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Research Article

Modelling the Impact of Vaccination on the Control of Measles in Nepal

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Abstract

Measles is a highly contagious disease in human caused by virus. Despite the accessibility of successful vaccines, measles outbreaks still occur, presumably because of the lack of compliance with vaccination. We developed a mathematical model to evaluate the effects of vaccines in different age structures particularly focusing on two groups, to control and eradicate the disease, that may help the planner. Using our model, we formulate the basic reproduction number R_0 that determines, whether the disease persists or dies out. In addition, we carry out sensitivity analysis to identify important parameters that can play a significant role in the control and prevention of measles in different groups of individuals. Furthermore, we investigate the behavior of the disease and effect of vaccination on disease dynamics over a long period.

Keywords: Measles, Vaccines, Age structures, Vaccinated Reproduction Number.
AMS(MOS) Subject Classification: 34K20, 34L30, 92B05, 92D30.

1 Introduction

Infectious diseases, also known as communicable diseases, have been spreading all over the world and pose a constant threat to human beings. Usually, individuals can be affected by a disease, which can be contracted through outside vectors, and may also be spread in

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the same manner. The emergence and re-emergence of infectious diseases have become a significant worldwide problem. Until a decade and a half ago, infectious diseases were the major cause of about 70% of morbidity and mortality [1].

Measles is one of the infectious disease that is highly contagious, caused by the Paramyxovirus, of genus Morbillivirus. It is transmitted through person-to-person with a high transmission rate, having over 90% attack rate among susceptible individuals, and is considered one of the most dangerous disease in children. Initially, the sign of illness typically appear 8-12 days after infection, with symptoms including high fever, a runny nose, bloodshot eyes, and small white spots inside the mouth. After about four days of fever rashes emerge, initially on the face and upper neck, gradually spreading downward. With such symptoms, the illness can lead to severe and deadly complications such as pneumonia, diarrhea, and encephalitis. Consequently, many children who get infected may later experience blindness, deafness, or vision problems. Measles provides lifelong immunity, preventing future occurrences [2].

Prior to the introduction of the measles vaccine in 1963 , significant epidemics emerged roughly every two to three years, resulting in an estimated 2.6 million deaths annually [25]. Moreover, it has been recognized as the leading cause of pediatric morbidity and mortality in the world. Particularly, in Nigeria, with 212,183 and 168,107 cases reported in 2000 and 2001, respectively, in France 22,178 cases were reported between 2008 and 2011 [4]. There were more than 170,000 cases globally in 2022, which increased to more than 320,000 cases in 2023, according to WHO's count. In the first several months of 2024, nearly 100,000 measles cases were recorded [9]. Additionally, it was recorded that in 2023, the measle outbreak occurred in Yemen (18,464 cases), Azerbaijan (13,721 cases), Kazakhstan (13,195 cases), India (12,301 cases), Ethiopia (10,060 cases), Russian Federation (7,720 cases), Iraq (7,601 cases), Pakistan (7,027 cases), Kyrgyzstan (5,777 cases), and Indonesia (3,205 cases) [8].

Measles has no specific treatment; the treatment is only for their complications. Measles is a vaccine preventable disease and the vaccination with the MMR (Measles, Mump, and Rubella) vaccine is the most effective way of preventing measles [3]. John F. Enders and Thomas C. Peebles discovered the measles virus in Boston, Massachusetts, in 1954. It took until 1968 for the US to develop a vaccine against the disease [5]. Before the introduction of the measles vaccine, almost all children got measles by the age of 15 years [2].

In Nepal, there were an estimated average of 90,000 cases of measles outbreaks per year from 1994 to 2002 [5]. While in 2004, from 1 March to 30 September, 137 measles outbreaks were reported through the routine surveillance system [6, 7]. Regarding the control of the disease, the single dose vaccine for measles in Nepal was introduce in 1979, initially in the three districts and then completed nationwide by 1989, and the second dose of vaccine was introduced in 2015. However despite the nationwide introduction of the measles vaccine in

1989, there was no proper implementation untill 2007. Before 2007, the coverage of first dose of measles vaccine (MCV1) was less than 85% nationally with no one district has more than 95% coverage of MCV1, which became a major cause of mortality and morbidity in childhood. During 2007-2014 the coverage of the first dose (MCV1) vaccine containing MCV1, raised from 71% to 88% [1]. Supplementary Immunization Activities (SIAs) carried out in 2008 and 2014, vaccinated around 3.9 and 9.7 million kids respectively. During 2007-2014, there was a decline in reported measles incidence by 13% i.e. 54 to 47 cases per 1 million population [1]. Despite the efforts by SIAs measles outbreaks persisted in some districts (Morang, Dang and Kapilvastu districts, Kathmandu and Lalitpur). The measles cases began to increase from 99 cases in 2017 to 247 in 2018 and 430 cases in 2019 in Nepal [7, 10] which is a cause of concern.

The World Health Organization (WHO) also has a great concern to eliminate the disease from the world. The South-East Asia Region (SEAR), World Health Organization (WHO) established a goal in 2013, to eliminate measles in SEAR by 2020. To declare the elimination of measles the number of measles cases should be less than five in every 1,000,000 population or no cases throughout the year. Nepal is one of the 11 SEAR member states that also adopted a goal of WHO for national measles elimination by 2019, which could not be achieved and extended by 2023 [1, 11].

As infectious diseases are major causes of morbidity and mortality worldwide, the study of these infectious diseases becomes very important. In particular, mathematical models, are crucial tools for understanding the dynamics of transmission, predicting the future outbreaks, and proposing control strategies. Consequently, many mathematical studies have been conducted to study the evolution and dynamics of infectious diseases. For the last few decades, researchers have developed many mathematical models for measles. Studies [2, 12, 13, 14] developed the SIR, SEIR, and SVEIRS deterministic model to study the dynamics of measles with different immunization strategies within the population characterized by size and age structures, vaccination, time vaccination, and pulse vaccination respectively.

In the context of Nepali literatures [1, 5, 7, 15] on advancements in measles control, the case fatality rate (CFR) of measles, and the genetic type of the Asian measles virus have been published, and most of these models have incorporated vaccination. Furthermore, Pokharel A. et.al 2022 studied the effect of monitored and un-monitored vaccination in Nepal by developing a deterministic model incorporationg monitored and un-monitored vaccination class [16]. Motivated by the model [17, 18], focused on the different age groups we also developed a $SVEIR$ model with the two groups of different age structures.

2 Methodology

In this work, we develop a deterministic model incorporating the vaccination class in two different age groups of population. We use the data taken from the official site of the World Health Organization (WHO) [19] and fit the model with the available data for analysis. Moreover, we perform existence and positivity analysis of the solutions, equilibria analysis (i.e. disease free equilibrium state and its stability), basic reproduction number, effective reproduction number, endemic equilibrium point etc. We also perform the sensitivity analysis.

2.1 Modeling of the Transmission dynamics

A deterministic mathematical model $SVEIR$ is developed to study the dynamics of measles transmission for the population of two different age groups (0-15 and above 15). The index used in the state variables $i = 1, 2$ represent the different age groups whereas $i = 1$ for the population of age fifteen years and below fifteen and $i = 2$ for the population of age above fifteen years. Each age group i is divided into five distinct compartments: S_i, V_i, E_i, I_i and R_i where, S_i: Susceptible, V_i: Vaccinated, E_i: Exposed, I_i: Infectious and R_i: Recovered population. The total population of each group N_i is the sum of the population in the i^{th} age group. The recruitment rate of the population in each age group is $\Lambda_i \delta_{i,1}$, where

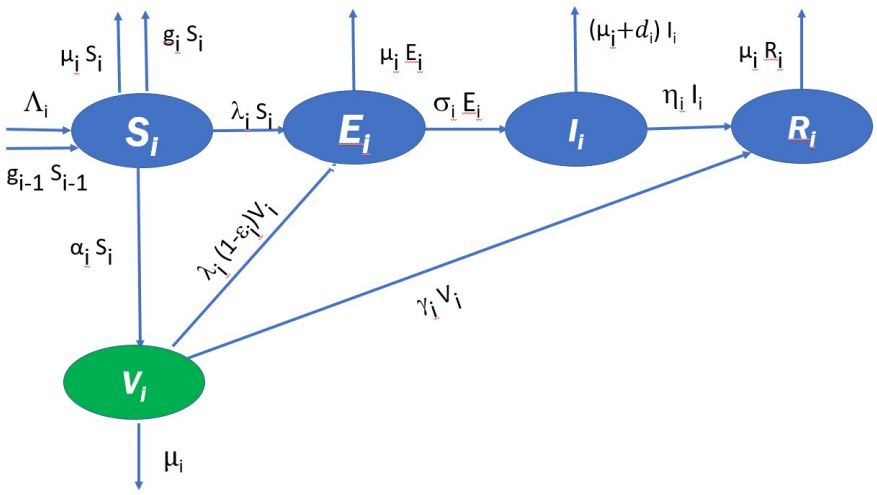


Figure 1: Schematic diagram of the model

$\delta_{i,1}$ is the Kronecker delta function, which is equal to 1 for $i = 1$ and zero for $i = 2$. So we assumed the first age group is recruited by $\Lambda_1 \delta_{1,1} = \Lambda_1 = \Lambda$ and second age group is recruited by $\Lambda_2 \delta_{2,1} = 0$. The susceptible individual in each group is vaccinated at a rate of α_i and unvaccinated population gets exposed (E_i) with the force of infection λ_i where

$\lambda_i = \left(\sum_{j=1}^{2} \beta_{i,j} \frac{I_j}{N}\right)$ for the rate of transmission $\beta_{i,j}$ between age class i and j. The infected individuals are recovered at the rate of η_i. Natural death and disease induced death rates are μ_i, and d_i respectively, however, we assume the equal natural and disease induced death rate for each group are μ and d respectively. The vaccinated population V_i is immunized and is removed at the rate of γ_i. As the vaccinated may be exposed due to the loss of immunity, we assume ϵ represents the effectiveness of the vaccine lying between [0 1], and the class V_i is exposed at the rate of $(1-\epsilon)\lambda_i$. The disease is progressed at the rate of σ. The aging rate from predecessor class i to its successor class, is g_i for $i = 1, 2$.

2.1.1 Dynamical Equations

The dynamical system of the model is:

$$\frac{dS_i}{dt} = \Lambda_i \delta_{i,1} - (\lambda_i + \mu + \alpha_i)S_i - g_i S_i + g_{i-1} S_{i-1}, \tag{2.1}$$

$$\frac{dV_i}{dt} = \alpha_i S_i - (\gamma_i + \mu + g_i)V_i - (1-\epsilon)\lambda_i V_i + g_{i-1} V_{i-1}, \tag{2.2}$$

$$\frac{dE_i}{dt} = \lambda_i (S_i + (1-\epsilon)V_i) - (\mu + \sigma + \eta + g_i)E_i + g_{i-1} E_{i-1}, \tag{2.3}$$

$$\frac{dI_i}{dt} = \sigma E_i - (\mu + d_i + g_i)I_i + g_{i-1} I_{i-1}, \tag{2.4}$$

$$\frac{dR_i}{dt} = \gamma_i V_i + \eta I_i - \mu R_i + g_{i-1} R_{i-1}, \tag{2.5}$$

$$N_i = (S_i + V_i + E_i + I_i + R_i),\ N = \sum_{i=1}^{2} N_i,$$

where $\delta_{i,1}$ is Kronecker delta function, $\forall\ i = 1, 2$.

2.2 Existence of Positive Solutions

Initially, we prove the positivity and the boundedness of the solution of the system of equations to establish the biological or epidemiological validation or the well-posedness of the model (2.1-2.5).

2.2.1 Positivity of the solutions

Theorem 2.1. *If* $\Omega = (S_i, V_i, E_i, I_i, R_i) \in R_+^{10}, S_i(0) > 0, V_i(0) \geq 0, E_i(0) \geq 0, I_i(0) \geq 0, R_i(0) \geq 0,\ \forall i = 1, 2$, *then the solutions* $\{S_i, V_i, E_i, I_i, R_i\}$ *of the system (2.1-2.5) are positive for all* $t \geq 0$.

Proof:

From (2.1), we get $\frac{dS_i}{dt} > -(\lambda_i + \mu + \alpha_i + g_i)S_i$,

$$S_i(t) > S_i(0)exp\left(-\int_0^t \left(\sum_{j=1}^{2} \beta_{i,j}\frac{I_j}{N} + (\mu + \alpha_i + g_i)\right) dt\right).$$

Similarly, solving the differential equations (2.2-2.5) we can show,

$$V_i(t) > V_i(0)exp\left(-\int_0^t \left((1-\epsilon)\sum_{j=1}^{2} \beta_{i,j}\frac{I_j}{N} + (\mu + \gamma_i + g_i)\right) dt\right).$$
$$E_i(t) \geq E_i(0)exp\left(-\left(\mu + \sigma + \eta + g_i\right)t\right),$$
$$I_i(t) \geq I_i(0)exp\left(-\left(\mu + d_i + \eta\right)t\right),$$
$$R_i(t) \geq R_i(0)exp\left(-\mu t\right).$$

Clearly $S_i, V_i, E_i, I_i, R_i \; \forall \; i = 1, 2$ are non-negative for all $t \geq 0$. Thus the positivity of the solutions $S_i(t), V_i(t), E_i(t), I_i(t), R_i(t)$ is established.

2.2.2 Boundedness and invariant region

We now show that the non-negative solutions of the system (Theorem 2.1) are bounded in an invariant region. Adding all differential equations in the system (2.1 - 2.5), we get $dN_i/dt = \Lambda_i\delta_{i,1} - \mu N_i - d_i I_i$, which provides $N_i(t) \leq N_i(0)e^{-\mu t} + \Lambda\delta_{i,1}/\mu(1 - e^{-\mu_i t})$ and $\limsup_{t\to\infty} N(t) = \sum_{i=1}^{2} N_i(t) \leq \Lambda/\mu$. This shows that the human population is ultimately bounded by Λ/μ. Thus all the state variables are bounded by Λ/μ ensuring the solution set of (2.1 - 2.5) remains positively invariant in the feasible region

$$\Omega = \left\{(S_i(t), V_i(t), E_i(t), I_i(t), R_i(t)) \in \mathbb{R}_+^{10} : \forall i = 1, 2, \; N(t) \leq \Lambda/\mu\right\}.$$

2.3 Equilibria Analysis

2.3.1 Disease Free of Equilibrium State

Our model is a system of nonlinear differential equation model having constant coefficients. If the equations have time-independent solutions, or remain unchanged over the time, are referred to as equilibrium points which play an important role in the long-term behavior of the solutions.

For each $i = 1, 2$ the equations (2.1-2.5) can be elaborated:

$$\frac{dS_1}{dt} = \Lambda - (\lambda_1 + \mu + \alpha_1)S_1 - g_1 S_1, \tag{2.6}$$
$$\frac{dV_1}{dt} = \alpha_1 S_1 - (\gamma_1 + \mu + g_1)V_1 - (1-\epsilon)\lambda_1 V_1, \tag{2.7}$$
$$\frac{dE_1}{dt} = \lambda_1(S_1 + (1-\epsilon)V_1) - (\mu + \sigma + g_1)E_1, \tag{2.8}$$
$$\frac{dI_1}{dt} = \sigma E_1 - (\mu + d + \eta + g_1)I_1, \tag{2.9}$$
$$\frac{dR_1}{dt} = \gamma_1 V_1 + \eta I_1 - \mu R_1 - g_1 R_1, \tag{2.10}$$
$$\frac{dS_2}{dt} = -(\lambda_2 + \mu + \alpha_2)S_2 + g_1 S_1, \tag{2.11}$$
$$\frac{dV_2}{dt} = \alpha_2 S_2 - (\mu + \gamma_2)V_2 - (1-\epsilon)\lambda_2 V_2 + g_1 V_1, \tag{2.12}$$
$$\frac{dE_2}{dt} = \lambda_2(S_2 + (1-\epsilon)V_2) - (\mu + \sigma)E_2 + g_1 E_1, \tag{2.13}$$
$$\frac{dI_2}{dt} = \sigma E_2 - (\mu + d + \eta)I_2 + g_1 I_1, \tag{2.14}$$
$$\frac{dR_2}{dt} = \gamma_2 V_2 + \eta I_2 - \mu R_2 + g_1 R_1. \tag{2.15}$$

Solving these equations with the disease compartments $E_i = 0$ and $I_i = 0,\ \forall i = 1, 2$ are zero, we obtain an equilibrium point called disease free equilibrium point,

$$E^0 = (S_1^0, V_1^0, 0, 0, R_1^0, S_2^0, V_2^0, 0, 0, R_2^0).$$

Where,

$$S_1^0 = \frac{\Lambda}{\alpha_1 + g_1 + \mu},\ V_1^0 = \frac{\alpha_1 \Lambda}{(\alpha_1 + g_1 + \mu)(\gamma_1 + g_1 + \mu)},\ R_1^0 = \frac{\alpha_1 \gamma_1 \Lambda}{(g_1 + \mu)(\alpha_1 + g_1 + \mu)(\gamma_1 + g_1 + \mu)},$$
$$S_2^0 = \frac{g_1 \Lambda}{(\alpha_2 + \mu)(\alpha_1 + g_1 + \mu)},$$
$$V_2^0 = \frac{g_1 \Lambda \left(\alpha_1 \mu + \alpha_1^2 + \alpha_2 (\gamma_1 + g_1 + \mu)\right)}{(\alpha_2 + \mu)(\gamma_2 + \mu)(\alpha_1 + g_1 + \mu)(\gamma_1 + g_1 + \mu)},$$
$$R_2^0 = \frac{g_1 \Lambda (\alpha_2 \gamma_2 (g_1 + \mu)(\gamma_1 + g_1 + \mu) + \alpha_1 (\alpha_2 + \mu)(\gamma_1 (\gamma_2 + \mu) + \gamma_2 (g_1 + \mu)))}{\mu (\alpha_2 + \mu)(\gamma_2 + \mu)(g_1 + \mu)(\alpha_1 + g_1 + \mu)(\gamma_1 + g_1 + \mu)}.$$

2.4 Basic Reproduction Number

Here we formulate the reproduction number in the presence of vaccination, using the Next Generation Matrix as method in [20, 21, 22, 23]. In the study, the population is not fully susceptible, so this R_0 is not basic reproduction number, while it is an effective reproduction number under vaccination but we still use R_0 to denote it. The system (2.1- 2.5) includes E_i and I_i the diseased compartments, which separates the terms with the new infection rate f_i: $(S_i + (1-\epsilon)V_i)\sum_{j=1}^{2} \beta_{i,j} I_j/N$ where $\sum_{j=1}^{2} \beta_{1,j} I_j/N = \lambda_1 = \beta_{1,1} I_1/N + \beta_{1,2} I_2/N$

and $\sum_{j=1}^{2}\beta_{2,j}I_j/N = \lambda_2 = \beta_{2,1}I_1/N + \beta_{2,2}I_2/N$. For the simplicity, we assume the contact of susceptible to the infected individual I_1 is taken as b_1 and to the infected individual I_2 is taken as b_2, and obtained $\lambda_1 = \lambda_2 = (b_1I_1 + b_2I_2)/N$. The children under 15 years are in school, so we assume they have a higher contact rate than the other class and for the simplicity of calculation and simulation we refer $b_1 = b$ the group of age < 15 years and $b_2 = b/2$ for group of age > 15 years and we use $\lambda_1 = \lambda_2 = b(I_1 + I_2/2)/N$. Whereas v_i: the transfer rate of individuals into and out of compartments E_i and I_i is given as:

$$f_i = \begin{pmatrix} (S_1 + (1-\epsilon)V_1)\frac{b(I_1+I_2/2)}{\sum_{i=1}^{2}N_i} \\ 0 \\ (S_2 + (1-\epsilon)V_2)\frac{b(I_1+I_2/2)}{\sum_{i=1}^{2}N_i} \\ 0 \end{pmatrix},\ v_i = \begin{pmatrix} E_1\left(g_1+\mu+\sigma\right) \\ I_1\left(d+g_1+\mu+\eta\right) - E_1\sigma \\ E_2\left(\mu+\sigma\right) - E_1g_1 \\ I_2\left(d+\mu+\eta\right) - g_1I_1 + E_2(-\sigma) \end{pmatrix},$$

The Jacobians F and V of f_i and v_i respectively at the steady state disease free equilibrium point E^0 are

$$F = \begin{pmatrix} 0 & \frac{b\mu\left(S_1^0 + V_1^0(1-\epsilon)\right)}{\Lambda} & 0 & \frac{b\mu\left(S_1^0 + V_1^0(1-\epsilon)\right)}{\Lambda} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{b\mu\left(S_2^0 + V_2^0(1-\epsilon)\right)}{\Lambda} & 0 & \frac{b\mu\left(S_2^0 + V_2^0(1-\epsilon)\right)}{\Lambda} \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} g_1+\mu+\sigma & 0 & 0 & 0 \\ -\sigma & d+g_1+\mu+\eta & 0 & 0 \\ -g_1 & 0 & \mu+\sigma & 0 \\ 0 & -g_1 & -\sigma & d+\mu+\eta \end{pmatrix},$$

$$V^{-1} = \begin{pmatrix} \frac{1}{g_1+\mu+\sigma} & 0 & 0 & 0 \\ \frac{\sigma}{Q_1\left(g_1+\mu+\sigma\right)} & \frac{1}{Q_1} & 0 & 0 \\ \frac{g_1}{\left(\mu+\sigma\right)\left(g_1+\mu+\sigma\right)} & 0 & \frac{1}{\mu+\sigma} & 0 \\ \frac{g_1\sigma\left(d+g_1+2\mu+\sigma\right)}{Q_1Q_2(\mu+\sigma)\left(2g_1+\mu+\sigma\right)} & \frac{g_1}{Q_1Q_2} & \frac{\sigma}{Q_2(\mu+\sigma)} & \frac{1}{Q_2} \end{pmatrix}.$$

Where, $Q_1 = \left(d+g_1+\mu+\eta\right),\ Q_2 = (d+\mu+\eta)$.

Now

$$FV^{-1} = \begin{pmatrix} b\mu\sigma xK_1 & b\mu xK_2 & \frac{b\mu\sigma x}{2(\mu+\sigma)\left(d+\eta+\mu\right)} & \frac{b\mu x}{2\left(d+\eta+\mu\right)} \\ 0 & 0 & 0 & 0 \\ b\mu\sigma yK_1 & b\mu yK_2 & \frac{b\mu\sigma y}{2(\mu+\sigma)\left(d+\eta+\mu\right)} & \frac{b\mu y}{2\left(d+\eta+\mu\right)} \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

$$\text{Where, } K_1 = \frac{\left(2(\mu+\sigma)\left(d+\eta+\mu\right)+g_1\left(d+\eta+2\mu+\sigma\right)+g_1^2\right)}{2(\mu+\sigma)\left(d+\eta+\mu\right)\left(g_1+\mu+\sigma\right)\left(d+g_1+\eta+\mu\right)},$$

$$K_2 = \frac{\left(2\left(d+\eta+\mu\right)+g_1\right)}{2\left(d+\eta+\mu\right)\left(d+g_1+\eta+\mu\right)},\ x = \frac{\left(\alpha_1\left(1-\epsilon\right)+\left(\gamma_1+g_1+\mu\right)\right)}{\left(\alpha_1+g_1+\mu\right)\left(\gamma_1+g_1+\mu\right)},$$

$$y = \frac{g_1\left(\left(\alpha_2\gamma_1+\alpha_1\mu+\alpha_2\mu+\alpha_2\alpha_1+\alpha_2 g_1\right)+\left(\gamma_1+\mu\right)\left(\gamma_1+g_1+\mu\right)\right)}{\left(\alpha_2+\mu\right)\left(\gamma_1+\mu\right)\left(\alpha_1+g_1+\mu\right)\left(\gamma_1+g_1+\mu\right)}.$$

The dominated eigenvalue or the spectral of $FV^{-1} = \rho(FV^{-1})$ is the Basic Reproduction Number (R_0) of the system, which is given as

$$R_0 = \frac{b\mu\sigma\left(S_1^0+V_1^0(1-\epsilon)\right)}{2\Lambda\left(g_1+\mu+\sigma\right)\left(d+\eta+g_1+\mu\right)} + \frac{b\mu\sigma\left(S_1^0+S_2^0+\left(V_1^0+V_2^0\right)(1-\epsilon)\right)}{2\Lambda(\mu+\sigma)(d+\eta+\mu).}$$

$$R_0 = \frac{bg_1^2\mu\sigma(x+y)+g_1(x+y)\left(d+2\mu+\sigma\right)+\left(\mu+\sigma\right)\left(2\eta x+(d+\mu+\eta)(2x+y)+\eta y\right)}{2(\mu+\sigma)\left(d+\eta+\mu\right)\left(g_1+\mu+\sigma\right)\left(d+g_1+\eta+\mu\right)}.$$

2.5 Local stability of disease free equilibrium point

Theorem 2.2. *The disease-free equilibrium point of the system 2.6 to 2.15 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

We have the Jacobian of the system at DFE is to be $J_{10\times10} = \begin{pmatrix} A_{5\times5} & C_{5\times5} \\ B_{5\times5} & D_{5\times5} \end{pmatrix}$ where

$$A_{5\times5} = \begin{pmatrix} -\alpha_1-g_1-\mu & 0 & 0 & -\frac{b\mu}{\alpha_1+g_1+\mu} & 0 \\ \alpha_1 & -\gamma_1-g_1-\mu & 0 & -\frac{\alpha_1 b\mu\left(1-\epsilon_1\right)}{\left(\alpha_1+g_1+\mu\right)\left(\gamma_1+g_1+\mu\right)} & 0 \\ 0 & 0 & -g_1-\mu-\sigma & b\mu x & 0 \\ 0 & 0 & \sigma & -d-g_1-\mu-\eta & 0 \\ 0 & \gamma_1 & 0 & \eta & -g_1-\mu \end{pmatrix},$$

$$B_{5\times5} = \begin{pmatrix} g_1 & 0 & 0 & -\frac{bg_1\mu}{\left(\alpha_2+\mu\right)\left(\alpha_1+g_1+\mu\right)} & 0 \\ 0 & g_1 & 0 & -\frac{bg_1\mu\left(1-\epsilon\right)\left(\alpha_1\left(\alpha_2+\mu\right)+\alpha_2\left(\gamma_1+g_1+\mu\right)\right)}{\left(\alpha_2+\mu\right)\left(\gamma_1+\mu\right)\left(\alpha_1+g_1+\mu\right)\left(\gamma_1+g_1+\mu\right)} & 0 \\ 0 & 0 & g_1 & b\mu y & 0 \\ 0 & 0 & 0 & g_1 & 0 \\ 0 & 0 & 0 & 0 & g_1 \end{pmatrix},$$

$$C_{5\times5} = \begin{pmatrix} 0 & 0 & 0 & -\frac{b\mu}{2\left(\alpha_1+g_1+\mu\right)} & 0 \\ 0 & 0 & 0 & -\frac{\alpha_1 b\mu\left(1-\epsilon_1\right)}{2\left(\alpha_1+g_1+\mu\right)\left(\gamma_1+g_1+\mu\right)} & 0 \\ 0 & 0 & 0 & \frac{b\mu x}{2} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$D_{5\times5}=\begin{pmatrix} -\alpha_2-\mu & 0 & 0 & -\dfrac{bg_1\mu}{2\left(\alpha_2+\mu\right)\left(\alpha_1+g_1+\mu\right)} & 0 \\ \alpha_2 & -\gamma_1-\mu & 0 & -\dfrac{bg_1\mu\left(1-\epsilon\right)\left(\alpha_1\left(\alpha_2+\mu\right)+\alpha_2\left(\gamma_1+g_1+\mu\right)\right)}{2\left(\alpha_2+\mu\right)\left(\gamma_1+\mu\right)\left(\alpha_1+g_1+\mu\right)\left(\gamma_1+g_1+\mu\right)} & 0 \\ 0 & 0 & -\mu-\sigma & \dfrac{b\mu y}{2} & 0 \\ 0 & 0 & \sigma & -d-\mu-\eta & 0 \\ 0 & \gamma_1 & 0 & \eta & -\mu \end{pmatrix}.$$

Among the ten eigenvalues of the Jacobian $J_{10\times10}$, six eigenvalues $\lambda_1=-\mu,\ \lambda_2=-\gamma_1-\mu,\ \lambda_3=-\mu-\alpha_1,\ \lambda_4=\mu-g_1,\ \lambda_5=-\alpha_1-g_1-\mu,\ \lambda_6=-\gamma_1-g_1-\mu$ are otained from inspection and the rest of sub matrix of the $J_{10\times10}$ is to be

$$\begin{pmatrix} -g_1-\mu-\sigma & b\mu x & 0 & \dfrac{b\mu x}{2} \\ \sigma & -d-g_1-\mu-\eta & 0 & 0 \\ g_1 & b\mu y & -\mu-\sigma & \dfrac{b\mu y}{2} \\ 0 & g_1 & \sigma & -d-\mu-\eta \end{pmatrix}.$$

The characteristics equations $P(\lambda)$ is obtained as

$$A_0\lambda^4+A_1\lambda^3+A_2\lambda^2+A_3\lambda+A_4=0.$$

Where,

$$\begin{aligned} &A_0=1,\ A_1=2(d+g_1+2\mu+\sigma)>0,\\ &A_2=(d+2\mu+\sigma)\left(\left(d+g_1+\mu+\eta\right)\left(g_1+\mu+\sigma\right)-\frac{1}{2}b\mu\sigma(2x+y)\right),\\ &A_3=(d+2\mu+\sigma)\left(\left(d+g_1+\mu+\eta\right)\left(g_1+\mu+\sigma\right)-\frac{1}{2}b\mu\sigma(2x+y)\right)\\ &\quad+(d+\mu+\eta)(\mu+\sigma)\left(d+2g_1+2\mu+\sigma\right)-bg_1\mu\sigma(x+y),\\ &A_4=\left(1-R_0\right)(d+\mu+\eta)(\mu+\sigma)\left(d+g_1+\mu\right)\left(g_1+\mu+\sigma\right). \end{aligned}$$

Since, $R_0<1$ follows $\left(d+g_1+\mu+\eta\right)\left(g_1+\mu+\sigma\right)>\frac{1}{2}b\mu\sigma(2x+y)$, and $(d+\mu+\eta)(\mu+\sigma)\left(d+2g_1+2\mu+\sigma\right)>bg_1\mu\sigma(x+y)$, clearly we obtained $a_0,\ A_1,\ A_2,\ A_3,\ A_4>0$ including the condition $A_1A_2A_3>A_3^2+A_1^2A_4$. This condition gives the positive determinate of Routh-Hurwitz Matrices and implies all the roots of characteristic equation $P(\lambda)$ i.e. Jacobian of the system at disease free equilibrium point $(J_{10\times10})$ has negative eigenvalues or eigenvalues with negative real parts. Concluding the result the disease free equilibrium point is locally asymptotically stable for $R_0<1$.

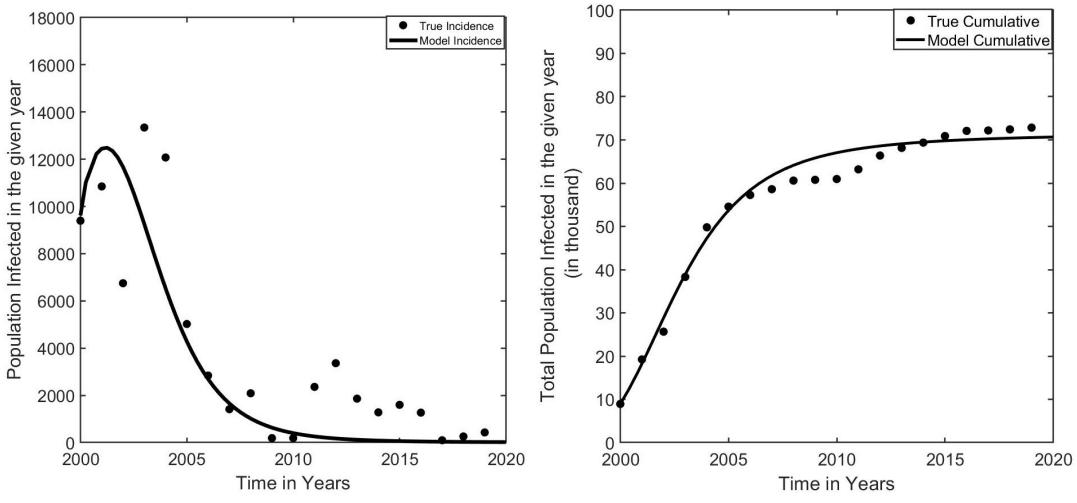
3 Data fitting and parameter estimation

3.1 Data Source

To validate the model, we fit the model with real time data and analyze any discrepancies. In this study, we utilize the reported yearly measles incidence cases from 2000 to 2019, accessible on the official website of the World Health Organization (WHO) [24]. Additionally, data from "Nepal Population Growth Rate 1950-2020" [19] is incorporated for the Crude Birth Rate (CBR) and Infant Mortality Rate (IMR) of Nepal.

3.2 Parameter estimation, data fitting and model validation

In 2000 (the base year), there were 23,941,110 population in Nepal among which 9,807,000 were children of age up to fifteen and 14,134,110 were above fifteen years, while in 2019 there were 28,608,710 population among which 8,460,000 were children under fifteen [19, 24]. It is not possible to determine the real population size in each of the classes S_i, V_i, E_i, I_i, and R_i. As in 2000 (the base year), 77 percent of the population was reported to have had vaccinations [24] among this we took 30% in V_1 class. For our base case simulation, among the 23% of the population, we took 22% in the susceptible class ($S_1(0) = 2,157,540$). We took 30% of the vaccinated population is in the vaccinated class ($V_1(0) = 2,206,575$).



(a) (b)

Figure 2: Recorded (a) yearly cases of measles data (dot) along with the best fit of the model prediction (line). (b) cumulative cases of data (dot) estimated using the model (line) along with the data.

From the data, the recorded cases were 9397 in the base year, among which we assume $E_1(0) = 300$, $I_1(0) = 340$ are in the exposed class in the infectious class under fifteen

and $E_2(0) = 50,\ I_2(0) = 50$ in the population above fifteen. We assume the remaining population under fifteen in $R_1(0) = 5,442,245$. In the same manner, we took $S_2(0) = 3,109,500,\ V_2(0) = 3,109,800$ and $R_2 = 7,914,710$.

The annual average birth rate as the recruitment rate (Λ = 612,328) is calculated by using the Crude Birth Rate (CBR) and Infant Mortality Rate (IMR) from the 2000-2019 data [19]. Whereas, we take the natural death rate (μ) = $1/71.74 \approx 1/72$ per year, as 71.74 years of average life expectancy in Nepal [19]. Since the population is divided into two groups, below and above fifteen years, we used the aging rate of the first group as $g_1 = 1/15 = 0.0667$ per year, while the first group is recruited by birth and the last group has no age limit we took $g_0 = g_2 = 0$. The incubation period of measles is 10-14 days [25, 26], and thus we cosidered the disease progression rate from the exposed class to the infectious class in each group $\sigma_1 = \sigma_2 = 1/12 \times 365 \approx 30$ per year and the disease takes about 18 days (within the range of 7 to 23 days) to recover [25], we used $\eta_1 = \eta_2 = 1/18 \times 365 \approx 20$ per year for both group of population. By using the secondary data [25, 26], the average disease-induced death rate is estimated to be $d = 0.01$ per year for each group. The children under 15 years are in school, so we assume they have higher contact rate than the other class and we refer b for < 15 and $b/2$ for $15 <$. Furthermore, to reduce the complexity of the parameter estimation we also assumed the equal efficacy and the immunization rate of the vaccine in each group i.e.$\epsilon_1 = \epsilon_2 = \epsilon$ and $\gamma_1, = \gamma_2 = \gamma$. We estimated the parameters of the model, $b, \alpha_1, \alpha_2,\ \gamma_1, \epsilon$ by fitting to the data of measles incidence cases in Nepal.

We calculate the yearly new infection at time t from our model by using the relation

$$h(t) = \sigma(E_1(t) + E_2(t)),$$

obtaining the numerical solution of the equations (2.6 to 2.15). Then the parameters are estimated by using [27] the nonlinear regression method involves minimizing the sum of the squares of the residuals.

$$\sum_{k=1}^{n} (t_k - \bar{t_k})^2$$

where t_k denotes yearly new infection predicted from the model and $\bar{t_k}$ denotes yearly new infection from data, and n is the number of data points. Our model aligns with the yearly incidence cases observed in Nepal Figure 4 which is also validated by the cumulative cases to describe the measles epidemic in Nepal. We estimated the parameters, $b, \alpha_1, \alpha_2, \gamma$, and ϵ. The values of the fixed parameter obtained from the fitting are mentioned in Table 1.

Table 1: Estimated and fixed parameters values.

Para meters	Baseline Value $(yr)^{-1}$	Sources	Para meters	Baseline Value $(yr)^{-1}$	Sources
α_1	0.1	Data Fitting	α_2	0.001	Data Fitting
ϵ	0.25 (Dim less)	Data Fitting	μ	0.0175	Assumed
g_1	.0667	Assumed	σ	30	[25]
η	20	[25]	d	0.01	[26]
b	75.8	Data Fitting	γ	0.10	Data Fitting

4 Numerical Results

4.1 Longterm dynamics

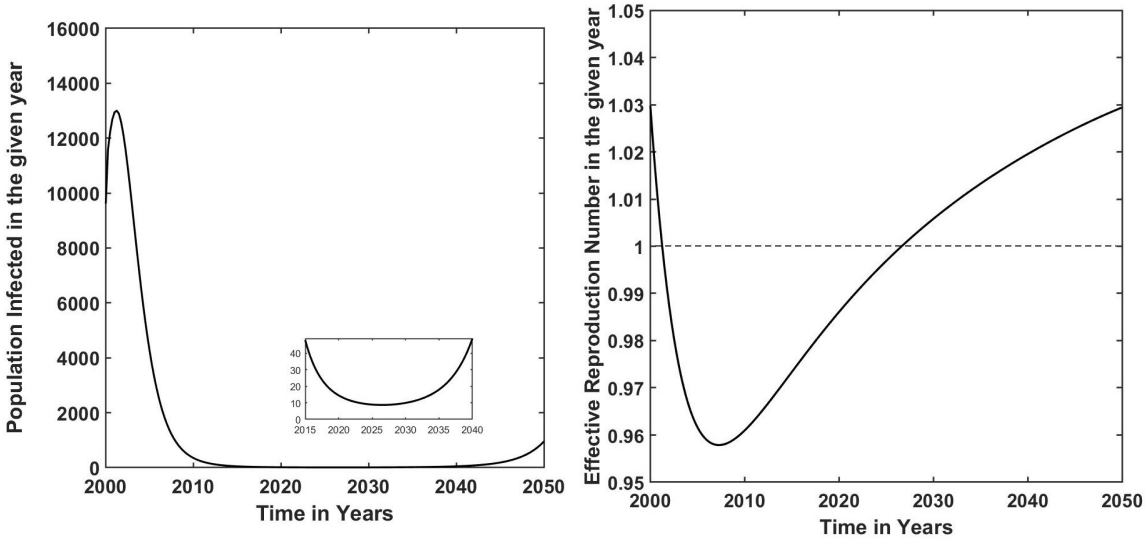
Observing the longterm dynamics of the disease the model predicts that there are still ten cases in 2023 in Nepal, so that the disease will not be die out by 2023 if the situation of vaccination remains same (Figure 3a). But the disease will decline by 2027 and will remain at nine cases, then it will increase.

4.2 Computation of effective reproduction number

We calculate the measles reproduction number in Nepal in the presence of vaccination to be $R_0 \approx 1.07$ using the estimated parameters (Table 1). Calculated R_0 is consistent with the ongoing measles endemic there, even though the magnitude is very small compared to the basic reproduction number of measles. This figure is our anticipated value because it was calculated using parameters which are influenced by the immunization program. Additionally, to track whether the epidemic is growing or shrinking, we compute the time-dependent effective reproduction number, R_t. The expression of R_t is given as:

$$\frac{b\sigma\left(S_1(t)+V_1(t)(1-\epsilon)\right)}{2N(t)\left(g_1+\mu+\sigma\right)\left(d+\eta+g_1+\mu\right)}+\frac{b\sigma\left(S_1(t)+S_2(t)+\left(V_1(t)+V_2(t)\right)(1-\epsilon)\right)}{2N(t)(\mu+\sigma)(d+\eta+\mu)}.$$

Using the estimated parameters (Table 1), we were able to determine the pattern of the time-dependent reproduction number R_t (Figure 3b). The pattern shows that the disease will decrease by 2027 where the $R_t < 1$ and then start to rise where the $R_t > 1$ indicating the disease starts to rise in the community if the current situation continues.



(a) Longterm dynamics of measles epidemic predicted in Nepal

(b) Time Varying effective reproduction number in the given year

Figure 3

4.3 Sensitivity analysis

Observing the local sensitivity of R_0 to the parameters $b, \epsilon, \alpha_1, \alpha_2, \gamma,$ and σ. For this we obtain the sensitivity index S_x, for the parameter x which is to be obtained, is given by

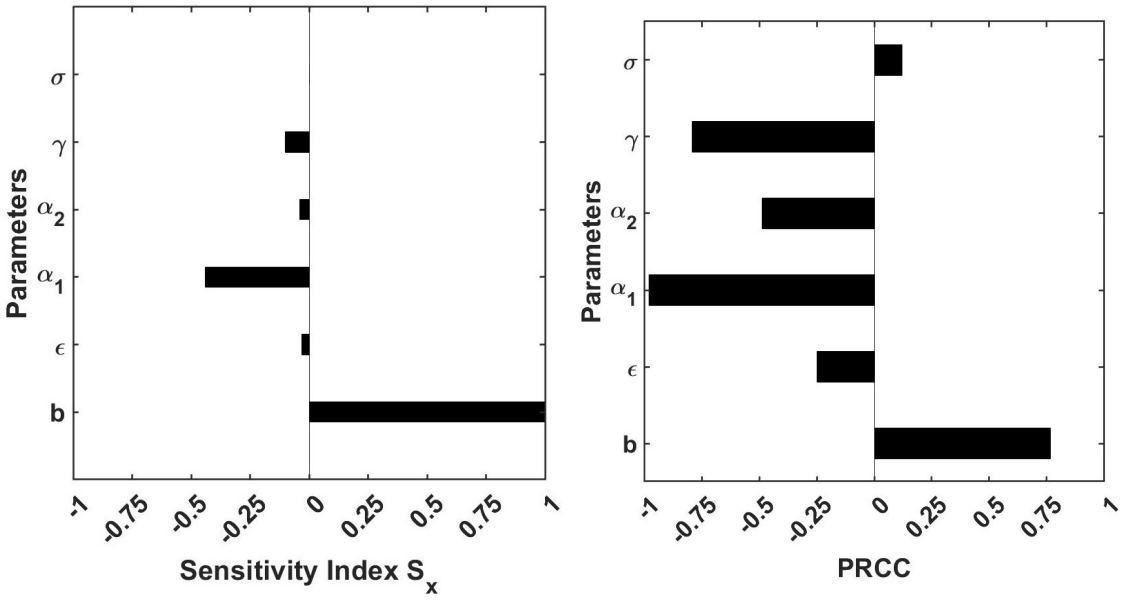
$$S_x = \left(\frac{x}{R_0}\right)\left(\frac{\partial R_0}{\partial x}\right).$$

On the basis of the sensitivity index S_x, we found that the parameter b affects R_0 highly than the other parameters. Then the second parameter affecting R_0 is α_1, and then it is followed by other parameters like $\epsilon, \alpha_2, \gamma,$ and σ, while the effect of σ to R_0 seems negligible Figure 4a.

By taking the 1000 sample points from the global parameters, the sensitivity analysis is extended to the global sensitivity by using Latin Hypercube Sampling (LHS) [28]. To Identify the most influential parameter to the R_0 we utilize the partial rank correlation coefficients (PRCC). in the global parameter space, we found that the parameter α_1 is the most strongly effective parameter to R_0, and then it is followed by $\gamma, b, \alpha_2, \epsilon$ and while σ is least effective (Figure 4b).

4.4 Effect of vaccination on disease dynamics

We performed the impact of the vaccination on the epidemic dynamics. After the reduction of children's vaccination (α_1) by 50%, the model predicts that the incidence cases will reach



(a) Local sensitivity of R_0

(b) Global sensitivity of R_0

Figure 4

the peak value of 13,251 hundred in 2037. In the absence of adult vaccination (α_2), the model prediction shows that rising of cases with a peak value of 2051 hundred in 2061. If the vaccination immunization rate is reduced by 33%, it will impact the increment of the cases and will reach to the peak value of about 4,435 hundred in 2054. And similarly the reduction of effectiveness of vaccination is decreased by 50%, the cases may rise and attain the peak value of 1960 hundred in 2050.

5 Conclusion

Despite the accessibility of vaccines, measles is growing as a global hazard to reducing child mortality and morbidity. More than 5.5 million people worldwide were not immunized between 2010 and 2017, including in high-income nations like the United States, the United Kingdom, France, Argentina, etc, so that, the vaccination rate is below the threshold of WHO-recommendation [29]. Additionally, there have been several anti-vaccine protests throughout the globe ([30, 31]) that have contributed to the epidemic in 2018-2019 (which mostly affected the USA) ([32, 33]).

To reduce mortality and morbidity rates due to measles, the Nepal government has implemented immunization programs like the Comprehensive Immunization Multi-Year Plan (2007-2011), (2011-2016), and (2012-2013) through Routine Immunization Program (RIP) and Supplementary Immunization Activities (SIAs). Behind these activities, the increasing

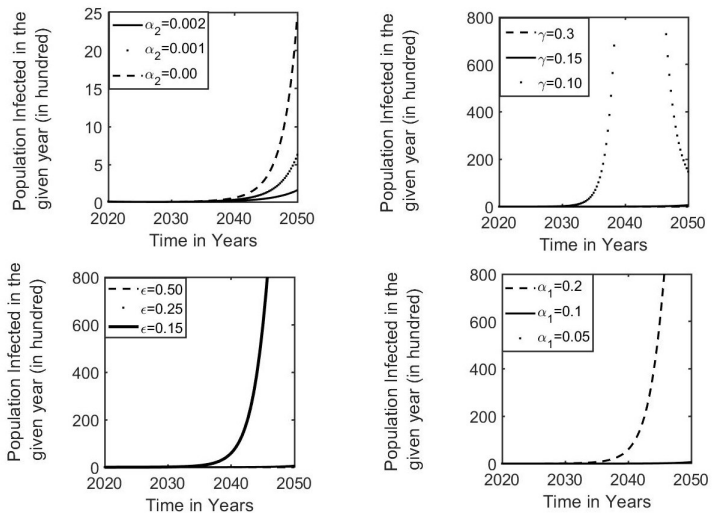


Figure 5: **Long run effect of control measures:** Model prediction of the present contest and model prediction after the reduction of the vaccines for children and adults, its immunization and effectiveness

number of ongoing measles cases in different ages of individuals after 2017 in various districts, including Rautahat, Kapilvastu, Morang, Bajura, etc.[7, 34, 35], became the primary focus of this study. We developed a deterministic model to explore the effect of vaccination in the different age groups particularly two different groups of age below and above fifteen years. We also incorporate the vaccinated population may skip the complete dose of vaccine (the two doses of vaccines are the complete dose for measles) and may lose the effectiveness of the vaccine so that they lose their immunity and can be back to susceptible.

From our study, in Nepal there will still be ten incidence cases in 2023, which would be eradicated by 2023 if child vaccination rates (α_1) increased by more than 50% or adult vaccination rates (α_2) increased by more than 400%. So we may infer that children's vaccination rates need to be raised to eradicate the disease by that year. Otherwise, the illness won't be able to be eradicated under the existing circumstances. Though the epidemic dynamic is extremely slow, the model forecasts that current trends will lead to a decline in cases to nine in 2027. Subsequently, there will be a gradual increase reaching the highest value of 153,967 cases in 2066.

Declaration of competing interest

The authors declare there is no conflicts of interest.

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