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## **A mathematical model to describe haemophilus influenzae type B within Western Australia**

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**A MATHEMATICAL MODEL TO DESCRIBE HAEMOPHILUS  
INFLUENZAE TYPE B WITHIN WESTERN AUSTRALIA**

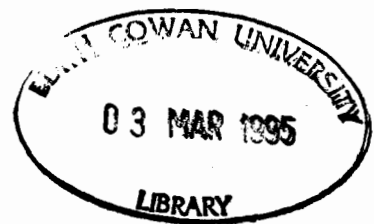
BY

Kevin Dennis BSc (Hons)

A Thesis Submitted In Partial Fulfilment of the  
Requirements for the Award of

Master of Applied Science  
Mathematics and Planning

at the Department of Mathematics, Edith Cowan University



## ABSTRACT

This work is primarily aimed at determining the effect that an immunisation policy is likely to have on the incidence of Haemophilus Influenzae Type B (HIB) and systematic HIB in Western Australia. There was a significant effort made to collect data pertinent to the estimation of parameter values but since HIB has only been a notifiable disease since 1992 there was a distinct lack of relevant data available. Private communication with individuals such as Dr Jeffrey Hanna and Dr Beryl Wild resulted in practical information being obtained that was used to estimate certain parameters. The deterministic mathematical models within the thesis are extensions of existing ideas tailored to suit the needs of this thesis.

Chapter one is a basic introduction to the pursuit of modelling infectious diseases with a brief description of basic epidemiology concepts. It also shows that even simple models may not deliver analytical results. Chapter two extends a model used by Angela McLean and allows some analytical results to be obtained by first simplifying the model and then solving using standard methods to give the equilibrium distributions for the proportions of people in each state within the model.

Chapter three introduces a second model that is age dependent and determines whether the equilibrium state of the model is stable by using the Routh Hurwitz criteria. Finally the conditions for the Hopf Bifurcation theorem to hold true are examined. This theorem is applied to determine whether periodic orbits exist in the vicinity of the equilibrium point of the model. Chapter four is concerned with estimating the parameters within the model used in chapter three and attempts to give values applicable to the Aboriginal and Torres Strait population as well as the non-Aboriginal population.

Chapter five uses an existing Fortran 77 computer algorithm to numerically solve the system of differential equations formed in chapter three. This involves using different scenarios such as before and after immunisation. The chapter also determines epidemiological parameters such as the average age of infection before and after immunisation is introduced. Finally there is a section covering suggestions for further study and recommendations as a result of this thesis.

## **DECLARATION**

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any institution of higher education; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

## **ACKNOWLEDGMENTS**

Firstly I need to thank my supervisor Dr Catherine Comiskey for her continued support and encouragement during the duration of this research thesis. She has introduced me to the world of research and given valuable lessons in how to gain information required during the development of the thesis. Secondly I wish to thank my wife Noni for putting up with me particularly during the final semester and for her assistance in presenting this thesis. Thirdly I'd like to thank Edith Cowan University for awarding a research scholarship that allowed me to spend a period of weeks in full time study during a critical stage of this thesis. Fourthly I must thank Chris and Cathy for their lively discussions during the last two academic years and Cathy for introducing me to the basic medical concepts of Haemophilus Influenzae Type B. Finally I should thank Paul Maisey for providing the computer equipment used in the production of this thesis.

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## CHAPTER ONE

### Introduction to the Thesis

#### 1.1 Background to Modelling Infectious Diseases

Infectious diseases have been the cause of countless numbers of deaths. In Europe during the fourteenth century there were in the order of twenty five million deaths from bubonic plague ( the black death ) alone. This was about one quarter of the total population of Europe at that time. Individual communities were devastated or completely wiped out. One well known example is the English community of Eyam. The inhabitants were persuaded by the Rector, William Mompesson to isolate themselves from the outside world so as not to pass infection to anyone in the wider community. It was recorded that out of a population of about 350 at least 258 died as a result of infection (Anderson and May, 1991).

In the years 1918-1921 there were approximately twenty five million cases of typhoid reported in Russia with an associated mortality rate of around ten per cent. During the world pandemic of influenzae in 1919 there were about twenty million influenzae associated deaths. The Aztec civilisation lost over three million people to smallpox in the early 1520's. This was more than the losses incurred as a result of the Spanish invasion led by Cortes in the same period (Anderson and May, 1991).

In contrast, life expectancy has risen from 25-30 years in 1700 to about 70-80 years in the contemporary age. Contributing factors have been increased personal hygiene and improved nutrition as well as the advancement of medical science. In particular the twentieth century has seen vaccination programmes introduced on a world wide scale. An example of a successful initiative was the eradication of Smallpox during the 1970's (Anderson and May, 1991). Even though understanding about the spread of infectious diseases has increased during this period the number and size of epidemics also increased. One explanation is the concentration of large numbers of people into large urban environments.

Development of the mathematical theory of infectious diseases is believed to have begun during the second half of the eighteenth century although all the major theoretical advancements have occurred during the

twentieth century. In 1760 Daniel Bernoulli gave a paper to the Academie Royale des Science in Paris in which he formulated the course of a smallpox epidemic in mathematical terms. This paper showed for the first recorded time how mathematics could be used to investigate the dynamics of a disease. Bernoulli also gave an assessment of how the risks and benefits of a preventative inoculation policy could be analysed using the model he had developed.

It was not until the early twentieth century that the modern theoretical framework of infectious diseases started to emerge. Individuals such as Hamer (1906), Ross (1908) and Mashkovski (1905) were among the first to develop specific theories about the transmission of infectious diseases. In 1906 Hamer suggested that the course of an epidemic depends on the contact rate between the number of susceptibles and the number of infectious individuals. This concept is called the "mass action principle" and has been at the centre of mathematical epidemiology ever since. The principle argues that the net rate of spread of infection is proportional to the product of the density of susceptible individuals times the density of infectious individuals. Soper (1929) further developed the theoretical framework by deducing why epidemics occur on a periodic basis. In basic terms his argument is as follows. When an epidemic occurs within a given population the people within the population either recover from infection and gain a degree of immunity from further infection or die as a result of infection. This immunity is a result of the body developing antibodies with which it can fight off further infection from the same disease. This immunity may be lifelong or it may give protection for a certain period of time. Once a suitable period of time has elapsed there will be a replenishment of susceptibles from newborns and perhaps from the recovered individuals losing temporary immunity from infection. The same infectious disease can then re-enter the population and cause another epidemic.

In 1927 Kermack and Mc Kendrick introduced the threshold theorem which sets out necessary conditions for an epidemic to occur within a given population. Essentially the theorem says that if a quantity of infectious individuals is introduced to a previously uninfected susceptible population then an epidemic will not occur unless the quantity of susceptible individuals is above a certain critical value. This theorem will be explained in more detail in section 4 of this chapter.

Early modelling techniques were based on the concept of compartmental mathematical models. Such models divide the total population into a finite number of distinct groups which describe the different states that individuals might belong to during the transmission dynamics of an infectious disease. Examples are the susceptible, infectious and recovered states. It was commonly assumed by Bailey (1975) and others that the total population under consideration was constant. This means that the total death rate is equivalent to the total birth rate within a given population. Such a convenient assumption will simplify any compartmental mathematical model since a logistic function does not have to be introduced in order to describe the net change in the total population.

A definitive introduction entitled "The Mathematical Theory of Infectious Diseases" was published by Norman T. J. Bailey in 1975. This single work defined the theoretical framework for modelling infectious diseases. Bailey outlined the rationale behind compartmental, stochastic and discrete modelling techniques. A discrete model is one that uses difference equations to describe the dynamics of a disease whereas a stochastic model is one that uses a probabilistic approach. Within Bailey's general theory of deterministic epidemics the models implied that an infectious disease would occur periodically but that the magnitude of the epidemics would become less pronounced as the epidemic repeated itself within a given constant population. This means that there is a type of harmonic damping predicted by the models. Such damping is not evident when considering common childhood diseases like measles. Diseases like these may result in a series of epidemics occurring periodically. However there is no obvious damping in the magnitude of an epidemic. This means that a more recent epidemic may be of greater magnitude than a earlier epidemic of the same disease. The theory did not predict future occurrences with great accuracy but Bailey's theory did provide a comprehensive building block for future development. Roy Anderson and Robert May published a textbook entitled " Infectious Diseases of Humans " in May 1991. This publication built on Bailey's work in advancing the theory and practice of mathematical epidemiology. The book is divided into two main areas covering microparasites and macroparasites. There is an obvious emphasis on the biological processes at work as well a pragmatic approach to the mathematical modelling process.

This thesis will demonstrate how mathematics can be applied to obtain predictions for the future incidence of Haemophilus Influenzae Type B. Models will be developed and we will determine the effectiveness of a vaccination policy in reducing the incidence of HIB in the Western Australia community.

## 1.2 Introduction to Modelling Infectious Diseases

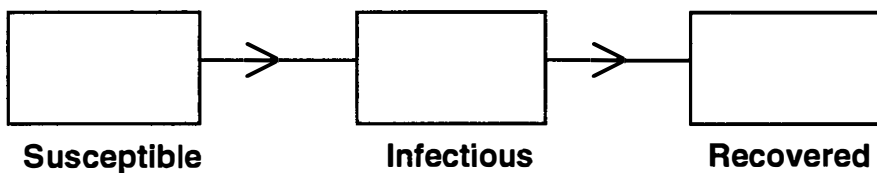
In their paper "Epidemics and the Spread of Disease" (1990, pg 147-180) Glynn James and Nigel Steele highlight a general approach to mathematically modelling infectious diseases. They begin by quoting the definition of an epidemic. " It is a disease that attacks in great numbers in one place, at one time, and itself travels from place to place." Another dictionary definition they state is that an epidemic " is a disease that is temporarily prevalent in a society ". They also say that an endemic disease " is one that is constantly or generally present in a society ". Widespread childhood diseases such as HIB tend to be constantly within a society but sometimes reach epidemic proportions so they are in a sense both endemic and epidemic.

James and Steele first assume that the population to be studied is large. This means that epidemiological processes within it can be considered as continuous. Therefore a deterministic methodology can be used to formulate in mathematical terms the dynamics of a disease. This means that differential equations can be introduced to model the different states an individual might belong to during the transmission dynamics of a disease. If a given population is small enough that epidemiological processes within it cannot be considered as continuous then it is necessary to use stochastic or probabilistic methods.

Another assumption they use is that a given population mixes in an homogeneous manner. This means that all epidemiological and demographic processes within a given population are averaged out. For example every individual has an equal probability of meeting any other individual within the community regardless of factors such as whether they live in a metropolitan or country region. The assumption also implies that any individual has an equal chance of being infected by a disease i.e. everyone is equally susceptible to infection regardless of age or previous infection. This assumption simplifies the task of measuring and defining parameters within a mathematical model and it therefore opens up the possibility of finding analytical solutions. However the assumption may not accurately reflect the dynamics of a

disease. For instance it may not be the case that a newborn child has the same probability of infecting an individual of school age as an individual in a school environment has of infecting another individual in the same school environment. Also there exists the possibility that recovery from infection might grant lifelong or temporary immunity from further infection. Homogeneous mixing can be used as a convenient place at which to begin the modelling process and it can then be refined as an appropriate model is developed.

To proceed with the development of a mathematical model it is necessary to define the states within the transmission dynamics of a disease. An individual might be susceptible to infection or infected and capable of passing on infection. The individual could also be recovered from infection. If we accept homogeneous mixing then recovered individuals would immediately become susceptible to further infection. However this assumption could be refined to say that recovered individuals have lifelong immunity from infection. Accepting this refinement we have a population where all members are considered as belonging to either the susceptible, infectious or recovered state. A suitable diagram is



If we initially accept that the total population is constant then a suitable set of equations describing the dynamics of a disease is provided by James and Steele, i.e.

$$\frac{dx(t)}{dt} = -\beta xy + \mu \quad 1.2.1 \quad \dots \text{Susceptibles } (x(t))$$

$$\frac{dy(t)}{dt} = \beta xy - \alpha y \quad 1.2.2 \quad \dots \text{Infected and infectious } (y(t))$$

$$\frac{dz(t)}{dt} = \alpha y - \mu \quad 1.2.3 \quad \dots \text{Recovered and immune } (z(t))$$

Here we have a set of three first order non-linear differential equations describing the rate of change between the three stages of the disease over time ,  $t$ . There are three parameters within this basic model. Firstly,  $\mu$

describes the death rate and allows the model to introduce a constant population by saying the birth rate is the same as the death rate. The parameter  $\alpha$  represents the recovery rate from infection. This parameter can be viewed as representing a constant time after which the infectious individual would recover from the infection. The final parameter  $\beta$  is commonly called the transmission rate of the disease. It is a complicated term since it is an attempt to measure aspects of human behaviour such as social interaction and personal hygiene. The purpose of the parameter is to quantify the rate at which the disease infects susceptibles. In this model it is considered to be both dependent on the number of susceptibles and the number of infected individuals. This relationship could be simplified by suggesting that the transmission rate is only dependent on the number of susceptibles. However it seems reasonable to expect the transmission rate of a disease to be influenced by both the number of infectious individuals and the number of susceptibles interacting within the general population. In the case where a disease is severe enough to stop infected individuals circulating within the community there could be a reasonable case for simplifying the relationship since infectious individuals could be considered as being removed from society for the period of infection. The question then is how long would it take before such a person is recognised as being infected by the disease and hence isolated. It seems that in most cases, if not all, an infected individual would be free to pass on infection for a period of time before it was recognised that the individual was infectious. It is obvious that the transmission rate is a complex parameter and will be discussed further in later chapters.

One of the main mathematical interests is the equilibrium state of the system of equations. In this situation everyone in the total population is characterised by belonging to a particular state of the disease and the numbers in each state do not change. When this occurs the dynamics of the disease can be considered as being in balance. It is possible for this to happen when an epidemic has settled down to a situation where any new infectious individual is balanced by a new susceptible ie a new birth, as well as a newly recovered individual and a death so that the numbers in each state remain the same. To determine the equilibrium values for the system of equations we set the rate of change between stages of the disease to be zero. The resulting equations should then yield appropriate values for the number of susceptibles and infectious individuals when the dynamics of the disease are in balance, we have,

$$-\beta xy + \mu = 0 \quad 1.2.4$$

$$\beta xy - \alpha y = 0 \quad 1.2.5$$

$$\alpha y - \mu = 0 \quad 1.2.6$$

One possible solution is that both  $x$  and  $y$  are zero. This particular solution is unrealistic since it implies there are no infectious or susceptible individuals. It could represent the situation where a disease has run through its life-span and everyone is immune to further infection or it may represent the time before the disease has been introduced to the population. However the solutions of interest are when we have at least some susceptible and infectious individuals. Therefore we are looking for non-zero positive values for the number of susceptible, infectious and recovered individuals. From 1.2.6 we have

$$\alpha y(t) - \mu = 0, \quad \therefore y(t) = \frac{\mu}{\alpha}$$

by substituting this value into 1.2.4 we get

$$x(t) = \frac{\alpha}{\beta},$$

using the relationship that  $N = x + y + z$ , where  $N$  is the total population, we can obtain a value for the number of recovered individuals at equilibrium i.e.

$$z(t) = N - \frac{\alpha}{\beta} - \frac{\mu}{\alpha}.$$

We have therefore obtained simple relationships for  $x(t)$ ,  $y(t)$  and  $z(t)$  in terms of the parameters within the model. Further to this a direct relationship between the susceptible and infectious individuals would be very useful since we could gain some insight into how one might affect the other. Assuming that the functions  $x(t)$  and  $y(t)$  are well behaved and that  $\mu \neq \beta xy$  we can divide 1.2.2 by 1.2.1 to give,

$$\frac{dy(t)}{dx(t)} = \frac{\beta xy - \alpha y}{\mu - \beta xy} \quad 1.2.7$$

This is a differential equation giving a relationship between the susceptibles and infected individuals but it doesn't allow a simple solution to be obtained. It is clear that even an apparently simple mathematical model may not allow analytical solutions to be obtained. Despite this we can still



employ methods that allow us to investigate the nature of the equilibrium point i.e. if the model reached its equilibrium will it stay close to its equilibrium values if any slight change is applied or will the model predict that any slight change to the equilibrium values would cause a significant shift away from the equilibrium values. James and Steele show how to employ perturbation techniques to this question by looking at what happens in the area immediately around the equilibrium. The aim is to show whether or not the equilibrium is stable or unstable. If a small change is applied to the equilibrium values and the system of equations move back towards the equilibrium after a period of time then the point is stable. However if the values move away from the equilibrium values then the point is unstable. Suppose,

$$x(t) = \frac{\alpha}{\beta} + \xi(t) \quad 1.2.8$$

$$y(t) = \frac{\mu}{\alpha} + \eta(t) \quad 1.2.9$$

where  $\xi(t)$  and  $\eta(t)$  are small perturbations away from the equilibrium values. Then by substituting 1.2.8 and 1.2.9 into 1.2.1 we have.

$$\frac{d\left(\frac{\alpha}{\beta} + \xi(t)\right)}{dt} = -\beta\left(\frac{\alpha}{\beta} + \xi(t)\right)\left(\frac{\mu}{\alpha} + \eta(t)\right) + u, \Rightarrow$$

$$\frac{d\xi(t)}{dt} = -\beta\left(\frac{\mu}{\beta} + \frac{\alpha}{\beta}\eta(t) + \frac{\mu}{\alpha}\xi(t) + \xi(t)\eta(t)\right) + \mu.$$

If we retain only linear terms in  $\xi(t)$  and  $\eta(t)$  we have

$$\frac{d\xi(t)}{dt} \approx -\frac{\beta\mu}{\alpha}\xi(t) - \alpha\eta(t) + \mu. \quad 1.2.10$$

and similarly from 1.2.2 we get

$$\frac{d\eta(t)}{dt} \approx \frac{\beta\mu}{\alpha}\xi(t). \quad 1.2.11$$

These can be further refined by eliminating one of the variables to give a second order differential equation. Differentiating 1.2.11 with respect to  $t$  gives

$$\frac{d^2\eta(t)}{dt^2} = \frac{\beta\mu}{\alpha} \frac{d\xi(t)}{dt} \quad 1.2.12$$

Equation 1.2.11 can also be arranged to give

$$\xi(t) = \frac{\alpha}{\beta\mu} \frac{d\eta}{dt} . \quad 1.2.13$$

Substituting 1.2.10 and 1.2.13 into 1.2.11 gives

$$\alpha \frac{d^2\eta(t)}{dt^2} + \beta\mu \frac{d\eta(t)}{dt} + \beta\mu\alpha\eta(t) = 0 . \quad 1.2.14$$

The characteristic equation of 1.2.14 is given by

$$\alpha n^2 + \beta\mu n + \beta\mu\alpha = 0, \quad \therefore$$

$$n = \frac{1}{2\alpha} (-\beta\mu \pm \sqrt{\beta\mu(\beta\mu - 4\alpha^2)})$$

If  $\beta\mu < 4\alpha^2$  then

$$n = -\frac{\beta\mu}{2\alpha} \pm \frac{i}{2\alpha} \sqrt{\beta\mu(4\alpha^2 - \beta\mu)} \quad 1.2.15$$

and the solution can be written in the form

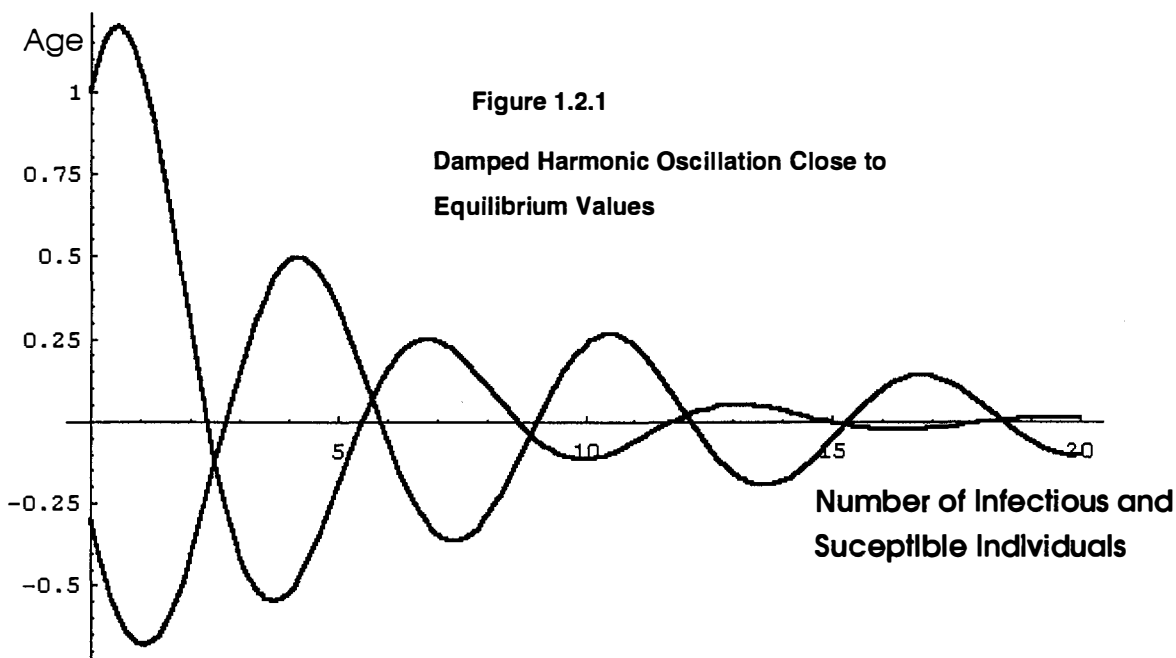
$$n(t) = e^{-\frac{\beta\mu}{2\alpha}t} (c_1 \cos t + c_2 \sin t) \quad 1.2.16$$

$$\xi(a) = e^{-\frac{\beta\mu}{2\alpha}t} \left( \frac{\alpha}{\beta\mu} (c_2 \cos t - c_1 \sin t) - \frac{1}{2} (c_2 \sin t + c_1 \cos t) \right) . \quad 1.2.17$$

The equation 1.2.14 is a well known standard form. If the parameters are real and positive as is the case when considering the transmission dynamics of a disease then it results in a damped harmonic oscillation about the equilibrium values. The period of oscillation when

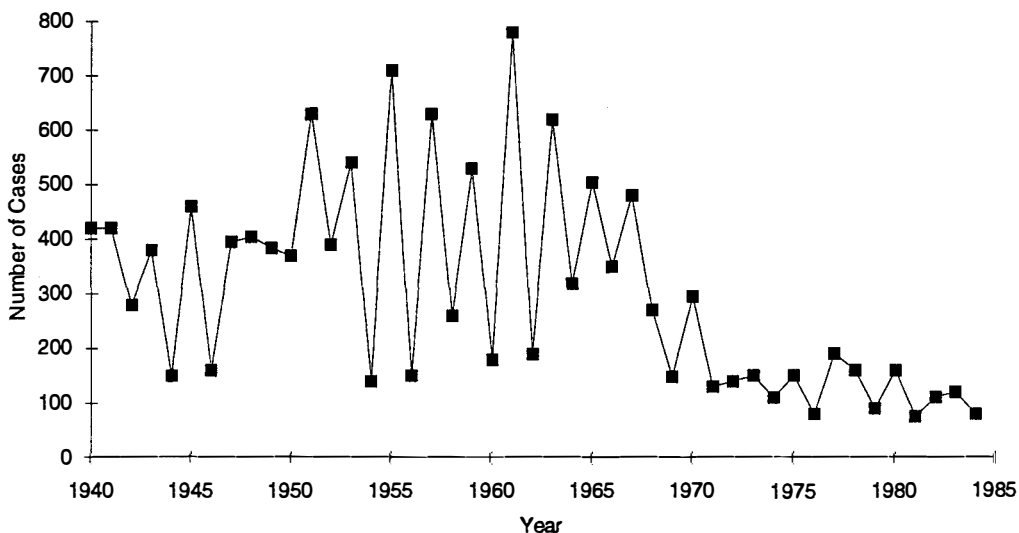
$$\beta^2 < 4\alpha^2 \text{ is } \frac{4\pi}{\sqrt{(4\alpha^2 - \beta\mu)\beta\mu}} .$$

As a result the equilibrium point is, in this case, stable. Figure 1.2.1 below illustrates how damped harmonic oscillation might occur close to the equilibrium point.



The main shortfall of such a convenient analysis is that the results predict that the disease will eventually die out. This may certainly be the case for some infections for which an immunisation policy has been introduced and applied in a widespread fashion but it certainly not true for diseases such as the common cold. Epidemics of diseases like the common cold tend to be periodic. Data gathered for measles indicate that there is a "three" yearly peak in the incidence of disease (Anderson and May, 1991), as figure 1.2.2 below shows.

**FIGURE 1.2.2, REPORTED CASES OF MEASLES PER ANNUM IN ENGLAND AND WALES 1940-1994**



This "three yearly peak" is often called the inter-epidemic period. What is clear however is that the incidence of disease does not tend to dampen down over a period of time, unless there are special conditions such as an immunisation policy. In conclusion James and Steele show how simple mathematical techniques can be used to model infectious diseases in a deterministic manner. However they also highlight the fact that a set of apparently simple differential equations can prove difficult to obtain analytical solutions from.

### **1.3 Background to Modelling Haemophilus Influenzae Type B**

Haemophilus Influenzae was first isolated by Pfeiffer in 1892 from the sputum of individuals during a flu epidemic. This disease only infects humans and the infection is predominantly in the upper respiratory tract ie above the Adam's apple. The disease is found world-wide being present in most societies at most times. As a result it is said to be endemic.

There are several strains of Haemophilus Influenzae with Haemophilus Influenzae type B (HIB) being the strain with which this thesis is concerned. This particular strain is a major concern to both parents and the medical profession since it can be the catalyst for infection from life threatening diseases. Dr P McIntyre ( Australian Family Physician, Vol 22, No 10, October 1993, pg 1782-1789) of Westmead Hospital states. " The most common type of invasive HIB are meningitis, epiglottitis and soft tissue infection." Further to this he says. "About one in four hundred non-aboriginal children develop invasive HIB diseases by the age of five years, but among some groups of aboriginal children up to one in fifty develop invasive HIB disease almost all before one year of age." In the same article Dr McIntyre goes on to say. "Meningitis accounts for about fifty per cent of invasive HIB disease and HIB causes about seventy per cent of childhood meningitis in Australia. The peak incidence of HIB meningitis is from six months to two years of age, but it remains the commonest cause of meningitis until at least ten years of age".

Systematic or invasive HIB cases appear to have a marked age relationship. (Systematic means that there is more than one part of the body infected, i.e. there is blood borne carriage to different sites within the body for example the meninges and the epiglottis.) Newborns, older children and

adults are not usually adversely affected by Systematic HIB. Strains of Haemophilus Influenzae can be found in up to eighty per cent of healthy individuals. However private communication with Dr Jeffrey Hanna of the Tropical Centre for Disease Control in Cairns indicated that it is not commonly type B that is found in older children and adults. This means that such people are unlikely to pass on infection of HIB to those susceptible to infection. Systematic Haemophilus Influenzae also appears to be seasonal. Within temperate climates it appears that invasive Haemophilus Influenzae diseases occur most frequently in late winter and early spring.

Amongst the various strains of Haemophilus Influenzae, type B is the most common. Bacterial meningitis, epiglottitis, pneumonia and swollen joints are examples of invasive HIB disease with meningitis being the most common. There is a high mortality rate amongst those infected by invasive HIB disease if the individuals concerned are not treated. This is especially true when considering meningitis and epiglottitis. Within Australia individuals who display signs of invasive HIB disease are usually hospitalised quickly, however there may be exceptions within remote or isolated communities. It is apparent that there is a life threatening risk associated with invasive HIB disease. Therefore it should prove worthwhile to study the transmission dynamics of the disease in order to attempt to increase understanding about the expected incidence after the introduction of the immunisation program.

#### **1.4 Basic Epidemiology Concepts**

If an infectious disease is to maintain a presence within a community then it must successfully reproduce infections at a rate greater than or equal to unity. This so called reproductive rate,  $R$ , is defined as the expected number of secondary cases produced by an infectious individual in a population of susceptibles. If this reproductive rate is less than unity i.e.  $R < 1$  then the disease will die out regardless of the number of susceptible individuals. The basic reproductive rate,  $R_0$ , of an infection is defined as the average number of secondary infections produced when one infectious individual is introduced into a population where everyone is susceptible. This definition is the same as the reproductive rate,  $R$ , when there is no disease present in a community. The basic reproductive rate is dependent on factors such as the contact rate between susceptibles and infectious individuals.

In order to derive epidemiological implications from the basic reproductive rate of an infectious disease Anderson and May ( Infectious Diseases of Humans, 1991 ) use the assumption of " weak homogeneous mixing " which says that the rate of new infections is linearly proportional to the total number of susceptibles,  $X$  ie  $\beta\bar{X}$  where  $\bar{X}(t) = \int_0^{\infty} X(a,t)da$ . Here  $X(a,t)$  is defined as the number of susceptibles of age  $a$  at time  $t$ . A more usual assumption is "strong homogeneous mixing" which means that the rate of new infections is proportional to both the number of susceptibles and infectious individuals ie  $\beta\bar{X}\bar{Y}$ , where  $\bar{Y}(t) = \int_0^{\infty} Y(a,t)da$ . Here  $Y(a,t)$  is defined as the number of susceptibles of age  $a$  at time  $t$ . Using the assumption of weak homogeneous mixing Anderson and May denoted the net fraction susceptible as  $\bar{x} = \frac{\bar{X}}{\bar{N}}$ , where  $\bar{N} = \int_0^{\infty} N(a,t)da$ . Here  $N(a,t)$  is defined as the total population of age  $a$  at time  $t$ .

Anderson and May then say that during the course of an epidemic of an infectious disease the number of secondary infections will decrease below the initial number occurring in a disease free community by a factor  $\bar{x}$ . We therefore have a relation between the basic reproductive rate and the effective reproductive rate which can be expressed mathematically as,

$$R = R_0 \bar{x} . \quad 1.4.1$$

If a disease is at its equilibrium or steady state position then the effective reproductive rate of the disease will be unity. In other words every infection present within the community would result in one secondary infection. Hence at this equilibrium value we have,

$$1 = R_0 \bar{x} . \quad 1.4.2$$

This relationship allows the estimation of the basic reproductive rate of an infectious disease. It can be used as an estimate regardless of the type of mixing assumed.

The next concept to be introduced is the Threshold Theorem. In order to illustrate the threshold theorem we can consider a community of constant size  $N$ . Within the population every individual is either susceptible,  $X$ , infected and infectious,  $Y$ , or recovered and immune from further infection,  $Z$ . A

simple system of equations describing the transmission dynamics of the disease is ,

$$\begin{aligned}\frac{dX}{dt} &= -\beta XY \\ \frac{dY}{dt} &= \beta XY - \alpha Y \\ \frac{dZ}{dt} &= \alpha Y\end{aligned}\tag{1.4.3}$$

which is the same system as 1.2.1-1.2.3 with birth and deaths removed. Here the transmission rate is  $\beta$  and the recovery rate is  $\alpha$  so that in time  $\nabla t$  there will be  $\beta XY \nabla t$  new infections and  $\alpha Y \nabla t$  recoveries in time  $\nabla t$ . If we assume  $x(t)$  and  $y(t)$  are well behaved and that  $\beta, x(t), y(t) \neq 0$  and then divided the second equation by the first we get

$$\frac{dY}{dX} = \frac{\beta XY - \alpha Y}{-\beta XY} = -1 + \frac{\alpha}{\beta X}\tag{1.4.4}$$

which can be rearranged and integrated to give

$$Y(X) = \frac{\alpha}{\beta} \ln X - X + c\tag{1.4.5}$$

where  $c$  is a constant dependent on the initial conditions of the model. We can also introduce a term  $\rho = \frac{\alpha}{\beta}$ , and call this term the "relative removal rate".

This term measures the recovery rate from infection divided by the transmission rate of the disease. As a consequence of the relative removal rate a description of the threshold theorem first introduced in 1927 by Kermack and Mc Kendrick ( Anderson and May, 1991 ) is as follows.

If the number of susceptibles,  $X$  is greater than the relative removal rate  $\rho$  ie  $X > \rho$  then  $Y(X)$  is an increasing function of  $X$  so the number of infectious individuals will increase. However if the number of susceptibles is less than the relative removal rate ie  $X < \rho$  then  $Y(X)$  will be a decreasing function of  $X$  and the number of infectious individuals will decrease. This can be seen from equation 1.4.4 in an obvious manner.

What this means in terms of epidemiology concepts is that an epidemic will not be able to occur unless the initial number of susceptibles is greater than the relative removal rate of the disease ie  $X_0 > \rho$ . If this condition is not satisfied then the disease will die out. An implication of the threshold theorem is that if immunisation rates can artificially reduce the number of susceptibles to a point where the relative removal rate is always greater than the number of

susceptibles then incidence of the infectious disease will diminish and may eventually die out. The disease will not be given the opportunity to reach epidemic proportions.

This chapter has introduced some of the developments in the history of mathematically modelling infectious diseases. A basic model was introduced and it was made clear that even simple models do not necessarily provide analytical solutions. Finally some basic epidemiological parameters were introduced that will be utilised in later chapters. The following chapter is concerned with introducing a more complex model that may more accurately represent the dynamics of HIB in Western Australia.



## CHAPTER TWO

### A MATHEMATICAL MODEL TO DESCRIBE THE TRANSMISSION DYNAMICS OF HAEMOPHILUS INFLUENZA TYPE B

#### 2.1 Introduction

When epidemics of common diseases like the common cold occur the majority of people affected suffer only mild personal inconvenience whilst the overall economic cost of the epidemic may be substantial. There are certain childhood diseases that can cause severe discomfort or even death in the worst cases. Haemophilus Influenzae type B (HIB) is predominantly a childhood disease that in itself is not particularly dangerous but it has the property that it can act as a catalyst for more serious infections such as bacterial meningitis or epiglottitis. It is therefore of practical relevance to try and determine why epidemics like HIB occur and investigate if it is possible to contain them through a public health strategy. If a disease can be transmitted from one person to another then the disease is said to be infectious or contagious. As a consequence it is possible for an epidemic of the disease to occur at some time. In order to minimise incidence of an infectious disease a common public health strategy is to implement a vaccination programme directly targeted at one or more infectious diseases. This thesis is an attempt to mirror the transmission dynamics of an infectious disease within a given population through the process of mathematical modelling. There are many issues that need to be addressed concerning the population to be studied. For this model the population is that of Western Australia and a selection of the relevant questions that need to be asked before the development of a models are as follows.

1. Is it necessary to study the total population?
2. Is the population constant?
3. Can the natural death rate be treated as constant?
4. How many initial infections would be needed for an epidemic to occur?
5. What is the average age of infection?
6. What effect would an immunisation policy have on the incidence of HIB?
7. How are parameters, such as the transmission rate of the disease, to be estimated?
8. Is it possible to obtain analytical results for the numbers of susceptible,

infectious and immune individuals or do we need to employ numerical methods?

Chapter four is dedicated to parameter estimation, the rest of the questions will be addressed during the development of suitable mathematical models in the next two chapters.

## 2.2 Definition of States and Parameters

To begin the modelling process we need to define distinct states during the transmission dynamics of HIB so that every individual within the given population will belong to only one of the states at any given age or time. Let

$M(a,t)$  = The number of individuals protected by maternal antibodies of age  $a$  at time  $t$

$X(a,t)$  = The number of susceptible individuals of age  $a$  at time  $t$

$H(a,t)$  = The number of latent individuals (infected but not yet infectious) of age  $a$  at time  $t$

$Y(a,t)$  = The number of infectious HIB individuals of age  $a$  at time  $t$

$K(a,t)$  = The number of systematic HIB individuals of age  $a$  at time  $t$

$Z(a,t)$  = The number of recovered or immune individuals of age  $a$  at time  $t$

$N(a,t)$  = The total population of age  $a$  at time  $t$ .

We now have several distinct states describing the transmission dynamics of HIB. It will be assumed that once an individual has recovered or has been successfully immunised then lifelong immunity is conferred on the individual. The next stage is to define the parameters associated with the transmission dynamics of HIB. Many of the compartmental models previously developed have assumed that the total population is constant i.e. the birth rate is equivalent to the death rate of the total population. Although this simplifies the resulting mathematical model, as will be seen in chapter 3, it is often an unrealistic assumption. Other parameters that will be introduced include the transmission rate, the recovery rate and the death rate associated with suffering systematic HIB diseases such as bacterial meningitis. A complete set of parameters is as follows.

- $\lambda(a)$  = The age dependent per capita force of infection  
 $\sigma(a)$  = The age dependent immunisation rate  
 $\mu(a)$  = The age specific death rate  
 $m(a)$  = The number of newborns with mothers of age  $a$   
 $\nu$  = The recovery rate from HIB infection  
 $\delta$  = Rate at which individuals lose protection due to maternal antibodies  
 $\theta$  = Rate at which people move from being in the latent class to the the infectious class  
 $\omega$  = Rate at which systematic HIB cases occur i.e. the rate at which people move from the infectious state to the systematic state.  
 $\phi$  = Recovery rate from systematic HIB  
 $\zeta$  = Systematic HIB death rate .

### 2.3 A Mathematical Model

With the parameters defined and the states of the model compartmentalised a set of partial differential equations describing the transmission dynamics of HIB can be constructed. Firstly, it is should noted that the following model is an extension of the one proposed by Angela McLean of Imperial College, London from a paper entitled "Dynamics of Childhood Infections in High Birth Rate Countries" presented at an international conference held at Mogilany, Poland, February 18-25, 1985. The following model extends A Maclean's model by adding an extra state that describes those individuals who suffer systematic HIB disease. The introduction of this additional state means that individuals who suffer HIB infection may acquire but do not necessarily acquire one of the systematic HIB diseases. Therefore such people may move either directly into the immune class or they may move into the systematic state. The assumptions that are used in the following of the model include the following.

1. The population is not constant.
2. The number of individuals in any class at a given time may change with age .
3. The number of individuals in any class at a given age may change with time.
4. All newborn individuals are born with immunity to infection due to the presence of maternal antibodies.
5. Once an individual has become immune to infection either as a result of

immunisation or recovery from the disease then lifelong immunity is conferred on the individual.

6. All individuals who acquire HIB infection remain in the latent state for a period of time and are therefore not capable of passing on infection until they move into the infectious state.

We can write the following system of equations,

$$\begin{aligned}
 \frac{\partial M(a,t)}{\partial a} + \frac{\partial M(a,t)}{\partial t} &= -(\delta + \mu(a))M(a,t) \\
 \frac{\partial X(a,t)}{\partial a} + \frac{\partial X(a,t)}{\partial t} &= \delta M(a,t) - (\lambda(a) + \sigma(a) + \mu(a))X(a,t) \\
 \frac{\partial H(a,t)}{\partial a} + \frac{\partial H(a,t)}{\partial t} &= \lambda(a)X(a,t) - (\theta + \mu(a))H(a,t) \\
 \frac{\partial Y(a,t)}{\partial a} + \frac{\partial Y(a,t)}{\partial t} &= \theta H(a,t) - (\nu + \omega + \mu(a))Y(a,t) \\
 \frac{\partial K(a,t)}{\partial a} + \frac{\partial K(a,t)}{\partial t} &= \omega Y(a,t) - (\phi + \zeta + \mu(a))K(a,t) \\
 \frac{\partial Z(a,t)}{\partial a} + \frac{\partial Z(a,t)}{\partial t} &= \sigma(a)X(a,t) + \nu Y(a,t) + \phi K(a,t) - \mu(a)Z(a,t) \\
 \frac{\partial N(a,t)}{\partial a} + \frac{\partial N(a,t)}{\partial t} &= -\mu(a)N(a,t) - \zeta K(a,t) .
 \end{aligned} \tag{2.3.1}$$

This system of equations describes the movement or flow of individuals between states during the transmission dynamics of HIB. The first equation describes the rate of change in the number of individuals protected by maternal antibodies with respect to age and time. The equation shows people leaving the class as a result of losing maternal antibody protection and also as a result of the background natural death rate. There is no need to explicitly include a term for newborns as this is taken care of by using suitable initial conditions.

The second equation describes the rate of change in the number of individuals in the susceptible class with respect to both age and time. Individuals enter the class as a result of leaving the maternal antibody class and they leave this class as a result of either becoming infected, dying or being immunised against HIB infection. In a similar fashion the third or latent class shows individuals entering as a result of becoming infected with HIB and leaving a result of becoming infectious or dying a natural death but not as a consequence of dying from HIB infection.

The fourth equation describes the rate of change in the number of individuals in the infectious state with respect to both age and time. Individuals enter this class when they leave the latent class and they leave this class as a consequence of either recovering from HIB infection, suffering systematic HIB infection or dying a natural death. The fifth equation shows the rate of change in the number of individuals in the systematic HIB class with respect to both age and time. Individuals enter when they suffer systematic HIB infection and leave as a result of either recovering from infection, dying a natural death or dying as a result of the systematic HIB disease.

The sixth equation shows the rate of change in the number of individuals in the recovered class with respect to both age and time. People can enter this class for three reasons. Firstly as a result of immunisation they move directly from the susceptible class to the immune class, secondly if they recover from HIB infection and thirdly if they recover from systematic HIB infection. Individuals only leave this class if they die a natural death. The final equation describes the rate of change in the total population with respect to both age and time. The total population decreases as a consequence of natural deaths and also because of systematic HIB deaths. Again there is no need for an explicit term to describe newborns since suitable initial conditions can be used that incorporate the birth rate.

We will now move on to the initial conditions. To begin, it is assumed that all newborn individuals are protected by maternal antibodies and therefore immune from infection for a certain period of time. Suitable initial conditions are,

$$M(0,t) = \int_0^{\infty} m(a)N(a,t)da \quad 2.3.2$$

$$X(0,t) = H(0,t) = Y(0,t) = K(0,t) = Z(0,t) = 0 \quad 2.3.3$$

and

$$M(a,t_0), X(a,t_0), H(a,t_0), Y(a,t_0), Z(a,t_0) \quad 2.3.4$$

are all known and fixed.

We therefore have the dynamics of the disease described at time  $t_0$ . The term  $m(a)N(a,t)$  describes the number of newborns with mothers of age  $a$ . If the total number of births is summed over all possible ages of the mother then the initial condition 2.3.2 is arrived at.

The per capita rate of infection is defined as (A. McClean, 1985)

$$\lambda(a,t) = \frac{\int_0^{\infty} \beta(a,a')Y(a',t)da'}{\int_0^{\infty} N(a',t)da'} \quad 2.3.5$$

where  $\beta(a,a')$  is the transmission rate of the disease from age  $a$  to  $a'$ . This term describes the probability that an infected person belonging to one age group will infect another individual belonging either to the same or another age group. A usual assumption is that individuals move from the susceptible to the infected state at a rate  $\beta XY$ . In this case the movement is at a rate proportional to the product of the number of susceptible and the number of infectious individuals. The term  $\beta$  also represents the combination of two epidemiological quantities. These are the degree of contact between the infectious and susceptible individual and the probability that contact between a susceptible and infected individual will result in a successful transmission of infection.

By the above definition for the per capita rate of infection it is clear that the transmission rate is no longer a constant of proportionality but is dependent upon the age groups that the susceptible and infectious individuals belong to. The transmission rate  $\beta(a,a')$  does combine two factors as in the simple proportional case but in an age dependent manner. The first is the degree of contact between susceptibles of age  $a$  and infectious individuals of age  $a'$ . It combines this with the likelihood that an infectious individual of age  $a'$  will successfully transmit infection to a susceptible of age  $a$ . This definition is an extension of the classical interpretation of the transmission rate.

The concept of an age structured model has been previously developed by Bailey, 1975 and Anderson and May, 1991. In these models we have a finite set of  $N$  discrete age groups or classes. Further it is usually assumed that for a susceptible in the  $i^{\text{th}}$  age class and an infectious person in the  $j^{\text{th}}$  age class the transmission rate would be constant i.e.  $\beta(a,a')$  would be a constant,  $\beta_{ij}$ . As a result of this assumption it is possible to construct a  $N \times N$  matrix which completely describes the transmission rates across all distinct age groups. This type of a matrix is commonly termed a Who Acquired Infection From Whom ( WAIFW ) matrix. However the task of finding  $N^2$

distinct components from only  $N$  distinct age groups remains. A common restriction placed upon this matrix is that it is in some form symmetrical. In the simplest scenario the element  $\beta_{ij} = \beta_{ji}$ , so that there are at most  $\frac{N^2 + N}{2}$  distinct elements to be found. Two examples of WAIFW matrices are below.

$$\beta_{ij} = \begin{bmatrix} \beta_1 & \beta_1 & \beta_3 & \beta_4 \\ \beta_1 & \beta_2 & \beta_3 & \beta_4 \\ \beta_3 & \beta_3 & \beta_3 & \beta_4 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 \end{bmatrix} \quad \beta_{ij} = \begin{bmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_2 & \beta_2 & \beta_2 & \beta_2 \\ \beta_3 & \beta_3 & \beta_3 & \beta_3 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 \end{bmatrix}$$

The first matrix can be used to describe the situation where the main route of transmission is through one particular age group, in this case age group two. Individuals in other age groups have their transmission rate described by the other terms  $\beta_1, \beta_3$ , and  $\beta_4$ . This could correspond to the situation described earlier where infectious individuals of school age, say age group two, are more likely to infect susceptibles within the same age group. The element  $\beta_2$  would reflect this by being larger than the other elements in the matrix. Further the elements  $\beta_1, \beta_3$ , and  $\beta_4$  reflect the other possible transmission routes. For instance the probability that an infectious person in age group one infects a susceptible in age group three would be given by the element  $\beta_3$ . The probability of the reverse situation is also given by the element  $\beta_3$ . In this manner the elements of a WAIFW matrix can be manipulated to simulate the probability of a successful transmission of infection across the different age groups. The design of the matrix will depend on empirical evidence about previous incidence of an infectious disease.

The second matrix can be used to describe the situation where the transmission rate depends only on the age of the susceptible and not on the age of the infectious individual. This can be seen by noticing that the probability of an infectious person in age group one successfully infecting a susceptible in any age group is given by the element  $\beta_1$ . Since all the elements in any row of the matrix are identical then the same is true for infectious individuals that belong to any of the other age groups. Other possible scenarios have been discussed by Anderson and May (1991) but the usual approach is to reduce the matrix to at most  $\frac{N^2 + N}{2}$  distinct elements so that collected data can be used to estimate the elements of the matrix. As previously mentioned one way of achieving this simplification is by assuming

that an individual in age group  $i$  has the same probability of being infected by an infectious individual in age group  $j$  as a susceptible in age group  $j$  has of being infected by an infectious individual in age group  $i$  so that  $\beta_{ij} = \beta_{ji}$ .

The system of equations 2.3.1 can be simplified in the following manner. Let the proportion of the total population in each state at a given age be denoted by  $\hat{M}, \hat{X}, \hat{H}, \hat{Y}, \hat{K}, \hat{Z}$  where  $\hat{M}(a, t) = \frac{M(a, t)}{N(a, t)}$  and similarly for the other proportions. In the set of equations 2.3.1, if we divide each equation by  $N(a, t)$ , then every right hand term will have a term describing the disease induced death rate. This is because the rate of change in the total population is affected by the disease induced death rate as well as the background death rate ie.

$$\begin{aligned} \hat{M}(a, t) &= \frac{M(a, t)}{N(a, t)}, \quad \therefore \\ \frac{\partial \hat{M}(a, t)}{\partial a} + \frac{\partial \hat{M}(a, t)}{\partial t} &= \frac{\left( \frac{\partial M(a, t)}{\partial a} + \frac{\partial M(a, t)}{\partial t} \right) N(a, t) - \left( \frac{\partial N(a, t)}{\partial a} + \frac{\partial N(a, t)}{\partial t} \right) M(a, t)}{(N(a, t))^2} \\ &= \frac{-(\delta + \mu(a))M(a, t)N(a, t) - (\mu(a)N(a, t) - \delta K(a, t))M(a, t)}{(N(a, t))^2} \\ &= -(\delta + \mu(a)) \frac{M(a, t)}{N(a, t)} \left( \frac{-\mu(a)N(a, t) - \delta K(a, t)}{N(a, t)} \right) \frac{M(a, t)}{N(a, t)} \\ &= -(\delta + \mu(a)) \hat{M}(a, t) + \mu(a) + \frac{\delta K(a, t)}{N(a, t)} \hat{M}(a, t) \\ &= -\delta \hat{M}(a, t) + \frac{\delta K(a, t)}{N(a, t)} \hat{M}(a, t). \end{aligned}$$

So every equation will have a term describing the systematic HIB death rate,  $\zeta K(a, t)$ . This extra term can be removed by defining an additional state within the model. Let this extra state be representative of those individuals who have died as a result of systematic HIB infection and who would not of died of another cause. If this extra class is denoted by  $E(a, t)$  then the numbers in this class of age  $a$  at time  $t$  will be given by the partial differential equation.

$$\frac{\partial E(a, t)}{\partial a} + \frac{\partial E(a, t)}{\partial t} = \zeta K(a, t) - \mu(a)E(a, t) \quad . \quad 2.3.6$$

The total population can then be altered to include this extra class. Let the new total population be given by



$$W(a,t) = N(a,t) + E(a,t).$$

2.3.7,

This equation is the original total population plus those who have died as a result of systematic HIB disease. This new total population can then be derived as a partial differential equation as follows.

$$\begin{aligned} \frac{\partial W(a,t)}{\partial a} + \frac{\partial W(a,t)}{\partial t} &= \frac{\partial N(a,t)}{\partial a} + \frac{\partial N(a,t)}{\partial t} + \frac{\partial E(a,t)}{\partial a} + \frac{\partial E(a,t)}{\partial t} \\ &= -\zeta(a)K(a,t) - \mu(a)N(a,t) + \zeta K(a,t) - \mu(a)E(a,t) \\ &= -\mu(a)W(a,t) \end{aligned}$$

since  $W(a,t) = N(a,t) + E(a,t)$ .

This new "total population" is only dependent on the background death rate so we can define a new set of variables that remove the dependency on the systematic HIB death rate. Let

$$\begin{aligned} M'(a,t) &= \frac{M(a,t)}{W(a,t)}, X'(a,t) = \frac{X(a,t)}{W(a,t)}, H'(a,t) = \frac{H(a,t)}{W(a,t)} \\ Y'(a,t) &= \frac{Y(a,t)}{W(a,t)}, K'(a,t) = \frac{K(a,t)}{W(a,t)}, Z'(a,t) = \frac{Z(a,t)}{W(a,t)} \end{aligned}$$

which describes the proportion of the new total population that belongs to any particular state within the transmission dynamics of HIB. From the first of these proportions we have

$M'(a,t)W(a,t) = M(a,t)$  which can be differentiated to give

$$\left( \frac{\partial}{\partial a} + \frac{\partial}{\partial t} \right) M'W = \frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} \text{ i.e.}$$

$$W \left( \frac{\partial M'}{\partial a} + \frac{\partial M'}{\partial t} \right) + M' \left( \frac{\partial W}{\partial a} + \frac{\partial W}{\partial t} \right) = -\delta M(a,t) - \mu(a)M(a,t).$$

But we know

$$\frac{\partial W(a,t)}{\partial a} + \frac{\partial W(a,t)}{\partial t} = -\mu(a)W(a,t), \text{ hence}$$

$$W(a,t) \left( \frac{\partial M'}{\partial a} + \frac{\partial M'}{\partial t} \right) = -(\delta + \mu(a))M(a,t) + \mu(a)W(a,t)M'(a,t).$$

$$\therefore \frac{\partial M'(a,t)}{\partial a} + \frac{\partial M'(a,t)}{\partial t} = -(\delta + \mu(a)) \frac{M(a,t)}{W(a,t)} + \mu(a) M'(a,t)$$

$$\text{since } \frac{M(a,t)}{W(a,t)} = M'(a,t).$$

Hence we have,

$$\frac{\partial M'(a,t)}{\partial a} + \frac{\partial M'(a,t)}{\partial t} = -\delta(a) M'(a,t). \quad 2.3.8$$

If this process is applied to the original system of equations we get.

$$\begin{aligned} \frac{\partial X'(a,t)}{\partial a} + \frac{\partial X'(a,t)}{\partial t} &= \delta M'(a,t) - (\lambda(a,t) + \sigma(a)) X'(a,t) \\ \frac{\partial H'(a,t)}{\partial a} + \frac{\partial H'(a,t)}{\partial t} &= \lambda(a,t) X'(a,t) - \theta H'(a,t) \\ \frac{\partial Y'(a,t)}{\partial a} + \frac{\partial Y'(a,t)}{\partial t} &= \theta H'(a,t) - (\nu + \omega) Y'(a,t) \\ \frac{\partial K'(a,t)}{\partial a} + \frac{\partial K'(a,t)}{\partial t} &= \omega Y'(a,t) - (\phi + \zeta) K'(a,t) \\ \frac{\partial Z'(a,t)}{\partial a} + \frac{\partial Z'(a,t)}{\partial t} &= \sigma(a) X'(a,t) + \theta K'(a,t) + \nu Y'(a,t) \\ \frac{\partial E'(a,t)}{\partial a} + \frac{\partial E'(a,t)}{\partial t} &= \zeta(a) K'(a,t). \end{aligned} \quad 2.3.9$$

The boundary conditions become,

$$M'(0,t) = 1$$

$$X'(0,t) = H'(0,t) = Y'(0,t) = K'(0,t) = Z'(0,t) = E'(0,t) = 0.$$

The equations are now in a form that is independent of both the background and systematic HIB death rates. To examine how the system behaves we must first look at the system when there is no longer any change in the rate of flow between the different states of the disease. In order to do this we can drop the time dependence from the model and find the age distribution of each of the states in terms of the parameters within the model. For the following calculations it will be assumed that the age dependent vaccination rate is actually a constant. This means that the susceptibles are immunised at a rate proportional to the number of susceptibles. It should also be noted that both the force of infection and the systematics HIB death rates are to be treated as constants within age groups. The equation governing the proportion of the population protected by maternal antibodies can then be solved using standard methods. We have

$$\frac{\partial M'(a,t)}{\partial a} + \frac{\partial M'(a,t)}{\partial t} = -\delta(a)M'(a,t)$$

which upon removing time dependence and applying the above assumptions reduces to a first order linear ordinary differential equation,

$$\frac{dM'(a)}{da} = -\delta M'(a).$$

$$\therefore \frac{dM'(a)}{M'(a)} = -\delta da \text{ i.e., } \ln M'(a) = -\delta a + c, \therefore$$

$$M'(a) = \exp(-\delta a + c).$$

But we have  $M'(0) = 1$ , i.e.,  $1 = \exp(c)$

hence  $c = 0$ , So the solution is,

$$M'(a) = \exp(-\delta a).$$

Similarly the rest of the equations reduce to,

$$\frac{dX'(a)}{da} = \delta M'(a) - (\lambda + \sigma)X'(a)$$

$$\frac{dH'(a)}{da} = \lambda X'(a) - \theta H'(a)$$

$$\frac{dY'(a)}{da} = \theta H'(a) - (\nu + \omega)Y'(a)$$

2.3.10

$$\frac{dK'(a)}{da} = \omega Y'(a) - (\phi + \zeta)K'(a)$$

$$\frac{dZ'(a)}{da} = \sigma X'(a) + \nu Y'(a) + \phi K'(a)$$

$$\frac{dE'(a)}{da} = \zeta K'(a).$$

These can be solved by the familiar integration factor method, for example the number of susceptibles is determined as follows,

$$\frac{dX'(a)}{da} = \delta M'(a) - (\lambda + \sigma)X'(a)$$

$$\therefore \frac{dX'(a)}{da} + (\lambda + \sigma)X'(a) = \delta \exp(-\delta a), \text{ since we have } M'(a) = \exp(-\delta a)$$

Applying a suitable integrating factor, i.e.  $\exp(\lambda + \sigma)a$ , we get

$$X'(a) = e^{-(\lambda + \sigma)a} \left( \int e^{(\lambda + \sigma)t} \delta e^{-\delta t} dt + c \right)$$

$$X'(a) = e^{-(\lambda + \sigma)a} \left( \frac{\delta e^{(\lambda + \sigma - \delta)a}}{\lambda + \sigma - \delta} + c \right).$$

We have the initial condition  $X'(0) = 0$ ,  $\therefore$

$$0 = \frac{\delta}{\lambda + \sigma - \delta} + c.$$

Hence the general solution at equilibrium is

$$X'(a) = c_1 \{ e^{-\delta a} - e^{-(\lambda + \sigma)a} \}$$

$$\text{where } c_1 = \frac{\delta}{\lambda + \sigma - \delta}$$

All of the ordinary differential equations can be solved in this manner.

The following solutions were obtained,

$$H'(a) = \lambda c_1 \left( \frac{e^{-\delta a}}{\theta - \delta} + \frac{e^{-(\lambda + \sigma)a}}{\lambda + \sigma - \theta} - c_2 e^{-\theta a} \right)$$

$$\text{where } c_2 = \frac{1}{\theta - \delta} + \frac{1}{\lambda + \sigma - \theta}.$$

$$Y'(a) = \lambda \theta c_1 \left( \frac{e^{-\delta a}}{(\theta - \delta)(v + \omega - \delta)} + \frac{e^{-(\lambda + \sigma)a}}{(\lambda + \sigma - \theta)(v + \omega - \lambda - \theta)} - \frac{c_2 e^{-\theta a}}{(v + \omega - \theta)} - c_3 e^{-(v + \omega)a} \right)$$

$$\text{where } c_3 = \frac{1}{(\theta - \delta)(v + \omega - \delta)} + \frac{1}{(\lambda + \sigma - \theta)(v + \omega - \lambda - \theta)} - \frac{c_2}{(v + \omega - \theta)}.$$

$$K'(a) = \lambda \omega \theta c_1 \left( \frac{e^{-\delta a}}{(\theta - \delta)(v + \omega - \delta)(\phi + \zeta - \delta)} + \frac{e^{-(\lambda + \sigma)a}}{(\lambda + \sigma - \theta)(v + \omega - \lambda - \sigma)(\phi + \zeta - \lambda - \sigma)} \right. \\ \left. - \frac{c_2 e^{-\theta a}}{(v + \omega - \theta)(\phi + \zeta - \theta)} - \frac{c_3 e^{-(v + \omega)a}}{(\phi + \zeta - v - \omega)} - c_4 e^{-(\phi + \zeta)a} \right)$$

$$\text{where } c_4 = \frac{1}{(\theta - \delta)(v + \omega - \delta)(\phi + \zeta - \delta)} + \frac{1}{(\lambda + \sigma - \theta)(v + \omega - \lambda - \sigma)(\phi + \zeta - \lambda - \sigma)} \\ - \frac{c_2}{(v + \omega - \theta)(\phi + \zeta - \theta)} - \frac{c_3}{(\phi + \zeta - v - \omega)}.$$

We can also obtain an expression for the recovered or immune equilibrium state, i.e.

$$\begin{aligned}
Z'(a) = & c_1 \left( \frac{1}{\lambda + \sigma} \left( \sigma - \left( \frac{\lambda \theta}{(\lambda + \sigma - \theta)} \left( v + \frac{\phi \omega}{(\phi + \zeta - \lambda - \sigma)} \right) \right) \right) \right) e^{-(\lambda + \sigma)a} \\
& - \frac{1}{\delta} \left( \sigma + \left( \frac{\lambda \theta}{(\theta - \delta)(v + \omega - \delta)} \left( v + \frac{\omega \theta}{(\phi + \zeta - \delta)} \right) \right) \right) e^{-\delta a} \\
& + \frac{\lambda \theta c_2}{\theta(v + \omega - \theta)} \left( v + \frac{\theta \omega}{(\phi + \zeta - \theta)} \right) e^{-\theta a} \\
& + \frac{\lambda \theta c_3}{(v + \omega)} \left( v + \frac{\theta \omega}{(\phi + \zeta - v - \omega)} \right) e^{-(v + \omega)a} + \frac{c_4}{\phi + \zeta} e^{-(\phi + \zeta)a} - c_5
\end{aligned}$$

$$\begin{aligned}
\text{where } c_5 = & \frac{1}{\lambda + \sigma} \left( \sigma - \left( \frac{\lambda \theta}{(\lambda + \sigma - \theta)} \left( v + \frac{\phi \omega}{(\phi + \zeta - \lambda - \sigma)} \right) \right) \right) \\
& + \frac{\lambda \theta c_2}{\theta(v + \omega - \theta)} \left( v + \frac{\theta \omega}{(\phi + \zeta - \theta)} \right) + \frac{\lambda \theta c_3}{(v + \omega)} \left( v + \frac{\theta \omega}{(\phi + \zeta - v - \omega)} \right) \\
& + \frac{c_4}{\phi + \zeta} .
\end{aligned}$$

Finally

$$E'(a) = \zeta \int K'(a) da$$

$$\begin{aligned}
E'(a) = & \lambda \omega \theta \zeta c_1 \left( \frac{-e^{-\delta a}}{\delta(\theta - \delta)(v + \omega - \delta)(\phi + \zeta - \delta)} - \frac{e^{-(\lambda + \sigma)a}}{(\lambda + \sigma)(\lambda + \sigma - \theta)(v + \omega - \lambda - \sigma)(\phi + \zeta - \lambda - \sigma)} \right) \\
& + \frac{c_2 e^{-\theta a}}{\theta(v + \omega - \theta)(\phi + \zeta - \theta)} + \frac{c_3 e^{-(v + \omega)a}}{(v + \omega)(\phi + \zeta - v - \omega)} + \frac{c_4 e^{-(\phi + \zeta)a}}{\phi + \zeta} + c_5
\end{aligned}$$

$$\begin{aligned}
\text{where } c_6 = & \left( \frac{1}{\delta(\theta - \delta)(v + \omega - \delta)(\phi + \zeta - \delta)} + \frac{1}{(\lambda + \sigma)(\lambda + \sigma - \theta)(v + \omega - \lambda - \sigma)(\phi + \zeta - \lambda - \sigma)} \right) \\
& - \frac{c_2}{\theta(v + \omega - \theta)(\phi + \zeta - \theta)} - \frac{c_3}{(v + \omega)(\phi + \zeta - v - \omega)} - \frac{c_4}{\phi + \zeta} .
\end{aligned}$$

We can then derive the relationship between the two new sets of variables. That is between the proportions of the population actually in each state at any particular age and the "extra state" defined by the set of equations that removes dependence on the disease induced death rate. We have ,

$W(a) = N(a) + E(a)$ , or alternatively

$$N(a) = W(a) - E(a).$$

We also know that

$$E(a) = W(a)E'(a).$$

$$\therefore N(a) = W(a)(1 - E'(a)).$$

$$\therefore \hat{M}(a) = \frac{M(a)}{W(a)(1 - E'(a))} = \frac{M'(a)}{(1 - E'(a))}.$$

The same method can be applied to the other states to give.

$$\hat{X}(a) = \frac{X'(a)}{1 - E'(a)}, \hat{H}(a) = \frac{H'(a)}{1 - E'(a)}, \hat{Y}(a) = \frac{Y'(a)}{1 - E'(a)}, \hat{K}(a) = \frac{K'(a)}{1 - E'(a)}, \hat{Z}(a) = \frac{Z'(a)}{1 - E'(a)}.$$

Given that seriological surveys or case notifications have been successful we have an estimate for  $\hat{X}(a)$ , the proportion of the population susceptible at a given age. If we have estimated values for all the parameters in the model except for the force of infection we can use this information to estimate the force of infection and a simple root finding routine can be used to achieve this objective. From the expression for the proportion of susceptibles we have, after rearrangement

$$0 = \hat{X}(a)(1 - E'(a)) - X'(a).$$

This formula could be used to find estimates for the age specific force of infection. We now have an expression for determining age specific values for the force of infection. Classical models such as that by Bailey 1975, did not take into account the disease induced death rate. Since the term  $(1 - E'(a))$  is dependent on the disease induced death rate it will have a direct effect on the age specific values for the force of infection. From before we have

$$\frac{dE(a)}{da} = \zeta(a)K'(a), \text{ i.e.}$$

$$E'(a) = \int_0^a \zeta(p)K'(p)dp.$$

We now need a method for incorporating the systematic HIB age dependent death rate. Mathematically this can be achieved quite easily. Let  $q_1, q_2, q_3, \dots, q_{n-1}, q_n$  represent the proportion of age specific case fatalities in the age groups  $0$  to  $a_1, a_1$  to  $a_2, a_2$  to  $a_3, a_{n-1}$  to  $a_n$ . The systematic HIB death rates for the same age groups can then be found in the following manner. We

know that  $q_i$  represents the proportion of people who leave the systematic state in the age group  $a_{j-1} - a_j$  and enter the introduced state  $E(a)$ . Mathematically this can be written as

$$q_j = \frac{\zeta_j}{(\phi + \zeta_j)}, \text{ where } \phi \text{ is the recovery rate from systematic HIB}$$

disease.

This equation says that the proportion of the population in the disease induced state from a particular age group is determined by the age independent rate at which individuals move into the systematic HIB state plus those people from the same particular age group who enter the disease induced state. We can rearrange to give,

$$\zeta_j = \frac{\phi q_j}{(1 - q_j)},$$

so that we have a method through which the age dependent disease induced death rate can be estimated. Therefore this method could be applied to estimate the age specific values for the force of infection. In turn this allows the age specific transmission rates of the disease to be estimated.

## 2.4 EPIDEMIOLOGICAL PARAMETERS

Three epidemiological parameters of real interest are the average age at infection, the basic reproductive rate of the disease and the critical vaccination proportion of the susceptibles that would eradicate or minimise incidence of the disease. The model in its current form can be used to calculate these values but any simplification would also be useful. One immediate choice is to remove the class of people protected by maternal antibodies by incorporating these newborns into initial conditions for the number of susceptibles. The boundary condition for this state becomes,

$$X(0, t) = \int_0^{\infty} m(a)N(a, t)da$$

This condition allows the susceptible state to take into account the individuals protected by maternal antibodies. Between  $0 - a_i$  months of age

there will be no individuals contributing to the number of susceptibles but once these individuals become older than  $a_i$  months they would become susceptible to infection.

For the approximation of the epidemiological parameters it will be assumed that the background and systematic HIB death rates are constant. Further it will be assumed that there is only one age group. Although this may simplify the analysis it allows the parameters to be analytically approximated.

Firstly the total number of susceptible and infectious individuals of all ages is given by,  $\bar{X}(t), \bar{Y}(t)$  respectively and the total population by  $\bar{N}(t)$ . Also since we know that the number of births in year  $t$  is given by  $N(0, t)$ , we can then state the following definition. The average birth rate  $B$  is defined as

$$B = \frac{N(0, t)}{N(t)}$$

This was first introduced by Anderson and May 1985. We also know that

$$\begin{aligned} N(0, t) &= \int_0^{\infty} m(a)N(a, t)da \\ &= \int_0^{\infty} m(a)(1 - E(a))W(a, t)da \\ &= \int_0^{\infty} \tilde{m}(a)W(a, t)da \end{aligned}$$

where  $\tilde{m} = m(a)(1 - E(a))$ .

Further  $W(0, t) = N(0, t)$ , because these are both measures of the same birth rate.

$$\therefore W(0, t) = \int_0^{\infty} \tilde{m}(a)W(a, t)da$$

This is a standard result ( McClean, 1985 ), on the growth of human populations and implies that the population will settle down to a stable age distribution. The growth rate is given by  $\tilde{g}$  and must satisfy the Euler condition.



$$\int \tilde{m}(a)e^{-(\tilde{g}+\mu)a} da = 1$$

The stable age distribution is given by.

$$W(a, t) = W(0, t)e^{-(\tilde{g}+\mu)a} .$$

The population  $\bar{N}(t)$  grows at a similar rate given by.

$$\begin{aligned} N(a, t) &= W(a, t) - E(a, t) \\ &= W(a, t)(1 - E(a)) . \end{aligned}$$

Therefore we have

$$\begin{aligned} \frac{d\bar{N}(t)}{dt} &= \int_0^{\infty} \frac{\partial N(a, t)}{\partial t} da \\ &= \tilde{g} \bar{N}(t) \end{aligned}$$

hence

$$\bar{N}(t) = \bar{N}(0)e^{\tilde{g}t} .$$

Where  $\bar{n}(0)$  denotes the initial condition that  $\bar{N}(0) = \bar{n}(0)$ .

The equilibrium value of the total number of susceptibles can be found by using the following equation,

$$\begin{aligned} \bar{X}(t) &= \int_0^{\infty} X(a, t) da \\ &= \frac{W(0, t)}{(\tilde{g} + \mu + \lambda)} . \end{aligned}$$

This gives the number of susceptibles present in the population when the rate of change of the proportion maternal, latent, susceptible, infectious systematic and immune is zero.

This chapter has shown how a set of partial differential equations can be used to describe the transmission dynamics of an infectious ideas, in this case HIB. It has also been seen that mathematical techniques can be applied to simplify the system of equations in order to find methods for estimating basic epidemiological parameters and the equilibrium distributions for the proportions in each class.

Finally the chapter has emphasised the complexity of the per capita force of infection and one possible way of determining the transmission rate of the disease across all age groups. The next chapter is concerned with using an alternative approach to building a suitable model and then analysing the model to determine whether the equilibrium points are stable.

## CHAPTER THREE

### AN ALTERNATIVE MODEL

#### 3.1 An Alternative Model

Instead of assuming that the age structured model depends on both age and time and then dropping the time dependence in order to find the equilibrium age distributions for the proportions in each state of the disease it is possible to define a model that is dependent on age only. In this case a set of first order ordinary differential equations will describe the transmission dynamics of HIB. The parameters from the first method can still be used but an explicit term describing the birth rate of the population needs to be included. This model is based upon existing principles such as those used by Bailey , 1975 and Anderson and May ,1991 but those ideas have been extended for the purpose of this thesis. During the period of research I have not found the following system of equations in any publication I have read. The assumptions in this model are similar to those used for the first model and include the following.

1. The population is not constant.
2. The number of individuals in any class at a given time may change with age .
3. All newborn individuals are born with immunity to infection due to the presence of maternal antibodies.
4. Once an individual has become immune infection either as a result of immunisation or recovery from the disease then lifelong immunity is conferred on the individual.
5. All individuals who acquire HIB infection remain in the latent state for a period of time and are therefore not capable of passing on infection until they move into the infectious state.

In this case a system of equations that describe how the rate of change in the numbers in each state changes in a small age period  $\Delta a$  is as below.

$$\begin{aligned}
\frac{dM(a)}{da} &= m(a)N(a) - (\delta + \mu(a))M(a) \\
\frac{dX(a)}{da} &= \delta M(a) - (\lambda + \sigma(a) + \mu(a))X(a) \\
\frac{dH(a)}{da} &= \lambda X(a) - (\theta + \mu(a))H(a) \\
\frac{dY(a)}{da} &= \theta H(a) - (v + w + \mu(a))Y(a) \\
\frac{dK(a)}{da} &= wY(a) - (\phi + \zeta + \mu(a))K(a) \\
\frac{dZ(a)}{da} &= \sigma(a)X(a) + vY(a) + \phi K(a) - \mu(a)Z(a) \\
\frac{dN(a)}{da} &= (m(a) - \mu(a))N(a) - \zeta K(a)
\end{aligned} \tag{3.1.1}$$

The first equation contains the explicit term for the newborns that needs to be included in this age dependent model. This term is  $m(a)N(a)$  and describes the birth rate as a fraction of the total population. In order to analyse how these equations behave it is convenient to allow the age dependent parameters to become constants so that these parameters are treated as being the same for the entire population. This means that the background death rate will be treated as being the same for the entire population. Similarly the birth rate will be made a constant fraction of the total population rather than being dependent on age. It will also be assumed that there is no vaccination programme in place. Further it will be assumed that there is no distinct maternal antibody state in the disease. This could mean that everyone is born susceptible or that initial conditions can be used to incorporate those protected by saying that the initial number of susceptibles of age zero is none and then allowing these newborns to become susceptible after a certain number of months. The state of latent individuals will also be removed and this corresponds to the situation where an individual is capable of passing on infection to others as soon as he/she is infected. Finally it will be assumed that there are no deaths as a result of systematic HIB disease. This means that any individual with systematic HIB receives medical attention that facilitates recovery from infection in all cases. The original set of equations reduce to.

$$\begin{aligned}
\frac{dX(a)}{da} &= mN(a) - (\lambda + \mu)X(a) \\
\frac{dY(a)}{da} &= \lambda X(a) - (v + w + \mu)Y(a) \\
\frac{dK(a)}{da} &= wY(a) - (\phi + \mu)K(a) \\
\frac{dZ(a)}{da} &= vY(a) + \phi K(a) - \mu Z(a) \\
\frac{dN(a)}{da} &= (m - \mu)N(a)
\end{aligned}
\tag{3.1.2}$$

The methodology that will be used begins by determining the equilibrium or steady state solution of the system of equations. We need positive non-zero values for a realistic situation since any negative values would mean a negative number of either susceptible, infective, systematic or recovered individuals. It should then be possible to examine the nature of the equilibrium point by using the Jacobian and the characteristic equation to check the stability of the equilibrium. The Routh Hurwitz criteria will be used to show that periodic solutions exist around the equilibrium point at least in the immediate vicinity around the bifurcation point to be determined. Since the algebra can become complex during the analysis it is worthwhile to make one more convenient assumption. This is that the population is constant, in other words the birth rate is equal to the background death rate. With this simplification the equations reduce to .

$$\frac{dX(a)}{da} = \mu N - (\lambda + \mu)X(a) \tag{3.1.3}$$

$$\frac{dY(a)}{da} = \lambda X(a) - (v + w + \mu)Y(a) \tag{3.1.4}$$

$$\frac{dK(a)}{da} = wY(a) - (\phi + \mu)K(a) \tag{3.1.5}$$

$$\frac{dZ(a)}{da} = vY(a) + \phi K(a) - \mu Z(a) \tag{3.1.6}$$

Since  $X = N - Y - K - Z$  equation 3.1.4 can be written as

$$\frac{dY(a)}{da} = \lambda(N - K - Z) - (v + w + \mu + \lambda)Y(a) \tag{3.1.7}$$

Equations 3.1.5 - 3.1.7 are now independent of  $X$  and we can therefore look for the equilibrium values of the three equations 3.1.5 - 3.1.7 . Once these have been determined it is a simple matter of subtraction to find the equilibrium value for the number of susceptibles. Setting 3.1.5 - 3.1.7 to zero we have,

$$\lambda(N - K - Z) - (\nu + \omega + \mu + \lambda)Y = 0 \quad 3.1.8$$

$$\omega Y - (\phi + \mu)K = 0 \quad 3.1.9$$

$$\nu Y + \phi K - \mu Z = 0 . \quad 3.1.10$$

From 3.1.9 and 3.1.10 we get,

$$Y = \frac{\phi + \mu}{\omega} K , \text{ and by substituting this into 3.1.10 we have}$$

$$K = \frac{\mu\omega}{(\nu(\phi + \mu) + \phi\omega)} Z .$$

Hence  $Y$  can be written in terms of  $Z$  i.e.

$$Y = \frac{\mu(\phi + \mu)}{\nu(\phi + \mu) + \phi\omega} Z .$$

Then by substituting these values into equation 3.1.8 we can obtain a solution for  $Z(a)$  in terms of the parameters within the model. This process yields

$$Z(a) = \frac{N}{C_1} , \text{ where}$$

$$C_1 = 1 + \frac{\mu\omega}{\nu(\phi + \mu) + \phi\omega} + \frac{\mu(\phi + \mu)(\nu + \omega + \mu + \lambda)}{\lambda(\nu(\phi + \mu) + \phi\omega)} .$$

Since all the parameters within the simplified model are positive then the equilibrium values are also positive and we therefore have a realistic equilibrium point. In order to determine whether this equilibrium point is stable we first need to find the Jacobian and Characteristic equation of the model.

### 3.2 Jacobian and Characteristic Equation

The Jacobian is given by  $\frac{\partial \left( \frac{dY, dK, dZ}{da \ da \ da} \right)}{\partial (Y, K, Z)}$ , which yields the following.

$$J = \begin{pmatrix} -(v + \omega + \mu + \lambda), & -\lambda, & -\lambda \\ \omega, & -(\phi + \mu), & 0 \\ v, & \phi, & -\mu \end{pmatrix}$$

The characteristic equation of a general cubic is given by

$$\begin{vmatrix} a - \alpha & b & c \\ d & e - \alpha & f \\ g & h & j - \alpha \end{vmatrix} \quad \text{which expands to give.}$$

$\alpha^3 - (a + e + j)\alpha^2 + (ae + aj + ej - bd - cg)\alpha - (aej + cdh - bdj - cge) = 0$ , when  $f=0$ .

This equation can be written in the form  $\alpha^3 + p_2\alpha^2 + p_1\alpha + p_0 = 0$ , whose roots we want to examine for stability. According to the Routh Hurwitz criterion (J.D. Murray, 1989) the equilibrium point is unstable if one or more roots of the characteristic equation has a positive real part. The Routh Hurwitz criterion states three necessary and sufficient conditions for roots of a cubic equation to have negative real parts. These are,

$$(1) p_2 > 0, \quad (2) p_0 > 0, \quad (3) p_2 p_1 - p_0 > 0.$$

Therefore we need to substitute all the previous values found for these coefficients of the cubic and then determine whether these conditions are satisfied.

$$(1) p_2 > 0.$$

We know  $p_2 = -(a + e + j)$ , and  $a = -(v + \omega + \mu + \lambda)$ ,  $e = -(\phi + \mu)$ ,  $j = -\mu$ .

$$\text{Hence } p_2 = v + \omega + \lambda + \phi + 3\mu. .$$

3.2.1 .

Since all parameters values have real positive values the first condition is satisfied.

(2)  $p_0 > 0$ .

We know  $p_0 = -(aej + cdh - bdj - ceg)$ , then by back substitution  
 $aej = -\mu(\phi + \mu)(v + \omega + \mu + \lambda)$ ,  $cdh = -\lambda\omega\phi$ ,  $bdj = \lambda\mu\omega$  and  $ceg = \lambda v(\phi + \mu)$ .  
Hence,  $p_0 = \mu(\phi + \mu)(v + \omega + \mu + \lambda) + \lambda\mu\omega + \lambda\omega\phi + \lambda v(\phi + \mu)$   
 $= (\mu + \phi)(\mu(v + \omega + \mu + \lambda) + \lambda(\omega + v))$   
 $= (\mu + \phi)(v + \omega + \mu)(\mu + \lambda)$ . 3.2.2.

Therefore since all parameters values are real and positive the second condition is satisfied.

(3)  $p_2 p_1 - p_0 > 0$ .

If we first determine the value for  $p_1$  i.e.  $p_1 = ae + aj + ej - bd - cg$ , the individual terms are,

$$ae = (\phi + \mu)(v + \omega + \mu + \lambda)$$

$$aj = \mu(v + \omega + \mu + \lambda)$$

$$ej = \mu(\phi + \mu)$$

$$bd = -\lambda\omega$$

$$cg = -\lambda\phi$$

Hence

$$p_1 = (\phi + \mu)(v + \omega + \mu + \lambda) + \mu(v + \omega + \mu + \lambda) + \mu(\phi + \mu) + \lambda\omega + \lambda v$$

$$= (\phi + 2\mu)(v + \omega + \mu + \lambda) + \mu(\phi + \mu) + \lambda(\omega + v)$$
. 3.2.3

Therefore this term is always positive. Continuing we have

$$p_2 p_1 = (v + \omega + \phi + 2\mu)\lambda^2 + ((v + \omega + \phi + 3\mu)(\phi + \omega + v + 2\mu) + (\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu))\lambda + (v + \omega + \phi + 3\mu)((\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu))$$

hence

$$p_2 p_1 - p_0 = (v + \omega + \phi + 2\mu)\lambda^2 + ((v + \omega + \phi + 3\mu)(\phi + \omega + v + 2\mu) + (\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu) - (\mu + \phi)(v + \omega + \mu))\lambda + (v + \omega + \phi + 3\mu)((\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu)) - \mu(\mu + \phi)(v + \omega + \mu)$$

We then need to determine for what values of  $\lambda$ , if any, this expression satisfies the third condition. The above equation can be rewritten in the form  $A\lambda^2 + B\lambda + C$ , where



$$A = v + \omega + \phi + 2\mu$$

$$B = (v + \omega + \phi + 3\mu)(v + \omega + \phi + 2\mu) + (\phi + 2\mu)(v + \omega + \mu) - (\mu + \phi)(\omega + v)$$

$$C = (v + \omega + \phi + 3\mu)((\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu)) - u(\phi + \mu)(v + \omega + \mu).$$

If we examine the final two terms for B we have

$$(\phi + 2\mu)(v + \omega + \mu) - (\omega + v)(\mu + \phi),$$

$\therefore$  we require that

$$(\phi + \mu)(v + \omega + \mu) + \mu(v + \omega + \mu) - (\phi + \mu)(v + \omega) > 0$$

for B to be positive. But we know that

$$(\phi + \mu)(v + \omega + \mu) - (\phi + \mu)(v + \omega) > 0 .$$

Since all parameter values are real and positive, hence B is always positive. Similarly by taking selective terms from C we can see that if

$(v + \omega + \phi + 3\mu)\mu(\phi + \mu) - u(\phi + \mu)(v + \omega + \mu) > 0$ , then C is always positive. By rearranging this expression we require that

$$\mu(v + \omega + \phi)(\phi + \mu) - u(\phi + \mu)(v + \omega + \mu) + 3\mu^2(\phi + \mu) > 0$$

which is always true, hence C is always positive. As a consequence it can be seen that the third condition will be satisfied for all real positive values of  $\lambda$ . This means that as long as the force of infection is greater than zero then the equilibrium values for the numbers in each state, prior to immunisation being introduced, are stable. If the force of infection is negative then we have an unrealistic situation and there is no need to determine for what negative values of  $\lambda$ , if any, the third condition is satisfied.

### 3.3 Hopf Bifurcation

The Hopf Bifurcation Theorem is concerned with the conditions necessary for the existence of real periodic solutions of the real system of ordinary differential equations

$$\frac{dX}{dt} = F(X, v).$$

Here  $F$  and  $X(v, t)$  are  $n$ -dimensional vectors and  $v$  is a real parameter. The bifurcation theorem is a very general tool in establishing the existence of periodic solutions and, in the neighbourhood of the bifurcation point, it also

gives their periods. However, it does not immediately provide any information as to the stability of the solutions, which is just as important as the existence of real periodic solutions. It is of practical importance in treating systems of dimension higher than two but can produce complex algebraic manipulation when applied to higher order systems. The following section is concerned with outlining how the method can be applied to a system of three ordinary differential equations. It should be noted that the three by three linear system that the theorem will be applied to can be solved explicitly and that the purpose is to simply illustrate the theorem. A more general discussion of the theorem can be found in either J.D. Murray's, 1989 or Sydel 1988.

To begin the illustration of the theorem we return to the quadratic equation in  $\lambda$  for the third condition to hold true i.e.

$$H(\lambda) = (v + \omega + \phi + 2\mu)\lambda^2 + ((v + \omega + \phi + 3\mu)(\phi + \omega + v + 2\mu) + (\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu) - (\mu + \phi)(v + \omega + \mu))\lambda + (v + \omega + \phi + 3\mu)((\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu)) - \mu(\mu + \phi)(v + \omega + \mu)$$

According to the Hopf Bifurcation theorem, bifurcation will occur at a point  $\lambda_0 > 0$  given by the solution to  $H(\lambda_0) = 0$ . This quadratic has roots given by

$$\lambda = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A} \quad 3.3.1$$

where as above

$$A = v + \omega + \phi + 2\mu$$

$$B = (v + \omega + \phi + 3\mu)(v + \omega + \phi + 2\mu) + (\phi + 2\mu)(v + \omega + \mu) - (\mu + \phi)(\omega + v)$$

$$C = (v + \omega + \phi + 3\mu)((\phi + 2\mu)(v + \omega + \mu) + \mu(\phi + \mu)) - \mu(\mu + \phi)(v + \omega + \mu) .$$

Since we have know that A, B and C are always positive then there are no real positive roots to equation 3.3.1 and hence the prerequisite condition for Hopf Bifurcation to take place is not satisfied.

However if we assume that there is a positive root to equation 3.3.1 and that the Hopf Bifurcation theorem is satisfied at this root then the characteristic equation must have a pair of complex conjugates given by

$$\alpha_2(\lambda) = g(\lambda) + it(\lambda)$$

$$\alpha_3(\lambda) = g(\lambda) - it(\lambda) .$$

Necessary and sufficient conditions for this to be true are

$$(1) \quad g(\lambda_0) = 0$$

$$(2) \quad t(\lambda_0) > 0$$

$$(3) \quad \frac{dg(\lambda)}{d\lambda} < 0 \quad \text{at } \lambda = \lambda_0 .$$

The characteristic equation at the bifurcation point is given by,

$$\alpha^3 + p_2(\lambda_0)\alpha^2 + p_1(\lambda_0)\alpha + p_0(\lambda_0) , \text{ but at } \lambda = \lambda_0$$

$$p_2(\lambda_0)p_1(\lambda_0) - p_0(\lambda_0) = 0,$$

therefore the characteristic equation becomes

$$\alpha^3 + p_2(\lambda_0)\alpha^2 + p_1(\lambda_0)\alpha + p_2(\lambda_0)p_1(\lambda_0) .$$

If the Hopf Bifurcation theorem holds at the bifurcation point then the characteristic equation can be written in the form

$$(\alpha - \alpha_1(\lambda_0))(\alpha^2 + (t(\lambda_0))^2) \quad \text{i.e.}$$

$$\alpha^3 - \alpha_1(\lambda_0)\alpha^2 + t^2(\lambda_0)\alpha - t^2(\lambda_0)\alpha(\lambda_0) .$$

By equating terms we have  $\alpha_1(\lambda_0) = -p_2(\lambda_0)$  , which is always less than zero. We also have  $t^2(\lambda_0) = p_2(\lambda_0)$  which is always greater than zero. Hence if

$t(\lambda_0) = \sqrt{p_1(\lambda_0)}$  ,  $\alpha_2(\lambda_0) = it(\lambda_0)$  and  $\alpha_3(\lambda_0) = -it(\lambda_0)$  , then the first two conditions are satisfied.

In order to show the third condition is satisfied we can use the continuation of the root  $\alpha_2$  in the neighbourhood of  $\lambda_0$ . This root satisfies the characteristic equation for all values of  $\lambda$  i.e.

$$\alpha_2(\lambda)^3 + p_2(\lambda)\alpha_2^2 + p_1(\lambda)\alpha_2 + p_0(\lambda) = 0$$

Therefore we require

$\left. \frac{dg(\lambda)}{d\lambda} \right|_{\lambda_0} = \operatorname{Re} \left\{ \left. \frac{d\alpha_2(\lambda)}{d\lambda} \right|_{\lambda_0} \right\}$ , evaluated at the bifurcation point. This

differentiation yields

$$\begin{aligned} & \frac{d\alpha_2(\lambda)}{d\lambda} (3\alpha_2(\lambda)^2 + 2p_2(\lambda)\alpha_2(\lambda) + p_1(\lambda)) \\ & + \alpha_2^2(\lambda) \frac{dp_2(\lambda)}{d\lambda} + \alpha_2(\lambda) \frac{dp_1(\lambda)}{d\lambda} + \frac{dp_0(\lambda)}{d\lambda} = 0 \end{aligned} \quad 3.3.1$$

Since we know that  $\alpha_2(\lambda) = g(\lambda) + it(\lambda)$ ,  $\therefore \operatorname{Re} \left\{ \left. \frac{d\alpha_2(\lambda)}{d\lambda} \right|_{\lambda_0} \right\} = \left. \frac{dg(\lambda)}{d\lambda} \right|_{\lambda_0}$

at the point  $\lambda = \lambda_0$  and that the root satisfies the characteristic equation for all  $\lambda$ , it follows from 3.3.1

$$\left. \frac{d\alpha_2(\lambda)}{d\lambda} \right|_{\lambda_0} = \left. \frac{-\alpha_2^2(\lambda) \frac{dp_2(\lambda)}{d\lambda} - \alpha_2(\lambda) \frac{dp_1(\lambda)}{d\lambda} + \frac{dp_0(\lambda)}{d\lambda}}{(3\alpha_2(\lambda)^2 + 2p_2(\lambda)\alpha_2(\lambda) + p_1(\lambda))} \right|_{\lambda_0}. \quad 3.3.2$$

What remains to be shown is that the real part of this equation is less than zero. From 3.2.1 we have  $p_2 = v + \omega + \lambda + \phi + 3\mu$ , therefore  $\frac{dp_2(\lambda)}{d\lambda} = 1$  and always positive. Similarly from 3.2.3 we know that

$$p_1(\lambda) = (\phi + 2\mu)(v + \omega + \mu + \lambda) + \mu(\phi + \mu) + \lambda(\omega + \phi)$$

$\therefore \frac{dp_1(\lambda)}{d\lambda} = (\phi + 2\mu) + (\omega + \phi) = 2\mu + 2\phi + \omega$ , which is always a positive quantity. We also know that,

$$p_0 = (\mu(\phi + \mu) + (\omega + v)(\mu + \phi))\lambda + \mu(\phi + \mu)(v + \omega + \mu)$$

$$\therefore \frac{dp_0}{d\lambda} = (\mu(\phi + \mu) + (\omega + v)(\mu + \phi))$$

which once again is always positive.

If we then rationalise and take the real part of equation 3.3.2 we get the following expression

$$\left. \frac{dg(\lambda)}{d\lambda} \right|_{\lambda_0} = \left. \frac{-p_1(\lambda) \frac{dp_2(\lambda)}{d\lambda} - p_2(\lambda) \frac{dp_1(\lambda)}{d\lambda} + \frac{dp_0(\lambda)}{d\lambda}}{2p_1(\lambda) + 2(p_2(\lambda))^2} \right|_{\lambda_0} \quad 3.3.3$$

which gives

$$\left. \frac{dg(\lambda)}{d\lambda} \right|_{\lambda_0} = \frac{-p_1(\lambda) - (2\phi + 2\mu + \omega)p_2(\lambda) + \mu(\phi + \mu) + (\omega + \nu)(\mu + \phi)}{2p_1(\lambda) + 2(p_2(\lambda))^2} \Big|_{\lambda_0} . \quad 3.3.4$$

Since  $p_1$  and  $p_2$  are always positive then the denominator is always positive. We require the numerator to be negative for the third condition to be satisfied. If we equate  $p_1(\lambda)$  to  $\mu(\phi + \mu) + (\omega + \nu)(\mu + \phi)$  then we have the requirement that

$$-((\phi + 2\mu)(\nu + \omega + \mu + \lambda) + \mu(\phi + \mu) + \lambda(\omega + \phi)) + \mu(\phi + \mu) + (\omega + \nu)(\mu + \phi) < 0 .$$

This simplifies to requiring that ,

$$-(\phi + 2\mu)(\nu + \omega) + (\omega + \nu)(\mu + \phi) < 0$$

which is always true since all parameters are real positive quantities. Hence the third condition is satisfied. The Hopf Bifurcation theorem then states that there exist periodic orbits around the equilibrium point, at least in the vicinity of the bifurcation point  $\lambda_0$ . The theorem also gives an estimate for the inter-epidemic period of the disease i.e.  $P = \frac{2\pi}{\tau(\lambda_0)}$ .

This chapter has shown how simplified models can prove difficult to obtain analytical results. It has also been seen that in this particular example the Hopf Bifurcation theorem does not need to be applied. However the conditions that need to be satisfied for Hopf Bifurcation to take place are examined. The next stage in the development of the model is to obtain estimates for the parameters within the model.

## CHAPTER FOUR

### PARAMETER ESTIMATION

#### 4.1 Introduction

Since HIB has only been a notifiable disease since 1992 there is a lack of data to which mathematical methods can be applied to estimate parameters within the model. However there are sources of information that can be used such as private communication with medical people in the field. The following discussion shows how various sources were used to further develop the mathematical model for HIB.

Parameters such as birth or death rates can be directly obtained from statistics provided by the Australian Bureau of Statistics ( ABS ). Other parameters such as the recovery or immunisation rate require a different method in order to estimate them. The recovery rate may be considered as a suitable time lag after infection during which an infected person will recover. This time lag would vary according to what infection the individual had suffered. Immunisation rates can be based on Health Department publications.

Private communication with Dr Beryl Wild from the Princess Margaret Hospital, Perth, has indicated how data relevant to the estimation of certain parameters can be collected . Dr Wild published a paper called Diagnosis and treatment of Meningitis in 1993 which also contained relevant information. This data includes the incidence of the disease and at what age individuals were infected. Another possible method of data collection is a seriological survey which would check for the presence of antibodies to the disease within the body i.e. an individual may be seropositive. However since HIB has only recently become a notifiable disease and that an immunisation programme against HIB has begun then a seriological survey could give unrealistic results for estimates of the proportion of the population susceptible to infection at particular ages.

One fundamental parameter that needs to be estimated is the per capita rate of infection or force of infection. This was defined by Muench (Comiskey, 1988) as the "instantaneous per capita rate at which susceptible individuals acquire infection". If this parameter is treated as a constant then it is a relatively simple task to estimate via either case notifications or

seriological surveys. However if it is treated as being dependent on age or time it becomes a more difficult parameter to estimate. In either case the per capita force of infection is dependent on the transmission rate of a disease. If the force of infection is age dependent then the transmission rate describes the probability that an infectious person of age  $a$  will infect a susceptible of age  $a'$ . The transmission rate is an attempt to quantify aspects of human behaviour such as social interaction and personal hygiene. For this reason the assumption of homogeneous mixing is commonly employed ( Anderson and May, 1991 ). This assumes that all aspects of social, epidemiological and demographic behaviour are averaged out. For instance the number of people that an individual interacts with is the same regardless of whether the person lives either in a metropolitan or rural area. Homogeneous mixing implies that the per capita rate of infection is the same for all individuals within a given population. This implies that the transmission rate is also the same for all individuals within the population regardless of age and can therefore be treated as a constant. Despite the generality of the assumption it permits a degree of simplicity to be introduced into the modelling process and may therefore allow analytical results to be obtained.

If this assumption is included the transmission rate will be the same for the entire population. One intuitive counter example can be highlighted when considering the school environment. In this environment, most individuals will be in the 5-12 year age group and will be mixing with others predominantly in the same age group. This necessarily implies that these individuals would be spending a significant amount of time away from individuals in other age groups. Therefore if we ignore the demographic position and possibly the density of children in different schools it may be reasonable to assume that the transmission rate could be considered as constant within the 3-10 year old age group. This simply says that different age groups do not mix in a uniform manner but that distinct age groups mix in a heterogeneous way or in a manner unlike other age groups. It may therefore be unreasonable to expect any particular individual to have an equal probability of transmitting infection to another individual independent of the age group that either belongs to. The likelihood is that an individual would have a greater chance of transmitting the infection to another person within the same age group, in this case within the same school environment.

Further, what if the main body of infectious individuals came from infants young enough not to be in a school environment. A suitable approach

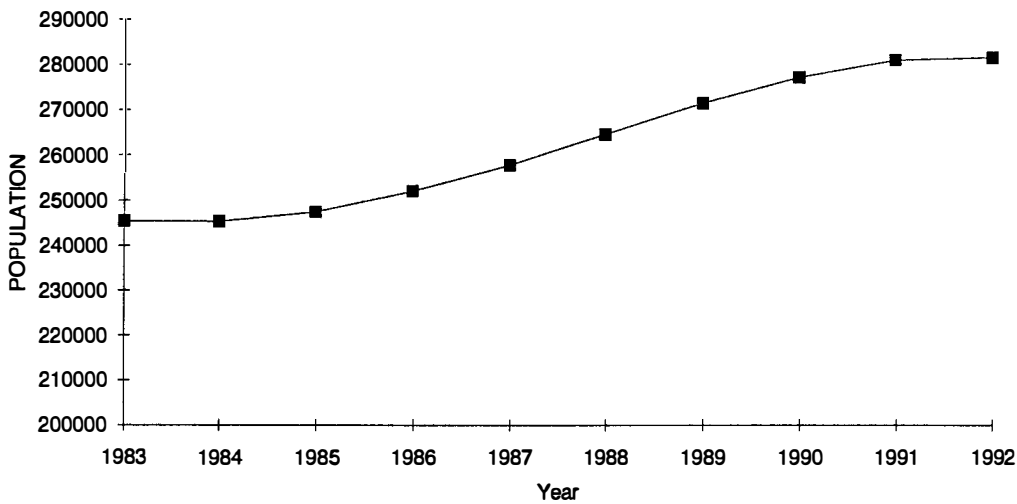
in this situation might be to subdivide the population into smaller groups. These groups could correspond to newborns, infants and those either at kindergarten or primary school. The age group 0-2 months could represent the newborns. Most of these individuals will have a degree of immunity from various infections even though their own immunity systems may not be fully developed. This immunity is due to the presence of maternal antibodies within the body. The majority of such antibodies would have entered the bloodstream via the mothers bloodstream during pregnancy. We now have the total population being compartmentalised into sub-populations. The purpose is to find similar characteristics, such as the transmission rate, within the sub-populations, so that different values can be applied to the distinct age groups. Whether or not the entire population needs to be considered depends on the incidence of the disease and in what age groups the incidence is concentrated. Since the vast majority of Hib and systematic Hib cases occur in young children this seems to be the age group in which the modelling process should be concentrated. This estimation process will study the age group 0-10 years and will compartmentalise this age group into subgroups in an attempt to mirror the incidence of Hib.

Figure 4.1.1 below shows that the population of Western Australia within the 0-10 year age group has significantly increased in the period 1983-1992. Therefore the population cannot be reasonably considered as constant. As a result the mathematical model will incorporate this population increase.

The next question to be considered is the number of initial infections needed to lead to an epidemic. This critical value is expressed by the well known "Threshold Theorem", first outlined by Kermack and McKendrick (Bailey, 1975). This theorem was illustrated during Chapter One. The theorem gives an adequate level of immunisation coverage that needs to be obtained for the disease to eventually die out rather than cause an epidemic or remain endemic. Intuitively this is because the pool of available susceptibles gets smaller as previously susceptible individuals are immunised. The ideal aim of an immunisation initiative is to eradicate the disease in question. However a more realistic goal is to minimise incidence levels of the disease. An example of a previously targeted disease is smallpox which was successfully removed as a significant threat to individuals within the developed world during the 1970's.



**FIGURE 4.1.1 , TOTAL POPULATION IN THE 0-10 YEAR AGE GROUP 1983-1992**



## 42 Parameters

From chapter two we have the following parameters that need to be estimated.

$\lambda(a)$  = The age dependent per capita force of infection

$\sigma(a)$  = The age dependent immunisation rate

$\mu(a)$  = The age specific death rate

$\nu$  = The recovery rate from HIB infection

$\delta$  = Rate at which individuals lose protection due to maternal antibodies

$\theta$  = Rate at which people move from being in the latent class to the the infectious class

$\omega$  = Rate at which systematic HIB cases occur i.e. the rate at which people move from the infectious state to the systematic state.

$\phi$  = Recovery rate from systematic HIB

$\zeta$  = Systematic HIB death rate

Private communication with Dr Jeffrey Hanna has shown how difficult it is to actually put a numerical value to many of these parameters. However Dr Hanna has suggested approximate values for some of these parameters. Firstly the recovery rate from systematic HIB disease depends on what

invasive HIB disease is suffered. If an individual is infected by Bacterial Meningitis then the recovery period may be of about two weeks duration once medical treatment begins. In chapter one it was said that bacterial meningitis accounts for about fifty per cent of invasive HIB disease and that invasive HIB meningitis accounts for about seventy per cent of the overall incidence of bacterial meningitis in the age group 0-10 years. Another common invasive HIB disease is epiglottitis from which individuals can recover in about 2-3 days. Since these two diseases account for the majority of invasive HIB disease the estimated values for the model will be based upon the recovery periods mentioned. If we have a specific recovery rate then the mean duration of infection is the inverse of the recovery rate hence the recovery rate for systematic HIB will be of the form

$$\phi \approx \frac{0.5}{0.5} + \frac{0.5}{0.1} = 1 + 5 = 6, \text{ measured in number of cases per month.}$$

Here it is assumed that 50 % of infected individuals suffer Bacterial Meningitis and the rest suffer epiglottitis infection and the time scale is in months. All of the following estimates will also be measured in months.

The recovery rate for individuals with only HIB infection is, according to Dr Hanna anywhere from a few days to a couple of months depending on the individual. For the purpose of this thesis we will take this value to be four weeks which may represent an average recovery period. During this time the individuals infected are at risk from invasive HIB disease. Since the purpose of this estimation is to numerically solve a system of equations this parameter as well as any other can be easily changed. We have  $v$  as the recovery rate and therefore  $\frac{1}{v}$  is the mean period of infectiousness. Hence

$$v \approx \frac{1}{1} = 1 \quad \text{is the estimate for the HIB recovery rate in one month.}$$

Next we will estimate the rate at which individuals move from the latent to infectious state. Since  $\theta$  represents this rate then  $\frac{1}{\theta}$  is the mean period of time spent in the latent class. Once again private communication with Dr Hanna has indicated this to be in the order of 3 days. Hence

$$\theta \approx \frac{1}{0.1} = 10 \quad \text{is the estimate for the latent to infectious rate}$$

The next parameter to estimate is the rate at which individuals lose immunity from infection due to maternal antibodies. For non-Aboriginals, the immunisation programme for a newborn starts ideally when an individual is two months old and consists of a triple dose vaccine at 2,4,6 months followed by a booster at 18 months. It will be assumed that every newborn is 100 per cent protected up to the age of 2 months. Therefore individuals could be viewed as losing maternal antibody protection over a period of 4 months at a uniform rate. If  $\delta$  is the rate at which individuals lose maternal antibodies then  $\frac{1}{\delta}$  is the mean period spent under the protection of maternal antibodies. In this case we have a period of 4 months to consider. The mean period that an individual will be covered by maternal antibodies is therefore approximately two months. Hence,

$$\delta \approx \begin{cases} 0 & \text{for } 0 < a < 2 \text{ months} \\ 0.5 & \text{for } 2 < a < 6 \text{ months} \end{cases}$$

### 4.3 Immunisation

Mass immunisation is the method used by Governments to try and minimise the incidence of diseases such as HIB. Immunisation programs differ in their effectiveness and methodology (Anderson and May, 1982). The policy directed at HIB is primarily a three stage program where newborns are immunised at three different ages during their growth. At each stage the level of resistance against the disease rises until a level approaching total immunity from infection is reached. For the purpose of this thesis it will be assumed that once an individual has been put through the program then one hundred per cent immunity is obtained. For those individuals who are beyond the age at which the immunisation program should of ideally began then a "catch up program" is implemented. This may mean that an individual passes through one or two stages of immunisation. Again, once this has been achieved the individuals concerned will be considered as totally immune. There are two main vaccines available for HIB these are HibTitter and PedVaxHIB. The manufacturers of the first have won the Australian contract via a federal government tender. However indigenous people are treated with the second because of the different effectiveness of the Vaccine at a young age. For HibTitter the schedule is based on the following.

1. First dose at 2 months of age with 15% protection

2. Second dose at 4 months of age with 84% protection
3. Third dose at 6 months of age with 98% protection
4. Booster at 18 months of age

For PedVaxHIB the immunisation schedule is as follows,

1. First dose at 2 months of age with 73% protection
2. Second dose at 4 months of age with 92% protection
3. Booster at 12 months of age.

There is a third vaccine called ProHIBit which can be administered to children over 18 months of age. This vaccine is of very little use to younger infants and therefore not appropriate for Aboriginal children since almost all cases of invasive HIB meningitis occur before 12 months of age. It is also only partly protective for non Aboriginal children since the peak incidence of invasive HIB disease appears to be between 6 and 24 months.

One problem associated with multiple stage vaccination programmes is whether an infant actually begins the programme and if so whether the infant receives all recommended doses. The Australian Bureau of Statistics (ABS, 1992) published, on 9th October 1992, the results of a National Health Survey carried out during 1989-1990. This suggested that the immunisation status of children depended of family characteristics, with a lower proportion of children from single parent families, and of lower income families being fully immunised. However these characteristics are beyond the scope of this thesis and will not be taken into account. From the survey of 22,000 private and special dwellings ( hospitals and nursing homes excluded ) an adult was asked to provide information about children in the household. Roughly equal numbers of households were interviewed each fortnight with up to 55 % of replies coming without consultation of immunisation cards.

Since the Diptheria, Tetanus, Polio (DTP) immunisation programme is implemented at 2,4,6 and 18 months then the statistics available for this could be applied to give likely levels of coverage for the HIB immunisation programme. For Western Australia the following results were published Diptheria and Tetanus.

**TABLE 4.3.1 IMMUNISATION STATISTICS FOR DIPHTHERIA AND TETANUS DURING 1989-1990**

% IMMUNISED	ALL DOSES	ONE DOSE	TWO DOSES	DON'T KNOW	TOTAL
DIPHTHERIA/TETANUS	85.6	5.1	3.6	5.7	100

In the absence of specific statistics for HIB immunisation rates these figures will be used as a guide-line for the numerical solution of the mathematical model. (There is at present a relevant survey being carried out by Dr Rob Condon of the Princess Margaret Hospital Perth. However the results of this research have yet to be published and therefore cannot be used in this thesis.) For those fully immunised we have,  $\sigma_1(a)$ , the age dependent immunisation rate given by,

#### 1. HibTitter

$$\sigma_1(a) = \begin{cases} 0.15 \times 0.856 \times X(a) = 0.1284X(a) & 2 < a < 4 \\ 0.69(0.85 \times 0.856)X(a) = 0.5020X(a) & 4 < a < 6 \\ 0.14(0.31 \times 0.85 \times 0.856)X(a) = 0.0316X(a) & 6 < a < 18 \end{cases}$$

This says that 98 per cent of the 85.6 per cent of susceptibles that began the programme at age 2 months are fully immunised at 6 months. However after the first dose only 15 per cent of those immunised can be considered as being immune. After the second dose another 69 per cent of the remainder of the original number of susceptibles i.e. the number of susceptibles at the beginning of the programme, can be considered as being recovered giving a total effective immunisation rate of 84 per cent of the original 85.6 per cent of susceptibles full immunised. The third dose sees another 14 per cent of the original susceptible population gaining immunity for a total protection of 98 per cent of those fully immunised. It will be assumed that all of these individuals have the 18 month booster and retain complete immunity to infection.

#### 2. PedVaxHIB

$$\sigma_1(a) = \begin{cases} 0.73 \times 0.856 \times X(a) = 0.6249X(a) & 2 < a < 4 \\ 0.19 \times 0.27 \times 0.856 \times X(a) = 0.0439X(a) & 4 < a < 18 \end{cases}$$

Again it will be assumed that all these individuals have the 12 month booster.

For the 5.1 per cent who are partially immunised it will be assumed that half receive one dose and the other half receive two doses. It will also be assumed that the first dose is always received at two months of age. Therefore the level of protection for these individuals is given by

### 1. HibTITER

#### a. One injection only

$$\sigma_2(a) = 0.50 \times 0.15 \times 0.051 X(a) = 0.0038 X(a) \quad 2 < a < 18$$

#### b. Two injections only

$$\sigma_3(a) = \begin{cases} 0.5 \times 0.15 \times 0.051 \times X(a) = 0.0038 X(a) & 2 < a < 4 \\ 0.5 \times 0.69 \times 0.85 \times 0.051 \times X(a) = 0.01496 X(a) & 4 < a < 18 \end{cases}$$

The equations could be extended to say that the immunisation of these partially immunised individuals begins at different ages but this will not be done here.

### 2. PedVaxHIB

Here it will be assumed that only one dose at two months is administered, then we have,

$$\sigma_2(a) = 0.50 \times 0.72 \times 0.051 X(a) = 0.0184 X(a) \quad 2 < a < 18$$

These rates can then be combined to give

#### 1. HibTitter

$$\sigma(a) = \begin{cases} (0.1284 + 2(0.0038))X(a) = 0.136 X(a) & 2 < a < 4 \\ (0.5020 + 0.0150)X(a) = 0.517 X(a) & 4 < a < 6 \\ 0.0316 X(a) & 6 < a < 18 \end{cases}$$

#### 2. PedVaxHIB

$$\sigma(a) = \begin{cases} (0.6249 + 0.0184)X(a) = 0.6433 X(a) & 2 < a < 4 \\ 0.0439 X(a) & 4 < a < 18 \end{cases}$$

It is also possible to combine these two types of vaccine into a combined rate. This can be achieved in the following way. The Aboriginal and Torres Strait Islanders make up approximately 5% of the cohort born in 1991. Therefore the PedVaxHib vaccine is applied to this proportion of the population. We will assume that this vaccine will act upon 5 % of any given cohort. Therefore the overall effect of PedVaxHib will be given by

$$\sigma(a) = \begin{cases} 0.05(0.6249 + 0.0184)X(a) = 0.032165X(a) & 2 < a < 4 \\ 0.05(0.0439)X(a) = 0.002195X(a) & 4 < a < 18 \end{cases}$$

Similarly the vaccine HibTitter will be concerned with 95% of the total population. Hence the overall effect of HibTitter is given by

$$\sigma(a) = \begin{cases} 0.95(0.1284 + 2(0.0038))X(a) = 0.1292X(a) & 2 < a < 4 \\ 0.95(0.5020 + 0.0150)X(a) = 0.49115X(a) & 4 < a < 6 \\ 0.95(0.0316)X(a) = 0.03002X(a) & 6 < a < 18 \end{cases}$$

If we then combine these values we have an overall expression for the proportion of susceptibles successfully vaccinated i.e.

$$\sigma(a) = \begin{cases} 0.161365X(a) & 2 < a < 4 \\ 0.493345X(a) & 4 < a < 6 \\ 0.0300X(a) & 6 < a < 18 \end{cases}$$

It has been assumed that the individuals who fall into the category of "Don't know" have not been immunised. We therefore have values for the immunisation programme which can be used in the numerical solution of system of differential equations. These values can easily be changed by simply substituting values for alternative levels of coverage into the equations formed. For individuals who have not begun the programme at 2 months there is a catch up schedule in place with the chart below describing the ideal programme that should follow as published by the manufacturers of HibTitter.

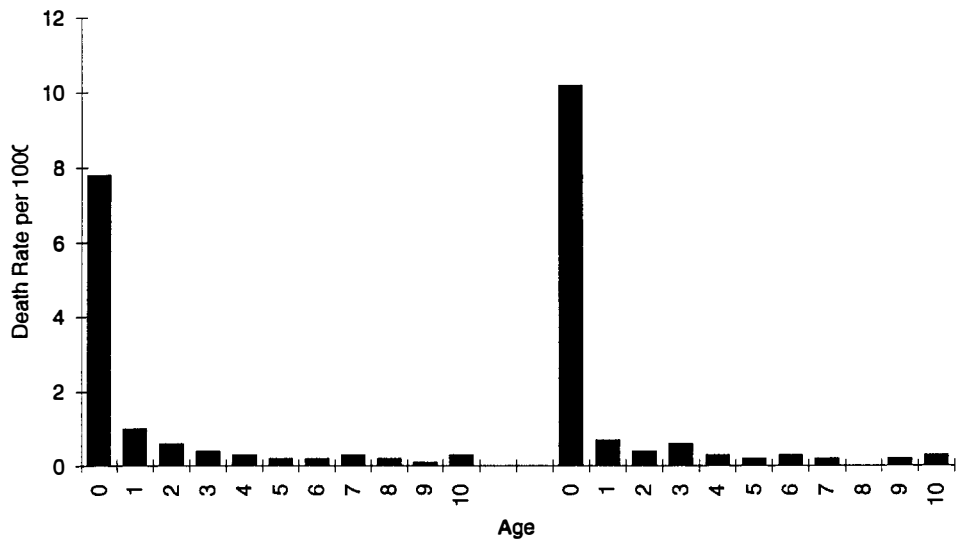
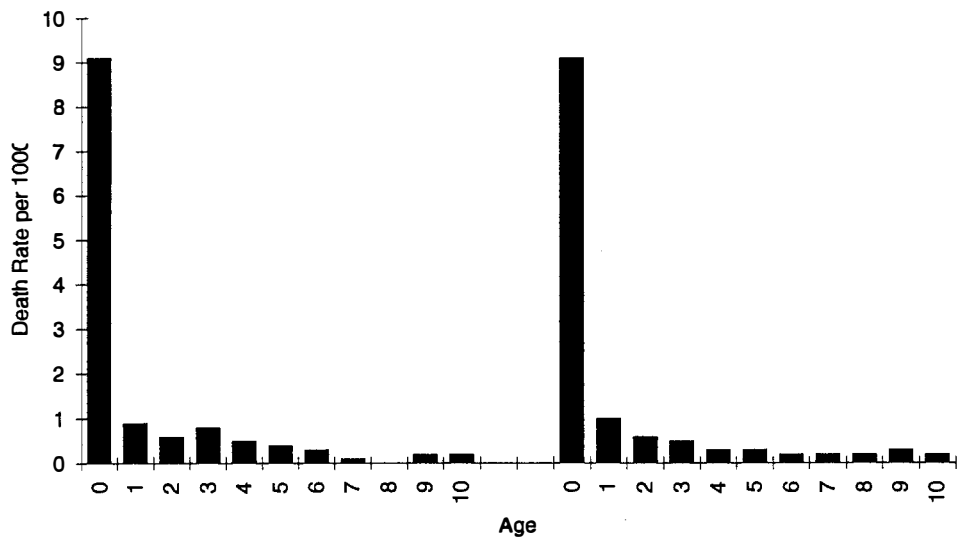
**TABLE 4.3.2 , IDEAL HibTITTER IMMUNISATION PROGRAMME**

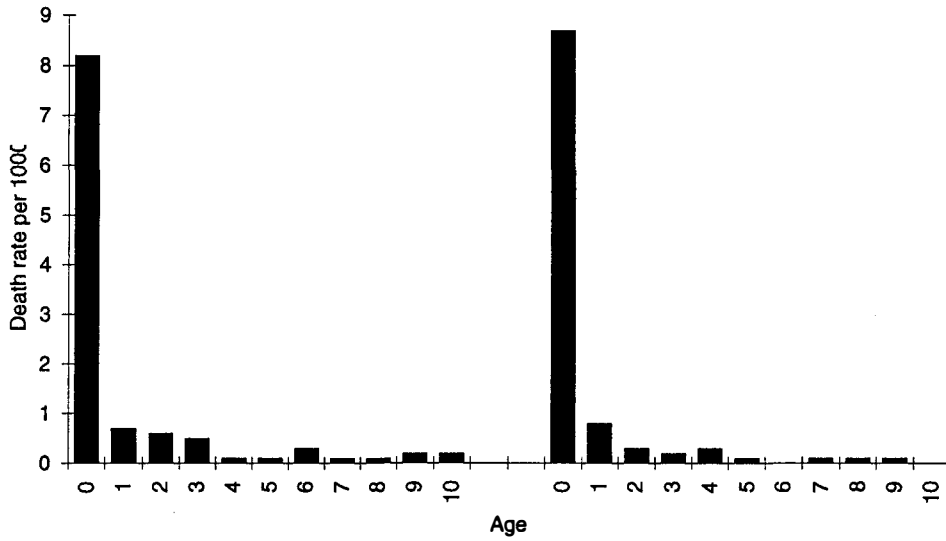
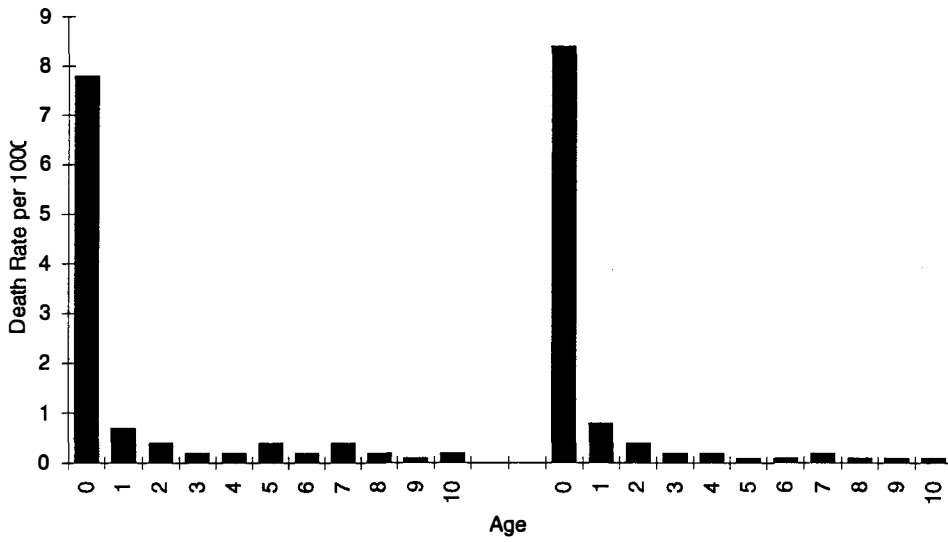
Age at Initial Immunisation in Months	Second Dose	Third Dose	Booster
15-59	none	none	none
14	none	none	16 or older
13	none	none	15 or older
12	none	none	15 or older
11	13	none	15 or older
10	12	none	15 or older
9	11	none	15 or older
8	10	none	15 or older
7	9	none	15 or older
6	8	10	15 or older
5	7	9	15 or older
4	6	8	15 or older
3	5	7	15 or older
2	4	6	15 or older

#### **4.4 Births and Age Specific Death Rates**

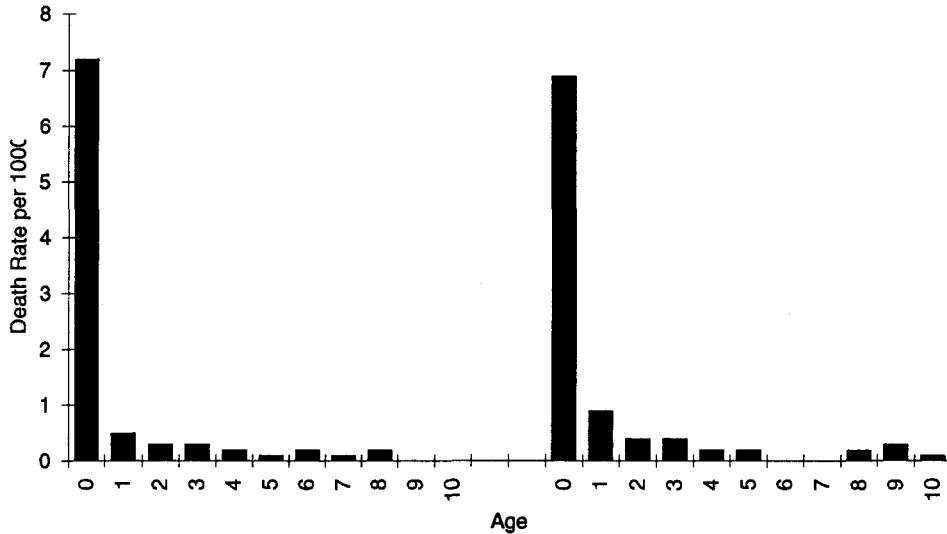
Basic demographic statistics were obtained from the Australian Bureau of Statistics (ABS). These gave the total population in the 0-10 year age group for the period 1983-1992, the age specific death rates and the number of births for each year. The charts below show the age specific death rate per 1000 for the age group 0-10.



**FIGURE 4.4.1, AGE SPECIFIC DEATH RATES 1983-1984****FIGURE 4.4.2, AGE SPECIFIC DEATH RATES 1985-1986**

**FIGURE 4.4.3, AGE SPECIFIC DEATH RATES 1987-1988****FIGURE 4.4.4, AGE SPECIFIC DEATH RATES 1989-1990**

**FIGURE 4.4.5, AGE SPECIFIC DEATH RATES 1991-1992**



It appears that the death rate is similar in the 0-1, 1-2, 2-4 and 5-10 year age groups. Therefore the death rate for these age groups has been averaged over the 10 years of available data obtained from the Australian Bureau of Statistics. We have

$$\mu(a) = \begin{cases} 0.693 & \text{per 1000} & 0 < a < 12 \\ 0.067 & \text{per 1000} & 12 < a < 24 \\ 0.038 & \text{per 1000} & 24 < a < 48 \\ 0.0151 & \text{per 1000} & 48 < a < 120 . \end{cases}$$

We also have approximate figures for the Aboriginal and Torres Strait age specific death rate and these are as follows

$$\mu(a) = \begin{cases} 2.675 & \text{per 1000} & 0 < a < 12 \\ 0.383 & \text{per 1000} & 12 < a < 24 \\ 0.150 & \text{per 1000} & 24 < a < 48 \\ 0.006 & \text{per 1000} & 48 < a < 120 \end{cases}$$

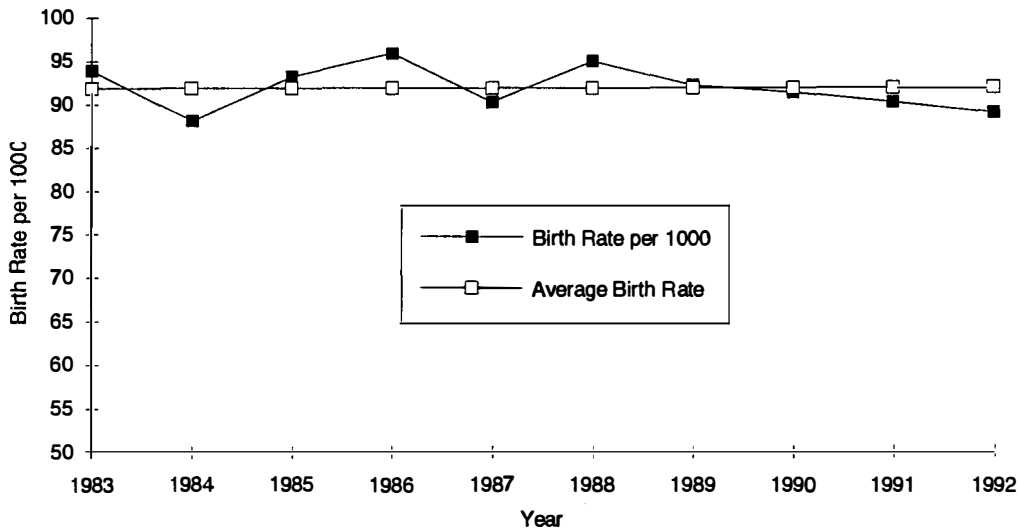
The following table describing the births in the periods 1983-1992.

**TABLE 4.4.1 BIRTH RATES in the PERIOD 1983-1992**

YEAR	NUMBER OF BIRTHS	POPULATION	BIRTH RATE PER 1000
1983	23046	245427	93.9
1984	21601	245268	88.07
1985	23066	247475	93.2
1986	24175	252152	95.87
1987	23271	257910	90.23
1988	25123	264541	94.97
1989	25019	271544	92.14
1990	25322	277266	91.33
1991	25349	281055	90.19
1992	25051	281714	88.92

The following chart illustrates the Birth Rate per Thousand

**FIGURE 4.4.6, BIRTH RATE PER 1000, 1983-1992**



An average value could be taken for the birth rate per 1000 and therefore the parameter could be treated as a constant in the numerical solution of the model. The average birth rate per 1000 over the ten year period 1983-1992 is 91.882.

## 4.5 The Age Specific Force of Infection

Private communication with Dr Jeffrey Hanna has indicated that close to 100 per cent of 5 year old children will test seropositive for the presence of H1B. The force of infection is therefore likely to be high during the first few years of life with the exception of the period that an individual is protected by maternal antibodies. The force of infection will be determined using the method described by Comiskey, 1988.

If there is a constant force acting on a given population of molecules where every molecule is susceptible to this force then Muench (Comiskey, 1988) says that the following differential equation describes the rate of change in the proportion of the original population,  $H$ , left at time  $t$  i.e

$$\frac{dH}{dt} = \lambda(1 - H) \quad \therefore \quad H(t) = 1 - e^{-\lambda t} \quad \text{given that } H(0) = 0 .$$

This notion of a catalytic process can be extended to modelling an infection acting on a given population. Firstly the proportion susceptible to infection in age class  $a$  is described by,

$$X(a) = e^{-\lambda a} .$$

This can be extended to the case where the force of infection is age dependent i.e

$$X(a) = e^{-\int_0^a \lambda(s) ds} .$$

The proportion of the total population not susceptible to infection is given by

$$Y(a) = 1 - X(a)$$

which can be used to describe the proportion of a particular cohort of people who were susceptible at birth and who have experienced infection by age  $a$ . We have

$$Y(a) = 1 - \exp \int_0^a \lambda(s) ds$$

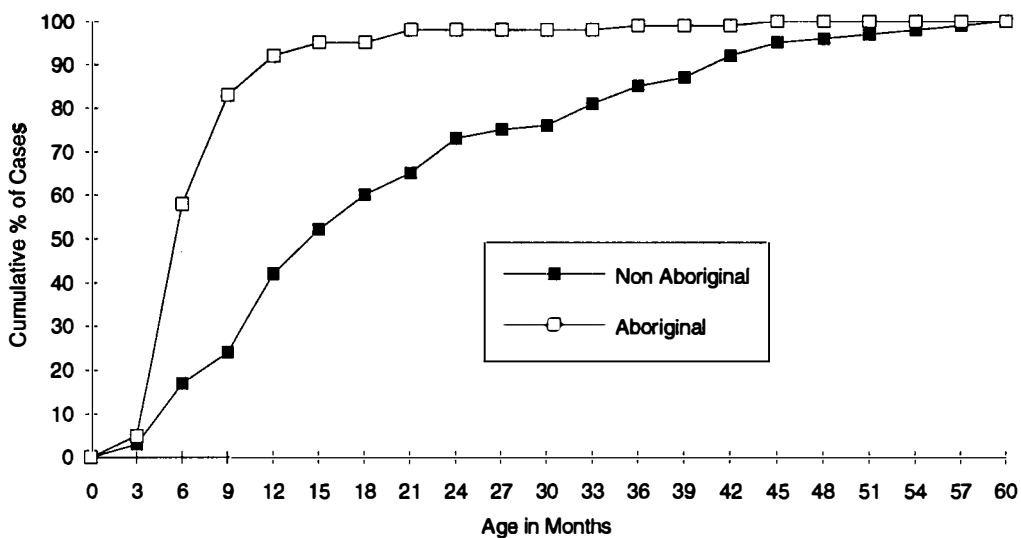
This equation is known as the cumulative distribution function of age at infection. Maternal antibodies can be allowed for by simply setting the force of infection to be zero below a certain age. A polynomial equation can be used to approximate values for the force of infection.

$$\lambda(a) = \sum_{i=0}^k b_i a^i \quad \text{for } m < a \leq j$$

$$\lambda(a) = 0 \quad \text{for } 0 < a \leq m$$

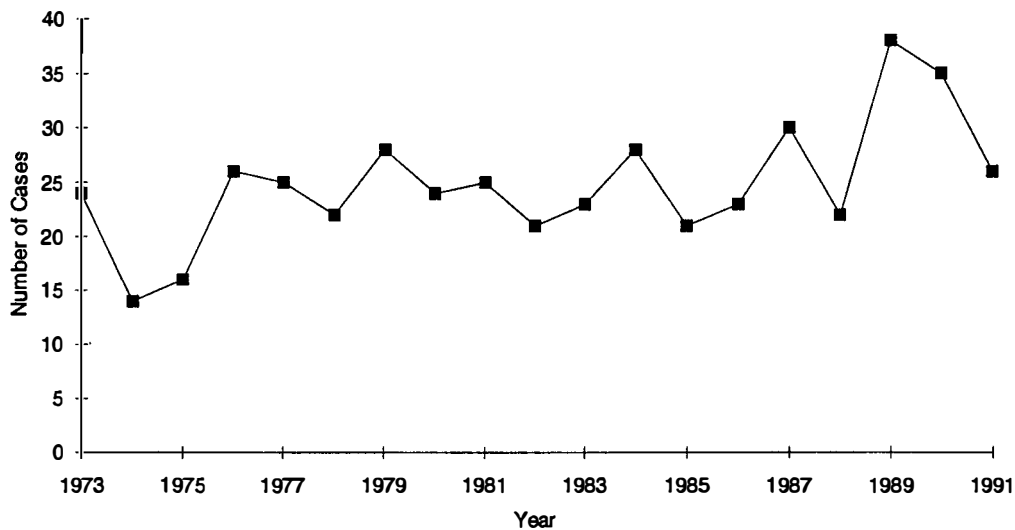
In the above expression  $m$  represents the age at which individuals begin to lose protection due to maternal antibodies. The term  $j$  represents the upper age limit for of the data to be used. We can now need fit a polynomial to a data set for the proportion susceptible to infection at certain ages. Since HIB was not a notifiable disease until 1993 there is a distinct lack of data available for this process. We do have the number of cases of HIB meningitis in children under five years of age at Princess Margaret Hospital (PMH) during the years 1984-1988 which can be used as a convenient place to start the calculations. The figure below illustrates this data.

**FIGURE 4.5.1, HIB MENINGITIS AT PMH 1984-1988**



The figure below describes the number of HIB meningitis cases at PMH during the years 1973-1991

**FIGURE 4.5.2, HIB MENINGITIS AT PMH 1973-1991**

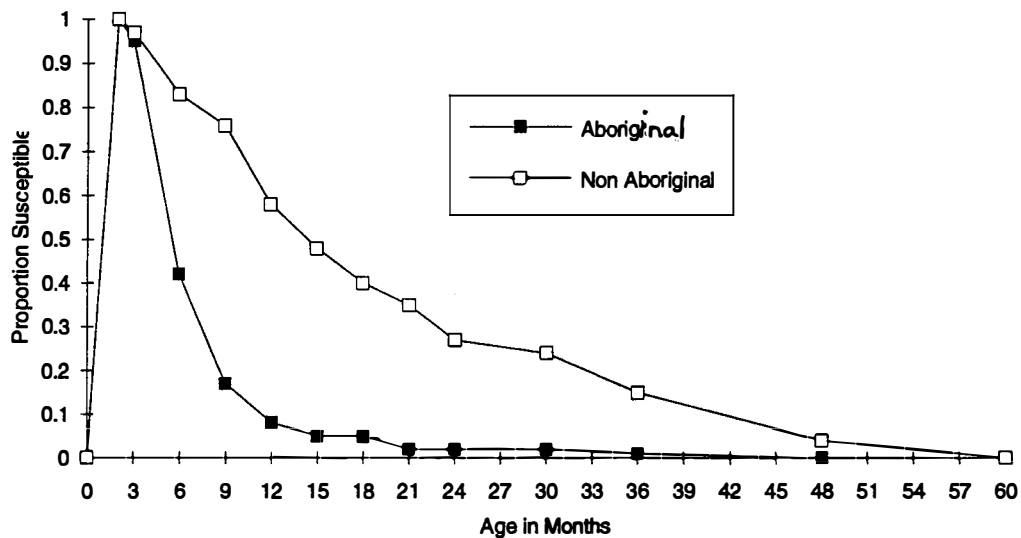


Even though PMH is only one of many Western Australian hospitals it specialises in children and would therefore see the majority of the individuals who suffer from infection from within the Perth metropolitan area. Dr Beryl Wild has provided the following data for the whole of WA in 1992-1994.

There were a total of 51 cases of invasive HIB disease in WA during 1992 with 15 being Aboriginals and thirty six being non Aboriginals. During 1993 there were 20 cases of invasive HIB with 3 being Aboriginals and 17 being non Aboriginals. Between January and June 1994 there have been 7 cases of invasive HIB disease with 2 Aboriginal and 5 non Aboriginal being infected. It should be recalled that the immunisation policy began in 1993.

One possible way of proceeding would be to calculate the age specific force of infection based on the figure for PMH. Figure 4.5.3 describes the proportion of the population susceptible to infection at age  $a$ .

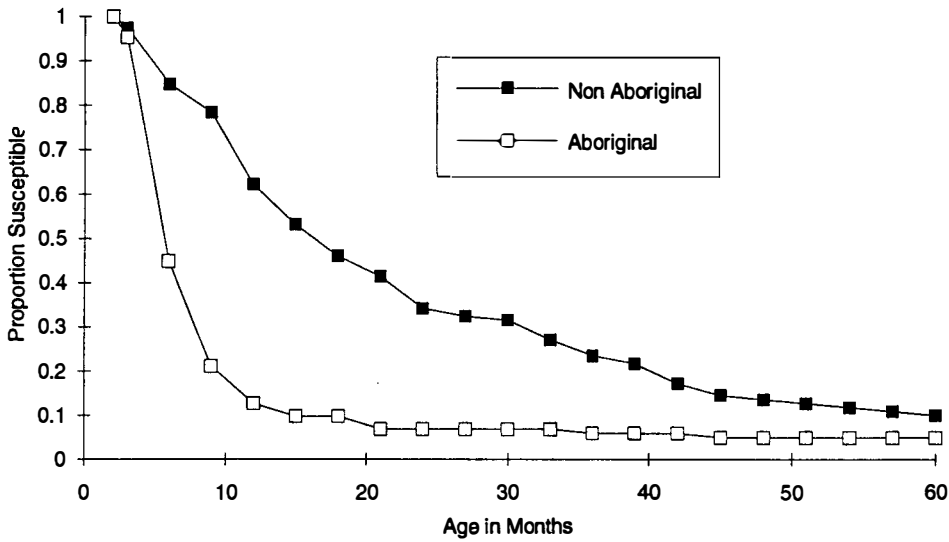
**FIGURE 4.5.3, PROPORTION SUSCEPTIBLE AT AGE A FOR THE UNDER FIVE YEAR OLD AGE GROUP**



However there are cases of invasive HIB disease in children older than five years of age. A paper by S. Iwarson titled "Strategies for immunisation against invasive Haemophilus Influenzae type b infection" (Vaccine, vol 9, Supplement, June 1991) shows a table describing the age distribution of invasive HIB meningitis in Sweden during the years 1971-80. The chart shows that of 147 cases, approximately 14 occurred in children between the ages of 5 and 10 years old. Therefore this data is used for suggesting that approximately 90 per cent of all such cases occur before 5 years of age in the absence of an immunisation programme.

We can then say that at the age of five years there are still ten per cent of individuals susceptible to HIB infection for non Aboriginal children. It will be assumed that five per cent of Aboriginal children are still susceptible to HIB infection at five years of age. This is because the vast majority of Aboriginal invasive HIB meningitis occurs at below one year of age. The five per cent then allows for the possibility of invasive HIB disease occurring in children older than five years of age. I have been unable to find any publications that give a breakdown of figures for the occurrence of invasive HIB disease within the Aboriginal and Torres Strait Islander population for the age group 5-10.



**FIGURE 4.5.4, PROPORTION SUSCEPTIBLE AT AGE A**

We can now fit suitable functions to these curves to give mathematical expressions for the proportion susceptible at age  $a$ . For the non Aboriginal data the following graph was obtained,

**FIGURE 4.5.5, CUBIC FIT FOR NON-ABORIGINAL DATA**

The function that gave the graph was a cubic, generated using Mathematica for Windows, (Wolfram, 1991) given by

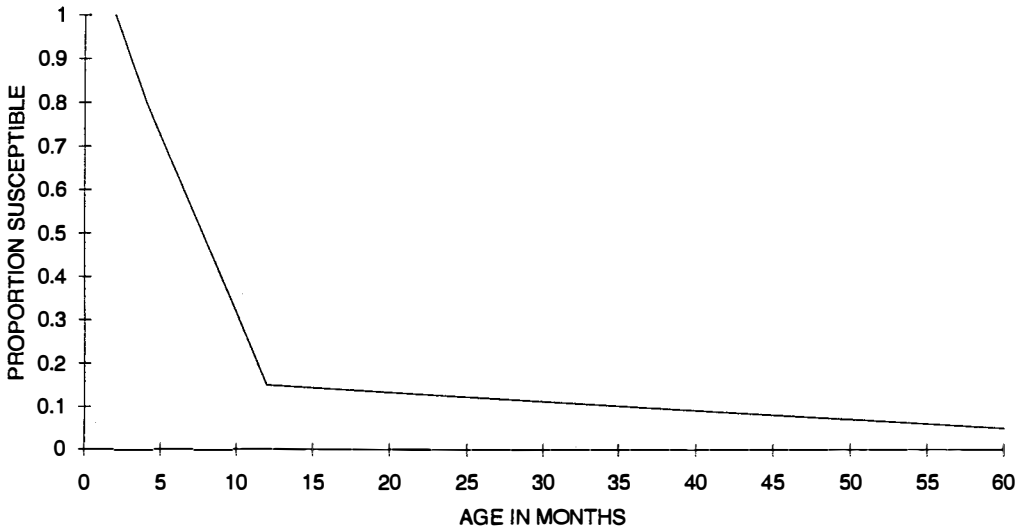
$$X(a) = c_0 + c_1a + c_2a^2 + c_3a^3, \quad \text{for } 2 \leq a \leq 60 \text{ months}$$

which becomes

$$X(a) = 1.10681 - 0.0488401a + 0.000893026a^2 - 0.00000603229a^3, \quad \text{for } 2 \leq a \leq 60 \text{ months.}$$

For the aboriginal data the following graph was obtained using Mathematica for Windows.

**FIGURE 4.5.6, LINEAR FIT FOR ABORIGINAL DATA**



The graph is a combination of two linear equations i.e.

$$X(a) = 1.15521 - 0.0840357a \quad \text{for } 2 \leq a < 12$$

$$X(a) = 0.10333 - 0.0011111a \quad \text{for } 12 \leq a \leq 60.$$

The force of infection is thereby given by the equation

$$X(a) = e^{\int_0^a \lambda(s) ds} \quad \text{which can be rewritten as}$$

$$\lambda(a) = -\frac{d \ln X(a)}{da},$$

which for the Aboriginal case becomes

$$\lambda(a) = \frac{0.0840357}{1.15521 - 0.0840357a} \quad \text{for } 2 < a < 12 \text{ months}$$

$$\lambda(a) = \frac{0.0011111}{0.10333 - 0.0011111a} \quad \text{for } 12 < a < 60 \text{ months.}$$

4.5.1

Similarly the force of infection for the non Aboriginal case is given by

$$\lambda(a) = \frac{3c_3a^2 + 2c_2a + c_1}{c_3a^3 + c_2a^2 + c_1a + c_0} \quad 4.5.2$$

where the constants are given by,

$$c_0 = 1.10681, \quad c_1 = -0.0488401, \quad c_2 = 0.000893026 \text{ and } c_3 = -0.00000603229.$$

We can apply this force of infection to both the proportion susceptible to HIB and the proportion susceptible to Systematic HIB. Since we now have estimates for all the parameters within the model we can begin the process of numerically solving the differential equations.

This chapter has estimated all parameter values within the model in order that a numerical simulation can take place. Available data provided by Beryl Wild showing the incidence of HIB meningitis has been used in order to estimate the proportion of the population susceptible at age  $a$ . The next chapter is concerned with various numerical simulations using the values estimated in this chapter.

## CHAPTER FIVE

### NUMERICAL RESULTS

#### 5.1 Introduction and Programme

This chapter is concerned with numerically solving the system of differential equations 3.1.1. We can then determine whether the equations predict realistic numbers of individuals in each state of the disease at different ages. We can also determine the effect that an immunisation policy will have on the incidence of HIB and systematic HIB disease. Another measurable quantity that can be estimated is the average age of infection and how it changes when an immunisation programme is introduced.

Before an appropriate computer simulation commences it is essential to understand what will actually be measured. The first stage will be to run the simulating without any immunisation factor being used. If we use as a starting point the total population in a particular year then we can see how the disease affects this particular cohort of people. Such a cohort will be considered as all being two months of age when the simulation begins. This is since it was previously assumed that all individuals will be 100 % protected from infection by maternal antibodies until two months of age. We can then run the simulation and see how the cohort of people are affected by HIB according to the system of equations. If we choose 1991 as the initial cohort to study then we can see how many people would be infected by HIB if the immunisation policy which began in that year is not included in the model. The same model can then be run with immunisation included and the results can be compared.

It should be noted that the simulation will initially run with aboriginal and non-aboriginal individuals grouped together and only be concerned with one type of vaccine, in this case HibTitter. These initial results may therefore not be truly representative of the overall immunisation policy since aboriginal children are given a different vaccine, PedVaxB, due to a lower average age of infection than non-aboriginal children. However the simulation will show how immunisation affects the general incidence of HIB and Systematic HIB. Before a suitable Fortran programme is introduced the parameters within the model are summarised below.

**TABLE 5.1.1 PARAMETER INTERPRETATION**

Parameter	Biological Interpretation	Age Dependence	Type of Data needed to measure	Range of Values
$\lambda(a)$	Per capita force of infection	dependent	age specific case notifications or seriological surveys	0.0259-0.3041
$\sigma(a)$	Immunisation rate	dependent	health surveys	0.0434-0.65
$\mu(a)$	Background death rate	dependent	demographic tables	0.000693-0.0000038
$\nu$	Recovery rate from HIB infection	independent	clinical observations	1
$\delta$	Rate of loss of maternal antibodies	independent	seriological surveys	0.5
$\theta$	Rate at which infected individuals become infectious	independent	clinical observations	10
$\omega$	Rate at which systematic HIB cases occur	independent	clinical observations	0.0259-0.3401
$\phi$	Recovery rate from systematic HIB	independent	clinical observations	6
$\zeta$	Systematic HIB death rate	independent	case fatality rates	0.00002

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$\phi$	Recovery rate from systematic HIB	independent	clinical observations	6
$\zeta$	Systematic HIB death rate	independent	case fatality rates	0.00002

The next stage was to develop a suitable Fortran programme that could be used to solve the system of differential equations. From the software package called Fortran PC50 an existing algorithm, D02CBF, was chosen and modified to suit the needs of this chapter. This routine uses the Adams Gear method to solve systems of ordinary differential equations. The modified routine that was used to run the simulation is documented at the end of this thesis.

## **5.2 Simulation with HibTitter Only**

The parameter values were changed as the model moved from a period that required certain values for parameters to another age period that required a different set of parameter values. To begin with the total number of individuals in the age group 0-10 in 1991 was used as the number of people protected by maternal antibodies. It was then assumed that the rate of change of individuals in this state would decline at an exponential rate given by the rate of loss of maternal antibodies as in the table above. At age zero there are considered to be no susceptible, latent, infectious, systematic or recovered individuals. The numbers in these classes appear as the simulation runs. If the force of infection was taken as proportional to the number of infectious individuals then there would need to be at least some infectious people at age zero otherwise the simulating model would simply predict zero infectious individuals for any simulation that was run under these conditions. Once the simulation began then appropriate values were fed into the algorithm as then need arose. For instance at age four months the efficacy of the vaccine changes and hence the new value was applied. Similarly after twelve months the background death rate would change. All of the simulations to follow used this method to ensure that the correct parameter values were applied when needed.

The following results were obtained from the simulation with around off error of 0.0001 for the situation where no immunisation programme was present.

D02CBF PROGRAM RESULTS WITH NO VACCINE PRESENT  
 CALCULATION WITH TOL= .1D-03

Age	M(a)	X(a)	H(a)	Y(a)	K(a)	Z(a)	N(a)
2.00	25051	00000	00000	00000	00000	00000	25051
3.00	15185	9608.2	40.701	146.80	83226	52.476	25034
4.00	9203.9	14995	65.820	407.67	2.7733	340.74	25016
5.00	5578.2	17844	80.463	613.22	4.4484	878.41	24999
6.00	3380.5	19173	87.497	743.49	5.5446	1591.8	24982
7.00	2048.6	19598	89.756	813.63	6.1488	2408.4	24964
8.00	1241.6	19492	89.468	842.36	6.4138	3274.9	24947
9.00	752.40	19082	87.761	844.78	6.4619	4156.3	24930
10.00	457.78	18501	85.027	831.42	6.3737	5030.4	24913
12.00	170.35	17130	79.358	780.77	6.0133	6711.3	24878
14.00	63.305	15716	73.236	727.70	5.6617	8292.0	24878
16.00	23.633	14363	66.972	667.61	5.1985	9750.6	24877
18.00	8.7937	13106	60.944	610.11	4.7481	11086	24877
20.00	3.2866	11952	55.732	556.47	4.3342	12304	24877
22.00	1.2361	10898	50.619	507.68	3.9501	13415	24876
24.00	.46245	9934.8	46.303	462.67	3.6033	14428	24876
36.00	00000	6112.1	24.975	248.77	1.6906	18487	24875
42.00	00000	5034.3	16.373	163.71	.88881	19650	24874
48.00	00000	4146.6	13.547	134.64	.73176	20569	24874
54.00	00000	3112.3	14.904	149.77	1.2037	21588	24874
60.00	00000	2336.1	11.247	112.49	.90569	22405	24874



The simulation predicted that almost all the cohort leave the maternal antibody class by the age of twelve months as expected. In fact in the twenty fifth month the equation describing the rate of change in the numbers in the maternal antibody class predicted negative results and therefore the number in this class was set to zero for all months greater than 24. It can also be seen that the number of susceptibles reached a peak of 19598 individuals after seven months. Thereafter the number of susceptibles decreases until there are some 2336 individuals susceptible after 60 months. This equates to approximately ten per cent of the total cohort. Further the number of infectious HIB individuals reached a peak of 845 at nine months with 112 individuals still being infectious at 60 months. There is always a number of people in the Systematic class peaking at around 6 in the 7-12 month range, and there is roughly one individual in the Systemic state at 60 months. The number of people in the recovered class rises steadily to about 22405, or approximately 90 %, are recovered after sixty months. Given that the vast majority of HIB and Systematic HIB cases occur in the first five years of life the simulation appears to produce reasonable results.

The next simulation involved introducing a immunisation factor. This simulation assumed that only the HibTitter vaccine was used. The initial conditions were similar to the first simulation with the total cohort of 25051 people considered as being protected by maternal antibodies for the first two months. It was assumed there were no susceptible, latent, infectious, systematic or recovered individuals at the start of the simulation. The immunisation parameter was introduced and would therefore influence the susceptible individuals as they moved from the maternal antibody state to the susceptible state. The following results were obtained.

D02CBF PROGRAM RESULTS WITH HIBTITTER VACCINE ONLY  
 CALCULATION WITH TOL= .1D-03

Age	M(a)	X(a)	H(a)	Y(a)	K(a)	Z(a)	N(a)
2.00	25051	00000	00000	00000	00000	00000	25051
3.00	15183	8940.1	37.897	140.56	.79774	731.76	25034
4.00	9202.1	12866	57.877	365.97	2.5329	2521.9	25016
5.00	5576.5	10027	47.008	455.12	3.4436	8890.0	24999
6.00	3379.2	73454	34.207	407.58	3.1908	13812	24981
7.00	2048.1	7241.8	32.965	330.15	2.5545	15219	24964
8.00	1241.2	7470.0	34.171	325.93	2.4895	15783	24947
9.00	752.17	7376.7	33.847	326.12	2.4925	16349	24929
10.00	457.68	7104.5	32.744	320.64	2.4602	16905	24912
12.00	170.15	6340.1	29.233	294.90	2.2730	17952	24878
14.00	62.599	5528.1	25.440	260.82	2.0137	18885	24852
16.00	23.309	4771.4	21.728	226.81	1.7478	19692	24825
18.00	8.7110	4100.9	18.978	195.14	1.5109	20383	24797
20.00	3.2652	3743.0	17.356	174.86	1.3606	20765	24794
22.00	1.2386	3413.9	15.895	159.03	1.2383	21110	24790
24.00	.46889	3112.6	14.438	145.03	1.1280	21425	24787
30.00	00000	2440.9	9.9192	99.458	.67495	22142	24781
36.00	00000	1914.3	7.9550	77.764	.53099	22686	24776
42.00	00000	1576.5	5.1825	51.205	.27883	23048	24770
48.00	00000	1298.3	4.3340	42.050	.22994	23331	24765
54.00	00000	974.36	4.7386	46.809	.37783	23647	24763
60.00	00000	731.36	3.8282	34.875	.28765	23901	24761

These results show how the introduction of an immunisation policy has affected the incidence of both HIB and Systematic HIB disease. For instance the number of susceptibles peaks at eight months with 7470 individuals susceptible to HIB infection. This is considerably lower than the seven month peak of 19598 individuals in the simulation without any immunisation. It can also be seen that the number of infectious HIB individuals peaks at 407 after five months compared to 845 after nine months in the pre-immunisation simulation. The number of Systematic HIB individual peaks at about 3-4 after the same time compared to approximately 6 in the 7-12 month range in the first simulation. The number of recovered individuals reaches about 90 % of the cohort after 34 months as opposed to 60 months in the first simulation. Clearly the introduction of an immunisation strategy is having a significant effect on the levels of HIB and therefore Systematic HIB disease. This leads to a fundamental question.

Is it possible for this immunisation campaign to eradicate all incidence of HIB and Systematic HIB disease?

In order to simulate this question it will be assumed that 100% of individuals begin and pass through the ideal immunisation schedule. It is obvious that we cannot simply change the effectiveness of the vaccine used but must use the proportions shown earlier. With this assumption the simulation gave the following results.

D02CBF PROGRAM RESULTS WITH 100 % VACCINATION RATES

CALCULATION WITH TOL= .1D-03

Age	M(a)	X(a)	H(a)	Y(a)	K(a)	Z(a)	N(a)
2.00	25051	00000	00000	00000	00000	00000	25051
3.00	15183	8874.5	37.647	139.91	.79461	798.19	25034
4.00	92021	12669	57.600	361.50	2.5158	2723.8	25016
5.00	55768	9339.5	44.568	439.49	3.3531	9595.4	24999
6.00	33795	6542.0	31.299	379.71	3.0065	14646	24981
7.00	20479	7289.4	32.928	332.22	2.5634	15259	24964
8.00	12411	7476.2	34.454	327.08	2.5044	15865	24946
9.00	752.08	7344.6	33.512	326.48	2.4926	16470	24929
10.00	457.11	7038.6	32.473	319.30	2.4523	17062	24912
12.00	168.89	6219.0	28.714	290.87	2.2443	18168	24877
14.00	62.157	5366.9	24.710	254.83	1.9909	19164	24874
16.00	23.267	4585.1	21.223	219.00	1.6964	20021	24870
18.00	8.7408	3900.6	18.013	186.89	1.4474	20752	24867
20.00	3.2754	3560.6	16.596	166.40	1.2969	21116	24864
22.00	1.2209	3247.4	14.896	151.54	1.1751	21445	24861
24.00	.45778	2960.8	13.787	137.89	1.0737	21744	24858
30.00	.00000	2321.8	9.2888	94.775	.64040	22425	24852
36.00	.00000	1820.9	7.4480	74.106	.50376	22943	24847
42.00	.00000	1499.5	5.0846	48.528	.26661	23287	24841
48.00	.00000	1234.8	4.0064	40.124	.21765	23555	24836
54.00	.00000	926.7.0	4.5611	44.459	.36008	23856	24834
60.00	.00000	695.5.7	3.2850	33.566	.26881	24097	24832

This simulation shows that even if everyone passes through the ideal immunisation programme there will still be some HIB and Systematic HIB incidence. The determining factor seems to be the effectiveness of the vaccine used. Since there are still some 85 % of the original cohort unprotected after the first dose of the immunisation programme and 16 % unprotected after the second dose these individuals are still susceptible to HIB infection and therefore Systematic HIB infection.

However since we have run the simulation using the HibTitter vaccine the added effect that the PedVaxB vaccine has on the incidence of HIB has not be taken into account. This vaccine could have a substantial effect since it is directed at aboriginal children. Cases of HIB and invasive HIB disease in this population occur almost always before one year of age. The effect of this vaccine on its own will be simulated in section 5.4.

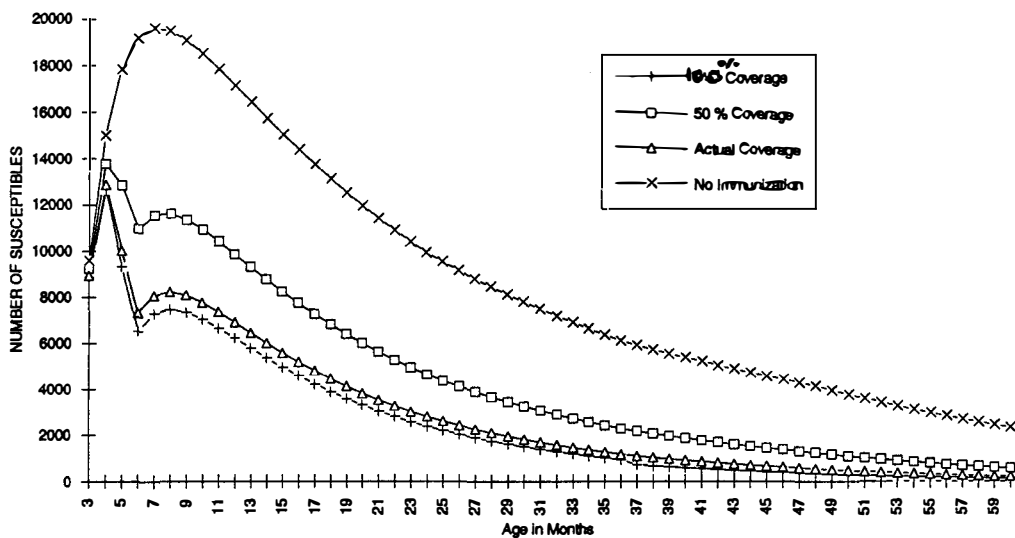
The next simulation is still concerned with the HibTitter vaccine only but when the immunisation rate is not as high as the published rate for DT. If we assume that the coverage rate is in fact fifty percent of the population then the following results were obtained.

D02CBF PROGRAM RESULTS FOR 50 % COVERAGE  
 CALCULATION WITH TOL= .1D-03

Age	M(a)	X(a)	H(a)	Y(a)	K(a)	Z(a)	N(a)
2.00	25051	00000	00000	00000	00000	00000	25051
3.00	15182	9233.2	39.017	143.45	.81171	434.78	25034
4.00	9202.1	13771	61.728	383.42	2.6428	1595.0	25016
5.00	5577.1	12830	59.477	516.03	3.8430	6012.8	24999
6.00	3379.5	10969	50.521	522.13	4.0037	10057	24981
7.00	2048.0	11563	52.828	505.23	3.8653	10792	24964
8.00	1241.2	11613	53.297	507.73	3.8772	11528	24946
9.00	752.18	11354	52.219	505.38	3.8689	12263	24929
10.00	456.27	10925	50.447	494.43	3.7985	12983	24912
11.00	279.03	10409	48.007	477.12	3.6710	13679	24895
12.00	170.14	9860.0	45.496	455.88	3.5127	14343	24877
14.00	62.674	8769.1	40.538	409.33	3.1604	15590	24874
16.00	23.412	7748.0	35.686	363.32	2.8041	16698	24870
18.00	8.7583	6827.4	31.462	320.69	2.4761	17677	24867
20.00	3.2822	6228.1	29.071	290.22	2.2617	18311	24864
22.00	1.2433	5679.1	26.518	264.43	2.0605	18888	24860
24.00	.47094	5177.5	24.084	241.16	1.8772	19413	24857
30.00	.00000	4060.5	16.623	165.33	1.1243	20608	24851
36.00	.00000	3184.7	12.898	129.75	.87959	21518	24846
42.00	.00000	2622.5	8.4413	85.378	.46221	22124	24840
48.00	.00000	2159.7	7.0250	70.157	.38084	22598	24835
54.00	.00000	1621.0	7.5617	78.228	.62421	23126	24833
60.00	.00000	1216.8	5.9678	58.471	.47320	23549	24831

This simulation shows the incidence of HIB and Systematic peaking at 6 months. The incidence of HIB and Systematic HIB has decreased when compared to the pre-immunisation simulation but does not decrease as much as either the published or ideal immunisation coverage rates. However it is clear that even a fifty per cent coverage rate is having a significant effect on the incidence of both HIB and Systematic HIB. The figure below shows the numbers susceptible with the different levels of coverage.

**FIGURE 5.2.1, NUMBER OF INDIVIDUALS SUSCEPTIBLE WITH DIFFERENT PROPORTIONS IMMUNISED**



### 5.3 Epidemiological Estimates

The next question to address is what happens to the average age of infection when an immunisation policy is introduced. Intuitively the average age of infection is the reciprocal of the force of infection. If we assume that the force of infection is a constant rather than age dependent then the average age of infection can be described mathematically by the equation.

$$A = \frac{\int_0^{\infty} a\lambda X(a) da}{\int_0^{\infty} \lambda X(a) da}, \quad (\text{Anderson and May 1991}). \quad 5.3.1$$

The age specific number of susceptibles  $X(a)$  can be written as

$$X(a) = N(0)l(a)e^{-\lambda a}, \text{ where } l(a) = e^{-\int_0^a \mu(s) ds}$$

is the survivorship function and describes the probability of surviving to age  $a$  and  $N(0)$  is the initial population. If we then assume that everyone survives to some age  $L$  and then dies we have

$$l(a) = 1 \text{ for } a < L$$

$$l(a) = 0 \text{ for } a > L$$

Hence substituting these relationships into 5.1 we get

$$A = \frac{\int_0^L ae^{-\lambda a} da}{\int_0^L e^{-\lambda a} da}$$

$$\therefore A = \frac{1}{\lambda} \left( \frac{1 - (1 + \lambda L)e^{-\lambda L}}{1 - e^{-\lambda L}} \right)$$

Then the larger the term  $\dots$ wrong... $e^{-\lambda L}$  the closer the equation is approximated by  $\frac{1}{\lambda}$ . The following table describes the age specific force of infection calculated using the equation 4.5.2.

**TABLE 5.3.1 ESTIMATES FOR THE FORCE OF INFECTION AT AGE A, IN MONTHS**

AGE	FORCE OF INFECTION	AGE	FORCE OF INFECTION	AGE	FORCE OF INFECTION	AGE	FORCE OF INFECTION
2	0.044774	15	0.047084	30	0.040875	45	0.030493
3	0.045080	18	0.046808	33	0.038306	48	0.031421
6	0.045909	21	0.046081	36	0.035617	51	0.034797
9	0.046562	24	0.044849	39	0.033129	54	0.041757
12	0.046977	27	0.043098	42	0.031257	57	0.054376

$\therefore$  The average force of infection = 0.043098



Since the average force of infection in the absence of an immunisation policy is 0.043167 then the average age of infection is approximately 23.15 months, which is the inverse of the force of infection.

Another important epidemiological parameter is the basic reproductive rate which is given by the equation,

$$R_0 = \frac{\frac{L}{A}}{(1 - e^{-\frac{L}{A}})}, \text{ (Anderson and May page 69, 1991).}$$

If  $A$  is much less than  $L$ , the average life expectancy, then

$R_0 \approx \frac{L}{A} = \frac{900}{23.15} = 38.876$ , where we assume the average life expectancy is of the order of 75 years. We have  $\frac{L}{A} = \frac{900}{23.15} = 38.876$  so that  $e^{-\frac{L}{A}}$  is very small and therefore the above approximation appears to be reasonable.

In order to eradicate a disease then the proportion of people successfully vaccinated must be great enough to exceed the effect of the basic reproductive rate of the disease. We know that the fraction of the population susceptible,  $\hat{x}$  must satisfy the inequality  $\hat{x} < 1 - p$ , so that the fraction susceptible is less than the total population minus those successfully vaccinated since there will be at least some people immune from infection due to natural antibody protection. We also know, from chapter one, that the equilibrium  $R_0 \hat{x} = 1$ . Hence we can obtain a condition that needs to be satisfied if the disease is to be eradicated. We have,

$$\frac{1}{R_0} < 1 - p .$$

Hence  $p > 1 - \frac{1}{R_0}$ , if the disease is to be eradicated. In our case we have a required immunisation level of 97.43 % to achieve eradication. This is saying that at least this proportion of people must be successfully vaccinated in order to eradicate the disease.

We can now determine what happens to the average age of infection and the effective reproductive rate of HIB after an immunisation policy has been introduced. The intrinsic reproductive rate after immunisation is given by the expression ( Comiskey, 1988)

$$R_0' = R_0 \left(1 - \frac{cp}{c + \mu}\right),$$

where  $p$  is the proportion vaccinated,  $c$  is the inverse of the average age at immunisation, therefore  $1/c$  is the average age at immunisation, and  $\mu$  the background death rate. If we assume that the death rate is a constant and choose 3 values for both  $p$  and  $c$  then the following table emerges.

**TABLE 5.3.2, ESTIMATES FOR REPRODUCTIVE RATE AFTER IMMUNISATION**

	1/c=2	1/c=6	1/c=12
p=0.5	Ro=22.48	Ro=26.4	Ro=29.69
p=0.75	Ro=14.29	Ro=20.16	Ro=25.09
p=0.95	Ro=7.74	Ro=15.17	Ro=21.42

The table shows the intuitive result that the intrinsic reproductive rate of the disease will become lower as the average age of immunisation decreases and the proportion immunised increases.

What will happen to the force of infection when an immunisation programme is introduced? Anderson and May (1991) give an approximate expression for the post immunisation force of infection as

$$R_0' = \frac{\lambda' L}{(1-p)(1-e^{-\lambda' L})}.$$

Since the exponential term contains a measure of age in months,  $L=900$ , we could approximate the post immunisation force of infection by

$$\lambda' = \frac{R_0'(1-p)}{L},$$

which in the case where  $L=900$ ,  $p=0.85$  and  $R_0'=38.876$  becomes,

$$\lambda' = \frac{38.876(0.15)}{900} = 0.0065$$

We can use this result to calculate the post immunisation average age at infection which is given by Anderson and May (1991) as below,

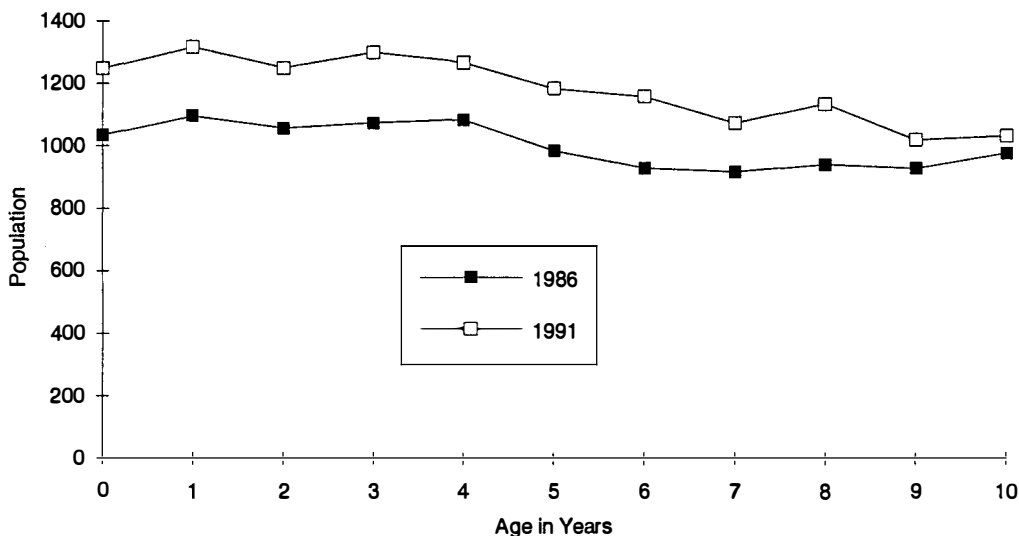
$$A' = \frac{1}{\lambda'} \left( \frac{1 - (1 + \lambda' L) e^{-\lambda' L}}{1 - e^{-\lambda' L}} \right).$$

This calculation yields  $A' = 151.25$  months, which appears to be very high since it means the average age of infection has jumped from approximately two years old to twelve years old. However it does highlight the fact that the average age at infection rises significantly when immunisation programmes are introduced. The determining factor is the post immunisation force of infection which we have taken to be a constant for all age groups in the previous estimation process. As has already been seen in chapter 4 this is not really a good interpretation of reality but it has allowed the simplified process above to be carried out.

#### 5.4 More Simulations

The simulations so far have been based on one vaccine only and have grouped both Aboriginal and non-Aboriginal children together. In order to reflect reality it is necessary to try and incorporate these individual populations separately. However there is a distinct lack of data concerning population levels of aboriginal people in Western Australia. Demographic tables published by the ABS give approximate population levels for both 1986 and 1991. The figure below shows the population for these two years.

**FIGURE 5.4.1, ABORIGINAL AND TORRES STRAIT ISLANDER POPULATION 1986 AND 1991**



We have also seen that Systematic Meningitis cases amongst Aboriginal children account for about 50% of the total number of cases and that nearly all of these cases occur before one year of age. We have also estimated the force of infection amongst this population. Therefore we can introduce the vaccine PedVaxB into the simulation process by concentrating on this group of people. If we substitute the appropriate parameter values into the simulation programme then we can simulate the effect that PedVaXB has on the Aboriginal and Torres Strait Islander community only. The initial conditions assumed that the total cohort in the 0-10 year age group in 1991 were protected by maternal antibodies at age zero. It is also assumed that there are no latent, susceptible, infectious, systematic or recovered individuals at the start of the simulation. The following table gives the results of the simulation when there is no immunisation programme present.

D02CBF PROGRAM RESULTS FOR ABORIGINAL AND TORRES STRAIT ISLANDERS WITH NO IMMUNISATION

Age	M(a)	X(a)	H(a)	Y(a)	K(a)	Z(a)	N(a)
2.00	1248.0	00000	00000	00000	00000	00000	1248
3.00	755.03	463.41	4.3908	15.772	.20064	5.8721	1244.7
4.00	456.68	697.66	6.9757	41.903	.64526	37.489	1241.4
5.00	276.22	797.71	8.1036	60.650	.99054	94.363	1238.0
6.00	167.06	820.76	8.3752	70.535	1.1815	166.83	1234.7
7.00	101.05	659.76	20.534	139.03	6.7067	304.37	1231.4
8.00	61.121	519.23	16.184	137.22	7.0662	487.34	1228.1
9.00	36.967	402.49	12.562	114.90	6.0247	651.95	1224.8
10.00	22.358	308.51	9.6372	91.033	4.8063	785.28	1221.6
11.00	13.523	234.48	7.3332	70.377	3.7286	888.93	1218.3
12.00	8.1787	177.05	5.5345	53.704	2.8498	967.80	1215.1
18.00	.42392	171.17	.21584	2.3009	.00488	1038.2	1212.3
24.00	.00000	158.79	.19461	1.9994	.00416	1048.5	1209.5
36.00	.00000	130.93	.19898	2.1019	.00552	1074.1	1207.3
48.00	.00000	103.16	.19141	2.0547	.00666	1074.8	1187.7
60.00	.00000	75.533	.15478	2.0113	.00823	1076.7	1186.8

The results show the incidence of HIB peaking after 7 months with approximately 139 individuals being infectious. The incidence of HIB rises from 0-139 cases in the 2-7 month period and then declines to about 54 infected individuals after 12 months. Thereafter the number of HIB cases declines until there are only 2 cases after 60 months. This is in accordance with case notifications that were described in chapter four. The incidence of systematic HIB peaks in the 7-9 month range with about 6-7 seven people infected. The incidence then decreases until it reaches negligible levels after 18 months. Since it is expected that almost all cases will occur before one year of age within this community then these appear to be reasonable results.

If we now introduce the PedVaxB vaccine into the simulation with the same initial conditions we get the following results

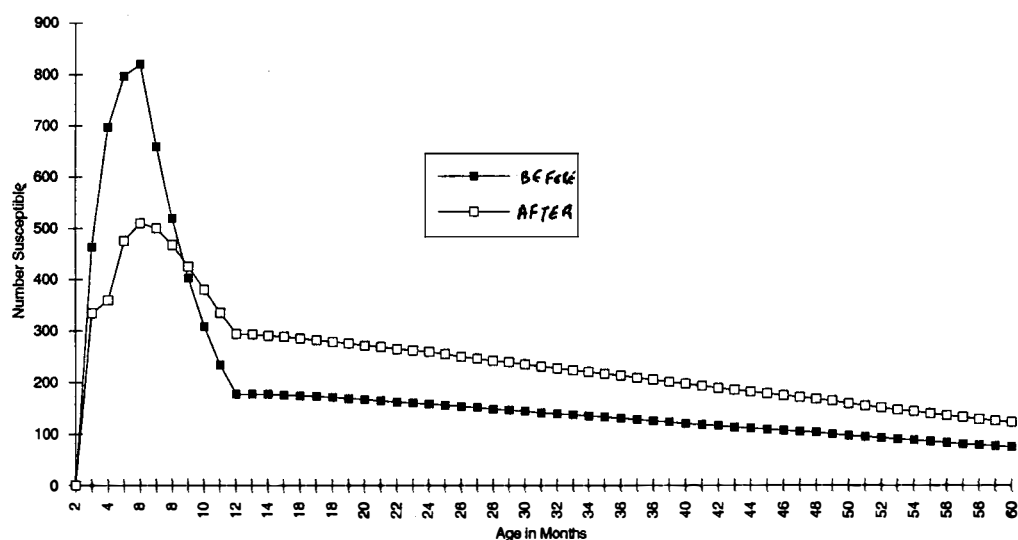
D02CBF PROGRAM RESULTS FOR PEDVAXHIB

Age	M(a)	X(a)	H(a)	Y(a)	K(a)	Z(a)	N(a)
2.00	1248.0	00000	00000	00000	00000	00000	1248.0
3.00	755.00	334.57	3.2526	12.849	.16655	138.84	1244.7
4.00	456.70	360.77	3.7529	26.557	.42623	393.14	1241.4
5.00	276.23	476.59	4.8037	35.282	.57595	444.56	1238.1
6.00	167.07	510.88	5.2343	42.536	.70976	508.30	1234.8
7.00	101.05	500.80	5.1498	45.602	.77320	578.07	1231.5
8.00	61.114	468.16	4.8261	45.228	.77500	648.06	1228.2
9.00	36.964	425.53	4.4028	42.722	.73743	714.53	1224.9
10.00	22.388	380.05	3.9390	39.137	.67861	775.43	1221.7
11.00	13.561	335.59	3.4856	35.147	.61139	829.97	1218.4
12.00	8.2520	294.15	3.0589	31.158	.54314	877.95	1215.2
18.00	.44484	279.59	.35550	3.5081	.00488	900.43	1212.5
24.00	.00000	259.14	.32550	3.2536	.00410	918.86	1209.8
36.00	.00000	213.66	.35157	3.4003	.00552	962.04	1207.7
48.00	.00000	168.33	.33374	3.3289	.00666	1005.3	1205.6
60.00	.00000	123.25	.33079	3.1948	.00823	1009.0	1204.8

In this scenario the incidence of Hib peaks after 7 months with about 45 cases. The incidence rise from 0-45 in the 2-7 month period and decreases from 45-31 after 12 months. After 18 months there are only about 3-4 cases predicted. The systematic Hib incidence is much lower than the pre-immunisation scenario. The simulation predicts that the incidence peaks after 8 months with maybe one case. However the simulation also predicts that there may be single cases from about the 4-12 month period.

These results predict that incidence of Systematic Hib disease amongst Aboriginals diminishes dramatically if the PedVaxHib vaccine is applied in the manner analysed in this numerical simulation. The numbers susceptible before and after immunisation are shown in the figure below.

**FIGURE 5.4.2 , NUMBER OF ABORIGINAL AND TORRES STRAIT ISLANDER SUSCEPTIBLES BEFORE AND AFTER IMMUNISATION**



Before these simulations are commented on in greater detail there is one final scenario that will be considered. That is the combined effect of the vaccines on the total population. In order to include this joint effect we will use the combined effect quantified in chapter 4. Using the appropriate proportions for those vaccinated we get the following results when applied to the cohort born in 1992.



D02CBF PROGRAM RESULTS FOR COMBINED VACCINES  
 CALCULATION WITH TOL= .1D-03

Age	M(a)	X(a)	H(a)	Y(a)	K(a)	Z(a)	N(a)
2.00	25051	00000	00000	00000	00000	00000	25051
3.00	15184	8820.3	38.496	138.36	.80444	852.14	25034
4.00	9202.1	12512	56.320	359.07	2.4882	2884.7	25016
5.00	5576.9	10028	47.190	447.81	3.3873	8896.4	24999
6.00	3379.5	7502.0	35.908	406.47	3.1953	13655	24981
7.00	2048.2	8225.2	37.169	368.72	2.8333	14283	24964
8.00	1241.2	8392.4	38.466	366.42	2.7988	14906	24946
9.00	752.18	8242.5	37.901	365.72	2.7981	15529	24929
10.00	457.09	7918.2	36.129	358.89	2.7473	16140	24912
11.00	278.56	7506.4	34.619	345.38	2.6581	16728	24895
12.00	170.15	7058.1	32.695	328.35	2.5345	17287	24877
14.00	63.333	6155.4	28.732	289.91	2.2469	18305	24843
16.00	23.629	5319.6	24.425	252.46	1.9497	19188	24808
18.00	8.8191	4579.6	21.042	217.88	1.6835	19946	24774
20.00	3.3011	4179.8	19.352	195.28	1.5189	20375	24744
22.00	1.2508	3812.5	17.900	177.44	1.3848	20764	24743
24.00	.47284	3476.3	16.128	161.97	1.2599	21118	24743
30.00	.00000	2726.6	10.948	111.25	.75250	21923	24742
36.00	.00000	2138.9	8.7941	86.995	.59223	22537	24742
42.00	.00000	1761.6	5.8323	57.167	.31193	22947	24741
48.00	.00000	1451.0	4.4930	47.389	.25383	23268	24741
54.00	.00000	1089.1	5.0493	52.595	.41899	23624	24741
60.00	.00000	817.56	3.8962	39.414	.31643	23910	24741

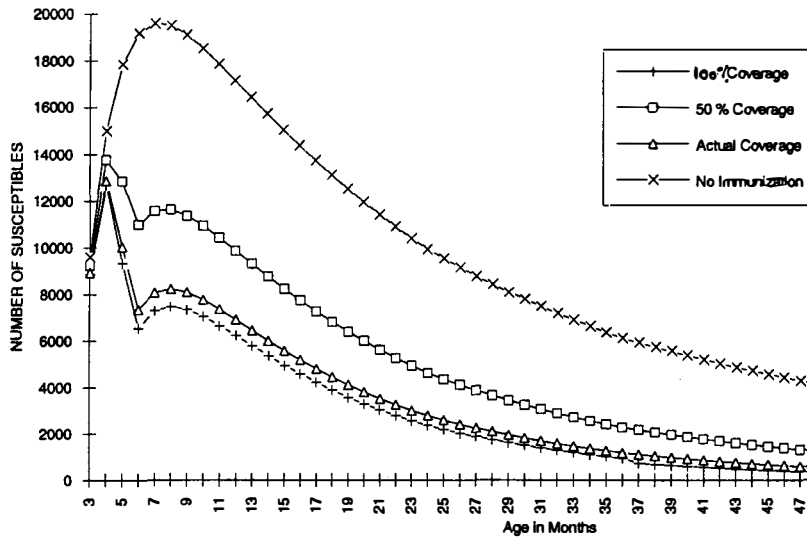
This simulation produces results that could possibly be considered as the most likely to reflect reality. They predict that the number of susceptible individuals peaks at 12512 after 4 months with 56 people in the latent class. This compares to 19598 susceptibles after 7 months and 90 individuals in the latent class after 7 months in the pre-immunisation simulation. The infectious HIB state peaks at 359 after 5 months compared to 845 cases after 9 months in the pre-immunisation case. Systematic HIB incidence peaks after 5 months with around 3 cases compared to about 6 cases in the 7-12 months age range in the pre-immunisation simulation. The number of recovered individuals reaches about 90% of the total cohort after 30 months compared with sixty months in the pre-immunisation simulation. After 60 months there are still some 817 individuals susceptibles to HIB infection and 23910 individuals can be considered as being immune to infection.

## **5.5 Conclusions**

This work has shown that the mass immunisation campaign now being implemented in Western Australia should significantly reduce the incidence of HIB. As a result the more serious threat to individuals from systematic HIB disease such as meningitis and epiglottitis will also diminish. If the coverage rate is actually as high as the statistics given in Table 4.3.1 then the incidence of HIB disease, as predicted in this model, will reduce to very low levels relative to the pre-immunisation incidence. It could be expected that the higher the immunisation coverage rate the lower the incidence of HIB will become. However this relationship does not appear to be linear since a series of incremental rises in the level of coverage will not all necessarily produce the same incremental reduction in the incidence of HIB. Figure 5.2.1, repeated below, shows how the number of susceptibles is affected by different coverage levels.

When the average age of infection was calculated in chapter five it was assumed that the average life expectancy to be of the order of 75 years or 900 months. If this was not so high then the reproductive rate of the disease would not be as high. As a result the average age of infection after immunisation could become lower than the figure calculated of approximately 150 months.

**FIGURE 5.2.1, NUMBER OF INDIVIDUALS SUSCEPTIBLE WITH DIFFERENT PROPORTIONS IMMUNISED**



One area of the thesis that offers room for further study concerns the age dependent force of infection. The concepts described in section 2.3 could be applied to give numerical values for the elements within an appropriate Who Acquired Infection From Whom matrix. Also the simulation process could be applied to the system of partial differential equations 2.3.1 or 2.3.9. Another area for further study is the Aboriginal and Torres Strait Islander Community. Since this population is small relative to the total Western Australian population it could be worthwhile to construct a stochastic model to examine the effects of the immunisation policy. Further this population has many isolated communities so that generalisations used in this model may not correctly reflect the demographics of such communities.

The simulation process in chapter five only took the population of one particular year as a starting point. This could be extended by performing the simulation for several starting values for the total population. It might also be worthwhile to run the simulation using several different numerical routines rather than the single algorithm used in this thesis. Comparison of the results would indicate if the routines predicted similar incidence of HIB and systematic HIB, and could therefore be treated as giving reliable results.

It might also be of benefit to test the sensitivity of the model, by using different initial conditions and parameter estimates. In this way we could see whether the model predicts very different results as different values are used to start the simulation process.

A difficult area within the study is the coverage rate of the immunisation policy. All that can really be used are official sources of information such as the Australian Bureau of Statistics (ABS) or the health department of Western Australia. However private communication with Beryl Wild and Jeffrey Hanna has thrown some doubts on the levels of coverage that were published by the ABS and used in this thesis as a guide-line. Both individuals indicated that the published rates seemed very high. The research currently been undertaken by Rob Condon should give some more realistic results and these could be used in the simulation process. The collection and analysis of data relevant to the study is of paramount importance in trying to understand the epidemiological trends in incidence of the disease. Any additional information that can be gained by either seriological surveys or case notifications would be highly desirable.

This work has shown that it is possible to apply standard mathematical techniques to the transmission dynamics of an infectious disease, in this case HIB. Providing that relevant information is available the models within this thesis could be used to simulate the incidence levels of other common childhood diseases like measles and many useful results can be obtained.

## APPENDIX

### FORTRAN 77 ALGORITHM USED IN CHAPTER FIVE

```

C  D02CBF PROGRAM TEXT
C  .. Parameters ..
  INTEGER      NOUT
  PARAMETER    (NOUT=6)
C  .. Scalars in Common ..
  DOUBLE PRECISION H, XEND
  INTEGER      I
C  .. Local Scalars ..
  DOUBLE PRECISION TOL, X
  INTEGER      IFAIL, IR, J, N
C  .. Local Arrays ..
  DOUBLE PRECISION W(7,36), Y(7)
C  .. External Subroutines ..
  EXTERNAL     D02CBF, FCN, OUT
C  .. Common blocks ..
  COMMON       XEND, H, I
C  .. Executable Statements ..
  WRITE (NOUT,FMT=99996)
  N = 7
  IR = 0
  DO 20 J = 4, 5
    TOL = 10.D0**(-J)
    WRITE (NOUT,FMT=99999) TOL
    WRITE (NOUT,FMT=99998)
    X = 2.D0
    XEND = 12.D0
    Y(1) = 25051.0D0
    Y(2) = 0.0D0
    Y(3) = 0.0D0
    Y(4) = 0.0D0
    Y(5) = 0.0D0
    Y(6) = 0.0D0
    Y(7) = 25051.0D0
    H = (XEND-X)/10.D0
    I = 9
    IFAIL = 1
    CALL D02CBF(X,XEND,N,Y,TOL,IR,FCN,OUT,W,IFAIL)
    WRITE (NOUT,FMT=99997) IFAIL
    IF (TOL.LT.0.D0) WRITE (NOUT,FMT=99995)
  20 CONTINUE
  STOP
C
99999 FORMAT (/,' CALCULATION WITH TOL=',D8.1)
99998 FORMAT (' X AND SOLUTION AT EQUALLY SPACED POINTS')
99997 FORMAT (' IFAIL=',I1)

```

```

99996 FORMAT (/,,/,/, ' D02CBF EXAMPLE PROGRAM RESULTS',/,1X)
99995 FORMAT (' RANGE TOO SHORT FOR TOL')
  END
  SUBROUTINE FCN(T,Y,F)
C   .. Array Arguments ..
  DOUBLE PRECISION F(7), Y(7)
C   .. Intrinsic Functions ..
  INTRINSIC    COS, SIN
C   .. Executable Statements ..
  F(1) = - (0.5 + 0.000693)*Y(1)
  F(2) = 0.5*Y(1) - ( 0.04586 + 0.000693 )*Y(2)
  F(3) = ( 0.04586 )*Y(2) - ( 10 + 0.000693 )*Y(3)
  F(4) = 10*Y(3) - (1 + 0.04586 + 0.000693)*Y(4)
  F(5) = 0.04586*Y(4) - (6 + 0.000021 + 0.000693)*Y(5)
  F(6) = 1*Y(4) + 6*Y(5) - 0.000693*Y(6)
  F(7) = F(6) + F(5) + F(4) + F(3) + F(2) + F(1)
  RETURN
  END
  SUBROUTINE OUT(X,Y)
C   .. Parameters ..
  INTEGER    NOUT
  PARAMETER  (NOUT=6)
C   .. Scalar Arguments ..
  DOUBLE PRECISION X
C   .. Array Arguments ..
  DOUBLE PRECISION Y(7)
C   .. Scalars in Common ..
  DOUBLE PRECISION H, XEND
  INTEGER    I
C   .. Local Scalars ..
  INTEGER    J
C   .. Intrinsic Functions ..
  INTRINSIC  DBLE, REAL
C   .. Common blocks ..
  COMMON     XEND, H, I
C   .. Executable Statements ..
  WRITE (NOUT,FMT=99999) X, (Y(J),J=1,7)
  X = XEND - DBLE(REAL(I))*H
  I = I - 1
  RETURN
99999 FORMAT (' ',F7.2,7D13.5)
  END

```

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