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Modeling the Impact of Immunization on the Epidemiology of Varicella Zoster Virus.

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Abstract

Chickenpox (also called varicella) is a disease caused by virus known as varicella-zoster virus (VZV) also known as human herpes virus 3. In this paper, a deterministic mathematical model for transmission dynamics of VZV with vaccination is formulated. The effective reproduction number is computed in order to measure the relative impact for individual or combined intervention for effective disease control. Numerical simulations of the basic reproduction number of the model shows that, the combination of vaccination and treatment is the most effective way to combat the epidemiology of VZV in the community.

Keywords: Modeling, Treatment, Vaccination, Epidemiology.

1. Introduction

Chickenpox (also called varicella) is a disease caused by virus known as varicella-zoster virus (VZV) also known as human herpes virus 3 (HHV -3) (Almuneef , 2006) . In non-vaccinated populations, primary infections tend to occur at a younger age (Gerson, 2008).

The main symptoms of chickenpox are fever, headache, stomach ache,itchy rash especially in the mouth, on chest, abdomen, back, face and upper arms and legs. The rash starts as small red spot, difficult breathing, malaise and anorexia.

Chickenpox is widely transmitted from touching the fluids from chickenpox blister. The virus is spread either by direct contact with a person with active chickenpox or shingles, or by direct contact with clothes or other articles infected with vesicle fluid, saliva, nasal discharge etc, or by air borne spread of small droplets of infected mucous of fluid.

There are different notions to the origin of the name of this disease. One is, once infected; the skin appeared as picked by chicken. Another is the rash resembles the seeds of Chick Peas. Most common explanation is that the disease is not that much dangerous compared to small pox so it is a 'chicken' version of pox.

The occurrence of chicken pox is different in different geographical zones. In temperate countries chickenpox is usually a mild, self-limiting infection, affecting pre-school children (Vyse, 2004), however, the incidence of chickenpox in these areas is increasing in adolescents and adults (Fairley &Miller, 1996), which may in part be due to increased world travel and economic migration of susceptible individuals. In many tropical countries the epidemiology is different, with about 60% of adults being immune (Lee, 1998).

In the past, the varicella zoster virus affected virtually the entire population and had substantial morbidity and mortality associated with both primary varicella and herpes zoster reactivation. Since the varicella vaccine was first approved in 1995, there has been a significant decline in incidence, morbidity, and mortality caused by primary varicella. Breakthrough disease with the one-dose vaccine schedule led to the recommendation in 2006 that children receive a two-dose vaccine series. Older adults have also benefited from the development of the

zoster vaccine. In 2006, the Food and Drug Administration approved the zoster vaccine, a higher concentration of the same live attenuated virus used in the primary varicella vaccine, for persons 60 years of age or older. It has the potential to help millions of people to avoid the pain associated with reactivation of the varicella zoster virus by reducing the incidence and severity of herpes zoster and postherpetic neuralgia.

The treatment for a patient with chickenpox is: reducing itches and irritation by keeping the skin cool with light clothing and tepid baths or sponging. Calamine lotion applied to spots, or antihistamine tablets may also help. Paracetamol or ibuprofen can be taken if lesions are painful and will lose fever.

The first vaccination was developed by Michiaki Takahash in 1974 derived from Oka strain. Some countries require the varicella vaccine for children before entering elementary school. Immunity derived from vaccine is not lifelong and subsequent vaccination is necessary usually after 5 years after initial vaccination. Chickenpox is characterized by long latent period (about two weeks), infectious period (one week) and permanent immunity after recovery.

2. Model Formulation

In this section we formulate a deterministic mathematical model for VZV which incorporates vaccination strategy. The total population is divided into the following epidemiological classes or subgroups: susceptible *S*, vaccinated V, Exposed E, infectious I, recovered R. Basically; we modify the SEIR model by adding a vaccination compartment which caters for immunization.

Let us assume that the per capita birth rate Π is constant, the natural fatality rate μ is time constant, there is no disease induced death, the members of the population mix homogenously (have the same interactions with one another to the same degree), and lastly assume that on recovery, there is a permanent immunity of the rate η. Furthermore, assume that individuals can be infected through direct contact c, with an infectious individual. Let β be the probability that a susceptible individual becomes infected by one infectious individual. Let Λ be the constant recruitment rate.

The susceptible and vaccinated individuals are recruited by both birth and immigration. A proportion ρ of the recruits are vaccinated, the remaining $1-\rho$ are not vaccinated so they join the susceptible compartment. Proportions of newborns ϕ are vaccinated, and the remaining $1-\phi$ newborns are not vaccinated and hence join the susceptible compartment. We consider that a proportion of the population of susceptible to receive a first dose vaccine at the rate θ_1, whereas the rest of it progress with the disease.

The primary vaccine wanes at the rate α after a fixed time t. After the first vaccine has expired, a proportion $1-f$ of the vaccinated individuals at dose one, join the susceptible compartment at the rate α while the remaining proportion f receive a second dose at the rate θ_2. Our assumption is that the individuals who have attended the first and the second dose consecutively receive permanent immunity; otherwise they become susceptible to the disease again. The susceptible individuals enter the exposed compartment at the rate λ which is a force of infection. The exposed individuals are the ones who are infected but not infectious. After some time the exposed become infectious, they move from exposed state to infectious at the rate δ. An infected individual recover at rate η, and according to the nature of the disease; the recovered individuals are permanently immune.

This description of dynamics of VZV can be summarized by compartmental diagram **Figure 1**

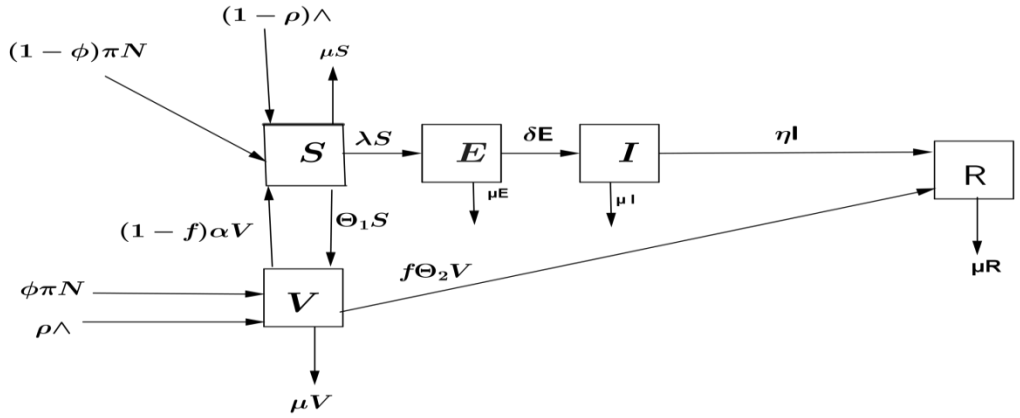

Figure 1.A Compartmental diagram for the dynamics of Varicella Zoster Virus (VZV) in a community with Immunization**.**

Table 1. Parameters used in the model formulation and their description

Parameter	Description
π	Per capita birth rate.
Λ	The recruitment rate of susceptible population.
ρ	Proportion of vaccinated immigrant babies.
c	Per capita contact rate.
β	The probability that a susceptible individual becomes infected by one infectious individual.
δ	The rate of progression from latent class to infectious class.
α	The rate of waning of a vaccine.
f	The proportion of vaccinated individuals who receive a second dose vaccine.
θ_1	The vaccine coverage rate for the first dose.
θ_2	The vaccine coverage rate for the second dose.
η	Recovery rate of treated infectious individuals.
μ	Per capita natural mortality death rate.

2.1 The *Model Equations*

From the assumptions and the dynamics between the compartments shown in the model compartments in **Figure1**, the impact of immunization on the epidemiology of VZV is modeled by following system of ordinary differential equations

$$\frac{dS}{dt} = (1-\phi)\pi N + (1-\rho)\Lambda + (1-f)\alpha V - (\lambda + \mu + \theta)S \quad (1)$$

$$\frac{dV}{dt} = \rho\Lambda + \phi\pi N + \theta_1 S - ((1-f)\alpha + f\theta_2 + \mu)V \quad (2)$$

$$\frac{dE}{dt} = \lambda s - (\mu + \delta)E \quad (3)$$

$$\frac{dI}{dt} = \delta E - (\eta + \mu)I \quad (4)$$

$$\frac{dR}{dt} = \eta I + f\theta_2 \text{v-}\mu R \quad (5)$$

where λ is the force of infection and is given by $\lambda = \frac{\beta cI}{N}$.

The total population sizes $N(t) = S(t) + V(t) + E(t) + I(t) + R(t)$ and

$$\frac{dN}{dt} = \Lambda + (\pi - \mu)N$$

determined by which are derived by adding Equation of the system (1-5).

2.2 Dimensionless transformation

For simplicity of analysis we normalized quantities. This can be done by scaling the population of each class by the total population.

We transforms follows $v = \frac{V}{N}, s = \frac{S}{N}, e = \frac{E}{N}, i = \frac{I}{N}$ and $r = \frac{R}{N}$ in classes V, S, E, I and R.

Hence the normalized model system becomes,

$$\frac{ds}{dt} = (1-\phi)\pi + (1-\rho)a + (1-f)\alpha v - (\lambda + \theta_1 + a + \pi)s \quad (6)$$

$$\frac{dv}{dt} = \phi\pi + \rho a + \theta_1 s - ((1-f)\alpha + f\theta_2 + a + \pi) \quad (7)$$

$$\frac{de}{dt} = \lambda s - (\delta + a + \pi)e \quad (8)$$

$$\frac{di}{dt} = \delta e - (\eta + a + \pi)i \quad (9)$$

$$\frac{dr}{dt} = \eta i + f\theta_2 v - (a + \pi)r \quad (10)$$

Subject to the restriction that leads to studying the system (6-10) in the region T where

$$T = \{(s,v,e,i,r) \in R^5_+ : 0 \le s, 0 \le v, 0 \le e, 0 \le i, 0 \le r, s+v+e+i+r \le 1\}$$

The feasible region (where the model makes biological sense) can be shown to be positively invariant.

3. Model analysis

The model system (6-10) is analyzed qualitatively to get insights into its dynamical features which give better understanding of the impact of immunization on the epidemiology of varicella zoster virus.

3.1 Disease Free Equilibrium (DFE), P_0

The disease free equilibrium of the model system (6-10) is obtained by setting $\frac{dv}{dt} = \frac{ds}{dt} = \frac{de}{dt} = \frac{di}{dt} = \frac{dr}{dt} = 0$ and in case there is no disease; $e = i = 0$ the sum of susceptible and vaccinated populations is equal to total population. That is to say $s_0{}^* + v_0{}^* + r_0{}^* = 1$

Consequently, system (3.2) is reduced to:

$$-(\lambda + \theta_1 + a + \pi)s + (1-f)\alpha v + (1-\phi)\pi + (1-\rho)a = 0$$

$$\theta_1 s - ((1-f)\alpha + f\theta_2 + a + \pi)v + \phi\pi + \rho a = 0$$

$$f\theta_2 v - (a+\pi)r = 0$$

which implies:

$$s^*{}_0 = \frac{(1-f)\alpha(a+\pi) + (f\theta_2 + a + \pi)[(1-\phi)\pi + (1-\rho)a]}{(a+\pi)(1-f)\alpha + (f\theta_2 + a + \pi)(\theta_1 + a + \pi)} \quad (11)$$

$$v_0{}^* = \frac{(a+\pi)(\theta_1 + \phi\pi + \rho a)}{\theta_1(f\theta_2 + a + \pi) + (a+\pi)[(1-f)\alpha + f\theta_2 + a + \pi]}$$

$$r_0{}^* = \frac{f\theta_2(\theta_1 + \phi\pi + \rho a)}{\theta_1(f\theta_2 + a + \pi) + (a+\pi)[(1-f)\alpha + f\theta_2 + a + \pi]}$$

Thus the Disease Free Equilibrium (DFE) point denoted by P_0 of the model system (6-10) exists and is given by:

$$P_0(s^*, v^*, e^*, i^*, r^*) = (s_0{}^*, v_0{}^*, 0, 0, r_0{}^*)$$

3.2 The Basic Reproduction Number,R_0

Diekmann et al (1990) defined the basic reproduction number denoted by R_0, as the average number of secondary infections caused by an infectious individual during his or her entire period of infectiousness. The

basic reproduction number is an important non-dimensional quantity in epidemiology as it sets the threshold in the study of a disease both for predicting its outbreak and for evaluating its control strategies. Thus, whether a disease becomes persistent or dies out in a community depends on the value of the reproduction number, R_0.

Furthermore, stability of equilibria can be analyzed using R_0. If $R_0 < 1$ it means that every infectious individual will cause less than one secondary infection and hence the disease will die out and when R0 > 1, every infectious individual will cause more than one secondary infection and hence the disease will invade the population. A large number of R_0 may indicate the possibility of a major epidemic. For the case of a model with a single infected class, R_0 is simply the product of the infection rate and the mean duration of the infection.

In more complicated epidemics we compute the basic reproduction number, R_0 using the next generation operator approach by van den Driessche and Watmough (2002).

From the system Eq. (6-10) we define $\mathcal{F}_i$ and $\mathcal{V}_i$ as

$$\mathcal{F}_i = \begin{bmatrix} \beta cis \\ 0 \end{bmatrix}, \mathcal{V}_i = \begin{bmatrix} (\delta + a + \pi)e \\ \delta e - (\eta + a + \pi)i \end{bmatrix}$$

We differentiate $\mathcal{F}_i$ with respect to e and i to get $F = \begin{bmatrix} 0 & \beta cs \\ 0 & 0 \end{bmatrix}$

We differentiate $\mathcal{V}_i$ with respect to e and i and get V

$$V = \begin{bmatrix} (\delta + a + \pi) & 0 \\ -\delta & (\eta + a + \pi) \end{bmatrix}$$

We find the inverse of V and get

$$V^{-1} = \begin{bmatrix} \frac{1}{\delta + a + \pi} & 0 \\ \frac{\delta}{(\delta + a + \pi)(\eta + a + \pi)} & \frac{1}{\eta + a + \pi} \end{bmatrix}$$

$$FV^{-1} = \left[\frac{\partial \mathcal{F}_i(E_0)}{\partial x_j} \right] \left[\frac{\partial \mathcal{V}_i(E_0)}{\partial x_j} \right]^{-1}$$

$$V^{-1}=\begin{bmatrix}0 & \beta cs_0^* \\ 0 & 0\end{bmatrix}\begin{bmatrix}\frac{1}{\delta+a+\pi} & 0 \\ \frac{\delta}{(\delta+a+\pi)(\eta+a+\pi)} & \frac{1}{\eta+a+\pi}\end{bmatrix}$$

$$=\begin{bmatrix}\frac{\beta cs_0^*\delta}{(\delta+a+\pi)(\eta+a+\pi)} & \frac{\beta cs_0^*}{\eta+a+\pi} \\ 0 & 0\end{bmatrix}? \quad ? \qquad (12)$$

and from eqn.(11)

$$s^*_0=\frac{(1-f)\alpha(a+\pi)+(f\theta_2+a+\pi)[(1-\phi)\pi+(1-\rho)a]}{(a+\pi)(1-f)\alpha+(f\theta_2+a+\pi)(\theta_1+a+\pi)}$$

The eigenvalues, λ of equation (11) can be computed from the characteristic equation:

$\left|FV^{-1}-\lambda I\right|=0$. And we see that from our matrix that $\lambda_1=\frac{\beta cs_0^*\delta}{(\delta+a+\pi)(\eta+a+\pi)}$ and $\lambda_2=0$

Obviously, λ_1 is the dominant eigenvalue and becomes equal to R_0 of the model.

Therefore, if we substitute s_0^* from eq. (12) into λ_1 we get effective reproduction number

$$R_e=\frac{\beta c\delta\{(1-f)\alpha(\phi\pi+\rho a)+[(1-f)\alpha+f\theta_2+a+\pi][(1-\phi)\pi+(1-\rho)a]\}}{\{\theta_1(f\theta_2+a+\pi)+(a+\pi)[(1-f)\alpha+f\theta_2+a+\pi]\}(\delta+a+\pi)(\eta+a+\pi)} \qquad (13)$$

When there is no any control strategy, then $\theta_1=\theta_2=\phi=\rho=0$ and hence $f=0,\alpha=0,$ so we get basic reproduction number

$$R_0=\frac{\beta c\delta}{(\delta+a+\pi)(\eta+a+\pi)} \qquad (14)$$

Now from the effective reproduction number R_e in equation (13) we can derive the other possible reproduction numbers with respect to different scenarios denoted by $R_{e1}, R_{e3}, R_{e4}R_e$ and R_0.

Consider a scenario when we do not give first vaccine to the susceptible individuals and also we do not give a second vaccine to the primary vaccinated individuals. Thus, we administered a first dose vaccine only to some newborns and the immigrants. We therefore set the parameters $\theta_1=\theta_2=f=0$ and obtain the reproduction number denoted by Re_1 and is given by

$$R_{e1}= \frac{(\alpha+a+\pi-(\phi\pi+\rho a))R_0}{(\alpha+a+\pi)} \quad (15)$$

We observe that the term $(\phi\pi+\rho a)>0$ makes Re_1 less than R_0 thus $R_{e1}<R_0$ and so we conclude that the endemicity of the infection is reduced more when vaccination is administered to newborns and immigrants.

Consider also the scenario when we give first dose vaccine to adult susceptible individuals, newborns and the immigrants. Now we set the parameters $\theta_1\neq 0,\alpha\neq 0,\rho\neq 0,\phi\neq 0,\theta_2=0,\ f=0$ and obtain the reproduction number denoted by Re_3 which is given by

$$R_{e3}= \frac{(\alpha+(1-\phi)\pi+(1-\rho)a)R_0}{(\theta_1+\alpha+a+\pi)} \quad (16)$$

since $\theta_1>0$ then $R_{e3}<R_{e1}<R_0$ thus we conclude that the endemicity of VZV is even more reduced when vaccination is administered to adult susceptible individuals , newborns and the immigrants.

Our last consideration is when we administer two dose vaccines to the susceptible adults only; we neglect the immigrants and newborns. We set the parameters:

$\theta_1\neq 0,\alpha\neq 0,\theta_2\neq 0,\rho=0,\phi=0,\ f=0$ therefore get reproduction number denoted by R_{e4} which is given by

$$R_{e4}=\frac{((1-f)\alpha+f\theta_2+a+\pi)(a+\pi)R_0}{\theta_1(f\theta_2+a+\pi)+(a+\pi)((1-f)\alpha+f\theta_2+a+\pi)} \quad (17)$$

The comparison between R_{e4}, with other reproduction numbers from equations (16-15) is not obvious analytically, so we opt for numerical simulation to see how they behave.

4. Simulation and Discussion

A VZV model with vaccination is formulated and analyzed. The main objective of this study was to assess the impact of immunization strategies on the transmission dynamics of the disease. In order to support the analytical results, graphical representations showing the variations in reproduction numbers with respect to exposure rate are provided in Figure 2. Since, most of the parameters are not readily available; therefore we estimated them just for the purpose of illustration. Table 3 shows the set of parameter values which were used.

Table 2. Parameters used in model simulations

Parameters	value	Source
f	0.5	Estimated
π	0.45/year	Estimated
θ_1	0.7/year	Estimated
θ_2	0.8/year	Estimated
α	0.36/year	Estimated
ρ	0.7	Estimated
η	0.6/year	Estimated
δ	0.3/year	Estimated
a	0.2/year	Estimated

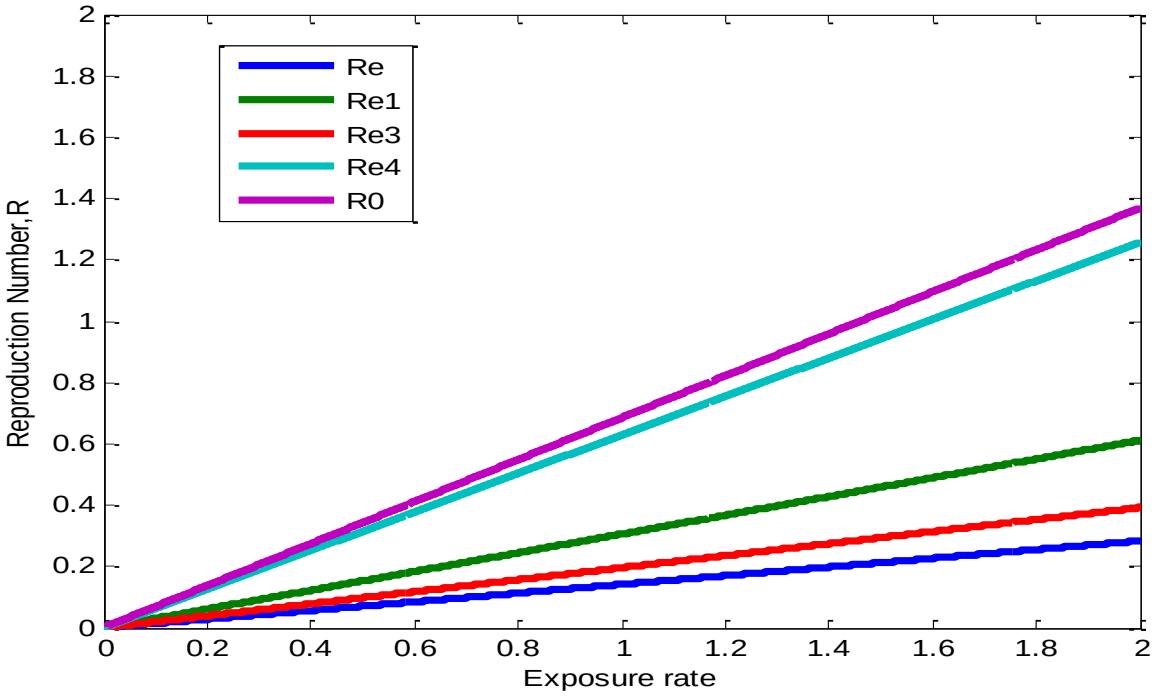

Figure 2: Variations in reproduction number with respect to exposure rate.

Figure 2 shows that, $R_e < R_{e3} < R_{e1} < R_{e4} < R_0$.

We see from the figure that R_0 is worst case scenario, it occurs when there is no vaccination strategy to control

the epidemic, here an individual recovers naturally. The basic reproduction number R_0 is at the peak, this implies that there is a high increase in reproduction number with respect to exposure rate. Such increase results in the eruption of VZV in the community.

The best case scenario occurs at graph R_e , here vaccination is offered to newborns, immigrants and the susceptible adults in two doses, we note that R_e has the least value of increase in reproduction number with respect to exposure rate, which implies that VZV can be eradicated from the community if at all two dose vaccination policies is seriously implemented.

The next to the best case scenario is R_{e3} which takes account for one dose vaccine for the adult susceptible, immigrants and newborns groups, in fact R_{e3} has a smaller rate of increase of reproduction number with respect to exposure rate than other consideration of reproduction numbers. Such a reduction in reproduction number indicates that VZV may not exist.

The middle line R_{e1} implies dose one vaccination is administered to newborns only. Here immigrants and adult susceptible are neglected in vaccination at all. It can be noted that the reproduction number R_{e1}, has bit much greater rate than R_{e3} and R_e. This means that the less we vaccinate the bigger is the reproduction number and as a result disease prevails.

The graph R_{e4} is line just below R_0, it represents the case when two doses of vaccine have been administered to susceptible adults only, no vaccine is given to newborns and recruits. We note that the rate of increase in reproduction number is growing up very sharp which implies that there is a need of vaccinating a large number of individuals in the community as for example newborns and recruits so as to eradicate VZV. Adult's vaccination alone is not sufficient to eradicate the disease from community.

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