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On the cholera therapy model, that incorporates *Vibrio cholerae* environmental reservoir

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Abstract
Cholera caused by toxigenic *Vibrio cholerae* is a major public health problem in developing countries, where outbreaks occur in regular seasonal patterns and are particularly associated with poverty and poor sanitation. The T *V. Cholerae* can thrive in marine environments for several months, alongside zooplanktons and other marine organisms. The infectious agent can assume a viable state, becoming undetectable to traditional microbiological techniques. The aquatic environment may be an habitat to the harmful *V. Cholerae* in affected regions. The Mathematical model incorporates important determinants of the *V. Cholerae* dynamics. Firstly, we study a basic S-I-R model together with an oceanic taxon of *V. Cholerae*. We aimed at exploring the purpose of the reservoir on the persistence of endemic cholera as well as the definition of minimum conditions for the development of epidemic and endemic cholera. We explore Mathematical model for the endemic and epidemic cholera. Thereafter verification within three suggested populations to estimate its characteristics in terms of; no disease or free, epidemic and endemic cases. We analyzed the proposed model fully by considering possible causes of endemic oscillations.

Keywords: Toxigenic *Vibrio cholera*, zooplankton, bacteriological, aquatic reservoir, epidemic, endemic

Introduction
Cholera is a waterborne disease, which mainly depicts itself with watery loose stool. The causal infectious substance is *Vibrio cholerae* O1 (or *VC* O139), which multiplies in the small intestines, producing enterotoxins which give rise to the looseness of the bowels. If medication is not immediate, the patient mainly dies due to dehydration within hours of infection. The main causal agents of cholera is contaminated food and water supplies. Cholera was predominant in the Indian sub-continent until the 19th century [1] where the eruptions are cyclical with one or two maximal in a year [2]. Since 1817, the disease has spread throughout the world seven times. The last pandemic began in 1961 in Indonesia, which spread through the Asian continent. It got as far as Africa in 1970 [4] and Latin America in 1991. The existence of consecutive eruptions in the whole of Africa and America in the 90's meant that it had thrived, hence persistently present but not limited to those particular regions.
There are three possible outcomes if the disease is detected in a new region; an orthodoxy or subordination, an outburst with subsequent waves, or a cyclic cholera flare up. Studies have indicated susceptible; subjection to contaminated water and refuse liquids; and existence of a habitat in which *V. Cholerae* lives, grows and multiplies are important demographic, environmental and sociological factors that give rise to the said outcomes [1, 3, 5]. The importance of these factors, on their interaction with each other and with others aids in the study of the distribution and determinants of health related states and events for the disease are key points in the model. In the proposed model, the following questions are resolved; function of marine reservoir in enhancing endemic cholera; best ways to prevent and control eruptions; forecasters of the eventual state of the infected, after the disease is noticed. They ably consolidate the knowledge derived from direct experience, observation and experimentation about the disease into a well-planned, clear and sensible view. The model will help in establishing the effects independent variables have on dependent variables.

Representation
The model is derived from the *Capasso's* model [8], which studied the 1973 cholera in Italy. In this model, two equations describe the dependence on the rate of transmission from infectious to susceptible hosts and marine bacteria. In the present model, the susceptible population is included since the long term dynamics is studied [7]. The model will take the form:

$$S' = n(H - S) - a\,\lambda\,(B)S \quad (1a)$$

$$I' = a\,\lambda(B)S - r\,I \quad (1b)$$

$$B' = B(n\,b - m\,b) + e\,I \quad (1c)$$

$$S_0 = H,\quad I_0 > 0,\quad B_0 = 0 \quad (2)$$

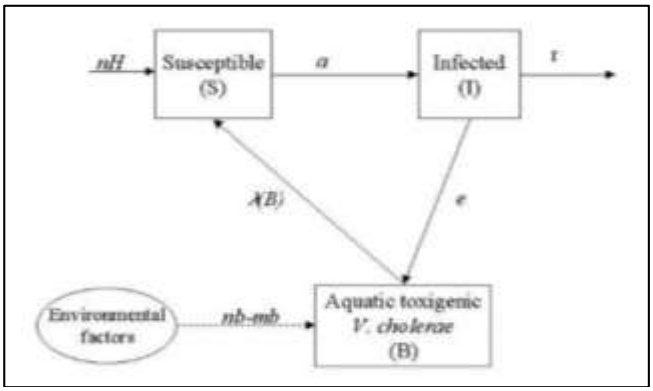

Fig 1: The diagrammatic representation of the model

Eqn. (1a) describes the exposed individuals of constant size *H*. The renewal rate of vulnerable persons is *n* and it can be due to birthing, mass exodus and/or brownout of adaptive immune system. Exposed persons are contaminated at a rate $a\,\lambda$ (B), where *a* is the rate of exposure with raw water and λ (B) is the likelihood of infection. This will be dependent on the engrossment of *V. Cholerae* in the taken water. Test trials have indicated that a high population *V. Cholerae* results in acquisition of the disease [9]. This can be shown by a coordinate graph relating the magnitude of a dose (stimulus) to the response of a biological system as in Fig. 2 below;

$$\lambda(B) = \frac{B}{B + K} \quad (3)$$

with *K* as the dense accumulation of *V. cholerae* in water.
The assumption here is that the only way to ingest the microbes is by taking the raw water.

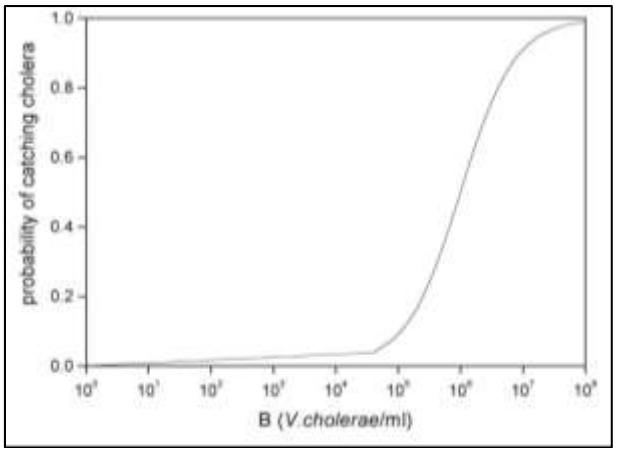

Fig 2: Dose Dependence Infection rate

Eqn. (1b) gives a measure of the number of new infections that arise, on average, from the introduction of one infected case into a susceptible population, which includes those with no signs or symptoms and those moderately infected. Putting together all infection types into a one- model compartment, with the assumption that the case-to-infection ratio remains constant throughout the epidemics. This is reasonable if infection virulence is strongly determined by host factors and bacterial infectivity, that are constant throughout the window period we are of interested in [11, 12, 13]. The probability is high that initial ratio of microorganisms in relation to the total working volume of the process can affect the ratio of the number of cases of a disease compared to the number of infections with the agent that causes the disease [14]. we take an assumption that there exists a correlation between the size of the inoculum and the probability or risk of an infection in a population and not intensity of disease signs. The equation simply shows the affected with disease-causing organism persons goes up as the ones likely or liable to be influenced or harmed by a disease become affected and goes down with recoveries or death.
Eqn. (1c) on the other hand, describes the dynamics of pathogenic *V. Cholerae* in the marine reservoir where the set of untreated waters is consumed by the population. Environmental *V. Cholerae* is found in ponds, wells, rivers, estuaries and coast waters. Here, the equation simply states that bacterial density in the water results from the balance between local birth and death processes and the inflow of contaminated sewage. The parameter *e* defines the average contribution of each infected person to the aquatic population of *V. Cholerae*. Eqns. 2 specifies the initial conditions i.e., all individuals are initially vulnerable.

Model validation
This model is predictive, that is., it uses known results to create, process, validate and forecast future events or patterns based on historical data of the disease. Once the affliction is noticed, there are three possibilities that can arise: it does not spread at all, widespread occurrence within a population or will regularly occur within an area.
In a population without the disease instances for a long time, all persons therein are susceptible. There are neither persons capable of infecting others, those very or partially resistant to the infectious disease or pathogen nor bacteria-producing toxin in the water;

$$\hat{S} = H \qquad \hat{I} = \hat{B} = 0 \quad (4)$$

where $\hat{S}$, $\hat{B}$ and $\hat{I}$ indicates a point at which the rates-of-change for all of these state variables are zero. We aim at knowing the response of a cholera free population in case a reasonable size of the affected persons with disease is put together with the susceptible. We wish to establish the effect of deviation or disturbance of the steady state $[\hat{S}, \hat{I}, \hat{B}] = [H, 0, 0]$. In case of stability, the disease will not and consequently, no recrudescence. Instability will definitely lead to an outbreak of the disease. The local stability analysis can address the issue efficiently [16].
The Jacobian matrix of system 1 is given by;

$$J = \begin{bmatrix} -r & \dfrac{a\hat{B}}{K + \hat{B}} & \dfrac{a\hat{S}}{K + B} - \dfrac{a\hat{B}\hat{S}}{(K + \hat{B})^2} \\ 0 & -n - \dfrac{a\hat{B}}{K + \hat{B}} & -\dfrac{a\hat{S}}{K + B} + \dfrac{a\hat{B}\hat{S}}{(K + \hat{B})^2} \\ e & 0 & (n\,b - m\,b) \end{bmatrix} \quad (a)$$

At the equilibrium point, this matrix becomes;

$$J_{[H,0,0]} = \begin{bmatrix} -r & 0 & \frac{a\,H}{K} \\ 0 & -n & -(\frac{a\,H}{K}) \\ e & 0 & (n\,b - m\,b) \end{bmatrix} \quad (b)$$

According to Routh-Hurwitz criterion, matrix (b) above will be deemed stable if;

$$Tra\ (J_{[H,0,0]}) = [-r - n + n\,b - m\,b < 0]$$

$$Det\ (J_{[H,0,0]}) = (\frac{n\,e\,a\,H}{K}) + n\,r(n\,b - m\,b) > 0$$

$$Tra(J_{[H,0,0]})\delta < Det\ (J_{[H,0,0]})$$

$$where\ \ \delta = -n(n\,b - m\,b + r) - \frac{r\,n\,b\,K - r\,m\,b\,K + a\,e\,H}{K} \quad (c)$$

Eqns. (c) holds if only if;

$$n\,b < m\,b$$

$$\frac{r\,K(m\,b - n\,b)}{a\,e} > H \quad (d)$$

There is the minimum number of people required to sustain indefinitely an infectious pathogen and this is given by;

$$S_c = \frac{r\,K(m\,b - n\,b)}{a\,e}$$

below which no recrudescence occurs. If $S_0 > S_c$, then the equilibrium will be unstable and the disease will spread. That is,

$$\frac{a\,e}{r\,K(m\,b - n\,b)} = \frac{R_0}{S_0}$$

The disease is likely to be transmitted in case the reproductive number is greater than one. On the other hand, the number of cases will decreases to zero. As seen above;

$$S_c = \frac{r\,K(m\,b - n\,b)}{a\,e} \quad (5)$$

The critical community size , S_c , is proportional to the blue death (*K*), and recovery (*r*) and net mortality rate of *V. Cholerae* in the water. Eqn. (5) can be re-arranged to take the form;

$$e = \frac{rK(mb - nb)}{aS_c} \quad (6)$$

On substituting quantities in matrix (a) by the endemic values as Eqn. (6) above and applying the Routh-Huwitz stability Criterion, we will get stability of the endemic equilibrium when $n\,b < m\,b$ and $S_c < S_0$. This model implies that with $S_0 > S_c$ there are higher chances of the disease outbreak which stabilizes into a state where the infection is constantly present or maintained with $n > 0$. To maintain this constant presence of infection, however, practically, *n* must be much greater than 0. This model therefore allows us to calculate a future event exactly, without the involvement of randomness allowing immeasurably steady state values. Coupled with the part of sepsis that is not showing signs, mild and intense, its possible to get to an estimate;

$$e = \frac{e_{asy}I_{asy} + e_{mi}\,\mathrm{I}_{mi} + e_{sev}I_{sev}}{I_{asy} + \mathrm{I}_{mi} + I_{sev}}$$

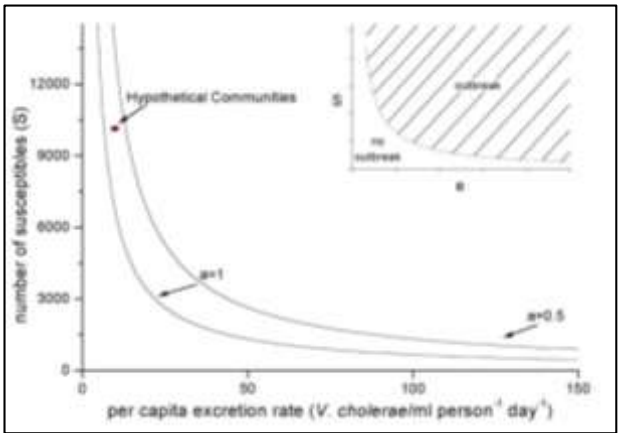

Fig 3: The effect of e on the threshold individuals size S_C

The curve for a = 0.5 and a = 1 utilizes the variables of population 1 and a = 1 from 2 and 3 respectively. The two curves displays the values of e and population threshold at which the reproduction number is equal to 1

Suppose that a contingent population of 10,000 members share the same water point which is contaminated with sewage. When a = 1, cholera outbreak is likely if individual contribution to water contamination exceeds ca. 7 cells/ml per day. When each infected person yields 1×10^4 cells per person per day, this water will remain infective unless diluted to a value less than 7 cells/ml. Such dilution requires $4 \times 10^4/7$ = ca. 5700 liters of water per infected person per day.

Then this model assumes that a real pond's contents are not mixed perfectly. In the case where the water for consumption is drawn from highly sewage concentrated point, there will be a higher chance of infection as much as the pond may be large enough. Notice that *V. Cholerae* is associated with phytoplankton, Macrophyte and other marine life. On the surface of these organisms, density of bacteria is much greater than in the aquatic medium.

Actually our seldom provides quantitative predictions on cholera dynamics in general. Its qualitative results leads to known alternative approaches to the aversion of the disease outbreak:

Minimization of water contamination and prohibition of consumption of untreated water, the classical approach to curb cholera outbreak. Proper and acceptable sanitation will definitely reduce the variable *e*. At the same time, proper water treatment before consumption reduces parameter *a*. Eqn, (5) implies that, the smaller the parameters, the larger

the susceptible pool so to curb cholera outbreak.

Consider a population with susceptible pool exceeding the threshold S_c. In case the infected are introduced, the probability of an outbreak is high. Fig.4 below shows the dynamics of infected, susceptible and bacteria in population 2; where cholera dynamics is epidemic,

$$H=10^4,\ n=10^{-4},\ a=1,\ K=10^6,\ r=2\times10^{-1},\ [n\,b-m\,b]=-33\times10^{-1},\ e=10,\ \text{and}\ S_c=6.6\times10^2$$

With this is with just a few cholera cases introduced. Two factors affect the starting reproduction rate of the cholera positively; the extent of pollution of the water supply (e) and the number of times the water is consumed (a):

$$\frac{R_0}{S_0}=\frac{a\,e}{r\,K(m\,b-n\,b)} \tag{7}$$

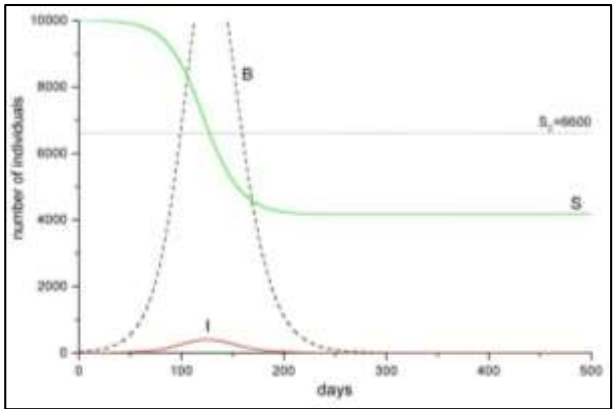

Fig 4: Dynamics of the infected, susceptible and bacteria in community 2

Infected individuals are likely to cause an outbreak. Bacterial density in the water increases as result of human excretion. The epidemic declines when the number of susceptible crosses down the threshold line.

Once the growth rate is negative, bacteria population will decline as the susceptible pool decreases below the critical size. Thereafter, bacteria annihilation rate exceeds sewage and the environmental V. Cholerae population finally dies off. The second population, then, regains its state of no Cholera

Next, consider the third population 3, with parameters similar to those in population two but for n greater. The introduction of infected in population 3 starts a cholera outbreak because $S_0 > S_C$. The disease returns in repeated occurrences without a break and finally gets to positive endemic equilibrium. We can equating system 1 to zero, solve to obtain;

$$\hat{S}=H-\frac{r}{n}\,\hat{I}$$

$$\hat{I}=\frac{n\,(r\,K\,m\,b-r\,K\,n\,b+a\,e\,H)}{e\,(n-a)\,r}$$

$$\hat{B}=\frac{e\hat{I}}{m\,b-n\,b} \tag{9}$$

A fraction ϕ of the excess population, that is $(H-S_c)$ gives the equilibrium figure of the infected persons in the population, that is.

$$\phi=\frac{an}{ra+n} \tag{10}$$

Eqn. (10) is a function of individual variables, only. To maintain an endemic state, we must have $\hat{I}$ 1 , otherwise infection will vanish due to random processes [7].

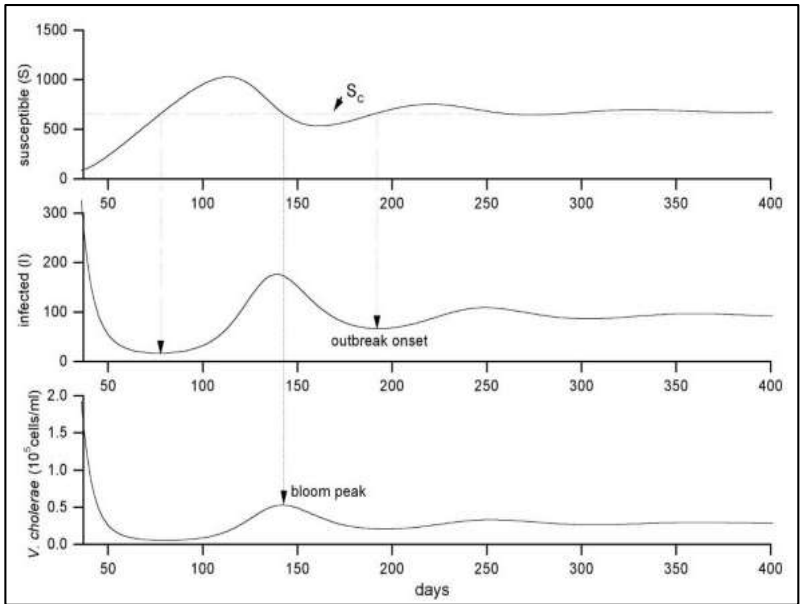

Fig 5: Positive endemic equilibrium

Facsimile of the measure of the number of new infections that arise on average, from introduction of one infected case into the susceptible population three using the variables;

$$H=10^4\ n=10^{-3},\ a=1,\ K=10^6,\ r=2\times10^{-1},\ (n\,b-m\,b)=-3.3\times10^{-1},\ e=10,\ \text{and}\ S_c=6.6\times10^3$$

After the starting outbreak, cholera ubiquity wavers towards a steady state.

Discussions

This model is a modification of a previous cholera model [8], with a population living and non-living reservoirs that harbor infectious pathogens outside the bodies of the susceptible. The model provides some insights into the importance of an environmental reservoir on cholera health surveillance. According to the model, a permanent environmental reservoir of toxigenic *V. Cholerae* increases the reproductive number without bound (Eqn. (8). Any susceptible persons exposed to the contaminated water are infected. The extent of this problem, in terms of public health, would depend on the probability of fecal-oral spread of the *V. Cholerae* organisms through person-to-person contact or through contaminated water and food. In a community with good sanitation, cholera would show up as occasional primary cases without fecal-oral spread of the organism through person-to-person contact or through contaminated water and food. In poor communities, on the other hand, endemism would result from the close contact between the susceptible and the source of contamination.

The instance when the disease is consistently present but limited to a particular region can be put under control if bacteria net loss rate is sufficiently low to maintain an aquatic population of *V. Cholerae* until the susceptible pool crosses the threshold S_c again. However, the best the sanitation condition, the longer-lived the reservoir must be. Alternatively, the worse the sanitation, the shorter can be the bacterial preference time in the water.

Conclusion

In the stability analysis, there is no effect of slight alteration of the equilibrium point to the endemic equilibrium. It remains stable even with small perturbations if $S_0 < S_c$ and $n\,b < m\,b$. Cholera waves would arise when the exposed population grows above the threshold population, which again gives rise to a fresh outbreak. Finally, the number of infected persons tends to a fixed part of the population.

In summation, this model prognosticates that the disease eruptions likely to occur in populations whose vulnerable pool is greater than the susceptible threshold. The intensity of the threshold is dependent on a combination of environmental, sociological and strain-specific factors. The environmental reservoir reduces the susceptible threshold. With the presence of a permanent reservoir of the pathogen, the threshold tend to zero, and population of any size in contact with the reservoir should depend on an outburst.

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