MATHEMATICAL ANALYSIS OF THE EFFECT OF MATERNAL IMMUNITY ON THE GLOBAL ERADICATION OF MEASLES

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ABSTRACT:Measles susceptibility depends largely on the influx of newborns. Besides, expectant women who contract measles are at the risks of early labor, miscarriage or babies with poor weight. On that ground, we propose a new deterministic mathematical model to study the effect of inborn immunity on the global eradication of measles. The model is based on dividing the entire human population into six disjoint subpopulations. The stability theory of nonlinear differential equation is used to analyse the model. We derive the reproduction number of the model by using the next generation matrix approach and conduct numerical simulations to verify the analytical results. One of the fundamental results of the study is that global eradication of measles is not feasible if efforts are only concentrated on getting more and more pregnant women immunised without taking measures to reduce the rate of exposure of the susceptible individuals to measles infections.
***KEYWORDS*:** Measles, Model, Immunity, Reproduction Number, Simulation.

1. INTRODUCTION

One of the global goals of health practitioners is the protection of children from measles and other vaccine-preventable diseases. Since vaccination has proved the best strategy against childhood illness, formulating a framework that would establish an adequate vaccine coverage required to manage the transmission of the disease is important and necessary. The only natural host for the measles virus is man. It is the leading cause of morbidity and mortality for children in Nigeria with 212 183 and 168 107 reported cases in 2000 and 2001 respectively ([OCA17]). Particularly in Adamawa State, there were 3 974 measles reported cases and 238 deaths in 2005 ([I+05]). Measles is a childhood disease and rarely threatens adults. It does not discriminate because it exists in all climates and races and its susceptibility is global. However, severe measles attacks are common among malnourished children especially children with insufficient vitamin A or those whose immune systems have been depleted by HIV/AIDS or other infections ([OCA17]). The disease has no specific treatment nevertheless infected individuals should be given enough rest, fluid and anti-fever therapy. Also, specific treatment should be administered to patients with complications ([Ame18]).

Measles is among the worst eruptive fever associated with children characterised by red rash and capable of resulting in complications which may be complemented with diarrhea, pneumonia or encephalitis. Infected children may suffer deafness, blindness or impaired vision. However, measles confers permanent immunity upon recovery ([F+14]). Since the implementation of vaccine programs is faced with a number of problems in Africa, measles becomes the leading killer of children in most African countries. In 2002, 614 000 deaths were attributed to measles of which more than half occurred in sub-Saharan Africa ([I+05]). In 2005, the World Health Assembly officially set a goal of reducing measles-related mortality by 90% worldwide between 2000 and 2001 ([Wor05]). A good number of organisations such as the Measles and Rubella Initiative have been promoting the plans of the World Health Organisation (WHO) to reduce measles death ([WHO12]) by fostering regular immunisation of children and ensuring a second dose chance for measles vaccines ([OHS06]). In the regions where measles routine immunisation strategies have attained good population coverage, the second dose is incorporated in the schedule of routine vaccination ([WHO09]). However, in regions where measles routine immunization systems have not attained sufficient coverage, the measles vaccines for the second dose is administered through the supplemental immunisation activities (SIA_S) ([WHO09]).

The global goal of reducing measles mortality by 90% by the WHO is becoming a reality. Reliable data had it that global measles-related mortality fell from 535 000 in 2000 to 139 000 in 2010, a reduction of over 75% in all regions except Southeast Asia ([S+12]). However, reports due to ([W+09]) had it that the estimates of measles mortality between 2000 and 2010 did not take into

consideration the measles mortality figures from low- and middle-income nations in general, particularly India, the nation with the leading measles burden worldwide. While measles incidence has reduced drastically in regions where vaccination programs have been implemented, upsurge in the measles incidence in the less developed countries has been attributed to poor vaccination rates.

In order to gain deeper understanding of the dynamics of measles disease, a good number of models have been developed. A mathematical model was designed in ([F+14]) by introducing vaccines to the susceptible population in order to study the dynamics of measles disease. The model was built on the assumption that each class in the population had variable size and the vaccinated individuals received permanent immunity against the infection. They conducted qualitative and quantitative analyses of the model and discovered that the model exhibited a locally asymptotically stable disease-free equilibrium when $R_0 < 1$, whereas, the disease-free equilibrium became unstable whenever $R_0 > 1$. A discrete-time, age-independent SIR-type epidemic model incorporating the effect of vaccination was designed in ([AJM91]). The researchers established three important mathematical properties for the model and discovered that every individual in the population at the end of the epidemic remained either susceptible or immune to the disease. The model was later applied to a university campus to investigate the possibility of measles outbreak. They carried out simulations and the outcome of their simulations showed that the outbreak of measles was sure to be prevented with the rate of immunity above 98%. The model had applications to various infectious diseases of SIR type.

In ([Bol14]), a compartmental model was designed to incorporate vaccination with a view to examining the dynamics of measles and to investigate the vaccination coverage and dosage required to eradicate the measles within a population. The model was formulated in terms of a system of first order ordinary differential equations and was premised on the assumption of permanent immunity for the successfully vaccinated individuals. The basic and the effective reproduction numbers were derived and the stability analysis was conducted. The author established that the infection-free was locally and globally asymptotically stable if $R_0 \leq 1$while the endemic equilibrium was stable if $R_0 > 1$. It was also discovered that the reproduction number under the influence of vaccination i.e. R_{0v}tended to zero as the population of successfully vaccinated individuals rises. Finally, the outcome of the study suggested the dosage and coverage of vaccination that were required to eradicate measles in a population. Works on measles also exist in ([KN10]), ([M+13]), ([AOK17]), ([OG14]).

Disease can spread in a population in various ways. However, the presence or absence of maternal immunity can shape the transmission of measles disease. The immunity received against measles infection by well immunised pregnant women can be passed on to their expecting babies therefore; two things are expected to happen if pregnant women are well immunised against measles. They will give birth to children who are immune to the infection for certain period of time. Besides, vertical transmission of the disease will be well prevented through passive immunisation. Based on this, the present study is conducted to investigate the effect of maternal immunity on the global eradication of measles. A P_1P_2SEIR compartmental model is formulated, where P_1 denotes the compartment for the pregnant women who are immunised against measles infections, P_2 denotes the compartment for the pregnant women who are not immunised against measles infections, S denotes the compartment for the individuals who have not been infected with measles at time t but are capable of being infected, E denotes the compartment for the individuals who have been infected with the disease and at the same time infectious but have not been manifesting measles symptoms, I denotes the compartment for the individuals who have not only been infected with measles but also infectious and at the same time have been fully showing measles symptoms and, R denotes the compartment that includes individuals who have been infected with measles at one time or the other but are now permanently cure of it, and the individuals who have acquired maternal immunity that is sufficient to move them to the recovered class at birth. Every individual in compartment R is free from measles attack throughout his life time.

2. MODEL FORMULATION

The P_1P_2SEIR model is partitioned into classes immunised pregnant women (P_1), unimmunised pregnant women (P_2), susceptible individual (S), exposed individuals (E), infectious individuals (I) and recovered individual (R). Recruitment into (P_1) is through the influx of the newborns whose mothers received immunisation at the rate $\theta_{1`}$ while the recruitment into ($P_2$) is through the influx of the newborns whose mothers did not receive immunisationat the rate $\theta_{2`}$. Some babies in the immunised compartment (P_1) who have enough immunity against infection move to the recovered compartment (R) at the rate ω while some others move to the (S) class at the rate $\beta_{1`}$ which may be as a result of inadequate immunity against infection or as a result of loss of acquired immunity. Babies in

(P_2) class move to S class at the rate β_2`. E class is generated when there is effective contact between individuals in the class (S) and individuals in the class (I) at the rate α. (I) class is generated when individuals in the (E) class move to it at the expiration of the latent stage at the rate ε while (I) class is reduced when some individuals in it are successfully cured and moved to R class at the rate τ and when some of them died due to the infection at the rate δ. (R) class is generated through the movement into it from (P_1) and (I) classes respectively. Natural mortality occurs for each compartment at the same rate μ.

The following set of first order ordinary differential equations is generated from the above assumptions and transmission diagram:

$$\frac{dP_1}{dt} = \theta_1 - \omega P_1 - \beta_1 P_1 - \mu P_1 \quad (1)$$

$$\frac{dP_2}{dt} = \theta_2 - \beta_2 P_2 - \mu P_2 \quad (2)$$

$$\frac{dS}{dt} = \beta_1 P_1 + \beta_2 P_2 - \alpha IS - \mu S \quad (3)$$

$$\frac{dE}{dt} = \alpha IS - \varepsilon E - \mu E \quad (4)$$

$$\frac{dI}{dt} = \varepsilon E - \tau I - (\mu + \delta) I \quad (5)$$

$$\frac{dR}{dt} = \omega P_1 + \tau I - \mu R \quad (6)$$

We shall drop Eqn. (6) and base our analysis on the reduced system (1) – (5) since permanent immunity is assumed and every flow into compartment R remains in compartment R throughout the analysis.

The numerical values assigned to the parameters to conduct the simulations are presented in Table 1.

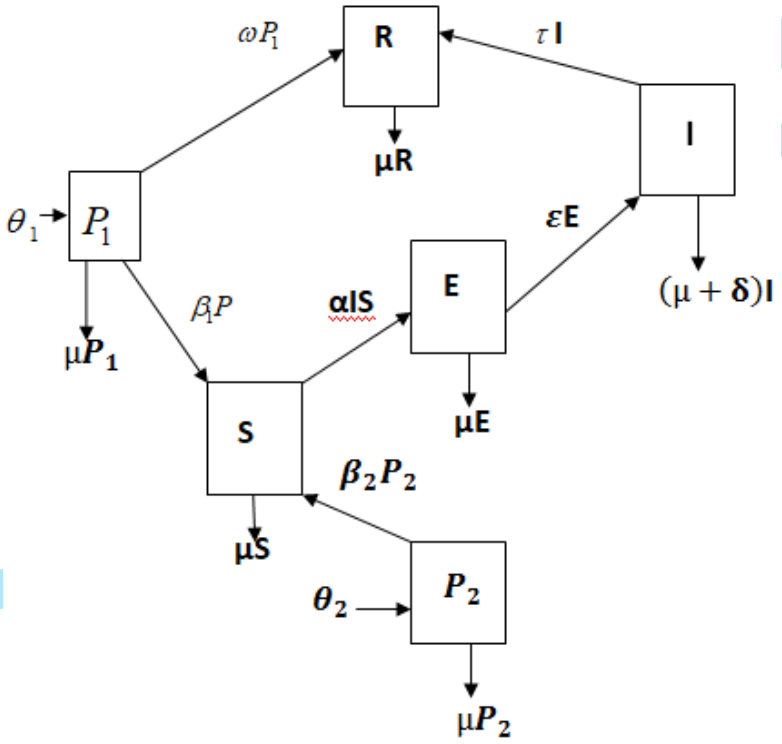

Figure 1. Transmission diagram of the model

Table 1. Parameters Description and Values

Parameters	Symbols	Values	Source
Rate at which $P_1(t)$are immunized	θ_1	0.237	Assumed
Rate at which $P_2(t)$are not immunized	θ_2	0.763	Assumed
Rate at which newborns from $P_1(t)$move to $R(t)$	ω	0.98	Assumed
Rate at which newborns from $P_1(t)$move to $S(t)$	β_1	0.02	Assumed
Rate at which newborns from $P_2(t)$move to $S(t)$	β_2	0.55	Assumed
Effective contact rate	α	0.09091	([F+14])
Progression rate into $I(t)$ from $E(t)$	ε	0.01	([OCA17])
Treatment rate	τ	0.14286	([F+14])
Disease induced death rate	δ	0.02	([OG14])
Natural mortality rate	μ	0.00875	([AOK17])

2.1. Model Basic Properties

In this subsection, the essential features of the system of equations (1) – (5) shall be verified.

Theorem 1: The model (1) – (5) preserves positivity of solutions.

Proof.

Suppose$\{P_1(t), P_2(t), S(t), E(t), I(t)\}$ are the solutions of the system for all $t \geq 0$ with positive initial conditions

$\{P_1(0) \geq 0, P_2(0) \geq 0, S(0) \geq 0, E(0) \geq 0, I(0) \geq 0\}$.

From equation (1),

$$\frac{dP_1}{dt} \geq -(\omega + \beta_1 + \mu)P_1 \quad (7)$$
$$\Rightarrow \quad lnP_1 \geq -(\omega + \beta_1 + \mu)t + k, \quad (8)$$
$$\Rightarrow P_1(t) \geq P_{1(0)}e^{-(\omega+\beta_1+\mu)t} \geq 0. \quad (9)$$

Following the same process,

$$\Rightarrow P_2(t) \geq P_{2(0)}e^{-(\beta_2+\mu)t} \geq 0 \quad (10)$$
$$\Rightarrow S(t) \geq S_0 e^{-(\alpha+\mu)t} \geq 0 \quad (11)$$
$$\Rightarrow E(t) \geq E_0 e^{-(\varepsilon+\mu)t} \geq 0 \quad (12)$$
$$\Rightarrow I(t) \geq I_0 e^{-(\tau+\delta+\mu)t} \geq 0. \quad (13)$$

Hence, the solutions of the system remain positive as long as the initial conditions of the state variables are positive sincee^q is positive for all real values of q.

Theorem 2: The solutions to the model remain bounded in the region Ω defined by

$$\Omega = \left\{ \left((P_1, P_2, S, E, I): 0 \leq P_1 + P_2 + S + E + I \leq \frac{\theta_1 + \theta_2}{\mu} \right) \right\}.$$

Ω is the region of attraction for the model which attracts every solution initiating in the interior of the positive octant.

Proof.

The sum of the compartments

$$= \frac{dP_1}{dt} + \frac{dP_2}{dt} + \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} \quad (14)$$
$$\Rightarrow \frac{d}{dt}(P_1(t) + P_2(t) + S(t) + E(t) + I(t)) = \theta_1 + \theta_2 - (\omega P_1 + \tau I + \delta I) - \mu(P_1 + P_2 + S + E + I)$$
$$\therefore \frac{d}{dt}(P_1(t) + P_2(t) + S(t) + E(t) + I(t)) \leq \theta_1 + \theta_2 - \mu(P_1 + P_2 + S + E + I) \quad (15)$$

By taking limit supremum

$$\lim_{t\to\infty} Sup(P_1(t) + P_2(t) + S(t) + E(t) + I(t)) \leq \frac{\theta_1 + \theta_2}{\mu} \quad (16)$$

3. MODEL ANALYSIS

We shall obtain the equilibrium solutions, derive the reproduction number, conduct the stability analysis of the disease-free equilibrium and perform the numerical simulations.

3.1. Existence of Disease-Free Equilibrium Point, P_0

This is obtained when there is no infection agent in the population such that nobody is exposed and nobody is infected i.e. $E = 0$ and $I = 0$. Solving Eqns (1) – (5) based on the condition $E = 0$ and $I = 0$ and using the representation $c_1 = \omega + \beta_1 + \mu$, $c_2 = \beta_2 + \mu$, $c_3 = \varepsilon + \mu$, $c_4 = \tau + \delta + \mu$, we obtained

$$P_0 = \left\{ \frac{\theta_1}{c_1}, \frac{\theta_2}{c_2}, \frac{c_1\beta_2\theta_2 + c_2\beta_1\theta_1}{c_1c_2}, 0, 0 \right\} \quad (17)$$

3.2. Existence of Endemic Equilibrium Point, P^*

The endemic equilibrium point of the model is denoted by $P^* = \{P^*_1, P^*_2, S^*, E^*, I^*\}$ where:

$$P_1^* = \left(\frac{\theta_1}{c_1}\right) \quad (18)$$
$$P_2^* = \left(\frac{\theta_2}{c_2}\right) \quad (19)$$
$$S^* = \left(\frac{c_3c_4}{\alpha\varepsilon}\right) \quad (20)$$
$$E^* = \left(\frac{c_1\alpha\beta_2\varepsilon\theta_2 - c_1c_2c_3c_4\mu + c_2\alpha\beta_1\varepsilon\theta_1}{c_1c_2c_3\alpha\varepsilon}\right) \quad (21)$$
$$I^* = \left(\frac{c_1\alpha\beta_2\varepsilon\theta_2 - c_1c_2c_3c_4\mu + c_2\alpha\beta_1\varepsilon\theta_1}{c_1c_2c_3c_4\alpha}\right) \quad (22)$$

3.3. The Basic Reproduction Number

The basic reproduction number of the model shall be computed following the next generational matrix method. The basic reproduction number is a non-dimensional quantity that measures the average number of new cases generated by an infected when introduced into the population of the susceptible. Measles generally has two disease states namely asymptomatic and symptomatic. The next generation matrix for the model shall therefore be derived from Eqns (4) and (5), the exposed and infectious classes respectively which monitor the two-disease state.

$$F_i = \begin{pmatrix} \alpha IS \\ 0 \end{pmatrix} \text{and} V_i = \begin{pmatrix} c_3E \\ -\varepsilon E + c_4 I \end{pmatrix} \quad (23)$$

F and V are obtained by finding the partial derivative of Eqn.(23) with respect to E and I respectively. Hence,

$$F = \begin{pmatrix} 0 & \alpha S \\ 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} c_3 & 0 \\ -\varepsilon & c_4 \end{pmatrix} \quad (24)$$

The inverse of V is obtained as

$$V^{-1} = \frac{1}{c_3 c_4}\begin{pmatrix} c_4 & 0 \\ \varepsilon & c_3 \end{pmatrix}$$

Therefore,

$$FV^{-1} = \begin{pmatrix} \frac{\alpha\varepsilon S}{c_3 c_4} & \frac{\alpha S}{c_4} \\ 0 & 0 \end{pmatrix} \quad (25)$$

Using the value of S at the DFE in Eqn. (17) to evaluate Eqn. (25), we have

$$FV^{-1} = \begin{pmatrix} \frac{\alpha\varepsilon[c_1\beta_2\theta_2 + c_2\beta_1\theta_1]}{\mu c_1 c_2 c_3 c_4} & \frac{\alpha[c_1\beta_2\theta_2 + c_2\beta_1\theta_1]}{\mu c_1 c_2 c_4} \\ 0 & 0 \end{pmatrix} \quad (26)$$

The reproduction number is the spectral radius (larger eigen-value) of the above matrix which is given as

$$R_0 = \frac{\alpha\varepsilon[c_1\beta_2\theta_2 + c_2\beta_1\theta_1]}{\mu} \quad (27)$$

The above is a threshold quantity for the outbreak or otherwise of measles in the population should an infected individual get into the population. If $R_0 > 1$, measles outbreak will take off in the population because on average, the infected individual generates more than one new infections before the expiration of his or her infectiousness but if $R_0 < 1$, measles outbreak will not take off in the population because on average, the infected individual could not infect a single individual throughout the period of his or her infectiousness.

3.4. Stability Analysis of the Disease-Free Equilibrium Point

To investigate the local stability of the infection free equilibrium of the model, the Jacobian matrix of the system of Eqns (1) – (5) is evaluated at the DFE of Eqn. (17) and the result is obtained as

$$J(P_0) = \begin{pmatrix} -c_1 & 0 & 0 & 0 & 0 \\ 0 & -c_2 & 0 & 0 & 0 \\ \beta_1 & \beta_2 & -\mu & 0 & -\alpha k \\ 0 & 0 & 0 & -c_3 & \alpha k \\ 0 & 0 & 0 & \varepsilon & -c_4 \end{pmatrix} \quad (28)$$

Where

$$k = S = \frac{c_1\beta_2\theta_2 + c_2\beta_1\theta_1}{\mu c_1 c_2}$$

Theorem 3: The disease-free equilibrium of the model is locally asymptotically stable if all the eigenvalues of Eqn. (28) are negative.

Proof. The characteristic polynomial of Eqn. (28) is

$$|J(P_0 - \lambda I)| = \begin{pmatrix} -(c_1+\lambda) & 0 & 0 & 0 & 0 \\ 0 & -(c_2+\lambda) & 0 & 0 & 0 \\ \beta_1 & \beta_2 & -(\mu+\lambda) & 0 & -\alpha k \\ 0 & 0 & 0 & -(c_3+\lambda) & \alpha k \\ 0 & 0 & 0 & \varepsilon & -(c_4+\lambda) \end{pmatrix} \quad (29)$$

The characteristic equation of Eqn. (29) is

$$-(\mu+\lambda)(c_2+\lambda)(c_1+\lambda)[(c_3+\lambda)(c_4+\lambda) - \alpha\varepsilon k] = 0 \quad (30)$$

But at the DFE, there is no infection term which reduces α and ε to zero in Eqn.(30)

$$\Rightarrow (\mu+\lambda)(c_2+\lambda)(c_1+\lambda)[(c_3+\lambda)(c_4+\lambda)] = 0 \quad (31)$$

Hence,

$$\lambda_1 = -\mu, \lambda_2 = -c_1,\ \lambda_3 = -c_2,\ \lambda_4 = -c_3,\ \lambda_5 = -c_4$$

Since all the eigenvalues are less than zero then the disease-free equilibrium of the model is locally asymptotically stable.

4. RESULTS AND DISCUSSION

The parameter values in Table 1 are used to obtain the numerical value for the reproduction number. The values of some of the key parameters are then varied to examine the effect of changes in their values on the reproduction number, the result of which is presented in Table 2 to three places of decimal. The trend of infectious population for the reproduction numbers in the serial numbers 4 and 8 in Table 2 is then supported graphically.

Table 2: Effect of Variations in the Values of the Key Parameters on the Reproduction Number

S/No	θ_1	θ_2	ω	β_1	β_2	α	ε	τ	δ	μ	R_0
1	0.237	0.763	0.98	0.02	0.55	0.09091	0.01	0.14286	0.02	0.00875	24.403
2	0.337	0.663	0.985	0.015	0.56	0.09091	0.01	0.14286	0.02	0.00875	21.240
3	0.437	0.563	0.99	0.01	0.57	0.09091	0.01	0.14286	0.02	0.00875	18.044
4	0.537	0.463	0.995	0.005	0.58	0.09091	0.01	0.14286	0.02	0.00875	14.814
5	0.337	0.663	0.985	0.015	0.56	0.08	0.005	0.2	0.019	0.00875	9.603
6	0.437	0.563	0.99	0.01	0.57	0.07	0.004	0.3	0.018	0.00875	4.292
7	0.537	0.463	0.995	0.005	0.58	0.06	0.003	0.4	0.017	0.00875	1.887
8	0.637	0.363	0.996	0.004	0.59	0.05	0.002	0.5	0.016	0.00875	0.730
9	0.737	0.263	0.997	0.003	0.60	0.04	0.001	0.6	0.015	0.00875	0.196

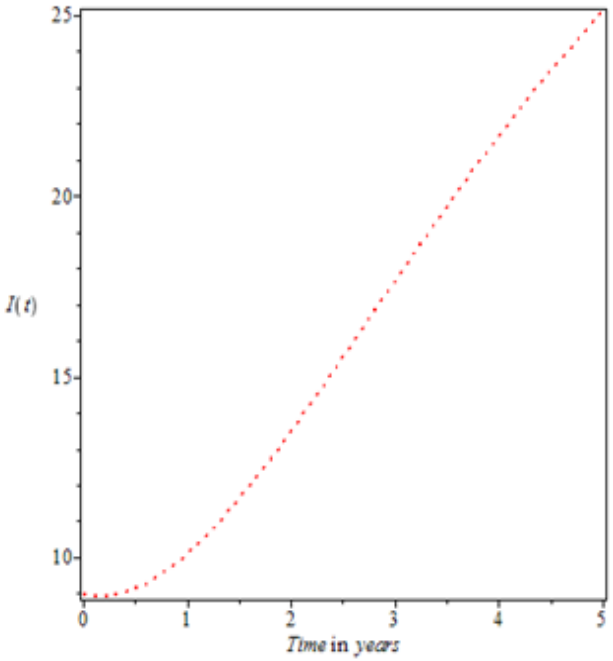

Figure 2. Simulation of *I(t)* for $R_0 = 14.814$

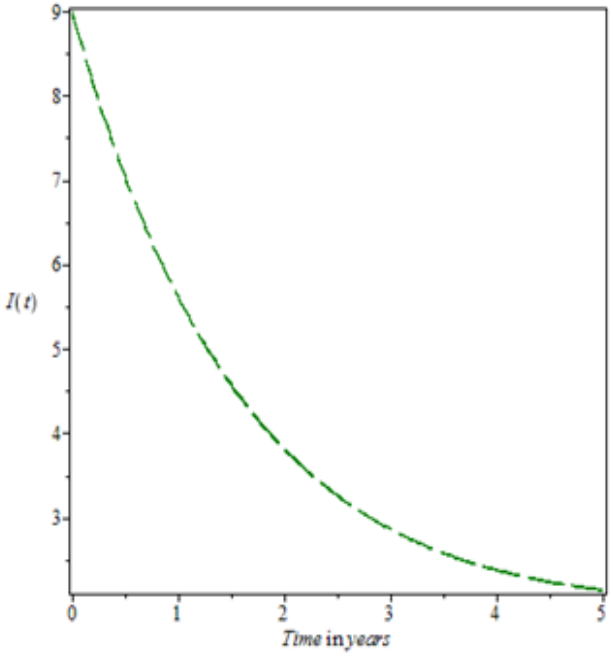

Figure 3. Simulation of *I(t)* for $R_0 = 0.730$

As regards the analytical result in subsection 3.4, the implication of stability of the disease-free equilibrium is that the reproduction number is less than unity and measles outbreak is doomed to a rapid failure even if an individual infected with the measles virus is introduced into the population. As for the numerical result in section 4.0, the basic reproduction number for measles is widely accepted as 18 ([OG14]). In Table 2, as the rate of immunisation of pregnant women increases without corresponding increase in the treatment rate of the infected and reduction in the contact rate between the susceptible and the infected (S/No 1 – 4 in Table 2), the disease free equilibrium is unstable and the population is plagued with measles even though R_0 falls from 24 to 14. However, as the increase in the rate of immunisation of pregnant women is matched with the increase in the treatment of the infected together with the reduction in the contact rate between the susceptible and the infected (S/No 5 – 9 in Table 2), the disease free equilibrium is stable and the outbreak of measles goes into extinction after some time. In Figure 2, infectiousness is directly related to time and the population of the infected rises continuously with time whereas in Figure 3, infectiousness is inversely related to time and the population of the infected tends to zero after five years. It is therefore discovered that high rate of immunisation of pregnant women, reduction in the contact rate between the susceptible and the infected together with the improvement in the treatment rate of measles cases above certain threshold (S/No 8 in Table 2) is capable of eradicating measles globally.

5. CONCLUSION

In this study, we have formulated a mathematical model for the global eradication of measles by considering the effect of maternal immunity. The analyses of the disease-free equilibrium and its stability in relation to the basic reproduction number are presented. Numerical simulation is carried out and the parameters space that guarantees global elimination of measles is established.

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