

Appendix

In the model we present, based on Codeço,¹ the basic reproductive number (R_0) and the rate of exponential growth (r), defined as the per capita change in number of new cases per unit of time, are:

$$R_0 = S_0 \frac{\xi\beta}{\delta\gamma\kappa}$$

$$r = \frac{1}{2} \left(-\gamma - \delta + \sqrt{\frac{4S_0\beta\xi}{\kappa} + \delta^2 - 2\delta\gamma + \gamma^2} \right)$$

These equations indicate that for a given growth rate, varying parameter values within their plausible range of uncertainty can lead to large changes in R_0 , with important consequences for the model's predictions about the effects of interventions.

As an example, take the starting point in which the duration of infection with cholera is 5 days, the lifespan of cholera in the water supply is 30 days, the size of the population is 10000 individuals, the concentration of *V. cholerae* in the water reservoir resulting in 50% probability of infection is 1×10^6 cells/mL, and the contact rate is 1 per day. Assuming an initial growth rate of 0.1 per day and solving for the contamination rate (ξ), then using the ξ term to derive R_0 , we calculate $R_0 = 6$.

Alternatively, assuming the lifespan of cholera in the water supply is 3 days, then, for the same growth rate, $R_0 = 1.95$. We consider the effect of giving 70% of the population a vaccine that gives full immunity to 70% of recipients, but has no effect on the remainder. We assume the vaccine is distributed prior to the introduction of

cholera. We model this as shifting individuals to the “Recovered” compartment in the model.

The examples above reflect the relationship among the growth rate, basic reproductive number, and disease-generation time, defined as the average amount of time between when an individual is infected and when the person who infected that individual was infected.² Given two of the three, one can determine the third. Because the generation time depends on the duration of cholera infection and the lifespan of cholera in the water reservoir, then, for a given positive growth rate, R_0 depends on these variables. Lack of knowledge of the lifespan of *V. cholerae* in a water reservoir then means we can only guess at the disease generation time, and hence a positive growth rate is compatible with a wide range of values of R_0 .

Note that in both expressions for R_0 and r , the terms ξ , β , κ , and S_0 appear only as the combination $\xi\beta S_0/\kappa$. If we were to assume δ and γ are fixed and fit the model to an observed value of r , then we are specifying the combination of $\xi\beta S_0/\kappa$, and so R_0 is uniquely determined. This holds regardless of how we allow ξ , β , S_0 , and k to vary in the fit; the relation between R_0 and r is not sensitive to these parameters. In other words, a sensitivity analysis of the impact of varying one of these parameters while fitting to another of the parameters is uninformative, as their product will remain the same. Introduction of terms to account for hyperinfectivity, differing infectivity for asymptomatic and symptomatic individuals, and person-to-person infection, will add terms to, and therefore influence, these relationships, but the core structure remains.

Combining these observations, the similar values for R_0 reported by several recent cholera models may reflect use of similar values of δ and γ and hence a similar serial interval. The variation seen in ξ and β likely then reflects differences in other parameter estimates and model differences. However, while we might know the distribution of duration of infection with cholera, we do not know the lifespan of cholera in a water supply. Because the relation between r and R_0 is sensitive to this parameter, and our knowledge of it is poor, sensitivity analyses should investigate wide ranges of this parameter.

The serial interval for the model discussed here can be calculated as follows. Start with one infected individual, who recovers at rate γ and increases the concentration of vibrios in the water reservoir at rate ξ . These vibrios decay at rate δ . The expected concentration of vibrios due to the infected individual at time t is given by:

$$B_I(t) = \frac{e^{-\delta t}(-1 + e^{(\delta - \gamma)t})\xi}{\delta - \gamma}$$

As infectiousness is proportional to vibrio concentration when concentrations are low, to obtain the serial interval distribution we can normalize $B_I(t)$ by its integral over time, which is

$$\frac{\xi}{\delta\gamma}$$

The serial interval has a mean equal to the sum of the mean duration of human infectiousness and the mean duration of vibrio viability in the water,

$$\frac{1}{\delta} + \frac{1}{\gamma}$$

Thus for these parameters, this ranges from 8 days (5 + 3) to 35 days (5+30) -- an uncertainty of almost 4.5 times. Plotting the serial interval distribution for the two sets of parameters used in the example above yields eFigure (<http://links.lww.com>).

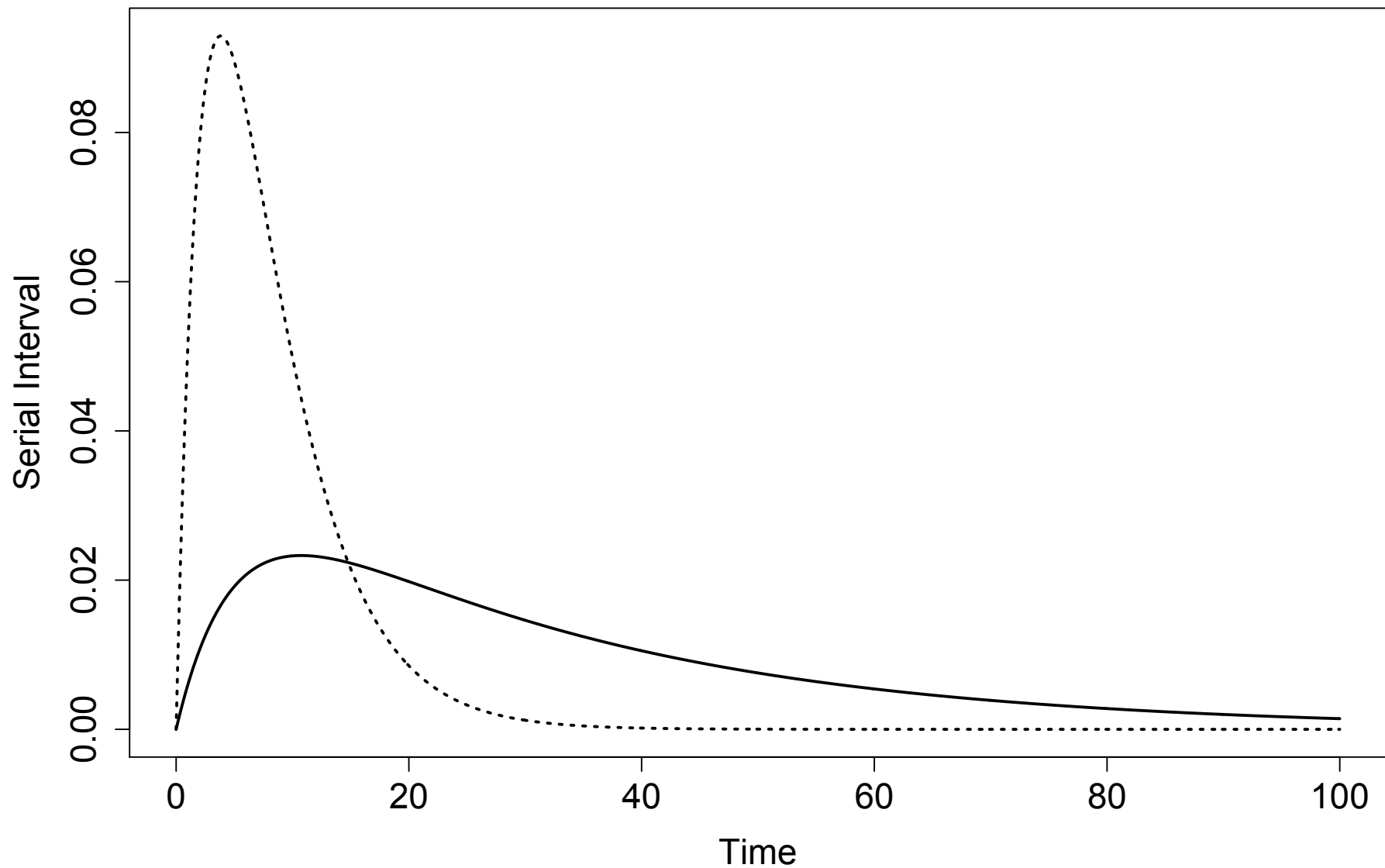
The parameter uncertainty emphasized here is importantly dependent on the most uncertain (and probably variable) parameter that influences timing of infectiousness, the decay rate of cholera infectivity in water. One might argue that this dependence is an artifact of assuming a purely waterborne transmission route, without accounting for person-to-person transmission, which in this context means transmission through contaminated food or water containers within households or at communal meals. The role of waterborne transmission is to extend the duration of infectiousness traceable back to one infected person from the duration of that person's shedding to the (possibly much longer) time that the vibrios shed by that person remain infectious in the water reservoir. In a model with primarily person-to-person transmission, the serial interval would be shorter and less uncertain.

If one were certain of the relative proportion of person-to-person and waterborne transmission of cholera within an epidemic (and if it could be assumed constant in space and time), then the parameter uncertainty described in the main text of this paper would be reduced. However, in models incorporating direct person-to-person transmission, the relative role of this route vs. waterborne transmission is either fitted, for which there may be an identifiability problem, or assumed, based on little

or no data, especially for any particular ongoing outbreak. In the absence of knowledge about the relative importance of person-to-person and waterborne transmission, the uncertainty in the serial interval remains unchanged.

References

1. Codeco CT. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. *BMC Infect Dis* 2001;1:1.
2. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proc Biol Sci* 2007;274(1609):599-604.



Supplemental Figure. Variation of serial interval over time with change in cholera lifespan in water reservoir. Serial interval as determined with cholera lifespan in water set at 30 days (solid line) and 3 days (dotted line) and duration of infection with cholera set at 5 days.