Determining the long term cost of vaccination schedules : a case study of measles in the United Kingdom

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Abstract

The antibody titre of vaccinated individuals are lower than those who gain immunity through infection. Consequently maternal antibody titre of infants born to vaccinated mothers are lower than those of recovered mothers. I consider the proportion of vaccinated and unvaccinated infants who are immune to measles at a given age, constructing models to account for vaccination and protective maternal immunity in infants. Using parameters established from UK data, I use these models to determine optimal vaccination schedules in terms of minimising long term cost of both vaccination and treatment for measles. Each model shows it is cheaper to over-vaccinate a population than to under-vaccinate by the same proportion from optimal. The realistic vaccination model presented does not indicate potential savings by the reduction of the initial vaccination to 9 months from 12 months in the current recommended vaccination scheme at high vaccination proportions. It also shows that single vaccination schemes at 9 and 12 months of age could offer approximately US $800 million (2001 levels) in savings over the next 50 years if over 95% of the population could be vaccinated. However, at the current levels of vaccination of 89% there is no reduction of costs in changing from a single to a double vaccination schedule. The model also suggests when vaccinating less than 88% of the population, it is more cost effective to use a double rather than a single vaccination scheme.

Contents

1 Introduction

Since the introduction of vaccination against measles in the United Kingdom in 1968, followed by replacement with MMR vaccine in 1988 [6], there has been a dramatic decline in notified cases. Fluctuating between 200,000-700,000 annually before 1968 [4], they have dropped down to just over 2000 in 2010 [5]. However in addition to these encouraging figures, changes to immunity dynamics has meant those under 1 year old, who are at serious risk of complications, now constitute 8.8% of cases in 2010 [2].

At birth, infants are protected against infectious diseases, such as measles, by maternal antibodies received via transplacental transfer. The quantity of antibodies received is related to the antibody titre of their mother, so infants of mothers with high antibody titre have high antibody titre at birth and vice versa [18, 33, 28, 22]. Adults who have vaccine based immunity have lower antibody titre than those who gain immunity through natural infection (referred to as unvaccinated or recovered). As such infants of vaccinated mothers have lower maternal antibody titre than those of unvaccinated mothers [31, 23, 24, 18]. Measles has been shown to have a threshold antibody titre, above which an individual is immune and below which they are susceptible to the disease [19, 13]. Protective maternal antibodies decay over time so those that receive fewer fall below the immunity threshold, becoming susceptible, earlier than their counterparts with higher antibody titre [23]. Consequently infants born to vaccinated mothers, become susceptible earlier than those infants born to unvaccinated mothers [38, 22, 20, 23].

Maternal antibodies are a major factor of vaccination failure in infants [30], as they target both live-attenuated and killed virus in the vaccine. Consequently the infant does not produce an adequate immune response to the vaccine. The current recommendation in the UK is initial vaccination at 12-13 months with a follow up vaccination between 3-5 years [6, 12]. As such infants of vaccinated mothers tend to have a larger window of susceptibility before vaccination than infants of unvaccinated mothers. As the majority of women of childbearing age have vaccine based immunity, the proportion of infants of vaccinated mothers is increasing. This could increase the number of susceptible individuals, contributing to an epidemic of measles once again in the UK.

In this study I develop a simple model for measles infections which I adapt to model introducing vaccination in a population. I then look in detail at protective maternal immunity in infants. Using this, I develop two further models including protective maternal immunity in infants. One of which looks at ideal vaccination schedules, where infants are vaccinated as soon as they become susceptible. The other models realistic vaccination schedules where infants are vaccinated at certain ages. Then using these models I examine various vaccination schemes and determine the long term cost.

2 Modelling methods

Throughout I will be using compartmental models to describe measles behaviour, in which individuals in the population are contained within groups and can transition between these groups as time progresses. It is these transitions that can be modelled

using a system of ordinary differential equations (ODEs), which can be numerically solved, or with simpler models solved analytically, to determine behaviour. As a basis of my models, I use SIR (Susceptible, Infectious, Recovered) dynamics, commonly used to model infectious diseases. SIR includes susceptible, infectious and recovered groups. The susceptible group are those without immunity and could become infected if they come into contact with infectious individuals. The infectious group are those currently with the disease. The recovered group are those that have been infected and now have immunity protecting them from the disease.

As this is a case study of the United Kingdom, I attempt to model a similar population. A constant population size of $N = 60,000,000$ is assumed. It is possible to examine models on populations of increasing size, however a constant population makes calculations easier and is a good approximation for the UK [14]. I assume homogeneous mixing, the chance of interaction between any two individuals is equal and I crudely assume life expectancy of 70 years which is similar to the UK [14]. As the average infectious period for measles is 9-12 days [29], I assume the upper limit of 12 days as there is often a latent infection period [27] which I do not account for otherwise. I assume the average age of infection in an unvaccinated population is 5 years [27]. It is possible to use different parameters for other countries.

Description	Value
Life Expectancy	70 Years
Avg. Infectious Period	$\frac{12}{365}$ Years
Avg. Age of Infection	5 Years
Population Size (N)	60,000,000

Table 1: Population assumptions

2.1 Numerical methods

I use a fourth-order Runge-Kutta method to numerically solve the systems ODEs in subsequent chapters. Given an Initial Value Problem (IVP) $u' = f(t, u)$ and $u(t_0) = u_0$.

$$t_{n+1} = t_n + h$$
$$u_{n+1} = u_n + \frac{h\left(k_1 + 2k_2 + 2k_3 + k_4\right)}{6}$$

where

$$k_1 = f\left(t_n, u_n\right)$$
$$k_2 = f\left(t_n + \frac{h}{2}, u_n + \frac{hk_1}{2}\right)$$
$$k_3 = f\left(t_n + \frac{h}{2}, u_n + \frac{hk_2}{2}\right)$$
$$k_4 = f\left(t_n + h, u_n + hk_3\right)$$

This method has $O(h^4)$ accuracy for time step h providing a good balance of accuracy and the amount of computation required [34]. For solving all models I assume $t_0 = 0$ and $h = \frac{1}{365}$ (i.e. one day).

2.2 General criticism

Although differential models are good for generating epidemic trends they have flaws which mean that results should be used cautiously. Numerically solving ODEs approximates the equilibrium point(s). As the method gets closer to equilibrium the oscillations, representing epidemics, decrease in magnitude. However in reality, the size of epidemics does not generally decrease in magnitude. Often differential models have a non-integer numbers of individuals within a group, meaning behaviour is not necessarily a true representation of reality. In some cases between epidemics there is less than 1 infectious individual, which in reality would result in eradication.

3 Simple SIR model

3.1 Purpose

Developing a simple SIR model for measles gives us a good understanding of measles behaviour within an unvaccinated population. It also allows us to establish parameters of transitions between groups using analytical methods. These parameters can then be assumed to be the same for more complex models.

3.2 Assumptions

A number of assumptions are made when setting up the simple SIR model :

- Exponential decay for death from each group at rate α.
- All births enter into the susceptible group.
- Stable population, so birth/death occurs at rate α. ODEs sum to 0.
- Homogeneous mixing, any two individuals have an equal chance of interaction. (e.g. infectious and susceptible individuals)
- Exponential decay from susceptible into infectious group with transmission rate β.
- Exponential decay from infectious into recovered group with recovery rate γ.
- Recovered immunity is lifelong.

3.3 System of differential equations

This simple SIR model is described by the set of differential equations.

$$\begin{aligned} N &= S + I + R \\ \frac{dS}{dt} &= \alpha N - \beta SI - \alpha S \\ \frac{dI}{dt} &= \beta SI - \gamma I - \alpha I \\ \frac{dR}{dt} &= \gamma I - \alpha R \end{aligned}$$

Alternatively, the differential equations can also be thought of pictorially (Figure 1).

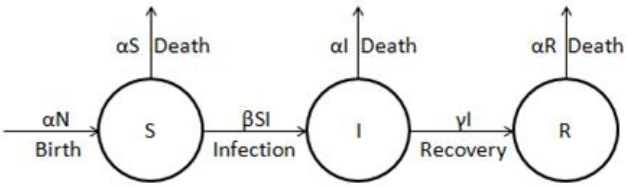


Figure 1: Simple SIR Model

3.4 Analytical results

Before numerically solving, I must establish parameters α, β and γ. Determining α is straight forward, I assumed life has exponential decay and life expectancy is 70 years, so $\alpha = \frac{1}{70}$ per person per year. Similarly, due to exponential decay and average infectious period of 12 days, so $\gamma = \frac{365}{12}$ per person per year. Establishing β is more difficult, as it is not directly measurable. Let us define the force of infection δ, the expected time in the susceptible group before infection, i.e. $\delta(t) = \beta I(t)$. As I have assumed exponential decay into the infectious group, the force of infection can be estimated. The average age of infection in an unvaccinated population is 5 years of age, so $\delta = \frac{1}{5}$. I can then determine $\beta = \frac{\delta(t)}{I(t)}$, which I assume to be constant; a crude estimate as there may be varying forces of infection at different times, e.g. during school term times. Solving at equilibrium we can determine I_e, the number infectious at equilibrium. Using I_e and the approximation for δ leads to (see Appendix)

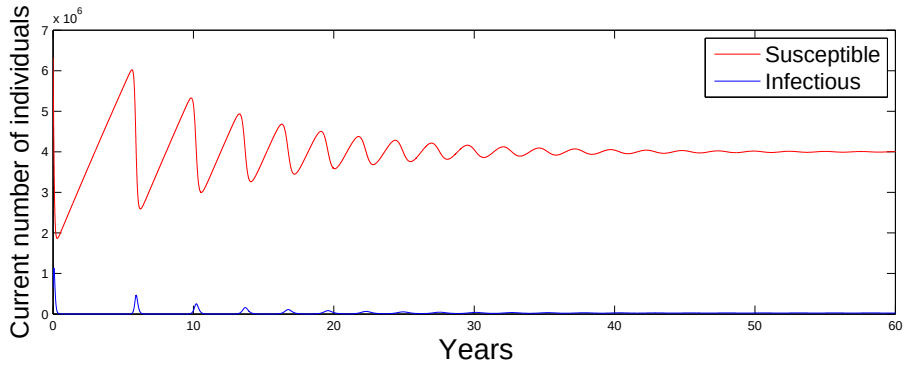
$$\beta = \frac{(\delta + \alpha)(\alpha + \gamma)}{\alpha N} \tag{1}$$

With $\alpha = \frac{1}{70}, \gamma = \frac{365}{12}, \delta = \frac{1}{5}$, and $N = 60,000,000$ I have $\beta = 7.61 \times 10^{-6}$. I now assume these values to remain the same throughout subsequent models.

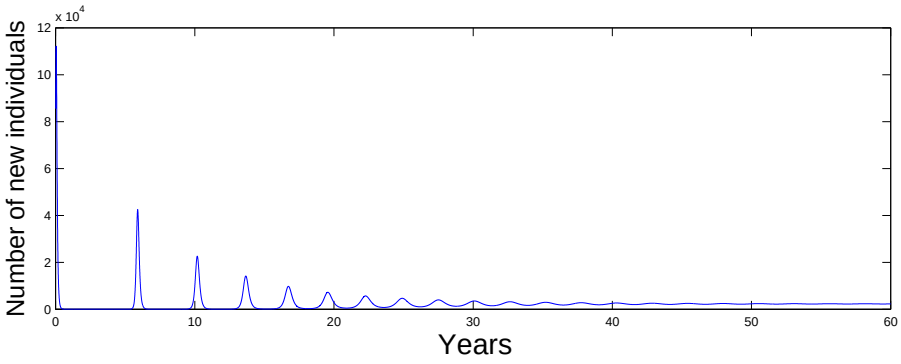
3.5 Numerical results

Solving the system numerically I determine the number of individuals in each group at a given time step. Considering the new infectious individuals βSI and simultaneously

numerically solving with the current numbers in the SIR model, I determine the new infectious individuals at each time step.



(a) The current number of infectious and susceptible individuals at each time step.



(b) The number of new infectious individuals at each time step.

Figure 2: Numerically solving the simple SIR system. Initial values of $S = 6,400,000$, $I = 600,000$ and $R = 53,000,000$. Parameters $\alpha = \frac{1}{70}$, $\beta = 7.61 \times 10^{-6}$,$\gamma = \frac{365}{12}$ and $\delta = \frac{1}{5}$. The system is run for 60 years at time step $h = \frac{1}{365}$.

Results from Figure 2 show peaks of infectious individuals corresponds to peaks in the number of new infections. Examining Figure 2, the troughs in susceptible individuals are at the same point as the peaks in infectious individuals, indicating epidemic like behaviour. Between the 10th and 25th year the period of peaks (epidemics) is approximately 2 to 3 years, a pattern observed in the United Kingdom before vaccination [4]. The system approaches equilibrium as time progresses and magnitude of peaks decreases with the model becoming less similar to the epidemics observed in the UK. In particular Figure 2b shows that near equilibrium the number of new infections is approximately 2200 cases at each time step h. Hence there are approximately 800,000 infections annually, similar to those observed during the greatest epidemics in UK[1]. Thus, near equilibrium this model overestimates the number of infections. However, even this result

[1]HPA data includes only England and Wales, this model includes the entire UK population so I expect slightly larger results

is of a similar magnitude to the number of infections observed pre-vaccination. Overall this model is highly simplistic, but as building block it matches measles infection rates adequately.

3.6 Criticism

Despite these good results in approximating measles in the UK pre-vaccination this model has many shortcomings. This model does not account for vaccination and is therefore not helpful for examining vaccination schedules. Protective maternal immunity is not accounted for, as individuals are born susceptible. Antibody levels are not used to determine protection from disease, nor does it account for natural boosting of antibodies when immune individuals come into contact with an infected individual. The homogeneous mixing assumption is clearly violated, as in reality there are various factors such as location that influence interactions. The model does not include a latent period, where an individual is infectious but not presenting symptoms, such individuals are generally more likely to come into contact with susceptible individuals than infectious individuals. Force of infection is likely to vary with time but is assumed to be constant. Population assumptions (e.g. mortality) are drastically unrealistic. Immunity may not be lifelong and length of immunity may vary for individuals [17]. Recently added 'infants' contribute to the birth rate of a group. This model does not account for gender in groups which could potentially contribute to birth groups. It also does not include immigration from other places. In addition the general criticism of differential models also applies.

4 Introduction of vaccination - SVIR

4.1 Purpose

I adapt the simple SIR model given in section 3 to include vaccination at birth by introducing a new group V, the vaccinated group. Vaccinated individuals could be added into the recovered group to obtain the same effect however the former is more suitable in the present study as I wish to distinguish between infants of vaccinated and recovered mothers. This model is referred to as SVIR (Susceptible, Vaccinated, Infectious, Recovered).

4.2 Assumptions

A number of assumptions are made to set up the SVIR model :

- Newborns are susceptible with p proportion being vaccinated (always successful) entering the vaccinated group and $1 - p$ entering the susceptible group.
- Exponential decay for death from each group at rate α.
- Stable population, so birth/death occurs at rate α. ODEs sum to 0

- Homogeneous mixing, any two individuals have an equal chance of interaction. e.g. infectious and susceptible individuals.
- Exponential decay from susceptible into infectious group with transmission rate β.
- Exponential decay from infectious into recovered group with recovery rate γ.
- Both vaccinated and recovered immunity is lifelong.

4.3 System of differential equations

The SVIR model is described by the following differential equations.

$$
\begin{aligned}
N &= S + V + I + R \\
\frac{dS}{dt} &= (1-p)\alpha N - \beta SI - \alpha S \\
\frac{dV}{dt} &= p\alpha N - \alpha V \\
\frac{dI}{dt} &= \beta SI - \gamma I - \alpha I \\
\frac{dR}{dt} &= \gamma I - \alpha R
\end{aligned}
$$

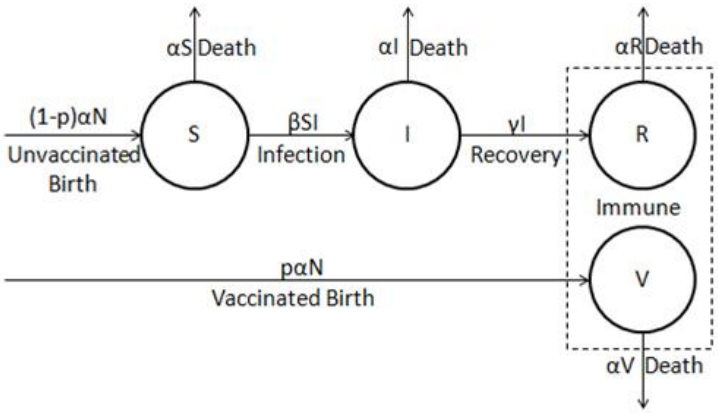


Figure 3: SVIR Model

4.4 Analytical results

It is a misconception that for eradication the entire population must gain immunity. Smallpox was eradicated with mass vaccination schemes that did not vaccinate the entire population [16]. This is due to a phenomenon known as herd immunity, where a large enough proportion of a population is immune to a disease (often through vaccination) protecting those individuals not immune. I can estimate p_E, the minimum proportion

of the population with immunity required for the eradication of measles. Let R_0 denote secondary cases, the number of infections occurring from introducing a single infectious individual into an entirely susceptible population. Consider the number of susceptible individuals infected βN in a given time, with the average time spent in the infectious group $\alpha + \gamma$ (combination of exponential decays death and recovery). It then follows that

$$R_0 = \frac{\beta N}{\alpha + \gamma} \tag{2}$$

For eradication it is required that $R_0 < 1$ [32]. This means that the number of infectious individuals is less than the infectious individual introduced so the number of infectious individuals tends to 0. Hence I deduce an estimate for the minimum proportion of individuals that must have immunity for eradication (see Appendix).

$$p_E = 1 - \frac{\alpha + \gamma}{\beta N} = \frac{14}{15} \tag{3}$$

This suggests to obtain eradication of measles one would need to vaccinate more than 14 in 15 people in the susceptible population, similar to figures found in literature [27, 16]. Due to loss of protective maternal immunity infants become susceptible and eradication may be achieved by vaccination of infants.

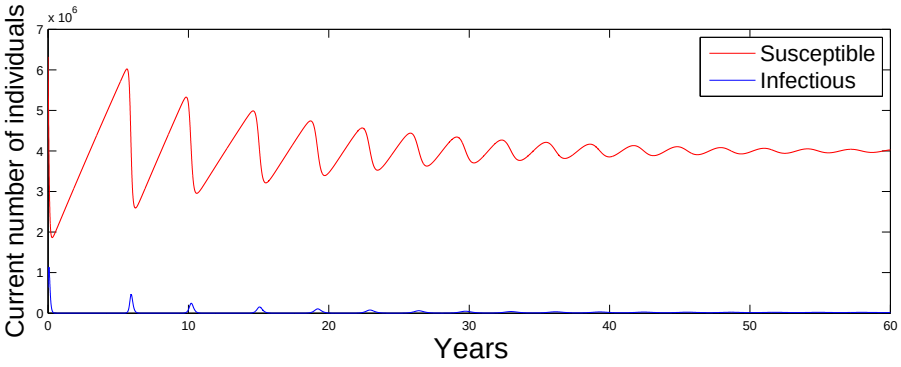
4.5 Numerical results

The model was solved numerically for a runtime of 60 years, introducing vaccination in the 10th year.

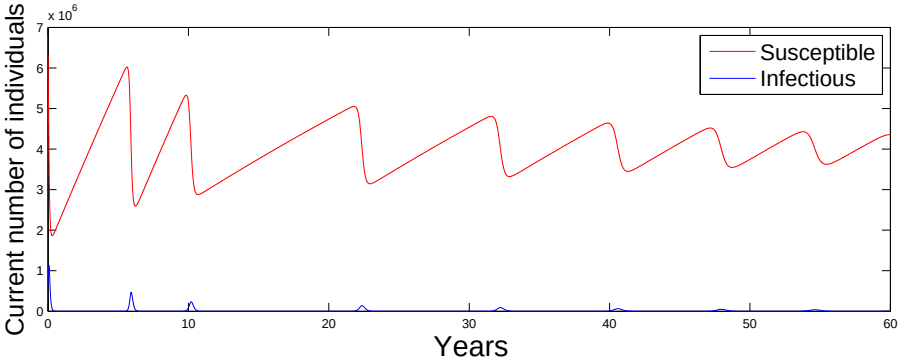
A damping effect in the frequency and size of epidemics can be observed after the year in which vaccination is introduced (see Figure 4). Figure 4a shows little difference to the unvaccinated population given in Figure 2, suggesting vaccination at low levels does not have significant effect. A 'honeymoon' period is observed in Figure 4b: After vaccination is introduced, there is long period before the next epidemic. However, eradication is not achieved with epidemics occurring at larger time intervals. Figure 4c shows vaccination proportions above p_E hitting stable numbers of susceptible and infectious individuals shortly after vaccination begins which indicates eradication.

4.6 Criticism

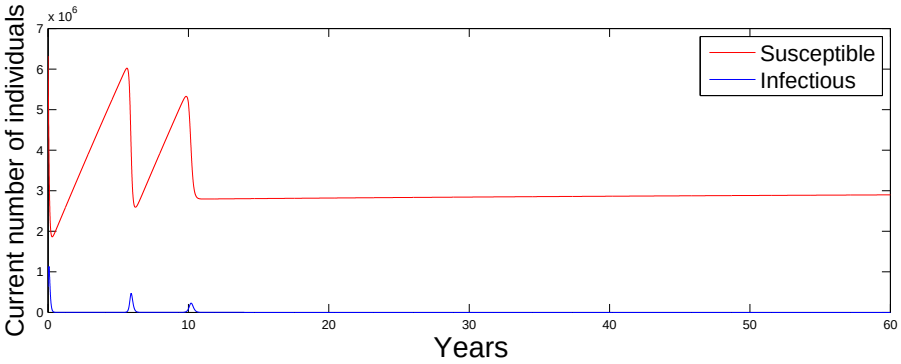
This model has allowed us to compare the disease dynamics that occur after various proportions of vaccination are applied to the population, but there are many issues with the model. Newborns are assumed to be susceptible at birth and without maternal immunity preventing infection and successful vaccination. Vaccination may not be successful on susceptible individuals due to maternal antibody interference. There is no difference in vaccinated and recovered immunity. Uniform vaccination is difficult to achieve, if not achieved can lead to susceptible pockets which are prone to infection which in turn can lead to resurgences in disease. As it shares some basics assumptions of the simple SIR model, the same criticisms still hold.



(a) The number of individuals at each time step. 30% vaccination.



(b) The number of individuals at each time step. 70% vaccination.



(c) The number of individuals at each time step. 95% vaccination.

Figure 4: Numerically solving the system. Initial values of $S = 6,400,000$, $V = 0$, $I = 600,000$ and $R = 53,000,000$. Parameters $\alpha = \frac{1}{70}$, $\beta = 7.61 \times 10^{-6}$, $\gamma = \frac{365}{12}$ and $\delta = \frac{1}{5}$. The system is run for a total of 60 years at time step $h = \frac{1}{365}$ with vaccination at birth being introduced in the 10th year.

5 Maternal immunity

Previously presented models have not accounted for protective maternal immunity. Before it is possible to model the impact of realistic vaccination schedules on a population, we must establish realistic parameters underpinning loss of infant immunity.

5.1 Experimental infant immunity

In order to determine the immunity function, the proportion of infants immune as a functions of age, I had to collect experimental data. I collected data involving infant immunity including maternal vaccination status from studies in countries which have undertaken a mass vaccination schemes against measles (Table 2). Antibody titre of blood taken from the umbilical cord is assumed to be the antibody titre of infants at birth. There were significant variations in the data available. Studies were carried out at different points in time relative to time after mass vaccination. A current hypothesis is that infant antibody titre decreases over time after mass vaccination due to the lack of natural boosting of antibodies in the population [17]. There were different methods of assessing maternal vaccination status, the majority using birth year rather than documented medical history. There were various exclusion criteria for infant weight and gestation period. Some studies have shown a strong link between gestation period and placental transfer of measles antibodies [24]. Different assays were used to assess antibody titre (Table 3) and there were various thresholds for immunity with the same assay, making it difficult to compare results. Additionally a number of studies did not have independent test data, i.e. samples were taken from the same infant more than once, implying a bias. Consequently it is not sensible to draw significant conclusions directly from the data.

				Exclusion Criteria	
Country[Ref.]	Study Years	Assay	Threshold	Weight (g)	Gestation (Weeks)
Belgium [23]	2006-8	ELISA	0.3 IU/ml	2500	36
Brazil [38][a]	1997	ELISA	10 AU	2500	37
Canada [11][b]	1991-2	ELISA PRN	0.3 IU/ml 15 Titre	2800	38
Poland [20]	1997-8	ELISA	0.12 IU/ml	2500	36
USA [21]	1990-1	ELISA	0.16 IU/ml	None	None
USA [26][c]	1990-1	PRN	8 Titre	None	None
UK [8]	1983-1991	PRN	0.2 IU/ml	None	None

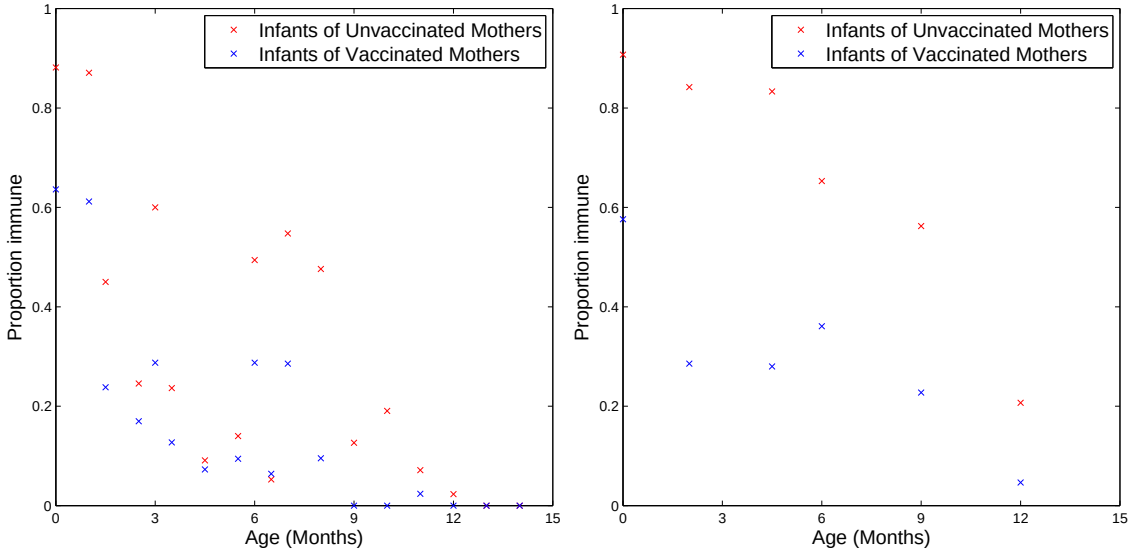
[a] Data only taken up to 6.5 months
[b] Groups 2 and 3 combined to form vaccinated group.
[c] Only data from USA born women. Women born between 1957-63 not included.

Table 2: Infant-mother measles immunity studies in mass vaccinated populations.

Most likely due to the various thresholds for immunity used, trends found in Figure 5

Assay	Description
ELISA	Enzyme linked immunosorbent assay. Serum is immobilised on microtitre plate. Detection antigen is added, which is linked to an enzyme or is detectable. Between steps the plate is washed removing non bound proteins or antibodies. The plate is developed by adding enzymatic substrate to produce a visible signal, indicating antibody titre in serum. Quick results but not as sensitive as PRN, more sensitive than HI. [35]
HI	Hemagglutination inhibition. Using standard amounts of antigen and red blood cells (RBC), by serially diluting the serum, antibody titre is determined as the greatest dilution of serum inhibiting hemagglutination, agglutination involving RBC. Agglutination, the clumping of cells. Less accurate than PRN but much quicker. [36]
PRN	Plaque Reduction Neutralisation Test. Diluted serum mixed with virus is incubated so antibodies react with the virus. This is poured over a confluent monolayer of cells, which are covered to prevent indiscriminant spreading. This is then left for a few days. The dilution to reduce number of regions of infected cells by 50% in comparison to serum free virus gives the antibody titre. Currently considered the most sensitive but time consuming. [37]

Table 3: Different assays used to assess antibody titre.



(a) ELISA [21, 23, 11, 38, 20]

(b) PRN [26, 8, 11]

Figure 5: Proportion of infants immune to measles using a different assays at a given age. Assumes cord titre is equivalent to infant birth titre.

are not strong. It shows that the proportion of infants immune to measles decreases as age increases. The proportion of infants of unvaccinated mothers with immunity is higher than their vaccinated counterparts at all ages. Figure 5a shows the majority of the infants of unvaccinated mothers have lost immunity at 12 months of age whereas for infants of vaccinated mothers it is 9 months.

5.2 Modelling proportion of immune infants using maternal antibody titre

It is useful to investigate long term effects of vaccination on populations protective maternal immunity. This is done by determining the immunity function in terms of maternal antibody titre. I assume cord antibody titre is equivalent to infant antibody titre at birth. Studies [18, 22, 33] suggest a linear relation between log maternal and log cord antibody titre.

$$\log_2(\text{cord}) = r \log_2(\text{mother}) + k \tag{4}$$

I suppose a gamma distribution for maternal antibody titre with scale parameter λ and shape parameter n. The CDF is given by

$$F_{\lambda,n}(x) = \frac{1}{\Gamma(n)}\gamma\Big(n, \frac{x}{\lambda}\Big), \tag{5}$$

I have assumed that infant antibodies exponentially decay at the same rate in all infants [15]. Given an infant's cord titre (i.e. antibody titre at birth), c, and the decay rate of infant antibodies, μ, we can determine an infant's antibody titre, A, at a given age (years), a:

$$A(a, c) = ce^{-\mu a} \qquad \mu \geq 0. \tag{6}$$

If I assume a threshold antibody titre, T, below which infants are susceptible to infection, I deduce the immunity function, J, for a given age with maternal antibody titre parameters λ and n (see Appendix). The constants k and r are given in Equation 4 and μ is the decay rate.

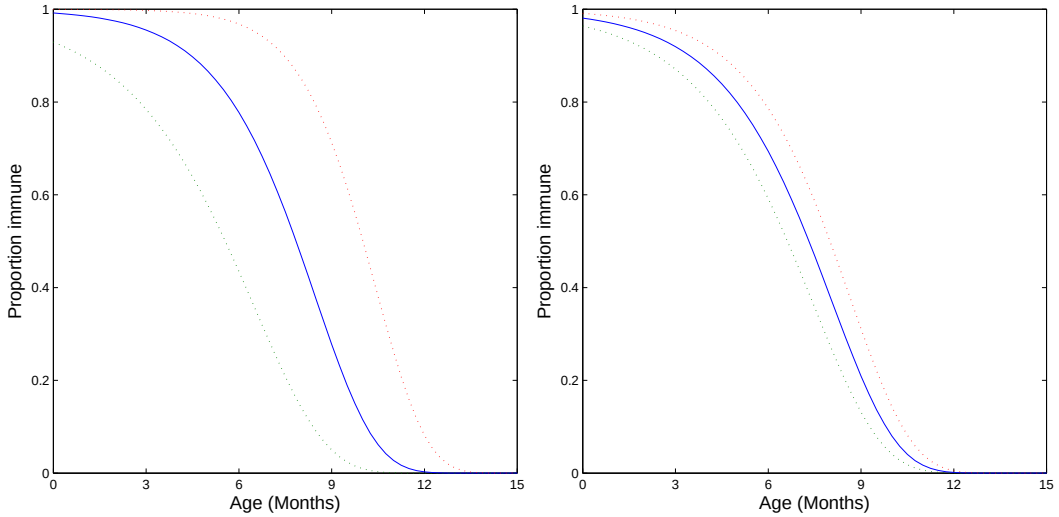
$$J_{\lambda,n}(a) = 1 - F_{\lambda,n}\left(\left(Te^{\mu a}2^{-k}\right)^{1/r}\right) \tag{7}$$

5.3 Comparison of modelled and experimental immunity functions

Parameters λ and n are obtained by parametrising available maternal antibody titre data[2] from Sato [33] and Lennon [22]. Whilst other parameters were obtained from various studies that were not included in Table 2 in order to maintain independence of modelled and experimental immunity. Assessment of antibody titre in Sato [33] and Lennon [22] were conducted using PRN and HI assays respectively, requiring different thresholds for immunity.

Figure 6 shows both immunity functions are similar to those found in infants of unvaccinated mothers in Janaszek [20] and importantly Lennon [22]. Figure 6a has a larger confidence interval than Figure 6b due to a smaller sample size. Other than that the

[2]Kindly provided by Duncan Palmer



(a) Sato Data. $T = 120$ [25], $\lambda = 1.26$ (0.84 to 1.89) and $n = 3075$ (1865 to 5069) [33]

(b) Lennon Data. $T = 5$, $\lambda = 1.06$ (0.94 to 1.2) and $n = 95.8$ (82.1 to 111.8) [22]

Figure 6: Modelled immunity function with parameters $\mu = 5.16$ [15], $r = 0.9216$ and $k = 1.1695$ [18]. 95% interval confidence dashed.

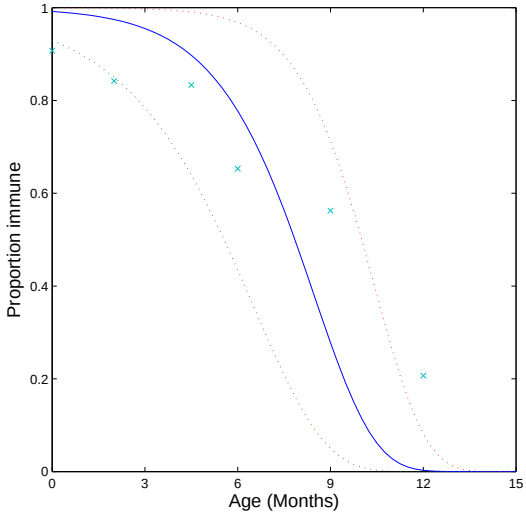


Figure 7: Experimental PRN data (crosses) compared with modelled immunity function using Sato data (95% confidence interval dashed). Immunity function has parameters $\mu = 5.16$ [15], $r = 0.9216$ and $k = 1.1695$ [18], $T = 120$ [25], $\lambda = 1.26$ (0.84 to 1.89) and $n = 3075$ (1865 to 5069) [33].

two are similar given different gamma parameters and thresholds. However, Figure 6 has a significantly higher proportion of unvaccinated immune infants than observed in Leuridan [23]. This could be due to waning of maternal antibodies or due to higher thresholds used in Leuridan.

Figure 7 compares data found in experiment against the modelled immunity function given in Equation 7. I have chosen to compare the experimental PRN data with the modelled immunity function using maternal antibody titre data from Sato [33], as they use the same assay. Most data points are within the 95% confidence interval or near it. This suggests a reasonable fit given the variation in thresholds and exclusion criteria used in the experimental data.

5.4 Criticism of modelled immunity function

The modelled immunity function has given us a good approximation of the proportion of immunity of infants based on maternal antibody titre parameters. However, the modelled immunity function ignores possible variation in relation between maternal and cord titre shown in Goncalves [18] which could go some way to explain variation between modelled immunity and experimental data. It also does not account for variation in gestation period of infants which can affect the birth antibody titre [24]. Both Lennon [22] and Sato [33] data only includes unvaccinated mothers, I do not have comparable data for vaccinated mothers. Additionally Lennon [22] and Sato [33] were both taken over 20 years ago as such maternal antibodies may have decline since then [17]. Large scale studies tend not to use PRN assays as they are time consuming and HI assays are less accurate than other assays.

6 Introduction of protective maternal immunity - Ideal BSVIR

6.1 Purpose

I account for protective maternal immunity, with vaccination occurring when individuals become susceptible. Evidence in section 5 suggests a difference in loss immunity between infants of vaccinated or recovered (unvaccinated) mothers. I introduce B_R and B_V groups, infants born from mothers in the recovered and vaccinated groups respectively. This is the ideal BSVIR model as individuals are vaccinated as they lose protective maternal immunity or at birth if born susceptible.

6.2 Assumptions

A number of assumptions are made setting up the ideal BSVIR model :

- Only Susceptible, Vaccinated and Recovered individuals can give birth with their infants entering the S, B_V and B_R respectively.
- Vaccination (always successful) occurs when maternal immunity is lost or for those born susceptible at birth, applied to p proportion of population.

- Exponential decay from B_V and B_R occurring at rates σ and ξ respectively.
- Stable population, birth/death occurs at rate α. Birth from Susceptible, Recovered and Vaccinated groups are weighted by $k = \frac{N}{(S+V+R)}$ so ODEs sum to 0.
- Exponential decay for death from each group at rate α.
- Homogeneous mixing, any two individuals have an equal chance of interaction. e.g. Infectious and susceptible individuals.
- Exponential decay from susceptible into infectious group with transmission rate β.
- Exponential decay from infectious into recovered group with recovery rate γ.
- Both vaccinated and recovered immunity is lifelong.

6.3 System of differential equations

The ideal BSVIR model is described by the following differential equations.

$$
\begin{aligned}
N &= B_R + B_V + S + V + I + R \\
\frac{dB_R}{dt} &= \frac{\alpha N R}{(S+V+R)} - \sigma B_R - \alpha B_R \\
\frac{dB_V}{dt} &= \frac{\alpha N V}{(S+V+R)} - \xi B_V - \alpha B_V \\
\frac{dS}{dt} &= (1-p)\left(\frac{\alpha N S}{(S+V+R)} + \sigma B_R + \xi B_V\right) - \beta S I - \alpha S \\
\frac{dV}{dt} &= p\left(\frac{\alpha N S}{(S+V+R)} + \sigma B_R + \xi B_V\right) - \alpha V \\
\frac{dI}{dt} &= \beta S I - \gamma I - \alpha I \\
\frac{dR}{dt} &= \gamma I - \alpha R
\end{aligned}
$$

6.4 Numerical results

The model was solved numerically for a runtime of 60 years, introducing vaccination in the 10th year. This gives behaviour of the 'ideal' vaccination when an infant is vaccinated with no window of susceptibility.

Vaccination occurs when infants become susceptible and is applied to a proportion p of these newly susceptible infants. Results in Figure 9 should therefore be similar to those in the SVIR model in Figure 4. Figure 9a shows minimal damping of infectious individuals in comparison to no vaccination, which is almost identical to Figure 4a. Figure 9b shows the number of infectious individuals is reduced by vaccination, with epidemics occurring approximately every 7-9 years, these results are similar to those of

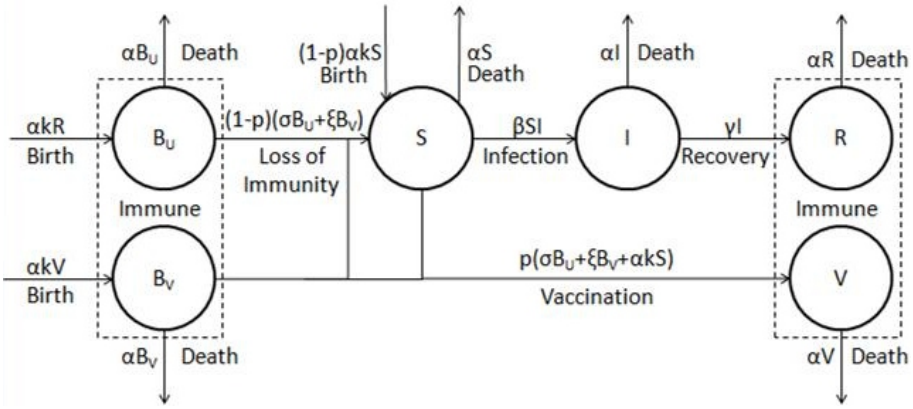


Figure 8: Ideal BSVIR Model

Figure 4b. Figure 9c shows that eradication is achieved like in Figure 4c but unlike it there is a decrease towards over 3 million susceptible individuals rather than a slight increase towards under 3 million.

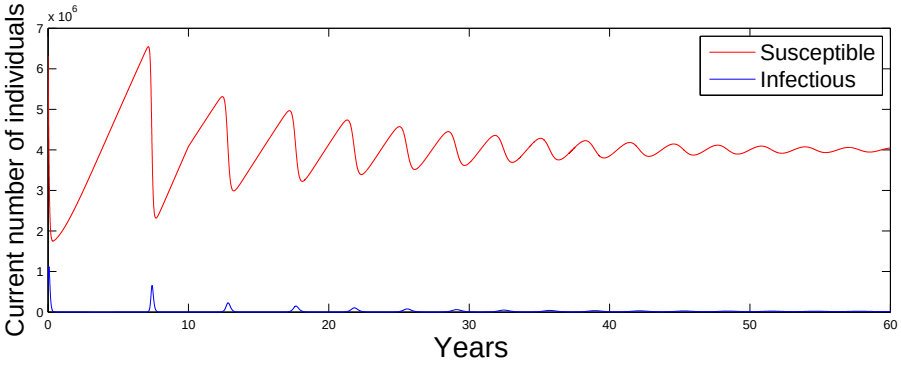
6.5 Criticism

This is the first model to account for protective maternal immunity and gives us an impression how this can effect disease dynamics. However, it still has numerous shortcomings. Vaccination applied in this model is currently unrealistic, as it is not possible to vaccinate individuals as they become susceptible. This is not helpful to model different vaccination schedules. The model assumes the decay of protective maternal immunity is an exponential, however, section 5 suggests this is not the case. This model in a small manner attempts to address infants contributing births, but as soon as they leave the birth immunity groups they still contribute. All criticism of the SVIR model in section 4 is equally applicable here apart from that of addressing maternal immunity.

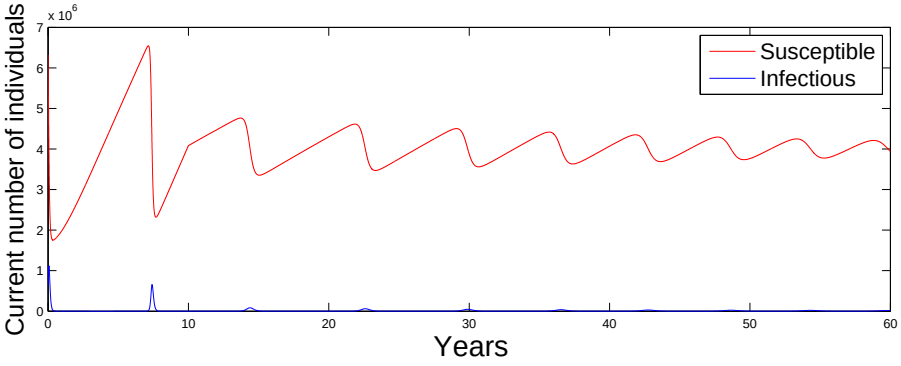
7 Realistic vaccination schedules - Realistic BSVIR

7.1 Purpose

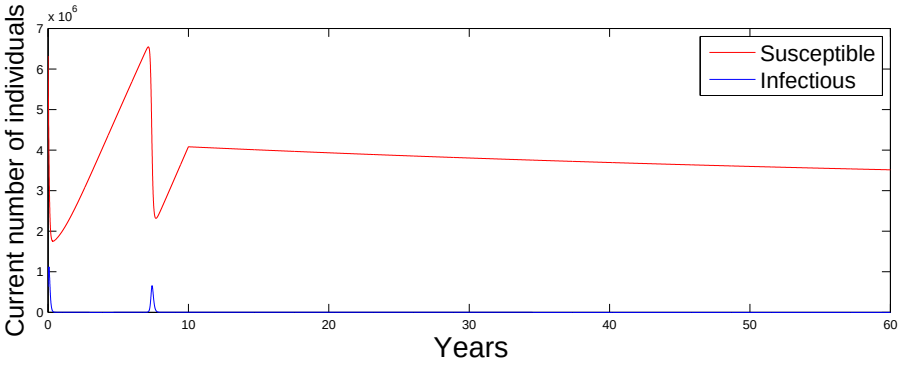
The previous models have two major flaws: loss of protective maternal immunity and unrealistic vaccination schedules. Loss of protective maternal immunity can be estimated using immunity functions established in section 5. Parametrising maternal antibody data found in Sato [33], gives us an approximation of unvaccinated maternal antibody parameters $\lambda = 3075$ and $n = 1.26$. As I could not obtain similar data for vaccinated individuals I assume that the shape parameter n remains constant and choose $\lambda = 1000$ and $n = 1.26$, which gives mean antibody levels similar to those in literature (ELISA) [23]. These parameters can (for more accurate models should) be improved by more accurate and relevant studies of antibody titre of mothers.



(a) The number of individuals at each time step. 30% vaccination.



(b) The number of individuals at each time step. 70% vaccination.



(c) The number of individuals at each time step. 95% vaccination.

Figure 9: Numerically solving the ideal BSVIR system. Initial values of $S = 6,400,000$, $I = 600,000$, $R = 53,000,000$ and $B_V = B_R = V = 0$. Parameters $\alpha = \frac{1}{70}$, $\beta = 7.61 \times 10^{-6}$, $\gamma = \frac{365}{12}$, $\delta = \frac{1}{5}$, $\sigma = 1$ and $\xi = \frac{4}{3}$. The system is run for a total of 60 years at time step $h = \frac{1}{365}$ with vaccination at birth being introduced in the 10th year.

Using $J_{\lambda,n}(a)$ from Equation 7, the proportion of infants immune at age a for with maternal antibody parameters λ and n. This gives the loss of recovered and vaccinated immunity $L_R(t_1, t_2)$ and $L_V(t_1, t_2)$ respectively, the proportion of immune infants that lose protective maternal immunity between ages t_1 and t_2.

$$L_R\left(t_1, t_2\right) = 1 - \frac{J_{3075,1.26}\left(t_2\right)}{J_{3075,1.26}\left(t_1\right)} \tag{8}$$

$$L_V\left(t_1, t_2\right) = 1 - \frac{J_{1000,1.26}\left(t_2\right)}{J_{1000,1.26}\left(t_1\right)} \tag{9}$$

To perform realistic vaccination schedules, immunity statuses of each age group are stored. This is done by using a matrix to keep track of those within the population. Let the rows of the matrix be the immunity statuses, so there are 6 rows each representing one of B_R, B_V, S, V, I and R respectively. Let the columns of the matrix be the age groups, with each age group one time step wide. In our particular case, each age group covers an interval of one day. In order to account for the ageing process, the matrix is simply shifted in each step. This gives a fully age-stratified model. However, these structures require large amounts of computation to numerically solve. As I am focusing on loss of protective maternal immunity and vaccinating infants/children as well as the time constraints of this study, I instead use a partially age-stratified model. Until four years of age, this model is identical to the fully-stratified model. However, above four years of age, all individuals are contained in a single age group which is represented by the final column in the matrix. This reduces the number of resulting differential equations and therefore the amount of computation required to numerically solve.

7.2 Assumptions

A number of assumptions are made to set up the realistic BSVIR model :

- Proportion of infants immune at given age is dependent on maternal status. Determined by L_R and L_V for infants of B_R and B_V respectively.
- Births occur separately forming a distinct age group.
- Vaccination is only successful on susceptible individuals. It is applied uniformly across each group to p proportion of the population at given age(s).
- Vaccination occurs at a certain age, happening before disease dynamics.
- Only Susceptible, Vaccinated and Recovered individuals in the > 4 years group give birth with infants entering the S, B_V and B_R respectively.
- Stable population, so birth/death occurs at rate α. Birth from Susceptible, Recovered Vaccinated groups are weighted by $k = \frac{N}{(S+V+R)}$ so ODEs sum to 0.
- Exponential decay for death from each group at rate α.

- Homogeneous mixing, any two individuals have an equal chance of interaction. e.g. Infectious and susceptible individuals.
- Exponential decay from susceptible into infectious group with transmission rate β.
- Exponential decay from infectious into recovered group with recovery rate γ.
- Both vaccinated and recovered immunity is lifelong.

7.3 System of differential equations

Unlike previous models the realistic BSVIR model it not just described by one differential equation. There are many operations that occur between time steps. Initially the births are calculated. The new births are given by the system of equations. Where n is age group > 4 years.

$$\begin{aligned}
B_R^{birth} &= \alpha J_R(0) N \frac{R(n)}{R(n) + S(n) + V(n)} \\
B_V^{birth} &= \alpha J_V(0) N \frac{V(n)}{R(n) + S(n) + V(n)} \\
S^{birth} &= \frac{\alpha N \left(S(n) + (1 - J_R(0)) R(n) + (1 - J_V(0)) V(n)\right)}{R(n) + S(n) + V(n)} \\
V^{birth} &= I^{birth} = R^{birth} = 0
\end{aligned}$$

So $B_R^{birth} + B_V^{birth} + Sbirth + V^{birth} + I^{birth} + R^{birth} = \alpha N$.

Vaccination is then applied to the appropriate age group(s), say v. It is successful on p proportion of the susceptible population in that age group(s).

$$\begin{aligned}
S(v) &= (1 - p) S(v) \\
V(v) &= pS(v) + V(v)
\end{aligned}$$

Typical SIR like dynamics then occurs to those in the population matrix. The system dynamics are given by the system of equations where a is an age group.

$$\begin{aligned}
\frac{dB_R(a)}{dt} &= -\alpha B_R(a) \\
\frac{dB_V(a)}{dt} &= -\alpha B_V(a) \\
\frac{dS(a)}{dt} &= -\beta S(a) I - \alpha S(a) \\
\frac{dV(a)}{dt} &= -\alpha V(a) \\
\frac{dI(a)}{dt} &= \beta S(a) I - \gamma I(a) - \alpha I(a) \\
\frac{dR(a)}{dt} &= \gamma I(a) - \alpha R(a)
\end{aligned}$$

Loss of protective maternal immunity is then applied to each age group. As modelled maternal immunity with current parameters reaches 0 above 15 months of age, there is no need to apply loss of immunity to the > 4 years group. For each age group a we have :

$$
\begin{aligned}
B_R(a) &= L_R(a, a+h)B_R(a) \\
B_V(a) &= L_V(a, a+h)B_V(a) \\
S(a) &= ((1 - L_R(a, a+h))B_R(a)) + ((1 - L_V(a, a+h))B_V(a)) + S(a)
\end{aligned}
$$

The ageing process then occurs, each age group is shifted by one step size, with those 4 years of age entering the > 4 years group. The new births now enter the population in the first column of the matrix.

Like all previous models this is more simply thought of pictorially (Figure 10). With transition into vaccinated group only occurring at certain ages.

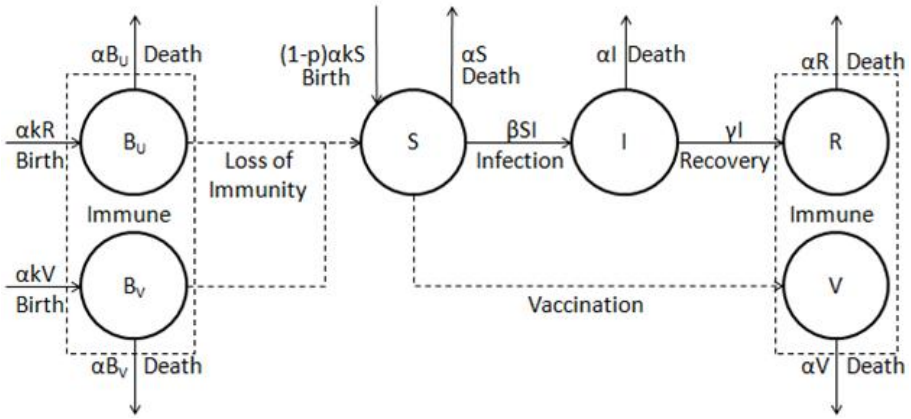
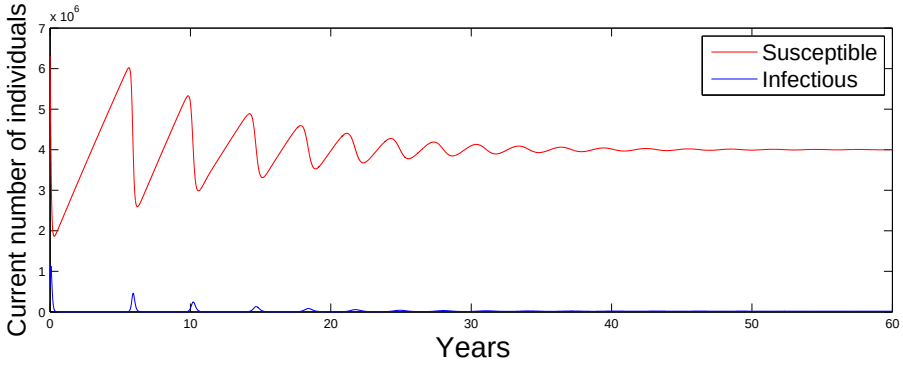


Figure 10: Realistic BSVIR Model

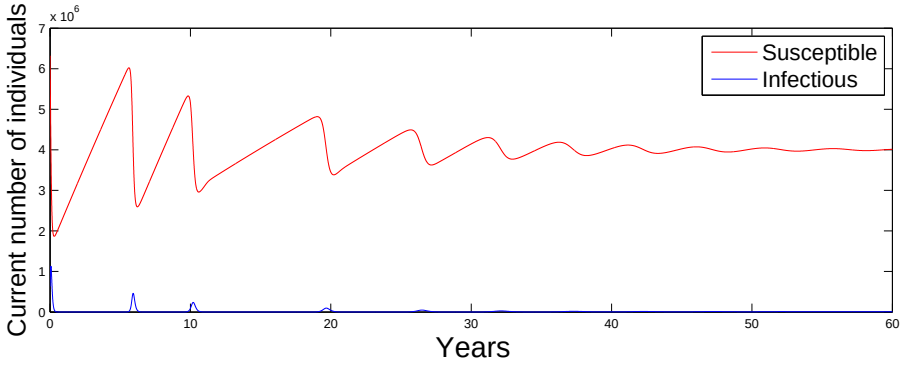
7.4 Numerical results

The births are numerically solved to determine the newborns. The system dynamics differential equations are also numerically solved. The system is run for a total of 60 years, introducing vaccination in the 10th year.

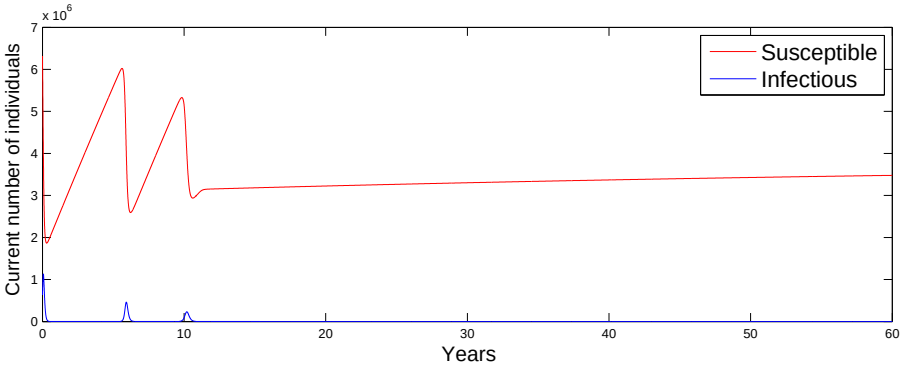
There are some small differences between Figure 11 and previous models. Figure 11a does not differ significantly from previous models with epidemics occurring 2-3 years and vaccination not significantly reducing infectious numbers. Figure 11b shows epidemics approximately every 5-8 years, whereas in previous models epidemics occur approximately every 8-10 years and magnitude of epidemics is reduced compared with earlier models. Like previous models in Figure 11c eradication is achieved at 95% vaccination despite the failure of some vaccinations.



(a) The number of individuals at each time step. 30% vaccination.



(b) The number of individuals at each time step. 70% vaccination.



(c) The number of individuals at each time step. 95% vaccination.

Figure 11: Numerically solving the realistic BSVIR system. Initial values of $S(n) = 6,400,000$, $I(n) = 600,000$, $R(n) = 53,000,000$ and $B_V(n) = B_R(n) = V(n) = 0$, where n is > 4 age group. $B_V(a) = B_V(a) = B_V(a) = B_V(a) = B_R(a) = V(a) = 0$ for all other age groups, a. Parameters $\alpha = \frac{1}{70}$, $\beta = 7.61 \times 10^{-6}$,$\gamma = \frac{365}{12}$ and $\delta = \frac{1}{5}$. The system is run for a total of 60 years at time step $h = \frac{1}{365}$ with single vaccination at 12 months of age is introduced in the 10th year.

7.5 Criticism

Even though this model is capable of modelling realistic vaccination schedule, which is an improvement on the previous models, it still contains flaws. The model does not account for natural boosting of immunity in the population. The assumptions related to maternal antibodies for vaccinated mothers are an educated guess, so the immunity function for infants of vaccinated mothers is not accurate and requires further investigation. Maternal antibody levels are constant and newborn antibody levels are not based on 'current' maternal antibody levels which would give a much more realistic model. This could be addressed using a stochastic model. Partial age-stratification the model assumes young infants (> 4 years old) immediately contribute to the reproduction, which not the case. A fully age-stratified model would rectify this. As vaccination is assumed to occur uniformly, when applying double vaccination, there is equal likelihood of second vaccination as first vaccination. This may not be the case as it assumes initial and follow up vaccinations are independent. However, individuals not vaccinated initially may be more likely not to be have a second vaccination as parents may not want vaccination of their child. Vaccination proportions are unlikely to be the same across both first and second stage of vaccination. This model assumes that all individuals get vaccinated on a particular day of their life, which is rarely the case in practice. In addition previous criticisms of models presented apply to this this model, apart from realistic vaccination and protective maternal immunity.

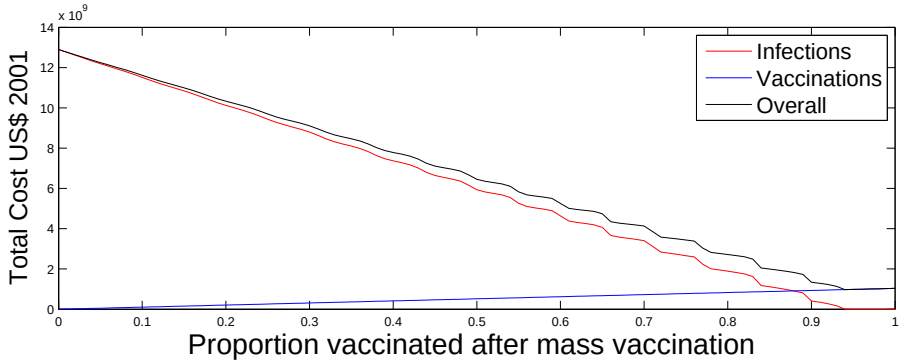
8 Economic impact

There are papers looking in great detail at the cost associated with vaccination and infection from the perspective of society [9, 10]. These studies include the UK as a case study, so may be used in combination with models presented in this study. By determining the number of new infectious and vaccinated individuals at each time step in the models provided in previous chapters, I estimate the cost for particular vaccination schemes over a period of time, the next 50 years in the present case. Using these results, it is possible to determine optimal vaccination schemes for each model in terms of long term cost on mass vaccinated populations. I assume mass vaccinated populations to be those that have undergone 85% vaccination for 20 years, a simplification applicable to the UK, which had low/medium levels of coverage of vaccination form 1968-1990, since 1990 vaccination coverage has been high fluctuating between 80-90% [1]. All models are run for 10 years without vaccination, mass vaccination is then applied for 20 years, then the particular vaccination scheme is applied for a further 50 years. The number of new infectious and vaccinated individuals is then calculated over this 50 year period, from which cost of each scheme can be determined.

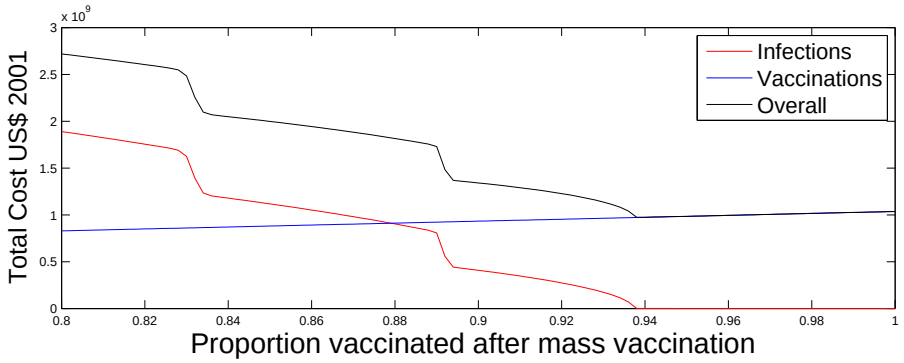
With the present models, only the cost of measles can be estimated. For true optimum vaccination schedules, one would need to develop models for mumps and rubella as well. However as measles requires the highest proportion of immunity to eradicate [27], I would suspect at high vaccination levels that optimum for measles should be similar to optimum for MMR vaccination.

8.1 Basic vaccination schedules - SVIR model

I use the model presented in section 4 to determine possible costs associated with vaccinating varying proportions of population. All criticism of the SVIR model still holds, so estimates are somewhat crude.



(a) 0% to 100% Vaccination



(b) 80% to 100% Vaccination

Figure 12: Total cost of the SVIR model (section 4) at varying proportions of vaccination. The system is run for 50 years after mass vaccination. US $307 (2001 levels) per measles case, US $22.1 (2001 levels) per vaccination and US $2.08 (2001 levels) per associated cost of vaccination [9, 10].

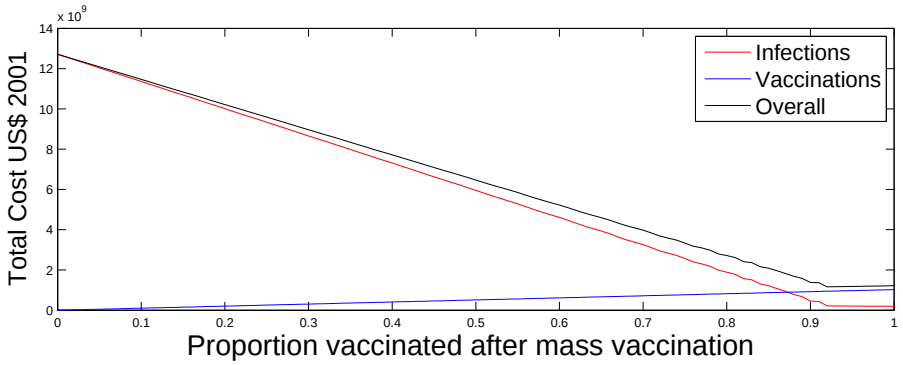
Figure 12 shows that optimal cost is achieved by vaccinating just under 94% of the infants born, at an approximate cost of US$ 1 Billion (2001 levels). Moreover this shows that vaccinating a greater proportion than this proportion results in a small increase in overall cost whereas vaccinating a lower proportion of the population results in a sharp increase cost. By vaccinating 86% of population results in a 2-fold increase in cost in comparison to optimum. This suggests vaccination schedules should aim to vaccinate over 94% of the population, e.g. around 97%, to determine near minimal cost. This is a similar approach when applying Kelly betting.

The model assumes that both the cost per measles case and cost of vaccination would remain constant for the next 50 years, but medical treatment can change over time.

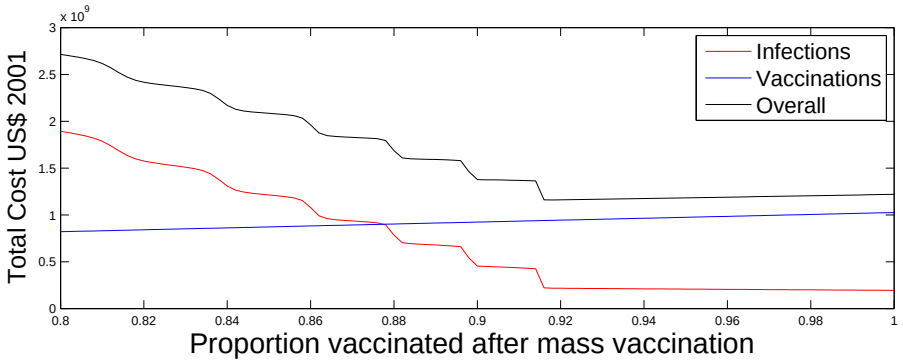
Nor does the model account for various economic factors such as inflation, which could have a significant impact. In addition replication of the mass vaccination program that occurred in the UK is a simplification.

8.2 Ideal vaccination schedule

I use the model presented in section 6 to determine costs associated with the ideal vaccination schedule. The criticisms associated with this model will also apply to the total cost model too.



(a) 0% to 100% Vaccination



(b) 80% to 100% Vaccination

Figure 13: Total cost of the ideal BSVIR model (section 6) at varying proportions of vaccination. The system is run for 50 years after mass vaccination. US $307 (2001 levels) per measles case, US $22.1 (2001 levels) per vaccination and US $2.08 (2001 levels) per associated cost of vaccination [9, 10].

Figure 13 shows that the minimum cost of US$ 1.16 billion occurs when 92% of the population are vaccinated. This is less than p_E and indicates either eradication or epidemics of period greater than 50 years. The cost associated with infections for proportions above 92% is the cost of measles cases of those infectious individuals before eradication. Like the previous cost model it is cheaper to over-vaccinate than it is to

under-vaccinate. This model suggests vaccination of approximately 95% would offer both eradication and near optimal cost.

The critical flaw in this model is that vaccination schedules are currently not ideal, as it is difficult/impossible to determine the exact moment at which an individual becomes susceptible and apply vaccination. Criticisms of the SVIR based cost model also apply.

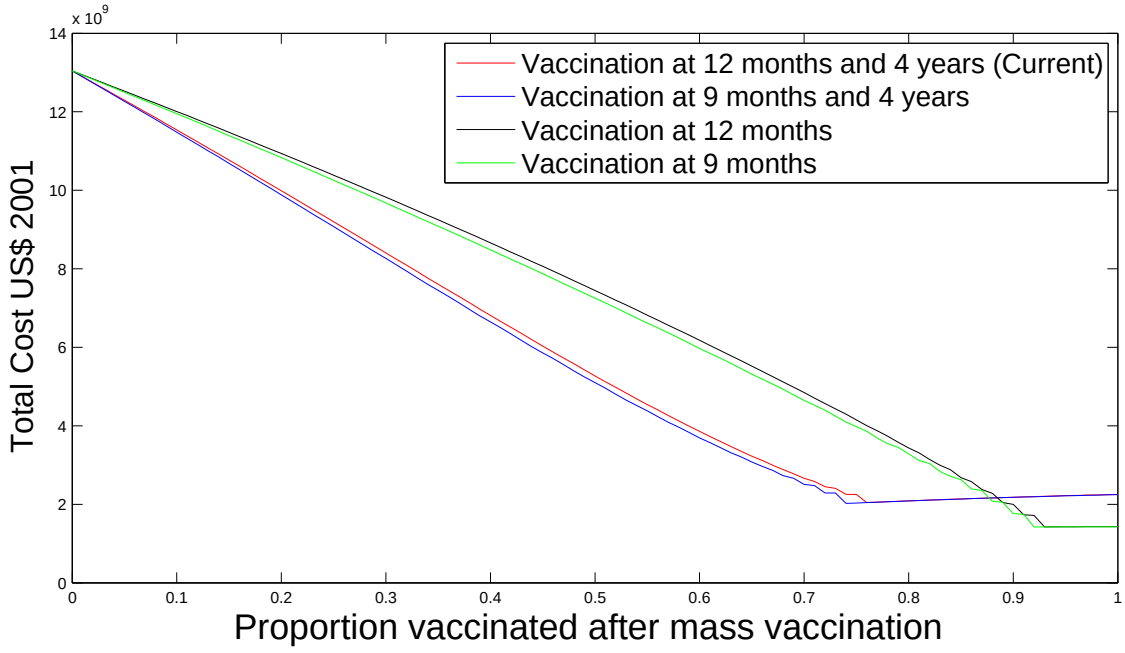
8.3 Realistic vaccination schedules

The previous definition of mass vaccination on this model must be refined for this cost model, at 12 months of age 85% vaccination is applied for 20 years, as this is the recommended age for initial vaccination [6]. Using the model provided in section 7, I compare estimated costs of different vaccination schedules against each other. I compare the current vaccination schedule (12 months and 4 years), reduction of initial vaccination to 9 months followed by second vaccination at 4 years, single vaccination at 9 months and single vaccination at 12 months. For those double vaccinations schedules, p proportion of the population are vaccinated at each age group. This supposes that vaccination at different age groups is independent and applied at equal proportions.

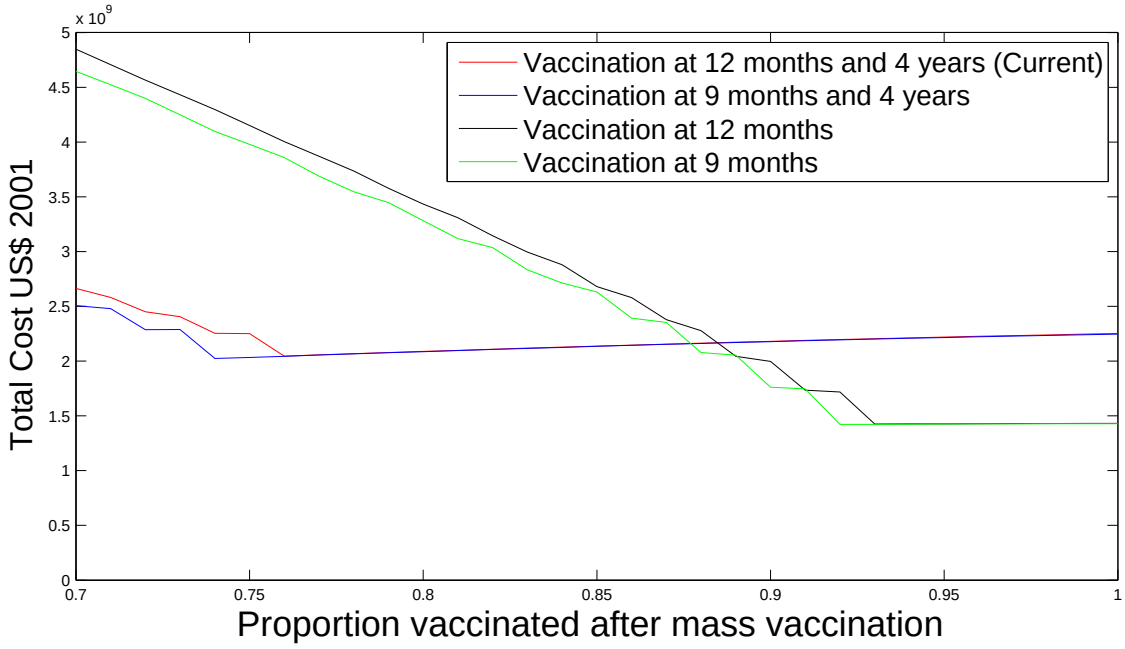
Figure 14 shows that optimum is obtained at 74% and 76% for double vaccinations schemes with initial vaccination at 9 and 12 months, respectively, costing approximately US$ 2 Billion over the next 50 years. It also shows optima for single vaccination schedules 9 month and 12 months are reached at 92% and 93%, respectively, costing approximately US$ 1.4 Billion over the next 50 years. Both single vaccination schemes obtain eradication, despite the 'failed' vaccinations. Like previous models, all vaccination schemes presented using the realistic vaccination model show that it is more expensive to under-vaccinate than it is to over-vaccinate a population.

At vaccination proportions below 88% of the population, double vaccination schemes offer an overall lower total cost. It suggests that near to optimum costs can be obtained above 80% on current vaccination schemes. At low vaccination levels, say 50% vaccination, reducing the initial age of vaccination to 9 months can reduce cost by approximately US$170 million over 50 years. However above the optimum proportion for the current vaccination scheme, there is no difference in overall cost offered by either double vaccination scheme. As reducing the initial vaccination age to 9 months offers lower overall costs for all the vaccination proportion below optimum, it may be considered as a potential area for further investigation, but at current levels of vaccination it seems to make no difference in cost.

For vaccination levels above 90%, single vaccination schemes seem to be more cost effective schedules than a double vaccination scheme. Similar to the double vaccination scheme, it seems that vaccination at low proportions at age of 9 months is more cost effective than vaccination at 12 months, but for greater accuracy, more detailed maternal antibody titres parameters must be established. However at high vaccination proportions, above 90%, where a single vaccination may be considered, the difference between the two different schemes is less clear. If a single vaccination campaign of 97% could be achieved, then a cost saving in the region of US $800 million (2001 levels) over 50 years could be achieved in comparison to a similar double vaccination scheme. Data



(a) 0% to 100% Vaccination



(b) 70% to 100% Vaccination

Figure 14: Comparison of various vaccination schedules total cost of the realistic BSVIR model (section 7) at varying proportions of vaccination. The system is run for 50 years after mass vaccination. $307 per measles case, US $307 (2001 levels) per measles case, US $22.1 (2001 levels) per vaccination and US $2.08 (2001 levels) per associated cost of vaccination [9, 10].

that should hopefully prompt further and more detailed study of the consequences of such schemes.

There are issues with this model that must be rectified before making recommendations about changing vaccination schedules. The fully age-stratified, leading to 'children' with age > 4 years contributing to births. Beutels [7] indicates cost per measles case is age dependant. Both these issues can be rectified with a fully age-stratified model. There is no accounting for antibody levels in the populations, so natural boosting of antibodies and varying antibodies of infants in relation to maternal antibodies have not been accounted for. Both of which could be dealt with using a stochastic model. Parameters used for maternal antibodies in this model are likely to be inaccurate as Sato data used for unvaccinated mothers was collected in 1979 and parameters used for vaccinated mother were estimates. A new study examining current measles antibody levels in the UK would be required in both vaccinated and unvaccinated mothers. The mass vaccination scheme applied is a simplification of the real vaccination applied in the UK. The assumption of independent vaccination in double vaccination seems to be false, which means that the accuracy of modelling single vaccination schemes will be higher than the double vaccination schemes presented. In addition the criticism of previous cost models also apply to this model.

9 Conclusion

The costs shown in Figure 12, Figure 13 and Figure 14 may seem unrealistic, as in previous 20 years we have had low numbers of measles cases, with only 1370 cases in 2008 [3]. There are numerous plausible reasons for this. First of all the majority of cost at high vaccination proportions are vaccination costs. The UK may currently be in a 'honeymoon' period of infections, observed in models with high vaccination proportions, where after vaccination the period between epidemics increases and as such the number of infections in a given year is low between epidemic years. These models are designed to be long term, as such it is possible for a measles epidemic in subsequent years. This has been observed for mumps, which in 2005 experienced a large epidemic [3].

All of the cost models described in section 8, show it is more cost effective to over-vaccinate than to under-vaccinated. For single vaccination schemes, figures around 97% vaccination of infants would ensure near optimal long term cost. The realistic BSVIR cost model shows that double vaccination schedules are more cost effective at lower vaccination proportions and there may be potential savings by reducing the initial age of vaccination down to 9 months and maintaining second vaccination. It also suggests there could be large savings in changing to a single vaccination schedule if high proportions of vaccination can be achieved, above 95%.

These results must be taken cautiously as there are many unrealistic assumptions about population and the cost models are not designed to give exact predictions for cost. Instead these models are designed for comparison of various vaccination schedules. For more accurate results I would have to address some the concerns of the realistic BSVIR model. Moreover, this study only looks at measles. For true analysis of cost

of vaccination schedules impact on mumps and rubella must also be examined, as the inclusion of rubella and mumps dynamics can only increase overall costs for lower vaccination proportions. This shows that even larger long term savings can be made by factoring these in if eradication is achieved of all three diseases. To be able to accurately predict long term cost I would need to account for various economic factors. Although this study a case study of the United Kingdom, it would be easy to change suitable parameters and determine similar results for any population.

The results of this study suggest increasing proportions vaccinated to reduce cost, this is itself a challenge, especially at ages at which this study advocates vaccination. One possible solution may be to require documented vaccination history before being able to attend reception or other pre-school. Alternatively it may also be possible to run mass vaccination days in a attempt to increase take up. Vaccination proportions for MMR are currently 7% lower than those observed for almost all other diseases [1]. This may be in part due to false links between the MMR vaccination and autism, which is a hard attitude shift. All models presented show for single vaccination schemes that eradication is not possible at current vaccination proportions, and it costs significantly more in the long term. This study does not account for antibody levels, and in particular suggestions of decline in antibody levels due to the lack of natural boosting. It would be interesting to see an investigation that looks to address this in a similar context as this study. Additionally it must be noted that this study looks at determining optimum vaccination schedules from a cost perspective. However, this may not be only factor that is considered when recommending vaccination schemes, e.g. minimizing infant infection may also be a consideration.

When obtaining experimental data to determine protective maternal immunity, the number of used various units and thresholds for immunity in different studies, made it extremely difficult to compare the studies. More recent studies have been becoming more standardised, making comparison easier. However, I feel there is still significant progress to be made, such as a on agreed antibody threshold for immunity for ELISA and PRN assays. This would allow direct comparison of studies, giving a much greater pool of data. One would therefore be able to draw more accurate conclusions.

It has been difficult to compare the results of my model with results observed in the real world. This is not due to poor data, as the HPA has been a great resource measles data. However, this does not include for Scotland or Northern Ireland (and sometimes even Wales), meaning I can only crudely assess my models in comparison to the UK. It must also be pointed out if eradication is to be achieved, high levels of vaccination must be achieved uniformly, with each area ensuring it sticks to target levels so that pockets of population are not under-vaccinated, which could cause a resurgence in the disease.

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Appendix

Proof of 1. Finding equilibrium point I_e I can deduce an estimate for constant β.
$\frac{dI}{dt} = 0 = I_e(\beta S_e - \alpha - \gamma)$
Trivially $I_e = 0$ ignoring this as implies if no one is infectious then no risk to the population, non-trivially $S_e = \frac{\alpha+\gamma}{\beta}$.
$\frac{dS}{dt} = 0 = \alpha(N - S_e) - \beta I_e S_e$
Hence $I_e = \frac{\alpha}{\beta}\left(\frac{N}{S_e} - 1\right) = \frac{\alpha\beta N - \alpha(\alpha+\gamma)}{\beta(\alpha+\gamma)}$.
To estimate β I have.

$$\begin{aligned}
\beta &= \frac{\delta}{I_e} \\
\beta &= \frac{\delta}{\frac{\alpha\beta N - \alpha(\alpha+\gamma)}{\beta(\alpha+\gamma)}} \\
\beta &= \frac{\delta\beta\left(\alpha+\gamma\right)}{\alpha\beta N - \alpha\left(\alpha+\gamma\right)} \\
1 &= \frac{\delta\left(\alpha+\gamma\right)}{\alpha\beta N - \alpha\left(\alpha+\gamma\right)} \\
\alpha\beta N - \alpha\left(\alpha+\gamma\right) &= \delta\left(\alpha+\gamma\right) \\
\alpha\beta N &= \left(\delta+\alpha\right)\left(\alpha+\gamma\right) \\
\beta &= \frac{\left(\delta+\alpha\right)\left(\alpha+\gamma\right)}{\alpha N}
\end{aligned}$$

□

Proof of 3. Suppose we could successful vaccinate a proportion of the susceptible individuals then the number vaccinated individuals is pS, and so the number remaining in the susceptible group in $(1-p)S$, hence the number of secondary cases of a single infected individual in our population is $(1-p)R_0$, which must be less than 1.

$$\begin{aligned}
(1-p)R_0 &< 1 \\
R_0 - pR_0 &< 1 \\
R_0 - 1 &< pR_0 \\
1 - \frac{1}{R_0} &< p \\
1 - \frac{\alpha+\gamma}{\beta N} &< p
\end{aligned}$$

As p_E is the minimum number of individuals that must gain immunity for eradication.

$$p_E = 1 - \frac{\alpha+\gamma}{\beta N}$$

□

Proof of 7.

$$\begin{aligned}
J_{\lambda,n}(a) &= \mathbb{P}\left(\text{Infant immune at age a}\right) \\
&= \mathbb{P}\left(A(c,a) \geq T\right) \\
&= \mathbb{P}\left(e^{-\mu a}c \geq T\right) \\
&= 1 - \mathbb{P}\left(e^{-\mu a}c < T\right) \\
&= 1 - \mathbb{P}\left(c < Te^{\mu a}\right) \\
&= 1 - \mathbb{P}\left(2^k m^r < Te^{\mu a}\right) \\
&= 1 - \mathbb{P}\left(m^r < Te^{\mu a}2^{-k}\right) \\
&= 1 - \mathbb{P}\left(m < \left(Te^{\mu a}2^{-k}\right)^{1/r}\right) \\
&= 1 - F_{\lambda,n}\left(\left(Te^{\mu a}2^{-k}\right)^{1/r}\right)
\end{aligned}$$

□

Matlab Code

Matlab code to generate current number of individuals in ideal BSVIR model (Figure 9). Similar code used for SIR (Figure 2) and SVIR (Figure 4) with different ODEs.

```
%Differential Model for ideal BVSIR.
%p – proportion of newly susceptible infants vaccinated as they become
%susceptible.
%Br–Birth Immunity Group. Of recovered mothers
%Bv–Birth Immunity Group. Of vaccinated mothers.
%S–Susceptable Group
%V–Vaccinated Group
%I–Infectious Group
%R–Recovered Group
%Population Assumptions
%lossrecoveredmatimmunityage – Avg. loss of immunity of maternally derived
%antibodies for infants of recovered mother. Years.
%sigma – recovered exposure rate. Per person per year.
%lossvaccinatedmatimmunityage – Avg. loss of immunity of maternally derived
%antibodies for infants of vaccinated mother. Years.
%xi – vaccinated exposure rate. Per person per year.
%lifexpt – Avg life expectancy. Years
%alpha – birth/death rate. Per person per year.
%infectiousperiod – Avg infectious period of measles.
%gamma – recovery rate. Per person per year.
%infectionage – avergage age of infection (without vaccination). years
%delta – Force of infection. per person person year
%beta – transmission rate. per person per year
%k – the proportion of people who make up the birth–able groups
function uprime = idealBSVIR(p,t,u)
Br=u(1);
Bv=u(2);
S=u(3);
V=u(4);
I=u(5);
R=u(6);
N = Br+Bv+S+V+I+R;
lossrecoveredmatimmunityage = 1;
sigma = 1/lossrecoveredmatimmunityage;
lossvaccinatedmatimmunityage = 0.75;
xi = 1/lossvaccinatedmatimmunityage;
lifeexpt = 70;
alpha = 1/lifeexpt;
infectiousperiod = 12/365;
gamma = 1/infectiousperiod;
infectionage = 5;
delta = 1/infectionage;
beta = ((delta+alpha)*(alpha+gamma))/(alpha*N);
k = N/(R+S+V);
brprime = (alpha*k*R)-(sigma*Br)-(alpha*Br);
bvprime = (alpha*k*V)-(xi*Bv)-(alpha*Bv);
sprime = ((1-p)*((sigma*Br)+(xi*Bv)))+((1-p)*alpha*k*S)-(beta*S*I)-(alpha*S);
```

```
vprime = (p*((sigma*Br)+(xi*Bv)+(alpha*k*S)))-(alpha*V);
iprime = (beta*S*I)-(gamma*I)-(alpha*I);
rprime = (gamma*I)-(alpha*R);
uprime = [brprime;bvprime;sprime;vprime;iprime;rprime];
```

```
%Solves the ideal BSVIR model using the fourth stage Runge-Kutta method.
%It then plots the number of susceptible and infectious individuals.
%u0 - intial distribution of population
%p - Proportion of population vaccinated
%vyear - year in which vaccination is introduced
%n - the number of years to run the system
%t - current time
%h - time step
%c - counter
%introvaccstep - the step at which vaccine is introduced
%l - length of t
%U - Store of population groups at each time step
function y = solveidealBSVIR(u0,p,vyear,n)
u = u0;
c = 1;
h = 1/365;
t = [0:h:n];
introvaccstep = vyear/h;
l = length(t);
U = zeros(6,l);
while ((c<= l)&&(c<=introvaccstep))
    %Runge-Kutta Method
    k1 = idealBSVIR(0,t(c),u);
    k2 = idealBSVIR(0,t(c)+h/2,u+(h*k1/2));
    k3 = idealBSVIR(0,t(c)+h/2,u+(h*k2/2));
    k4 = idealBSVIR(0,t(c)+h,u+(h*k3));
    u = u + (h*(k1+(2*k2)+(2*k3)+k4)/6);
    U(:,c)=u;
    c = c+1;
end
while (c<=l)
    %Runge-Kutta Method
    k1 = idealBSVIR(p,t(c),u);
    k2 = idealBSVIR(p,t(c)+h/2,u+(h*k1/2));
    k3 = idealBSVIR(p,t(c)+h/2,u+(h*k2/2));
    k4 = idealBSVIR(p,t(c)+h,u+(h*k3));
    u = u + (h*(k1+(2*k2)+(2*k3)+k4)/6);
    U(:,c) = u;
    c = c+1;
end
y = U;
%Display the resulting susceptible and infectious individuals.
%S = U(3,:);
%I = U(5,:);
%plot(t,S,'r',t,I,'b')
%h_legend=legend('Susceptible','Infectious');
%set(h_legend,'FontSize',14);
```

```
%x_label = xlabel('Years');
%set(x_label,'FontSize',18);
%y_label = ylabel('Current number of individuals');
%set(y_label,'FontSize',16);
```

Matlab code to generate new infectious and vaccinated individuals in ideal BSVIR model (No Figure). Similar code used for SIR (Figure 2) and SVIR (No Figure) with different ODEs. Similar methods also used for realistic BSVIR (No Figure).

```
%Differential Model estimating the new infectious and vaccinated
%individuals in the ideal BSVIR model.
%Br—Birth Immunity Group. Of recovered mothers
%Bv—Birth Immunity Group. Of vaccinated mothers.
%S—Susceptable Group
%V—Vaccinated Group
%I—Infectious Group
%R—Recovered Group
%The Population assumptions
%lossrecoveredmatimmunityage — Avg. loss of immunity of maternally derived
%antibodies for infants of recovered mother. Years.
%sigma — recovered exposure rate. Per person per year.
%lossvaccinatedmatimmunityage — Avg. loss of immunity of maternally derived
%antibodies for infants of vaccinated mother. Years.
%xi — vaccinated exposure rate. Per person per year.
%lifexpt — Avg life expectancy. Years
%infectiousperiod — Avg infectious period of measles. Years
%infectionage — avergage age of infection (without vaccination). Years
%alpha — birth/death rate. Per person per year.
%gamma — recovery rate. Per person per year.
%delta — Force of infection. per person person year
%beta — transmission rate. per person per year
%k — the proportion of people who make up the birth—able groups
%p — proportion of newly susceptible infants vaccinated as they become
%susceptible.
function uprime = newinfectiousandvaccidealBSVIR(p,t,u)
Br=u(1);
Bv=u(2);
S=u(3);
V=u(4);
I=u(5);
R=u(6);
N = Br+Bv+S+V+I+R;
lossrecoveredmatimmunityage = 1;
sigma = 1/lossrecoveredmatimmunityage;
lossvaccinatedmatimmunityage = 0.75;
xi = 1/lossvaccinatedmatimmunityage;
lifeexpt = 70;
alpha = 1/lifeexpt;
infectiousperiod = 12/365;
gamma = 1/infectiousperiod;
infectionage = 5;
delta = 1/infectionage;
beta = ((delta+alpha)*(alpha+gamma))/(alpha*N);
```

```
k = N/(R+S+V);
brprime = 0;
bvprime = 0;
sprime = 0;
vprime = (p*((sigma*Br)+(xi*Bv)+(alpha*k*S)));
iprime = (beta*S*I);
rprime = 0;
uprime = [brprime;bvprime;sprime;vprime;iprime;rprime];
```

```
%Solves the new number of infectious and vaccinated individuals in
%the ideal BSVIR model using the fourth-stage Runge-Kutta method. It
%then solves the ideal BSVIR model using the fourth stage Runge-Kutta
%method to track overall system behaviour. It then plots the new number
%infectious and vaccinated individuals.
%u0 - initial values
%p - Proportion of population vaccinated
%vyear - year in which vaccination is introduced.
%n - the number of years to run the system
%t - current time
%h - time step
%c - counter
%introvaccstep - the step at which vaccine is introduced
%l - length of t
%U - Stores the number of individuals in each group at each time step.
%newinfectiousindivuals - stores the number of newly infected individuals
%as time progresses.
%newvaccinatedindivuals - stores the number of newly vaccinated individuals
%as time progresses.
%delta - temporarily stores the changes in the newinfectiousandvaccSVIR
%differential model. i.e. the newly infected and vaccinated individuals.
function y = solvenewinfectiousandvaccidealBSVIR(u0,p,vyear,n)
u = u0;
c = 1;
h = 1/365;
t = [0:h:n];
introvaccstep = vyear/h;
l = length(t);
U = zeros(6,l);
newinfectiousindividuals = zeros(1,l);
newvaccinatedindividuals = zeros(1,l);
while ((c<= l)&&(c<=introvaccstep))
    %Runge-Kutta Method for the number of new infectious individuals
    k1 = newinfectiousandvaccidealBSVIR(0,t(c),u);
    k2 = newinfectiousandvaccidealBSVIR(0,t(c)+h/2,u+(h*k1/2));
    k3 = newinfectiousandvaccidealBSVIR(0,t(c)+h/2,u+(h*k2/2));
    k4 = newinfectiousandvaccidealBSVIR(0,t(c)+h,u+(h*k3));
    delta = (h*(k1+(2*k2)+(2*k3)+k4)/6);
    newvaccinatedindividuals(c) = delta(4);
    newinfectiousindividuals(c) = delta(5);
    %Runge-Kutta Method
    k1 = idealBSVIR(0,t(c),u);
    k2 = idealBSVIR(0,t(c)+h/2,u+(h*k1/2));
```

```
    k3 = idealBSVIR(0,t(c)+h/2,u+(h*k2/2));
    k4 = idealBSVIR(0,t(c)+h,u+(h*k3));
    u = u + (h*(k1+(2*k2)+(2*k3)+k4)/6);
    U(:,c)=u;
    c = c+1;
end
while (c<=l)
    %Runge—Kutta Method for the number of new infectious and vaccinated
    %individuals
    k1 = newinfectiousandvaccidealBSVIR(p,t(c),u);
    k2 = newinfectiousandvaccidealBSVIR(p,t(c)+h/2,u+(h*k1/2));
    k3 = newinfectiousandvaccidealBSVIR(p,t(c)+h/2,u+(h*k2/2));
    k4 = newinfectiousandvaccidealBSVIR(p,t(c)+h,u+(h*k3));
    delta = (h*(k1+(2*k2)+(2*k3)+k4)/6);
    newvaccinatedindividuals(c) = delta(4);
    newinfectiousindividuals(c) = delta(5);
    %Runge—Kutta Method
    k1 = idealBSVIR(p,t(c),u);
    k2 = idealBSVIR(p,t(c)+h/2,u+(h*k1/2));
    k3 = idealBSVIR(p,t(c)+h/2,u+(h*k2/2));
    k4 = idealBSVIR(p,t(c)+h,u+(h*k3));
    u = u + (h*(k1+(2*k2)+(2*k3)+k4)/6);
    U(:,c) = u;
    c = c+1;
end
y = [newinfectiousindividuals;newvaccinatedindividuals];
%Display the number new infectious and vaccinated individuals at each time
%step.
%plot(t,newvaccinatedindividuals,'r',t,newinfectiousindividuals,'b')
%legend('Vaccinated','Infectious')
%x_label = xlabel('Years');
%set(x_label,'FontSize',14);
%y_label = ylabel('Number of new individuals');
%set(y_label,'FontSize',14);
```

Matlab code to generate scatter graph of experimental infant immunity data (Figure 5).

```
%The function takes data containing the age of sampling, number of infants
%and number with immunity from both vaccinated and unvaccinated
%mothers, in the form of a matrix, and returns scatter graph of the
%proportion of infants immune as a function of their age.
%data — n x 5 matrix. 1st column is age (months).2nd column is number of
%infants of unvaccinated mothers. 3rd column is number of infants of
%unvaccinated mothers with immunity. 4th column is number of
%infants of vaccinated mothers. 5th column is number of infants of
%vaccinated mothers with immunity.
%a — age vector. The ages at which data was taken.
%nu — number of infants of unvaccinated mothers vector.
%iu — number of infants of unvaccinated mothers with immunity vector.
%nv — number of infants of vaccinated mothers vector.
%iv — number of infants of vaccinated mothers with immunity vector.
function datatoscatter (data)
```

```
a = data (:,1);
nu = data (:,2);
iu = data (:,3);
nv = data (:,4);
iv = data (:,5);
plot (a,iu./nu,'rx',a,iv./nv,'bx');
axis ([0 15 0 1]);
axis square;
set(gca,'XTick',0:3:15);
set(gca,'YTick',0:0.2:1);
hlegend = legend ('Infants of Unvaccinated Mothers','Infants of Vaccinated Mothers');
set(hlegend,'FontSize',14);
x_label = xlabel('Age (Months)');
set(x_label,'FontSize',14);
y_label = ylabel('Proportion immune');
set(y_label,'FontSize',14);
```

Matlab code to generate modelling immunity functions (Figure 6).

```
%Takes a set of maternal antibody data and plots the resulting immunity
%function as well as the lower and upper confidence bounds that would
%be obtained from parameterising the data and inputting parameters into the
%immuniy function.
%T – Threshold of immunity
%data – Vector of datapoints of maternal antibody titre.
%est – estimated scale and shape parameters for the data
%conf – 95% lower and upper bounds for the scale and shape parameters for
%the data
%k – constant term to translate maternal into infant antibody titre.
%r – linear coefficient to translate maternal into infant antibody titre.
%mu – decay rate of infant antibody titre
%x – input values for gammacdf.
function datatoimmunityfunc (T,data)
%Parameterise the data
[est,conf] = gamfit(data);
k = 1.1695;
r = 0.9216;
mu = 0.43;
a = (0:0.25:15);
x = ((T.*exp(mu.*a)/(2^k)).^(1/r));
prop = 1– gamcdf(x,est(1),est(2));
proplow = 1– gamcdf(x,conf(1,1),conf(1,2));
prophigh = 1– gamcdf(x,conf(2,1),conf(2,2));
plot (a,prop,'–',a,proplow,':',a,prophigh,':');
axis ([0 15 0 1]);
axis square;
set(gca,'XTick',0:3:15);
set(gca,'YTick',0:0.2:1);
xlabel('Age (Months)')
ylabel('Proportion immune')
x_label = xlabel('Age (Months)');
set(x_label,'FontSize',14);
y_label = ylabel('Proportion immune');
```

```
set(y_label,'FontSize',14);
```

Matlab code to generate current number of individuals in realistic BSVIR model (Figure 11).

```
%Differential Model for realistic BSVIR births as a vector.
%Br—Birth Immunity Group. Of recovered mothers
%Bv—Birth Immunity Group. Of vaccinated mothers.
%S—Susceptable Group
%V— Vaccinated Group
%I—Infectious Group
%R—Recovered Group
%N — Total population size
%lifexpt — Avg life expectancy. Years
%alpha — birth/death rate. Per person per year.
%k — the proportion of people who make up the birth—able groups
function uprime = birthBSVIR(t,u)
Br=u(1);
Bv=u(2);
S=u(3);
V=u(4);
I=u(5);
R=u(6);
N = 60000000;
lifeexpt = 70;
alpha = 1/lifeexpt;
k = N/(R+S+V);
ui = unvaccinatedimmunity(0);
vi = vaccinatedimmunity(0);
brprime = ui*(alpha*k*R);
bvprime = vi*(alpha*k*V);
sprime = (alpha*k*S)+((1—vi)*(alpha*k*V))+((1—ui)*(alpha*k*R));
vprime = 0;
iprime = 0;
rprime = 0;
uprime = [brprime;bvprime;sprime;vprime;iprime;rprime];
```

```
%Differential Model for realistic BSVIR system dynamics storing the
%differences as a matrix.
%u — matrix containing values
%totalI—Total in Infectious Group
%Population Assumptions
%N — total population size.
%lifexpt — Avg life expectancy. Years
%alpha — birth/death rate. Per person per year.
%infectiousperiod — Avg infectious period of measles.
%gamma — recovery rate. Per person per year.
%infectionage — avergage age of infection (without vaccination). years
%delta — Force of infection. per person person year
%beta — transmission rate. per person per year
%k — the proportion of people who make up the birth—able groups
%l — length of u
```

```
%c — counter
%Br—Birth Immunity Group. Of recovered mothers
%Bv—Birth Immunity Group. Of vaccinated mothers.
%S—Susceptable Group
%V—Vaccinated Group
%I—Infectious Group
%R—Recovered Group
function uprime = matrixBSVIR(t,u)
totalI=sum(u(5,:));
N = 60000000;
lifeexpt = 70;
alpha = 1/lifeexpt;
infectiousperiod = 12/365;
gamma = 1/infectiousperiod;
infectionage = 5;
delta = 1/infectionage;
beta = ((delta+alpha)*(alpha+gamma))/(alpha*N);
l = length(u);
c = 1;
brprime = zeros(1,l);
bvprime = zeros(1,l);
sprime = zeros(1,l);
vprime = zeros(1,l);
iprime = zeros(1,l);
rprime = zeros(1,l);
while (c<=l)
    Br = u(1,c);
    Bv = u(2,c);
    S = u(3,c);
    V = u(4,c);
    I = u(5,c);
    R = u(6,c);
    brprime(c) = -alpha*Br;
    bvprime(c) = -alpha*Bv;
    sprime(c) = -(beta*S*totalI)-(alpha*S);
    vprime(c) = -alpha*V;
    iprime(c) = (beta*S*totalI)-(gamma*I)-(alpha*I);
    rprime(c) = (gamma*I)-(alpha*R);
    c=c+1;
end
uprime = [brprime;bvprime;sprime;vprime;iprime;rprime];
```

```
%immunitydays return the proportion of infants still immune after a certain
%number of days given the day, scale and shape value for the gamma distn
%of the maternal antibody titre.
%Maternal antibodies are assumes to be linearly related by
%log(cord)=r*log(maternal)*k
%lambda — Scale parameter of gamma distribution.
%n — Shape parameter of gamma distribution.
%r — ratio of linear relationship between log(cord) and log(maternal).
%Taken as the corrected values from Transplacental transfer of measles and total IgG.
%k — constant term of the linear relationship between log(cord) and
```

```
%log(maternal). %Taken as the corrected values from Transplacental transfer
%of measles and total IgG.
%mu — rate of decay
%T — Threshold for immunity. Taken from standard mIU/ml
%a — the time/age in months
function y=immunityyears (years,n,lambda)
k = 1.1695;
r = 0.9216;
mu = 5.16;
T = 120;
x = ((T*exp(mu*years)/(2^k))^(1/r));
y = 1— gamcdf(x,n,lambda);
```

```
%Returns the proportion of infants who have lost maternal immunity between
%two time intervals given they are born to unvaccinated mothers . Years.
%t1 — lower time interval
%t2 — upper time interval
%p1 — lower time interval immunity function
%p2 — upper time interval immunity function
function y = lossofunvaccinatedimmunity(t1,t2)
n = 1.26;
lambda = 3075;
p1 = immunityyears(t1,n,lambda);
p2 = immunityyears(t2,n,lambda);
%Numerical errors occur if we try to divide by 0 or close to 0. So we want
%everyone to lose it
if (p1 == 0)
    y=1;
else
    y =1—(p2/p1);
end
```

```
%Returns the proportion of infants who have lost maternal immunity between
%two time intervals given they are born to vaccinated mothers . Years.
%t1 — lower time interval
%t2 — upper time interval
%p1 — lower time interval immunity function
%p2 — upper time interval immunity function
function y = lossofvaccinatedimmunity(t1,t2)
n = 1.26;
lambda = 1000;
p1 = immunityyears(t1,n,lambda);
p2 = immunityyears(t2,n,lambda);
%Numerical errors occur if we try to divide by 0 or close to 0. So we want
%everyone to lose it
if (p1 == 0)
    y=1;
else
    y =1—(p2/p1);
end
```

```
%Solves the realistic BSVIR model using the fourth stage Runge–Kutta
%method. Storing the partially age stratified model as a matrix
%It then plots the number of susceptible and infectious individuals.
%n – the number of years to run the system
%vage – the age at which vaccination schedual is applied
%vyear – year in which vaccination is introduced.
%p – Proportion of population vaccinated
%u0 – intial number individuals in each group. u0=[br0;bv0;s0;v0;i0;r0]
%population – the matrix which stores age information and status
%information.
%t – current time
%h – time step
%c – counter
%introvaccstep – the step at which vaccine is introduced
%vagegroup – the age group at which vaccination is applied.
%l – length of t
%U – tracks the total number in each group over time.
%***Due to computation required to calulate, it is effective to store
%values and reference them when required.***
%lossofunvaccimmunityvalues – Store proportion of infants of unvaccinated
%mothers that lose immunity between time steps.
%lossofvaccimmunityvalues – Store proportion of infants of vaccinated
%mothers that lose immunity between time steps.
function y = solverealisticBSVIR(u0,p,vage,vyear,n)
c = 1;
h = 1/365;
t = [0:h:n];
l = length(t);
trackage = 4;
trackagegroup = trackage/h;
introvaccstep = vyear/h;
vagegroup = vage/h;
%Population matrix stores information about infants until they reach
%vaccination age. After that they are added to the general group, the last
%column of the matrix.
population = zeros(6,trackagegroup+1);
population(:,end) = u0;
lossofunvaccimmunityvalues = zeros (1,trackagegroup);
for i=1:length(lossofunvaccimmunityvalues)
   lossofunvaccimmunityvalues(i) =  lossofunvaccinatedimmunity(i*h,(i+1)*h);
end
lossofvaccimmunityvalues = zeros (1,trackagegroup);
for i=1:length(lossofvaccimmunityvalues)
   lossofvaccimmunityvalues(i) =  lossofvaccinatedimmunity(i*h,(i+1)*h);
end
U = zeros(6,l);
while ((c<= l)&&(c<=introvaccstep))
    %Runge–Kutta Method for new birth group
    kbirth1 = birthBSVIR(t(c),population(:,end));
    kbirth2 = birthBSVIR(t(c)+h/2,population(:,end)+(h*kbirth1/2));
    kbirth3 = birthBSVIR(t(c)+h/2,population(:,end)+(h*kbirth2/2));
    kbirth4 = birthBSVIR(t(c)+h,population(:,end)+(h*kbirth3));
    births = (h*(kbirth1+(2*kbirth2)+(2*kbirth3)+kbirth4)/6);
    %Runge–Kutta Method for change in population dynamics
```

```
    k1 = matrixBSVIR(t(c),population);
    k2 = matrixBSVIR(t(c)+h/2,population+(h*k1/2));
    k3 = matrixBSVIR(t(c)+h/2,population+(h*k2/2));
    k4 = matrixBSVIR(t(c)+h,population+(h*k3));
    population = population + (h*(k1+(2*k2)+(2*k3)+k4)/6);
    for i=1:(length(population)-1)
        brnum = population(1,i);
        bvnum = population(2,i);
        population(1,i) = lossofunvaccimmunityvalues(i)*brnum;
        population(2,i) = lossofvaccimmunityvalues(i)*bvnum;
        population(3,i) = population(3,i)+((1-lossofunvaccimmunityvalues(i))*brnum)...
        +((1-lossofvaccimmunityvalues(i))*bvnum);
    end
    %Shift data
    population = [births,population(:,1:(end-2)),(population(:,end-1)+population(:,end))];
    U(:,c) = sum(population,2);
    c = c+1;
end
while (c<=l)
    %Runge-Kutta Method for new birth group
    kbirth1 = birthBSVIR(t(c),population(:,end));
    kbirth2 = birthBSVIR(t(c)+h/2,population(:,end)+(h*kbirth1/2));
    kbirth3 = birthBSVIR(t(c)+h/2,population(:,end)+(h*kbirth2/2));
    kbirth4 = birthBSVIR(t(c)+h,population(:,end)+(h*kbirth3));
    births = (h*(kbirth1+(2*kbirth2)+(2*kbirth3)+kbirth4)/6);
    %Apply Vaccination
    population(4,vagegroup) = p*population(3,vagegroup);
    population(3,vagegroup) = (1-p)*population(3,vagegroup);
    %Runge-Kutta Method for change in population dynamics
    k1 = matrixBSVIR(t(c),population);
    k2 = matrixBSVIR(t(c)+h/2,population+(h*k1/2));
    k3 = matrixBSVIR(t(c)+h/2,population+(h*k2/2));
    k4 = matrixBSVIR(t(c)+h,population+(h*k3));
    population = population + (h*(k1+(2*k2)+(2*k3)+k4)/6);
    for i=1:(length(population)-1)
        brnum = population(1,i);
        bvnum = population(2,i);
        population(1,i) = lossofunvaccimmunityvalues(i)*brnum;
        population(2,i) = lossofvaccimmunityvalues(i)*bvnum;
        population(3,i) = population(3,i)+((1-lossofunvaccimmunityvalues(i))*brnum)...
        +((1-lossofvaccimmunityvalues(i))*bvnum);
    end
    %Shift data
    population = [births,population(:,1:(end-2)),(population(:,end-1)+population(:,end))];
    U(:,c) = sum(population,2);
    c = c+1;
end
y = U;
%Display the resulting susceptible and infectious individuals.
%S = U(3,:);
%I = U(5,:);
%plot(t,S,'r',t,I,'b')
%h_legend=legend('Susceptible','Infectious');
%set(h_legend,'FontSize',14);
```

```
%x_label = xlabel('Years');
%set(x_label,'FontSize',18);
%y_label = ylabel('Current number of individuals');
%set(y_label,'FontSize',16);
```

Matlab code used to generate total cost of realistic BSVIR single vaccination schedule (Figure 14), similar methods are used for double vaccination schemes, SVIR (Figure 12) and ideal BSVIR (Figure 13).

```
%Determines the cost of vaccinating varying proportions of the population
%against measles, using the realistic BSVIR model as a basis for the number of
%infections and vaccinations occured. The system is run for 10 years
%without vaccination, vaccination is then applied at 85% for 20 years to
%give a mass-vaccinated population. The system is then run for an
%additional 50 years to determine the long term behaviour. The number of
%new infectious individuals and vaccinations that occured is then summed to
%determine those incidence which incur cost. This is then multiplied by the
%associated cost to give total cost of the 50 year period from mass-vaccination.
%Parameters
%vage - the age in which vaccination schedule is administered.
%costpermeaslescase - the cost of a measles case in US $ (2001) to the UK.
%costpervaccination - the cost of measles vaccination in US $ (2001) to the UK.
%associatedcostpervaccination - the additional associated cost of each
%vaccination, e.g. any side effects of the vaccine.
%infections - the number of new infections that occur at each proportion of
%the population vaccinated.
%vaccinations - the number of vaccinations that occur at each proportion of
%the population vaccinated.
%intromassvaccyear - the year in which mass vaccination is introduced.
%massvaccperiod - the time which mass vaccination occured for. Years
%massvaccprop - the proportion of the population that is vaccinated during
%massvaccage - the age at which the population is vaccinated during mass
%vaccination. Assumed to be 1 and with a single vaccination.
%the mass period.
%s0 - intial number susceptable in population
%v0 - intial number vaccinated in population
%i0 - intial number infected in population
%r0 - intial number recovered in population
%U - store of the values for each group obtained during the mass
%vaccination period.
%postmassvacc - Is a vector giving the 'intial' values after the mass
%vaccination period. This is the intial values for the next 50 years.
%p - current proportion of population vaccinated.
%temp - tempory store of vaccinated and infectious individuals of a
%particular vaccination scheme.
function y = proportionrealisticBSVIRcost (vage)
costpermeaslescase = 307;
costpervaccintion = 22.1;
associatedcostpervaccination = 2.08;
prop = [0:1/100:1];
l = length(prop);
c = 1;
infections = zeros (1,l);
```

```
vaccinations = zeros (1,l);
%To save on time run the system for 10 years, then 20 years at 85%
%vaccination to determine the intial condiations once. Then these initial
%conditions can be used again in each model. (Avoiding repeat calculations)
intromassvaccyear = 10;
massvaccperiod = 20;
massvaccprop = 0.85;
massvaccage = 1;
br0 = 0;
bv0 = 0;
s0 = 6400000;
v0 = 0;
i0 = 600000;
r0 = 53000000;
u0 = [br0;bv0;s0;v0;i0;r0];
%More Efficient as avoids recalculation 100 times.
%solverealisticBSVIRpop same as solverealisticBSVIRpop apart from returns
%the population matrix instead of group history.
postmassvaccpop = solverealisticBSVIRpop(u0,massvaccprop,massvaccage,...
    intromassvaccyear,(intromassvaccyear + massvaccperiod));
while (c<=l)
    p = prop(c);
    temp = solvenewinfectiousandvaccrealisticsingleBSVIR(postmassvaccpop,p,vage,0,50);
    infections(c)=sum(temp(1,:));
    vaccinations(c)=sum(temp(2,:));
    c = c+1;
end
totalinfectioncost = costpermeaslescase*infections;
totalvaccinationcost = (costpervaccintion+associatedcostpervaccination)*vaccinations;
totalcost = totalinfectioncost+totalvaccinationcost;
y = totalcost;
%plot (prop,totalinfectioncost,'r',prop,totalvaccinationcost,'b',prop,totalcost,'k');
%legend ('Infections','Vaccinations','Overall');
%x_label = xlabel('Proportion Vaccinated after mass-vaccination');
%set(x_label,'FontSize',14);
%y_label = ylabel('Total Cost US$ 2001');
%set(y_label,'FontSize',14);
```