CoMPLEX
University College London

Summer Project

How To Increase The Benefits of Childhood Vaccination in The UK

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Abstract

The current vaccination schedule for childhood vaccination in the UK consists of vaccinating children age 0-5 against 11 vaccine preventable diseases including measles, mumps and rubella. Under the current schedule a single MMR vaccine is given to prevent against all of these three diseases: measles, mumps and rubella and it is administered as a single dose at 12 months of age and a top-up second dose at 40 months old. Changes to the current MMR vaccination schedule may affect the impact of the MMR vaccine and in this project we aim to explore this. Specifically, within the scope of this work we will develop, calibrate and analyse a mathematical model for transmission of measles, mumps or rubella. The model will allow us to explore the impact as the number of disease cases under different MMR vaccination scenarios including changes to vaccine coverage orscheduled timing of vaccine administration.

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Chapter 1

Introduction & Motivation

1.1 Childhood vaccination in the UK

The current childhood vaccination in the UK includes vaccinating children ages 0 to 5 years, immunizes children against 11 preventable infectious diseases and is offered is freely as part of the childhood health care supplied by the National Health Service (NHS). This childhood immunisation programme starts at 2 months and extends to 40 months with administration of different vaccines at different times over this period [6]. The full details of the current schedule are contained in Figure 1.1

<table>
<tr><th>Vaccine</th><th>2 mo.</th><th>3 mo.</th><th>4 mo.</th><th>12 mo.</th><th>3–4 yrs</th></tr>
<tr><td>Diphtheria, pertussis, and tetanus</td><td rowspan="3">DTaP +
IPV +
Hib</td><td rowspan="3">DTaP +
IPV +
Hib</td><td rowspan="3">DTaP +
IPV +
Hib</td><td></td><td rowspan="2">DTaP +
IPV</td></tr>
<tr><td>Polio vaccine (inactivated)</td><td></td></tr>
<tr><td>Haemophilus influenzae type b</td><td rowspan="2">Hib +
MenC</td><td></td></tr>
<tr><td>Meningococcus</td><td></td><td>MenC</td><td></td><td></td></tr>
<tr><td>Rotavirus (from July 2013)</td><td>Rotavirus</td><td>Rotavirus</td><td></td><td></td><td></td></tr>
<tr><td>Pneumococcal</td><td>PCV</td><td></td><td>PCV</td><td>PCV</td><td></td></tr>
<tr><td>Measles, mumps, and rubella</td><td></td><td></td><td></td><td>MMR</td><td>MMR</td></tr>
</table>

Figure 1.1: Current childhood vaccination schedule in the UK from 2 month to 4 years of age.

Although the vaccine programme is effective in preventing a vast amount of disease cases across different disease and population groups, in the recent years there have been outbreaks in a number of the diseases included in the current vaccine programme, even though none of these diseases are in an endemic state in the UK. Specifically there have been large outbreaks of measles, mumps and whooping cough (pertussis) in 2011, 2012 and 2013 and the again mumps and pertussis

in 2014. In additionsome smaller and irregular outbreaks of rubella have also been observed in [5] .

These recent outbreaks might have been a result of a decline in vaccine uptake. Specifically for measles, mumps and rubella the vaccination was introduced in the UK in 1988 [7] and although the currently reported coverage is high at 92% [8], the vaccine uptake fell in the late 1990s from 92% in 1996 to 80% in 2003 [10]. This was a consequence of the suggestion of a potential link between this vaccine and the onset of autism in children as reported in the study by Wakefield and collegues [18]. This study was subsequently proved to be unfounded, falsely obtained and discredited on many occasions [13, 9, 15].

The presence of the outbreaks brought into questioning the influence of vaccine coverage on the vaccine impact and how possible changes to schedule (e.g. missing a dose of a vaccine) can affect the overall impact and effectiveness of the vaccination programme across different target groups. Possible questions were raised around how any changes in the programme such as altering the vaccination timing or adding a new vaccine, which is currently done on a case-by-case basis, can influence the effectiveness of the immunisation programme as a whole.

1.2 Modelling vaccination-preventable diseases

Mathematical modelling combined with numerical simulations provide a platform for understanding the dynamics of vaccine-preventable diseases and evaluating the impact of different vaccine scenarios. Specifically mathematical equations can be designed to describe the transmission of the disease and then using simulations it is possible to investigate the effect of different scenarios and vaccination strategies impossible without the use of these tools. Moreover, such experimentations in real life would be unethical and impossible to do. Hence, mathematical and computational modelling provides a theoretical laboratory for diseases and their vaccines. A general approach in modelling of infectious diseases is the development of an SIR compartmentalised model where each compartment describes the population of Susceptible (S), Infected (I) and Recovered (R) individuals and hence represent the different stages of the infection of the disease. In addition to these three compartments a fourth compartment can also be used, called the Latent stage, to account for the period where individuals are infected but not yet infectious. Since different diseases are more dangerous to different age groups vaccines are given to specific age-cohorts and hence when modelling vaccine-preventable diseases and vaccines there is a need to include different age groups. Then by monitoring the distribution of infected individuals in each age group the model can determine which age-cohort drives the epidemic.

Mathematical models for infectious disease can be categorised as deterministic or stochastic (or Markov processes) models. Both methods have their advantages and disadvantages. Stochastic models are used often when the disease is not at an endemic steady state and $R_0 < 1$ .In that case while a deterministic model can, by design, only give a continuously declining infection, a stochastic model can capture the probabilistic nature of the infectious disease, such as outbreaks, and represent the dynamics better. On the other hand deterministic models are simpler and allow for more analytical results and are good at capturing steady state epidemics. Furthermore due to the absence of noise, it is often easier to calibrate deterministic model and also their simplicity can often be helpful in providing insight into the basic dynamics of a disease but there are also highly complex and complicated deterministic models. In our project we will use a deterministic model for disease spread.

One of the most important factors concerning a disease is its ability to spread within a population. If the spread can be controlled then the infection will not reach pandemic state and can be constraint. One of the key things in halting the spread of infectious disease is the rate at which additional (secondary) infections can originate from the primary infection. If no secondary infections can occur, or they occur and are controlled then the spread of the infection can also be controlled. A parameter that can capture this analytically is the reproduction number R_0 defined as the number of secondary infections produced due to an individual entering a disease free population. Within the mathematical models infectious disease transmission the value of R_0 controls the fate of the epidemic [12], with R_0 value less than 1 yielding a disease-free steady state and controlled epidemic whereas a value of R_0 greater than 1 allows for a secondary spread of the infections and the infectious disease reaching an endemic steady state.

1.3 Aims of the project

In this project we will not have the platform to evaluate the whole childhood vaccination programme in the UK as a whole, but instead we will focus on the vaccine against measles, mumps and rubella in the UK. Measles, mumps and rubella are highly contagious viral diseases which are very dangerous for young children and pregnant mothers. But all three diseases can effectively be prevented through the single measles- mumps-rubella (MMR) vaccine [11]. The MMR vaccine in the UK is known under the brand name Priorix or MMR-VAXPRO [11] and is currently given as a two dose vaccine with the first dose given in the first month of the first birthday and the second dose between 3 and 4 years old .

Within the scope of this project we will develop a mathematical framework that provides a platform for the assessment of this MMR vaccine. We will construct and analyse a mathematical model for transmission of infectious diseases and apply the model specifically to measles by parameterising the equations to this disease. We will use the model to project the impact of changes in the vaccine coverage and timing on the measles disease burden quantified as the number of disease cases per year.

Chapter 2

Description of the mathematical model and model parameters

2.1 Mathematical model for transmission of measles with and without MMR vaccine

The model we develop is a general model for transmission of infectious diseases such as measles, mumps and rubella. In its skeleton the model describes the transmission of any infectious disease from susceptible to infected individuals for different age-cohorts and constitutes a system of ordinary differential equations (ODEs). The model is stratified into four age-cohorts: 0-1 year old, 1-5 years old, 5-15 years old and 15-30 years old. We note that there is an upper limit in the fourth age group to account for the fact that people over certain age are immune. Each age compartment is divided into susceptible, infected and recovered-immune with the exception of the first age group where there is the maternal immunity subpopulation (M). Since they do not affect the impact of the vaccination, the recovered-immune populations are not included in our model. Also for simplicity we assume that after infection an individual is infectious hence we do not consider a latent infection period.

The system of equations that constitute our model is;

Age Group	**Age Range**
1	0-1
2	1-5
3	5-15
4	15-30

There is an upper limit in the fourth age group to account for the fact that people over a certain age are already immune. Of course further exploration and data are needed to decide which the appropriate cut-off age is. Each age compartment is divided into susceptible, infected and recovered-immune with the exception of the first age group where there is the maternal immunity subpopulation (M). The recovered-immune populations are not included in our model since their are not needed for our analysis. For simplicity we assume that after infection an individual is infectious hence we do not consider a latent infection period.

$$\frac{dM}{dt} = B - \mu M - \alpha_1 M$$

$$\frac{dS_1}{dt} = \mu M - \lambda_1 S_1 - \alpha_1 S_1$$
$$\frac{dS_2}{dt} = \alpha_1(1 - e\nu)S_1 + \alpha_1(1 - e\nu)M - \lambda_2 S_2 - \alpha_2 S_2$$
$$\frac{dS_3}{dt} = \alpha_2 S_2 - \lambda_3 S_3 - \alpha_3 S_3$$
$$\frac{dS_4}{dt} = \alpha_3 S_3 - \lambda_4 S_4 - \alpha_4 S_4$$

$$\frac{dI_1}{dt} = \lambda_1 S_1 - \gamma I_1 - \alpha_1 I_1$$
$$\frac{dI_2}{dt} = \lambda_2 S_2 + \alpha_1 I_1 - \gamma I_2 - \alpha_2 I_2$$
$$\frac{dI_3}{dt} = \lambda_3 S_3 + \alpha_2 I_2 - \gamma I_3 - \alpha_3 I_3$$
$$\frac{dI_4}{dt} = \lambda_4 S_4 + \alpha_3 I_3 - \gamma I_4 - \alpha_4 I_4$$

Here M represents the first population as the maternally immune population of age 0-1. In this population people are born with a constant rate per year B and either lose their immune with a rate or age above the first year of age and move directly to the susceptible population of age 1-5 (S2). The main transfer in and out of susceptible population is done by infection or ageing. The infection term will be explained explicitly later on. In the first two susceptible population of age 0-1 and 1-5 there are some extra terms not present in the older susceptible populations. Individuals who lose their maternal immunity are transferred in S1 with a rate μ. Furthermore, in S2 individuals enter the population after being vaccinated at the end of year one (in the case of measles, mumps and rubella) and hence the uptake is the percentage of the population that was not vaccinated plus that where the vaccine was ineffective (1-e), where e is the effectiveness and is the uptake. These individuals come from both S1 that have not being infected and M that have lost their immunity before the end of year 1. We make the assumption here that the vaccine on the 12 months of age has the same effectiveness to people that have lost their immunity and people that have not. This is sufficiently simple for the purposes of this project, but further investigation beyond the scope of this project is needed to fully confirm this. Finally, individuals move to the infected population groups by infection from the susceptible population and either age to move to an older infected population or recover with a rate . Since the order of magnitude of the recovery rate is much larger than the ageing rate, the ageing terms can potentially be ignored to a leading order. But for completeness also aging effect is insignificant, we have included it in our model.

The force of infection, i , is given by the following equation:

$$\lambda_i = \beta \sum_j \rho_{ij} \frac{I_j}{N_j}$$

Here, ρ is the mixing matrix that contains the average number of contacts of an individual in

age group i (row) with the each age group j (column) per year. These values are given in table below and were taken from [14]. represent the infectivity and $\frac{I_j}{N_j}$ represents the fraction of the population in cohort j (given by N_j) that is infected (I_j).

	0 - 1	**1 - 5**	**5 - 15**	**15 - 30**
0 - 1	0	60.6	24.1	31.4
1 - 5	226.3	647.1	176.3	127
5 - 15	234.7	458.4	2652.1	470.9
15 - 30	503	543.5	774	2403.1

2.2 Parameter definition and values

Although the model developed in 2.1 can readily be applicable to measles, mumps and rubella in this project we parametrise the model to measles. The model parameters and their values specific to measles are contained in the next table. As mentioned before the mixing matrix is populated with values from [14]. The rest of the values were taken from he available literature and beta was varied as part of the calibration of the model.

Parameter Description	**Parameter Symbol**	**Value**	**Reference**
Birth rate	B	698,512	[1]
Loss of maternal immunity rate per individual	μ	1(per year)	[2]
Ageing rate for each age group	α_i	$1, 0.25, 0.1, 0.066$	model paramater
Vaccination coverage	ν	97%	[16]
Vaccination efficacy	e	95%c	[16]
Infectivity	β	found through calibration	model parameter
Contact rate matrix between the different age groups	ρ_{ij}	see specific table	[14]
Recovery rate (one over the infectiousness period)	γ	disease specific (infectiousness period)	[4]

All rates are given as per year.

2.3 Defining different vaccination scenario

Every vaccine is characterised by vaccine coverage and vaccine effectiveness. The proportion of people who are vaccinated makes up the coverage of the vaccination program and this can vary per year, across age groups and risk groups. The proportion of the vaccinated population who become fully immune is determined by the efficacy. The coverage of the current MMR vaccine is high at 92% and its efficacy is around 95%. The product of vaccine coverage and vaccine efficacy represents effective vaccine coverage and in our model this is the product $e\nu$.

Currently the MMR vaccine in the UK is given as a 2-dose vaccine with the first dose administered around the 1^{st} birthday and the second dose at around 40 months old. There are currently discussions whether earlier administration of the vaccine can impact the effectiveness of the vaccine. Furthermore, following the reduced uptake of MMR vaccine in the late 1990s worries exist if this might happen again. Hence within this project we will explore the impact of shifting timing of the MMR 1^{st} dose vaccine from 12 months to 9 months and also what if the second dose of the vaccine is not taken. Details of these 4 different scenarios are given in the next 4 subsections

2.3.1 Scenario 1: Single dose MMR vaccination at 12 months old

The first scenario assumes that only a single dose of the MMR vaccine is given at the age of 12 months and that individuals do not show for the top-up second dose at 40 months. This represents the simplest scenario with the model to be used without further modifications. We project the number of measles cases for different levels of effective coverage of the vaccine when we vary v and assume vaccine efficacy is 95%.

2.3.2 Scenario 2: Single dose MMR vaccination at 9 months old

The second scenario is again a single dose scenario but the vaccine in given on the 9th month instead of the 12th. In order to account for the earlier vaccination there are a few changes and assumptions that need to be made in order to modify the model.

The second scenario assumes an earlier administration of the vaccine (9th instead of the 12th month) but again a single dose scenario. In accommodate for this we stratified the 0-1 years old age cohort into two age cohort 0-9 months and then incorporated the 9-12 months population in the 2nd age-cohort. Hence in this case we have the following age groups: 0-9 months, 9 months to 5 years, 5 years to 15 years and 15 to 30 years old. The only differences with the previous case (12 month vaccine) are the first two ageing rates, α_1, α_2 the first two total population sizes as well as the mixing rates between that include these age groups. Since the data available for the mixing rates have year precision the new rates were found by increasing or decreasing the appropriate rates. To see this we first have to make some basic assumptions. (a) By decreasing the duration of the first group from 12 months to 9 months we are taking one quarter of the population off and adding it to the second group which now extends from 9 months to 5 years. (b) Reducing the population of the first group does not affect the contact patterns of the individuals in this group and hence ρ_{1j} stay exactly the same. As a result ρ_{j1} decreases by one quarter due to the balance equation. (c) The contact rates of individuals from other groups with group 2 increase due to the increased population. (d) The mixing patterns of group 2 change due to the fact that the composition of the groups changes due to the addition of the individuals of age (9-12

months) which have the same contact patterns as group 1 individuals. In mathematical terms the assumption are as follows:

Balance Equation:

$$N_i \rho_{ij} = N_j \rho_{ji} \tag{2.1}$$

$$N_1' = \frac{3}{4} N_1 \tag{2.2}$$

$$N_2' = N_2 + \frac{1}{4} N_1 \tag{2.3}$$

Mixing rates of individuals from group j wih group 1 (assumption b):

$$N_1' * \rho_{1j} = N_j \rho_{j1}'$$

$$\rho_{j1}' = \frac{N_1'}{N_1} \rho_{1j} \implies (2.2), (2.1)$$

$$\rho_{j1}' = \frac{3}{4} \rho_{j1} \tag{2.4}$$

Mixing rates of individuals from group j with group 2 (assumption c):

$$\rho_{j2}' = \rho_{j2} + \frac{1}{4} \rho_{j1} \tag{2.5}$$

Mixing rates of individuals from group 2 with other groups (assumption c)

$$\rho_{2j}'(N_2 + \frac{1}{4} N_1) = \rho_{j2}' N_j \implies (2.5), (2.1)$$

$$\rho_{2j}' = \frac{N2}{N_2 + \frac{1}{4} N_1} \rho_{2j} + \frac{N1}{N_2 + \frac{1}{4} N_1} \rho_{1j} \tag{2.6}$$

The new mixing matrix for vaccination at 9 months is given at the **Mixing Matrices** section.

Simulations of these model give the infected population for each age group but the first two age groups have different time windows, as already mentioned (1-9 months, 9-60 months). Hence, in order to be able to compare our results with the earlier scenario we needed the cases for the initial age groups (0-1,1-5,5-15,15-30). This was achieved by dividing the number of cases of the second group (I_2) into 51 months, $I_2/51$. 3/51 of I_2 were given to I_1 to account for the three month difference (9 to 12 months) and the rest was the new I_2 ($48/51 * I_2$) which represented the infected population of age 1-5. Of course this is not the most effective way of finding which percentage of the infected individuals in I2 belong to the age of 9-12 months but there was currently no other way of tracking them without introducing a separate age group.

2.3.3 Scenario 3: Two dose MMR vaccination with 1^{st} dose at 12 months old and 2nd dose at 40 months old

This scenario represents the current vaccination strategy in the UK. We add a second vaccine dose to the model by splitting the second age cohort. Initially it was 1-5 year but to account for the second dose at 40 months the second age group was broken down to two, 1- $\frac{1}{\alpha_{2ndD}}$ and $\frac{1}{\alpha_{2ndD}}$ -5. Due to this division of the second age group there was the need to use a new mixing matrix which was given for the contacts between the groups 0-1, 1-3 ,3-5, 5-15 and15-30 giving a total of five age groups. The second dose is given at 40 months and hence 4 months needed to be added to the second age group and subtracted from the third. The procedure we used to do this and find the new mixing matrix was the same described earlier for the 9 months scenario. The 12-40 scenario mixing matrix is given at the Mixing Matrices section and the modifications are given by the following equations:

Mixing rates of individuals from group j wih group 1 (assumption b):

$$\rho'_{j3} = \frac{5}{6}\rho_{j3} \tag{2.7}$$

Mixing rates of individuals from group j with group 2 (assumption c):

$$\rho'_{j2} = \rho_{j2} + \frac{1}{6}\rho_{j3} \tag{2.8}$$

Mixing rates of individuals from group 2 with other groups (assumption c)

$$\rho'_{2j} = \frac{N2}{N_2 + \frac{1}{6}N_1}\rho_{2j} + \frac{N3}{N_2 + \frac{1}{6}N_3}\rho_{3j} \tag{2.9}$$

For the two dose vaccination there are two cases depending on the current vaccination policy.

CASE A. The second dose is available to everyone even if they did not take the first. For this case no further modification is needed to the model other than the addition of a new group for each part of the model (susceptible, infected and recovered). The age groups are:

Age Group	**Age Range**	**Ageing Rate**
1	0-1	1
2	1-3.3	0.43
3	3.3-5	0.6
4	5-15	0.1
5	15-30	0.066

Again in order to have consistency in the age groups, the two groups of age 1-3.3 and 3.3-5 are added to a single group 1-5.

CASE B. In this case people who got the first dose of vaccine can get or want to get the second. To model case B we have to break the susceptible population of the new second age group into two subpopulations. The first subpopulation is the susceptible that got vaccinated but the vaccine did not work due to not perfect efficacy, S_2^{eff}. The second subpopulation is the susceptible that did not take the vaccine at all, S_2^{no}. As a result susceptibles from these two subpopulation move to the next susceptible age group with different rates. The second population moves with an ageing rate of $\alpha_{2ndD} S_2^{no}$ in contrast to the first which moves with a rate similar to what we had in our original model, $\alpha_{2ndD}(1 - e\nu)$. The effective coverage of the second dose is different than that of the first. The relevant part of the model is:

$$\frac{dS_2^{eff}}{dt} = \alpha_1 \nu (1-e)(S_1 + M) - \lambda_2 S_2^{eff} - \alpha_2 S_2^{eff}$$
$$\frac{dS_2^{no}}{dt} = \alpha_1 (1-\nu)(S_1 + M) - \lambda_2 S_2^{no} - \alpha_2 S_2^{no}$$

The mixing matrix can be found at the **Mixing Matrices** section.

2.3.4 Scenario 4: Two dose MMR vaccination with 1^{st} dose at 9 months old and 2nd dose at 40 months old

The changes in the model are equivalent to those in section 2.3.3 except for instead of splitting the 1st age cohort to 0-12 and 12-40 months we now split it to 0-9months and 9-40 months old. The rest of the methodology remains the same. Again the mixing matrix can be found at the **Mixing Matrices** section.

Chapter 3

Methods

3.1 Calculation of R_0 for measles

R_0 as mentioned in the introduction is defined as the average number of secondary infection produced from an infected individual when entering a disease-free environment. This definition is clear for single population models and R_0 is generally given by the contact rate times the infectious period or death-adjusted infectious period, depending on the model [12]. Hence, it is usually given by the simple formula:

$$R_0 = \frac{\beta}{\gamma + \alpha} \tag{3.1}$$

Here, α is an ageing rate (death rate) and γ is the recovery rate.

The situation is more complicated for models where there is more than one compartments. For these models a more general definition is appropriate where R_0 is defined as the number of new infections produced by a typical infective individual in a population at a disease free equilibrium [17].Van den Driessche and Watmough [17] addressed this problem and proposed a general method for calculating R_0 for compartmental models. Their method was used to derive the reproduction number for our models . Here we derive R_0 for the original model intented for single vaccination at 12 months and measles. The same method is used to derive it the other scenarios as well.

First let us define $\mathcal{F}_i$ as the rate of new infections for compartment i and $\mathcal{V}_i$ the transfer of individuals from compartment i by means other than infection. For our model there are 9 compartments or 13 if we include the recovered/immune populations. Hence we have the following two matrices:

$$\mathcal{F} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \beta \sum_{j=1}^{4} \rho_{1j} \frac{I_j}{N_j} S_1 \\ \beta \sum_{j=1}^{4} \rho_{2j} \frac{I_j}{N_j} S_2 \\ \beta \sum_{j=1}^{4} \rho_{3j} \frac{I_j}{N_j} S_3 \\ \beta \sum_{j=1}^{4} \rho_{4j} \frac{I_j}{N_j} S_4 \end{pmatrix}$$

$$\mathcal{V} = \begin{pmatrix} -B + \mu M + \alpha_1 M \\ \mu M + \beta \sum_{j=1}^{4} \rho_{1j} \frac{I_j}{N_j} S_1 + \alpha_1 S_1 \\ -\alpha_1(1 - e\nu)(M + S_1) + \alpha_2 S_2 + \beta \sum_{j=1}^{4} \rho_{2j} \frac{I_j}{N_j} S_2 \\ -\alpha_2 S_2 + \alpha_3 S_3 + \beta \sum_{j=1}^{4} \rho_{3j} \frac{I_j}{N_j} S_3 \\ -\alpha_3 S_3 + \alpha_4 S_4 + \beta \sum_{j=1}^{4} \rho_{4j} \frac{I_j}{N_j} S_4 \\ \gamma I_1 + \alpha_1 I_1 \\ \gamma I_2 - \alpha_1 I_1 + \alpha_2 I_2 \\ \gamma I_3 - \alpha_2 I_2 + \alpha_3 I_3 \\ \gamma I_4 - \alpha_3 I_3 + \alpha_4 I_4 \end{pmatrix}$$

To proceed let us also define F and V, where $F = \frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)$ and $F = \frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)$. Only the infected compartments are taken into account for this calculation, so {i,j,k}=I_c, I_{sw}. x_0 is the value of the population in each compartment at the disease free equilibrium, so in this case $x_0 = (M_0, S_1^0, S_2^0, S_3^0, S_4^0, 0, 0, 0, 0, R_1^0, R_2^0, R_3^0, R_4^0)$. From these formulas we can see that the {i,j} component of F gives the rate at which infected individuals from compartment j produce new infections in compartment i and the {j,k} component of V^{-1} gives the time an individual from compartment k spends at compartment j. Hence, FV^{-1} admits the average number of new infections in compartment i produced by an individual introduced in compartment k. This is called the next generation matrix [**?**] and its spectral radius gives R_0 for the system. In our particular model F and V are:

$$F = \begin{pmatrix} \beta \frac{S_1^0}{N_1} \rho_{11} & \beta \frac{S_1^0}{N_2} \rho_{12} & \beta \frac{S_1^0}{N_3} \rho_{13} & \beta \frac{S_1^0}{N_4} \rho_{14} \\ \beta \frac{S_2^0}{N_1} \rho_{21} & \beta \frac{S_2^0}{N_2} \rho_{22} & \beta \frac{S_2^0}{N_3} \rho_{23} & \beta \frac{S_2^0}{N_4} \rho_{24} \\ \beta \frac{S_3^0}{N_1} \rho_{31} & \beta \frac{S_3^0}{N_2} \rho_{32} & \beta \frac{S_3^0}{N_3} \rho_{33} & \beta \frac{S_3^0}{N_4} \rho_{34} \\ \beta \frac{S_4^0}{N_1} \rho_{41} & \beta \frac{S_4^0}{N_2} \rho_{42} & \beta \frac{S_4^0}{N_3} \rho_{43} & \beta \frac{S_4^0}{N_4} \rho_{44} \end{pmatrix}$$

$$V = \begin{pmatrix} \gamma + \alpha_1 & 0 & 0 & 0 \\ -\alpha_1 & \gamma + \alpha_2 & 0 & 0 \\ 0 & -\alpha_2 & \gamma + \alpha_3 & 0 \\ 0 & 0 & -\alpha_3 & \gamma + \alpha_4 \end{pmatrix}$$

Substituting values to all parameters except β and the disease-free values of the susceptible populations yields:

$$FV^{-1} = \begin{pmatrix} 4.33 * 10^{-8} S_1^0 \beta & 2.014 * 10^{-6} S_1^0 \beta & 8.054 * 10^{-7} S_1^0 \beta & 1.044 * 10^{-6} S_1^0 \beta \\ 2.118 * 10^{-6} S_2^0 \beta & 5.754 * 10^{-6} S_2^0 \beta & 1.57 * 10^{-6} S_2^0 \beta & 1.131 * 10^{-6} S_2^0 \beta \\ 8.279 * 10^{-7} S_3^0 \beta & 1.615 * 10^{-6} S_3^0 \beta & 9.079 * 10^{-}6 S_3^0 \beta & 1.613 * 10^{-6} S_3^0 \beta \\ 1.058 * 10^{-6} S_4^0 \beta & 1.137 * 10^{-6} S_4^0 \beta & 1.622 * 10^{-6} S_4^0 \beta & 5.007 * 10^{-6} S_4^0 \beta \end{pmatrix}$$

To find the eigenvalues with respect to β we need to give values to the disease-free steady state values for the susceptible populations. This is done by numerically solving the model for the disease free steady state with an effective coverage of 92%. The final results is:

$$R_0 = 5.7\beta \tag{3.2}$$

3.2 Calibration of the model using measles specific UK data

We calibrate the model using UK data for the transmission and spread of measles in 2013 [3]. Specifically, we fix all the model parameters to known values as per Table 1 and only vary the transmission probability β. It represents how infectious is a disease and need to be calibrated for each disease specifically since this is a very important parameter of the model that affects the steady state solution for the infected cases, as evident from Figure 2.1 showing the number of cases in the single dose (12 months) scenario with respect to β.

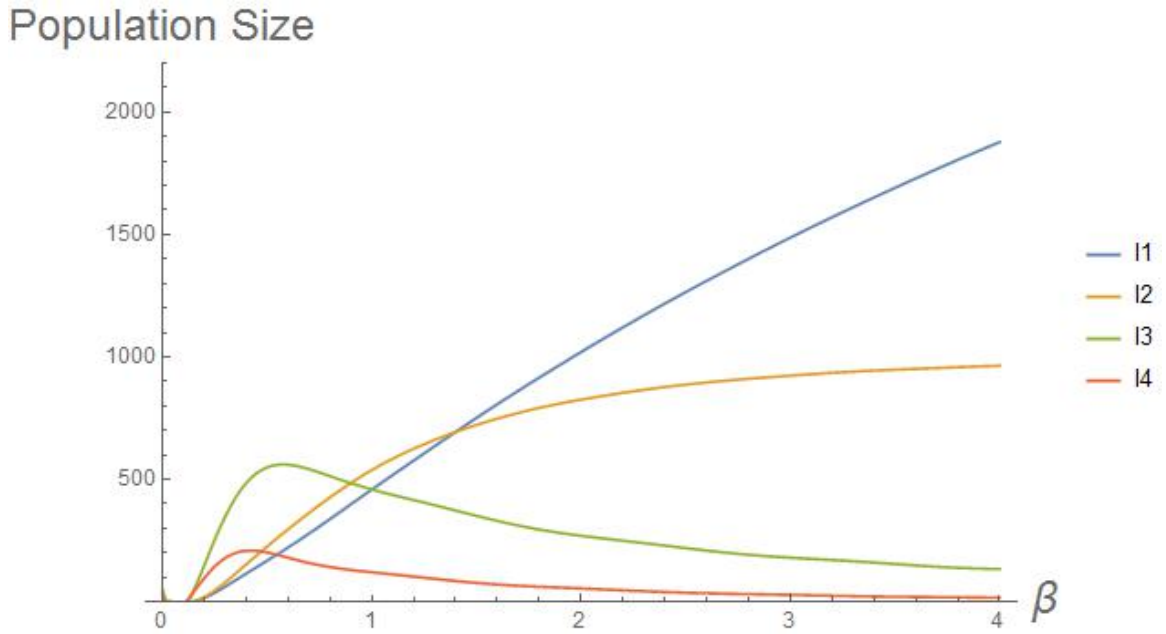


Figure 3.1: Population sizes of infected population per age group with respect to β.

The model was calibrated against the UK data for 2013, stratified per age cohort. The vaccination efficacy and coverage was kept constant both for the single and double dose models and at a level of 97% coverage and 95% efficacy as reported from previous work [16].

The model calibration includes calculation of the number of measles cases in each age-cohort for each scenario from the model and comparing these to the number of cases from the 2013 data. We do a two step calibration by first restricting R_0 to be within (10,20) (as adviced by Matt Keeling) and this gives us a range for β. We then calculate the optimal β in the best fit case. We define a best-fit measure as the minimal value of the sum of the absolute difference between model and data values. This best-fit measure is called the score and is given by:

$$Score = |I_1^{model} - I_1^{real}| + |I_2^{model} - I_2^{real}| + |I_3^{model} - I_3^{real}| + |I_4^{model} - I_4^{real}|$$

The minimal value of the score gives an optimal value of β and optimal β then induces a value for R_0.

Of course each scenario admits different R_0 as a function of beta and hence different β range and different optimal β_s, but it is not possible to have a valid comparison between the four scenarios if each has each own β. In order to resolve that after finding the optimal β for each scenario we examined which of these produces acceptable R_0 values for all four scenarios. The optimal β values that did were then simulated in all four scenarios so as to have a common base for comparison. Finally the calibrated model was used to project the number of cases for each age cohorts as well as the percentage of averted cases due to each vaccination scenario.

3.3 Defining the burden of measles

The burden of measles is defined as the total number of infected cases (number of infected cases per age group added to a total number) as found by the endemic steady-state solution of the model.

3.4 Calculating the impact of the MMR vaccine

We asses the impact of vaccination by calculating the disease burden with and without vaccine and for all four vaccination scenarios. The comparison is done both on an age cohort basis as on a total number of cases basis.

3.5 Analysis of the model

The model is solved for its endemic steady state. The endemic steady was chosen al though most of the vaccine-preventable diseases are not endemic in the UK. The reason behind that is that there seems to be an almost fixed number of cases for measles, mumps and rubella in the UK in the last few years. Despite the fact that the dynamics of these diseases are complex and the seasonality of the mixing patterns at the end of each year the number of cases accumulated for each age group is confined a specific range making it almost constant. Moreover, we are not interested in the dynamics and what happen in between the year but in the total number cases so as to use it as a measure of the benefit of different vaccination scenarios.

Chapter 4

Results

4.1 Finding the optimal beta and R_0 for measles

The tabla below contains the optimal values of beta and the corresponding R_0 values for each of the four vaccination scenarios. We note that these optimal β_s are specific for each scenario 1-4.

Scenario	$R_0(\beta)$	**Optimal** β	R_0
Single dose 12 months	5.7β	2.31	13.2
Single dose 09 months	57β	3.15	18
Two doses 12 - 40 months	2.7β	3.7	10
Two doses 09 - 40 months	2.66β	4.08	10.8

4.2 Number of measles cases for each scenario and different optimal β

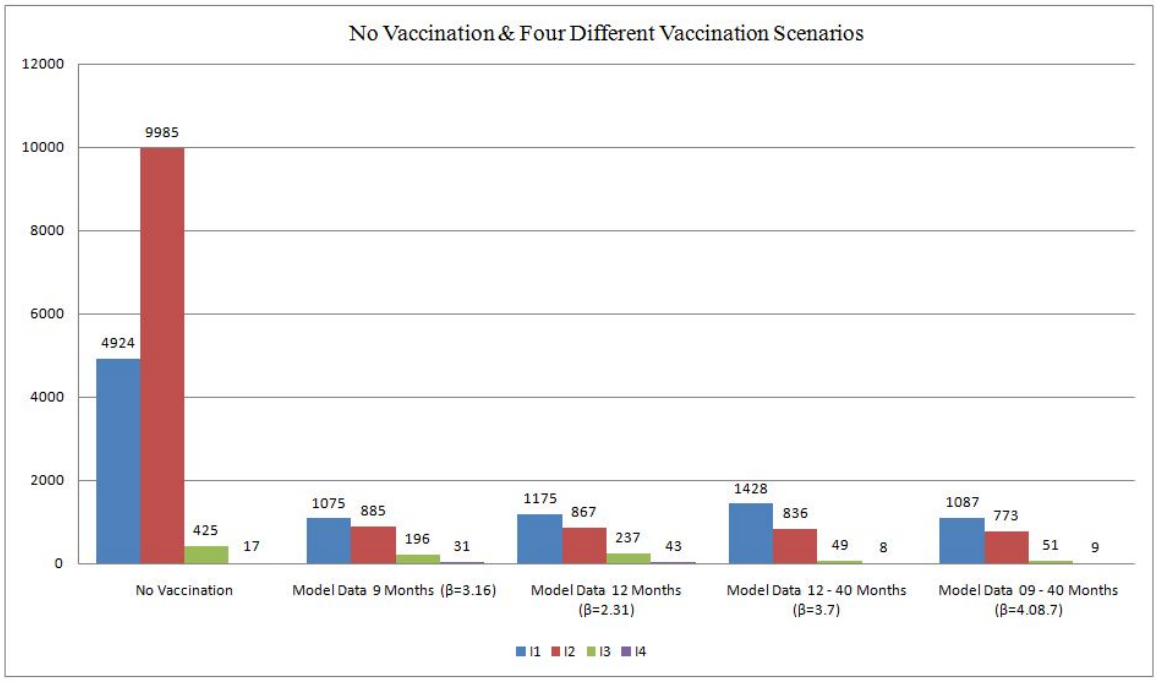


Figure 4.1: Histogram of the number of cases for each age cohort for each of the four vaccination scenarios for their respective optimal β and the no vaccine case.

4.3 Number of measles for same optimal β.

In order to compare the number of measles cases across different scenarios we need to choose a single optimal β and run the model for that beta. In order to restrict the value of R_0 within the realistic range [10,21] we need to choose a beta of 3.7 in which case the R_0 is respectively (21.1, 21.1, 10, 10) for the different scenario. This is the optimal β for the current vaccination schedule of 12-40 scenario. The results are contained in the following table and illustrated in Figure 4.2.

Scenario	R_0	N. of Cases	N. of Cases Averted per age group	Total n. of cases averted
Single dose 12 months	21.1	1768/955/145/19	3156/9030/280/-2	12464
Single dose 09 months	21.1	1231/915/167/23	3693/9070/258/-6	13015
Two doses 12 - 40 months	10	1428/836/49/8	3496/9149/376/9	13030
Two doses 09 - 40 months	10	1063/746/60/17	3861/9239/365/0	13471

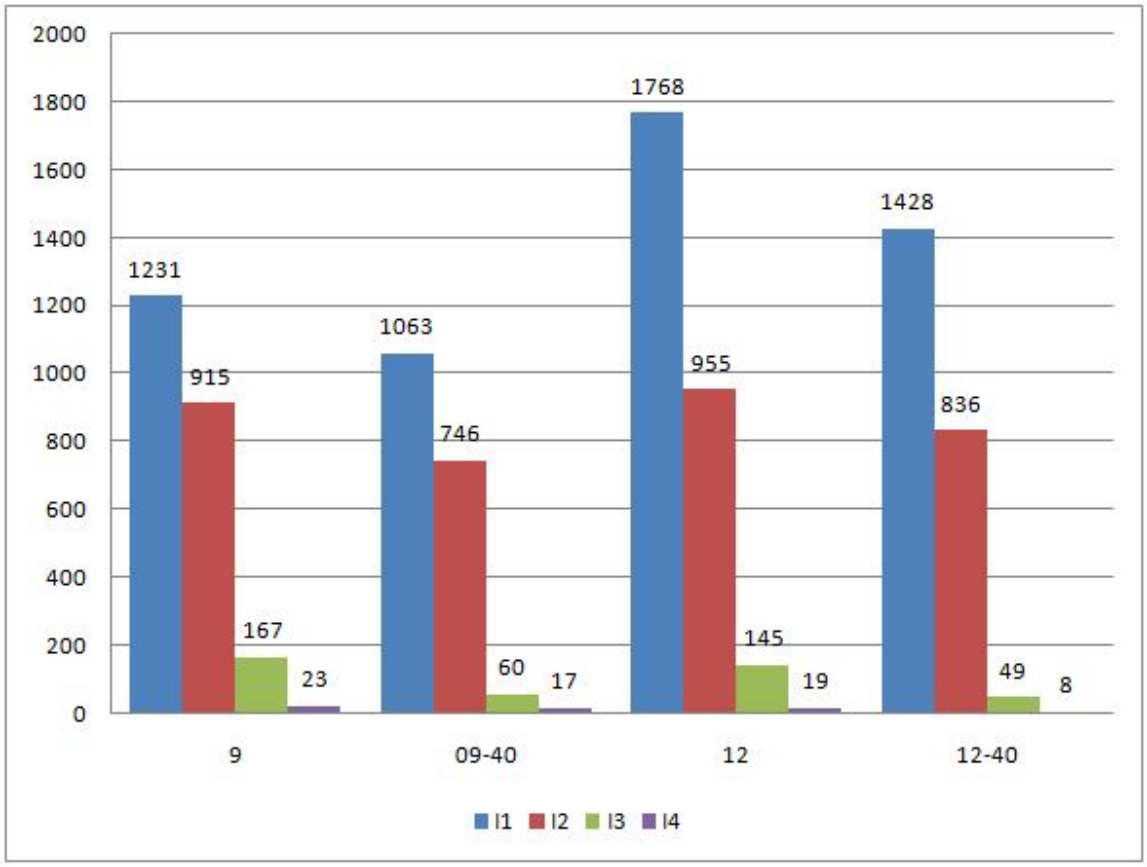


Figure 4.2: Histogram of the number of cases for each age group in the four vaccination scenarios for β=3.7.

It is interesting to compare this with the projections when the optimal value of β for the 9-40 vaccination scenario. In this case the optimal β is larger (β=4.08) but the values of R_0 are out of the realistic bounds (8.4, 8.4, 10, 10.8 respectively). Results are shown in Figure 4.3.

Scenario	R_0	N. of Cases	N. of Cases Averted per age group	Total n. of cases averted
Single dose 12 months	8.4	1907/966/130/16	3017/9019/295/1	12332
Single dose 09 months	8.4	1334/929/151/20	3590/9056/274/-3	12917
Two doses 12 - 40 months	11	1571/862/41/6	3353/9123/384/11	12871
Two doses 09 - 40 months	10.8	1087/773/51/9	3837/9212/374/8	13431

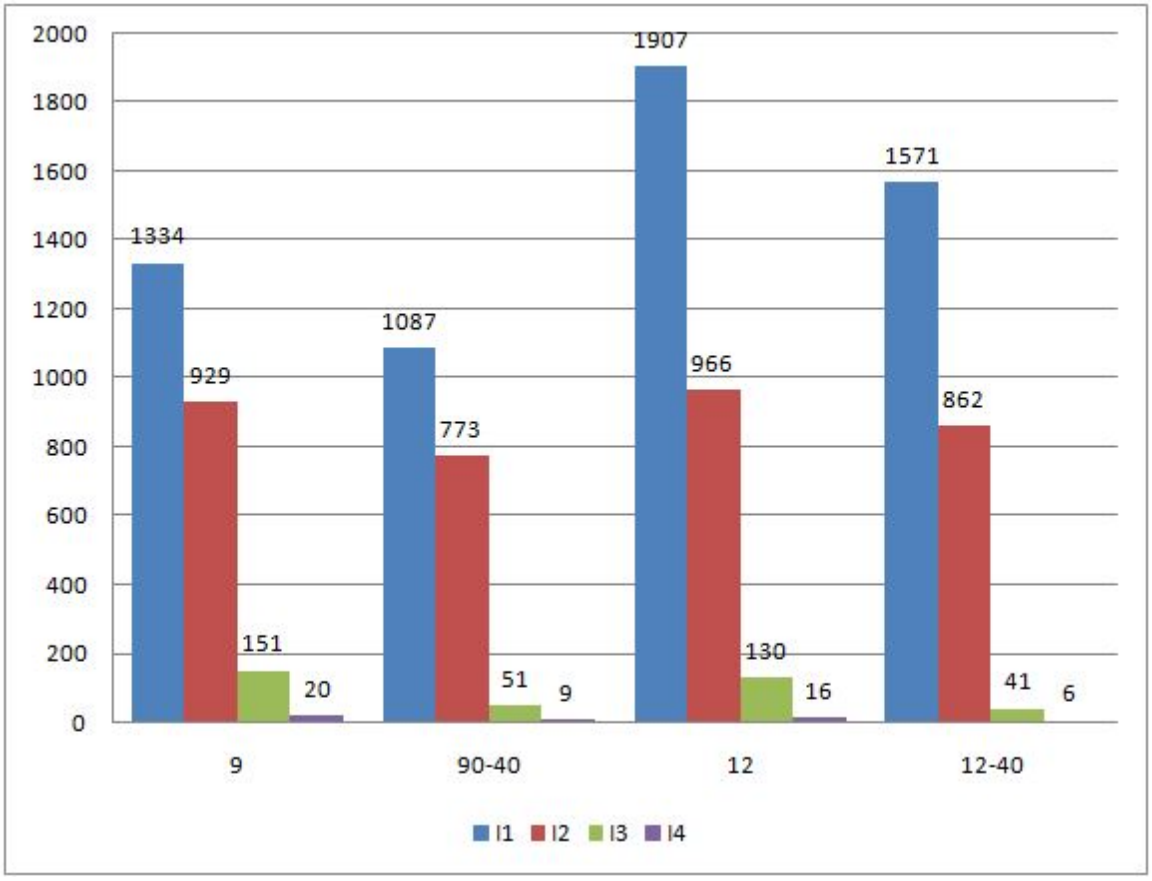


Figure 4.3: Histogram of the number of cases for each age group in the four vaccination scenarios for β=4.08.

We note that the optimal β of the single dose cases were not used as the R_0 in this case is even smaller than the lower limit of the acceptable range.

4.4 Impact of vaccinating everyone with a second dose of the MMR vaccine

When we simulated the Case A for both scenarios 12-40 and 9-40 our results show that zero number of measles cases for the steady state. Therefore the impact of such a vaccine is to diminish the disease. However this is not realistic and hence we have in the remainder of these results focused on exploring only Case B, where the second dose of the vaccine is given only to those that had the 1st vaccine.

4.5 Projections of the number of measles cases in absence of vaccination

When we run the model without any MMR vaccine the number of cases at the long-time steady state are shown in Figure 4.4. We note that the majority of measles cases are in the youngest

age-cohorts with a very small number of cases in the adult (15+) cohort.

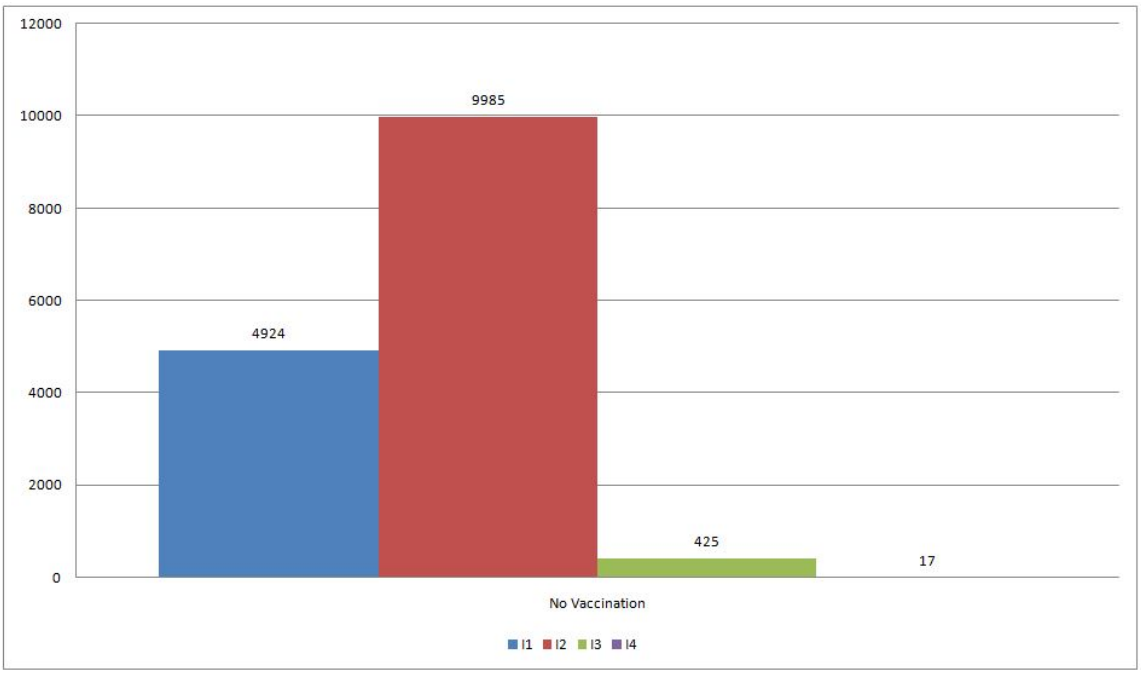
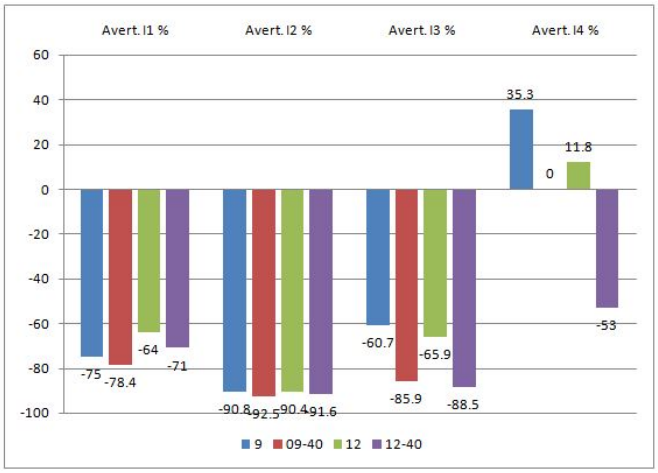


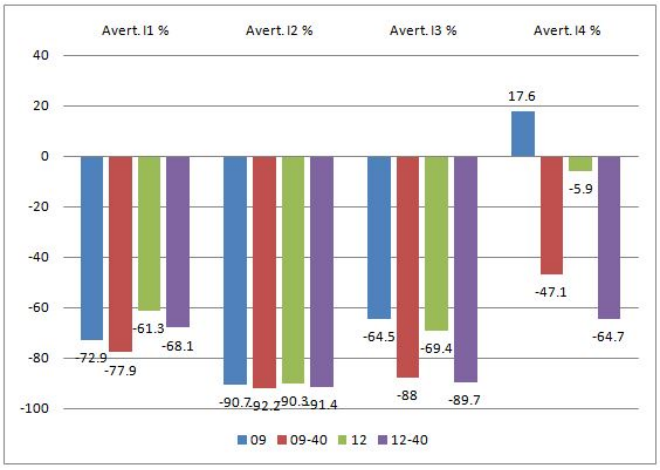
Figure 4.4: Histogram of the number of cases without vaccination.

4.6 Projections of the burden of measles under different vaccination scenarios

Under any of the vaccination scenarios there is a dramatic reduction in number of measles cases (Figure 4.5). The biggest decline in cases is observed in the second age group, young children between 1-5 years of age, were the most cases were found without vaccination (9985).



(a)



(b)

Figure 4.5: (a)Histogram of percentage of averted cases for each vaccination scenarion in the four different age groups for β=3.7. (b)Histogram of percentage of averted cases for each vaccination scenarion in the four different age groups for β=4.08.

4.6.1 Is adding a second dose of MMR vaccine more effective?

Adding of the second dose of the vaccine also reduces the number of cases.There is an evident decrease in the number of cases and hence an increase of the averted cases between the single dose and the respective two dose scenarios. For both β_s there is an increase in the total number of averted cases of 566 and 539 (4.5% and 4.3%) for the 12-40 scenario in comparison to the 12 scenarioand an increase of 456 and 514 (3.5% and 4%) for the 09-40 scenario in comparison to the 09 scenario. The main difference is due to the decreases number of cases in the third age group, children and teenagers between 5-15 years of age, due to the addition of the second dosage a few months before that age window.

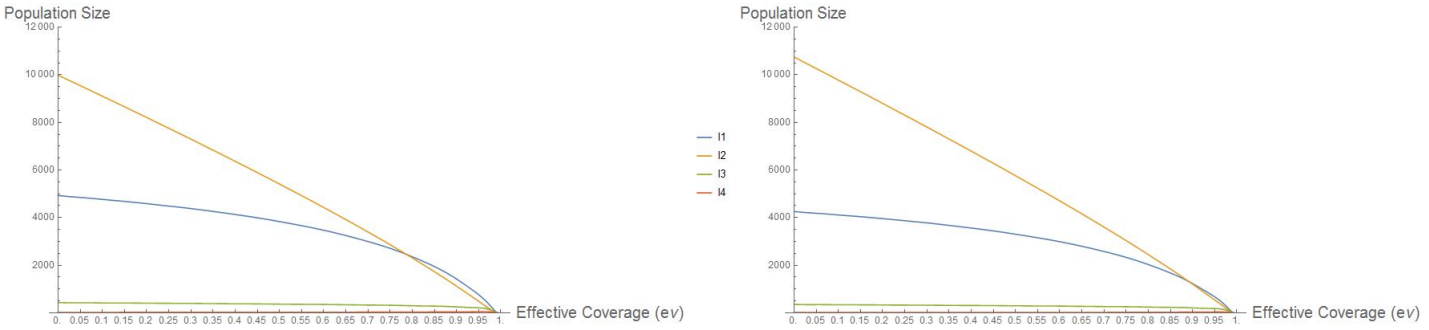
4.6.2 Should the 1st dose of the MMR vaccine be administered at 9 months instaed of 12?

When we compare the number of measles cases with a vaccines 1st dose at 9 months instead of 12, we observe a reduction in the number of cases in some age-cohorts. For example in the case where β=3.7, with earlier vaccination there is a reduction in the number of measles cases in the two young age-cohorts (25% reduction from 1063 to 1428 in I1 and 11% reduction from 746 to 836 in I2) but there is a slight increase in the number of cases in the older age cohorts (18% from 49 to 60 in I3 and 53% 8 to 17 in I4) for the single dose scenarios. The same holds for the two-dose scenario as it is evident also evident from percentages of averted cases in Figure 4.5 (7.3% less cases in I1 and 0.9% less cases in I2). We observe that the main difference between the earlier first dose scenarios comes from the first age group as is expected due to the earlier vaccination.

Moreover, three months earlier vaccination increases the number of cases in the older age groups, I3 and I4. Despite the fact that the increase is large as a percentage for I4 (35% increase with 09 scenario for $\beta = 3.7$) as an absolute number is very small and not comparable with the benefits earlier vaccination has in decreasing the number of cases for infants and very young children in I1. So to sum up our model clearly shows that earlier vaccination is beneficial and it might even suggest that single dose 09 vaccination might be comparable to two-dose 12-40 vaccination.

4.6.3 What is the effect of vaccine effective coverage on the burden of measles?

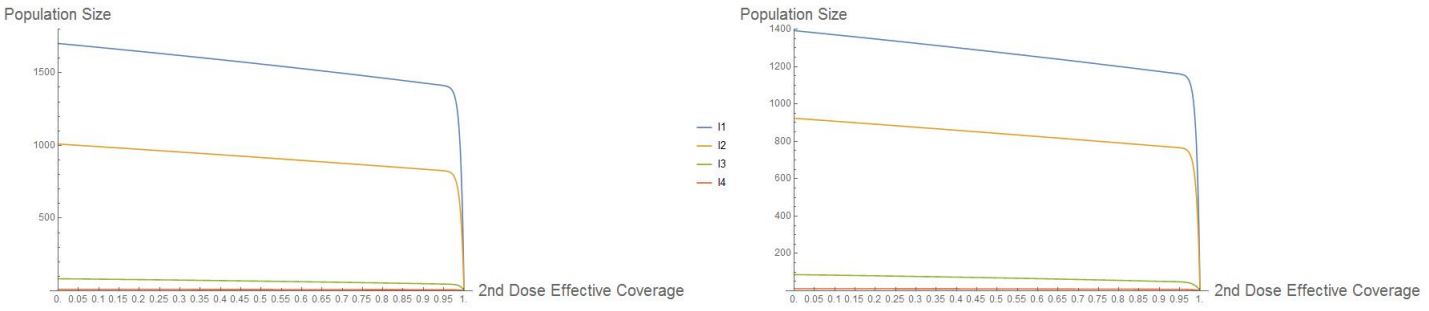
Finally, we demonstrate what is the effect of changing the effective coverage on the number of cases.



(a) (b)

Figure 4.6: (a)Plot of number of cases per age group versus effective coverage in the 12 months single dose scenario. (b)Plot of number of cases per age group versus effective coverage in the 9 months single dose scenario.

The observed behavior is expected and what we can see is that as we move to older age groups the changing effective coverage has diminishing effect. The same behavior is obsrved in the two dose scenarios and as it is expected the second dose plays only a very small part in the overall outcome as seen from the figures below:



(a) (b)

Figure 4.7: (a)Plot of number of cases per age group versus the second dose effective coverage in the 12-40 months scenario. (b)Plot of number of cases per age group versus the second dose effective coverage in the 9-40 months scenario.

The sudden drop at near 100% effective coverage is due to the fact that for effective coverage of the second dose equal to 100% the steady state gives zero infected populations but this is probably a simulation artifact rather than a result.

Chapter 5

Discussion

5.1 Summary of results

The aim of this project was to develop and apply a mathematical model for transmission of measles to explore the impact as the number of disease cases under different MMR vaccination scenarios. The modelling framework we have developed was parameterised with UK data and calibrated against number of measles cases for 2013. The calibrated model was then used to explore the impact of different vaccination scenarios. Such scenarios include changes to vaccine coverage or scheduled timing of vaccine administration.

Currently the MMR vaccine in the UK is given as a 2-dose vaccine with the first dose administered around the 1st birthday and the second dose at around 40 months old . Currently considerations are given whether earlier administration of the vaccine can impact the effectiveness of the vaccine. Furthermore, following the reduced uptake of MMR vaccine in the late 1990s worries exist if this might happen again. Hence within this project we explored the impact of shifting timing of the MMR 1st dose vaccine from 12 months to 9 months and also what if the second dose of the vaccine is not taken.

Our results suggest that bringing the MMR 1st dose vaccine to 9 months instead of 12 months can reduce the number of cases in the younger age but it might induce an increase in the number of cases in the older age-cohorts. But as an absolute number these are still very small and not comparable with the benefits earlier vaccination has in decreasing the number of cases for infants and very young children.

Adding the second dose of the MMR vaccine is also more effective: there is a an increase in the total number of averted cases of 566 and 539 (4.5% and 4.3%) for the 12-40 scenario in comparison to the 12 scenario and an increase of 456 and 514 (3.5% and 4%) for the 09-40 scenario in comparison to the 09 scenario.

In summary our results show that a two- dose MMR vaccines more beneficial than a single dose MMR vaccine. Moreover, our results indicate that earlier first dose results in less infected cases per year and hence is more beneficial. In addition, our framework captures correctly the differences induced in the number of cases for each age group due to the different vaccination scenarios. Hence, these results suggest that our framework is effective in evaluating a vaccine and the effect of changing its timing and could potentially be used for more vaccines.

5.2 Future work

Further work is needed to explore whether different upper age limit after which individuals are immune can affect the model results. In our model we have used the upper age limit of 30 year of age. Additionally, there is need for investigating how the effectiveness of a vaccine is affected by maternal immunity. In our model we have assumed that there is no change in the efficacy of the vaccine whether it is given at 9 or 12 months but that is up to a lot of discussion and in need for verification by biological data. Another important factor is the mixing rates between individuals in age group 0-1. Although the number is in reality very small it is not zero. The zero in the mixing matrix is a result of under sampling. There is a lot of variation for this value, as seen from the figure below, and hence there is the need for sensitivity analysis but it does not make much difference between zero and a small value close to zero.

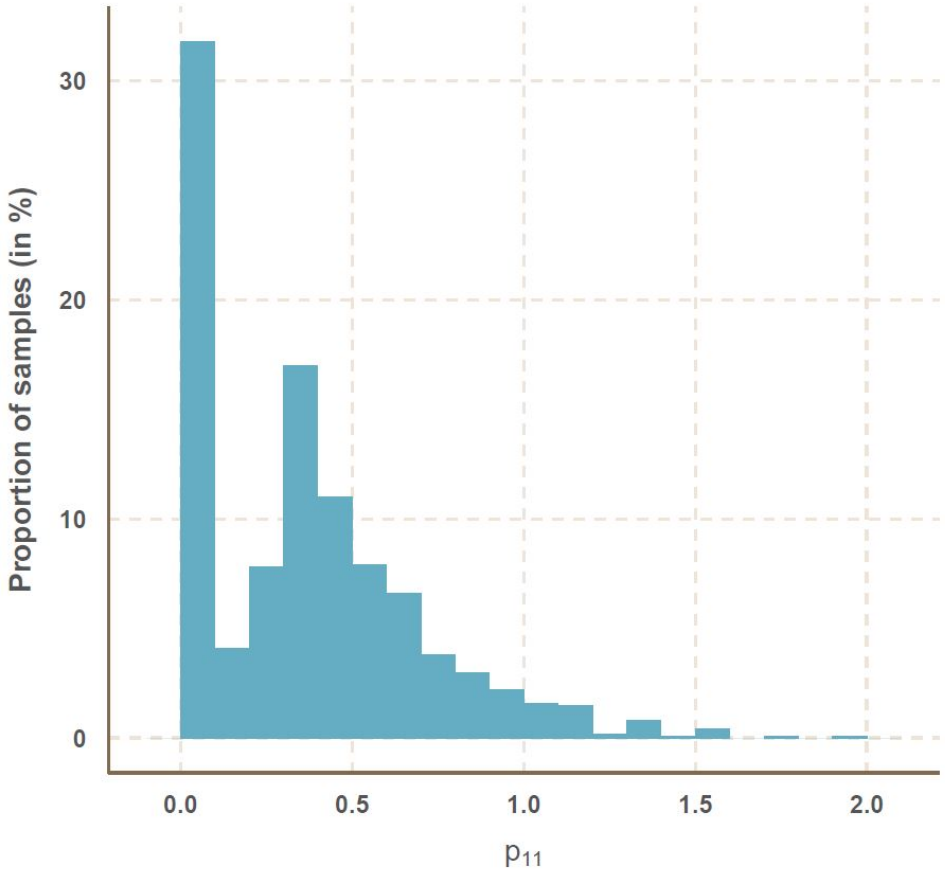


Figure 5.1: Distribution of the value for p_{11} generated from 1000 bootstrap samples from POLYMOD

5.3 Extension to this work

There is a potential of this work to be used as a tool in a evaluating different vaccines as art of the childhood vaccination schedule. To attain this the mathematical model presented here needs to be combined with a previously developed Markov model [16] .The Markov gives the possible childhood vaccination scheduling options and hence the combination of both models can give a formal way of assessing a schedule as a whole and not on a case by case basis.

Bibliography

[1] Births in England and Wales, 2013 - ONS. http://www.ons.gov.uk/ons/rel/vsob1/birth-summary-tables--england-and-wales/2013/stb-births-in-england-and-wales-2013.html.

[2] How long do babies carry their mother's immunity? - Health questions - NHS Choices. http://www.nhs.uk/chq/Pages/939.aspx?CategoryID=62.

[3] Measles notifications in England and Wales, by age group - GOV.UK. https://www.gov.uk/government/publications/measles-notifications-by-age-group-region-and-sex/measles-notifications-in-england-and-wales-by-age-group.

[4] Measles (Rubeola) - Chapter 3 - 2014 Yellow Book | Travelers' Health | CDC. http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/measles-rubeola.

[5] Public health england, research and analysis. https://www.gov.uk/government/publications?keywords=&publication_filter_option=research-and-analysis&topics%5B%5D=public-health&departments%5B%5D=all&official_document_status=all&orld_locations%5B%5D=all&from_date=&to_date=.

[6] Department of health (2010) health protection legislation (england). http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/HealthProtectionRegulations/, 2010.

[7] Health protection agency (2010) hpa national measles guidelines local & regional services. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1274088429847, 2010.

[8] Nhs (2012) the health and social care information centre, nhs immunisation statistics, england 2011-12. http://www.hscic.gov.uk/catalogue/PUB09125, 2011-2012.

[9] Robert T Chen and Frank DeStefano. Vaccine adverse events: causal or coincidental? *The Lancet*, 351(9103):611–612, 1998.

[10] Yoon H Choi, Nigel Gay, Graham Fraser, and Mary Ramsay. The potential for measles transmission in england. *BMC Public Health*, 8(1):338, 2008.

[11] N. H. S. Choices. About the MMR vaccine - Vaccinations - NHS Choices. http://www.nhs.uk/conditions/vaccinations/pages/mmr-vaccine.aspx, April 2015.

[12] Herbert W Hethcote. The mathematics of infectious diseases. *SIAM review*, 42(4):599–653, 2000.

[13] MR Kiln. Autism, inflammatory bowel disease, and mmr vaccine. *The Lancet*, 351(9112):1358, 1998.

[14] Jol Mossong, Niel Hens, Mark Jit, Philippe Beutels, Kari Auranen, Rafael Mikolajczyk, Marco Massari, Stefania Salmaso, Gianpaolo Scalia Tomba, Jacco Wallinga, and others. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med*, 5(3):e74, 2008.

[15] Sarah J O'Brien, Ian G Jones, and Peter Christie. Autism, inflammatory bowel disease, and mmr vaccine. *The Lancet*, 351(9106):906–907, 1998.

[16] Guy Walker Jasmina Panovska-Griffiths Peter Grove Sonya Crowe, Martin Utley and Christina Pagel. A novel approach to evaluating a national childhood immunisation schedule (in review). *BMC Infectious Diseases*.

[17] Pauline Van den Driessche and James Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1):29–48, 2002.

[18] Andrew J Wakefield, Simon H Murch, Andrew Anthony, John Linnell, DM Casson, Mohsin Malik, Mark Berelowitz, Amar P Dhillon, Michael A Thomson, Peter Harvey, et al. Retracted: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *The Lancet*, 351(9103):637–641, 1998.

Chapter 6

Mixing Matrices

Single dose at 9 months mixing matrix:

	0 - 1	**1 - 5**	**5 - 15**	**15 - 30**
0 - 1	0	45.5	18.1	23.6
1 - 5	226.3	621.9	182.3	134.9
5 - 15	234.7	445	2652.1	470.9
15 - 30	503	541.1	774	2403.1

Two doses at 12-40 months mixing matrix:

	0 - 1	**1 - 3.3**	**3.3 - 5**	**5 - 15**	**15 - 30**
0 - 1	0	44.6	74.4	21.9	18.7
1 - 3.3	99.5	243	136.1	107.3	95.7
3.3 - 5	116.8	103	665	109.5	46.5
5 - 15	286.5	445.8	684.3	2934.4	483.9
15 - 30	401.9	656.6	477.4	795.3	2348.9

Two doses at 09-40 months mixing matrix:

	0 - 0.75	**0.75 - 3.3**	**3.3 - 5**	**5 - 15**	**15 - 30**
0 - 1	0	33.5	55.8	29.2	24.9
1 - 3.3	99.5	254.2	154.7	100	89.5
3.3 - 5	116.8	104.6	665	109.5	46.5
5 - 15	286.5	428.1	684.3	2934.4	483.9
15 - 30	401.9	628.3	477.4	795.3	2348.9