Predicting the impact of childhood vaccines: health and economics

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Abstract

In this paper we focus on the mathematical modelling of the so-called childhood diseases, namely Measles, Mumps, and Rubella, for which a tri-effective vaccine is administered in the UK (MMR vaccine). The first objective of such work is to specify a model and model parameters that can predict realistic infection levels according to the retrieved data on notified cases. An age-structured SIRV model is formulated to allow for different levels of vaccination and infection over the age groups. Subsequently, simulations and optimisation procedures have been carried out to select the level of susceptibility of the population to each of the three diseases in current times. In the context of health economics, our second research goal is to carry out economic evaluations on the cost-effectiveness of vaccination policies based on the current costs of prevention, vaccination, and healthcare. We were able to build a pipeline capable of using the predicted infection levels and of calculating the QALY gain. The latter can potentially reveal relevant information on the monetary value that the government saved by preventing the population from MMR outbreaks.

Introduction

This project aims to investigate the health and economic impact of childhood vaccines in the United Kingdom. Specifically, we are looking at the MMR vaccine. This is a vaccine against Measles, Mumps, and Rubella (MMR), three diseases most commonly affecting children. Some background information regarding the diseases is given in the subsection that follows.

The mathematical model constructed for the purposes of this project is an age-structured SIRV (Susceptibles, Infected, Recovered, Vaccinated) compartmental model. The model required the collection of a lot of real-life data in order to determine the multiple parameters present. The data collection and the model itself are presented in the next section, 'Materials and methods', and a brief mathematical background is discussed further on.

In terms of the health economics aspect of the project some background information regarding economic evaluation is provided and the relevance to vaccinations is explained.

Biological background

A brief summary of the three diseases we are focusing on follows. The information presented has been found on the NHS website, [1–3].

Measles is an infectious disease whose symptoms develop approximately 10 days after infection. The initial symptoms are cold-like, i.e. blocked nose, sneezing, fever, and

are followed by the *"measles rash"* which consists of small red/brown spots. The rash covers most of the body, starting from the neck. When the rash first appears is when the infected person usually feels the most ill. Some infected people will develop small grey/white spots in their mouth before the rash appears. In the case of no serious complications the infection generally clears up in about 7-10 days. Complication of measles can affect anyone, but the lowest risk of developing them is held by children above 1 year old who are generally healthy. Common complications include middle ear infections, conjunctivitis, laryngitis, and pneumonia. Less common ones include hepatitis, meningitis, and encephalitis. More rarely, complications can lead to vision loss, heart problems, and in extreme cases death. There are some potential risks for a pregnant woman who gets infected with measles that include a miscarriage and premature birth.

Moving on to mumps, a disease noticeable by its distinct symptom of painful swellings of the parotid glands (parotitis), we are dealing with an infectious disease that has a 2-3 weeks incubation period. Other symptoms that develop before the swelling include headaches, joint pain, fever, and fatigue. It is worth mentioning that 1 in 3 cases do not have any obvious symptoms. Again, the infection clears up in about 1 to 2 weeks. Some complications include orchitis, i.e. swelling of one testicle, which affects 25% of males infected after puberty. Similarly, about 5% of females who are infected after puberty experience oophoritis, i.e. swelling of the ovaries. There is a chance of mumps causing viral meningitis or pancreatitis, and, more rarely, encephalitis.

Lastly, rubella's main symptom is a rash consisting of red/pink spots. This forms about 2-3 weeks after infection and lasts for 3 days [4]. Like measles, the rash covers most of the body starting from behind the ears. Other symptoms of rubella include fever, joint pain, and sore eyes. Rubella causes concern if acquired during pregnancy, especially in the early stages, because it gives rise to serious complications. These include a miscarriage or the baby being born with Congenital Rubella Syndrome (CRS) [4]. CRS can lead to brain, heart, vision, or hearing problems [5].

The three diseases discussed above are all airborne. They travel through droplets, e.g. from a sneeze or cough, and survive on surfaces for many hours. A person who was infected with these diseases then most commonly is immune for life. However, one can get immunity through the aforementioned vaccine. This is administered in two doses in the UK. The first dose is given at around the first birthday of a child and the second at around 3 years and 4 months old [6]. After the two doses, the MMR vaccine is 99% effective against measles and rubella and 88% effective against mumps [6].

Mathematical background

As mentioned earlier, we have constructed an age-structured SIRV compartmental model in order to investigate the dynamics of the Susceptible, Infected, Recovered, and Vaccinated proportions of the population. An SIRV model is quite similar to a typical SIR model, with the addition of the Vaccinated group, whose main purpose is to keep track of the number of people who get vaccinated. Reviewing the literature, we have come across many SIR and SEIR (adding the "Exposed" compartment to include the incubation period) models, some taking into account vaccination rates. The papers that influenced the formulation of our model include [7–18].

The authors of [7] study the dynamics of an age-structured SIR model which is further used to analyse measles data in India and evaluate some strategies regarding controlling the epidemic with vaccination. Schenzle, [8], formulates an age-structured SEIR model and emphasises the importance of age dependency in the contact rates, which had not been focused on at the time, and special attention is given on the fact that school children transmit infection among themselves at a much higher rate than the rest of the population, given schools are open. This is thought to be why there are

recurrent epidemics with various periods. Moving on, [9], [10], and [11], three papers by the same authors initially exploring the dynamics of measles with SEIR models including age structure and seasonal forcing, then comparing epidemics from different parts of the world, and lastly investigating the impact of vaccination and its correlation to epidemic patterns.

Furthermore, [12–14] all have similar models focusing on mumps. In particular, the authors of [12] modelled the transmission dynamics and control of mumps in China, using an SVEILR (Susceptible, Vaccinated, Exposed, severely Infectious, mildly infectious, Recovered) model, whereas in [13] formulated a SVEIAR model, with the difference of having Infectious and Asymptomatic compartments instead of severely infectious and mildly infectious. And finally, in [14] an SVEILHR model (addition of Hospitalised compartment) was constructed, including seasonality, where again mumps data from China was used to analyse the dynamics.

For rubella disease models, Anderson and May [15] focused on the effect of different vaccination policies on CRS incidences both in the short and long run through the analysis of the deterministic model with age structure. They divided the human community into four compartments consisting of susceptible, latent, infectious, and immune individuals and a partial differential system was established for describing each compartment change with respect to time and age. They also discussed the ways of evaluating force of infection through the analysis of equilibrium and the role of maternal antibodies in the endemic. An agent-based model for rubella ourbreaks [16] was explored by Kurahashi, revealing the contact process among people. He analysed the infection by male and female in workplace and railway and proved the importance of vaccinating men against rubella in Japan. Furthermore, rubella metapopulation dynamics and the risk of CRS with repect to spacial coupling in Peru were also discussed in [17] and spatial heterogeneous vaccination coverage in South Africa was taken into consideration by Metcalf et al [18].

Keeping all this in mind and given the data we were able to find for the UK, we decided to formulate an SIRV model, which is outlined in the next section. However, we shall first have an introduction for the health economics aspect of this project.

Health Economics

Economic evaluation in different fields aims to provide a means to estimate and quantify the consequences of different interventions or projects based on their costs and effects and thus compare and suggest the best alternative based on evidence available using different measures. The objective is to estimate economic values and costs in order to evaluate various interventional programmes ultimately to identify the best course of action. Since our interests lie within health economics, the economic evaluation is in relation to health care resources.

Economic evaluation includes various methods, namely *cost-effectiveness analysis*, *cost-benefit analysis*, and *cost-utility analysis*. The three methods differ in the aspects that are considered when quantifying costs and implications, they attach different values to each of them.

Cost-effectiveness analysis: Attaches no monetary value to outcomes and compares costs with benefits in natural biomedical units of outcomes, such as the number of cases avoided, life-years gained, disability years averted, lives saved, life-years saved, or quality-adjusted life-years (QALYs) [19].

Cost-benefit analysis: Attaches monetary values to the measure of effect. The method focuses more on the financial aspect and is applied to pharmacoeconomics. It attaches monetary vale to health benefits by the 'willingness-to-pay' approach which estimates a value that could represent reduced mortality or morbidity rates or on impact of life [19].

Cost-utility analysis: A particular type of cost-effectiveness analysis. The outcomes are measured based on QALYs gained. QALYs combine the changes in quantity and quality of life into a single composite measure that is independent of the programme or disease being assessed [19]. Cost per QALY is one measure in cost-utility analysis that is used to directly compare the costs associated with an intervention and its effects in QALYs. Current threshold for treatments, suggested by the National Institute for Health and Care Excellence (NICE), is £20,000 to £30,000 per QALY [20]. An intervention which has a cost per QALY within this threshold is considered to be 'cost-effective'.

Costs and benefits

The different types of costs include direct and indirect costs:
Direct costs: Costs that are directly associated with the intervention, such as direct labour, materials, medicines, facilities, etc. [21].
Indirect costs: Also called societal costs; arise as a consequence of introducing the intervention, including volunteer services, cost of work loss etc. [21].

In our case, we look at the costs associated to immunisation which includes cost of vaccines, administration costs, parent travel and work-time lost, adverse effects associated with vaccination etc. Benefits of vaccination are usually savings in direct and indirect costs as a result of averting morbidity and mortality. This could be life-years gained, life-years saved, disability averted etc. [19].

Materials and methods

In order to carry out our analysis, after reviewing the literature, we first collected the data to feed into our ODE system model. Such data are used to approximate model parameters and initial conditions. For clarity, the model is presented first and then a subsection regarding the various data used follows. Further on, there is a subsection regarding the economic evaluation strategy used for this project and a detailed outline is presented.

Model

Let us define a k-age group compartmental SIRV model for the infection dynamics of the diseases covered by the MMR vaccine. This model takes the form of a system of four vectorised Ordinary Differential Equations. Each of the k vector entries then corresponds to a given age subgroup with span a_i, $i \in 1...k$. Each equation then governs the dynamics of what proportion of the sub-populations is Susceptible, Infected, Recovered, or of those who have been Vaccinated. The model can be represented in matrix form:

$$\begin{aligned}
\frac{d\mathbf{s}}{dt} &= (\mathbf{I}-\mathbf{V})\mathbf{b} - \mathbf{ds} - \mathbf{s} * (\boldsymbol{\beta}(t)\mathbf{Ci}) + \delta(t-t_{\text{end}})(\mathbf{L}-\mathbf{I}-\mathbf{VL})\mathbf{As} \\
\frac{d\mathbf{i}}{dt} &= \mathbf{s} * (\boldsymbol{\beta}(t)\mathbf{Ci}) - (\mathbf{d}+\boldsymbol{\gamma})\mathbf{i} + \delta(t-t_{\text{end}})(\mathbf{L}-\mathbf{I})\mathbf{Ai} \\
\frac{d\mathbf{r}}{dt} &= \boldsymbol{\gamma}\mathbf{i} - \mathbf{dr} + \delta(t-t_{\text{end}})(\mathbf{L}-\mathbf{I})\mathbf{Ar} \\
\frac{d\mathbf{v}}{dt} &= \mathbf{Vb} - \mathbf{dv} + \delta(t-t_{\text{end}})[(\mathbf{L}-\mathbf{I})\mathbf{Av} + \mathbf{VLAs}]
\end{aligned} \tag{1}$$

where

$\mathbf{s} * \mathbf{i}$	*Denotes the element-wise product*
$\mathbf{L}, \quad (L)_{ij} = \delta_{i,j+1}$	*Denotes the lower shift matrix and δ_{ij} is the Kronecker delta*

$$\delta(t - t_{\text{end}}) = \begin{cases} 0 & \text{if } t \neq t_{\text{end}} \\ \infty & \text{if } t = t_{\text{end}} \end{cases} \qquad \textit{and} \qquad \int_{t_{\text{end}}-\epsilon}^{t_{\text{end}}+\epsilon} \delta(t - t_{\text{end}})\,\mathrm{d}t = 1$$

$\mathbf{s}, \mathbf{i}, \mathbf{r}, \mathbf{v} \in \mathbb{R}^k$	k-age group compartment vectors
$\mathbf{b} := (b, 0, ..., 0)$	Birth rate
$\mathbf{V} := diag(v_1, ..., v_k)$	Vaccination rates
$\mathbf{d} := diag(d_1, ..., d_k)$	(Natural) death rates
$\boldsymbol{\beta}(t) := diag(\beta_1(t), ..., \beta_k(t))$	Age-based force of infection
$\boldsymbol{\gamma} := diag(\gamma_1, ..., \gamma_k)$	Recovery rates
$\mathbf{C} \in \mathbb{R}^{k\times k}, \mathbf{C} := (c)_{ij}$	*Who Interacts With Who matrix*
$\mathbf{A} \in \mathbb{R}^{k\times k}$	The age group transition matrix

where $\mathbf{A}$ has the structure

$$\mathbf{A} = \begin{bmatrix} a_1^{-1} & & & & \\ & a_2^{-1} & & & \\ & & \ddots & & \\ & & & a_{k-1}^{-1} & \\ & & & & 0 \end{bmatrix}$$

The model can also be represented in indexed form:

$$\begin{aligned}
\frac{dS_i}{dt} &= \delta_{1i}(1 - v_1)B + \delta(t - t_{\text{end}})a_{i-1}(1 - v_i)S_{i-1} \\
&\qquad - \sum_{j=1}^{k} \beta_i c_{ij} S_i I_j - (d_i + \delta(t - t_{\text{end}})a_i + v_i)S_i \\
\frac{dI_i}{dt} &= \delta(t - t_{\text{end}})a_{i-1}I_{i-1} + \sum_{j=1}^{k} \beta_i c_{ij} S_i I_j - (d_i + \gamma_i + \delta(t - t_{\text{end}})a_i)I_i \\
\frac{dR_i}{dt} &= \delta(t - t_{\text{end}})a_{i-1}R_{i-1} + \gamma_i I_i - (d_i + \delta(t - t_{\text{end}})a_i)R_i \\
\frac{dV_i}{dt} &= \delta(t - t_{\text{end}})a_{i-1}(V_{i-1} + v_i S_{i-1}) + \delta_{1i}v_1 B + v_i S_i - (d_i + \delta(t - t_{\text{end}})a_i)V_i
\end{aligned} \tag{2}$$

where $i = 1, ..., k$, $a_0 = a_k = 0$, and $I_0 = S_0 = R_0 = V_0 = 0$.

The underlying assumptions of the model are twofold:

1. The total population size remains constant throughout time;
2. The disease mortality is negligible thus omitted in the model formulation.

It is worth to mention that, with the outlined model, our aim is to specify the level of susceptibility for each disease ($\boldsymbol{\beta}$) separately in order to predict realistic infection levels compared to the real ones. The diagonal entries of $\boldsymbol{\beta}$ are the unknown parameters to estimate.

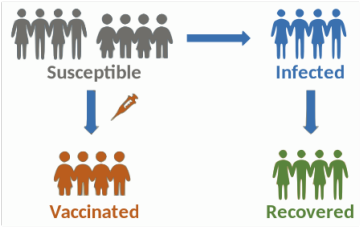


Fig 1. Diagram of disease dynamics of the model.

Data for model

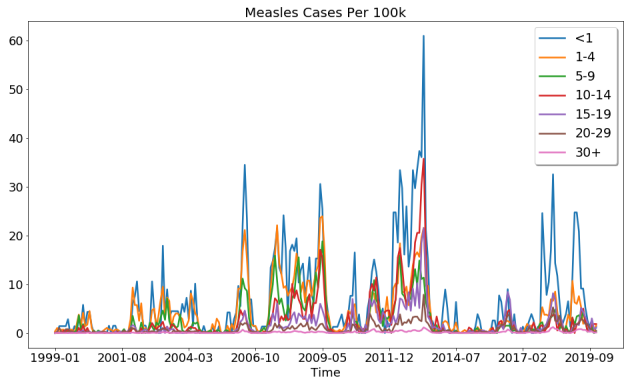
There are several sources of age-structured epidemiological data for the MMR diseases available. By far the highest temporal resolution for measles and rubella is offered by the ECDC Surveillance Atlas of Infectious Diseases dataset [22], which offers age-standardised rates with monthly resolution, spanning years 1999-2019 for measles, and 2007-2019 for rubella. Unfortunately for mumps this dataset only offers yearly resolution for years 2000-2017. The data is plotted in the graphs displayed in Fig 2. The aforementioned data are used to perform numeric optimisation of the unknown diagonal entries of $\boldsymbol{\beta}$ in our model, which represent the level of susceptibility in each age group. This can also be seen as the chance of getting the disease after one physical contact with an infected individual. The parameters in $\boldsymbol{\beta}$ will be associated to each disease according to the real retrieved data thus each having a specific susceptibility level, respectively.

Realistic data are important to determine the other parameters in the model as well. First, we partitioned the population into 7 age groups: '< 1', '1-4' '5-9', '10-14','15-19', '20-29', and '30+' thus we gathered demographics according to these classes and the total population size:

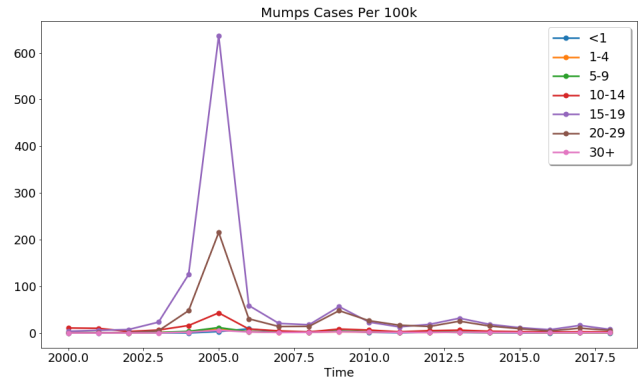
- A time series of the mid-year population estimates of the UK from mid-2019 back to mid-1991 is available from the website of the Office for National Statistics (ONS), [23]. Additionally, the United Nations Statistics Division publishes the estimated population of the UK from 1982 to 1990, [24];
- Crude birth rates from 1938 to 2018 have been provided by the ONS website [25];
- Death registrations by single age between the year of 1978 and 2012, [26]. Annual data on deaths registered by age from 2013 to 2018 are collected from the ONS, [27], National Records of Scotland, [28], and the Northern Ireland Statistics and Research Agency, [29]. The death rate per age band from 1982 to 2018 is obtained by dividing the death per age class by the number of individuals in each age class.

Crude birth rate is slightly larger than the total death rate so, in order to keep the population size constant over time, we opted to remove the excess proportional to the age distribution. A plot for the birth and death rates can be found in Fig 3.

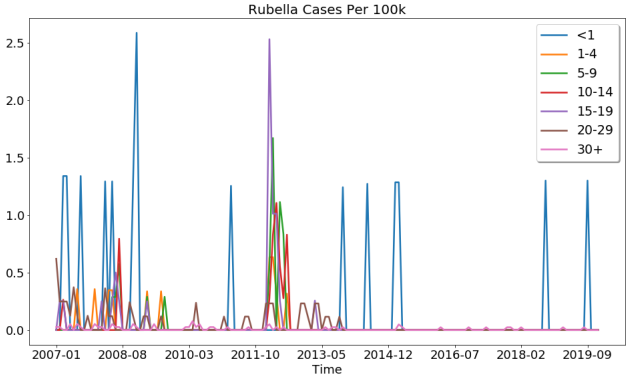
Additionally, the age structured pattern of physical contacts was gathered from the POLYMOD survey [30] conducted between May 2005 and September 2006. These data has been used as a proxy for matrix $\mathbf{C}$ of daily contacts. In the study, the authors partitioned the population into 5 year bands and grouped all individuals aged 70 years and older together. To fit to the underlying grouping in our model, we averaged over the contacts made by participants in the age bands of '20-24' and '25-29' towards the other age groups to obtain a new contact rate for the age band '20-29'. The contact rate for the '30+' group is obtained in a similar way, by taking the weighted average of the



(a) Monthly reported cases of Measles.



(b) Annually reported cases of Mumps.



(c) Monthly reported cases of Rubella.

Fig 2. Reported MMR new cases by age group per 100 thousand individuals. Fig 2(a) shows the time series of monthly notifications for Measles which has been characterised by several peaks over all age groups. In particular, it has been encountered mainly in the two lower age classes with major outbreaks in 2011. In Fig 2(b) the annual number of cases of Mumps is reported. We can distinguish one major outbreak in 2015 which involved teenagers in the "15-19" age group and "20-29". In fact, the rise of Mumps cases involved individuals under 25, particularly in university towns. For this reason, a catch-up campaign was then administered. Monthly cases of Rubella are plotted in Fig 2(c) for which we can notice that the highest levels of infection involve children under one year of age. However, Rubella has been recognised to have a fairly chaotic behaviour due to absence of symptoms, apart from CRS, and thus the possibility of it being notified and traced is limited.

contacts made by the participants whose age is over 30 according to the number of participants in these age groups. In absence of further information and granularity for the '< 1' age group, the assumption is made that babies in this age group have the same contact pattern as children in the '0-4' age class. The figures in Fig 4 show the contact rates for the age groups of the survey and the pooled age groups for this project.

Furthermore, childhood vaccination coverage statistics for England are published on NHS Digital, [31], and the data relating to the first dose of the MMR vaccine are reported by birth cohort. The coverage of the second dose of the MMR vaccine in England, together with the catch up campaign coverage, are published on the PHE UK Measles and Rubella elimination strategy report, [32]. Due to the limited resources of the coverage data, we assume the coverage rate in the UK is equal to that in England. The coverage for the first (MMR1) and second (MMR2) dose is reported by the child's

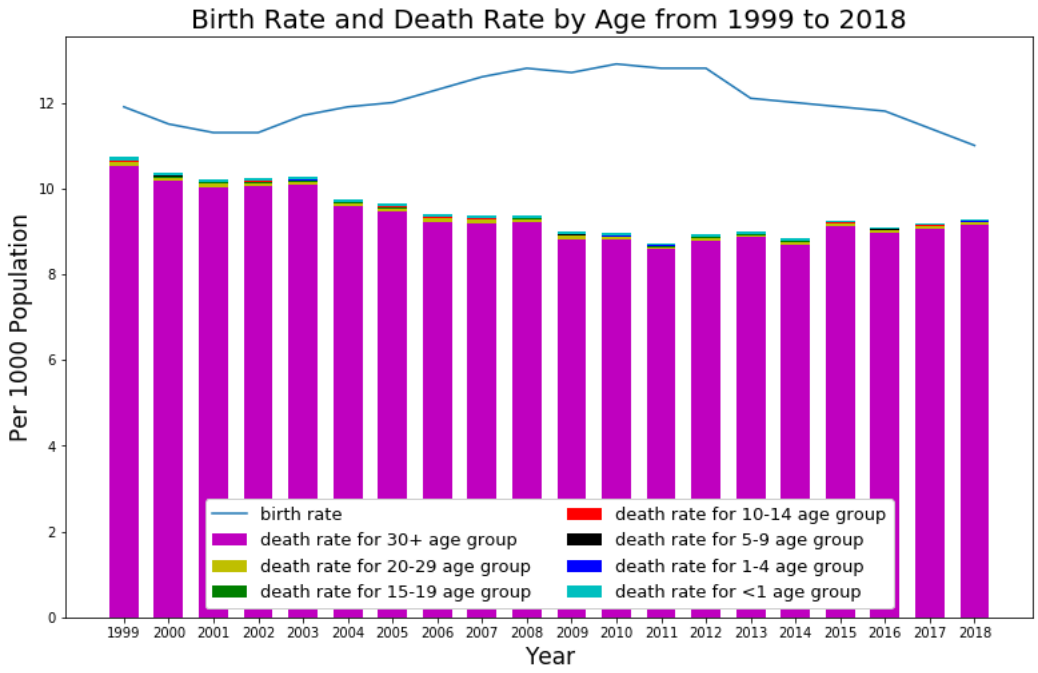
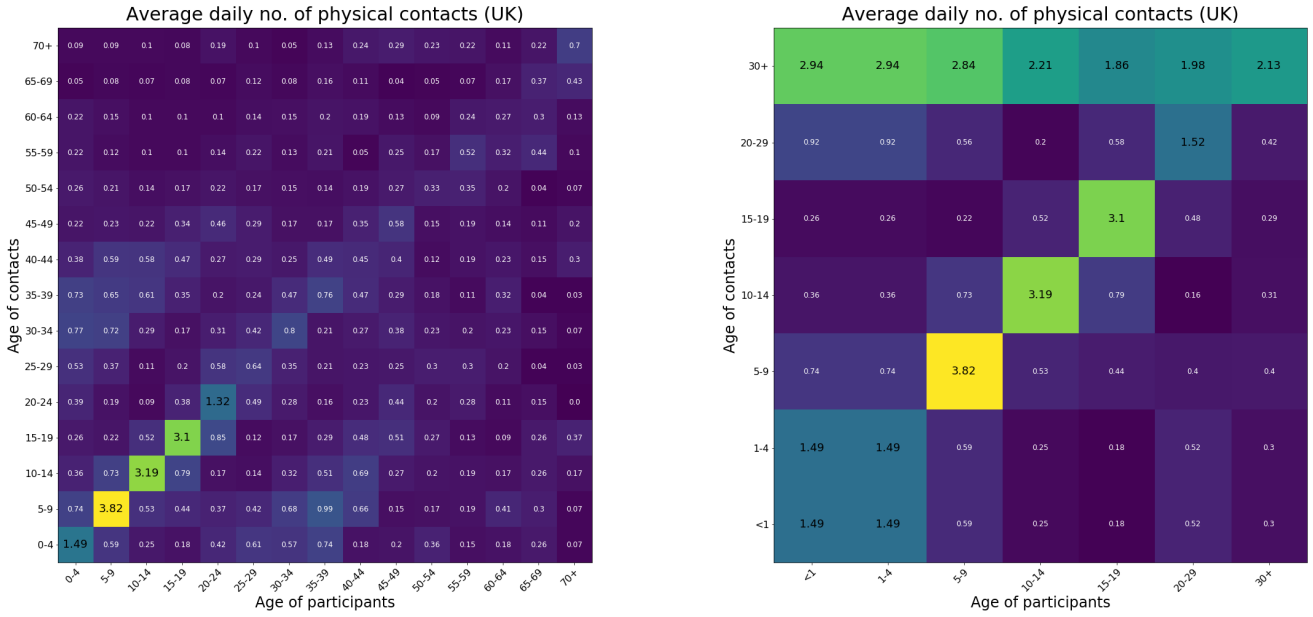


Fig 3. Plot for birth and death rates. Here we can see the birth and death rates over the period of interest (1999 – 2018). These tend to have an opposite trend with the former slightly increasing and the latter decreasing over the years.



(a) Original contact matrix.

(b) Pooled contact matrix for 7 age groups.

Fig 4. Contact rates heatmaps for the various age classes. Fig 4(a) reports the original matrix of physical contacts showing that the younger age classes tend to mix and gather mostly between each other and represent the highest rates in the matrix. Fig 4(b) shows the results of merging some of the age group together, leading the '30+' to have higher physical contact levels due to being the most numerous group. However, primary school children '5-9' remain the most prone to mixing.

second and fifth birthday year, therefore, we assume that children in age class '< 1' and '1-4' would get vaccinated by MMR1 and MMR2, respectively, and the vaccination rates for those two age classes are calculated according to the coverage data. Meanwhile, the vaccinated rate for each age band in 1999 are computed for the initial conditions of the model based on the historic coverage data. Furthermore, historic measles notifications data can be obtained from the Health Protection Agency (HPA) archives [33]. This dataset spans years 1940-2013 which offers an insight into the effect of vaccine on preventing disease transmission. Fig 5 shows the vaccination coverage along with notifications of measles cases over the years.

Lastly, given the information mentioned in the "Biological Background" earlier on, the recovery rates are taken to be the inverse of the average infectious period: 8.5 days for measles, 11 for rubella and 10.5 for mumps.

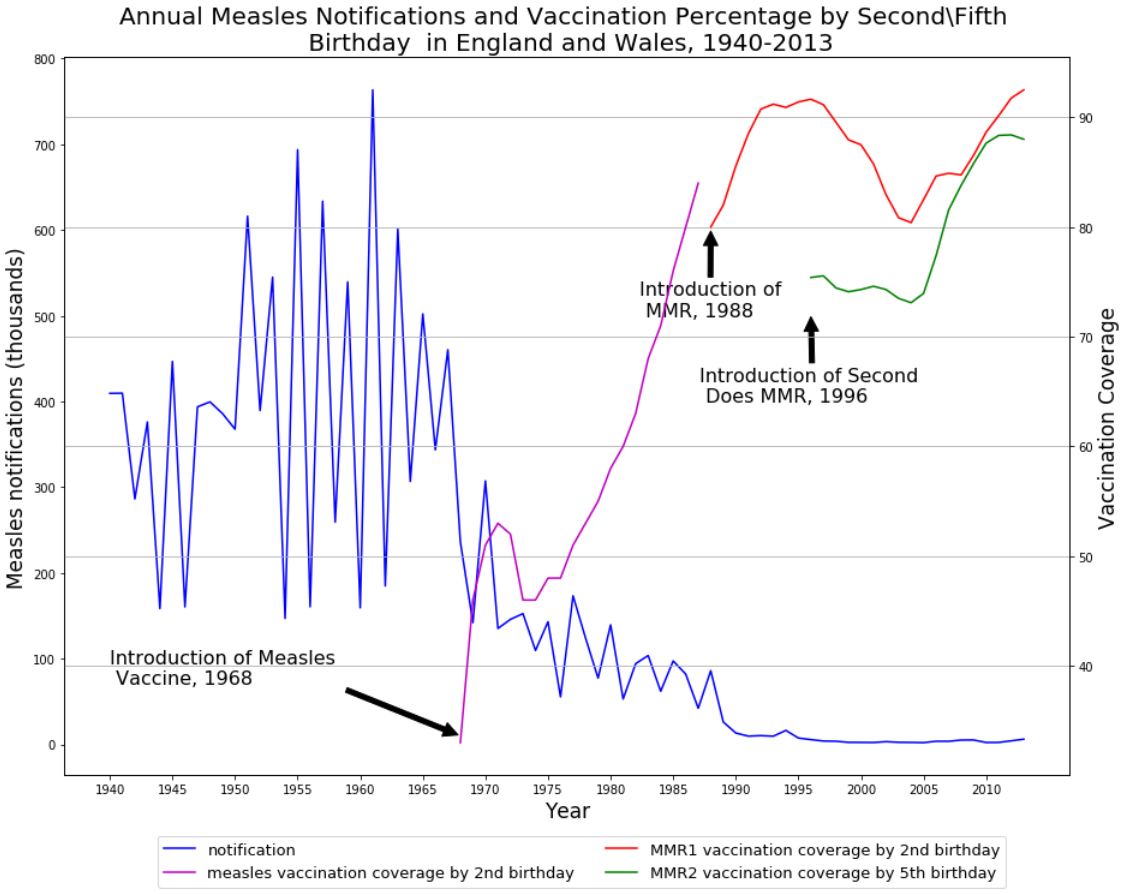


Fig 5. Plot for vaccination rates and notifications. The plot reports the number of notifications of Measles per thousands of individuals in England and Wales from early 1940 (blue line). Such values significantly decreased after the introduction of vaccine for Measles, the coverage data (in percentage) regarding the vaccines administered in England and Wales between 1968 and 1977 are shown (purple line). In 1979, the MMR vaccine was introduced first with a single (1988−1996) and after with a double dose, as is currently practiced. The coverage numbers for the two doses in England are reported in red and green lines, respectively.

Economic Evaluation

Measure used for economic evaluation

The plan for the economic evaluation associated with the MMR vaccination is to use the incremental cost-effectiveness ratio (ICER), which is the ratio of the difference between costs of intervention (i.e. vaccination) with a base case, no intervention in our case, and the difference between the effects of these two cases [34]. ICER is similar to the cost per QALY in a cost-utiliity analysis. ICER is given by the formula [35]:

$$\text{ICER} = \frac{C_1 - C_0}{E_1 - E_0}, \tag{3}$$

where C_1, E_1 are the costs and effects after intervention and C_0, E_0 are the costs and effects before intervention. We compute ICER by taking the costs before vaccination as treatment costs for the diseases and the costs after vaccination as the vaccination costs added to the treatment costs for each incidence. The effects are measured in QALYs and hence the denominator will be aimed at a QALY gain.

QALY

QALY gain/loss is the quality-adjusted life-years gained/lost by the population as a result of the intervention [36]. In our case, we look at the QALY gain as a result of immunisation. QALY can be calculated using the formula:

$$\text{Number of QALYs} = \text{Number of life years} \times \text{Utility value} \tag{4}$$

Utility value is a measure of indicating the health of a person, on a scale from 0 to 1 [37]. An individual having perfect health is said to have a utility value of 1 and an individual with utility value 0 is considered dead. Here, QALY is calculated to see how many years has been gained with respect to the health of an individual.

We will compute ICER, using Eq 3, but we will keep the vaccination costs unknown. We will then equate this to £20,000−£30,000 which is, as already mentioned, the cost per QALY threshold for an intervention to be cost-effective, to try and estimate the cost of vaccination.

Discounting

In any measure associated with economic evaluation, discounting is an important part that has to be considered especially while looking at long term interventions [38]. It is also recommended to use different discount rates for costs and effects since we have to consider that some health effects, like QALYs, are not calculated in monetary value but in health terms. If the value of an item changes and it was measured in monetary terms, it will directly reflect in the value, yet, since it is measured in health terms, it will have a different change [39].

In the UK, usually the costs and effects are discounted at the same rate of 3.5%. However, in the case of a public health intervention the effects are discounted at the rate of 1.5% [39]. Thus, in our case, we will use differential discounting with 3.5% for the costs and 1.5% for the effects.

Calculations outline

Here we present an outline of the calculations to be used for the economic evaluation part. We start by defining the two costs for Eq 3:

$$\textbf{Cost without vaccination} = \begin{array}{l}\text{Treatment costs for all incidences}\\ \text{of Measles/Mumps/Rubella in}\\ \text{a year without vaccination}\end{array}$$

$$\textbf{Cost with vaccination} = \begin{array}{l}\text{Cost of vaccination of } n\% \text{ of newborns for MMR1}\\ \text{and } m\% \text{ of second age group for MMR2}\\ +\,(\text{Cost due to adverse effects per vaccine}\\ \qquad \times \text{ population vaccinated})\\ +\,\text{Treatment costs for all incidences}\\ \quad \text{of Measles/Mumps/Rubella in}\\ \quad \text{a year without vaccination}\end{array}$$

where n and m are the percentages of newborns and children we are considering to vaccinate, respectively.

Hence, ICER is calculated as:

$$\text{ICER} = \frac{\textbf{Cost with vaccination} - \textbf{Cost without vaccination}}{\textbf{QALY gain}} \tag{5}$$

For each person that dies in age group A, QALY loss can be calculated as:

$$Q_A = \sum_{a=A}^{\text{FLE}} U_a e^{-(a-A)\times d_e} \tag{6}$$

where

$$\begin{aligned}\text{FLE} &: \text{Future life expectancy}\\ U &: \text{Utility}\\ d_e &: \text{Discount rate for effects}\end{aligned}$$

For our scenario we make the assumption that the entire population lives to be 85 years as the last age group that we are considering is '30+'.

Total QALY loss of the population in a year can therefore be written as:

$$TQ = \sum_{A=0}^{\text{FLE}} N_A \times Q_A \tag{7}$$

where $N_A =$ Number of deaths of people belonging to age group A. From Eq 7 it is easy to see that the discounted total QALY loss at time t (i.e. at t years from the start) is given by:

$$TQ_d(t) = e^{-t\times d_e} \sum_{A=0}^{\text{FLE}} N_A(t) \times Q_A(t) \tag{8}$$

To calculate $N_A(t)$, which is the number of deaths of people belonging to age group A at time t, we look at the number of deaths per infection for each of the diseases, i.e. the case fatality rate [40]. Using this, we can rewrite Eq 8 as:

$$TQ_d(t) = e^{-t \times d_e} \sum_{A=0}^{\text{FLE}} N_A(t) \times D \times Q_A(t) \tag{9}$$

where we now redefine the terms as:

$N_A(t)$: Number of people belonging to age group A at time t

D : death rate associated with each disease

$Q_A(t)$: QALY loss associated with the death of a person in age group A at time t

The data was collected by looking for deaths per measles/mumps/rubella case and in cases where this information was not available we looked at the symptoms that led to the most number of deaths and looked at the mortality rates due to them.

Returning to ICER and Eq 5, we want to calculate the ICER in t years from now, so we obtain the following:

$$\text{ICER}(t) = \frac{VC_d(t) + TC_{d,1}(t) - TC_{d,0}(t)}{TQ_{d,1}(t) - TQ_{d,0}(t)} \tag{10}$$

where the subscript 1 represents the quantities in the case after immunisation and 0 represents no immunisation. Here, $TQ_{d,1}(t)$ and $TQ_{d,0}$ are the discounted total QALY loss at time t with the immunisation intervention and without the immunisation intervention respectively, as defined in Eq 9. Additionally, $VC_d(t)$ is the discounted vaccination cost at time t calculated as:

$$VC_d(t) = (x + v_c) \times \left\{ \frac{n}{100} \times g_1(t) + \frac{m}{100} \times g_2(t) \right\} \times e^{-t \times d_c} \tag{11}$$

where

x : cost of one unit of vaccination

v_c : average cost due to adverse effects of vaccination

d_c : cost discount rate

$g_1(t)$: number of infants in age group 1 at time t

$g_2(t)$: number of children in age group 2 at time t

Lastly, $TC_{d,1}(t) = TC_1(t) \times e^{-t \times d_c}$, the discounted treatment costs with immunisation at time t, and hence $TC_{d,0}(t) = TC_0(t) \times e^{-t \times d_c}$, the discounted treatment costs without immunisation at time t. TC_1 and TC_0 consist of various direct and indirect costs, found in the literature.

Now, we can compute

$$\textbf{ICER} = \sum_{t=0}^{T} \text{ICER}(t) \qquad \text{(substituting in Eq 10 and Eq 11)} \tag{12}$$

$$= \sum_{t=0}^{T} \left[\frac{(x + v_c) \times \left\{ \frac{n}{100} \times g_1(t) + \frac{m}{100} \times g_2(t) \right\} \times e^{-t \times d_c} + TC_{d,1}(t) - TC_{d,0}(t)}{TQ_{d,1}(t) - TQ_{d,0}(t)} \right] \tag{13}$$

where T = Number of years we are considering from now.

Equating Eq 13 to the current threshold approved by NICE, say Y, and rearranging for x, to give us the cost of vaccination, yields:

$$x = \frac{Y - \left[\sum_{t=0}^{T} \frac{TC_{d,1}(t) - TC_{d,0}(t)}{TQ_{d,1}(t) - TQ_{d,0}(t)}\right]}{\sum_{t=0}^{T} \frac{e^{-t \times d_c}\left(\frac{n}{100} \times g_1(t) + \frac{m}{100} \times g_2(t)\right)}{TQ_{d,1}(t) - TQ_{d,0}(t)}} - v_c \tag{14}$$

which is equivalent to

$$x = \frac{Y - \sum_{t=0}^{T} e^{-t \times (d_c - d_e)} \left[\frac{TC_1(t) - TC_0(t)}{TQ_1(t) - TQ_0(t)}\right]}{\sum_{t=0}^{T} e^{-t \times (d_c - d_e)} \left[\frac{\frac{n}{100} \times g_1(t) + \frac{m}{100} \times g_2(t)}{TQ_1(t) - TQ_0(t)}\right]} - v_c \tag{15}$$

where Y = £20,000 or £30,000.

Data for calculations

To carry out the above calculations we need some data, namely for treatment costs (TC_1, TC_0 and v_c), and also death rates, discount rates and utility values.

Treatment costs due to adverse effects of vaccines: The average costs following the adverse effects of vaccination for the MMR vaccine was $1.93 in 2002 [41]. Converting [42] and inflating [43] the value gives us £2.11 (as of 2019).

Treatment costs for measles: The average costs per measles case were found to be $307 [41]. Since this was the cost in 2002, applying conversion rates from 2002 [42] and inflating the costs to 2019 gives us £335.46.

Treatment costs for mumps: The estimated cost for each mumps case is comprised of hospitalisation, drug treatment cost, and societal productivity losses. According to the clinical features and sequelae of mumps [44], we choose 20% as the proportion of asymptomatic and sub-clinical infections, 70% developing parotitis, 9.84% causing orchitis, and 0.16% leading to encephalitis. Among those who have symptoms, we assume all the encephalitis cases and 9% of parotitis cases will seek medical treatment in hospitals while others will take painkillers like paracetamol and rest at home. We suppose the average stay in hospitals is 7 days for encephalitis cases, with a proportion of 50% staying in the ICU, and 5 days for those who are hospitalised due to parotitis. The average cost of hospitalisation and ICU is based on the study in 2002 [41] and the price of paracetamol is taken from Boots [45]. Furthermore, we take the societal productivity losses into consideration since people should avoid school or work at least 5 days after symptoms first develop [2]. This loss is computed by multiplying the GDP per capita [46] by $\frac{5}{365}$, which is the proportion of quarantine over the whole year. The costs were converted [42, 47] and inflated [43] to match the costs to 2019. Therefore, the average estimated cost for a mumps case is £494.21. The treatment costs are shown in more detail in Table 1 further on.

Treatment costs for rubella: The estimated total cost for rubella cases is also comprised of three parts which are societal productivity losses, drug treatment, and life-long cost for the newborn babies with CRS. Since up to 50% of rubella infections are asymptomatic [48], the societal productivity losses are calculated for half of the infected cases. According to the NHS suggestions [3], paracetamol could help for the treatment and patients should stay off school or work for 5 days after the rash appears. As the most serious situation rubella would cause is the infection in early pregnancy, we estimate the ratio of pregnant women who contact rubella in the first 20 weeks in the age groups of '15-19', '20-29', and '30+' based on the fertility rate for women between the ages of 15-44 [25], and compute the number of babies with CRS through the risk

Table 1. Treatment costs for mumps.

Cost Type	Symptoms				Days	Costs*
	Asymptomatic	Parotitis	Orchitis	Encephalitis		
	20%	70%	9.84%	0.16%		
Productivity loss	No	Yes	Yes	Yes	5 days	£368.761
Hospitalisation General	-	9%	-	50%	5 for parotitis, 7 for encephalitis	£122
Hospitalisation ICU	-	-	-	50%	7 days	£2.6948
Drug Treatment**	-	91%	100%	-	5 days	£0.75
	Total cost per mumps case = £494.2058					

*Costs per case of mumps. **£0.75 for 32 500mg Paracetamol tablets.

data [49]. Furthermore, CRS was estimated to cost up to $140,000 over a lifetime in high-income countries in 2012 [50]. We calculated the risks associated to pregnant women contracting rubella and passing it on to babies, who will then be born with CRS. The proportion of women contracting rubella was assumed to be 50% after comparing the proportion of male infection and female infection. For ease of computation according to our model, we then divide the proportion of females into age groups 15-20, 20-29 and 30+ (0.4 was used as the ratio of women in the age group 30-44 in all of 30+ age groups), and compute the risks. The fertility rate of women in the age group 15-44 is 0.0585 (58.5 live births per 1000 women [25]) and out of the 40 weeks of pregnancy, the risk of giving birth with CRS is 90% for those who contacted rubella in their first 10 weeks of pregnancy ($0.9 \times \frac{10}{40}$) and 15% percent for those who contacted rubella in 11-16 weeks of pregnancy($0.15 \times \frac{6}{40}$). It is very rare to have this complication during weeks 17-20 of the pregnancy, and after week 20 it will not affect the baby even if they contract rubella. Thus, the total risk factor for an infected pregnant woman to give birth to a baby with CRS is $[0.9 \times \frac{10}{40} + 0.15 \times \frac{6}{40}]$. This combined with the proportion of women in each age-group and their fertility rate will give the risk. More details can be found in Tables 2 and 3 below.

Table 2. Treatment costs for rubella.

Cost Type	Symptoms		Days	Costs*
	Asymptomatic	Typical Symptoms		
	50%	50%		
Productivity loss	-	Yes	5 days	£230.473
Drug Treatment	-	Yes	32 tablets in 5 days	£0.75
	Total treatment cost per rubella case = £231.223			

*Costs per case of rubella.

Table 3. Life-long costs for rubella.

Rubella in Pregnancy (Age Group)	Risk	Life-long cost for CRS for age group **A** = $N_A \times$ Risk $\times \text{CRS}^{\dagger}_{\text{cost}}$
15-20	0.0072	£$(N_{15-20} \times 1029.4096)$
20-29	0.0072	£$(N_{20-29} \times 1029.4096)$
30+	0.0029	£$(N_{30+} \times 414.6233)$

†(in £) The life-long costs for CRS are calculated as $140,000 (2012) [50] which is £142,973.56 as of 2019 after conversion [51] and inflation [43].

As mentioned earlier, the discount rates are taken to be as: $d_c = 3.5\%$ and $d_e = 1.5\%$ [39]. The death rates can be found in Table 4 below. In addition, we have utility values as: [0.928 0.928 0.928 0.928 0.928 0.915 0.915 0.877 0.877 0.844 0.844 0.799 0.799 0.795 0.795 0.723 0.723 0.723 0.723 0.723....] for 5-year age classes. [52] gives the utility values only for ages above 15. Hence the utilities in the initial age classes spanning ages 0-15 have essentially been assumed to be the same as those in the 16-20 year-old age bracket. Lastly, the QALY loss values for ages from 0 to 100 for discounting rates 3.5%, 1.5%, 0% can be obtained from [53] and [54]. Here, the QALY loss associated with the death of a person A is calculated using Eq 6 and substituting the different discount rates 3.5%, 1.5% and 0% in the place of d_e.

Table 4. Death rates of measles, mumps, and rubella

Disease	Symptoms/Associated death rates	Mortality rate
Measles	1 death in 5000 cases [55]	0.02% deaths per case
Mumps	5 Encephalitis cases in 1000 mumps cases [56] Mortality rate of encephalitis is 1.4% [56]	0.007% deaths per case
Rubella	1 Encephalitis case per 6000 rubella cases [57] Mortality rate of encephalitis is 1.4% [56]	0.000233% deaths per case

Results

Implementation

The code was implemented in Python and all the simulations and optimisation procedures were carried out in Jupyter Notebook [58].

Estimation of the initial conditions

In order to estimate the initial proportion of population that is infected, susceptible, or recovered, while avoiding an initial erroneous epidemic peak, the system was solved for a period of one year with the initial proportion of infected persons equal to 0.05, vaccinated individuals were set to the coverage level of the immediately previous year, and everyone else was left as susceptible. The final proportions for the individual classes, excluding the vaccinated class as that one is available from the data, were then used as initial conditions for the simulation.

Implementation details

The system was integrating using method "RK45" with SciPy [59]. 120 time steps per year were used and the relative tolerance was set to 10^{-4}. An auxiliary differential equation was used to track the cumulative number of infected individuals in each age class throughout time.

Optimisation procedure

Our first approach has been to compute the Sum of Square Differences (SSD) between the monthly (or yearly in the case of mumps) infections obtained from numerically integrating the system, and the observed cases recorded in the ECDC datasets [22]. This was used as an objective function in order to optimise the individual β_i values (susceptibility) for each age class. The minimiser used was a simplex-based optimisation

routine `optimize.fmin` available in package `scipy` [59]. Additionally, the feasible set was bounded such that it would only involve positive values on the basis of their biological meaning.

The approach, however, proved ill-suited for this problem, and proved incapable of meaningfully capturing the dynamics in the data. Furthermore, it exhibited a high degree of sensitivity to initial conditions and would frequently get stuck in local minima. This was exacerbated by the level of noise in the data and the lack of temporal forcing in the model, as well as the chaotic behaviour of real-life outbreaks due to extraneous complexity, such as spatial structure or the nature of reporting cases. In fact, giving the same weight to observation in a scarce dataset would likely lead to unreasonable estimates.

For this reason, we then opted for a more qualitative approach by first using some sensible guesses based on recent studies [60], and by trying several initial values before selecting one that gave the most sensible results. In the case of the simulation for rubella, the initial guess provided by the algorithm was then further adjusted manually to obtain a qualitatively better fit. Due to the data for mumps being available only yearly, and also being the scarcest, we were unable to fit any set of values that corresponded to meaningful behaviour.

Results of numerical simulations

An attempt at automatic fitting was made as described in the previous section. The routine for the measles data reported an SSD of 59562.997 while it failed to converge for rubella with a final SSD value of 34871.128. The optimised estimates for the 7-dimensional $\boldsymbol{\beta}$ vector describing the level of susceptibility for each age class, that is the likeliness of getting the disease after one physical contact, are reported in Table 5 below.

Table 5. Optimised $\boldsymbol{\beta}$ values for Measles and Rubella.

Disease/ Age Class	<1	1-4	5-9	10-14	15-19	20-29	30+
Measles	7.7182	142.14992	213.80122	242.81186	205.76573	232.21351	272.00709
Rubella	66.86849	459.51148	105.56413	18.33344	1.76295	142.51446	285.49631

From the obtained estimates, we can recognise that the level of susceptibility is fairly low for the first age group as, biologically, newborns benefit from maternal immunity to infections for a limited time period. A similar observation can be made for rubella, although teenagers report even lower rates than for newborns. However, all other β values are unrealistically high, by several orders of magnitude. This has proven to be due to an inconsistency in the vaccination data used.

Carrying out an optimisation procedure for the mumps data turned out to be infeasible due to low granularity of only annual case notifications. Indeed, it would be impossible to temporally locate when the number of cases rose and compare it to the pooled results of a simulation. Nonetheless, the simulations for measles and rubella are presented, alongside with the real data, in Figs 6, 7, 8, and 9 in the following two pages.

We then proceeded by using the optimised estimated vector to solve the system in absence of vaccination. Unfortunately, the high instability of the system made it impossible to obtain a simulation for such scenario for Measles and Rubella.

We further investigated such issue and discovered that the collected data on vaccine coverage for both doses represented a cumulative statistics. The vaccination rate would then be extremely high thus, in order to obtain simulated infections close to the recorded real ones, would require very large values for the level of infection over all age groups.

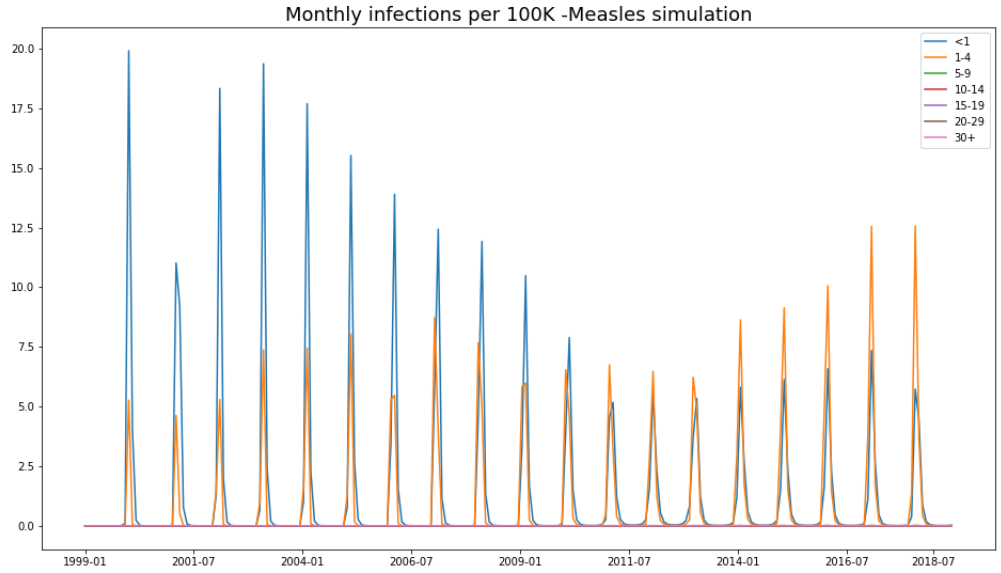


Fig 6. Measles simulation. Monthly new infection cases generated by the SIRV model using the optimised β values.

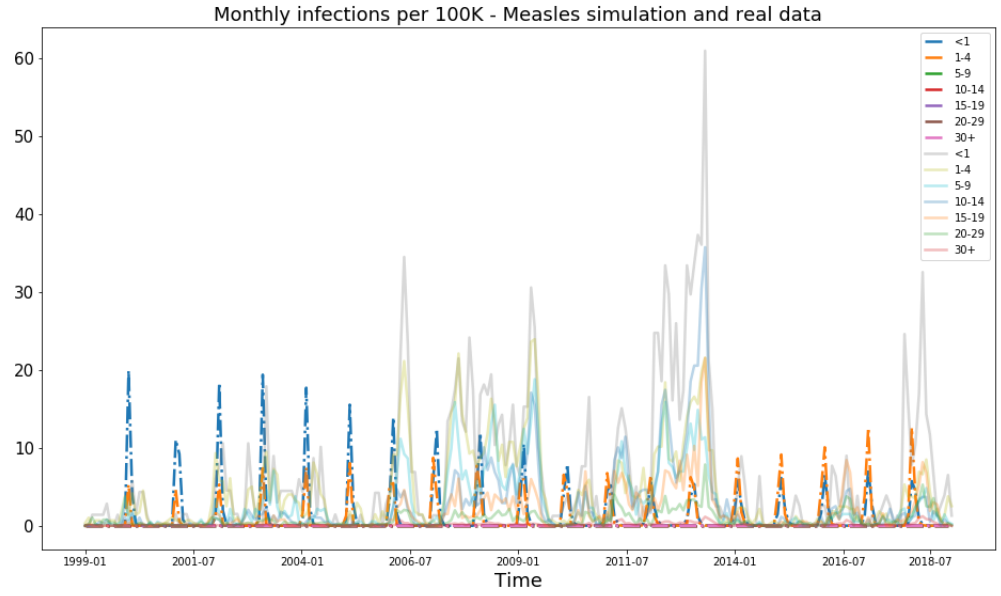


Fig 7. Measles simulation and real data. Monthly new infection cases generated by the SIRV model using the optimised β values (dotted lines) over-imposed on the real monthly cases (shaded lines). The order of magnitude between simulated and real data is fairly diverse and the behaviour of the simulate model predicts a gradual decrease from high infection levels for age class '< 1' until the level of infections in the second age class becomes higher.

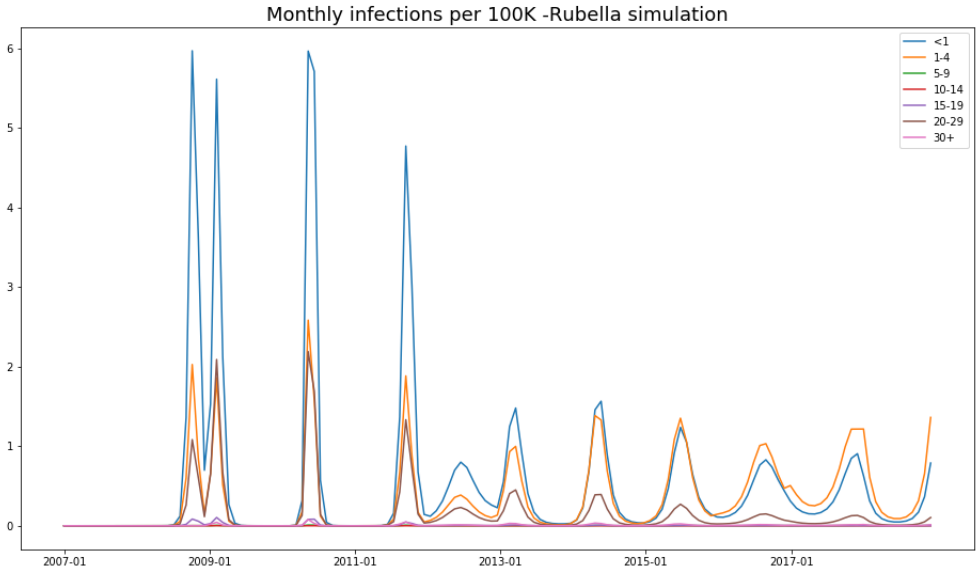


Fig 8. Rubella simulation. Monthly new infection cases generated by the SIRV model using the optimised β values.

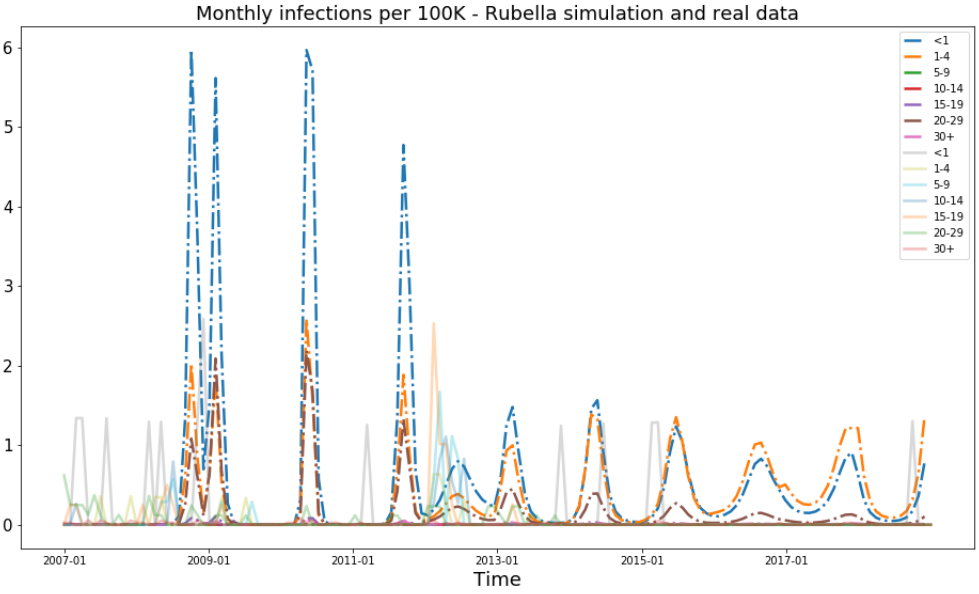


Fig 9. Rubella simulation and real data. Monthly new infection cases generated by the SIRV model using the optimised β values (dotted lines) over-imposed on the real monthly cases (shaded lines). The figures for simulated and real cases are in the same order of magnitude and similar periodic behaviours for age classes '< 1' and '1-4' are observed. However, the simulation predict multiple spiky data points in 2009 and 2010. This could be due to the absence of a temporal switch for the force of infection.

Discussion

It turns out that there was a bug present in the code responsible for transforming and extracting vaccination rate data that went unnoticed until the very end. This caused vaccination coverage for all age classes except for the first two to be significantly higher than in the real world. As such, all β values fitted, except for the one for the first age class, were several orders of magnitude higher than biologically feasible. This also caused the model to fail to converge for the scenario where no vaccinations are present.

Furthermore, the system we constructed has proven to have serious convergence and stability issues for a wide range of parameters, that we suspect may be related to the discrete cohort structure and aging.

Another problematic aspect involved the goodness of the collected data regarding the notification of new cases. In fact, such figures are known to be particularly noisy because in times when a significant number of people get tested after having the symptoms, many other individual are lead to also get tested. This increases the discrepancy between periods with a low and high infection levels.

The health economics study carried out gave us an insight into the *"willingness-to-pay"* method. So far we believe that the formulae we have proposed should be able to give a fairly good estimate for the unit price of vaccination. Data regarding measles was easily available whereas it proved to be quite challenging to obtain similar data for mumps and rubella. The estimates for the average costs for these which we have calculated can be improved by taking into account more costs, such as the public health costs, GP costs etc. However, due to time constraints and insufficient data this could not be done here, as it would require an in-depth study to extract such information. Including these would definitely give more accurate results for vaccination costs. We hope that all the information we collected will be helpful for anyone who wishes to pursue this work in the future.

Further work

There is a suite of options to tackle the objective of modelling MMR disease outbreaks more precisely and efficiently. On the mathematical modelling side, one could include delayed dynamics by adding an Exposed compartment, taking into account the latent period of each disease. This would probably improve the prediction about the time of the highest peak. Moreover, considering a continuous vaccination rate instead of the assumption of discrete vaccination at the end of each age class would give a more realistic description and again would lead to more realistic observed cases for age classes '1-4' and '5-9' which according to the simulations were fairly low.

Additionally, it has been noted by previous research that temporal forcing coinciding with school term times greatly improves model fits such as this one [61]. Lastly, it would be worth to take into account spatial heterogeneity, especially for Rubella [17, 18, 62].

In order to numerically optimise the fit of the model, a better loss function would be required, as well as a minimiser capable of coping with a highly non-convex space. It would be beneficial to attempt Approximate Bayesian Computation (ABC) fitting [63].

Conclusion

In this project a model for describing the dynamics of the MMR diseases for multi-age structure has been formulated. The model describes simple interactions between the compartments by keeping a constant population and does not involve temporal forcing.

The drawback of modelling such dynamics resides in retrieving good data for the demographics and other model parameters such as vaccination rates and coverage. This

has proved to be crucial and unfortunately lead us to a poor specification of the level of susceptibility for the three diseases.

Fitting such a complex, yet simplified, model to fit the available data revealed to be challenging. Monthly and yearly notification data carry a lot of uncertainty and identifying a winning optimisation strategy for the generating process is still the subject of several discussions.

However, we are confident that, having reliable data at hand, will lead us to a simplistic yet realistic description of the MMR disease dynamics in the UK. This piece of work could indeed be a starting point to extend the existing studies on modelling the chaotic behaviour of rubella and could possibly raise interest in further studies on mumps, for which literature was particularly limited.

Finally, extended research on economic evaluation for the calculation of QALY gain has been conducted and could be readily available once fed with annual infected predictions that can be reliable. It will then be accessible to use for any further study carried out in such context.

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