An epidemic model for Acute Hemorrhagic Conjunctivitis: Application to a 2003 outbreak in Mexico

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Abstract

We use a simple epidemic model that includes susceptible, infectious, reported, and recovered classes to model an outbreak of Acute Hemorrhagic Conjunctivitis (AHC). Our model considers the impact of under-reporting and behavior changes on the transmission rate and is applied to a recent epidemic of Acute Hemorrhagic Conjunctivitis in Mexico. Model parameters are estimated from a fit to the cumulative number of cases. Epidemiological parameters are in agreement with those derived from clinical studies. Our model predicts a "mean time from symptom onset to diagnosis" of 1.43 days (95% CI: $1-2.5$) which is consistent with an estimate of 1.55 days (95% CI: $1.46-1.63$) obtained using maximum likelihood methods on the distribution of the "times from symptom onset to diagnosis" of the clinical records of AHC cases reported during the epidemic. Our model predicts that the final epidemic size was under-reported by 38.68%. We estimate that a primary infectious case generates approximately 3 secondary cases ($R_0 = 2.64$, SD 0.65). Furthermore, our model predicts a 36.36% reduction in the transmission rate due to behavior changes which started to be effective 21.90 (SD 0.19) days after the first reported case. We explore the expected impact of how quickly interventions are implemented and estimate an approximate of 11 person-years of productivity losses from diagnosed cases. Our results are in agreement with current public health policy including informing the population about the presence of the outbreak as quickly as possible, instructing individuals via press releases with public health information on how to avoid contagion, and encouraging infectious individuals to get diagnosed in hospital clinics.

Keywords: epidemic model; parameter estimation; parameter identifiability; under-reporting; acute hemorrhagic conjunctivitis; reproductive number; benign disease; Colima, Mexico.

1 Introduction

Acute hemorrhagic conjunctivitis (AHC) is a highly communicable disease typical of tropical, coastal cities. AHC outbreaks usually last 1-2 months and secondary attack rates within households are greater than 50% [1]. A susceptible individual exposed to the virus enters a short incubation period ($1-2$ days) followed by the rapid onset of painful, swollen, red eyes, lacrimation, foreign-body sensation, and subconjunctival hemorrhaging in many cases [2]. Transmission occurs primarily via person-to-person contact or contact with contaminated objects (i.e towels). Symptoms persist usually for 3-7 days with no consequences. Therefore, many cases are not properly reported to public health institutions [3] which contributes to its further spread. Properly reported individuals are advised on how to avoid further transmission of the disease.

Furthermore, in developing countries like Mexico, proper diagnosis in health institutions is necessary to obtain an appropriate number of sick days for home isolation, which not only allow for faster recovery but also help infectious individuals avoid contact with co-workers, which could potentially increase the final epidemic size.

There have been identified different viruses as the causing agent of AHC including enterovirus 70, coxsakievirus A24 variant (CA24v) and adenovirus 11. The etiologic agent has been identified using different methodology including modification of centrifugation enhanced culture and neutralization tests [4]. The first outbreak of AHC was identified in western Africa in 1969 and reported to be due to enterovirus 70. The enterovirus 70 invaded the western hemisphere in 1981 when several outbreaks of AHC occurred in Central America [5], South America [6], and Florida [7]. The coxsakievirus A24 variant (CA24v) was first identified in Singapore in 1970 [8]. The first AHC outbreak in the western hemisphere occurred on the islands of Trinidad, Jamaica and St. Croix, US in the fall of 1986 [9]. Only months later, an outbreak of AHC caused by the same agent CA24v was observed in the Yucatan Peninsula of Mexico where the secondary attack rate in households was 37% [10]. A subsequent outbreak in Mexico occurred in Delicias, Oaxaca and a third outbreak occurred in Tampico, Tamaulipas (a town in northern Mexico along the gulf coast and about 250 miles south of Brownsville, Texas) [10]. The agent CA24v caused all three outbreaks and the attack rates were observed to be considerably higher in schoolchildren. The most recent reported epidemics of AHC have occurred in Dheli, North India in August-September of 1996 caused by the enterovirus 70 [4]. In September 1998, another outbreak by CA24v in Saint Croix, US left 1051 cases by the end of October. The average self-reported duration of symptoms was 5 days [1]. In 2002, more than one million people were infected with AHC (CA24v) in South Korea from late August to early October [11].

In this paper we model an outbreak of Acute Hemorrhagic Conjunctivitis that developed in the state of Colima, Mexico in 2003. Using a simple model, we estimate epidemiological and control parameters. We give an estimate of the number of secondary cases generated by a primary case in a fully susceptible population. We also explore the role of AHC cases that are never reported in hospital clinics (under-reporting) and the effects of behavioral changes in the population due to increasing awareness of the outbreak and education on how to avoid contagion. Model parameters are estimated from a fit to the cumulative number of cases. We compare our model estimate of the "mean time to diagnosis" with that obtained using maximum likelihood methods from the clinical records of AHC cases reported during the epidemic. We also estimate the number of secondary cases generated by a primary case. Moreover, we explore

the impact of behavior changes in the population on the transmission rate of the disease and the reporting rate. We also carried out a sensitivity analysis of the impact of delays in the implementation of interventions on the final epidemic size. This article is organized as follows: Section 2 presents the model, gives an expression for the basic reproductive number (R_0), and describes epidemic data; Section 3 explains our parameter estimation procedure, derives an expression for the variance of R_0, presents an analysis on parameter identifiability, and gives a model-free estimate of the diagnostic rate; Section 4 presents our results and Section 5 discusses our results and concludes our work.

2 Model

2.1 Epidemic Model

We model an outbreak of Acute Hemorrhagic Conjunctivitis that developed in the state of Colima, Mexico in 2003 in order to estimate epidemiological and control parameters. We also use this model to estimate the number of secondary cases generated by a primary case in a fully susceptible population, explore the role of under-reporting during the epidemic and the effects of behavioral changes in the population on the transmission dynamics of AHC.

The model (Figure 1) for the transmission dynamics of Acute Hemorrhagic Conjunctivitis classifies individuals in one of five classes: Susceptibles (S), exposed (E), infectious (I), diagnosed/reported (J), and recovered but not reported (U). Susceptible individuals in contact with the virus enter the exposed class at the rate $\beta(t)I(t)/N$ where $\beta(t)$ is the time-dependent transmission rate, $I(t)$ is the number of infectious individuals at time t, and $I(t)/N$ is the probability that a contact is made with an infectious individual at time t. That is, we assume a homogeneously mixing population of size N. The duration of the AHC outbreak studied here is on a time scale much faster than that of birth and deaths and the final epidemic size is small compared to N. Hence, assuming a constant population size at risk is a reasonable assumption. During the outbreak, only diagnosed individuals in hospital clinics were capable of obtaining sick days. The typically high underreporting rates observed during AHC outbreaks [12] lead to higher mixing of individuals in work places and schools. This supports our homogeneous mixing assumption as a reasonable approximation to the underlying real structure (see for example [13, 14, 15, 16, 17]). Incorporating a more realistic population structure into the model (see for example [18, 19, 20] and references therein) would increase its complexity and the number of parameters that need to be estimated. Once individuals are diagnosed/reported and hence educated on how to avoid further contact with susceptible individuals, we assume

their contribution to further disease transmission to be negligible. Exposed individuals enter the infectious class at constant rate k (mean incubation period is $1/k$). Infectious individuals are either diagnosed (class J) at the time dependent rate $\alpha(t)$ or recover at rate γ without being diagnosed (class U). Recovered individuals acquire immunity to the causing AHC virus strain for at least the duration of the outbreak, in agreement with the epidemiology of AHC [21].

The transmission process (single outbreak) can be modeled using the system of nonlinear differential equations:

$$\begin{aligned} \dot{S}(t) &= -\beta(t)S(t)I(t)/N \\ \dot{E}(t) &= \beta(t)S(t)I(t)/N - kE(t) \\ \dot{I}(t) &= kE(t) - (\alpha(t)+\gamma)I(t) \\ \dot{J}(t) &= \alpha(t)I(t) \\ \dot{U}(t) &= \gamma I(t), \end{aligned} \tag{1}$$

where the dot denotes time derivatives. In order to account for behavioral changes in the population, the transmission rate $\beta(t)$ is defined as follows:

$$\beta(t) = \begin{cases} \beta_0 & t < \tau \\ \beta_1 & t \geq \tau \end{cases},$$

where $\beta_1 < \beta_0$ and τ is the day at which behavioral changes started to have an effect on the transmission rate. Moreover, we consider a time-dependent diagnostic rate $\alpha(t)$ as the distribution of cases by date of case notification (Figure 2) shows a low reporting rate at the beginning of the outbreak before behavioral changes started to have an effect on the transmission dynamics of AHC. Hence, similarly, we assume the diagnostic rate $\alpha(t)$ as follows:

$$\alpha(t) = \begin{cases} \alpha_0 & t < \tau \\ \alpha_1 & t \geq \tau \end{cases},$$

where $\alpha_0 < \alpha_1$. We found that our model fails to reproduce the beginning of the epidemic if we assume that the diagnostic rate is constant throughout the epidemic.

2.2 The basic reproductive number, R_0

The number of secondary cases generated by a primary infectious case or basic reproductive number (R_0) [22, 23, 24] is a measure of the power of an infectious disease to spread in a suscep-

tible population. Once an epidemic is underway, the reproductive number (R^*) decreases due to reductions in the susceptible population and public health interventions which could include contact tracing followed by quarantine, vaccination (if available), surveillance controls at ports of entry, and education of the population by dissemination of fact sheets. Of course, control measures will depend on the disease in question and availability of resources. For an emerging infectious disease, a vaccine may not be available and control would rely on basic public health measures such as contact tracing followed by quarantine, isolation of infectious individuals in hospital wards and education of the public to avoid contagion.

For the case of benign diseases like AHC, recommendations include: avoiding direct or indirect (object sharing) contact with AHC cases, restriction of infected individuals from attending school or work while symptomatic, and increase hand-washing [1]. Control of the AHC epidemic in Florida in 1981 was facilitated by closing affected schools. During the 2002 AHC epidemic in South Korea, 1100 schools were closed [11]. Moreover, disease symptoms vary among individuals and individuals with mild symptoms may never look for proper diagnosis in hospital clinics. Mild cases may lead to higher incidence of infection among co-workers who would then carry the disease to their households.

The basic reproductive number (R_0) depends upon the typical activity of an uninfected susceptible population. Because a minimal number of the initially infected people will be diagnosed with a rate α_0 (our estimate $\alpha_0 \approx 0.08$ per day), this behavior will affect the initial spread of the disease and is included in the definition of R_0. Hence for our model, the basic reproductive number is given by $R_0 = \beta_0/(\gamma + \alpha_0)$ (Appendix I), which is the product of the initial transmission rate (β_0) with the inverse of the sum of the recovery (γ) and the initial diagnostic rate (α_0).

2.3 Epidemic data

We consider data from a recent outbreak of Acute Hemorrhagic Conjunctivitis (AHC) that developed in the state of Colima, Mexico during the period of September-November, 2003. The state of Colima is located on the pacific coast, with a tropical climate, a mean annual temperature of $23 - 26$ degrees Celsius, and an approximate population of 488,028 [25]. The outbreak was caused by an Adenovirus [12]. The data were extracted from 1310 clinical records generated by the Mexican Institute of Public Health (IMSS) which provides service to 60% ($87,472$ individuals) of the total population in the state of Colima. We have reported elsewhere [12] on the relative frequency of symptoms presented, the spatial and age-specific incidence distri-

butions and the distribution of the time from onset of symptoms to notification distributions. The daily number of AHC cases by time of onset of symptoms and by time of notification is shown in Figure 2.

3 Parameter Estimation

We estimate the disease-related parameters (β_0, β_1 k, and γ), the time at which behavioral changes start to take place (τ), and the mean time from symptom onset to diagnosis before and after interventions started to have an effect ($1/\alpha_0$ and $1/\alpha_1$) by least-squares fit of $J(t, \mathbf{\Theta})$ in model (1) (where $\mathbf{\Theta}$ is the vector of fitting parameters) to the cumulative number of AHC cases by date of case notification (Figure 2) with appropriate initial conditions. Four our least-squares fitting procedure, we used the Levenberg-Marquardt method with line-search [26] implemented in the built-in routine `lsqcurvefit.m` of MATLAB (The MathWorks, Inc.). The best fitting parameters were obtained by repeating 10 times our fitting procedure with different initial conditions for the parameters which were randomly drawn from the appropriate parameter ranges ($0 < \beta_0 < 10$, $0 < \beta_1 < 10$, $0 < \tau < 100$, $0 < k < 2$,$0 < \gamma < 1$, $0 < \alpha_0 < 1$, $0 < \alpha_1 < 1$). The resulting parameter estimates are given in Table 1 and the model fit to the data is shown in Figure 3.

We estimate the standard deviation of the parameters by computing the asymptotic variance-covariance $AV(\hat{\Theta})$ matrix of the least-squares estimate by:

$$\mathbf{AV}(\hat{\mathbf{\Theta}}) = \sigma^{\mathbf{2}}\ \mathbf{B}(\mathbf{\Theta_0})\ \nabla_{\mathbf{\Theta}}\mathbf{J}(\mathbf{\Theta_0})^{\mathbf{T}}\ \mathbf{G}\ \nabla_{\mathbf{\Theta}}\mathbf{J}(\mathbf{\Theta_0})\ \mathbf{B}(\mathbf{\Theta_0}),$$

where $\mathbf{B}(\mathbf{\Theta_0}) = [\nabla_{\mathbf{\Theta}}\mathbf{J}(\mathbf{\Theta_0})^{\mathbf{T}}\ \nabla_{\mathbf{\Theta}}\mathbf{J}(\mathbf{\Theta_0})]^{-\mathbf{1}}$. An estimate of which is

$$\hat{\sigma}^2\ \hat{\mathbf{B}}(\hat{\mathbf{\Theta}})\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{J}}(\hat{\mathbf{\Theta}})^{\mathbf{T}}\ \mathbf{G}\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{J}}(\hat{\mathbf{\Theta}})\ \hat{\mathbf{B}}(\hat{\mathbf{\Theta}}),$$

where $\hat{\mathbf{B}}(\hat{\mathbf{\Theta}}) = [\nabla_{\mathbf{\Theta}}\hat{\mathbf{J}}(\hat{\mathbf{\Theta}})^{\mathbf{T}}\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{J}}(\hat{\mathbf{\Theta}})]^{-\mathbf{1}}$, $\hat{\sigma}^2 = \sum(y_i - J(t_i, \hat{\mathbf{\Theta}}))^2/(I_{1xn}\ \ \mathbf{G}\ \ I_{nx1})$, and $\nabla_{\Theta}\hat{\mathbf{J}}$ are numerical derivatives of $J(\hat{\mathbf{\Theta}})$. The error structure [27] is modeled by a Brownian bridge ($\mathbf{G}$) to account for the stochastic temporal dependence of the cumulative number of cases. Here $\mathbf{G}$ is an n x n matrix such that $G_{i,j} = (1/n)\ \min(i, j) - (ij)/n^2$ and n is the total number of observations. That is, G captures the higher variability in the cumulative number of cases observed on the middle course of the epidemic and the smaller variability observed at the beginning and

the end of the epidemic.

3.1 Estimation of the variance of R_0

We obtained an expression for the variance of the estimated basic reproductive number (R_0) using the Taylor series approximation of our R_0 expression (delta method [28]). Let $T_1, T_2, ..., T_3$ be random variables with means β_0, α_0, γ_0 and define $\mathbf{T} = (T_1, T_2, T_3)$ and $\mathbf{\Phi} = (\beta_0, \alpha_0, \gamma)$. The first-order Taylor series expansion of R_0 about $\mathbf{\Phi}$ is:

$R_0(\mathbf{t}) \approx g(\mathbf{\Phi}) + \sum_{i=1}^{3} g'(\mathbf{\Phi})\ (t_i - \phi_i)$. We can approximate the variance of $R_0(\mathbf{T})$ by:

$V(R_0(\mathbf{T})) \approx \sum_{i=1}^{3} [g_i'(\mathbf{\Phi})]^{\mathbf{2}}\ V(T_i) + 2\sum_{i>j} g_i'(\mathbf{\Phi})\ g_j'(\mathbf{\Phi})\ Cov(T_i, T_j)$.

The resulting expression for the variance of the estimated R_0 is given by:

$$\begin{aligned} V(\hat{R_0}) \ \approx\ & \hat{R_0}^{\,2} \left\{ \frac{V(\hat{\beta}_0)}{\hat{\beta}_0^{\,2}} + \frac{V(\hat{\gamma})}{(\hat{\gamma} + \hat{\alpha_0})^2} + \frac{V(\hat{\alpha_0})}{(\hat{\gamma} + \hat{\alpha_0})^2} \right. \\ & \left. - \left(\frac{2}{\beta_0(\gamma + \alpha_0)} \right) \left(Cov(\hat{\gamma}, \hat{\beta}_0) - \frac{\beta_0 Cov(\hat{\alpha_0}, \hat{\gamma})}{\gamma + \alpha_0} + Cov(\hat{\alpha_0}, \hat{\beta}_0) \right) \right\}. \end{aligned} \tag{2}$$

The corresponding values for the variance and covariance terms are directly obtained from the estimated variance-covariance matrix $\mathbf{AV}(\hat{\mathbf{\Theta}})$.

3.2 Parameter identifiability analysis

When estimating parameters from models, it is important to quantify how reliably the model parameters are determined by a given data set. We estimate this uncertainty by a comprehensive simulation study to explore the identifiability of the model parameters from data. We perturb our best fit of the cumulative number of reported cases $J(t, \mathbf{\Theta})$ to the data by simulating alternate realizations. We add to our best fit curve $J(t, \mathbf{\Theta})$ a simulated Brownian bridge error structure, which we compute using the increment in the "true" $J(t, \mathbf{\Theta})$ from day i to day $i + 1$ as the Poisson mean for the number of new cases observed in the i to $i + 1$ interval. We applied our parameter estimation procedure (described above) for each of 1000 simulated realizations. The histograms of the parameter estimates from the 1000 simulations are shown in

Figure 5. The nominal confidence intervals are in close agreement with those obtained from the asymptotic variance-covariance matrix $\mathbf{AV}(\mathbf{\Theta})$ (Table 1). In order to study the applicability of the epidemic model for other outbreaks of AHC, we explore the identifiability of model parameters by performing a large number of simulations with parameter values randomly drawn from plausible ranges. Our results can be summarized from the simulations of 20 sets of parameter values obtained by dividing the plausible range of each parameter ($\beta_0 : 0.5 - 5$, $\beta_1 : 0.3 - 5$, $\tau : 15 - 30$, $k : 0.1 - 2$,$\gamma : 0.1 - 1$, $\alpha_0 : 0.05 - 0.5$, $\alpha_1 : 0.1 - 1$) into 20 equal parts which are then randomly permuted to generate 20 different sets of parameter values. For each set of parameter values, we simulate 100 alternate realizations of the cumulative number of reported cases $J(t, \mathbf{\Theta})$ by adding the simulated Brownian bridge error structure. We then generate the nominal 95% confidence intervals for the estimated parameters for each of the simulated realizations using our parameter estimation procedure (Table 2). We present the implications of our results in the Results.

3.3 Model-free estimate of the diagnostic rate

We estimated the mean time from symptom onset to diagnosis independently of our ordinary differential equation model (1) from clinical record data via maximum likelihood methods [29]. The date of onset of symptoms was missing or not properly recorded in 22 clinical records and therefore we only considered 1288 (out of 1310) clinical records in the estimation. Let $t_1, \ldots, t_n$ be the "times from symptom onset to diagnosis" (days) obtained from clinical records of each of the diagnosed individuals during the epidemic. The distributions of the"times from onset to diagnosis" is well approximated by an exponential (Figure 4). Hence, we can consider estimating the mean time to diagnosis (θ) by maximizing the log-likelihood equation

$$\ell(\theta|t_1, \ldots, t_n) = -[\sum_{i=1}^{n} t_i + n \ln(\theta)], \tag{3}$$

and the maximum likelihood estimator (MLE) of θ is the sample mean $\hat{\theta} = \frac{1}{n}\sum_{i=1}^{n} t_i$ whose variance is $Var(\hat{\theta}) = \hat{\theta}^2/n$.

4 Results

Using our simple epidemiological model, we estimate relevant epidemiological and control parameters, which can in turn be used to estimate the reproductive number and the final epidemic size. Our model agrees well with the data (see Figure 3) with a coefficient of determination of

approximately 0.99 [30]. We estimate a final epidemic size of 2115 AHC cases with an under-reporting rate of approximately 38.68%.

We estimate that behavior changes in the population started to have an effect on the transmission rate approximately 21.9 (SD 0.19) days after the first reported case. Our model predicts that the initial transmission rate $\beta_0 = 0.99$ (days^{-1} infective^{-1}) is reduced by 36.36% to $\beta_1 = 0.63$ due to behavior changes in the population and a jump in the diagnostic rate from 0.08 to 0.70 (days^{-1}) (Table 1). We estimate the incubation period ($1/k$) and the infectiousness period ($1/\gamma$) to be approximately 3.65 days and 3.37 days, respectively (see Table 1). Our estimate of the time from onset of symptoms to diagnosis is $1/\alpha_1 \approx 1.43$ days (95% CI: $1-2.5$). This estimate of $1/\alpha_1$ can be compared to an independent estimate of 1.55 days (95% CI $1.46-1.63$) obtained using the dates of notification and dates of onset of symptoms of the 1310 individual clinical records via maximum likelihood methods (Figure 4). Hence, our two independent estimates are consistent.

Our simulation study supports our parameter estimates (See Figure 5) for the 2003 AHC epidemic in Colima, Mexico. However, the parameter β_1 is not well identified in 8 out of the 20 sets of possible parameter values for other potential epidemics. Hence, β_1 may not be estimated using this model for other epidemic settings (Table 2) and caution should be exercised when quantifying the role of interventions using the decay in the transmission rate from β_0 to β_1.

We performed a sensitivity analysis on the final epidemic size (Appendix II) to changes in the time (τ) at which interventions start to have an effect on the transmission and diagnostic rates (Figure 6). Our model predicts an increase in the final epidemic size of 3609 cases if the effects of interventions had been observed 5 days after the actual estimate of the time to behavior changes (τ) and a reduction of 1320 cases if behavior changes had been in effect 5 days prior the actual estimated time. We also carried out a sensitivity analysis of the effective population size N on the parameter estimates. We found that our parameter estimates are stable to changes in N.

We derived an expression to estimate the average number of secondary cases that a primary infectious AHC case generates in a fully susceptible population or R_0. We also derived an expression to estimate the variance of R_0 (formula 2). The reproductive number depends on the transmission rate (β), the infectious period ($1/\gamma$) and the initial mean time from onset of symptoms to diagnosis ($1/\alpha_0$). The reporting rate was very low at the beginning of this outbreak

(Figure 2) . Our estimate of the basic reproductive number (R_0) is 2.64 with standard deviation 0.65.

5 Discussion

We developed a relatively simple epidemic model (Figure 1) to assess underreporting, behavioral changes in the population, and the effects of basic public health interventions during an outbreak of acute hemorrhagic conjunctivitis in Mexico. Our model captures the time course dynamics of the outbreak. We formulated the force of infection using the mass-action assumption for the mixing between susceptible and infectious individuals ($\beta SI/N$) [31]. Similar epidemic models have been used for the analysis of other epidemics [13, 14, 15, 16, 17]. When additional data is available, more realistic population structures could be explicitly modeled and tested. The first mathematical model incorporating household information was used to study an epidemic of bubonic plague [32] and age-structured models have been able to capture the seasonal dynamics of measles [22, 33]. Some models with household structure have been introduced to study the distribution of the total number of cases in households using *Variola minor* [34], influenza and common cold data [18, 35] but these models do not incorporate the role of interventions.

We use data on a recent outbreak of AHC in Mexico. We estimated epidemiological and control parameters through least squares fitting of our model to the cumulative number of cases. We estimate that 38.68% of the total number of cases were not reported. Undiagnosed individuals are more likely to pass the disease due to their lack of information on how to avoid further transmission. We also consider a reduction in the transmission rate of undiagnosed individuals due to public health information (fact sheets) disseminated via TV and radio on how to avoid contagion. Since it usually takes some time before public health information is disseminated to the public, we consider the average time elapsed (τ) before interventions started to have an effect on the transmission and diagnostic rates. We estimate a 36.36% reduction in the transmission rate and an increase in the reporting of 89% due to behavioral changes in the population. Hence, launching an awareness campaign about the presence of the outbreak as quickly as possible, instructing individuals via press releases on how to avoid contagion (including indirect contact with contaminated objects such as utensils, glasses, towels, or wash clothes) and about the importance of staying home from work or school until symptoms disappear, and decreasing the fraction of under-reported individuals are promising means of control.

Parameter estimates from models should ideally be corroborated using empirical data. However, empirical data is not available in many situations or available empirical data partially validates model parameter estimates. Our estimate of the infectious period and the incubation period agree with the epidemiology of AHC [36, 37]. However, some variability in epidemiological aspects has been reported which might be due to the different etiological agents causing outbreaks of AHC (i.e Enterovirus 70, coxsakievirus A24 variant (CA24v), adenovirus 11). Our estimate from model (1) of the "mean time to diagnosis" ($1/\alpha_1$) is in agreement with an independent estimate obtained using maximum likelihood methods on the individual times to diagnosis of the clinical records of AHC cases generated during the epidemic.

Estimates of the final epidemic size can be obtained using our analytical expression (Appendix II) for the final epidemic size (10) which relies on estimates of the number of susceptible individuals about the time interventions are implemented (S_τ) and at the end of the epidemic (S_∞). Our model predicts that if the impact of interventions had been delayed an additional five days then there would have been 63% more cases. If interventions had been in effect 5 days prior to the actual date, our model predicts the epidemic would have been reduced by 62% (Figure 6). We also studied the sensitivity of our model parameters to changes in the effective population size (N), an uncertain quantity at the moment of modeling real disease outbreaks. Our parameter estimates are not sensitive to changes in the effective population size N, an observation we have also made elsewhere [17].

The high infectiousness characteristic of Acute Hemorrhagic Conjunctivitis is well captured in the basic reproductive number. We estimate that an infectious case generates on average approximately 3 secondary cases during its period of infectiousness in a population of mostly susceptible individuals. Our model predicts that behavioral changes in the population along with a strategy of contact tracing followed by quarantine of infectious cases are effective means of control. During the AHC outbreak reported here, the Mexican Institute of Public Health granted three sick days (isolation period at home) to each infected worker [12]. We estimate an approximate of 11 person-years of missed work from the 1310 reported cases (out of our estimated total of 2115 cases including unreported cases). However, more data would be needed to assess the productivity losses for child care, the impact of unreported cases on productivity losses, medical costs, and costs incurred by the public health department for epidemic control. Even though AHC is regarded as a self-limiting disease, its control should be taken seriously as its tightly linked economic impact can be significant.

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Appendix I: The basic reproductive number, R_0

Using the approach of P. van den Driessche and J. Watmough [24], we obtain an expression for the basic reproductive number for our system with the transmission and the diagnostic rates fixed to their initial values β_0 and α_0, respectively. First, one can consider the disease transmission model consisting of initial conditions and the following system of equations:

$$\dot{x}_i = f_i(x) = F_i(x) - V_i(x), \qquad i = 1, \ldots, 5$$

where

$$F = \begin{pmatrix} \beta_0 SI/N \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \qquad V = \begin{pmatrix} kE \\ -kE + (\alpha_0 + \gamma)I \\ \beta_0 SI \\ -\alpha_0 I \\ -\gamma I \end{pmatrix}$$

.

Let x_0 denote the disease-free equilibrium of (1) and define $DF(x_0)$ and $DV(x_0)$ as follows:

$$DF(x_0) = \begin{pmatrix} 0 & \beta_0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$DV(x_0) = \begin{pmatrix} k & 0 & 0 & 0 & 0 \\ -k & \gamma + \alpha_0 & 0 & 0 & 0 \\ 0 & \beta_0 & 0 & 0 & 0 \\ 0 & -\alpha_0 & 0 & 0 & 0 \\ 0 & -\gamma & 0 & 0 & 0 \end{pmatrix}$$

where F and V are the 2×2 matrices consisting of the first two rows and columns of $DF(x_0)$ and $DV(x_0)$ respectively. The basic reproductive number is given by the largest eigenvalue of

FV^{-1}:

$$
\begin{aligned}
FV^{-1} &= \begin{pmatrix} 0 & \beta_0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} k & 0 \\ -k & \gamma+\alpha_0 \end{pmatrix}^{-1} \\
&= \frac{1}{k(\gamma+\alpha_0)} \begin{pmatrix} 0 & \beta_0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \gamma+\alpha_0 & 0 \\ k & k \end{pmatrix} \\
&= \frac{1}{k(\gamma+\alpha_0)} \begin{pmatrix} \beta_0 k & \beta_0 k \\ 0 & 0 \end{pmatrix}
\end{aligned}
$$

$$
\rho(FV^{-1}) = \frac{\beta_0}{\gamma+\alpha_0}. \tag{4}
$$

Appendix II: The final epidemic size

The final size of an epidemic is tightly linked to its economic impact. Hence, it is of importance to be able to estimate the final size of epidemics. For the case of benign diseases, the number of reported cases highly underestimates the final epidemic size. The expression for the final epidemic size has been derived for the standard SIR models and extensions [38].

We derive an expression for the final epidemic size for our model with time dependent transmission and diagnostic rates ($\beta(t)$ and $\alpha(t)$). From model (1), one can divide $\dot{U(t)}$ by $\dot{S(t)}$ to get

$$
\frac{dU(t)}{dS(t)} = \frac{\gamma N I(t)}{-\beta(t)S(t)I(t)} = -\frac{\gamma}{\beta(t)}\frac{N}{S(t)}. \tag{5}
$$

Using the fact that $\beta(t)$ is defined as a step function,

$$
\begin{aligned}
U(t) - U(0) &= -\gamma N \left[\int_0^\tau \frac{1}{\beta_0 S(t)} dS + \int_\tau^t \frac{1}{\beta_1 S(t)} dS \right] \\
&= -\gamma N \left[(\frac{1}{\beta_0} - \frac{1}{\beta_1}) \ln(S(\tau)) - \frac{1}{\beta_0}\ln(S(0)) + \frac{1}{\beta_1}\ln(S(t)) \right].
\end{aligned}
$$

Since $U(0) = 0$, it follows that

$$
U(t) = -\gamma N \left[(\frac{1}{\beta_0} - \frac{1}{\beta_1}) \ln(S(\tau)) - \frac{1}{\beta_0}\ln(S0) + \frac{1}{\beta_1}\ln(S(t)) \right]. \tag{6}
$$

If we use the fact that $\lim_{t\to\infty} I(t) = 0$ and $\lim_{t\to\infty} E(t) = 0$ and let $U_\infty = \lim_{t\to\infty} U(t)$ and $S_\infty = \lim_{t\to\infty} S(t)$ then we obtain

$$
U_\infty = -\gamma N \left[(\frac{1}{\beta_0} - \frac{1}{\beta_1}) \ln(S(\tau)) - \frac{1}{\beta_0}\ln(S_0) + \frac{1}{\beta_1}\ln(S_\infty) \right], \tag{7}
$$

which gives the final number of unreported cases. We obtain similarly an expression for the total number of reported cases. By dividing $J(t)$ by $U(t)$, we obtain:

$$\frac{dJ(t)}{dU(t)} = \frac{\alpha(t)I(t)}{\gamma I(t)} = \frac{\alpha(t)}{\gamma}$$

Using the fact that $\alpha(t)$ is defined as a step function,

$$\begin{aligned} J(t) - J(0) &= \frac{1}{\gamma}\left[\int_0^\tau \alpha_0 \, dU + \int_\tau^t \alpha_1 \, dU\right] \\ &= \frac{1}{\gamma}\left[(\alpha_0 - \alpha_1)U(\tau) - \alpha_0 U_0 + \alpha_1 U(t)\right]. \end{aligned}$$

Since $U(0) = 0$ and $J(0) = 0$, it follows that

$$J(t) = \frac{1}{\gamma}\left[(\alpha_0 - \alpha_1)U(\tau) + \alpha_1 U(t)\right]. \tag{8}$$

If we let $J_\infty = \lim_{t\to\infty} J(t)$ then we obtain

$$J_\infty = \frac{1}{\gamma}\left[(\alpha_0 - \alpha_1)U(\tau) + \alpha_1 U_\infty\right], \tag{9}$$

which gives the final number of reported cases. With equations (7) and (9), one can obtain an expression for the final epidemic size:

$$U_\infty + J_\infty = \frac{1}{\gamma}(\alpha_0 - \alpha_1)U(\tau) + (\alpha_1 + \gamma)N\left[(-\frac{1}{\beta_0} + \frac{1}{\beta_1})\ln(S(\tau)) + \frac{1}{\beta_0}\ln(S_0) - \frac{1}{\beta_1}\ln(S_\infty)\right]. \tag{10}$$

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Tables & Figures

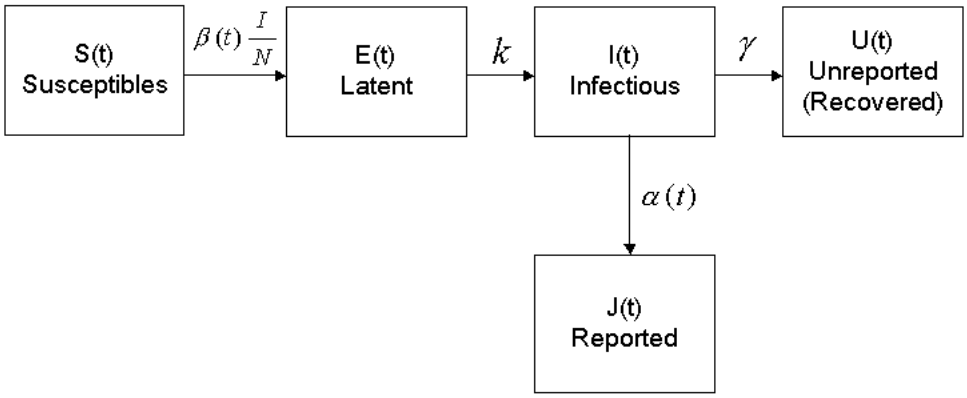

Figure 1: Schematic representation of the flow of individuals among the different classes. Susceptible individuals in contact with the virus enter exposed class at the rate $\beta(t)I/N$ where $\beta(t)$ is the time-dependent transmission rate, I is the number of infectious individuals, and I/N is the probability that a contact is made with an infectious individual. The AHC outbreak reported here is on a time scale much faster than that of birth and deaths and the final epidemic size was small compared to N. Hence, assuming a constant population size at risk is a reasonable assumption. Diagnosed/reported individuals are assumed educated on how to avoid further contact with susceptible individuals, hence, their contribution to further disease transmission is assumed to be negligible. Exposed individuals enter the infectious class at constant rate k (mean incubation period is $1/k$). Infectious individuals are either diagnosed at the time dependent rate $\alpha(t)$ or recover at rate γ without being diagnosed (under-reported). Recovered individuals acquire immunity to the causing AHC virus strain for at least the duration of the outbreak, in agreement with the epidemiology of AHC [21].

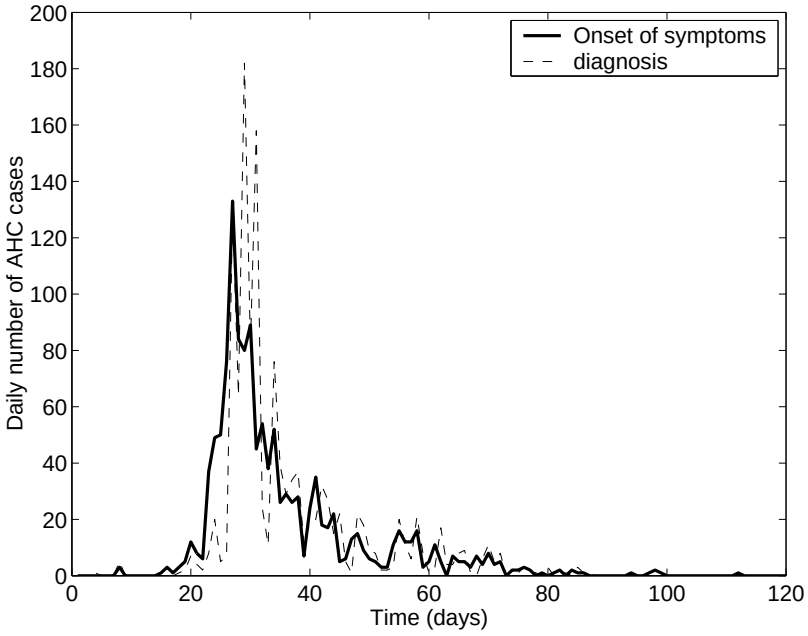

Figure 2: Daily number of Acute Hemorrhagic Conjunctivitis reported cases by date of symptom onset and date of case notification from the 2003 outbreak in Colima, Mexico.

Parameter	Definition	Estimate	S.D.
β_0	Mean transmission rate before behavior changes take place (days^{-1} infective^{-1})	0.99	0.29
β_1	Mean transmission rate after behavior changes take place (days^{-1} infective^{-1})	0.63	0.11
τ	Approximate time at which behavior changes take place (days)	21.90	0.19
k	Rate of progression from exposed to infectious state (days^{-1})	0.27	0.07
γ	Recovery rate (days^{-1})	0.30	0.09
α_0	Diagnostic rate before behavior changes take place (days^{-1})	0.08	0.01
α_1	Diagnostic rate after behavior changes take place (days^{-1})	0.70	0.15

Table 1: Definitions and estimates for parameters in model (1) obtained from the best least-squares fit to the cumulative number of reported AHC cases.

Sim.	β_0	β_1	k	γ	α_0	α_1
1	0.5(0.495-0.506)	3.52(3.5-3.53)	0.763(0.757-0.769)	0.811(0.806-0.814)	0.0737(0.0704-0.079)	0.526(0.521-0.53)
2	0.737(0.73-0.743)	1.54(1.53-1.55)	0.432(0.405-0.451)	0.526(0.524-0.53)	0.5(0.496-0.505)	0.384(0.369-0.396)
3*	5(4.91-5.08)	3.27(0.00812-7.1)	0.811(0.797-0.827)	0.479(0.464-0.495)	0.405(0.394-0.418)	0.621(0.581-0.664)
4*	4.05(3.98-4.13)	2.28(0-6.21)	0.337(0.333-0.341)	0.147(0.144-0.151)	0.311(0.304-0.318)	0.716(0.688-0.75)
5	1.92(1.88-1.96)	3.76(3.7-3.83)	0.716(0.691-0.745)	0.668(0.66-0.678)	0.334(0.322-0.35)	1(0.977-1.03)
6	3.58(3.57-3.58)	3.02(3.01-3.03)	0.147(0.147-0.148)	0.574(0.572-0.576)	0.121(0.12-0.122)	0.763(0.758-0.767)
7*	4.29(4.2-4.39)	2.53(0.742-5.23)	0.195(0.192-0.197)	0.289(0.281-0.298)	0.0974(0.0936-0.101)	0.289(0.28-0.298)
8	2.16(2.15-2.17)	4.01(4-4.02)	0.1(0.099-0.101)	1(0.993-1.01)	0.358(0.35-0.367)	0.432(0.427-0.437)
9	0.974(0.968-0.98)	5(4.98-5.02)	1(0.996-1)	0.858(0.854-0.861)	0.453(0.451-0.455)	0.574(0.569-0.578)
10	2.39(2.36-2.42)	2.03(2.02-2.04)	0.384(0.373-0.396)	0.905(0.887-0.92)	0.476(0.466-0.489)	0.811(0.794-0.828)
11	1.45(1.44-1.45)	0.547(0.547-0.548)	0.289(0.286-0.293)	0.337(0.336-0.338)	0.192(0.191-0.194)	0.147(0.146-0.15)
12*	4.53(4.42-4.64)	4.75(2.83-7.01)	0.574(0.564-0.587)	0.763(0.742-0.793)	0.287(0.278-0.299)	0.953(0.837-1.14)
13	1.21(1.2-1.22)	4.51(4.42-4.59)	0.668(0.657-0.679)	0.195(0.193-0.197)	0.239(0.235-0.243)	0.195(0.193-0.197)
14*	3.11(3.02-3.19)	0.3(0.159-0.466)	0.242(0.236-0.249)	0.432(0.426-0.44)	0.216(0.206-0.226)	0.858(0.828-0.894)
15*	3.34(3.16-3.5)	0.795(0-6.19)	0.953(0.888-1.03)	0.384(0.376-0.392)	0.145(0.142-0.148)	0.905(0.19-1.57)
16	2.87(2.79-2.93)	2.77(2.68-2.86)	0.479(0.455-0.508)	0.953(0.946-0.958)	0.263(0.251-0.279)	0.1(0.0981-0.102)
17	2.63(2.61-2.65)	4.26(4.2-4.31)	0.621(0.611-0.632)	0.716(0.713-0.719)	0.429(0.424-0.435)	0.337(0.335-0.339)
18	1.68(1.68-1.69)	1.04(1.04-1.04)	0.526(0.519-0.532)	0.621(0.621-0.622)	0.168(0.168-0.169)	0.479(0.477-0.48)
19*	3.82(3.52-4.07)	1.29(0-9.48)	0.858(0.786-0.947)	0.242(0.231-0.252)	0.382(0.364-0.398)	0.242(-0.417-1.14)
20*	4.76(4.65-4.89)	1.78(0-10.2)	0.905(0.855-0.952)	0.1(0.0993-0.101)	0.05(0.0496-0.0503)	0.668(0.659-0.678)

Table 2: The nominal 95% confidence intervals (in parenthesis) obtained from our simulation study for 20 different sets of parameter values as explained in the text. For each set of parameter values, we simulated 100 alternate realizations of the cumulative number of reported cases $J(t, \mathbf{\Theta})$ by adding the Brownian bridge error structure and estimated parameters for each of the simulated realizations using our parameter estimation procedure. The parameter β_1 is not well identified in 8 (marked with *) out of the 20 sets of possible parameter values for other potential epidemics.

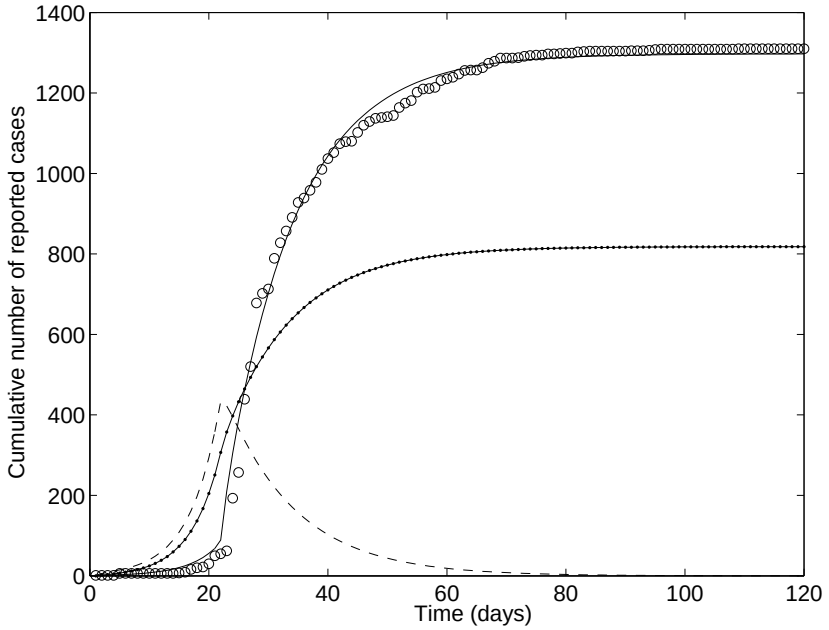

Figure 3: The best fit solution obtained by fitting $J(t, \Theta)$ (solid line) in model (1) to the cumulative number of reported AHC cases (circles) as explained in the text (coefficient of determination is approximately 0.99 [30]). The dash-dot curve is the cumulative number of AHC unreported cases and the dash-dash curve is the number of cases incubating the disease. Our model predicts that behavior changes started to have an effect on the transmission rate approximately 22 days after the first reported case.

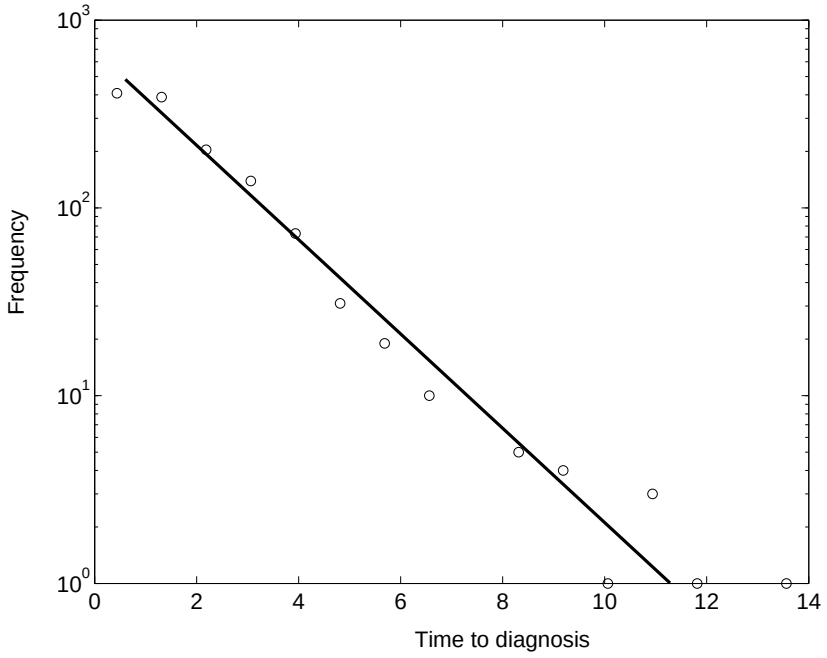

Figure 4: Semilog plot of the distribution of the "time from onset to diagnosis" obtained from the 1310 clinical records of Acute Hemorrhagic Conjunctivitis. Circles are the data and the solid straight line supports an exponential distribution. The maximum likelihood estimates of the mean and variance for the time of onset to diagnosis are 1.55 days (95% CI $1.46 - 1.63$) and 2.39 days^2, respectively.

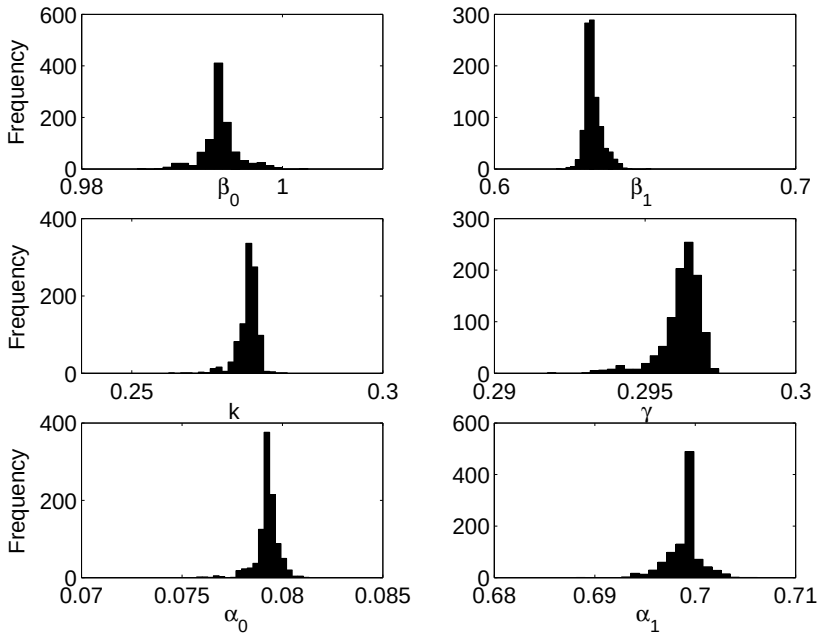

Figure 5: Distributions of the model parameter estimates obtained from our simulation study when considering our be st fit of the cumulative number of reported cases $J(t, \mathbf{\Theta})$ to the data. We simulate alternate realizations by adding a simulated Brownian bridge error structure, which we compute using the increment in the "true" $J(t, \mathbf{\Theta})$ from day i to day $i+1$ as the Poisson mean for the number of new cases observed in the i to $i+1$ interval. We simulated 1000 different realizations and applied our parameter estimation procedure for each of the simulated realizations. The nominal confidence intervals are in close agreement with those obtained from the asymptotic variance-covariance matrix $\mathbf{AV}(\mathbf{\Theta})$ (Table 1).

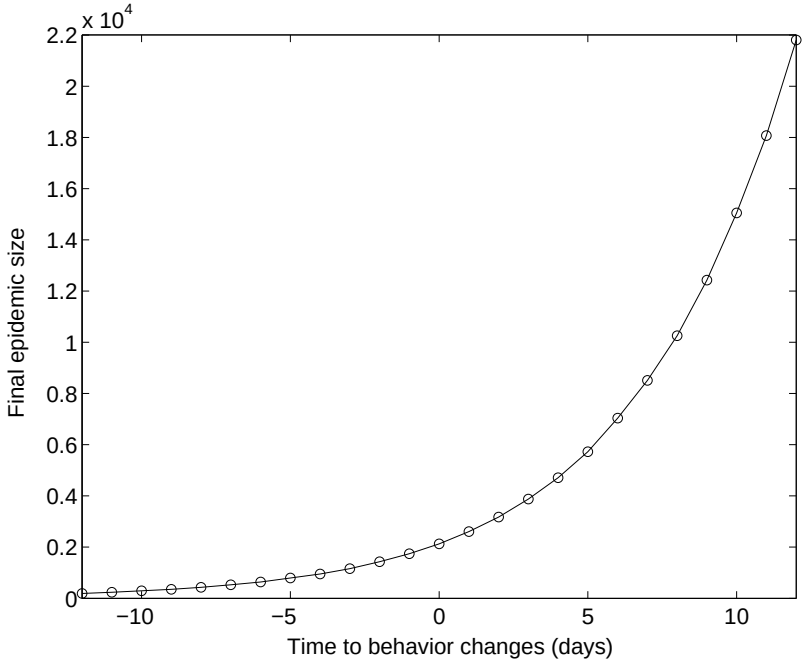

Figure 6: The Sensitivity of the final epidemic size (reported and unreported cases) to the time of start of behavior changes due to public health interventions. Negative numbers represent number of days before the actual estimated intervention time (Table 1) and positive numbers represent a delay after the estimated intervention time. All other parameters have been fixed to their baseline values (Table 1).