**Discrete age-structured mathematical model for application of 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 contagious and serious viral infection caused by the virus for infants [1], however it can be prevented with a vaccine [2]. The respiratory system becomes infected by the virus, which subsequently spreads to the rest of the body. 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 [3]. Transmission occur during direct contact with infectious droplets or airborne spread caused by an infected person's breathing, coughing, or sneezing [4]. After exposure, symptoms of measles don't begin to develop for 10 to 14 days. Clinically, the incubation period from exposure to early symptom onset of disease averages 10 - 12 days from exposure to the virus and it last about 7 – 10 days [5]. It is estimated that 90% of exposed susceptible individuals are exposed to measles [6]. The majority of healthy infants who contract the measles virus recover fully, and there is a low fatality rate. About 30% of measles cases in children under the age of five can result in serious complications [7]. However, despite successful immunization, which led to a decline in measles-related fatalities worldwide between 2000 and 2011 [8]. More than 140,000 individuals died from measles in 2018 alone. 52,600 of these deaths, according to the WHO, happened in Africa [9].

Prior to the measles vaccine was created in the 1960s, the disease was a leading risk factor for mortality worldwide [10]. Since the creation of safe and effective vaccinations in 1963, infant measles infections have declined. It is estimated each year, 2.6 million individuals worldwide are afflicted and killed by measles. [11]. Measles remains the most cause of mortality among children younger than the age of five, despite the availability of vaccinations [7]. In places like Liberia, Madagascar, and Somalia, where vaccination rates are poor, measles outbreaks continue to occur [12]. According to the WHO, global effort to increase vaccination coverage lowered deaths by 73% in 2018. The Measles Eradication Initiative was updated by WHO in 2012 with the intention of eliminating measles in at least five of the world's six regions by 2020 [13]. The World Health Organization defines measles eradication as the absence of indigenous measles cases in a given area for at least 12 months while elevated monitoring systems are present. In addition, the WHO mandates a 95% nationwide measles vaccination rate across all districts, with two doses administered to each kid. At least 80% of districts must investigate at least one suspicious case within a year, and there must be at least 2 non-measles cases per 100,000 inhabitants nationwide. [14].

A vaccine is the most effective public health intervention for combatting vaccine-preventable infectious diseases such as measles [15]. Between 2000 and 2017, measles mortality decreased by 80% as a result of vaccination, and as of 2017, 85% of children globally have received their first dose [16]. The measles vaccine is commonly administered to two doses of the Measles-Mumps-Rubella (MMR) vaccination and it is scheduled for two doses each child. Infants frequently receive their first dose of the measles vaccine at 6 months, followed by second dose at 12 months [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 [13].

Age distribution is the significant element that makes contributions to the heterogeneity of populations, with a substantial impact on the timing and effects on the spread and transmission of infectious diseases [17]. 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 [18]. Age-related differences in immune capacity to infectious disease are also possible. These changes may have an impact on age-specific fatality and infection recovery rates [17].

This study will focus on the transmission of measles in a host population with an age structure. We will examine a mathematical model with discrete age structure and the use of measles vaccination strategies. The effectiveness and vaccination coverage varies depending on the age group. The first dose of the measles vaccination is recommended for infants 6 months of age, and the second dose is recommended for infants 12 months of age. Both doses of measles vaccine are intended to lower the incidence rate [18].

To conduct this study, we will construct a discrete age-structured SEIR model to analyse measles outbreaks that occurred in South Africa. We further evaluate and discuss the effectiveness of various vaccination strategies for control of measles epidemics. The model is 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 to comprehend the dynamics of infection spread in an age-structured host population, an epidemic model with different ages is required.

**Main objective of the research**

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

**Research objectives**

* To explore transmission dynamics of measles in age-structured host population.
* To study the vaccination strategies for measles with discrete age structure.
* To analyse South African measles data and evaluate the effectiveness of various vaccination strategies for measles epidemic control.
* To compare the outcomes of the effect various measles vaccination strategies.
* To modify an age-structure model for measles vaccination on measles incidence.

**Study benefits**

The efficiency of vaccination strategies and measles elimination targets will be shown by the discrete age structure epidemic model when used in conjunction with the measles vaccination strategy for future predictions. The modified two age groups that includes the current measles vaccination in the measles vaccination programs will help with the analysis of the immunological profile of the population and in each age group to establish the base and make predictions.

The model will then demonstrate that two doses of vaccination given to each person has an effect that is more or equivalent to 95% vaccine coverage. The study will also demonstrate the effects of boosting the effectiveness of two doses in lowering measles incidence at a modest vaccination coverage.

**Literature review**

**Measles**

The measles virus is the cause of this extremely contagious disease that is caused by Morbilli virus. Patients who have measles show up with a rash and a fever. The rash appears as small, flat, red spots that first appear on the face or head before moving down the body. The rash is neither unpleasant or itchy, nor does it produce blisters. Cough, conjunctivitis (red eyes), and coryza are further symptoms (running nose). Measles can result in mortality, dehydration, encephalitis, middle ear infections, blindness, and other complications. The red rash that appears a few days after the fever starts and the high fever that manifests after an incubation period of 9–10 days are the main signs of the disease. Measles may also cause ocular symptoms in addition to particular generic symptoms. It is a highly (approximately 95%) contagious disease that mostly affects children but can potentially infect adults if they have not had the recommended immunizations.

One of the earliest documented descriptions of the measles sickness was published in the ninth century by a Persian physician. Scottish physician Francis Home established in 1757 that a pathogen found in patients' blood is what causes measles. Measles became a nationally reportable disease in the United State in 1912, necessitating the reporting of all cases by healthcare professionals and laboratories. During the first ten years of reporting, 6,000 deaths attributable to the measles were reported annually on average. Before a vaccine was developed in 1963, the majority of kids had the measles by the time they were 15 years old. According to estimates, 3 to 4 million Americans contract the disease annually. In addition to recorded cases, 400 to 500 deaths, 48,000 hospitalizations, and 1,000 instances of encephalitis (brain swelling) from measles are predicted to occur annually.

Measles infections can occur wherever in South Africa and are not restricted to certain risk groups or geographic locations. Communities and institutions like daycare facilities and crèches may contain cases. When visiting regions where measles cases have been documented or where measles is a very common disease, adult travelers who were not immunized as children run the risk of contracting the disease. An outbreak is when there are several measles cases in a given location within a short period of time (three or more cases in a health district within four weeks), at which point public health efforts are needed to stop the disease's spread. In 2009, there was a significant measles outbreak in South Africa, with over 18,000 cases being confirmed.

**Measles vaccination**

Vaccination is the strongest protection against measles. Before the introduction of a successful vaccine in 1963, measles infection was almost endemic in children and was considered to be the cause of 2.6 million annual fatalities. As part of the Expanded Programme on Immunization (EPI), single-dose measles vaccination was introduced to South Africa in 1975. After that, in 1995, a two-dose plan was implemented, with additional immunization drives taking place every three to four years. The two-dose measles vaccination regimen was modified to 6 and 12 months in 2016. The disease's high morbidity and mortality rates in early infancy are intended to be prevented by giving the first dose at 6 months of age.

It is recommended that the population immunization rate be at least 95% to minimize measles outbreaks. Only 85% of children worldwide, according to estimates from the World Health Organization (WHO), had received the first dose of the measles vaccine by the time they turned one and 64% had received the second dose by that time. South Africa has experienced numerous measles outbreaks throughout the years; from 2003 to 2005, there were 1 676 laboratory-confirmed case-patients, and from 2009 to 2011, there were more than 18 000.

**Age distribution**

Discrete and continuous methods have been used to study the age-structure of epidemic models. Ordinary differential equation (ODE) models with discrete age groups and partial differential equation (PDE) models with continuous age structure are used in this research. In an effort to comprehend why measles outbreaks repeat, Hamer created and examined a discrete time model in 1906. It's possible that his model was the first to make the assumption that the incidence (number of new cases per unit of time) depended on the sum of the densities of the susceptible individuals and infectives [1].

Much of the recent theoretical progress for PDE models has been inspired by the models' well-posedness and the characteristics of the semigroups they are connected with. ODE models present a mathematical analytical problem because of the high dimensionality and huge scale of the ODE system, despite the fact that the mathematical framework is rather straightforward due to the finite dimensionality of the phase space. It is extremely difficult to establish the global dynamics of age-structured epidemic models using either approach.

It is possible to think about epidemic models on transmission networks as coupled systems of nonlinear differential equations with discrete age structures. Each age group in this scenario can be thought of as a node, and inter-group transmissions and aging are what determine the connections between nodes. Models with discrete age groups can be created using the graph-theoretic method introduced in [], which constructs Lyapunov functions for coupled systems on networks.

**Mathematical modelling of infectious diseases**

Mathematical modelling of infectious disease started out in 1760 whilst Daniel Bernoulli adopted epidemic models to determine whether or not inoculation of healthy individuals with smallpox changed into a powerful approach of preventing the unfold of the disease (Bernoulli 1760). Bernoulli changed into the first to represent the proportion of healthy individuals which might be at risk of an infectious disease in phrases of the force of infection and the lifestyles expectancy. Deterministic epidemic modelling started to be normally used within the 20th century, with mathematicians together with Ross, Kermack and McKendrick contributing significantly to this discipline. Prior to the 20th century, an essential result was determined by Hamer who establish that the progression of an epidemic is dependent upon the quantity of susceptible individual in a population and the rate at which infectious individual and susceptible individuals come into contact with each other (Hamer 1906). Early in the 20th century, Ross developed fundamental deterministic epidemic model where in differential equations are used to explain modifications within the range of susceptible and infectious hosts, in addition to the full wide variety of hosts within the population, through the time (Ross 1916). Deterministic models offer affordable approximations to the adjustments in the number of susceptible and infectious hosts over the time while the numbers of each type of host are large. This basic model can be actually extended to bear in mind other functions of the sickness under observe.

**Kermack and McKendrick model**

In 1927, Kermack and McKendrick prolonged the simple model of Ross to attempt to constitute the adjustments in the quantity of infected people located in epidemics together with the plague and cholera (Kermack and McKendrick 1927). The Kermack and McKendrick model keeps the fundamental structure of the model with the aid of Ross, with non-linear ordinary differential equations used to describe the rate of exchange of the quantity of susceptible (S) and infectious (I) hosts. However, a third magnificence of host is taken into consideration on this model for recovered hosts (R). Recovered hosts are those individuals who recovered from the contamination infection and developed an immunity and thus do not return to the susceptible elegance. The non-linear equations that correspond to this model can be described as follows:

In the model notation, β is the rate of contamination infection and γ is the recovering rate. This model describes the adjustments in a closed population through the years, as no births or deaths are considered. The Kermack and McKendrick model assumes that there is an immediate incubation duration for the infection and that the population is homogeneously mixed.

**Mathematical Model**

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 received the second dose of vaccine and those who have enduring infection-acquired immunity) classes. Compartments with labels the epidemiology classes include and .

For the age group, the influx susceptible individuals are specified by the rate of . is the transmission coefficient between and . 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 mortality rate of an age group is represented by , while case mortality of an age group is represented by a rate of . Individuals gain of immunity at rate .

It is assumed that proportion of infants who received the first dose of the vaccination joined the class of recovered infants 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.

In this section, we construct a vaccination model with two age divisions to evaluate the vaccination strategies for two dose of measles vaccination [21,22].

Figure 1: Model for a measles vaccination model with two vaccination doses.

In this section, a mathematical model to describe the dynamics of measles transmission is developed. It is deterministic and compartmental. The host population is assumed to be homogeneous mixed for both age groups and reflecting to 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 both measles vaccine dose consecutively develop a permanent immunity to the disease.

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. During the incubation period, the susceptible joins the exposed class E of infants who are affected but not yet infectiou, 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 that they can transfer measles infection. The infant enters the recovered class when the infectious period ends if they have gained an 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.

The model is shown in the transmission diagram in Figure 1. Two doses of measles vaccine were incorporated: first dose (6 months), and second dose (12 months). The differential equations given below provide a description of the model.

**Application of measles vaccination methods**

Measles is a disease that can be prevented with a vaccine [7]. It typically takes two doses to fully protect against measles, which is included in the Measles, Mumps, and Rubella (MMR) vaccine. Infants generally receive their first dose of the measles vaccine at 6 months of age, the second dose is administered at 12 months [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].

**Measles vaccination model**

The MMR vaccine helps protect against measles. Children should take the MMR vaccine twice, according to the WHO. The first dose has been taken for six months, and the second for 12 months [6]. After one dosage, the measles vaccine is 93% efficient against the disease, and after two doses, it is 97% effective. [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].

* Age-group 1 – 6 months olds
* Age-group 2 – 12 months olds

We subdivide the host population into two age groups, taking into consideration variations in vaccination programs strategies and interaction patterns according to age. The model is described by the following system of differential equations.

Differential equations for age group 1:

Differential equations for age group 2:

**Parameter estimation**

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 has two parts , the mean of interactions between infants in age groups k and k is represented by the variable . The likelihood of transmission for a typical encounter from susceptible infants in age group k and an infectious infant is , and . Be aware that the age difference between and may prevent the interaction matrix from being symmetrical.

As indicated in Table 1, several model parameters and the starting values of state variables are estimated computed from published data. Other parameter values are estimate by fitting the model outcomes to measles data using the nonlinear least squares method [11]. The measles data used for model fitting include annual incidence rate and age-specific incidence of measles in South Africa [12].

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameters | Values/Range | Unit | Description | Ref |
|  | 650 |  | Influx of susceptible | fitting |
|  | 0.0241 |  | Mortality rate of age group k | [20] |
|  | 0.2859 |  | Aging rate for age group k | [19] |
|  | 0.024368 |  | Recovery rate for age group k | fitting |
|  | 0.72 |  | Exposed rate of age group | [13] |
|  | 0.2 |  | Induced mortality rate of age group k | fitting |
|  | 0.717 |  | Vaccination coverage of first dose | [10] |
|  | 0.764 |  | Vaccination coverage of second dose | [10] |
|  | 0.93 |  | Efficacy of first dose | [9] |
|  | 0.95 |  | Efficacy of second dose | [9] |
|  | 0.1679 |  | Likelihood of transmission rate for age group 1 | fitting |
|  | 0.5154 |  | Likelihood of transmission rate for age group 2 | fitting |
|  | 0.004 |  | Gain of immunity of age group k | fitting |
|  | 13.3 |  | Mean of interactions between age groups j and k | fitting |

Table 1: Model parameters and estimated values.

**Immune profile analysis**

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 percentage of population that has received vaccination and the percentage that has immunity from prior infection. This will demonstrate the effectiveness of the second dose of vaccination at the population level. This will show the population level efficacy of the second dose of vaccination. We may also project the population's level of immunity using this model to make future projections.

In our model, for each age group and the host population, we will create the measles immunological profile. The primary focus is the current level of endemic measles vaccination strategies in South Africa, which is a single dose at 6 months o and a second dose at 12 months. In South Africa, children under 12 months old had an average vaccination coverage of 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].

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

In our model, we will explore different possibility where vaccine coverage rate of first dose and second dose will be increased, while vaccine efficacies is kept the same as in Table 1. 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.

The purpose of improving vaccination coverage and efficacy of measles to is observe the influence of increasing the vaccination coverage and efficacy to examine the effectiveness in reducing the measles incidences. The model prediction will indicate good alternative strategies for measles control in South Africa.

**Code design**

The model will be run in R studio (version 4.2.1) running R statistical software (version 4.2.1). The R package tidyverse (version 1.3.2) 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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