**Discrete age-structured SEIR epidemic model with applications to measles vaccination strategies**

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A Research Proposal for the Biomathematics Honours Project

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15 August 2022

**Introduction**

Measles is a Vaccine-Preventable Disease (VPD) [8]. Infants are most susceptible to measles infections, which can cause lifelong problems like severe brain damage, blindness, or hearing loss as well as complications including pneumonia and encephalitis [18]. Transmission occurs through direct contact with infectious droplets or by airborne spread when an infected person breathes, coughs, or sneezes [19]. The African Region of the World Health Organization (WHO) announced a measles eradication target for 2020 in 2011. About 90% of exposed susceptible individuals are exposed to measles [3]. Clinically, the incubation period from exposure to early symptom onset of disease averages 10 - 12 and 14 days from exposure to the rash. Serious complications caused by measles can occur in approximately 30% of measles cases, children under 5 years of age [4]. However, despite successful immunization, which led to a decline in measles-related fatalities worldwide between 2000 and 2011 [20]. More than 140,000 individuals died from measles in 2018 alone. 52,600 of these deaths, according to the WHO, happened in Africa [18].

Prior to the development of the measles vaccine in the 1960s, measles was a major cause of morbidity and mortality globally [4]. Childhood measles infections have become practically universal since the development of safe and effective vaccines in 1963, killing an estimated every year, 2.6 million people are affected. [5]. Despite the availability of vaccines, measles continues to be the leading cause of death in children under the age of five [6]. Measles outbreaks are still occurring in countries where vaccination coverage is low, such as Liberia, Madagascar and Somalia [7]. According to the WHO, global effort to increase vaccination coverage lowered deaths by 73% in 2018. In 2012, WHO updated the Measles Eradication Initiative with the goal of eradicating measles in at least five of the six regions of the world by 2020 [8]. Measles elimination is defined by the World Health Organization as the absence of indigenous measles cases in a certain area for at least 12 months in the presence of high-quality surveillance systems. WHO also requires a national measles vaccination rate of 95% in all districts with two vaccinations per child. Within a year, at least 80% of districts should examine at least one suspicious case and report a nationwide non-measles case rate of at least 2 cases per 100,000 people. [9].

A vaccine is the most effective public health intervention for combatting vaccine-preventable infectious diseases such as measles [8]. The measles vaccine is commonly administered to infants as part of the Measles-Mumps-Rubella (MMR) vaccination and requires two doses. However, the measles vaccine is normally administered to children at 6 months old age, and the second dose is administered at 12 months old age [6]. World Health Organization (WHO) strongly encouraged the usage of MMR vaccines to get rid of the measles virus inside the nations by enforcing large-scale vaccination programs [17].

Age distribution is the significant element that makes contributions to the heterogeneity of populations, with a substantial impact on the timing and effects of the transmission and spread of infectious diseases [5]. Most crucially, there is a considerable degree of non-uniformity in transmission rates due to the patterns and frequency of individual encounters, which can range dramatically between age groups [6]. Individuals of different ages can also have different levels of immunity against infectious diseases. Age-specific mortality and recovery rates from an infection may be impacted by these variations [7].

For this study, we are interested in the spread of an infectious disease in a host population with an age structure. We therefore examine an SEIR epidemic model with discrete age groups and the application of measles vaccination strategies. Each age group has different vaccine coverage and efficacy. The efficacy of the first dose of the measles vaccine is scheduled for 6 months old, whilst the second dose of the measles vaccine is scheduled for 12 months old age. Vaccine coverage of first and second doses is meant to reduce the measles incidence rate [18].

To conduct this study, we will build an SEIR model to analyse measles data in South Africa and evaluate the effectiveness of several vaccination strategies for the control of measles epidemics. The model will be fitted to real-life data and the model can be used to answer our desired research question. We should be able to use our model to distinguish between different scenarios of efficacy and vaccine coverage.

**Research question**

How different vaccination strategies would influence the transmission of measles in population?

**Aim of the research**

The proposed research question is investigating the Measles SEIR epidemic model with discrete age groups to understand the transmission dynamics of an infectious disease in a host population with an age structure.

**Main objective of the research**

The main objective of the research is to develop a mathematical model for vaccination strategies and transmission dynamics of measles.

**Research objectives**

* To explore the transmission dynamics of an infectious disease in a host population with an age structure.
* To study the vaccination strategies for measles with discrete age structure.
* To analyse the measles data in South Africa and evaluate the effectiveness of several vaccination strategies for the control of measles epidemics in South Africa.
* To modify an age-group model for measles vaccination using published data by The National Institute for Communicable Diseases on measles incidence from South Africa [19, 20], and compare the effects of two different measles vaccination strategies proposed by the NICD together with the World Health Organisation.

**Study benefits**

The discrete age structure epidemic model with the application of the measles vaccination strategy will bring to light the effectiveness of vaccination strategies and measles eradication targets for future predictions. The modified measles vaccination model with two age groups that incorporated the current measles vaccination programs will assist in the analysis of the immune profile of the population and in each age group to establish the baseline and make projections.

The model will subsequently reveal the effect of increasing vaccine coverage to be greater or equal to 95% with two doses administered for each person. The study will also show the impact of increasing the efficacy of two doses in reducing the effectiveness of measles incidence at a moderated vaccine coverage rate.

**Mathematical Model**

In this section we developed a deterministic, compartmental, mathematical model to describe the transmission dynamics of measles is formulated. It is assumed that the host population is homogeneous mixed for both age groups and reflecting increasing dynamics such as birth [29]. Natural death and birth rates per capita are both consistent over time [30]. Direct contact with an infectious person can result in infection [31]. After recovery, the person develops a permanent infection-acquired immunity, meaning they can never contract the disease again. Infants who receive the first and second doses of the vaccine consecutively develop a permanent immunity to the disease.

The model is dividing a host population of a constant size into susceptible (infants who may be infected), exposed (infants who are exposed to the infection), infected (infants who are infected and can transfer infection) and recovered (infants who have permanent infection-acquired immunity and those who received the second dose of vaccine) classes. Compartments with labels and R are used for the epidemiology classes. It is assumed that proportion of infants who received first dose of vaccine join the recovered class whilst infants who received second dose of vaccine join the recovered class . The compliments  and joins the susceptible classes of and respectively. Since the disease is severe, those who contract it may pass away from the disease or naturally pass away.

We consider that infants at 6 months enters directly in the susceptible class. We assume all infants between 0 months to 6 months are susceptible for age group 1 and infants between 6 months to 12 months are susceptible for age group 2. The susceptible enters the exposed class of individuals in the incubation period, who are affected but not yet infectious, when sufficient contact between a susceptible and an infective result in transmission. The individual joins the class of infectives after the incubation period, which makes them infectious in the sense that they can spread the virus. The infant enters the recovered class when the infectious period ends if they have gained a permanent immunity to infection, otherwise passes away. These are the classical assumptions based on SEIR model. This model assumes that an infant will be protected from measles by a successful vaccination.

**An application to vaccination strategies for measles**

Measles is a contagious and serious viral infection for infants, but it can be prevented with a vaccine. The respiratory system becomes infected by the virus, which subsequently spreads to the rest of the body. The disease isspread through the air through droplets produced when coughing or sneezing. After exposure, symptoms of measles don't begin to develop for 10 to 14 days. These include coughing, runny nose, sore eyes, sore throat, fever, and a red, patchy rash [23]. Healthy children and adults who get the measles virus have a low mortality rate, and the majority make a full recovery. The children under the age of 5 years have an increased risk of complication [24].

Measles is a disease that can be prevented with a vaccine [7]. The measles vaccine, given as part of the measles, mumps, and rubella (MMR) vaccine, usually requires two doses. The first dose of the measles vaccine is commonly given to infants at 6 months of age and the second dose is administered at 12 months of age [8]. The efficacy of two doses of the measles vaccine ranges from 93% to 99% [9]. In South Africa, vaccine coverage requires a maximum of 95% or higher to be sustained with both doses administered per person [10].

In this section, we develop a two-dose vaccination model with two age corporations to observe the vaccination strategies for measles epidemics.

**Measles vaccination model**

Measles can be prevented with the MMR vaccine. The WHO recommends that children receive the MMR vaccine twice. The first dose is 6 months old and the second dose is 12 months old [6]. One dose of MMR vaccine is 93% effective against measles while two doses of MMR vaccine are 97% effective against measles [10]. In South Africa, vaccine coverage for children at 12 months old age averaged 71.1%, while the second dose averaged 68.8% between the year 2012 to 2017. The coverage of the second dose increased to 76.4% in 2018 [9].

We subdivide the host population into two age groups, considering age-specific differences in vaccination schedules, mortality, and contact patterns [21, 22].

Figure 1: Model diagram for a measles vaccination model with two age group

The model structure is shown in the transmission diagram in Figure 1. Two doses of measles vaccine were incorporated: MMR1 for age group 1 (6 months), and MMR2 for age group 2 (12 months). The model is described by the following system of differential equations.

Differential equations for age group 1:

Differential equations for age group 2:

The model parameters are shown in Table 1 along with their description and units. Specifically, and are the vaccination rates of MMR1 and MMR2, respectively, and are the efficacy of MMR1 and MMR2, respectively, and and are the effective coverage of MMR1 and MMR2, respectively.

To incorporate vaccination, assume a proportion, , of 6-month-old into the population are vaccinated (and thus immune to infection). Vaccinated people bypass the susceptible class and go directly to the recovered class, while unvaccinated people go to the susceptible class as before. If is the proportion vaccinated, then is the proportion left unvaccinated.

The transmission coefficient between and is decomposed into two factors where is the probability of transmission for an average contact between a susceptible individual in age group with infected individual, and is the mean number of contacts between people in age group and people in age group . Note that and are not the same and the contact matrix may not be symmetric because of different ages.

The influx susceptible individuals are specified by the rate of . Exposed individuals move to the infectious class at a rate of an age group of . Infectious individuals move to the recovered compartment at a rate of an age group of . Individuals are aging at a rate . Natural fatality rate of an age group is represented by , while case fatality of an age group is represented by a rate of . The aging rate of age group is and individuals gain of immunity at rate

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameters | Values/Range | Unit | Description | Ref |
|  | 650 |  | Influx of susceptible | fitting |
|  | 0.00029 |  | The natural mortality rate of age group k | fitting |
|  | 0.00385 |  | Aging rate of age group k | fitting |
|  | 0.024368 |  | Recovery rate of age group k | fitting |
|  | 0.72 |  | Exposed rate of age group | [13] |
|  | 0.2 |  | Case mortality rate of age group k | fitting |
|  | 0.717 |  | Vaccination coverage of Measles vaccine | [10] |
|  | 0.764 |  | Vaccination coverage of Measles vaccine | [10] |
|  | 0.93 |  | Efficacy of MMR1 | [9] |
|  | 0.95 |  | Efficacy of MMR2 | [9] |
|  | 0.1679 |  | Probability of transmission per contact for age group 1 | fitting |
|  | 0.5154 |  | Probability of transmission per contact for age group 2 | fitting |
|  | 0.004 |  | Gain of immunity of age group k | fitting |
|  | 13.3 |  | Average number of contacts from age group j to age group k | fitting |

Table 1: Model parameters and estimated values.

**Parameter’s estimation**

As indicated in Table 1, some parameter values and initial values of state variables in the model are estimated directly from published data. Other parameter values, especially those of the probability of transmission per contact and the recovery rate from measles for each age group, are estimated by fitting the model outcomes to measles data using the nonlinear least squares method [11]. The measles data used for model fitting include the reported annual incidence and age specific incidence of measles in South Africa [12]. The values of measles case mortality ratio are and . By the end of 2020, the values of , are the actual vaccination rates published by NICD [9].

**Immune profile analysis**

In our model, we will generate the measles immune profile for the total population and for different age groups. The baseline is the current endemic level of measles vaccination strategies in South Africa, namely, a single-dose vaccine at 6 months old (age group 1) and the second dose vaccine at 12 months old (age group 1). In South Africa, vaccination coverage of children under 1 year averaged 71.1% , whilst measles second dose vaccination coverage is 76.4% [9]. The efficacy of two doses of measles vaccine ranges from to 93-99%. We therefore assume that the efficacy of the first dose is 93% and for the second dose is 95% [10].

The purpose of immune profile analysis for the population and two age group is to evaluate sustained effort of measles vaccination strategies, particularly after introduction of second dose of vaccination. We will examine the fraction of population that is protected by vaccination and the fraction that is protected by immunity due to past infection. This will demonstrate the effectiveness of the second dose of vaccination at the population level. This model will also allow us to project the level of immunity in the population for future predictions.

**Effect of increasing measles and improving vaccination coverage**

In our model, we will explore different scenarios in which the vaccine coverage rate of first dose or second dose will be increased to , while vaccine efficacies is kept the same as in Table 1 and we will implement the efficacy of to the first dose that is administered to 6 months old. This will indicate the effectiveness of increasing vaccine coverage in reducing the measles incidence.

**Code design**

The model will be run in R studio (version 4.2.0) running R statistical software (version 4.2.0). The R package tidyverse (version 4.2.0) will be used.

We define a function to calculate the rate of change in each state variable. This function solves the Ordinary Differential Equations (ODE’s) (specify the equation numbers), taking parameters of the model system. The system will be updated at each time step. The change in state variables is calculated and returned.

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