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The Impact of Hospitalization in the Management of Cholera: A mathematical Modelling Approach

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Abstract: **Cholera is an infectious water borne disease caused by the gram-negative bacterium Vibrio Cholerae. It is manifested in signs and symptoms such as severe rice-water diarrhea and vomiting. It is mainly a disease of countries and regions with high inequality levels, conflict and resource starved. Globally, it affects more than 2.8 million people and kills about 95000 people annually. This thesis seeks to investigate the impact of management of cholera through hospitalization with a major focus on Baringo county. It has a model for mathematical epidemiological modelling to investigate the disease dynamics and the consequential impact of hospitalization as a measure to manage outbreaks. The stability of the cholera dynamics was determined analytically indicating that for cholera outbreaks to be managed effectively the basic reproduction should be less than one. The basic reproduction number was determined and analyzed analytically. The sensitivity analysis of the parameters was conducted with respect to their contribution to the basic reproduction number. The numerical solution was determined and used to draw conclusion on future trends of the disease dynamics under different prevailing conditions.**

Keywords: **Cholera dynamics, mathematical modelling, epidemiological modelling, hospitalization modelling, sensitivity analysis.**

1. INTRODUCTION

Waterborne infections are one of the leading causes of death in the African continent. Cholera is one of the most prominent waterborne diseases having a great impact in the rural counties, provinces and townships of the continent. Cholera is caused by the gram negative bacterium Vibrio Cholerae through consumption of contaminated food or water. In particular, the cholera toxin (CT)-producing V. cholerae strains of O139 and O1 serogroups [5] are responsible for the majority of cholera outbreaks in the world.

Some of the common symptoms of cholera include vomiting and severe rice-water like diarrhea. The diarrhea is very severe to extent of outputting as high as 1 L/h of diarrheal fluids. As a consequence of the cumulative impact of vomiting and diarrhea, patients are always at a high risk of dehydration and hypovolemic shock which often results in a high fatality rate if treatment is not offered in good time.

Oral rehydration solution (ORS) is the mainstay therapy prescribed to cholera patients since it is effective in increasing hydration and can reduce the mortality rate from around 50% to 1%. ORS can effectively be administered in a hospital environment to maximize its effectiveness since it has limitations. The limitations include lack of capacity to reduce stool output, ineffectiveness in severe diarrhea cases, which account for about 20% of cholera cases, and lastly lack of clean water supply in epidemic areas.

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Administration of antibiotics is another intervention recommended but often used in moderate and severe occasions. Antibiotic administration has been proven to reduce the duration of diarrhoea and stool by about 50% thus reducing the amount of intravenous fluid necessary for rehydration as well as reduce the period of V. Cholerae excretion to 1-2 days from 5 days [5]. However, the utilization of antibiotics is not a sustainable solution since the bacteria becomes more resistant to the antibacterials thus making it hard to treat cholera. It should be noted that the most effective environment to administer both treatment option is the hospital environment.

2. MODEL DESCRIPTION AND FORMULATION

This project considered a compartmental model with a total population (N) to analyze the transmission dynamics of Cholera. The total population (N) is categorized into five compartments; the susceptible individuals (S), who are not colonized by cholera bacterium but are at risk of infection; the vaccinated individuals (V), who are individuals vaccinated against cholera. The vaccination rate is denoted by ξ while φ denotes the vaccination immunity waning rate. The susceptible individuals get infected at a rate of β while the vaccinated individuals get infected after their vaccine has waned or failed at a rate of ρ, governed by the law of mass action. The infectious compartment (I) contains people infected with cholera. The hospitalized individuals are contained in the Hospitalization compartment (H) while the recovered compartment (R) contains individuals with temporary immunity.

The infected individuals are hospitalized at the rate α. The infected individuals recover at a rate of τ without being hospitalized while the hospitalized individuals recover at a rate of ω. The recovered individual's temporary immunity wanes at a rate of ψ. The recruitment rate of individuals into the model is given by Λ. Lastly, the individuals under study die at a natural rate μ while the infected ones dies at a rate of σ.

2.1 Model diagram

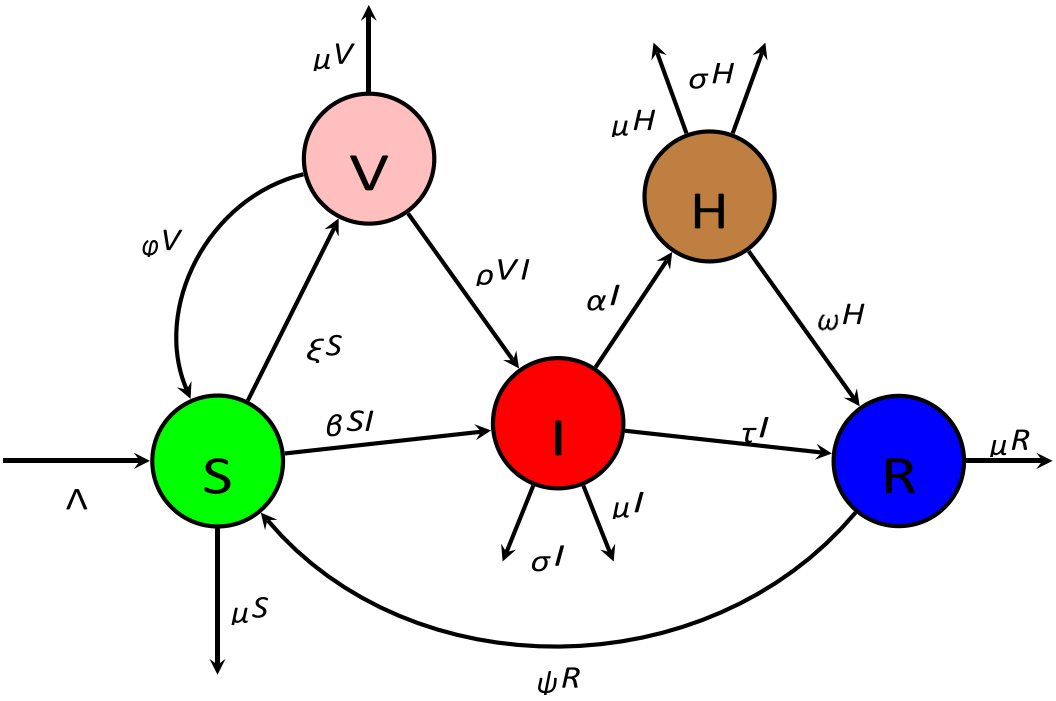

Figure 1: The Model

The time evolution state of the susceptible (S), vaccinated (V), infected (I), hospitalized (H), and recovered (R) populations can be expressed by the following deterministic ordinary differential equations:

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Lambda + \phi V - \xi S - \beta SI - \mu S + \psi R \\
\frac{dV}{dt} &= \xi S - (\phi + \mu)V - \rho VI \\
\frac{dI}{dt} &= \beta SI + \rho VI - (\mu + \sigma + \tau + \alpha)I \\
\frac{dH}{dt} &= \alpha I - (\sigma + \mu + \omega)H \\
\frac{dR}{dt} &= \tau I + \omega H - (\psi + \mu)R
\end{aligned}\right\} \qquad (2.1)$$

3. POSITIVITY AND BOUNDEDNESS

This section analyzed the positivity and boundedness of the epidemiological model to ensure that it is well posed mathematically [3]. We assumed that the initial conditions lie within a closed bounded set Ω thus 2.1 has a closed and bounded solution in ω at all time $t \geq 0$ given by

$$\Omega = \left\{(S,V,I,H,R) \in \mathbb{R}^5_+ : S + V + I + H + R = N\right\}$$

The total population is given by N(t)= S(t)+V(t)+I(t)+H(t)+R(t), therefore

$$\frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dV(t)}{dt} + \frac{dI(t)}{dt} + \frac{dH(t)}{dt} + \frac{dR(t)}{dt}$$

Utilizing the equation 2.1, we get

$$\begin{aligned}
\frac{dN(t)}{dt} &= \Lambda + \phi V - \xi S - \beta SI - \mu S + \psi R + \xi S - (\phi + \mu)V - \rho VI + \beta SI + \rho VI \\
&\quad -(\mu + \sigma + \tau + \alpha)I + \alpha I - (\sigma + \mu + \omega)H + \tau I + \omega H - (\psi + \mu)R
\end{aligned}$$

which reduces to

$$\frac{dN(t)}{dt} = \Lambda - \mu S - \mu V - (\sigma + \mu)H - \mu R$$

which can be reduced into,

$$\frac{dN(t)}{dt} = \Lambda - \mu(S(t) + V(t) + I(t) + H(t) + R(t)) + (\sigma + \mu)H(t)$$

but $N(t)= S(t)+V(t)+I(t)+H(t)+R(t)$. Therefore,

$$\frac{dN(t)}{dt} \leq \Lambda - \mu(N(t)) + (\sigma + \mu)H(t) \qquad (3.1)$$

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At the initial conditions there is no hospitalization thus 3.1 reduces to

$$\frac{dN(t)}{dt} \leq \Lambda - \mu N(t) \tag{3.2}$$

Which is a separable differential equation. As such,

$$\frac{dN(t)}{\Lambda - \mu N(t)} \leq dt$$

Integrating both sides we obtain

$$-\ln(\Lambda - \mu N(t)) \leq t + A$$

$$\ln \frac{1}{\Lambda - \mu N(t)} \leq t + A$$

Raising both sides to power e

$$e^{\ln \frac{1}{\Lambda - \mu N(t)}} \leq e^{(t+A)}$$

$$\frac{1}{\Lambda - \mu N(t)} \leq Ae^{t}$$

taking inverses on both sides

$$\Lambda - \mu N(t) \geq \frac{1}{A} e^{-t}$$

$$\Lambda - Ae^{-t} \geq \mu N(t)$$

$$\mu N(t) \geq \Lambda - Ae^{-t}$$

Which simplifies to

$$N(t) \leq \frac{\Lambda}{\mu} - \frac{A}{\mu} e^{-t}$$

at $t = 0$ we have

$$N(t) \leq \frac{\Lambda}{\mu} - \frac{A}{\mu} e^{-t}$$

which simplifies to

$$A = \Lambda - \mu N_0$$

Therefore,

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

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

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simplifying, we have

$$N(t) \le N_0 e^{-t} + \frac{\Lambda}{\mu}\left(1 - e^{-t}\right)$$

as $t \to \infty$

$$\lim_{t\to\infty} N(t) = \frac{\Lambda}{\mu}$$

4. THE DISEASE FREE EQUILIBRIUM

At the equilibrium point we have no variation with time thus the dynamical system 2.1 reduces to

$$\left.\begin{aligned} 0 &= \Lambda + \phi V - \xi S - \beta SI - \mu S + \psi R \\ 0 &= \xi S - (\phi + \mu)V - \rho VI \\ 0 &= \beta SI + \rho VI - (\mu + \sigma + \tau + \alpha)I \\ 0 &= \alpha I - (\sigma + \mu + \omega)H \\ 0 &= \tau I + \omega H - (\psi + \mu)R \end{aligned}\right\} \quad (4.1)$$

At the disease free equilibrium (DFE) $I = 0$ implying that $H = 0$ and $R = 0$. by extension $V = 0$ since cholera vaccination is given to targeted populations [2]. As such 4.1 reduces to

$$0 = \Lambda - \xi S_0 - \mu S_0 \quad (4.2)$$

and

$$0 = \xi S_0 \quad (4.3)$$

Implying that $\xi = 0$ since S_0 is not equal to 0. Applying this result to 4.2 above we get

$$0 = \Lambda - \mu S_0 \quad (4.4)$$

Thus

$$S_0 = \frac{\lambda}{\mu} \quad (4.5)$$

Which can be written as $(S_0, V_0, I_0, H_0, R_0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$

5. BASIC REPRODUCTION NUMBER

The next generation matrix method is used to determine the basic reproduction number R_0 [7] which gives a measure of every secondary infection arising from primary novel infection [4].

$$f = \begin{bmatrix} \beta SI + \rho VI \\ 0 \end{bmatrix} \quad (5.1)$$

$$v = \begin{bmatrix} (\mu + \sigma + \tau + \alpha)I \\ -\alpha I + (\sigma + \mu + \omega)H \end{bmatrix} \quad (5.2)$$

$$F = \begin{bmatrix} \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial E} \\ \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial E} \end{bmatrix} = \begin{bmatrix} \beta SI + \rho VI & 0 \\ 0 & 0 \end{bmatrix} \tag{5.3}$$

$$V = \begin{bmatrix} \frac{\partial v_1}{\partial I} & \frac{\partial v_1}{\partial E} \\ \frac{\partial v_2}{\partial I} & \frac{\partial v_2}{\partial E} \end{bmatrix} = \begin{bmatrix} (\mu + \sigma + \tau + \alpha) & 0 \\ -\alpha & (\sigma + \mu + \omega) \end{bmatrix} \tag{5.4}$$

At DFE given by $(S_0, V_0, I_0, H_0, R_0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$

$$F = \begin{bmatrix} \frac{\beta\Lambda}{\mu} & 0 \\ 0 & 0 \end{bmatrix} \tag{5.5}$$

and

$$V = \begin{bmatrix} (\mu + \sigma + \tau + \alpha) & 0 \\ -\alpha & (\sigma + \mu + \omega) \end{bmatrix} \tag{5.6}$$

The inverse V^{-1} is given by

$$\begin{bmatrix} \frac{1}{(\tau + \sigma + \alpha + \mu)} & 0 \\ \frac{\alpha}{(\tau + \sigma + \alpha + \mu)(\omega + \sigma + \mu)} & \frac{1}{(\omega + \sigma + \mu)} \end{bmatrix} \tag{5.7}$$

The next generation matrix FV^{-1} is given by

$$FV^{-1} = \begin{bmatrix} \frac{\beta\Lambda}{(\tau + \sigma + \alpha + \mu)\mu} & 0 \\ \frac{\alpha\beta\Lambda}{(\tau + \sigma + \alpha + \mu)(\omega + \sigma + \mu)\mu} & 0 \end{bmatrix} \tag{5.8}$$

whose eigen vectors are given as

$$\begin{bmatrix} 0 \\ \frac{\beta\Lambda}{(\tau + \sigma + \alpha + \mu)\mu} \end{bmatrix} \tag{5.9}$$

The most dominant eigenvalue of the next generation matrix FV^{-1} gives the basic reproduction number R_0 [1]. Therefore

$$R_0 = \frac{\beta\Lambda}{(\tau + \sigma + \alpha + \mu)\mu} \tag{5.10}$$

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6. LOCAL STABILITY OF THE DISEASE FREE EQUILIBRIUM

At the stable condition $\frac{d}{dt} = 0$ that is, the system does not change with time. As such, we have

$$\left.\begin{aligned} 0 &= \Lambda + \phi V - \xi S - \beta SI - \mu S + \psi R \\ 0 &= \xi S - (\phi + \mu)V - \rho VI \\ 0 &= \beta SI + \rho VI - (\mu + \sigma + \tau + \alpha)I \\ 0 &= \alpha I - (\sigma + \mu + \omega)H \\ 0 &= \tau I + \omega H - (\psi + \mu)R \end{aligned}\right\} \quad (6.1)$$

It follows that the jacobian matrix [8] of any dynamical system is given by

$$J = \begin{bmatrix} \frac{\partial s}{\partial S} & \frac{\partial s}{\partial V} & \frac{\partial s}{\partial I} & \frac{\partial s}{\partial H} & \frac{\partial s}{\partial R} \\ \frac{\partial v}{\partial S} & \frac{\partial v}{\partial V} & \frac{\partial v}{\partial I} & \frac{\partial v}{\partial H} & \frac{\partial v}{\partial R} \\ \frac{\partial i}{\partial S} & \frac{\partial i}{\partial V} & \frac{\partial i}{\partial I} & \frac{\partial i}{\partial H} & \frac{\partial i}{\partial R} \\ \frac{\partial h}{\partial S} & \frac{\partial h}{\partial V} & \frac{\partial h}{\partial I} & \frac{\partial h}{\partial H} & \frac{\partial h}{\partial R} \\ \frac{\partial r}{\partial S} & \frac{\partial r}{\partial V} & \frac{\partial r}{\partial I} & \frac{\partial r}{\partial H} & \frac{\partial r}{\partial R} \end{bmatrix} \quad (6.2)$$

The jacobian matrix of 2.1 is given by

$$J = \begin{bmatrix} -\beta i - \mu - \xi & \phi & -\beta S & 0 & \psi \\ \xi & -\rho i - \mu - \phi & -\rho V & 0 & 0 \\ \beta i & \rho i & \beta S + \rho V - \alpha - \mu - \sigma - \tau & 0 & 0 \\ 0 & 0 & \alpha & -\omega - \mu - \sigma & 0 \\ 0 & 0 & \tau & \omega & -\psi - \mu \end{bmatrix} \quad (6.3)$$

The jacobian evaluated at the disease free equilibrium yields

$$J_{\left(\frac{\Lambda}{\mu},0,0,0,0\right)}=\begin{bmatrix} -\xi-\mu & \phi & -\frac{\beta\Lambda}{\mu} & 0 & \psi \\ \xi & -\mu-\phi & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta\Lambda}{\mu}-\alpha-\mu-\sigma-\tau & 0 & 0 \\ 0 & 0 & \alpha & -\omega-\mu-\sigma & 0 \\ 0 & 0 & \tau & \omega & -\psi-\mu \end{bmatrix} \tag{6.4}$$

Whose eigen values are given by

$$\begin{bmatrix} -\mu \\ -\psi-\mu \\ -\mu-\phi-\xi \\ -\omega-\mu-\sigma \\ \frac{-\mu^2+(-\tau-\alpha-\sigma)\mu+\beta\Lambda}{\mu} \end{bmatrix} \tag{6.5}$$

For the system to be asymptotically stable all the eigenvalues should be negative. The first three eigenvalues of 6.4 are negative. The last eigenvalue is not strictly negative, as such the system can only be asymptotically stable under given conditions. For the system to be locally asymptotically stable

$$\frac{-\mu^2+(-\tau-\alpha-\sigma)\mu+\beta\Lambda}{\mu}<0 \tag{6.6}$$

$$\frac{-(\mu+\tau+\alpha+\sigma)\mu}{\mu}+\frac{\beta\Lambda}{\mu}<0 \tag{6.7}$$

Dividing all through by (μ+τ+α+σ) we get

$$-1+\frac{\beta\Lambda}{\mu(\mu+\tau+\alpha+\sigma)}<0 \tag{6.8}$$

Multiplying through by -1 we get

$$1-\frac{\beta\Lambda}{\mu(\mu+\tau+\alpha+\sigma)}<0 \tag{6.9}$$

Therefore, we have

$$1>\frac{\beta\Lambda}{\mu(\mu+\tau+\alpha+\sigma)} \tag{6.10}$$

implying that following condition

$$\frac{\beta\Lambda}{\mu(\mu+\tau+\alpha+\sigma)}<1 \tag{6.11}$$

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must be met for the dynamical system to locally asymptotically stable. But from 5.10

$$R_0 = \frac{\beta\Lambda}{(\tau+\sigma+\alpha+\mu)\mu} \tag{6.12}$$

thefore the system is loacally asymptotically stable if and only if

$R_0 < 1$

7. SENSITIVITY ANALYSIS

Sensitivity analysis is done to evaluate the parametric contribution of parameters to the reproduction number. It measures the sensitivity of the reproduction number in response to changes in parameters and errors arising from formulation errors. The sensitivity analysis of a model parameter is usually determined through the relationship between the individual parameter and the basic reproduction number (R_0). Given a variable w, its sensitivity is given by relation;

$$S_w^{R_0} = \frac{\partial R_0}{\partial w} \cdot \frac{w}{R_0} \tag{7.1}$$

The sensitivity analysis of the threshold number (Basic reproduction number R_0) with respect to the individual parameters is given in the table below

Table 1: Summary of parameter sensitivity indices

Parameter	Description	Sensitivity Index (+ve or -ve)
Λ	Recruitment rate	+ve
ξ	Vaccination rate	0
ϕ	Vaccination waning rate	0
ρ	Infection rate of the vaccinated compartmnet due to waning or Vaccination failure	0
β	Infection rate of the susceptible compartment	+ve
α	Hospitalization rate	-ve
σ	Disease mortality rate	-ve
μ	Natural death rate	-ve
τ	Recovery rate	-ve
ω	Recovery rate of the hospitalized individuals	-ve
ψ	Temporary immunity waning rate	0

8. NUMERICAL SOLUTIONS

This section explores the numerical simulations of the disease spread dynamics using the Runge-Kutta order four numerical method. The simulations consider the spread of the disease within a period of seventy months.

8.1 Cholera disease dynamics

The figure 2 indicates the cholera dynamics within each compartment. Majority of the susceptible individuals are not infected by the disease in long run, however the number of unaffected individuals decreases significantly after the first 30 months after an outbreak. After 30 months of the disease in the community, the over 50% of the population would have been in various stages of recovery after infection or exposure to cholera disease. As such, immediate intervention measures are necessary when cholera is detected in the community to prevent a heavy disease burden.

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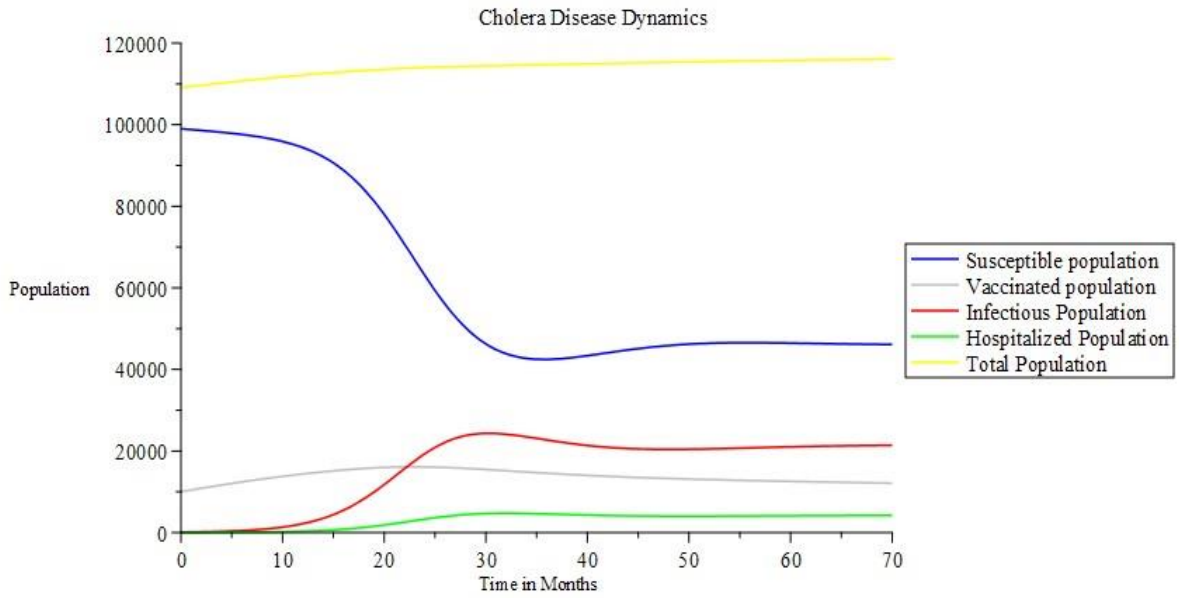

Figure 2: Counties Affected by Cholera Outbreaks

The vaccinated population remains stable at low levels since vaccinations are given to targeted individuals who are at high risk of spreading the disease. At the stable state the hospitalized population accounts for the compartment with the lowest population with the infectious populations very high at the same state.

8.2 Hospitalization dynamics

One of the early interventions of cholera management are increasing the hospitalization levels. Figure 3 illustrates the infectious population at different hospitalization levels.

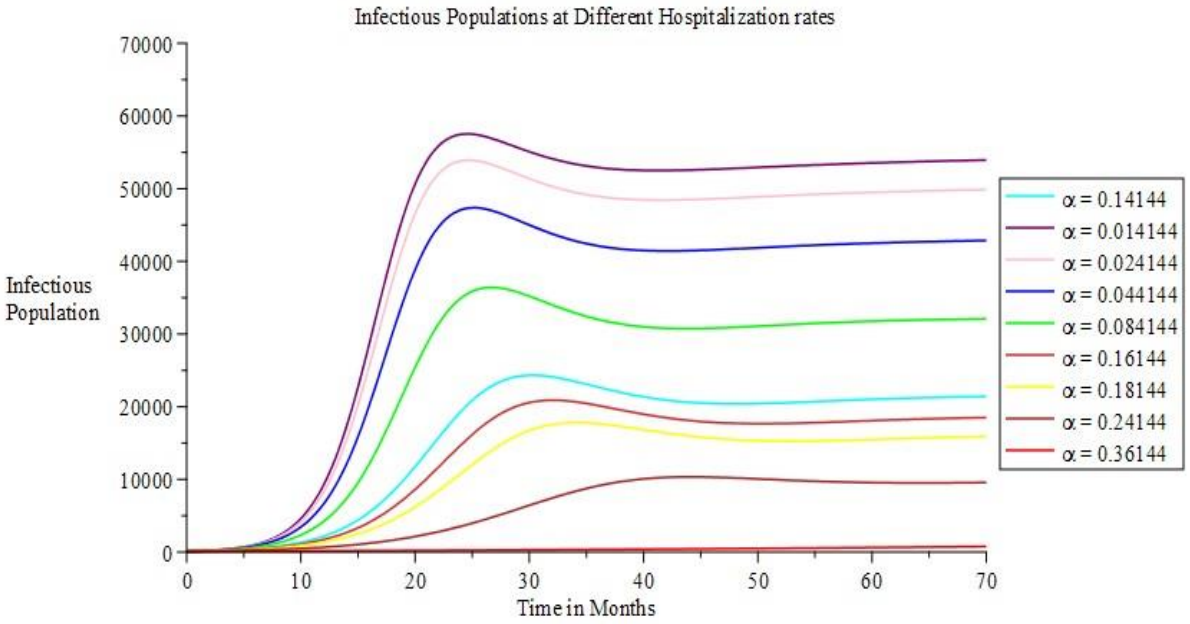

Figure 3: Counties Affected by Cholera Outbreaks

When the hospitalization levels are very high, α = 0.36144 the infectious population stabilize at very low levels thus accounting for very low disease burden over time. As the hospitalization decrease, the disease burden increases proportionately in the community as illustrated by figure 3. When the hospitalization rates are at their lowest levels α = 0.014144 the infection rates are their highest.

9. CONCLUSION AND RECOMMENDATIONS

9.1 Conclusion

A deterministic SVIHR model for cholera transmission was developed that incorporated the hospitalization compartment as an interventionary measure to combat the spread of cholera. The model was analyzed analytically and the analytical threshold number determined. The equilibrium points were determined pointing to the fact that for effective management of cholera transmission the basic reproduction number should always be less than one.

Sensitivity analysis of each parameter and its contribution towards the basic reproduction was conducted. It was found that the effective contact rate increased the spread of the disease in the communities. As such, interventions decreasing effective contact rate should be employed in the fight against cholera. In addition, the increase of the recruitment rate contributes to the increase of the disease thus interventions that ensure that the infectious population do not interact with the new recruits such as quarantining should be employed for effective management of the disease.

9.2 Recommendation

The cholera model can further be improved to include new compartments with new interventionary measures such as quarantined population. Local health officers in rural counties should hold more campaigns focused on public health and personal hygiene as a measure of reducing contact rate between infectious individuals together with the environment around them and the susceptible individuals.

From the sensitivity analysis, both the recruitment rate and contact rate drive up the infection rates. As such, local health authorities should focus on providing hospitals for the infected individuals to contain the spread of cholera in the communities. Hospitalization is one of the key intervention measures since it isolates the sick individuals from the susceptible individuals effectively lowering the contact rate. Additionally, the hospital environment is a controlled environment that minimizes the diseases transmission to other individuals thus effectively breaking the disease dynamics cycle.

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