Mathematical Modeling of Delayed Pulse Vaccination Model of Infectious Diseases

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ABSTRACT

This study concerns the theoretical determination of a mathematical model of delayed pulse vaccination of infectious diseases that affects children. In this study, a delayed SEIR epidemic model with impulsive effect and the global dynamic behaviors of the model will be analyzed. Using the discrete dynamical systems determined, it's shown that there exists an 'infection-free' periodic solution which is globally attractive when the period of impulsive effect is less than some critical value. The sufficient condition for the permanence of the epidemic model with pulse vaccination is given, which means the epidemic disease is to spread around. The study has concluded that time delay and pulse vaccination brings great effects of shortening 'infection period' on the dynamics of the model. The results indicate that a large vaccination rate or a short period of pulsing leads to the eradication of the disease. Numerical simulation has been used together with the analytical results. The results shall be presented in tabular and graphical form.

Keywords:

Basic reproduction ratio-R_o,Compartmental model, Infectious diseases, Disease-free, Equilibrium Mathematical modeling, Pulse vaccination, Time delay

INTRODUCTION

Infectious diseases are disorders caused by pathogenic microorganisms. Many organisms live in and on our bodies. Most infectious diseases could be driven towards eradication, if adequate and timely steps (e.g. vaccination, treatment, etc.) are taken in the course of an epidemic. However, many of these diseases eventually become endemic in many societies due to lack of adequate policies and timely interventions to mitigate the spread of the diseases. Consequently, there is the

need for proactive steps towards controlling the spread of infectious diseases, particularly those ones for which both vaccine and cure are available.

The ultimate goal of an epidemic model would be to closely follow and predict real-life disease outbreaks, with the aim of informing public policy and related government agencies. It will focus on looking at control methods, i.e. ways to keep the infective population low or to eradicate the infection altogether. One such control method is vaccination. Some vaccination campaigns are run continuously, for example with people of a certain age receiving their vaccine. Another way is to organize large campaigns in which a large proportion of the population is vaccinated over a short time; this technique is known as pulse vaccination.

In modeling of delayed pulse vaccination of infectious diseases, the study focuses on deterministic models and dynamical systems used to model epidemics, using deterministic compartmental models, in which a given population is divided into compartments based on the disease status (susceptible, exposed etc.). The transfers between compartments, as well as the entrance to the population of new individuals and the exit of others are modeled as terms in a differential equation governing the time-evolution of each compartmental value. After the infectious individuals lived through an infection period, they recover completely and transfer to the 'removed' class, R, so, the number of the death of the infectious should be considered during convalescence, which is called the phenomena of 'time delay'.

Pulse vaccination is gaining prominence as a strategy for the elimination of childhood viral infectious diseases such as measles, hepatitis, parotitis, smallpox and phthisis, and was considered in many literatures in D'Onofrio (2002, 2004) and Gao (2008). Known theoretical results showed that the pulse vaccination strategy can be distinguished from the conventional strategies in leading to disease eradication at relatively low value of vaccination.

Therefore, this study will consider an epidemic model with impulsive vaccination and time delay and study their dynamic behaviors (the 'infection-free' periodic solution, the permanence and the global attractive behavior) under pulse vaccination. The main aim of this study is to introduce time delay, pulse vaccination in an epidemic model and to obtain some important qualitative properties and valid pulse vaccination strategy.

LITERATURE SURVEY

Wencai *et al* (2015) researched on dynamical analysis of SIR epidemic model with non-linear pulse vaccination and lifelong immunity. In this study, due to the limited medical resources, vaccine immunization rate is considered as a nonlinear saturation function and their findings were enriching medical resources the disease will be in extinction, otherwise the disease will be permanent.

Onyejekwe and Kebede (2015), studied the epidemiological modeling of measles infection with optimal control of vaccination and supportive treatment, in which they concluded that the optimal combination of the strategies required to achieve the set objective depend on the relative cost of

each of the control measures and the resulting optimality system. The use of both vaccination and supportive treatment gives the highest possible rate to the control of epidemics.
Tongqian *et al* (2014), in their study SVEIRS a new epidemic disease model with time delays and impulsive effects realized that global dynamical behavior of the model with pulse vaccination and impulsive population inputs effects at two different periodic moments, existence and global attractivity of the infection free periodic solution and also permanence of the model. Their results shows that time delay, pulse vaccination and pulse population input can exert a significant influence on the dynamics of the systems which confirms the availability of pulse vaccination strategy for the practical epidemic prevention.
Shulgin *et al* (2014) considered a simple SIR model with pulse vaccination and have shown that if certain conditions regarding the magnitude of vaccination proportion and on the period of pulses are satisfied then the pulse vaccination leads to epidemic eradication.

Yanke and Rui (2010), investigated a delayed SIR epidemic model with nonlinear incidence rate and pulse vaccination, they noted that the global attractiveness of infection free periodic solution was analyzed and sufficient conditions are obtained for permanence of the system. Their results indicated that a large vaccination rate or a short period of pulsing leads to the eradication of the disease.

An epidemic HIV/AIDS model with treatment has been investigated in the study by Cai *et al* (2009). The model allows some infected individuals to move from symptomatic phase to the asymptomatic phase by all kinds of treatments. The authors introduced the time delay to the model in order to investigate the effect of the time delay on the stability of the endemically infected equilibrium. This discrete time delay has also been used to the model to describe the time from the start of the treatment in the symptomatic stage until the treatment effects becomes clear. It was found that treatment can be used to make the disease free equilibrium (E_0) stable when it would be unstable in the absence of treatment. On the other hand using the time delay can induce oscillation in the system. Biologically, this means that there is a critical value for the treatment-induced delay which determines the stability of the infected equilibrium $E*$. That is, the infected equilibrium $E*$ is asymptotically stable when antiretroviral drugs on average show positive effects in patients within less than time delay.

D'Onofrio *et al* (2007) presented simple epidemiological models with information dependent vaccination functions which can generate sustained oscillations via Hopf bifurcation of the endemic state. The onset of these oscillations depends on the shape of the vaccination function. They used "global" approach to characterize the instability condition and identify classes of functions that always lead to stability/instability. The analysis allows the identification of an analytically determined "threshold vaccination function" having a simple interpretation: coverage functions lying always above the threshold always lead to oscillations, whereas coverage functions always below never lead to instability.

Meng *et al* (2008) and Jin *et al* (2008) studied an SIR model with some people failing to obtain immunity after first dose but gained immunity after later doses. As it's known immunity to infectious diseases after being vaccinated against them might not be life long, so in this study it's

assumed that the latent and immunity (not permanent) period are constants.

The control of epidemics by vaccination, by Verriest *et al* (2011), they used recently developed results on optimal impulsive control for time delay systems in the problem of control of an epidemic through pulse vaccination. For added realism, delays are explicitly incorporated in the epidemiological model. It was shown that the conditions for optimality are easily amenable by an iterative gradient type numerical algorithm. They recommended future work to include multipulse strategies. They expected that current policies of *periodic* vaccination pulses can be improved upon. This will then provide a 'proof of principle' with which more realistic models for disease may be attacked.
The combination of pulse vaccination in an epidemic model with time delay is the main objective of this study, focusing on pulse vaccination. The study of the pulse vaccination model with delay as given by Gao (2009) will be the basis of this research.

Purpose of the study

Infectious diseases have been a major concern in health sector, as it affects children and young borns adversely. Constant vaccination have been used mostly as a method of controlling infectious diseases e.g. measles, polio, etc. Pulse vaccination is the latest advancement in health sectors hence its study.

Objectives of the study

The main objective of this study is to model the infectious diseases, come up with the control measures to enable their eradication and determine the effect of the various population parameters on the delayed pulse vaccination using delayed differential equations, also to:
To determine and analyze contact rate parameters which are piecewise constant or time-varying of epidemiological modeling for the disease eradication or become incurable.
To determine the effects of delay and non-delay pulse vaccination models in the control of an epidemic outbreak.
To obtain the model for simulating delayed pulse vaccination of infectious diseases.
To obtain the threshold values for which an outbreak will die or persist in the population.
To discuss the implications of the model for the management of the infectious diseases.

METHODS/DISCUSSION

In this study we analyse the deterministic compartmental model of the infectious disease on the population. A deterministic compartmental model is one in which the individuals in a population are classified into compartments depending on their status with regard to the infection, the compartments are; Susceptible – $S(t)$, Exposed/latent but not yet infectious – $E(t)$, Infected – $I(t)$ and the Removed – $R(t)$ for *SEIR* model. There are many different compartmental epidemic models for example we have *SEIR*, *SIR*, *SI* model and others. The differential equations (DE) will be assigned initial conditions (IC) and boundary conditions (BC) which will help to solve them. The time-varying or constant parameters will be determined for the dynamical system. The partial

differential equations governing the deterministic models have been used. In mid-19th century, the Xinzhi L and Peter S (2009) discussed different theorems of aiding in solving partial differential equations.

The existence and uniqueness theorem,
The stability theorems, and
The Comparison theorems.

After presenting theorems applicable to very general systems of differential equations, then apply them to the following systems based on the equations of D'Onofrio *et al* (2005).
Non-delay SIR Model

$$\left.\begin{aligned} \frac{dS}{dt} &= b(N(t)-S(t)) - \beta\frac{I(t)}{N(t)}S(t) \\ \frac{dI}{dt} &= \beta\frac{I(t)}{N(t)}S(t) - (\mu+\gamma)I(t) \\ \frac{dR}{dt} &= \gamma I(t) - \mu R(t) \end{aligned}\right\} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots 2.1$$

Delay SEIR Model:

$$\left.\begin{aligned} \frac{dS}{dt} &= b(N(t)-S(t)) - \beta\frac{I(t)}{N(t)}S(t) \\ \frac{dE}{dt} &= \beta\frac{I(t)}{N(t)}S(t) - \beta e^{-\mu r}\frac{I(t-r)}{N(t-r)}S(t-r) - \mu E(t) \\ \frac{dI}{dt} &= \beta e^{-\mu r}\frac{I(t-r)}{N(t-r)}S(t-r) - (\mu+\gamma)I(t) \\ \frac{dR}{dt} &= \gamma I(t) - \mu R(t) \end{aligned}\right\} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots 2.2$$

The DELAY SEIR model with Pulse vaccination

$$\left.\begin{aligned} dS/dt &= bN(t) - \mu S(t) - \beta\frac{I(t)}{N(t)}S(t) \\ dE/dt &= \beta\frac{I(t)}{N(t)}S(t) - \beta e^{-\mu r}\frac{I(t-r)}{N(t-r)}S(t-r) - \mu E(t) \\ dI/dt &= \beta e^{-\mu r}\frac{I(t-r)}{N(t-r)}S(t-r) - (\mu+\gamma)I \\ dR/dt &= \gamma I - \mu R \end{aligned}\right\} t \neq \kappa\tau$$

$$\left.\begin{aligned} S(t) &= (1-p)S(t^-) \\ E(t) &= E(t^-) \\ I(t) &= I(t^-) \\ R(t) &= R(t^-) + pS(t^-) \end{aligned}\right\} t = \kappa\tau \qquad \dots\dots\dots\dots\dots\dots\dots\dots\dots 3.1$$

Ordinary Differential Equations

An ordinary differential equation (ODE) is an equation that involves some ordinary derivative of a function which can be solved by integration.

$x'(t) = f(t, x)$ ……2.3

Here theorems for a general ordinary differential equation (ODE) are discussed, which will be relevant to later analysis. This equation is non-autonomous since it depends explicitly on the time variable *t* in addition to the state variable *x (t)*. It's assumed that the ODE is subject to the initial condition (IC)

$x(t_0) = x_0$. ……2.4

These theorems are:

The Existence and uniqueness theorem

Local existence theorem

Peano's existence theorem gives conditions for when a solution to equation 2.3 exists:

Theorem 1:Peano's Existence Theorem: Let $f \in C(F, R^n)$, that is, *f* is a continuous function from *F* to R^n where

$F = \{(t, x) \in R \times R^n : |t - t_0| \leq a, \|x - x_0\| \leq c, a, c > 0\}$ ……2.5

and let, $\|f(t,x)\| \leq M$ on *F* for some $M > 0$. Then the IVP (2.3-2.4) has at least one solution *x (t)* defined on $[t_0 - \alpha, t_0 + \alpha]$ where $\alpha = \min(a, \frac{c}{M})$.

Equal Birth and Death Rates

If $\mu = b$ and the population is normalized to $N(t) = S(t) + I(t) + R(t) \equiv 1$, equation (2.1) becomes:

$$\left.\begin{aligned} dS/dt &= \mu(1 - S(t)) - \beta I(t)S(t) \\ dI/dt &= \beta I(t)S(t) - (\mu + \gamma)I(t) \\ dR/dt &= \gamma I(t) - \mu R(t) \end{aligned}\right\} \text{……2.6}$$

Defining $x = [S, I, R]^T$ and $f(t, x) := [x^1, x^2, x^3]T$. Then (2.1) is equivalent to $x'(t) = f(t, x)$.

In this normalized case, the physical region is $x \in \Omega_1 := \{(S, I, R) \in [0, 1]^3 : S + I + R = 1\}$since *S, I,* and *R*, are fractions of the population. This region is positively invariant.

Since $S(t), I(t), R(t) \geq 0$ and $S(t) + I(t) + R(t) = 1$. Thus $||f(t, x)|| \leq M_1$ for all $x \in \Omega_1$. If we choose any compact region $F = \{(t, x) \in R^+ \times \Omega_1 : |t - t_0| \leq a, ||x - x_0|| \leq c\}$, then we have $f \in C(F, \Omega_1)$ and $||f(t, x)|| \leq M_1$ on *F*. Therefore by Peano's Existence Theorem, Equation (2.3) has at least one solution on $[t_0 - \alpha, t_0 + \alpha]$, where $\alpha = \min(a, \frac{c}{M})$. Notice that if we choose $c \geq 3$ then $\{x : ||x - x_0|| \leq c\} \supseteq \Omega_1$

Allowance for Population Growth

If the birth and death rates are unequal, $b \neq \mu$, then the boundedness of the model is slightly more difficult to prove, since the population sizes may grow. The physical region of interest is now (potentially) unbounded; thus we define $\Omega_N := R^3_+$ (where $R^+ = [0, \infty)$). The region Ω_N is positively invariant with respect to the DE 2.3:

$S(t) = 0 \Rightarrow S' = \mu > 0$ $I(t) = 0 \Rightarrow I' = 0:$ $R(t) = 0 \Rightarrow R' = \gamma I(t) \geq 0$
so with these initial conditions in Ω_N, the trajectory of the solution will never leave Ω_N.This analysis assumes the total population will undergo exponential growth or decay depending on the relative values of b and μ.

Seir Model Without Vaccination
The differential equations for this model are;
$\frac{dS}{dt} = bN(t) - \beta S(t)\frac{I}{N} - \mu S(t)$ (1)
$\frac{dE}{dt} = \beta S(t)\frac{I}{N} - (\sigma+\mu)E(t)$ (2)
$\frac{dI}{dt} = \sigma E(t) - (\gamma + \mu + \delta)I(t)$ (3)
$\frac{dR}{dt} = \gamma I(t) - \mu R(t)$ (4)
$\frac{dN}{dt} = 0$, and $N = S+E+I+R$ is thus constant.

Properties of the SEIR Model Equations
The basic properties of the of the model equations 1-4 are feasible solutions and positivity of solutions.

Feasible solution
The feasible solution set which is positively invariant set of the model is given by,
$\emptyset = \left\{(S, E, I, R) \in R: S + E + I + R = N \leq \frac{b}{\mu}\right\}$ R_+^4

Positivity of solutions

A first-order linear differential equation of the form,

$\frac{dN}{dt} = (b - \mu)N$. Thus $N(t) = Ce^{(b-\mu)t}$ at $t = 0$ $N(0) = C$
Hence the solution of the linear differential equation then becomes
$N(t) = N(0)e^{(b-\mu)t}$ Therefore, $\emptyset$ is positively invariant.

Existence of steady states of the system
The equilibrium points of the system can be obtained by equating the rate of changes to zero.

$$\frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$$

Global asymptotic stability of the model
In proving the global stability of the SEIR Model, there is need to find the equilibrium points of the system 5-8.

Assuming that the birth rate, b is equal to death rate, μ i.e. b=μ.

1. The Analysis of the SEIR Model without pulse vaccination
This section gives an illustration of the analytical results of the SEIR model without pulse vaccination by carrying out stability analysis and numerical simulations of the model using the

parameter values pertinent to Kenya given in Table 4.1 below. These parameters were obtained from different sources in the literature

Table 4.1: Parameter symbol, values and their sources

Parameter symbol	Parameter value	Literature source
b	0.02755 per year	Gao et al(2009)
μ	0.00875 per year	Gao et al(2009)
β	0.09091 per day	D'onofrio (2004
σ	0.125 per day	Gao et al(2009)
α	0.14286 per day	Momoh et al(2013

Stability analysis of the Model

From model 3.1 when no time delay then the equations becomes

$$\frac{dS}{dt} = b(N(t) - S(t)) - \beta \frac{I(t)}{N(t)} S(t)$$

$$\frac{dI}{dt} = \beta \frac{I(t)}{N(t)} S(t) - (\mu + \gamma) I(t)$$

$$\frac{dR}{dt} = \gamma I(t) - \mu R(t)$$

Endemic Model

$\frac{ds}{dt}$ = μ -(μ+βi)s

$\frac{de}{dt}$ = βsi-(μ+σ)e

$\frac{di}{dt}$ = σe -(μ+$\gamma + \delta$)i

$\frac{dr}{dt}$ = $(\gamma + \delta)i$ -μr

Linearising the system of the differential equations, the Jacobian matrix is given as

$$\text{J(s,e,i,r)} = \begin{bmatrix} \mu + \beta i & \mu & 0 & \mu\beta \\ \beta i & \mu + \sigma & \mu & b \\ 0 & b & \mu + \gamma + \delta & 0 \\ 0 & 0 & 0 & \gamma + \delta \end{bmatrix}$$

For the infection free equilibrium (s,e,i) = (1,0,0), the Jacobian matrix then becomes

$$\text{J(1,0,0)} = \begin{bmatrix} -\mu & 0 & -\beta \\ 0 & -(\mu - \delta) & \beta \\ 0 & \delta & -(\mu - \sigma) \end{bmatrix} = \begin{bmatrix} -0.0875 & 0 & -0.09091 \\ 0 & -0.2125 & 0.09091 \\ 0 & 0.125 & -0.230336 \end{bmatrix}$$

The important sub-matrix is the second 2x2 matrix. From this, the trace (T) < 0, but if R_0 < 1, then the determinant (D) > 0 and if R_0 > 1 then (D) < 0 for all parameters

Routh-Hurwitz stability condition for T and D is given as follows:

T = - $(2\mu + \sigma + \alpha)$ = - 0.44286 and D = $(\mu + \alpha)$ $(\mu + \sigma)(1\text{-}R_0)$ = 0.02488
Hence the disease free study state when $R_0 < 0$, and unstable when $R_0 > 0$. The eigenvalues at the disease free equilibrium are given by$\{-\mu, -(\mu + \sigma), -(\mu + \alpha),\}$. All the eigenvalues are negative meaning the disease free equilibrium (1, 0, 0, 0) is asymptotically stable. The endemic equilibrium $(s^*, e^*, i^*) = \left(\frac{1}{R_0}, \frac{\mu(R_0-1)}{R_0(\mu-\sigma)}, \frac{\mu(R_0-1)}{\beta}\right)$
The Jacobian matrix for the endemic equilibrium is given as

$$J_{endemic} = \begin{pmatrix} -\mu R_0 & 0 & -(\mu+\alpha)(\mu+\sigma) \\ \mu(R_0-1) & -(\mu+\sigma) & (\mu+\alpha)(\mu+\sigma) \\ 0 & \sigma & -(\mu+\alpha) \end{pmatrix}$$

Whose Characteristic equation is given as $X^3+a_1X^2+a_2X+a_3 = 0$
Routh-Hurwitz criteria for stability, all the roots of the Characteristic equation have negative real part which means stable equilibrium is attained.

Optimal Vaccination Strategies

Herd immunity
Herd immunity is the level of immunity in a population which prevents epidemics, even if some transmission may still occur. It is well-known that the higher R_0 is for a disease, the higher the proportion of the population will have to be vaccinated to achieve herd immunity as seen by Hethcote (1989). Although, this statement could seem theoretical, it was almost the perspective followed by *WHO's Technical Working Group*(2000), when devising strategies to control a full range of diseases; for instance, this procedure has succeeded during the worldwide campaign for measles and smallpox eradication in the 1960s.

The condition for control.
Let p be the proportion immune after a vaccination campaign. To reach the so-called critical proportion p_c, we need the control condition $R_0(1 - p_c) < 1$ to be fulfilled. For instance, in most sub-Saharan Africa countries, the basic reproductive number for measles R_0 is approximately around 18 by Hethcote (1989) and Grais (2006), so $p_c = 0.94$.Under the schedule of an unique dose, the minimal coverage to control infectious diseases is such that everyone does not need be immune through vaccination to control infectious diseases.

Numerical simulations and Analysis of the Simulations of the SEIR model equations.

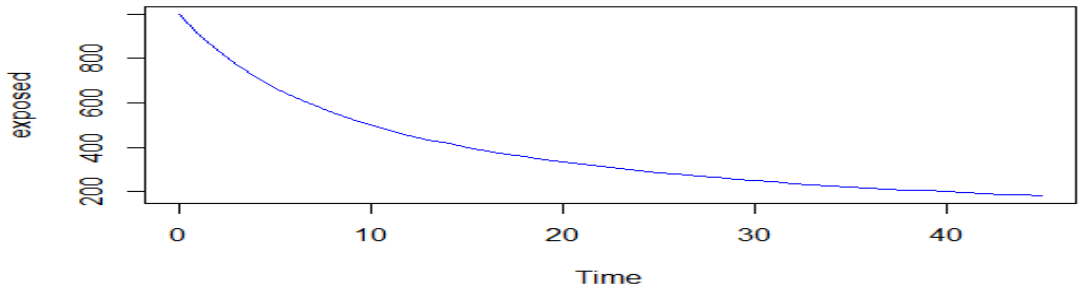

Figure 1: Simulation of the Exposed Population

In Figure 1 it can be observed that as the rate increases, the population of exposed individuals shows some rapid decrease after the earlier intervals of rise. The decrease in the exposed population could be due to early detection and also possibly due to those who enter the infective class. This decrease could also be due to the education about the infectious diseases transmission, very few individuals are coming out as infected individuals. Also the dynamics of the exposed population depend on the contact number.

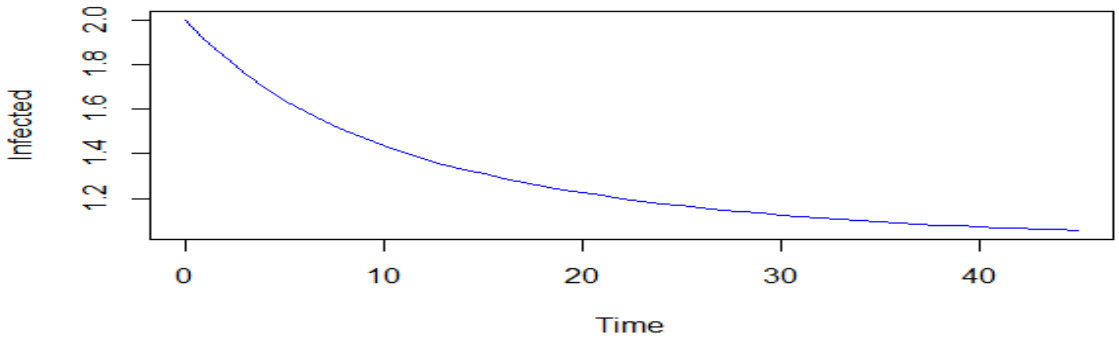

Figure 2: Simulation of the Infected Population

In Figure 2, it is realized that the population of infected individuals at the very beginning rise sharply as the rate increases and then fall uniformly as time increases. This rapid decline of the infected individuals may be due to early detection of the measles and partly due to those who revert to the Exposed class. This graph also demonstrates that the contact rate has large impact on the spread of the disease through population. If the contact rate is observed to be high then the rate of infection of the disease will also be high as would be expected logically. However, there exists another parameter to consider as more individuals are infected with the disease and I(t) grows, as some individuals are leaving the infected class by being cured and joining the recovered class.

Conditions for control of infectious diseases

Herd immunity

Herd immunity is defined as the level of immunity in a population which can prevents epidemics of a disease, even if some transmission of that particular disease may still occur in a population. If the percentage or proportion of the population that is immune exceeds the herd immunity level for the disease, then the disease can no longer persist in that particular population. Thus, if this level of immunity can be exceeded by means of mass vaccination, then the disease can indeed be eliminated.

Assuming that, the herd immunity level is denoted by v. Recall that, for a stable state: $R_0 \times S = 1$ so that, S will be (1-v), since v is the proportion of the population that are immune and v + S must be equal to one (since in the simplified model everyone one susceptible or immune). Then:

R_0X (1-v) =1, 1-v = $\frac{1}{R_0}$, v = 1- $\frac{1}{R_0}$ and therefore, v = (1- 0.0625) x 100 = 93.75%

Now let me assume that, in a given population if the average age at which a disease is contracted is *A* and the average life expectancy in that same population is given as *L.*

And it is assumed that everyone in the population lives to age *L* and then dies. If the average age of infection is *A*, then on average, individuals younger than *A* are susceptible and those older than *A* are immune. Thus the proportion of the population that is susceptible is given by

S= $\frac{A}{L}$.

But mathematical definition of the endemic steady state can be arranged to give;

S = $\frac{1}{R_0}$, therefore, $\frac{1}{R_0} = \frac{A}{L}$ and this implies that $R_0 = \frac{L}{A}$.

By using the available data,R_0 can be estimated.

When mass vaccination cannot exceed the herd immunity

If the mass vaccination due to the outbreak of a disease is insufficiently effective or the required coverage cannot be reached due to some reasons, for example in some community where the people have agree not to permit their children to be vaccinated due to some personal reasons, the programme may not be able to exceed q_c.

Suppose that a proportion of the population *v* (where $v < q_c$) is immunised at birth against an infection with $R_0 > 1$. The vaccination programme changes R_0 to Rq where Rq = R_0 (1- *v*), this change is as a result of now fewer susceptible will be in the population who can be infected. Rq is simply R_0 minus those that would normally be infected but that cannot be now since they are immune. As a consequence of this lower basic reproduction number, the average age of infection *A* will also change to some new value *A*q in those who have been left unvaccinated. Assuming that life expectancy has not changed, now

$R_Q = \frac{L}{A_Q}$, $A_Q = \frac{L}{R_Q}$, $A_Q = \frac{L}{R_0(1-V)}$

But R = $\frac{L}{A}$ So $A_Q = \frac{L}{\frac{L}{A}(1-V)}$,$A_Q = \frac{AL}{L(1-V)}$, $A_Q = \frac{A}{1-V}$, $A_Q = \frac{A}{S}$.

The vaccination programme caused the lowering of basic reproductive number, and this will also produce an increase in the average age of infection. Unvaccinated individuals now experience a reduced force of infection due to the presence of the vaccinated group.

When mass vaccination exceeds the herd immunity
If a vaccination programme causes the proportion of immune individuals in a population to exceed the critical threshold for a significant length of time, transmission of the infectious disease in that population will gradually come to a halt.

Discussion
The main objective of this study is to model delayed pulse vaccination of infectious diseases and also establish a possible way of reducing the disease transmission.
The basic reproductive number has been computed to determine the stability of the disease because theoretical determination of threshold conditions for R_0 is of important public heath interest. It was established qualitatively that the model has the disease- free equilibrium and endemic equilibrium points. It was realized that whenever $R_0 < 1$, the disease- free equilibrium point is locally asymptotically stable and unstable whenever $R_0 > 1$.
It was also realized that, in the absence of mass vaccination programme as well as early detection and supervised treatment, the transmission of the disease cannot be eradicated from the population. The introduction of proper treatment and education about the disease transmission as well as early detection of the disease can help reduce the disease in a population. The results has also shown that effective contact with the infectious individual cause a major increase of the disease transmission, hence individuals with active infectious disease must be detected as early as possible to reduce high rate of transmission in a population. Education about infectious disease can help many appear for diagnosis and get detected early.

1. The SIS Model

This model is for diseases which the infection does not confer immunity. It is called an SIS Model since individuals return to the susceptible class when they recover from the infection. Naturally occurring births and deaths (vital dynamics) are included, but the behavior of solutions is similar when vital dynamics are not included.

2. The SIR Model without vital dynamics

In this model, the diseases considered for which the infection confers permanent immunity. When such an SIR disease goes through a population in a relatively short time (less than one year) then this disease outbreak is called an epidemic. Since an epidemic occurs relatively quickly, the model does not include births and deaths (vital dynamics). Epidemics are common for diseases such as influenza, measles, rubella and chickenpox.

3. The SIR Model with vital dynamics
In this section an SIR epidemiological Model is considered, but here a model of the disease behavior in the population over a long time period. A disease is called endemic if it is present in a population for more than 10 or 20 years. Because of the long period involved, a model for an endemic disease must include births as a source of new susceptible and natural deaths in each class.

By Theorem 2 and above discussions, we know that the set Ω_0 is a global attractor in Ω, and of course, every solution of system (3.11) with initial conditions (3.12) will eventually enter and remain in region Ω_0. Therefore, system (3.11) is permanent. The proof of Theorem 3 is complete.

$$S^* = \frac{(\sigma+\alpha+\mu)(\gamma+\mu+\delta)}{\alpha\beta} \quad ,V^* = \frac{(\sigma+\alpha+\mu)(\gamma+\mu+\delta)}{\alpha\beta(\varphi+\mu)},\ I^* = \frac{\alpha\beta B(\varphi+\mu)+\varphi\lambda(\sigma+\alpha+\mu)(\gamma+\mu+\delta)}{\beta(\varphi+\mu)(\sigma+\alpha+\mu)(\gamma+\mu+\delta)} - (\frac{\lambda+\mu}{\beta})$$

$$E^* = \frac{\alpha\beta B(\varphi+\mu)+\varphi\lambda(\sigma+\alpha+\mu)(\gamma+\mu+\delta)}{\beta(\varphi+\mu)(\sigma+\alpha+\mu)} - (\frac{\lambda+\mu(\gamma+\mu+\delta)}{\alpha\beta})$$

$$E^* = \frac{\sigma\alpha\beta}{\mu(\sigma+\alpha+\mu)(\gamma+\mu+\delta)} + \frac{\lambda\sigma\varphi(\gamma+\mu+\delta)}{\mu\beta(\varphi+\mu)} - (\lambda+\mu)\frac{(\gamma+\mu+\delta)}{\alpha\beta\mu} + \frac{\alpha\gamma\beta}{\mu(\sigma+\alpha+\mu)}$$

$$dE/dt = \beta S(t)I(t) - (\sigma+\alpha+\mu E\ (t)$$
$$dI/dt = \beta S(t)I\ (t) - (\mu+\gamma+\alpha)I$$

We have analyzed the SIR epidemic model with pulse vaccination and distributed time delay. Two thresholds have been established, one for global stability of the infectious-free solution and one for persistence of the endemic solution.

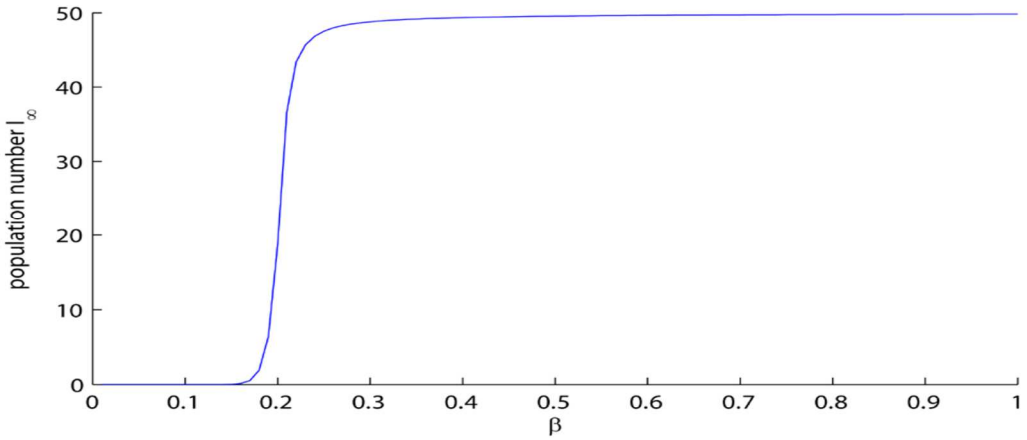

Figure 3 The bifurcation diagram the unique endemic equilibrium (the component *I* of infectious individuals regarding β as the bifurcation parameter, all other parameters are same as in model (5.1)).

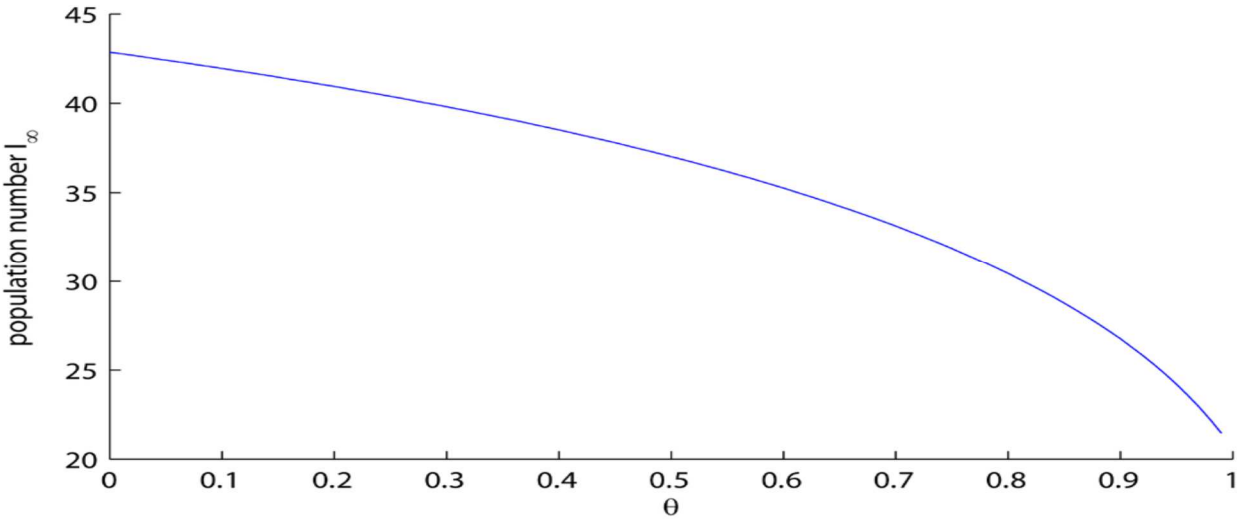

Figure 4. The bifurcation diagram the unique endemic equilibrium (the component *I* of infectious individuals regarding θ as the bifurcation parameter, all other parameters are same as in model (5.1) except for β = 0.214).

From Figures 1 and 2, we can observe the following:

(i) R^* and R_* are inversely proportional to θ value and directly proportional to τ value and R_0value, which implies that pulse vaccination measures the inhibition effect from the behavioral change of the susceptible when they transfer to the infectious class (*I*).

(ii) R^* is a directly proportional to μ value, which implies that the natural birth or death rate measures the inhibition effect from the behavioral change of the susceptible class (with *S*) when it moves into the infectious class (*I*).

(iii) R_* is inversely proportional to *h* value, which implies that the maximum infectious period of the disease measures the inhibition effect from the behavioral change of the susceptible class (with *S*) when it moves into the infectious class *I(t).*

(iv) There is a value μ^* such that R_* is directly proportional to μ when $\mu < \mu^*$ and is inversely proportional to μ when $\mu > \mu^*$. Therefore the larger death rate is sufficient for the global attractivity of infection free periodic solution *(S̃e(t), 0)*. It is easy to verify. In fact, we can calculate the derivative of R_* with respect to μ

$$\frac{dR*}{d\mu} = \frac{(1-\theta)e^{-\mu h}R_0}{[1-(1-\theta)e^{-\mu h}]^2} g(\mu), \quad \text{.....3.52}$$

Where $g(\mu) = \theta\tau e^{-\mu\tau} - h(1 - e^{-\mu\tau})(1 - (1 - \theta)e^{-\mu\tau})$. Obviously, $g'(\mu) < 0$ and $g(0) > 0$, $lim\mu \to +\infty\ g(\mu) < 0$. Hence, there exists a μ^* such that $dR^*/d\mu > 0$ for $\mu \in (0, \mu*)$, whereas $dR^*/d\mu < 0$ for $\mu \in (\mu^*, +\infty)$.

Epidemic models with time delays have received much attention since delays can often cause some complicated dynamical behaviors. Delays in many models can destabilize equilibrium and thus lead to periodic solutions by Hopf bifurcation Hethcote *et al* (1981), Cooke L. and Busenberg S. (1993). It is well known that periodic forcing can drive SIR and SEIR models into a behavior which looks chaotic, Smith L. and Schwartz B.(1983).

The impulsive model with distributed time delay (3.11) will be analyzed, in particular paying attention to the following points:

(i) The global asymptotic stability for SIR model with pulse vaccination and distributed time delay;

(ii) The behavior of the model when an insufficient level of people undergoes the vaccination: bifurcation and chaotic solutions;
(iii) Whether periodic or pulse vaccination does a better job than constant vaccination at the same average value.

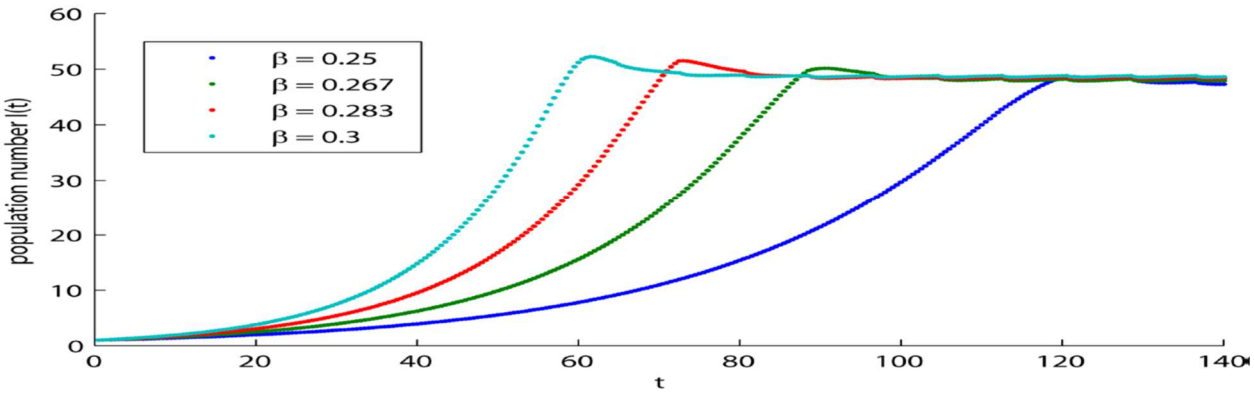

Figure 5: Time series of system (2.1) * θ = 0.214, *R* =1.0529

Figure 5The tendency of the infected individuals *I* with different values of β

Therefore, an interesting open problem is proposed whether we can prove that the positive periodic solution of model (2.1) is globally attractive as * *R* >1.

Finally, the numerical simulations of the stroboscopic map of model on the number of infected individuals with different values of β are shown in Figure 5. It shows that the number of infected individuals will increase steadily in next few days, then reach the peak and begin a slow decline, and finally become stable. The greater the value β , the bigger the peak value and the earlier the peak appears. Our result implies that decreasing infection rate can put off the disease outbreak and reduce the number of infected individuals.

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