risk communities within a generally low-prevalence population; examples include New Zealand (249) and New York City (250). In both these instances those with the highest burden of infection were people born in the Asia Pacific region, as is the case in Australia (ch.1,4).

• The recently published CDC guidelines demonstrate that screening for HBV infection in populations with a prevalence of 2% or greater (which would include approximately 3 million Australians on the country of birth criterion alone (49)) is cost effective when compared to other diseases for which screening programs are routine in both the United States and Australia (27).

• Recent research from Stanford University demonstrated that screening people born in high-prevalence countries for HBV infection, together with vaccination of those that remain susceptible, is not only cost-effective but could greatly reduce the burden of HBV-associated liver cancer and chronic liver disease in these groups (133). The cost
effectiveness of treatment is likely to increase over time as more effective treatments become available (27), and a better evidence base behind clinical guidelines is established.

- The significant geographic differences in HBsAg prevalence noted in the Victorian Hepatitis B Serosurvey 1995 – 2005 (ch.3) and the underlying differences in country of birth they reflect can be used to maximise the efficiency and appropriateness of targeted screening programs, as well as community and clinician education (7.2.6 and 7.2.7), vaccination (7.2.4), and expanded treatment access (7.2.5).
- Identification, education and treatment of those with chronic infection, and vaccination of contacts all act to avert further transmission of infection (ch.1,6).

Recommendations
- Immediate design and implementation of pilot HBV screening programs in various Australian jurisdictions, targeting communities and areas with high prevalence of infection, responsive to local conditions and diversity, with the meaningful involvement of CALD and Indigenous communities from the outset.
- The detailed conduct of such pilot studies will depend largely on local circumstances; what might be appropriate for migrant communities residing in inner Melbourne may be completely inappropriate for Indigenous people living in central Australia.
- Objectives would include;
  - to diagnose people with previously unknown chronic HBV infection
  - to provide appropriate follow up for those diagnosed
  - to provide vaccination for those at risk of HBV infection
  - to increase general practitioner (GP) and community awareness of the importance of testing for HBV infection, particularly for people born in high prevalence regions and Indigenous people
  - to establish the prevalence of chronic HBV infection according to collected risk factor data in order to inform population prevalence estimates and expanded public health interventions
  - to assess the feasibility of a broader community based HBV screening program
  - to identify barriers and best practices in the pilot program to optimise the design of future, broader population HBV screening programs as appropriate.
7.2.3 Encourage appropriate opportunistic screening with adequate follow up for all patients

**Rationale**

- In addition to defined community-based screening programs, appropriate opportunistic testing for serological correlates of HBV infection and immunity is important, to improve diagnostic rates for those at particular risk, to facilitate immunisation for those at risk who remain susceptible, and to exclude HBV where the consequences of infection are greatest (ch. 1).

**Recommendations**

- Examples of where such opportunistic testing should occur include:
  - All patients of acute care hospitals (including all inpatients, and all ongoing outpatients) with risk factors for chronic HBV infection, particularly those born in endemic areas or who identify as Aboriginal or Torres Strait Islanders. Availability of interpreting services, ease of referral to hepatitis services, and barriers to accessing pathology collection are all much less in the hospital environment than in community practices.
  - All patients who are to undergo immunosuppressive therapy, including transplantation, chemotherapy, or for autoimmune diseases (80). This allows preemptive therapy to be undertaken in those diagnosed with chronic HBV infection, an approach which is associated with reduced mortality (251). It also permits vaccination of those remaining susceptible.
  - All pregnant women. Although this is current policy, coverage should be optimised and case management of all women diagnosed with chronic HBV infection should be undertaken by the Health Department (7.2.1).
  - All patients with risk factors as presented in table 1.1 (ch. 1), plus Indigenous people should be offered testing by all clinicians recurrently involved in their care, not only primary care clinicians, and appropriate referral arranged should chronic HBV infection be diagnosed.
7.2.4 Expand vaccination for those most at risk

*Rationale*

- Universal vaccination of Australian infants cannot protect susceptible migrants from regions of HBV endemicity against infection (*ch.1, 6*).
- Migrants from endemic areas (≥2% HBsAg prevalence) constitute a large proportion of the Australian population – over 10% in the 2006 census (49).
- These Australians have a significantly greater risk of acute HBV infection than their Australian-born peers, reflecting increased likelihood of contact with people with chronic HBV infection (*ch.1*).
- Although the cohort of Australian children born since 1985 has been targeted by adolescent catch-up program, serological evidence suggests coverage is poor, of the order of 50-60% of eligible adolescents (*ch.3*). This group (now aged between 10 and 23 years) are in or about to enter the age range of highest HBV infection rates, predominantly through sexual contact or IDU (*ch.1*).
- The impact of the neonatal vaccination program on acute HBV infections will not start to be realised for another six years, when the first cohort of infants will reach 15 years of age. Following this watershed, selective vaccination programs (which have historically failed to adequately address incident HBV infections in rich countries (*ch.1*)) will need to be refocussed and reinforced to improve access by those groups remaining at greatest risk of infection, which will increasingly become people born in countries without universal hepatitis B vaccination programs (*ch.1*).
- Health Departments have variable funding rules for non-NIP hepatitis B vaccination. In Victoria, funded vaccination is available for:
  - Catch up for secondary school students who were missed in the adolescent program
  - Household contacts of people with chronic infection
  - IDUs
- A number of groups at higher risk of chronic HBV infection or of more serious consequences if infected are not eligible for funded vaccine. These include susceptible adults born in high prevalence areas, susceptible Indigenous adults, non-household sexual
partners of people with chronic infection, MSM, and people with chronic HCV infection or other liver diseases (ch. 1).

- Many clinicians are unaware of existing eligibility criteria for free vaccination. Furthermore, complexities around vaccine ordering and provision (in Victoria, three separate vaccine order forms are required for various indications for funded vaccination, and none of the links are appropriate to the household contact indication), and doctors and clinics must register and obtain Department of Human Services account numbers, Doctor Registration numbers and/or Health Services Permit numbers prior to ordering vaccines.

Recommendations

- Health departments and epidemiological researchers should continually assess under-vaccinated sections of the community at risk of HBV infection, particularly once the first cohort of universal infant vaccinees enters the peak age of HBV acquisition.

- Health Departments should formulate programmatic responses to improve vaccination coverage amongst those people at high risk of infection, particularly CALD and Indigenous people who are also subject to health care access inequity and in some instances may not have received vaccinations that their non-Indigenous Australian-born peers have been provided.

- Adequately resourced and universal vaccination programs in all custodial settings should be implemented as part of broader screening, educational and treatment service provision.

- Health departments should fund vaccine provision to susceptible members of high risk groups.

- This is particularly the case for non-household susceptible contacts of people diagnosed with chronic HBV infection who are currently ineligible. ‘Ring vaccination’ around people diagnosed with chronic infection has been demonstrated to be cost effective (133).

- Other groups who should receive free vaccination include susceptible Indigenous adults and adults born in endemic areas.

- Streamlining of processes for provision of funded hepatitis B vaccine should be undertaken, both in community settings and especially in the hospital context.

- Primary care practitioners (medical and nursing), and relevant hospital medical, nursing and pharmacy staff should receive effective communications regarding the indications for funded vaccine and how to access it.
7.2.5 Expand access to HBV treatment

Rationale

- The number of people living with chronic HBV infection rises by several thousand each year, the vast majority (>95%) through migration (ch.1,4,6).
- The incidence of complications such as HCC is also rising (ch.1), with this cancer now increasing in incidence faster than any other internal malignancy in New South Wales (24).
- Evidence is mounting that appropriate management of HBV infection – including, but not limited to specific antiviral therapy, and also HCC screening where indicated – is associated with modification of the natural history of disease, and reduced morbidity and mortality (ch.2).
- Treatment options are expanding rapidly, complicating management algorithms and increasing the difficulty of delivering optimal care for clinicians (general and specialist) who do not have a substantial caseload of patients with chronic HBV infection (ch.1,2).
- Only a small fraction of patients living with chronic HBV infection who could benefit from antiviral treatment have received it (25).
- Existing hepatitis clinics in tertiary hospitals often have waiting periods for new referrals of many months and in some instances greater than one year. For those with marked necroinflammatory activity, this period may result in significant deterioration in their condition (ch.2). In a patient with undiagnosed HCC (the annual incidence of which is between 5-10% in cirrhotic patients (24)), such delays following referral could result in death prior to the first scheduled appointment (67).
- Viral hepatitis services in regional and remote areas are very limited. The need for increased public services is most acute in regions of Australia with significant proportions of Indigenous people living with chronic HBV infection. Indigenous people have been identified as having greater barriers to accessing hepatitis services than any other affected community for a range of reasons (26).
- Expanding testing through screening programs and related testing recommendations, if successful, will rapidly increase pressure on existing hepatitis services, which are also struggling to meet the needs of the approximately 200,000 Australians living with chronic hepatitis C virus (HCV) infection (244).
• As discussed in 1.4.3 (ch.1), expansion of appropriate treatment for those with chronic HBV infection not only has the potential to affect their own health outcomes, but to reduce HBV transmission to susceptible contacts.

Recommendations

• Immediate and adequately funded investment in expansion of existing public hepatitis services is essential. This intervention is likely to result in the most rapid reduction in delays to specialist assessment for most patients whilst the development of more innovative models of care delivery are explored and implemented. Governments, hospital management and specialist clinicians must work collaboratively and urgently to make this outcome a reality and remove the inevitable administrative and bureaucratic obstacles.
• Such an expansion will also most rapidly address the worsening workforce shortage in specialist medical and nursing staff with expertise in the management of viral hepatitis.
• Public hepatitis services in regional and remote areas must be expanded, and specific clinical programs for Indigenous people with HBV infection must be created and supported in partnership with the Indigenous community.
• Where appropriate, delivery of care in the community can reduce costs, is potentially more convenient for patients, and would allow existing hepatitis clinic resources to be prioritised for patients with complex care requirements.
• Such community-based care could include primary care clinicians with improved access to HBV resources (see below) and also the creation of community-based hepatitis clinics, ideally staffed with multidisciplinary teams of GPs, specialist physicians and nursing staff, along with CALD workers, interpreters and other allied health practitioners (including drug and alcohol workers and nutritionists) as dictated by local needs and resources. Such community clinics should be established in areas where the burden of chronic HBV infection is highest, such as areas with large proportions of the population having been born in endemic areas of Asia, Africa and the Pacific, and areas with large Indigenous Australian communities. In the Victorian context, these areas would include inner western Melbourne, and the Greater Dandenong area, as evidenced by the Victorian Hepatitis B Serosurvey (see figure 3.1, ch.3).
• Significant work will need to be undertaken to adequately educate, resource and support GPs in order to improve management of HBV infection in primary care (26, 30) – 7.2.6.
• Innovative models of care, including expanding the role of specialist nurses in hospital clinics, and practice nurses in the community, and the creation of shared care models between hospitals and community clinicians will be critical to enable adequate servicing of the increasing numbers of people living with chronic HBV infection in the community.

• There was a greater focus on preventive health ($448 million over four years) and funding for increased hospital outpatient throughput (2.5 million extra services over four years) in the most recent Council of Australian Governments meeting in November 2008 (http://www.coag.gov.au/coag_meeting_outcomes/2008-11-29/index.cfm#health). These initiatives must be harnessed to contribute to improved health outcomes for Australians with chronic HBV infection.

• Adequately funded screening, prevention and treatment services for people serving custodial sentences (who are more likely to be Indigenous, and also more likely to use injected drugs than those not in custody (ch.1)) should be established.

• The requirement for liver biopsy prior to S100 funded therapy was removed for people infected with HCV in 2006 as a barrier to treatment access. Although in many instances assessment of liver histology is important for patients with hepatitis B and C, the requirement for biopsy prior to treatment of HBV infection (excluding patients with clotting disorders) remains a significant problem for some patients. This is most acute in remote areas of Australia – such as Alice Springs, where no facility for liver biopsy is currently available at all. Thus Indigenous people in central Australia who experience a huge burden of HBV-related mortality (17) are completely unable to access funded treatment for this infection under S100 guidelines unless they are able to travel a thousand kilometres to the nearest capital city. This policy failure helps cement the burden of chronic liver disease due to HBV infection in Indigenous people in this area and must be rectified immediately.

7.2.6 Health care provider education

Rationale

• Our understanding of HBV epidemiology, virology, natural history and treatment paradigms is rapidly evolving (ch.1,2). This is particularly so for clinical approaches to HBV infection, with new agents rapidly becoming available, and evidence regarding
treatment outcomes emerging. Therapeutic endpoints are becoming controversial, and it is increasingly difficult for specialists to keep abreast of emerging research, let alone GPs.

- 70% of responding GPs in a recent survey identified their need to strengthen their professional skills with respect to HBV (26).

- Illustrative of this need is that while 55% of clinicians in the survey felt confident about when to refer patients for specialist opinion, 29.5% of all those surveyed believed a positive anti-HBs test result (i.e., immunity through vaccination or prior infection) should result in referral to a specialist. Were this to actually occur, the 9 million Australians (42% of the population, see 6.2.2 ch.6) who have been immunised are going to be competing with the 160,000 with chronic HBV infection (ch.6) for available resources.

- Primary care clinicians are central to the health care experience of people living with chronic HBV infection, from diagnosis through education and monitoring to referral for specialist review and ongoing management (30).

- Without an improved level of awareness among primary care physicians generally, and significant numbers of GPs with particular interest and expertise in HBV management, the recommendations outlined above including public health responses to notified infections, screening programs, opportunistic testing and vaccination, and especially community based care and associated shared care models will be either difficult or impossible to implement.

Recommendations

- The Commonwealth Government must make GP education regarding HBV infection a priority and fund programs accordingly.

- Education and training specific for HBV infection must be developed and delivered to primary care practitioners (including GPs and practice nurses). The differences between HBV and the other blood borne viruses (BBVs) in terms of epidemiology and the predominantly affected communities, and also prevention and treatment strategies are such that HBV-specific approaches are required, rather than attempting to ‘peg’ HBV to existing HCV and HIV programs – which has been the case previously due to specific funding for these other BBVs under the auspices of their respective National Strategies (see 7.2.9).
The tiered approach used in several Commonwealth and State funded educational programs for HCV and HIV could also be implemented for HBV education in primary care.

Ongoing engagement of GPs in this educational process at all levels will require involvement of many supporting structures including Commonwealth and State/Territory Governments, Colleges of General Practice, and GP Divisions.

### 7.2.7 Community education and empowerment

**Rationale**

- Providing health information to affected individuals and communities is a process of empowerment, providing personal and collective opportunities for choice, for engagement, and for achieving desired outcomes. This is central to the practice of health promotion (247).
- Communities predominantly affected by HBV infection in Australia have been repeatedly shown to lack information or understanding of important aspects of HBV including modes of transmission, natural history, and treatment options available \((ch.1)\). This lack of information has the potential for significant harm, including ongoing transmission of infection and increased morbidity and mortality from chronic infection.
- The high prevalence of HBV infection in particular communities including migrants from endemic areas and Indigenous people \((ch.1)\) mandates that these Australians are involved in the design and conduct of community HBV programs from the outset. If this does not occur, the relevance and impact of these programs will be impaired, and the risks of disengagement and stigmatisation will be greater (252).

**Recommendations**

- Health Departments should engage with and involve representatives of affected communities, and agencies with demonstrated cultural competency in health program and education delivery in the development of diverse community HBV education initiatives.
- Such initiatives should be targeted initially on groups experiencing the highest burden of chronic HBV disease in the community. These include migrants from high prevalence areas of Asia and Africa, and Indigenous people \((ch.1)\).
Ongoing assessment of program impacts (positive and negative) with continual readjustment and refining of message delivery is essential.

Australians with a refugee background often have a very different history of health care access than other migrants, and also different and very challenging social and financial circumstances. The approach to HBV education and care in this context may need to be very different and should not be attempted in isolation from other immediate concerns common in recently arrived refugees (252).

7.2.8 Provide Australian financial aid for birth dose inclusive vaccination programs in high prevalence countries

Rationale

- Universal vaccination of all Australians would prevent less than 5% of all chronic infections entering the population each year, with the remainder incurred through migration from HBV endemic countries (ch.6).
- Vaccination against HBV in Australia saves one life for every 23,000 people vaccinated up to the end of the simulation in 2050 (ch.6).
- In contrast, vaccination against HBV in a country with 10% HBsAg prevalence would be expected to save one life for every 30 to 40 people vaccinated (ch.1). Thus universal vaccination in high prevalence countries is more than 500 times as effective as it is in Australia on a lives-saved-per-course basis.
- The differential impact of vaccination in resource-poor high HBV prevalence countries is even more profound on a cost effectiveness basis, with a price per dose of hepatitis B vaccine only 20 to 30 US cents (115), orders of magnitude less than in rich countries such as Australia and the United States (53, 133). Even were vaccine costs here only 10 times the UNICEF supply cost, this would still result in a ratio of cost effectiveness for hepatitis B vaccine prevented deaths in a low-income high prevalence country of 5000 times that in Australia as a conservative estimate.
- Taking Vietnam as a illustration:
  - Vietnamese-born Australian population in 2006 Census: approximately 160,000 (241)
  - Estimated Vietnamese population in 2006: approximately 85,000,000
  - Proportion of Vietnamese-born population that has migrated to Australia (excluding migration to other countries): 160,000/85,000,000 = 0.19%.
- Number of Vietnamese-born lives saved for every Australian-born life saved (same total vaccine purchase price): 5000

- Number of Vietnamese-born Australian residents’ lives saved for every Australian-born life saved through universal infant vaccination: 9.4

- That is, if the same resources were devoted to Vietnamese universal vaccination programs by the Australian Government that are to our domestic National Immunisation Program, not only would 5000 lives be saved for every life saved currently, but nearly 10 times as many lives would be saved here in Australia as are currently through domestic vaccination, due to protection of future Australian migrants against infection.

- Hence on self interest as well as humanitarian grounds, Australia (and other rich net migrant importing countries) should be investing as much as possible in comprehensive vaccination programs in HBV endemic countries. If universal vaccination of our own infants is cost saving to society (table 1.9, ch.1) despite the number needed to vaccinate to avert each death, such program support in endemic countries we source migrant intake from is likely to represent an even more effective investment – even if one discounts the ‘collateral’ benefit of saving an extra 4990 lives not destined to be lived in Australia.

- This comparison is relatively insensitive to the number of Vietnamese migrants to other countries. As an extreme example, if the number of Vietnamese born people world-wide is 100 million (15 million emigrants), then the number of Australian lives saved through vaccination in Vietnam compared with in Australia becomes \((160,000/100,000,000) \times 5000 = 8\). Furthermore, the total number of lives saved is unchanged at 5000.

- Under the optimised model (high dynamic FoI, intermediate migration) the number of chronic infections averted under the expanded NIP is 14,135. If one assumes that future treatments available in Australia beyond 2050 have no impact on the mortality of chronic HBV infection, total future attributable deaths (beyond the simulated period) in people with chronic HBV infections acquired up to 2050 will be \(0.225 \times 14,135 = 3180\). If this is added to acute deaths averted (n=362), total projected mortality averted due to the expanded NIP for infections acquired in Australia to 2050 would be 3,542 deaths. This gives an estimate of number needed to vaccinate to avert each death of \(18,000,000/3,542 = 5081\). The number of Australian lives saved through vaccination in Vietnam for every life saved through vaccination in Australia falls to 2.4, and the total lives saved falls from 5,000 to 1,270. Thus even under the most extreme assumptions to favour domestic
Australian vaccination, more than 1,000 lives can be saved for every life saved currently, including more than double the number of Australian lives.

- It turns out this idea is not new. Over a decade ago Gay and Edmunds reported a similar analysis in a letter to the British Medical Journal entitled “Developed countries could pay for hepatitis B vaccination in developing countries” (253). Their analysis considered chronic infections averted, rather than resultant deaths, and considered British support for universal vaccination in Bangladesh would be four times more effective for the United Kingdom than a domestic infant vaccination program.

- As observed by Gay and Edmunds in 1998, since future migration is unable to be predicted with precision, global co-ordination would be required to enable all high prevalence countries to introduce vaccination against HBV, funded by rich low prevalence countries, to the benefit of all. A vehicle for this co-ordination came into being two years later, in the form of the GAVI Alliance.

- As discussed in 1.4.2.3, the birth dose of hepatitis B vaccine is critical to the prevention of vertical transmission. In 2006, the WHO reported that although 84% of high HBV prevalence countries had hepatitis B vaccine in their childhood schedules, only 36% of the estimated 62,658,651 infants born in these countries in that year received a dose of vaccine at birth (118). With reference to the example of Vietnam given, GAVI-supported programs have resulted in 93% coverage for infant hepatitis B vaccination, and 64.3% coverage for the birth dose as of 2006 (http://www.gavialliance.org/resources/Vietnam_Progress_Report_2006_VTN.doc).

**Recommendations**

- Additional resources should be provided to Australian development aid to support hepatitis B vaccination in high prevalence, resource poor countries of the world, particularly for programs to expand timely birth dose vaccine provision.

- The GAVI Alliance provides an effective route to channel such funds. Australia’s total commitment to the GAVI Alliance since its creation stands at US$20 million, which is modest compared with the contributions of many countries with comparable or smaller economies. Furthermore, as a country with particularly high migration levels from HBV endemic countries in the Asia Pacific region, Australia stands to gain relatively more from contribution to these programs as outlined above.
7.2.9 Urgent creation and implementation of a comprehensive National Hepatitis B Strategy

Rationale

- None of the recommendations listed above are likely to be implemented without a whole-of-government approach providing co-ordination, governance structures and adequate resourcing for implementation.
- The piecemeal and largely uncoordinated response to chronic HBV infection in Australia has been attributed to the lack of a National Strategy to resource and channel these efforts (25, 26, 30). This provides a stark contrast with the other blood borne viruses, for which National Strategies have existed for many years and are credited with significant progress made in fostering collaboration, prevention of transmission, care of those infected, and ongoing education and research (30).

Recommendations

- Australia must immediately engage in the creation and implementation of a broad-based, adequately funded National Hepatitis B Strategy with involvement of all key stakeholders. This could be a standalone strategy, or be part of an inclusive Viral Hepatitis Strategy following the imminent review of the National Hepatitis C Strategy 2005-2008. In the latter case, given the fundamental differences between the viruses (7.2.6) the HBV component cannot simply be appended to a new Hepatitis C Strategy, otherwise the institutionalised ‘poor cousin’ status of efforts to address the expanding burden of HBV infection will remain.
- This strategy must define responsibilities for defined outcomes, with pre-determined success and failure criteria, and must have a dedicated implementation plan as exists for existing National Strategies.
- An essential element of a National Hepatitis B Strategy, as in existing HCV and HIV strategies, would be linkage to dedicated public research funds for dedicated HBV research, including epidemiological, socio-cultural, clinical and basic science including virology and immunology.
7.3 Addressing the research questions

- **What is the current understanding of the burden of HBV infection in Australia?**

It is well recognised that the incidence of acute HBV infection in this country is falling, partly due to the evolving universal vaccination program of infants and adolescents. The contrasting increase in the prevalence of chronic HBV infection in Australia is also recognised, as is the root cause of the greatest proportion of this increase, migration from endemic areas.

The notable and rising burden of complications of chronic HBV infection have been well documented to be visited disproportionately on members of our community who are known to be less well served by our health care system, namely migrants from Asia and Africa, and Indigenous Australians.

- **What are the population, individual and viral factors which influence the outcome of HBV infection?**

The level of HBV endemicity in a population naturally affects the ongoing likelihood of transmission, with those chronically infected being the source of the majority of incident infections in all populations. Furthermore, with increasing prevalence, the average age at infection falls. This is so for most infectious diseases and reflects the likelihood of effective contact between a susceptible individual with an infectious individual over time. However the unique relationship between age at infection and likelihood of progression to chronicity that is a fundamental determinant of HBV epidemiology worldwide means that the patterns of endemicity have been self-perpetuating. It is only with the advent of vaccination, and more recently effective antiviral agents, that these feedback loops can be interrupted.

- **How can a serological survey of a convenience sample be made more representative of the general population, and how can this representativeness be assessed? Can a serosurvey conducted in this manner improve our estimates of the population prevalence of chronic HBV infection, and of immunisation coverage?**
The Victorian Hepatitis B Serosurvey attempted to address the problem of bias by excluding samples ever referred for serological testing for blood borne viruses. An attempt to improve representativeness was also undertaken by selecting samples proportional to the age and gender structure of the Victorian population. Representativeness was assessed by comparison of raw serosurvey results with those standardised by age group and geographic location. Despite the fact that no attempt was made to select samples by residential area, the serosurvey matched the geographic distribution of the Victorian population very closely.

It cannot be stated with certainty whether the resulting estimates are an improvement on National Serosurvey results for example. When assessed using the mathematical model described in this thesis (which was not parameterised using these serosurvey data) as described in 6.2.2, it would appear that the serosurvey reported in this thesis most closely approximated results for the proportion of susceptible, vaccinated and cleared HBV infections in the population, whereas the National Serosurveys better reflected the numbers with chronic HBV infection.

It is not certain why this is the case, but with respect to HBsAg status it is possible that the status of VIDRL as a virology reference laboratory influenced these results. It should be noted, however, that the trends in HBsAg prevalence over the three test years spanning 1995-2005 did correspond with changes in unspecified HBV notifications to NNDSS (4.3.1), and led to investigation of parallels between these trends with migration estimates that became the foundation of the regression model presented in chapter 4.

Finally, the ability to connect samples with residential postcode allowed the analysis of differences in HBsAg prevalence across Melbourne, and between Melbourne and the rest of Victoria, data which provide critical information for targeting of policy responses to address the expanding burden of HBV infection in the community.

- **How can existing demographic data be used to extend our understanding of HBV epidemiology in Australia?**

This thesis – particularly chapters 4, 5 and 6 – made extensive use of demographic data in the public domain, predominantly from the Australian Bureau of Statistics (ABS) website (http://www.abs.gov.au/) but also from the (currently so named) Department of Immigration
and Citizenship (http://www.immi.gov.au/media/publications/statistics/). These data included migration by birth country, census data, and a wide range of demographic parameters used to parameterise the complex mathematical model of HBV infection in Australia including births, deaths, immigration and emigration, and age distribution of the population from 1951-2004 and projections from 2005 to 2050. Without these data, the model could not have been constructed.

As such, the Gift to the Nation announced on the 100th birthday of the ABS, 8th December 2005 by former Treasurer Peter Costello – that all statistics on the ABS website would thereafter be provided free of charge – was instrumental in the realisation of this thesis. Furthermore, this investment in statistical availability is likely to be returned many times over through innovative research in any way touching on population statistics and demography.

Finally, detailed information not available on the ABS website for migration to Victoria by country of birth and by age group, was commissioned from the ABS by the Communicable Diseases Prevention and Control Unit, Public Health Branch, Department of Human Services Victoria.

- Can mathematical modelling be used to establish estimates of the burden of HBV infection in Australia over time, and how can the accuracy and reliability of such models be tested?

The mathematical model, constructed as described in chapter 5 with outcomes and validation presented in chapter 6, has provided realistic and very useful information about the evolution of the epidemiology of HBV in Australia over the last six decades, with projections ahead another forty years. It provided a means of assessing the impact of vaccination programs. In addition, estimates of the proportion of people with chronic HBV infection that have been diagnosed, the proportion of chronic infections arising domestically, and the numbers of deaths attributable to this infection have been derived. These inferences were not conceived when the model was being designed, but were incorporated once the structure of the simulation was established and further questions of interest were developed in discussions with a range of colleagues, and with my supervisory panel. These discussions have also helped to lay foundations for future extensions to the model, described in 6.5.
The model has been validated against available data including notifications and serosurvey information and has been shown to be robust. Sensitivity analyses conducted for the force of infection, future migration estimates, and in the nature of the simulation itself (static versus dynamic force of infection, with various contact matrices tested within the dynamic model) have allowed the range of uncertainty to be explored and quantified.

- Finally, following synthesis of the findings of this doctoral research, can priorities for public health policy be identified that could address the increasing burden of chronic HBV infection?

This question has been the subject of 7.2 above.

### 7.4 Closing statement

Australia is experiencing a large and expanding epidemic of chronic HBV infection. The public health response to HBV has so far revolved around universal infant vaccination. This strategy simply cannot address the more than 95% of chronic HBV infections in Australia that are acquired overseas prior to migration. Community-based screening of those at risk of chronic infection such, including migrants from endemic areas and Indigenous people, and improving access to treatment for these groups, are critical elements of an adequate public health response to HBV infection that are yet to be addressed.

The natural history of chronic HBV infection is determined by the dynamic interplay between viral replication and the immune response of those infected. The long asymptomatic period prior to the onset of any illness, and the typically very high viral load for the first few decades of life (immune tolerance) increase the potential for transmission to susceptible contacts, but also afford the ability to diagnose and treat prior to both these outcomes.

Of the estimated 160,000 people living with chronic HBV infection in Australia as of 2009, more than 60,000 remain undiagnosed. One quarter of these people will die of complications related to HBV infection.

The estimated number of deaths due to HBV infection annually is three times the number caused by HIV/AIDS. However HBV remains grossly under-represented in research and
public health funding in Australia when compared with HCV and HIV and unlike these other blood borne viruses no National Hepatitis B Strategy exists to address the significant and growing burden of HBV infection in Australia. This burden will clearly be felt most by those infected and their families and communities, but will also challenge the resources of the health care system as a whole.

The title of this doctoral thesis refers to the novelty of the approaches taken in developing an improved understanding of HBV infection in Australia. The convenience sample serosurvey reported in chapter 3 is the largest conducted in Australia for markers of HBV infection, the first to apply the same sampling strategy to serum specimens collected over a 10 year time span around the introduction of universal childhood vaccination, and the first to use an automated selection strategy designed to improve representativeness and reduce bias. The regression model presented in chapter 4 comparing a variety of disparate data sources is the first time this analysis has been applied to deriving lag periods between migration and surveillance notifications of a communicable disease. Finally, the complex mathematical model described in chapters 6 and 7 is unique in many respects. It is the first mathematical model of HBV infection to simulate the entire population of Australia, and the first dynamic FoI model of HBV infection for this country. In the specific modelling of migration trends over decades, vaccination uptake at various ages at different times, and specific comparison of static and dynamic FoI model outputs to assess which best fit observed data, the model is novel to the body of international literature.

These novel approaches have afforded new information of relevance to the future public health response to HBV infection in Australia. This chapter has summarised the results of this research, and presented recommendations grounded in these results that would help address the burden of HBV infection in Australia. Unless these or other effective measures are undertaken to provide essential policy and practice outcomes to assist and empower Australians living with chronic HBV infection, the costs to our community in health care expenditure, lost productivity and related social outcomes will become great. The human costs will be even greater.
Bibliography


186. Lurie Y, Manns MP, Gish R, Chang TT, Yurdaydin C, Lai CL, et al. The efficacy of entecavir is similar regardless of disease-related baseline subgroups in treatment of nucleoside-naive, HBeAg(+) and HBeAg(-) patients with chronic hepatitis B. Journal of Hepatology 2005;42(Suppl 2):184.


231.  Massad E. Why bother with modelling? Introduction to Infectious Disease Modelling and its Applications. London School of Hygiene and Tropical Medicine; 2006.


Appendix 1  Serosurvey failed HBsAg test run resolution

A1.1 Description of run error

On the second run of HBsAg testing of anti-HBc positive samples, conducted on 28 March 2007, many low-level positive results were obtained. Of the entire run of 91 anti-HBc positive samples, 43 were positive – of which 60% had an optical density (OD) of less than 1.0 (table A1.1). This is a much higher proportion of HBsAg positive samples than expected on epidemiologic grounds, and also than on the first HBsAg test run which was 13.4%. It is also a very large proportion of low-level positive samples.

Further evidence of testing error was obtained when the plate was read by a separate stand-alone plate reader in the Serology Laboratory. In the penultimate well of the tray, which was not used in the test run and therefore should have been empty, the reader gave an OD result of 0.291, indicating a positive result. This is categorical evidence of cross-well contamination of either sample or reagents leading to false positive results.

Automated HBsAg EIA assay 28/03/07 – test conditions and result summary:

<table>
<thead>
<tr>
<th>Results</th>
<th>OD group range</th>
<th>Number</th>
<th>Percentage of samples with same result in OD group range</th>
<th>Percentage of samples with result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.05 – 0.069</td>
<td>19</td>
<td>47.5</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>0.07 – 0.089</td>
<td>17</td>
<td>42.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.09 – 0.119</td>
<td>4</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0.09 – 0.119</td>
<td>8</td>
<td>100.0</td>
<td>9%</td>
</tr>
<tr>
<td>Positive</td>
<td>0.12 – 0.149</td>
<td>8</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.15 – 0.199</td>
<td>6</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 – 0.39</td>
<td>9</td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.4 – 0.99</td>
<td>3</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 – 2.99</td>
<td>2</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OWR</td>
<td>15</td>
<td>34.9</td>
<td>47%</td>
</tr>
</tbody>
</table>

Table A1.1 – HBsAg run 28/03/07 – results by OD range
A1.2 Actions taken

1. Discussion with Serology Senior Scientist, another Serology Scientist and then the Head of the Serology Laboratory. Consensus that as there was no obvious pattern of positive results on the plate (i.e. well contents not ‘carried’ along tray by wash, and weak positive wells suspected of being erroneous not uniformly clustered around strong positive wells) that there was no obvious explanation such as a wash cycle error.

2. The Triturus EIA Analyzer was examined by a service technician (attending to address a wash cycle error in the Serology laboratory’s other Triturus Analyzer on that day) in whose opinion the problems were not obviously caused by a wash issue. The technician did not offer any other explanations other than plate might have been knocked at some stage during the test run within the machine.

3. Entry of sample data into Stata v8.2 for descriptive statistics and comparison on 28 March 2007.

4. Comparison of HBsAg results with anti-HBs results of the same samples (see table A1.2 for relevant Stata output) revealed that many of the samples with HBsAg positive results were also anti-HBs positive (at estimated anti-HBS titres of both 10-100 IU/L, and >100IU/L). This is biologically implausible (HBsAg rarely co-exists with anti-HBs as this causes immune complex formation resulting in a lack of available anti-HBs to react during the EIA testing and hence a negative test result). In the rare circumstance when both surface antigen and antibody do co-exist, the antibody titre is typically low and not >100IU/L. These co-existent antigen and antibody results suggest contamination during or after the testing (but before reading).

5. The decision was made to repeat a representative portion of the tests manually, including:
   a. at least one negative sample
   b. as many adequate volume IND and low positive samples as possible
   c. at least one strong positive and one of the OWR (‘Out (of reader) Working Range’: samples with such a strong OD that the reader is unable to further quantify the result)
   d. a spread of samples with negative, positive (10-100 IU/L) and strongly positive (>100 IU/L) anti-HBs results

6. Consequently a manual run of 35 representative samples (tables A1.3 and A1.4) and 5 controls (3 negative, 2 positive) was undertaken on 29 March 2007. Criteria for selection:
   a. number of strips able to be used = 5 (40 wells)
b. to optimise result security, decision made to include 5 controls

c. samples had to have sufficient volume of remaining serum (at least 75μL) for the manual run

d. A representative sample of remaining samples used: as per 5. above

<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2</td>
<td>824</td>
<td>.067</td>
<td>Neg</td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>854</td>
<td>.067</td>
<td>Neg</td>
</tr>
<tr>
<td>3.</td>
<td>6</td>
<td>2101</td>
<td>.068</td>
<td>Neg</td>
</tr>
<tr>
<td>4.</td>
<td>19</td>
<td>2217</td>
<td>.064</td>
<td>Neg</td>
</tr>
<tr>
<td>5.</td>
<td>22</td>
<td>2264</td>
<td>.065</td>
<td>Neg</td>
</tr>
<tr>
<td>6.</td>
<td>27</td>
<td>2298</td>
<td>.058</td>
<td>Neg</td>
</tr>
<tr>
<td>7.</td>
<td>30</td>
<td>2325</td>
<td>.068</td>
<td>Neg</td>
</tr>
<tr>
<td>8.</td>
<td>31</td>
<td>2355</td>
<td>.064</td>
<td>Neg</td>
</tr>
<tr>
<td>9.</td>
<td>33</td>
<td>2364</td>
<td>.056</td>
<td>Neg</td>
</tr>
<tr>
<td>10.</td>
<td>38</td>
<td>2423</td>
<td>.065</td>
<td>Neg</td>
</tr>
<tr>
<td>11.</td>
<td>39</td>
<td>2429</td>
<td>.064</td>
<td>Neg</td>
</tr>
<tr>
<td>12.</td>
<td>43</td>
<td>2459</td>
<td>.067</td>
<td>Neg</td>
</tr>
<tr>
<td>13.</td>
<td>54</td>
<td>2563</td>
<td>.069</td>
<td>Neg</td>
</tr>
<tr>
<td>14.</td>
<td>55</td>
<td>2567</td>
<td>.066</td>
<td>Neg</td>
</tr>
<tr>
<td>15.</td>
<td>62</td>
<td>2608</td>
<td>.066</td>
<td>Neg</td>
</tr>
<tr>
<td>16.</td>
<td>63</td>
<td>2623</td>
<td>.065</td>
<td>Neg</td>
</tr>
<tr>
<td>17.</td>
<td>70</td>
<td>2700</td>
<td>.067</td>
<td>Neg</td>
</tr>
<tr>
<td>18.</td>
<td>71</td>
<td>2701</td>
<td>.066</td>
<td>Neg</td>
</tr>
<tr>
<td>19.</td>
<td>74</td>
<td>2725</td>
<td>.068</td>
<td>Neg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>7</td>
<td>2122</td>
<td>.07</td>
<td>Neg</td>
</tr>
<tr>
<td>2.</td>
<td>10</td>
<td>2143</td>
<td>.07</td>
<td>Neg</td>
</tr>
<tr>
<td>3.</td>
<td>13</td>
<td>2185</td>
<td>.084</td>
<td>Neg</td>
</tr>
<tr>
<td>4.</td>
<td>14</td>
<td>2195</td>
<td>.07</td>
<td>Neg</td>
</tr>
<tr>
<td>5.</td>
<td>21</td>
<td>2263</td>
<td>.089</td>
<td>Neg</td>
</tr>
<tr>
<td>6.</td>
<td>23</td>
<td>2267</td>
<td>.072</td>
<td>Neg</td>
</tr>
<tr>
<td>7.</td>
<td>32</td>
<td>2362</td>
<td>.07</td>
<td>Neg</td>
</tr>
<tr>
<td>8.</td>
<td>36</td>
<td>2409</td>
<td>.078</td>
<td>Neg</td>
</tr>
<tr>
<td>9.</td>
<td>37</td>
<td>2411</td>
<td>.071</td>
<td>Neg</td>
</tr>
<tr>
<td>10.</td>
<td>42</td>
<td>2452</td>
<td>.085</td>
<td>Neg</td>
</tr>
<tr>
<td>11.</td>
<td>46</td>
<td>2485</td>
<td>.07</td>
<td>Neg</td>
</tr>
<tr>
<td>12.</td>
<td>66</td>
<td>2650</td>
<td>.075</td>
<td>Neg</td>
</tr>
<tr>
<td>13.</td>
<td>67</td>
<td>2661</td>
<td>.077</td>
<td>Neg</td>
</tr>
<tr>
<td>14.</td>
<td>75</td>
<td>2726</td>
<td>.08</td>
<td>Neg</td>
</tr>
<tr>
<td>15.</td>
<td>82</td>
<td>2775</td>
<td>.081</td>
<td>Neg</td>
</tr>
<tr>
<td>16.</td>
<td>86</td>
<td>2804</td>
<td>.071</td>
<td>Neg</td>
</tr>
<tr>
<td>17.</td>
<td>88</td>
<td>2808</td>
<td>.082</td>
<td>Neg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>246</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-> od_grp = 0.05-0.069

-> od_grp = 0.07-0.089

-> od_grp = 0.09-0.119

<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

246
<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>8</td>
<td>2136</td>
<td>.101</td>
<td>Ind</td>
</tr>
<tr>
<td>2.</td>
<td>29</td>
<td>2321</td>
<td>.106</td>
<td>Ind</td>
</tr>
<tr>
<td>3.</td>
<td>35</td>
<td>2401</td>
<td>.115</td>
<td>Ind</td>
</tr>
<tr>
<td>4.</td>
<td>45</td>
<td>2465</td>
<td>.099</td>
<td>Ind</td>
</tr>
<tr>
<td>5.</td>
<td>50</td>
<td>2507</td>
<td>.102</td>
<td>Ind</td>
</tr>
<tr>
<td>6.</td>
<td>52</td>
<td>2555</td>
<td>.106</td>
<td>Ind</td>
</tr>
<tr>
<td>7.</td>
<td>56</td>
<td>2574</td>
<td>.107</td>
<td>Ind</td>
</tr>
<tr>
<td>8.</td>
<td>61</td>
<td>2596</td>
<td>.091</td>
<td>Neg</td>
</tr>
<tr>
<td>9.</td>
<td>77</td>
<td>2730</td>
<td>.114</td>
<td>Ind</td>
</tr>
<tr>
<td>10.</td>
<td>79</td>
<td>2749</td>
<td>.096</td>
<td>Neg</td>
</tr>
<tr>
<td>11.</td>
<td>89</td>
<td>2813</td>
<td>.095</td>
<td>Neg</td>
</tr>
<tr>
<td>12.</td>
<td>90</td>
<td>2816</td>
<td>.097</td>
<td>Neg</td>
</tr>
</tbody>
</table>

-> od_grp = 0.12-0.149

+-+----------------+-----+-----+-----+
<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>11</td>
<td>2150</td>
<td>.128</td>
<td>Pos</td>
</tr>
<tr>
<td>2.</td>
<td>12</td>
<td>2153</td>
<td>.127</td>
<td>Pos</td>
</tr>
<tr>
<td>3.</td>
<td>20</td>
<td>2223</td>
<td>.134</td>
<td>Pos</td>
</tr>
<tr>
<td>4.</td>
<td>24</td>
<td>2275</td>
<td>.121</td>
<td>Pos</td>
</tr>
<tr>
<td>5.</td>
<td>49</td>
<td>2502</td>
<td>.126</td>
<td>Pos</td>
</tr>
<tr>
<td>6.</td>
<td>68</td>
<td>2681</td>
<td>.141</td>
<td>Pos</td>
</tr>
<tr>
<td>7.</td>
<td>73</td>
<td>2723</td>
<td>.127</td>
<td>Pos</td>
</tr>
<tr>
<td>8.</td>
<td>81</td>
<td>2753</td>
<td>.132</td>
<td>Pos</td>
</tr>
</tbody>
</table>

-> od_grp = 0.15-0.199

+-+----------------+-----+-----+-----+
<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>18</td>
<td>2212</td>
<td>.152</td>
<td>Pos</td>
</tr>
<tr>
<td>2.</td>
<td>41</td>
<td>2433</td>
<td>.18</td>
<td>Pos</td>
</tr>
<tr>
<td>3.</td>
<td>57</td>
<td>2575</td>
<td>.174</td>
<td>Pos</td>
</tr>
<tr>
<td>4.</td>
<td>65</td>
<td>2644</td>
<td>.184</td>
<td>Pos</td>
</tr>
<tr>
<td>5.</td>
<td>72</td>
<td>2705</td>
<td>.173</td>
<td>Pos</td>
</tr>
<tr>
<td>6.</td>
<td>76</td>
<td>2728</td>
<td>.189</td>
<td>Pos</td>
</tr>
</tbody>
</table>

-> od_grp = 0.2-0.39

+-+----------------+-----+-----+-----+
<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4</td>
<td>856</td>
<td>.356</td>
<td>Pos</td>
</tr>
<tr>
<td>2.</td>
<td>5</td>
<td>2100</td>
<td>.308</td>
<td>Pos</td>
</tr>
<tr>
<td>3.</td>
<td>25</td>
<td>2279</td>
<td>.395</td>
<td>Pos</td>
</tr>
<tr>
<td>4.</td>
<td>28</td>
<td>2300</td>
<td>.209</td>
<td>Pos</td>
</tr>
<tr>
<td>5.</td>
<td>51</td>
<td>2544</td>
<td>.211</td>
<td>Pos</td>
</tr>
<tr>
<td>6.</td>
<td>58</td>
<td>2576</td>
<td>.376</td>
<td>Pos</td>
</tr>
<tr>
<td>7.</td>
<td>60</td>
<td>2583</td>
<td>.228</td>
<td>Pos</td>
</tr>
<tr>
<td>8.</td>
<td>64</td>
<td>2631</td>
<td>.221</td>
<td>Pos</td>
</tr>
<tr>
<td>9.</td>
<td>69</td>
<td>2682</td>
<td>.223</td>
<td>Pos</td>
</tr>
</tbody>
</table>

-> od_grp = 0.4-0.99

+-+----------------+-----+-----+-----+
<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1</td>
<td>625</td>
<td>.648</td>
<td>Pos</td>
</tr>
<tr>
<td>2.</td>
<td>9</td>
<td>2140</td>
<td>.478</td>
<td>Pos</td>
</tr>
<tr>
<td>3.</td>
<td>44</td>
<td>2461</td>
<td>.487</td>
<td>Pos</td>
</tr>
</tbody>
</table>
Table A1.2 - HBsAg run 28/03/07: Sample ID, OD, Result and anti-HBs status by OD group

<table>
<thead>
<tr>
<th>number</th>
<th>id</th>
<th>od</th>
<th>result</th>
<th>sAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>17</td>
<td>2199</td>
<td>1.951</td>
<td>Pos</td>
</tr>
<tr>
<td>2.</td>
<td>40</td>
<td>2432</td>
<td>1.814</td>
<td>Pos</td>
</tr>
</tbody>
</table>

Table A1.3 – Worksheet replica for manual HBsAg EIA assay 29/03/07

<table>
<thead>
<tr>
<th>20062701</th>
<th>20062122</th>
<th>20062452</th>
<th>20062321</th>
<th>20062401</th>
</tr>
</thead>
<tbody>
<tr>
<td>20062730</td>
<td>20062816</td>
<td>20062150</td>
<td>20062153</td>
<td>20062325</td>
</tr>
<tr>
<td>20062275</td>
<td>20062502</td>
<td>20062401</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20062723</td>
<td>20062753</td>
<td>20062212</td>
<td>20062433</td>
<td>20062575</td>
</tr>
<tr>
<td>20062644</td>
<td>20062705</td>
<td>20062100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20062279</td>
<td>20062544</td>
<td>20062583</td>
<td>20062631</td>
<td>20062682</td>
</tr>
<tr>
<td>20062625</td>
<td>20062140</td>
<td>20062365</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20062199</td>
<td>20062432</td>
<td>20062789</td>
<td>20062507</td>
<td>20062574</td>
</tr>
<tr>
<td>20062813</td>
<td>Control 4</td>
<td>Control 5</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>ID</td>
<td>OD</td>
<td>S/CO</td>
<td>Result</td>
<td>OD group</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>2701</td>
<td>.066</td>
<td>.6</td>
<td>Neg</td>
<td>0.05-0.069</td>
</tr>
<tr>
<td>2122</td>
<td>.07</td>
<td>.63</td>
<td>Neg</td>
<td>0.07-0.089</td>
</tr>
<tr>
<td>2452</td>
<td>.085</td>
<td>.77</td>
<td>Neg</td>
<td>0.07-0.089</td>
</tr>
<tr>
<td>2321</td>
<td>.106</td>
<td>.96</td>
<td>Ind</td>
<td>0.9-0.119</td>
</tr>
<tr>
<td>2401</td>
<td>.115</td>
<td>1.04</td>
<td>Ind</td>
<td>0.9-0.119</td>
</tr>
<tr>
<td>2730</td>
<td>.114</td>
<td>1.03</td>
<td>Ind</td>
<td>0.9-0.119</td>
</tr>
<tr>
<td>2816</td>
<td>.097</td>
<td>.88</td>
<td>Neg</td>
<td>0.9-0.119</td>
</tr>
<tr>
<td>2150</td>
<td>.128</td>
<td>27.1</td>
<td>Pos</td>
<td>0.12-0.149</td>
</tr>
<tr>
<td>2153</td>
<td>.127</td>
<td>27.1</td>
<td>Pos</td>
<td>0.12-0.149</td>
</tr>
<tr>
<td>2325</td>
<td>.068</td>
<td>.62</td>
<td>Neg</td>
<td>0.05-0.069</td>
</tr>
<tr>
<td>2275</td>
<td>.121</td>
<td>1.1</td>
<td>Pos</td>
<td>0.12-0.149</td>
</tr>
<tr>
<td>2502</td>
<td>.126</td>
<td>1.14</td>
<td>Pos</td>
<td>0.12-0.149</td>
</tr>
<tr>
<td>2681</td>
<td>.141</td>
<td>1.28</td>
<td>Pos</td>
<td>0.12-0.149</td>
</tr>
<tr>
<td>2723</td>
<td>.127</td>
<td>1.15</td>
<td>Pos</td>
<td>0.12-0.149</td>
</tr>
<tr>
<td>2753</td>
<td>.132</td>
<td>1.19</td>
<td>Pos</td>
<td>0.12-0.149</td>
</tr>
<tr>
<td>2212</td>
<td>.152</td>
<td>1.38</td>
<td>Pos</td>
<td>0.15-0.199</td>
</tr>
<tr>
<td>2433</td>
<td>.18</td>
<td>1.63</td>
<td>Pos</td>
<td>0.15-0.199</td>
</tr>
<tr>
<td>2575</td>
<td>.174</td>
<td>1.57</td>
<td>Pos</td>
<td>0.15-0.199</td>
</tr>
<tr>
<td>2644</td>
<td>.184</td>
<td>1.67</td>
<td>Pos</td>
<td>0.15-0.199</td>
</tr>
<tr>
<td>2705</td>
<td>.173</td>
<td>1.57</td>
<td>Pos</td>
<td>0.15-0.199</td>
</tr>
<tr>
<td>2100</td>
<td>.308</td>
<td>2.79</td>
<td>Pos</td>
<td>0.2-0.39</td>
</tr>
<tr>
<td>2279</td>
<td>.395</td>
<td>3.57</td>
<td>Pos</td>
<td>0.2-0.39</td>
</tr>
<tr>
<td>2544</td>
<td>.211</td>
<td>1.91</td>
<td>Pos</td>
<td>0.2-0.39</td>
</tr>
<tr>
<td>2583</td>
<td>.228</td>
<td>2.06</td>
<td>Pos</td>
<td>0.2-0.39</td>
</tr>
<tr>
<td>2631</td>
<td>.221</td>
<td>2</td>
<td>Pos</td>
<td>0.2-0.39</td>
</tr>
<tr>
<td>2682</td>
<td>.223</td>
<td>2.02</td>
<td>Pos</td>
<td>0.2-0.39</td>
</tr>
<tr>
<td>625</td>
<td>.648</td>
<td>5.86</td>
<td>Pos</td>
<td>0.4-0.99</td>
</tr>
<tr>
<td>2140</td>
<td>.478</td>
<td>4.33</td>
<td>Pos</td>
<td>0.4-0.99</td>
</tr>
<tr>
<td>2365</td>
<td>3</td>
<td>27.1</td>
<td>Pos</td>
<td>OWR</td>
</tr>
<tr>
<td>2199</td>
<td>1.951</td>
<td>17.7</td>
<td>Pos</td>
<td>1.0-2.99</td>
</tr>
<tr>
<td>2432</td>
<td>1.814</td>
<td>16.4</td>
<td>Pos</td>
<td>1.0-2.99</td>
</tr>
<tr>
<td>2789</td>
<td>3</td>
<td>27.1</td>
<td>Pos</td>
<td>OWR</td>
</tr>
<tr>
<td>2507</td>
<td>.102</td>
<td>.92</td>
<td>Ind</td>
<td>0.9-0.119</td>
</tr>
<tr>
<td>2574</td>
<td>.107</td>
<td>.97</td>
<td>Ind</td>
<td>0.9-0.119</td>
</tr>
<tr>
<td>2813</td>
<td>.095</td>
<td>.86</td>
<td>Neg</td>
<td>0.9-0.119</td>
</tr>
</tbody>
</table>

Table A1.4 – Characteristics of samples selected for manual HBsAg EIA assay 29/03/07
Unfortunately an error in performance of the manual test procedure (extra wash step inserted between 1st incubation and addition of conjugate) invalidated the results.

The manual test procedure was performed again (late afternoon 29th March 2007), but 4 further samples (20062275 + 20062212 (low pos samples) and 20062365 + 20062199 (strong pos samples)) had been exhausted and were unable to be retested.

Second manual HBsAg EIA assay 29/03/07 – test conditions:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg control</td>
<td>0.81</td>
</tr>
<tr>
<td>Pos control</td>
<td>1.68</td>
</tr>
<tr>
<td>Cut-off</td>
<td>0.131</td>
</tr>
</tbody>
</table>

Validation conditions met: yes

The results of the second manual HBsAg EIA assay performed on 29/03/07 on the samples selected as described are shown in table A1.5 together with the results of the original erroneous automated run and the anti-HBs status of the samples.

As can be seen in table A1.5:

1. All results with OD<1.0 on initial run returned negative results on the manual run (and all had an OD less than that of the negative controls)
2. Both results with an OD>1.0 on the initial run remained positive on the manual run (and both had an OD above the positive control)

### A1.3 Resolution

Based on the results of manual retesting and applying the OD=1 cut-off value established as described for presumed positivity for samples unable to be retested to the initial Triturus run results, the final results for the second manual HBsAg EIA assay were:

- Samples - 91
- Negative – 74
- Indeterminate – 0
- Positive – 17
<table>
<thead>
<tr>
<th>ID</th>
<th>Initial OD</th>
<th>Initial Result</th>
<th>Manual OD</th>
<th>Manual Result</th>
<th>Anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2701</td>
<td>.066</td>
<td>Neg</td>
<td>.067</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>2325</td>
<td>.068</td>
<td>Neg</td>
<td>.071</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2122</td>
<td>.07</td>
<td>Neg</td>
<td>.071</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>2452</td>
<td>.085</td>
<td>Neg</td>
<td>.074</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2813</td>
<td>.095</td>
<td>Neg</td>
<td>.074</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2816</td>
<td>.097</td>
<td>Neg</td>
<td>.068</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2507</td>
<td>.102</td>
<td>Ind</td>
<td>.068</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2321</td>
<td>.106</td>
<td>Ind</td>
<td>.072</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2574</td>
<td>.107</td>
<td>Ind</td>
<td>.073</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2730</td>
<td>.114</td>
<td>Ind</td>
<td>.077</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2401</td>
<td>.115</td>
<td>Ind</td>
<td>.073</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>2502</td>
<td>.126</td>
<td>Pos</td>
<td>.063</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2153</td>
<td>.127</td>
<td>Pos</td>
<td>.07</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2723</td>
<td>.127</td>
<td>Pos</td>
<td>.067</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>2150</td>
<td>.128</td>
<td>Pos</td>
<td>.072</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2753</td>
<td>.132</td>
<td>Pos</td>
<td>.071</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>2681</td>
<td>.141</td>
<td>Pos</td>
<td>.077</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2705</td>
<td>.173</td>
<td>Pos</td>
<td>.063</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2575</td>
<td>.174</td>
<td>Pos</td>
<td>.068</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>2644</td>
<td>.184</td>
<td>Pos</td>
<td>.072</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2544</td>
<td>.211</td>
<td>Pos</td>
<td>.07</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2631</td>
<td>.221</td>
<td>Pos</td>
<td>.063</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2682</td>
<td>.223</td>
<td>Pos</td>
<td>.071</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2583</td>
<td>.228</td>
<td>Pos</td>
<td>.069</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2100</td>
<td>.308</td>
<td>Pos</td>
<td>.103</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2279</td>
<td>.395</td>
<td>Pos</td>
<td>.067</td>
<td>Neg</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2140</td>
<td>.478</td>
<td>Pos</td>
<td>.069</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>625</td>
<td>.648</td>
<td>Pos</td>
<td>.08</td>
<td>Neg</td>
<td>Pos:&gt;100</td>
</tr>
<tr>
<td>2432</td>
<td>1.814</td>
<td>Pos</td>
<td>1.747</td>
<td>Pos</td>
<td>Pos:10-100</td>
</tr>
<tr>
<td>2789</td>
<td>3</td>
<td>Pos</td>
<td>5.951</td>
<td>Pos</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Table A1.5 – Results of second manual HBsAg EIA assay 29/03/07 compared to initial automated HBsAg EIA assay 28/03/07
The distribution of OD results from the initial erroneous automated HBsAg EIA assay by final result status was as follows:

**Final result = Negative**

<table>
<thead>
<tr>
<th>OD group</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05-0.069</td>
<td>19</td>
<td>25.68</td>
</tr>
<tr>
<td>0.07-0.089</td>
<td>17</td>
<td>22.97</td>
</tr>
<tr>
<td>0.09-0.119</td>
<td>12</td>
<td>16.22</td>
</tr>
<tr>
<td>0.12-0.149</td>
<td>8</td>
<td>10.81</td>
</tr>
<tr>
<td>0.15-0.199</td>
<td>6</td>
<td>8.11</td>
</tr>
<tr>
<td>0.2-0.39</td>
<td>9</td>
<td>12.16</td>
</tr>
<tr>
<td>0.4-0.99</td>
<td>3</td>
<td>4.05</td>
</tr>
</tbody>
</table>

**Total** | **74** | **100.00**

**Final result = Positive**

<table>
<thead>
<tr>
<th>OD group</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-2.99</td>
<td>2</td>
<td>11.76</td>
</tr>
<tr>
<td>OWR</td>
<td>15</td>
<td>88.24</td>
</tr>
</tbody>
</table>

**Total** | **17** | **100.00**

Therefore the percentage of anti-HBc positive samples positive for HBsAg in the second manual EIA assay was 18.7% - not 47.3% as per the initial automated assay, and more similar to the first automated HBsAg test run of 9/67 = 13.4% positive. Furthermore, as is more biologically plausible, all of the remaining HBsAg positive samples with an OD on the initial run of >3.0 were anti-HBs negative; interestingly however one of the positive samples (confirmed on the second manual assay) with an OD of 1.7-1.8 (sample ID 20062432) had a positive anti-HBs in the 10-100 range. Thus both HBsAg and anti-HBs were positive in this sample, but neither was strongly (OWR) positive.

The final resolution of the impact of the failed automated EIA assay was therefore to enter the results in the final table using manual retest results whenever possible, with application of the OD=1.0 cut-off where samples were unable to be retested. No reason for the failed automated run was ever found; fortunately this problem was not encountered again for any of the remaining automated assays in the rest of the serosurvey.
Appendix 2  Equations for the deterministic model of HBV infection in Australia

This appendix presents the equations used in the model to describe the initial conditions, the flows through the model compartments, the population, infection and vaccination parameters, and the derived summary variables for the static FoI model and sub-models. The differences in the dynamic model structure are described in 5.4.8.

A2.1  Equation key

All Reservoirs, Flows, Parameters and Variables with Age-group Specificity

| [X]_0 | [X] for 0 – 4 year age group |
| [X]_1 | [X] for 5 – 14 year age group |
| [X]_2 | [X] for 15 – 44 year age group |
| [X]_3 | [X] for 45 plus year age group |

(all examples that follow this syntax are represented below as the 0 – 4 age group)

Primary Model Reservoirs

- **Sus_0**: Susceptible individuals
- **Acute_0**: Acutely infected individuals
- **Chronic_0**: Chronically infected individuals
- **Cleared_0**: Individuals with resolved HBV

Primary Model Flows

- **inf_0**: New infections in susceptible individuals
- **prog_0**: Progression from acute to chronic HBV
- **recov_0**: Progression from acute HBV to clearance
- **clear_0**: Progression from chronic HBV to clearance
- **vac_0**: Progression from susceptible to immunised through vaccination
- **births**: Newborns entering population
- **mig_sus_0**: Migration of susceptible individuals into population
- **mig_imm_0**: Migration of immunised into population
- **mig_chron_0**: Migration of individuals with chronic HBV into population
- **mig_cleared_0**: Migration of individuals with resolved HBV into population
- **age_sus_0**: Ageing of susceptibles into next age group
- **age_imm_0**: Ageing of immunised into next age group
- **age_ac_0**: Ageing of individuals with acute HBV into next age group
- **age_chr_0**: Ageing of individuals with chronic HBV into next age group
- **age_cleared_0**: Ageing of individuals with resolved HBV into next age group
- **sus_mort_0**: Removal of susceptibles from population due to death
- **imm_mort_0**: Removal of immunised from population due to death
- **ac_mort_0**: Removal of individuals with acute HBV due to death
- **chr_mort_0**: Removal of individuals with chronic HBV due to death
- **cleared_mort_0**: Removal of individuals with resolved HBV due to death

Demographic Parameters

- **tot_0**: Total population in 0 – 4 age group
- **tot_pop**: Total population in model
- **init_pop**: Starting population for model in the year 1951
- **pop_prop_0**: Proportion of starting population in the 0 – 4 age group
- **mig_series**: Multiplier allowing sensitivity analysis for migration projections
Expression to ensure migration sensitivity analysis only applies to migration projections (from 2005) and not past migration figures

Infection and Vaccination Related Parameters

- **dis_rate**: $1 / \text{[Incubation period]}$ (years) - not ultimately used model
- **ac_res_rate**: $1 / \text{[Duration of acute infection]}$ (years)
- **f_o_i_0**: Force of Infection
- **Fol_mult**: Multiplier allowing sensitivity analysis for Fol assumptions
- **prog_chron_0**: Proportion of acute infections progressing to chronicity
- **clr_rate_0**: Rate of clearance of chronic infections (years)
- **ac_mort_rate_0**: Annual probability of death due to acute infection
- **chr_mort_rate_0**: Annual probability of death due to chronic infection
- **vacc_eff_0**: Proportion of vaccinated individuals that attain immunity
- **vacc_avail**: Test for existence of vaccine – set to 1985, see 5.4.5
- **vac_tog**: Toggle to allow comparison of outcomes with and without vaccination
- **vacc_prog_0**: Test for existence of NIP in age group: see 5.4.5
- **vacc_prop_0**: Proportion of those targeted by NIP that are vaccinated

Submodel Reservoirs

- **Cum_acute_0**: Cumulative acute infections
- **Cum_chronic_0**: Cumulative chronic infections
- **Cum_deaths_uninf_0**: Cumulative deaths in uninfected individuals
- **Cum_acute_deaths_0**: Cumulative deaths in people with acute HBV
- **Cum_chronic_deaths_0**: Cumulative deaths in people with chronic HBV

Submodel Flows

- **J1**: Acute infections in 0 – 4 age group
- **J2**: Acute infections in 5 – 14 age group
- **J3**: Acute infections in 15 – 44 age group
- **J4**: Acute infections in 45 plus age group
- **J5**: Chronic infections in 0 – 4 age group
- **J6**: Chronic infections in 5 – 14 age group
- **J7**: Chronic infections in 15 – 44 age group
- **J8**: Chronic infections in 45 plus age group
- **J9**: Mortality in uninfected individuals in 0 – 4 age group
- **J10**: Mortality in uninfected individuals in 5 – 14 age group
- **J11**: Mortality in uninfected individuals in 15 - 44 age group
- **J12**: Mortality in uninfected individuals in 45 plus age group
- **J13**: Mortality in acute HBV infection in 0 – 4 age group
- **J14**: Mortality in chronic HBV infection in 0 – 4 age group
- **J15**: Mortality in acute HBV infection in 5 – 14 age group
- **J16**: Mortality in chronic HBV infection in 5 – 14 age group
- **J17**: Mortality in acute HBV infection in 15 – 44 age group
- **J18**: Mortality in acute HBV infection in 15 – 44 age group
- **J19**: Mortality in chronic HBV infection in 45 plus age group
- **J20**: Mortality in chronic HBV infection in 45 plus age group

Summary Variables

- **tot_sus**: Total population of susceptible individuals
- **tot IMMUNE**: Total population of immunised individuals
- **tot_acute**: Total population of individuals with acute HBV
- **tot_chronic**: Total population of individuals with chronic HBV
- **tot_cleared**: Total population of individuals with resolved HBV
- **sAg_prev**: HBsAg prevalence (proportion of population infected with HBV)
- **sAg_prev_0**: HBsAg prevalence in 0 - 4 age group
- **tot_cum_acute**: Total cumulative acute infections
- **tot_cum_chronic**: Total cumulative chronic infections
- **tot_prog**: Number of acute infections progressing to chronicity annually
- **tot_mig_chron**: Number of migrants with chronic HBV entering population annually
- **prop_chron_aust**: Proportion of chronic HBV cases that are due to domestic infection
tot_cum_deaths_uninf: Total cumulative deaths in uninfected individuals

tot_cum_deaths_acute: Total cumulative deaths in individuals with acute HBV

tot_cum_deaths_chronic: Total cumulative deaths in individuals with chronic HBV

deaths_uninf_0: Deaths in uninfected 0–4 age group

tot_deaths_uninf: Total deaths in uninfected individuals

deaths_acute_0: Deaths in 0–4 age group with acute HBV

tot_deaths_acute: Total deaths in individuals with acute HBV

deaths_chronic_0: Deaths in 0–4 age group with chronic HBV

tot_deaths_chronic: Total deaths in individuals with chronic HBV

HBV_mort_chronic: Annual mortality in individuals with chronic HBV

HBV_mort_chronic_0: Annual mortality in 0–4 age group with chronic HBV

uninf_mort: Annual mortality in uninfected individuals

prop_chronic_mort: Mortality ratio of those with chronic HBV to uninfected individuals

rel_mort_0: Mortality ratio of those in 0–4 age group with chronic HBV to uninfected individuals

attrib_deaths_chronic: Annual deaths attributable to chronic HBV infection

attrib_cum_deaths_chronic: Cumulative deaths attributable to chronic HBV infection

ever_chronic: The number of people ever chronically infected with HBV

not_prop: The proportion of all chronic infections notified

not_sys: Toggle for the existence of a HBV notifications system (1971-2006)

Vector datasets
(used to supply model with external data to govern model behaviours which change over time)

#births(TIME): Number of births for given year

#mig0sus(TIME): Entry of susceptible migrants for given year

#mig0chron(TIME): Entry of migrants with chronic HBV for given year

#mig0cleared(TIME): Entry of migrants with resolved HBV for given year

#bgmort0(TIME): Background mortality rate for given year

#notifications(TIME): Annual surveillance notifications of chronic HBV

#not_cumulative(TIME): Cumulative surveillance notifications of chronic HBV

A2.2 Equations

\[
\begin{align*}
\text{Reservoirs} \\
\text{INIT } & \text{Sus}_0 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_0 \cdot .998 \\
\text{INIT } & \text{Acute}_0 = 0 \\
\text{INIT } & \text{Chronic}_0 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_0 \cdot .001 \\
\text{INIT } & \text{Cleared}_0 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_0 \cdot .001 \\
\text{INIT } & \text{Sus}_1 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_1 \cdot .994 \\
\text{INIT } & \text{Acute}_1 = 0 \\
\text{INIT } & \text{Chronic}_1 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_1 \cdot .002 \\
\text{INIT } & \text{Cleared}_1 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_1 \cdot .004 \\
\text{INIT } & \text{Sus}_2 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_2 \cdot .94 \\
\text{INIT } & \text{Acute}_2 = 0 \\
\text{INIT } & \text{Chronic}_2 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_2 \cdot .007 \\
\text{INIT } & \text{Cleared}_2 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_2 \cdot .053 \\
\text{INIT } & \text{Sus}_3 = \text{init}_\text{pop} \cdot \text{pop}_\text{prop}_3 \cdot .94
\end{align*}
\]
\[
d/dt (Acute_3) = + age_{ac_3} - prog_3 - recov_3 - ac_mort_3 + inf_3 \\
INIT Acute_3 = 0 \\
d/dt (Chronic_3) = + age_{chr_3} - clear_3 + mig_chron_3 - chr_mort_3 + prog_3 \\
INIT Chronic_3 = init_pop*pop_prop_3*.005 \\
d/dt (Cleared_3) = + vac_2 + mig_cleared_3 + recov_3 + clear_3 - cleared_mort_3 \\
INIT Cleared_3 = init_pop*pop_prop_3*.055 \\
d/dt (Immune_0) = + vac_0 + mig_imm_0 - age_imm_0 - imm_mort_0 \\
INIT Immune_0 = 0 \\
d/dt (Immune_1) = + vac_1 + age_imm_0 + mig_imm_1 - age_imm_1 - imm_mort_1 \\
INIT Immune_1 = 0 \\
d/dt (Immune_2) = + vac_2 + mig_imm_2 + age_imm_1 - age_imm_2 - imm_mort_2 \\
INIT Immune_2 = 0 \\
d/dt (Immune_3) = + vac_3 + mig_imm_3 + age_imm_2 - imm_mort_3 \\
INIT Immune_3 = 0 \\
\]

\{(Flows)\}

\[
inf_0 = Sus_0*f_{o_i-0} \\
prog_0 = Acute_0*ac_res_rate*prog_chron_0 \\
recov_0 = Acute_0*ac_res_rate*(1-prog_chron_0) \\
clear_0 = Chronic_0*clr_rate_0 \\
births = #births(TIME) \\
mig_sus_0 = #mig0sus(TIME)*mig_series*mig_pred \\
mig_chron_0 = #mig0chron(TIME)*mig_series*mig_pred \\
sus_mort_0 = Sus_0*#bgmort0(TIME) \\
ac_mort_0 = Acute_0*(#bgmort0(TIME)+ac_mort_rate_0) \\
chr_mort_0 = Chronic_0*(#bgmort0(TIME)+chr_mort_rate_0) \\
cleared_mort_0 = Cleared_0*#bgmort0(TIME) \\
mig_cleared_0 = #mig0cleared(TIME)*mig_series*mig_pred \\
age_sus_0 = Sus_0*(1/5) \\
age_ac_0 = Acute_0*(1/5) \\
age_chr_0 = Chronic_0*(1/5) \\
age_cleared_0 = Cleared_0*(1/5) \\
inf_1 = Sus_1*f_{o_i-1} \\
prog_1 = Acute_1*ac_res_rate*prog_chron_1 \\
recov_1 = Acute_1*ac_res_rate*(1-prog_chron_1) \\
clear_1 = Chronic_1*clr_rate_1 \\
mig_sus_1 = #mig1sus(TIME)*mig_series*mig_pred \\
mig_chron_1 = #mig1chron(TIME)*mig_series*mig_pred \\
sus_mort_1 = Sus_1*#bgmort1(TIME) \\
ac_mort_1 = Acute_1*(#bgmort1(TIME)+ac_mort_rate_1) \\
chr_mort_1 = Chronic_1*(#bgmort1(TIME)+chr_mort_rate_1) \\
cleared_mort_1 = Cleared_1*#bgmort1(TIME) \\
mig_cleared_1 = #mig1cleared(TIME)*mig_series*mig_pred \\
age_sus_1 = Sus_1*(1/10) \\
age_ac_1 = Acute_1*(1/10) \\
age_chr_1 = Chronic_1*(1/10) \\
age_cleared_1 = Cleared_1*(1/10) \\
inf_2 = Sus_2*f_{o_i-2} \\
prog_2 = Acute_2*ac_res_rate*prog_chron_2 \\
recov_2 = Acute_2*ac_res_rate*(1-prog_chron_2) \\
clear_2 = Chronic_2*clr_rate_2 \\
mig_sus_2 = #mig2sus(TIME)*mig_series*mig_pred \\
mig_chron_2 = #mig2chron(TIME)*mig_series*mig_pred \\
sus_mort_2 = Sus_2*#bgmort2(TIME) \\
ac_mort_2 = Acute_2*(#bgmort2(TIME)+ac_mort_rate_2) \\
chr_mort_2 = Chronic_2*(#bgmort2(TIME)+chr_mort_rate_2) \\
cleared_mort_2 = Cleared_2*#bgmort2(TIME) \\
mig_cleared_2 = #mig2cleared(TIME)*mig_series*mig_pred \\
age_sus_2 = Sus_2*(1/10) \\
age_ac_2 = Acute_2*(1/10) \\
age_chr_2 = Chronic_2*(1/10) \\
age_cleared_2 = Cleared_2*(1/10) \\
inf_3 = Sus_3*f_{o_i-3} \\
prog_3 = Acute_3*ac_res_rate*prog_chron_3 \\
recov_3 = Acute_3*ac_res_rate*(1-prog_chron_3) \\
clear_3 = Chronic_3*clr_rate_3 \\
mig_sus_3 = #mig3sus(TIME)*mig_series*mig_pred
\]
\begin{align*}
mig_{\text{chron}}_{3} &= \#mig3chron(TIME)\cdot mig\_series\cdot mig\_pred \\
sus\_mort\_3 &= Sus\_3\cdot \#bgmort3(TIME) \\
ac\_mort\_3 &= Acute\_3\cdot (\#bgmort3(TIME)\cdot ac\_mort\_rate\_3) \\
chr\_mort\_3 &= Chronic\_3\cdot (\#bgmort3(TIME)\cdot chr\_mort\_rate\_3) \\
cleared\_mort\_3 &= Cleared\_3\cdot \#bgmort3(TIME) \\
mig\_cleared\_3 &= \#mig3cleared(TIME)\cdot mig\_series\cdot mig\_pred \\
vac\_0 &= Sus\_0\cdot \text{vacc\_eff\_0}\cdot \text{vacc\_prop\_0}\cdot \text{vacc\_prog\_0}\cdot \text{vacc\_avail} \\
vac\_1 &= Sus\_1\cdot \text{vacc\_eff\_1}\cdot \text{vacc\_prop\_1}\cdot \text{vacc\_prog\_1}\cdot \text{vacc\_avail} \\
vac\_2 &= Sus\_2\cdot \text{vacc\_eff\_2}\cdot \text{vacc\_prop\_2}\cdot \text{vacc\_avail} \\
vac\_3 &= Sus\_3\cdot \text{vacc\_eff\_3}\cdot \text{vacc\_prop\_3}\cdot \text{vacc\_avail} \\
mig\_imm\_0 &= 0\cdot \#mig\_series\cdot \#mig\_pred \\
imm\_mort\_0 &= Immune\_0\cdot \#bgmort0(TIME) \\
mig\_imm\_1 &= 0\cdot \#mig\_series\cdot \#mig\_pred \\
mig\_imm\_2 &= 0\cdot \#mig\_series\cdot \#mig\_pred \\
mig\_imm\_3 &= 0\cdot \#mig\_series\cdot \#mig\_pred \\
age\_imm\_0 &= Immune\_0\cdot \#bgmort0(TIME) \\
age\_imm\_1 &= Immune\_1\cdot \#bgmort1(TIME) \\
age\_imm\_2 &= Immune\_2\cdot \#bgmort2(TIME) \\
age\_imm\_3 &= Immune\_3\cdot \#bgmort3(TIME) \\
\end{align*}

{Submodel "Cum cases SM"}

{Reservoirs}
\begin{align*}
\frac{d}{dt} (\text{Cum\_acute\_0}) &= + J1 \\
\text{INIT Cum\_acute\_0} &= 0 \\
\frac{d}{dt} (\text{Cum\_acute\_1}) &= + J2 \\
\text{INIT Cum\_acute\_1} &= 0 \\
\frac{d}{dt} (\text{Cum\_acute\_2}) &= + J3 \\
\text{INIT Cum\_acute\_2} &= 0 \\
\frac{d}{dt} (\text{Cum\_acute\_3}) &= + J4 \\
\text{INIT Cum\_acute\_3} &= 0 \\
\frac{d}{dt} (\text{Cum\_chronic\_0}) &= + J5 \\
\text{INIT Cum\_chronic\_0} &= 0 \\
\frac{d}{dt} (\text{Cum\_chronic\_1}) &= + J6 \\
\text{INIT Cum\_chronic\_1} &= 0 \\
\frac{d}{dt} (\text{Cum\_chronic\_2}) &= + J7 \\
\text{INIT Cum\_chronic\_2} &= 0 \\
\frac{d}{dt} (\text{Cum\_chronic\_3}) &= + J8 \\
\text{INIT Cum\_chronic\_3} &= 0 \\
\end{align*}

{Flows}
\begin{align*}
J1 &= Sus\_0\cdot \text{f\_o\_i\_0} \\
J2 &= Sus\_1\cdot \text{f\_o\_i\_1} \\
J3 &= Sus\_2\cdot \text{f\_o\_i\_2} \\
J4 &= Sus\_3\cdot \text{f\_o\_i\_3} \\
J5 &= \text{Acute\_0}\cdot \text{ac\_res\_rate}\cdot \text{prog\_chron\_0} \\
J6 &= \text{Acute\_1}\cdot \text{ac\_res\_rate}\cdot \text{prog\_chron\_1} \\
J7 &= \text{Acute\_2}\cdot \text{ac\_res\_rate}\cdot \text{prog\_chron\_2} \\
J8 &= \text{Acute\_3}\cdot \text{ac\_res\_rate}\cdot \text{prog\_chron\_3} \\
\end{align*}

{Submodel "Cum deaths SM"}

{Reservoirs}
\begin{align*}
\frac{d}{dt} (\text{Cum\_deaths\_uninf\_0}) &= + J9 \\
\text{INIT Cum\_deaths\_uninf\_0} &= 0 \\
\frac{d}{dt} (\text{Cum\_deaths\_uninf\_1}) &= + J10 \\
\text{INIT Cum\_deaths\_uninf\_1} &= 0 \\
\frac{d}{dt} (\text{Cum\_deaths\_uninf\_2}) &= + J11 \\
\text{INIT Cum\_deaths\_uninf\_2} &= 0 \\
\frac{d}{dt} (\text{Cum\_deaths\_uninf\_3}) &= + J12 \\
\text{INIT Cum\_deaths\_uninf\_3} &= 0 \\
\frac{d}{dt} (\text{Cum\_acute\_deaths\_0}) &= + J13 \\
\text{INIT Cum\_acute\_deaths\_0} &= 0 \\
\frac{d}{dt} (\text{Cum\_chronic\_deaths\_0}) &= + J14 \\
\text{INIT Cum\_chronic\_deaths\_0} &= 0 \\
\frac{d}{dt} (\text{Cum\_acute\_deaths\_1}) &= + J15 \\
\text{INIT Cum\_acute\_deaths\_1} &= 0 \\
\end{align*}
\[
\begin{align*}
\frac{d}{dt} (\text{Cum\_chronic\_deaths\_1}) &= + J_{16} \\
\text{INIT} & \quad \text{Cum\_chronic\_deaths\_1} = 0 \\
\frac{d}{dt} (\text{Cum\_acute\_deaths\_2}) &= + J_{17} \\
\text{INIT} & \quad \text{Cum\_acute\_deaths\_2} = 0 \\
\frac{d}{dt} (\text{Cum\_chronic\_deaths\_2}) &= + J_{19} \\
\text{INIT} & \quad \text{Cum\_chronic\_deaths\_2} = 0 \\
\frac{d}{dt} (\text{Cum\_acute\_deaths\_3}) &= + J_{18} \\
\text{INIT} & \quad \text{Cum\_acute\_deaths\_3} = 0 \\
\frac{d}{dt} (\text{Cum\_chronic\_deaths\_3}) &= + J_{20} \\
\text{INIT} & \quad \text{Cum\_chronic\_deaths\_3} = 0
\end{align*}
\]

\{Flows\}
\[
\begin{align*}
J_9 &= (\text{Cleared\_0} + \text{Immune\_0} + \text{Sus\_0}) \times \#bgmort0(TIME) \\
J_{10} &= (\text{Cleared\_1} + \text{Immune\_1} + \text{Sus\_1}) \times \#bgmort1(TIME) \\
J_{11} &= (\text{Cleared\_2} + \text{Immune\_2} + \text{Sus\_2}) \times \#bgmort2(TIME) \\
J_{12} &= (\text{Cleared\_3} + \text{Immune\_3} + \text{Sus\_3}) \times \#bgmort3(TIME) \\
J_{13} &= \text{Acute\_0} \times (\#bgmort0(TIME) + \text{ac\_mort\_rate\_0}) \\
J_{14} &= \text{Chronic\_0} \times (\#bgmort0(TIME) + \text{chr\_mort\_rate\_0}) \\
J_{15} &= \text{Acute\_1} \times (\#bgmort1(TIME) + \text{ac\_mort\_rate\_1}) \\
J_{16} &= \text{Chronic\_1} \times (\#bgmort1(TIME) + \text{chr\_mort\_rate\_1}) \\
J_{17} &= \text{Acute\_2} \times (\#bgmort2(TIME) + \text{ac\_mort\_rate\_2}) \\
J_{18} &= \text{Acute\_3} \times (\#bgmort3(TIME) + \text{ac\_mort\_rate\_3}) \\
J_{19} &= \text{Chronic\_2} \times (\#bgmort2(TIME) + \text{chr\_mort\_rate\_2}) \\
J_{20} &= \text{Chronic\_3} \times (\#bgmort3(TIME) + \text{chr\_mort\_rate\_3})
\end{align*}
\]

\{Globals\}
\[
\begin{align*}
\text{DEMOGRAPHIC PARAMETERS AND VARIABLES} \quad \text{-------------------------------------------------------------------------------}
\text{tot\_0} &= \text{Sus\_0} + \text{Immune\_0} + \text{Acute\_0} + \text{Chronic\_0} + \text{Cleared\_0} \\
\text{tot\_1} &= \text{Sus\_1} + \text{Immune\_1} + \text{Acute\_1} + \text{Chronic\_1} + \text{Cleared\_1} \\
\text{tot\_2} &= \text{Sus\_2} + \text{Immune\_2} + \text{Acute\_2} + \text{Chronic\_2} + \text{Cleared\_2} \\
\text{tot\_3} &= \text{Sus\_3} + \text{Immune\_3} + \text{Acute\_3} + \text{Chronic\_3} + \text{Cleared\_3} \\
\text{tot\_pop} &= \text{tot\_0} + \text{tot\_1} + \text{tot\_2} + \text{tot\_3}
\end{align*}
\]
\[
\begin{align*}
\text{init\_pop} &= 8421775 \\
\text{pop\_prop\_0} &= 0.110963345 \\
\text{pop\_prop\_1} &= 0.160490162 \\
\text{pop\_prop\_2} &= 0.443568401 \\
\text{pop\_prop\_3} &= 0.284978092
\end{align*}
\]
\[
\begin{align*}
\text{mig\_series} &= 1 \\
\text{mig\_pred} &= \text{IF} (\text{TIME}\geq2005) \text{ THEN } 1 \text{ ELSE } (1/\text{mig\_series})
\end{align*}
\]
\[
\begin{align*}
\text{INFECTION AND VACCINATION-RELATED PARAMETERS} \quad \text{-------------------------------------------------------------------------------}
\text{dis\_rate} &= 6 \\
\text{ac\_res\_rate} &= 4
\end{align*}
\]
\[
\begin{align*}
\text{Fol\_mult} &= 1 \\
\text{prog\_chron\_0} &= 0.5 \\
\text{prog\_chron\_1} &= 0.2 \\
\text{prog\_chron\_2} &= 0.06 \\
\text{prog\_chron\_3} &= 0.04 \\
\text{clr\_rate\_0} &= 0 \\
\text{clr\_rate\_1} &= 0.005
\end{align*}
\]
clr_rate_2 = 0.01
clr_rate_3 = 0.025
ac_mort_rate_0 = 0.001
ac_mort_rate_1 = 0.0014
ac_mort_rate_2 = 0.0035
ac_mort_rate_3 = 0.0035
chr_mort_rate_0 = 0
chr_mort_rate_1 = 0.0003
chr_mort_rate_2 = 0.002
chr_mort_rate_3 = 0.006
vacc_eff_0 = 0.95
vacc_eff_1 = 0.95
vacc_eff_2 = 0.9
vacc_eff_3 = 0.75
vacc_avail = (IF(TIME>=1985) THEN 1 ELSE 0)*vacc_tog
vacc_tog = 1
vacc_prog_0 = IF(TIME>=2000) THEN 1 ELSE 0
vacc_prog_1 = IF(TIME>=1998) AND (TIME < 2012) THEN 1 ELSE 0
vacc_prop_0 = 0
vacc_prop_1 = 0
vacc_prop_2 = 0
vacc_prop_3 = 0

USEFUL SUMMARY VARIABLES

\[
\begin{align*}
tot_sus &= sus_0 + sus_1 + sus_2 + sus_3 \\
totimmune &= immune_0 + immune_1 + immune_2 + immune_3 \\
totacute &= acute_0 + acute_1 + acute_2 + acute_3 \\
totchronic &= chronic_0 + chronic_1 + chronic_2 + chronic_3 \\
totcleared &= cleared_0 + cleared_1 + cleared_2 + cleared_3 \\
sAg_prev &= tot_chronic/tot_pop \\
sAg_prev_0 &= chronic_0/tot_0 \\
sAg_prev_1 &= chronic_1/tot_1 \\
sAg_prev_2 &= chronic_2/tot_2 \\
sAg_prev_3 &= chronic_3/tot_3 \\
totcumacute &= Cum_acute_0 + Cum_acute_1 + Cum_acute_2 + Cum_acute_3 \\
totcumchronic &= Cum_chronic_0 + Cum_chronic_1 + Cum_chronic_2 + Cum_chronic_3 \\
totprog &= prog_0 + prog_1 + prog_2 + prog_3 \\
totmigchron &= (#mig0chron(TIME) + #mig1chron(TIME) + #mig2chron(TIME) + mig3chron(TIME)) * (mig_series*mig_pred) \\
prop_chron_aust &= tot_prog/(tot_prog + tot_mig_chron) \\
totcumdeathsuninf &= Cum_deaths_uninf_0 + Cum_deaths_uninf_1 + Cum_deaths_uninf_2 + Cum_deaths_uninf_3 \\
totcumdeathsaacute &= Cum_acute_deaths_0 + Cum_acute_deaths_1 + Cum_acute_deaths_2 + Cum_acute_deaths_3 \\
totcumdeathschronic &= Cum_chronic_deaths_0 + Cum_chronic_deaths_1 + Cum_chronic_deaths_2 + Cum_chronic_deaths_3 \\
deaths_uninf_0 &= Sus_0*#bgmort0(TIME) + Immune_0*#bgmort0(TIME) + Cleared_0*#bgmort0(TIME) \\
deaths_uninf_1 &= Sus_1*#bgmort1(TIME) + Immune_1*#bgmort1(TIME) + Cleared_1*#bgmort1(TIME) \\
deaths_uninf_2 &= Sus_2*#bgmort2(TIME) + Immune_2*#bgmort2(TIME) + Cleared_2*#bgmort2(TIME) \\
deaths_uninf_3 &= Sus_3*#bgmort3(TIME) + Immune_3*#bgmort3(TIME) + Cleared_3*#bgmort3(TIME) \\
totdeathsinf &= deaths_uninf_0 + deaths_uninf_1 + deaths_uninf_2 + deaths_uninf_3 \\
deaths_acute_0 &= Acute_0*#bgmort0(TIME)*ac_mort_rate_0)
deaths_acute_1 = Acute_1*(#bgmort1(TIME)+ac_mort_rate_1)
deaths_acute_2 = Acute_2*(#bgmort2(TIME)+ac_mort_rate_2)
deaths_acute_3 = Acute_3*(#bgmort3(TIME)+ac_mort_rate_3)
total_deaths_acute = deaths_acute_0 + deaths_acute_1 + deaths_acute_2 + deaths_acute_3

deaths_chronic_0 = Chronic_0*(#bgmort0(TIME)+chr_mort_rate_0)
deaths_chronic_1 = Chronic_1*(#bgmort1(TIME)+chr_mort_rate_1)
deaths_chronic_2 = Chronic_2*(#bgmort2(TIME)+chr_mort_rate_2)
deaths_chronic_3 = Chronic_3*(#bgmort3(TIME)+chr_mort_rate_3)
total_deaths_chronic = deaths_chronic_0 + deaths_chronic_1 + deaths_chronic_2 + deaths_chronic_3

HBV_mort_chronic = total_deaths_chronic/tot_chronic
uninf_mort = tot_deaths_uninf/(tot_sus+tot_immune+tot_cleared)
prop_chronic_mort = HBV_mort_chronic/uninf_mort

rel_mort_0 = (chr_mort_rate_0+#bgmort0(TIME))/#bgmort0(TIME)
rel_mort_1 = (chr_mort_rate_1+#bgmort1(TIME))/#bgmort1(TIME)
rel_mort_2 = (chr_mort_rate_2+#bgmort2(TIME))/#bgmort2(TIME)
rel_mort_3 = (chr_mort_rate_3+#bgmort3(TIME))/#bgmort3(TIME)

attrib_deaths_chronic = total_deaths_chronic*0.225
attrib_cum_deaths_chronic = tot_cum_deaths_chronic*0.225

ever_chronic = tot_chronic + tot_cum_deaths_chronic
not_prop = (#not_cumulative(TIME) / ever_chronic)*not_sys
not_sys = IF(TIME>=1971) AND (TIME < 2007) THEN 1 ELSE 0

(End Globals)
Appendix 3  Articles published in peer-reviewed journals related to PhD research

A3.1
Cowie BC.
Is there an optimal genetic target for molecular analysis of hepatitis B virus transmission?
*Journal of Clinical Microbiology* 2006; 44 (8): 3051
Letter to the Editor

Is There an Optimal Genetic Target for Molecular Analysis of Hepatitis B Virus Transmission?

A recent report of an outbreak investigation in this journal (1) explored the heterogeneity of variability across the hepatitis B virus (HBV) genome. As expected, genomic regions encoding a single gene product tended to be more variable than overlapping open reading frames (ORFs) with multiple translated products. The investigators recommend the use of the most rapidly evolving regions, such as nonoverlapping stretches of core and pol genes, for transmission investigations or studies of sequences deriving from a recent common source.

There have been many investigations of HBV transmission using sequencing of various genome targets. In a recent study of occult HBV infection in household contacts of carriers (2), S-gene sequencing was undertaken for the purpose of transmission analysis. It was observed that the sequences from some (presumably epidemiologically unconnected) families clustered together, a phenomenon it was suggested may be due to gene flow through the extensive mixing of HBV strains as was hypothesized for precore/core sequence similarities in an investigation of HBV transmission in Gambia (3).

An alternative explanation is the high degree of conservation in the S region, and in the Gambian study the authors reported that S-gene sequence analysis was unsuitable for demonstration of common source infections due to this conservation, which is related to the overlapping S and reverse transcriptase domain of pol ORFs in this region (5, 9, 11). Indeed, multiple epidemiologically unrelated S-gene sequences were found to be identical.

Similar findings were reported from Australia 3 years earlier than the Gambian study (1). In this study of recently emigrated families, separate analysis of S- and X-gene sequences were performed. The S genes allowed categorization of HBV strains into dominant strains related to country of origin, which were not recognized by distal-Xprecore sequence analysis, but the latter was better able to discriminate between family groups. Both observations are presumably due to the differing variability in this regions, with the distal-X-precore being more variable and therefore preferred by the authors for tracing recent HBV transmission events.

Discussion of the optimal genetic targets for sequence analysis of transmission is neither new nor restricted to HBV (6, 8, 10). In response to the controversy surrounding single-gene sequence analysis of human immunodeficiency virus type 1 (HIV-1) transmission, González-Candelas and Mora (4) state that given the heterogeneity of the evolutionary rate along the genome of this virus, analysis of phylogenetic relationships must be based on a domain with an appropriate level of evolution for the issue under investigation. Assessing recent transmission events requires the analysis of fast-evolving regions, whereas older events must be studied by sequencing more-stable regions. Thus, in the HBV context, conserved areas, such as the S gene, are useful for determining genotypes and strains associated with particular regions or communities (where common ancestor virus strains are more distant) but potentially less so for studying the chain of transmission between individuals, where a more mutable and therefore variable area of the genome is preferable. Bracho and colleagues reinforce this argument in their recent article (4).

Again drawing from the controversy surrounding HIV-1 transmission, it perhaps could also be said for HBV that "there is no such thing as an ultimate gene for evolutionary analysis . . . indeed, full-length sequences should be used for the investigation of potential linkages by phylogenetic means" (7) and that no single region is equal to them all.

I thank Heath Kelly for comments and suggestions to improve this letter.

This work was financially supported by the Centre for Clinical Research Excellence in Infectious Diseases and by a Public Health Postgraduate Scholarship from the National Health and Medical Research Council, Australia.

I had no conflict of interest.

REFERENCES


Benjamin C. Cowie
Victorian Infectious Diseases Reference Laboratory
19 Wrexham Street, North Melbourne
Victoria 3051, Australia
Phone: (03) 9342 2000
Fax: (03) 9342 2666
E-mail: Benjamin.Cowie@vms.org.au
A3.2

Cowie BC.

Selecting a genetic region for molecular analysis of hepatitis B virus transmission – Author’s reply.

*Journal of Clinical Microbiology* 2007; 45 (2): 688 - 689
Selecting a Genetic Region for Molecular Analysis of Hepatitis B Virus Transmission

The optimal genetic regions for the phylogenetic analysis of hepatitis B virus (HBV) transmission continue to be a matter of debate, with different investigators preferring different regions. However, full-length HBV sequence analysis is the gold standard for the purpose. But in developing countries, such as ours, where HBV infections are endemic, the added cost of full-length sequencing becomes a limiting factor for studying large numbers of samples. Thus, the search for a suitable genetic region of HBV is important.

Initially clustering of HBV serumers (7, 12) and subsequently clustering of well-established mutations (e.g., HBsAgG145R or HBsAg2259934) were used to demonstrate that (11, 13, 15, 18, 19). Recently, to increase the confidence level of detection of true transmission events, phylogenetic analysis with the bootstrap resampling/maximum-likelihood test of surface/precore (preC) core region sequences was carried out (6, 8, 22). However, clustering of sequences from epidemiologically unrelated families was suggested to be due to a high degree of conservation of surface (S) gene sequence (8), which led to the region being considered unsuitable for transmission studies.

Thus, analysis of nonoverlapping, fast-evolving regions was recommended (3, 5). Interestingly, 67% of the HBV genome is overlapping (16), leaving distal XpreC partial core regions nonoverlapped. These regions encode important RNA structural elements, such as the epsilon signal (10), that are essential for HBV replication. Thus, one can assume that high variability in these regions might have negative selection pressure; on the other hand, variability in the HDAg is positively selected to evade host immune pressure. Recently, using statistical models, Szomol noted and colleagues (17) found that overlapping sites have slightly higher substitution rates than nonoverlapping regions, which supports the above assumption.

Further, variability of a genetic region or prevalence of certain mutations varies with the study population, infecting genotype (10), immune status, chronically (20), clinical outcome (21), duration (associated time frame), and mode of infection (heterospecies, vertical, or intrahost horizontal). Thus, as recommended by Bracho and colleagues (3) for investigating the chain of recent heterospecies fumigant cases, analysis of highly variable preC/core region sequence associated with fumigant hepatitides B (14) should be preferred.

Our population shows a low preC mutation prevalence (2), and S gene sequence analysis provided more phylogenetic signal, which is more appropriate for tracing horizontal transmission patterns among HDAg-negative family members (6). High S gene variability has been documented in previous studies among HDAg-negative subjects (20) or among chronic virus carriers or their families (18). In fact, different specific variability levels for the S gene (genotype, subgenotype, and subtype), in addition to mutations, can provide enough confidence to prove transmission events. Actually, in one of our earlier studies, where the preC/core region of all the isolates was identical, genotype, subtype, and mutation analysis of S gene sequences proved two different sources and evidence of horizontal transmission of HBV infection in a family (4).

Thus, before selecting a genetic region for investigations of transmission, it is more reasonable to consider the genetic variability of HBV among the study population, their serological profile, and the mode of probable transmission rather than to adhere to a specific genetic region, found to be more variable in a study of different population groups with different HBV genotypes, disease severity, or serological patterns.

S.D.A.B., and P.K.C. are supported by research scholarships from UGC, ICMR, Government of India, and WISSAPS, Government of West Bengal, India, respectively.

REFERENCES

The molecular epidemiology of HBV infection is indeed complex, and phylogenetic analysis is complicated by the compact genomic structure comprising four partially overlapping open reading frames with no noncoding regions in the genome—all regulatory signals also encode proteins (2, 10). Many of the products of these genes are important to viral structure and function and may be subject to significant selection pressure, such as host immune responses acting on the HBsAg and HBeAg products or antiviral medications acting directly on the viral polymerase (with corresponding changes in overlapping S gene sequences) (3, 8, 11–13). Much care must therefore be taken in analyzing sequence heterogeneity in putatively related HBV strains. As noted by Datta and colleagues in the preceding letter, particular regard must be given to the influence of host immune pressure on the infecting virus, ranging from little or no selection pressure being exerted during the immune-tolerant phase of infection, to a correspondingly lower rate of mutations in genes encoding immunodominant epitopes, to much greater pressure during and after immune clearance, with subsequent selection of mutations providing escape from this pressure. Examples of these mutations include the classic precore mutation resulting in loss of HBeAg and the range of S-gene polymorphisms that have been implicated in immune escape (1, 7–10, 14, 15).

In the interesting study by these authors published earlier this year (5), contacts of known HBsAg-positive patients were screened to detect those with occult HBV infection—detectable HBV DNA in the serum in the absence of HBsAg. The S gene of the infecting HBV was sequenced to determine potential significant mutations and was also used for phylogenetic analysis of transmission within families—in their letter, they state that it is a more appropriate target for tracing transmission patterns among HBsAg-negative family members, with more "phylogenetic signal" in the S gene than in other areas. However, in this study population, this signal may represent the polymorphisms evolved within individual hosts in response to immune pressure on HBsAg (8), and as stated in the introduction to their study, "occult HBV infection is often explained by low levels of HBV DNA and a significant increase in genetic variability in the [S] determinant" (5, 16). Such variability arising within the host in response to immune pressure, could complicated attempts to define phylogenetic relatedness at the time of infection years before (15), and conversely similar patterns of mutations in unrelated viral strains could potentially explain some of the clustering of genetically unconnected individuals in this population. This idea is supported by the observation made by the authors that the phylogenetic tree shows clustering by whether the sequenced viruses were wild-type or variant strains (5).

There is evidence that the S gene can be a relatively conserved region (outside the context of immune selection as discussed above), impairing the ability to distinguish transmission patterns (4, 6, 14). The assumption that distal Xprecore/core region variability is deleterious to the virus and therefore will not be observed is not supported by other transmission investigations (2, 6, 14, 17), and in the Australian and Gambian studies previously cited (4), these regions revealed transmission patterns where S gene analysis did not, due to a lack of sufficient variability (6, 14).

Full genome sequencing is the gold standard for phylogenic analysis of HBV transmission, but the increased cost is certainly a consideration, particularly in many regions where the burden of HBV infection is highest. The search for a suitable genetic target for transmission analysis is important. However, before selecting a convenient single gene target for such analysis, I would concur with Bracho and colleagues (2) that consideration of the heterogeneity of variability across the HBV genome in the study population is important and that a systematic way to define this is to use whole-genome sequencing. Finally, regard must be given to the stage of HBV infection in the patients being studied, with the presence or absence of significant immune pressure being critical to the rate of mutation in genomic regions encoding immunologically important structures, such as the S gene.

B.C.C. is financially supported by the Centre for Clinical Research Excellence in Infectious Diseases and by a Public Health Postgraduate Scholarship from the National Health and Medical Research Council, Australia.

There is no conflict of interest.

REFERENCES


Benjamin C. Cowie*
Victorian Infectious Disease Reference Laboratory
10 Wreckys Street, North Melbourne
Victoria 3051, Australia

*Phone: (61 3) 9342 2606
Fax: (61 3) 9342 2666
E-mail: benjamin.cowie@mh.org.au
Appendix 4  Published chapters in monographs related to PhD research

A4.1

Cowie BC.

Chapter 10: Managing hepatitis B virus infection in complex situations.


Darlinghurst; Australasian Society for HIV Medicine.
MANAGING HEPATITIS B VIRUS INFECTION IN COMPLEX SITUATIONS

Benjamin Cowie  
Victorian Infectious Diseases Service, Royal Melbourne Hospital and Victorian Infectious Diseases Reference Laboratory, North Melbourne, VIC.

Links to:  
Chapter 3: Hepatitis B virus testing and interpreting test results  
Chapter 4: Natural history of chronic hepatitis B virus infection  
Chapter 5: Primary prevention of hepatitis B virus infection  
Chapter 7: Treatment of chronic hepatitis B virus infection  
Chapter 8: Managing patients with advanced liver disease  
Chapter 9: Hepatitis B virus-related hepatocellular carcinoma

KEY POINTS

Facts
- Ninety per cent of the mother-to-child transmission of hepatitis B virus (HBV) is preventable.
- Several antiviral drugs used in the treatment of human immunodeficiency virus (HIV) infection are also effective against HBV.
- The reactivation of HBV infection in the setting of immunosuppression can also occur in people who have a history of resolved acute HBV infection.

Myths
- Mothers with HBV infection should not breastfeed.
- Children with HBV do not develop cirrhosis, hepatocellular carcinoma (HCC) or other manifestations of advanced liver disease.
- People with HIV should not be concerned about viral hepatitis, as complications take many years to develop.

There are a number of special situations in which the complexity of managing the care of a patient with hepatitis B virus (HBV) infection is increased. Primary care practitioners are optimally placed to recognise and respond to these situations, and coordinate a management plan that maximises the health and wellbeing of the patient with HBV infection.

Pregnant women and HBV

Worldwide, the majority of people with chronic HBV infection acquire the infection at birth or in early childhood. Given that age at infection determines the risk of progression to chronicity (see Chapter 4: Natural history of chronic hepatitis B virus infection), with 90% of neonatal infections resulting in chronic infection, averting the vertical transmission of HBV is critical. For many women with HBV infection who are pregnant or planning pregnancy, the possibility of HBV transmission to their child is a cause of significant distress. Adequate counselling and addressing the mother’s concerns are crucial, emphasising the availability of highly effective treatment to prevent transmission. It is also an opportunity to assess the HBV status of other family and household members and to vaccinate all those who are susceptible.
Routine antenatal HBsAg screening is essential to allow the identification and treatment of as many neonates at risk of infection as possible. If pre-test counselling identifies maternal risk factors for HBV infection, but serology indicates HBsAg negativity and no immunity, plans should be made to initiate vaccination of the mother following delivery.

The risk of vertical transmission is determined by the intensity of maternal HBV replication, with highly replicative infection characterised by a high HBV DNA viral load and HBeAg positivity (see Chapter 3: Hepatitis B virus testing and interpreting test results). Up to 90% of infants born to HBeAg-positive mothers acquire the infection if untreated, compared to less than 10% of those born to HBeAg-negative mothers. When the appropriate prophylactic treatment is given, there is no evidence that mode of delivery (vaginal or caesarean) affects the risk of infection, and although HBsAg and HBV DNA are detectable in breast milk, breastfeeding is not associated with an increased risk of transmission and should not be discouraged.

A pregnant woman diagnosed with HBV should be referred to a physician experienced in the management of viral hepatitis. Pregnant women with established chronic hepatitis, especially those with cirrhosis, should be monitored for any deterioration in their liver disease throughout their pregnancy. A flare in the mother's hepatitis is sometimes seen after delivery, presumably secondary to the recovery from the pregnancy-induced immune tolerance state. Although HBV antiviral therapy is not approved in pregnancy, lamivudine has been taken by many pregnant women for the treatment of HIV infection without evidence of adverse foetal effects.

For a susceptible woman exposed to HBV during pregnancy, prophylaxis should be initiated immediately (Table 10.1). If acute HBV infection occurs during pregnancy, the risk of infection to the foetus is low in the first two trimesters but rises to 75% in the third trimester. The mother should be referred for supportive care and monitored for features of fulminant hepatitis (see Chapter 4: Natural history of chronic hepatitis B virus infection, and Chapter 7: Treatment of chronic hepatitis B virus infection). The infant should receive hepatitis B vaccine and HBIG at birth as described in the next section.

### Table 10.1: Prophylaxis for women exposed to hepatitis B virus during pregnancy

| 1. HBIG* 400 IU, IM, single dose |
| 2. Hepatitis B vaccine 1.0 mL, IM, 3 doses at 0, 1 and 6 months |

#### Other considerations:
- Both HBIG and hepatitis B vaccine should be administered without delay.
- HBIG and HBV vaccine can be administered simultaneously at different sites.
- Serological monitoring for infection must extend to at least six months post-exposure.
- Vaccinate infant at usual schedule unless infection occurs in the mother.
- If mother acquires infection, manage the infant as per maternal chronic HBV infection.

* Hepatitis B immunoglobulin (HBIG) is only available through the Australian Red Cross Blood Service.

---

76 R. Positive - all you wanted to know about hepatitisB: a guide for primary care providers.
Paediatric management
For a neonate born to a mother with HBV infection, hepatitis B vaccination reduces the risk of infection by 70%; the addition of HBIG, derived from the plasma of blood donors with high anti-HBs levels, augments this risk reduction to 90%. This combined active and passive vaccination approach for the prevention of perinatal infection is outlined in Table 10.2. Children diagnosed with HBV infection should be referred to a paediatrician experienced in viral hepatitis.

All susceptible household members should be vaccinated against HBV, and the affected child should also be vaccinated against hepatitis A. As with adults with chronic HBV infection, children should be periodically monitored for disease activity, progression and the development of hepatocellular carcinoma. Although there are even less data informing the frequency of monitoring in children than in the adult context, annual screening for HCC with serum alpha fetoprotein testing has been recommended, together with periodic liver ultrasounds, and clinical and biochemical monitoring of disease activity every six to 12 months.

The selection of patients for antiviral therapy is similar to the adult context. Treatment is generally reserved for patients with ALT values repeatedly more than twice the upper level of normal, as treatment efficacy is much higher in this setting (see Chapter 7: Treatment of chronic hepatitis B virus infection). The available treatments are conventional interferon-alfa and lamivudine. The advantages of interferon-alfa are the finite duration of therapy and the lack of induction of antiviral resistance. Both efficacy and toxicity profiles in children are similar to those in adults, and patients with normal ALT (being the majority of children who acquired the infection at birth) are unlikely to achieve favourable outcomes. The use of pegylated interferon to treat HBV in children has not yet been investigated but was examined.

Table 10.2: Prophylaxis for perinatal hepatitis B virus exposure

| 1. HBIG* 100 IU, IM, single dose |
|---|---|
| 2. Hepatitis B vaccine 0.5 mL, IM, 4 doses at 0, 2, 4 and 6 or 12 months |
| 3. Other considerations: |
| ▪ Preferably both HBIG and hepatitis B vaccine should be administered immediately after birth in opposite thighs (i.e. not into the same site) |
| ▪ HBIG should not be delayed beyond 12 hours after birth |
| ▪ Hepatitis B vaccine should be given within 24 hours of birth; if delay is unavoidable, vaccine must be given within seven days |
| ▪ Doses of hepatitis B vaccine subsequent to the birth dose are combined vaccines as per the standard schedule (final dose at 6 or 12 months depending on vaccine used) |
| ▪ Serological assessment for infection (HBsAg and anti-HBs) should be performed three months after the final dose of hepatitis B vaccine (not before nine months of age) |

*Hepatitis B immunoglobulin (HBIG) is only available through the Australian Red Cross Blood Service.
in children with hepatitis C virus (HCV) infection. Lamivudine is an alternative that is well tolerated and effective at suppressing viral replication, but this antiviral therapy is associated with the relatively rapid emergence of viral resistance. Paediatric use of adefovir remains under investigation.²

Co-infections
An estimated 0.5–1% of Australians with chronic HBV infection also have HIV infection; 4–9% of HbsAg-positive people are believed to be co-infected with HCV. These rates are higher than in the general population, related to the shared modes of transmission and hence epidemiological associations of these viruses. Hepatitis B virus (HBV) only exists as a co-infection with HBV.

HBV/HIV co-infection
The majority of HIV-positive men who have sex with men (MSM) have serological evidence of past or chronic HBV infection. In the Australian HIV Observational Database cohort of more than 2000 HIV-positive participants, over 6% of those tested were seropositive for HBsAg.² The progression to chronic infection following acute HBV is much more common in people with HIV infection, with the likelihood of failing to clear HBV related to the degree of immunodeficiency.²⁰

Co-infection with HIV has a significant impact on the natural history of chronic HBV infection. High HBV DNA levels and detectable HbsAg are more common in patients with HIV co-infection, and the rate of viral reactivation is also higher, particularly in more immunocompromised patients.²⁰ Even anti-HBs-positive patients with a history of resolved HBV infection can experience reactivation, with reappearance of HbsAg and HBV DNA in the setting of advanced immunodeficiency. Occult chronic HBV infection (HbsAg negative but HBV DNA positive) is also more common in patients with HIV infection.

In the setting of HBV/HIV co-infection, the progression to advanced liver disease, such as cirrhosis and HCC, is more rapid and liver-related mortality is higher, despite typically lower ALT values and reduced inflammatory activity on biopsy. This disparity of less necro-inflammatory activity but faster disease progression is incompletely understood. In contrast to the significant impact of co-infection on the natural history of HBV, there is little evidence to suggest that HBV affects the progression of HIV infection.

With the profound reduction in acquired immune deficiency syndrome (AIDS)-related mortality and in the incidence of opportunistic infections since the introduction of highly active antiretroviral therapy (HAART), liver-related morbidity and mortality has assumed an increasing burden on the health of people with HIV infection. The co-infection with hepatitis viruses explains a significant proportion of this burden. Another cause of hepatic damage in people with HIV infection is the toxicity of a number of antiretroviral agents; this toxicity is more pronounced in patients with pre-existing liver disease, such as chronic viral hepatitis.²¹

The selection of patients requiring treatment for HBV in the setting of HIV co-infection is similar to the HIV-negative context, and the aims are essentially the same. One very important consideration is that some of the agents used to treat HIV (such as lamivudine, tenofovir and emtricitabine) are also active against HBV. Thus, the incorporation of one or more of these drugs into a HAART regimen allows treatment of both infections without increasing the therapy burden. Furthermore, co-infection is the only context in which combination therapy for HBV is possible under the PBS, an approach which is likely to delay the development of HBV antiviral resistance (as it does in HIV).²² In patients not requiring HIV therapy, monotherapy for HBV with agents also active against HIV (such as lamivudine) should be avoided, as this can induce resistance mutations that will make designing subsequent HAART regimens more difficult. It was previously thought that the anti-HBV drug entecavir, had no anti-HIV activity, however, recent reports indicate that entecavir can induce resistance mutations in HIV²² and its use as HBV monotherapy in the context of HIV co-infection is being re-evaluated. Pegylated
interferon-alfa, as a non-nucleoside-based therapy, can be considered for patients in this context, provided they have adequate hepatic reserve, although its efficacy is reduced in the context of HIV infection, particularly with more advanced immunodeficiency.11

Another reason to incorporate HBV active agents in a HAART regimen is to avert immune reconstitution hepatitis. The immune reconstitution inflammatory syndrome describes a pathology deriving from resurgent immune attacks on chronic infections in patients with HIV, following the commencement of HAART. HBV flares in the setting of immune reconstitution are more common in patients with a high baseline HBV viral load, and can result in significant liver disease and mortality, particularly in patients with advanced liver disease and poor hepatic reserve. However, flares can also lead to HBsAg clearance and the suppression of viral replication in some patients.2 Caution when changing HAART regimens in co-infected patients is also necessary, as ceasing HBV-active agents can cause reactivation. Continuation of these antivirals should be considered even if they add little to the patient’s HIV therapy.

HBV/HCV co-infection
In contrast to the co-infection with HIV, it is common for patients with HCV co-infection to have a reduced replication of HBV, with lower viral loads than in patients with HBV mono-infection. This is because HCV directly interferes with the HBV replication. It is a common finding in HBV/HCV co-infection that one of the viruses predominates in terms of viral replication, with the suppression of the other virus.4 As with HIV, occult (HBsAg-negative) HBV infection is also seen more commonly in patients with HCV co-infection.

Acute co-infection (usually arising through injecting drug use) has been associated with an increased incidence of fulminant hepatitis. Chronic HBV/HCV co-infection is usually associated with a more severe liver disease, an increased risk of progression to cirrhosis and a higher incidence of HCC. A recent Australian study showed that co-infection with HBV and HCV was associated with much higher mortality rates (liver-related and all cause) than infection with either HBV or HCV alone; patients with co-infection had mortality rates approximately three times higher than patients with HBV infection only.13

In patients with chronic HBV/HCV co-infection meeting the criteria for therapy for either infection, consideration should be given to combination therapy with pegylated interferon-alfa plus ribavirin, even if the HBV infection predominates. Reactivation of previously suppressed HBV replication following treatment of HCV with standard interferon plus ribavirin has been reported, leading to suggestions that combination with additional anti-HBV agents should be considered. This approach is not universally followed.

HBV/HDV co-infection
In non-endemic countries such as Australia, HDV infection is most commonly associated with injecting drug use (IDU). HDV is a defective virus that requires co-infection with HBV to synthesise new virions. Similar to the situation of HBV/HCV co-infection, HDV infection results in the suppression of HBV replication with sometimes low or even undetectable HBsAg levels.

Acute co-infection with HBV/HDV is typically indistinguishable from HBV mono-infection, but has been associated with a higher incidence of fulminant hepatitis. The rate of progression to chronicity is no different from that for HBV infection alone. HDV superinfection of a patient with existing chronic HBV can present as an acute hepatitis flare, and progression to chronic HDV infection is almost universal. Chronic HBV/HDV co-infection has been associated with a more severe liver disease and the increased incidence of HCC and mortality. Treatment of HBV/HDV co-infection is with interferon-alfa, conventional or pegylated, for a period of one year, although treatment eradicates the virus in only a minority of patients and relapse following therapy is common. Lamivudine is ineffective against HDV and the addition of ribavirin to interferon also confers no benefit.
**Reactivation during Immunosuppression**

The natural history of HBV infection is fundamentally related to the dynamic balance between the viral replication and the host's immune response (see Chapter 4: Natural History of chronic hepatitis B virus infection). Therefore, it is not surprising that immunosuppressive therapy can have a marked impact on chronic HBV infection. Reactivation of HBV replication is common during cancer chemotherapy and following immunosuppression for transplantation or for the treatment of autoimmune diseases. It is particularly associated with glucocorticoid therapy as, in addition to suppressing host immunity, glucocorticoids act directly on the virus to enhance transcription.

HBV reactivation due to the institution of immunosuppressive medication is initially associated with a rise in the serum HBV DNA viral load. A hepatitis flare with a rise in ALT levels can follow, particularly when the immunosuppressive therapy is reduced or withdrawn; restoration of the immune function causes a sudden increase in the destruction of infected hepatocytes. This is similar to the immune reconstitution inflammatory syndrome seen with HAART for HIV infection.

Although most hepatitis flares in the context of immunosuppression are asymptomatic, a full spectrum of presentations is possible, through to liver failure and death. Suggested risk factors for reactivation have included use of glucocorticoids, high baseline HBV DNA viral load, HBeAg positivity, young age and male gender.4 The rate of withdrawal of immunosuppression is an important determinant of the severity of flares. The increased incidence of flares observed in the setting of cancer chemotherapy, compared with other immunosuppressive regimens, may relate to the cyclical nature of such therapy, with repeated episodes of immunosuppression and restoration.

Prophylaxis with lamivudine has been shown to markedly reduce the incidence of reactivation, hepatic flares and associated mortality. Prophylaxis should be given to all HBsAg-positive patients prior to chemotherapy or other immunosuppressive therapy; such pre-emptive treatment has been shown to be superior to starting treatment once reactivation has been detected.4 To allow prophylaxis to occur, all patients being prepared for such treatment should be screened for the presence of HBsAg, anti-HBs and anti-HBc. Although most experience in such prophylaxis has been with lamivudine, the possibility of inducing drug resistance mutations is a significant concern. Entecavir is associated with a lower rate of resistance induction and is likely to assume an increasing role in this setting. Interferon is contraindicated in patients with significant autoimmune disease or in the post-transplantation setting due to its immunomodulatory activity.

HBV is detectable in the hepatocytes of any person who has ever had the infection, even those who are anti-HBs positive. In the setting of profound immunosuppression, HBsAg-negative patients can also reactivate and develop severe flares. This situation is more common in isolated anti-HBc-positive patients than in those with detectable anti-HBs, but the occurrence in the latter group is also described. Some protocols extend the recommendation for antiviral prophylaxis to isolated anti-HBc-positive patients, but few recommend prophylaxis in anti-HBs-positive patients. Recognising the possibility of reactivation and acting promptly is therefore important in all patients undergoing immunosuppression.
References


E Positive - all you wanted to know about hepatitis B: a guide for primary care providers
A4.2

Cowie BC.

Chapter 9: Viral hepatitis.

VIRAL HEPATITIS

Overview:
Viral hepatitis is an important health problem worldwide. It is estimated that over 350,000 Australians are chronically infected with viral hepatitis B (HBV) or C (HCV) or both. The sexual route of transmission is important for hepatitis A (HAV). HBV and hepatitis D (HDV). Sexual transmission of HCV is much less common. For people living with chronic viral hepatitis, approximately 26% will develop advanced liver disease such as cirrhosis or hepatocellular carcinoma (HCC). People living with HIV/AIDS are at increased risk of also having chronic viral hepatitis B or C or both, and the rate of progression to severe liver disease is higher. As safe and effective vaccines are available for both HAV and HBV (including in a combined formulation), immunisation should be encouraged for all patients at risk of infection.

Medical Issues:
Although symptoms and signs of acute or chronic hepatitis are important to recognise, in many cases patients are asymptomatic or exhibit mild or non-specific symptoms. Therefore, a thorough exploration of potential risks of transmission with patients is critical to enable diagnosis. Knowledge of the risk factors for infection, and of particular groups in the community at higher risk, should also be the foundation for a comprehensive and pro-active vaccination policy. Some risk factors for infection and related information appear in the table below:

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Risk Factors for Infection and Related Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>(a) Parenteral and sexual transmission. People with multiple sex partners (or current or recent sexual partners of people with multiple sex partners) and people who engage in oral-anal sexual contact. Sexual transmission is possible in heterosexual couples. People with sexual partners who are infected with HBV may be at risk. Sexual transmission may occur during oral-anal sexual contact. People with sexual partners who are infected with HBV may be at risk. Sexual transmission may occur during oral-anal sexual contact.</td>
</tr>
<tr>
<td>HAV</td>
<td>(a) Parenteral and sexual transmission. People with multiple sex partners (or current or recent sexual partners of people with multiple sex partners) and people who engage in oral-anal sexual contact. Sexual transmission is possible in heterosexual couples. People with sexual partners who are infected with HAV may be at risk. Sexual transmission may occur during oral-anal sexual contact. People with sexual partners who are infected with HAV may be at risk. Sexual transmission may occur during oral-anal sexual contact.</td>
</tr>
</tbody>
</table>

History:
It is generally not possible to distinguish between acute viral hepatitis infections on clinical features alone. It is also important to remember that subclinical infection or non-specific clinical features are very common. These tests reinforce the importance of eliciting relevant epidemiological clues and having a low threshold for testing. Symptoms and signs of chronic viral hepatitis do not reliably reflect disease activity; their absence does not preclude significant pathology.

Symptoms of viral hepatitis can include malaise, lethargy, anorexia, nausea and vomiting, fever, jaundice, headache and myalgia, abdominal pain particularly in the right upper quadrant, pruritus, and icterus, and jaundice, spider nevi, palmar erythema, and gynecomastia. Features of portal hypertension such as ascites, splenomegaly, and encephalopathy may be present. With the onset of liver failure (acute or chronic), symptoms can include intractable nausea, excessive bruising and bleeding, and with hepatic encephalopathy, reversal of the diurnal sleep pattern, increasing lethargy and behavioral changes. Signs include bruising and bleeding, peripheral edema, jaundice, hepatosplenomegaly, and alterations in consciousness state.

The extraparenchymal manifestations of viral hepatitis are protein; common clinical features include vasculitis, rash, other skin conditions, arthritis, abnormally pain, peripheral neuropathy, and dry eyes and mouth. People living with chronic HCV in particular have a high prevalence of depression.

Investigations:
The diagnosis of viral hepatitis is established by blood tests. The cornerstone of first-line testing remains serology, although newer molecular tests are assuming an increasing role...
Some find these tests confusing (particularly those for HAV), but a systematic approach to testing makes interpreting the results more straightforward.

**HAV**

**Acute:** anti-HAV IgM positive

**Past infection:** anti-HAV total or IgG positive and anti-MHAV IgM negative

**HBV**

Consideration should be given to ordering a panel of HBV serology including HBSAg, anti-HBe and anti-HBc for any patient with risk factors for HBV infection. This avoids both missing chronic HBV infections and unnecessary vaccination. Unlike HCV RNA PCR (see below), at the time of writing there was no Medicare rebate available for HBV DNA PCR testing; hence outside a hospital or institutional setting where the cost is covered, the patient will be liable to pay for the test (typically over $100).

<table>
<thead>
<tr>
<th>Serologic test</th>
<th>Results</th>
<th>Typical interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBSAg anti-HBs</td>
<td>negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>HBSAg negative</td>
<td>negative</td>
<td>Vaccinated, if titre &gt;10 mIU/mL and has had complete course of vaccination, no further immunisation required.</td>
</tr>
<tr>
<td>HBSAg positive</td>
<td>negative</td>
<td>Early acute infection</td>
</tr>
<tr>
<td>HBSAg positive</td>
<td>positive</td>
<td>Vaccinated, if titre &gt;10 mIU/mL and has had complete course of vaccination, no further immunisation required.</td>
</tr>
</tbody>
</table>


* IgM anti-HBc can be positive during a flare of chronic HBV infection.

**HCV**

Anti-HCV is a marker of ever having been infected with HCV; up to 20% of anti-HCV positive patients will have cleared the infection. Due to the availability of a Medicare rebate for HCV RNA PCR, this test to establish the replicative status i.e., whether the infection persists or has been cleared, of an anti-HCV positive patient is possible in the primary care setting. Repeatedly negative PCR and persistently normal ALT suggests cleared infection.

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
<th>Alternative interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-HCV HCV RNA PCR negative</td>
<td>no infection</td>
<td>previous infection with clearance and seroreversion during incubation period</td>
</tr>
<tr>
<td>anti-HCV HCV RNA PCR positive</td>
<td>acute infection</td>
<td>chronic infection with transient undetectable RNA PCR, false positive antibody result</td>
</tr>
</tbody>
</table>

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.

Effective therapies exist to treat both chronic HBV and HCV. For patients with chronic HAV with persistently elevated ALT and biopsy evidence of chronic hepatitis, possible treatments include nucleoside analogues (lamivudine, entecavir, adefovir) or pegylated interferon. The aim of therapy is to suppress viral replication. Induction HBSAg seroreversion, and prevent progressive fibrosis and HCC. In the case of HAV, cromovir therapy with pegylated interferon and ribavirin elicits a sustained virologic response (SVR, defined as remission HCV RNA PCR negative 6 months after cessation of therapy). In 45 – 60% of patients depending on HCV genotype. Achievement of an SVR is associated with improvement in liver histology, reduction in incidence of HCC and reduced mortality. SVR appears durable in >95% of patients. The former requirements for a liver biopsy and raised ALT to access treatment no longer apply to chronic HCV infection.
and if necessary minimisation is also important, as is a harm minimisation approach in the setting of ongoing IDU.

Other Considerations:

Notification:

Any newly diagnosed viral hepatitis must be notified by the treating doctor and the testing laboratory to enable an appropriate public health response.

Screening of contacts:

Discussion with the newly diagnosed patient regarding relevant contact tracing and screening is advisable. Contacts to consider include sexual, blood-to-blood (e.g., IDU), and household contacts (in the case of HAV and HBV). Occupational contact tracing may be relevant (e.g., food preparation for HAV, healthcare workers involved in exposure prone procedures for HBV and HCV). Commonwealth and State Territory guidelines should be followed and assistance can be sought from State or Territory public health authorities.

Serosexual follow-up for people exposed to HBV or HCV should extend to 6 months following exposure (typically performed at 1, 2, and 6 months).

Immunisation:

Vaccination against HAV or HBV, or both (combined formulation) should be proactively offered to all people with risk factors for infection.

People with chronic viral hepatitis should be protected against further liver injury. A person with chronic HBV requires vaccination against HAV; a person with chronic HCV should be vaccinated against both HAV and HBV.

Sexual and household contacts of a person infected with either HAV or HBV should be immunised.

HAV sexual and household contacts (during the 2 weeks prior to and for 1 week after the onset of jaundice) should receive single human immunoglobulin (HIG) and non-immune individuals at ongoing risk of HAV infection can commence active vaccination against HAV simultaneously. HIG should be administered as soon as possible, certainly within 2 weeks.

HBV, following significant exposure to an HBsAg positive source, a non-immune individual should receive hepatitis B immune globulin (HBIG) as soon as possible and commence hepatitis B vaccination simultaneously. HBIG can only be obtained from the Australian Red Cross Blood Service.

Sexual exposure: HBIG and commence vaccination within 14 days.

Perinatal exposure: HBIG within 12 hours, commence vaccination within 7 days.

Perinatal exposure: HBIG within 12 hours. Commence vaccination within 24 hours, repeat vaccines doses at 2, 4 and 6 or 12 months. This regimen reduces the risk of infection by 60%. The child should be screened for HBV infection with HBsAg and anti-HBs 2 months after completing the vaccine series.

Exposure with lesser risk (e.g., susceptible household contacts of people with chronic HAV, susceptible long-term partners of patients with latent HAV infection) usually do not warrant HBIG but hepatitis B vaccination should still be strongly encouraged.

People presenting following unprotected sexual or needle-sharing contact with a person of unknown HBsAg status should be offered vaccination against HBV (consider vaccination against HAV also) as should patients presenting for STI screening or treatment.

For more detailed discussion see the Australian Immunisation Handbook 8th edn.

References and further reading:


Appendix 5  Other publications

A5.1

Cowie BC.

Review of:

By:
Dr Benjamin Cowie
Physician, Victorian Infectious Diseases Service, Royal Melbourne Hospital
Medical Epidemiologist, Victorian Infectious Diseases Reference Laboratory

The Centers for Disease Control and Prevention (CDC) in the United States recently published revised recommendations for the identification and management of people living with chronic hepatitis B virus (HBV) infection (1). A fundamental component of these recommendations is the expansion of routine testing to include many more people at risk of having chronic HBV than was previously the case (see box).

The impact of these new testing recommendations will be profound if implemented in Australia. Approximately 30 per cent of us were born overseas, the majority in countries with intermediate or high prevalence of HBsAg (2). Therefore some 3.4 million Australians, being among the nearly 90 per cent of humans born in areas with HBsAg prevalence above 2 per cent (1) would be candidates for routine HBV screening under this single criterion alone.

In the Australian context it is imperative to include Indigenous people in such testing recommendations given the higher prevalence of chronic HBV in Indigenous Australians (3). There are other groups for whom testing has been recommended which are not included in the CDC criteria; the recently published ASHM/Cancer Council NSW monograph B Positive - all you wanted to know about hepatitis B: a guide for primary care providers (4) (available at http://www.ashm.org.au/b-positive/) includes extensive information on HBV epidemiology and testing recommendations, particularly in chapters 1 and 3.

These new recommendations come at a time when there are increasing calls in Australia for a profound shift in both public policy and clinical management relating to chronic HBV infection. This year has seen the publication of both the B Positive monograph and the National Hepatitis B Needs Assessment (5) (available at http://alliance.hepatitis.org.au/index.php?page=research). Both documents describe the failure of Australia’s public health response to HBV. There is still no National Strategy to co-ordinate an urgently needed, broad-based approach to this “poor cousin” of HCV and HIV. The prevalence of HBV infection is increasing in Australia, with the most recent national sero-prevalence data suggesting 160,000 Australians are chronically infected (6), one quarter of whom can be expected to die as a result of cirrhosis and/or hepatocellular carcinoma (HCC) (7). The disease burden in this country cannot be overstated; in New South Wales, HCC incidence is rising faster than any other cancer (8).

The CDC document goes much further than simply advising more people be tested for chronic HBV. A rationale for this expansion is provided, including favourable cost effectiveness analysis, and it is demonstrated that testing for chronic HBV meets long-established World Health Organisation criteria for disease screening (9). Critically, with the recent rapid expansion of effective treatment options for chronic HBV, the opportunities for modifying the natural history of the disease – and reducing further transmission - have improved. Enrolment in regular monitoring to assess disease activity and for HCC screening where appropriate is also most important, with randomised controlled trial evidence supporting previous observational data that HCC surveillance significantly reduces cancer mortality (10).
Finally, the new recommendations call for a change in the way public health authorities respond to notifications of chronic HBV – a disease which has only been nationally notifiable in the USA since 2005 (11). Significantly expanding the role of surveillance registries of notified cases of chronic HBV is advised, with the ‘minimum’ approach being similar to that undertaken in Australia. The CDC recommends building on this foundation in a tiered fashion, to develop chronic HBV registries into tools for public health intervention and clinical management. The expanded roles discussed include:

- Facilitating and tracking the follow-up of notifications with chronic HBV
- Assisting with notification of contacts and co-ordinating testing and vaccination as indicated
- Communication with or referral to health care providers
- Providing geographic and temporal estimates of the epidemiology of chronic HBV
- Linkage with cancer registries and mortality data to establish robust disease burden estimates

Such an expansion would obviously require significantly increased funding devoted to hepatitis programs, and the first three elements are more akin to the approach taken for HIV and tuberculosis notifications in the USA and also in Australia. Depending on the intensity of the expansion, the resources required could be considerable, not least when one considers annual notifications of non-incident HBV currently range between 8000 and 8000 in Australia, some three times the number for HIV and tuberculosis combined. However the current approach involves little or no public health follow up of notified cases of chronic HBV infection, despite the fact that these people have a treatable disease associated with significant mortality. It could be argued that our standard practice of compiling lists of infected people andarchiving their contact details without making any attempt to help inform them regarding their illness or their options is programmatically flawed, and even ethically questionable.

Perhaps the most important point to reflect on when considering the new CDC recommendations is that policy changes can only make a difference if implemented. Reference is made to a study from New York of over 18,000 primary care clinic attendees in 2005-2006, which demonstrated nearly half of those born in high HBV prevalence countries had not been tested in line with the existing CDC recommendations at that time (12). There is no reason to suspect we do any better in Australia. Most clinicians would probably agree that failing to opportunistically test patients with a 1 in 50 or greater chance of having a communicable, treatable and potentially fatal disease is unacceptable.

References


Box – existing and new CDC recommendations for chronic HBV testing.

<table>
<thead>
<tr>
<th>Existing recommendations</th>
<th>New recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>People born in regions of high HBsAg prevalence (&gt;8%)</td>
<td>People born in regions of intermediate and high HBsAg prevalence (&gt;2%)</td>
</tr>
<tr>
<td>Blood and tissue donors</td>
<td>People not vaccinated as infants whose parents were born in regions with high HBsAg prevalence</td>
</tr>
<tr>
<td>Haemodialysis patients</td>
<td>Injection-drug users</td>
</tr>
<tr>
<td>All pregnant women</td>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>Infants born to HBsAg positive mothers</td>
<td>Patients needing immunosuppressive therapy e.g. chemotherapy or for autoimmune diseases or following transplantation</td>
</tr>
<tr>
<td>Household, needle-sharing, or sexual contacts of HBsAg positive people</td>
<td>People with elevated ALT or AST for unknown reasons</td>
</tr>
<tr>
<td>Sources of blood/body fluid for exposures that might require PEP</td>
<td></td>
</tr>
<tr>
<td>People living with HIV/AIDS</td>
<td></td>
</tr>
</tbody>
</table>
A5.2

Cowie BC.

Trends in hepatitis B virus surveillance data in Victoria.


**TRENDS IN HEPATITIS B VIRUS SURVEILLANCE DATA IN VICTORIA**

Hepatitis B virus (HBV) infection – both acute and chronic (for surveillance purposes termed ‘unspecified’) – is a notifiable disease in Victoria. Notification to the Department of Human Services (DHS) by both testing laboratory and referring doctor is essential, as is tracing for all notifiable diseases.

It has been estimated that only a minority of cases of chronic HBV are notified. Despite this fact between 1500 and 1900 people are notified each year with unspecified HBV in Victoria alone (Figure 1).

**150 NOTIFICATIONS PER MONTH IN 2008**

So far in 2008, an average of 150 notifications of unspecified HBV infection has been received each month by DHS. More than 90% of those notified reside in metropolitan Melbourne. Figure 2 shows the municipality of residence of people notified with chronic HBV infection in Melbourne between 1 January and 31 August 2008, with the colours indicating the approximate numbers notified in each area.

*HBV surveillance data from the Communicable Diseases Prevention and Control Branch, Department of Human Services, Victoria.*

![Figure 1. Notifications of HBV infection in Victoria 2000-2007*](image1)

![Figure 2. Number of notifications of HBV infection in Victoria January-August 2008 by local government area*](image2)
Appendix 6  Presentations of PhD research at national conferences

6th Australasian Viral Hepatitis Conference, Brisbane, Queensland, October 2008
- The Victorian hepatitis B serosurvey 1995-2005
- Mapping hepatitis B at the crossroads: The correlation between seroprevalence, notifications and migration and predictions from a parsimonious linear regression model

11th National Immunisation Conference, Gold Coast, Queensland, September 2008
- Hepatitis B virus seroprevalence and vaccination uptake in Victoria, 1995 to 2005
Appendix 7  Other presentations related to PhD research

Inaugural meeting of the Viral Hepatitis Taskforce, Sexual Health and Viral Hepatitis Forum, Department of Human Services Victoria, Melbourne, March 2009
- The burden of chronic viral hepatitis in Victoria

Royal Melbourne Hospital / Western Hospital Cluster Meeting, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, February 2009
- Novel approaches to an improved understanding of the epidemiology and control of hepatitis B virus infection in Australia (Completion Seminar)

Forbes Week Research Seminar, The Alfred Hospital, Melbourne, November 2008
- Novel approaches to an improved understanding of an old (old) foe

Monash Medical Centre Infectious Diseases Meeting, Clayton, September 2008
- The Victorian Hepatitis B Serosurvey 1995 - 2005

SH3ED (Sexual Health, HIV and Viral Hepatitis Education) Program, General Practice Victoria “BBV Intermediate Course” Melbourne, September 2008
- Hepatitis B: Epidemiology, natural history and public health issues
- Hepatitis B: Diagnosis and management in primary care

Communicable Diseases Prevention and Control Meeting, Department of Human Services Victoria, Melbourne, August 2008
- The Victorian Hepatitis B Serosurvey 1995 - 2005

Victorian Infectious Diseases Service Meeting, Royal Melbourne Hospital, Parkville, February 2008
- The Victorian Hepatitis B Serosurvey 1995 - 2005
Centre for Clinical Research Excellence in Infectious Diseases Colloquium, Royal Melbourne Hospital, November 2007
- The Victorian Hepatitis B Serosurvey 1995 - 2005

Australasian Society for HIV Medicine “Short Course in Viral Hepatitis Medicine”
Sydney, NSW, July 2007
- Epidemiology, natural history & public health issues in HBV infection
- Diagnosis and management of HBV infection in primary care

Australasian Society for HIV Medicine “Update on HIV, hepatitis B and C and sexually transmitted infections” Albury, NSW, March 2007
- HBV: natural history, clinical features, diagnosis, management and PEP

Australasian Society for HIV Medicine “Short Course in Viral Hepatitis Medicine”
Melbourne, October 2006
- Epidemiology, natural history & public health issues in HBV infection

Department of Medicine Meeting (RMH/WH), Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, May 2006
- The seroprevalence, molecular characterisation, and mathematical modelling of hepatitis B virus infection in Victoria (Confirmation of Candidature)
Appendix 8  Participation in committees related to PhD research

Australian Government Ministerial Advisory Committee on Blood Borne Viruses and Sexually Transmissible Infections, National Strategies 2009-2013
http://www.ashm.org.au/nationalstrategies

Member, Viral Hepatitis Expert Writing Reference Group

Viral Hepatitis and Sexual Health Forum, Department of Human Services Victoria –

Member, Viral Hepatitis Taskforce
Chair, Hepatitis B Working Group

Australian Academy of Science and Royal Society United Kingdom ‘Theo Murphy High Flyers Think Tank 2008 – Preventive Health: Science and technology in the prevention and early detection of disease”. Sydney, NSW, November 2008 -

Invited participant


Member, Clinical Reference Panel


Member, Board of Directors
Member, Education and Resources Advisory Committee
Member, Hepatitis B Reference Committee

SH³ED (Sexual Health, HIV and Viral Hepatitis Education) Program,

Member, Expert Reference Group
Member, Clinical Advisory Group
Appendix 9  Awards related to PhD research

ASHM Junior Researcher Support Award in Viral Hepatitis, 2008

Awarded Lifetime Membership of the John Snow Society, London School of Hygiene and Tropical Medicine, Introduction to Infectious Disease Modelling & Its Applications, London, United Kingdom, July 2006
http://www.johnsnowsociety.org/
(Presented to the group constructing the best mathematical model of pandemic influenza)
Appendix 10  Human Research Ethics Committee approval

Melbourne Health Human Research Ethics Committee
Meeting date: 15 June 2005
Approved: 15 June 2005
Project Status: Completed  December 2007
Research Directorate - Human Ethics Committee Approval Form

Telephone: 9342 8530 Facsimile: 9342 8548

This is to certify that

HREC Project No: 2005.096 Approval date: 15/06/2005 Expiry date: 15/06/2008

Project Title: Victorian hepatitis B serosurvey 1995-2005

Principal Investigator: Dr. Benjamin Cowie
Victorian Infectious Diseases Reference Laboratory
Locked Bag 815
CARLTON SOUTH VIC 3053

Sponsored by:

Protocol No:

Participant Information and Consent Form:

Investigator Brochure:

Other enclosures (please describe e.g. advertisement etc.):

Conducted at: Royal Melbourne Hospital has been approved

It is now your responsibility to ensure that all people conducting this research project are made aware of which documents have been approved.

This approval is subject to ongoing, current and valid insurance coverage throughout the duration of the conduct of the study.

You are required to notify the Secretary of the Human Research Ethics Committee of:

- Any change in the protocol and the reason for that change together with an indication of ethical implications (if any) by submitting an amendment to the study.
- Serious adverse effects on subjects and the action taken to manage them, including amended Plain Language Statement and Consent Form where appropriate.
- Any unforeseen events.
- Your inability to continue as Principal Investigator, or any other change in research personnel involved in the study
- A delay of more than 12 months in the commencement of the project.
- The actual date of commencement of the study.

You are required to submit to the Human Research Ethics Committee:

- An Annual Report every twelve months for the duration of the project.
- A detailed Final Report at the conclusion of the project.

The Human Research Ethics Committee may conduct an audit at any time.

An extension of the project beyond the stated conclusion date should be sought from the Human Research Ethics Committee.

Signed: [Signature]
Dr. Angela Watt
Secretary – Human Research Ethics Committee

Incorporating: The Royal Melbourne Hospital (City Campus and Royal Park Campus), North Western Mental Health, North West Dialysis Service, Victorian Infectious Diseases Reference Laboratory, NW Shared Support Service
RESEARCH DIRECTORATE

17 June 2005

Dr. B. Cowie
Victorian Infectious Diseases
Reference Laboratory
Locked Bag 815
CARLTON SOUTH VIC 3053

Dear Dr. Cowie


The above study was approved (Approval Certificate enclosed) with the following comments:

1. The committee discussed the ethical dilemma presented by the issue of not contacting people whose serum samples tested positive for HBV infection to provide such information to individuals that could potentially affect their health significantly. After much discussion, the committee agreed with your suggested option of proceeding with permanent de-identification of the data following collection to best ensure confidentiality for all study subjects. In this way, the research can proceed without the requirement for written informed consent.

Yours sincerely

[Signature]

Dr. Angela Watt
Manager – Human Research Ethics Committee

Interpreting: The Royal Melbourne Hospital, Melbourne Extended Care & Rehabilitation Service, North Western Mental Health, North West District Service, Victorian Infectious Disease Reference Laboratory, NIMR Shared Support Service
Author/s:
Cowie, Benjamin Campbell

Title:
Novel approaches to an improved understanding of the epidemiology and control of hepatitis B virus infection in Australia

Date:
2009

Citation:
Cowie, B. C. (2009). Novel approaches to an improved understanding of the epidemiology and control of hepatitis B virus infection in Australia. PhD thesis, Faculty of Medicine, Dentistry & Health Sciences, Medicine - Royal Melbourne and Western Hospitals, The University of Melbourne.

Publication Status:
Published

Persistent Link:
http://hdl.handle.net/11343/35269

File Description:
Novel approaches to an improved understanding of the epidemiology and control of hepatitis B virus infection in Australia

Terms and Conditions:
Terms and Conditions: Copyright in works deposited in Minerva Access is retained by the copyright owner. The work may not be altered without permission from the copyright owner. Readers may only download, print and save electronic copies of whole works for their own personal non-commercial use. Any use that exceeds these limits requires permission from the copyright owner. Attribution is essential when quoting or paraphrasing from these works.