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**.

First author, year, and reference	Model type	FoI	Population +/- type	Notes
Wong 1995 (143)	Stochastic (Markov model)	None (all infected at baseline)	Patients with chronic HBV	Meta-analysis of clinical trials of interferon α-2b and treatment cost effectiveness analysis using a Markov model.
Edmunds 1996 (140)	Deterministic	Dynamic	High prevalence	Models vertical, horizontal and sexual transmission.
Williams 1996 (120)	Deterministic	Dynamic	Low prevalence	Models vertical and sexual transmission across a variety of sexual activity strata. Transmission due to IDU and impact of migration/ethnicity not assessed.
Fendrick 1999 (123)	Stochastic (Markov model)	Static	Low prevalence	Vaccine cost effectiveness analysis. A very high FoI is assumed in this and a related study (see **5.4.4**).
Zhao 2000 (232)	Deterministic	Dynamic	High prevalence	Informed by very large epidemiological datasets from China.
Harris 2001 (53)	Stochastic (Markov model)	Static	Low prevalence	Vaccine cost effectiveness analysis for Australia (see **5.2.2**) predominantly adapted from (123), including the high FoI (see **5.4.4**)
Medley 2001 (113)	Deterministic	Dynamic	Theoretical populations – low and high prevalence	Theoretical model exploring catastrophic dynamics of HBV transmission based on population seroprevalence and perturbations thereof.
Kretzschmar 2002 (122)	Deterministic	Dynamic	Low prevalence	Extension of (120) modelling vertical and sexual transmission but also incorporating the effect of

				migration from higher prevalence areas. Transmission due to IDU not assessed.
Goldstein 2005 (114)	Deterministic	Static	Global population	Model analysing the burden of chronic HBV and resultant mortality worldwide, and impact of vaccination.
Kanwal 2005 (142)	Stochastic (Markov model)	None (all infected at baseline)	Patients with chronic HBV	Cost effectiveness analysis for treatment alternatives for chronic HBV with abnormal ALT. No FoI as all infected at baseline.
Sutton 2006 (233)	Deterministic	Dynamic	High incidence sub-population	Model assessing the impact of prison-based vaccination on HBV transmission amongst IDUs in England and Wales.
Hutton 2007 (133)	Stochastic (Markov model)	Static	High prevalence sub-population	Cost effectiveness analysis of HBV screening and vaccination of Asians and Pacific Islanders in the USA.
Hu 2008 (234)	Stochastic (Markov model)	Static	High incidence sub-population	Cost effectiveness analysis of HBV screening and vaccination of IDUs.

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,

$FoI = k$ - 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,

$FoI = k'I$ - 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.

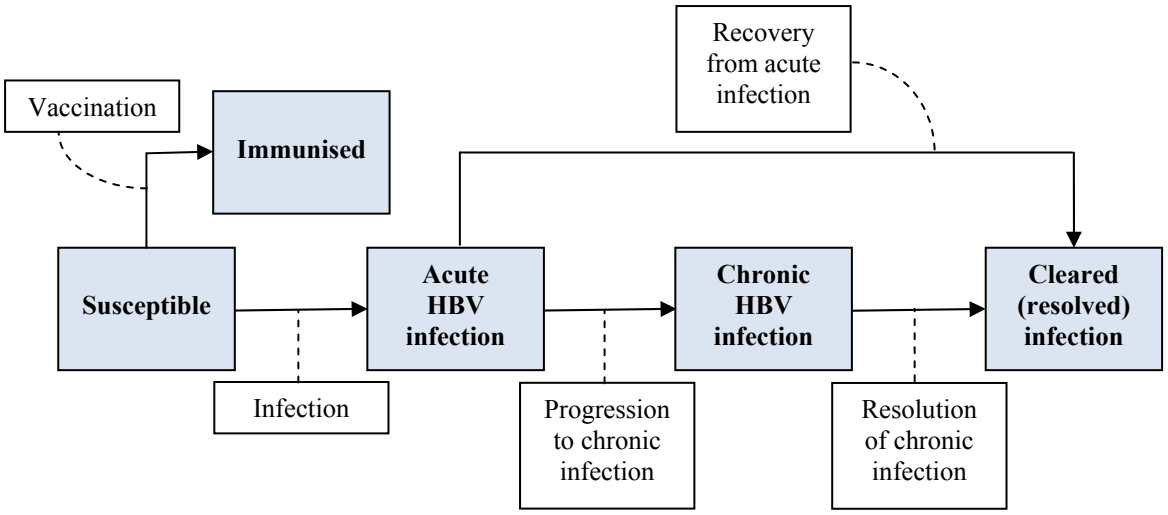

Figure 5.1 – Schematic representation of modelled transition between HBV infection states. Blue boxes represent these states, and arrows represent the flow of individuals defined by the natural history of HBV infection, with the white boxes defining the respective transitions.

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 purposed 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.

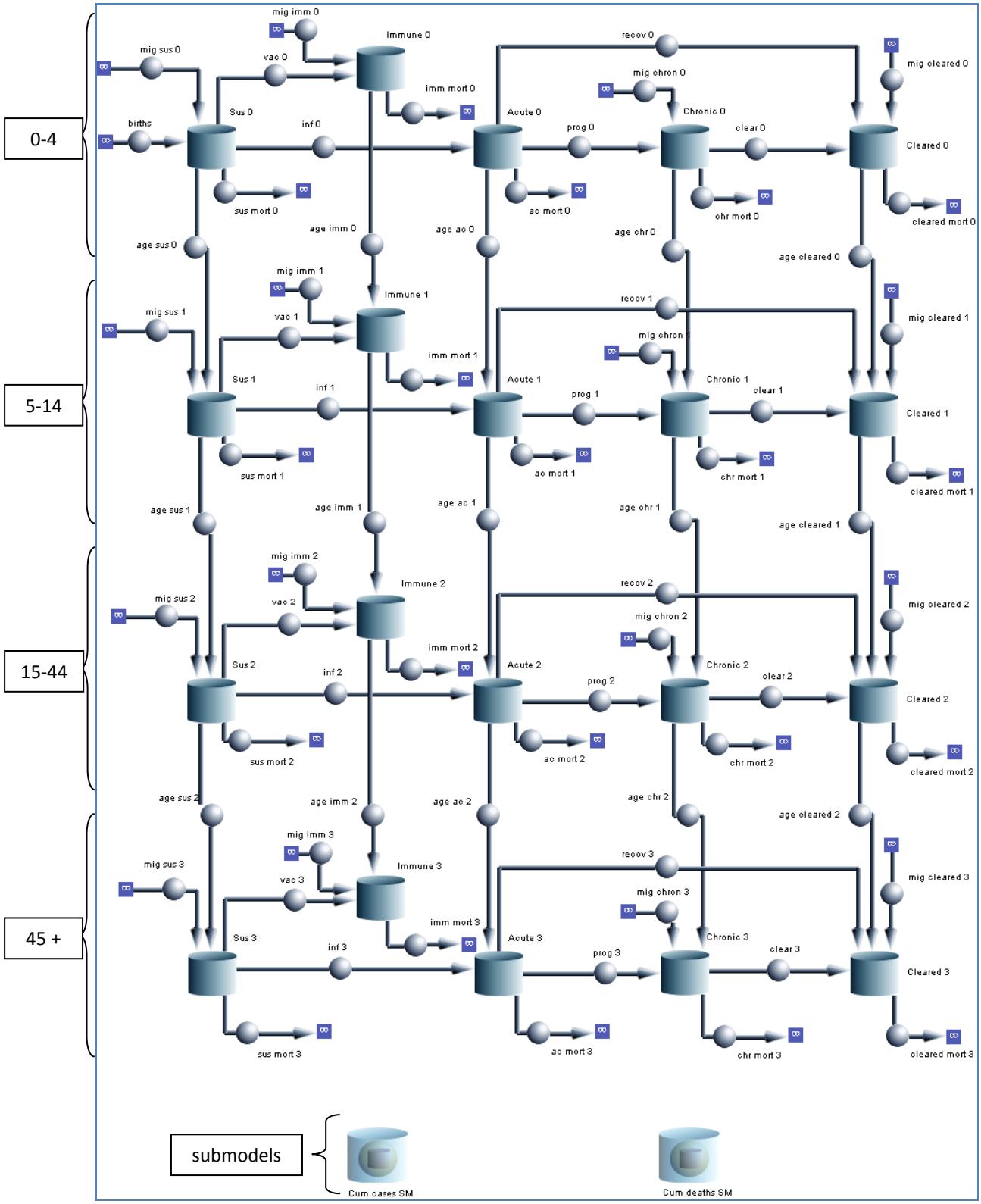

Figure 5.2 – Simplified flowchart of the structure of the mathematical model of HBV infection constructed. Flow across rows represents transition between infection states; downward flow between rows represents ageing between the four age groups (0-4, 5-14, 15-44 and 45+). The sub-models allowing assessment 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 [∞]).

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

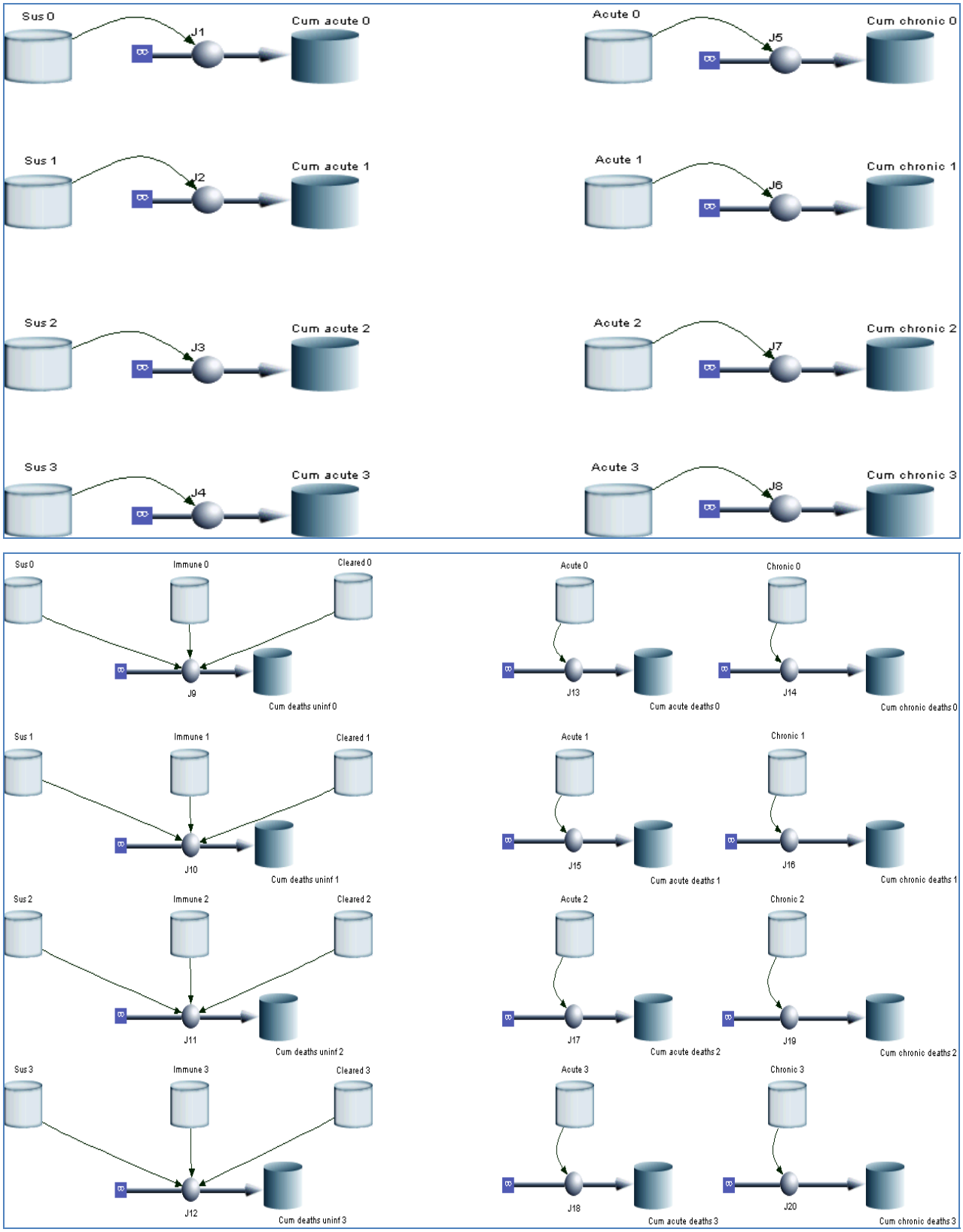

Figure 5.3 – Sub-models for assessment of (a) cumulative cases and (b) cumulative deaths. The lighter-coloured reservoirs are 'aliases' of reservoirs in the primary model. This flowchart image is an output from Berkeley Madonna.

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).

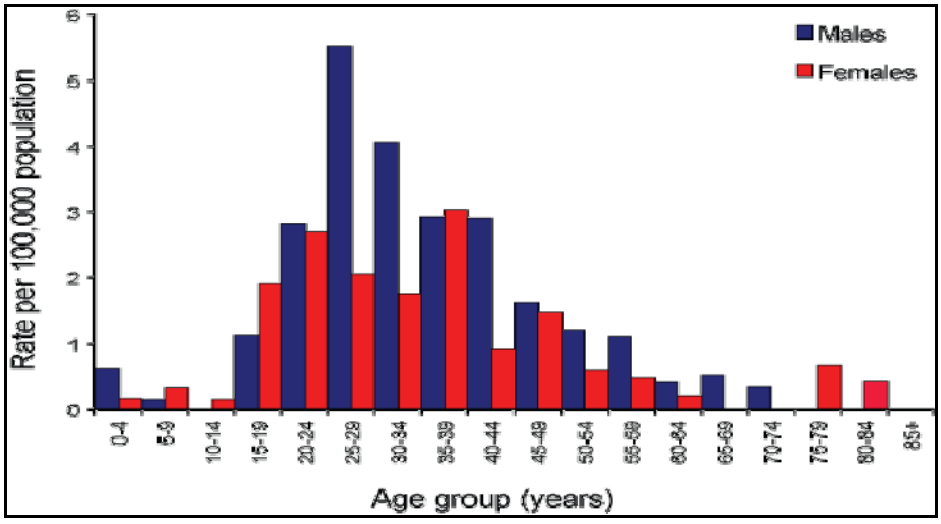

Figure 5.4 – Notification rate for incident HBV infections in Australia by age group and gender, 2006. Taken from (40).

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.

Variable	Years	Sources	Notes
Births	1951 – 2004	ABS 3105.0.65.001 Table 36: Births registered by sex, 1824 onwards	
	2005 – 2050	ABS 3222.0 Table 1. Projected population, Components of change and summary statistics—Australia Series B	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.
Background mortality rates	1951 – 2004	ABS 3105.0.65.001 Table 43. Deaths 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 & 56. Probability of dying between exact age x and exact age x+1, females & males (qx), 1881 onwards ABS 3302.0 Table 1.9 Deaths, Summary, 1996-2006	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

	2005 – 2050	As above, plus ABS 3222.0 Table 1. Projected population, Components of change and summary statistics—Australia Series B	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**.
Total migration (Net Overseas Migration)	1951 – 1974	Immigration: Federation to Century's End, DIMA 2001	HBV status and age distribution of migrants derived according to methods described in **5.4.3.2**.
	1975 – 2004	ABS 3412.0	
	2005 - 2050	ABS 3222.0 Table 1. Projected population, Components of change and summary statistics—Australia	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.
Total population and age distribution	1951 – 2004	ABS 3105.0.65.001 Table 19. Population, age and sex, Australia, 1901 onwards	Total population and age group proportions for 1951 used for initial model conditions. Subsequent years used to validate model and calculate annual deaths
	2005 – 2050	ABS 3222.0 Table B9. Population projections, By age and sex, Australia - Series B	Used to validate model outputs

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 μ_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 (r^2). 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.

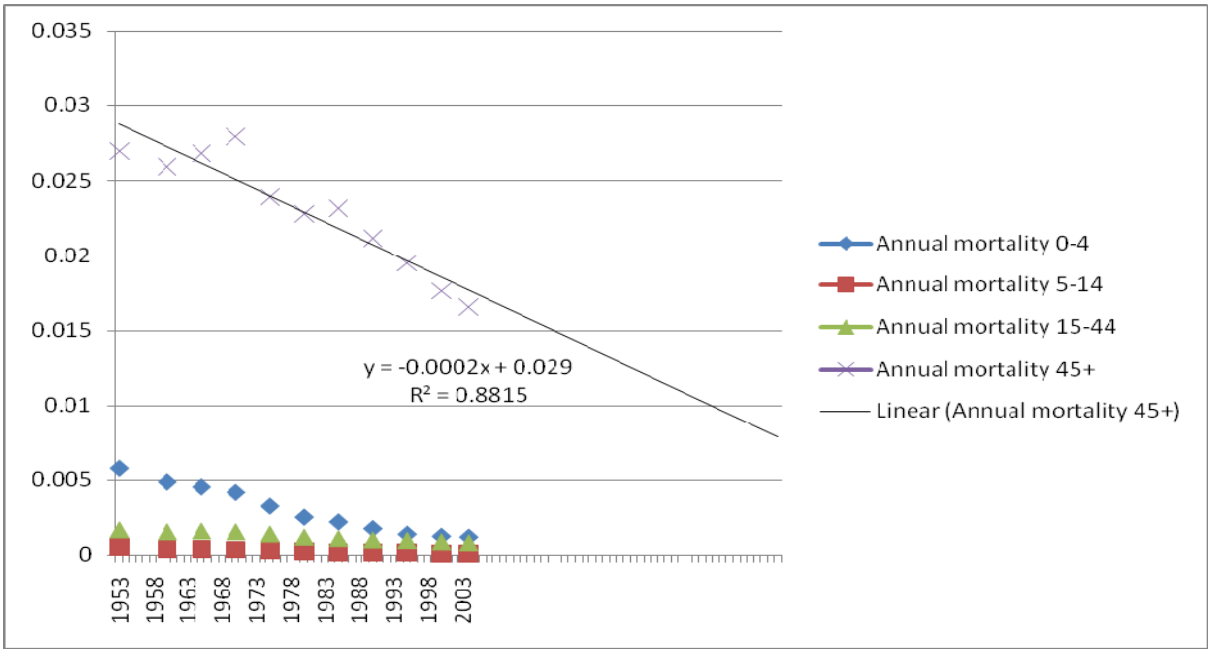

Figure 5.5 – Annual mortality rate by age group, Australia, 1951 to 2004; plus linear trend of mortality rate in 45+ age group with forward projection.

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.

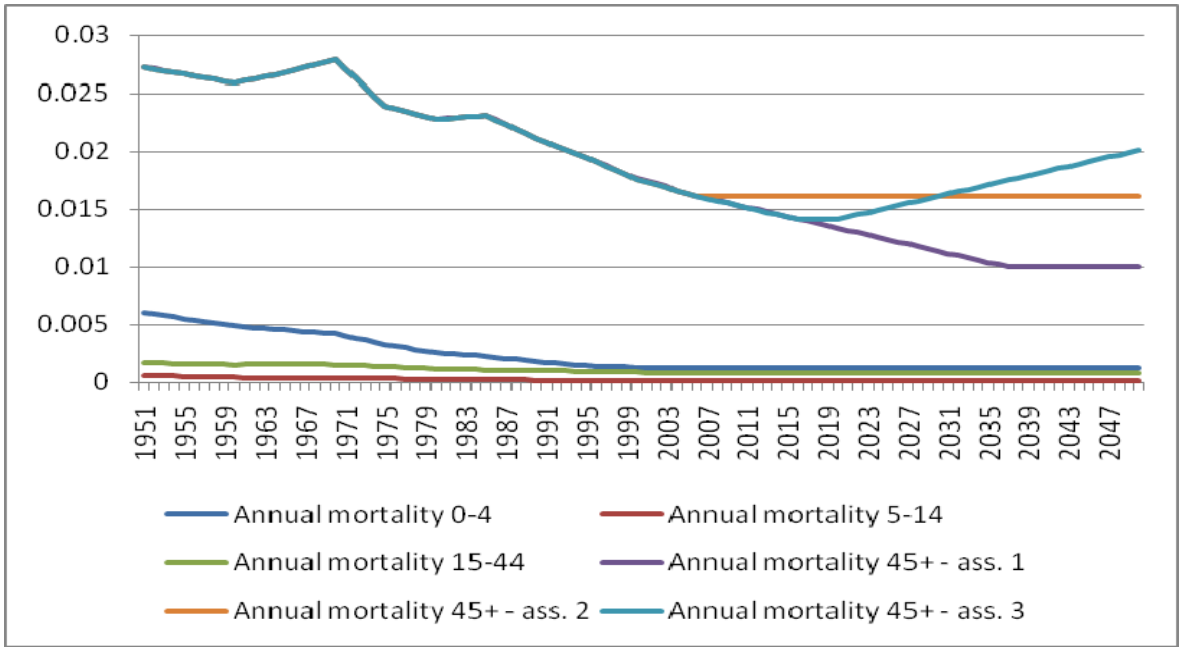

Figure 5.6 – Annual mortality rate by age group, Australia, 1951 to 2004 plus projections to 2050. Different mortality assumptions for the 45+ age group are shown; refer to text for details.

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.

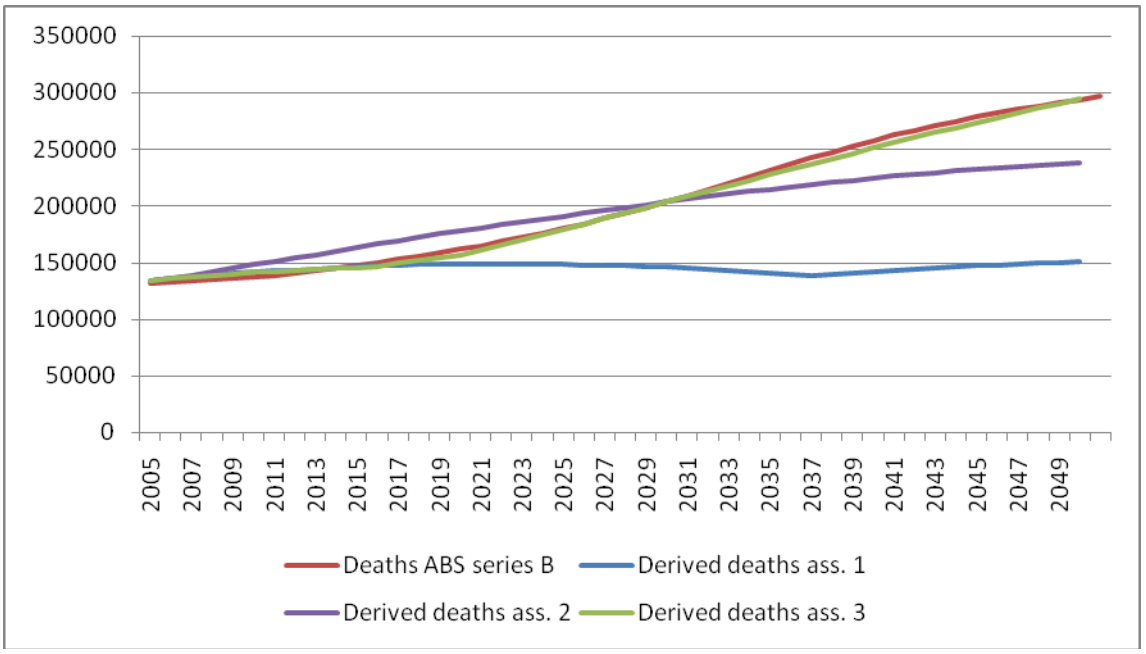

Figure 5.7 – Projected annual deaths, Australia, 2005 - 2050 under different 45+ age group mortality assumptions (see text) compared with ABS series B projections.

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.

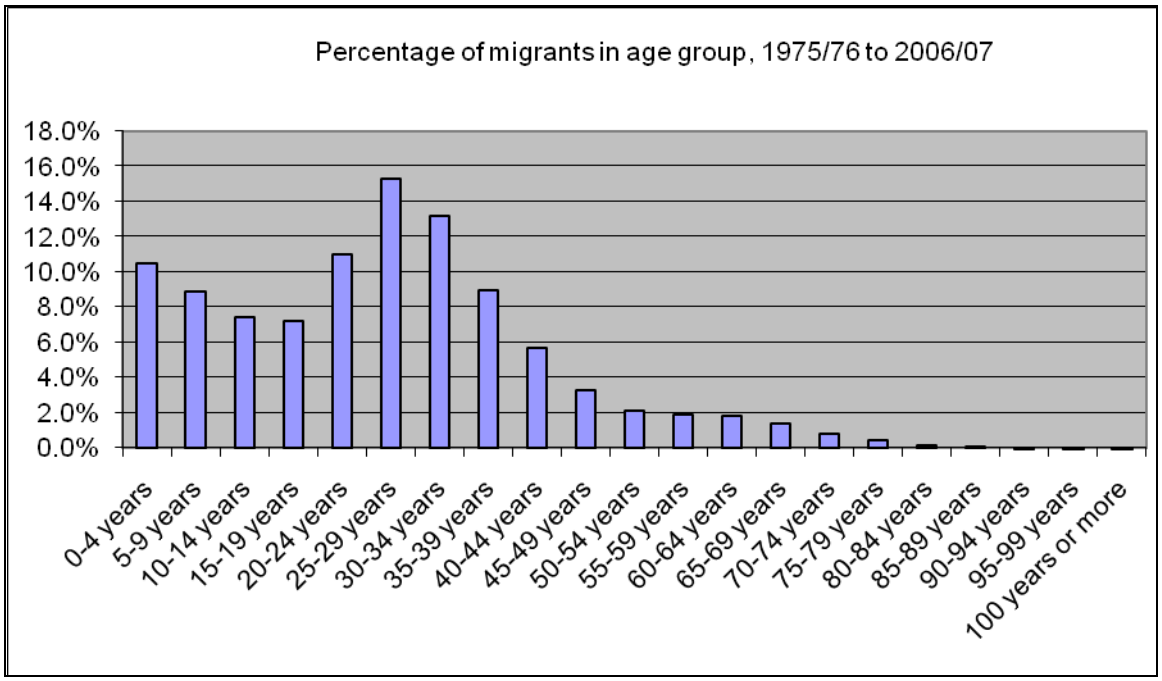

Figure 5.8 – Age distribution of all migrants to Victoria, 1975 – 2006.

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).

	Susceptible	**Infected**	**Resolved**
Low	94.5%	0.5%	5%
Intermediate	60%	5%	35%
High	20%	10%	70%

Table 5.3 – Estimated HBV infection status of migrants by source country HBsAg prevalence.

	1945 - 2005	1945 – 1985	1985 - 2005
Low prevalence	*49.9*	57.2	34.5
Intermediate prevalence	*26.4*	28.2	22.7
High prevalence	*18.1*	8.1	39.3
Unknown	*5.5*	6.5	3.6
Estimated HBsAg positive migrants	*3.5*	*2.7*	*5.4*

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.

	Group	**Summary point estimate**	**Individual point estimates**
Force of Infection (FoI) (infections/million/year)	0-4 years	6	2 (38, 44) 3 (237-239) 25 (131) 700 (53, 123)
	5-14 years	6	2 (38, 44) 3 (237-239) 25 (131) 700 (53, 123)
	15-44 years	80	30 (38, 44) 40 (237-239) 48 (133) 150 (131) 400 (234) 1800 (53, 123)

	45 plus years	20	10 (38, 44) 10 (237-239) 25 (131) 48 (133) 400 (234) 500 (53, 123)
Duration of acute infection (weeks)	All patients	13	13 (113, 140, 232, 233) 15 (120)
Acute infection mortality (proportion)	0-4 years	0.001	Derived from combined probabilities of fulminant infection and death in fulminant infection from: (53, 114, 123, 133, 234)
	5-14 years	0.0014	
	15-44 years	0.0035	
	45 plus years	0.0035	
Progression to chronicity (proportion)	Neonate	0.5	0.85 (232) 0.88 (123) 0.885 (96, 120, 122) 0.9 (53, 114, 133)
	0-4 years		0.07 – 0.9 (53) 0.08 – 0.9 (123) 0.1 – 0.85 (232) 0.3 (114) 0.35 (96)
	5-14 years	0.2	0.06 (114) 0.06 – 0.8 (123) 0.07 – 0.9 (53) 0.1 (232) 0.16 (122) 0.2 (96)
	15-44 years	0.06	0.05 (122, 233, 234) 0.06 (114) 0.06 – 0.1 (53) 0.06 – 0.08 (123) 0.075 (96) 0.1 (120, 232)
	45 plus years	0.04	0.03 (122) 0.04 (53, 123) 0.05 (96, 233, 234) 0.06 (114, 133) 0.1 (120, 232)
Chronic infection mortality (proportion dying /year)	0-4 years	0	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)
	5-14 years	0.0003	
	15-44 years	0.002	
	45 plus years	0.006	
Resolution of chronic infection	0-4 years	0	0 (114) 0.01 (143, 232)

(proportion clearing /year)			0.015 (120) 0.018 (123) 0.02 (53) 0.025 (113, 140, 233)
	5-14 years	0.005	0 (114) 0.01 (143, 232) 0.015 (120) 0.018 (123) 0.02 (53) 0.025 (113, 140, 233)
	15-44 years	0.01	0.005 (114) 0.01 (143, 232) 0.015 (120) 0.018 (123) 0.02 (53) 0.025 (113, 140, 233) 0.1 (234)
	45 plus years	0.025	0.005 (114) 0.01 (143) 0.015 (120) 0.018 (123) 0.02 (53) 0.025 (113, 140, 233) 0.05 (232) 0.1 (234)
Efficacy of vaccination (proportion)	0-4 years	0.95	(95)
	5-14 years	0.95	
	15-44 years	0.90	
	45 plus years	0.75	

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).

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" 3x base = "intermediate FoI" 5x base = "high FoI"
	5 - 14 years	6	
	15 - 44 years	80	
	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:

*Sus_0*vacc_eff_0*vacc_prop_0*vacc_prog_0*vacc_avail*

With:

Sus_0 representing all susceptible children in the age group at a given time
vacc_eff_0 being the efficacy of vaccine in the age group (95% for these children)
vacc_prop_0 being the proportion of susceptibles vaccinated
vacc_prog_0 being an indicator variable to instruct the model in what year to commence the NIP, coded for this age group as:

vacc_prog_0 = IF(TIME>=2000) THEN 1 ELSE 0

Similarly, *vacc_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 *vacc_avail* term is coded as:

*vacc_avail = (IF(TIME>=1985) THEN 1 ELSE 0)*vacc_tog*
vacc_tog = 1

The *vacc_tog* variable was included to allow comparison of outcomes with and without vaccination in a single run using batch runs with *vacc_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

(118). 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

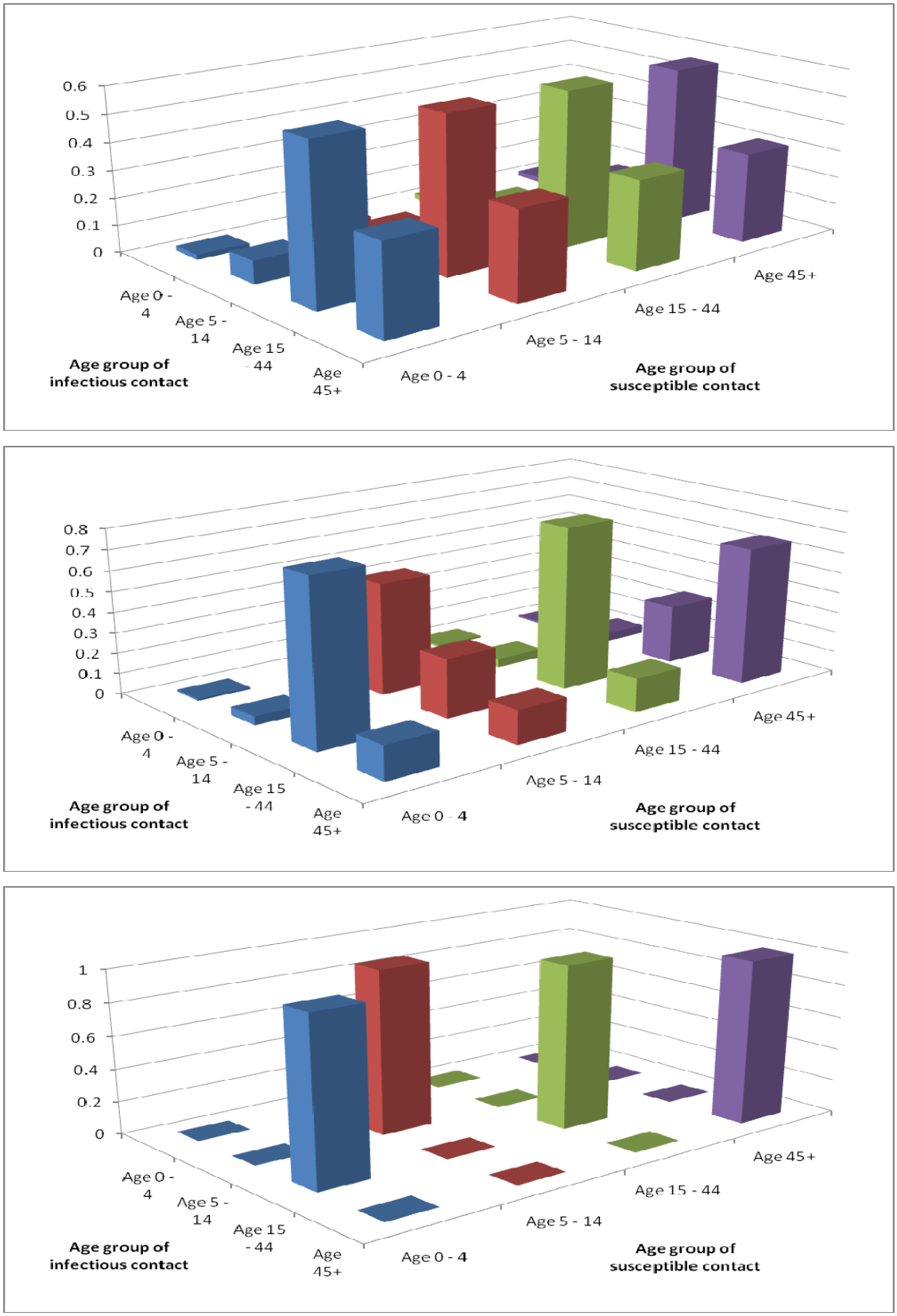

Figure 5.9 – Proportion of total FoI acting on susceptible contacts by age group of infectious contact under different WAIFW structures; (a) WAIFW 1 assuming homogeneous mixing, (b) WAIFW 2 with increased within-age group mixing and (c) WAIFW 3 with completely heterogeneous mixing based on age group 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

Age 0 – 4		*Age 5 – 14*		*Age 15 – 44*		*Age 45+*	
Acute	*Chronic*	*Acute*	*Chronic*	*Acute*	*Chronic*	*Acute*	*Chronic*
1.82	*2460*	*3.85*	*11404*	*143.69*	*76679*	*35.58*	*43880*

Assuming infectiousness of chronically infected individual is 0.16 that of acutely infected
Composite infectious units per age group in year 2000 =

Age 0 – 4: *1.82 + (0.16*2460) = 395.42*
Age 5 – 14: *3.85 + (0.16*11404) = 1828.34*
Age 15 – 44: *143.69 + (0.16*76679) = 12413.26*
Age 45+: *35.58 + (0.16*43880) = 7056.38*

For base WAIFW risk is proportional to age distribution of infectious units (homogeneous mixing) therefore relative contribution is:

Age 0 – 4: 395.42 / 21693.4 = 0.018228
Age 5 – 14: 1828.34 / 21693.4 = 0.084281
Age 15 – 44: 12413.26 / 21693.4 = 0.572214
Age 45+: 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.

WAIFW 1	From 0 - 4	From 5 - 14	From 15 - 44	From 45+
On 0 – 4	2.7797E-10	2.7796E-10	2.7796E-10	2.7796E-10
On 5 -14	2.7797E-10	2.7796E-10	2.7796E-10	2.7796E-10
On 15 – 44	3.7062E-09	3.7061E-09	3.7061E-09	3.7061E-09
On 45+	9.2655E-10	9.2653E-10	9.2653E-10	9.2653E-10

WAIFW 2	From 0 - 4	From 5 - 14	From 15 - 44	From 45+
On 0 – 4	1.3827E-10	1.3840E-10	3.8084E-10	1.38695E-10
On 5 -14	1.3827E-10	1.7805E-09	1.3861E-10	1.38695E-10
On 15 – 44	1.8436E-09	1.8454E-09	5.0778E-09	1.84927E-09
On 45+	4.6090E-10	4.6134E-10	4.6202E-10	1.88362E-09

WAIFW 3	From 0 - 4	From 5 - 14	From 15 - 44	From 45+
On 0 – 4	0	0	4.8444E-10	0
On 5 -14	0	3.2843E-09	0	0
On 15 – 44	0	0	6.4592E-09	0
On 45+	0	0	0	2.8426E-09

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**.

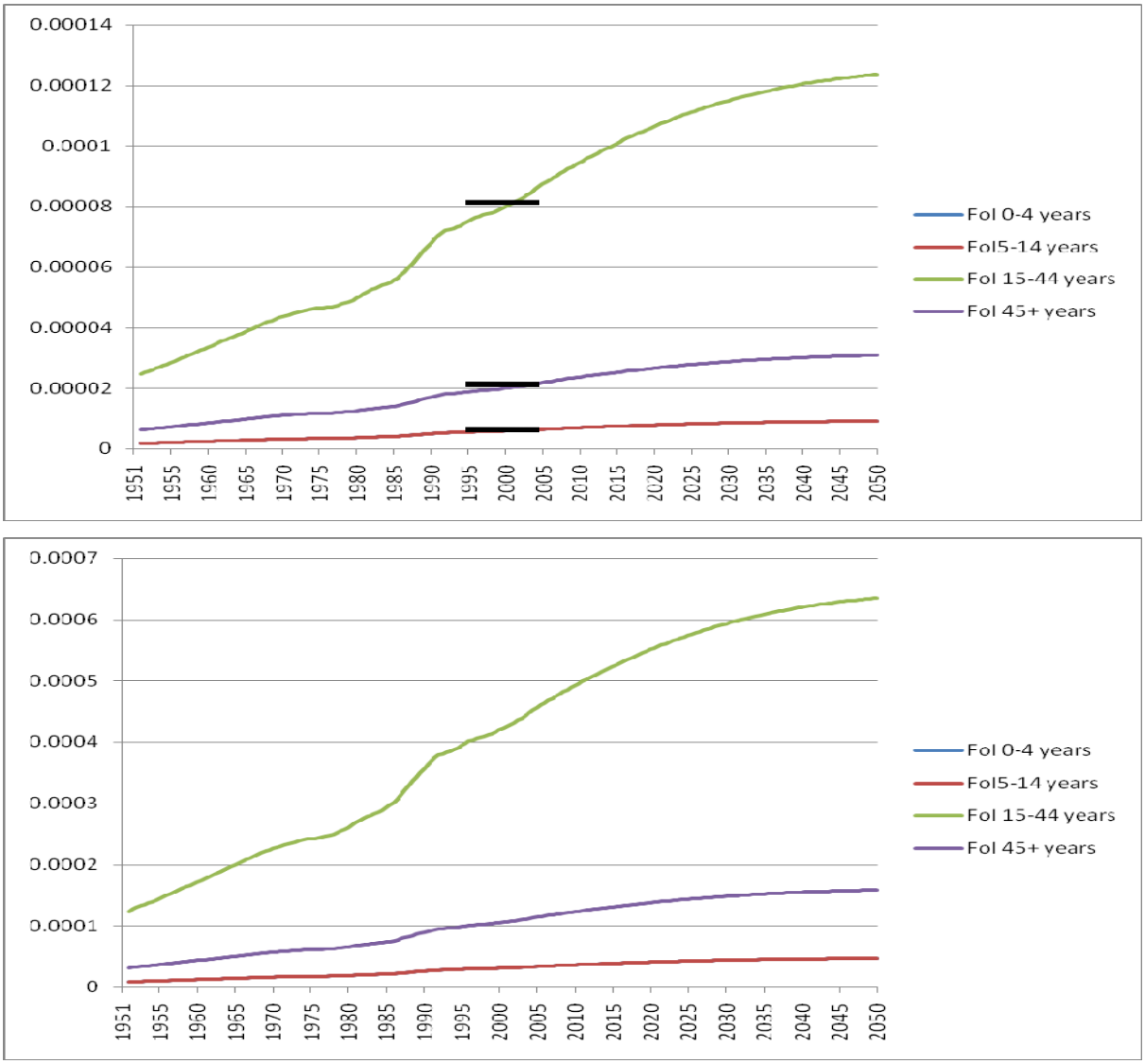

Figure 5.10 – Dynamic (a) base FoI and (b) high FoI acting on each age group over time. Assumes base migration and no immunisation. FoI estimates over time are similar for the two youngest age groups and therefore overlap on these charts.

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.

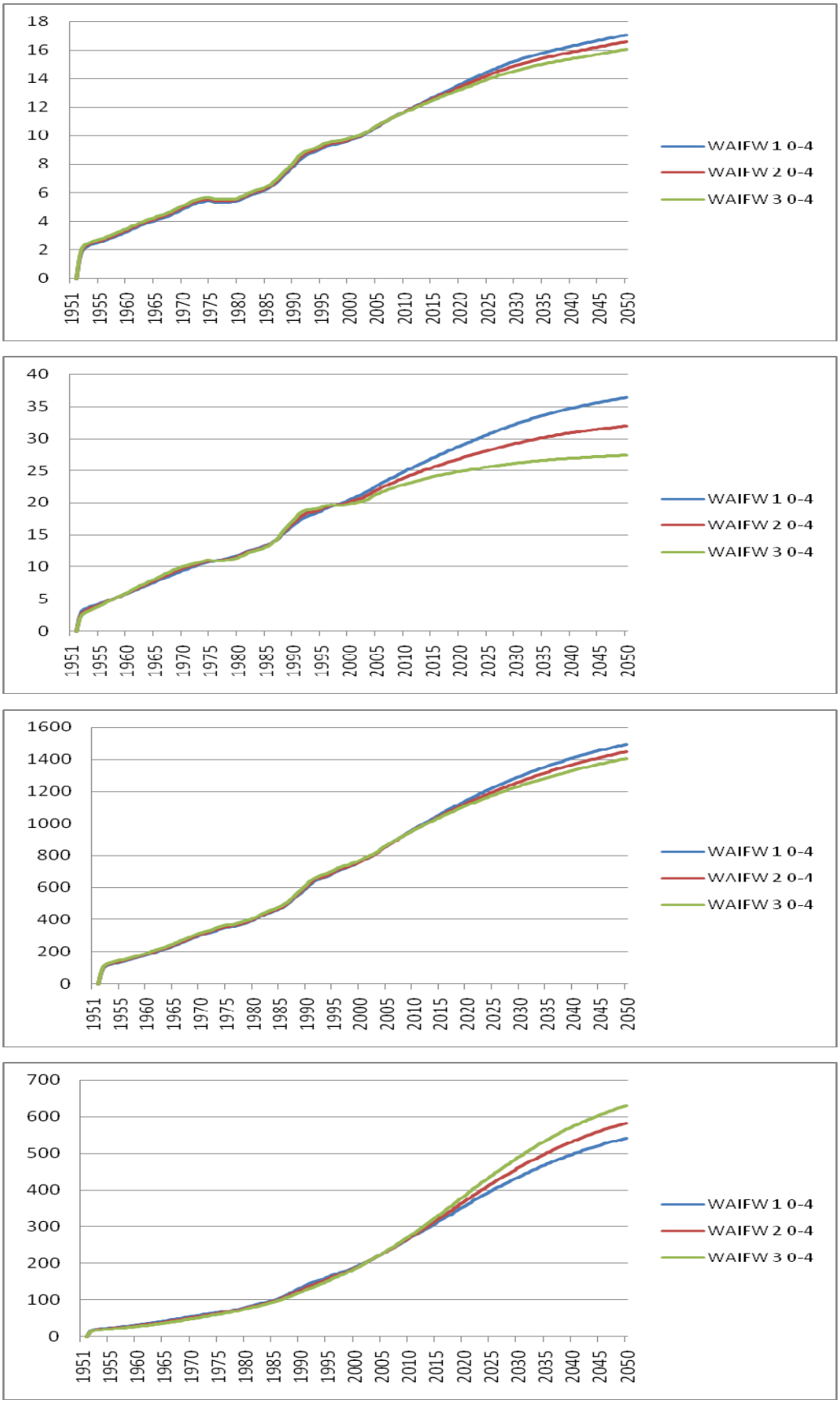

Figure 5.11 – Number of people with acute HBV Infection by WAIFW matrix used in high dynamic FoI model over time for people aged (a) 0-4 years (b) 5-14 years (c) 15-44 years and (d) over 45 years.

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.

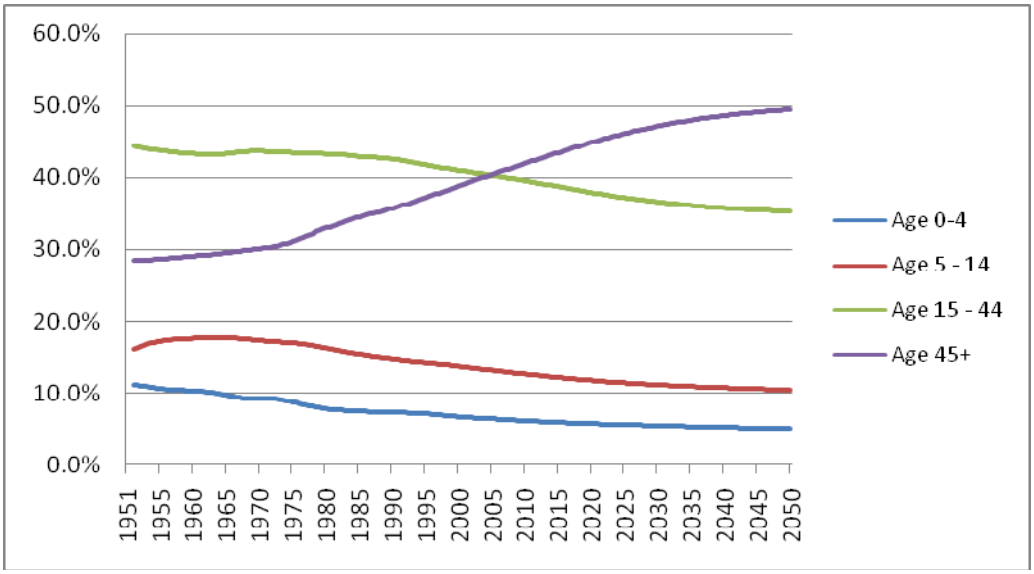

Figure 5.12 – Age distribution of the Australian population in the model (base migration assumption), 1951 - 2050.

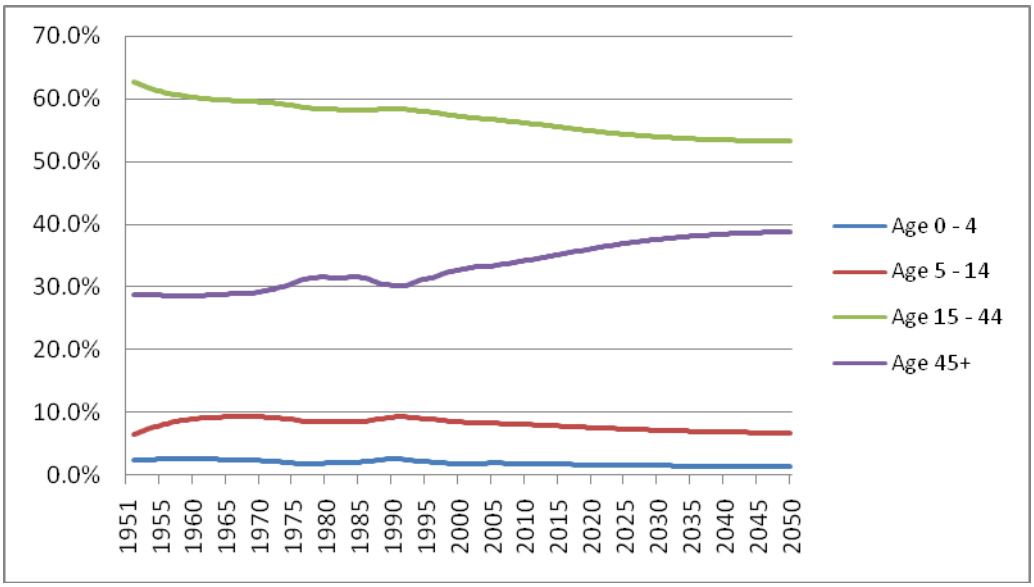

Figure 5.13 – Age distribution of people with chronic HBV infection in the high static FoI model (base migration), 1951 – 2050.

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.

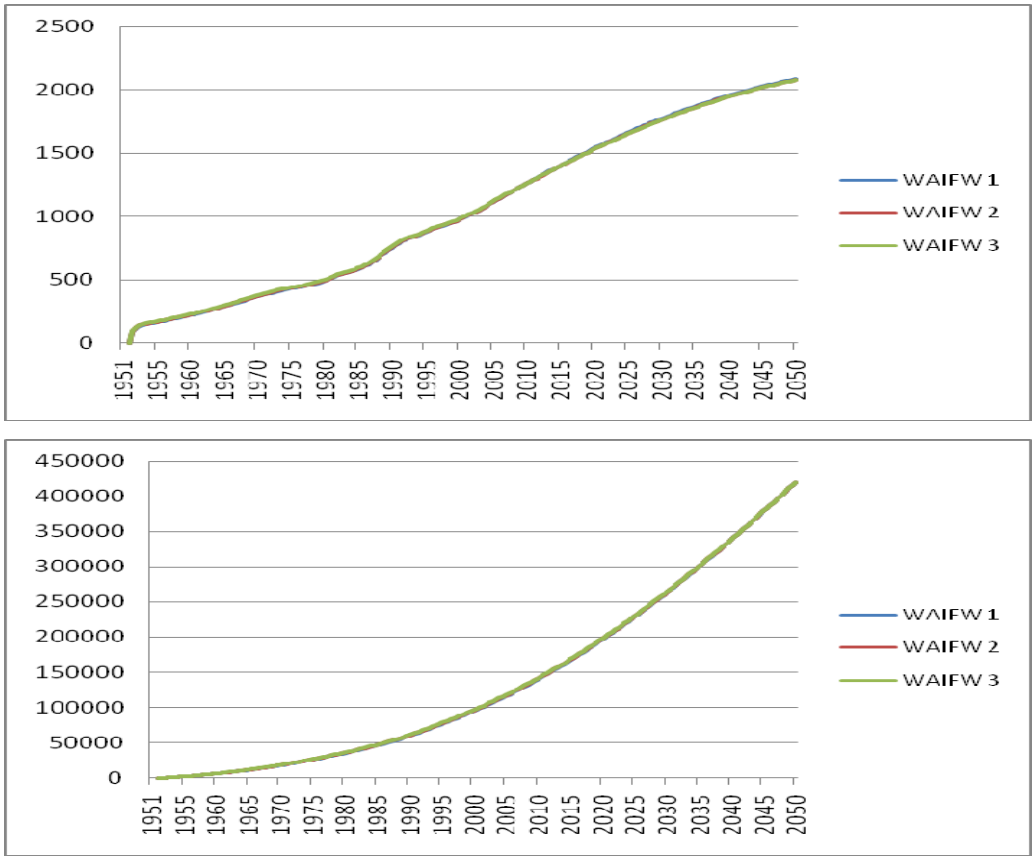

Figure 5.14 – (a) Number of people with acute HBV infection and (b) cumulative acute HBV infections by WAIFW over time in high dynamic FoI model, base migration, no immunisation.

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.

	HBV infection status		
	Susceptible	**Chronic infection**	**Cleared infection**
0-4 years	**99.8%**	**0.1%**	**0.1%**
5-14 years	**99.4%**	**0.2%**	**0.4%**
15-44 years	**94%**	**0.7%**	**5.3%**
45+ years	**94%**	**0.5%**	**5.5%**
All ages	**95.5%**	**0.5%**	**4.0%**

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.

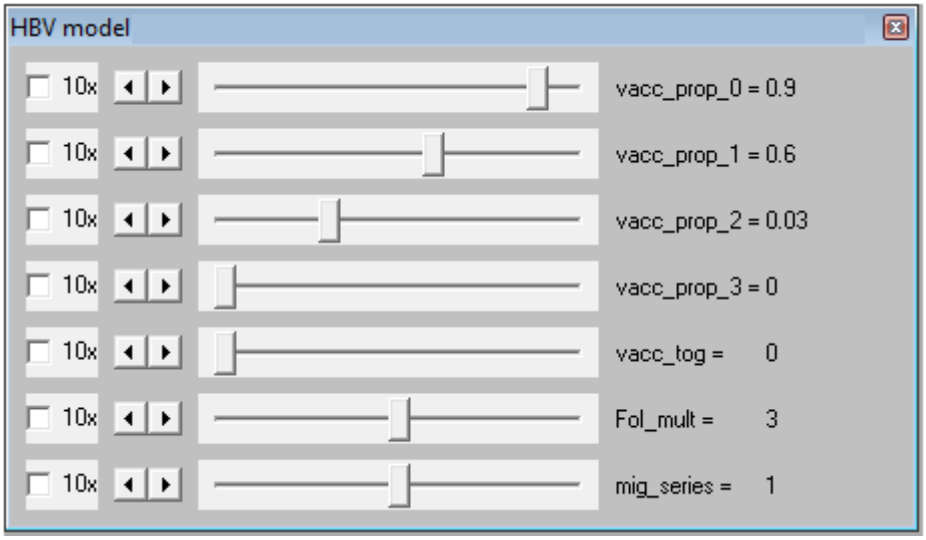

Figure 5.15 – Slider window for the HBV model showing sliders to control (from top down): proportion of susceptible members of different age groups vaccinated annually, a 'vaccine toggle' with binary values of 0 or 1, and two sliders to allow sensitivity analysis by multiplying the FoI and migration projection assumptions within the range described in **5.4.4**.

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).

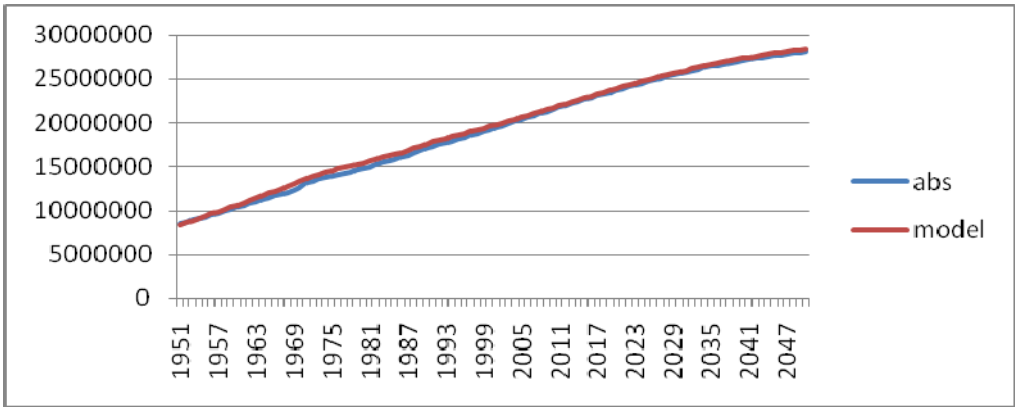

Figure 5.16 – Comparison between the modelled population of Australia and ABS records and projections, 1951 – 2050.

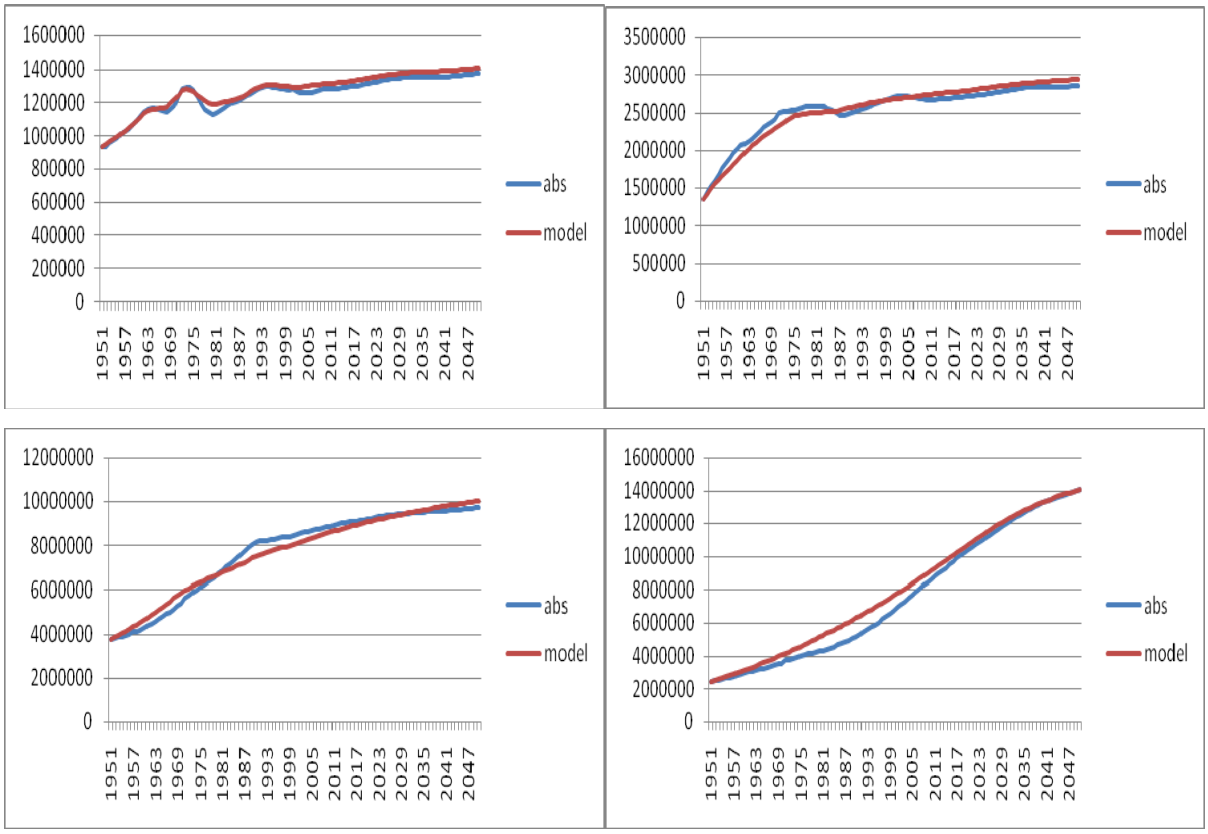

Figure 5.17 – Comparison between the modelled population of Australia and ABS records and projections for 1951 – 2050 for people aged (a) 0-4 (b) 5-14 (c) 15-44 and (d) 45 plus.

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.

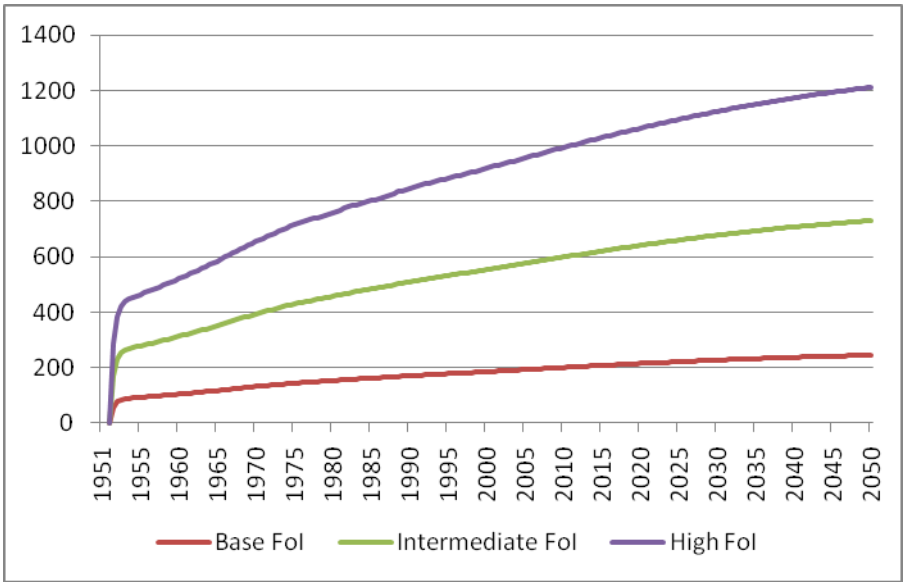

Figure 6.1 – Number of people with acute HBV infection by FoI over time.
Static FoI model, base migration assumption.

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.

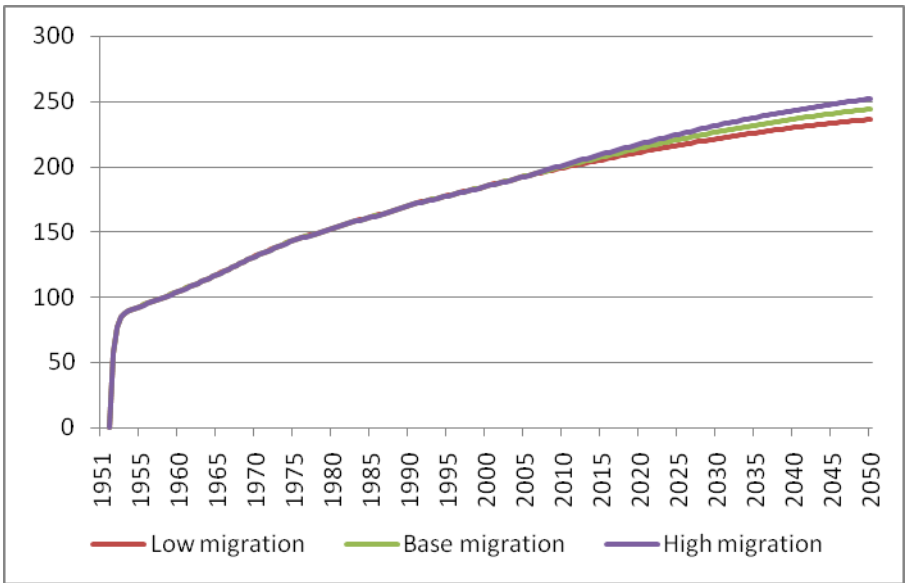

Figure 6.2 – Number of people with acute HBV infection by migration over time.
Static FoI, base FoI assumption.

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.

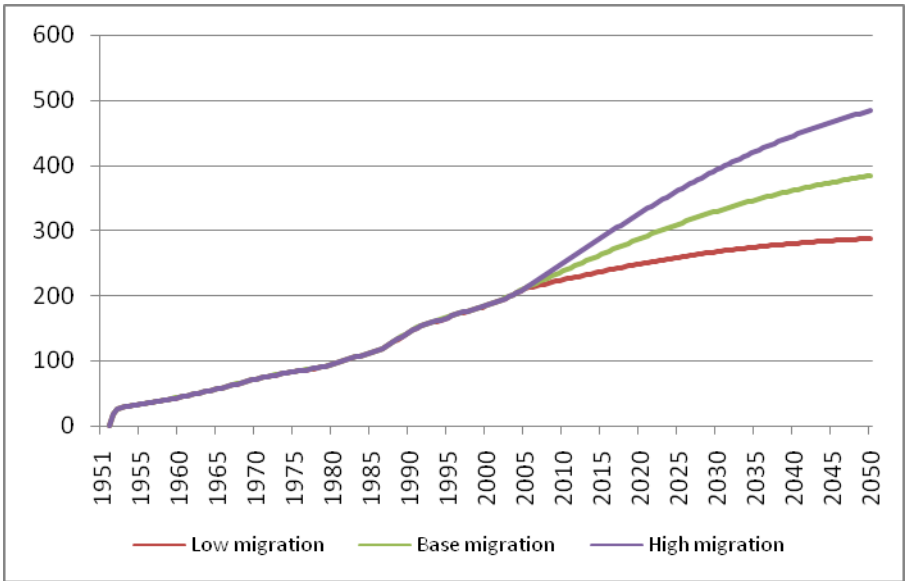

Figure 6.3 – Number of people with acute HBV infection by migration assumption over time. Dynamic FoI model (WAIFW 1), base FoI assumption.

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.

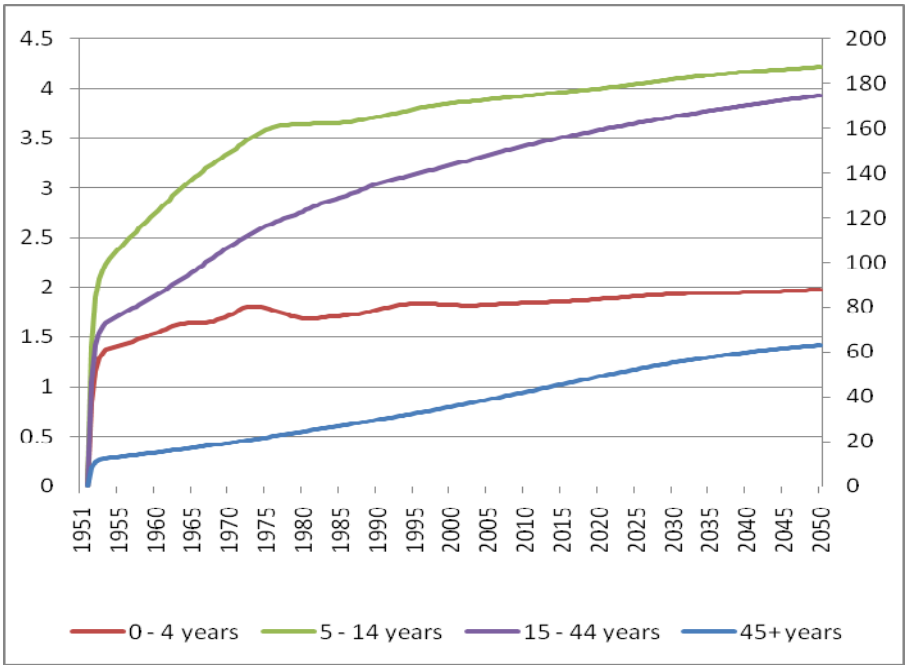

Figure 6.4 – Number of people with acute HBV infection by age-group over time.
Static FoI, base FoI and migration assumptions. Age groups 0-4 and 5-14 use primary Y axis, 15-44 and 45+ use secondary Y axis.

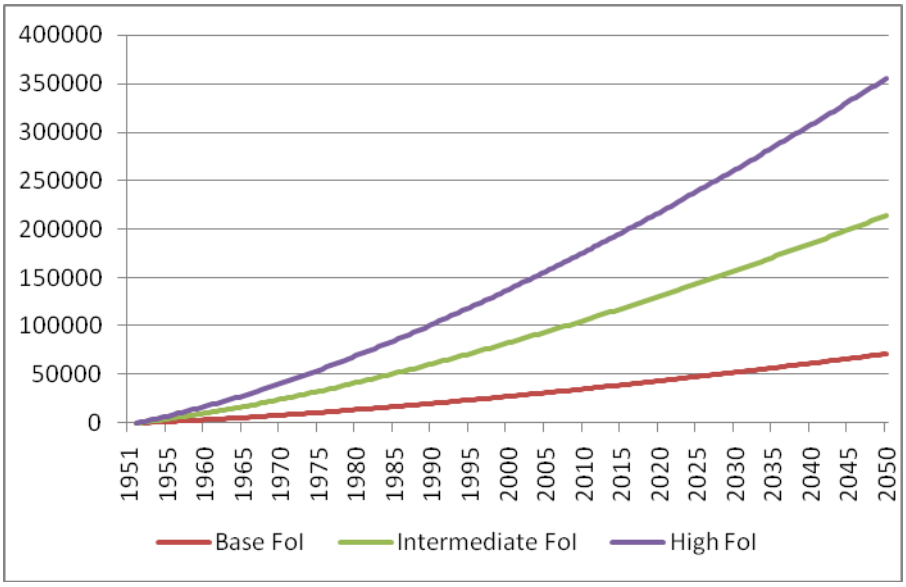

Figure 6.5 – Cumulative number of acute HBV infections by FoI over time. Static FoI, base migration assumption.

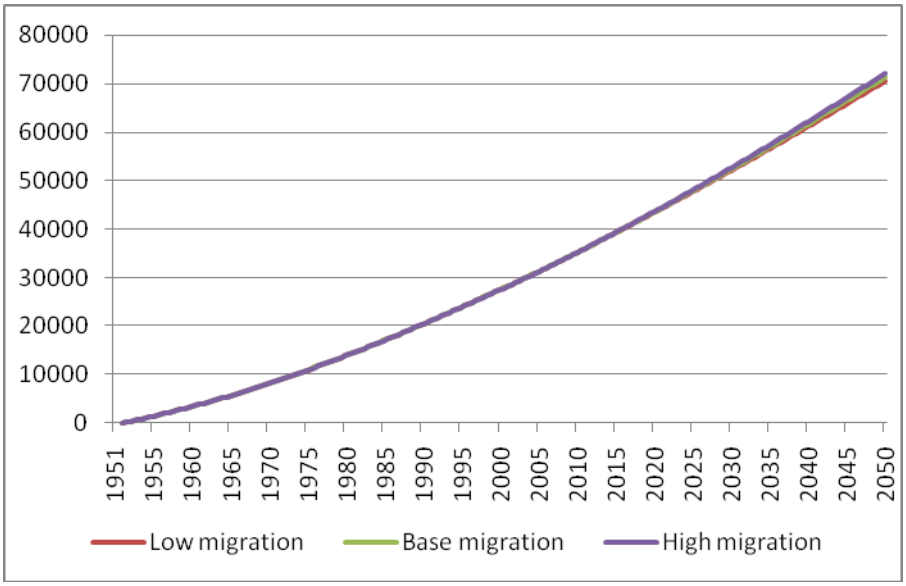

Figure 6.6 – Cumulative number of acute HBV infections by migration over time. Static FoI, base FoI assumption.

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.

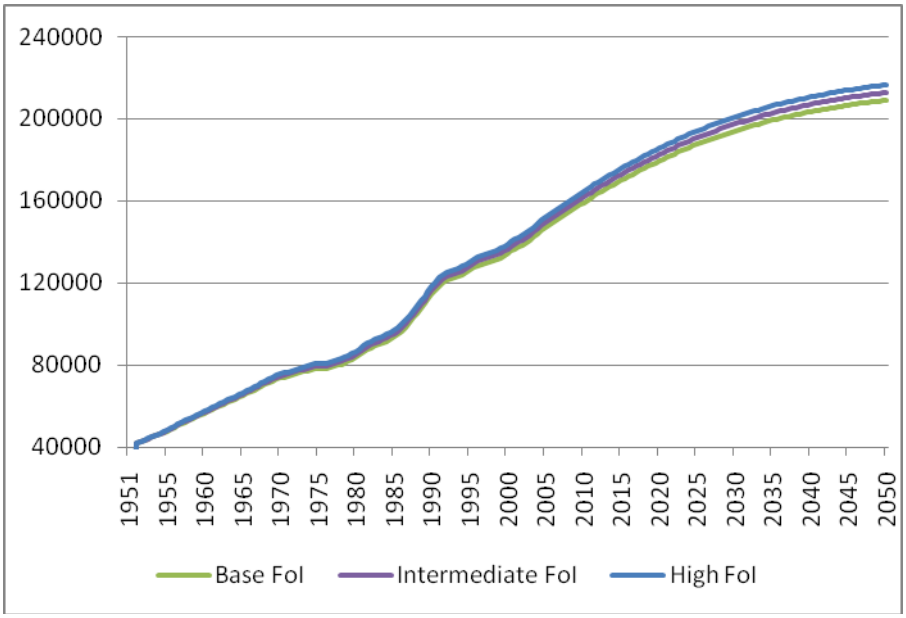

Figure 6.7 – Number of people with chronic HBV infection by FoI over time.
Static FoI, base migration assumption.

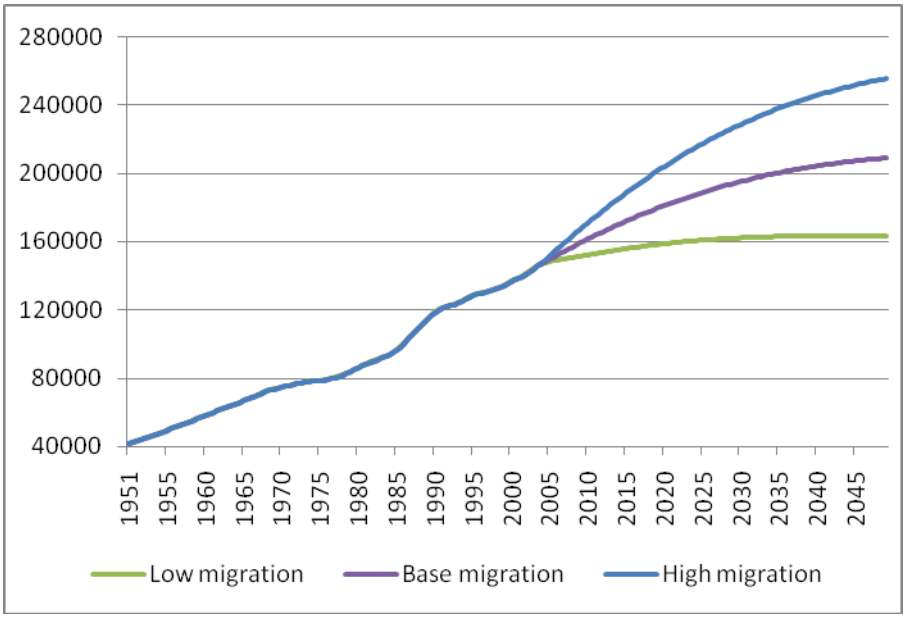

Figure 6.8 – Number of people with chronic HBV infection by migration over time. Static FoI, base FoI assumption.

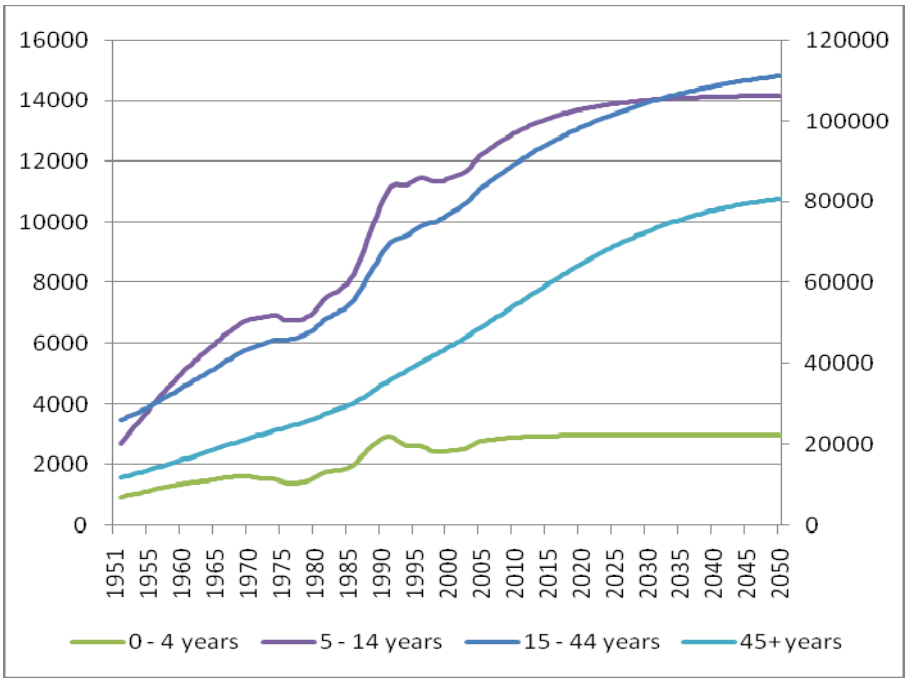

Figure 6.9 – Number of people with chronic HBV infection by age-group over time. Static FoI, base FoI and migration assumptions. Age groups 0-4 and 5-14 use primary Y axis, 15-44 and 45+ use secondary Y axis.

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.

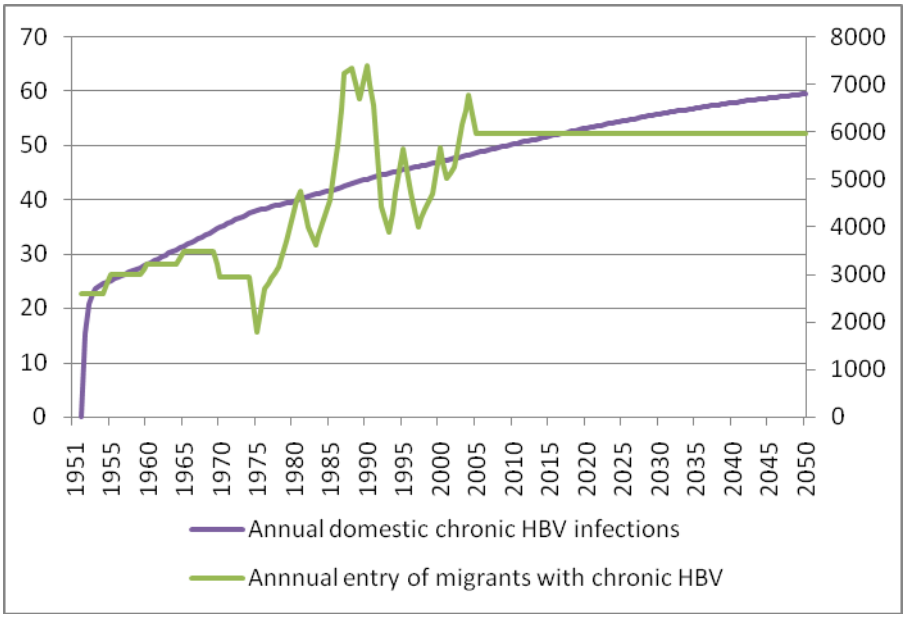

Figure 6.10 – Annual domestic chronic HBV infections (primary Y axis) and annual entry of migrants with chronic infection (secondary Y axis) over time. Static FoI, base FoI and migration assumptions.

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.

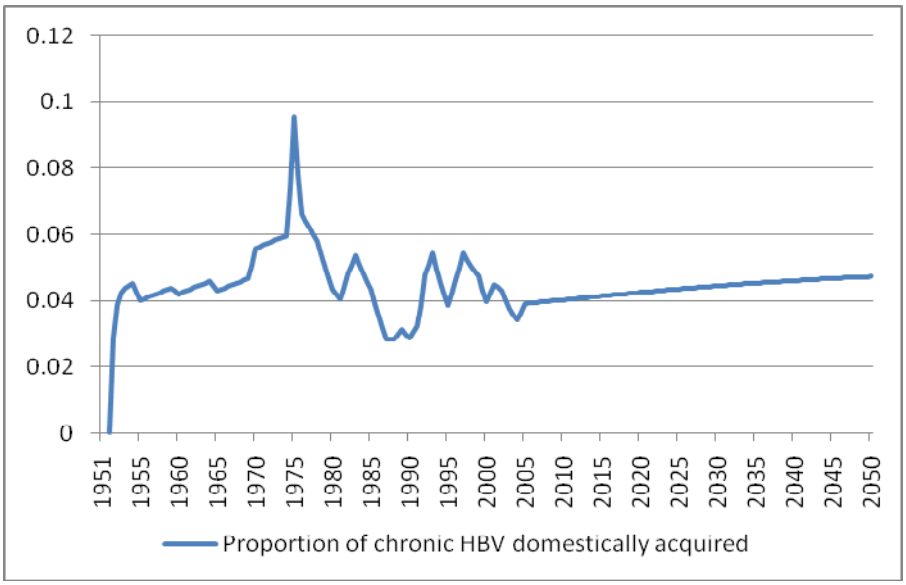

Figure 6.11 – Proportion of chronic HBV infections which are domestically acquired over time. Static FoI, high FoI and base migration assumption.

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.

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

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.

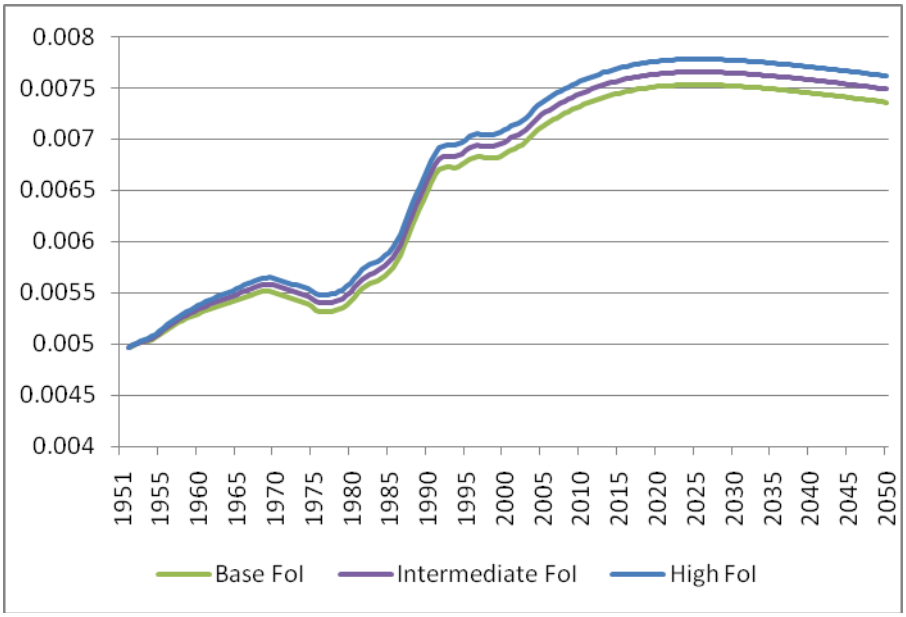

Figure 6.12 – HBsAg prevalence by FoI over time. Static FoI, base migration assumption.

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.

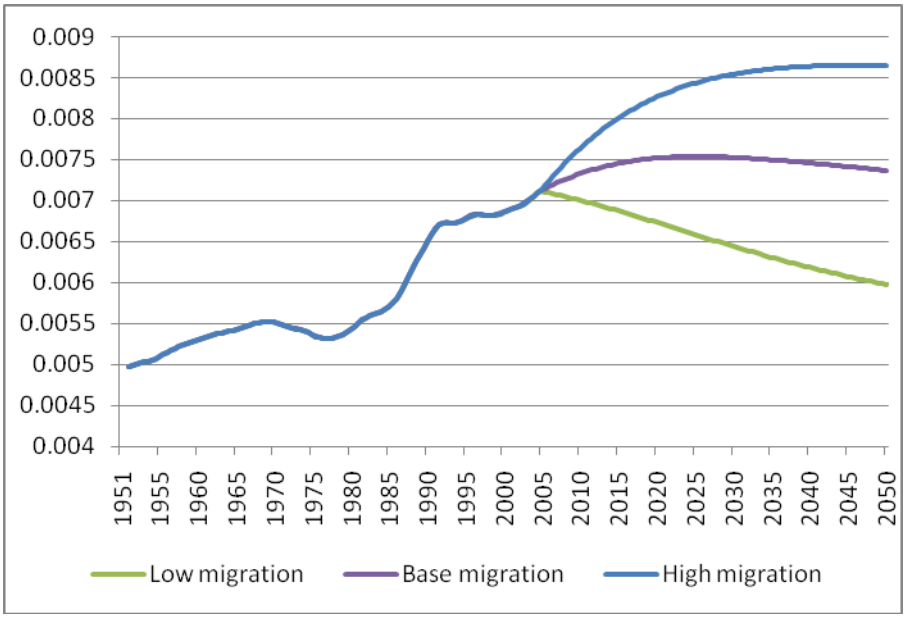

Figure 6.13 - HBsAg prevalence by migration over time. Static FoI, base FoI assumption.

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.

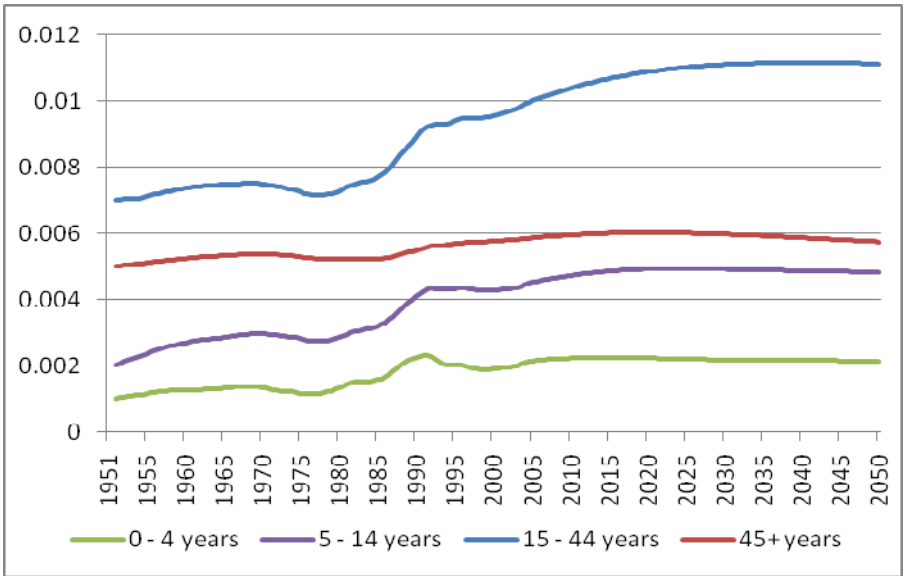

Figure 6.14 – HBsAg prevalence by age group over time.
Static FoI, base FoI and migration assumptions.

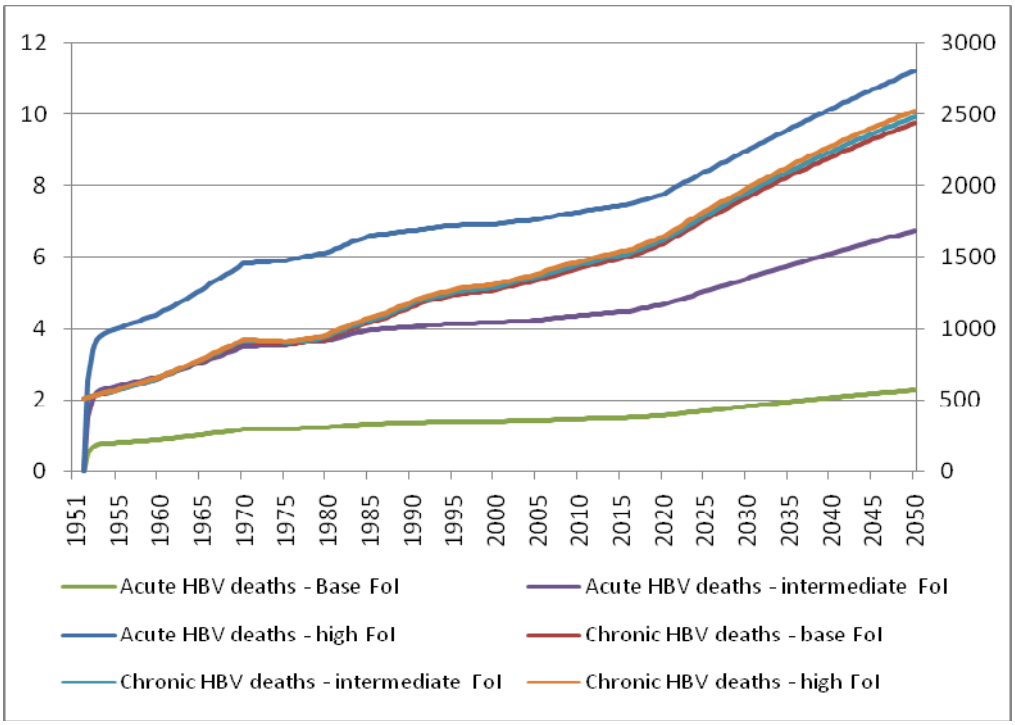

Figure 6.15 – Deaths in people with acute (primary Y axis) and chronic HBV infection (secondary Y axis) by FoI over time. Static FoI, base migration assumption.

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.

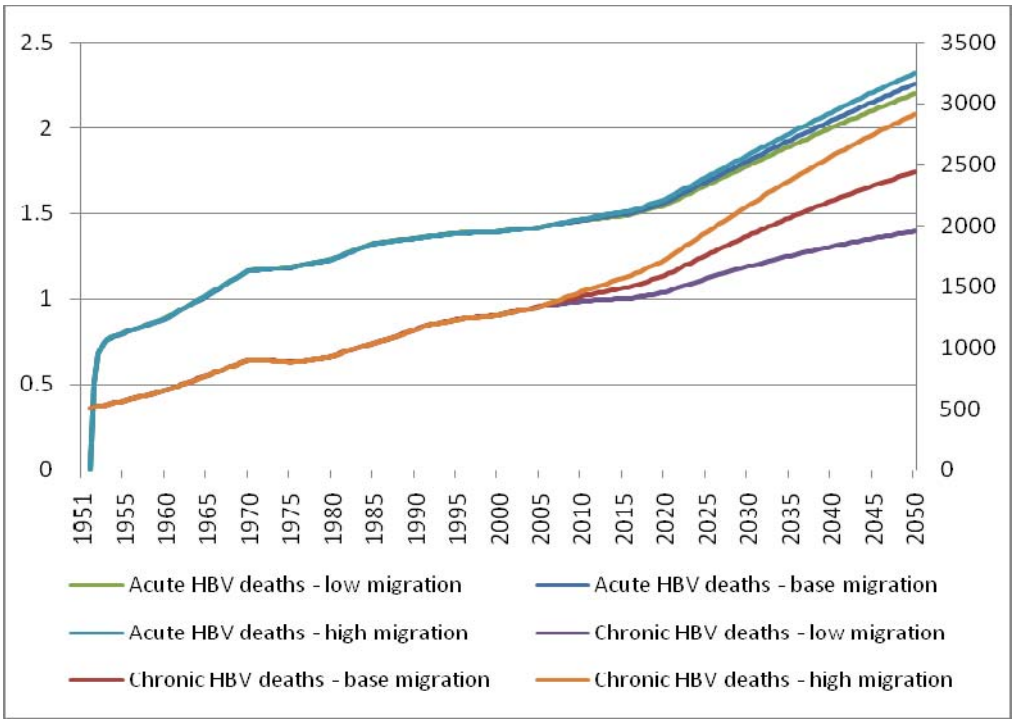

Figure 6.16 – Deaths in people with acute (primary Y axis) and chronic HBV infection (secondary Y axis) by migration over time. Static FoI, base FoI assumption.

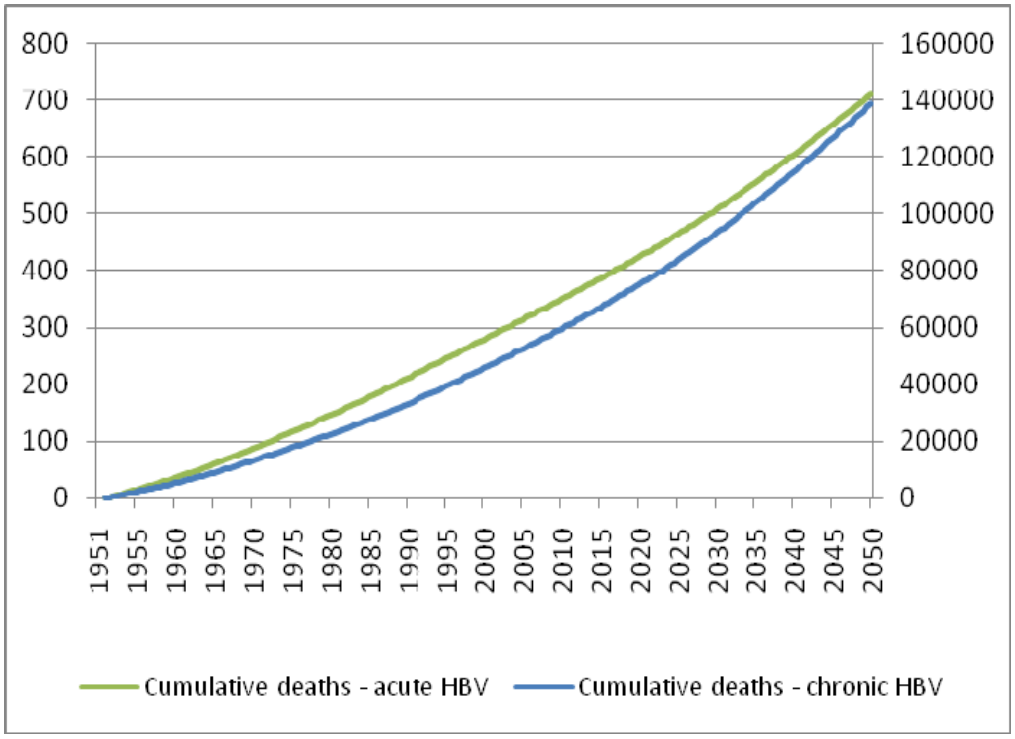

Figure 6.17 – Cumulative deaths in acute (primary Y axis) and chronic HBV infection (secondary Y axis) over time. Static FoI, high FoI and base migration assumptions.

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:

HBV mortality rate = deaths in chronic HBV / number chronically infected / year
Uninfected mortality rate = deaths in uninfected / number uninfected / year
HBV mortality ratio = HBV mortality rate / Uninfected mortality rate

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).

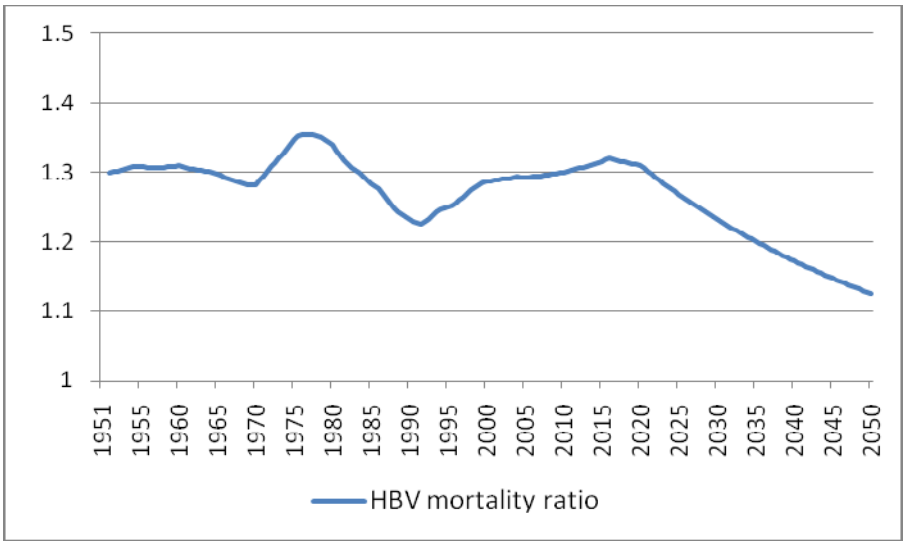

Figure 6.18 – HBV mortality ratio over time. Dynamic FoI model, high FoI and base migration assumptions.

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.

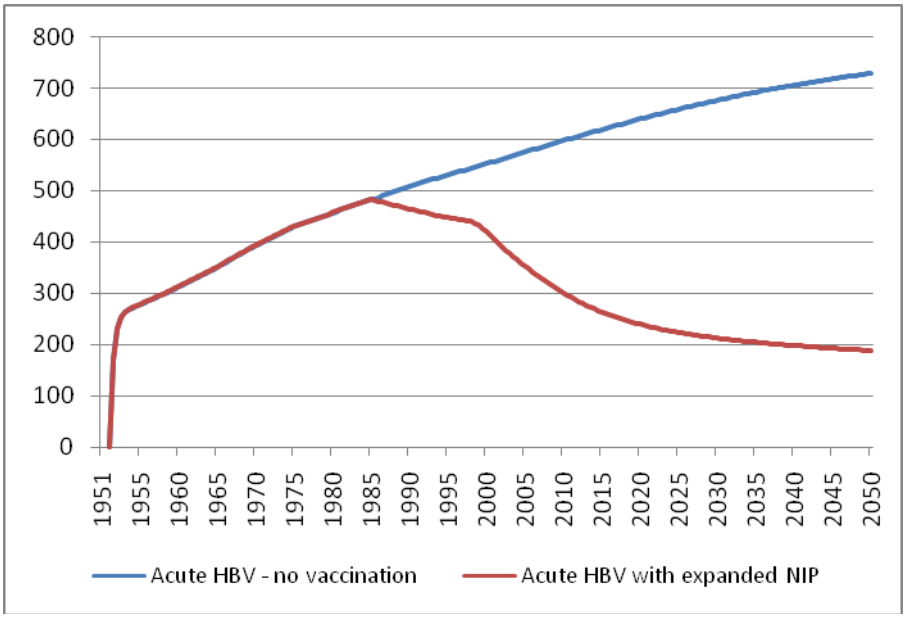

Figure 6.19 – Impact of immunisation on the number of people with acute HBV infection over time. Static FoI, intermediate FoI and base migration assumptions.

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).

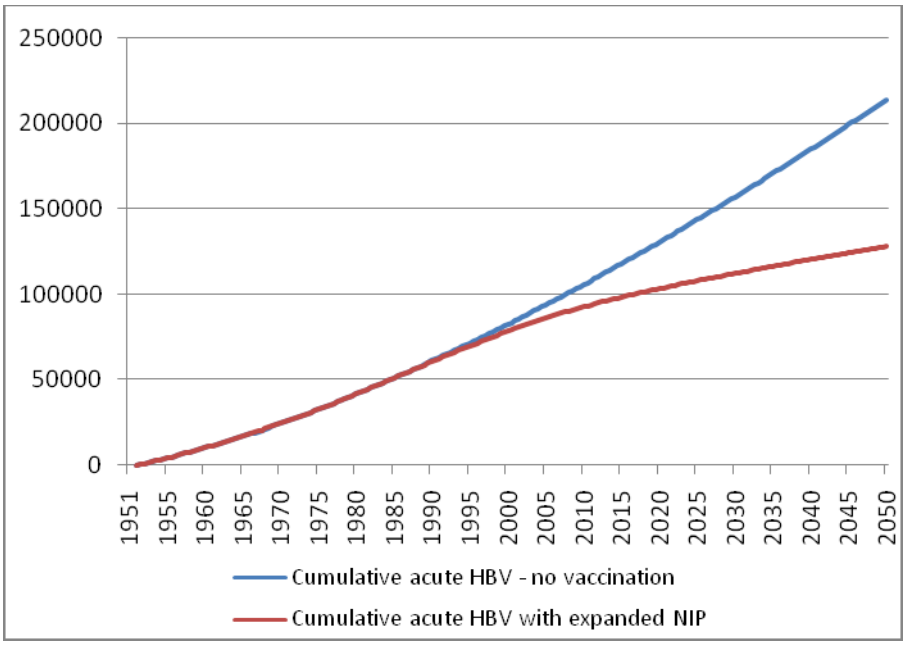

Figure 6.20 – Impact of immunisation on the cumulative number of acute HBV infections over time. Static FoI, intermediate FoI and base migration assumptions.

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.

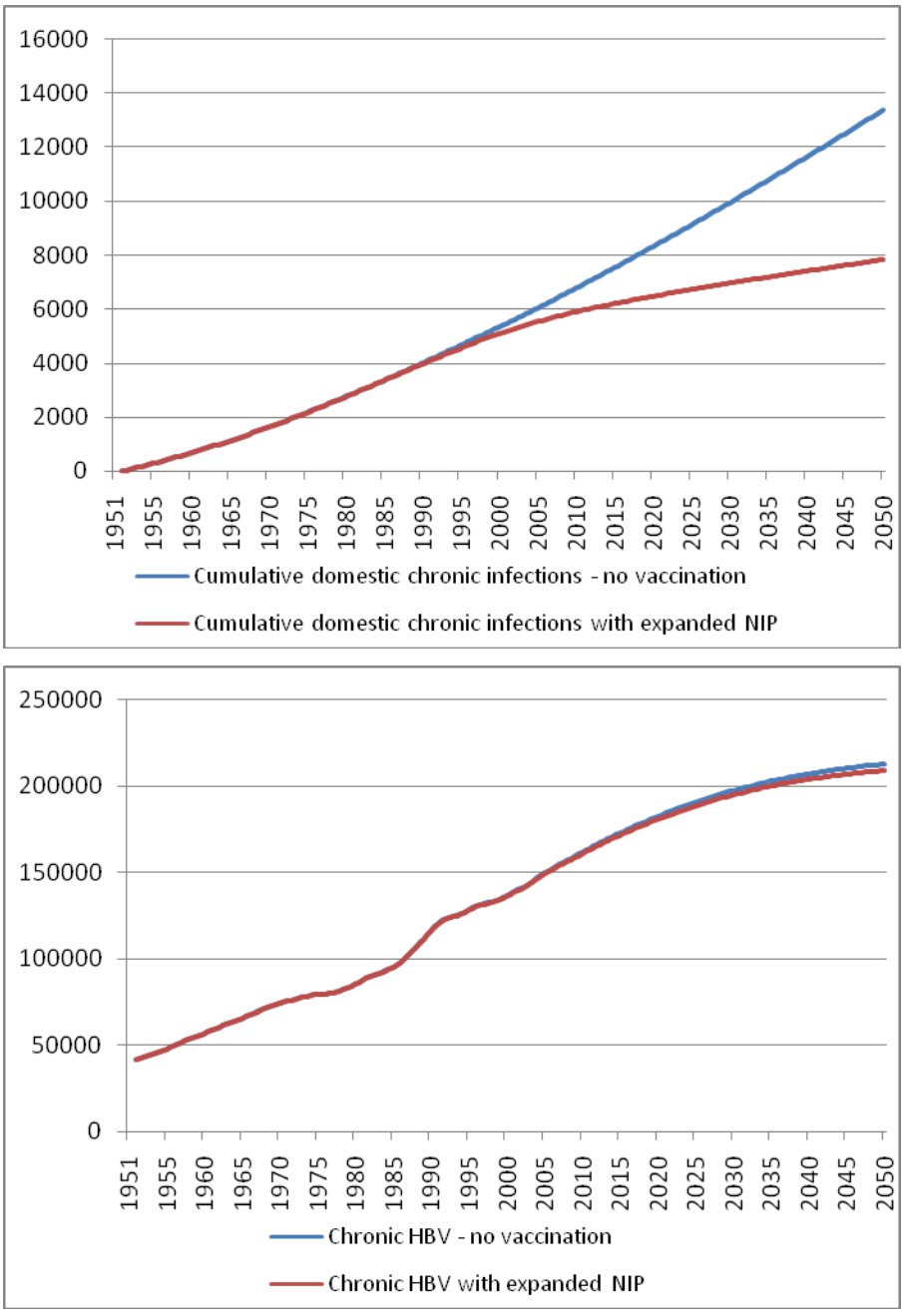

Figure 6.21 – Impact of immunisation on (a) cumulative number of domestically acquired chronic HBV infections and (b) the number of people with chronic HBV infection over time. Static FoI, intermediate FoI and base migration assumptions.

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 .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**).

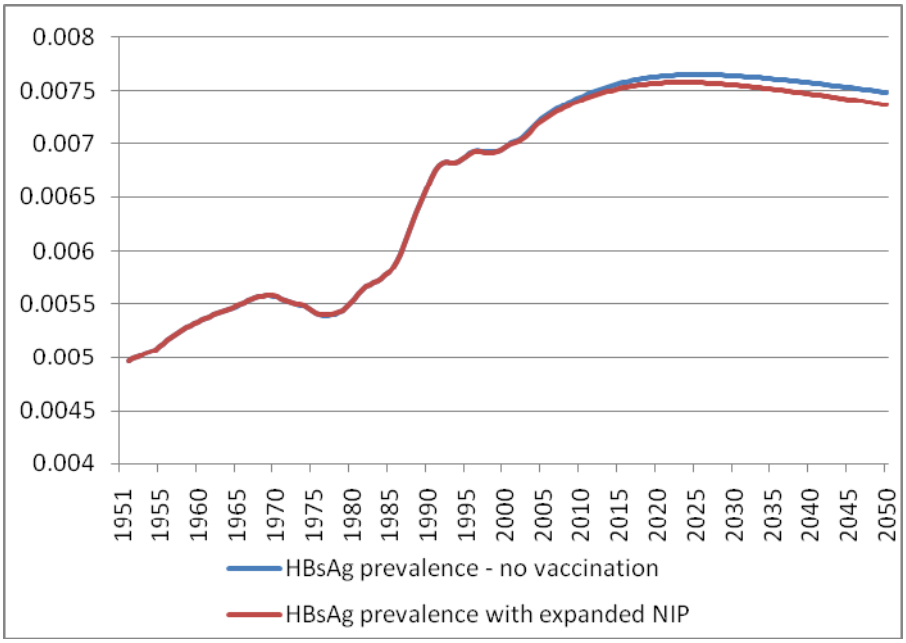

Figure 6.22 – Impact of immunisation on the HBsAg prevalence over time. Static FoI, intermediate FoI and base migration assumptions.

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.

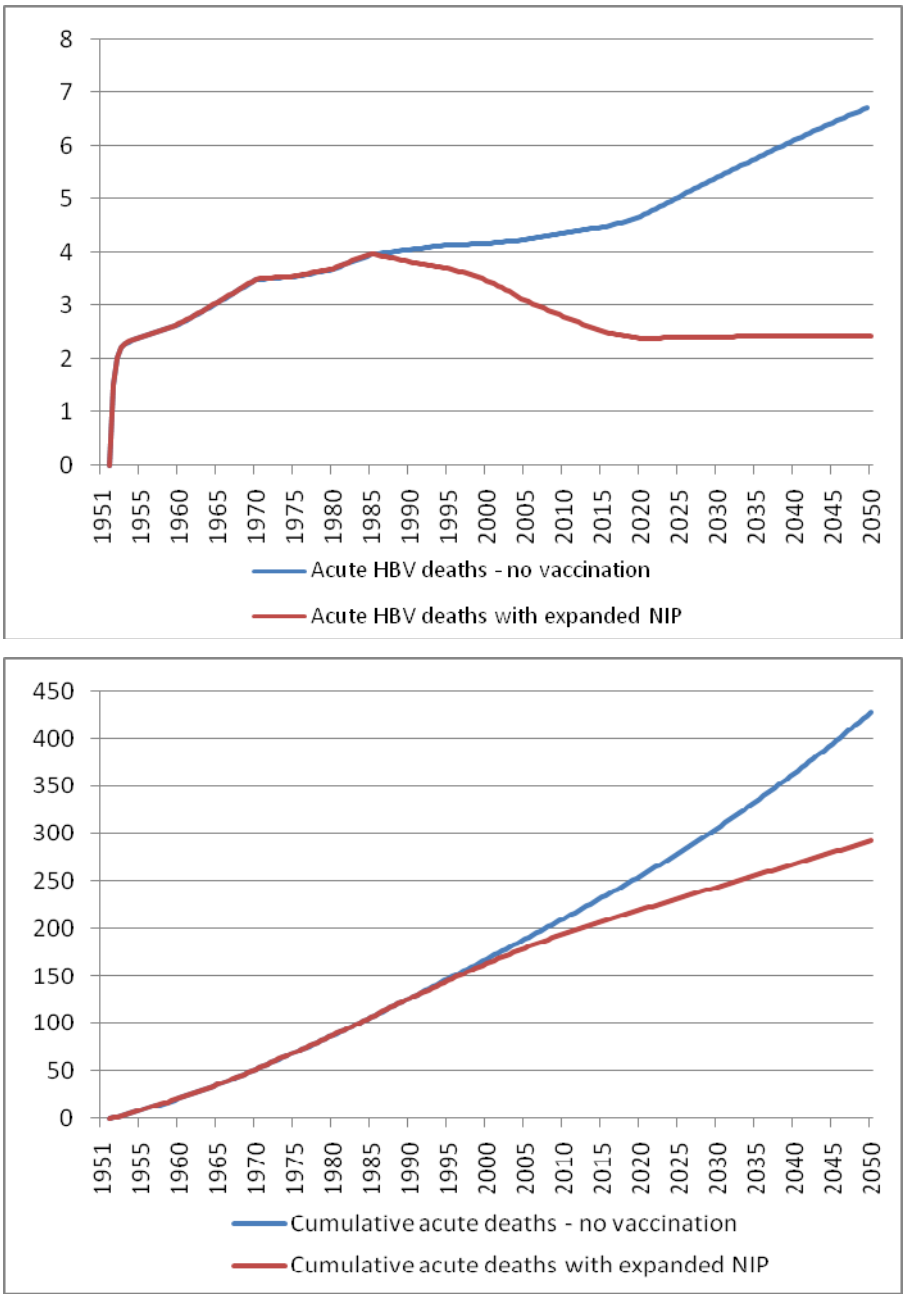

Figure 6.23 – Impact of immunisation on (a) annual deaths in acute HBV infection and (b) number of cumulative deaths in acute HBV infection over time. Static FoI, intermediate FoI and base migration assumptions.

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.

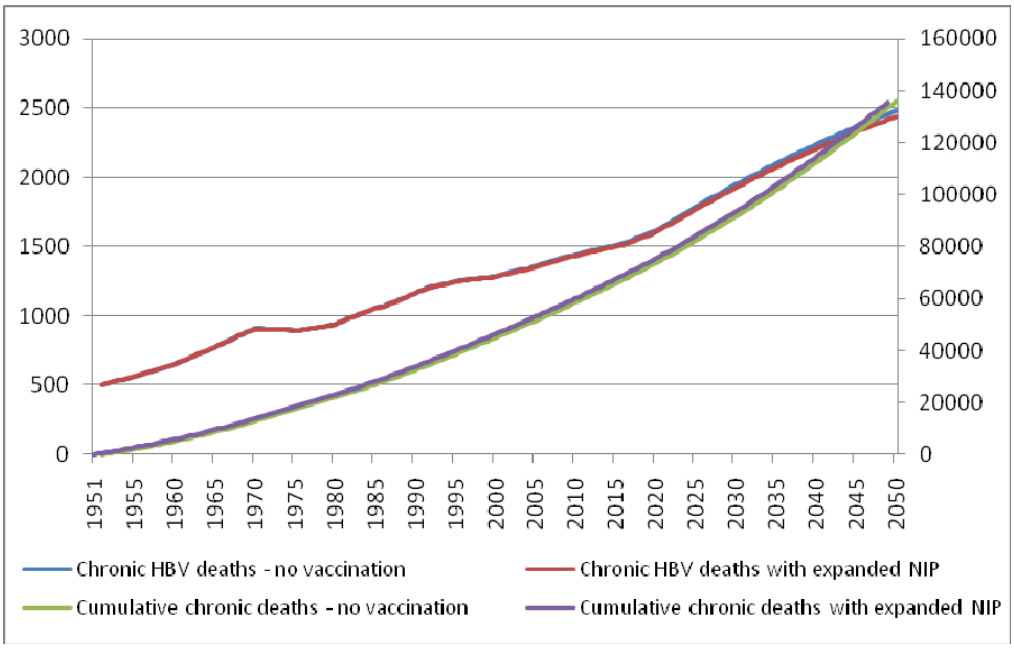

Figure 6.24 – Impact of immunisation on annual deaths in people with chronic HBV infection (primary Y axis) and cumulative deaths in people with chronic HBV infection (secondary Y axis) over time. Static FoI, intermediate FoI and base migration assumptions.

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.

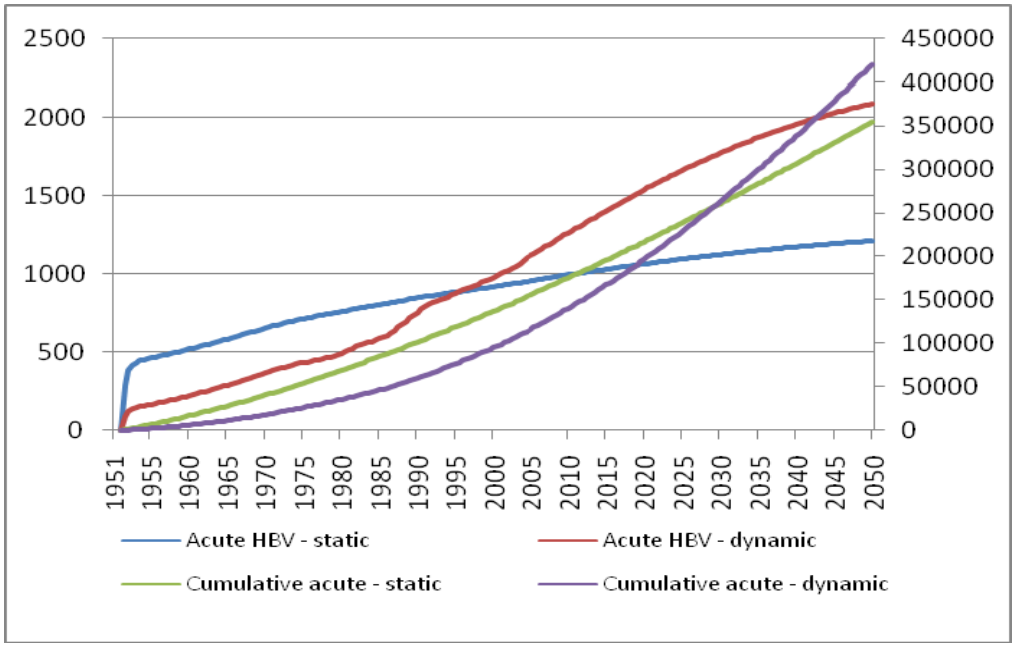

Figure 6.25 – Number of people with acute HBV infection (primary Y axis) and cumulative number of acute HBV infections (secondary Y axis) over time. Static versus dynamic FoI model, high FoI and base migration assumptions.

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).

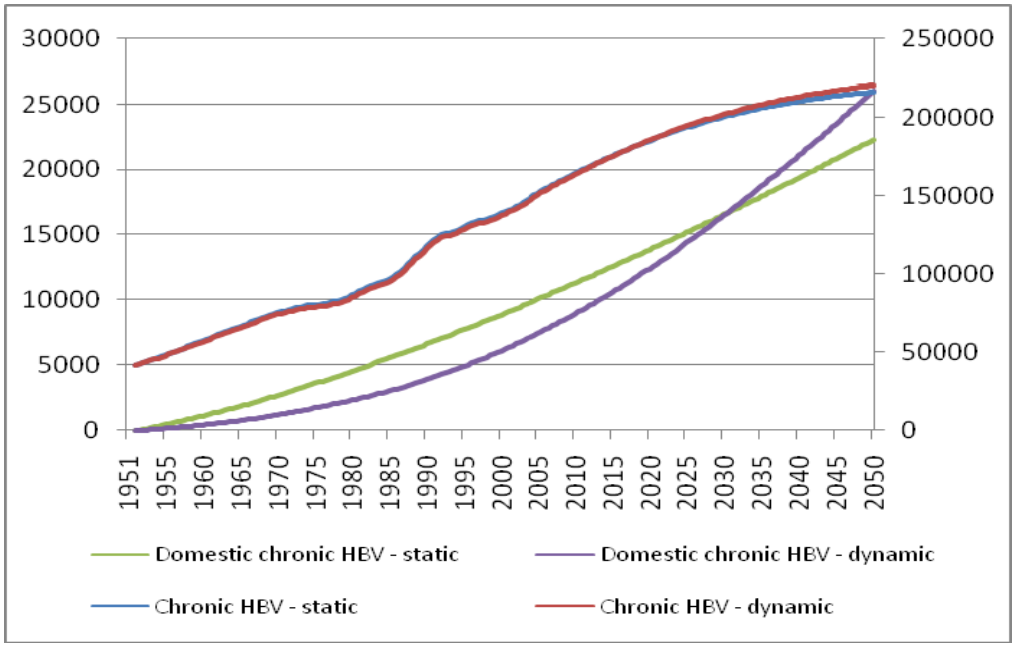

Figure 6.26 – Cumulative domestically acquired chronic HBV infections (primary Y axis) and total number of people with chronic HBV infection (secondary Y axis) over time. Static versus dynamic FoI model, high FoI and base migration assumptions.

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.

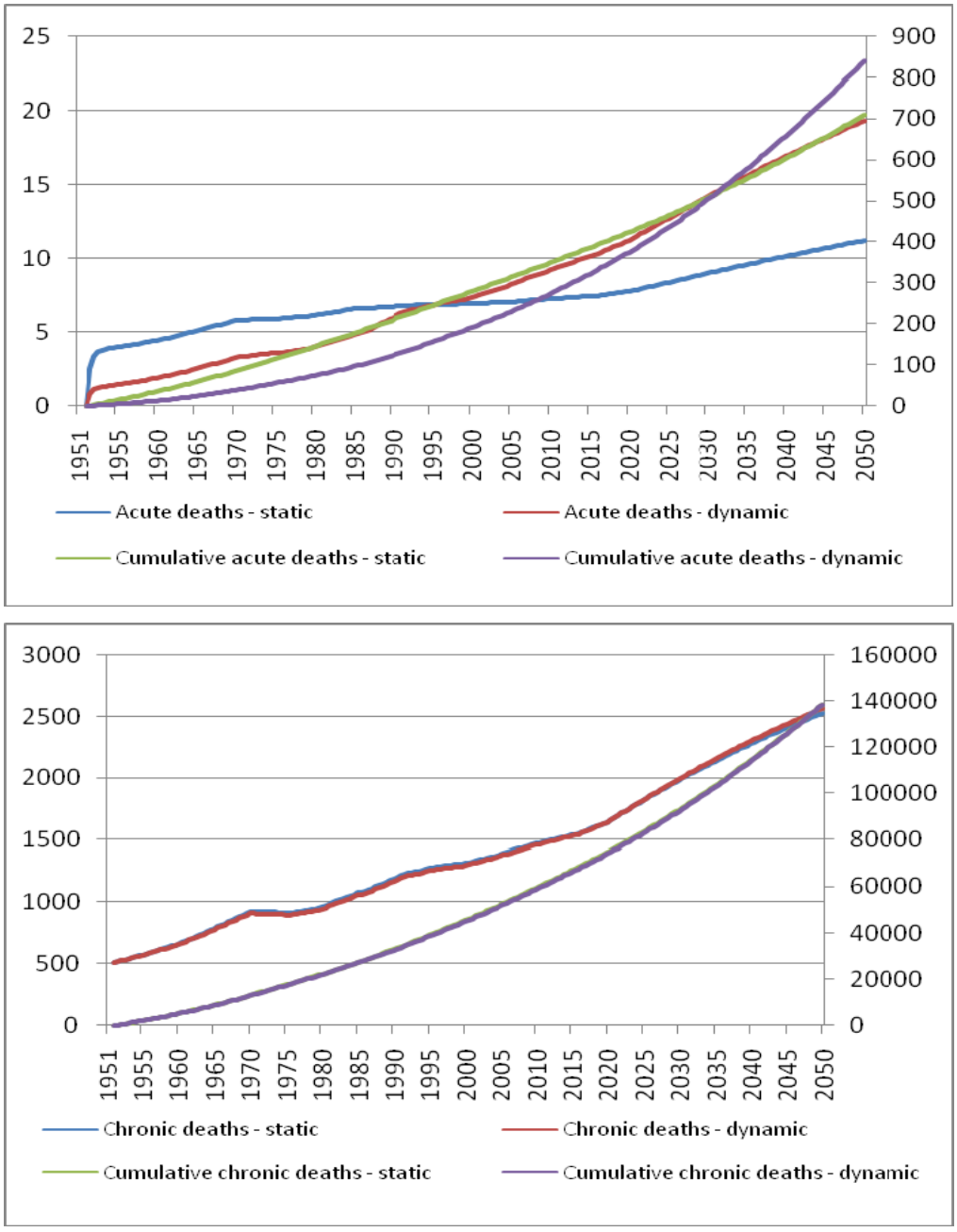

Figure 6.27 – Annual (primary Y axes) and cumulative (secondary Y axes) deaths in (a) acute and (b) chronic HBV infection over time. Static versus dynamic FoI model, high FoI and base migration assumptions.

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 *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.

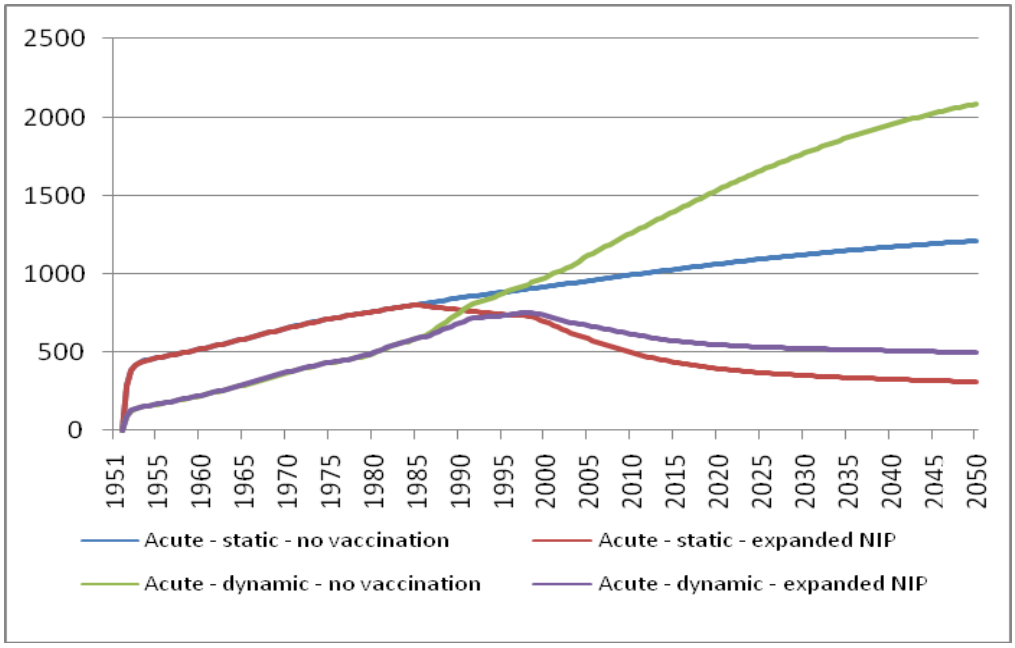

Figure 6.28 – Impact of immunisation on the number of people with acute HBV infection over time. Static versus dynamic FoI model, high FoI and base migration assumptions.

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.

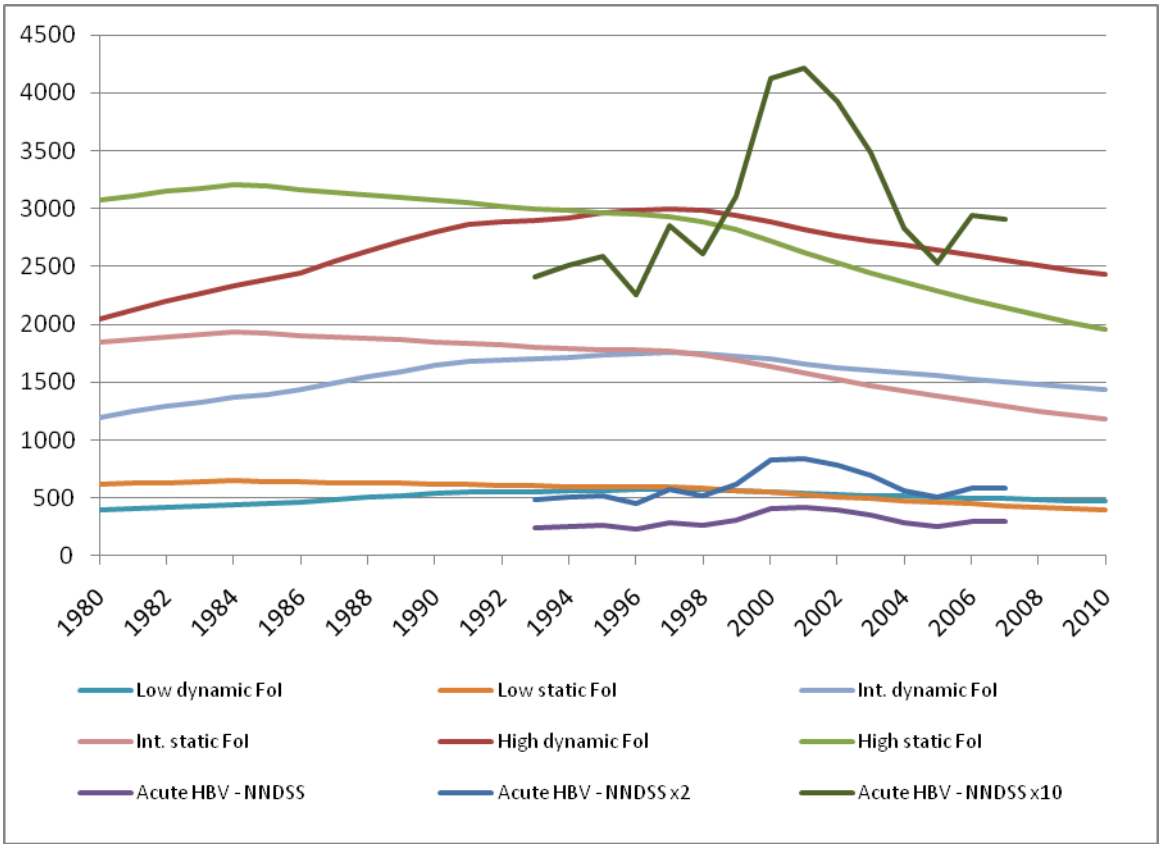

Figure 6.29 – Comparison of the number of people with acute HBV infection by FoI with acute notifications to NNDSS (242) and 2x- and 10x-notifications (see text) over time. Static versus dynamic FoI model, base migration assumption.

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

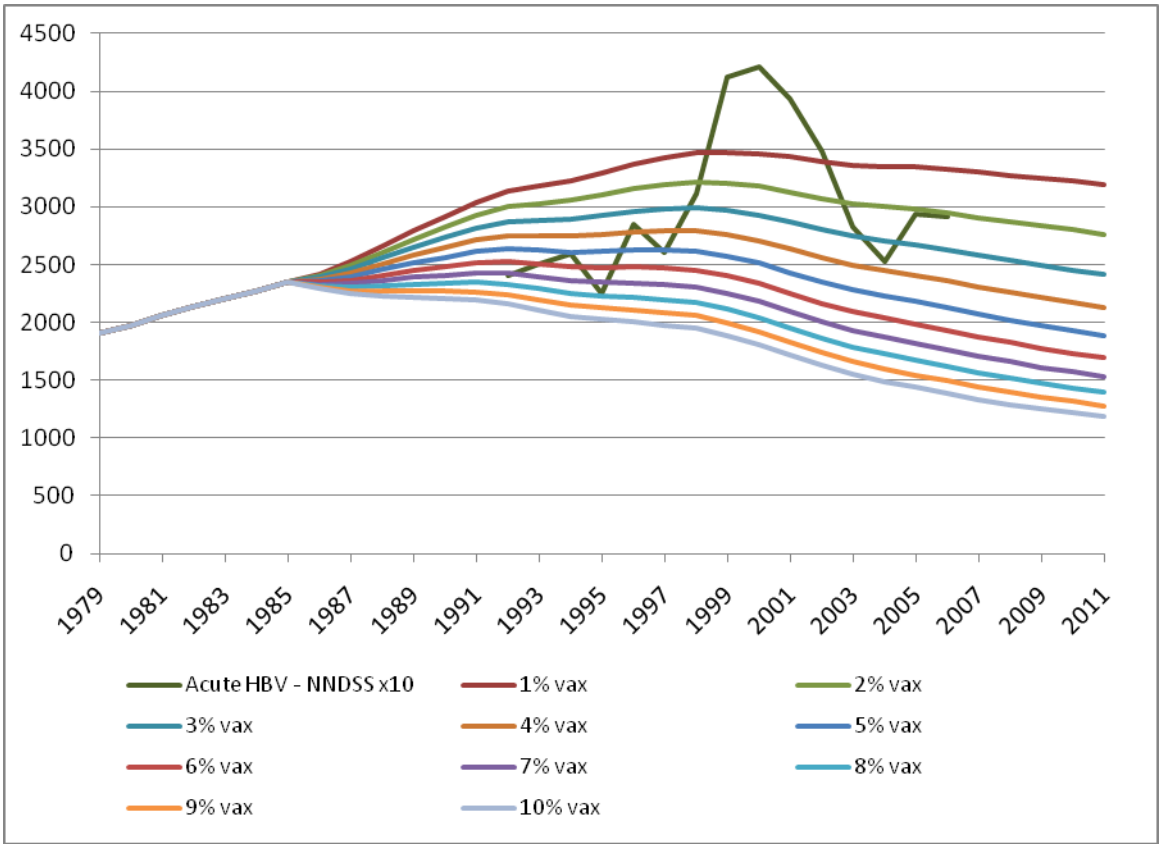

Figure 6.30 – Comparison of acute HBV infections under a range of vaccination uptake values (1-10%) for adults aged 15-44 with actual notification data (NNDSS x10). Dynamic high FoI model, base migration assumption, vaccination according to expanded NIP parameters other than in 15-44 age group.

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)).

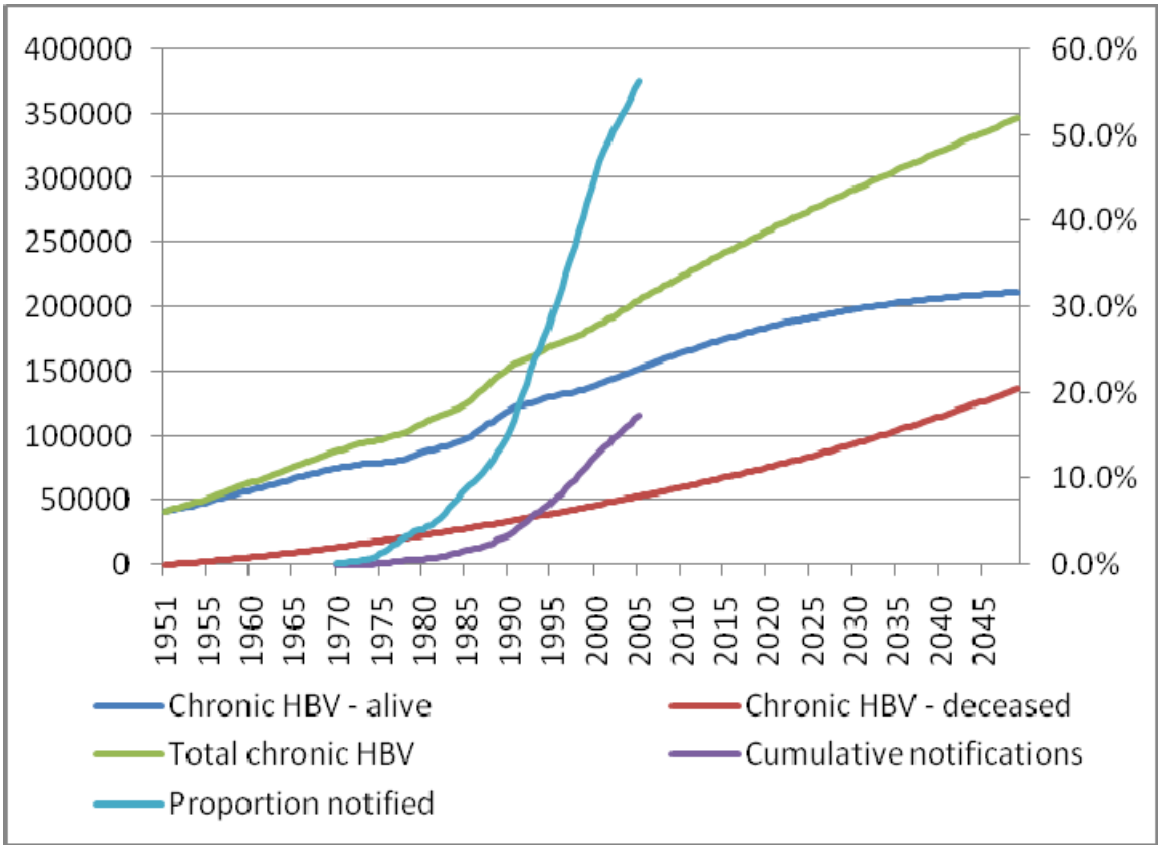

Figure 6.31 – Comparison of people with chronic HBV infection (alive, deceased, and the sum of both) compared with the cumulative number of notifications to the NNDSS since 1971 (primary Y axis). Also shown is the resultant estimate of the proportion of all people with chronic HBV who have been diagnosed 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).

	1995		2000		2005	
	Serosurvey	**Model**	Serosurvey	**Model**	Serosurvey	**Model**
Susceptible	79.1%	**83.5%**	66.6%	**70.1%**	55.2%	**54.2%**
Vaccinated	13.6%	**8.7%**	23.2%	**21.7%**	33%	**37.2%**
Chronic infection	*0.9%*	***0.69%***	*1.9%*	***0.70%***	*0.6%*	***0.73%***
Cleared	5.3%	**7.1%**	7.8%	**7.5%**	10.2%	**7.9%**

Table 6.2 – Comparison of results from Victorian serosurvey with outcomes of high dynamic FoI model with base migration assumption incorporating expanded NIP (see **6.1.4**).

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.

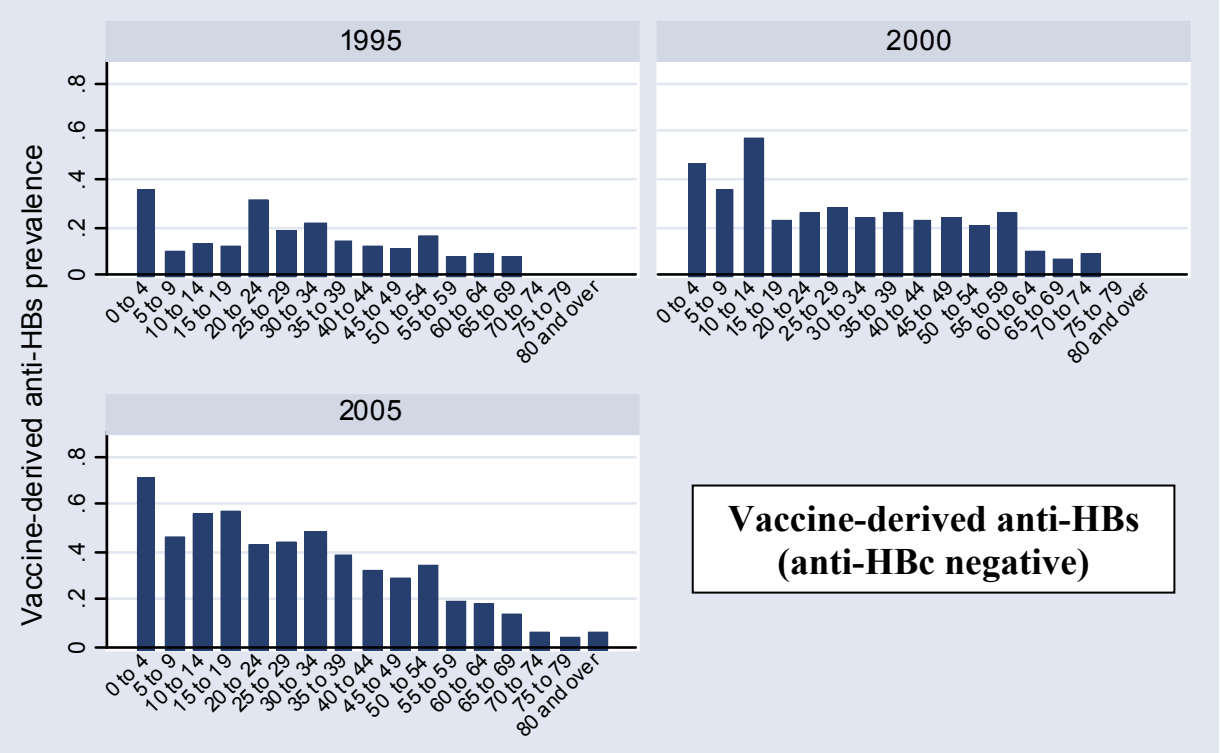

Figure 6.32 – Prevalence of vaccine derived anti-HBs (anti-HBc negative samples) in Victorian serosurvey by age-group by test year.

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.

	Serosurvey vaccine-derived anti-HBs prevalence (%)	**95% C.I. for serosurvey estimate (exact binomial) (%)**	**Predicted vaccinated proportion from mathematical model using 'expanded NIP'**
1995	**18.7**	**15.1 – 22.6**	**17.8**
2000	**24.8**	**20.9 – 29.1**	**25.5**
2005	**43.5**	**38.8 – 48.4**	**40.0**

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	*1 – ([anti-HBs]+[HBsAg]+[0.25*[anti-HBc])*
Vaccinated	*[Anti-HBs] – 0.75*([Anti-HBc]-[HBsAg])*
Chronic infection	*[HBsAg]*
Cleared infection	*[Anti-HBc] – [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.

	1996-1999		2002	
	Serosurvey Ref: (11)	**Model (1998)**	Serosurvey Ref: (12)	**Model (2002)**
Susceptible	68.9%	**80.7%**	65.4%	**60.2%**
Vaccinated	24.2%	**11.3%**	28.5%	**31.4%**
Chronic infection	*0.65%*	***0.70%***	*0.75%*	***0.71%***
Cleared	6.3%	**7.3%**	5.4%	**7.6%**

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

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:

Mortality ratio in those with chronic HBV relative to uninfected = 1.29 : 1
Therefore fraction of mortality attributable to HBV = (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**.

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

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**.

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

mig_pred	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 / [Incubation period] (years) - not ultimately used model
ac_res_rate	1 / [Duration of acute infection] (years)
f_o_i_0	Force of Infection
FoI_mult	Multiplier allowing sensitivity analysis for FoI 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
total_deaths_acute	Total deaths in individuals with acute HBV
deaths_chronic_0	Deaths in 0 – 4 age group with chronic HBV
total_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

```
================================================================================
{Reservoirs}
d/dt (Sus_0) = - inf_0 + births + mig_sus_0 - sus_mort_0 - age_sus_0 - vac_0
    INIT Sus_0 = init_pop*pop_prop_0*.998
  d/dt (Acute_0) = + inf_0 - prog_0 - recov_0 - ac_mort_0 - age_ac_0
    INIT Acute_0 = 0
  d/dt (Chronic_0) = + prog_0 - clear_0 + mig_chron_0 - chr_mort_0 - age_chr_0
    INIT Chronic_0 = init_pop*pop_prop_0*.001
  d/dt (Cleared_0) = + recov_0 + clear_0 - cleared_mort_0 + mig_cleared_0 - age_cleared_0
    INIT Cleared_0 = init_pop*pop_prop_0*.001
  d/dt (Sus_1) = + age_sus_0 - age_sus_1 - sus_mort_1 - inf_1 + mig_sus_1 - vac_1
    INIT Sus_1 = init_pop*pop_prop_1*.994
  d/dt (Acute_1) = + age_ac_0 - ac_mort_1 - recov_1 - prog_1 - age_ac_1 + inf_1
    INIT Acute_1 = 0
  d/dt (Chronic_1) = + age_chr_0 - clear_1 + prog_1 - chr_mort_1 - age_chr_1 + mig_chron_1
    INIT Chronic_1 = init_pop*pop_prop_1*.002
  d/dt (Cleared_1) = + age_cleared_0 + mig_cleared_1 + clear_1 - age_cleared_1 - cleared_mort_1 + recov_1
    INIT Cleared_1 = init_pop*pop_prop_0*.004
  d/dt (Sus_2) = + age_sus_1 - inf_2 + mig_sus_2 - age_sus_2 - sus_mort_2 - vac_2
    INIT Sus_2 = init_pop*pop_prop_2*.94
  d/dt (Acute_2) = + age_ac_1 - recov_2 - age_ac_2 + inf_2 - prog_2 - ac_mort_2
    INIT Acute_2 = 0
  d/dt (Chronic_2) = + age_chr_1 - age_chr_2 + mig_chron_2 - clear_2 - chr_mort_2 + prog_2
    INIT Chronic_2 = init_pop*pop_prop_2*.007
  d/dt (Cleared_2) = + age_cleared_1 + recov_2 - cleared_mort_2 + clear_2 - age_cleared_2 + mig_cleared_2
    INIT Cleared_2 = init_pop*pop_prop_2*.053
  d/dt (Sus_3) = + age_sus_2 - sus_mort_3 + mig_sus_3 - inf_3 - vac_3
    INIT Sus_3 = init_pop*pop_prop_3*.94
```

```
d/dt (Acute_3) = + age_ac_2 - prog_3 - recov_3 - ac_mort_3 + inf_3
  INIT Acute_3 = 0
d/dt (Chronic_3) = + age_chr_2 - clear_3 + mig_chron_3 - chr_mort_3 + prog_3
  INIT Chronic_3 = init_pop*pop_prop_3*.005
d/dt (Cleared_3) = + age_cleared_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*(1/30)
age_ac_2 = Acute_2*(1/30)
age_chr_2 = Chronic_2*(1/30)
age_cleared_2 = Cleared_2*(1/30)
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
```

```
mig_chron_3 = #mig3chron(TIME)*mig_series*mig_pred
sus_mort_3 = Sus_3*#bgmort3(TIME)
ac_mort_3 = Acute_3*(#bgmort3(TIME)+ac_mort_rate_3)
chr_mort_3 = Chronic_3*(#bgmort3(TIME)+chr_mort_rate_3)
cleared_mort_3 = Cleared_3*#bgmort3(TIME)
mig_cleared_3 = #mig3cleared(TIME)*mig_series*mig_pred
vac_0 = Sus_0*vacc_eff_0*vacc_prop_0*vacc_prog_0*vacc_avail
vac_1 = Sus_1*vacc_eff_1*vacc_prop_1*vacc_prog_1*vacc_avail
vac_2 = Sus_2*vacc_eff_2*vacc_prop_2*vacc_avail
vac_3 = Sus_3*vacc_eff_3*vacc_prop_3*vacc_avail
mig_imm_0 = 0*mig_series*mig_pred
age_imm_0 = Immune_0*(1/5)
imm_mort_0 = Immune_0*#bgmort0(TIME)
mig_imm_1 = 0*mig_series*mig_pred
mig_imm_2 = 0*mig_series*mig_pred
mig_imm_3 = 0*mig_series*mig_pred
age_imm_1 = Immune_1*(1/10)
age_imm_2 = Immune_2*(1/30)
imm_mort_1 = Immune_1*#bgmort1(TIME)
imm_mort_2 = Immune_2*#bgmort2(TIME)
imm_mort_3 = Immune_3*#bgmort3(TIME)

{Submodel "Cum cases SM"}
  {Reservoirs}
  d/dt (Cum_acute_0) = + J1
    INIT Cum_acute_0 = 0
  d/dt (Cum_acute_1) = + J2
    INIT Cum_acute_1 = 0
  d/dt (Cum_acute_2) = + J3
    INIT Cum_acute_2 = 0
  d/dt (Cum_acute_3) = + J4
    INIT Cum_acute_3 = 0
  d/dt (Cum_chronic_0) = + J5
    INIT Cum_chronic_0 = 0
  d/dt (Cum_chronic_1) = + J6
    INIT Cum_chronic_1 = 0
  d/dt (Cum_chronic_2) = + J7
    INIT Cum_chronic_2 = 0
  d/dt (Cum_chronic_3) = + J8
    INIT Cum_chronic_3 = 0

  {Flows}
  J1 = Sus_0*f_o_i_0
  J2 = Sus_1*f_o_i_1
  J3 = Sus_2*f_o_i_2
  J4 = Sus_3*f_o_i_3
  J5 = Acute_0*ac_res_rate*prog_chron_0
  J6 = Acute_1*ac_res_rate*prog_chron_1
  J7 = Acute_2*ac_res_rate*prog_chron_2
  J8 = Acute_3*ac_res_rate*prog_chron_3

{Submodel "Cum deaths SM"}
  {Reservoirs}
  d/dt (Cum_deaths_uninf_0) = + J9
    INIT Cum_deaths_uninf_0 = 0
  d/dt (Cum_deaths_uninf_1) = + J10
    INIT Cum_deaths_uninf_1 = 0
  d/dt (Cum_deaths_uninf_2) = + J11
    INIT Cum_deaths_uninf_2 = 0
  d/dt (Cum_deaths_uninf_3) = + J12
    INIT Cum_deaths_uninf_3 = 0
  d/dt (Cum_acute_deaths_0) = + J13
    INIT Cum_acute_deaths_0 = 0
  d/dt (Cum_chronic_deaths_0) = + J14
    INIT Cum_chronic_deaths_0 = 0
  d/dt (Cum_acute_deaths_1) = + J15
    INIT Cum_acute_deaths_1 = 0
```

```
    d/dt (Cum_chronic_deaths_1) = + J16
      INIT Cum_chronic_deaths_1 = 0
    d/dt (Cum_acute_deaths_2) = + J17
      INIT Cum_acute_deaths_2 = 0
    d/dt (Cum_chronic_deaths_2) = + J19
      INIT Cum_chronic_deaths_2 = 0
    d/dt (Cum_acute_deaths_3) = + J18
      INIT Cum_acute_deaths_3 = 0
    d/dt (Cum_chronic_deaths_3) = + J20
      INIT Cum_chronic_deaths_3 = 0

    {Flows}
    J9 = (Cleared_0+Immune_0+Sus_0)*#bgmort0(TIME)
    J10 = (Cleared_1+Immune_1+Sus_1)*#bgmort1(TIME)
    J11 = (Cleared_2+Immune_2+Sus_2)*#bgmort2(TIME)
    J12 = (Cleared_3+Immune_3+Sus_3)*#bgmort3(TIME)
    J13 = Acute_0*(#bgmort0(TIME)+ac_mort_rate_0)
    J14 = Chronic_0*(#bgmort0(TIME)+chr_mort_rate_0)
    J15 = Acute_1*(#bgmort1(TIME)+ac_mort_rate_1)
    J16 = Chronic_1*(#bgmort1(TIME)+chr_mort_rate_1)
    J17 = Acute_2*(#bgmort2(TIME)+ac_mort_rate_2)
    J18 = Acute_3*(#bgmort3(TIME)+ac_mort_rate_3)
    J19 = Chronic_2*(#bgmort2(TIME)+chr_mort_rate_2)
    J20 = Chronic_3*(#bgmort3(TIME)+chr_mort_rate_3)

{Globals}
{=============================================================================}
{        DEMOGRAPHIC PARAMETERS AND VARIABLES                                 }
{=============================================================================}

tot_0 = Sus_0 + Immune_0 + Acute_0 + Chronic_0 + Cleared_0
tot_1 = Sus_1 + Immune_1 + Acute_1 + Chronic_1 + Cleared_1
tot_2 = Sus_2 + Immune_2 + Acute_2 + Chronic_2 + Cleared_2
tot_3 = Sus_3 + Immune_3 + Acute_3 + Chronic_3 + Cleared_3
tot_pop = tot_0 + tot_1 + tot_2 + tot_3

init_pop = 8421775
pop_prop_0 = 0.110963345
pop_prop_1 = 0.160490162
pop_prop_2 = 0.443568401
pop_prop_3 = 0.284978092

mig_series = 1
mig_pred = IF(TIME>=2005) THEN 1 ELSE (1/mig_series)

{=============================================================================}
{        INFECTION AND VACCINATION-RELATED PARAMETERS                         }
{         (note that these are in YEARS, unless otherwise specified )         }
{=============================================================================}

dis_rate = 6
ac_res_rate = 4

f_o_i_0 = FoI_mult*0.000006
f_o_i_1 = FoI_mult*0.000006
f_o_i_2 = FoI_mult*0.00008
f_o_i_3 = FoI_mult*0.00002

FoI_mult = 1

prog_chron_0 = 0.5
prog_chron_1 = 0.2
prog_chron_2 = 0.06
prog_chron_3 = 0.04

clr_rate_0 = 0
clr_rate_1 = 0.005
```

```
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                                            }
{=============================================================================}

tot_sus = sus_0 + sus_1 + sus_2 + sus_3
tot_immune = immune_0 + immune_1 + immune_2 + immune_3
tot_acute = acute_0 + acute_1 + acute_2 + acute_3
tot_chronic = chronic_0 + chronic_1 + chronic_2 + chronic_3
tot_cleared = 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

tot_cum_acute = Cum_acute_0 + Cum_acute_1 + Cum_acute_2 + Cum_acute_3
tot_cum_chronic = Cum_chronic_0 + Cum_chronic_1 + Cum_chronic_2 + Cum_chronic_3

tot_prog = prog_0 + prog_1 + prog_2 + prog_3
tot_mig_chron = (#mig0chron(TIME) + #mig1chron(TIME) + #mig2chron(TIME) + mig3chron(TIME))*
(mig_series*mig_pred)
prop_chron_aust = tot_prog/(tot_prog + tot_mig_chron)

tot_cum_deaths_uninf = Cum_deaths_uninf_0 + Cum_deaths_uninf_1 + Cum_deaths_uninf_2 +
Cum_deaths_uninf_3
tot_cum_deaths_acute = Cum_acute_deaths_0 + Cum_acute_deaths_1 + Cum_acute_deaths_2 +
Cum_acute_deaths_3
tot_cum_deaths_chronic = 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)
tot_deaths_uninf = 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}
================================================================================
```