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Sensitivity Analysis of the parameters of a Cholera Model

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ABSTRACT: In this paper, a deterministic mathematical model is formulated to analyse the degree of sensitivity of some factors that aid cholera transmission and management. We obtain the disease-free equilibrium point and conduct the local stability of the disease-free and endemic equilibria of the model. Reproduction number with interventions is stated and the method of normalised forward sensitivity index is employed to determine the numerical value of the key model parameters with respect to the effective reproduction number in order to determine their relative importance to cholera transmission and management. The results obtained show that the most important parameter to cholera transmission is the contact rate between susceptible and infectious individuals while the most crucial parameter to cholera management is the rate of cholera awareness.

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Sensitivity analysis in Mathematical Biology tells us how important each parameter is to disease transmission and is used to assess how sensitive a model is to variations in the value of the parameters of the model and to changes in the structure of the model (Rodrigues *et al*., 2013 and Numfor, 2010). It identifies which parameters are important in contributing to the prediction imprecision (i.e., how do changes in the values of the input parameters alter the value of the outcome variable (Blower and Dowlatabadi, 1994). Besides, it is used to discover parameters that have high impact on the basic reproduction number R_0 so that it is directly targeted by intervention strategies. Over the years, sensitivity analysis of cholera models has received attention of modelers and has become a subject of intense study. A good number of models has been developed to assess the sensitivity of each factor driving the disease in order to determine the major factors to be targeted by the appropriate interventions in order to eradicate the disease that has been in existence for more than 200 years (Neilan *et al*., 2010).

Edward and Nyerere, 2015 formulated a mathematical model that captured some essential dynamics of cholera transmission with public health educational campaigns, vaccination, sanitation and treatment as control strategies in limiting the disease. They carried out sensitivity analysis on the basic reproduction number with all control strategies and discovered that the most sensitive parameters are the educational campaign, therapeutic treatment, effective contact between the susceptible and infected individuals, bacteria carrying capacity, and recruitment rate. They concluded that any strategy aimed at eliminating cholera should target these parameters. Mondal and Kar, 2013 presented a water-borne disease epidemic model amenable to cholera dynamics including multiple transmissions namely, water- to- person and person-to-person transmission. They studied the sensitivity analysis of the system in refer to some crucial parameters and discovered that the number of infected individuals and concentration of pathogens are directly proportional to the two type disease transmission rate. They also found that if person-to-person contact is not applied, then the disease may be transmitted initially through the contaminated reservoir and within a very tiny time it can spread into the population. Kadaleka, 2011 conducted a study by formulating a basic mathematical model to assess the effects of nutrition and treatment in cholera dynamics, with reference to Malawi and the numerical results indicated that the cholera epidemic can be reduced when both interventions, nutrition and treatment, are implemented.

The present work is aimed at conducting sensitivity analysis on a cholera model by incorporating possible

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transmission modes as well as all the available prevention and control strategies for effective management of cholera transmission.

MATERIALS AND METHODS

The model is built around the following assumptions:(1) There is no permanent immunity after recovery; (2) All the recruited individuals are susceptible;(3) Water contamination occurs only through the release of *V. Cholerae* into the water body;(4) Recovery occurs either by immunity acquired through vaccination or successful treatment after vaccination and;(5) The total human population is closed which is a reasonable assumption for a relatively short period of time and for low mortality diseases like cholera. For example, WHO states that "In 2012, the overall case fatality rate for cholera was 1.2%" (Wang and Wang, 2014). In view of the above assumptions, the cholera model can be generated by the following system of first order ordinary differential equations 1, 2, 3 and 4. In these equations, S(t), I(t), R(t) and B(t) are compartments for each state variable and they represent the number of susceptible individuals at time t, the number of infected individuals at time t, the number of recovered individuals at time t and the population of bacteria in the aquatic environment at time t respectively.:

$$\frac{dS}{dt} = \pi - \mu S - (1-\theta)\frac{\beta_1 B}{B+\aleph}S - (1-\theta)\beta_2 IS + \sigma R - \upsilon S \quad (1)$$

$$\frac{dI}{dt} = (1-\theta)\frac{\beta_1 B}{B+\aleph}S + (1-\theta)\beta_2 IS - (\mu + \mu_c + \rho)\mathrm{I} \quad (2)$$

$$\frac{dR}{dt} = \upsilon S - \mu R - \sigma R + \rho \mathrm{I} \quad (3)$$

$$\frac{dB}{dt} = (1-\theta)\varepsilon I - (\delta + \omega)B \quad (4)$$

The definition for the model parameters, their values, units and sources are presented in Table1.

Table 1: Definitions and sources of the model parameters

Parameter	Symbol	Value	Unit	Source
Human recruitment rate	π	10	day $^{-1}$	Kadaleka, (2011)
Rate of human contribution to the population of *V.cholerae*	ε	10	cells/ml/day	Isere *et al.,* (2014)
Rate of human exposure to contaminated water	β_1	0.075	day $^{-1}$	Wang and Modnak, (2011)
Pathogen concentration that yields 50% chance of catching cholera	$\aleph$	10^5	cells/ml	Edward and Nyerere, (2015)
Natural death rate for *V.cholerae*	δ	0.4	day $^{-1}$	Isere *et al.,* (2014)
Death rate unrelated to cholera	μ	0.02	day $^{-1}$	Kadaleka, (2011)
Human Death rate due to cholera	μ_c	0.015	day $^{-1}$	Kadaleka, (2011)
Rate of contact between susceptible and infectious individuals	β_2	0.00011	day $^{-1}$	Wang and Modnak, (2011)
Rate of cholera awareness	θ	0.6	Dimensionless	Assumed
Rate of vaccination	υ	0.2	Dimensionless	Assumed
Rate of sanitation	ω	0.5	Dimensionless	Ochoche, (2013)
Rate of cholera treatment	ρ	0.98	day $^{-1}$	Kadaleka, (2011)

Equilibrium Analysis: Two equilibria shall be discussed- disease-free equilibrium and the endemic equilibrium. At the disease-free equilibrium, it is assumed that the population is free from cholera bacteria which makes compartments I, R and B to be zero. Hence, the disease-free equilibrium (DFE) for the model is given by

$$\mathrm{E}_0 = \left(\frac{\pi}{\mu+\upsilon}, 0, 0, 0\right) \quad (5)$$

At the endemic equilibrium, the cholera bacteria are present in the population and there exists cholera infection which makes each compartment to be greater than zero. Besides, all the compartments of the population coexist for the differential equations. Suppose $E^* = (S^*, I^*, R^*, B^*)$ is the endemic equilibrium for the model where S^*, I^*, R^* and B^* denote the endemic state for each state variable then eqns (1) – (4) can be written in terms of endemic state of each state variable at equilibrium as

$$\pi - \mu S^* - (1-\theta)\frac{\beta_1 B^*}{B^*+\aleph}S^* - (1-\theta)\beta_2 I^* S^* + \sigma R^* - \upsilon S^* = 0 \quad (6)$$

$$(1-\theta)\frac{\beta_1 B^*}{B^*+\aleph}S^* + (1-\theta)\beta_2 I^* S^* - (\mu + \mu_c + \rho)\mathrm{I}^* = 0 \quad (7)$$

$$\upsilon S^* - \mu R^* - \sigma R^* + \rho I^* = 0 \quad (8)$$

$$(1-\theta)\varepsilon I^* - (\delta + \omega)B^* = 0 \quad (9)$$

From eqn. (9), $B^* = (1-\theta)\frac{\varepsilon}{\delta+\omega}I^*$ (10)

Following the method of (Driessche and Watmough, 2002), the effective reproduction number for the model system (1) – (4) is obtained as

$$R_e = \frac{\pi\{1-\theta\}[\varepsilon\beta_1(1-\theta)+\aleph\beta_2(\delta+\omega)]}{\aleph(\delta+\omega)(\mu+\nu)(\mu+\mu_c+\rho)} \quad (11)$$

*Stability Analysis of the Disease Free Equilibrium***:** To conduct the local asymptotic stability of the disease-free equilibrium point E_0, the Variational matrix of the system of equations (1) – (4) is derived and then evaluated at the disease-free equilibrium point E_0 i.e. eqn. (5) to obtain

$$J(E_0) = \begin{pmatrix} -a_4 & -b_1\aleph\beta_2 & \sigma & -b_1\beta_1 \\ 0 & b_1\aleph\beta_2 - a_2 & 0 & b_1\beta_1 \\ \nu & \rho & -a_5 & 0 \\ 0 & a_1\varepsilon & 0 & -a_3 \end{pmatrix} \quad (12)$$

In eqn. (12), $a_1 = (1-\theta)$, $a_2 = (\mu+\mu_c+\rho)$, $a_3 = (\delta+\omega)$, $a_4 = (\mu+\nu)$, $a_5 = (\mu+\sigma)$, $b_1 = \frac{\pi a_1}{\aleph a_4}$

Generally, the disease-free equilibrium of the system (1) – (4) is locally asymptotically stable if $R_e < 1$ and is unstable if otherwise. This theorem can be established and the condition will be satisfied if all the eigenvalues of eqn. (12) can be proved negative. These eigenvalues can be determined by solving the characteristic equation

$$\left|J(E_0) - \lambda I\right| = 0 \quad (13)$$

Which leads to $c_0\lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4 = 0$ (14)

Where $c_0 = 1$, $c_1 = (a_3+a_5)$, $c_2 = \frac{a_2a_3a_4a_5+\sigma\nu}{a_2a_4}$, $c_3 = \frac{\sigma\nu(a_2+a_3)}{a_2a_4}$, $c_4 = \frac{a_3\sigma\nu}{a_4}$ (15)

Bearing in mind that the analysis is at the DFE so β_1 and β_2 are reduced to zero to arrive at equation (14). Following Routh-Hurtwitz stability criteria outlined in (Okyere, 2012), the eigenvalues of eqn. (14) are all negative if

$c_1 > 0$, $c_3 > 0$, $c_4 > 0$ and $c_1c_2c_3 > c_3^2 + c_1^2c_4$ (16)

Obviously, $c_1 > 0$, $c_3 > 0$ and $c_4 > 0$. Hence, the disease-free equilibrium of the system (1) – (4) is locally asymptotically stable if and only if $c_1c_2c_3 > c_3^2 + c_1^2c_4$.

*Stability Analysis of the Endemic Equilibrium***:** We obtain the Variational matrix of the system (6) – (9) as

$$J(E^*) = \begin{pmatrix} -K-a_4 & -a_1\beta_2S^* & \sigma & -L \\ K & a_1\beta_2S^* - a_2 & 0 & L \\ \nu & \rho & -a_5 & 0 \\ 0 & a_1\varepsilon & 0 & -a_3 \end{pmatrix} \quad (17)$$

Where $K = a_1\left[\frac{\beta_1B^*}{B^*+\aleph} + \beta_2I^*\right]$ and $L = a_1\left[\frac{\beta_1S^*}{B^*+\aleph} - \frac{\beta_1B^*S^*}{(B^*+\aleph)^2}\right]$

Unlike the disease-free equilibrium, the endemic equilibrium E^* of the system (1) – (4) is locally asymptotically stable if $R_e > 1$ and is unstable if otherwise. The theorem can be proved in two ways: (1) If we can show that $\det\{J(E^*)\} > 0$ whenever $\text{tr}\{J(E^*)\} < 0$ and (2) If all the eigenvalues of $|J(E^*) - \lambda I| = 0$ have negative real parts.

The characteristic polynomial eqn. (17) is thus evaluated as

$$p_0\lambda^4 + p_1\lambda^3 + p_2\lambda^2 + p_3\lambda + p_4 = 0, \quad (18)$$

Where

$p_0 = 1$

$p_1 = a_2 - a_1\beta_2S^* + a_3 + a_5$

$p_2 = \frac{[(a_4+K)\{(a_3+a_5)(a_2-a_1\beta_2S^*) - a_1\varepsilon L + a_3a_5\} + \sigma\nu]}{(a_4+K)}$

$p_3 = \frac{[(a_4+K)\{a_3a_5(a_2-a_1\beta_2S^*) - a_1a_5\varepsilon L\} + \sigma\nu(a_3+\{a_2-a_1\beta_2S^*\})]}{(a_4+K)}$

$p_4 = -\sigma\nu\frac{[a_3(a_2-a_1\beta_2S^*)+\varepsilon L]}{(a_4+K)}$

Following Routh-Hurwitz stability criteria for polynomial of degree four, the eigenvalues are all negative if $p_1 >$

0, $p_3 > 0$, $p_4 > 0$ and $p_1p_2p_3 > p_3^2 + p_1^2p_4$ (19)

$p_1 > 0$ is true and $\text{tr}\{J(E^*)\} < 0$ is also true therefore, the endemic equilibrium of the model is locally asymptotically stable if $\det\{J(E^*)\} > 0$ or $p_3 > 0$, $p_4 > 0$ and the inequality $p_1p_2p_3 > p_3^2 + p_1^2p_4$ is true.

*Sensitivity Analysis***:** Sensitivity indices allow us to measure the relative change in a variable when a parameter changes. If the model is simple, it may be possible to differentiate the outcome with respect to each parameter in turn. The derivatives are the rate of change of predictions with respect to the parameters. Like (Edward and Nyerere, 2015), (Numfor, 2010), (Adewale *et al*., 2017) and (Okosun and Smith, 2017). This work adopts the normalized forward sensitivity index to conduct the sensitivity analysis. The normalized forward sensitivity index of a variable with respect to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively

defined using partial derivative. For instance, the normalized forward sensitivity index on R_0, which depends differentially on a parameter p, is defined by

$$\gamma_p^{R_0} = \frac{\partial R_0}{\partial p} \text{x} \frac{p}{R_0} \qquad (20)$$

The parameter values displayed in table 1 are taken as the baseline values and they are used to evaluate the sensitivity indices of some parameters which are responsible for the transmission and management of cholera disease to three places of decimal in relation to the effective reproduction number,R_e using eqn. (20) as a guide, the result of which is presented in table 2.

Table2. Sensitivity indices of the effective reproduction number to model parameters.

Parameter	Sensitivity index
θ	-1.544
β_2	1.078
π	1.000
ρ	-0.966
v	-0.909
ε	0.029
β_1	0.029
ℵ	-0.029
ω	-0.002

It is observed in table 2 that these parameters have either positive or negative effects on the effective reproduction number though the magnitude of negative indices is considered to investigate the size of the effect of changing the parameters with negative indices.

RESULTS AND DISCUSSION

We established the existence of disease-free equilibrium and endemic equilibrium for the model and the two equilibria were proved to be locally asymptotically stable under certain conditions. The implication of these equilibria is that in a population (e.g. country), it is possible to have some communities that are free from cholera and other communities that are prone to cholera due to some prevailing conditions. The privilege communities in a country are likely to free from cholera while the less privilege communities may be prone to cholera. Nigeria, despite being a cholera endemic country, has some places in Lagos that are free from cholera e.g. Ikoyi, Victoria Island, Banana Island, e.t.c. On the other hand, a number of places is cholera hotspots especially in the Northern part of the country (UNICEF, 2014).

As regards the stability of the two equilibria, the epidemiological interpretation of the stability of the disease-free equilibrium is that cholera outbreak will not take off even if an individual infected with the cholera bacteria is introduced into the cholera free community whereas, for a stable endemic equilibrium, cholera outbreak will take off but may not persist in a cholera prone community if a person living with the cholera bacteria is introduced into the community. The United States of America is one of the several countries that has been maintaining stability in terms of cholera outbreak for more than a country. Even though there are occasional sporadic cases of cholera resulting from several people who travelled abroad to countries where cholera is endemic and contracted the disease either by drinking the water or eating some food that was contaminated and developed illness on returning to the United States but at large no secondary transmission has been recorded within the United States.

From table 2, the most sensitive parameter to cholera transmission is the contact rate between susceptible and infectious individuals followed by the recruitment rate into susceptibility while the most sensitive parameter to cholera management is the rate of cholera awareness followed by the rate of cholera treatment. The results in table 2 have serious implications to cholera transmission and management. Firstly, it shows that vaccination plays an indispensable role in curtailing the menace of cholera outbreak. This is corroborated by the outcome of the study conducted by the research arm of the international medical humanitarian organization Me'decins San Frontier'res (MSF), and the Guinean Ministry of Health where an oral cholera vaccine (i.e Shanchol) protected individuals by 86% during the 2012 cholera outbreak in Guinea (MSF, 2012). Secondly, the lowest sensitivity index for sanitation does not imply that sanitation is not relevant to cholera management. It implies that cholera prevention is achievable provided that the level of sanitation is high enough as in the case of the developed countries of the world. For cholera outbreak to be prevented through sanitation, the level of sanitation must above 0.5 that is used for simulation in this work. In view of the outcome of this work, public health educational campaigns, sensitization programs and all form of cholera education are recommended to the general public on the dangers of cholera outbreak and the needs for environmental sanitation. Information about cholera and its management can influence nearly all the transmission parameters. Apart from awareness of the dangers of cholera outbreak, immediate medical attention to the cholera infected individuals and measures (e.g. quarantine) capable of limiting contact between the susceptible and the wastes of the cholera infected individuals should be encouraged for effective management of cholera cases in time of cholera outbreak.

On the issue of vaccination, oral cholera vaccine was added to the WHO recommendation for cholera prevention and control in 2010. However the vaccine has not been commonly used as a public health tool for control of the disease. Concern about its feasibility, timeliness, and acceptability by communities, as well as fear of diverting resources to other medical programs has discouraged its use (MSF, 2012). Above all, since vaccination is the only intervention parameter that reduces susceptibility by limiting recruitment rate π which is one of the most sensitive parameters to cholera transmission, this study recommends removal of all barriers to its application by the appropriate authority. The use of oral cholera vaccine should greatly improve our ability to prevent and control epidemics, and ultimately, to save more lives.

*Conclusion***:** In this work, a deterministic cholera model is employed to investigate the relative influence of key factors to cholera transmission and management. A careful equilibrium analysis of the model is conducted and the disease free equilibrium point is obtained. The disease-free equilibrium and the endemic equilibrium are also analysed for stability and the conditions that guarantee the stability of the two equilibria are established. The effective reproduction number R_e is stated and the sensitivity analysis is performed. The sensitivity indices of the effective reproduction number, R_e with respect to the key model parameters are evaluated to determine the relative importance of the parameters to the disease transmission and management and the result is presented in tabular form.

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