

Modeling Cholera Outbreaks

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Abstract Mathematical modeling can be a valuable tool for studying infectious disease outbreak dynamics and simulating the effects of possible interventions. Here, we describe approaches to modeling cholera outbreaks and how models have been applied to explore intervention strategies, particularly in Haiti. Mathematical models can play an important role in formulating and evaluating complex cholera outbreak response options. Major challenges to cholera modeling are insufficient data for calibrating models and the need to tailor models for different outbreak scenarios.

Contents

1	Introduction.....	196
2	Mathematical Models of Cholera Transmission	196
2.1	Modeling Cholera Transmission Within a Well-Mixed Population	197
2.2	Spatial Modeling and Pathogen Movement.....	198
2.3	Transmission Within Households and Hyperinfectivity	200
2.4	Modeling Interventions.....	201
3	Modeling the 2010 Cholera Outbreak in Haiti	202
4	Discussion and Conclusions.....	203
	References.....	205

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1 Introduction

Although early studies of cholera have become exemplars of modern epidemiology (e.g., Snow 1855; Koch 1886, 1893), predicting and managing cholera outbreaks is still a major challenge in the developing world. Improvements in sanitation and the use of oral rehydration therapy have greatly reduced the burden of disease, but we lack a predictive framework for anticipating outbreaks and planning for interventions. Mathematical modeling is one approach to synthesizing our knowledge of cholera into a quantitative framework. Mathematical models have been used to study the dynamics of disease outbreaks and predict the effectiveness of potential intervention strategies (Garnett et al. 2011; Hutubessy et al. 2011).

Recommendations for the response to cholera outbreaks have evolved over the past decade. Earlier guidelines emphasized case management and discouraged the use of vaccines until post-emergency (Connolly 2005). Later, pre-emptive vaccination was proposed for use during complex emergencies (Chaignat and Monti 2007), and mass vaccination was being considered for containing outbreaks (Global Task Force on Cholera Control 2010). However, vaccination is usually not a practical option because of the small global supply of cholera vaccine. Recent massive and prolonged outbreaks of cholera in Haiti and several countries in Africa renewed interest in creating a global cholera vaccine stockpile, which would increase availability of the vaccine for emergency use as well as for seasonal epidemics (Waldor et al. 2010; World Health Organization 2010, 2012; Holmgren 2012; International Vaccine Institute 2012; Martin et al. 2012). But even if more vaccine were available, there is a lack of guidance for its use. Mathematical modeling can help fill this gap.

As the options for cholera outbreak responses become more complex, there is a greater need for quantitative frameworks such as mathematical modeling to both evaluate and help formulate them (Clemens 2011). In particular, the ongoing multi-year epidemic in Haiti has challenged us to plan for more comprehensive, integrated, and long-term strategies for cholera outbreaks that would involve improved identification and treatment of cases, increased access to clean water, and vaccine (Ivers et al. 2010; Farmer et al. 2011). Because cholera vaccine has rarely been used *during* an outbreak, modeling may be needed to extrapolate what little *has* been observed. Because there are many competing needs for scarce resources during complex emergencies, modeling may be required to help weigh the costs and benefits of different options (Miller Neilan et al. 2010). In this chapter, we describe how mathematical models have been applied to study cholera.

2 Mathematical Models of Cholera Transmission

Here, we describe basic mathematical models of cholera transmission, then we discuss approaches to making more detailed cholera outbreaks models, including the addition of contaminated water supplies, spatial effects, within-household transmission, and interventions.

2.1 Modeling Cholera Transmission Within a Well-Mixed Population

Basic mathematical models of infectious disease transmission describe the transitions of individuals among susceptible, infectious, and recovered states. In a susceptible-infected-recovered (SIR) model, susceptible individuals become infected at a rate proportional to the number of infected individuals, infected individuals recover at a constant rate, and recovered individuals are immune to infection (Kermack and McKendrick 1927). To account for the incubation period of a disease, one may introduce a transient “exposed” state for infected individuals before they become infectious (e.g., an SEIR model). This basic model generates a single epidemic peak, but variants that include the waning of immunity or the introduction of new susceptibles can produce cyclical dynamics (Hethcote 2000).

This basic modeling framework can be adapted to specific infectious agents by tuning infectiousness and recovery rate parameters to match the known natural history parameters or outbreak dynamics of a pathogen. A mathematical model of cholera could include an incubation period of a few hours to a few days and an infectious period of one or two weeks (Longini et al. 2007; Chao et al. 2011). To include multi-season dynamics, waning immunity can be added to the model (e.g., an SIRS model) (Koelle and Pascual 2004; Koelle et al. 2005; Rinaldo et al. 2012). One may also add symptomatic and asymptomatic infections, which could play different roles in disease transmission and surveillance (Longini et al. 2007; King et al. 2008; Nelson et al. 2009; Andrews and Basu 2011).

Many cholera models assume that individuals become infected by consumption of *V. cholerae* from the environment and therefore include an explicit environmental compartment (Codeço 2001; Tien and Earn 2010). A susceptible individual’s risk of infection, λ , at time t can be expressed as $\lambda(t) = \mu I(t) + \beta B(t)$, where μ is the rate of exposure between individuals, $I(t)$ is the number of infectious individuals at time t , β is the rate of exposure to the environment, and $B(t)$ is the level of contamination of the environment. Note that the first term is proportional to the number of infectious individuals, and we refer to this as the *ciclo corto* (“short cycle”) transmission pathway. This route is also known as “person-to-person” transmission and accounts for infections occurring during the short time window of an infected close contact’s infectious period. The second term is proportional to the level of contamination in the environment and is also known as *ciclo largo* (“long cycle”) transmission, which could be caused by exposure to sewage or contaminated water not necessarily traceable to an infected contact. A cholera model can include either or both of these terms. Inserting the environment into the chain of cholera transmission can create a lag in the generation time and allows for cholera transmission to occur in the absence of infected individuals, which can help the disease persist in a population. Figure 1 diagrams a modeling framework that includes both *ciclo corto* and *ciclo largo* transmission.

Different models based on alternative sets of assumptions may be able to fit observations equally well. For example, simple SIR models of cholera can produce

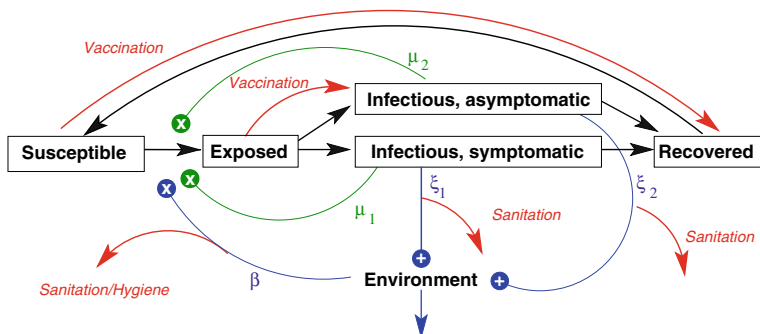


Fig. 1 Basic cholera model diagram. Individuals can be Susceptible to cholera, Exposed, Infectious (either symptomatically or asymptotically), or Recovered (and immune to infection). *Black arrows* indicate transitions between these states. Infectious individuals shed cholera into the environment (indicated by the “+”s). Susceptible individuals become infected by exposure to *Vibrio cholerae* from the Environment (the *ciclo largo* route indicated by blue “x”) at the rate of β or “directly” from Infectious individuals at the rate of μ (the *ciclo corto* route indicated by green “x”s). After an incubation period, individuals transition from the Exposed to the Infectious state. Infectious individuals shed vibrios into the environment at rate ξ . Symptomatic and asymptomatic may have different levels of infectiousness, indicated by the subscripts following ξ and μ . *Red arrows* indicate possible effects of interventions labeled in italics, including vaccination, sanitation, and improved hygiene

outbreak dynamics nearly indistinguishable from those that include *ciclo largo* transmission. However, a particular intervention may target one of these routes of transmission more than the other. Therefore, to accurately predict the effectiveness of interventions, one should include the major routes of exposure.

With high quality surveillance data, models might be used to determine the relative contribution of *ciclo corto* and *ciclo largo* transmission. In regions with seasonal cholera epidemics, outbreaks may be triggered by *V. cholerae* in the aquatic reservoir while secondary transmission (*ciclo corto*) drives dramatic local outbreaks (Franco et al. 1997; Ruiz-Moreno et al. 2010). King et al. (2008) used over 50 years of cholera mortality data from Bengal to test alternative models of disease transmission and found support for a large role for *ciclo largo* transmission in certain districts. Mukandavire et al. (2011) used weekly surveillance data to estimate the relative contributions of *ciclo corto* and *ciclo largo* transmission of a major outbreak in Zimbabwe that started in 2008. They concluded that the relative contributions of these two routes of transmission were different by province, which may be due to differences in the modes of transmission. Studies such as these reveal spatial heterogeneities in cholera transmission.

2.2 Spatial Modeling and Pathogen Movement

For disease outbreaks in small, tightly connected communities, models of single well-mixed populations may be the most appropriate and parsimonious approach.

However, if an outbreak encompasses a large population or if the geographic region includes heterogeneities relevant to disease transmission, such as population density, socioeconomic differences, or geographic features that could block or enhance transmission, then models may need to include multiple interacting populations.

There are several options for geographically subdividing a population for modeling purposes. An obvious choice would be to match the spatial resolution of available surveillance data, so that each reporting area is a single subpopulation within a “metapopulation” or “patch” model (Tuite et al. 2011; Andrews and Basu 2011). However, surveillance data may be coarse, and disease outbreaks may occur on a much finer scale. One could instead use finer political boundaries [e.g., districts or other administrative boundaries (Bertuzzo et al. 2011)], geographical/geological features [e.g., watersheds (Rinaldo et al. 2012)], or a fine regular grid (Longini et al. 2007; Chao et al. 2011). Using smaller geographic units may better capture spatial heterogeneity relevant to cholera transmission, but can complicate the model with excessive parameters and lead to a loss of generality of modeling results.

Perhaps the spatial resolution of the model should not be determined by convenient political boundaries, but instead by the “natural scale” of cholera outbreaks. Cholera outbreaks are known to be fast and produce sharply peaked epidemic curves, but when case reporting is aggregated by large geographic regions, such as at the country-level, sharp epidemic spikes and outbreak dynamics in general can be masked. Trying to fit a single epidemic curve that is actually the aggregate of multiple spatially separated outbreaks will result in misleading results (Grad et al. 2012). Unfortunately, the scale of an outbreak probably depends on local environmental and sociological factors. Spatial analyses and sequencing of cholera isolates may help identify distinct outbreaks in endemic settings (Stine et al. 2008), which could help modelers dis-aggregate concurrent but distinct outbreaks.

Metapopulation models include mechanisms governing the flow of the infectious agent among the populations. Many models assume that pathogens are transported primarily by infectious people. In such models, susceptible people in one community can be infected by infectious people in neighboring communities. This is usually implemented by setting the force of infection in a community to be a function of both the number of infectious individuals residing in the community and the number of infectious individuals in neighboring communities. Thus, an infectious person contributes to infections in co-located susceptibles and in neighboring populations, often with a force of infection inversely proportional to distance (Bertuzzo et al. 2011; Tuite et al. 2011; Mari et al. 2012). In addition to using geographic distance, one can assume that individuals living along major transportation routes are more mobile and can spread disease farther than those who are more isolated (Chao et al. 2011). In agent-based, or individual-based, models in which each person is individually represented, infectious individuals can move from location to location, infecting individuals as they travel (Longini et al. 2007; Chao et al. 2011). Eventually, studies that track cell phones and other

mobile devices might tell us how people actually move during an outbreak (Chunara et al. 2012; Bengtsson et al. 2011; Khan et al. 2012).

Alternatively, models can assume that the pathogen moves via the environment. The environmental reservoirs of adjacent populations can be linked, which would cause *V. cholerae* shed by one population to diffuse to neighboring populations (Bertuzzo et al. 2010, 2011; Mari et al. 2012), or hydrology can be modeled so that communities can infect populations that are downstream (Chao et al. 2011; Rinaldo et al. 2012). Including realistic hydrology may be important when rivers play a major role in cholera transmission. Some cholera models include the transport of the pathogen through both people and the environment (Chao et al. 2011; Rinaldo et al. 2012).

2.3 *Transmission Within Households and Hyperinfectivity*

High secondary attack rates have been observed within households of cases (Mosley et al. 1965, 1968; McCormack et al. 1968; Harris et al. 2008; Weil et al. 2009; Kendall et al. 2010). Although a common source of exposure could account for many of these heavily infected households, studies of the time intervals between cases or that genotype infecting strains have found patterns of transmission consistent with *ciclo corto* transmission (Snow 1855; Tamayo et al. 1965; Kendall et al. 2010). A tell tale sign of *ciclo corto* transmission would be the rapid appearance of secondary cases consistent with the incubation period of cholera.

A large inoculum of *V. cholerae* is required to infect an individual (Cash et al. 1974; Levine et al. 1979; Suntharasamai et al. 1992), which makes *ciclo corto* transmission appear to be physiologically challenging. There are several possible mechanisms for transmission within a household. For example, a household's food or water supply could be contaminated by an infected individual (St Louis et al. 1990; Albert et al. 1997; Rabbani and Greenough 1999; Roberts et al. 2001; Palit et al. 2012). Another possibility is that *V. cholerae* "hyperinfectious" state facilitates *ciclo corto* transmission. *V. cholerae* can be orders of magnitude more infectious within the first several hours after excretion from its host (Merrell et al. 2002). This *hyperinfectious* state of the pathogen would have a much lower infectious dose, which could allow for rapid transmission among close contacts.

Hartley et al. (2006) modeled the effects of hyperinfectivity by including two environmental reservoirs; infectious individuals contribute to a highly infectious environmental reservoir, which transitions to a second, less infectious reservoir. Including the hyperinfectious reservoir allowed the model to replicate the "explosive" dynamics of outbreaks (Hartley et al. 2006; Morris 2011). However, rapid cholera outbreaks can also be modeled using simple SIR models without explicitly including hyperinfectivity (Pascual et al. 2006). It may be impossible to resolve the role of hyperinfectivity in actual outbreaks using models alone—careful epidemiological studies are required. Conversely, it is not obvious which

modeling framework should be used, and it may depend on the particular scenario and possible interventions being considered.

Regardless of the actual mechanism invoked, models can include cholera transmission within households in order to capture the elevated attack rates within households with index cases (Chao et al. 2011). Including within-household transmission may be necessary to model certain household-level interventions, such as targeting certain individuals for vaccination in order to protect their families (Ali et al. 2008).

2.4 Modeling Interventions

Models can be used to estimate the effectiveness of intervention strategies. Interventions in the cholera modeling literature have included vaccination and improvements in sanitation and hygiene.

The effect of vaccines can be modeled in several ways, depending on assumptions about the vaccine's mode of protection (Halloran et al. 1999). Most cholera models assume that vaccination has the same protective effect as natural infection, so vaccinated susceptibles are simply treated as resistant individuals (Miller Neilan et al. 2010; Bertuzzo et al. 2011; Tuite et al. 2011; Andrews and Basu 2011; Azman et al. 2012), as shown in Fig. 1. However, vaccination may have immunological consequences different from natural infection (Leung et al. 2012; Arifuzzaman et al. 2012). In one challenge study, vaccine appears to protect against symptomatic illness but not necessarily against infection (Black et al. 1987). If one assumes that asymptotically infected individuals are infectious, then those protected by vaccine could still transmit disease. The model described in Chao et al. (2011) assumes that vaccinees are not protected against infection but have a lower probability of becoming symptomatic upon infection, as shown in Fig. 1.

Unvaccinated individuals may be indirectly protected when a sufficient number of their contacts are vaccinated (Fox et al. 1971). Models can be used to compute the critical vaccination fraction, or the fraction of the population that needs to be vaccinated to essentially stop local transmission (Hill and Longini 2003). If the basic reproductive number, R_0 is known, then the critical vaccination fraction is approximately $(1/VE)(1 - 1/R_0)$, where VE is the vaccine efficacy against infection. More detailed transmission models can be used to make more refined estimates for the critical vaccination fraction and other measures of indirect protection. In a large cholera vaccine trial, herd immunity was observed (Ali et al. 2005), and a modeling study used these results to explore the effectiveness of different levels of vaccine coverage (Longini et al. 2007). The Longini et al. (2007) study estimated that the critical vaccination fraction of the study population was about 70 %.

Improvements in sanitation and hygiene are essential non-pharmaceutical measures for cholera outbreak control. Interventions that reduce the consumption

of contaminated water, such as the provision of clean water or the promotion of chlorination, can be modeled as a reduction in the exposure to cholera from the environment (Miller Neilan et al. 2010; Tuite et al. 2011; Chao et al. 2011; Mari et al. 2012). Interventions that better manage the waste of infected individuals, such as the cleaning or building of latrines, could be modeled as a reduction in the contribution of infected individuals to the environmental reservoir (Chao et al. 2011; Mari et al. 2012). Both of these approaches to modeling improved sanitation and hygiene are depicted in Fig. 1.

3 Modeling the 2010 Cholera Outbreak in Haiti

In October 2010, cases of cholera began appearing in central Haiti, the start of a massive and prolonged epidemic that spread across the country and sickened over half a million people within a year (Walton and Ivers 2011; Cravioto et al. 2011). The conditions in Haiti seemed perfect for cholera transmission, with unrepaired damage from a major earthquake earlier in the year and Hurricane Tomas striking soon after the first cases of cholera were identified. Public health workers were trained to treat cases, and temporary cholera treatment centers were quickly established. Haiti's Ministère de la Santé Publique et de la Population (MSPP) launched a media campaign to promote better sanitation and hygiene (Centers for Disease Control and Prevention (CDC) 2010).

Several modeling efforts began soon after the first cases were reported (Bertuzzo et al. 2011; Tuite et al. 2011; Andrews and Basu 2011; Chao et al. 2011; Abrams et al. 2012). All of these studies attempted to reproduce the dynamics of the epidemic for a single season at the department level, the spatial resolution of reported case and hospitalization counts publicly released by MSPP. Two modeling groups divided the departments into much smaller regions to implement more realistic cholera transmission dynamics (Bertuzzo et al. 2011; Chao et al. 2011). All of these modeling studies focused on the size and duration of the first, and largest, wave of the epidemic, but the first were published in March of 2011, months after the peak actually occurred.

What emerged from the modeling community was a set of models and a small body of literature on modeling cholera during an outbreak. Common themes were the spatial coarseness of the surveillance data, the limited impact a small supply of vaccine would have on a nationwide outbreak, and the need for better surveillance. Most of the modeling groups used the case and hospitalization estimates from the MSPP, but one of the studies attempted to estimate and correct for the different reporting rates by department (Andrews and Basu 2011).

Chao et al. (2011) modeled scenarios in which there was much more vaccine than was actually available at the time. The study suggested that achieving high levels of coverage in regions with high exposure to cholera, particularly along rivers, could have had a major impact on the course of the epidemic. However, the study found that mass vaccination alone would have been insufficient to stop the

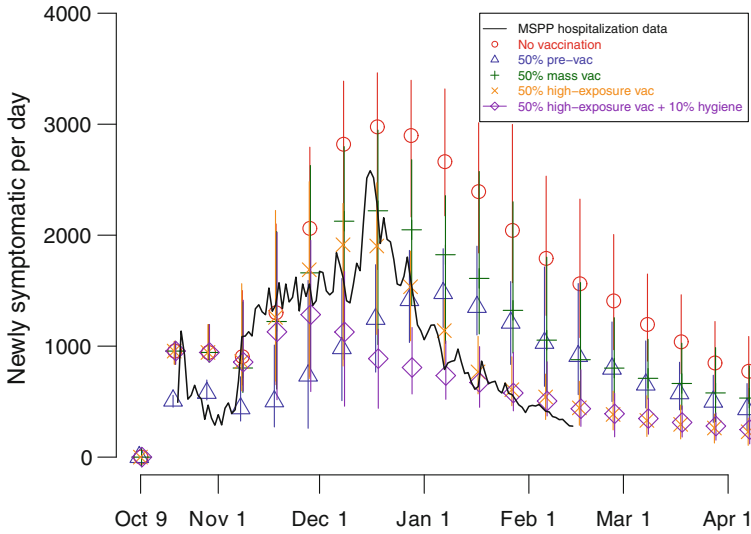


Fig. 2 Simulated effects of interventions during the first wave of the 2010 cholera epidemic in Haiti. The stochastic model described in Chao et al. (2011) was run 50 times per scenario, and the points plot the median attack rates for the stochastic simulations and the lines represent the range of the minimum and maximum attack rates. Several intervention scenarios were modeled: no intervention (in red), vaccination well before the epidemic (pre-vaccination, in blue), vaccination after the first cholera cases were confirmed (mass vaccination, in green), vaccination targeted to communities near rivers after the first cholera cases were confirmed (high-exposure vaccination, in yellow), and prioritizing vaccination and educational campaigns to improve hygiene and sanitation to communities near rivers after the first cholera cases were confirmed (in purple). Note that pre-vaccination delays the epidemic peak, while reactive strategies tend to reduce but not delay the peak

spread of cholera—improving sanitation and hygiene to reduce the public’s exposure to the pathogen was also necessary to greatly reduce cholera transmission in Haiti (Fig. 2). The results highlight the need to target vaccination campaigns and other interventions efficiently when resources are scarce.

4 Discussion and Conclusions

We have described a variety of approaches to modeling cholera outbreaks. The same modeling frameworks can be used to describe both epidemic and endemic cholera, but the modeler must make the appropriate choices of initial conditions, parameterization, and possibly model structure. For cholera outbreaks in non-endemic regions, there may be little prior immunity, a high attack rate, similar attack rates among age groups, and high symptomatic fractions (Sack 2003; Sack et al. 2004). The issues more important in endemic regions, such as drivers of seasonality and environmental predictors of outbreaks, may be of little concern

and can be omitted from models when one is interested solely in outbreaks in non-endemic settings. Therefore, when formulating a model, one should consider the population of interest (e.g., size, heterogeneity, prior exposure history), available interventions (e.g., vaccination, sanitation improvements), available surveillance data (e.g., spatial scale, age distributions, reporting rates), and time-scale (e.g., days, months, or years).

Models with different assumptions may fit the dynamics of a particular outbreak equally well. In some cases, model selection might not be an important issue. But when one wants to perturb the dynamics of cholera transmission by simulating interventions, different models could produce dramatically different projections of the effectiveness of interventions. Complex models will also encounter problems of identifiability, making it impossible to find a unique “best” set of parameters. More detailed epidemiological studies of cholera transmission are needed in order to better parameterize transmission models. Sensitivity analyses of cholera models may help us prioritize such studies by identifying the most important gaps in our understanding of the disease (Grad et al. 2012).

In general, infectious disease modelers find it difficult to find epidemic data of sufficient quality for model-fitting. Public health departments generally release surveillance data aggregated over large spatial scales. More detailed outbreak data is usually obtainable only through direct collaborations with the outbreak investigators, which is rare in the modeling world. Therefore, there are few modeling studies of real outbreaks and many studies of the properties of the models themselves. The dearth of data and well-parameterized models may lead to the overgeneralization of modeling results. There is a clear need for more modeling studies of actual outbreaks, which would require either more direct collaborations between modelers and surveillance groups or more receptiveness to sharing outbreak data with modelers and other analysts.

Modeling studies can be a valuable source of information for public health officials evaluating potential interventions for cholera outbreaks (Garnett et al. 2011; Hutubessy et al. 2011). Most published studies that evaluate the cost-effectiveness of cholera vaccination do not include a dynamic model of disease transmission (Sack 2003; Jeuland et al. 2009; Cook et al. 2009; Kim et al. 2011; Reyburn et al. 2011). Dynamic transmission models such as those described here capture indirect protection, which increases the estimated effectiveness of mass vaccination and other interventions (Brisson and Edmunds 2003). Based on earlier studies, many concluded that reactive vaccination would not be helpful during outbreaks (Sommer and Mosley 1973; Naficy et al. 1998). However, large and prolonged outbreaks could be mitigated using reactive vaccination, particularly if interventions target key populations (Chao et al. 2011; Azman et al. 2012). Models could and should be used to weigh the costs and benefits of different interventions for a range of scenarios, from seasonal endemic cholera outbreaks to epidemics exacerbated by natural disasters (Legros et al. 1999; Calain et al. 2004; Jeuland et al. 2009; Chaignat and Monti 2007; Global Task Force on Cholera Control 2010).

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