

Controlling measles transmission dynamics with optimal control analysis

Chinwendu E. Madubueze*

Isaac O. Onwubuya†

Iorwuese Mzungwega‡

Abstract

In this paper, a deterministic model for the transmission dynamics of measles infection with two doses of vaccination and isolation is studied. The disease-free equilibrium state and basic reproduction number, R_0 , of the model are computed. The sensitivity analysis of the model parameters is carried out using the Latin Hypercube Sampling (LHS) scheme in order to ascertain the parameters that contribute to the spread of measles in the population. The result of the sensitivity analysis shows that transmission rates, vaccination rates and isolation of the infected persons in the prodromal stage are significant parameters to be targeted for the eradication of measles infection. Based on the result of sensitivity analysis, an optimal control model with nutritional support as a control is developed. The analysis of optimal control model is carried out using Pontryagin's maximum principle to identify the optimal control strategies to be adopted by public health practitioners and policy health makers in curtailing the spread of measles infection. The result of the optimal control analysis via numerical simulations revealed that combined timely implementation of correct administration of the two doses of vaccination, isolation of infected persons in the prodromal stage and mass distribution of nutritional support would curtail the measles disease outbreak in the population. However, in a situation where there is a limited facility to isolate the infected persons in the prodromal stage, the combined implementation of mass distribution of nutritional support and administration of the two doses of vaccination will still eradicate measles infection in the population.

Keywords: Measles; Nutritional Support; Vaccination; Isolation; Sensitivity Analysis; Pairwise Comparison; Optimal Control Analysis.

2010 AMS subject classification: 49K15, 49K40, 90C31, 34D20, 34C60.

* Joseph Sarwuan Tarka Univerisity, Makurdi, Nigeria; ce.madubueze@gmail.com.

† Joseph Sarwuan Tarka Univerisity, Makurdi, Nigeria; isaacobiajulu@gmail.com.

‡ Joseph Sarwuan Tarka Univerisity, Makurdi, Nigeria.

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1. Introduction

Measles is a viral infectious disease caused by a single-stranded RNA virus that belongs to the group of Morbilliviruses of the Paramyxoviridae family. It is a seasonal disease that occurs mostly during the dry season in tropical zones where it is endemic and it peaks during late winter and early spring in temperate zones [24]. Non-immune people are infected via direct contact with the nasal and oral secretions or inhaling the aerosol droplets of an infected person. 90% of non-immune people are exposed to an infective and have the chance of being infected with measles disease [24, 27]. Measles has an average of 10 - 12 days incubation from exposure to the prodromal stage [28], which spans for seven days of the infection period, after which the infective recovers with lifelong immunity against the disease. The symptoms of measles are based on different stages of the disease. Prodromal stage symptoms include high fever, runny nose (coryza), cough, and red eyes (conjunctivitis) that lasts 2 to 4 days with a range of 1- 7 days, while the rash stage symptoms occur a few days after the initial symptoms. The rash stage can lead to fatal complications or death if not treated early [10,12].

Annually, measles affects up to 20 million people worldwide and most cases are from Africa and Asia [24]. According to a report from World Health Organization and United State Center for Diseases Control and Prevention (CDC) [44, 45], 869,770 infection cases with 207,500 deaths of Measles were recorded globally in 2019, making it the highest number since the 1996 outbreak and has 50% increment as of 2016. For sub-Saharan Africa, about 134,200 measles deaths were recorded in 2015, while Nigeria recorded a significant increase of 28,400 cases in 2019 compared with 5,067 cases in 2018. Despite the cases dropping to 9,316 in 2020, the confirmed cases of measles remain high, and the case fatality is yet to be eased anytime there is an outbreak. This implies a need for comprehensive efforts and intervention strategies to reduce the menace of measles is crucial. Therefore, it is necessary to examine the optimal strategy that can be implemented to control measles disease in high-burden countries.

According to WHO, the two major strategies to eradicate measles are vaccine and treatment [21, 23]. Isolation of infected people is also important in preventing further spread of the disease but increasing population immunity through vaccination remains the most effective way to prevent outbreaks of measles in a community [22]. The vaccination is mainly based on MMR (measles, mumps, and rubella) and MMRV (measles, mumps, rubella, and varicella) vaccines. These vaccines are about 95% effective as they globally prevent 4.5 million deaths yearly [16]. There are two doses of MMR vaccine. The first dose produces 90 to 95% immunity to measles while the second dose produces a stronger immunity for those that do not respond to the first dose [17]. Among the childhood vaccine-preventable diseases, measles causes the most deaths in children. Measles outbreaks is prevented in a community if 90% to 95% of children are vaccinated.

Mathematical models of infectious diseases are useful in studying transmission dynamics of diseases, testing theories, planning, implementing, evaluating and comparing various control programs that will prevent the further spread of diseases and their epidemics. A notable number of mathematical models have been elaborated and applied to infectious diseases like measles [4, 7, 9, 18, 25]. Some authors, like [8, 10, 19],

developed an SEIR model of measles where testing and diagnosis therapy was incorporated as in [10] at the latent period. Authors [15, 20] considered the effect of supplemental immunization activities as an optimal policy for measles using an age-stratified compartmental model. Stephen *et al.* [17] revealed that the spread of measles disease largely depends on the contact rates with infected people within a population and the disease dies out in the population if the proportion of the population that is immune exceeds the herd immunity level. Vaccination is considered in the autonomous models [3, 4, 11, 13, 19, 29] as constant parameter or compartment for vaccinated people, while in [27-31], it is examined as a time-dependent control function to determine the optimal vaccination strategy that can be implemented to control measles in high-burden countries. Although [30 – 35] considered optimal control of vaccination for measles but the effect of two doses of vaccination and nutritional support are not examined. However, the authors [3, 37, 40] examined the effect of two doses of vaccination and isolation on measles disease as constant parameters without nutritional support impact and optimal control analysis. As advised by WHO [46], it is important to consider the effect of two doses of vaccination and nutritional support on measles transmission dynamics, which forms the study's motivation. This involves modification of the model by [3] to investigate the impact of the two doses of vaccination, nutritional support and isolation on measles dynamics using sensitivity analysis and optimal control analysis approaches. This will help to provide the mathematical analysis of the possible control strategy (vaccine and nutritional support) that will help the public health practitioners to achieve the best strategy for the prevention and control of the spread of measles in community.

The rest of the paper is organized as follows: Section 2 is the model formulation for measles with constant control measures. The model analysis is discussed in Section 3 which includes sensitivity analysis. We obtained the optimal control of the formulated model in Section 4. In Section 5, we carried out numerical simulation to verify some analytic results and their discussion, while Section 6 is the conclusion.

2. Model formulation

A deterministic model for measles disease is presented by modifying the model by Aldila and Asrianti [3]. The total population at any time (t) denoted by $N(t)$, is subdivided into Susceptible persons, $S(t)$, Exposed persons, $E(t)$, Infected persons in prodromal stage, $P(t)$, Infected persons in rash stage, $I(t)$, Isolated persons, $J(t)$, 1st dose of vaccinated persons, $V_1(t)$, 2nd dose of vaccinated persons, $V_2(t)$, and Recovered persons, $R(t)$ such that

$$N = S + E + P + I + J + V_1 + V_2 + R. \quad (1)$$

The susceptible persons, $S(t)$, decreases when they come in contact with the infected persons at a force of infection, λ_1 and become exposed person or by vaccination with 1st dose vaccine at a rate, ε_1 . The persons vaccinated with 1st dose vaccine may be

infected at a force of infection, λ_2 since vaccine is not 100% efficacy. The force of infections, λ_1 and λ_2 , are given by

$$\left. \begin{aligned} \lambda_1 &= \frac{\beta_1(P+n_1I+n_2J)}{N} \\ \lambda_2 &= \frac{\beta_2(P+n_1I+n_2J)}{N} \end{aligned} \right\} \quad (2)$$

where β_1 and β_2 are the transmission rate for the susceptible and 1st dose vaccinated persons respectively, n_1 and n_2 are the parameters that reduce the infectivity of the infected persons in the rash stage and isolated persons respectively.

The 1st dose of vaccinated persons, $V_1(t)$ receive 2nd dose vaccine at a rate, ε_2 and achieve immunity at the rate, σ . The exposed persons, $E(t)$, becomes infected persons in the prodromal stage, $P(t)$ at a rate, k after incubation period of measles disease. The infected persons in the prodromal stage, $P(t)$, then progress to rash stage at a rate, α while some are isolated for further treatment at a rate, φ_1 or they recovered at a rate, δ_1 . In a similar way, the infected persons at the rash stage, $I(t)$, are isolated at a rate, φ_2 or recovered from measles at a rate, δ_2 . Meanwhile, the isolated persons recovered at a rate, δ_3 . It is assumed that all the subpopulations experience natural death at a rate, μ and the subpopulations, $I(t)$ and $J(t)$ may die of measles disease at d_1 and d_2 respectively.

The model description and details of the model parameters are presented in Figure 1 and Table 1. respectively.

With Figure 1 and Table 1, the transition within subpopulations are expressed by the following system of first order differential equations;

$$\left. \begin{aligned} \frac{dS}{dt} &= \Lambda - \lambda_1 S - (\varepsilon_1 + \mu)S, \\ \frac{dV_1}{dt} &= \varepsilon_1 S - (\lambda_2 + \varepsilon_2 + \mu)V_1, \\ \frac{dV_2}{dt} &= \varepsilon_2 V_1 - (\mu + \sigma)V_2, \\ \frac{dE}{dt} &= \lambda_1 S + \lambda_2 V_1 - (\mu + k)E, \\ \frac{dP}{dt} &= kE - (\alpha + \mu + \varphi_1 + \delta_1)P, \\ \frac{dI}{dt} &= \alpha P - (\varphi_2 + \delta_2 + \mu + d_1)I, \\ \frac{dJ}{dt} &= \varphi_1 P + \varphi_2 I - (\delta_3 + \mu + d_2)J, \\ \frac{dR}{dt} &= \sigma V_2 + \delta_1 P + \delta_2 I + \delta_3 J - \mu R \end{aligned} \right\} \quad (3)$$

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where $\lambda_1 = \frac{\beta_1(P+n_1I+n_2J)}{N}$, $\lambda_2 = \frac{\beta_2(P+n_1I+n_2J)}{N}$ and the initial conditions, $S(0) > 0, V_1(0) \geq 0, V_2(0) \geq 0, E(0) \geq 0, P(0) \geq 0, I(0) \geq 0, J(0) \geq 0, R(0) \geq 0$. The model parameters are assumed to be nonnegative except recruitment rate, Λ , that is strictly positive.

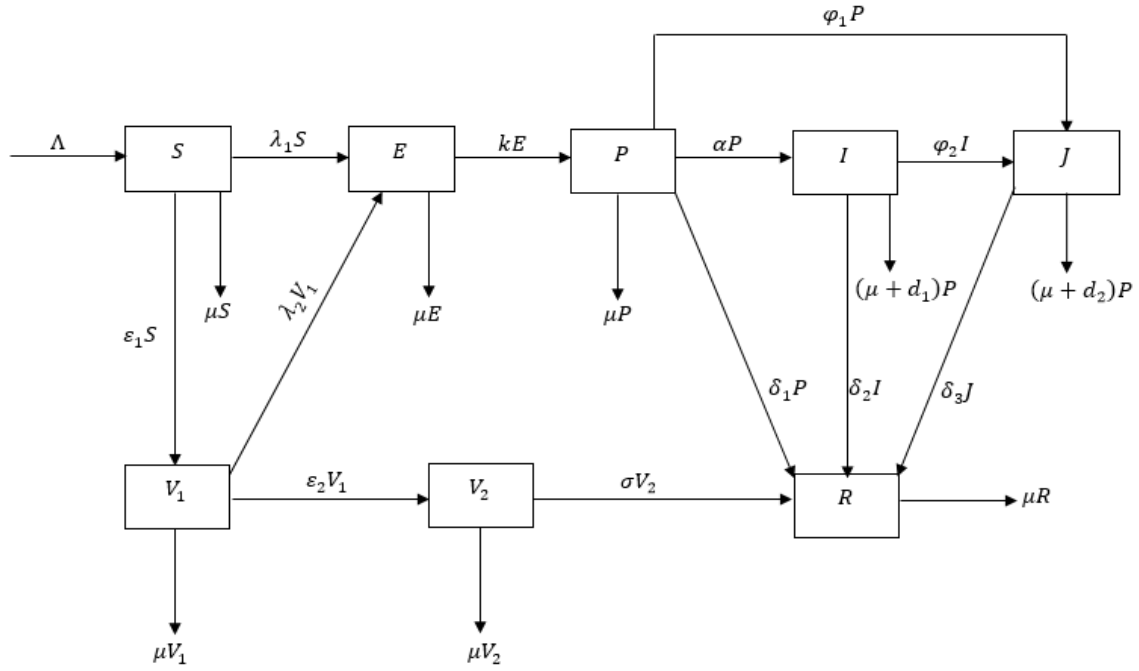


Figure 1. Model flow diagram for transmission dynamics of measles disease.

Table 1. Parameters and their descriptions

Parameters	Parameters Description	(Ranges)Nominal values	Sources
Λ	Recruitment rate	(-)2000	[1]
β_1	Transmission rate for $S(t)$	(0.0004 – 0.5)0.6	Assumed
β_2	Transmission rate for $V(t)$	(0.0003 – 0.4)0.5	Assumed
ε_1	Vaccination rate of first dose vaccine	(0.01 – 0.95)0.6	[38]
ε_2	Vaccination rate of second dose vaccine	(0.01 – 0.95)0.01	Assumed
n_1	Infectivity reduction rate of $I(t)$	(-)0.1	[3]
n_2	Infectivity reduction rate of $J(t)$	(-)0.01	[3]
μ	Natural death rate	(-) 1/65.365	[3]
k	Progression rate from $E(t)$ to $P(t)$	(-)0.09	[1]
δ_1	Recovery rate for $P(t)$ class	(-)0.2	[3]
δ_2	Recovery rate for $I(t)$ class	(-)0.06	Assumed
δ_3	Recovery rate for $J(t)$ class	(-)0.3121	[36]
d_1	Disease-related death rate for $I(t)$ class	(-)0.125	[39]
d_2	Disease-related death rate for $J(t)$ class	(-)0.1	[1]
α	Progression rate from $P(t)$ to $I(t)$	(-)0.003	Assumed
ω_1	Isolation rate for $P(t)$ class	(0.0001 – 0.05)0.01	[1]
ω_2	Isolation rate for $I(t)$ class	(0.001 – 0.5)0.001	Assumed
σ	Recovery rate due to 2 nd dose of vaccine	(-)0.01	[38]

3. Model analysis

Here, the system (3) is establish to show well-posedness of the model that makes biological sense. This is done by proving the existence of nonnegative solution and its boundedness given initial solutions of the model.

Theorem 1. With the initial solutions, $S(0) > 0$, $V_1(0) \geq 0$, $V_2(0) \geq 0$, $E(0) \geq 0$, $P(0) \geq 0$, $I(0) \geq 0$, $J(0) \geq 0$, $R(0) \geq 0$, the model equation (3) has non-negative solutions for all time, $t > 0$.

Proof. Let $t_1 = \sup\{t > 0: S(0) > 0, V_1(0) \geq 0, V_2(0) \geq 0, E(0) \geq 0, P(0) \geq 0, I(0) \geq 0, J(0) \geq 0, R(0) \geq 0\} \in [0, t]$.

From the first equation of system (3), we have

$$\frac{dS}{dt} = \Lambda - \lambda_1 S - \varepsilon_1 S - \mu S \geq -(\varepsilon_1 + \mu + \lambda_1)S.$$

Applying the method of integrating factor with initial condition, $S(0)$, we have

$$S(t) \geq S(0) \exp \left\{ - \int_0^t (\varepsilon_1 + \mu + \lambda_1) t_1 \right\} > 0$$

which is always positive for $t > 0$.

In similar way, $V_1(t) > 0, V_2(t) > 0, E(t) > 0, P(t) > 0, I(t) > 0, J(t) > 0, R(t) > 0$ for $t > 0$. This means that the solution set $\{S(t), V_1(t), V_2(t), E(t), P(t), I(t), J(t), R(t)\}$ of the system (3) is non-negative for all $t > 0$.

To show the boundedness of the solutions of the system (3), we state and prove feasible region of the system (3).

Theorem 2. The solutions of system (3) are contained in the feasible region, $\Omega = \{(S, V_1, V_2, E, P, I, J, R) \in \mathfrak{R}_+^8: N \leq \frac{\Lambda}{\mu}\}$ with the non-negative initial conditions.

Proof. To obtain the total population, $N(t)$, we sum up the equations of system (3) to yields

$$\frac{dN}{dt} = \Lambda - \mu N - d_1 I - d_2 J \leq \Lambda - \mu N. \quad (4)$$

Applying Gronwall's inequality with the initial condition, $N(0) = N_0$ in equation (4) gives

$$N(t) \leq \frac{\Lambda}{\mu} + \left[N_0 - \frac{\Lambda}{\mu} \right] e^{-\mu t}. \quad (5)$$

If $N_0 > (<) \frac{\Lambda}{\mu}$, the total population, N , tends to $\frac{\Lambda}{\mu}$ as $t \rightarrow \infty$. Thus, in either case, the total population, $N(t) \rightarrow \frac{\Lambda}{\mu}$ as $t \rightarrow \infty$ in (5). Hence, the solution set of system (3) will enter the feasible region, Ω that is positively invariant.

3.1 Existence of disease-free equilibrium state and basic reproduction number

Disease-free equilibrium state occurs when there is no infection in the population, that is when the infected state variables are zero.

Solving simultaneously at equilibrium state, $\frac{dS}{dt} = 0$, $\frac{dV_1}{dt} = 0$, $\frac{dV_2}{dt} = 0$, $\frac{dE}{dt} = 0$, $\frac{dP}{dt} = 0$, $\frac{dI}{dt} = 0$, $\frac{dJ}{dt} = 0$, $\frac{dR}{dt} = 0$ of the system (3) gives the disease-free equilibrium state,

$$E_0 = (S^0, V_1^0, V_2^0, E^0, P^0, I^0, J^0, R^0) \\ = \left(\frac{\Lambda}{(\varepsilon_1 + \mu)}, \frac{\varepsilon_1 \Lambda}{f(\varepsilon_1 + \mu)}, \frac{\varepsilon_1 \varepsilon_2 \Lambda}{f(\sigma + \mu)(\varepsilon_1 + \mu)}, 0, 0, 0, 0, \frac{\sigma \varepsilon_1 \varepsilon_2 \Lambda}{\mu f(\sigma + \mu)(\varepsilon_1 + \mu)} \right) \quad (6)$$

with $f = \varepsilon_2 + \mu$.

Basic Reproduction Number, R_0

The basic reproduction number is a threshold quantity that determines the persistence and eradication of the infectious disease in the population, making it the most important quantity in infectious disease epidemiology. It is defined as the mean number of persons infected when a single infective is introduced into a wholly susceptible population [6]. R_0 is computed using the next-generation matrix approach [6].

Following the approach in [6], the rate of new infection, $\mathcal{F}_i$, and the rate of transitional terms, $\mathcal{V}_i$, in compartment i , of the system (3) are given as

$$\mathcal{F}_i = \begin{pmatrix} \frac{\beta_1(P+n_1I+n_2J)S}{N} + \frac{\beta_2(P+n_1I+n_2J)V_1}{N} \\ 0 \\ 0 \\ 0 \end{pmatrix}, \mathcal{V}_i = \begin{pmatrix} gE \\ -kE + hP \\ -\alpha P + pI \\ -\varphi_1 I - \varphi_2 P + qJ \end{pmatrix},$$

where $i = 1, \dots, 4$ is the number of infected compartments and

$$g = (\mu + k), h = (\alpha + \varphi_1 + \delta_1 + \mu), p = (\varphi_2 + \delta_2 + \mu + d_1), q = (\delta_3 + \mu + d_2). \quad (7)$$

Taking the partial derivative of $\mathcal{F}_i$ and $\mathcal{V}_i$ with respect to E, P, I and J at DFE, E_0 , we have respective Jacobian matrices

$$F = \begin{pmatrix} 0 & \frac{(\beta_1 S^0 + \beta_2 V_1^0)}{N^0} & \frac{n_1(\beta_1 S^0 + \beta_2 V_1^0)}{N^0} & \frac{n_2(\beta_1 S^0 + \beta_2 V_1^0)}{N^0} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \\ V = \begin{pmatrix} g & 0 & 0 & 0 \\ -k & h & 0 & 0 \\ 0 & -\alpha & p & 0 \\ 0 & -\varphi_1 & -\varphi_2 & q \end{pmatrix},$$

where

$$N^0 = S^0 + V_1^0 + V_2^0 + E^0 + P^0 + I^0 + J^0 + R^0 = \frac{\Lambda}{\mu}.$$

The inverse of V is given as

$$V^{-1} = \begin{pmatrix} \frac{1}{g} & 0 & 0 & 0 \\ \frac{k}{gh} & \frac{1}{h} & 0 & 0 \\ \frac{\alpha k}{ghp} & \frac{\alpha}{hp} & \frac{1}{p} & 0 \\ \frac{k(\alpha\varphi_2+p\varphi_1)}{ghpq} & \frac{(\alpha\varphi_2+p\varphi_1)}{hpq} & \frac{\varphi_2}{pq} & \frac{1}{q} \end{pmatrix}.$$

With definition of basic reproduction number, R_0 , as the spectral radius of matrix, FV^{-1} , we have

$$R_0 = \frac{(\beta_1 S^0 + \beta_2 V_1^0)}{N^0} \left[\frac{k}{gh} + \frac{\alpha k n_1}{ghp} + \frac{k n_2 (\alpha\varphi_2 + p\varphi_1)}{ghpq} \right].$$

With the substitution of $S^0 = \frac{\Lambda}{\varepsilon_1 + \mu}$, $V_1^0 = \frac{\varepsilon_1 \Lambda}{f(\varepsilon_1 + \mu)}$ and $N^0 = \frac{\Lambda}{\mu}$, we have

$$R_0 = \frac{\mu(\beta_1 f + \beta_2 \varepsilon_1)}{f(\varepsilon_1 + \mu)} \left[\frac{k}{gh} + \frac{\alpha k n_1}{ghp} + \frac{k n_2 (\alpha\varphi_2 + p\varphi_1)}{ghpq} \right].$$

By the virtue of next-generation matrix approach [6], the disease-free equilibrium, E_0 , of system (3) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. This means that the measles infection will die out in the population if $R_0 < 1$ while it will persist in the population when $R_0 > 1$.

3.2 Sensitivity analysis

Sensitivity analysis plays an important role in examining the effect, influence and contribution of the parameters of a mathematical model to the model output. To know the type of intervention strategies to adopt in reducing the transmission and prevalence of any disease, sensitivity analysis is carried-out to determine the biological significance of the model parameters in relation to the reproduction number, R_0 . We adopt the Latin Hypercube Sampling (LHS) scheme used by [41,42,43] with the Partial Rank Correlation Coefficients (PRCCs) procedure to assess the biological implications of each input parameter to the output parameter, the disease threshold, R_0 . This type of approach provides numerical results that enable us to explore the entire parameter space simultaneously, thereby producing an unbiased selection of the parameter values. The

sign (positive or negative) of the PRCCs indicates the precise strength of the relationship between the input variables (parameters of the model) and the output variable, R_0 in this case. It also provides an insight to the degree of monotonicity between the parameters of the model and R_0 . Thus, comparing the values of PRCC enabled us to directly evaluate the impact of the model parameters on R_0 .

Figure 2 shows the PRCCs for some important parameters of the model. The parameters β_1 and β_2 have positive PRCCs meaning increasing their values increase R_0 , which in return increase the spread of measles infection in the population. Whereas, the parameters ε_1 , ε_2 , ω_1 and ω_2 with negative PRCCs reduce the value of R_0 when they are increased. They have the capacity of ameliorate the spread of measles infection in the population, which leads to the eradication of the disease in the population. However, the parameter ω_2 has a small magnitude of PRCC that is non-monotonically related to R_0 but it can still produce a change in the transmission dynamics of measles infection. In other to identify the model parameters that are significant in curtailing or enhancing the spread of measles disease, the Fisher Transformation is applied to the PRCCs to compute the p-values of each of the model parameters as used in [42]. This is shown in Table 2. It is observed in Table 2 that the parameters, $(\beta_1, \beta_2, \varepsilon_1, \varepsilon_2, \omega_1)$ have p-values that are significant while the parameter, ω_2 , has an insignificance p-value. This is further shown in Figure 3 as scatterplots for R_0 against some model parameters. From Figure 3, it is observed that the parameters $(\beta_1, \beta_2, \varepsilon_1, \varepsilon_2, \omega_1)$ have a significant impact on R_0 than ω_2 .

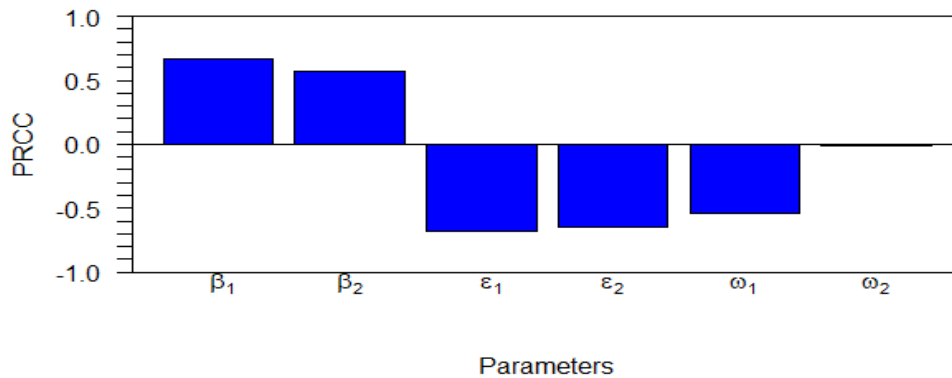


Figure 2. Tornado plot for some significant model parameters.

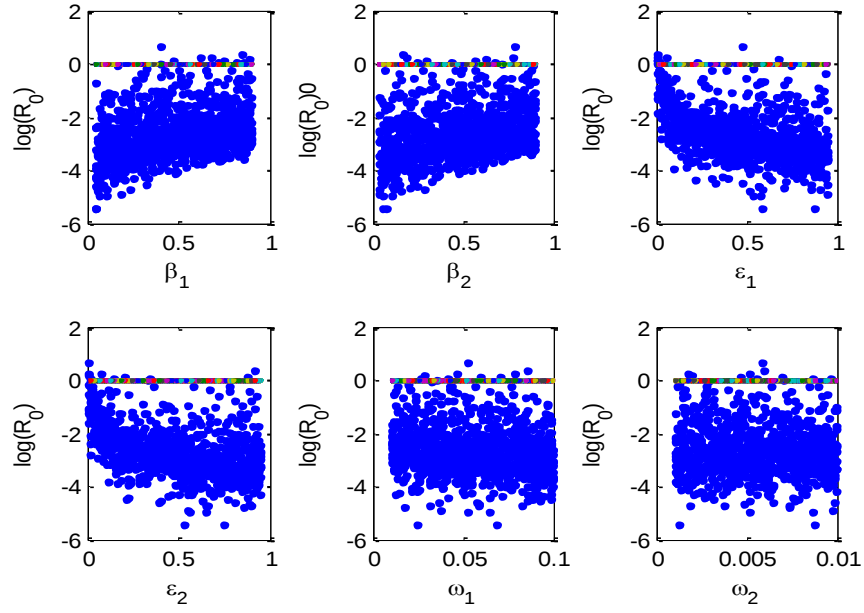


Figure 3. Monte Carlo simulations for some important parameters of the model generated using the parameter values in Table 1. In each simulation run, 1000 randomly selected parameters were used.

Table 2. Parameter PRCC significance (unadjusted p-value)

Parameter	PRCC	p-value	Keep
β_1	0.65564141	0.0000	TRUE
β_2	0.57787305	0.0000	TRUE
ϵ_1	-0.67496222	0.0000	TRUE
ϵ_2	-0.65937154	0.0000	TRUE
ω_1	-0.54171573	0.0000	TRUE
ω_2	-0.01142558	0.7049	FASLE

Table 3. Pairwise PRCC Comparisons (unadjusted p-values)

	β_1	β_2	ε_1	ε_2	ω_1
β_1		0.00506	0	0	0
β_2			0	0	0
ε_1				0.5314	2.048×10^{-6}
ε_2					3.743×10^{-5}
ω_1					

Table 4. Pairwise PRCC Comparisons (FDR Adjusted p-values)

	β_1	β_2	ε_1	ε_2	ω_1
β_1		0.005622	0	0	0
β_2			0	0	0
ε_1				0.5314	2.926×10^{-6}
ε_2					4.679×10^{-5}
ω_1					

Table 5. Parameters different after FDR adjustment?

	β_1	β_2	ε_1	ε_2	ω_1
β_1		TRUE	TRUE	TRUE	TRUE
β_2			TRUE	TRUE	TRUE
ε_1				FASLE	TRUE
ε_2					TRUE
ω_1					

Tables 3 and 4 show the pairwise comparison of the important parameters of the model, whose p-values are less than 0.05, in other to establish if there exist any difference between the processes describing the compared parameters. The results of the pairwise PRCC comparison for the unadjusted p-values and the false discovery rate (FDR) adjusted p-values are presented in Table 3 and Table 4, respectively. With the FDR adjusted p-values in Table 4, we present the parameters different in Table 5. If the p-values of the compared pair of significant parameters are less than 0.05, we say that they

are different (TRUE); otherwise not different (FALSE). We also noted from Table 5, that apart from $\epsilon_1 - \epsilon_2$ pair, all other pairs of parameters are significantly different.

The parameters $\beta_1, \beta_2, \epsilon_1, \epsilon_2, \omega_1$ play a vital role in the eradication of the measles disease. The spread of measles infection will reduce drastically if the value of R_0 is less than a unity ($R_0 < 1$), which implies reducing the values of β_1 and β_2 as well as increasing the values of $\epsilon_1, \epsilon_2, \omega_1$. This establishes that isolating the infected individuals in the prodromal stage and minimizing contact with infected persons (both at the prodromal and rash stage) will eradicate the spread of measles in the population. Also, increasing the rate of correct administration of vaccines (first and second dose) will go a long way in reducing the number of infected individuals as many susceptible people will be protected by vaccination thereby minimize the spread of measles before and during the epidemic.

4. Optimal control analysis

Optimal control has been extensively applied as a strategy in controlling many epidemic outbreaks. The main idea of applying the optimal control to measles epidemics is to choose among the available strategies, the most suitable and effective strategies that will reduce the measles infection rate to a minimum level while optimizing the cost of deploying these strategies [26]. In terms of measles epidemics, such strategy can include therapies, vaccines, isolation and educational campaigns [5].

Based on the result of the sensitivity analysis, the functions, $u_1(t), u_2(t), u_3(t), u_4(t)$, are considered as time-dependent control functions where $u_1(t)$ is mass distribution of nutrition (supplement) support that reduces the transmission rates, $u_2(t)$ is the first dose vaccination control, $u_3(t)$ is the second dose vaccination control and $u_4(t)$ is isolation of infected people in the prodromal stage. The nutritional support is to boost the immune system of the body. Thus, the optimal control model of the system (3) is given by

$$\left. \begin{aligned} \frac{dS}{dt} &= \Lambda - \frac{(1-u_1(t))\beta_1(P+n_1I+n_2J)S}{N} - \epsilon_1 u_2(t)S - \mu S, \\ \frac{dV_1}{dt} &= \epsilon_1 u_2(t)S - \frac{(1-u_1(t))(1-u_2(t))\beta_2(P+n_1I+n_2J)V_1}{N} - \epsilon_2 u_3(t)V_1 - \mu V_1, \\ \frac{dV_2}{dt} &= \epsilon_2 u_3(t)V_1 - (\mu + \sigma)V_2, \\ \frac{dE}{dt} &= \frac{(1-u_1(t))\beta_1(P+n_1I+n_2J)S}{N} + \frac{(1-u_1(t))(1-u_2(t))\beta_2(P+n_1I+n_2J)V_1}{N} - (\mu + k)E, \\ \frac{dP}{dt} &= kE - (\alpha + \mu + \varphi_1 + u_4(t) + \delta_1)P, \\ \frac{dI}{dt} &= \alpha P - (\varphi_2 + \delta_2 + \mu + d_1)I, \\ \frac{dJ}{dt} &= \varphi_1 P + u_4(t)P + \varphi_2 I - (\delta_3 + \mu + d_2)J, \\ \frac{dR}{dt} &= \sigma V_2 + \delta_2 I + \delta_1 P + \delta_3 J - \mu R. \end{aligned} \right\} \quad (8)$$

These control functions are bounded, Lebesgue integrable functions that satisfy $0 \leq u_1 \leq 1$, $0 \leq u_2 \leq 0.95$, $0 \leq u_3 \leq 0.95$ and $0 \leq u_4 \leq 1$ with assumption that the highest vaccination coverage will be 95%.

The goal is to minimize the number of infected people $(P(t), I(t), J(t))$ and maximize the number of susceptible people $S(t)$ while minimizing the cost of controls. Therefore, the objective function is given as

$$\Gamma(u_1, u_2, u_3, u_4) = \int_0^{t_f} \left(bP + cI + dJ + \frac{1}{2} \sum_{i=1}^4 m_i u_i^2(t) \right) dt \quad (9)$$

and is subject to equation (8) with the initial conditions of the system (3).

In equation (9), the constants, $b, c, d, m_1, m_2, m_3, m_4$, are positive weights to balance the size of the terms attached with them and t_f is the final time to implement the controls, $u_1(t), u_2(t), u_3(t), u_4(t)$. The terms, bP, cI, dJ are the cost related to reducing the number of infected people, (P, I, J) such as cost of the mass distribution of nutrition (supplement) support, isolation and vaccination, first dose and second dose vaccination at the due time.

We seek optimal controls $u_1^*, u_2^*, u_3^*, u_4^*$ such that

$$\Gamma(u_1^*, u_2^*, u_3^*, u_4^*) = \min\{\Gamma(u_1, u_2, u_3, u_4) | u_1, u_2, u_3, u_4 \in U\}. \quad (10)$$

With the application of Pontryagin's maximum principle [14], the equations (8) and (9) are converted into a problem of minimizing pointwise a Hamiltonian, H with respect to u_1, u_2, u_3, u_4 . This is given by

$$\begin{aligned} H = & bP + cI + eJ + \frac{m_1 u_1^2(t)}{2} + \frac{m_2 u_2^2(t)}{2} + \frac{m_3 u_3^2(t)}{2} + \frac{m_4 u_4^2(t)}{2} + \zeta_1 \left(\Lambda - \right. \\ & \left. \frac{(1-u_1(t))\beta_1(P+n_1I+n_2J)S}{N} - \varepsilon_1 u_2(t)S - \mu S \right) + \zeta_2 \left(\varepsilon_1 u_2(t)S - \right. \\ & \left. \frac{(1-u_1(t))(1-u_2(t))\beta_2(P+n_1I+n_2J)V_1}{N} - \varepsilon_2 u_3(t)V_1 - \mu V_1 \right) + \zeta_3 (\varepsilon_2 u_3(t)V_1 - (\mu + \sigma)V_2) + \\ & \zeta_4 \left(\frac{(1-u_1(t))\beta_1(P+n_1I+n_2J)S}{N} + \frac{(1-u_1(t))(1-u_2(t))\beta_2(P+n_1I+n_2J)V_1}{N} - (\mu + k)E \right) + \zeta_5 (kE - \\ & (\alpha + \mu + \varphi_1 + u_4(t) + \delta_1)P) + \zeta_6 (\alpha P - (\varphi_2 + \delta_2 + \mu + d_1)I) + \zeta_7 (\varphi_1 P + \\ & u_4(t)P + \varphi_2 I - (\delta_3 + \mu + d_2)J) + \zeta_8 (\sigma V_2 + \delta_2 I + \delta_1 P + \delta_3 J - \mu R) \end{aligned}$$

with $\zeta_1, \zeta_2, \zeta_3, \zeta_4, \zeta_5, \zeta_6, \zeta_7, \zeta_8$ as respective adjoint variables for the state variables, $S, V_1, V_2, E, P, I, J, R$.

The system of adjoint variables are derived by taking the partial derivative of H with respect to each of their corresponding state variables. This is given by

$$\left. \begin{aligned}
 \frac{d\zeta_1}{dt} &= -\frac{\partial H}{\partial S} = a + A \left(1 - \frac{S}{N}\right) (\zeta_1 - \zeta_4) + BV_1(\zeta_4 - \zeta_2) \\
 &\quad + \zeta_1\mu + \varepsilon_1 u_2(t)(\zeta_1 - \zeta_2), \\
 \frac{d\zeta_2}{dt} &= -\frac{\partial H}{\partial V_1} = BN \left(1 - \frac{S}{N}\right) (\zeta_2 - \zeta_4) + \frac{AS}{N} (\zeta_4 - \zeta_1) + \zeta_2\mu \\
 &\quad + \varepsilon_2 u_3(t)(\zeta_2 - \zeta_3), \\
 \frac{d\zeta_3}{dt} &= -\frac{\partial H}{\partial V_2} = BV_1(\zeta_4 - \zeta_2) + \frac{AS}{N} (\zeta_4 - \zeta_1) + \sigma(\zeta_3 - \zeta_8) + \zeta_3\mu, \\
 \frac{d\zeta_4}{dt} &= -\frac{\partial H}{\partial E} = BV_1(\zeta_4 - \zeta_2) + \frac{AS}{N} (\zeta_4 - \zeta_1) + (\zeta_4 - \zeta_5)k + \zeta_4\mu, \\
 \frac{d\zeta_5}{dt} &= -\frac{\partial H}{\partial P} = -b + BV_1(\zeta_4 - \zeta_2) + \frac{AS}{N} (\zeta_4 - \zeta_1) + (\zeta_5 - \zeta_8)\delta_1 \\
 &\quad + \frac{(1-u_1(t))(1-u_2(t))\beta_2 V_1}{N} (\zeta_2 - \zeta_4) + (\zeta_5 - \zeta_7)(\varphi_1 + u_4(t)) \\
 &\quad + \frac{(1-u_1(t))\beta_1 S}{N} (\zeta_1 - \zeta_4) + (\zeta_5 - \zeta_6)\alpha + \zeta_5\mu, \\
 \frac{d\zeta_6}{dt} &= -\frac{\partial H}{\partial I} = -c + BV_1(\zeta_4 - \zeta_2) + \frac{AS}{N} (\zeta_4 - \zeta_1) + \zeta_6(\mu + d_1) \\
 &\quad + \frac{(1-u_1(t))(1-u_2(t))n_1\beta_2 V_1}{N} (\zeta_2 - \zeta_4) + (\zeta_6 - \zeta_7)\varphi_2 \\
 &\quad + \frac{(1-u_1(t))n_1\beta_1 S}{N} (\zeta_1 - \zeta_4) + (\zeta_6 - \zeta_8)\delta_2, \\
 \frac{d\zeta_7}{dt} &= -\frac{\partial H}{\partial J} = -d + BV_1(\zeta_4 - \zeta_2) + \frac{AS}{N} (\zeta_4 - \zeta_1) + \zeta_7(\mu + d_2) \\
 &\quad + \frac{(1-u_1(t))(1-u_2(t))n_2\beta_2 V_1}{N} (\zeta_2 - \zeta_4) + \zeta_8\mu + (\zeta_7 - \zeta_8)\delta_3 \\
 &\quad + \frac{(1-u_1(t))n_2\beta_1 S}{N} (\zeta_1 - \zeta_4), \\
 \frac{d\zeta_8}{dt} &= -\frac{\partial H}{\partial R} = BV_1(\zeta_4 - \zeta_2) + \frac{AS}{N} (\zeta_4 - \zeta_1),
 \end{aligned} \right\} \quad (11)$$

where $A = \frac{(1-u_1(t))\beta_1(P+n_1I+n_2J)}{N}$ and $B = \frac{(1-u_1(t))(1-u_2(t))\beta_2(P+n_1I+n_2J)}{N^2}$ with transversality conditions

$$\zeta_1(t_f) = \zeta_2(t_f) = \zeta_3(t_f) = \zeta_4(t_f) = \zeta_5(t_f) = \zeta_6(t_f) = \zeta_7(t_f) = \zeta_8(t_f) = 0. \quad (12)$$

Furthermore, the respective controls, $u_1^*, u_2^*, u_3^*, u_4^*$ are obtained by solving $\frac{\partial H}{\partial u_1} = 0$, $\frac{\partial H}{\partial u_2} = 0$, $\frac{\partial H}{\partial u_3} = 0$, $\frac{\partial H}{\partial u_4} = 0$ and these are given by

$$\begin{aligned}
 u_1^* &= \frac{(P+n_1I+n_2J)(\beta_1 S(\zeta_4 - \zeta_1) + (1-u_2(t))\beta_2 V_1(\zeta_4 - \zeta_2))}{m_1 N}, \\
 u_2^* &= \frac{(P+n_1I+n_2J)(1-u_1(t))\beta_2 V_1(\zeta_4 - \zeta_2)}{m_1 N} + \frac{(\zeta_1 - \zeta_2)\varepsilon_1 S}{m_2},
 \end{aligned}$$

$$u_3^* = \frac{(\zeta_2 - \zeta_3)\varepsilon_2 V_1}{m_3}, \quad u_4^* = \frac{(\zeta_5 - \zeta_7)P}{m_4}.$$

With the controls $u_1^*, u_2^*, u_3^*, u_4^*$, the optimality condition is given by

$$\left. \begin{aligned} u_1^{opt} &= \max\{0, \min(1, u_1^*)\}, \\ u_2^{opt} &= \max\{0, \min(0.95, u_2^*)\}, \\ u_3^{opt} &= \max\{0, \min(0.95, u_3^*)\}, \\ u_4^{opt} &= \max\{0, \min(1, u_4^*)\}. \end{aligned} \right\} \quad (13)$$

The optimality system consists of the state system (8), the adjoint system (11) with initial conditions of (3) and transversality condition (12) together with the characterization of the optimality condition (13).

The restrictions of obtaining the uniqueness of the optimal control based on the length of time follow the technique in [2, 9, 14].

5. Numerical simulations

In this section, the solutions of the optimality system are solved numerically using the forward and backward fourth-order Runge-Kutta method that is coded in MatLab software. The parameter values in Table 1, $b = c = d = 100$, $m_1 = 10000$, $m_2 = 2000$, $m_3 = 2000$, $m_4 = 5000$ and the initial conditions, $S(0) = 200000$, $V_1(0) = 2000$, $V_2(0) = 1800$, $E(0) = 80$, $P(0) = 60$, $I(0) = 100$, $J(0) = 20$, $R(0) = 10000$ are used for the numerical simulations purpose.

Controlling measles transmission dynamics with optimal control analysis

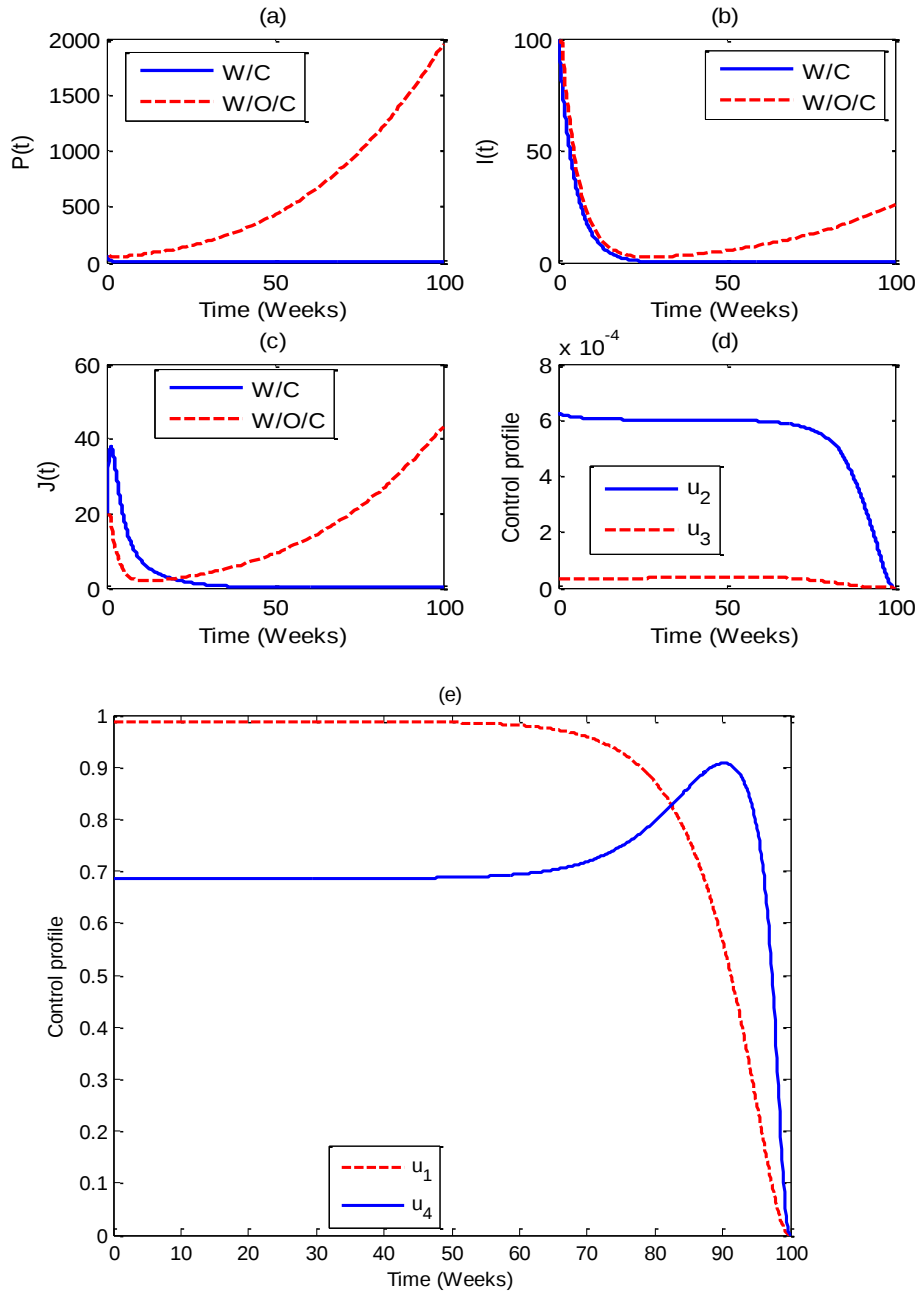


Figure 4. The population dynamics of (a) infected persons in the prodromal stage, $P(t)$, (b) infected persons in the rash stage, $I(t)$, (c) Isolated persons, $J(t)$, (d) Controls, u_2 , u_3 , and (e) Controls, u_1 , u_4 . Here, W/C means “With Control” while W/O/C means “Without Control”.

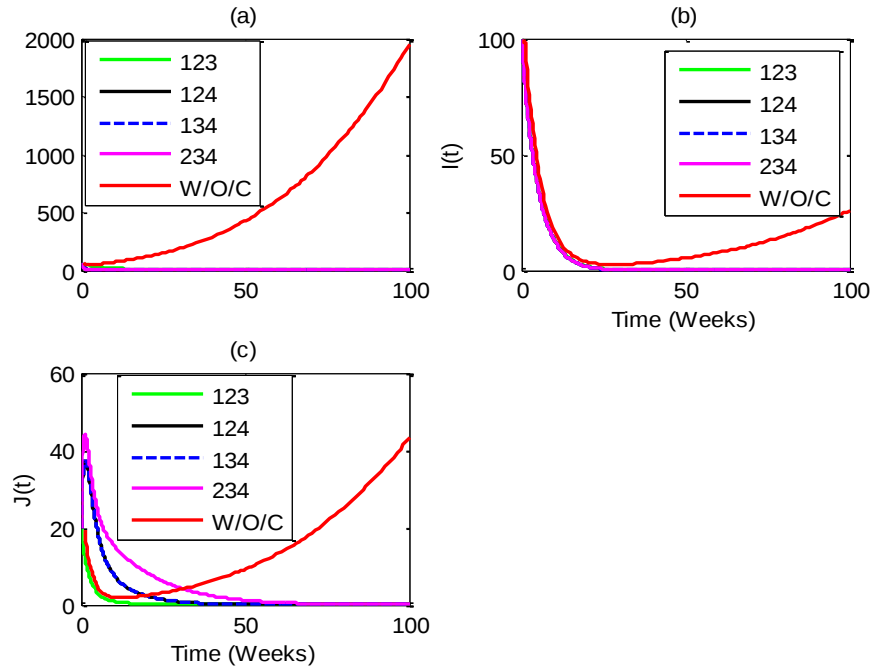


Figure 5. The population dynamics of (a) infected persons in the prodromal stage, $P(t)$, (b) infected persons in the rash stage, $I(t)$, (c) Isolated persons, $J(t)$ when triple controls are implemented together. Here, the numbers 1,2,3, and 4, are subscripts of the control functions, u_1, u_2, u_3, u_4 while W/O/C means “Without Control”.

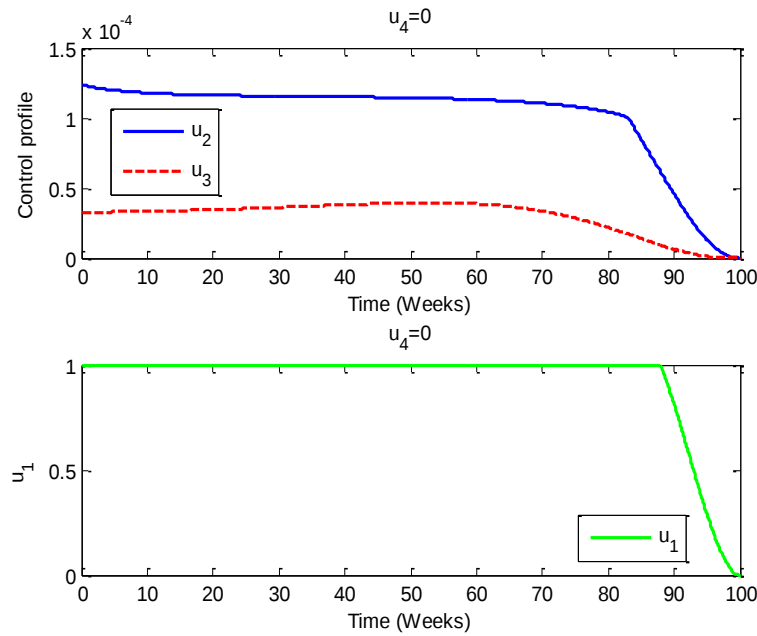


Figure 6. Control profile for implementation of triple optimal controls.

5.1 Discussion

Figure 4 shows the population dynamics of infected persons in the prodromal stage, $P(t)$, infected persons in the rash stage, $I(t)$, isolated persons, $J(t)$, for with and without control and the control profile. According to Figure 4a, with control measures, measles-free population is achieved for $P(t)$ population immediately, and thus reducing the number of persons moving to the infected people in the rash stage, while Figure 4b, the number of infected persons in the rash stage, $I(t)$, decrease to zero within 25 weeks with control measures in place. Also, Figure 4c reveals that with the implementation of the control measures, there is a sharp increase in the number of isolated persons before decreasing to zero by 25 weeks and achieves measles-free population. The control profile for achieving the result in Figures 4a-4c are display in Figures 4d and 4e. They show that the upper bounds for u_1, u_2, u_3 are 9.9, 6.1×10^{-4} and 2×10^{-5} , respectively, where the control, u_3 maintains a bound of 6.9 for 50 weeks before it gradually increases to 0.9 as at 90 weeks. For without control measures, Figures 4a – 4c show the endemicity of the measles infection in the population.

In Figure 5, the implementation of triple control measures for the dynamics of the infected compartments ($P(t), I(t), J(t)$) are evaluated. We observed in Figures 5a -5b that simultaneous implementation of any triple control measures reduce the number of infected persons ($P(t), I(t)$) in the population as they achieve a measles-free population within a short time while for isolated persons, $J(t)$, the combine implementation of u_1, u_2, u_3 (123) yields a faster and better result in achieving a measles-free population compared with other combinations (see Figure 5c). With this, it implies that combined implementation of control measures, u_1, u_2, u_3 (123), reduces the number of infected persons in the prodromal stage, $P(t)$, rash stage, $I(t)$ and the isolated persons, ($J(t)$) compare with any other combination of control measures. The control profile for triple control measures are display in Figure 6. The control profile when $u_4 = 0$ is the combined implementation of u_1, u_2, u_3 (123) that gives the best result in Figure 5, which indicates that mass distribution of nutritional (supplement) support, administration of first and second dose vaccine control measures have much effect on controlling measles in the population. To achieved this, u_1 maintains an upper bound that declines after 85 weeks, whereas u_2 maintains a bound of 1.2×10^{-4} that decreases gradually till 85 weeks where it declines to the final time. For u_3 , it starts with a bound of 3.2×10^{-5} that slightly increases to 4.0×10^{-5} at 70 weeks before declining to the final time.

The numerical simulations imply that combined implementation of mass distribution of nutritional support, complete vaccination with the first and second dose of vaccine and isolation of infected persons in the prodromal stage will help eradicate the spread of measles in the population. This is in agreement with the sensitivity analysis result and the results in [3]. This indicates that implementation of control measures will help prevent the spread of measles infection in the population. However, if there are limited facilities to isolate the infected persons in the prodromal stage, the triple control measures, mass distribution of nutritional support and complete vaccination with first and second doses of vaccine will reduce the spread of measles infection as fewer people will

be infected and thus help the health practitioners achieve the best strategy in the control of the spread of measles in the community.

6. Conclusion

In this paper, an autonomous system for the transmission dynamics of measles disease involving isolated persons and two doses of vaccination is formulated. The model disease-free equilibrium and basic reproduction number (R_0) are computed. The sensitivity analysis of the basic reproduction number, which includes the pairwise comparison and scatterplots of important parameters of the basic reproduction number is carried out using Latin Hypercube Sampling (LHS) scheme. LHS scheme is also used to compute and compare the values of Partial Rank Correlation Coefficients (PRCCs) of the model parameters. The result of the sensitivity analysis indicates that transmission rates, first and second-dose vaccination rates and isolation rate of the infected persons in the prodromal stage are significant parameters in eradicating the spread of measles infection. Furthermore, the optimal control model of the autonomous system is developed and analysed with four control measures, mass distribution of nutritional support, administration of first and second dose vaccination and isolation of infected persons in the prodromal stage. From the numerical simulations, we found out that the combined implementation of the four control measures achieves a measles-free population on time than without control measures. However, if there are limited facilities to isolated the infected persons in the prodromal stage, the triple control measures, mass distribution of nutritional support and complete vaccination with first and second doses of vaccine will reduce the spread of measles infection as fewer people will be infected and thus help the health practitioners achieve the best strategy in the control of the spread of measles in the community.

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