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ORIGINAL ARTICLE

The Role of Immunity and Seasonality in Cholera Epidemics

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Abstract This paper presents a mathematical model for cholera epidemics which comprises seasonality, loss of host immunity, and control mechanisms acting to reduce cholera transmission. A collection of data related to cholera disease allows us to show that outbreaks in endemic areas are subject to a resonant behavior, since the intrinsic oscillation period of the disease (∼1 year) is synchronized with the annual contact rate variation. Moreover, we argue that the short period of the host immunity may be associated to secondary peaks of incidence observed in some regions (a bimodal pattern). Finally, we explore some possible mechanisms of cholera control, and analyze their efficiency. We conclude that, besides mass vaccination—which may be impracticable—improvements in sanitation system and food/personal hygiene are the most effective ways to prevent an epidemic.

Keywords Cholera · Mathematical model · Endemic state · Resonance · Bimodal · Control mechanisms

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1 Introduction

Cholera is a water-borne disease characterized by severe diarrhea. Its spatial distribution includes the Indian sub-continent, parts of Asia, Africa, and Latin America.

The etiological agent is *Vibrio cholerae* which colonizes the small intestine and produces an enterotoxin responsible for the disease. Treatment with fluid replacement therapy and antibiotics may reduce the number of deaths to 1% of the diagnosed cases. In fact, antibiotics are useful in abbreviating the course of infection and decreasing disease severity, but in most cases they are not necessary. The incubation period of the disease is very short, ranging from a few hours up to 5 days, with symptoms varying greatly, from mild and asymptomatic to intense diarrhea, vomiting, thirst, loss of skin elasticity, and muscle cramps (Zuckerman et al. 2007).

Disease transmission is mainly environment-to-human, although a secondary, less important, route exists, in the form of human-to-human transmission. So far, the most important and common routes of cholera transmission are water and food (especially seafood) contaminated with the bacterium (Colwell and Huq 1994; Hartley et al. 2006). Classical control efforts to prevent cholera outbreaks encompass improvements in sanitation system, safer water treatment, and improved food/personal hygiene. Vaccines constitute near-term options for cholera control, but so far an inexpensive and effective vaccine is still under developed (Longini et al. 2007; Seidlein 2007; Mahalanabis et al. 2008; Sur et al. 2009), with optimistic prospects for the future (World Health Organization 2010).

One of the central challenges in cholera epidemiology is the explanation of why the outbreaks can be so explosive and, at the same time, self-limiting, with recurrence patterns that can be unimodal or bimodal (twice a year). So far, the explosive nature of the outbreaks has been associated to a hyper-infectious state of the organism (a short-lived competitive advantage; Hartley et al. 2006) and to asymptomatic infections with short-term protection against the pathogen so that depletion of the susceptible pool brings the epidemic to a halt (King et al. 2008).

Furthermore, in regions where cholera is endemic, its dynamics displays one or two annual peaks with pronounced inter-annual variability (Pascual et al. 2002). Like other endemic diseases, cholera outbreaks are associated with seasonality, environment deterioration, bacterial virulence and host immunity. The interplay between these factors determines cholera occurrence patterns in a specific region (Koelle et al. 2005).

Compartment models for cholera are usually based on the work of Codeço (2001) which besides the usual susceptible-infected-recovered compartments, includes a fourth compartment for bacterial population in order to represent the natural reservoir of *V. chorelae*. This assumption allowed to explain the endemic cholera state as well as to define a threshold for the existence of an endemic and epidemic cholera state. The same author added seasonality to this model assuming a periodic variation of the parameters, and showed that this seasonality is responsible for annual outbreaks of the disease (a unimodal pattern). Further, important contributions in cholera modeling were the study of serotype dominance and the influence of epidemiological factors on the period of these serotype cycles (Koelle et al. 2006),

and the use of optimization techniques to carry out control strategies (Neilan et al. 2010).

In this paper, we propose an extension of Codeço's model (Codeço 2001) to describe the dynamics of cholera transmission taking into account the loss of host immunity and its interplay with seasonality and control mechanisms. First, we give a resonance approach to the problem, in line with recent results for influenza (Dushoff et al. 2004). We show that the natural period between outbreaks may be, under some conditions, close to 1 year. This supports the idea of an intensification of outbreaks by a resonance effect due to annual variations of contact rates.

We find that immunity loss change the resonance period. In particular, we show that a second peak corresponding to a secondary outbreak, may appear when the immunity period is small. This indicates that loss of immunity may be a possible triggering mechanism behind the bimodal pattern observed in some regions. Moreover, these additional peaks show up only in certain range of parameters, which is consistent with the fact that secondary outbreaks are not always present. Indeed, as the parameter model depend upon regional factors, two cholera outbreaks do not always occur in the same year.

We also consider cholera control in the model. We include four different control mechanisms, namely, reduction of contact parameter, sanitation, water treatment, and vaccination. Efficiency of both continuous and periodic control strategies is analyzed. It turns out that besides vaccination, improvements in sanitation system and food/personal hygiene are the most effective way of cholera prevention.

The paper is structured as follows: in Sect. 2, we formulate the model and discuss the significance of the equations; in Sect. 3, we analyze the autonomous model without seasonality to provide a basis for further developments; in Sect. 4, we present a resonance approach to the non-autonomous problem and discuss seasonal behaviors; in Sect. 5, it is shown that host immunity effects in addition to seasonal ones could be the reason for the existence of biannual outbreaks; in Sect. 6, control mechanisms and their efficiency are analyzed, and finally, Sect. 7 is devoted to the concluding remarks.

2 Mathematical Model for Cholera Transmission

The model proposed in this section is a modified version of Codeço's model (Codeço 2001). The main point in the model presented in Codeço (2001) is to take into account an aquatic reservoir where toxigenic *V. cholerae* can survive, a fact that has been observed (Colwell and Huq 1994) and is now well established (Vezzulli et al. 2010). Here, we take this modeling rationale and extend it to consider host loss of immunity. Besides, we further address the question of control mechanisms, that has not been studied in the context of the basic model. Thus, let us consider the following system of differential equations for the number of susceptible hosts, S, infected hosts, I, recovered hosts, R, and number of toxigenic bacterial cell per ml, B:

$$
\begin{aligned}
\frac{dS}{dt} &= \mu(H - S) - (\theta_1\beta)\frac{B}{K+B}S + r_1 R - \theta_4 S,\\
\frac{dI}{dt} &= (\theta_1\beta)\frac{B}{K+B}S - (r+\mu)I,\\
\frac{dR}{dt} &= rI + \theta_4 S - (r_1+\mu)R,\\
\frac{dB}{dt} &= (\theta_2 e)I - (\theta_3\gamma)B.
\end{aligned}
\tag{1}
$$

In the first equation, susceptible individuals are renewed at a rate μ. They become infected at a per capita rate β multiplied by the probability that a susceptible individual becomes infected which is modeled by a Michaelis–Menten functional form since such probability depends on the concentration of *V. cholerae* (Cash et al. 1974). We do not consider human-to-human transmission, since an aquatic environment is accepted as playing a pivotal role in persistence, dispersion, transmission, as well as on the evolution of this bacterium (Vezzulli et al. 2010). The parameter $\theta_1 \in [0, 1]$ represents the decrease in the contact rate due to the effect of individual sanitary measures (hands washing, correct food care, filter pond water through sari cloth) on the transmission of the infection. It is an aggregate measure of these effects on the probability of contact between susceptibles and bacteria. Susceptibles are transferred by vaccination to the recovered compartment at a rate $\theta_4 = PQ$, where $0 \leq P \leq 1$ and $0 \leq Q \leq 1$ are, respectively, the population proportion that is vaccinated and vaccine efficacy, which is in the order of 65%–80% (Longini et al. 2007). The susceptible population also increases by the return of individuals that lose immunity at a rate r_1 and decreases by natural death at a rate μ. The infected population increases through contact of the susceptibles with *V. cholerae*, and decreases through recovery from the disease, r, and by natural death, μ. In the third equation, the immune class increases due to the arrival of new immune individuals that recovered of the infection or were vaccinated at rates r, and θ_4, respectively. It decreases by loss of immunity and natural death of the individuals. Finally, the last equation describes the dynamics of *V. cholerae* in the aquatic reservoir, which increases through the contribution of infected individuals by a rate $\theta_2 e$ and decreases by the bacterial mortality γ. We are not considering bacterial replication in the natural environmental because, in the context of cholera transmission the major contribution to the disease spread is the contact between human and a hyper-infectious state of the bacterial that occurs few hours after the passage of the vibrio by the human organisms (Hartley et al. 2006; Merrell et al. 2002). The parameters $\theta_2 \in [0, 1]$, and $\theta_3 \geq 1$ represent the effects of health measures in reducing the amount of bacterial, in the first case by educational programs, construction of drainages, water treatment, or directly by killing bacterial using chemical substances in the second case (Curtis et al. 2009). For example, filter pond water through sari cloth before drinking reduce the risk of cholera infections by approximately 50% (Lipp et al. 2002). The model parameters are summarized in Table 1.

We will allow the contact rate to be a function of time, representing the seasonal effects (floods, droughts, temperature variation) that potentially drive cholera dynam-

Table 1 Parameters used in the model and their meaning (Codeço 2001; Brayton et al. 1987; Kaper et al. 1995; King et al. 2008; Neilan et al. 2010)

Parameter	Biological meaning	Range of values
μ	Natural mortality rate	$[0.012, 0.033]$ (years^{-1})
β	Contact rate between bacterial and susceptible hosts	$[1.05, 10.5]$ days^{-1}
K	Concentration of bacterial in water that yields 50% change of catching *V. cholerae*	$[10^3, 10^6]$ (cells/ml)
r_1	Rate at which people lose immunity	$[0.001, 0.03]$ (days^{-1})
r	Rate at which people recover from the disease	$[0.07, 0.20]$ (days^{-1})
γ	Bacterial mortality rate	$[0.02, 1.0]$ (days^{-1})
e	Contribution of each infected person to the population of *V. cholerae* in the aquatic environment	$[1, 100]$ (cell/ml day^{-1} person^{-1})

ics (Codeço 2001; Pascual et al. 2002). The contact rate β will be taken to vary sinusoidally according to

$$\beta = \beta_0(1 + \delta \sin(2\pi t/365)).$$

In this case, β_0 is the mean contact rate and δ describes the relative amplitude of seasonal variations. In fact, modeling seasonality as a sine wave is the simplest way to incorporate an external forcing parameter in infectious diseases, which appear to be synchronized and periodic in time. This allows us to pursue a generic study of the system. Of course, to attain predictability concerning a specific geographic location, more complicated and realistic seasonal forcing functions that describe the processes underlying the seasonal transmission in a particular region can be added, but the qualitative aspects that we want to address here will be preserved.

We also consider that the total human population, H, is constant (natality replacing mortality), and therefore, $H = S + I + R$, so that the system can be reduced to a three-dimensional one.

Although the splitting of the infective class, in symptomatic and asymptomatic, can explain sporadic cholera outbreak in a population, as well as disease dispersion and, depending on the parameter set, has a positive or negative impact on the estimation of the epidemic size (Neilan et al. 2010; Hsu and Hsieh 2008), we decided not distinguish between symptomatic and asymptomatic individuals, since our main interest in this work is to investigate other aspects of the disease dynamics that have not yet been explored, like the intensification of outbreaks by resonance effects, as well as the role of the immunity in cholera pattern. In this way, the epidemiological parameters β, r, and e can be interpreted as the weighted average of its possible values, where the weight assigned to each possible value is the size of symptomatic and asymptomatic class.

3 Preliminary Analysis: the System Without Seasonal Effects

In order to set the stage for the analysis of the seasonally forced equation in the next section, we first consider the case where $\delta = 0$, that is, the contact rate is constant

and equal to β_0. In this case, the corresponding model has two equilibrium points, namely, the disease-free equilibrium, $E_0 = (\frac{\mu+r_1}{\mu+r_1+\theta_4}H, 0, 0)$, and the endemic equilibrium. The stability of the disease-free equilibrium is given by the eigenvalues of the characteristic equation $P(\lambda) = \det(J^* - \lambda I) = 0$ evaluated in E_0, where J^* is the Jacobian matrix, and I is the identity matrix. In this case the corresponding characteristic equation is

$$P(\lambda) = P_1(\lambda)P_2(\lambda) = 0$$

where

$$\begin{cases} P_1(\lambda) = -\mu - r_1 - \theta_4 - \lambda, \\ P_2(\lambda) = \lambda^2 + (r + \mu + \theta_3\gamma)\lambda + (r + \mu)(\theta_3\gamma) - \frac{(\theta_2 e)(\theta_1\beta_0)(\mu+r_1)H}{(\mu+r_1+\theta_4)K}. \end{cases}$$

Using the Routh–Hurwitz stability criterion (Hurwitz 1895) and defining

$$R_c = \frac{(\theta_1\beta_0)(\theta_2 e)(\mu + r_1)H}{(\mu + r_1 + \theta_4)(\theta_3\gamma)(r + \mu)K}, \tag{2}$$

the disease-free equilibrium is locally asymptotically stable if $R_c < 1$. On the other hand, if no control mechanisms are applied, that is, $\theta_1 = \theta_2 = \theta_3 = 1$ and $\theta_4 = 0$, R_c becomes $R_0 = (\beta_0 eH)/(K\gamma(r + \mu))$, the *basic reproductive number* for cholera disease.

The second equilibrium point is given by $E_1 = (\bar{S}, \bar{I}, \bar{B})$ where

$$\begin{cases} \bar{S} = \frac{(r+\mu)(K(\gamma\theta_3)+(e\theta_2)I)}{(\beta_0\theta_1)(e\theta_2)}, \\ \bar{I} = \frac{(\mu+r_1)K(\theta_3\gamma)((r+\mu)(R_c-1)-\theta_4)}{(\theta_2 e)((\mu+r_1+\theta_4)(r+\mu)+(\theta_1\beta)(r_1+r+\mu))} \quad \text{and} \\ \bar{B} = \frac{\theta_2 e}{\theta_3\gamma}I. \end{cases}$$

From the expressions above, we see that in the absence of vaccination ($\theta_4 = 0$), the condition for $\bar{I} > 0$ is $R_c > 1$. In this case, the endemic equilibrium E_1 is feasible, and standard linear analysis of system (1) indicates that E_1 is locally asymptotically stable, and E_0 becomes unstable. When $R_c \leq 1$, the solutions approach the disease-free equilibrium E_0, and the disease dies out. However, when vaccination is in course ($\theta_4 > 0$), the threshold value for cholera outbreaks is situated at $R = R_c^* > 1$, where

$$R_c^* = \frac{(\mu + r)(R_c - 1)}{\theta_4}. \tag{3}$$

The steady-state stability analysis shows that control mechanisms on the parameters β_0, e, μ, and γ can reduce the value of R_c below 1, stopping cholera transmission in the population. Also, reducing $R_c^* < 1$ (with vaccination) prevents cholera outbreaks.

Similar to Codeço model, the endemic equilibrium is attained through a succession of epidemic peaks of decreasing amplitude. Therefore, an oscillatory mechanism is already present in the model, due to the continuous entrance of susceptible individuals, with an intrinsic period of outbreaks peaks. A natural inquiry is to examine the

effects of seasonal forcing on these oscillations. In analogy to mechanical oscillators, we would expect that an external forcing will sustain the oscillations, whose amplitude should depend on the frequency of the forcing, and resonance phenomenon could appear (Nayfeh and Mook 2004). Therefore, to examine the case where the system is subject to seasonal forcing, we take an approach based on resonance studies.

4 Seasonal Cycles on Cholera Transmission: a Resonance Approach

A dynamical system with damped natural oscillations under the action of a periodic forcing develops sustained cycles, whose amplitude usually depends on the period and amplitude of the forcing. The seasonality of cholera outbreaks will be analyzed according to a resonance approach (Dushoff et al. 2004; Greenmam et al. 2004). The parametric forcing depends on three parameters: the frequency, the amplitude and the mean value. The mean value is approximately known and we will take it as known. We thus have a two-dimensional parameter space for the seasonality related effects. Examining the dependence on the amplitude would lead us to the realm of nonlinear effects, as is usual in the study of parametrically forced systems. However, we have no reason to proceed in this way as there are no evidences for strong nonlinear behavior coming from data. On the other hand, varying the frequency is the usual way to perform a resonance analysis, and was been done so in epidemiology. We begin by scaling the parameters of the model by a constant factor p^{-1}: $\mu' = \frac{\mu}{p}, \beta_0' = \frac{\beta_0}{p}, r_1' = \frac{r_1}{p}, r' = \frac{r}{p}, e' = \frac{e}{p}, \theta_4' = \frac{\theta_4}{p}, \gamma' = \frac{\gamma}{p}$ and time as $t' = tp$. Dropping the primes, for convenience, the new rescaled equations have the same form of system (1) with

$$\beta = \beta_0\left(1 + \delta \sin\left(\frac{2\pi t}{365p}\right)\right).$$

The model parameters used in the simulations are $\mu = 0.00007$ days^{-1}, $\beta_0 = 1.2$ days^{-1}, $\delta = 0.3$, $K = 10^6$ cell/ml, $r_1 = 0.0035$ days^{-1}, $r = 0.12$ days^{-1}, $\gamma = 0.4$ days^{-1} and $e = 10$ cells/ml days^{-1} person^{-1}. The total population H is assumed equal to 10,000. To go step by step, we analyze first the case with no control.

To determine the existence of a resonance phenomenon in cholera transmission dynamics, in Fig. 1a, we look at the local maxima of the infectious population $I_{\max}$, which is periodic as shown in Fig. 1b, plotted against the external force period p. The value of a variable at time t is a local maximum if it is higher than the values measured at times $(t-3)$, $(t-2)$, $(t-1)$, and not lower than that ones measured at times $(t+1)$, $(t+2)$, $(t+3)$.

Now, it is known that the usual SIRS model with immunity loss and vital dynamics has an intrinsic period of oscillation $T \sim 2\pi/\sqrt{((r_1+\mu)(r+\mu)(R_0-1))}$ (Keeling and Rohani 2008). This period is a good approximation to the one of our model. Suppose, for instance, that the bacterial population reaches equilibrium values much faster than the human population, and that the number of infected human individuals is much smaller than $K\gamma/e$. Then the proposed model can be view as a SIRS model

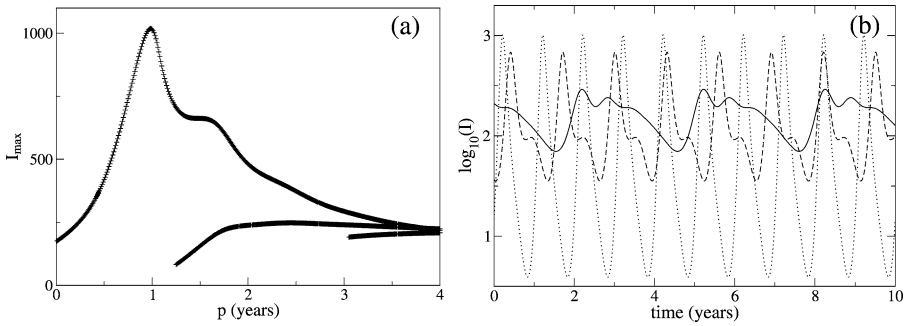

Fig. 1 In (**a**), the local maxima of the temporal evolution of the infected individuals are plotted against the external force period. In (**b**), the temporal evolution of the logarithm (base 10) of the infected individuals is plotted for $p = 1.0$ (*dotted line*), $p = 1.3$ (*dashed line*), and $p = 3.03$ (*continuous line*)

and the result obtained for the period of the oscillation is in good agreement with the above expression.

Resonance phenomena can occur for T near the period of the seasonal forcing producing amplified oscillations in the disease incidence (Dushoff et al. 2004). Substituting the parameters given above in model (1) without seasonality (i.e. $\delta = 0$) and control mechanisms, we estimate $R_0 = 2.50$ with an intrinsic or natural period of oscillation of $T \sim 0.70$, and maximum number of infected individuals $I_{\max} = 172.8$ (the correct value is 2π divided by the modulus of the imaginary part of the complex conjugate eigenvalues of the Jacobian of (1)). On the other hand, the numerical results for the model with seasonality show that maximum response is given at $p \sim 1.0$ day with $I_{\max} = 1024$. As expected, without seasonal forcing, the maximum number of infected individuals is smaller than that obtained with $\delta \neq 0$. Interesting, Fig. 1b shows that for $0 < p < 1.25$ the temporal evolution of the number of infected individuals (plotted in base 10 logarithm) is unimodal, for $1.25 \leq p \leq 3.0$ it is bimodal and finally, for $3.0 < p \leq 4.0$ it is trimodal. In all cases, the system responds with oscillations of the same period as the external force.

In the range of parameters explored, which correspond to typical values (Codeço 2001; Brayton et al. 1987; Kaper et al. 1995; King et al. 2008), sustained peaks of cholera outbreaks can be explained by seasonal forcing in a nearly linear regime. The value of p obtained in this way is close to one, implying a near-resonant matching of periods if the origin of infective periodicity is related to annual variations, which is a reasonable assumption. We notice, however, that cholera is subject to many region-specific factors. Therefore, a more precise case-specific analysis should be performed to effectively propose strategic decision-making assessments. For instance, natural defense mechanisms against the disease are more common in populations continually exposed to cholera vibrios, or survivors of severe infections. Also, depending on sanitary conditions of the region, as well as water treatment, the amount of bacterial can increase. All these factor may be important under certain conditions. Over this work, we aim to explore the general features in the cholera transmission, rather than analyze specific cases.

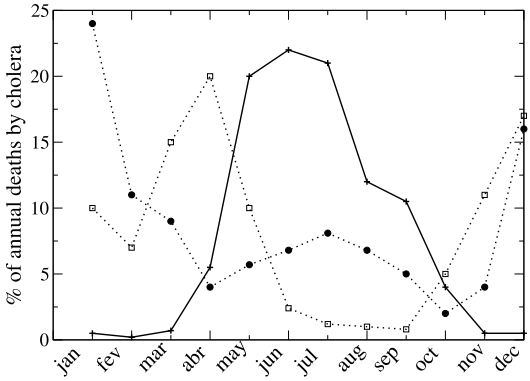

Fig. 2 Variability of seasonal cholera in the endemic provinces Bengal (□) and Madras (•)—bimodal pattern—and in the epidemic Punjab province (+)—unimodal pattern. Figure taken from (Pascual et al. 2002)

5 Effects due to Loss of Host Immunity

Cholera dynamics have been the object of many studies, but until now unsolved puzzles still remain about its mode of transmission and the role of host immunity in its dynamics. For instance, King et al. (2008) fitted a SIRS model to data from the province of Bengal over the period 1891–1940 and showed that immunity must wane on a time scale of weeks to months and that most exposures do not result in severe forms of cholera, but in mild or asymptomatic infection with shorted-lived immunological memory. Systematic changes on their basic model could explain the data significantly better, but their conclusions about low $R_0 \sim 1.5$, rapid loss of immunity and high prevalence of asymptomatic infection remain unchanged. They also associated the disease persistence to environmental reservoirs which provide an extrinsic force of infection, whose strength varies geographically following a pattern, reinforcing the idea that extrinsic factors can trigger cholera outbreaks (an hypothesis already discussed in Sect. 4). These results contrast with the belief that infection-derived immunity to cholera wanes on a time scale of 3–10 years, and with the much higher values of $R_0 \sim 8.7$ proposed by other authors (Hartley et al. 2006; Koelle and Pascual 2004).

In this section, we will address the different patterns observed in cholera epidemics peaks, using the model parameters given in King et al. (2008), and relate the one or two annual epidemics peaks observed in the endemic regions of cholera to different periods of host immunity (Fig. 2).

In order to explore the role of immunity loss in cholera dynamics we show in Fig. 3 the effect of the variation of r_1 in cholera periodicity and severity. The parameter values are the same as used before. First, we note that the number of infected individuals always increases when r_1 increases. Since r_1^{-1} is the typical period of time that an individual remains immune, it is not surprising that the fast recovery of the susceptible pool by return of the immune individuals increases the number of infected individuals in the population. The numerical results obtained for p times r_1 corroborate the analytical results given by $T \propto \sqrt{1/r_1}$ (for the SIRS model), as we expect that the resonance occurs at $p \sim T$ (Keeling and Rohani 2008). Finally, for small value of r_1, resonance occurs for largest values of p, because the susceptible pool takes more time to recover.

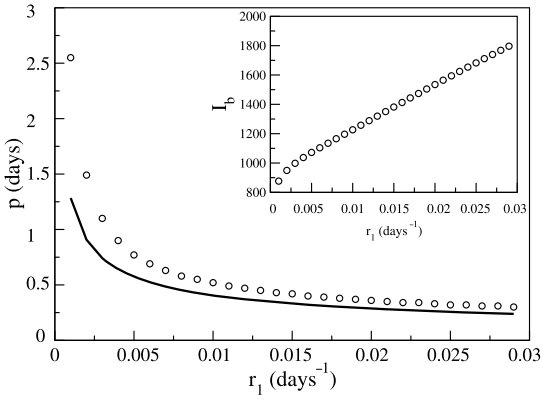

Fig. 3 Resonance period, p, and the number of infected individuals, I_b (*in the inset*), as a function of the immune rate, r_1. The p value is the one that maximizes the number of infected individuals for each parameter set, and I_b is the biggest value of I obtained from the time series of the infected individuals. The symbol (∘) corresponds to the simulation and the *continuous line* to the analytical results given by $T \sim 2\pi/\sqrt{((r_1+\mu)(r+\mu)(R_0-1))}$ for the usual SIRS model with immunity loss and vital dynamics

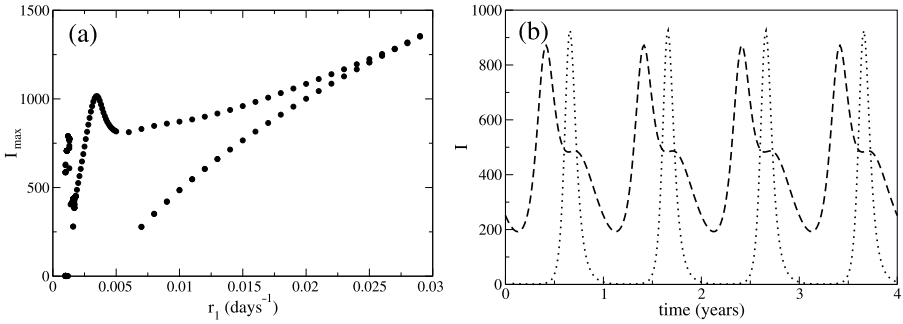

Fig. 4 In (**a**), the region of the parameter space where a unimodal or bimodal curve for the infectious individuals versus time appears. In (**b**), the temporal evolution of the infected individuals for $r_1 = 0.003$ days^{-1} (*dotted line*) and $r_1 = 0.01$ days^{-1} (*dashed line*)

Figure 4a shows the local maxima obtained from the time evolution of the infectious population as r_1 varies for distinct initial conditions (it was obtained from the derivative of the curve of infected individuals in time). Observe that there is a region in the parameter space where two local maxima occur in a period, which characterizes a bimodal curve. We can note that for $r_1 < 0.0068$ the curve of the number of infected individuals versus time is unimodal. On the other hand, for $0.0068 \leq r_1 \leq 0.03$, the curve of the number of infected individuals versus time is bimodal. Also, for $r_1 < 0.002$, the projection of the attractor of the infected individuals versus the susceptible total population shows that the system dynamics can depend on the initial conditions (result not shown).

To emphasize the existence of unimodal and bimodal curves in the parameter space, in Fig. 4b, we have depicted the number of infected individuals versus time for $r_1 = 0.003$ days^{-1} (dotted line) and $r_1 = 0.01$ days^{-1} (dashed line). Disease severity is not the same for the different set of parameters. Following the disease for one year, we can see that we have one peak of incidence for $r_1 = 0.003$ days^{-1} (which can be related to a community with long-lasting immunity) and two peaks of incidence for $r_1 = 0.01$ days^{-1} (which can be related to a community with short immunity). In fact, different patterns can be generated by distinct r_1, reinforcing the idea that immunity has an important role on cholera transmission, and also that it can be the basis of the explanation of the different patterns observed on cholera disease. We conclude that the seasonal forcing parameter alone is not sufficient to explain the annual bimodal pattern, it is triggered by a seasonal force plus host immunity.

6 Control Mechanisms

In this section, our aim is to compare the efficiency of different control mechanisms acting at the periodic model (i.e. $\delta \neq 0$) to stop or decrease cholera transmission. Therefore, we introduce an index, J_i, defined as

$$J_i = \left(1 - \frac{A_i}{A_0}\right) \times 100 \quad \text{where } A_i = \int_0^\tau I(t)\,dt, \text{ with } i = 1, 2, 3, 4.$$

Hence, A_0 and A_i are the area below the curve of the infected individuals measure between $t = 0$ to τ without and with control mechanisms, respectively. The index J_i measures the reduction of the infected individuals obtained by the application of a specific control mechanism during τ years (Ferreira et al. 2008). To simplify the analysis, we will discuss the effects of each one of the control mechanisms separately.

Control mechanisms can be applied using several distinct strategies. We analyzed two of them:

1. periodic: in this case, specific control mechanisms are applied during the period of the year when cholera has the highest probability of appearing. The period was determined by measuring the slope of the number of infected individuals in time. Therefore, the control is applied when cholera infection starts to grow (positive slope) and is stopped when it starts to decay (negative slope);
2. continuous: in this case, specific control mechanisms are applied all the time.

The parameters values are the same used before and $p = 1$ day. Initially, the simulation is carried on until the time evolution of the population achieves a periodic regular pattern. Then a specific control is applied and disease dynamics with and without control is compared during 5 years of simulation, i.e. $\tau = 5$ years (Ferreira et al. 2008).

Figure 5 shows control efficiency measurement as a function of θ_1. In this case, the control has been applied directly on the rate of cholera transmission and can be seen as an improvement of individual behavior, like hand washing. An interesting example is a common practice of the habitants of the Amazonian region consisting of

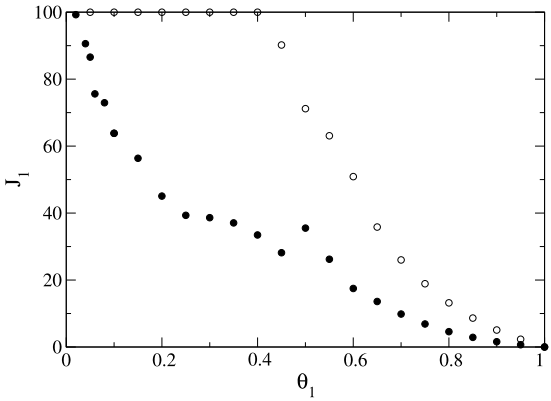

Fig. 5 Control efficacy, J_1, measured as a function of θ_1. The other control parameters are $\theta_2 = \theta_3 = 1$ and $\theta_4 = 0$. As an example, θ_1 can be thought of as the protective effect of hand hygiene. In (○) for continuous control and (●) for periodic one

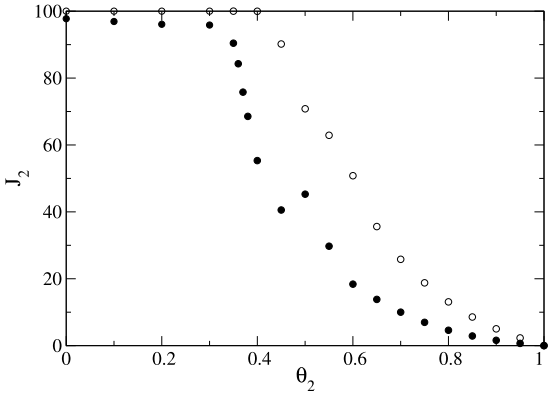

Fig. 6 Control efficacy, J_2, measured as a function of θ_2. The other control parameters are $\theta_1 = \theta_3 = 1$ and $\theta_4 = 0$. The parameter θ_2 can be related to an increase of sanitation conditions. In (○) for continuous control and (●) for periodic one

add citrus juice to water, because the acid in the fruit kills the *Vibrio* bacterial (Tauxe et al. 1995). In fact, this practice protects the susceptible individuals from cholera disease. If control is applied continuously, a 60% of efficiency is obtained with 4.6 times less effort compared to periodic control. For this parameter set, periodic control cannot eradicate cholera transmission. On the other hand, for continuous control, eradication is achieved with $\theta_1 = 0.4$. This threshold value represents a reduction of 40% in the contact rate, and corroborates the analytic results obtained using (2), assuming a constant transmission rate $\beta = \frac{1}{\tau}\int_0^\tau \beta_0(1+\delta\sin(2\pi t/365))\,dt = \beta_0$, i.e., for this parameter set $R_c = 0.9994$.

Figure 6 shows control efficiency measurement as a function of θ_2. Good sanitary conditions drive cholera to extinction if continuous control is applied. Unfortunately, during wars and complex humanitarian emergencies the provision of safe water and sanitation break down leaving the susceptible individuals exposed to cholera *Vibrio*. If continuous control is applied, using (2) and, as before, assuming a constant transmission rate $\beta = \beta_0$, eradication is achieved with $\theta_2 = 0.4$ which gives $R_c = 0.9992$. This threshold value represents a reduction of 40% in the amount of bacterium expelled by a infected human into the environment. Also, continuous control gives a 60% of efficiency with 1.4 times less effort compared to periodic one.

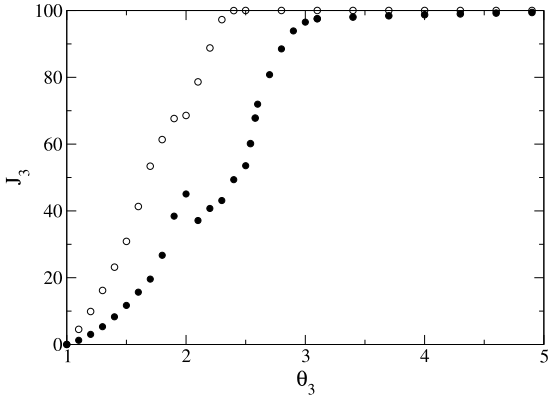

Fig. 7 Control efficacy, J_3, measured as a function of θ_3. The other control parameters are $\theta_1 = \theta_2 = 1$ and $\theta_4 = 0$. The parameter θ_3 can be related to an improvement of water treatment. In (○) for continuous control and (●) for periodic one

Figure 7 shows control efficiency measurement as a function of θ_3 which can be related to water treatment. If continuous control is applied, using (2) and assuming a constant transmission rate $\beta = \beta_0$, eradication is achieved with $\theta_3 = 2.5$ which gives $R_c = 0.9994$. This threshold value represents an increase of $2,5$ times in bacterium mortality. As before, continuous control gives a 60% of efficiency with 1.4 times less effort compared to periodic one. The anomalous behavior observed in the curves (like at $\theta_3 \sim 2$) is related to the J definition (integration interval) and to the applied of control mechanisms which cause oscillation in the infective curves.

Figure 8 shows control efficiency measurement as a function of θ_4. Mass immunization programs are not in view presently because an effective and low-cost vaccine has not been developed yet. Nonetheless, during cholera outbreaks (periodic control) vaccination campaigns can be a good strategy to control cholera epidemics. In Longini et al. (2007), a spatial stochastic model was used to asses the efficiency of vaccination campaigns in cholera transmission. They assumed that the vaccine induces immunity, which results in a reduction of the probability of infection per contact with an infectious source. For endemic cholera, where population-level immunity is relatively high, it was shown that relatively low vaccine coverage levels (50%–70%) can control cholera transmission. Using a different approach, i.e. a compartmental model plus the assumption that vaccination reduces the number of susceptible individuals in the total population, our results agree with theirs; periodic control can suppress cholera outbreaks if $\theta_4 > 0.015$ which accounts for the number of recovered individuals $R \sim 6{,}000$. Therefore, in a total population of $H = 10{,}000$ and considering a effective vaccine efficiency of 0.8, it means a coverage reach of 60% of the population.

As shown before, the continuous control is always more efficient than the periodic one. In particular, control measures related to individual behavior when made in a non-continuous way greatly diminishes the effectiveness of this control on cholera transmission (see Fig. 5). Also, comparing Figs. 5, 6, 7, and 8, we obtain that vaccination and improvements in the sanitation system and food/personal hygiene are the most efficient control strategies to prevent cholera transmission and outbreaks. Indeed, the real contribution of each one can only be measured by knowledge of the parameter set that characterizes a specific region.

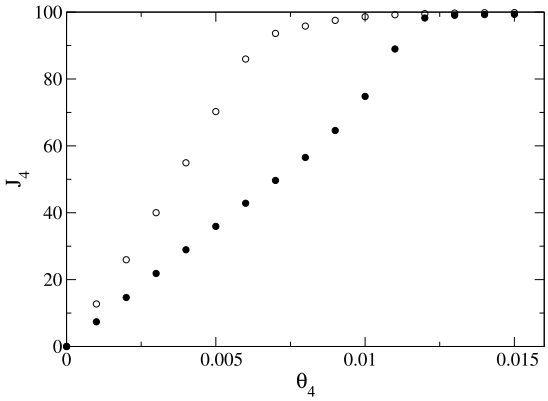

Fig. 8 Control efficacy, J_4, measured as a function of θ_4. The other control parameters are $\theta_1 = \theta_2 = \theta_3 = 1$. The parameter θ_4 can be seen as the proportion of individuals immunized. In (○) for continuous control and (●) for periodic control

7 Conclusion

The model developed here is an extension of Codeço's model and captures essential features of cholera epidemics. We show that extrinsic (e.g. environmental) and intrinsic factors correlate in time with components of the epidemic cycle. The interplay of time-scales of the incidence cycles and the annual variations of contact rates may give rise to resonant behavior, which shows up as an increase of the number of infected individuals. When a third typical time-scale is also considered, that of immunity duration, possible complex behavior may emerge.

Our model offers a clue to the existence of secondary outbreaks. They appear as a consequence of the finite duration of immunity to the disease. When this is not taken into account, the model does not show a bifurcation to a two-maxima-per-year regime. On the other hand, we note that solutions of the model showing secondary peaks only exist in a certain range of parameters. Because these parameters are regulated by regional policies, some regions may exhibit secondary peaks and others may not.

For the autonomous model, a threshold value given by R_c^*, which depends on the biological parameters of the pathogen and the host and also on population size, separates disease-free equilibrium and endemic equilibrium. Control mechanisms, such as vaccination, improved sanitary conditions, and water treatment applied continuously, can diminish $R_c^* < 1$ and prevent cholera transmission. Indeed, an effective cholera prevention strategy addresses individual behavior and public health practices. We analyzed the application of different control mechanisms and emphasized the importance of sanitary conditions, better water treatment, and hand/food hygiene in the disease dynamics. If mass vaccination is possible (maybe in a critical situation or in a endemic area), periodic application of this kind of control can eradicate or reduce cholera outbreaks. As in Longini et al. (2007) model, the range of vaccination coverage depends on a population's level of immunity.

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