Modeling measles in vaccinated populations

Joël Mossong

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Contents

List of Tables

List of Figures

Acknowledgments

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Finally I am most indebted to my parents for their relentless encouragement and continued support. I dedicate this thesis to them.

Declaration

This thesis is the result of original research conducted by myself unless stated in the text. The research was carried out under the supervision of Dr. David James Nokes at the University of Warwick. All sources of information and individuals who provided data sets have been fully acknowledged. No part of this thesis has been submitted for a degree at any other university.

So far one article based on chapter 4 has been published in the *American Journal of Epidemiology* (Mossong *et al.*, 1999). One article based on chapter 2 is in press and is due to appear shortly in *Epidemiology & Infection*. A third manuscript based on chapter 3 has been submitted to *Vaccine*.

Summary

This thesis focuses on a series of aspects related to measles control in vaccinated populations, particularly in view of future elimination goals from a mathematical modeling perspective.

The first investigation describes a recent measles outbreak in a vaccinated primary school population in Luxembourg and attempts to estimate the basic reproduction number during the outbreak using information from a school survey. From this, we go on to estimate the coverage that would have been necessary to prevent the outbreak.

Next, we analyze measles antibody data from vaccinated Canadian school children to investigate factors associated with seropositivity and magnitude of prevailing antibody titers using a mixed Bernoulli/log-gamma regression model. We show that age at immunization and time since vaccination are the most important determinants of the magnitude of anti-measles antibody titers in vaccinees. Highest titers are observed in children vaccinated at later ages. In absence of exposure to circulating virus and while controlling for all other significant factors, we observed that measles antibody titres decline at a mean rate of 5.6% per annum equivalent to a half life of 12 years indicating waning of humoral immunity.

The third research chapter examines the potential impact of waning of immunity from an epidemiological perspective with a simple deterministic mathematical model. Parameters for this model are estimated using regression analysis on the same Canadian serological data set. Based on a putative protective threshold titer we estimate the mean duration of vaccine-induced protection in absence of re-exposure to be 25 years. After long term absence of circulating virus, the mathematical model predicts that 80% of all seroconverted vaccinees will have titers below the protective threshold. In this case elimination of measles virus cannot be achieved by a single-dose routine vaccination strategy if the basic reproduction number in vaccinated individuals exceeds 1.24. For this reason there is a need to establish the intensity and duration of infectiousness in infected vaccinated individuals.

In the final chapter, we examine a particular strategy proposed by the WHO for elimination of measles in WHO Region Europe. We use a widely-used and tested age-structured mathematical model of measles transmission to investigate under which demographic or epidemiologic conditions the proposed strategy leads to elimination and when it is insufficient to break the chains of transmission. Furthermore, we apply these modeling techniques to show that the proposed strategy ought to be refined to take account of the fact that some countries in the WHO Region Europe in Central Asia have much higher birth rates than most Western European countries.

Abbreviations and acronyms

CI Confidence Interval

CAR Central Asian Republics

CDC Centers for Disease Control and Prevention

EIA Enzyme immunoassay

ELISA Enzyme-linked immuno-sorbent assay

HI Haemagglutination inhibition

HLA Human leukocyte antigen

IgG Immunoglobulin G

IgM Immunoglobulin M

LDL Lower detection limit

MMR Measles, mumps and rubella

NT Neutralization test

PRN Plaque reduction neutralization

SIR Susceptible Immune Recovered

SE Standard error. The standard error of a statistic is the standard deviation of the sampling distribution of that statistic.

VMMI Vaccine-modified measles infection

WAIFW Who acquires infection from whom

WHO World Health Organization

Chapter 1

Introduction: rationale and background

1.1 Introductory remarks

This first chapter aims to set the scene by giving a brief introduction to the concepts and background information which are important for modeling measles in immunized populations. It is not intended to be a comprehensive review of the published research literature of the epidemiology of measles, nor of the history of measles vaccine or vaccination policies. For this, I refer the interested reader to the excellent review by Markowitz & Katz (1998). Where necessary, further background information will be given in the introductions of the respective individual research chapters. The aims and the structure of the thesis are dealt with at the end of the chapter following the background.

1.2 Rationale

Measles, which is highly infectious viral disease, remains one of the leading causes of deaths in children globally despite the fact that a safe, inexpensive and relatively effective vaccine has existed for more than thirty years. Before the measles vaccine was first licensed (in the United States) in the 1960s, it has been estimated that around 5.7 million deaths were associated with the viral infection annually (World Health Organization, 1996b). Current estimates from the World Health Organization (WHO) suggest that around 30 million measles cases and approximately 900000 measles-related deaths occurred worldwide in 1998 (World Health Organization, 1999). The majority of this tremendous burden is shared between African and South-East Asian countries.

In those countries who have maintained high levels of immunization coverage over several decades measles-related mortality and morbidity have been enormously reduced. Some countries have even achieved elimination. Elimination refers to the fact that transmission was interrupted on a sizable geographic scale for a substantial period of time. For example, several countries in the Americas, the United Kingdom and Finland have been able to control measles due to intense vaccination efforts (often through mass campaigns) such that most new cases in these countries can be traced back to introductions from countries where measles remains endemic (Centers for Disease Control and Prevention, 1997). Based on this success, calls for global eradication (i. e. the interruption of measles on a global scale so that immunization can be stopped) have gathered momentum in recent years (World Health Organization, 1996a). Indeed, three WHO regions have set themselves targets for elimination: the Region of the Americas by 2000, the European Region by 2007 and the Eastern Mediterranean Region by 2010 (World Health Organization, 1999; Wild, 1999).

1.3 Biological, clinical and immunological characteristics

Measles is a spherical RNA virus member of the *Morbillivirus* genus in the *Paramyxoviridae* family and is closely related to the viruses of rinderpest, phocine and canine distemper and peste des petits ruminants (Markowitz & Katz, 1998). Clinical symptoms are usually overt and include high fever, malaise, conjunctivitis, coryza, cough and erythematous maculopapular rash (Markowitz & Katz, 1998). Following exposure, infected individuals incubate the virus for a period of 7 to 12 days before they become contagious. The typical measles rash appears after about 14 days after exposure and individuals are thought to cease being infectious 4 to 6 days after the appearance of the rash. The end of the rash coincides with the appearance of virus-specific immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody. The IgG antibody can persist for decades and is often used in serology as a marker of past exposure to measles infection (or immunization as shall be explained below). IgM, on the other hand, disappears a few months after infection and can therefore be used as a marker of *recent* infection. Recovery from infection is also associated with the production of interferon as well as the establishment of cellular immunity (Markowitz & Katz, 1998). Children who have experienced natural measles infection are generally thought to be immune from the disease for life.

1.4 Measles vaccine

Most currently used measles vaccine are further attenuated live measles vaccine derived from the Edmonston strain (Markowitz & Katz, 1998). The attenuation of the virulence was achieved by passaging the virus sequentially through diverse human and chicken embryo cell cultures. Although very promising results have been obtained recently

with aerosol administration of vaccine (Dilraj *et al.*, 2000), the recommended route of administration is subcutaneous injection. At least in developed countries, immunization is often combined with other live vaccines that contain attenuated rubella and mumps viruses resulting in the measles, mumps and rubella (MMR) vaccine.

Given that vaccine is a live virus, the immune response to the vaccine is thought to be very similar to that arising from natural infection, that is, immunization induces both humoral antibodies (transient IgM and persisting IgG) and cellular immunity (Markowitz & Katz, 1998). However, it is thought that vaccine-induced antibody titers are lower than those induced by natural infection and it is not clear whether boosting is required in later life to maintain protection from reinfection. This aspect will be discussed in more detail in chapter 5.

1.5 Is global eradication feasible?

Given that global eradication has been advocated, several authors have discussed the problems and merits of this goal (Hopkins *et al.*, 1982; Henderson, 1982; de Quadros *et al.*, 1998; Cutts & Steinglass, 1998; Hinman, 1999; Omar, 1999; Cutts *et al.*, 1999). First of all, eradication of measles, although possible at least theoretically because there is no known large animal reservoir for the virus (Markowitz & Katz, 1998), is thought to be be more difficult than was the case for smallpox (which was eradicated in the late 1970s) because measles is more contagious (Anderson & May, 1991). Studies have indicated that the virus can remain endemic in populations as small as 250000 persons, so that any eradication attempt must be truly on a global scale (Markowitz & Katz, 1998). Furthermore, because the virus is extremely contagious, empirical and theoretical epidemiological studies have estimated that up to 95% of the population

need to be successfully vaccinated to achieve immunity levels high enough to prevent continued transmission (Anderson & May, 1991). As a comparison only 70-75% was judged necessary for smallpox and indeed this level of coverage was achieved on a global scale in the eradication campaign in the 1960s and 1970s (Arita *et al.*, 1986). Also, symptoms of smallpox are more obvious, which coupled to its lower contagiousness allowed for a "ring-fence" vaccination approach around an index case in the later stages of the eradication campaign.

However, other challenges have been identified which could threaten elimination and these can be loosely grouped into 2 categories.

1. *Is vaccine-induced immunity really as good as immunity from natural infection?*

   Although the vaccine has been shown over and over again in the field to protect from clinical disease, it's not clear how vaccine-induced immunity compares to natural immunity in the long term. In particular, there is a concern that the lower antibody response in some vaccinees in combination with waning of vaccine-induced immunity could result in large pool of individuals susceptible to a milder form of reinfection being able to contribute to measles transmission.

2. *What age is best for vaccinating and how many doses are necessary?*

   First, young infants below 6 months of age cannot receive the currently used live vaccine because passively acquired maternal antibodies present in a high proportion of infants at this age prevent an adequate immune response. However, if vaccination is delayed too long, such that passive antibodies will have waned in all children, many are at risk from infection in early infancy with high risk of serious complications. This "optimal window" poses a serious problem in developing countries where the average age of infection can be very low (McLean

& Anderson, 1988a) and the risk of serious complications from infection at very young ages is considerable (Samb *et al.*, 1997; Burstrom *et al.*, 1995). Second, given that the vaccine is only about 90-95% effective (Markowitz & Katz, 1998), many countries have opted for a multiple (usually two) dose strategy either by giving a second dose at a certain age (usually before entering primary or secondary school) or by doing a periodical mass campaign of a given age range (also known as pulse vaccination) (Nokes & Swinton, 1995; Agur *et al.*, 1993). Hence the main question is what age is optimal and what proportion needs to be revaccinated to ensure the interruption of transmission.

It is these two aspects of measles elimination that this thesis is attempting to address. The main tool in this investigation is a series of deterministic mathematical and statistical regression models, which will be discussed in more detail in the research chapters themselves.

1.6 Structure of the thesis

This thesis is divided into one introductory chapter followed by four research chapters and a final discussion chapter.

The second chapter illustrates a situation likely to occur if an immunization policy is not optimal (in terms of question 2 raised on page 5) by describing an outbreak in an immunized primary school population in Luxembourg in 1996. A novel approach is taken to estimate the basic reproduction number during the outbreak which allows to predict which vaccination coverage would have been necessary to prevent it.

Chapter 3 looks at the various factors that influence antibody titers in an immunized school-aged population in Canada which has had little exposure to circulating virus

using a mixed Bernoulli/generalized log-gamma regression model.

Chapter 4 examines the potential impact of waning of immunity from an epidemiological perspective with a simple deterministic mathematical model and thus addresses the question of whether the difference, if it exists, between vaccine- or natural infection-induced immunity is at all relevant for measles elimination.

Chapter 5 investigates a particular elimination strategy advocated by the WHO Region Europe in view of extending it to the Central Asian Republics and gives suggestions for policy refinements.

Finally, chapter 6 aims to synthesize these findings by reviewing the major results, by suggesting directions for future research and and by emphasizing the rôle of mathematical models in infectious disease epidemiology.

Chapter 2

Analysis of a measles outbreak in a vaccinated population in Luxembourg and estimation of the basic reproduction number

2.1 Introduction

This first research chapter has essentially two aims: first it attempts to illustrate some of the issues and concepts treated in later chapters by describing a measles outbreak in a partially vaccinated school population which occurred in the spring and early summer of 1996 in Luxembourg. This particular episode occurred several years after the introduction of the measles, mumps and rubella (MMR) vaccine into the national immunization schedule primarily because vaccination coverage was too low to prevent transmission in a primary school environment, where conditions for spreading the measles virus are extremely favorable.

Apart from setting the rest of the thesis into context, the second purpose is to provide some insight into how this outbreak might have been prevented if more children had been vaccinated. The question is thus what pre-epidemic vaccination coverage would have been necessary to prevent transmission in this high-risk environment. The method for this is based on estimating the basic reproduction number of measles R_0 during the outbreak. This measure of the contagiousness of the virus in combination with estimates of vaccine efficacy can be linked to the vaccine coverage necessary to minimize the chances of a major outbreak. As far as I am aware the application of these techniques to epidemics in vaccinated populations has not been done before and as such provides novel insights into the practical issues of measles control.

The actual data collection (serology and school surveys) was initiated and conducted by a team headed by Prof. Claude Muller from the WHO Reference Center for Measles in the National Health Laboratory (Laboratoire National de Santé) in Luxembourg to whom I am very grateful for providing me with the serological and the survey data.

The structure of this chapter is as follows: first I will give some background information on the outbreak and vaccination policy in Luxembourg. The second section contains some definitions and describes the statistical methods used. A results section includes the analysis of the survey and provides estimates of vaccine coverage, vaccine efficacy as well as the basic reproduction number of measles during the outbreak. Finally, I discuss relevant issues related to the outbreak and the estimation procedure which could prove helpful to future investigators.

2.2 Background

In Luxembourg, routine vaccination with MMR vaccines was introduced in 1987. Measles control measures have in the past relied solely on routine immunizations, recommended

at the age of 15-18 months which are performed free of charge by the pædiatrician or family doctor. A second dose is now recommended at the age of 5-6 years. According to a representative survey of 6 year old school children in 1992, vaccine coverage was estimated to be 80%. A more recent survey done in 1996 of children aged 26 to 30 months has shown that coverage has increased to 91.1% (Division de la Médicine Préventive et Sociale, 1997). However, there is evidence that after the introduction of the MMR vaccine, a few medical doctors have not recommended its routine use and this has resulted in localized pockets of susceptibility in certain geographical areas.

It is in this setting that the measles outbreak occurred in the spring and early summer of 1996 based around 2 primary schools in the North of Luxembourg. In addition to the serological investigation to confirm measles infection, a questionnaire-based survey at the 2 primary schools was initiated to obtain information on the vaccination coverage and immune status of the children to be able to determine vaccine efficacy.

2.3 Methods

2.3.1 Case definition: confirmed and suspected case

Cases were classified as having typical clinical measles if their symptoms were in accordance with the Centers for Disease Control and Prevention (CDC) definition of a clinical case, i.e having a fever of $\geq 38.3^o$ C with a generalized rash lasting at least 3 days and combined with at least one of cough, coryza, or conjunctivitis. Furthermore, wherever possible, blood samples were taken from patients for confirmation of infection by specific IgM enzyme-linked immuno-sorbent assay (ELISA) (Enzygnost, Dade, Mannheim, Germany).

2.3.2 Case notification and school survey

Notifications were ascertained in several ways: A measles hot-line was setup during the outbreak and advertised to doctors for notification of suspected cases. Other cases were identified during regular visits to the schools during the outbreak or were reported by family, friends or neighbours of known cases.

Additional suspected cases, for whom no blood samples were available, were later identified from a school questionnaire distributed to all parents of children attending the 2 primary schools in Reuler and Wincrange. Parents were requested to supply information on children's history of past measles infection as well as history of measles immunization by either including a copy of a vaccine certificate or indicating the date of most recent vaccination. No data on repeat vaccination was available. Teachers agreed to collect the questionnaires and return them to the investigators.

2.3.3 Vaccine efficacy

Vaccine efficacy was estimated according to the criteria set by the World Health Organization for the field evaluation of vaccine efficacy. Vaccine efficacy was calculated separately for the cohorts in either school as well as a pooled estimate using the formula: $VE = 1 - AR_v/AR_u$. Here AR_v denotes the attack rate among vaccinated children, that is the number of cases who were vaccinated divided by the total number of vaccinated children. AR_u similarly denotes attack rates among unvaccinated children, that is the number of cases among unvaccinated children divided by the total number of unvaccinated children.

Confidence intervals for vaccine efficacy were obtained with Epi Info, Version 6 (Dean *et al.*, 1995). As case misclassification can have a significant effect on vaccine efficacy (Orenstein *et al.*, 1988), vaccine efficacy was recalculated using confirmed cases

only.

2.3.4 Inference of children's immune status

The number of immune and susceptible children before the epidemic in each school were estimated using the information parents provided from the survey.

Children at a school were considered susceptible before the epidemic if:

1. They were a case during the epidemic.

2. They had not received vaccine and they had no previous experience of measles. Since these children have come into contact with neither measles virus nor vaccine, they ought to be considered susceptible.

3. As measles vaccine does not protect 100% of vaccine recipients and because not all susceptible unvaccinated children became cases, we must also assume that not all susceptible vaccinated children were infected during this episode. Hence we have to assume that a certain fraction of vaccinees remains susceptible after the epidemic. To estimate this fraction, we assume that the proportion of susceptible vaccinees and susceptible non-vaccinees who were infected during the epidemic were identical. This is equivalent to saying that a proportion $(1 - VE)$ of all vaccinated children were considered susceptible before the epidemic.

Children were considered immune before the epidemic if:

1. They were not a case during the epidemic.

2. If they had experienced previous measles infection regardless of vaccination status.

3. A proportion VE of those vaccinated were also considered immune as explained in the previous paragraph.

It is clear that children who were susceptible before the epidemic and were not a case were also considered susceptible after the epidemic. Moreover children who were immune before the epidemic were necessarily immune after the epidemic.

2.3.5 Independence of RxC tables

Heterogeneity in RxC contingency tables was checked using either Fisher's exact test or a Monte-Carlo version of Fisher's exact test if the exact test proved to be too computationally intensive. Calculations were performed on a PC using StatXact-3, Version 3.1 (Cytel Software Company, MA). The Monte Carlo estimates of mean and 99% confidence intervals (CI) of the p-value were based on 100000 generated tables.

2.3.6 Critical vaccination coverage

The critical vaccination coverage p necessary for minimizing the chances of a major epidemic was estimated using the formula $p = (1 - 1/R_0)/VE$, where R_0, the basic reproduction number of the infection, is the average number of secondary cases due to an index case in a completely susceptible population (Anderson & May, 1991) and VE represents vaccine efficacy. Although this result stems from the analysis of deterministic models, it is nevertheless a useful reference for stochastic outbreaks.

2.3.7 Basic and effective reproduction numbers

To estimate the basic reproduction number R_0 I followed the martingale approach by Becker (1989) which uses 3 statistics of the epidemic: the final number of cases (C), the number of susceptibles before the epidemic (S) and the total community size (N). As most transmissions can be expected to occur inside the schools, we take N to be the total number of pupils at either school. The mean estimate, $\hat{R}_0$, is then given by

the formula

$$\hat{R}_0 = \frac{N-1}{C} \sum_{i=S-C+1}^{S} 1/i \tag{2.1}$$

with standard error

$$\text{s.}e.(\hat{R}_0) = \frac{N-1}{C} \sqrt{\sum_{i=S-C+1}^{S} 1/i^2 + \frac{C\hat{R}_0^{\,2}}{(N-1)^2}}. \tag{2.2}$$

The effective reproduction number R_e was simply defined to be the product of the basic reproduction number and the actual proportion of the total population which is susceptible, i. e.

$$R_e = R_0 \frac{S}{N} \tag{2.3}$$

2.3.8 Monte Carlo simulations of stochastic SIR epidemic process

The formula for the standard error of R_0 in equation 2.2 stems from the martingale central limit theorem and is an approximation when the number of susceptibles S at the start of the epidemic is "sufficiently" large (Becker, 1989). To see whether the number of susceptibles at either school is sufficient enough to make this approximation, I compared these estimates to those derived from numerical Monte Carlo simulations of a simple stochastic SIR epidemic model in an approach similar to Becker & Hasofer (1997).

This stochastic model, which describes the epidemic process in a discrete, finite and closed population of susceptibles (S), infectives (I) and recovereds (R) has two types of transition events: infections ($S \to S-1,\ I \to I+1,\ R \to R$) occur at a rate βIS, whereas recoveries ($S \to S,\ I \to I-1,\ R \to R+1$) occur at a rate νI. β and ν denote the transmission and recovery parameters, respectively, which combine to make up the basic reproduction number $R_0 = \beta(S+I+R)/\nu$ (for more details on stochastic

modeling of epidemic processes, see for example Bartlett (1956) or Bailey (1975)).

A batch of 5000 outbreaks was run with the same initial distribution of susceptibles and immunes as was found at the school of Reuler for values of R_0 ranging from 3 to 18 in steps of 0.5. The frequency distribution of the final number of cases was recorded for each value of R_0. In these simulations, the average infectious period was assumed to be 7 days and the transmission parameter was then calculated using $\beta = \nu R_0/(S+I+R)$.

2.4 Results

2.4.1 Description of the outbreak

A total of 113 suspected cases of measles were reported from March 1st to July 20th 1996 over a period of 20 weeks. 88 (77.9 %) reported cases attended primary schools in two villages (Wincrange and Reuler) in a rural area of Northern Luxembourg. Both in terms of size and class structure, the two schools were similar: 346 and 363 pupils were registered at Wincrange and Reuler, respectively, divided among 20 classes. Most of the remaining 25 cases occurred in the nearby community of the 2 schools in siblings of pupils. The distance by road between these two villages is about 13 kms (8 miles). Both primary schools take their catchment from several communes and include infant schools.

The epidemic curve in figure 2.1 shows how the outbreak started off at the primary school in Reuler before spreading into the rest of the community and eventually sparking off another epidemic at the primary school in Wincrange. It is clear that all suspected cases occurred during the main peaks and it is therefore not unlikely that these suspected cases had indeed measles. It is also interesting to note that transmission seems to have been interrupted temporarily at both schools. Although the reasons

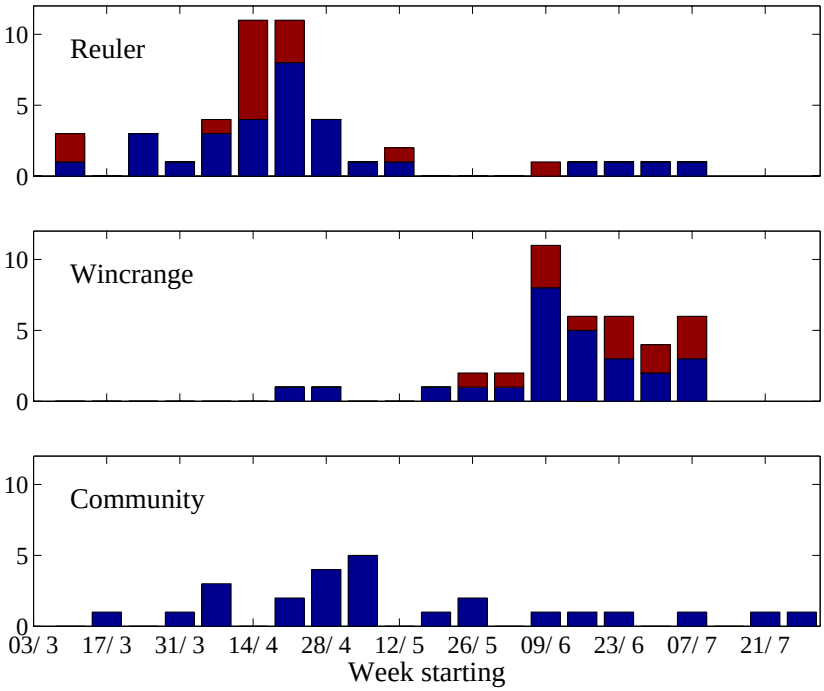


Figure 2.1: Epidemic curve with weekly number of measles cases based on onset of rash. Suspected cases are shown in red and confirmed cases in blue. The epidemic first took off at Reuler primary school before spreading to Wincrange. Measles cases who were not pupils at the schools occurred throughout the two episodes. 2 confirmed and 1 suspected measles cases in Wincrange without an exact date of onset of rash are not included in this graph.

for these interruptions are somewhat unclear, it is possible that school holidays (Easter break from 6th-21st April and Pentecost break from 26th May-5th June) have played a role. A recent study has identified that the measles virus isolated from both schools belonged in fact to the same genetic strain (Hanses *et al.*, 1999). Since the 2 schools are so geographically close, it is probable that some transmission occurred between the schools at the peak of the epidemics.

The age distribution of suspected and confirmed cases is shown in figure 2.2. No effect of age on classification of cases can be detected. The median age at infection of all reported cases was 8 years. 5 cases occurred in infants less than 2 years old and 4 cases in adults. 84 blood samples were taken from the 113 suspected cases and all

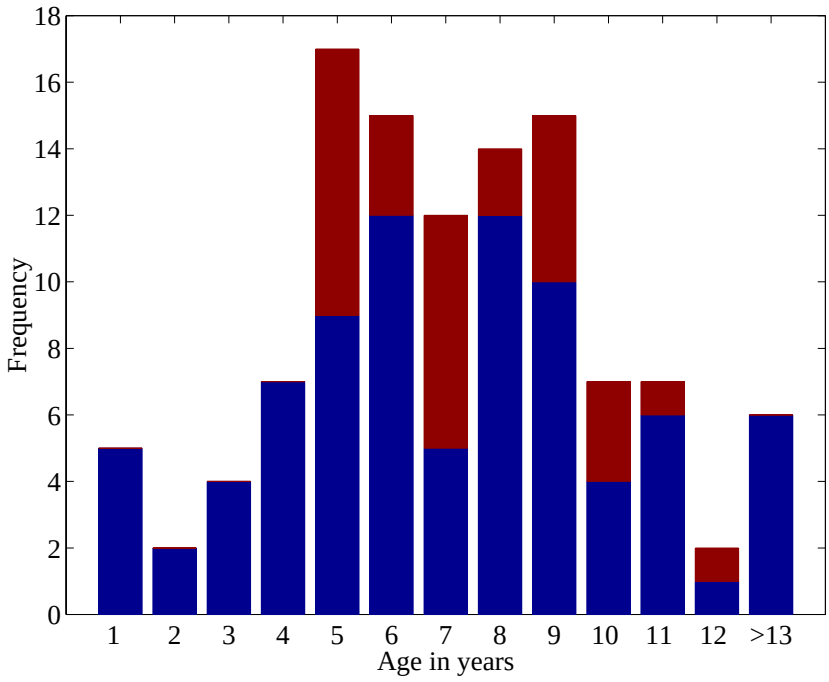


Figure 2.2: Age distribution of all 113 notified measles cases during the outbreak. Suspected cases are shown in RED and confirmed cases in BLUE.

showed evidence of recent measles infection. No blood samples were available from the other 29 suspected cases. Among the 84 serologically confirmed cases, 79 (94 %) had typical clinical measles according to the CDC case definition of clinical measles, but 5 did not meet all of the criteria. In addition 4 (4.8%) children had otitis media and 13 (15.5%) had diarrhoea. 59 (70.2%) were prescribed at least one drug by their doctor (mainly antibiotics, antipyretics or antitussiva).

Among the 8 (9.5%) confirmed cases which occurred among immunized individuals, 2 children (25%) did not have typical clinical measles compared to 3 (4%) among 76 unvaccinated cases (p=0.095). All 5 atypical cases failed to have a generalized rash lasting for at least 3 days.

	Vaccinated			
Previous case	No	Yes	Unknown	Total
No	49	207	4	260
Yes	15	10	0	25
Unknown	2	10	0	12
Total	66	227	4	297

Reuler

	Vaccinated			
Previous case	No	Yes	Unknown	Total
No	67	194	2	263
Yes	12	9	7	28
Unknown	2	8	1	11
Total	81	211	10	302

Wincrange

Table 2.1: Vaccination and infection status in survey responders in Reuler and Wincrange prior to the outbreak.

2.4.2 Post-outbreak school surveys

From the 709 pupils registered at the 2 schools, 599 (84.5%) questionnaires were returned. Either a copy of the vaccination certificate or the date of vaccination was given for 415 (94.7%) of the 438 children reportedly vaccinated.

The response rates were only marginally different between schools - 81.8 % at Reuler and 87.3 % at Wincrange (p=0.0488). Response rates were statistically different by class at either school (Reuler: p=0.014 (99% CI 0.0131-0.015); Wincrange: p=0.0024 (99% CI 0.002-0.0027)). This could be explained by the fact that some teachers might have been less conscientious about collecting questionnaires. Parents' compliance with supplying evidence of vaccination was very good: at Reuler either a copy of the vaccination certificate or the date of vaccination was given for 217 (95.6%) of the 227 vaccinated children. This figure was similarly high at Wincrange with 198 of 211 (93.8%) documented vaccinations.

Vaccination and infection status among survey responders prior to the outbreak is shown in Table 2.1. At Reuler, 25 (8.4%) survey responders had a previous history of

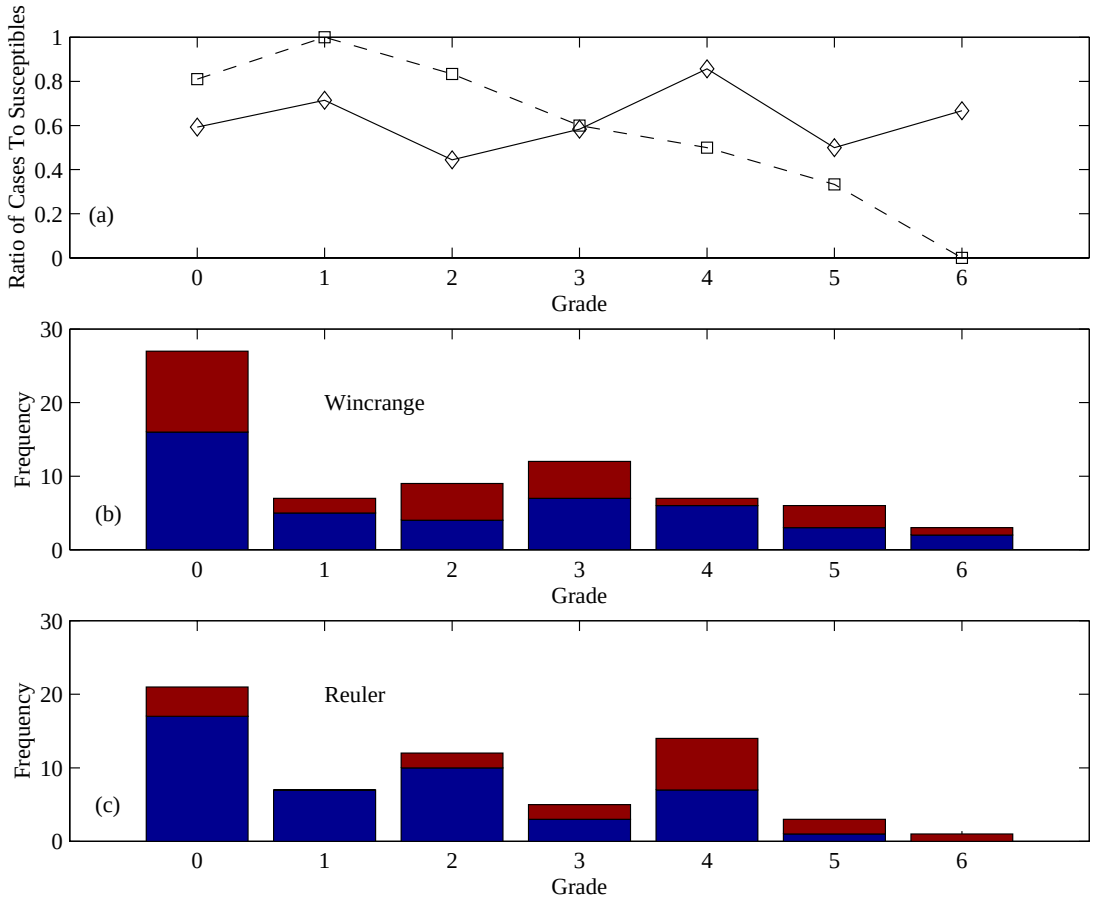


Figure 2.3: (a) Ratio of cases to susceptibles (prior to outbreak) by school grade at Wincrange (diamonds/solid line) and Reuler (squares/dashed line) among survey responder children. Grade 0 represents children at kindergarten, i. e. those aged 4 and 5 years; most children in grade 1 have 6 years, 7 years in grade 2, etc. Whereas the proportion of infected susceptibles was more or less constant in Wincrange, younger children in Reuler had a higher chance of being infected than their older schoolfriends. (b) and (c) show the total number of susceptibles (in red) and cases (in blue) after the epidemic among respondents. Here susceptible children after the epidemic refer to children who have not been vaccinated, have had no prior experience of measles before the epidemic and of course were not a case during the epidemic.

measles and 227 (76.4%) were vaccinated. At Wincrange, 28 (9.2%) gave a history of previous measles infection and 211 (69.9%) had received immunization. Inspection of the dates and ages at previous infection suggests that neither school had experienced a major outbreak in the 1990s. 49 (16.5%) of respondent children at Reuler and 67 (22.2 %) of respondent children at Wincrange were not vaccinated and had no previous experience measles and hence could be considered susceptible before the outbreak.

The actual proportion of susceptibles that were infected differed slightly between the two schools at the class level. Whereas infection rates were homogeneous at Wincrange (p=0.5369; 99% CI 0.5328-0.5410), there is a significant difference at Reuler (p=0.0197; 99% CI 0.0186-0.0208). Figure 2.3 shows this infection pattern after classes have been grouped into yearly grades indicating that higher measles transmission occurred among younger children at Reuler primary school.

2.4.3 Vaccine efficacy

At Reuler, 10 cases of measles occurred among the 217 vaccinated children, compared with 35 cases among 64 unvaccinated children yielding a vaccine efficacy of 91.6% (95% CI 83.9-95.6). At Wincrange, 2 cases were recorded among 203 vaccinated children, compared with 41 cases among 79 unvaccinated children giving an estimate of 98.1% vaccine efficacy (95% CI 92.3-99.5). By pooling the two schools together, we obtain an overall vaccine efficacy of 94.6% (95% CI 90.4-97.0), which is comparable to estimates reported in the literature from outbreaks in developed countries (Markowitz *et al.*, 1990). If we limit ourselves to only using confirmed cases for the calculation of vaccine efficacy (there were 7 confirmed cases among 420 vaccinated children and 51 confirmed cases among 145 unvaccinated children), we obtain a pooled vaccine efficacy estimate of 95.3% (95% CI 89.8-97.8), which is not significantly different from that obtained when using both suspected and confirmed cases. Thus there is little evidence that misclassifications (if they indeed existed) had any impact on estimates of vaccine efficacy.

Figure 2.4 shows vaccine efficacy and 95% confidence intervals as a function of the different grades. Although it appears that older children might have been marginally more protected than younger children, this trend could be simply explained by the

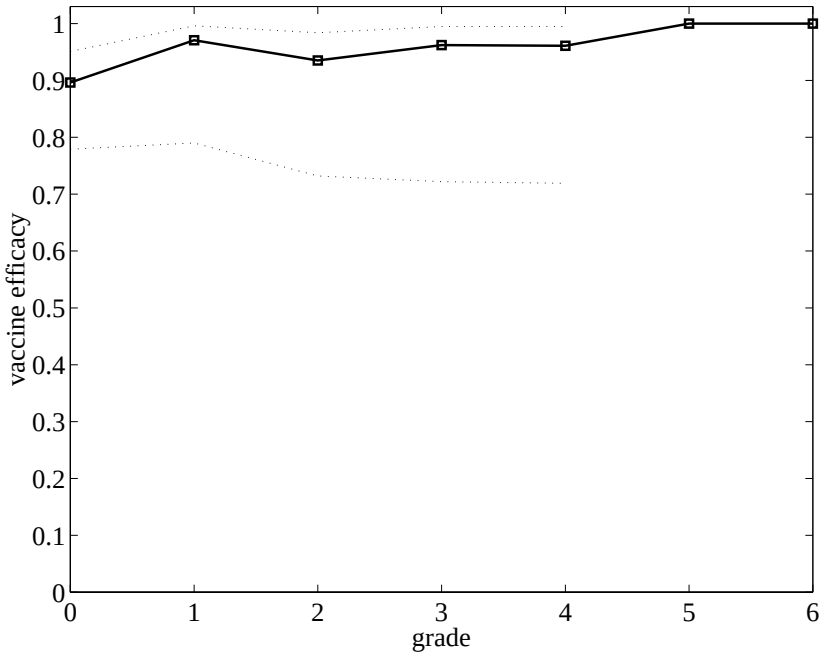


Figure 2.4: Grade-specific vaccine efficacy with 95% confidence intervals (dashed line). Although the mean estimate appears to increase with grade, the wide confidence intervals for grade 0 to 4 suggest that there is little evidence that this trend could be statistically significant.

fact that the incidence rate (i.e. the proportion of susceptibles who were infected) was higher in general among the younger children as shown in figure 2.3. Moreover, the 95% confidence region associated with these estimates in grades 0 to 4 is so wide that it can be doubted whether a trend would reach statistical significance.

2.4.4 Martingale estimates of the basic reproduction number

From the information of the survey, it is possible to estimate the immune status of the 2 school populations at Reuler and Wincrange. As shown in table 2.2, at Reuler we were able to identify 45 cases of which 10 had been vaccinated, 25 immune children who had previous experience of measles, 14 unvaccinated susceptible children, 207 vaccinated children who did not get infected during the epidemic and 72 children with unknown immune status. In addition to the 14 unvaccinated susceptible children we would also

Vaccinated?	No				Yes				Unk.	
Previous case?	No		Yes	Unk.	No		Yes	Unk.	No	Unk.
Case in 1996?	No	Yes	No	Unk.	No	Yes	No	Unk.	No	Unk.
Children	14	35	15	2	197	10	10	10	4	66
Immune Status	Sus.	Case	Imm.	Unk.	Vacc.	Case	Imm.	Vacc.	Unk.	Unk.

Reuler

Vaccinated?	No				Yes				Unk.		
Previous case?	No		Yes	Unk.	No		Yes	Unk.	No	Yes	Unk.
Case in 1996?	No	Yes	No	Unk.	No	Yes	No	Unk.	No	No	Unk.
Children	26	41	12	2	192	2	9	8	2	7	45
Immune Status	Sus.	Case	Imm.	Unk.	Vacc.	Case	Imm.	Vacc.	Unk.	Imm.	Unk.

Wincrange

Table 2.2: Extrapolation of children's immune status in Reuler and Wincrange from the survey information. 3 criteria are used to determine pupils' immune status after the epidemic: whether they were vaccinated, whether they had previous history of measles infection and whether they were a recent case in the 1996 epidemic. The immune status shown above refers to after the epidemic. The following abbreviations were used: sus. - susceptible; imm. - immune; vacc. - vaccinated; unk. - unknown immune status.

expect to have a certain fraction of vaccinated children remaining susceptible after the epidemic. Using the previously calculated estimate of vaccine efficacy of 91.6% at Reuler, we would expect 8.4% of the 217 vaccinated children which did not have previous experience of measles to be susceptible prior to the epidemic, i. e. 18 children. As only 10 of these children were indeed infected during the epidemic, the other 8 vaccinated children ought to be considered susceptible. We can thus summarize the immune status of the school population in Reuler after the epidemic as follows: 45 children were cases, 224 children were immune, 22 children were susceptible and the immune status of 72 children could not be determined. The same calculation for Wincrange with an estimate of vaccine efficacy of 98.1% yields a total of 28 susceptibles, 43 cases, 226 immunes and 49 children with unknown immune status.

If only those children with known immune status are included for the estimation of R_0, i.e. leaving out children with unknown immune status, equations 2.1-2.2 yield

estimates of R_0 of 7.1 (95% CI 4.1-10.1) at Reuler, and 6.3 (95% CI 3.6-9.1) at Wincrange. At the beginning of the epidemic, the corresponding estimates of the effective reproduction number R_e are 1.6 (95% CI 0.9-2.3) at Reuler and 1.5 (95% CI 0.9-2.2) at Wincrange, whereas at the end of the epidemic they are, respectively, 0.5 (95% CI 0.3-0.8) and 0.6 (95% CI 0.3-0.9). The low effective reproductive numbers at the start of the outbreaks could explain the relatively prolonged duration of the epidemics and might have contributed to the fact that the epidemic failed to take off the first time at Wincrange (the lower the effective reproduction number, the higher the chance of a quick fadeout after introduction).

Assuming a 95% vaccine efficacy, the estimates of the basic reproduction number above correspond to vaccine coverages of 91.6% (95% CI 81.4-95.7) at Reuler and 88.3 (95% CI 75.5-93.4) at Wincrange, respectively, which would have minimized the chance of the outbreak to occur. Note that these minimal coverage estimates are 15-20% higher than the actual vaccine coverage among responders which was 76.4% at Reuler and 69.9% at Wincrange and similarly high levels to achieve elimination have also been suggested by other authors (Anderson & May, 1991).

However, the above method for estimating R_0 is very sensitive to the distribution of susceptibles and immunes among the non-responders. Figure 2.5 shows the mean and 95% confidence limits of R_0 at the 2 schools as a function of the proportion of susceptibles among the non-responders assuming that all cases were identified during the epidemic, so that survey non-responders were either susceptible or immune. It is clear that estimates of R_0 could increase substantially if all non-responders happened to be immune.

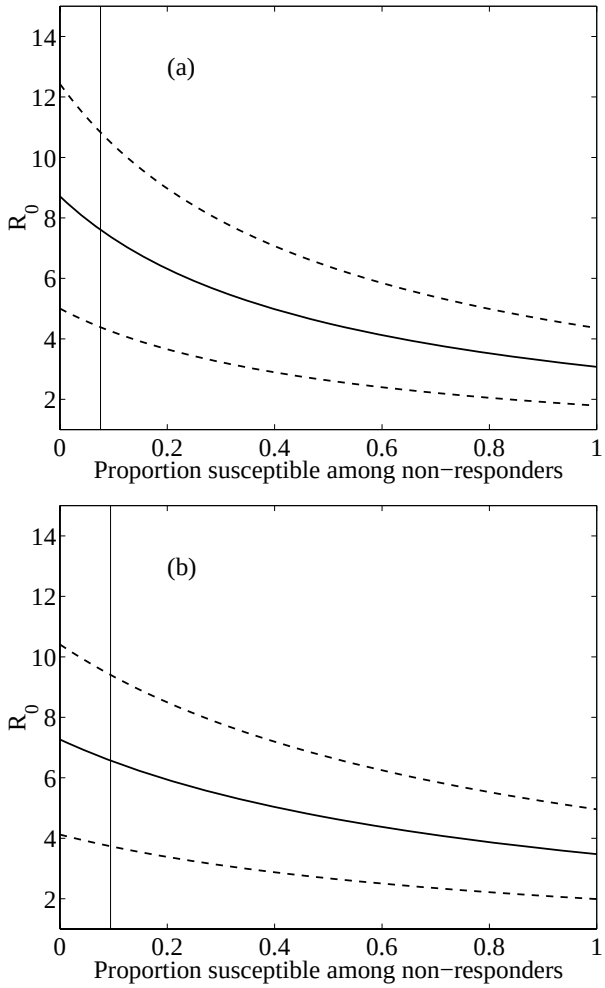


Figure 2.5: Estimates of the basic reproduction number R_0 at Reuler (a) and Wincrange (b) depend on the proportion of susceptibles among the survey non-responders. The solid line represents the mean estimate and the dotted lines the 95% confidence region for the mean. For comparison, the vertical line indicates the actual proportion of susceptibles among the survey responders at the end of the epidemic. Note that even if the proportion of susceptibles among survey responders and non-responders were identical, the mere fact of having the same final size in a larger population increases the estimates of R_0 if compared to those in section 2.4.4.

2.4.5 Comparing martingale and Monte Carlo estimates of the basic reproduction number

It is possible to compare the estimates of the martingale method with numerical output from Monte Carlo simulations of the simple stochastic SIR epidemic process in a population where the susceptibility levels were similar to those obtained from the sur-

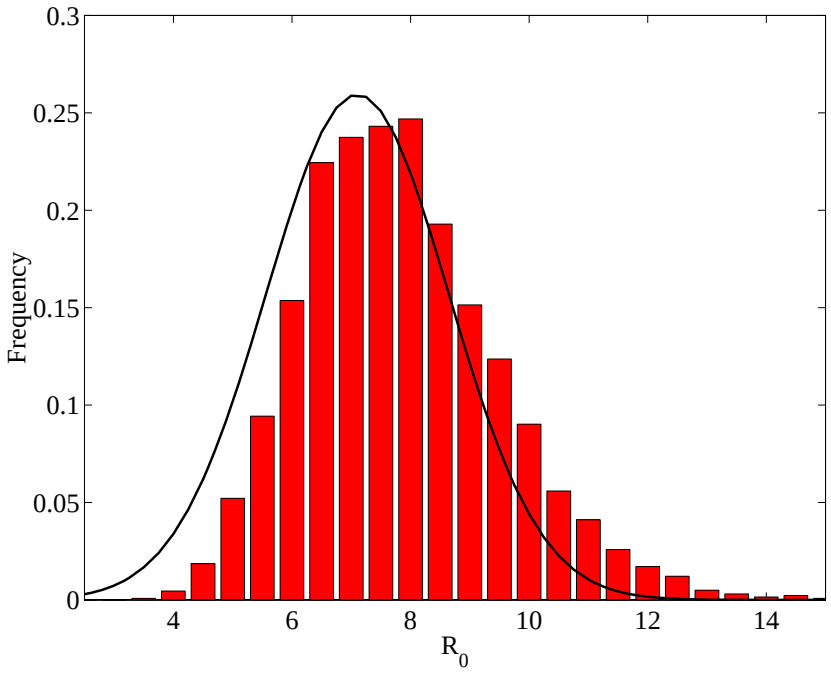


Figure 2.6: Comparison of the estimated distribution of R_0 in Reuler using the Martingale method (normal distribution in thick line) and scaled likelihood of having a final size of 45 cases in 50000 Monte Carlo simulations of a stochastic SIR epidemic process (red histogram). The starting conditions for the Monte Carlo simulations were that one infectious individual is introduced in a population of 67 susceptible and 224 immune school children.

vey estimates. The likelihood distribution of R_0 represents the proportion of the total stochastic epidemics which have a final size of 45 given that one infectious individual is introduced into a population of 67 susceptible and 224 immune children. To avoid unnecessary duplication, only the results of the simulations in Reuler are presented here, the pattern for Wincrange being identical.

Figure 2.6 shows that the distributions obtained from the Monte Carlo method and the normal approximation of the martingale method overlap considerably. Whereas the "peaks" of both distributions occur close to each other, the Monte Carlo distribution is skewed with a noticeable tail on the right hand side. This could be due to the fact that being an approximate result for large populations, the martingale method might underestimate the proportion of rapid fade-outs that occur when the initial proportion

of susceptibles is small and the effective basic reproduction number is close to one.

The main implication is that estimates of the mean and 95% confidence region using the Monte Carlo method (mean 7.8, 2.5 percentile-97.5 percentile 4.8-11.4) are somewhat greater than that of the martingale method (mean 7.1, 95% CI 4.1-10.1), particularly so for the estimate of the upper limit.

2.5 Discussion

While some developed and developing countries have been able to control or eliminate measles through intensive vaccination efforts additional to high single-dose routine coverage (eg. mass campaigns in the UK and the Americas, multidose regimes in the USA and Scandinavia), several authors (Olivé, 1997; Helwig *et al.*, 1998; Lévy-Bruhl *et al.*, 1998; Guérin & Roure, 1997) have stressed the need for all EU countries to increase coverage to target levels of 95% as recommended in the *Health for all in the year 2000* programme of WHO Europe. The epidemic we have reported herein is therefore further evidence that vaccination levels of 70-75% are insufficient to prevent outbreaks, especially in school settings.

To my knowledge, no other study has previously attempted to estimate the basic reproduction number R_0 of measles during an outbreak in a vaccinated population. Becker & Hasofer (1998) applied a related but slightly more sophisticated technique to outbreak data from a measles epidemic in a German village in 1861. They obtained an estimate of R_0 of the order of 11 (no confidence interval given). The most commonly used method to estimate the basic reproduction number R_0 relies on age-serological profiles obtained prior to the start of routine immunization rather than from outbreak data. Estimates of R_0 derived using this technique have been of the order of 15 (Anderson & May, 1991), which is roughly twice the value of the estimates herein. There

are several explanations for the apparent discrepancy between these and the estimates presented in this chapter:

1. The martingale method for estimating R_0 is very sensitive to the number of susceptibles remaining after the epidemic which might have been underestimated due to parental recall bias.

2. As indicated in Figure 2.5, both the mean estimate as well as the 95% confidence region of R_0 could increase substantially if all survey non-responders happened to be immune.

3. Similarly, as shown in section 2.4.5, estimates of the basic reproduction number and confidence region obtained from the martingale method are lower than those from the Monte Carlo simulations of a stochastic SIR epidemic process.

4. Neither method for estimating R_0 assumes heterogeneity in mixing: each child has the same probability of contacting any other child, which does not take into account the class structure of schools, nor the contact patterns among siblings. Adding heterogeneity to mathematical models in the form of variable contact rates generally has the effect of increasing the basic reproduction number.

5. The outbreaks at both schools were temporarily interrupted and this has not really been considered in the estimation method. I have investigated this complication by only counting cases which occurred during the main epidemic and found that estimates of the basic reproduction number only changed marginally, especially with respect to the wide confidence intervals.

6. I have only considered measles transmission within the schools, whereas it is certain that some transmissions have occurred outside of the school environment

(e.g. from older to younger siblings at home). These out-of-school contacts are not taken into account for our estimation purposes, but could clearly increase the basic reproduction number.

Even so, regardless of the possibility of underestimating the basic reproduction number, the estimates of R_0 generally correspond to a vaccination coverage of greater than 90% which would have been necessary to minimize the chances of an outbreak occurring.

More reliable estimates of R_0 could only be obtained if a more detailed investigation of the immune status of the whole school population and possibly their family contacts had been initiated before and after the epidemic. Whereas questionnaire-based surveys are adequate to estimate vaccine coverage and vaccine efficacy, it is possible, as Lyons *et al.* (1994) have pointed out, that we could have underestimated the proportion of immune children due to recall bias: some parents might not remember whether their child received measles vaccine or whether it had measles in the past. In fact, several studies have shown that historical information (as given by the parents) is unreliable for identifying susceptibles and with under-reporting of measles disease being the main problem, rather than false positive diagnoses (Cutts *et al.*, 1995; Scott *et al.*, 1984; Preblud *et al.*, 1982).

To improve estimates of the basic reproduction number, post-outbreak immunity should be serologically confirmed. A recently described immunoassay which relies on oral fluid samples (Nigatu *et al.*, 1999) would be suitable if blood samples cannot be obtained.

Although not statistically significant due the small sample size, the association between non-classical symptoms and vaccination has also been reported from other outbreak investigations both in developed countries (Chen *et al.*, 1990; Centers for Disease

Control and Prevention, 1999) and developing nations (Aaby *et al.*, 1986; Tayil *et al.*, 1998). Albeit vaccinated individuals tend to have a milder form of the disease, there is a growing concern, that in the long run they could make a substantial contribution to overall transmission, particularly if vaccine-induced immunity wanes in absence of exposure to wild type virus. This issue of waning of vaccine-induced immunity and its relevance from a public health perspective will be one of the central themes of the next two chapters.

Chapter 3

Modeling antibody response to measles vaccine and subsequent waning of immunity in a low exposure population

3.1 Introduction

Investigations of measles serum antibody responses are an important tool for monitoring levels of immunity in vaccinated populations. The main aim of this chapter is to investigate using regression analysis some of the factors associated with antibody response and persistence in a vaccinated population of school children who had minimal exposure to circulating wild virus. In particular it examines the phenomenon of waning of vaccine-induced antibody titers the implications of which are a central theme in chapter 4.

The first section attempts to give some background information by reviewing some

of published serological studies of antibody responses to measles vaccine and some statistical modeling issues related to this kind of assay data. The method section then briefly describes the study population, the lab methods and in more detail the statistical model. In the results section, I compare goodness of fit and parameter estimates from the different statistical models and attempt to specify the most parsimonious model of the data. The implications of these results, both from public health perspective and for the work presented in later chapters are discussed in a final section.

3.2 Background

3.2.1 Associations found in published serological studies

Previous serological studies have shown that measles antibody titers in vaccinated individuals decline in the absence of natural "booster" infections (Gustafson *et al.*, 1987; Christenson & Bottiger, 1994; Boulianne *et al.*, 1995; Davidkin & Valle, 1998; Whittle *et al.*, 1999a). Furthermore, age at vaccination and gender have been shown to have an influence on the immune response: a study in England and Wales involving 475 children who received a single dose of measles vaccine 12-18 months of age reported that titers were twofold higher in girls vaccinated after 14 months of age, whereas in boys these were intermediate and showed no age effect (Miller *et al.*, 1995). In a large vaccine safety and immunogenicity trial, at 12 months of age, children vaccinated at 8 months of age were found to have 22% higher titers than children vaccinated at 6 months of age after controlling for all other significant covariates (Moulton & Halsey, 1996).

Gans *et al.* (1998) have found that even in absence of detectable passively acquired antibodies, titers were lower in infants vaccinated at 6 months compared with those

in 9 and 12-month-old infants. They report that a developmental maturation of the immune response to measles may occur during the first year of life, which affects the immunogenicity of measles vaccine. Hayney *et al.* (1998) have reported that genetic makeup plays an important role in the antibody response: Poland (1999) and Poland *et al.* (1998) found that the allele distribution of human leukocyte antigen (HLA) - B alleles differed significantly between non-responders and hyper-responders. In particular several class I alleles were associated with non-response (HLA-B13, HLA-B44, HLA-C5) and hyper-response (HLA-B7, HLA-B51). Moreover, for the allele HLA-B7 they detected a dose-response relationship.

3.2.2 Statistical approaches for modeling quantitative assay data

The statistical analysis of antibody data is fraught with methodological difficulties. The main problem is that assays used to measure antibody concentration have a lower limit of detection, that is they are unable to detect antibodies at low concentrations. This lower detection limit (LDL) varies of course between the various assay methods: it is higher for enzyme-linked immuno-sorbent assays (ELISA) and haemagglutination inhibition (HI) assays than for the "gold standard" plaque reduction neutralization (PRN) test. Often this limitation means that tests with a high LDL are unable to distinguish between individuals with low but positive antibody concentrations and those who have no antibody present at all in their blood, which is the case when infants fail to respond to vaccine.

How are observations below the LDL to be incorporated into a statistical analysis? There are essentially two possibilities. Deleting or ignoring this data (e.g. using the argument that they are non-responders) could potentially yield biased parameter estimates placing their validity into question. Including them in the analysis, however,

poses the additional problem of how to do it. The most commonly found approach consists of assigning these observations with values, usually the LDL divided by factor of 2 or 4. It is evident that this somewhat arbitrary choice could lead to substantial bias in regression analyses or when calculating geometric means, especially if a substantial fraction of all observations are below the detection cut-off.

Fortunately, Moulton & Halsey (1996) have presented a flexible regression model which deals with censored observations (i.e. below a LDL) and the possibility of an additional population of non-responders among those individuals whose titer is also below the LDL. Moreover their approach allows for the distribution of log-transformed titers not to be normally distributed, but to display skewness (i.e. a "heavy" tail on one side of the distribution), as is often found with biological assay data.

3.3 Methods

3.3.1 Study population and laboratory methods

The study population consisted of children in kindergarten to grade nine who were in the age bracket 4 to 16 years enrolled through a two-stage cluster sampling done in each of the five health regions in the province of Newfoundland, Canada in the winter of 1994-95. Three schools were selected at random in each health region, and up to four classes within each grade were approached to enroll volunteers. Measles antibody was measured using the plaque reduction neutralization (PRN) test. The LDL of this test was 8 units such that samples with titers < 8 were classified as being undetectable.

Serum samples from a total of 1177 children were obtained. Of these, 36 (3.1%) were excluded from subsequent analyses because no date of vaccination was recorded in their official record. The present study, therefore, is based on 1141 children. Exposure to

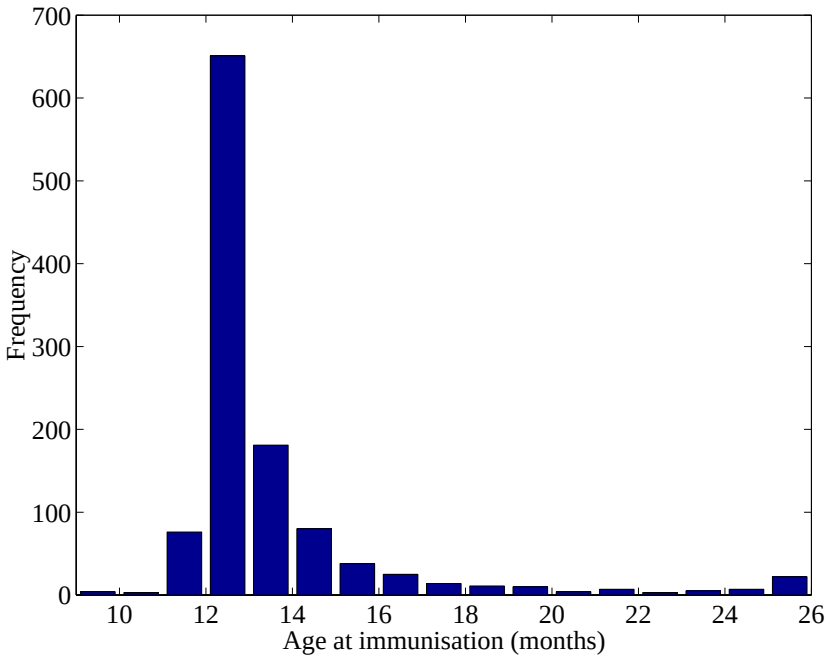


Figure 3.1: Histogram indicating age (in months) at first immunization of the 1141 children included in statistical analyses.

circulating wild virus was considered to be minimal within the Newfoundland provincial population as demonstrated by the fact that only one minor outbreak of measles was recorded between 1982 and 1996 (Ratnam *et al.*, 1996).

3.3.2 Statistical methods

The dependent outcome variable consisted of logarithm base 10 of measles PRN antibody titers. Independent variables available for the analysis were: gender (FEMALE: 1 for females, 0 for males), age at time of sample collection (AGESAM: recorded in continuous years), age at vaccination (AGEIMM: in continuous years), health district (dummy variables STJOHN, EAST, CENTRL & NORTH with health district WEST as reference), second measles immunization (SECIMM: 1 for immunized twice, 0 for immunized once) and history of prior measles infection based on parental recall (dummy variables MSLYES for positive history, MSLUNC for uncertain history *versus* absence of

Variable	Short name	Counts of dummy = 1
Sex	FEMALE	564
Health District	STJOHN	316
Health District	EAST	237
Health District	CENTRL	211
Health District	NORTH	192
Health District	WEST	185
Immunized Twice	SECIMM	45
Previously infected	MSLYES	59
Uncertain history of measles	MSLUNC	146

Table 3.1: Summary of dummy variables used in the models

reported measles as reference). The reference intercept (i.e. the constant in the model) is coded as INTERG for the log-gamma component and INTERB for the Bernoulli component. A summary of all the dummy variables including counts is shown in table 3.1. Frequency distributions of age at immunization and age at sample collection are presented in Figures 3.1 and 3.2, respectively. Most children were immunized at 12 months of age.

The data were analyzed using a mixed Bernoulli/log-gamma regression model proposed by Moulton & Halsey (1996) for the analysis of quantitative assay data. This modeling framework is highly flexible in that it incorporates: (a) the existence of a separate population of children who did not respond to measles vaccine (i.e. primary vaccine failures); (b) the LDL of antibody assays (8 PRN units for this study); (c) a flexible distributional assumption of the residuals: i.e. they can have a normal or a skewed distribution, subsequently referred to as Mixture Normal and Mixture Skewed, respectively.

There are two separate components to this particular model which is the reason it is called a "mixed" regression model:

1. The first component is called the Bernoulli component and attempts to model the

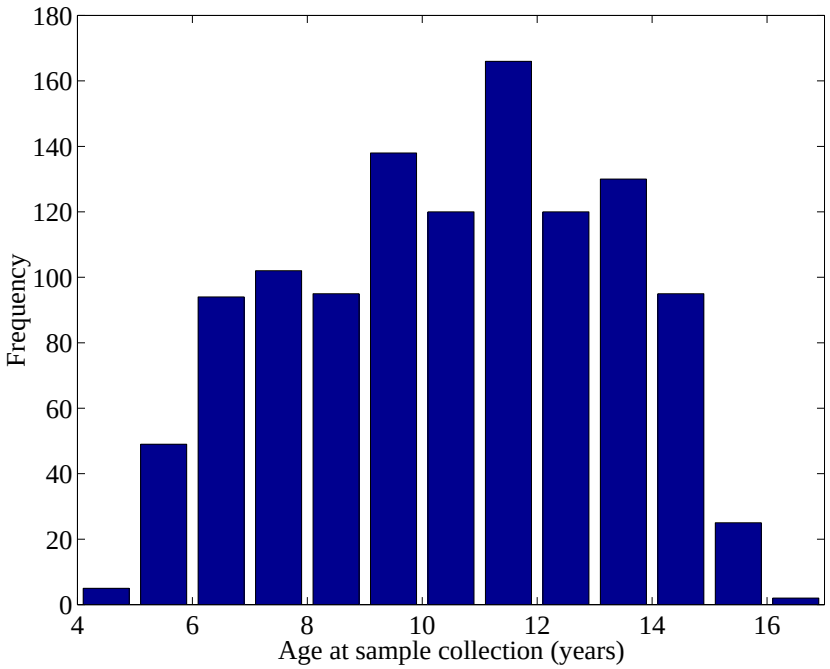


Figure 3.2: Histogram of the age of the study population (in years) at the time when serum samples were collected.

proportion of non-responders. Essentially, it is assumed that a certain proportion of children respond to vaccine and one minus that proportion do not. If children do not respond to the vaccine, one would expect them to have zero neutralizing antibody titer (after their maternal antibody titers have waned), so that their log titers are theoretically $-\infty$. So it is clear that all non-responders are expected to have titers below the LDL. However, observations below the LDL could also come the population of responders whose titer are non-zero, but just happen to lie below the LDL. This particular model solves this complication by assuming that a certain proportion of the observations below the LDL contribute to the left tail of the responder distribution (see below), whereas the rest of the observations below the LDL are simply from the non-responders. Moreover, apart from simply estimating the proportion, the modeling framework enables us to find risk factors for non-response status using a logistic regression on non-response status

as dependent variable and the set of variables described above as explanatory covariates. An alternative to the logistic link function to model the binary response status would have been a probit link function, although either approach is generally thought to yield very similar results.

2. The log-gamma component attempts to model the frequency distribution of the vaccine responders, i.e. those having a titer above the LDL. This is achieved by assuming a linear relationship between the logarithm of the neutralization titer (i.e. the dependent variable) and the explanatory variables described above (i.e. the independent variables). For the AGESAM variable, the fact that we are using the logged titers means that we are assuming an exponential decay (or increase) of the titers. Whereas in ordinary regression, the error distribution (of the log titers) is assumed to be normal, Moulton & Halsey (1996) have argued that the generalized gamma distribution is more appropriate for skewed data. In addition to estimating the spread of the errors (characterized by the parameter σ), the generalized gamma distribution also estimates its skewness (parameter δ). In fact, normality of errors corresponds to δ being 0. As such, this additional skewness parameter can be used to check the assumption of normality. More details on this particular error distribution can be found in Prentice (1974) and Farewell & Prentice (1977). Moreover, as alluded to in point 1 above, a proportion of responders could be expected to have titers below the detection limit. Even if it's not clear what their exact titers were, observations below the LDL contribute to the left tail (from $-\infty$ to the LDL) of the responder distribution.

The log likelihood function of the model proposed by Moulton & Halsey (1996) is

given by:

$$\mathcal{L}(\boldsymbol{\beta}, \boldsymbol{\gamma}, \sigma, \delta) = \sum_{i=1}^{n} \log\left(\tau_i + (1-\tau_i)F\left(\frac{\log(LDL) - \boldsymbol{x_i'\gamma}}{\sigma}\right)\right) + \sum_{i=n+1}^{N} \log\left(\frac{(1-\tau_i)f(w_i)}{\sigma}\right) \tag{3.1}$$

where the titers below the LDL are indexed from 1 to $n = 80$ and titers above the LDL from $n+1 = 81$ to $N = 1141$. $w_i = (y_i - \boldsymbol{x_i'\gamma})/\sigma$, where y_i are the log titers, $\boldsymbol{x_i}$ are the vectors of explanatory variables for the log-gamma component and $\boldsymbol{\gamma}$ is the corresponding parameter vector; σ is the parameter estimate of the square root of the residual error; f represents the probability density function of the log-gamma density function which is defined by

$$f(w) = \begin{cases} |\delta|[\exp(\delta w)/\delta^2]^{1/\delta^2} \exp[-\exp(\delta w)/\delta^2]/\Gamma(1/\delta^2) & \text{if } \delta \neq 0 \\ \exp(-w^2/2)/\sqrt{(2\pi)} & \text{if } \delta = 0 \end{cases} \tag{3.2}$$

F represents the cumulative distribution function corresponding to f and δ is the shape parameter which estimates the skewness of the error distribution. The non-reponders in the Bernoulli component are specified using the logistic model by $\tau_i = \exp(\boldsymbol{z_i'\beta})/[1+\exp(\boldsymbol{z_i'\beta})]$, where $\boldsymbol{z_i}$ is the vector of explanatory variables and $\boldsymbol{\beta}$ is the corresponding parameter vector. Thus in equation 3.1 τ_i represents the contribution of each observation i to estimating the proportion of non-responders in the population.

The results of this model is contrasted with more traditional or standard regression techniques, namely simple multiple variable regression (i.e. assuming normality of residuals but where observations below the LDL were assigned the extreme values of either 1, 8 PRN units or deleted, subsequently referred to as models "Simple 1", "Simple 8" and "Deleted", respectively) and a tobit model (often encountered in econometrics) where observations below the LDL are considered to be censored but contribute to the left tail of the normal distribution of residuals (i.e. there is no population of non-responders).

Maximum likelihood methods were employed for all model fitting using PROC NLP (SAS v6.12, SAS Institute, Cary, NC, USA) and a SAS Macro program (kindly supplied by Dr. L.H. Moulton). Good convergence was obtained using the Dual Quasi-Newton Method of maximization. Parameter estimates and standard errors were robust to initial starting values.

Model fit and adequacy of distributional assumptions were assessed by comparing log likelihood values and by inspection of residuals. Nested models were compared using the likelihood ratio test, that is the difference between two times the log likelihood of 2 nested models is compared to a χ^2 reference distribution with n degrees of freedom, where n is the difference in total number of parameters estimated of the two models compared. Preliminary screening of significance of variables was by means of t ratios utilizing approximate standard errors. Subsequent selection of variables for the most parsimonious model relied on likelihood ratio testing of nested models. 95% confidence intervals (CI) of parameter estimates are only approximate so that some of them include zero (or unity for odds ratios) although the variables are significant by the likelihood ratio test.

3.4 Results

Figure 3.3 shows the frequency distribution of the base 10 logarithm of measles antibody titers for the 1141 children included in the analyses. The distribution of the log titers above the LDL ($\log_{10}(8) = 0.903$) appears to approximate normality. However, 80 children (7.0%) failed to demonstrate a detectable PRN titer (i.e. possibly had titers below 8), raising the questions i) how could these be best classified according to their immune status, i.e. non-responders *versus* low responders and ii) how to incorporate this information in the analysis of the titers. One of the advantages of the mixture

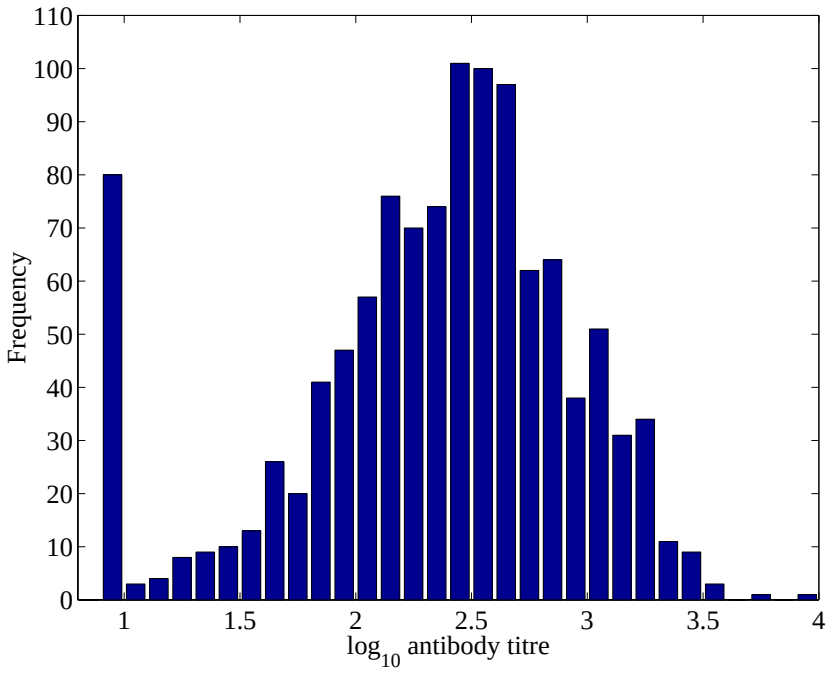


Figure 3.3: Frequency distribution of the $\log_{10}$ antibody titers of the 1141 children included in statistical analyses. The left most bar represents those titers below the LDL.

model is that it not only allows for this distinction, but provides a mechanism for estimating their relative proportions.

Table 3.2 compares the output produced by standard one-distribution regression models and the mixture models by providing parameter estimates and their approximate standard errors for maximally specified models containing all available variables but where, for purposes of comparison, the Bernoulli component which estimates the fraction of non-responders in the mixture models is estimated using the intercept (INTERB) only with no other explanatory variables.

Based on the log likelihood values, Mixture Normal and Mixture Skewed models clearly provided a significantly superior fit to any single distribution model for the addition of one and two degrees of freedom, respectively. When comparing models "Simple 1" and "Simple 8" which differ only by which value observations below the

	Model					
	Simple 1	Simple 8	Tobit	Deleted†	Mixture Normal	Mixture Skewed
Covariates						
INTERG	2.3263	2.3897	2.3722	2.5211	2.5208	2.5939
	(0.1178)	(0.0916)	(0.0382)	(0.0734)	(0.0738)	(0.0745)
FEMALE	-0.0067	0.0188	0.0124	0.0656*	0.0655*	0.0447
	(0.0458)	(0.0356)	(0.0382)	(0.0288)	(0.0290)	(0.0289)
AGESAM	-0.0193*	-0.0205*	-0.0204*	-0.0244*	-0.0245*	-0.0258*
	(0.0089)	(0.0069)	(0.0074)	(0.0055)	(0.0056)	(0.0054)
AGEIMM	0.1116*	0.1019*	0.1048*	0.0908*	0.0911*	0.0984*
	(0.0447)	(0.0347)	(0.0372)	(0.0276)	(0.0277)	(0.0284)
STJOHN	0.0551	0.0427	0.0461	0.0239	0.0243	0.0581
	(0.0716)	(0.0557)	(0.0597)	(0.0448)	(0.0451)	(0.0449)
EAST	-0.0421	-0.0199	-0.0256	0.0207	0.0206	0.0523
	(0.0771)	(0.0599)	(0.0643)	(0.0486)	(0.0489)	(0.0489)
CENTRL	0.0022	0.0138	0.0111	0.0374	0.0374	0.0550
	(0.0778)	(0.0604)	(0.0649)	(0.0489)	(0.0492)	(0.0485)
NORTH	0.0528	0.0667	0.0641	0.1026*	0.1031*	0.1233*
	(0.0796)	(0.0618)	(0.0664)	(0.0501)	(0.0504)	(0.0498)
MSLYES	0.2493*	0.1943*	0.2087*	0.1051	0.1063	0.1248*
	(0.1050)	(0.0816)	(0.0873)	(0.0643)	(0.0646)	(0.0636)
MSLUNC	-0.0100	-0.0075	-0.0078	0.0014	0.0018	0.0006
	(0.0693)	(0.0538)	(0.0578)	(0.0437)	(0.0440)	(0.0434)
SECIMM	0.2169	0.1704	0.1826	0.0949	0.0958	0.1099
	(0.1182)	(0.0919)	(0.0984)	(0.0726)	(0.0729)	(0.0719)
σ	0.7667	0.5959	0.637057	0.4643	0.4657	0.4569
	(0.0161)	(0.0125)	(0.0143)	(0.0101)	(0.0104)	(0.0108)
δ	0	0	0	0	0	0.3697
	(0)	(0)	(0)	(0)	(0)	(0.0893)
INTERB	$-\infty$	$-\infty$	$-\infty$	$-\infty$	-2.5928	-2.6267
	(0)	(0)	(0)	(0)	(0.1175)	(0.1225)
-2 * log likelihood	2631.80	2056.70	2289.34	1382.77†	1961.11	1942.60

* P-value < 0.05 shown for covariates only

† As the Deleted model uses only a subset of the complete data set its log-likelihood value cannot be compared with the other models.

Table 3.2: Comparison of mixture models and single distribution models: approximate standard errors are shown in parentheses below the parameter estimates.

LDL are assigned, it is noticeable that some model parameters varied significantly, in particular σ, the estimate of the standard deviation of the errors, thus illustrating the bias generated by the arbitrary choice of assigning values to observations below the LDL.

Further, the improvement within the mixture model by allowing for a skewed distribution of residuals was more moderate, although still highly statistically significant ($\chi^2_{1\text{d.f.}} = 18.51, p \ll 0.001$). Note that the log likelihood value for the Deleted model is not directly comparable to the other models, as it was derived from a subset of the data, i.e. only those observations above the LDL.

In terms of the significance of individual variables on preliminary screening, it is notable that in all models, age at sample collection and age at immunization were consistently statistically significant factors based on significance level of 0.05. However, considering models based on the complete data set, the magnitude of the parameter estimates and the degree of significance differed between the single distribution and mixture models. Specifically, the rate of decay by age estimated in the mixture models (AGESAM variable) is approximately 25% greater. In contrast, the parameter estimates in the Deleted model are virtually identical to those derived for the Mixture Normal model. This is a consequence of the fact that the number of observations lying below the LDL which can be attributed to non-responders is estimated as being $\exp(-2.5928)/(1+\exp(-2.5928)) * 1141 = 79.4$, i.e. virtually all 80 children were likely to be non-responders as opposed to low responders. No other variables met the criteria for significance in all models.

Table 3.3 presents the maximally specified mixed skewed model with respect to both log-gamma and Bernoulli components (Model A) and contrasts this with the most parsimonious reduced model (Model B). Models C and D are further reduced versions

Covariates	Model A		Model B		Model C		Model D		Model E	
	Log-gamma	Bernoulli	Log-gamma	Bernoulli	Log-gamma	Bernoulli	Log-gamma	Bernoulli	Log-gamma	Bernoulli
INTERCEPT	2.5836	-2.4009	2.6205	-2.7634	2.6205	-2.5851	2.6558	-2.5851	2.5077	-2.5851
	(0.0740)	(0.6493)	(0.0673)	(0.1807)	(0.0672)	(0.1164)	(0.0654)	(0.1163)	(0.0231)	(0.1160)
FEMALE	0.0490	0.4369	0.0535	0.4142	0.0535					
	(0.0287)	(0.2392)	(0.0284)	(0.2367)	(0.0284)					
AGESAM	-0.0254	-0.0209	-0.0248		-0.0248		-0.0237			
	(0.0054)	(0.0460)	(0.0052)		(0.0052)		(0.0051)			
AGEIMM	0.0961	-0.2006	0.0918		0.0918		0.0927			
	(0.0281)	(0.3095)	(0.0278)		(0.0278)		(0.0280)			
STJOHN	0.0512	-0.2573								
	(0.0445)	(0.3997)								
EAST	0.0466	0.3592								
	(0.0484)	(0.3918)								
CENTRL	0.0519	0.1978								
	(0.0482)	(0.4019)								
NORTH	0.1188	0.2260	0.0755		0.0755					
	(0.0495)	(0.4036)	(0.0380)		(0.0379)					
MSLYES	0.1186	-1.5887	0.1167	-1.5399	0.1167					
	(0.0633)	(1.0329)	(0.0626)	(1.0206)	(0.0625)					
MSLUNC	-0.0003	0.0511								
	(0.0431)	(0.3580)								
SECIMM	0.1037	-1.2460								
	(0.0716)	(1.0342)								
σ	0.4542		0.4561		0.4561		0.4580		0.4660	
	(0.0105)		(0.0103)		(0.0103)		(0.0104)		(0.0105)	
δ	0.3013		0.2778		0.2778		0.2894		0.2563	
	(0.0795)		(0.0769)		(0.0769)		(0.0760)		(0.0772)	
-2 * log likelihood	1933.89		1944.64		1951.52		1962.72		1993.29	

Table 3.3: The most parsimonious mixture skewed model: approximate standard errors of parameter estimates are shown in parentheses.

	Model A	Model B	Model C	Model D
Model B	10.75 12 d.f. p=0.5505			
Model C	17.63 15 d.f. p=0.2826	6.88 2 d.f. p=0.0321		
Model D	28.83 18 d.f. p=0.0505	18.08 5 d.f. p=0.0028	11.2 3 d.f. p=0.0107	
Model E	59.9 20 d.f. p < 0.0001	48.65 7 d.f. p < 0.0001	41.77 5 d.f. p < 0.0001	30.57 2 d.f. p < 0.0001

Table 3.4: Likelihood ratio tests beween the different nested models shown in table 3.3. The top line of each cell displays the absolute difference of 2 * log likelihood between row and column model, the second line the difference in degrees of freedom and the bottom line the associated p-value of the χ^2 distribution.

of Model B to illustrate the relative contribution to model fit of the more marginally significant variables (FEMALE, NORTH, MSLYES). Model E is the intercept only model. The two most significant variables based on the likelihood ratio test contrasting Model D and Model E are age at sample collection (AGESAM) and age at immunization (AGEIMM) ($\chi^2_{2\text{d.f.}} = 30.57, p \ll 0.001$). However, additional significant model fit is gained by the inclusion of variables FEMALE, NORTH and MSLYES in the log-gamma component (Models C *vs* D: $\chi^2_{3\text{d.f.}} = 11.2, p = 0.011$), as well FEMALE and MSLYES in the Bernoulli component (Models B *vs* C: $\chi^2_{2\text{d.f.}} = 6.88, p = 0.032$). A table of likelihood ratio tests between these different nested models is shown in table 3.4.

Table 3.5 shows the parameters of the most parsimonious reduced model B, but where the variable age at sample collection (AGESAM) is replaced by a new variable time since immunization (TIMIMM=AGESAM-AGEIMM). The definition of this new variable allows us to model the decay rate of antibody titers following immunization directly. From the comparison of this model with model B in table 3.3, we notice that

Covariates	Log-gamma	Bernoulli
INTERCEPT	2.6205	-2.7634
	(0.0670)	(0.1798)
FEMALE	0.0535	0.4142
	(0.0283)	(0.2356)
AGEIMM	0.0669	
	(0.0278)	
TIMIMM	-0.0248	
	(0.0052)	
NORTH	0.0755	
	(0.0378)	
MSLYES	0.1167	-1.5424
	(0.0623)	(1.0162)
σ	0.4561	
	(0.0103)	
δ	0.2778	
	(0.0765)	
-2 * log likelihood	1944.64	

Table 3.5: The most parsimonious skewed model where the variable AGESAM has been replaced by the variable TIMIMM=AGESAM-AGEIMM. Standard errors are shown in parentheses.

the parameter estimate of age at immunization AGEIMM decreases by 30% whereas all other parameter estimates are very similar. This difference can be explained by the fact AGEIMM and AGESAM are positively correlated (Spearman's rank correlation coefficient $\rho = 0.0981$, $p = 0.0009$), i. e. children who were vaccinated at an older age must also be relatively older at sample collection. Note on the other hand that the new variable time since immunization (TIMEIMM) and age at immunization (AGEIMM) are no longer correlated (Spearman's rank correlation coefficient $\rho = 0.0221$, $p = 0.4567$). This suggests that TIMEIMM rather than AGESAM is more appropriate as an independent explanatory variable.

Figure 3.4 shows the distribution of the standardized residuals of titers above the LDL from the fit of Model B, together with the expected distribution from the log-gamma curve with $\delta = 0.2778$ indicating a good model fit.

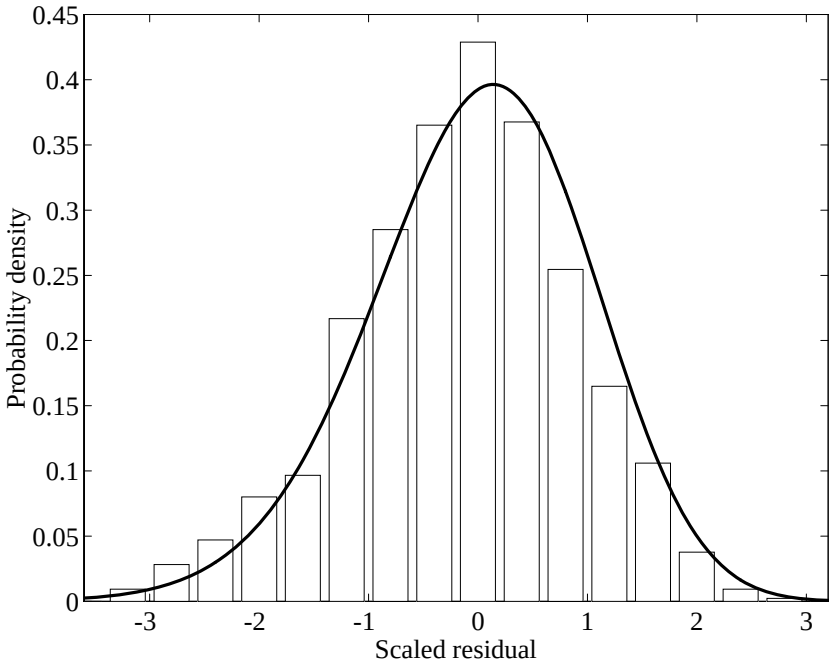


Figure 3.4: Comparison between the frequency distribution of the standardized residuals (in bars) from the fit of the most parsimonious mixture-skewed model (model B in table 2) and the estimated log-gamma density distribution (thick line) indicating a good model fit. Only residuals of titers above the detection limit are included for the histogram.

Based on the parameter estimates of the most parsimonious in Table 3.5, measles antibody titers decay at an average rate equivalent to a reduction of $1-10^{-0.0248} = 5.6\%$ per annum (approx. 95% CI; $3.3-7.7$). Further, there is a detectable linear relationship with respect to age at immunization such that the average increase in titer of an infant who responds to vaccination gained by delaying vaccination from 12 months to 18 months of age is $10^{0.0669/2} - 1 = 8.0\%$ (approx. 95% CI; $1.4 - 15.0$).

With respect to other variables estimated by this most parsimonious model, it is of interest to note that although girls are on average one and a half times more likely to be non-responders than boys (odds ratio= 1.51; approx. 95% CI; $0.95-2.41$), girls who did respond to vaccination possess an average titer 13.1% higher than boys (approx. 95% CI; -0.5 – 28.6). Not unexpectedly, children who were reported to have had a

history of measles were nearly five times less likely to be classified as non-responders (odds ratio= 4.68; approx. 95% CI; $0.64 - 34.3$) and exhibited average titers 30.8% (approx. 95% CI; $-1.4 - 73.5$) higher than children with an uncertain or no history of measles. Finally, children from the northern health district exhibited average titers 19.0% (approx. 95% CI; $0.24 - 41.2$) higher than children from all other health districts combined, controlling for other significant variables.

3.5 Discussion

The similarity of the parameter estimates from the log-normal mixture model and the deleted model may be a unique feature of this particular data set. One possible explanation for this is that the PRN assay used for measuring antibody titers is highly specific and sensitive so that virtually all observations below the LDL were true negatives. As most other studies on large populations rely on less work- and time-consuming serological methods of lesser specificity and sensitivity (eg. HI or ELISA), simply deleting observations below the LDL or assigning to them an arbitrary value cannot be recommended in general. An additional strength of the mixture modeling method is that it provides a mechanism of simultaneously assessing those factors associated with whether or not an individual exhibits a detectable response to vaccination as well as those associated with the magnitude of this response.

An important finding of this study is that antibody titers were subject to substantial waning following immunization, at an estimated rate of 5.6% per annum which corresponds to a half-life of approximately 12 years. This poses the question of how long vaccinated children are protected from measles infection and whether it might be necessary to give a booster vaccination later in life to keep up individual and *inter alia* herd immunity in absence of exposure to wild virus. The relative importance of boost-

ing of titers, either through natural infection or through immunization, for maintaining protective immunity needs to be investigated further.

The question remains open to what extent vaccine-induced antibodies against measles virus measured in sera correlate with protection against either clinical, mild or asymptomatic infection. Whereas children with high antibody levels seem to be completely protected against clinical disease, children with low or intermediate titers are more susceptible to either mild or clinical infection (Chen *et al.*, 1990). Hence, large population-based serological studies measuring antibody levels before and after large outbreaks are required to elucidate and quantify the relationship between antibody levels and protection from infection.

In addition, the work presented in this chapter indicates that age at immunization is a significant factor associated with the magnitude of vaccine-induced antibody titers. In particular, vaccination at an older age tends to increase the antibody response, although it is not possible with the current analysis framework to detect if this effect stops after a certain age. A biological explanation for this could be that the immune system of older children is more mature and they therefore develop higher and possibly longer-lasting antibody levels. This finding is agreement with previous work (Moulton & Halsey, 1996; Gans *et al.*, 1998) and suggests that a delay of immunization could be beneficial in terms of magnitude of antibody levels. However this potential individual benefit ought to be carefully balanced against the additional risk of complications which arise if children acquire measles infection before they are due to receive the vaccine. This is especially a cause of concern in infants of vaccinated mothers whose passively acquired immunity has been shown to decay faster than those of infants born to mothers with experience of natural infection (de Francisco *et al.*, 1998; Brugha *et al.*, 1996; Markowitz *et al.*, 1996). The relative benefit gained in terms of magnitude and duration of protection

versus the potentially serious effect of an accumulation of a pool of young susceptibles must be evaluated at the population level.

Moreover, the parameter estimates derived herein will be used for calibrating a mathematical model which attempts to account for the potential contribution of subclinical infection in vaccinees to measles transmission in vaccinated populations which is the subject of the following chapter.

Chapter 4

Modeling the impact of subclinical measles transmission in vaccinated populations

4.1 Introduction

One of the main findings of the analysis in the previous chapter is that, unless immunized individuals get re-exposed, their antibody titers can be expected to wane after they have received the vaccine. The main thrust of this chapter is to see whether or not this noticeable waning of immunity might be of epidemiological relevance, if individuals with low antibody titers are susceptible to a mild vaccine-modified infection which would enable them to transmit the virus. The tool for doing this analysis is a simple deterministic mathematical model which attempts to describe the important aspects of subclinical measles transmission in a vaccinated population.

The first section of this chapter presents some background material about vaccine-derived immunity, boosting responses, subclinical infection and their relation to previ-

ous mathematical modeling. The methods section describes the mathematical model in more detail and how the data presented in chapter 3 can be utilized for estimating some model parameters. Next, a stability analysis identifies the important parameters and the results from the regression analysis are presented along with a prediction of how long vaccinated individuals might stay protected. The final section addresses the implications of these results and gives recommendations for future research.

4.2 Background

Several studies have shown that measles epidemics can occur even in highly vaccinated populations (Shasby *et al.*, 1977; Gustafson *et al.*, 1987; Nkowane *et al.*, 1987; Pedersen *et al.*, 1989). A variety of factors are likely to contribute to this observation including failure to seroconvert and waning of vaccine-induced immunity (Boulianne *et al.*, 1995). It is well documented from outbreak investigations that current measles vaccines protect between 90-95 percent of vaccinees from typical measles in developed countries (Nkowane *et al.*, 1987; Farrington, 1992; Markowitz *et al.*, 1990; Miller, 1987). However, evidence is accumulating which suggests that vaccine-derived immunity might be somewhat less protective than previously assumed. There is a growing concern that among individuals who have responded to vaccine, a substantial proportion are or will become susceptible to clinical (symptomatic) or subclinical (asymptomatic) infection. I adopt the terminology of Edmonson *et al.* (1990) of vaccine-modified measles infection (VMMI) to indicate any measles infections occurring in individuals who have seroconverted upon immunization. Although VMMI can occasionally result in full-blown clinical disease (i.e. secondary vaccine failures) especially after intensive exposure (Paunio *et al.*, 1998; Centers for Disease Control and Prevention, 1999), the majority of infections in vaccinated individuals are thought to be mild or subclinical (Helfand *et al.*,

1998; Chen *et al.*, 1990; Huiss *et al.*, 1997; Whittle *et al.*, 1999b). It is the estimation of the potential contribution towards overall measles transmission from these individuals who experience VMMIs which forms the basis of this study.

The evidence for this distinct group of vaccinated individuals comes from outbreak studies describing a boosting of measles-specific antibody titers in exposed vaccinees who do not show the full range of typical symptoms associated with measles infection (Chen *et al.*, 1990; Pedersen *et al.*, 1989; Bin *et al.*, 1991; Huiss *et al.*, 1997; Wild, 1999; Lisse *et al.*, 1998) (for the CDC criteria, see section 2.3.1 page 10). By definition such immunized individuals have some pre-exposure antibodies, and in general this is found to be of low level. Boosting does not generally occur in individuals with high neutralizing antibody titers (Huiss *et al.*, 1997; Muller *et al.*, 1996; Chen *et al.*, 1990). There is probably no precise range in antibody level within which individuals will experience a VMMI following exposure, below which individuals are fully susceptible and above which they are fully immune. Nevertheless, various authors have given approximate guidelines for this range (Muller *et al.*, 1996; Chen *et al.*, 1990; Huiss *et al.*, 1997; Cox *et al.*, 1998) from which it is possible to estimate the prevalence of individuals susceptible to VMMI as illustrated in Table 4.1. These estimates are typically two to six fold higher than those derived from previous vaccine-efficacy studies in which efficacy is usually determined by protection against overt clinical disease (see Markowitz *et al.*, 1990).

Although it is generally accepted that immunized individuals who develop typical clinical measles following exposure (i.e. vaccine failures) are able to shed and transmit measles virus, it is currently unclear to what extent, if at all, individuals with a milder or subclinical form of VMMI can also be infectious (Chen *et al.*, 1990; Christenson & Bottiger, 1994; Miller *et al.*, 1995; Ratnam *et al.*, 1996; Damien *et al.*, 1998; Whittle

Source	(%) susceptible	Sample size	Age range	Assay	Susceptibility criteria	Country
Cox *et al.*, 1998*	30	306	9 m.-15 y.	EIA	≥ 50 & ≤ 255 mIU/ml	Brazil
Damien *et al.*, 1997	33	368	11-15 y.	HI, NT & ELISA	†	Luxembourg
Ratnam *et al.*, 1996	28	1075	5-17 y.	PRN	≤ 120	Canada
Boulianne *et al.*, 1995	19	468	6-7 y.	PRN	≤ 120	Canada
Miller *et al.*, 1995	31	475	4-6 y.	PRN	≤ 200 mIU/ml	England
Christenson *et al.*, 1994	19	332	12 y.	ELISA	≤ 0.3	Sweden

* Not all individuals in this study were vaccinated, although this age group had direct experience of high levels of routine and campaign vaccination.

† ELISA Enzygnost IgG$\leq$870 mOD_{450}, NT$\leq$250 mIU/ml and HI$\leq$1:128.

Table 4.1: Estimated prevalence of susceptibility to either clinical or sub-clinical re-infection in vaccinated populations.

et al., 1999b; Wittler *et al.*, 1991; Bennett *et al.*, 1999). Even if this type of vaccine-modified infection might not be of importance from a clinician's point of view (because it might not cause substantial disease), it could be of crucial relevance from a public health and epidemiological perspective by having an effect on overall levels of measles transmission.

In this chapter the potential impact of VMMIs on persistence of measles virus is investigated using a simple mathematical model of measles transmission in a large vaccinated population. One of the main aims is to analyze how different degrees of vaccine-modified transmission could affect the critical vaccine coverage necessary for elimination and prevention of future epidemics. This model differs from the standard SIR (susceptible-infected-recovered) model (see Anderson & May, 1991) in two important aspects. First, it is assumed that not all individuals who respond to vaccination are protected from developing VMMI. Vaccine responders are divided into three groups according to the degree of protection conferred by their vaccine-induced immune response: 1) those unprotected from and immediately susceptible to VMMI (weak response); 2) those temporarily protected, but who become susceptible to VMMI due to waning of vaccine-induced immunity (intermediate response); 3) those permanently protected from VMMI (strong response).

This 3-way stratification is based on the empirical evidence that: 1) levels of antibody following immunization show a substantial degree of variation which may be an indication that they confer different levels of protection: whereas higher titers have been shown to correlate with full immunity, lower titers might only protect from full-blown illness but not necessarily mild or subclinical infection (Chen *et al.*, 1990); 2) In absence of circulating natural infection in the population, antibody titers have been shown to decrease gradually after immunization as shown in chapter 3 and in other

studies (Christenson & Bottiger, 1994; Ratnam *et al.*, 1996; Davidkin & Valle, 1998).

The second major difference between this modeling framework and the standard SIR approach is that vaccinated individuals with VMMI are assumed to be less infectious, on average, than unvaccinated individuals with classical measles. This is incorporated into the model by taking their average duration of infectiousness to be less than that of unvaccinated measles cases. This reduced infectiousness is based on the observation that symptoms in vaccinated individuals—if they occur at all—generally tend to be milder and of shorter duration than those in unvaccinated individuals (Aaby *et al.*, 1986; Nkowane *et al.*, 1987; Chen *et al.*, 1990; Edmonson *et al.*, 1990; Kawamoto *et al.*, 1995). Hence it is assumed that duration of symptoms and duration of infectiousness correlate to some degree.

4.3 Methods

4.3.1 Structure of the mathematical model

I consider a simple deterministic compartmental model with the standard assumptions of measles transmission in a large homogeneous population subject to a routine vaccination programme. By taking the birth rate μ equal to the overall death rate, the total population is assumed to be constant which is a valid approximation of the demographic situation of a developed nation (Anderson & May, 1991).

As shown in figure 4.1 the population is divided into 6 classes depending on their immune and vaccination status: susceptible to classical measles infection (X_c), susceptible to VMMI (X_v), infectious due to classical infection (Y_c), infectious due to VMMI (Y_v), permanently immune and resistant to re-infection (Z) and temporarily protected from VMMI (W) but experiencing waning of vaccine-induced immunity at a constant

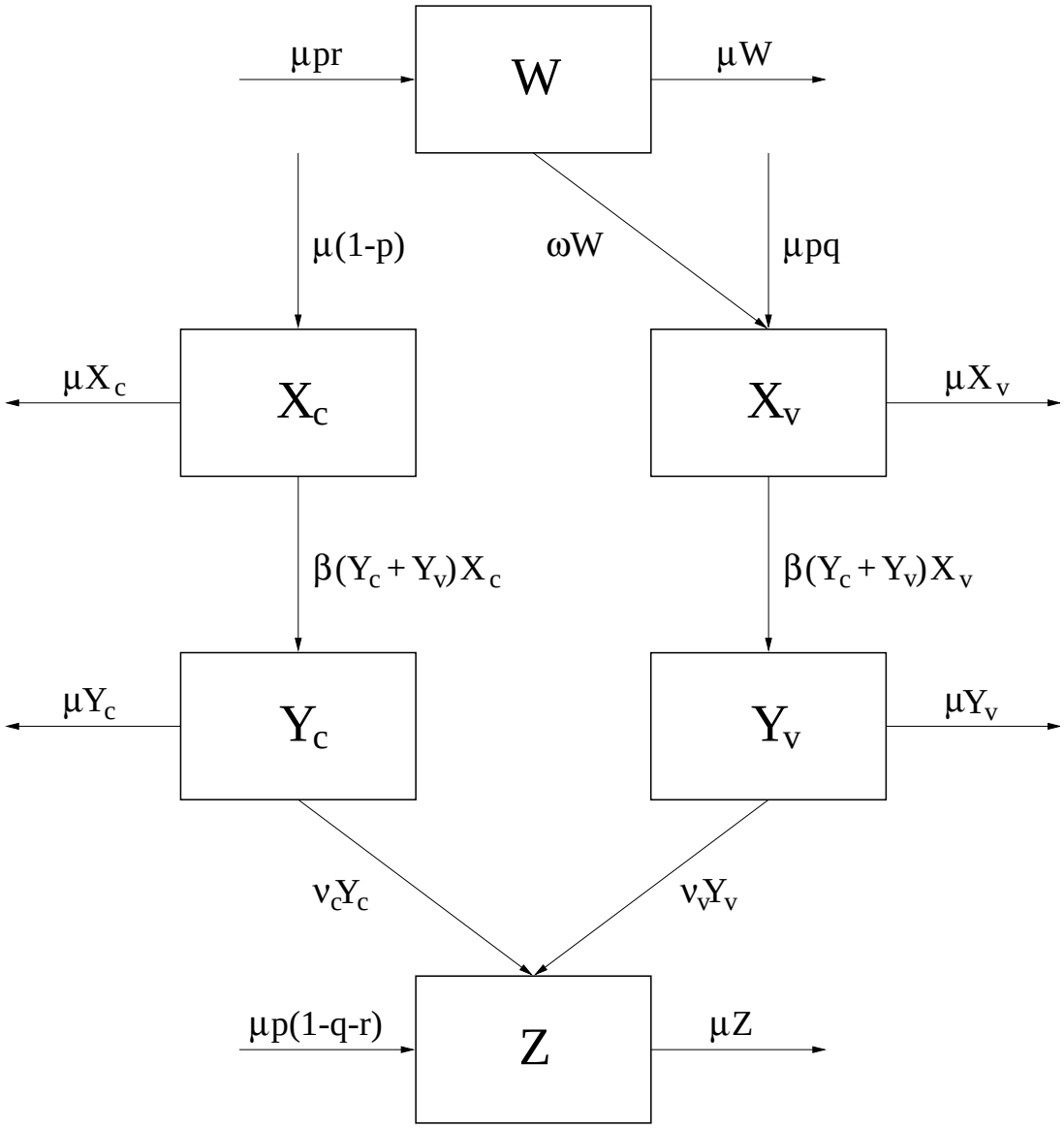


Figure 4.1: Model structure: The model describes transitions among 6 classes of individuals: susceptible to classical infection (X_c), individuals with classical infection (Y_c), susceptible to VMMI (X_v), individuals with vaccine-modified infection (Y_v), completely resistant (immune) individuals (Z) and vaccinated individuals who are temporarily protected from vaccine-modified infection but experience gradual waning of vaccine-derived immunity (W).

rate.

For the purpose of this model, routine vaccination is implemented by inoculating infants at birth. Although children usually receive their first dose of vaccine at 12-18 months in industrialized countries, the assumption of vaccinating children at birth has

symbol	immune response to vaccine	degree of protection from vaccine-modified infection	fraction
X_v	low	none	q
W	intermediate	temporary	r
Z	high	permanent	$1-q-r$

Table 4.2: Stratification of vaccinees according to their immune response and resulting degrees of protection.

no impact on model results. A proportion p of the children from each birth-cohort are vaccinated and seroconvert (i.e. "take"). The remaining proportion $1-p$ of children enter the class X_c and are considered to be susceptible to classical measles infection either because they were not vaccinated or because they failed to respond to the vaccine (primary vaccine failure).

Individuals who respond to the vaccine are stratified according to the level of protection conferred by their immune response (see table 4.2). First, it is assumed that a proportion q of vaccinees have a weak immune response to the vaccine which makes them immediately susceptible to VMMI (they enter class X_v). Next, a fraction r of vaccinees who have an intermediate immune response enter class W. They are taken to be temporarily protected but will become susceptible to VMMI at a constant rate as a result of waning of vaccine-induced immunity (they move from class W to X_v). Finally, the remaining fraction $(1-q-r)$ are assumed to develop a strong immune response similar to those unvaccinated individuals following classical measles and are taken to be permanently protected from VMMI.

For reasons of mathematical convenience no difference is made between suscepti-

bility to infection of unvaccinated (X_c) and vaccinated (X_v) susceptible individuals as well as no difference in infectivity. Both types of susceptibles have the same probability of being infected and each type of infective has the same probability of infecting either type of susceptible. For reasons explained above, the mean duration of infectiousness of the VMMI, $1/\nu_v$, is assumed to be less than that of the classical infection, $1/\nu_c$.

Transmissions occur according to the mass action law with parameter β (Anderson & May, 1991). I chose not to incorporate any effects of waning immunity following either natural infection or VMMI (i.e. individuals in Z remain there until death) and I consider only waning of immunity following vaccination. Although waning of natural immunity can be important in the context of vaccination (Rouderfer *et al.*, 1994), this aspect as well as effects of maternal antibodies, latency, age-structure and spatial heterogeneity are not considered for analytical tractability.

The above model assumptions can be written as a system of 5 ordinary differential equations:

$$dX_c/dt = \mu(1-p) - \beta(Y_c + Y_v)X_c - \mu X_c \tag{4.1}$$

$$dY_c/dt = \beta(Y_c + Y_v)X_c - (\mu + \nu_c)Y_c \tag{4.2}$$

$$dX_v/dt = \mu pq + \omega W - \beta(Y_c + Y_v)X_v - \mu X_v \tag{4.3}$$

$$dY_v/dt = \beta(Y_c + Y_v)X_v - (\mu + \nu_v)Y_v \tag{4.4}$$

$$dW/dt = \mu pr - \omega W - \mu W \tag{4.5}$$

The quantities X_c, Y_c, X_v, Y_v, W and Z represent the fractions in the total population of the different types of individuals described above. β is the transmission coefficient (Anderson & May, 1991), ν_c and ν_v are the recovery rates from classical measles and VMMI respectively, and ω is the rate at which temporarily protected vaccinees W lose their immunity and become susceptible to VMMI. Note that no equation

for the resistant class Z is necessary as it can be obtained from the fact that the total population density is kept constant: $Z(t) = 1 - X_c(t) - Y_c(t) - X_v(t) - Y_v(t) - W(t)$.

The long-term behaviour of the model is obtained by first calculating the steady-states (by putting all time derivatives equal to 0 in equations 4.1-4.5) and then by determining their stability to small perturbations (by calculating the Jacobian matrix, see appendix).

4.3.2 Estimating the rate of waning of vaccine-induced immunity

The data presented in chapter 3 can be used to estimate several parameters of the mathematical model as will be shown in section 4.4.3. In particular, these are q (the fraction of vaccinees who are immediately susceptible to VMMI), r (the fraction who are initially protected but gradually lose protective titers during their lifetime) and ω (the rate at which these initially protected individuals become susceptible to VMMI).

To estimate the rate of decay of titers post immunization, a regression analysis was performed on the log of antibody titers using the Bernoulli/lognormal mixture model proposed by Moulton & Halsey (1995). As explained in chapter 3 this model accounts for the fact that 1) the observations are left-censored due to the lower detection limit of the PRN test and 2) there is evidence for a population of non-responders, i.e. some vaccinees fail to produce neutralizing antibodies. For reasons of simplifying the subsequent analysis, the complication of skewed residuals has been ignored. Although I showed in chapter 3 that controlling for skewness improved the fit of the model significantly, it had no significant impact on the coefficient estimates of the most significant explanatory variables (see table 3.2 page 41).

Although age at sample collection and age at vaccination were both found to be significant explanatory variables in previous models (see table 3.3), for the purposes

of estimating the rate of waning of immunity following vaccination it is appropriate to combine these two variables into a single variable "time since immunization" (AGESAM-AGEIMM) which is of primary interest for our mathematical model.

However, to avoid any potential biases arising from multiple vaccinations and/or natural infections, only those children were selected from the original data set (described in chapter 3) who had been documented receiving a single dose of vaccine between 10 and 36 months (mean 13 m.) of age and whose parents confirmed on a questionnaire that their child had no history of measles infection. Of the 883 selected study subjects, 66 (7.5 percent) children had no detectable measles antibody, i.e. their PRN titer was known to be less than 8.

Similar to Woolhouse *et al.* (1996) the log-transformed antibody titers of the responders are assumed to have a normal distribution function $N(A(t), \sigma^2)$, where $A(t)$ is the mean log antibody titer at time t after vaccination and the variance σ^2 is independent of both $A(t)$ and t. The mean log antibody titer at time t, $A(t)$, can then be expressed as a linearly decreasing function of t, i.e. $A(t) = \gamma_0 + \gamma_1 t$ where γ_1 is the constant rate of decay and γ_0 is the mean log antibody titer at the intercept $t = 0$ (time of vaccination).

The log likelihood function of the lognormal mixture model is given by:

$$\begin{aligned} \mathcal{L}(\boldsymbol{\beta}, \boldsymbol{\gamma}, s) &= \sum_{i=1}^{n} \log\left(\tau_i + (1-\tau_i)\Phi\left(\frac{\log(T) - \boldsymbol{z_i'\gamma}}{s}\right)\right) + \\ &\quad \sum_{i=n+1}^{N} \log\left(\frac{(1-\tau_i)\exp\left(\frac{-(log(y_i) - \boldsymbol{z_i'\gamma})^2}{2s^2}\right)}{y_i\sqrt{2\pi}s}\right) \end{aligned} \tag{4.6}$$

where i indexes the $N = 883$ data points, y_i are the observed titers, $\boldsymbol{z_i'\gamma} = \gamma_0 + \gamma_1 t_i$ (t_i are the observed values for time post immunization and γ_0, γ_1 the intercept and coefficient of the time variable, respectively). $\tau_i = \exp(\beta_0)/(1+\exp(\beta_0))$ represents the Bernoulli component and models non-response status (β_0 being the intercept), $T = 8$

is the assay detection limit, s is the standard error, $\Phi(x)$ is the integral from $-\infty$ to x of the normal distribution with mean 0 and standard deviation 1 and for convenience the censored observations are given by the indices $i = 1 \ldots n$, where $n = 66$ is the total numbers of observations at or below the detection limit.

Regression parameters γ_0, γ_1, β_0 and s were estimated by maximizing the log likelihood function in equation 4.6 using the built-in optimization function on Quattro Pro 7 (Corel Corporation Limited). Standard errors were obtained on Maple V3 (Waterloo Maple Software) using the Hessian matrix of the log-likelihood function (Greene, 1993).

4.3.3 Duration of protective immunity

As discussed in section 4.1, there is probably no definite threshold level of antibody titers which confers protection from VMMI. However, several authors (Ratnam *et al.*, 1996; Chen *et al.*, 1990) have suggested that a PRN titer > 120 might be protective and the analysis in this chapter is based on this criterion. Hence for purposes of this analysis individuals with antibody titers below 120 are assumed to be susceptible to VMMI and individuals with titers above this level are protected. As titers wane following immunization, this criterion determines how the proportion of the population which is protected decreases as a function of time following immunization.

Assuming that PRN titers are log-normally distributed among those who respond, the proportion of the population fully protected (i.e. with titers > 120) at time t post immunization, $\rho(t)$ is given by the integral

$$\rho(t) = \int_{\log(120)}^{\infty} \frac{1}{\sqrt{2\pi}s} \exp\left(-\frac{(x - \gamma_0 - \gamma_1 t)^2}{2s^2}\right) dx. \tag{4.7}$$

By assuming that the variance estimate s^2 is constant, 95 percent upper and lower confidence bounds for the prediction $\rho(t)$, denoted by $\rho_u(t)$ and $\rho_l(t)$, respectively, can be obtained from replacing the mean regression line $A(t)$ in equation 4.7 by the upper

and lower bounds of the 95% confidence region, $A_u(t)$ and $A_l(t)$, respectively, which is given by (see Draper & Smith, 1981):

$$A_u(t) = A(t) + (2F(2, N-2, 0.95))^{1/2} s\sqrt{1/N + (t-\bar{t})^2/\Sigma(t_i - \bar{t})^2} \quad (4.8)$$

$$A_l(t) = A(t) - (2F(2, N-2, 0.95))^{1/2} s\sqrt{1/N + (t-\bar{t})^2/\Sigma(t_i - \bar{t})^2} \quad (4.9)$$

where N is the total number of observations, s is the square root of the residual mean square, t_i are the observed values of time post immunization, $\bar{t}$ is the mean of all such observed values and F represents the F-distribution. As the curves $\rho(t)$, $\rho_u(t)$, $\rho_l(t)$ can be interpreted as survivorship functions for immunity, estimates of the mean duration of protection M can be obtained by numerically evaluating the integral of $\rho(t)$, $\rho_u(t)$, $\rho_l(t)$ from $t = 0$ to $t = \infty$.

4.4 Results

4.4.1 Steady state analysis of the mathematical model

The mathematical system described by equations 4.1-4.5 has 2 steady states (equilibria), the first one corresponding to absence (or elimination) of infection.

$$\mathcal{X}^{(1)} = (X_c^{(1)}, Y_c^{(1)}, X_v^{(1)}, Y_v^{(1)}, W^{(1)}) \quad (4.10)$$

$$= (1-p, 0, \kappa p, 0, \frac{\mu p r}{\mu + \omega}) \quad (4.11)$$

where the summary parameter $\kappa = q + r\omega/(\mu+\omega)$ represents the fraction of vaccinated individuals who will eventually be susceptible to VMMI after long-term absence of infection in the population. Note that κ includes the fraction q of vaccinees who immediately became susceptible to VMMI due to their low immune response as well as the fraction of individuals $r\omega/(\mu+\omega)$ who gradually lost their protective vaccine-induced immunity due to waning. Note r is the fraction of vaccinees who after vaccination are

temporarily protected from VMMI whereas $\omega/(\mu+\omega)$ is simply the proportion of these individual who will survive to become susceptible to VMMI.

The second steady state describes the equilibrium densities in each class when the infection persists in the population: $\mathcal{X}^{(2)} = (X_c^{(2)}, Y_c^{(2)}, X_v^{(2)}, Y_v^{(2)}, W^{(2)})$, where

$$X_c^{(2)} = \frac{1-p}{(1-p\phi)R_c} \tag{4.12}$$

$$Y_c^{(2)} = \frac{\mu(1-p)}{\mu+\nu_c}\left(1-\frac{1}{(1-p\phi)R_c}\right) \tag{4.13}$$

$$X_v^{(2)} = \frac{\kappa p}{(1-p\phi)R_c} \tag{4.14}$$

$$Y_v^{(2)} = \frac{\mu\kappa p}{\mu+\nu_v}\left(1-\frac{1}{(1-p\phi)R_c}\right) \tag{4.15}$$

$$W^{(2)} = \frac{\mu p r}{\mu+\omega} \tag{4.16}$$

and

$$R_c = \frac{\beta}{\mu+\nu_c} \tag{4.17}$$

$$R_v = \frac{\beta}{\mu+\nu_v} \tag{4.18}$$

$$\phi = 1-\kappa\frac{R_v}{R_c} = 1-\left(q+\frac{\omega r}{\mu+\omega}\right)\frac{R_v}{R_c} \tag{4.19}$$

R_c and R_v represent the basic reproduction numbers of the two types of infection. R_c is defined to be the average number of secondary infections due to one individual with classical measles in a completely susceptible population (Anderson & May, 1991) and, similarly, R_v is the average number of secondary infections coming from one VMMI in a completely susceptible population. As the average duration of infectiousness of VMMI, i.e. $1/\nu_v$, is assumed to be less than the average duration of classical infection, $1/\nu_c$, R_v is less than R_c.

Similar to McLean & Blower (1993), one can define the summary parameter $\phi = 1-\kappa R_v/R_c$ in equation 4.19 to represent the vaccine impact. This parameter is an important determinant of the vaccine coverage level necessary for elimination of the

infection from the population. It can be easily seen from equation 4.19 that if a vaccine is perfect (i.e. it confers complete and permanent immunity to vaccinees), so that q and r are 0, then vaccine impact ϕ equals 1. Conversely, if the vaccine is imperfect in some sense (either q or r greater than 0), then vaccine impact ϕ is less than 1. Note that in contrast to McLean and Blower's model, vaccine impact does not only depend on the fraction susceptible to VMMI (as represented by κ) but also on the ratio of respective basic reproduction numbers R_v/R_c. Thus higher values of R_v have the effect of decreasing vaccine impact.

The effect of a vaccination strategy is best summarized by an overall reproductive number, R, defined as the average number of secondary cases generated from an infectious individual in a population where a fraction p has been immunized with a vaccine of impact ϕ and the other fraction $1-p$ is susceptible to classical infection. There is some ambiguity about what is meant by an "infectious" individual here as two types of infection are considered: classical and vaccine-modified. This can be resolved by noting that in the above population only a proportion κp of vaccinees would be susceptible to VMMI, so that a total of $1-p+\kappa p$ are susceptible to either form of measles infection. Hence the initial infectious individual has classical infection with probability $(1-p)/(1-p+\kappa p)$ and VMMI with probability $\kappa p/(1-p+\kappa p)$.

If a vaccination strategy reduces the overall reproductive number R to less than 1, then the infection cannot persist in the population, each index case giving rise, on average, to less than one secondary case (McLean & Blower, 1993).

Thus the elimination criterion is defined as (see Appendix A):

$$p > \frac{R_c - 1}{R_c - \kappa R_v} = \frac{1}{\phi}\left(1 - \frac{1}{R_c}\right). \tag{4.20}$$

subject to:

$$\kappa R_v < 1 \tag{4.21}$$

It is important to note that if $\kappa R_v > 1$, then p is also forced to be greater than 1, which is impossible as coverage can never exceed 100 percent, and so elimination is mathematically impossible. In this case measles infection can persist in a fully vaccinated population entirely in its vaccine-modified form. If $\kappa R_v < 1$ then elimination depends critically on the vaccination coverage as determined by inequality 4.20. The overall reproductive number R can be deduced by simply re-arranging inequality 4.20:

$$R = (1 - p\phi)R_c \tag{4.22}$$

$$= (1-p)R_c + p\left(q + \frac{r\omega}{\mu+\omega}\right)R_v \tag{4.23}$$

Note that the overall reproductive number R consists of the sum of two terms: the first, $(1-p)R_c$, represents the average number of cases due to a classical infection and the second, $p(q+r\omega/(\mu+\omega))R_v$, represents the average number of secondary cases coming from an individual with VMMI.

Figure 4.2 shows the equilibrium proportion of individuals susceptible to either classical or VMMI as a function of routine vaccination coverage p and impact ϕ where standard parameter values are assumed for classical infection. The fraction of susceptibles can be expected to remain largely unaffected until vaccination coverage gets sufficiently large.

Figure 4.3 shows the same graph but this time for the equilibrium proportion of individuals with either type of infection. Note that by differentiating Y_v in equation 4.15 with respect to p, the vaccination coverage with the highest prevalence of VMMIs can be determined analytically, which occurs when $p = (1 - 1/\sqrt{R_c})/\phi$. For example, if $R_c = 15$ and the vaccine impact is high enough to allow eradication with a single

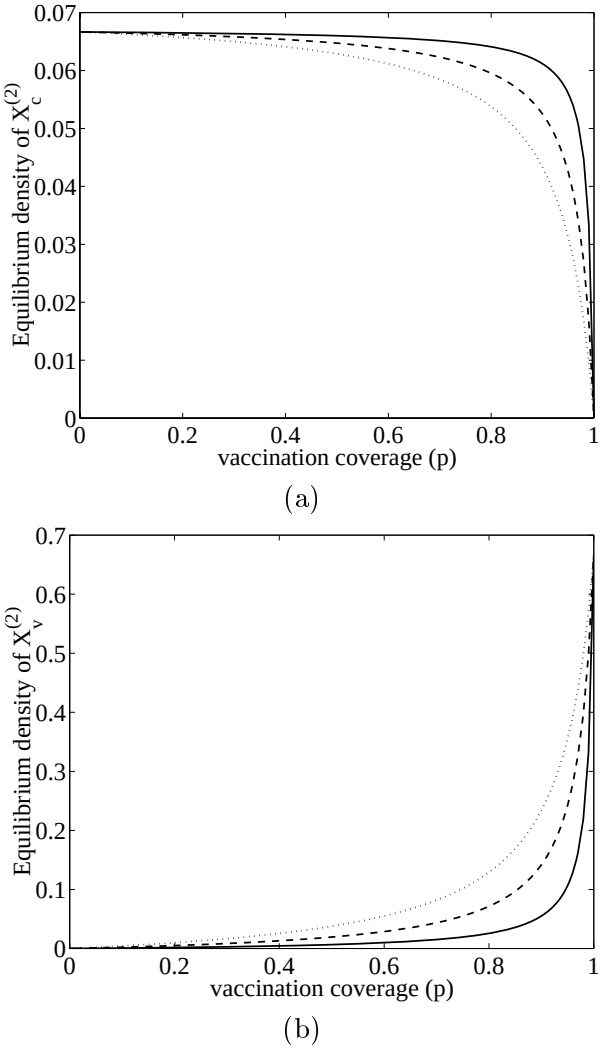


Figure 4.2: The equilibrium proportion of the population susceptible to either classical $X_c^{(2)}$ (a) or vaccine-modified infection $X_v^{(2)}$ (b) as a function of vaccination coverage (p) when vaccine impact $\phi = 0.99$ (solid), 0.97 (dashed), 0.94 (dotted). It is clear that the equilibrium fraction of susceptibles to either type of infection is affected only when vaccine coverage gets sufficiently high. Other parameter values: $R_c = 15$, $\mu = 1/75$ year^{-1}, $\nu_c = 52$ year^{-1}, $R_v = 1.5$.

routine dose, i.e. $0.933 < \phi \leq 1$, one would expect the highest prevalence of VMMI in populations where routine coverage is between 74 and 79 percent.

To summarize the findings of this analysis, the main effect of VMMI is to increase the effective reproduction number of measles virus. However, the current modeling framework can also quantify its impact on the equilibrium proportions of susceptible and infected individuals of either type. In particular the critical coverage was shown

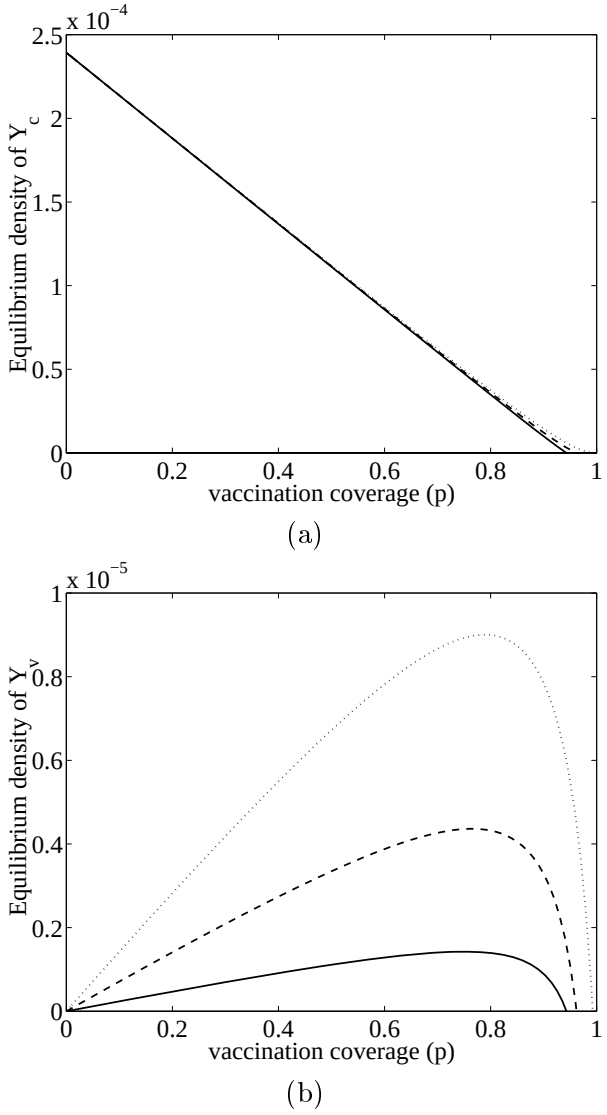


Figure 4.3: The equilibrium proportion of the population infected with classical (a) or vaccine-modified measles (b) as a function of vaccination coverage (p) when vaccine impact $\phi = 0.99$ (solid), 0.97 (dashed), 0.94 (dotted). Whereas the proportion of classical measles infections decreases continually with increasing vaccine coverage, the proportion with VMMI reaches a peak for a certain vaccine coverage, which can be found analytically to be $p = (1 - 1/\sqrt{R_c})/\phi$ (see main text). Other parameter values as in figure 4.2.

not only to depend on the reproduction number of the natural infection R_c but also on the variation of immune responses to vaccination at a population level (which is summarized by the parameter κ) as well as the reproduction number of vaccine-modified measles infection R_v. Elimination of measles virus with a single dose routine vaccination

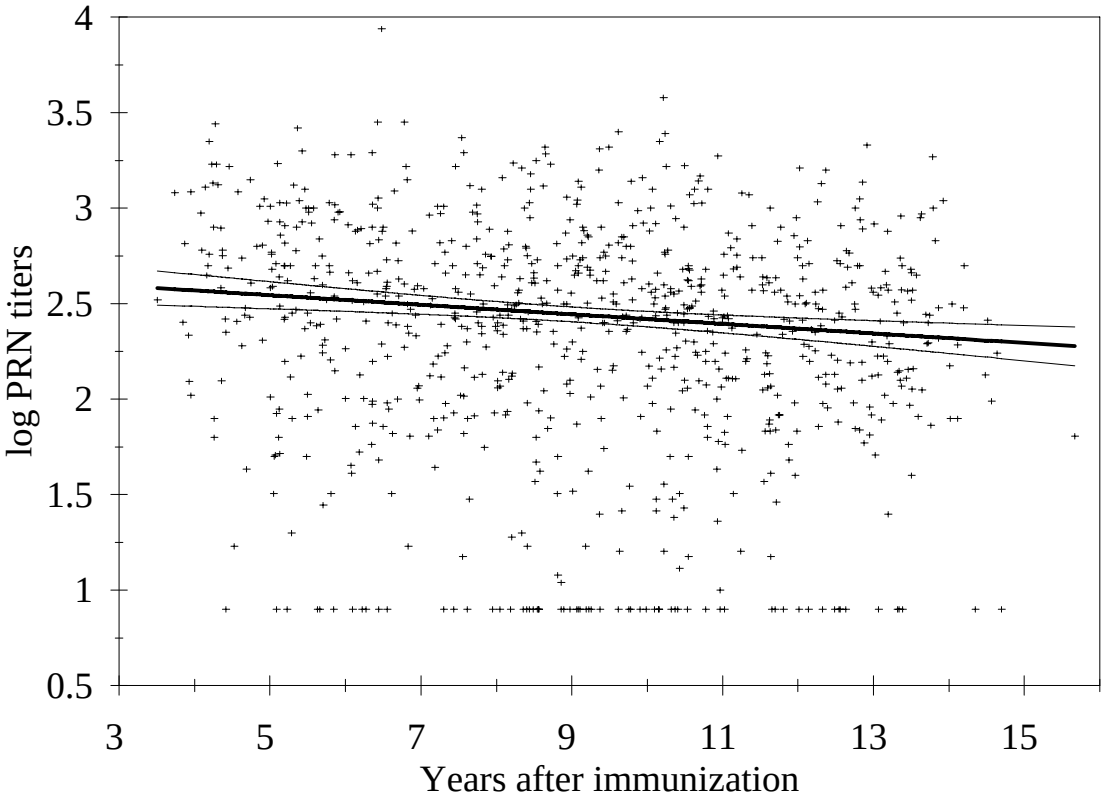


Figure 4.4: Log of antibody titers of the 883 selected children are plotted against time post immunization. The thick line represents the best fit regression line of the mixture model: $A(t) = 2.6699 - 0.025t$. The thin lines $A_u(t)$ and $A_l(t)$, indicate the upper and lower boundary, respectively of the 95 percent confidence region for the mean regression line.

strategy is furthermore mathematically impossible if κR_v is greater than 1, even when 100 percent coverage is attained.

4.4.2 Regression results

As expected from the results in chapter 3, the Bernoulli-lognormal model with time after vaccination as an explanatory variable of the lognormal component provided a significantly better fit to the data ($-2*$loglikelihood $= 1544.34$) than the Bernoulli-lognormal model without covariates ($-2*$loglikelihood $= 1561.26$).

The fitted regression line through the log of antibody titers had slope $\gamma_1 = -0.025$ (standard error (SE) 0.0061) per year which corresponds to antibody half-life of 12.0

years (95 percent confidence interval (CI) 8.2-23.1). The intercept of the regression line (the predicted log antibody titer at vaccination) is -2.6699 (SE 0.0577) and the estimate for residual standard deviation is $s = 0.4691$ (SE 0.0118). The estimate of the proportion of non-responders τ is 7.4 percent (95 percent CI 5.9 to 9.4), which indicates that most—if not all—observations below the detection limit come from a separate population of non-responders (66 out of 883 titers (7.5%) were below the LDL).

Figure 4.4 shows the log of titers of all selected samples and the best fit regression line derived from the mixture model responders (thick line) which takes account of non-responders and the left-censored data. The upper and lower curves around the regression line (normal lines), $A_u(t)$ and $A_l(t)$, indicate the 95 percent confidence region of the mean regression line $A(t) = 2.6699 - 0.025t$.

The proportion of vaccinees who develop an antibody response, but whose antibody titers are below the susceptibility threshold immediately after immunization is given by $1 - \rho(0)$, which is calculated to be 10.4 percent (95 percent CI 6.0-16.7). Predictions of the proportion immune subsequent to immunization are plotted in figure 4.5 and compared to the observed proportion of children with titers > 120 grouped into yearly classes. Note that the proportion non-immune in this graph includes the non-responders which was estimated to be 7.4 percent of the total population so that the displayed curves correspond to $\rho(t)$, $\rho_u(t)$ and $\rho_l(t)$ multiplied by 0.926. The mean duration of protective immunity is estimated to be $M = 24.5$ years with 95 percent CI of $M_l = 17.9$ to $M_u = 47.5$ years.

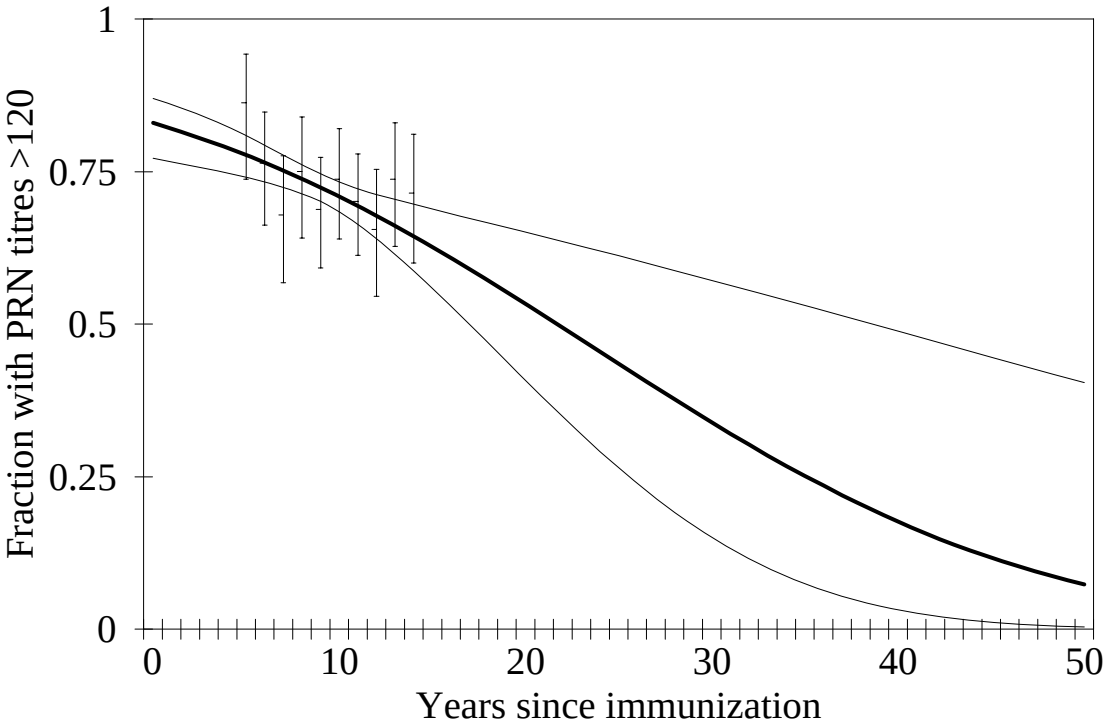


Figure 4.5: Comparison of the mixture model prediction of the proportion immune (i.e. who have PRN titers > 120) and the observed proportion of immune children grouped into yearly classes post immunization. 95 percent confidence limits for the observed proportions were obtained using the F-distribution (Zar, 1996). The thick line represents the mean prediction based on $A(t)$ whereas the thin lines indicate the 95 percent confidence region for the mean prediction based on $A_u(t)$ and $A_l(t)$. The mixture model's mean prediction is consistent with the data from 4 to 15 years post immunization as their confidence regions overlap. Note also that the prediction is most accurate for 9-10 years post-immunization but that accuracy decreases as t increases. Nevertheless, the model predicts that, in absence of natural infection, 50% of the initial vaccinated population will have lost fully protective immunity (i.e. have PRN titers < 120) 24.5 years post immunization (95 percent confidence interval 17.9-47.5).

4.4.3 Relating regression results to the mathematical model

The mean and 95% CI for the summary parameter

$$\kappa = q + r\omega/(\mu + \omega) \tag{4.24}$$

can be obtained by noting that all the unknown parameters which make up κ, i.e. q, r and ω are themselves functions of the regression parameters γ_0, γ_1 and s.

To see this, note that q, the fraction of vaccinees having a titer less than the thresh-

old of 120 immediately after vaccination, is given by

$$q = \int_{-\infty}^{\log(120)} \frac{1}{\sqrt{2\pi}s} \exp\left(-\frac{(x-\gamma_0)^2}{2s^2}\right) dx. \tag{4.25}$$

and is a therefore a function of γ_0 and s only.

If all vaccinated individuals are assumed to experience a decay of titers, then r is equal to $1-q$. This corresponds to the situation where no vaccinee is able to maintain high titers indefinitely in absence of reexposure. Since $r = 1-q$, r is also a function of γ_0 and s only.

Finally of the average rate, ω, at which temporarily protected individuals W move into the susceptible-to-VMMI compartment X_v, is estimated by the inverse of the average duration of immunity of those individuals who had titers > 120 after immunization. This stems from the fact that the integral from 0 to ∞ of the survivorship function is equal to the average age in that population. Thus

$$\omega = \frac{r}{\int_0^\infty \int_{\log(120)}^\infty \frac{1}{\sqrt{2\pi}s} \exp\left(-\frac{(x-\gamma_0-\gamma_1 t)^2}{2s^2}\right) dxdt} \tag{4.26}$$

which is a function of the parameters γ_0, γ_1 and s. By now substituting our previous estimates of the mean duration of immunity (24.5 years) and r (0.896) from section 4.4.2, we get an estimate of the decay rate of 0.0366 per year.

However, from the assumptions underlying any regression model, the 3 parameters γ_0, γ_1 and s approximately follow a multivariate normal distribution with a mean vector equal to the maximum likelihood estimates (i.e. 2.6699, -0.025 and 0.4691 respectively) and with a covariance matrix obtained using the Hessian matrix of the log-likelihood function (Greene, 1993). Hence an estimate of the distribution of κ can be obtained by generating random vectors of this multivariate normal distribution and substituting them into the equations for q, r and ω to calculate κ. An approximate distribution of

κ was thus generated using 5000 random vectors which had a mean of 80.4 percent and 95 percent CI of 65.3-90.8.

This means that after long-term absence of circulating measles virus (i.e. several decades) and with a single dose of vaccine, the model would predict that the large majority of antibody titers in a vaccinated population would fall below the protective threshold of 120. In view of eradication it is therefore important to investigate whether current vaccines perform well enough to prevent persistence of wild virus in highly or even fully vaccinated populations. Given that we have an estimate of what the likely proportion of suceptibles to VMMI is going to be, it is possible to determine the characteristics of VMMI—in particular its infectiousness—which could enable persistence of virus in highly vaccinated populations.

From inequality 4.21, long-term elimination under a single dose vaccination programme is only possible if $\kappa R_v < 1$. Rearranging this inequality and using the upper CI estimate for κ above, it is clear that elimination with a single dose of vaccine is possible as long as the basic reproduction number of the VMMI R_v is less than $1/0.908 = 1.10$ and coverage is above the critical threshold defined in inequality 4.20. Furthermore, using the lower CI estimate of κ elimination with a single dose is unlikely even at 100 percent coverage if R_v exceeds $1/0.653 = 1.53$, which is roughly about one tenth of the estimate of the basic reproduction number of measles in industrialized countries (Anderson & May, 1991). Hence, even if individuals with VMMI are on average ten times less infectious than individuals with natural infection, their contribution to overall transmission can be sufficient to allow persistence of measles virus.

4.5 Discussion

Although mathematical modeling approaches have been extensively used to investigate the consequences of various vaccination strategies on patterns of measles transmission and incidence (Anderson & May, 1991) the impact of variation in individuals' immune responses to vaccine have not been taken into account in the context of measles. To my knowledge only Eichner *et al.* (1996) explicitly include subclinical infection in their model of measles transmission. Their investigation, however, focuses on the effects of vaccination coverage on the lifetime risk of measles for non-vaccinated individuals, rather than on the impact of VMMI transmission on persistence.

The modeling framework is similar to that of McLean & Blower (1993) in defining the impact of a vaccine in terms of different forms of vaccine imperfections, which in the context of HIV used in their study were: 1) take (vaccine only works for a fraction of the population), 2) degree (vaccine reduces the probability of being infected) and 3) duration (waning immunity).

There are nevertheless important differences between their modeling framework and the framework presented in this chapter. First, vaccine "take" is not incorporated into vaccine impact, rather it is subsumed into a term for the proportion receiving vaccine who also respond by producing specific antibodies. Second, degree and duration apply to the vaccine responders only in relation to susceptibility to VMMI, rather than susceptibility to classical measles infection. Third, we assume that if infection occurs in vaccine responders, they are less infectious in the sense that they shed virus on average for a shorter duration albeit with the same intensity than unvaccinated naturally infected individuals. Finally, we model the two classes of individuals susceptible to VMMI and of individuals with VMMI explicitly which enables us to predict the prevalence of

VMMI as a function of routine vaccination coverage.

There are several ways in which the current mathematical model could be improved. The assumption that there is no difference between susceptibility to natural infection and to VMMI as well as no difference between the intensity of both types of infection is probably unrealistic. The main effect, however, of a lower susceptibility to VMMI or of a lower intensity during VMMI would be to increase the vaccine impact ϕ and thereby reduce the overall reproduction number R. From the modeling point of view, it is however less critical what the exact mechanism of a lower reproduction number is. Indeed as far as the reproduction number is concerned both shorter infectiousness and reduced intensity are essentially interchangeable. What is important and what is different in our modeling approach is to assume that infected vaccinated individuals have a lower reproduction number than naturally infected cases.

It is also possible to extend the rather simplistic SIR-model framework to include age-structure (age-dependent mortality and contact rates as in Anderson & May (1991)) or a continuous range of immunity levels (White & Medley, 1998). However, including these factors would significantly increase the complexity of the model and preclude any analytic stability analysis. Numerical techniques would then be necessary to investigate model behaviour.

Using regression analysis on a data set from a serological study of vaccinated children in Canada and a threshold criterion derived from a serological outbreak study (Chen *et al.*, 1990) the mean duration of protection conferred by currently used measles vaccines was estimated to be 24.5 years (95 percent CI 17.9-47.5). Furthermore in absence of exposure to wild virus, one would expect that 80 percent (95 percent CI 65-91) of the vaccinated population would eventually have titers which make them susceptible to VMMI. On the basis of that, it is not surprising that even a greatly reduced trans-

mission potential in these individuals (basic reproduction number of 1.24 (95 percent CI 1.10-1.53)) could prevent control by a single dose strategy.

From a public health perspective, this work has highlighted three important aspects which warrant further investigation. First, serological data from individuals over a greater interval of time since vaccination are needed to complement the existing data in order to confirm or correct estimates of the rate of antibody decay. Second, larger serological pre- and post-outbreak studies are required to elucidate and quantify the relationship between antibody titers and protection from clinical, mild and asymptomatic infection (Lee, 1999). Finally there is a need to identify the transmission capacity of vaccinated individuals during outbreaks. This study has shown that it is important to establish whether individuals with mild or subclinical VMMI are able to transmit infection, and if so, how the characteristics of VMMI (duration and intensity) compare to those of classical measles infection.

Chapter 5

A mathematical investigation of a vaccination strategy to eliminate measles in WHO Region Europe

5.1 Introduction

As stated in chapter 1, based on the success of measles control in countries with high immunization levels, several WHO Regions have declared elimination targets: the Americas want measles eliminated by 2000, Europe by 2007 and the Eastern Mediterranean Region by 2010 (Wild, 1999; World Health Organization, 1999).

In this chapter, a particular strategy will be focussed upon which has been proposed by a WHO meeting to achieve measles elimination in the WHO Region Europe (WHO Regional Office for Europe, 1997; World Health Organization, 1999). The main premise of this strategy is to eliminate virus by immunizing more people by vaccine than would have been infected due to virus from natural transmission. The central idea is to create an immune profile in the population which is higher than that created by the circulation

of virus prior to the introduction of the vaccine. In particular, the criteria state that at least 85% of 1-4 year olds, 90% of 5-9 year olds and 95% of ten-year olds and above should have lifelong immunity (WHO Regional Office for Europe, 1997). Conversely, susceptibility needs to be reduced to $< 15\%$ for ages 0-4, $< 10\%$ for ages 5-9 and $< 5\%$ for ages ≥ 10 years.

Although one would expect most countries to apply a 2-dose policy in practice, this 3-tiered criterion allows some flexibility for the modeling, in particular as some countries give the second dose before children enter primary school when around 5-6 years old (e. g. Luxembourg) and others at 10 years of age (12 years in Sweden for example).

These immunity (or susceptibility) criteria have been established using preliminary results from an age-structured mathematical model of measles transmission based on patterns of demography and epidemiological characteristics of measles in the UK. While they are thought to be also applicable to other Western European countries with similar demographics and transmission patterns, it is currently unclear to what extent this strategy also works for other countries of the WHO Region Europe, in particular the Central Asian Republics (CAR), where demographics are substantially different due to higher birth rates, lower life expectancy and a young population and where little is known about the epidemiology of measles transmission (e. g. the force of infection or average age at infection).

The principal aim of this chapter is therefore to investigate using a mathematical model under which demographic or epidemiologic conditions the strategy proposed for WHO Region Europe leads to elimination and when it is insufficient to break the chains of transmission. The tool used for this investigation is a partial differential equation model of measles transmission which has been used in a wide variety of contexts for

studying the impact of vaccination (McLean & Anderson, 1988b; Anderson & May, 1991; Babad *et al.*, 1995; Gay *et al.*, 1995; Nokes & Swinton, 1995; Gay *et al.*, 1997, 1998). Furthermore, we apply these modeling techniques to see whether elimination with the current criteria can be achieved in the CAR or whether the immunization policy needs some refinements.

The structure of the remainder of this chapter is as follows: a methods section describes the anatomy of the mathematical model, its underlying assumptions and basic definitions. The second section investigates some of the factors crucial for achieving elimination, in particular the effects of mortality patterns, population growth and the relevance of age-dependent transmission rates. The next section focuses in more detail on the situation of the CAR in view of establishing whether the suggested vaccination strategy is also applicable for the CAR. Finally, conclusions are drawn in a discussion section and recommendations made for a policy refinement.

5.2 Anatomy of the age-structured transmission model

5.2.1 Model structure

To model the dynamics of measles transmission in an age-structured population, we use the standard model which can be described by a set of five partial differential equations (Anderson & May, 1991). At birth, infants are initially protected by maternally derived antibodies (M) for an average period of 3.5 months, after which we assume that they become fully susceptible to measles infection (X). After contact with infectious individuals, susceptible individuals become infected. They stay non-infectious during a latency period of 7 days on average while incubating the disease (H) before becoming infectious for the same period (Y). After their infectious period, individuals are

assumed to become immune and to remain so for the rest of their lives (Z).

5.2.2 Model Equations

The equations for the model follow standard lines as presented in Anderson & May (1991):

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = -(\mu(a) + \delta)M(a,t) \tag{5.1}$$

$$\frac{\partial X}{\partial t} + \frac{\partial X}{\partial a} = \delta M(a,t) - (\mu(a) + \lambda(a,t))X(a,t) \tag{5.2}$$

$$\frac{\partial H}{\partial t} + \frac{\partial H}{\partial a} = \lambda(a,t)X(a,t) - (\mu(a) + \sigma)H(a,t) \tag{5.3}$$

$$\frac{\partial Y}{\partial t} + \frac{\partial Y}{\partial a} = \sigma H(a,t) - (\mu(a) + \gamma)Y(a,t) \tag{5.4}$$

$$\frac{\partial Z}{\partial t} + \frac{\partial Z}{\partial a} = \gamma Y(a,t) - \mu(a)Z(a,t) \tag{5.5}$$

The boundary conditions are given as:

$$M(0,t) = \int_0^\infty mN(a,t)da \tag{5.6}$$

$$X(0,t) = H(0,t) = Y(0,t) = Z(0,t) = 0 \tag{5.7}$$

where $N(a,t)$ represents the total population of age a at time t and m is the constant birth rate of the population. $\lambda(a,t)$ is the force of infection at age a and at time t, which is defined to be:

$$\lambda(a,t) = \frac{\int_0^\infty \beta(a,a')Y(a',t)da'}{\int_0^\infty N(a',t)da'} \tag{5.8}$$

where $\beta(a,a')$ is the effective contact rate between susceptibles of age a with infectious individuals of age a'. Here we make the implicit assumption that the per capita force of infection is independent of the total population size (Anderson & May, 1991; McLean & Anderson, 1988b), as the integral of N with respect to age is in the denominator of equation 5.8. This assumption is often made on the basis that a growing population doesnot necessarily mean that its density (and therefore the number of contacts per person) is growing (McLean & Anderson, 1988b).

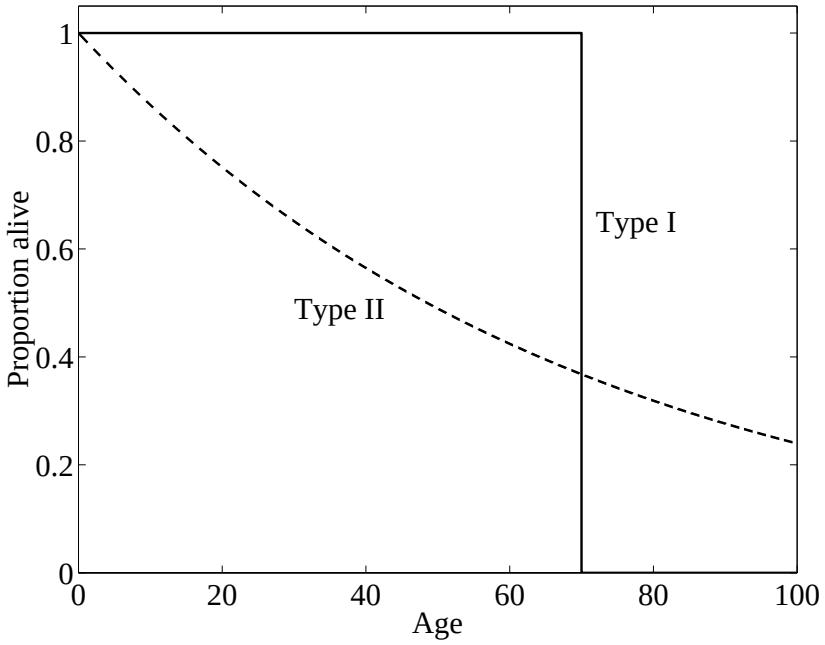


Figure 5.1: Two types of simplified survivorship profiles used for modeling mortality patterns in human populations. Rectangular type I represents populations in developed countries and exponential type II is more representative of developing nations. Both populations have an average life expectancy of 70 years.

5.2.3 Mortality patterns

For mathematical modeling of infectious diseases in human populations, it is common practice to consider two extreme types of mortality. Individuals exhibiting type I survival (or type I mortality) survive until they reach life expectancy L, i.e. everybody lives to age L then dies. As shown in figure 5.1, the corresponding survivorship function for this type of mortality is a rectangular box and is a simplified model of the mortality pattern observed in developed countries. Individuals exhibiting type II survival, on the other hand, are subject to a constant risk of dying after birth, resulting in an exponentially declining survivorship profile. This profile is thought to reflect more accurately mortality patterns in developing countries.

5.2.4 Population Growth

Whereas it is clear that the age structure of the population doesn't change for a non-growing population with either type I or type II mortality, this is not true when the population experiences growth. If the growth rate stays constant, the population will eventually settle to a stable age distribution experiencing net population growth at a rate r determined by the Euler equation $\int_0^\infty \exp(-ra)l(a) = 1/m$, where $l(a)$ is the survivorship function and m the birth rate (Anderson & May, 1991). We have used this stable age distribution in all subsequent analysis and as a starting condition for numerical simulations.

5.2.5 Transmission rates

For our study, two forms for $\beta(a, a')$ have been looked at, depending on the underlying epidemiological assumptions. The first is to assume no age-dependence in transmission rates. In this case, individuals of all ages have the same number of contacts per unit time and $\beta(a, a') = \beta$, a constant. This assumption is often used in epidemiological settings when insufficient data is available to detect age-dependent mixing in the force of infection.

The second approach is to divide the population into 5 age classes $(a_{i-1}, a_i]$ (for our model we have used $a_0 = 0$, $a_1 = 5$, $a_2 = 10$, $a_3 = 15$, $a_4 = 20$, $a_5 = L_{max}$) and describe the contact patterns between these age groups by a "who acquires infection from whom" (WAIFW) matrix. In this case $\beta(a, a')$ takes the form of a two-dimensional step function ($\beta(a, a') = \beta_{ij}$, $i, j = 1..5$) and the force of infection is assumed to be constant on each age group, i.e. $\lambda(a, t) = \lambda_i(t)$ if $a \in (a_{i-1}, a_i]$.

Although individual components of this matrix cannot be estimated in a unique fashion, they can be calculated from the age-specific forces of infection (λ_i,i=1..5)

prior to immunization by constraining the form of the matrix to be epidemiologically plausible (Anderson & May, 1991; Gay *et al.*, 1995; Babad *et al.*, 1995). Unfortunately very few studies have actually tried to obtain precise estimates of the force of infection of measles in developing countries prior to the introduction of vaccine. As a starting point we have used estimates of measles in the UK which are shown in table 5.1 which were derived from England and Wales pre-vaccination notifications (Babad *et al.*, 1995).

age class	force of infection per person per year
0-4	0.154
5-9	0.518
10-14	0.255
15-19	0.102
20+	0.095

Table 5.1: Force of infection estimates of measles in the UK prior to immunization

5.2.6 WAIFW matrices

Once the force of infection estimates have been obtained, the exact form of the mixing WAIFW matrix remains to be specified and ought to reflect epidemiologically realistic mixing patterns. The 6 different types of mixing matrices shown in table 5.2 were taken from a variety of sources and were chosen to provide an indication of the range of possible outcomes. Matrices 1, 2, 3 and 4 given in table are all taken from Anderson & May 1991. Matrices 5 and 6 on the other hand are derived from Babad et al. The estimated values of β_1-β_4 relative to the general mixing parameter β_5 using the force of infection estimates for the UK (table 5.1) are shown in table 5.3. From these, it is noticeable that the β values are very similar for matrices 1, 2 and 3. Matrix 4 represents the situation where contacts in the first 4 age classes occur primarily within their own age class against a general background common to all individuals. For the UK data set,

WAIFW 1

		infectious age class				
		0-4	5-9	10-14	15-19	20+
	0-4	β_1	β_1	β_3	β_4	β_5
	5-9	β_1	β_2	β_3	β_4	β_5
susceptible	10-14	β_3	β_3	β_3	β_4	β_5
age class	15-19	β_4	β_4	β_4	β_4	β_5
	20+	β_5	β_5	β_5	β_5	β_5

WAIFW 2

		infectious age class				
		0-4	5-9	10-14	15-19	20+
	0-4	β_1	β_1	β_1	β_4	β_5
	5-9	β_1	β_2	β_3	β_4	β_5
susceptible	10-14	β_1	β_3	β_3	β_4	β_5
age class	15-19	β_4	β_4	β_4	β_4	β_5
	20+	β_5	β_5	β_5	β_5	β_5

WAIFW 3

		infectious age class				
		0-4	5-9	10-14	15-19	20+
	0-4	β_1	β_1	β_1	β_1	β_1
	5-9	β_2	β_2	β_2	β_2	β_2
susceptible	10-14	β_3	β_3	β_3	β_3	β_3
age class	15-19	β_4	β_4	β_4	β_4	β_4
	20+	β_5	β_5	β_5	β_5	β_5

WAIFW 4

		infectious age class				
		0-4	5-9	10-14	15-19	20+
	0-4	β_1	β_5	β_5	β_5	β_5
	5-9	β_5	β_2	β_5	β_5	β_5
susceptible	10-14	β_5	β_5	β_3	β_5	β_5
age class	15-19	β_5	β_5	β_5	β_4	β_5
	20+	β_5	β_5	β_5	β_5	β_5

WAIFW 5

		infectious age class				
		0-4	5-9	10-14	15-19	20+
	0-4	β_1	β_1	β_1	β_1	β_5
	5-9	β_1	β_2	β_3	β_4	β_5
susceptible	10-14	β_1	β_3	β_3	β_4	β_5
age class	15-19	β_1	β_4	β_4	β_4	β_5
	20+	β_5	β_5	β_5	β_5	β_5

WAIFW 6

		infectious age class				
		0-4	5-9	10-14	15-19	20+
	0-4	β_1	β_5	β_5	β_5	β_5
	5-9	β_5	β_2	β_3	β_5	β_5
susceptible	10-14	β_5	β_3	β_3	β_4	β_5
age class	15-19	β_5	β_5	β_4	β_4	β_5
	20+	β_5	β_5	β_5	β_5	β_5

Table 5.2: WAIFW matrices used for the modeling.

	β_1	β_2	β_3	β_4	β_5
WAIFW 1	1.60	10.11	2.70	1.07	1.00
WAIFW 2	1.63	10.01	3.86	1.07	1.00
WAIFW 3	1.62	5.45	2.68	1.07	1.00
WAIFW 4	2.21	10.89	64.49	19.03	1.00
WAIFW 5	1.62	10.01	3.86	0.49	1.00
WAIFW 6	2.21	10.68	4.51	3.41	1.00

Table 5.3: Estimates of the β values for the various forms of WAIFW matrices based on the UK force of infection data set in table 5.1.

this matrix yields probably unrealistically high values for the transmission coefficients β_3 and β_4: it is difficult to justify that 10-14 year olds have 65-fold higher contact rates among themselves than adults do among themselves. Matrix 5 yields a β_4 value lower than the β_5 value which also seems unrealistic. Matrix 6, on the other hand, a variation of matrix 5, appears to have reasonable transmission coefficients, with highest contact rate among 5-9 year olds and then a gradual decrease towards adulthood.

5.2.7 Implementing the vaccination strategy

The WHO Europe immunization strategy in the model is implemented by constantly vaccinating 85% of 1 year-olds, 33% of 5 year olds and 50% of 10 year-olds, i.e. by putting the above proportion of individuals at their respective ages from the X class into the Z class. After running this vaccination program for $L-1$ years, this achieves the desired effect of having at least 85% of 1-4 year olds, 90% of 5-9 year olds and 95% of 10+ year olds immune. Note that for simplicity we assume that all one year-olds have lost their maternal antibody protection, i.e. all one-year-olds go from class M to class X. The motivation for this is to avoid having more than 85% of one-year-olds being immune due to a vanishing fraction of them still being protected by maternal antibodies. Note also that vaccine is assumed to be 100% efficacious and to be given at random independently of previous history of vaccination or infection.

Constant population with type I	$R_0 = \lambda L$
Constant population with type II	$R_0 = 1 + \lambda L$
Growing population with type I	$R_0 = \lambda / m$
Growing population with type II	$R_0 = 1 + \lambda / m$

Table 5.4: Relationship between the basic reproduction number and force of infection depending on survival and growth type (Anderson & May, 1991). R_0 represents the basic reproduction number, λ denotes the per capita force of infection (per year), L is the life expectancy (in years) and m is the yearly per capita birth rate of the growing population.

5.2.8 Establishing whether the vaccination programme leads to elimination

No age-dependent transmission rates

In the absence of age-dependent transmission rates, it is possible to establish whether elimination occurs for the different types of mortality by calculating explicitly what proportion of the total population have not been vaccinated successfully. This can be achieved with analytical integration methods by taking account of the underlying mortality pattern. Using the formula for the basic reproduction number $R_0 = 1/x^*$, where x^* is the critical fraction of susceptible individuals in the population, we can estimate the critical basic reproduction number R_0^* which would enable an infection to persist in the vaccinated population. Furthermore, using the relationships between the basic reproduction number and the force of infection in table 5.4 (taken from (Anderson & May, 1991)), we can deduce the equivalent critical force of infection estimates pre-vaccination above which infection can persist and below which it dies out. These elimination criteria are based on equilibrium results, i.e. they refer to long term dynamics and do not necessarily prevent a temporary epidemic or consider epidemic/stochastic fade out.

Age-dependent transmission rates

If we assume that the transmission rates are dependent on age (as described by a WAIFW matrix), the elimination criterion becomes analytically intractable and we have to resort to numerical methods. Gay *et al.* (1995) and Babad *et al.* (1995) have proposed to use the effective reproductive number in this case. The effective reproduction number R is defined to be the average number of secondary cases arising from a "typical" primary case (Gay *et al.*, 1995). It is clear that to achieve elimination of an infection, R must be kept below unity. More details on the method for calculating R can be found in appendix B.

There are, however, at least 2 ways to define whether a particular vaccination programme is successful. First of all one could take a long term view and ask to achieve elimination in the long run, i.e. that $R < 1$ after some time interval. One of the problems that might occur for example is that that those individuals who were too old to be vaccinated at the beginning (i.e. those older than 10 years old) could eventually build up a pool of susceptibles large enough to fuel an epidemic in the older age classes. This build up is likely to occur if the vaccination programme is initially very successful in reducing the force of infection to such a low level as to prevent infection in the older age groups.

The second approach is to judge a vaccination programme successful only if it keeps the effective reproduction number below unity at all times following the start of the vaccination programme. This will ensure that no temporary outbreaks can occur thereby ensuring rapid elimination of infection. This latter criterion is clearly more desirable from a public health perspective as epidemics after the start of vaccination programmes could undermine the public's perception of the effectiveness of the vaccination policy.

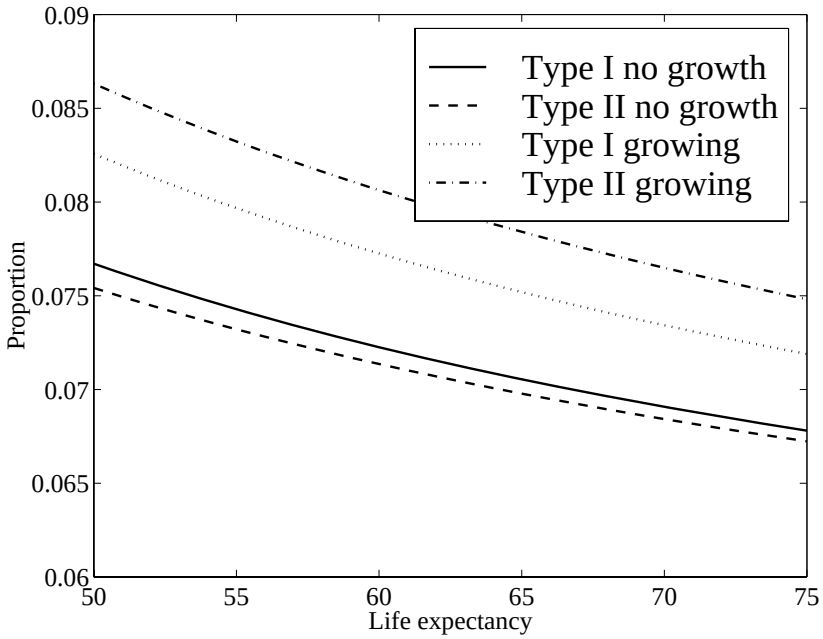


Figure 5.2: The fraction of the total population which remains susceptible (in absence of infection) if 85% of 1-4 year olds, 90% of 5-9 year olds and 95% of 10+ year olds are immunized by vaccine is shown as a function of life expectancy, survival type and population growth. For the non-growing populations, the birth rate is equal to the inverse of life expectancy. For the growing populations, the respective birth rates were increased by 25%.

5.3 Results

5.3.1 No age-dependent transmission

There are essentially 4 parameters which can determine whether elimination occurs. The only epidemiological parameter is the force of infection estimate λ which is assumed to be independent of age and the demographic variates are mortality pattern (type I *vs.* type II), life expectancy, birth rates (constant *vs.* growing).

Figure 5.2 shows the relationship between life expectancy, mortality pattern and population growth and the total proportion of the susceptible population under the proposed vaccination programme when infection is ignored. Three observations can be made:

1. The proportion of susceptibles decreases with increasing life expectancy. In populations with higher life expectancy, a higher fraction of the total population are among those with most immune individuals (95% of those aged 10+).

2. For the non-growing population, the proportion of susceptibles is always lower in type II than in type I populations. This at first somewhat unexpected result can be explained by considering that a type II mortality population has a larger fraction of the total population which is older than 10 years (for a more detailed explanation including a formal proof see Appendix D page 118).

3. The proportion of susceptibles in a growing population is generally higher than in an equivalent non-growing population. This is due to the fact that a higher proportion of the total population is found in the younger age classes where susceptibility levels are highest. Figure 5.3 shows how increasing population growth increases the proportion of susceptibles in the population with type I and type II mortality, when life expectancy is 50 years. In particular we can see that a doubling of the birth rate from 0.02 to 0.04 has the effect of increasing the proportion of susceptibles by about 30% for populations with type I and by 50 % for populations with type II mortality. Notice that except for the lowest birth rates, the effect of growth is more important for type II populations than for those of type I.

Hence it is clear that both mortality and growth patterns influence susceptibility levels in the vaccinated population with potentially important implications for the introduction of the proposed WHO Europe elimination policy to the CAR.

Using the relationship $R_0 = 1/x^*$, where x^* represents the susceptible fraction of the population, it is now possible to determine what level of *infectiousness*, as indicated

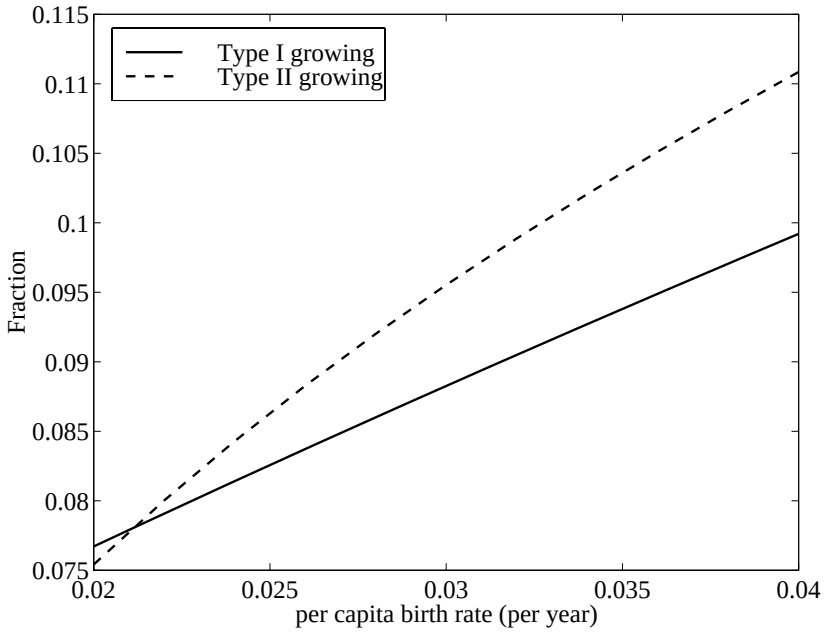


Figure 5.3: The fraction susceptible in the population when the birth rate is increased from 0.02 to 0.04 per year while keeping life expectancy fixed at 50 years.

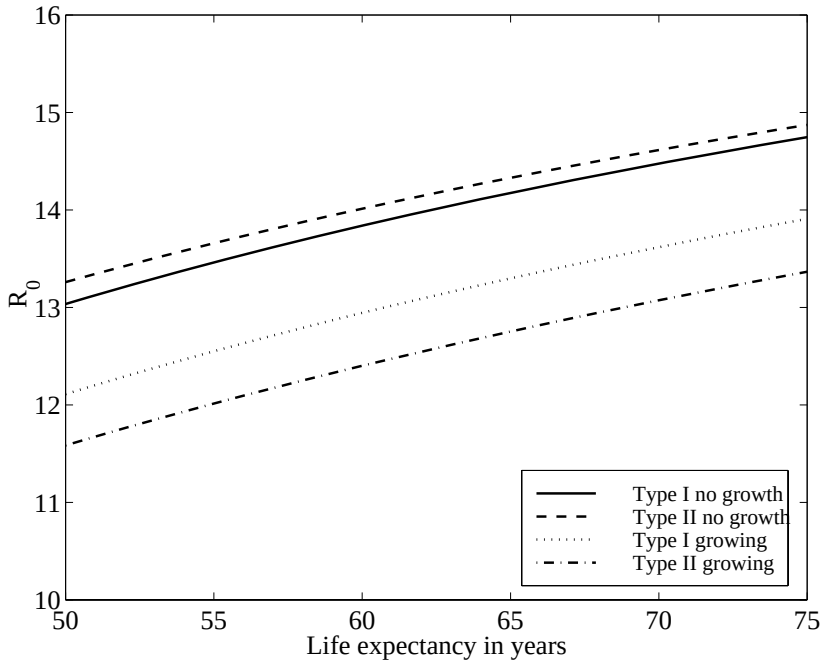


Figure 5.4: The critical basic reproduction number R_0 above which the infection can persist and below which the immunity profile ensures elimination when no age-dependent transmission is assumed. Other parameters as in figure 5.2.

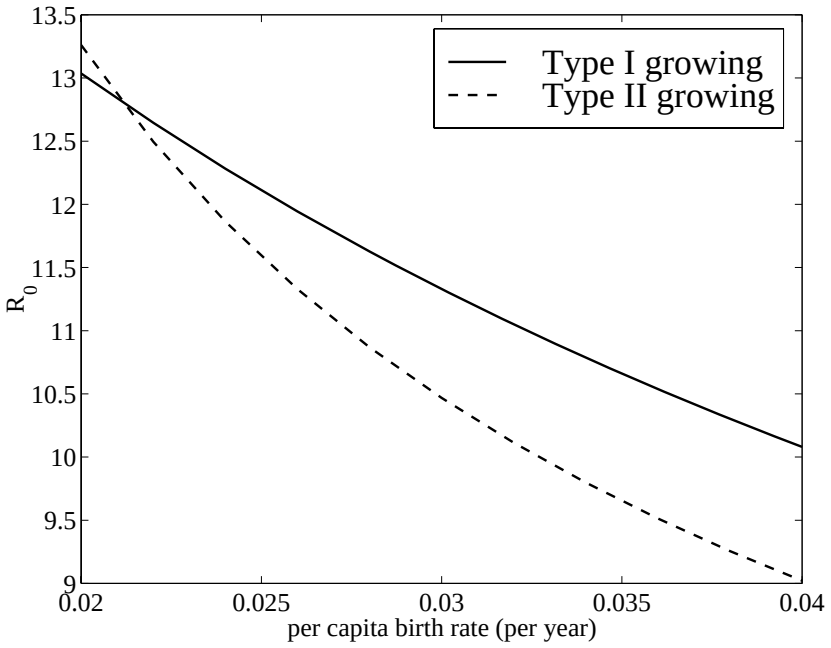


Figure 5.5: The critical basic reproduction number where elimination is achieved with the proposed immunity profile as a function of the birth rate in growing populations. Life expectancy is kept fixed at 50 years.

by R_0, could be eliminated using the WHO-Europe immunity profile. Figure 5.4 shows that infections with higher basic reproduction numbers can be eliminated in those populations with higher life expectancy, due to the inverse relationship between the basic reproduction number and the proportion susceptible. Furthermore, the critical basic reproduction number decreases substantially in growing populations with either mortality type as shown in figure 5.5. For example whereas in a constant population with 50 years life expectancy and type I mortality, the critical R_0 is 13, this decreases to a value of only about 10 if the birth rate doubles.

To conclude, if age-dependence in transmission rates is ignored, elimination of the infection due to the proposed vaccination immunity profile depends on the interplay between the intrinsic basic reproduction number of the infection and the demographic setting. In particular, the critical basic reproduction is higher in populations with higher life expectancies, but lower in populations experiencing growth. The mortality

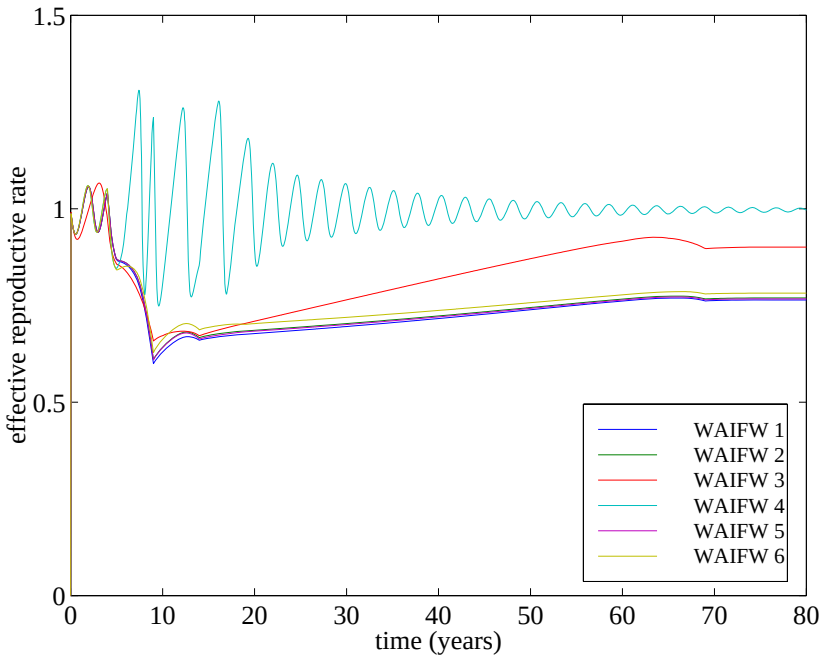


Figure 5.6: Reproductive rate R of measles as a function of the 6 transmission matrices under the proposed vaccination strategy in a demographically stable population with type I mortality and a life expectancy of 70 years.

pattern (i.e. type I *vs.* type II) plays generally a less important rôle than either life expectancy or population growth for determining whether elimination occurs or not.

5.3.2 Age-dependent transmission

When contact rates are assumed to vary between ages, the particular choice of the WAIFW matrix turns out to be an important factor for determining whether elimination occurs under the proposed strategy. Figure 5.6 shows a time series over 80 years of the effective reproductive rate R and figure 5.7 the corresponding average age at infection for WAIFW matrices 1 to 6 in a non-growing population with type I mortality and life expectancy of 70 years. Elimination occurs rapidly for all transmission matrices except matrix 4, which represents the situation when the majority of contacts are within the same age-class (i.e. βs along the diagonal dominate).

It is interesting to note that matrix 3 (when transmission depends only on the age

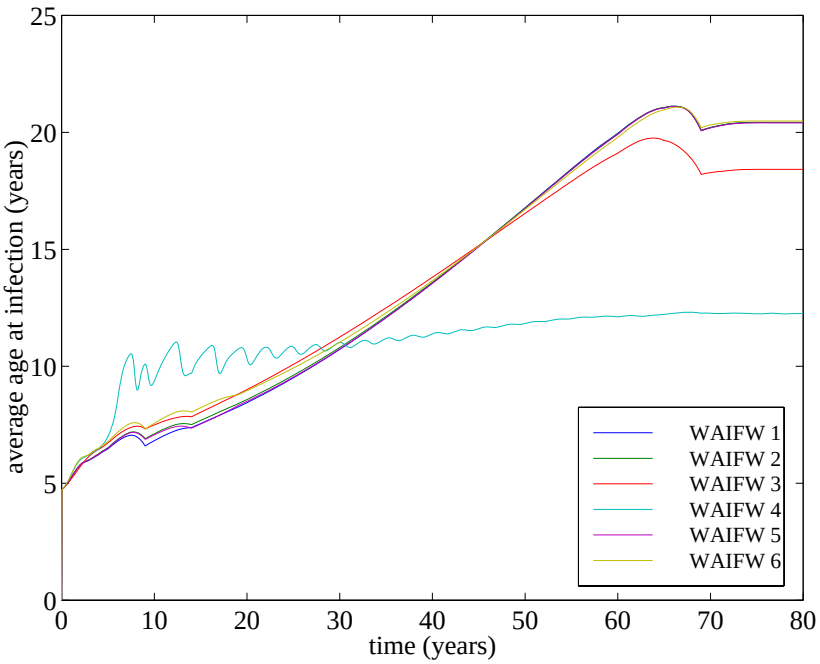


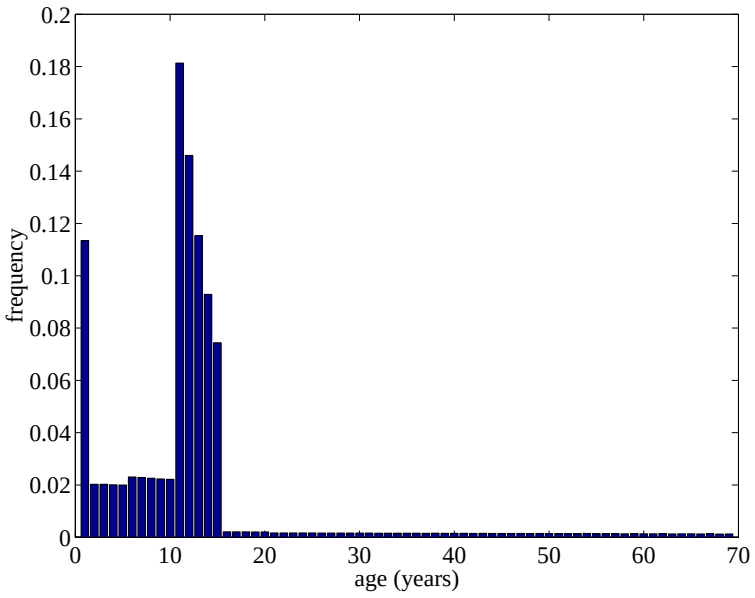
Figure 5.7: Average age of infection as a function of the 6 transmission matrices under the proposed vaccination strategy in a demographically stable population experiencing type I mortality with life expectancy of 70 years.

of the susceptible) has a higher effective reproduction in the long run than the other matrices 1, 2, 5 and 6, which all yield very similar patterns.

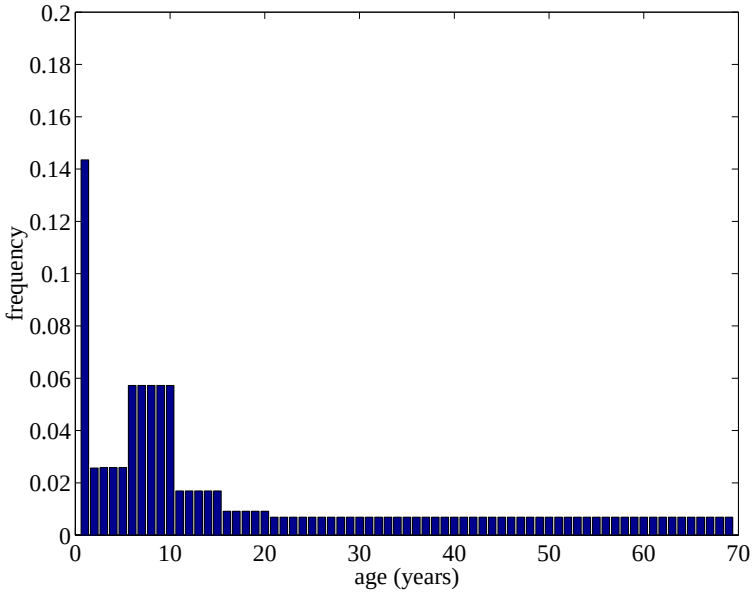
The average age of infection after 70 years of infection is depicted in figure 5.7: when elimination occurs (for matrices 1, 2, 3, 5 and 6) the average age of infection rises virtually linearly to about 20 years. If infection persists, on the other hand, in the case of matrix 4, the average age of infections remains much lower at 12 years.

If we look at the age distribution of cases after 80 years (note that figure 5.6 suggests that the dynamics have converged to a steady state) as shown in figure 5.8, it becomes clearer why the average age is much lower for WAIFW matrix 4: the extremely high β_3 among 10-14 year olds enables infection to persist virtually exclusively in this age-class, so that no individuals remain susceptible by the age of 15 (part a of figure 5.8).

On the other hand, when elimination occurs as in the case of matrix 6 shown in



(a)



(b)

Figure 5.8: Age distribution of cases of model output as in figure 5.6 after 80 years. (a) for WAIFW-matrix 4 when infection can persist most cases occur in the age class of 10-15 year olds; (b) for WAIFW-matrix 6 when transmission cannot be sustained most cases occur in the first year of life and in children aged 5 to 9 years. Note that the age distributions are normalized, i.e. the figure shows the number of cases in each class divided by the total number of cases in all age classes.

part b) of figure 5.8, a higher proportion of cases occur in the oldest age-classes thereby having the effect of increasing the average age of infection.

5.3.3 Sensitivity analysis

All of the age-dependent results presented above are derived using the England & Wales force of infection estimates. As it is likely that these estimates are not identical in other countries of the WHO Region Europe, a natural question to ask then is by how much these estimates of λ have to be changed to threaten elimination. For this scenario, we have used the WAIFW mixing matrix 6 in a population with type I mortality and a life expectancy of 70 years. However, as there are 5 different age classes, there are many combinations for changing the λs individually or in pairs, triples, quadruples or all at once.

The first problem then looked at was to see by what percentage all 5 λs need to be increased by simultaneously (i. e. all 5 λ_is multiplied by the same factor) to threaten elimination. Model simulations show that an increase of 20% or more of each λ simultaneously would suffice to sustain continued transmission.

Second, if only the λ of a single age-class is changed while leaving the other four unchanged, we can determine which component of the force of infection is most sensitive: simulations show that λ_1 needs to be increased by 53%, λ_2 by 48% λ_3 by 132 % λ_4 by 44%. λ_5 on the other hand cannot be increased indefinitely while keeping λ_1 to λ_4 fixed as this causes some of the components of the transmission matrix to become negative. However, this technical problem can be solved by increasing both λ_4 and λ_5 at the same time: in this case, an increase by 68% of both yields sustained transmission.

To sum up, elimination with the WHO strategy might not be threatened in those countries where the force of infection estimates in the age categories 0-4, 5-10, 15-20,

20+ exceed those of the UK by about 50% individually or 20% simultaneously. An increase of the force of infection estimate in the age class of 10-15 year has lowest impact when compared with other age groups.

5.4 Case Study: the Central Asian Republics

The following section tries to synthesize some of the theoretical insights gained in the previous section and apply them to the particular question whether the immunity profile suggested by WHO Europe for elimination of measles in Western nations is also applicable for the Central Asian Republics (CAR).

5.4.1 Demographic characteristics of the Central Asian Republics

The Central Asian Republics consist of Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan. Following the breakup of the USSR these countries joined the WHO Region Europe. Table 5.5 shows recent demographic characteristics of the CAR according to WHO *Health or All* statistical database (WHO Regional Office for Europe, 1999).

It is clear that life expectancy in the CAR is on average ten years less than those living in the European Union (EU) which had an average life expectancy of 77.6 years in 1996. More importantly, the population age structure differs remarkably as the CAR population is much younger on average: whereas in 1996, 17.33% of the average EU population were aged less than 15, the average in the CAR is more than twice that value at 37.42%, indicating that the CAR have a "young" population much like most developing countries. For our purposes of doing the mathematical modeling, it is important to note that 4 out of the 5 countries have a fertility rate (i.e. the average number of offspring from a women during her lifetime) substantially higher than two

	Kazakhstan	Kyrgyzstan	Tajikistan	Turkmenistan	Uzbekistan	EU average[1]
population	15.8 m.	4.6 m.	6.0 m.	4.6 m.	23.8 m.	-
life expectancy at birth, in years	64.81	66.77	68.3[2]	63.95[3]	67.88[2]	77.59
life expectancy at age 1	65.48	67.72	69.44[2]	65.79[3]	68.69[2]	77.03
life expectancy at age 15	52.27	54.98	57.00[2]	53.85[3]	56.21[2]	63.24
life expectancy at age 45	26.41	28.13	30.04[2]	26.61[3]	28.61[2]	34.66
life expectancy at age 65	13.32	13.98	15.16[2]	12.18[3]	14.02[2]	17.71
% of population aged 0-14	29.54	36.98	43.67[1]	39.67[3]	40.64[2]	17.33
% of population aged 15-64	63.61	57.44	52.40[1]	56.73[3]	55.16[2]	67.05
% of population aged 65+	6.85	5.58	3.93[1]	3.60[3]	4.20[2]	15.62
total fertility rate	2.00	2.8	4.1[2]	3.8[2]	3.4	-[4]
population density per km^3	5.86[1]	22.83[1]	40.98[1]	9.36[1]	52.23[1]	178.74

[1] Estimated for 1996. [2] Estimated for 1995. [3] Estimated for 1994. [4] Not given.

Table 5.5: Some demographical parameters of Central Asian Republics and the EU average according to WHO *Health for All* statistical database (WHO Regional Office for Europe, 1999). All estimates are for 1997, except indicated otherwise.

indicating that that these countries experience significant population growth. Only the population of Kazakhstan has had a fertility rate around 2 in recent years, which means that the their population remains stable.

The fact that those countries with a high fertility rate also have a high proportion of 0-15 year olds is not unexpected. If more people are born than die, which is essentially the definition of population growth, than one would expect a higher proportion of people in the younger age classes. Figure 5.9 shows the relationship of fertility rate and proportion of 0-15 year olds in the five CAR. From this, it is clear that those countries with a high fertility rate also have a higher proportion of 0-15 year olds. The fact that compared with the EU average, Kazakhstan also has a relatively high proportion of 0-15 year olds can be explained that Kazakhstan's fertility rate has also been consistently

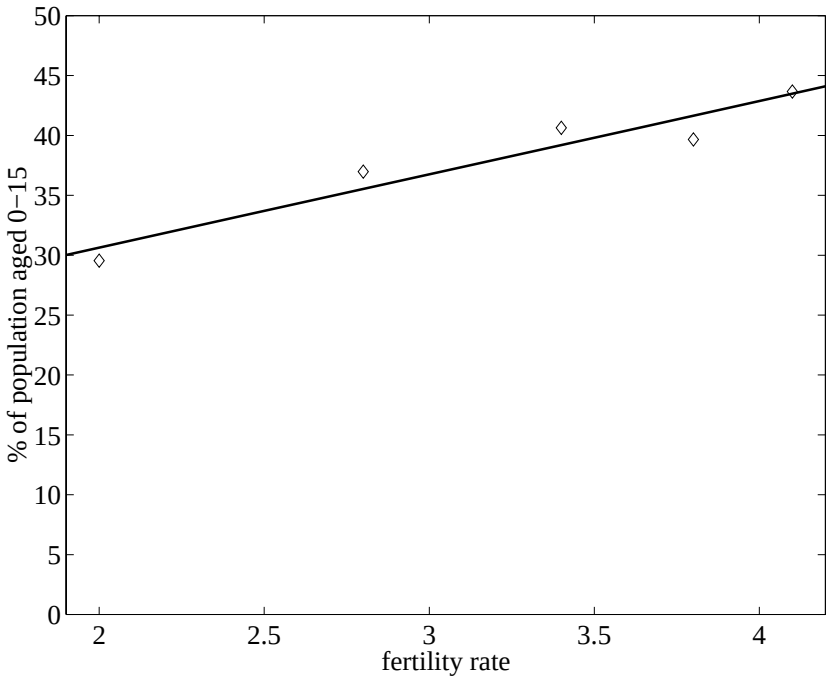


Figure 5.9: Relationship between the fertility rate and the proportion of the population aged 0-15 in the 5 Central Asian Republics. Also shown for reference is the least square linear regression. It is clear that those CAR with higher fertility rates also tend to have a younger population.

greater than 2 until 1995 (see figure 5.13 (a) page 102).

The next important question is to investigate mortality patterns in the CAR. Given that the age structure in these countries (i.e. comparatively young population) corresponds to those of developing countries, one might expect to find the same mortality pattern, that is type II survival. Even if published age-dependent mortality rates in the CAR are not easily available, it is possible to approximate the mortality patterns from the WHO *Health for All* database on the basis of life expectancies at birth and at ages 1, 15, 45 and 65. Using a method explained in the appendix C, approximate survivorship profiles in the CAR are shown in figure 5.10.

It is striking that the proportion of people surviving up to age 65 does not vary substantially between the 5 countries. On this graph, between 80-85% of the population in the CAR can expect to survive until the age of 65. This is indicative that mortality

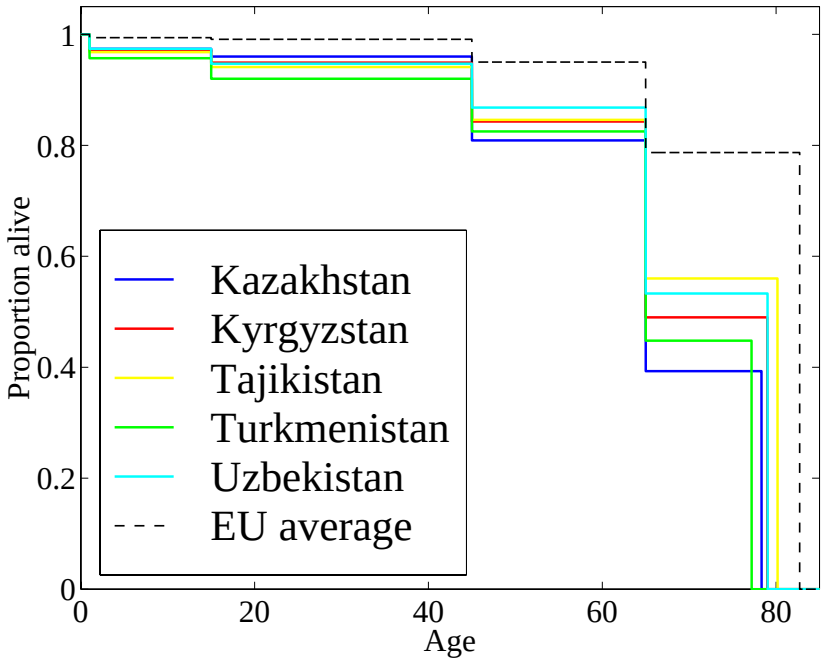


Figure 5.10: Survivorship profiles of Central Asian Republics and the EU average in mid 1990s, based on the step-wise type I mortality survivorship function.

rates up to the age of 65 are relatively low, which is incompatible with type II mortality. The only substantial differences are seen in the proportions surviving from age 65 to the maximum age.

As a consequence, all 5 countries have an overall survivorship function that is closer to type I than to type II. As such the mortality patterns in the CAR are more similar to those observed in developed countries than in developing countries.

5.4.2 Can measles be eliminated in the CAR?

To see whether the WHO Region Europe immunity profile leads to elimination in each of the five CAR, a mathematical model with the following features was used:

1. The populations have the survivorship profiles as shown in figure 5.10 which reflects the data we have on life expectancies at ages 0, 1, 15, 45 and 65.

2. It is assumed that the population is undergoing growth as given by the current

fertility rate of these countries. The starting conditions for the model are given by the stable age distributions under the respective fertility rate and mortality regime. In practice, this means that the model is first run for 2 generations after which it has converged to the stable age distribution. During this initial phase, the model also includes transmission of infections, but without the immunization programme. Thus, initial conditions are those of a demographic and epidemiological equilibrium.

3. As there is no data available on the force of infection in the CAR prior to immunization programmes, we use the UK estimates of measles transmission prior to vaccination. For similar reasons, we use the WAIFW matrix 6, which has the most plausible parameter values.

4. Immunization leads to an immunity profile such that 15% of 1-4 year olds, 10% of 5-9 year olds and 5% of 10+ year olds remain susceptible to measles.

Figure 5.11 shows the effective reproduction number following the start of the vaccination programme in each of the five republics. In Kazakhstan, Kyrgyzstan and Uzbekistan, the effective reproduction number stays below one following a transitional epidemic period. Thus elimination of measles can be expected to occur in these republics. In Tajikistan and Turkmenistan, however, the immunity profile is insufficient to keep infection at bay in the long run. Notice that if one ranks the countries' effective basic reproduction number after 10-15 years, one obtains the same ranking order as that of the countries' fertility rate. This shows that of all demographic characteristics considered, the fertility rate is probably the most important in determining elimination. Essentially these results suggest that elimination becomes more likely as the fertility rate decreases.

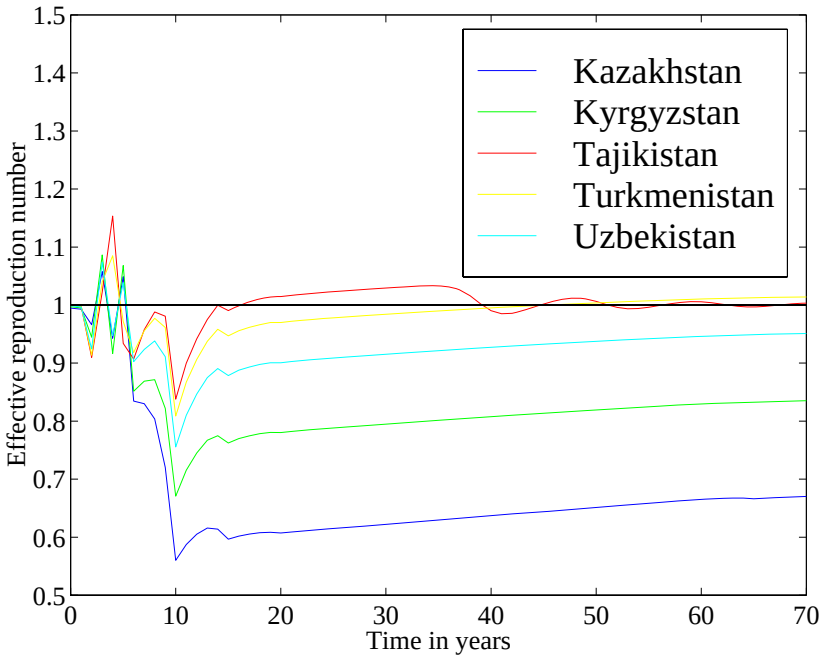


Figure 5.11: Effective reproductive rate after starting the 3-dose vaccination programme in year 0 in the 5 Central Asian Republics.

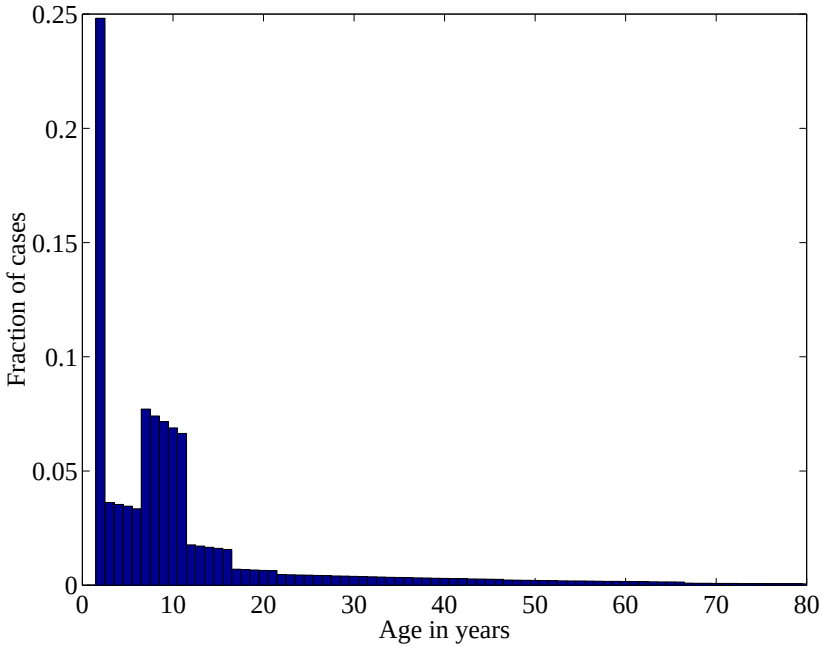


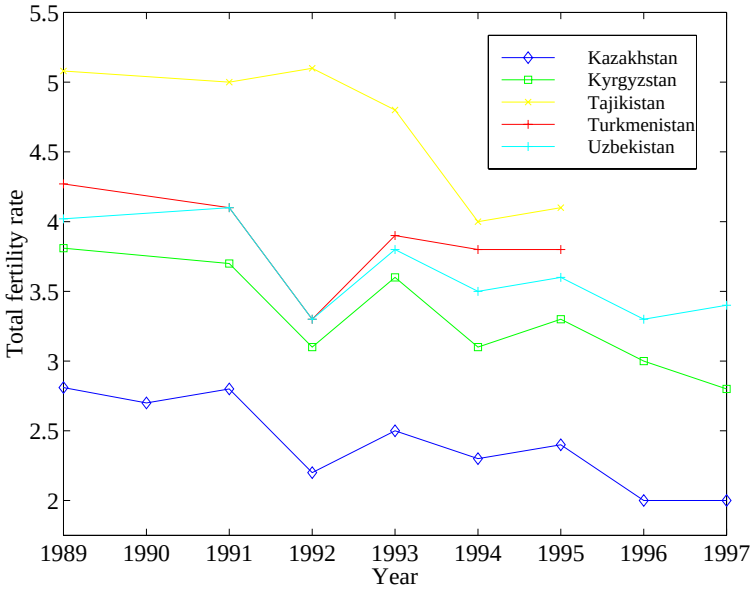
Figure 5.12: Age distribution of cases in Tajikistan under the proposed immunity profile at equilibrium.

As the proposed immune profile seems to be insufficient for Tajikistan and Turkmenistan, a natural question to ask is then by how much immunity has to be increased to get elimination in these countries. The age distribution of cases for Tajikistan at equilibrium is shown in figure 5.12. Whereas in this scenario 25% of all new cases can be expected to occur in under-ones, the age category of 5-9 year olds shares much of the burden. Hence one might consider increasing the immunity profile at age 5 from 90% to 95%, while leaving the proportion immune the same at ages 1 and 10. And indeed, model simulations show that this increase will reduce the effective reproduction number to 0.8 and 0.75 in Tajikistan and Turkmenistan, respectively. On the other hand, rather than increasing the vaccination coverage at age 5, it might be easier logistically to immunize 90% at one years of age, followed by 95% immune at 10 years. This strategy is, however, less successful because elimination would only just be achieved in Turkmenistan (reducing the effective rate R to 0.99), but measles would persist in Tajikistan which has the highest birth rates.

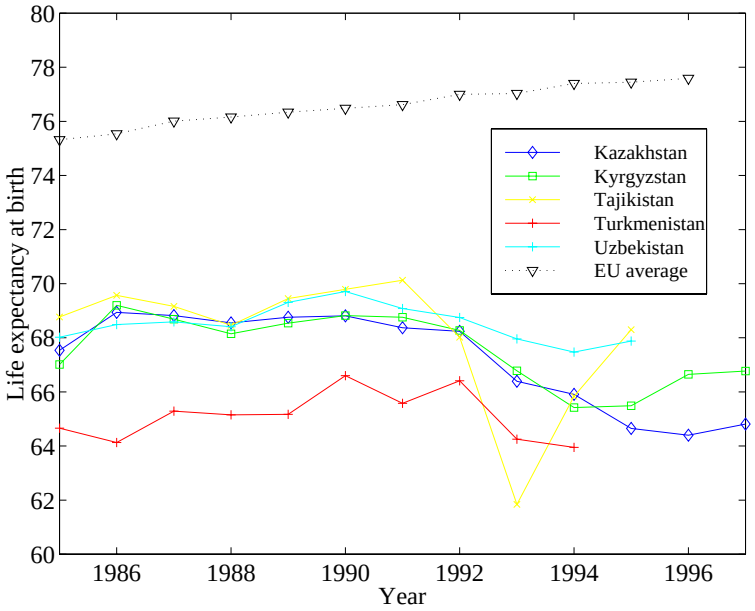
To sum up, the mathematical model indicates that while the suggested immunity profile might be sufficient to lead to measles elimination in Kazakhstan, Uzbekistan and Kyrgyzstan this is not necessarily true for those nations with very high birth rates, Turkmenistan and Tajikistan. In this situation, 85% of 1-4 year olds and 95% of 5+ year olds need to be protected to be sure of achieving elimination.

5.5 Discussion

There are several assumptions in the modeling which need careful consideration. First, vaccine is assumed to be given at random, independently of previous history of vaccination or infection. It is probable that this is not realistic and that children who receive a first dose are more likely to receive multiple doses compared to children who miss the



(a)



(b)

Figure 5.13: Total fertility rate (a) and life expectancy at birth (b) in Central Asian Republics in recent years.

first dose. This would mean, for example, that more than 33% of children would need to be vaccinated at the age of 5 to increase immunity from 85 to 90%.

Second, demographic parameters of the model are assumed to remain constant over time. However data from the *Health for All* Database (WHO Regional Office for Europe, 1999) shows a decreasing trend in fertility rates in recent years (figure 5.13 (a)), and a well-documented decrease in life expectancy (Reamy & Oreskovic, 1999) in the CAR following the break-up of the USSR (figure 5.13(b)). If these trends continue, particularly if birth rates continue to fall then the proposed WHO strategy might nevertheless be sufficient for elimination.

Another major assumption was the use of the England & Wales force of infection (or β values) as an estimate of the force of infection in the CAR. It is unclear how appropriate this assumption is: for a start, the lower observed population density in the CAR could result in less mixing and a lower force of infection. Again this would increase the likelihood of elimination under the proposed WHO strategy. However, the low population density might simply be due to large areas being uninhabitable (e.g. deserts and mountainous regions). The population density (and therefore mixing patterns) in inhabited areas might on the other hand be very similar to those observed in England & Wales. The only way to check the validity of extrapolating values observed in the UK to the CAR would be to obtain seroepidemiological immunity profiles or case notification data in these countries prior to the introduction of the vaccine.

Nevertheless, the above theoretical work demonstrates that both epidemiologic and demographic characteristics of a country are crucial for achieving elimination under the proposed WHO strategy. In particular the models show that elimination might be thwarted if the population experiences strong population growth. Life expectancy and survival type on the other hand play a minor role in comparison. The suggested

immunity profile for WHO Region Europe seems to work well in non-growing but not necessarily in rapidly growing populations, such as Tajikistan and Turkmenistan. In the latter, we recommend a refinement of the susceptibility criteria: no more than 15% of 1-4 year olds and less than 5% of 5+ year olds ought to be susceptible to ensure elimination of measles virus.

A more widespread utilization of the logic underlying the European elimination method would therefore require careful consideration of the demographic profiles of such countries. This is particularly relevant in the case of many developing world countries in Asia and Africa with very high growth rates. Further numerical work would be be useful in evaluating combined multidose and campaign vaccination strategies, as the use of the latter has gained prominence, particularly in the Americas (de Quadros *et al.*, 1996, 1998).

Chapter 6

Discussion and future work

6.1 Review

In this thesis I have investigated several issues related to the control of measles in view of the goal of future measles elimination from a mathematical modeling perspective. The following major conclusions can be drawn from the various research chapters:

- The estimation of the basic reproduction number R_0 of measles during an epidemic in a vaccinated school-aged populations can be used to determine what vaccine coverage is necessary to prevent future outbreaks in similar settings. Estimates of the basic reproduction number derived with this rarely used method are comparable to those derived from standard sero-epidemiological techniques. The results show that the outbreaks could only have be prevented if vaccine coverage had exceeded 90%.

- Statistical regression analysis of antibody titers in vaccinated children shows that age at immunization and time since vaccination are important determinants of the magnitude of anti-measles antibody titers in vaccinees. Highest titers are observed in children vaccinated at later ages. In absence of exposure to circulating virus,

antibody titers are subject to significant decay which indicates waning of humoral immunity.

- Mathematical models show that if vaccinated individuals with low antibody titers are able to be re-infected and transmit virus even at a ten-fold lower rate than those experiencing classical measles, their contribution to overall transmission could nevertheless be sufficient to threaten the success of measles elimination strategies.

- The criteria proposed by the WHO for elimination of measles in WHO Region Europe ought to be refined to take account of the fact that some countries in this WHO Region in Central Asia have much higher birth rates than most Western European countries. Mathematical modeling shows that high population growth generally gives rise to a large proportion of susceptible individuals in the younger age classes, where transmission is thought to be highest.

6.2 Future Directions

There are a number of areas in which the work in this thesis could be extended:

It would be interesting to apply the techniques presented in chapter 2 of estimating the basic reproduction number for other measles outbreaks in vaccinated populations, particularly if a serological study of the immunity levels was carried out at the start of the epidemic. The methodology is of course not only limited to measles and could be applied to other infectious agents which result in lifelong immunity.

In chapter 3 we described various factors influencing antibody response following immunization. We were able to observe that the rate of antibody decay was more or less constant from 3 to 12 years following immunization. However it is not clear whether

this decay continues in later life in absence of exposure or whether decay rates increase or decrease after long-term absence of exposure. Lee (1999), for example, has suggested that the rate of waning decreases in the first couple of years following immunization. More studies are needed which focus on the kinetics of antibody titers in immunized and naturally infected individuals.

Detailed serological investigations prior to and after an outbreak are necessary to elucidate the relationship between antibody titers and risk from asymptomatic or symptomatic re-infection after exposure. Although some preliminary work has been done in this direction (Lee, 1999), our knowledge of the epidemiological and immunological impact of subclinical infection and boosting responses for maintaining immunity both in naturally infected and vaccinated individuals is still limited. This issue becomes more relevant as a recent study has shown that infectious virus has been isolated from a "naturally-immune", asymptomatically re-infected individual (Vardas & Kreis, 1999).

Finally, the work presented in chapter 5 on the elimination of measles in WHO Region Europe is to a large extent based on transmission patterns and demographics found in Western European countries. Whereas some insights could be gained by inferring similar epidemiological transmission patterns in Central Asian countries with high birth rates, this work would benefit considerably if basic epidemiological data (e.g. average age of infection prior to vaccination) were to become available in these countries.

Other key aspects associated with the spread and control of measles infection could be investigated, especially spatial dynamics and pulse campaign strategies. The main problem in these areas is the fundamental lack of understanding of spatial-temporal spread of measles infection in communities for which recently developed salivary based surveillance methods would be of use (Nokes *et al.*, 1998; Nigatu *et al.*, 1999).

6.3 Rôle of mathematical modeling in infectious disease epidemiology

I am never content until I have constructed a mechanical model of the subject I am studying. If I succeed in making one, I understand; otherwise I do not.

Lord Kelvin.

Even if Lord Kelvin refers here to mechanical models, it certainly applies also to mathematical modeling in infectious disease epidemiology. One of the primary aims of all modeling is to gain further insights from all available epidemiological observations. At best, mathematical models are simplified descriptions of complex phenomena whose dynamics can be investigated to enhance our understanding (Fine, 1994). Both chapters 4 and 5 are examples of how modeling can assist in hypothesis formulation and testing.

Often mathematical models can help in the process of recognizing those areas where crucial information is lacking and thus identifying the most important directions for future research. An example of this aspect in this thesis is given in chapter 4 which clearly demonstrates that subclinical infection, although relatively unimportant and uninteresting from a medical (or clinician's) perspective, ought to receive more attention as it might have a significant impact on measles elimination strategies.

Finally, if particular models have been shown to mimic the dynamics of infection appropriately, they can be extremely useful tools for evaluating immunization policy options, prior to making a decision. In chapter 5, for example, a widely used and tested model was used to point out a deficiency of the current WHO Region Europe strategy and to suggest a further refinement. Hence, results from mathematical modeling ought

to be considered as an important element along with all other considerations in the decision making process of the design of future elimination strategies.

Appendix A

Stability analysis

The Jacobian matrix A of the system 4.1-4.5 evaluated at $\mathcal{X}^{\mathbf{1}}$ is given by:

$$A = \begin{pmatrix} -\mu & -\beta(1-p) & 0 & -\beta(1-p) & 0 \\ 0 & \beta(1-p)-(\mu+\nu_c) & 0 & \beta(1-p) & 0 \\ 0 & -\beta\kappa p & -\mu & -\beta\kappa p & \omega \\ 0 & \beta\kappa p & 0 & \beta\kappa p-(\mu+\nu_v) & 0 \\ 0 & 0 & 0 & 0 & -(\mu+\omega) \end{pmatrix}$$

The steady state $\mathcal{X}^{\mathbf{1}}$ is stable if all 5 eigenvalues of the above matrix have negative real parts. The eigenvalues are obtained by finding the roots of the characteristic polynomial which is given by $\det(A-\lambda I)=0$. Three of the 5 eigenvalues are easily found to be $-(\mu+\omega)$ and $-\mu$(occurs twice), which are all negative. The last 2 eigenvalues are those of the smaller 2 by 2 matrix:

$$B = \begin{pmatrix} \beta(1-p)-(\mu+\nu_c) & \beta(1-p) \\ \beta\kappa p & \beta\kappa p-(\mu+\nu_v) \end{pmatrix}$$

Rather than determining the last 2 eigenvalues explicitly, we are only interested in the condition when their real parts are negative. Note that the eigenvalues of a 2 by 2 real matrix have negative real parts if and only if the trace of the matrix is negative and

the determinant is positive,i.e.

$$\beta(1-p) - (\mu+\nu_c) + \beta\kappa p - (\mu+\nu_v) \quad < \quad 0 \tag{A.1}$$

$$(\mu+\nu_c)(\mu+\nu_v) - \beta(1-p)(\mu+\nu_v) - \beta\kappa p(\mu+\nu_c) \quad > \quad 0 \tag{A.2}$$

After substituting $R_c = \beta/(\mu+\nu_c)$, $R_v = \beta/(\mu+\nu_v)$, $\phi = 1-\kappa R_v/R_c$, we can simplify these conditions to:

$$p \quad > \quad \frac{1}{(1-\kappa)}\left(1 - \frac{1}{R_v} - \frac{1}{R_c}\right) \tag{A.3}$$

$$p \quad > \quad \frac{1}{\phi}\left(1 - \frac{1}{R_c}\right) \tag{A.4}$$

However, for the parameter regime we are considering ($0 < R_v < R_c$, $0 \leq p, \kappa, \phi \leq 1$), it is possible to show that the inequality (A.3) is automatically satisfied whenever inequality (A.4) also holds.

For notational convenience let us call the right hand side of (A.3) $h(\kappa, R_v, R_c)$ and the right hand side of (A.4) $g(\kappa, R_v, R_c)$. We want to show that $g(\kappa, R_v, R_c) \geq h(\kappa, R_v, R_c)$ whenever $0 < R_v < R_c$ and $0 \leq \kappa, g(\kappa, R_v, R_c), h(\kappa, R_v, R_c) \leq 1$. Note that if $\kappa = 0$, then $g(0, R_v, R_c) > h(0, R_v, R_c)$. Furthermore $g(\kappa, R_v, R_c) = h(\kappa, R_v, R_c)$ if and only if

$$\kappa = \kappa^* = \frac{R_c^2}{R_v(R_c^2 + R_c R_v - R_v)} > 0$$

Since both g and h are continuous with respect to κ in their respective domains, $g(\kappa, R_v, R_c) < h(\kappa, R_v, R_c)$ can only be true for $\kappa > \kappa^*$. However by substituting $\kappa = \kappa^*$ back into g, we get

$$g(\kappa^*, R_v, R_c) = \frac{R_c^2 - R_c R_v - R_v}{R_c(R_c - R_v)}$$

which is strictly greater than 1 whenever $0 < R_v < R_c$. Since g is an increasing function of κ, $g(\kappa, R_v, R_c)$ must also be strictly greater than 1 whenever κ is greater than or

equal to κ^*. This implies that, within the chosen parameter regime, $g(\kappa, R_v, R_c)$ is always greater than $h(\kappa, R_v, R_c)$.

Appendix B

Calculating the effective reproduction number

Consider the situation of the model described in section 5.2.2 where the population is divided into N age classes $(a_{i-1}, a_i]$, with $a_0 = 0$ and $a_N = L_{max}$. The force of infection is is assumed to be constant across each age class such that $\lambda(a,t) = \lambda i(t)$ if $a \in (a_{i-1}, a_i]$.

Using an approach by Diekmann & Hesterbeek (1990), Gay *et al.* (1995) have shown that up to higher terms involving negligible contributions in the parameter space we are considering, $\lambda_i(t)$ can be written as:

$$\lambda_i(t) = \sum_j \frac{\beta_{ij} X_j(t)}{\gamma R(t) \bar{N}(t)} \lambda_j(t) \tag{B.1}$$

where number $X_j(t)$ is the number of susceptibles in age group j, $R(t)$ is the effective reproduction number at time t, $\bar{N}(t)$ is the total population (integral of N over all ages) at time t and β_{ij} and γ are defined as in sections 5.2.5 and 5.2.2, respectively.

Then a simple calculation shows that $R(t)$ is the dominant eigenvalue of the matrix with elements $\beta ij X_j(t)/(\gamma \bar{N}(t))$ and the corresponding eigenvector has elements $\lambda_j(t)$.

The eigenvalues are computed using standard routines from the Numerical Recipes series (Press *et al.*, 1997).

Appendix C

Estimating survivorship profiles

We can determine approximate survivorship profiles in the CAR from the basis of life expectancy estimates at ages 0, 1, 15, 45 and 65 by assuming that the population has a step-wise type I profile between these ages, i.e. deaths occur only at ages 1, 15, 45, 65 and then at the maximum age L_{max} as shown in figure C.1. Let E_0, E_1, E_{15}, E_{45} and E_{65} denote the known life expectancies at ages 0, 1, 15, 45 and 65, respectively and let p_{15}, p_{45}, p_{65} and $p_{L_{max}}$ be the corresponding proportions of people who survive up to age 15, 45, 65 and L_{max}, respectively, where L_{max} is again the maximum age. Note that p_1, the proportion surviving up to age 1 is assumed to be equal to 1. From figure C.1 we can see that the total life expectancy at birth is given by the total area below the suvivorship curve , i.e.

$$E_0 = 1 + (15-1)p_{15} + (45-15)p_{45} + (65-45)p_{65} + (L_{max}-65)p_{L_{max}} \quad \text{(C.1)}$$

$$= 1 + 14p_{15} + 30p_{45} + 20p_{65} + (L_{max}-65)p_{L_{max}} \quad \text{(C.2)}$$

Now L_{max} is simply given to be 65 + life expectancy at age 65, ie.

$$L_{max} = 65 + E_{65}. \quad \text{(C.3)}$$

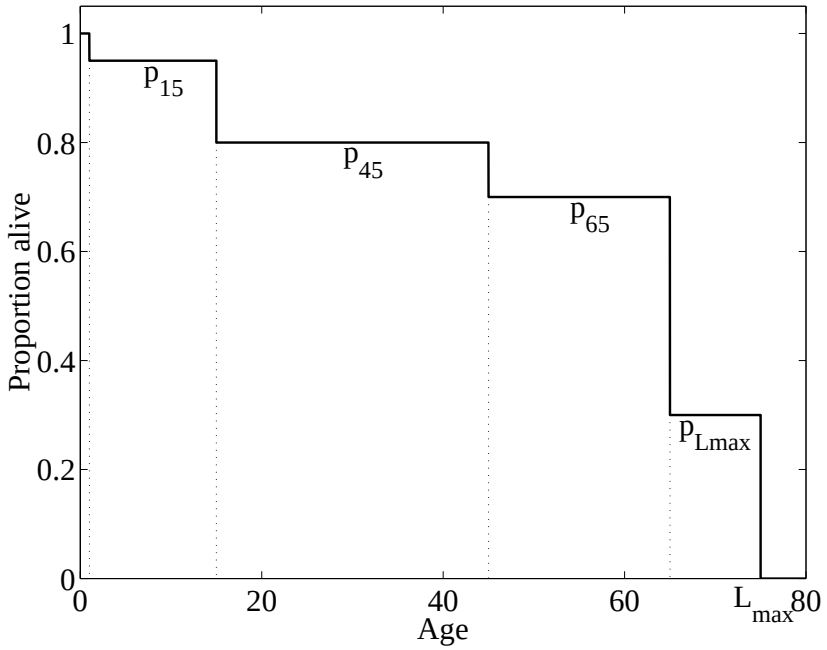


Figure C.1: Determining the survivorship profile from the knowledge of life expectancies at ages 0, 1, 15, 45 and 65. In this survivorship model, all individuals survive to age 1. Thereafter a fraction p_{15} survive to age 15, a fraction p_{45} to age 45, a fraction p_{65} to age 65 and finally fraction $p_{L_{max}}$ survive to the maximum age L_{max}.

Substituting into the equation C.2 yields:

$$E_0 = 1 + 14p_{15} + 30p_{45} + 20p_{65} + E_{65}p_{L_{max}} \tag{C.4}$$

However, we can also rewrite life expectancy at birth as

$$E_0 = 1 + p_{15}E_1 \tag{C.5}$$

which after rearranging yields that $p_{15} = (E_0 - 1)/E_1$. With the knowledge of p_{15}, we can proceed to estimate p_{45} by the same argument by rearranging $E_0 = 1 + 14p_{15} + p_{45}E_{15}$. The remaining unkowns p_{65} and $p_{L_{max}}$ can then be evaluated in a similar iterative fashion. The results of this calculations, based on the estimates of life expectancies given in table 5.5 are shown in the table C.1.

	Kazakhstan	Kyrgyzstan	Tajikistan	Turkmenistan	Uzbekistan
p_{15}	0.974	0.971	0.968	0.957	0.974
p_{45}	0.960	0.949	0.941	0.920	0.947
p_{65}	0.809	0.843	0.846	0.825	0.868
$p_{L_{max}}$	0.393	0.490	0.560	0.448	0.533

Table C.1: Estimates of the proportion of individuals surviving up to age 15, 45, 65 and L_{max} as denoted by p_{15}, p_{45}, p_{65} and $p_{L_{max}}$, respectively.

Appendix D

Vaccination in type I and type II populations

Suppose that one considers vaccinating two populations, one with type I mortality and the other with type II mortality, albeit both with the same life expectancy L. Let us assume that a proportion p of the the population are vaccinated at an age a. A natural question to ask is in whether, in the long run, our 2 equivalent vaccination programmes will result in the same proportion of susceptibles in the 2 populations. If not, in which population would one expect to find the highest proportion of susceptibles. Figure D.1 shows a sketch of the vaccination programme on the two populations. Intuitively one might expect that the the higher proportion of younger individuals in the type II population could lead to a higher proportion of susceptibles. However, this is not the case and in fact the exact opposite is true, namely that the proportion of susceptibles in the type II population will also be lower than in the type I population. From the figure D.1 it is easy relatively easy to work out the fraction of of susceptibles of the total population analytically.

In the population with type I mortality, the proportion of susceptibles can be written

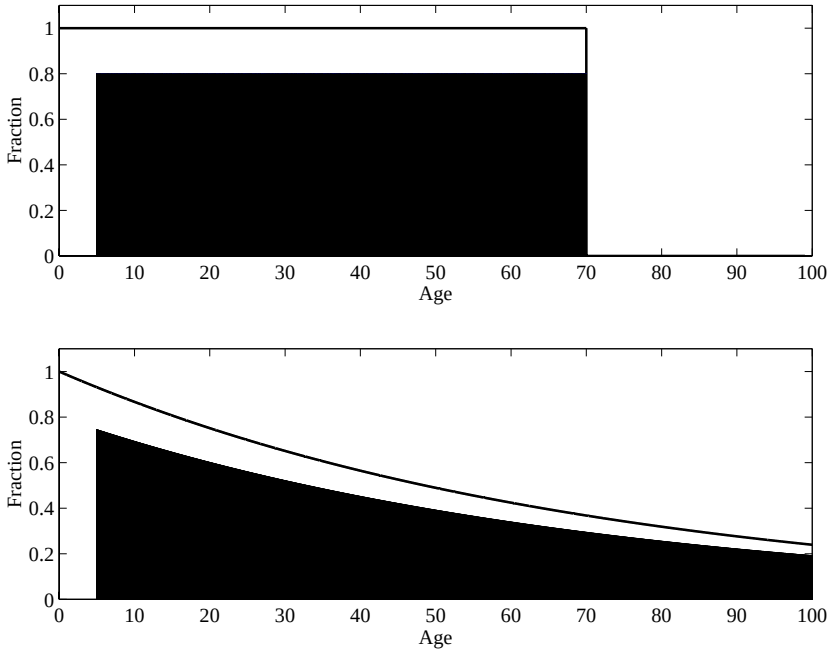


Figure D.1: Immunity profiles resulting from vaccinating 80% of 5 year olds in populations with type I and type II mortality.

as

$$s_I = \frac{a + (1-p)(L-a)}{L} \tag{D.1}$$

$$= 1 - p + pa/L. \tag{D.2}$$

In the population with type II mortality, the fraction susceptible s_{II} is given by

$$s_{II} = \frac{(1 - \exp(-a/L))L + (1-p)\exp(-a/L)L}{L} \tag{D.3}$$

$$= 1 - p\exp(-a/L) \tag{D.4}$$

Then the difference $s_I - s_{II} = -p + pa/L - p\exp(-a/L)$ is easily shown to be positive as long as $0 < a < L$ and $p > 0$, by graphical means. Figure D.2 shows the graph of $f(x) = \exp(-x) + x - 1$, which is greater than 0 if $0 < x < 1$.

The fact that the proportion of susceptibles under this vaccination strategy will always be greater in type I than in type II can also be seen from a more heuristic argument. First, we note that from age 5 onwards, the proportion of suceptibles in

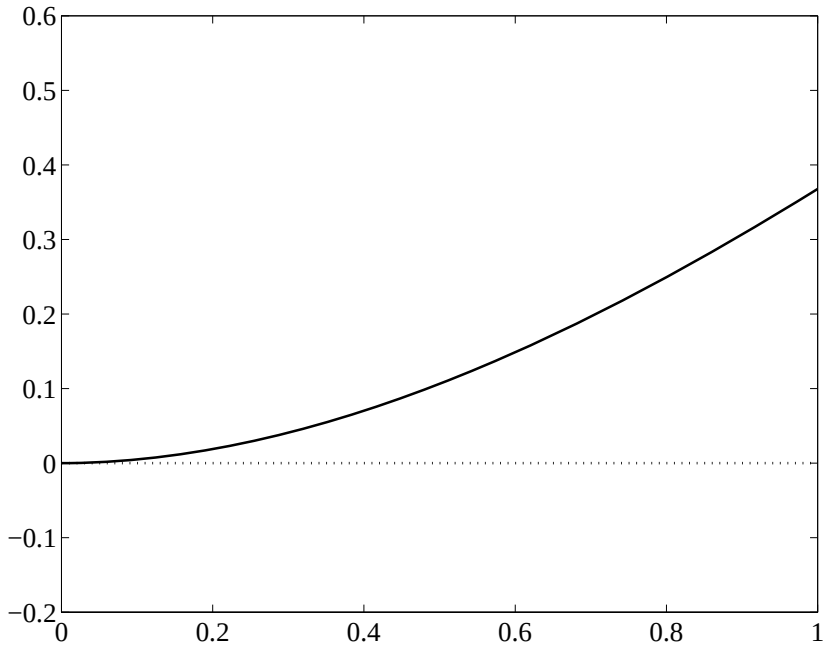


Figure D.2: Shown is the function $f(x) = \exp(-x) + x - 1$, which is greater than 0 if $0 < x < 1$

.

both populations is exactly 80%. Similarly, 100% of individuals in both populations aged less than 5 are susceptible. The only difference lies therefore in the fact that the fraction of less than five year olds (with respect to the total population) is lower in the population with type II mortality, than in that with type I mortality.

The same argument can also be applied when vaccination occurs at several stages like the strategy suggested by the WHO-Europe for having 85%, 90% and 95% at ages 1-4, 5-9 and 10+ year olds immune.

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