

## ADDENDUM

### NOTES ON THE COLLECTION OF IRISH DATA

As has been said in the main text the collection of accurate and appropriate data in Ireland is a very difficult and tedious task. Data on survival rates for the Irish people in chapter four was collected during the Winter of 1985 and Spring 1986. Records contained in the Central Statistics Office were not always readily available. Also in many instances the access to records which recorded the age of the population and the number of deaths within each age group of the population although available were recorded in different reports. More details of the specific difficulties encountered are described in chapter 4. One must also point out that often the census figures were recorded at irregular intervals (usually every 5 years but this was not always the case) and that the most recent figures available on the numbers in each age group were to be found in the 1981 census reports.

The collection of data on the proportions immunised in each age group was also very difficult. No official figures were available to me, however I was very fortunate to have received information and assistance from Community Care Area 8. This area kept details on the numbers of children vaccinated, the age of each child vaccinated and the total number of children in each age group.

The collection of this immunisation data occupied all of Summer 1986. Community Care Area 8 had all the above data computerised for those children in the General Medical Service (G.M.S.) It remained for me to computerise the remaining cases of non G.M.S.

data This was achieved by coding, for use with the statistical package SPSSX, all immunisations forms returned by doctors in the area In order to be paid for administering the vaccine all doctors had to complete and return these forms (A copy of one such form is attached) The data contained in this form was then transcribed onto a computer data entry sheet (see attached) Data from over 4000 vaccinations was coded and computerised in this way

As the total numbers of children in each age group was available I then estimated the proportions vaccinated in each of the age groups I must stress that this would not have been possible were it not for the excellent records kept within Community Care Area 8.

I was very fortunate that I could estimate the exact proportions susceptible to measles infection prior to mass immunisation. This was due to the fact that unvaccinated blood samples were available in the Department of Medical Microbiology in University College Dublin From the records made available to me I drew a sample of over 140 bloods These were taken from children between the ages of 1 and 13 years These blood samples were then tested using the Critical Flicker Fusion test (CFF) for measles antibodies. The proportions susceptible in each of the age groups was then derived from the results of these tests. I should point out that although this is the best way to estimate the proportion susceptible to measles it is not always possible due to the fact other countries have been immunising for several years and that unvaccinated blood is unavailable. In such cases the proportion susceptible must be estimated from cases notifications, these

however are notoriously unreliable

As has been said above the collection of data can be a very laborious and time consuming task, especially where records are scarce or simply non-existent. Therefore I must stress to all health authorities the necessity of keeping accurate and detailed records (especially of age). I must also caution other mathematicians that working with mathematical models for diseases in Ireland can be very difficult, but I must say, also very interesting, rewarding and I hope of some benefit to the community.

NATIONAL INSTITUTE OF HIGHER EDUCATION

SCHOOL OF MATHEMATICAL SCIENCES

MSc THESIS

A Mathematical Model for  
Measles Epidemics in Ireland

Catherine Comiskey B A (Mod )

Supervisor  
Prof A D. Wood  
School of  
Mathematical Sciences

This thesis is based on the candidates own work

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Finally, I wish to thank Ms Geraldine Comyn for her excellent work of typing the manuscript.

To My Parents

For their continued support throughout  
my education

## ABSTRACT

The aim of this work is to establish a mathematical model for measles epidemics and to predict levels of vaccination coverage required in Ireland in order to eradicate the disease. The emphasis throughout has been to derive the parameters of the model using data collected in Ireland. To achieve this a non-linear differential equation model first proposed by Anderson R.M. and May R.M. has been adopted and adjusted to meet our application.

In Chapter 1 we introduce the concept of mathematically modelling the dynamics of an infectious disease and we also propose a simple constant parameter model. We then move on in Chapter 2 to discuss what is known as "the force of the infection". This is then calculated for Ireland by testing over 100 blood samples for measles antibodies.

In Chapter 3 we estimated the Irish interepidemic period using Hopf's bifurcation theorem. In Chapter 4 we move on to the more detailed model with age dependence. We also estimate the age dependent survival rate  $\mu(a)$  for the Irish population.

Finally, in Chapters 5 and 6, we look at immunisation and the results predicted by the model. In Chapter 5 we derive  $c(a)$ , the Irish age dependent vaccination rate. This is accomplished by computerising over 4,000 immunisations.

We also predict how the reproductive rate,  $R_0$ , of the disease will change with vaccination. In Chapter 6 we numerically analyse the model with the Irish age dependent parameters and we predict the levels of vaccination required in order to eradicate measles in Ireland.

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## Preface

This research was motivated by the implementation of the measles vaccination program in Ireland in October 1985. At that time there was much discussion and confusion over the safety and efficacy of vaccines. With this in mind Professor Alastair Wood, (Wescan Professor of Applied Mathematics), N I H E Dublin, and I decided to investigate the effects of the measles vaccination program on the Irish population.

This work was aided by the works and papers of R.M. Anderson and R.M. May. They have shown, by many practical examples how mathematics can model endemic diseases such as measles and can accurately predict future epidemiological parameters. Throughout this thesis the aim has been to assess these population and epidemic parameters for measles in Ireland. These parameters were then inserted into a mathematical model in order to predict:

- a) future trends in measles epidemics in Ireland and
- b) the levels of vaccination required in order to eradicate the disease.

It is hoped that this thesis will stimulate other mathematicians to tackle the problems of epidemiology in a practical way. It is also hoped that the results provided in this work will assist those of the medical profession in their difficult task of estimation and prediction of epidemiological parameters.

Catherine Comiskey

CHAPTER 1  
INTRODUCTION TO EPIDEMIOLOGY AND  
MATHEMATICAL MODELLING

In the preface we discussed the motivation for this particular research. We shall now expand on this and show how mathematical modelling of epidemics has evolved and developed. We shall do this by giving, (a) a brief historical outline of mathematical epidemiology and (b) an account of the development of mathematical theories on the spread of epidemic diseases. We shall then move on to discuss some more recent work, namely that of N.T.J. Bailey, who in a single work (6) describes in detail the mathematical basis of the population dynamics of infectious diseases. We shall be looking mainly at his work on deterministic models and also at the information on the dynamics of a disease that can be gained from these models. Finally we shall move on to introduce a non linear deterministic differential equation model by R. Anderson and R. May. We shall discuss this particular model in detail and shall see what we can learn from this simple constant parameter model.

First recorded accounts of epidemics go back as far as the ancient Greeks of approximately 400 B.C. Genuine progress in epidemiology was not made until the 19th Century. This was due to the research of Pasteur (1822-1895) and Koch (1843-1910) both of whom made great progress in the

science of bacteriology. Medical and vital statistics were first compiled as early as the 17th Century, at this stage it was still too early for any theory of epidemics. Also, at this time, the necessary mathematical techniques were themselves then only in the process of development and no sufficiently precise hypotheses about the spread of disease suitable for expression in mathematical terms had been proposed. However in 1760 Daniel Bernoulli used a mathematical method to evaluate the effectiveness of the technique of variolation against smallpox with a view to influencing public health policy. Some curve fitting methods were used by Evans(1875) on the smallpox outbreak of 1871-2, but this met with little success.

By the end of the 19th century the general mechanism of epidemic spread as revealed by bacteriological research made possible some new developments. Hammett(1906) believed that the course of an epidemic must depend on the number of susceptibles and the contact rate between the susceptibles and infectious individuals. The simple mathematical assumptions made by Hammett are basic to all subsequent deterministic theories. Hammett by using these simple ideas deduced the existence of periodic recurrences. These ideas were later taken up by Soper(1929)(20). In the meantime Ross(1911) was working out a deterministic mathematical model for the transmission of malaria. From his model we can deduce the future state of the epidemic given the initial

numbers of susceptible and infectious individuals, together with the attack, recovery, birth and death rates. For the first time it was possible to use a well organised mathematical theory as a research tool in epidemiology.

More detailed and elaborate mathematical studies of the same type were later developed by Kermack and McKendrick (1927-1939). These authors also considered the problems of endemic diseases. Their most important result was the well known threshold theorem, according to which the introduction of infectious cases into a community of susceptibles would not give rise to an epidemic outbreak if the density of susceptibles was below a certain critical value. If, on the other hand, the critical value were exceeded, then there would be an epidemic of sufficient magnitude to reduce the density of susceptibles as far below the threshold as it originally was above. We shall look closer at this critical value or threshold later in this chapter.

Work specifically associated with measles was carried out by Soper (1929). With his deterministic model he made the very important discovery that the basic assumptions entailed, as far as recurrent epidemics were concerned, a damped train of harmonic waves. Published data on measles although exhibiting marked variations in incidence from year to year showed no tendency to damping. We shall be looking at the

inter-epidemic period of measles incidence in Ireland later in Chapter 3. First, let us examine some of the work of Bailey in, "The Mathematical Theory of Infectious Diseases", first published in 1957, (6)

In the above work Bailey introduces a simple deterministic model for recurrent epidemics. He models common infectious diseases such as measles, diseases which are really endemic, that is they are constantly with us although often presenting considerable fluctuation in prevalence. Bailey introduces a basic deterministic model, which under appropriate conditions yields a steady state about which natural periodic oscillations are possible. However these oscillations are damped in contradiction with observed epidemiological phenomena. This as we have seen was first observed by Soper

Bailey considers a community of  $N$  individuals comprising of at time  $t$ ,  $X$  susceptibles,  $Y$  infectives in circulation and  $Z$  individuals who are isolated, dead or recovered and immune. Thus  $X + Y + Z = N$ . The infection rate is  $\beta$  and the recovery rate is  $\gamma$  so giving  $\beta XY \Delta t$  new infections and  $\gamma Y \Delta t$  removals in time  $\Delta t$ . He further assumes that there is a continuous stock of new susceptibles. The basic set of differential equations is given by

$$\frac{dX}{dt} = -\beta XY$$

$$\frac{dY}{dt} = \beta XY - \gamma Y \quad (1.1)$$

$$\frac{dZ}{dt} = \gamma Y$$

As the first two equations do not depend on  $Z$  we can consider the system

$$\frac{dX}{dt} = -\beta XY \quad (1.2)$$

$$\frac{dY}{dt} = \beta XY - \gamma Y$$

From this we can determine  $X(t)$  and  $Y(t)$  and we can obtain  $Z(t)$  from the fact that  $N = X(t) + Y(t) + Z(t)$

We have from system (1.2)

$$\frac{dY}{dX} = \frac{dY/dt}{dX/dt} = \frac{\beta XY - \gamma Y}{-\beta XY} = -1 + \gamma/\beta X$$

which when separating the variables and integrating gives

$$Y(x) = Y_0 + x_0 - x + \gamma/\beta \ln X/x_0 \quad (1.3)$$

where  $X_0$  and  $Y_0$  are the initial numbers of susceptibles and infectives and  $p = \gamma/\beta$  is the removal rate. As we can see from figure (1.1)  $Y(x)$  is an increasing function of  $x$ , that is  $dY/dX > 0$  for  $x < p$  and is decreasing for  $x > p$  also  $Y(x_0) = y_0 > 0$ . Hence there exists a unique point  $x_u$  with  $0 < x_u < x_0$  such that  $y(x_u) = 0$ . Since for  $y = 0$ ,  $y' = x' = 0$  then the equilibrium points lie on the  $x$  axis. The conclusions drawn from this analysis and from figure (1.1) are that an epidemic will occur only if the number of susceptibles in a population exceeds the threshold value  $p = \gamma/\beta$  and the disease dies out only for lack of infectives and does not stop for lack of susceptibles. This leaves us at the Kermack and McKendrick threshold theorem, proof of which can be found in Bailey(6) or Braun(8).

In describing a deterministic model for the endemic measles infection Bailey returns to the model described above. He introduces a birth parameter  $\mu$  so giving  $\mu\Delta t$  new susceptibles in time  $\Delta t$ . He takes the population  $N$  to remain constant by assuming that the new susceptibles are balanced by an appropriately defined death rate. Constructing the simple model he concentrates on the groups of susceptibles and infectives making the further assumption that the death

FIGURE 1 1  
 ILLUSTRATION OF THE BASIC THRESHOLD THEOREM

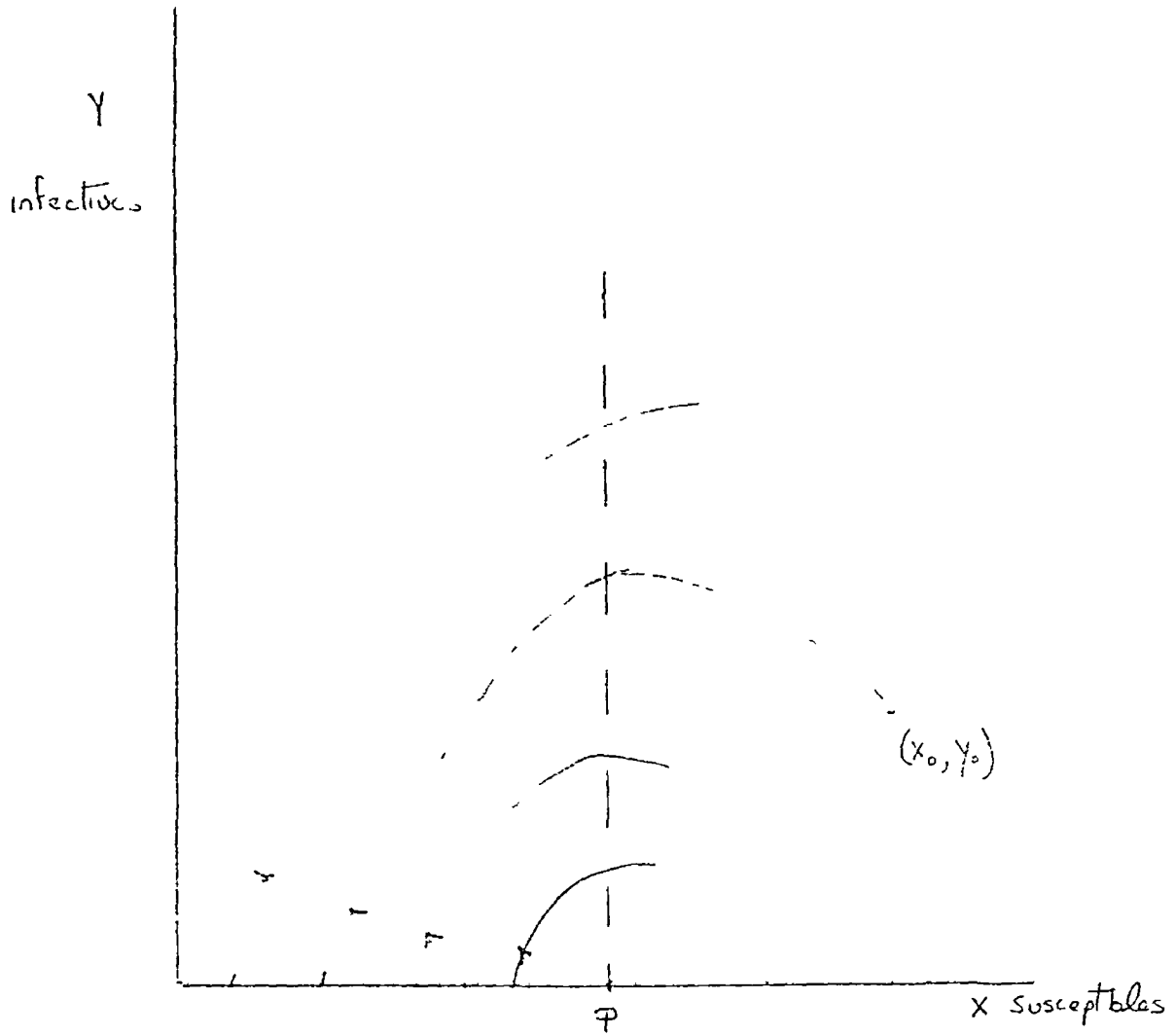


Figure (1 1) showing the trajectories of the solution curves of the first order equation  $dY/dX = -1 + \gamma/(\beta X)$



rate of susceptibles is negligible compared to that of the infected population. This is equivalent to assuming that on average the deaths of removed individuals are just balanced by the births of new susceptibles. These assumptions lead to the following set of differential equations

$$\frac{dx}{dt} = -\beta xy + \mu \quad (1.4)$$

$$\frac{dy}{dt} = \beta xy - \gamma y$$

By equating the differential equations to zero we find the

equilibrium values  $x_0 = \frac{\gamma}{\beta}$

$$y_0 = \frac{\mu}{\gamma} \quad (1.5)$$

The equations for small departures from these equilibrium values are obtained by writing  $x = x_0 (1 + u)$

$$y = y_0 (1 + v) \quad (1.6)$$

and substituting these into our system (1.4) above gives

$$\sigma \frac{du}{dt} = - (u + v + uv) \quad (1.7)$$

$$r \frac{dv}{dt} = u (1 + u)$$

where  $\sigma = \frac{\gamma}{\beta \mu}$        $r = \frac{1}{\gamma}$  .

By neglecting the product  $uv$  and eliminating  $u$  from the equations we obtain the second order differential equation in  $v$ ,

$$\frac{d^2v}{dt^2} + \left(\frac{1}{\sigma}\right) \frac{dv}{dt} + \left(\frac{1}{\sigma r}\right)v = 0 \quad (1.8)$$

which has the solution

$$v_1 = v_0 e^{-t/2\zeta} \cos \zeta t \quad \text{where } \zeta = \left(\frac{1}{\sigma r} - \frac{1}{4\sigma^2}\right)^{1/2} \quad (1.9)$$

for a suitably chosen origin of time. We then obtain the solution for  $u$  given by  $u_1 = v_0 (r/\sigma)^{1/2} e^{-t/2\zeta} (\cos(\zeta t + \psi))$  where  $\cos \psi = \frac{-1}{(r/\sigma)^{1/2}}$   $0 \leq \psi \leq \pi$  (1.10)

2

These linearised solutions involve damped harmonic trains of waves with period  $\frac{2\pi}{\zeta}$ . Soper believed that the allowance for an incubation period of 2 weeks, as is the case with measles, would remove the damping. This, however, was found to be incorrect. An important consequence of Baileys work is that while the additional assumption of a constant fresh supply of new susceptibles accounts for the epidemic waves, it does not explain the damping down to a steady endemic state, which is not in accordance with observed epidemiological data. We shall be looking at the Irish interepidemic period in Chapter 3.

Moving ahead to some of the more recent work in mathematical epidemiology we shall now study the deterministic models proposed by R M Anderson and R May, (1,2,3,4) They address many of the important epidemiological questions which still remain to be answered For example, what proportion must be immunised in order to eradicate the disease? What reduction in disease incidence is to be expected given an age specific vaccination schedule? What is the effect of vaccination on the average age at which individuals acquire infection and on the time between epidemics (termed the interepidemic period)? Anderson and May draw from both deterministic modelling theory and from the data that is available to them in England and Wales to answer these and other related questions. We shall consider their work in relation to the Irish situation and Irish data We shall see what knowledge of the aetiology of measles in Ireland is to be found from an adaptation of one of their simple deterministic models.

In order to devise a mathematical model describing the dynamics of measles Anderson and May make several assumptions, these are as follows:

- (1) The population is divided into discrete classes where -  
 $X(t)$  = the number of susceptibles at time  $t$ ,  
 $H(t)$  = the number of those who are infected but not yet  
infectious,  
 $Y(t)$  = the number of infectious and  
 $Z(t)$  = the number of recovered or immune
- (2) The size of the population (or density)  $N$  remains roughly constant on a time scale appropriate to the pathology of the disease or at least changes on a time scale long compared with other time scales of interest. This is a reasonable assumption for the Irish population as can be seen from figures(1.2) Note also that  $N = X+H+Y+Z$ . This assumption corresponds to the assumption that the net input of susceptibles into the population by birth is roughly equal to the net mortality  $\mu N$ , where  $\mu$  is the death rate and life expectancy is  $1/\mu$ .
- (3) The net rate at which infections are acquired is proportional to the number of encounters between susceptible and infectious individuals,  $\beta XY$   $\beta$  is called the transmission coefficient

FIGURE 1 2 (a)  
VARIATION IN POPULATION FIGURES IN THE  
0-4 AGE GROUP OVER THE PERIOD 1926 - 1981

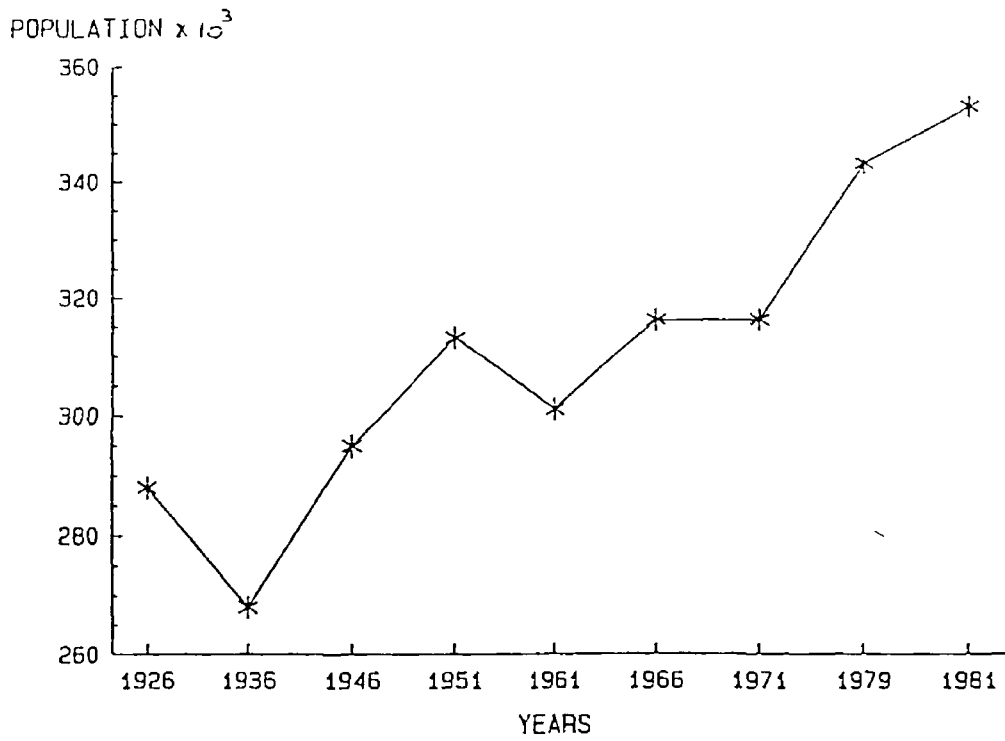


FIGURE 1 2 (b)  
VARIATION IN POPULATION FIGURES IN THE  
5-9 AGE GROUP OVER THE PERIOD 1926 - 1981

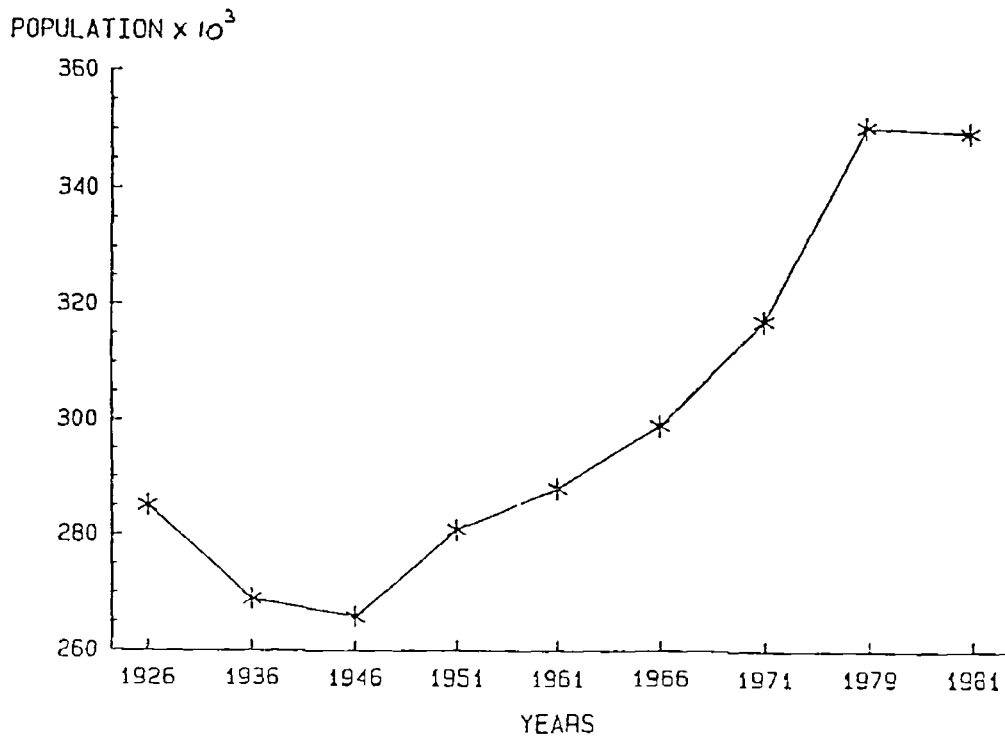


FIGURE 1 2 (c)  
 VARIATION IN POPULATION FIGURES IN THE  
 10-14 AGE GROUP OVER THE PERIOD 1926 - 1981

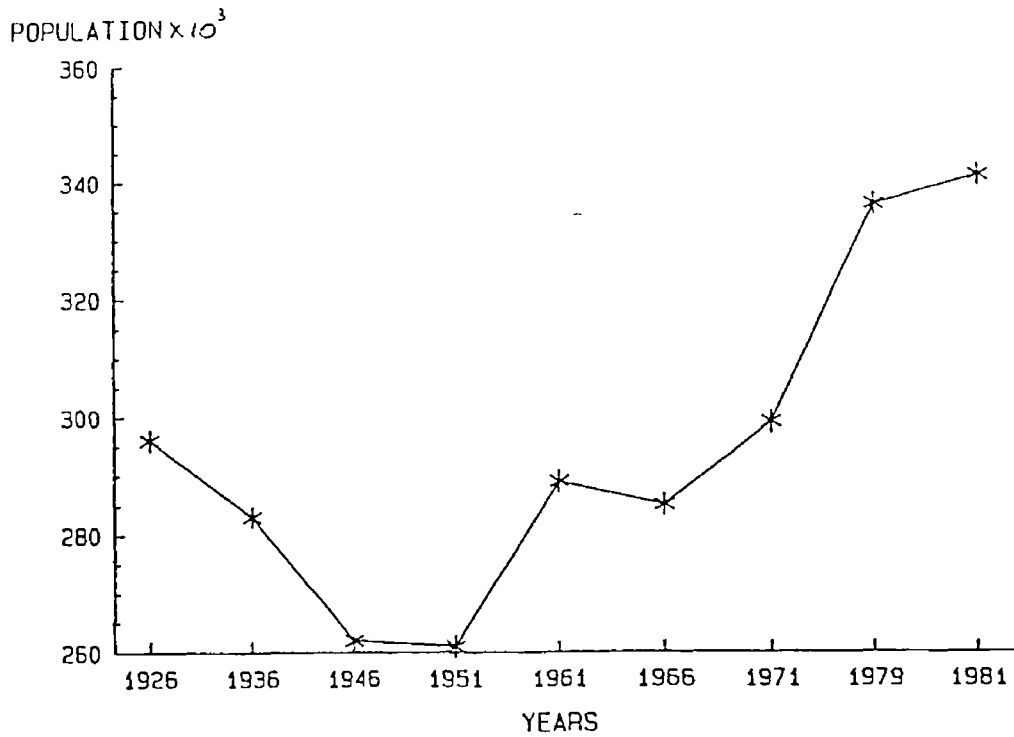
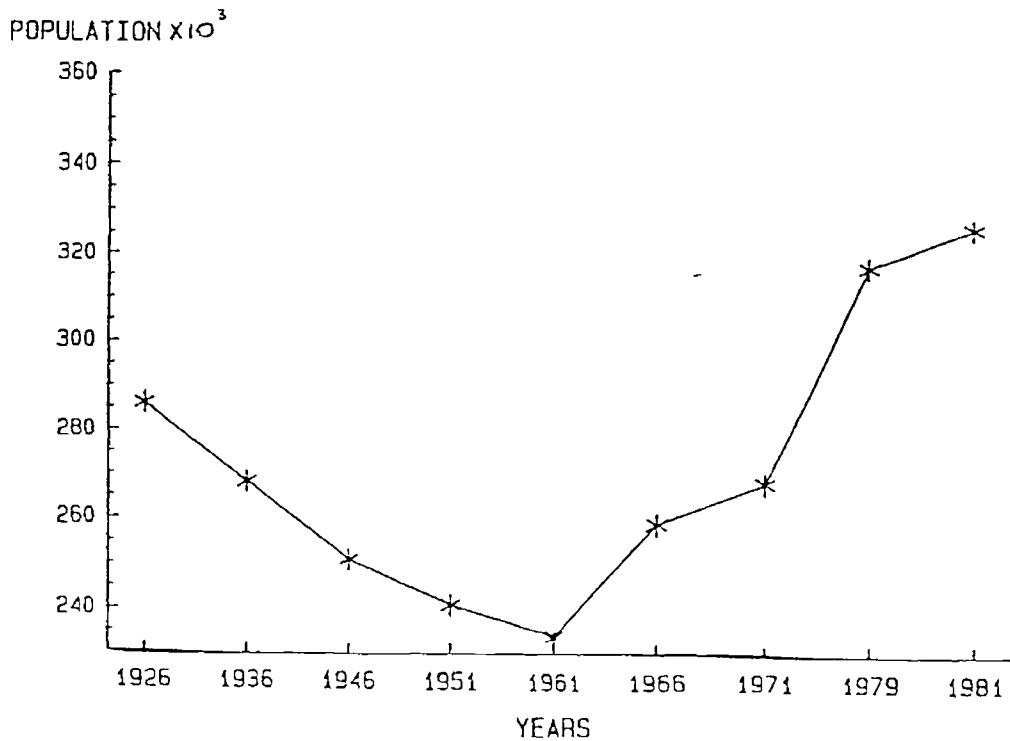


FIGURE 1 2 (d)  
 VARIATION IN POPULATION FIGURES IN THE  
 15-19 AGE GROUP OVER THE PERIOD 1926 - 1981



(4) Individuals pass from the latent state to the infectious state at a per capita rate  $\sigma$  (such that the average latent period is  $1/\sigma$ ) and recover to join the immune class at a per capita rate  $\gamma$  (where  $1/\gamma$  is the average infectious period) Estimates for these constant parameters are set out in table (1.1) below

Table 1.1

Infectious Disease	Latent Period $1/\sigma$ (days)	Infectious Period $1/\gamma$ (days)
Measles	6 to 9	6 to 7

(5) Immunity is lifelong. This is the case with measles

(6) Finally we assume homogeneous mixing

It is important to note at this stage that the assumption that the parameters  $\beta$ ,  $\sigma$ ,  $\gamma$  and  $\mu$  are simple constants is artificial but these parameters used as such in a time dependent model can provide useful and illuminating results. Using these assumptions we construct a set of four first order non linear differential equations,

$$\frac{dX}{dt} = \mu N - \mu X - \beta XY$$

$$\frac{dH}{dt} = \beta XY - (\mu + \sigma) H \quad (1.11)$$

$$\frac{dY}{dt} = \sigma H - (\mu + \gamma) Y$$

$$\frac{dZ}{dt} = \gamma Y - \mu Z$$

Adding all four equations gives  $\frac{dN}{dt} = 0$ , corresponding to

the original assumption that  $N$  is constant. We also note that this model does not incorporate any vaccination program that may be in operation. This is the case for Ireland from October 1985. We shall see in Chapter 5 how the above model can be developed to include such a program.

A disease such as measles will maintain itself within a population provided the reproductive rate  $R$ , of the infection is greater than or equal to unity. This reproductive rate is defined as the expected number of secondary cases produced by an infectious individual in a population of  $X$  susceptibles. If  $R < 1$  the disease will die out even if there



are susceptible people in the community. This concept of the reproductive rate is also discussed by Dietz(10)

For the time dependent model above we define

$$R = \frac{\sigma \beta X}{(\sigma + \mu)(\gamma + \mu)} \quad (1.12)$$

This definition is biologically intuitive for we know that secondary infections are produced at a rate of  $\beta X$ , (transmission coefficient by population of  $X$  susceptibles) throughout the expected lifetime,  $\frac{1}{\gamma + \mu}$ , of an infectious individual. Of these a fraction,  $\frac{\sigma}{\sigma + \mu}$ , will survive the latent period to become the second generation of infectious individuals.

We have said that the reproductive rate must exceed unity for the disease to establish itself within a community. That is to say that each infectious individual must infect at least one susceptible. This requirement is equivalent to the criterion that the population of susceptibles must exceed some threshold density, that is  $X > N_T$ . This has been discussed in great detail by Waltman (19). We seen from (1.12) that  $N_T$  is defined as

$$N_T = \frac{(\gamma + \mu)(\sigma + \nu)}{\beta\sigma}, \quad (1.13)$$

We can now express equation (1.12) above

$$\text{as } R = \frac{X}{N_T}. \quad (1.14)$$

For measles in developed countries the duration of the latent and infectious periods,  $1/\sigma$  and  $1/\gamma$  is of the order of a few days while  $1/\mu$  is of the order of approximately 70 to 75 years

Under these circumstances equations (1.12) and (1.13) above can be approximated as  $R = \frac{\beta X}{\gamma}$  and  $N_T = \frac{\gamma}{\beta}$ . We

note here that the same threshold value is derived in Bailey's work above. However we cannot as yet find estimates for these parameters because of the difficulty in estimating the transmission coefficient,  $\beta$ .

We now introduce the important concept of the basic reproductive rate of an infection, denoted  $R_0$ . This is introduced in order to illuminate further the ideas discussed above. For a directly transmitted viral infection  $R_0$  is defined as the average number of secondary infections

#### Footnote

(1) We shall see in Chapter 3 that at equilibrium  $\beta > 0.00095$ , taking  $1/\gamma = 6$  days and  $\mu = 61 \text{ years}^{-1}$  gives us a threshold value of  $N_T > 64,211$

produced when one infectious individual is introduced into a population where everyone is susceptible. Equivalently it may be defined as the value of  $R$  in a disease free population. The value of  $R_0$  depends both on biological factors related to the aetiology of the infection and on environmental and social factors, having to do with contacts among susceptible and infectious individuals.

Anderson and May (2) derive some interesting relations between  $R_0$  of an endemic infection such as measles and the epidemiological parameters. Parameters are the fraction of the population that is susceptible and the average age of first infection. These they derive under the assumption they call 'weak homogeneous mixing'. This says that the rate of appearance of new infections is linearly proportional to the number of susceptibles  $X$ . In their model the age structure is included, so that  $X$  is now a function of the two variables, age,  $a$  and time,  $t$ . This is in contrast to what they call the assumption of 'strong homogeneous mixing', which assumes that the rate is

proportional to both  $\bar{X}$  and  $\bar{Y}$ , that is  $\beta \bar{X} \bar{Y}$ . Where  $\bar{X}$  is defined, as  $\bar{X}(t) = \int_0^{\infty} X(a, t) da$  (1.15) the total number of susceptibles and  $\bar{Y}$  is similarly defined.

Under the assumption of weak homogeneous mixing Anderson and May argue as follows. As the infection becomes

established the fraction of the population who remain susceptible will decrease. The net fraction susceptible may be denoted  $\bar{x}$ , where  $\bar{x} = \frac{\bar{X}}{\bar{N}}$ . (1.16)

On average, under the assumption that the rate of appearance of new infections is linearly proportional to the number of susceptibles, the number of secondary infections will be diminished below the number occurring when all are susceptible by the factor  $\bar{x}$ . That is, the value of the effective reproductive rate  $R$  is:

$$R = R_0 \bar{x} \quad (1.17)$$

If an infection is established at roughly steady equilibrium value, the effective reproductive rate will be unity. This is because at equilibrium each infection on average produces exactly one secondary infection. This common sense result has been established rigorously by Nold (17) in 1979. Therefore, at equilibrium,  $R_0$  and the fraction susceptible  $\bar{x}$  are related by:

$$R_0 \bar{x} = 1 \quad (1.18)$$

This is a very useful result, for if the equilibrium fraction of the population who are susceptible can be determined from serological data or otherwise we can use equation (1.18) above to estimate  $R_0$ . We have established that at equilibrium  $R_0 \bar{x} = 1$ . In deriving this we have

made no assumptions about how individuals acquire infection. At equilibrium before vaccination, susceptibility is lost only by natural infection, at equilibrium after a vaccination program is in place susceptibility can be lost either by immunisation or by acquiring the infection. Provided no other social or environmental changes have taken place  $R_0$  will remain unaltered and equation (1.18) provides the surprising conclusion that the fraction of the population who are susceptible to infection will remain the same after a vaccination program has been implemented as it was before.

We shall explore further estimates of  $R_0$  and relate this parameter to Irish data in our next chapter on  $\lambda$ , the force of infection. We shall demonstrate the relationships between  $\lambda$ ,  $A$ , the average age of first infection and  $R_0$ . We shall also see, in our chapter on mortality, the effect that the Irish mortality curve has on  $R_0$ .

CHAPTER TWO  
ON THE FORCE OF INFECTION  $\lambda(a)$  AND ESTIMATION  
FOR IRISH DATA

We shall now discuss the estimation of age related rates of infection from case notification and serological data, with particular emphasis on estimating the age related rate of infection or force of infection of measles in Ireland. This we shall estimate by means of a serological survey.

In a study of the transmission dynamics and epidemiology of measles or any such viral or bacterial infection of man, case reports and serological data stratified according to age are an important source of information. Because the dimensions of age and time are equivalent, age-related changes can reflect temporal changes in the rate or force of disease transmission within a community. Data from case reports have many limitations one of which is a possible age-related bias in case reporting. It is believed that the probability of a case being reported in the very young is higher than that for the adult age class. Data from age stratified serological surveys carried out before the implementation of a vaccination program can provide accurate information on the proportion of immunes.

One of the earliest serological surveys was carried out by Collins<sup>\*</sup> in 1924 and again in 1929. His analysis was

\* Collins, S O (1929)  
Age incidence of the common communicable diseases of children  
US Public Health Reports 44

based on an age specific "incidence rate" This was defined as the number of reported cases per unit of time in a given age class, divided by the total number of individuals in that age class Today this is termed the age specific "attack rate" and is often defined per 1,000 head of population This statistic has many limitations as it takes no account of the numbers in each age class who are actually susceptible to infection. A precise measure of the rate at which susceptibles acquire infection was first proposed by Muench (14) in 1959. He employed simple mathematical models to mirror age related changes in the proportion of individuals who had experienced infection Muench used a parameter termed "the force of infection" defined as the instantaneous per capita rate at which susceptible individuals acquire infection It is this force of infection that we shall estimate for measles in Ireland. This in turn will lead us to a further estimate of the previously defined parameter,  $R_0$

It is both interesting and illuminating to see how Muench developed the idea of "a force of infection" as the concept can be difficult to understand. Muench draws an analogy between a catalytic process in chemistry and the individuals in a population The simplest picture of a catalytic process in chemistry involves molecules of an original substance, this, he says, may be equated with individuals in a population that has not yet been in contact

with an infective force. In chemistry, the original molecules are subjected to a contact with molecules of a catalytic substance, a contact between the two implies the creation of another substance. Similarly the uninfected individuals of a population can be conceived as subjected to a force of infection which changes them to infected individuals. The basic rate at which molecules are changed depends on -

- (a) the relative number of molecules of catalyst and
- (b) the number of contacts made by each per unit time.

Thus (a) and (b) make a force which can be expressed as the number of effective contacts per unit time. The force of infection acting on the population can similarly be measured in terms of effective contacts per unit time (usually a year) per individual. "Effective contact" here has the meaning used by Wade Frost - a contact sufficient to produce infection if the subject is susceptible.

Muench proposes the following hypothesis in order to derive mathematically the force of infection. We begin with a quantity of unchanged molecules or individuals. This quantity we shall make equal to 1 and deal with the fraction changed at any time  $t$ . This fraction we designate  $y$  so that  $1 - y$  is the relative amount still left unchanged at time  $t$ . This then is the part on which the catalytic or infective force can still work, at the rate of  $r$  effective contacts per individual per unit of time. The speed at which the



reaction acts on will then be measured by

$$\frac{dy}{dt} = r(1 - y) \quad (2.1)$$

This is a simple linear differential equation which has the general solution

$$y = 1 + ce^{-rt}, \quad (2.2)$$

If we substitute  $y = 0$  and  $t = 0$  (i.e. starting at time = 0) we have  $y = 1 - e^{-rt}$ , (2.3)

This form of the equation describes the expected behaviour of a group of molecules, or persons, starting entirely unchanged, or susceptible at the beginning of observation or at birth (when  $t=0$ ) and exposed to a continuous bombardment of catalysis or infection at a constant rate of  $r$  effective contacts per individual per unit time.

In order to transfer the catalytic picture to a model of infection acting on a population it is necessary to include some assumptions, namely

- (a) The population is entirely susceptible to infection at birth
- (b) A constant force of infection to which this population is exposed

(c) Evidence which will show that infection has taken place, allowing the estimate of  $y$ , or the fraction infected at any time  $t$ . This may consist of positive histories or the results of laboratory findings

With regard to measles, assumption (a) is unfulfilled as it is believed that children possess their maternal antibodies up to the age of 6 months. However, we shall see that this can easily be overcome. We shall also see that the force of infection is in fact not a constant but rather a function of age. Finally, we shall look at the findings of our Irish serological survey in order to estimate  $y$ , the fraction infected and subsequently  $\lambda$ , (or  $r$ ) the force of infection

In order to estimate the Irish force of infection we shall follow some guidelines set out by B.T. Grenfell and R.M. Anderson (12). We have seen from the simple catalytic model of Muench that the proportion susceptible  $x(a)$  in age class  $a$  is given by

$$x(a) = \exp(-\lambda a) \quad (2.4)$$

More generally, if the force of infection  $\lambda(a)$  is age-dependent then

$$x(a) = \exp\left[-\int_0^a \lambda(s) ds\right] \quad (2.5)$$

The proportion immune at age  $a$ ,  $y(a)$  is simply

$$y(a) = 1 - x(a). \quad (2.6)$$

Equation (2.5) can be expressed in terms of the cumulative distribution function of age at infection,  $F(a)$  (the proportion of a cohort all of whom were susceptible at birth who have experienced infection (i.e. who are immune by age,  $a$ ), where

$$F(a) = 1 - \exp \left[ - \int_0^a \lambda(s) ds \right] \quad (2.7)$$

To account for maternally derived antibodies in children born to mothers who have experienced the infection,  $\lambda(a)$  can be set to zero below a lower age threshold  $m$  (This is usually assumed to be in the region of 0.5 years for measles) We note at this stage that we have succeeded in modifying the 3 assumptions set out by Muench

Muench (14) as we have seen, assumed  $\lambda$  (or  $r$ , as he used) to be constant and independent of host age Griffiths (13) noted in an analysis of the age distribution of infection for measles in England and Wales that  $\lambda$  tends to rise linearly with age between the ages of 0 and 10 years. Anderson and May (1) also discuss the estimation of  $\lambda$  as a linear function of age In Grenfell and Anderson (12) we see that  $\lambda$  can be expressed as a polynomial of degree  $k$  where

$$\lambda(a) = \sum_{i=0}^k b_i a^i \quad (m < a \leq u) \quad (2.8)$$

$$\lambda(a) = 0 \quad (a \leq m)$$

where the upper age limit  $u$  denotes human life expectancy or the oldest age class for which data is available. The lower age limit  $m$  represents the age to which a child is protected by the maternally derived antibodies.

Table 2.1 below shows estimates for the force of infection from several studies (12). *The coefficients were obtained as in Grenfell, by assuming a binomial distribution for  $F(a)$  and estimating the parameters (the  $b_i$ 's) by maximum likelihood.*

We shall now look at an estimation of  $\lambda$  within an Irish context. As we have said the proportion infected by age can be derived from two different sources. One, case notifications, as we have seen, can be biased, with cases being reported more frequently among the younger age groups. In Ireland there is the further problem in that before the introduction of an extensive publicity campaign and vaccination, measles was not considered to be a serious infection. Often children were not attending their G.P. especially if more than one child in the household had the infection. However, in Ireland we had one major advantage and that was the availability of unvaccinated blood samples. Data arising from age-stratified serological surveys provide information on the proportion of immunes. In the absence of vaccination such data in principle correspond directly to the proportion of infecteds.

Table 2 1

Details of the Polynomial Relationships Between Force of Infection  
and Age of Contacting Measles

Data Source	Upper Age Limit	Polynomial Degree	$b_0$	$b_1$	$b_2$	$b_3$	$b_4$	Mean Age at Attack, Years
Baltimore 1906-15	25	3	-0 00594	0 0679	-0 00561	0 000122	--	6 72
Rural Maryland 1908-17	20	4	0 0663	-0.0228	0 0102	0 000951	0 000261	9 27
Aberdeen 1883-1902	15	4	0 429	-0.325	-0 113	-0.0124	0 00042	4 76
England and Wales 1948-68	25	2	-0.0105	0.0864	-0 0411	--	--	4 96
New Haven Small Families	15	2	-1 475	0 411	-0 021	--	--	8 01
New Haven Large Families	15	2	-0 261	0.186	-0 0125	--	--	5 51

The data that we shall use for our estimation of  $\lambda$  was collected from childrens' blood samples that were sent to the Department of Medical Microbiology, University College Dublin, for different kinds of tests. There was nothing in the nature of these suspected diseases to render the children more or less likely (than the general age group) to have had measles. 145 samples were collected. All of these samples were dated pre October 1985 (i.e. pre the implementation of the vaccination program). For each sample we found the age and the sex of the child. These samples were then tested for measles antibodies using the CFF test. Figure (2.1) shows the age distribution of the samples.

We can see from figure (2.1) that all samples used were taken from children more than 1 year old. This was to allow for the possible presence of maternally derived antibodies. As there were more samples available for some ages samples were grouped into the following age categories, 1 year, 2 years, 3 years, 4 years, the proportion susceptible at ages 5, 6 and 7 years were grouped and the mean proportion susceptible for ages 6 years is expressed, ages 8, 9 and 10 and 11, 12 and 13 were similarly grouped. A table of the grouped proportions susceptible is shown in tables 2.2 below and a plot of these is shown in figures (2.2).

FIGURE 2.1  
SHOWING THE AGE DISTRIBUTION OF NUMBER OF  
AVAILABLE BLOOD SAMPLES

FREQUENCY

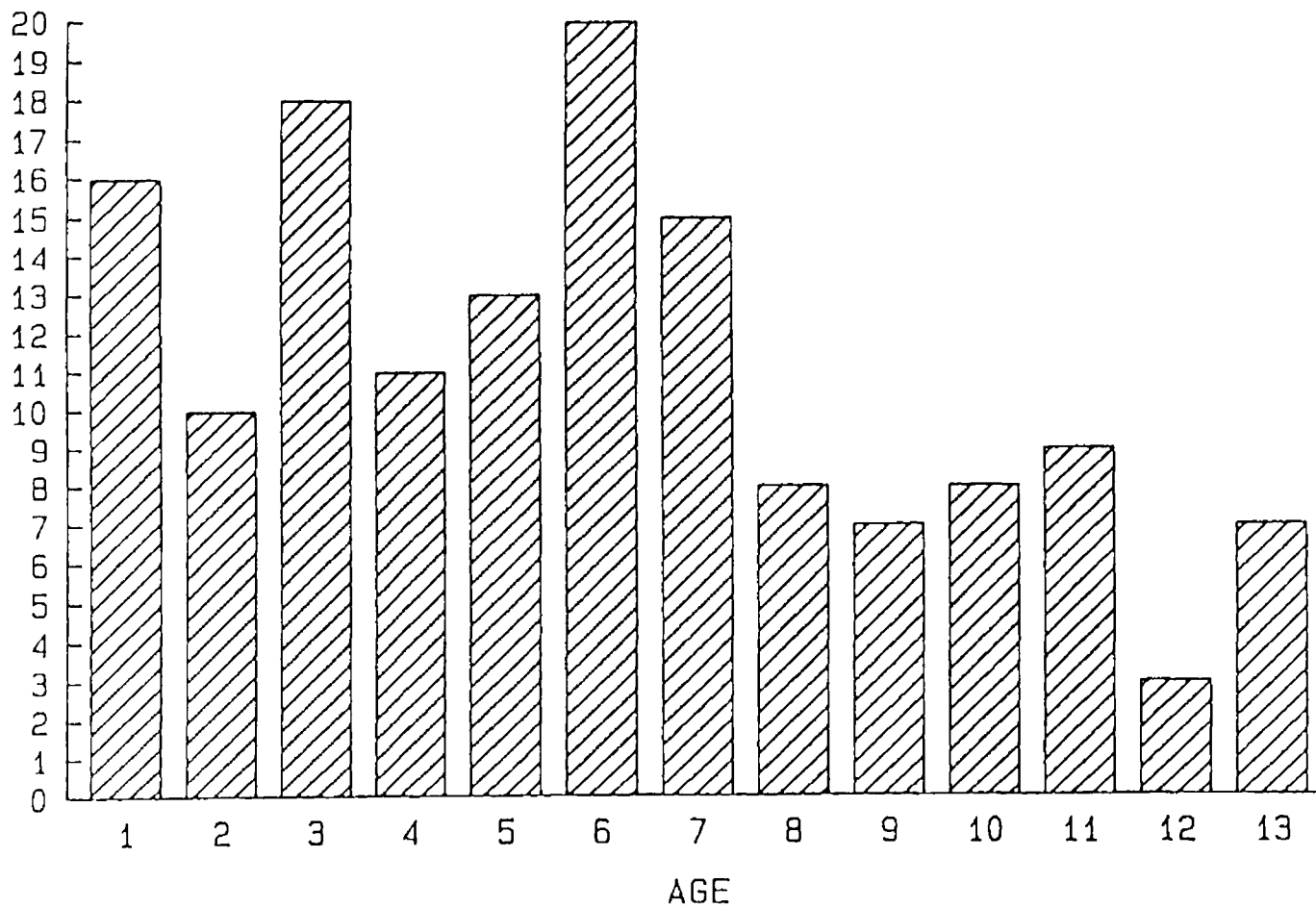


Table 2.2(a)

<u>Age in Years</u>	<u>Proportion Susceptible to Measles</u>
1	0 37500
2	0 60000
3	0 33300
4	0 272700
5	0.230670
6	0 15000
7	0 33330
8	0.00000
9	0 142857
10	0.375000
11	0.33300
12	0.00000
13	0 00006

Table 2.2(a) showing the proportion susceptible to measles at each age from a sample of 145 bloods.

Table 2.2(b)

<u>Age in Years</u>	<u>Proportion Susceptible</u>
<u>Grouped</u>	<u>to Measles</u>
1	0.37500
2	0.60000
3	0 33300
4	0.27270
6	0 22916
9	0.17390
12	0.15789

Table 2.2(b) as for 2.2(a) but data is grouped for ages 5 to 13 years.



FIGURE 2 2a  
SHOWING PLOT OF PROPORTIONS SUSCEPTIBLE  
(NON-GROUPED)

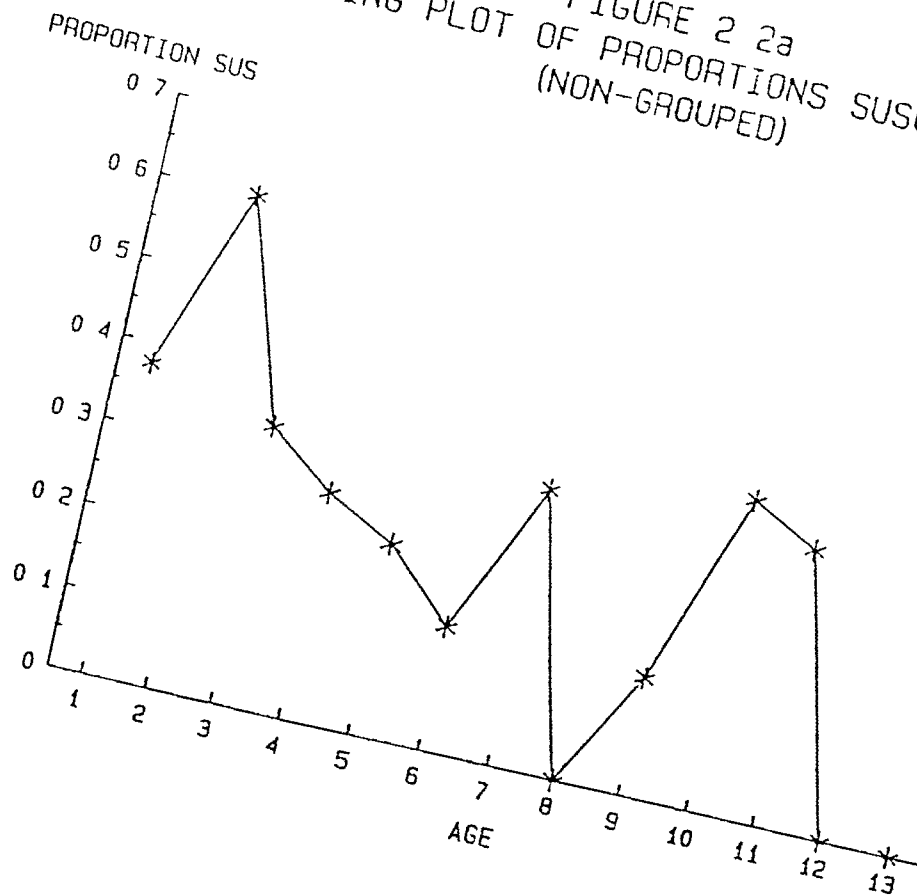
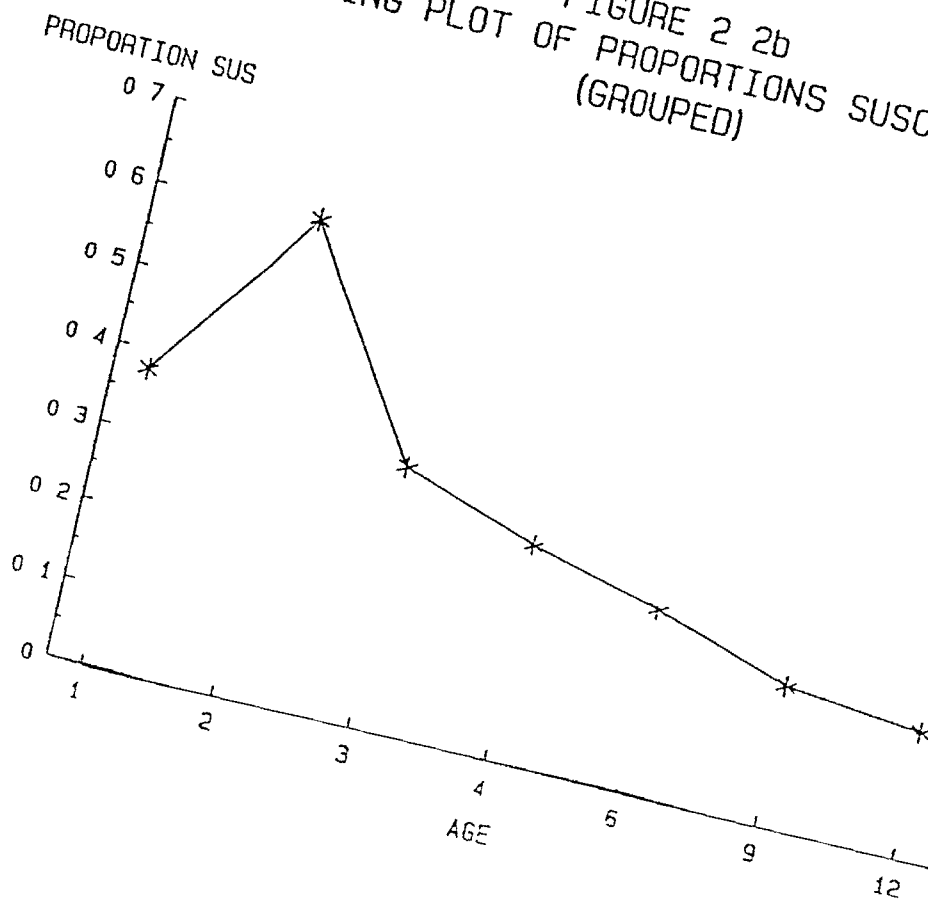


FIGURE 2 2b  
SHOWING PLOT OF PROPORTIONS SUSCEPTIBLE  
(GROUPED)



Figures (2 2) showing the proportion of children susceptible to measles infection in Ireland. A sample of 145 bloods was drawn from the records of the Medical Microbiology department at University College Dublin by kind permission of Professor Irene Hillary.

We see from Figure (2 2b) that the proportion susceptible follows a negative exponential distribution from the age of two years. This is as expected from Muench's original model where he expresses the fraction infected as

$$y = 1 - e^{-rt}$$

with  $\exp(-rt)$  as the fraction susceptible.

However what is very unexpected is the fact that the proportion susceptible is still rising sharply between the age of 1 and 2 years. This would seem to imply that the maternal measles antibodies are still present in a large proportion of children at this age or else reflects the fact that measles epidemics are periodic. For example, although a child may lose immunity at six months, there may not be a measles epidemic to infect that child for another 1 - 2 years. (See section on the interepidemic period). As it is the policy to vaccinate children at the age of 15 months it would appear that it is possible for the antibodies in the children's blood to destroy the virus and render the child susceptible to measles at a later date. We should

also note that this age group constitutes the largest number of samples

We now utilise the above data to estimate the force of infection,  $\lambda$ . We know that the proportion susceptible is given by

$$x(a) = \exp \left[ - \int_0^a \lambda(s) ds \right] \quad (2.9)$$

If we assume a linear force of infection we can fit a function of the form.

$$x(a) = \exp[ra^2 + sa] \quad (2.10)$$

to the proportion susceptible. Using the method of least squares we have.

$$x(a) = \exp[0.0012439 a^2 - 0.326783 a] . \quad (2.11)$$

Several other methods, including fitting quadratics and cubics, can be shown not to yield such a close fit.

Note that the data for 1 to 2 year olds was not included in the estimation of this function. From the above estimation of the proportion susceptible we can compute  $\lambda(a)$ , the force of infection. We have

$$\lambda(a) = -0.0024878a + 0.326783,$$

for  $2 \leq a \leq 12$

This is a linear function with a very small negative slope

In Table 2.3 below we have set out the estimates for  $\lambda(a)$  at the various ages.

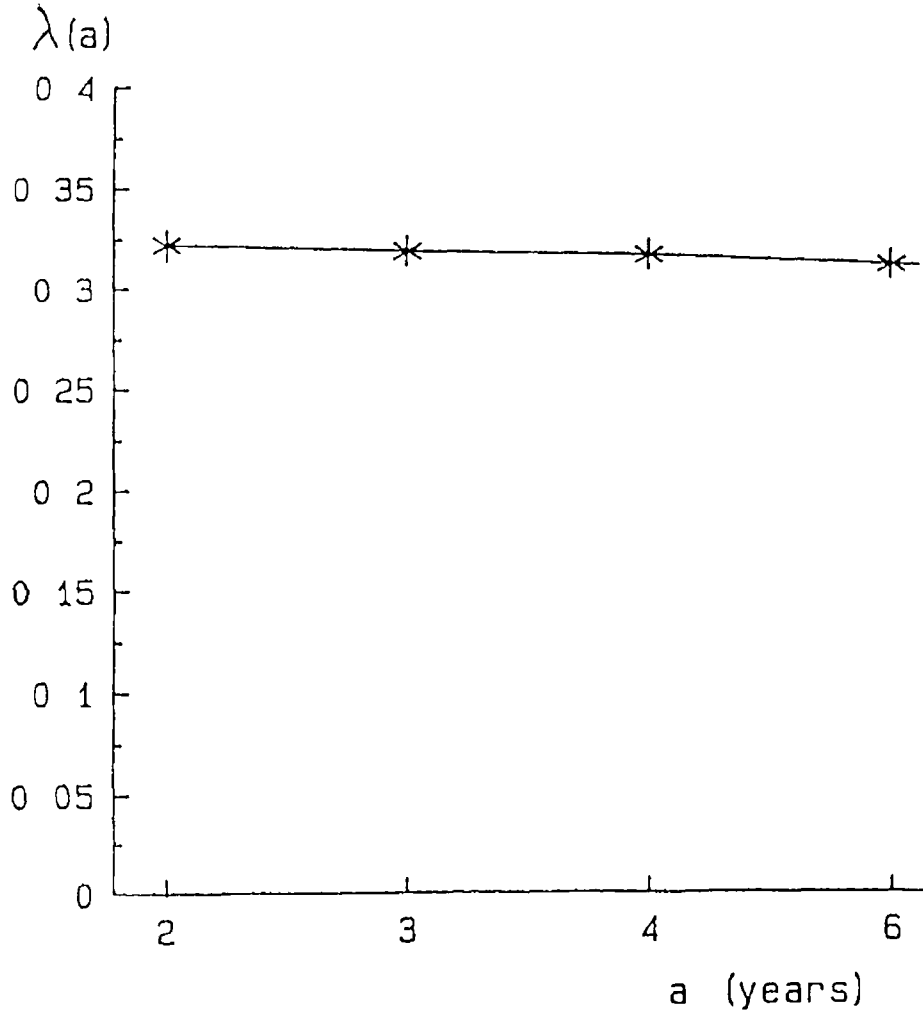
Table 2.3

<u>Age, a Years</u>	<u><math>\lambda(a)</math></u>
2	0.322
3	0.319
4	0.317
6	0.312
9	0.304
12	0.297

We can see from Table 2.3 that in Ireland the force of infection is almost constant.

We have said that Muench believed  $\lambda$  to be independent of age. Griffiths believed it to rise linearly with age and Anderson and Grenfell believed that  $\lambda$  could be polynomial. However, looking at figure 2.3 we see that  $\lambda(a)$  in Ireland is almost constant. For measles in England and Wales of 1965 - 1975,  $\lambda(a)$  was linear as can be seen from figure 2.4

FIGURE 2.  
 $\lambda(a)$  FOR MEASLES

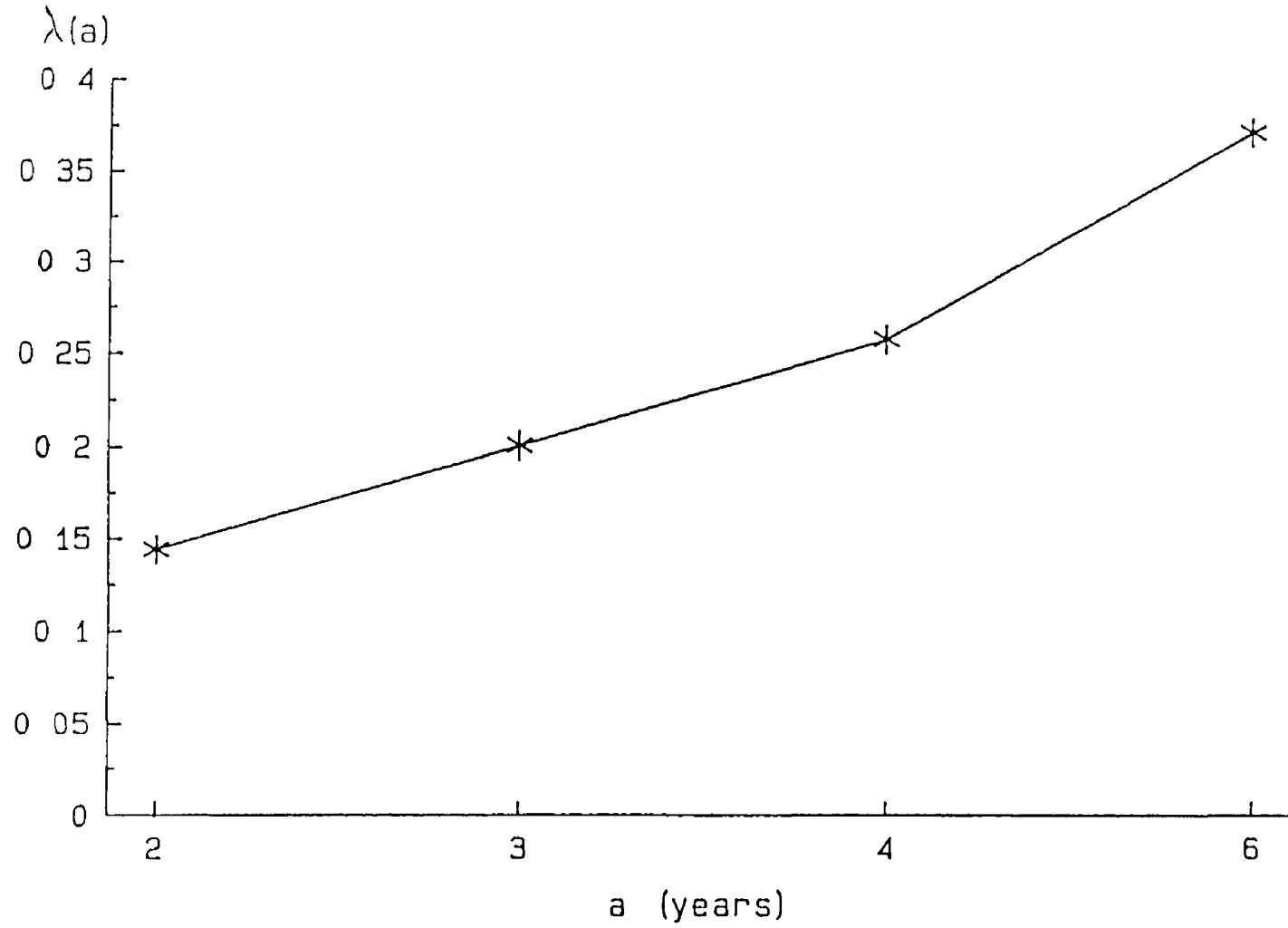


.3

IN IRELAND



FIGURE 2.4  
 $\lambda(a)$  FOR MEASLES IN ENGLAND AND WALES  
1965 - 1975



Having estimated  $\lambda(a)$  for measles in Ireland we now can derive another very important parameter from this estimation. The parameter in question is the average age at infection,  $A$ . This in turn will lead us to further estimates for  $R_0$ , the basic reproductive rate, of which we will see more later.  $A$  is given by

$$\begin{aligned}
 A &= \frac{\int_0^{\infty} a \lambda(a) x(a) da}{\int_0^{\infty} \lambda(a) x(a) da} & (2.12) \\
 &= \int_0^{\infty} x(a) da
 \end{aligned}$$

From this we can derive the average force of infection,  $\bar{\lambda}$

$$\bar{\lambda} = \frac{1}{A} \tag{2.13}$$

If we treat  $\lambda$  as independent of age we can relate it to the more observable  $A$ . If we know  $A$  from previous case studies, we have a rough estimate of  $\lambda$ . We have from equation

$$\begin{aligned}
 (2.12) \quad A &= \int_0^{\infty} \exp\left[-\int_0^a \lambda(s) ds\right] da \\
 &= \int_0^{\infty} \exp[0.0012439 a^2 - 0.326783 a] da
 \end{aligned}$$

Numerically integrating the above gives us the average age at infection for measles in Ireland, we have

$$\begin{aligned}
 A &= 3.14 \text{ years} \\
 &\approx 38 \text{ months}
 \end{aligned}$$



This would appear to be very young in comparison with other European countries. The average family size in Ireland being greater than other European countries could also reduce the average age at infection (for example the whole family is infected when the eldest child is exposed to an epidemic at school). In England and Wales the average age at infection was seen to be between 4 and 5 years. However, upon further research into regional measles susceptibility surveys carried out in Ireland prior to October 1985 we find that M. O' Boyle<sup>(1)</sup> carried out a survey in Waterford City. He questioned 2,132 children between the ages of 0 to 16 years. He found that 65% of all cases occurred in the pre-school group (under 4 years) also 92% of cases occurred before the age of 6. However, what is most interesting about his survey is that he found the mean age of attack to be 41 months, a difference of only + 3 months as predicted by our mathematical model and serological survey.

We have successfully shown that the mathematical model can reflect and predict important epidemiological parameters. In our next chapter we shall discuss the interepidemic period of measles incidence in Ireland and we shall use the mathematical model along with parameter estimates to demonstrate and predict the interepidemic period for Ireland.

<sup>(1)</sup> O' Boyle, M (1985)

*Irish Medical Journal, September Vol 78, No 9*

## CHAPTER THREE

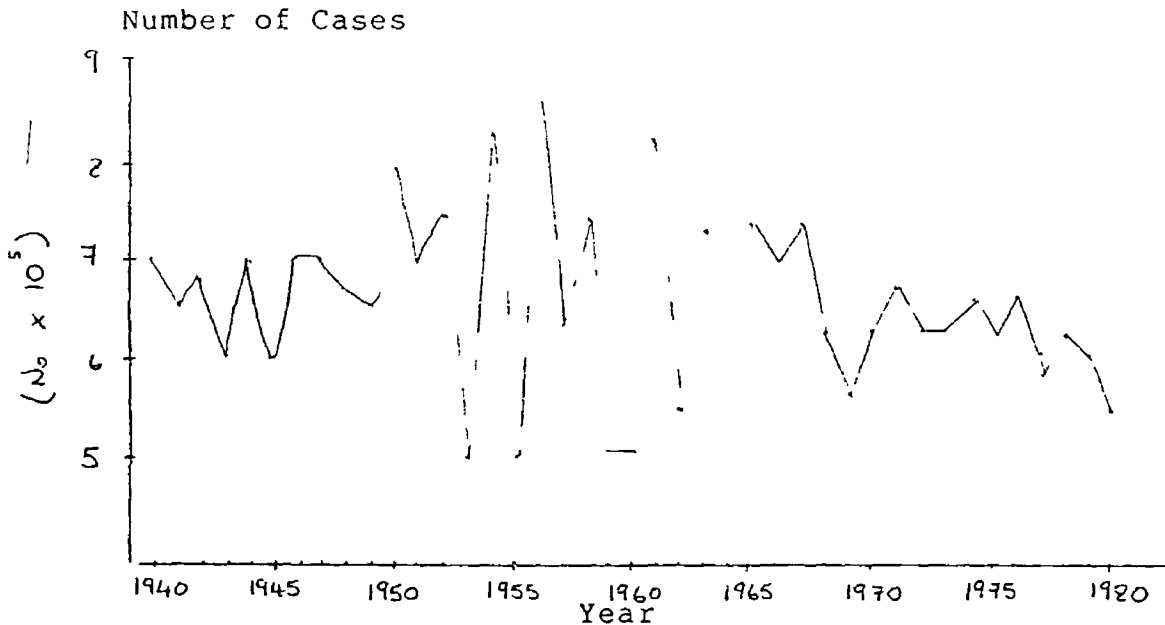
### THE INTER-EPIDEMIC PERIOD OF MEASLES INCIDENCE IN IRELAND

Long term records of measles exhibit marked variation in incidence from year to year. These fluctuations tend to be of a regular nature. With measles a major epidemic is experienced every two to three years. This interval between epidemics is termed the interepidemic period. These fluctuations are influenced by the fact that the number of susceptible children decreases as immunity is acquired by recovering from infection, then the number of susceptibles increases slowly as children are born.

We have seen in Chapter One how compartment models consisting of systems of non linear differential equations can be used to describe the dynamics of the childhood disease measles. We shall now see how the fluctuations in incidence can be found by analysing the equilibrium points of the system and their behaviour. We shall also see how the interepidemic period is related to the parameters that characterise the infection, such as the latent and infectious periods and the average age of infection. Figure 3.1 shows how the 2 to 3 year cycle of measles can be seen in data from case notifications in England and Wales.

Figure 3 1

Showing the Number of Cases of Measles in England and Wales from 1940 to 1980 (Note the 2-3 year interepidemic period)



Figures 3.2 show the fluctuations in the numbers of case notifications in Irish data. The 2 to 3 year cycle is not as clear here due to inconsistencies in reporting

For a compartment model to mirror a real oscillating process it must possess stable limit cycle solutions of the equations. Also the system must possess at least one physically realistic singular point. We shall now examine our compartment model for such properties. *The non mathematician may prefer to turn directly to page 53*

FIGURE 3.2a  
 SHOWING THE CYCLIC PATTERN IN MEASLES INCIDENCE  
 IN IRELAND FROM 1945 TO 1985

MEASLES - IRELAND

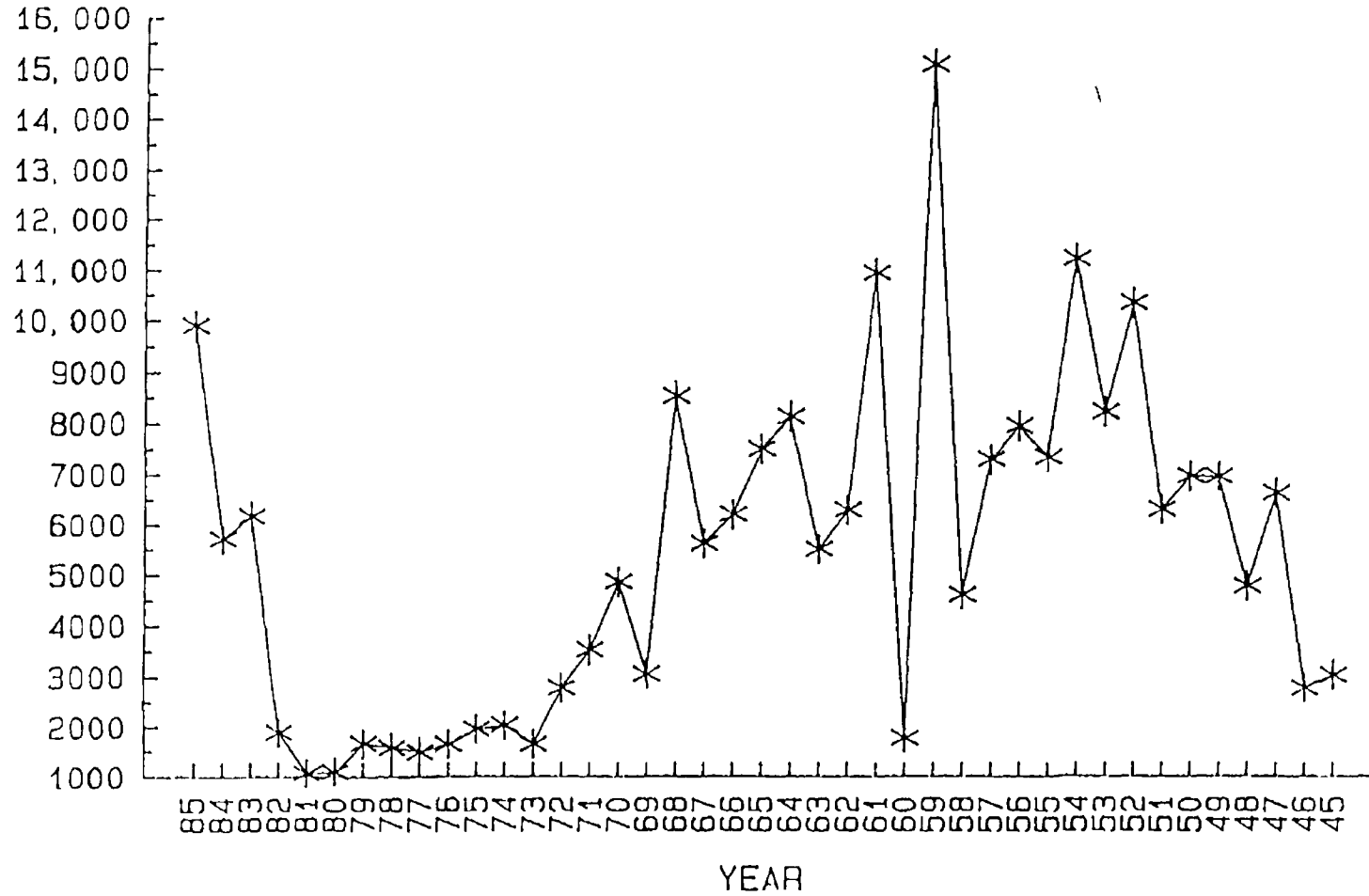
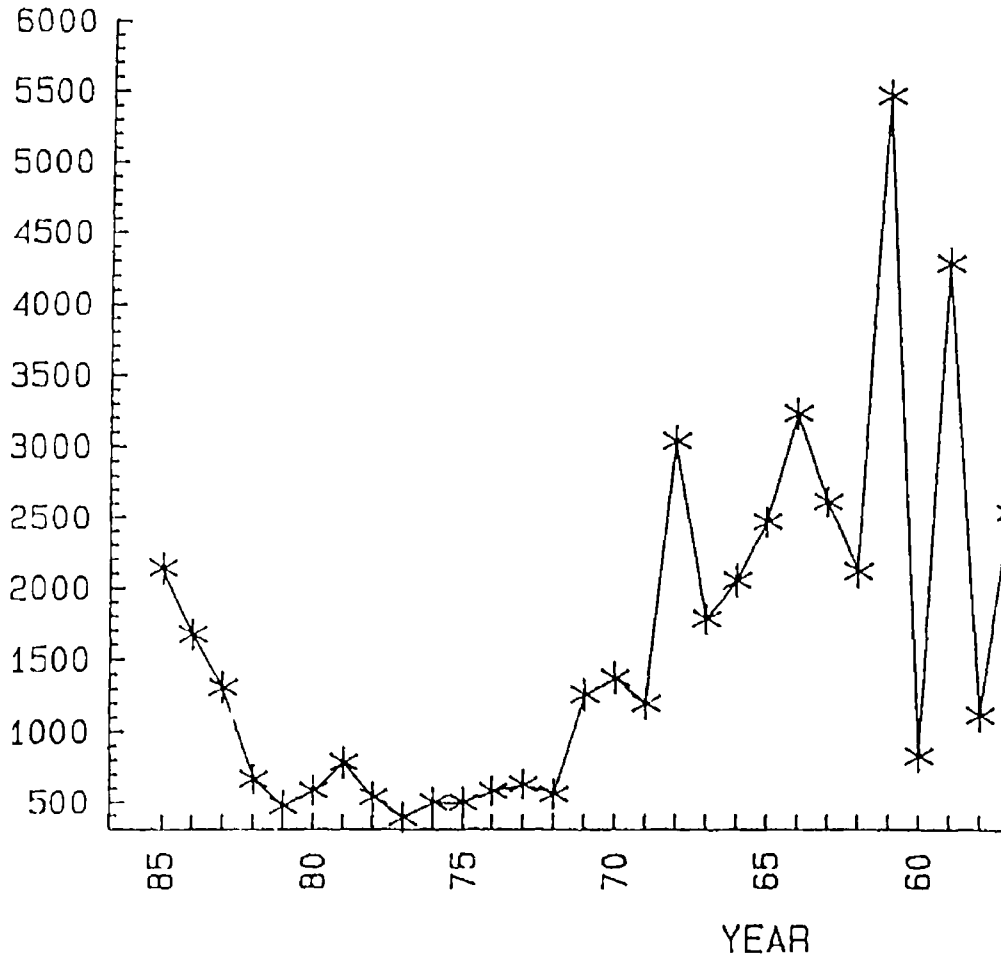
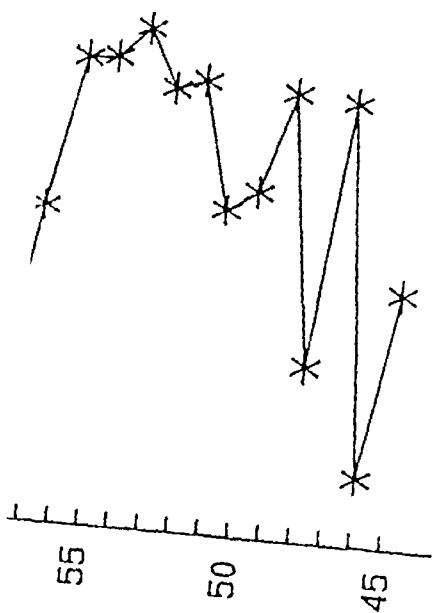


FIGURE 3.2b  
SHOWING THE CYCLIC PATTERN IN  
IN DUBLIN FROM 1945

MEASLES - DUBLIN



# MEASLES INCIDENCE TO 1985



We have the system

$$\frac{dX}{dt} = \mu H + \mu Y + \mu Z - \beta XY \quad (3.1)$$

$$\frac{dH}{dt} = \beta XY - (\mu + \sigma)H \quad (3.2)$$

$$\frac{dY}{dt} = \sigma H - (\mu + \gamma)Y \quad (3.3)$$

$$\frac{dZ}{dt} = \gamma Y - \mu Z \quad (3.4)$$

The equilibrium points can be found by setting:

$$dX/dt = dH/dt = dY/dt = dZ/dt = 0$$

This gives us the simple critical point  $(X, H, Y, Z) = (0, 0, 0, 0)$ .

However we are looking for a physically realistic critical point. The existence of a limit cycle around the simple critical point would entail negative values of  $X, H, Y$  and  $Z$  that is susceptible, infected, infectious and immune.

Looking again at the system of equations we see that

$N = X + H + Y + Z$  or  $X = N - H - Y - Z$ , substituting this into our system (3.1) to (3.4) we have

$$\dot{H} = \beta NY - \beta YH - \beta Y^2 - \beta ZY - (\mu + \sigma)H \quad (3.5)$$

$$Y = \sigma H - (\mu + \gamma)Y \quad (3.6)$$

$$\dot{Z} = \gamma Y - \mu Z \quad (3.7)$$

From (3.7) we see that at equilibrium  $Y = (\mu/\gamma)Z$  (3.8)

and we have in turn from (3.6) and (3.5) respectively

$$H = \frac{(\mu + \gamma)\mu}{\sigma\gamma} Z \quad (3.9)$$

$$Z = \frac{\beta\sigma N\sigma\gamma - (\mu + \sigma)(\mu + \gamma)\sigma\gamma}{\beta\sigma((\mu + \gamma)\mu + \mu\sigma + \sigma\gamma)} = N - \frac{\gamma}{\beta} + E_1 \quad (3.10)$$

where  $E_1$  is very small as it contains terms containing  $\mu$  which is small in comparison to other terms, also  $E_1 < 0$ .<sup>(1)</sup>

We note here that  $Z$  is positive (and hence so is  $H$  and  $Y$ ) provided that:

$$\beta > \frac{\mu^2 + \mu\sigma + \mu\gamma + \sigma\gamma}{\sigma N} > 0.00095 \quad (3.10a)$$

Assuming this to be so we now have a physically realistic critical point of the system (3.5) to (3.7).

We consider the nature of this equilibrium point by looking at the Jacobian matrix of the system above. We have

$$J = \frac{\partial(\dot{H}, \dot{Y}, \dot{Z})}{\partial(H, Y, Z)} = \begin{pmatrix} -\beta Y - (\mu + \sigma) & \beta N - \beta H - \beta Z - 2\beta Y & -\beta Y \\ \sigma & -(\mu + \gamma) & 0 \\ 0 & \gamma & -\mu \end{pmatrix} \quad (3.11)$$

(1) The details of this computation may be found on page 55



For simplicity we write the characteristic equation as

$$\begin{vmatrix} a - \lambda & b & c \\ d & e - \lambda & 0 \\ 0 & f & g - \lambda \end{vmatrix} = 0 \quad (3.12)$$

with obvious definitions for  $a, b, c, d, e, f,$  and  $g$

The characteristic polynomial is a cubic algebraic equation given by

$$\lambda^3 - (e + g + a) \lambda^2 + (ga + ge + ae - db) \lambda + (gdb - gae - cdf) = 0, \quad (3.13)$$

which we write more simply as

$$\lambda^3 + p_2 \lambda^2 + p_1 \lambda + p_0 = 0. \quad (3.14)$$

We are interested in the nature of the roots of the above cubic. For the equilibrium point of the system to be unstable, at least one root of the above cubic must have a positive real part. From the Routh-Hurwitz criterion we know that for all solutions of a cubic to have negative real parts three necessary and sufficient conditions must be satisfied they are

- (i)  $p_2 > 0$
- (ii)  $p_0 > 0$  and
- (iii)  $p_2 p_1 - p_0 > 0$

We consider first condition (i)  $p_2 > 0$ . We have

$$p_2 = 3\mu + \gamma + \sigma + B(\mu/\gamma)^2; \quad (3.15)$$

this is positive as all the terms are positive. Looking at condition (11),  $p_0 > 0$ , we have

$$\begin{aligned}
 p_0 &= -\sigma BN + \sigma B \frac{(\mu + \gamma)}{\sigma} \frac{\mu}{\gamma} Z + \sigma BZ + 2\sigma B \frac{\mu}{\gamma} Z \\
 &+ \frac{B\mu}{\gamma} (\mu + \gamma)Z + (\mu + \sigma)(\mu + \gamma) + 3\sigma Z \\
 &= -\sigma BN + \sigma BZ + \sigma\gamma + B\sigma Z + E_2, \tag{3.16}
 \end{aligned}$$

where  $E_2^{(4)}$  is small as it is the collection of terms containing the parameter  $\mu$ . Also we can show that for current parameter estimate  $-1.44 < E_2 < 0$ . By simple algebraic manipulations we see that  $p_0 > 0$  provided  $B > \frac{\sigma\gamma - E_2}{\sigma(N + 2E)}$  = 0.00095 (for current estimates), (3.17)

We also know that this is always positive as both  $E_1$  and  $E_2$  are small compared to the other terms.

We now wish to consider condition (11) of the Routh Hurwitz criterion, that is, is  $p_2 p_1 - p_0 > 0$ , to do this we first examine the sign of  $p_1$ . We have

$$p_1 = \mu BY + \mu(\mu + \sigma) + (\mu + \gamma)BY + (\mu + \sigma)(\mu + \gamma) + \mu(\mu + \gamma) + \sigma B[H + Z + 2Y] - \sigma BN \tag{3.18}$$

We know that  $Y = (\mu/\gamma)Z$ , therefore we have:

$$\begin{aligned}
 p_1 &= \mu B(\mu/\gamma)Z + \mu(\mu + \sigma) + (\mu + \gamma) B(\mu/\gamma)Z + (\mu + \sigma)(\mu + \gamma) + \\
 &\mu(\mu + \gamma) + \sigma B \left[ \frac{(\mu + \gamma)\mu}{\sigma\gamma} + 1 + 2 \frac{\mu}{\gamma} \right] Z - \sigma BN, \tag{3.19}
 \end{aligned}$$

Which we write as,

(1) See page 55

$$p_1 = \sigma\gamma + \sigma\beta Z + E_3 - \sigma\beta N, \quad (3.20)$$

where  $E_3^{(1)}$  contains all terms that contain a multiple of  $\mu$ . We know that  $E_3$  is small and we can see that it is positive. We know from (3.10) that  $Z = N - \gamma/\beta + E_1$ , we can therefore write

$$p_1 = \sigma\gamma + \sigma\beta(N - \gamma/\beta + E_1) + E_3 - \sigma\beta N \quad (3.21)$$

$$= \sigma\beta E_1 + E_3. \quad (3.22)$$

We see that  $p_1 > 0$  provided that  $|E_3| > |\sigma\beta E_1|$ ; this is true for the current parameter estimates. Returning to condition (111),  $p_2 p_1 - p_0 > 0$ ? We have

$$\begin{aligned} p_2 p_1 - p_0 = & \\ \beta^2 \left( \frac{\mu N}{\gamma} + E_1 \frac{\mu}{\gamma} \right) \sigma E_1 + \beta [E_3 \left( \frac{\mu N}{\gamma} + E_1 \frac{\mu}{\gamma} \right) + E_1 \sigma (\gamma + \sigma + 2\mu) - & \\ (\sigma N + 2\sigma E_1)] + E_3 (\gamma + \sigma + 2\mu) - (E_2 - \sigma\gamma) & \end{aligned} \quad (3.23)$$

We now have a quadratic in  $\beta$  which we may write as:

$$F(\beta) = A\beta^2 + B\beta + C \quad (3.24)$$

where

$$A = \sigma E_1 \frac{\mu}{\gamma} (N + E_1) < 0 \quad (3.25)$$

$$B = \frac{\mu}{\gamma} E_3 (N + E_1) + \sigma E_1 (\gamma + \sigma + 2\mu) - (\sigma N + 2\sigma E_1) < 0 \quad (3.26)$$

$$C = E_3 (\gamma + \sigma + 2\mu) - (E_2 - \sigma\gamma) > 0 \quad (3.27)$$

Bifurcation will occur at a critical value  $\beta_0 > 0$  defined by the equation

$$F(\beta) = 0 \quad (3.28)$$

which has two solutions, but only one of them, namely-

$$\beta_0 = \frac{-B - \sqrt{B^2 - 4AC}}{2A}$$

is positive. Hence,

(1) See page 56

$F(\beta) > 0$  if  $\beta > \beta_0$  and

$F(\beta) < 0$  if  $0 < \beta < \beta_0$  (3.29)

Consequently, the equilibrium point  $(H, Y, Z)$  is stable for  $\beta > \beta_0$  and unstable for  $0 < \beta < \beta_0$

We shall now prove that the conditions of the Hopf Bifurcation theorem are fulfilled at  $\beta = \beta_0$ . Namely, the characteristic equation has a pair of complex conjugate roots

$$\lambda_2(\beta) = \alpha(\beta) + i\omega(\beta)$$

$$\lambda_3(\beta) = \alpha(\beta) - i\omega(\beta) \quad (3.30)$$

and the conditions to be fulfilled are:

$$(i) \quad \alpha(\beta_0) = 0$$

$$(ii) \quad \omega(\beta_0) > 0$$

$$(iii) \quad \left. \frac{d\alpha(\beta)}{d\beta} \right|_{\beta = \beta_0} < 0 \quad .$$

Given that these conditions hold, then we know from the Hopf Bifurcation theorem that there exist periodic orbits around the equilibrium point (at least in the vicinity of the bifurcation point  $\beta = \beta_0$ ).

The characteristic polynomial takes the following form for

$$\beta = \beta_0$$

$$\begin{aligned} & \lambda^3 + p_2(\beta_0)\lambda^2 + p_1(\beta_0)\lambda + p_0(\beta_0) \\ = & \lambda^3 + p_2(\beta_0)\lambda^2 + p_1(\beta_0)\lambda + p_2(\beta_0)p_1(\beta_0) \end{aligned} \quad (3.31)$$

for at  $\beta = \beta_0$ ,  $f(\beta_0) = p_2(\beta_0)p_1(\beta_0) - p_0(\beta_0) = 0$

Therefore our characteristic polynomial evaluated at  $\beta = \beta_0$  takes the form

$$[\lambda - \lambda_1(\beta_0)] [\lambda^2 + (w(\beta_0))^2],$$

from this we know

$$\lambda_1(\beta_0) = -p_2(\beta_0) < 0 \quad (3.32)$$

$$w^2(\beta_0) = p_1(\beta_0) = \frac{p_0(\beta_0)}{p_2(\beta_0)} > 0 \quad (3.33)$$

Thus the conditions (1) and (11) are satisfied if:

$$w(\beta_0) = +\sqrt{p_1(\beta_0)}$$

$$\text{and } \lambda_2(\beta_0) = iw(\beta_0) \text{ and } \lambda_3 = -iw(\beta_0)$$

To investigate the requirement (111) we use the continuation of the root  $\lambda_2$  in the neighbourhood of  $\beta_0$ . The root  $\lambda_2(\beta)$  satisfies the equation:

$$[\lambda_2(\beta)]^3 + p_2(\beta)[\lambda_2(\beta)]^2 + p_1(\beta)[\lambda_2(\beta)] + p_0(\beta) = 0 \quad (3.34)$$

for every  $\beta$ .

$$\begin{aligned} \text{We require } \left. \frac{d\lambda_2(\beta)}{d\beta} \right|_{\beta_0} &= \left. \frac{d[\text{Re } \lambda_2(\beta)]}{d\beta} \right|_{\beta_0} \\ &= \left. \text{Re } \frac{d\lambda_2(\beta)}{d\beta} \right|_{\beta_0} \end{aligned} \quad (3.35)$$

Differentiating with respect to  $\beta$  we arrive at:

$$\begin{aligned} \frac{d\lambda_2(\beta)}{d\beta} [3[\lambda_2(\beta)]^2 + 2p_2(\beta)\lambda_2(\beta) + p_1(\beta)] \\ + [\lambda_2(\beta)]^2 \frac{dp_2(\beta)}{d\beta} + \lambda_2(\beta) \frac{dp_1(\beta)}{d\beta} + \frac{dp_0(\beta)}{d\beta} = 0 \end{aligned} \quad (3.36)$$

As we have seen

$$\lambda_2(\beta) = \alpha(\beta) + iw(\beta)$$

$$\text{therefore } \text{Re} \frac{d\lambda_2(\beta)}{d\beta} \Big|_{\beta_0} = \frac{d\alpha(\beta)}{d\beta} \Big|_{\beta_0}$$

and thus we have from equation (3.36) above

$$\begin{aligned} \frac{d\lambda_2(\beta)}{d\beta} \Big|_{\beta_0} &= \\ & \frac{-[\lambda_2(\beta)]^2 \frac{dp_2(\beta)}{d\beta} - \lambda_2(\beta) \frac{dp_1(\beta)}{d\beta} - \frac{dp_0(\beta)}{d\beta}}{3[\lambda_2(\beta)]^2 + 2p_2(\beta)\lambda_2(\beta) + p_1(\beta)} \Big|_{\beta_0} \quad (3.37) \end{aligned}$$

the real part of  
if the above is less than zero than the third condition of the Hopf Bifurcation theorem is satisfied and there will exist periodic orbits around the equilibrium point

We shall now prove that this is indeed the case.

We have seen in (3.15) that

$$p_2(\beta) = 3\mu + \gamma + \sigma + \beta(\mu/\gamma)Z, \text{ which when substituting in for } Z \text{ gives, } p_2(\beta) = 2\mu + \gamma + \sigma + (\mu N/\gamma)\beta + E_1(\mu/\gamma)\beta.$$

Differentiating with respect to  $\beta$  gives,

$$\frac{dp_2(\beta)}{d\beta} = \frac{\mu N}{\gamma} + E_1 \frac{\mu}{\gamma} > 0 \quad (3.38)$$

We also have,

$$p_1(\beta) = \sigma\beta E_1 + E_3 \text{ which on differentiating gives,}$$

$$\frac{dp_1(\beta)}{d\beta} = \sigma E_1 + \frac{dE_3(\beta)}{d\beta} > 0 \text{ for } \beta > \beta_0. \quad (3.39)$$

Finally we have,

$$p_0(\beta) = -\sigma N\beta + \sigma BZ + \sigma\gamma + \sigma BZ + E_2$$

When we substitute in for Z we have,

$$p_0(\beta) = \sigma N\beta - \sigma\gamma + 2\sigma E_1\beta + E_2$$

Differentiating the above  $p_0(\beta)$  with respect to  $\beta$  gives,

$$\frac{dp_0(\beta)}{d\beta} = \sigma N + 2\sigma E_1 + \frac{dE_2(\beta)}{d\beta} > 0, \text{ for } \beta > \beta_0 \quad (3.40)$$

Finally, we substitute equations (3.38) to (3.40) into (3.37)

rationalising and taking the real part only gives

$$\left. \frac{d\alpha(\beta)}{d\beta} \right|_{\beta_0} = \frac{\left\{ -p_1(\beta) \left[ \frac{\mu N}{\gamma} + E_1 \frac{\mu}{\gamma} \right] - p_2(\beta) \left[ \sigma E_1 + \frac{dE_3(\beta)}{d\beta} \right] - \left[ \sigma N + 2\sigma E_1 + \frac{dE_2(\beta)}{d\beta} \right] \right\}}{\left\{ 2p_1(\beta) + 2[p_2(\beta)]^2 \right\}} \bigg|_{\beta=\beta_0} \quad (3.41)$$

As  $p_1(\beta_0)$ ,  $\frac{[\mu N + E_1 \mu]}{\gamma}$ ,  $[\sigma E_1 + \frac{dE_3(\beta)}{d\beta}]$ ,  $[\sigma N + 2\sigma E_1 + \frac{dE_2(\beta)}{d\beta}]$ ,

and  $p_2(\beta_0)$  are all positive, we have,

$$\left. \frac{d\alpha(\beta)}{d\beta} \right|_{\beta_0} < 0 \quad (3.42)$$

and the third condition of the Hopf bifurcation theorem is fulfilled. Hence according to the Hopf bifurcation theorem, there exist periodic orbits around the equilibrium point, at least in the vicinity of the bifurcation point  $\beta = \beta_0$ .

We have seen that the Hopf bifurcation theorem provides us with the conditions necessary for the existence of real periodic solutions for a system of ordinary differential equations,

$$\frac{dX}{dt} = F(X, v), \quad (3.43)$$

where  $F$  and  $X(v, t)$  are  $n$  dimensional vectors and  $v$  a real parameter. The theorem also provides us with the approximate period of the solution. We have.

$$\text{Period, } T = \frac{2\pi}{\omega} \quad (3.44)$$

given that the characteristic equation of  $A(v)$  has purely imaginary roots  $\pm i\omega$ , where

$A(v)$  is the linearised matrix of (3.43) about the singular point  $a(v)$ , that is

$$A(v) = \left[ \nabla_x F(X, v) \right]_{x=a(v)} \quad (3.45)$$

We have seen that  $\omega = \sqrt{\rho_1(\beta_0)}$ , and

we have therefore from the Hopf bifurcation theorem an estimate of  $T$ . We have,

$$T = 4.2$$

We shall now compare this with estimates from numbers of reported cases of measles in Ireland and in Dublin from 1945 to 1985. From figure 3.2a and figure 3.2b we can derive the average interepidemic period for measles. These are set out in Table 3.1 below



Table 3.1  
Shows the Interepidemic Periods (in years) in Ireland and  
in Dublin between the years 1945 to 1985

Ireland	Dublin
2	2
2	2
3	3
2	2
2	5
3	2
2	3
3	4
4	2
2	6
4	3
5	6
4	-
2	-
-	-
Average Interepidemic Period Ireland 2.86 years	Average Interepidemic Period Dublin 3.33 years

We see from Table (3.1) that the Hopf bifurcation theorem estimate of the interepidemic period is slightly higher than the actual as derived from Irish records. This may be due to the fact that throughout our calculations pertaining to the theorem we have been using a death rate of  $\mu = 1/75$  years. For those in the 0 - 15 years old age bracket this death rate may in fact be lower.

We have succeeded in showing how the fluctuation in the incidence of measles in Ireland is reflected in the non-linear differential equation compartment model by the study of the equilibrium points and their behaviour. We have also successfully shown how the Hopf Bifurcation theorem provides an estimate for this interepidemic period.

APPENDIX

Throughout Chapter three we have used the following parameter estimates

(i)  $N = 64,000$ , this is the number of births in 1985 that is the total population of the cohort studied

(ii)  $1/\sigma$  is the average latent period, we have

$$1/\sigma = 9 \text{ days} = 0.025 \text{ years, we have therefore}$$

$$\sigma = 41 \text{ years}^{-1}$$

(iii)  $1/\gamma = 6 \text{ days} = 0.016 \text{ years}$  which implies

$$\gamma = 61 \text{ years}^{-1}$$

(iv)  $1/\mu$  is the average life expectancy, we have

$$1/\mu = 70 \text{ years which implies } \mu = 0.014 \text{ years}^{-1}$$

(v)  $E_1$  of equation (3.10) equals

$$\frac{N\sigma\gamma}{\sigma\gamma + (\mu^2 + \mu\gamma + \mu\sigma)} - N,$$

for the parameter estimates given above we have

$$E_1 = -36.5$$

(vi)  $E_2$  of equation (3.16) equals

$$\beta \left( \frac{\mu + \gamma}{\sigma} \right) \frac{\mu}{\gamma} Z + 2\beta \frac{\mu}{\gamma} Z + \beta \frac{\mu(\mu + \gamma)Z}{\gamma} + \mu^2 + \mu\sigma + \mu\gamma$$

Substituting in the parameter values gives us

$$E_2 = 3198.18\beta - 4.48$$

We know from (3.10a) that  $\beta > 0.00095$  for  $Z$  to be positive, we have therefore

$$E_2 > -1.44$$

(vii)  $E_3$  of equation (3.20) equals

$$\frac{\mu\beta\mu z}{\delta} + \mu^2 + \mu\sigma + (\mu+\gamma) \frac{\beta\mu z}{\delta} + \mu^2 + \mu\sigma + \mu\gamma + \mu^2 + \mu\gamma +$$

$$\left( \frac{\sigma\beta(\mu+\gamma)\mu}{\sigma\gamma} + \frac{\sigma\beta 2\mu}{\delta} \right) z$$

On substitution of parameter values we have,

$$E_3 = 3006\ 28458 - 0.013$$

Given that  $\beta > 0.00095$  we have

$$E_3 > 2\ 843$$

(viii) The co-efficients of equation (3.24) are as follows.

$$A > -21,968\ 841$$

$$B > -2776642.1$$

$$C > 2792.51$$

(ix) The roots  $\beta_1$  and  $\beta_0$  of equation (3.24) are as follows

$$\beta_1 > -126.39, \quad \beta_0 > 0\ 001$$

## CHAPTER 4

### ON INTRODUCING THE AGE DEPENDENT MODEL AND THE MORTALITY PARAMETER $\mu(a)$

We have examined a time dependent model and found it useful in illuminating certain basic principles. However the assumption that the parameters of the model are simple age independent constants is an over simplification.

We can generalise the time dependent model to include the effects of age independence, particularly in mortality rates, vaccination rates and transmission rates. This will allow us to give a more rigorous discussion of  $R_0$  and later in chapter 5, a more rigorous discussion of our vaccination policy.

Our analysis of the transmission of measles will involve a compartment model with age structure. The population is again divided into discrete classes, at age  $a$  and at time  $t$  we have

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

$H(a,t)$  = number infected but not yet infectious

$Y(a,t)$  = number infectious.

$Z(a,t)$  = number recovered and immune.

The partial differential equations for this system are first order nonlinear. They describe the rates of change of  $X, H, Y, Z$  with respect to both age  $a$  and time  $t$ . They are

$$\frac{\partial X(a,t)}{\partial t} + \frac{\partial X(a,t)}{\partial a} = -[\mu(a) + \lambda(a,t) + c(a)] X(a,t) \quad (4.1)$$

$$\frac{\partial H(a,t)}{\partial t} + \frac{\partial H(a,t)}{\partial a} = \lambda(a,t) X(a,t) - [\mu(a) + \sigma] H(a,t) \quad (4.2)$$

$$\frac{\partial Y(a,t)}{\partial t} + \frac{\partial Y(a,t)}{\partial a} = \sigma H(a,t) - [\mu(a) + \gamma] Y(a,t) \quad (4.3)$$

$$\frac{\partial Z(a,t)}{\partial t} + \frac{\partial Z(a,t)}{\partial a} = \gamma Y(a,t) + c(a) X(a,t) - \mu(a) Z(a,t) \quad (4.4)$$

with initial and boundary conditions,

$t = 0$  specify  $X(a,t)$ ,  $H(a,t)$ ,  $Y(a,t)$ ,  $Z(a,t)$ .

$a = 0$  specify  $X(0,t) = N(0,t)$ , the total population at age 0,

that is all newborn individuals are susceptible to infection.

This assumption can be modified to include protection from maternal antibodies

Also  $H(0,t) = Y(0,t) = Z(0,t) = 0$ , for all  $t$

The parameters  $\gamma$ , the recovery rate and  $\sigma$ , the rate of passing from infected to the infectious state are as before in Chapter 1. However we now assume that all individuals are subject to an age dependent mortality rate  $\mu(a)$  and that individuals are vaccinated at an age dependent rate  $c(a)$ . We have also assumed, as before, that immunity is lifelong, as is the case with measles.

By considering the equilibrium state of this general model we can gain further understanding of the temporal

behaviour or dynamics of the general model To do this we make the further assumption that births and deaths exactly balance That is, we are assuming that the population remains roughly constant on the time scale appropriate to the pathology of the disease This is not an unreasonable assumption for Ireland as can be seen from figures(4.1) below, these show the population age structure of Ireland over several decades

At equilibrium the partial differential equations (4.1) to (4.4) reduce to.

$$\frac{dX}{da} = - [\lambda(a) + \mu(a) + c(a)] X(a) \quad (4.5)$$

$$\frac{dH}{da} = \lambda(a) X(a) - [\sigma + \mu(a)] H(a) \quad (4.6)$$

$$\frac{dY}{da} = \sigma H(a) - [\gamma + \mu(a)] Y(a) \quad (4.7)$$

$$\frac{dZ}{da} = \rho Y(a) + c(a)X(a) - u(a) Z(a) \quad (4.8)$$

where  $N(a) = X(a) + H(a) + Y(a) + Z(a)$ , with initial conditions

$$X(0) = N(0), \quad H(0) = Y(0) = Z(0) = 0$$

When discussing the time dependent model we assumed that all the parameters including mortality were independent of age We did this in order to make the mathematics of the

FIGURE 4 1  
POPULATION CLASSIFIED BY AGE GROUP AT  
CENSUS 1951

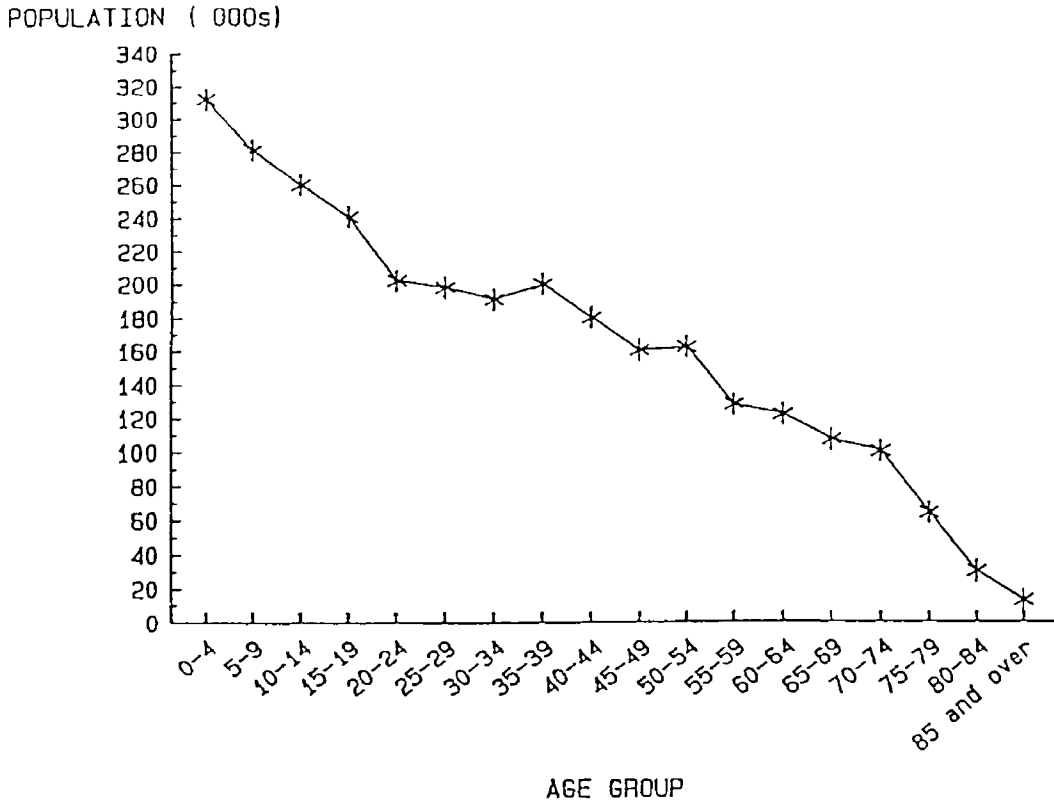


FIGURE 4 1  
POPULATION CLASSIFIED BY AGE GROUP AT  
CENSUS 1961

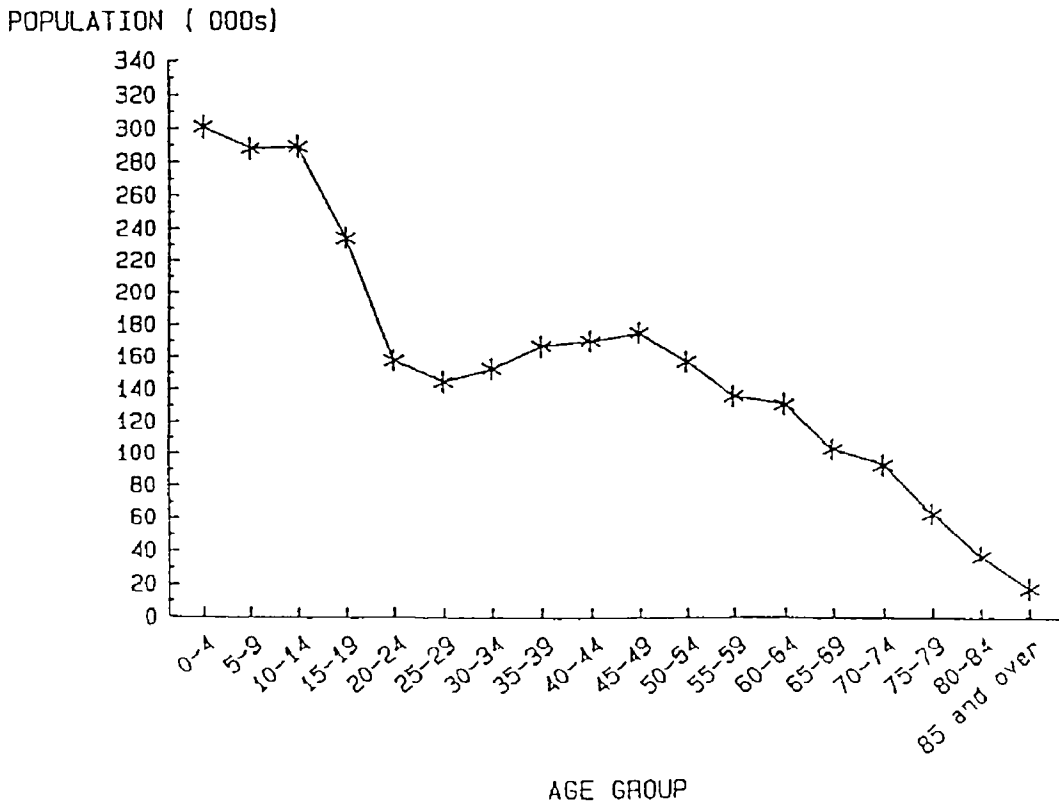


FIGURE 4 1  
 POPULATION CLASSIFIED BY AGE GROUP AT  
 CENSUS 1971

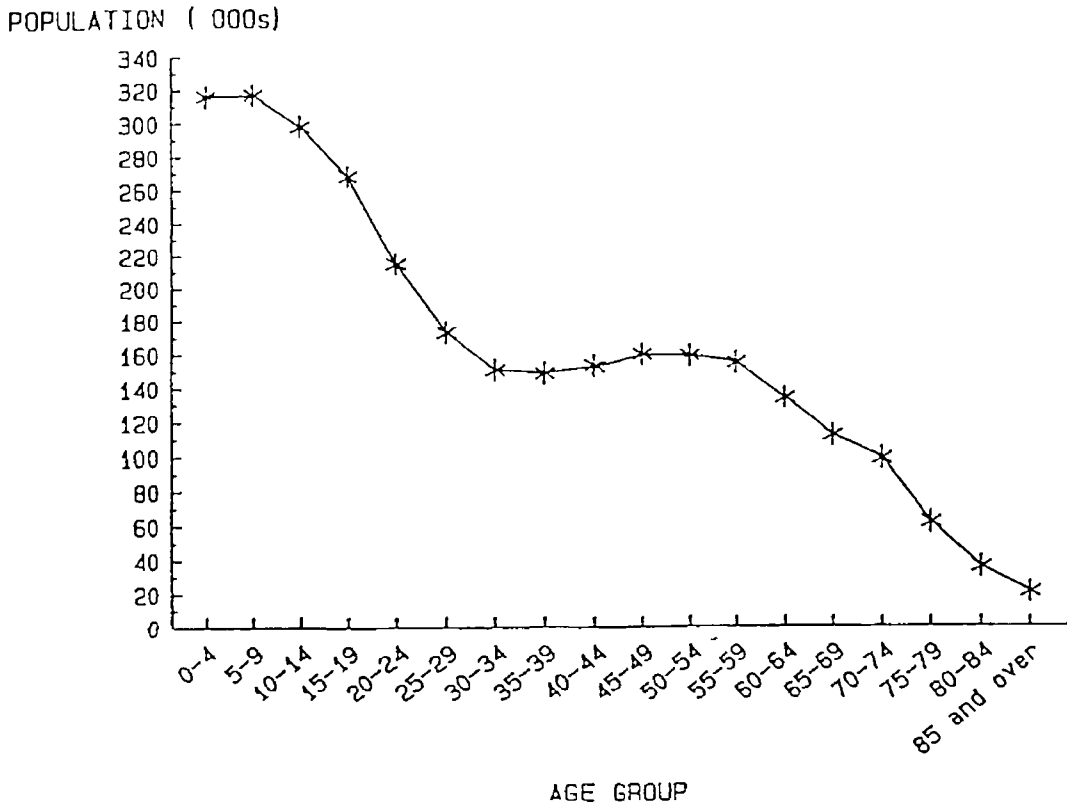
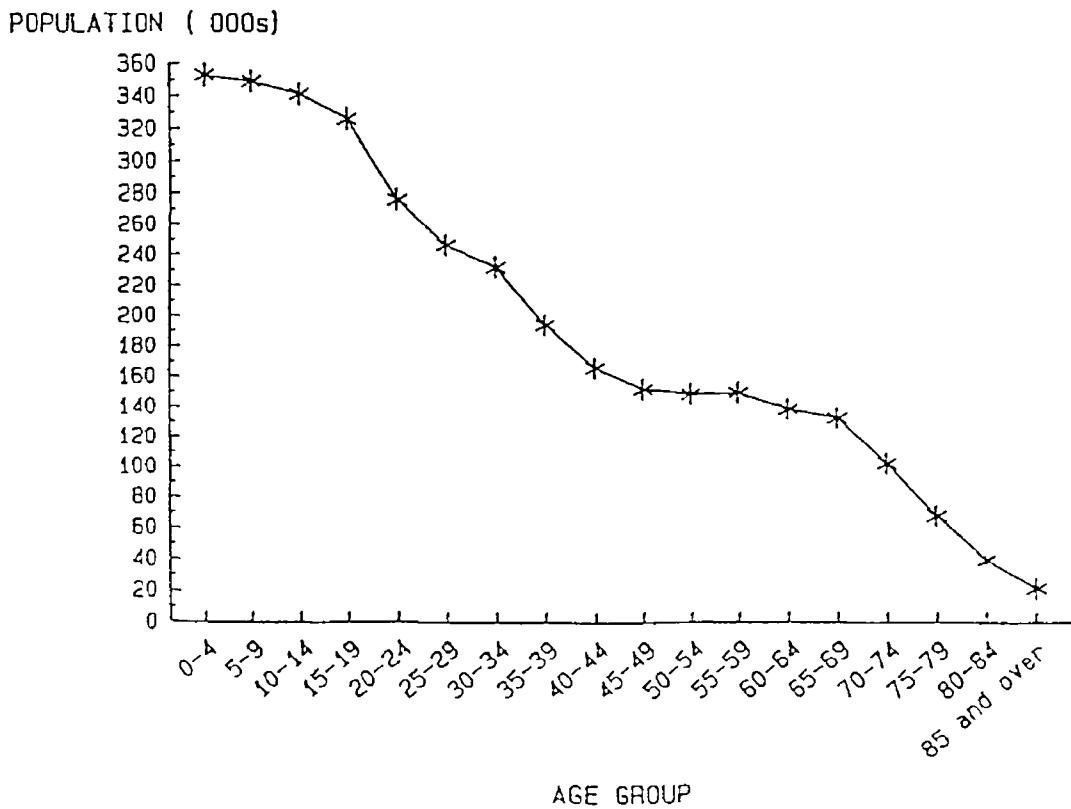


FIGURE 4 1  
 POPULATION CLASSIFIED BY AGE GROUP AT  
 CENSUS 1981





model easier and more elegant rather than because real populations have age independent death rates. This assumption of age independence is frequently made and can be found in the works of Dietz (4), Bailey (6) and Anderson and May (1). We have also assumed that the population remains constant and that the birth rate equals the death rate. We shall now examine the mortality rate in Ireland and its dependence on age.

Our aim is to derive an age dependent mortality rate for Ireland so that the model will represent the dynamics of the measles infection within the Irish population in a more realistic way. We shall finally in chapter six insert this realistic parameter back into the model and numerically solve the above equations (4.5) to (4.8) for  $X$ ,  $H$ ,  $Y$  and  $Z$  that is, susceptibles, infecteds, infectious and recovered and immune respectively.

To derive the age independent mortality rate we need to study the numbers and hence proportions of people remaining in various cohorts. These are set out in table 4.1 below.

Table 4 1

Proportion Remaining in Each Cohort Born from 1900 to 1980

<u>Age in</u> <u>1981</u>	<u>Number Born</u> <u>into Cohort</u>	<u>Number Remaining</u> <u>in each Cohort</u>	<u>Proportion</u> <u>Remaining</u> <u>in each</u> <u>Cohort</u>
81	70453 0	8875 0	0 125970
80	70184.0	11537 0	0.164240
79	71156.0	11150.0	0.156698
78	71541 0	12181.0	0.170266
77	72261.0	13521.0	0.187113
76	71427.0	15153.0	0.212147
75	72147.0	16446.0	0.227951
74	70773.0	17631.0	0.249120
73	71439 0	18274.0	0.255799
72	72119.0	20288.0	0.281313
71	71774.0	22066 0	0.307437
70	71351 0	24879.0	0.348685
69	70835.0	25649.0	0.362095
68	70214 0	26583.0	0.378600
67	69097 0	26426.0	0 382448
66	67501.0	28444.0	0.421386
65	64814 0	26781 0	0 413198
64	61421 0	27214.0	0.443073
63	61092 0	24632.0	0 403195
62	61829.0	24471.0	0 395785
61	67015.0	29479.0	0 439887
60	61010.0	30470.0	0.499426
59	58849.0	29983 0	0.509490
58	61690 0	30499.0	0.494391
57	63402.0	29360 0	0.463077
56	62069.0	30275.0	0.487764
55	61176.0	29489.0	0 482035
54	60054 0	29823.0	0 496603
53	59176 0	28840.0	0.487360
52	58280 0	29945.0	0.513813
51	58353.0	29942.0	0.513118
50	57086.0	31130.0	0.545318
49	56240.0	29016.0	0.515932
48	57364.0	31320.0	0.545987
47	57897.0	29761.0	0 514034
46	58266 0	30337 0	0 520664
45	58115.0	31416.0	0.540583
44	56488 0	32781.0	0 580318
43	56925.0	30911.0	0 543013
42	56070 0	33108 0	0 590476
41	56594 0	34811 0	0 615101
40	56780 0	34313 0	0 604315

Table 4.1 (Contd )

Proportion Remaining in Each Cohort Born from 1900 to 1980

39	66117.0	33995 0	0 514164
38	64375 0	37676 0	0 585258
37	65425.0	38254 0	0.584700
36	66861 0	40333 0	0 603267
35	67922 0	43571.0	0 641486
34	68978.0	44343 0	0 642857
33	65930.0	46410 0	0 703928
32	64153.0	46976 0	0 732249
31	63565.0	46505 0	0.731613
30	62878.0	47724 0	0.758994
29	64631.0	46885 0	0 725426
28	62558.0	49713.0	0 794671
27	62534.0	48800.0	0.780375
26	61622.0	50584.0	0.820876
25	60740.0	50071.0	0.824350
24	61242.0	51945.0	0.848192
23	59510.0	52683 0	0.885280
22	60188.0	53832.0	0 894398
21	60735.0	57213.0	0.942010
20	59825.0	57308.0	0 957927
19	61782.0	59342.0	0.960506
18	63246.0	60986 0	0.964267
17	64072.0	61779 0	0.964212
16	63525.0	61443.0	0.967225
15	62215.0	60207 0	0 967725
14	61307.0	59386.0	0.968666
13	61004.0	59368.0	0.973182
12	62912.0	61217 0	0.973058
11	64284.0	62643.0	0.974473
10	67551.0	65992.0	0.976921
9	68500.0	66937.0	0.977183
8	68700.0	67186.0	0.977962
7	68900.0	67430.0	0 978694
6	67200.0	65862.0	0.980089
5	67700.0	66413.0	0.980990
4	68900.0	67665.0	0.982075
3	70300.0	69096.0	0.982873
2	72500.0	71457 0	0.985610
1	74100.0	73213.0	0.988030

Table 4.1 shows the following.

- a) The age of each cohort in 1981. 1981 was used as it was then the most recent census year We start studying

cohorts from 1900 on. This raises some problems that are peculiar to Ireland. Due to the partition of the country in 1921 records of births prior to this contain those for the 6 counties of Northern Ireland but death figures after this date do not contain the northern figures. Hence we must subtract off individual figures for the 6 northern counties. This is mentioned in order to show how politics can effect studies and one must keep this in mind.

- b) The number of births in the Republic of Ireland in each year from 1900 to 1980.
- c) The number of those aged 81 years down to those aged 1 remaining in 1981. Some problems were also experienced at this stage. We find that in the age range of 20 years to 1 year there are more children remaining than were actually born! It is possible that this is due to the in-migration of families in the 1970's. However this problem can be overcome by looking at, first, the number of deaths of those aged  $< 1$  in 1961, those aged  $< 1$  and aged 1 in 1962, those aged  $< 1$ , aged 1 and those aged 2 in 1963 and so on until we find the number of deaths of those aged 20, 19, 18, .. 1, and  $< 1$  in 1981. By performing this task we can find the correct number of deaths in the cohort born in 1961. These figures (on deaths) can then be subtracted from the numbers born in 1961 up to 1981 to arrive at the correct numbers of 20 year olds remaining in 1981. This can be repeated for

each of the cohorts

- d) The correct proportions remaining in each of the cohorts aged 81 years to 1 year

Once the correct proportion remaining in each of the cohorts is found we can plot the data and subsequently fit a suitable function to the resulting plot. The above data was plotted using the Minitab statistical package. The shape of the curve can be seen in figure (4.2) below

Figure (4.2) shows the age dependent survival curve for Ireland in 1981. The age specific mortality rate  $\mu(a)$  is the logarithmic derivative of this curve with respect to  $a$ . We shall derive this result mathematically later in this chapter.

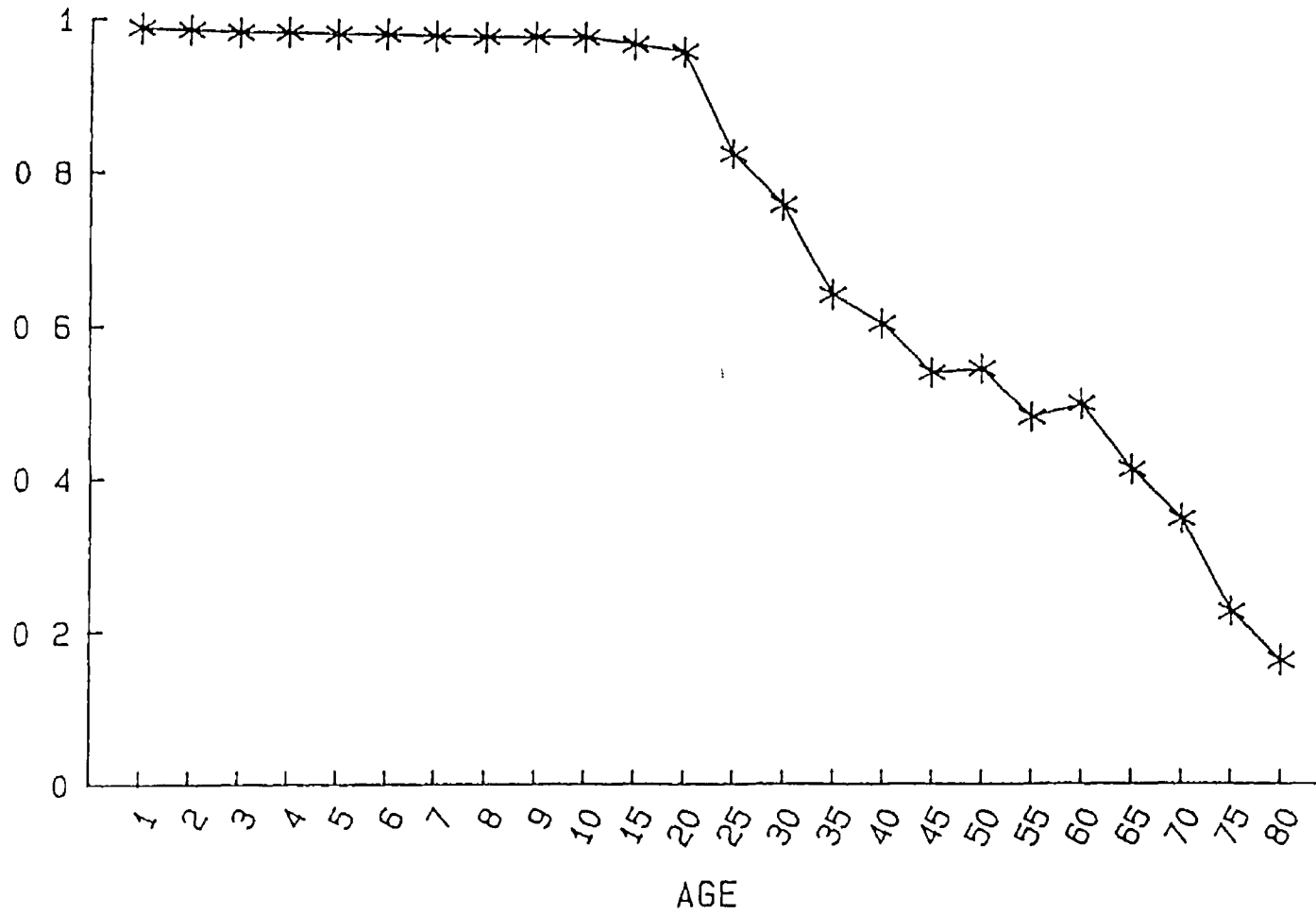
We can see from figure (4.2) that most people survive up to the age of 25 years. After this there is a decline in the proportions remaining. This is most likely due to emigration rather than to death. The data suggests that a suitable function for those remaining in the 1 year to 25 year age bracket would be,

$$S(a)=1 \quad a < 25 \quad (4.9)$$

in other words all survive up to and including the age of 25 years. A suitable function for the remaining data can be derived from Newton's Interpolating Formula for a polynomial

FIGURE 4.2  
PLOT OF SURVIVAL CURVE

PROPORTION REMAINING



of degree 3 Working from grouped averages we have table 4.2 below

Table 4.2

AGE(years)    PROPORTION REMAINING

29.5	0.756017
45.5	0.543876
61.5	0.449806
77.5	0.186688

Using Newtons method of divided differences we have

X	f(x)	f(x <sub>1</sub> x <sub>2</sub> )	f(x <sub>1</sub> x <sub>2</sub> x <sub>3</sub> )	f(x <sub>1</sub> x <sub>2</sub> x <sub>3</sub> x <sub>4</sub> )
x <sub>1</sub> 29.5	0.756017	-0.0132588		
x <sub>2</sub> 45.5	0.543876		0.000230609	
x <sub>3</sub> 61.5	0.449806	-0.0058793	-0.0003017	-0.000011089
x <sub>4</sub> 77.5	0.186688	-0.0164448		

Newton tells us that the required polynomial is of the form:

$$P(x) = f(x) + f(x_1 x_2)(x - x_1) + f(x_1 x_2 x_3)(x - x_1)(x - x_2) + f(x_1 x_2 x_3 x_4)(x - x_1)(x - x_2)(x - x_3)$$

This gives us:

$$P(x) = 0.756017 - 0.0132588(x - 29.5) + 0.00023061(x - 29.5)(x - 45.5) - 0.0000111(x - 29.5)(x - 45.5)(x - 61.5)$$

We now have

$$\begin{aligned} S(a) &= 1 && \text{for } a \leq 25 \\ S(a) &= P(a) && a > 25 \end{aligned}$$

Where  $P(x) = Ax^3 + Bx^2 + Cx + D$  where

$$A = -1.0 \times 10^{-5}, B = 1.565 \times 10^{-3}, C = -8.785 \times 10^{-2},$$

$$D = 2.242$$

We shall see in chapter 5 how a generalisation of this survival curve will effect our immunisation policy. We said above that the age specific mortality rate  $\mu(a)$  is the logarithmic derivative of the age dependent survival curve  $S(a)$ . We shall now prove this by looking closer at some basic reliability theory

Consider the compartment model with age structure. We assume that individuals are subject to an age dependent mortality rate  $\mu(a)$  in age class  $a$ . We also assume that the number of births equals the number of deaths. How then does the parameter  $\mu(a)$  relate to reliability theory?

Let  $\mu(a)$  = age specific death rate.

$S(a)$  = probability of surviving to age  $a$ .

$N(a)$  = the number in the population at age  $a$

Consider  $(a, a + \Delta a)$ ,  $\Delta a$  small, then the number of deaths in

$$(a, a + \Delta a) = \mu(a) * N(a) * \Delta a$$

For example



The number of deaths in say the (12 months, 18 months) age group that is the (12 months, 12+6 months) age group would be  $\mu(12) * N(12) * 6$  months, that is, (the death rate of those aged 12 months) \* (the number of 12 month olds) \* (6 months)

The probability of death in  $(a, a + \delta a)$  is  $(\mu(a) * N(a) * \delta a) / N(a) = \mu(a) \delta a$  that is, (expected number of deaths)/(number at risk), therefore the probability of an individual alive at  $a$ , surviving to  $a + \delta a$  is

$$1 - [\mu(a) \delta a]$$

Now the probability of individual alive at  $a + \delta a$ , that is surviving to age  $a + \delta a$

$$= S(a + \delta a)$$

= probability (alive at  $a$ ) \* probability (survives from  $a$  to  $a + \delta a$ )

$$= S(a) * (1 - [\mu(a) * \delta a])$$

that is

$$S(a + \delta a) = S(a) * (1 - [\mu(a) * \delta a]).$$

Rearranging we get-

$$[S(a + \delta a) - S(a)] / \delta a = -\mu(a) * S(a).$$

Letting  $\delta a \rightarrow 0$  implies  $dS/da = -\mu(a) * S(a)$

Separating the variables we have,  $dS/S(a) = -\mu(a) * da$

Integrating from 0 to a gives us  $\int_0^a 1/S(a) dS = - \int_0^a \mu(a) da$

which implies  $[\ln (S(a))] - [\ln (S(0))] = - \int_0^a \mu(t) dt$

But  $S(0) = 1$ , which implies  $\ln S(0) = 0$  therefore we have

$$\ln S(a) = - \int_0^a \mu(t) dt$$

which implies  $S(a) = \exp[- \int_0^a \mu(t) dt]$ .

We have related our survivor function to our compartment model parameter  $\mu(a)$ . Can we perhaps derive this result in another way? Consider the following

Let  $F(a)$  = probability of death before age a

We know  $S(a) + F(a) = 1$  therefore (4 11)

$$F(a) = 1 - \exp [- \int_0^a \mu(t) dt]$$

In fact  $F(a)$  equals the cumulative distribution function of ages to death. From reliability theory we know

$$f(a) = dF(a) / da \quad (4 12)$$

which equals the probability density function of ages to

death. Because  $f(a)$  = (probability of dying at age a) (probability of surviving up to age a), we have  $f(a) = \mu(a) S(a)$ . Using (4 12) we can say  $F'(a) = \mu(a) S(a)$  and from (4 11) we know that  $F'(a) = -S'(a)$

We now have

$$\begin{aligned} -S'(a) &= \mu(a) S(a) \text{ which implies} \\ &= -[dS/da] / S(a) = -d[\ln S(a)]/da = \mu(a) \text{ as required} \end{aligned}$$

We have shown how the compartment parameter  $\mu(a)$  relates to reliability theory and we have also shown that it is indeed the logarithmic derivative of the survival curve. We shall now state the age specific mortality rate for Ireland using the survival curve derived above.

We have from (4.10):

$$\mu(a) = 0 \quad a \leq 25 \text{ years,}$$

$$\mu(a) = -\frac{d \ln P(a)}{da} \quad a > 25$$

In Chapter 6 we shall use the Irish mortality rate derived above to estimate the proportions of children susceptible, and immune to measles in the coming years.

CHAPTER FIVE  
ON IMMUNISATION AND ESTIMATION OF  $c(a)$ , THE VACCINATION  
RATE IN IRELAND

We shall now see how the introduction of the age dependent model with age dependent parameters enables us to give a more rigorous description of the values of  $A$ ,  $R_0$  and  $N_T$ . We shall also examine the effect of introducing immunisation into the model. We shall look at

- 1) the prediction of the levels of immunity required to eradicate the disease given a specific vaccination program,
- 11) the effect of vaccination on  $A$ , the average age of infection,
- 111) the effect of vaccination on the numbers of cases of measles and of measles encephalitis.

Prior to October 1985 no such program existed in Ireland. All newborn infants were and still are immune to infection as a consequence of the protection provided by their maternal antibodies, these are passed via the placenta into the blood stream of the baby during pregnancy. For measles, infants remain protected for roughly their first six months of life. The recommended age for vaccination is 15 months because it is believed that the rate of seroconversion is

maximised at this age. Vaccination at a lower age gives lower seroconversion rates due to the protection of the maternal antibodies. The policy of vaccinating all children at this optimum age has been adopted by the Irish Health Boards.

How then do we describe this parameter? Prior to October 1985 we had:

$$(a) \quad C(a) = 0 \quad 0 \leq a \leq L \quad L = 70 \text{ years} \quad (5.1)$$

and from 1985 to the present it is hoped that:

$$(b) \quad C(a) = \begin{array}{ll} 0 & a < 15 \text{ months} \\ 1 & a = 15 \text{ months} \\ 0 & a > 15 \text{ months} \end{array} \quad (5.2)$$

In other words no children are vaccinated before the age of 15 months, all or most children are vaccinated at the age of 15 months and no children are vaccinated after this age. This is of course an ideal situation which will not occur. In reality it does however give us many insights into the levels of immunity required to eradicate the disease if we adopt such a policy. This we shall discuss later. First we consider the situation as it actually occurred in one Community Care Area of Dublin.

Community Care Area 8 in Dublin, lies on the northern outskirts of the city, it contains densely populated urban areas and rural areas with sparse population. Prior to the introduction of the measles immunisation program, in October

1985, a survey of 2936 children between the ages of 1 and 5 years was carried out. The aim of this survey was to test for the proportions susceptible to measles and hence establish a target figure for the initial immunisations. The results of this survey are set out in Table 5.1 below. Some similar surveys were conducted in other parts of the country with the similar results.

*For these reasons we feel justified in*  
Taking Community Care Area 8 (C C A.8) as a sample <sup>and</sup> population representative of the general population, we examine the numbers of actual vaccinations at specific ages in the area. Assuming that the distribution of vaccinations is similar throughout the country we shall take this sample data and estimate  $C(a)$ , the vaccination rate for all of Ireland.

Patient files for children in the General Medical Service in C C A.8 were computerised, this gave over 2,000 medical card cases. From these we saw what proportions were immunised in the various age groups. Using immunisation forms returned by doctors in the area we computerised over 2,000 immunisations of those in the non General Medical Service sector. This gives us over 4,000 records of children immunised in the various age groups. As the total population figures were available for these age groups in this area the proportion immunised in each of the age groups was derived. *This lengthy process occupied 3 months in the Summer of 1986*

TABLE 5.1

AGE in years	Immunised	Status Unknown	Had Measles	Vacc before 1/10/85	Left Area	Refused	Contra- Indicat	Other	Row Total
1	12 37.5%	11 34.4%	6 18.8%	2 6.3%	0 0.0%	0 0.0%	0 0.0%	1 3.1%	32 100.0%
2	315 44.4%	225 31.7%	107 15.1%	22 3.1%	34 4.8%	1 0.1%	1 0.1%	4 0.6%	709 24.1%
3	298 40.1%	209 28.1%	168 22.6%	18 2.4%	36 4.8%	2 0.3%	2 0.3%	10 1.3%	743 25.3%
4	270 31.7%	194 22.8%	309 36.3%	20 2.4%	51 6.0%	1 0.1%	1 0.1%	5 0.6%	851 29.0%
5	158 26.3%	145 24.1%	244 40.6%	7 1.2%	38 6.3%	1 0.2%	3 0.5%	5 0.8%	601 20.5%
Total	1053 35.9%	784 26.7%	834 28.4%	69 2.4%	159 5.4%	5 0.2%	7 0.2%	25 0.9%	2936 100.0%

Results of survey carried out by Dr Z Johnson in C C A 8 prior to the introduction of measles vaccination

He finds that approximately 30% of children in the 1 - 5 year age group need to be immunised

The results of this work are shown in Table 5.2 below

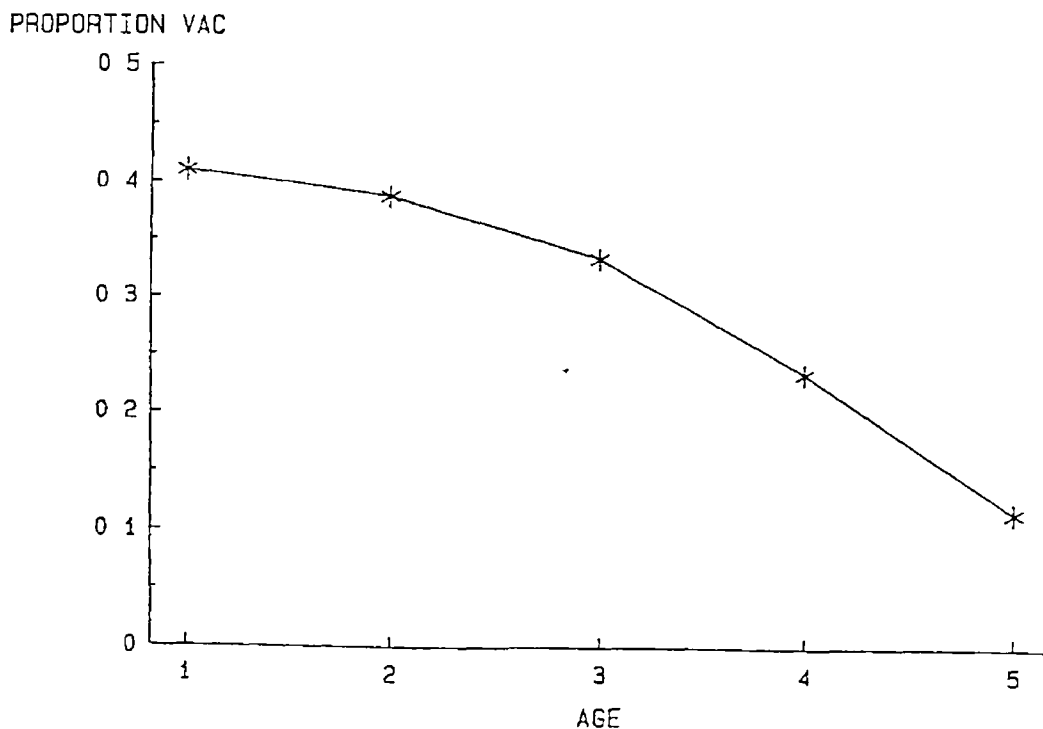
Table 5.2

Age at Vaccination (years)	Proportion Vaccinated
1	0.410
2	0.387
3	0.333
4	0.233
5	0.115

Table 5.2 showing the proportion vaccinated in each age group for Community Care Area 8 from October 1985 to June 1986.

A plot of the proportion vaccinated versus age can be seen in figure 5.1 below

FIGURE 5.1  
PROPORTIONS VACCINATED IN C C A 8  
Vs AGE AT VACCINATION





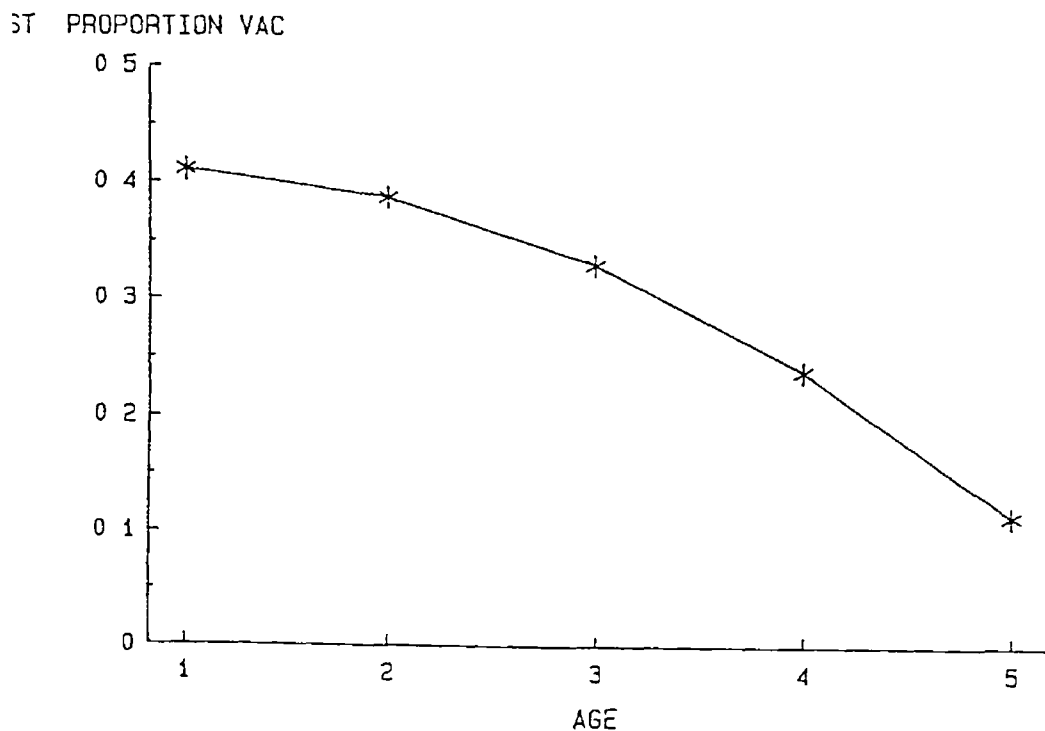
The method of least squares was used to fit as quadratic to the original data on the proportions vaccinated giving

$$C(a) = ra^2 + sa + t$$

with  $r = -0.01686$ ,  $s = 0.026743$   $t = 0.40083$

A plot of the estimated proportion vaccinated versus age is given in figure 5.2 below

FIGURE 5  
ESTIMATED PROPORTIONS VACCINATED IN C.C A 8  
Vs AGE AT VACCINATION



The derived vaccination rate gives the following estimates of proportions vaccinated

Table 5.3

<u>Age at Vaccination</u> (years)	<u>Estimated Proportion</u> <u>Vaccinated (%)</u>
1	0.411
2	0.387
3	0.329
4	0.238
5	0.113

Table 5.3 as for Table 5.2 but shows estimated proportions vaccinated

Since March 1986, we know that the Health Board's policy has been to vaccinate all or most children at the age of 15 months. What are the effects of this vaccination and given this policy what proportion must we immunise in order to eradicate the disease? Must we vaccinate all children?

Vaccination has two effects, first we have the obvious effect that those immunised are protected against infection. We also have a less obvious effect, that is that a susceptible child has less chance of acquiring the disease in a partially vaccinated community than in an unvaccinated one. This is because there are fewer people infectious in the community to give the disease to the child. Therefore it is not necessary to immunise all children in order to eradicate the disease.

(1) Confidence Interval on estimated proportion vaccinated at age 1  
 $CI = p - (N_{1/2} \times SE) \text{ to } p + (N_{1/2} \times SE) \quad SE = \sqrt{p(1-p)/n}$

We have  $p = 0.411$ ,  $n = 3062$ ,  $SE = 0.000791$

$CI = 0.4108 \text{ to } 0.4112$  79

As the sample sizes are very large and the standard errors very small no other confidence intervals were estimated

As measles is endemic we can find some interesting relations between  $R_0$  and the fraction of the population that are susceptible or the average age at first infection. This in turn will allow us to discuss  $P$ , the proportion of the population immunised, in more detail.

As the infection becomes established the fraction of the population who remain susceptible will decrease. The net fraction susceptible may be denoted by  $\bar{x}$ , where

$$\bar{x} = \bar{X}/\bar{N} \quad (5.3)$$

$\bar{X}$  is the total number of susceptibles and  $\bar{N}$  is the total population. If we make the Anderson and May (2) assumption of weak homogeneous mixing, we are assuming that the rate of appearance of new infections is linearly proportional to the number of susceptibles. Therefore, on average the number of secondary infections will be diminished below the number occurring when all individuals are susceptible, by the factor  $\bar{x}$ . That is, the effective reproductive rate,  $R$ , is

$$R = R_0 \bar{x} \quad (5.4)$$

If the infection is established at a roughly steady equilibrium value the effective reproductive rate will be unity (at equilibrium each infection on average produces exactly one secondary infection). *As we saw in <sup>chapter 1</sup> at equilibrium*  $R_0$  and the fraction susceptible,  $\hat{x}$ , are related by

$$R_0 \hat{x} = 1 \quad (5.5)$$

If the equilibrium fraction of the population who are susceptible can be determined, equation (5.5) can be used to estimate  $R_0$ . (Estimates of  $R_0$  shall be discussed in the next section and again in more detail in Chapter 6)

Equation (5.5) cannot be satisfied if the proportion of the population who are successfully vaccinated,  $p$ , exceeds some critical value. As the fraction susceptible cannot exceed the fraction not successfully vaccinated ( $\bar{x} < 1-p$ ) the equation can only be satisfied if  $R_0(1-p)$  exceeds unity. It follows that if the proportion vaccinated exceeds the value:

$$p > 1 - 1/R_0^* \quad (5.6)$$

then the effective reproductive rate of the infection will necessarily be less than unity and the infection will die out. In other words equation (5.6) gives a rough criterion for eradication of an infection by a vaccination program

We also see that infections with high  $R_0$  values, as in the case with measles, require a higher proportion of children to be vaccinated in order to eradicate the disease.

Dietz (9,10) has derived the relation:

$$R_0 \approx \frac{\lambda L}{A} = \underline{L} \quad (5.7)$$

or more realistically for a step function mortality curve

(i.e. everyone lives up to the age,  $L$ ) we have

\* This is a very important result for the medical profession  
 We require  $R_0 \bar{x} < 1$  for eradication. Therefore if we vaccinate a proportion  $p$  we will have a proportion  $1-p$  not vaccinated i.e.  $\bar{x} = 1-p$   
 We now require  $R_0(1-p) < 1$ , if we rearrange this we see that  
 $p > 1 - 1/R_0$  for eradication of the infection

$$R_0 = (L/A) / [1 - \exp(-L/A)] \quad (5.8)$$

which approximates to

$$R_0 = \frac{L}{A} \quad (\text{for } A < L, \text{ as is the case with measles in Ireland})$$

To give a feeling for these parameters, we consider some typical values for A, taking L = 70 years, we have Table 5.4 below

A	$R_0$	P (greater than)
3	23.33	0.957
3.5	20.00	0.950
4	17.50	0.943

In areas of lower age of acquiring infection,  $R_0$  will be larger, implying that a larger proportion of children should be immunised in order to eradicate the disease. This should be kept in mind in Ireland where we have both large urban and rural areas. Higher levels of coverage may be *required* to eradicate the disease within these urban areas. These figures are very high and will be very difficult to achieve in practice. In the United States of America where pre-school vaccinations is compulsory to the extent that a certificate of immunisation is an entry requirement for

school, measles has virtually disappeared as more than 95% of children are vaccinated before going entering school. In the United Kingdom immunisation is not enforced by law and high levels of vaccination have proved difficult to achieve.

We have estimated the proportions we need to vaccinate given the values of  $\mu(a)$ ,  $A$ , and  $R_0$  before vaccination. We have seen the importance of  $R_0$  and  $A$  in determining these proportions. We shall now address the questions, what happens to this reproductive rate,  $R_0$ , of the disease if we immunise, will it increase or decrease? Also, what happens to,  $A$ , the average age of acquiring the infection, after the introduction of an immunisation program?

To see this we return to our original set of differential equations given by

$$\frac{dX}{da} = -(\lambda + \mu(a)) X(a) \quad (5.9)$$

$$\frac{dH}{da} = \lambda X - (\sigma + \mu(a)) H(a) \quad (5.10)$$

$$\frac{dY}{da} = \sigma H - (\gamma + \mu(a)) Y(a) \quad (5.11)$$

$$\frac{dZ}{da} = \gamma Y - \mu(a) Z(a) \quad (5.12)$$

By introducing the set of starred variables

$$X(a) = X^*(a) \phi(a) \quad (5.13)$$

Where

$$\phi(a) = \exp\left[-\int_0^a \mu(s) ds\right]. \quad (5.14)$$

With  $\gamma^*$ ,  $H^*$  and  $Z^*$  defined analogously,  
 - We arrive at a set of equations identical to the above but  
 with mortality factored out,

we now have

$$X(a) = X^*(a) \phi(a)$$

$$\text{Hence. } \frac{dX}{da} = -(\lambda + \mu(a)) X^*(a) \phi(a) \quad (5.15)$$

$$\text{But } \frac{dX}{da} = \frac{d[X^*(a) \phi(a)]}{da}$$

$$= X^* \phi'(a) + \phi(a) X^{*'} \quad \text{Where ' denotes differentiation with respect to } a \quad (5.16)$$

$$\begin{aligned} \text{Also. } \phi(a) &= \exp\left[-\int_0^a \mu(s) ds\right] \\ &= \exp\left[-(U_1(a) - U_1(0))\right] \end{aligned}$$

which implies

$$\begin{aligned} \phi'(a) &= -\mu(a) \exp\left[-\int_0^a \mu(s) ds\right] \\ &= -\mu(a) \phi(a) \end{aligned} \quad (5.17)$$

Therefore

$$\frac{dX}{da} = X^* (-\mu(a) \phi(a)) + \phi(a) X^{*}$$

But

$$\frac{dX}{da} = -(\lambda + \mu(a)) X^*(a) \phi(a) \quad \text{from (5.15)}$$

da

Hence

$$X^* (-\mu(a)\phi(a)) + \phi(a) X^{*'} = -(\lambda + \mu(a)) X^*(a)\phi(a) \quad (5.18)$$

which when both divided by  $\phi(a)$  gives

$$-(\lambda + \mu(a)) X^*(a) = -\mu(a) X^* + X^{*'}$$

On re-arranging

$$X^{*'} = -X^*(a) - \mu(a) X^* + \mu(a) X^*$$

which gives, on dividing by  $\phi(a) \neq 0$

$$\frac{dX^*}{da} = -\lambda X^*(a) \quad (5.19)$$

Mortality has disappeared as required.

Introducing an age specific vaccination rate into our set of starred equations gives us

$$\frac{dX^*}{da} = -(\lambda' + c(a)) X^*(a) \quad (5.20)$$

$$\frac{dH^*}{da} = \lambda' X^* - \sigma H^*(a) \quad (5.21)$$

$$\frac{dY^*}{da} = \sigma H^* - \gamma Y^*(a) \quad (5.22)$$

$$\frac{dZ^*}{da} = \gamma Y^* + c(a) Z^*(a) \quad (5.23)$$

here  $\lambda$  is the force of infection at equilibrium after the immunisation program is established. Also we are taking  $\lambda$



independent of age for simplicity. The above set of differential equations has boundary conditions

$$X^*(0) = N(0), \quad H^*(0) = Y^*(0) = Z^*(0) = 0$$

We can easily find  $X^*(a)$  from the above. Using an integrating factor we have:

$$X^*(a) = N(0) \exp[-\lambda' a + \int_0^a c(s) ds] \quad (5.24)$$

As  $X(a) = X^*(a) \phi(a)$  we have the number of susceptibles at age,  $a$ , given by:

$$X(a) = N(0) \exp[-\lambda' a + \int_0^a c(s) ds] \phi(a) \quad (5.25)$$

and

$$N(a) = N(0) \phi(a) \quad (5.26)$$

By integrating equation (5.25) for  $X(a)$  over all ages we can compute  $\bar{X}$  (the total number susceptible) for any specific vaccination program  $c(a)$  and any mortality rate  $\mu(a)$ . We can then discover  $\hat{x}$  the fraction susceptible and we can find  $R_0$ .

The policy for vaccination in Ireland is to vaccinate a proportion,  $P$  of children at age  $b$ ,  $b$  being 15 months.  $c(a)$  in this case can be taken to be a Dirac- $\delta$  function centred on  $a = b$ . Using such a  $c(a)$  we obtain.

$$\begin{aligned} X(a) &= N(0) \exp[-\lambda' a] \phi(a) & a < b \\ X(a) &= (1 - p) N(0) \exp[-\lambda' a] \phi(a) & a > b \end{aligned} \quad (5.27)$$

Where

$$\phi(a) = \exp\left[-\int_0^a \mu(s) ds\right] = 1$$

given that

$$\mu(a) = 0 \text{ for } a < L, \quad \mu(a) = \infty \text{ for } a = L$$

The total number susceptible,  $\bar{X}$ , is given by  $\int_0^{\infty} X(a) da$  where,

$$\int_b^L X(a) da = \int_b^L (1-p) N(0) \exp[-\lambda' a] da \quad (5.28)$$

$$\begin{aligned} &= (1-p) N(0) (1/\lambda') \exp(-\lambda' a) \Big|_b^L \\ &= (1-p) N(0) (1/\lambda') \exp[-\lambda' L] - (1-p) N(0) \\ &\quad (1/\lambda') \exp(-\lambda' b) \end{aligned}$$

$$= \frac{N(0)}{\lambda'} [(1-p) \exp(-\lambda' b) - (1-p) \exp(-\lambda' L)] \quad (5.29)$$

$$\text{and } \int_0^b X(a) da = \frac{N(0)}{\lambda'} \exp(-\lambda' b) + \frac{N(0)}{\lambda'}$$

$$\text{We now have } \bar{X} = \frac{N(0)}{\lambda'} [1 - p \exp(-\lambda' b) - (1-p) \exp(-\lambda' L)] \quad (5.29a)$$

Using equation (5.29a) we can give estimates for the total numbers susceptible under our given immunisation policy and the proportions actually vaccinated

We have seen above that

$$R_0 = 1/\hat{x}, \quad \hat{x} = \bar{X}/\bar{N} \text{ which implies } R_0 = \bar{N}/\bar{X},$$

$$\text{where } \bar{N} = N(0)L.$$

This now provides an estimate for the reproductive rate of the disease given our estimated Irish mortality curve and immunisation policy.

$$R_0 = \frac{\bar{N}}{\bar{X}} = \frac{N(0)L}{N(0) [1-p \exp(-\lambda' b) - (1-p) \exp(-\lambda' L)] / \lambda'}$$

$$= \frac{\lambda' L}{(1-p) \exp(-\lambda' b) - (1-p) \exp(-\lambda' L)} \quad (5.30)$$

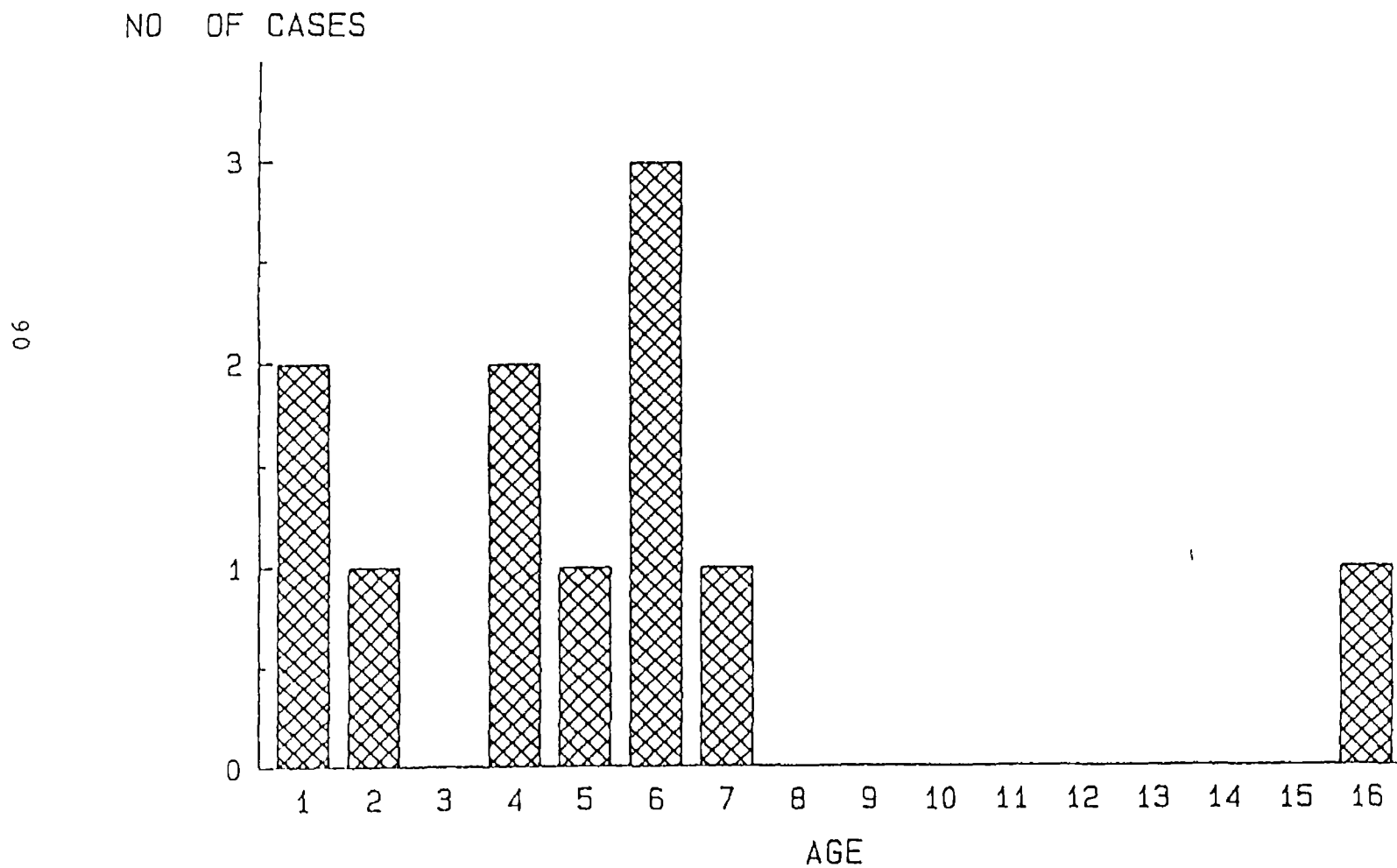
Various estimates of  $R_0$  given the Irish data are discussed in Chapter 6. Note we must keep in mind that we require  $R_0$  to be below unity in order for the disease to die out. We should find that  $R_0$  decreases with vaccination, the extent of the decrease depending on  $P$ , the proportion immunised.

We have observed the effects of vaccination on the reproductive rate of the disease. We shall now look at the effects of vaccination on  $A$ , the average age of infection with measles. This average age  $A$  can vary greatly depending on the degree of urbanisation, being much higher in areas of dense population. In Ireland we believe  $A$ , to be in the range of 3 to 5 years. This is in accordance with similar populations in England and Wales. Direct estimates of  $A$  are best obtained from either serological surveys or case notifications, neither of which are readily available in Ireland and, where available, case notifications may be seriously underestimated.

Infection of any child with measles can lead to the more dangerous infection of measles encephalitis. The risk of measles encephalitis is a very serious one. Survivors often have permanent brain damage and mental retardation. It is

known that the risk of this disease varies with age, the older child being at a higher risk. Wide spread immunisation within a community increases the average age  $A$  at which an infection is acquired, therefore we must examine our vaccination policy with this in mind. If we vaccinate a proportion  $P$ ,  $P < 1$ , of all children then there will remain a proportion,  $1-P$  of children at risk to infection. These may develop the infection at a later age due to the fact that there will be fewer susceptible children in circulation and hence fewer infectious. Given this situation will more or less children in Ireland develop measles encephalitis? As yet there is no data available on the numbers of post-vaccination cases of measles encephalitis. However in the coming years these should be carefully monitored in order to check that our immunisation policy is indeed a safe one and that our levels of coverage are adequate. Figure (5.3) below shows the number of cases of measles encephalitis in the years 1981 to 1985, prior to mass immunisation. We shall discuss the effects of vaccination on the average age of first infection and on the numbers of cases of measles encephalitis when we examine our numerical results in Chapter 6.

NUMBER OF CASES OF MEASLES ENCEPHALITIS  
IN THE YEARS 1981 TO 1985  
PRIOR TO MASS IMMUNISATION



CHAPTER SIX  
NUMERICAL RESULTS, CONCLUSIONS AND RECOMMENDATIONS

In the preceding chapters we introduced a constant parameter, time dependent model. We saw now this simple model was useful in illuminating certain basic principles. In particular providing us with estimates of.

- (1) The average age at infection,  $A$ .
- (11) The basic reproductive rate,  $R_0$ .
- (111) The interepidemic period,  $T$ .

In chapters 2, 4 and 5 we found the age dependent force of infection, the mortality rate and the vaccination rate for Ireland. We used this information to derive the average age at first infection in Ireland. We shall now use these parameters to derive the intrinsic reproductive rate before and after the advent of the Irish vaccination program. Finally, we shall estimate from the above the fraction of the population which must be vaccinated in order to eradicate measles in Ireland.

In the second half of this chapter we shall present the model with Irish parameters. We shall numerically solve the system, (a set of non-linear differential equations) and we will show how the model predicts, (given certain specified initial conditions) the proportion of a particular cohort susceptible to measles infection before and after the

introduction of the Irish vaccination program

We have seen that the disease will maintain itself within the population provided the reproductive rate,  $R$ , of the infection is greater than or equal to unity.  $R$ , is the expected number of secondary cases produced by one infectious individual in a population of  $X$  susceptibles. The intrinsic reproductive rate of the disease  $R_0$  may be defined as the value of  $R$  in a disease-free population. We shall see that  $R_0$  can be estimated from the relation:

$$R_0 = 1 + L/A \quad (6.0)$$

Where  $L$  is the human life expectancy and  $A$  is the average age at first infection.

For the model described in equations 4.3 to 4.8 we can use a result obtained by Dietz(9,10) and generalised by Anderson and May (2). They have:

$$R_0 = \frac{\int_0^{\infty} \exp\left\{-\int_0^a [\mu(v) + c(v)] dv\right\} da}{\int_0^{\infty} \exp\left\{-\int_0^a [\lambda(v) + \mu(v) + c(v)] dv\right\} da} \quad (6.1)$$

For Ireland we have from page 78,

$$\mu(v) = 0, \quad v < 70,$$

$$c(v) = -0.01686v^2 + 0.026743v + 0.40083$$

$$\lambda(v) = -0.0024878v + 0.326783.$$

Looking at the simple case when all the rate parameters are constants and there is no vaccination program, equation (6.1) reduces to

$R_0 = 1 + (\lambda/u)$ , as the average age at first infection is  $A = 1/\lambda$  and  $L = 1/\mu$  we have the simplified equation for  $R_0$  given in (6.0) above

Let us now insert the Irish parameters into (6.1) and examine the intrinsic reproductive rate for Ireland We have before the implementation of the vaccination program  $c = 0$  so giving

$$R_0 = \frac{\int_0^{70} \exp [0] da}{\int_0^{70} \exp \left[ - \int_0^a -0.0024878v + 0.326783 \right] da}$$

$$= \frac{70}{3.13711} = 22.3135.$$

We can now see that this figure for  $R_0$  is very close to our first approximation of  $R_0 = 1 + L/A = 1 + 70/3.25 = 22.54$ .

After the implementation of our vaccination program we have:

$$R_0 = \frac{\int_0^6 \exp \left[ - \int_0^a c(v) dv \right] da + \int_6^{70} \exp \left[ - \int_0^a c(v) dv \right] da + \int_6^{70} \exp \left[ - \int_6^a c(v) dv \right] da}{\int_0^6 \exp \left[ - \int_0^a \lambda(v) dv - \int_0^a c(v) dv \right] da + \int_6^{70} \exp \left[ - \int_0^a \lambda(v) dv - \int_0^a c(v) dv \right] da + \int_6^{70} \exp \left[ - \int_0^a \lambda(v) dv - \int_6^a c(v) dv \right] da}$$

which implies that:

$$R_0 = \frac{1 + 238929 + 182402}{0.853368 + 102249 + 0.138279} = 10738838$$

The above estimate is based on  $c(v)$  as derived from our sample of vaccination rates. If we assume that all children up to the age of 6 years are vaccinated at a constant rate,  $c = 1$  we have



$$R_0 = \frac{\int_0^b [\exp\{-\int_0^a c(v) dv\}] da + \int_6^{70} \exp[-\int_0^b c(v) dv] da}{\int_0^b [\exp\{0.0012439a^2 - 1.326783a\}] da + \int_6^{70} \exp[-\int_0^a \lambda(v) dv - \int_0^b c(v) dv] da}$$

which implies,

$$R_0 = 1.529$$

We can see from the above that the introduction of vaccination has reduced the intrinsic reproductive rate considerably. However, we must remember that for the eradication of measles in Ireland we must ensure that  $R_0 < 1$ .

More generally if it is the policy to vaccinate a proportion of the population at a constant rate  $c$  while the remaining fraction  $1 - p$  is not covered by the vaccination program it has been shown that the intrinsic reproductive rate  $R'_0$ , Anderson and May (2), is:

$$R'_0 = R_0 [1 - cp/(c + \mu)] \quad (6.2)$$

where  $R'_0$  is the intrinsic reproductive rate after the vaccination program and  $R_0$  is the rate before,  $c = 1/v$  with  $v$  equalling the average age at vaccination.

If then we decide before the start of the vaccination program (by means of surveys etc) that on average half of our children have had measles and therefore we target our vaccination policy at  $p = 0.5$  we shall have in Ireland after initial vaccinations

$$R'_0 = 22.3135 [1 - (1/2.6)(0.5)/(1/2.6)] = 11.156$$

What proportion then, need we immunise in Ireland in order to reduce  $R_0$  below unity? From equations (6.0) and (6.2) we can prove that the fraction of the population that must be protected must exceed

$$p > \frac{1 + v/L}{1 + A/L} \quad (6.3)$$

where  $v$  is the average age at which individuals are vaccinated (i.e.  $v = 1/c$ ). Since  $p$  cannot be greater than 1 we see that eradication is possible only if  $A > v$ . This is an important result when we consider that in Ireland  $A = 3.16$  years. Irish children need to be vaccinated at an early age however immunisation at too early an age can lead to poor seroconversion and hence loss of immunity.

We can estimate  $v$  from our sample data on vaccination we have  $v = 2.6$  years Taking  $L = 70$  years gives

$$p > 0.9923$$

if we manage to reduce  $v$  to 15 months or 1.25 years we then have

$$p > 0.9738$$

which is still a very large proportion. One of the main reasons for this is our very low average age at first infection. On a still more pessimistic note it has been found that outbreaks of measles can still occur even when more than 99% of children have been vaccinated. The reported outbreak in question arose in Texas among school children, the first being a fifteen year old girl

99% of the school children were documented as having been immunised however upon measles antibody tests they found that 5% were not protected. Vaccination may have failed for several reasons. These include administering the vaccine to infants under 15 months, administering it in conjunction with immunoglobulin or improperly storing it. For these reasons the Irish medical profession must be aware of the possibility of an outbreak even where all children have been vaccinated.

It is interesting to note the age of the girl in which the infection arose. It is well known that vaccination increases the average age at infection. A susceptible has less chance of acquiring the infection in a partially vaccinated community than in an unvaccinated population. There are less infectious individuals around from whom one can contract the disease. However, it is also well known that the risk of acquiring measles encephalitis as a complication is also higher amongst those who contract the disease at an older age.

In Ireland the severity of the disease in terms of mortality and morbidity has not changed in 20 years. The rate of deaths to notification is 1.5 per 10,000. There has been 82 deaths in 15 years and at least 25 cases of encephalitis in 10 years in Ireland. However, we can take some comfort from the fact that Anderson and May have shown in (2) that vaccination at whatever level always acts to reduce the

number of encephalitis cases. Taking parameter values appropriate to the U.K. population i.e.  $A = 5$  years,  $v = 2.2$  years and  $p = 0.5$  they find that immunisation levels of 50% result in only a 25% reduction in the number of encephalitis cases. A 90% coverage results in a 75% reduction, while higher levels of vaccination result in eradication. The reduction in the number of cases is non-linearly related to the proportion of the cohort immunised. This non-linear effect is important because substantial reductions in the number of cases of encephalitis will only occur as the overall level of herd immunity begins to approach the critical level for eradication.

We have seen what proportion we need to immunise in order to eradicate measles in Ireland. We shall now return to the model. We shall see what proportions of susceptible, infected, infectious and immunes the model will predict given the Irish age dependent parameters. These we shall compare with the results of our seriological survey.

We have the system as described in (4.5) to (4.8). This system can be solved numerically for  $X$ ,  $H$ ,  $Y$  and  $Z$  given the following initial conditions:

- (1)  $X(0.5) = 64,000$ . This is the number of births in 1984. We choose this year as vaccination was introduced into Ireland in 1985. We shall be following the movement of this particular cohort in the model.

- (11)  $H(0.5) = Y(0.5) = Z(0.5) = 0$  There are no infected, infectious, recovered and immune at the age of 6 months We note here that  $X + H + Y + Z = N$  as required
- (111) We take  $\mu(a) = 0$  as the death rate amongst those in the age range of interest i.e. 6 months to 10 years is negligible
- (iv)  $C(a) = 0$  We wish to examine the proportions the model will predict as susceptible prior to the implementation of a vaccination program
- (v)  $\lambda(a)$  is a linear function for  $a > 0.5$  years. The force of infection acts only on those not protected by the maternal antibodies These are thought to last for 6 months
- (vi) Finally  $0.5 \leq a \leq 10$  as most of the parameters have been estimated for the younger age groups. Also measles in Ireland is a childhood disease.

These parameter values are substituted into the program below. (Note: the program below is a modification of an NAG Library program).

```

PROGRAM ODE SOLVER
IMPLICIT REAL*8(A-H,O-Z)
REAL *8 X, XEND, SSIZE, X1
REAL *8 Y(4), Z(4)
N = 4
X = 0 5D0
XEND = 1 0D1
SSIZE = 0. 5D0
Y(1) = 64 0D3
Y(2) = 0 0D0
Y(3) = 0.0D0
Y(4) = 0.0D0
WRITE (28,99) X,(Y(I),I = 1,N)
DO 100 I = 1,19
X1 = X + SSIZE
CALL GEAR (N,X,X1,Y)
X = X + SSIZE
WRITE (28,99) X,(Y(J), J = 1, N)
- 100 CONTINUE
99 FORMAT (/, ' T = ', D13 6,' Y(I) = ' 4D13.6)
END

```

C

```

SUBROUTINE GEAR (N,X,XEND,Y)
IMPLICIT REAL*8 (A-H,O-Z)
REAL *8 TOL, X, XEND, OLDX
INTEGER I, IFAIL, IW, J, N, NOUT
REAL *8 W(4,22), Y(4)

```

C

```

EXTERNAL FCN
IW = 22
TOL = 1. 0D-7
IFAIL = 1
OLDX = X
CALL DO2EAF(X,XEND,N,Y,TOL,FCN,W,IW,IFAIL)
X = OLDX
IF (TOL.LT.0 0D0) WRITE (6,99994)
WRITE (6,99996) IFAIL
99994 FORMAT (/,' RANGE TOO SMALL FOR TOL ')
99996 FORMAT (/,' IFAIL = ', I1)
END

```

C

```

SUBROUTINE FCN (T,Y,F)
IMPLICIT REAL *8(A-H, O-Z)
REAL *8 T
REAL *8 Y(4), F(4)
ZLMDA = -2 4878D-3* T+3.26783D-1
ZMUA = 0.0D0
CA = 0.0D0
SIGMA = 40.556D0
GAMMA = 60 833D0

```

C

```
F(1) = -Y(1) * (ZLMDA + ZMUA + CA)
F(2) = -Y(2) * (SIGMA + ZMUA)+ ZLMDA * Y(1)
F(3) = SIGMA * Y(2) - (GAMMA + ZMUA) * Y(3)
F(4) = GAMMA * Y(3) + CA*Y(1) - ZMUA * Y(4)
RETURN
END
```

This program uses the Gear method in order to solve the system. The results can be seen in Table 6.1 and Table 6.1a below.

TABLE (6.1a)

SHOWS THE PROPORTION SUSCEPTIBLE TO MEASLES OF THE ORIGINAL COHORT OF 64,000 CHILDREN, AT AGE a

Age years	No. Susceptible	No. Immune	Proportion Susceptible
0.5	64000.0	0.0	1.00000
1.0	54403.3	8864.1	0.85005
1.5	46274.4	17104.9	0.72304
2.0	39384.5	24089.2	0.61538
2.5	33541.4	30012.1	0.52408
3.0	28583.0	35038.1	0.44661
3.5	24372.7	39305.5	0.38082
4.0	20795.5	42931.0	0.32493
4.5	17754.4	46013.0	0.27741
5.0	15167.4	48634.7	0.23699
5.5	12965.4	50866.0	0.20258
6.0	11090.1	52766.4	0.17328
6.5	9491.8	54385.8	0.14831
7.0	8129.0	55766.6	0.12702
7.5	6966.2	56944.8	0.10885
8.0	5973.4	57950.5	0.09333
8.5	5125.3	58809.7	0.08008
9.0	4400.3	59544.1	0.06875
9.5	3780.2	60172.2	0.05907
10.0	3249.6	60709.7	0.05077

Several important results should be noted from this table:

- (a) By the age of 10 years there are still over 3,000 of the original cohort of 64,000 children, susceptible to measles infection.

TABLE 6 1

SHOWS THE PREDICTED NUMBERS OF SUSCEPTIBLE, INFECTED,  
INFECTIOUS AND RECOVERED AND IMMUNE AT AGE a

A	X	H	Y	Z
AGE (years)	NO s SUSCEPTIBLE	INFECTED	INFECTIOUS	RECOVERED/ IMMUNE
0.500000D+00	0.640000D+05	0.000000D+00	0 000000D+00	0 000000D+00
0.100000D+01	0.544033D+05	0.438612D+03	0.294018D+03	0 886409D+04
0.150000D+01	0.462744D+05	0.371633D+03	0 249114D+03	0.171049D+05
0.200000D+01	0.393845D+05	0.315073D+03	0.211196D+03	0.240892D+05
0.250000D+01	0.335414D+05	0.267283D+03	0.179159D+03	0.300121D+05
0.300000D+01	0.285830D+05	0.226880D+03	0.152073D+03	0.350381D+05
0.350000D+01	0.243727D+05	0.192701D+03	0.129161D+03	0.393055D+05
0.400000D+01	0.207955D+05	0.163770D+03	0.109768D+03	0.429310D+05
0.450000D+01	0.177544D+05	0.139267D+03	0.933428D+02	0.460130D+05
0.500000D+01	0.151674D+05	0.118502D+03	0.794237D+02	0.486347D+05
0.550000D+01	0.129654D+05	0.100895D+03	0 676211D+02	0.508660D+05
0.600000D+01	0.110901D+05	0.859553D+02	0 576074D+02	0.527664D+05
0 650000D+01	0.949184D+04	0.732723D+02	0 491063D+02	0.543858D+05
0.700000D+01	0 812899D+04	0.624986D+02	0.418851D+02	0.557666D=05
0 750000D+01	0.696616D+04	0.533414D+02	0 357474D+02	0 569448D+05
0 800000D+01	0.597338D+04	0.455534D+02	0.305276D+02	0 579505D+05
0.850000D+01	0.512527D+04	0.389261D+02	0.260857D+02	0 588097D+05
0.900000D+01	0.440031D+04	0.332831D+02	0.223037D+02	0.595441D+05
0.950000D+01	0.378025D+04	0.284753D+02	0.190815D+02	0.601722D+05
0.100000D+01	0.324958D+04	0.242768D+02	0.163348D+02	0.607097D+05



FIGURE 6 1  
 SHOWING PLOT OF NO SUSCEPTIBLE US AGE  
 (WHERE  $C(a) = 0$ )

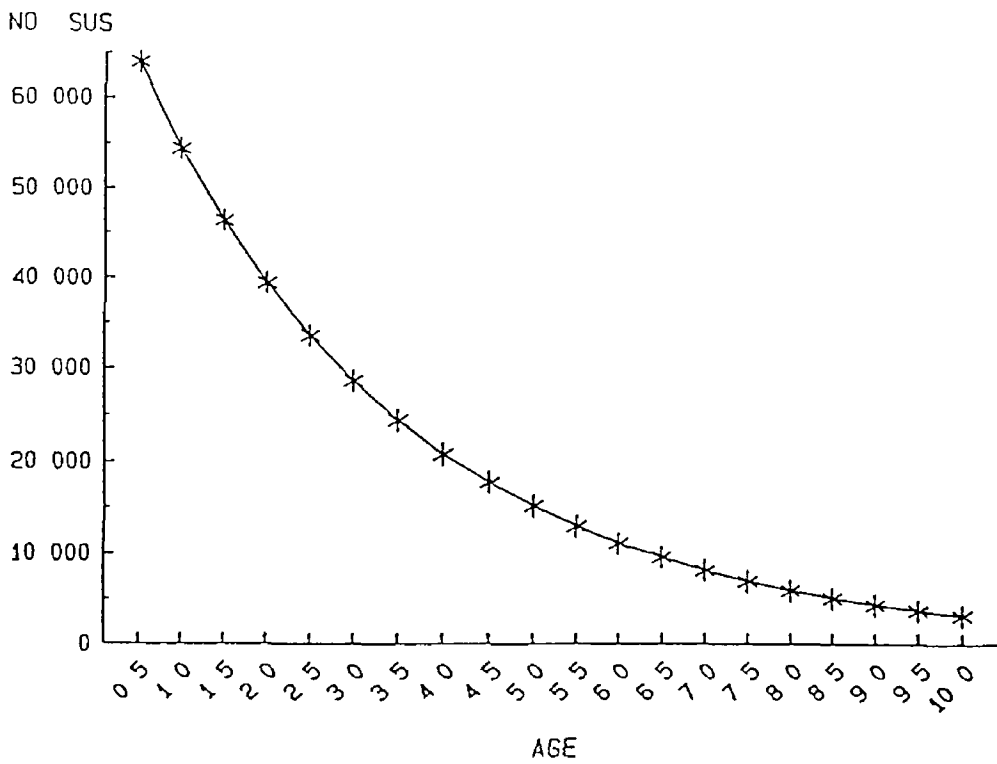
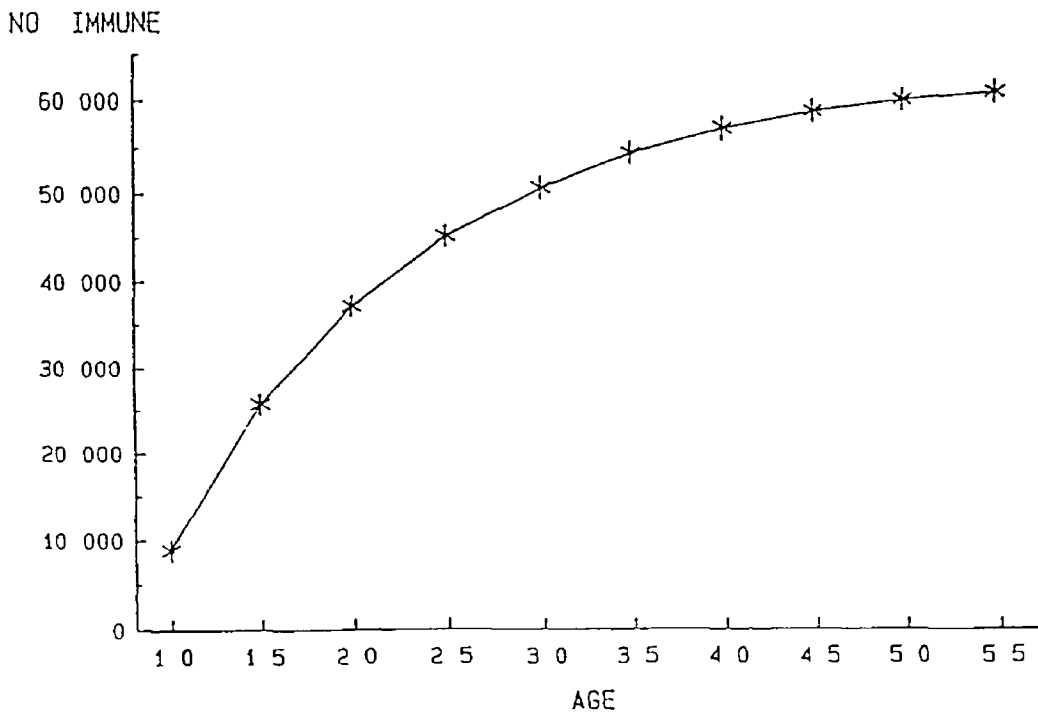


FIGURE 6 1a  
 SHOWING PLOT OF NO IMMUNE AT AGE A  
 (WHERE  $C(a) = 0$ )



- (b) Between the ages of 3 and 3.5 years there is an average of 26,000 susceptible to infection. This is a very large number when we consider the fact that the average age of infection is 3.25 years.
- (c) The number of infected is always larger than the number of infectious. This is due to the fact that the latent period is longer than the infectious period.
- (d) At each age point  $X + H + Y + Z = N$ , where  $N$  is the total population of the original cohort.

Figures (6.1) and (6.1a) show plots of the numbers susceptible at age  $a$  and numbers immune at age  $a$ . We see that there is a sharp decline in the numbers susceptible in the early years. This decrease then slows down in the older years. Similarly with the numbers of immune, these rise steadily up to the age of 6.

How then do the pre-vaccination results predicted by the model compare with the existing situation? From our sample of 145 cases we have estimates of the proportions immune and susceptible to measles infection in Ireland before the introduction of the vaccination program. The predicted proportions susceptible at age  $a$  and the sample estimates of the proportions susceptible are given in Table 6.2 below.

Table (6 2) shows the predicted and estimated proportions susceptible to measles infection in Ireland prior to the introduction of the vaccination program in October 1985

TABLE 6 2

Age a in Years	Sample Estimates	Model Estimates
2	0.6	0.61538
3	0.33	0.44661
4	0.2727	0.32493
5	0.229	0.17328

As we can see the model predictions are extremely close to those proportions estimated from the sample.

We now take the model a step further by introducing vaccination into the model. We adapt the above program to solve the system given the following initial conditions.

- (i) We start at age  $a = 1$  year as vaccinations start at the age of 15 months
- (ii) Some children will have contacted the disease between the ages of 6 months (when the maternal antibodies start to wear off) and 15 months (when immunisation starts). We therefore do not have all of the original cohort of 64,000 susceptible. We know from our predictions earlier that the force of infection acting on susceptibles from six months to

1 year gives us the following numbers of susceptible, infected, infectious and recovered and immune respectively

$$a = 1 \quad X(a) = 54,403$$

$$H(a) = 439$$

$$Y(a) = 295$$

$$Z(a) = 8,864$$

(111) $C(a) = -0.01686a^2 + 0.026743a + 0.40083$  This is estimated from the sample vaccination program discussed in chapter 5. Also  $1 \leq a \leq 6$  years.

These conditions with program (6.1) yield the following results. See Table (6.3).

TABLE 6.3

SHOW PROPORTIONS SUSCEPTIBLE TO MEASLES INFECTION  
AT AGE  $a$  GIVEN  $C(a) = \text{QUADRATIC}$

Age years	No. Susceptible	No. Immune	Proportion Susceptible
1.0	54403.0	8865.0	0.850047
1.5	37743.0	25746.2	0.589734
2.0	26357.8	37287.7	0.411841
2.5	18606.7	45144.8	0.290730
3.0	13333.7	50489.7	0.208339
3.5	9740.5	54131.7	0.152195
4.0	7284.3	56621.1	0.113818
4.5	5600.3	58327.9	0.087505
5.0	4445.0	59498.8	0.069453
5.5	3657.7	60296.7	0.057152

We now note from Table (6.3) that

(a) The numbers susceptible are decreasing at a faster

rate However, by the age 5 5 years there are still over 3,500 susceptible to measles

(b) With regard to the proportions susceptible we see that at the age of 3 years there is still almost 21% susceptible to measles. Again this is a very high percentage given that the average age at infection is 3 25 years. It would be desirable to reduce the proportion susceptible at this age considerably

TABLE 6.4

PROPORTIONS SUSCEPTIBLE BEFORE AND AFTER VACCINATION

AGE	PRE-VACCINATION PROPORTION SUS.	AGE	POST-VACCINATION PROPORTION SUS
0.5	1.00000	1 0	0 850047
1.0	0.85005	1.5	0.589734
1.5	0.72304	2.0	0 411841
2.0	0 61538	2.5	0.290730
2.5	0.52408	3.0	0 208339
3.0	0.44661	3.5	0.152195
3.5	0.38082	4.0	0.113818
4.0	0 32493	4.5	0.087505
4.5	0.27741	5.0	0.069453
5.0	0.23699	5.5	0.057152
5.5	0.20258		
6.0	0.17328		
6.5	0.14831		
7.0	0.12702		
7.5	0.10885		
8.0	0.09333		
8.5	0.08008		
9.0	0.06875		
9.5	0.05907		
10.0	0 05077		

Comparing the proportions susceptible pre and post vaccination we see in Table (6.4) and from Figure (6 2) that

(1) Vaccination reduces the proportions susceptible considerably Before vaccination 5% of the

FIGURE 6 2a  
PROPORTION SUSCEPTIBLE BEFORE VACCINATION

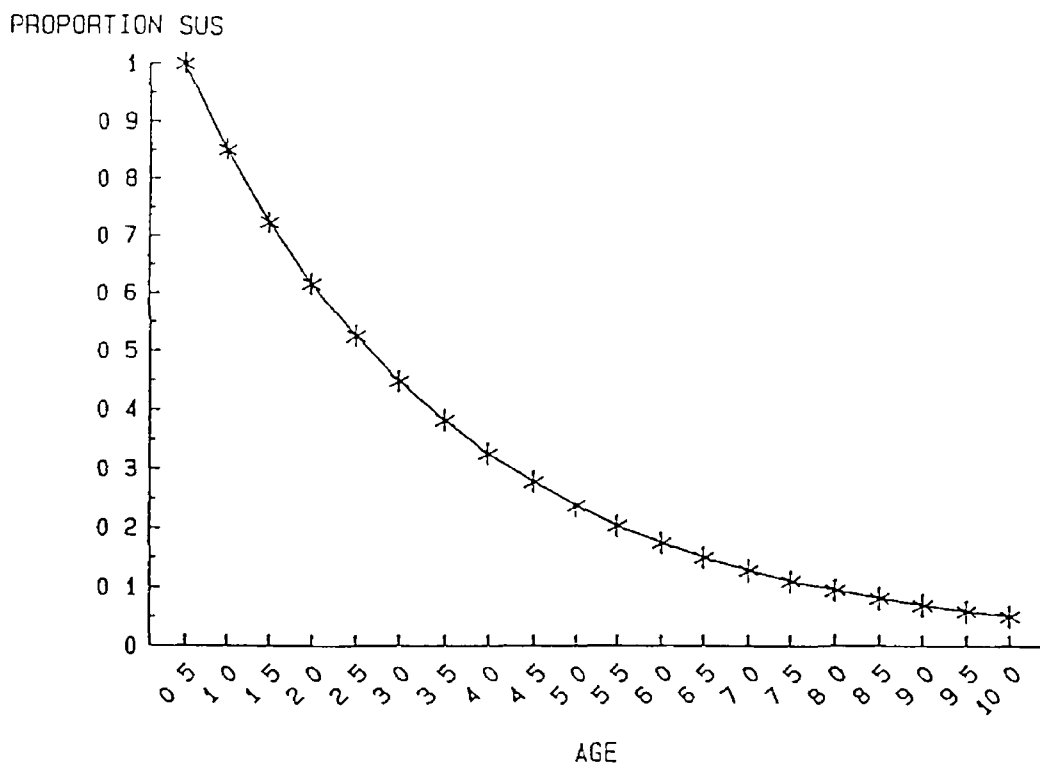
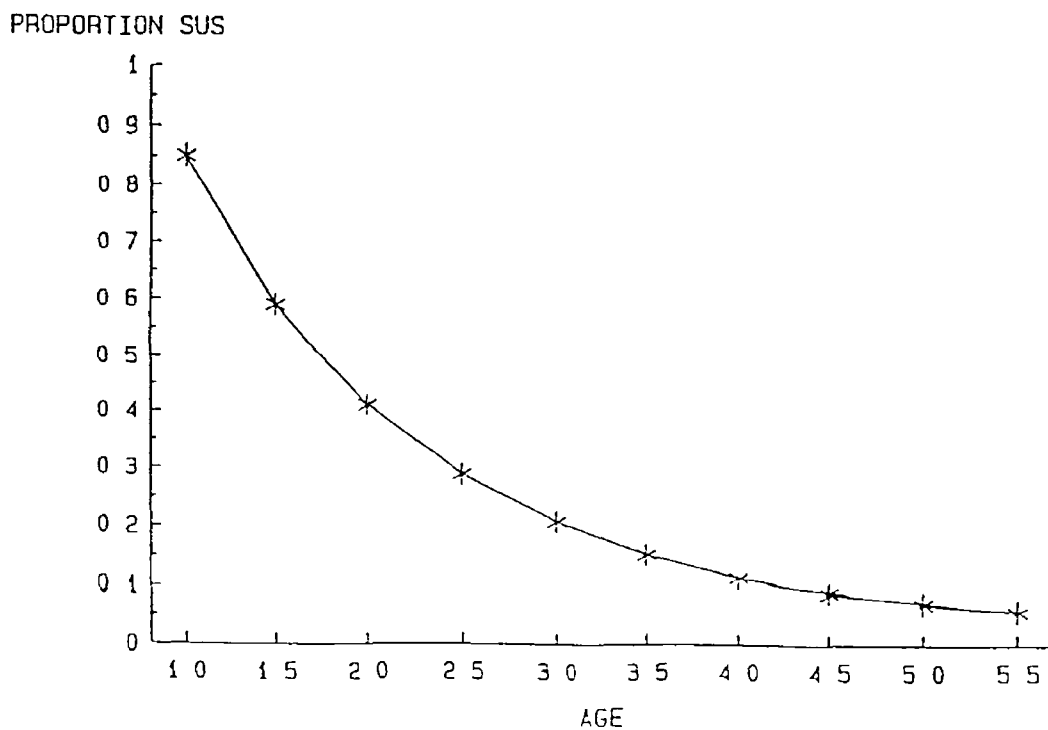


FIGURE 6 2b  
PROPORTION SUSCEPTIBLE AFTER VACCINATION



original cohort remained susceptible at the age of 10. With vaccination approximately 5% remain susceptible by the age of 5.5 years. This represents a considerable improvement.

(11) In the earlier, younger age groups we see that vaccination has reduced the number of 1.5 year olds susceptible to measles by approximately 13%, the number of 2 year olds by 20.5%, the number of 2.5 year olds by 22.5%, the number of 3 year olds by approximately 23% and the number of 3.5 year olds by 23%. These are not large improvements. The current vaccination program should be aiming to immunise the children at as young an age as possible for we have a very young average age at infection. We have seen earlier in this chapter that for the successful eradication of an infectious disease such as measles  $V < A$ .

(111) Vaccination raises the average age at infection and hence reduces  $R_0$ . As we have seen for eradication  $R_0 < 1$ . For our vaccination program to succeed we must increase our levels of coverage. The required levels for eradication are in the region of 97%.

Finally, what then should be the aims of future policy and further research? With regard to policy we should aim for

(a) Widespread immunisation with a coverage of 97% to

- (b) Immunisation at as young an age as possible, in order to ensure that the average age at vaccination is less than the average age at infection
- (c) The reduction of  $R_0$  to less than unity. If such were the case measles in Ireland would die out.
- (d) The collection and compilation of appropriate data. There is an urgent need for the collection of seriological data (by surveys with fine age stratification) and vaccination data (also with age stratification). These are very important for the interpretation of epidemiological trends in disease incidence under the given vaccination policy.

With regard to future research we have in our model made the assumption of homogeneous mixing. That is that the population mixes in a homogeneous manner, at a given point in time, each susceptible has an equal probability of encountering an infectious person. In natural communities there will be groups of individuals who are less at risk of exposure to infection than other groups. There is a need for further work on the impact of inhomogeneous mixing. Similar comments also apply to vaccination coverage, since this is rarely uniform throughout the different regions of the country. Finally, our analysis is based on measles infection, the methods, however, can be applied to the epidemiological study of a wide variety of infectious



diseases in Ireland Provided the researcher is willing to apply his mathematical skills and collect the appropriate data, many useful results can be predicted for the common infectious diseases in Ireland

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