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The epidemiological dynamics of infectious trachoma may facilitate elimination

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ABSTRACT

Introduction: Trachoma programs use mass distributions of oral azithromycin to treat the ocular strains of *Chlamydia trachomatis* that cause the disease. There is debate whether infection can be eradicated or only controlled. Mass antibiotic administrations clearly reduce the prevalence of chlamydia in endemic communities. However, perfect coverage is unattainable, and the World Health Organization's goal is to control infection to a level where resulting blindness is not a public health concern. Here, we use mathematical models to assess whether more ambitious goals such as local elimination or even global eradication are possible.

Methods: We fit a class of non-linear, stochastic, susceptible–infectious–susceptible (SIS) models which allow positive or negative feedback, to data from a recent community-randomized trial in Ethiopia, and make predictions using model averaging.

Results: The models predict that reintroduced infection may not repopulate the community, or may do so sufficiently slowly that surveillance might be effective. The preferred model exhibits positive feedback, allowing a form of stochastic hysteresis in which infection returns slowly after mass treatment, if it returns at all. Results for regions of different endemicity suggest that elimination may be more feasible than earlier models had predicted.

Discussion: If trachoma can be eradicated with repeated mass antibiotic distributions, it would encourage similar strategies against other bacterial diseases whose only host is humans and for which effective vaccines are not available.

Introduction

Trachoma is the leading infectious cause of blindness worldwide (Resnikoff et al., 2004). Sustained transmission of its etiological agent, *Chlamydia trachomatis*, is possible only in humans. While no effective vaccine exists, a single dose of oral azithromycin can clear ocular chlamydial infection from an individual (Bailey et al., 1993). Mass treatment of entire communities dramatically reduces the prevalence of infection (Schachter et al., 1999; Chidambaram et al., 2006), but the extent to which infection returns over time is still under study. Some have predicted that infection would gradually disappear after an antibiotic distribution, and others that infection would return (Schachter et al., 1999; Lietman et al., 1999; Zhang et al., 2004).

Longitudinal reports of single communities have not resolved the issue. In some villages, infection has faded away (Gaynor et al., 2003; Solomon et al., 2004), but elsewhere, it has persisted or returned (Schachter et al., 1999; West et al., 2005). Supplemental treatments, inter-community variance (either due to random effects or underlying differences), seasonal effects, and secular trends make these single-community reports difficult to interpret. Multiple-community studies in severely affected areas have revealed marked variation in how communities respond to treatment (Chidambaram et al., 2006; Melese et al., 2008); on average, infection has returned, although to lower levels than those observed prior to treatment (Chidambaram et al., 2006; Lakew et al., 2009). Yet possible transmission from untreated neighboring areas (Chidambaram et al., 2006; Lakew et al., 2009) renders even these larger studies inconclusive.

How quickly and to what extent infection returns after a single treatment may dictate the appropriate long-term goal for trachoma programs (Lietman et al., 1999; Melese et al., 2008). If infection tends to disappear, then local elimination or even global eradication may be

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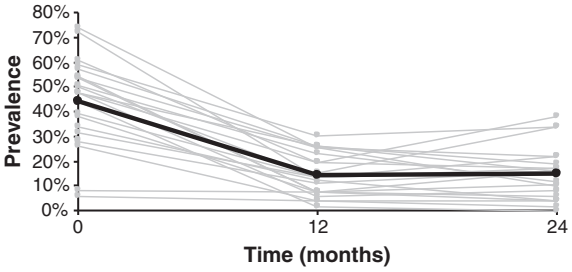

Fig. 1. Clinical data. The prevalence of ocular chlamydial infection determined by PCR in 24 Ethiopian communities after a single mass oral azithromycin distribution at time zero (TANA, U10 EY016214). Individual communities are displayed in gray, and the mean of the 24 communities in black. Communities were re-treated, by design, after the 24 month survey.

feasible. If infection returns quickly, repeated suppression of infection to low levels may be all that can be achieved. Proper assessment requires monitoring multiple communities without subsequent antibiotic treatment, in the absence of a secular trend or confounding transmission from untreated neighboring areas. Conducting annual longitudinal assessments in the same month eliminates the contribution of seasonal effects. A recent, NIH-supported, cluster-randomized clinical trial provides just such data (Fig. 1) (House et al., 2009), offering a unique opportunity to assess the dynamics of chlamydial infection after mass treatment.

Classically, susceptible–infectious–susceptible (SIS) models have assumed that the hazard of infection experienced by each susceptible is proportional to the prevalence of infection in the community (the *mass action* assumption) (Brauer et al., 2008; Ray et al., 2009). SIS models incorporating the mass action assumption have been used to estimate the coverage and frequency of mass treatments necessary to eliminate trachoma and the optimal season to treat (Lietman et al., 1999; Melese et al., 2008; Ray et al., 2007). Other modifications have explored household transmission and progression of trachoma through its clinical stages (Blake et al., 2009; Gambhir et al., 2009; Grassly et al., 2008). However, the behavior of a mass-action model is limited, allowing neither positive nor negative feedback of the prevalence of infection on the proportionality constant for transmission. In the absence of secular changes in transmission, any infection remaining after mass treatment of an endemic community will necessarily repopulate the community to equilibrium levels. In this paper, we use a straightforward extension of the mass action model which allows a more general dependence of the infection hazard on the prevalence (van den Driessche and Watmough, 2000; Alexander and Moghadas, 2004; Moghadas and Alexander, 2006).

Methods

We assume that a community has an effective population size of N, with I infectious cases. Susceptible individuals $(N-I)$ can be exposed to both linear $(\beta\frac{I}{N})$ and non-linear hazards of infection $(\beta\nu_2\left(\frac{I}{N}\right)^{\phi+2})$ from within the community, and to infection from outside $(\beta\nu_1\frac{\bar{I}}{N}$, where $\frac{\bar{I}}{N}$ is the average prevalence of infection in other communities). If not treated, cases recover at a rate γ. Thus:

$$\frac{dI}{dt}=\beta\left(\nu_1\frac{\bar{I}}{N}+\frac{I}{N}+\nu_2\left(\frac{I}{N}\right)^{\phi+2}\right)(N-I)-\gamma I \tag{1}$$

The implications of adding the non-linear term have been explored in detail for this deterministic model (van den Driessche and Watmough, 2000; Alexander and Moghadas, 2004; Moghadas and Alexander, 2006). At a low prevalence, this behaves similarly to the mass-action model, but with increasing prevalence, transmission can exhibit either positive or negative feedback, depending on whether ν_2 is positive or negative (van den Driessche and Watmough, 2000; Moghadas and Alexander, 2006). Kolmogorov forward equations describing a stochastic version of the 5-parameter model are (Brauer et al., 2008; Ray et al., 2007, 2009):

$$\frac{dp_0(t)}{dt}=-\beta\nu_1\frac{\sum_{j=0}^{N}jp_j}{N}Np_0(t)+\gamma p_1(t) \tag{2}$$

for $1\le i\le N-1$,

$$\frac{dp_i(t)}{dt}=\beta\left(\nu_1\frac{\sum_{j=0}^{N}jp_j}{N}+\frac{i-1}{N}+\nu_2\left(\frac{i-1}{N}\right)^{\phi+2}\right)(N-i+1)p_{i-1}(t)+\gamma(i+1)p_{i+1}(t)$$
$$-\left(\beta\left(\nu_1\frac{\sum_{j=0}^{N}jp_j}{N}+\frac{i}{N}+\nu_2\left(\frac{i}{N}\right)^{\phi+2}\right)(N-i)+\gamma i\right)p_i(t)$$
$$\frac{dp_N(t)}{dt}=\beta\left(\nu_1\frac{\sum_{j=0}^{N}jp_j}{N}+\frac{N-1}{N}+\nu_2\left(\frac{N-1}{N}\right)^{\phi+2}\right)p_{N-1}(t)-\gamma Np_N(t)$$

where $p_i(t)$ is the probability of a community having i infections at time t.

We estimated the optimal values of all five parameters (β, ν_1, ν_2, ϕ, and γ) by maximizing the likelihood of having observed the baseline

Table 1
Model selection. We tested 6 models, corresponding to the 6 possible subsets of the parameters in Eq. (2), β, ν_1, ν_2, γ, and ϕ, which have terms for both transmission (β) and recovery (γ), and where ϕ is included only if ν_2 is included. The parameter values for each subset that resulted in the maximum likelihood of the observed data (Fig. 1) are displayed and ranked by the AIC_c (Burnham and Anderson, 1998). Models 1–4 were considered in the confidence set, which here we have defined as those models which had an AIC_c of within 4 AIC_c-units of the optimal model (Burnham and Anderson, 1998). Models were weighted by the AIC_c for the model averaging in Fig. 2. The parameters β and γ have the units 1/week, and ν_1, ν_2, and ϕ are dimensionless.

Model	Transmission				Recovery			
	Outside	Within community						
	ν_1 (95% CI)	β (95% CI)	ν_2 (95% CI)	ϕ (95% CI)	γ (95% CI)	Loglikelihood	AIC_c	AIC_c weight
1	0.1047 (0.0111, 0.2951)	0.0139 (0.0072, 0.0214)	2.706 (1.402, 5.261)	*	0.0168 (0.0100, 0.0243)	−142.40	291.38	0.467
2	0.0747 (0.0178, 0.2412)	0.0192 (0.0156, 0.0522)	2.673 (1.238, 6.127)	0.8064 (−0.5674, 1.591)	0.0173 (0.0133, 0.0414)	−141.84	292.66	0.245
3	*	0.0143 (0.0072, 0.0287)	1.779 (0.694, 3.241)	*	0.0136 (0.0087, 0.0231)	−144.64	293.56	0.157
4	*	0.0191 (0.0149, 0.0368)	2.321 (1.565, 6.638)	1.3137 (−0.5517, 3.131)	0.0140 (0.0114, 0.0240)	−143.67	293.92	0.131
5	*	0.0190 (0.0140, 0.0382)	*	*	0.0109 (0.0079, 0.0226)	−152.81	307.72	0.000
6	0.0112 (−0.0020, 0.0310)	0.0196 (0.0129, 0.0302)	*	*	0.0113 (0.0073, 0.0179)	−151.99	308.25	0.000

TANA data as an equilibrium, and of having collected the 24 month TANA data given the 12 month results. We performed the following steps: (a) determination of the maximum likelihood estimate using the Nelder–Mead downhill simplex algorithm, (b) repeat optimization using 25 randomly chosen starting points, and (c) determination of interval estimates (and correlation) using the Metropolis–Hastings algorithm (a Markov chain Monte Carlo method) using the maximum likelihood estimate as the starting point for the chain (O'Neill, 2002). Convergence was assessed graphically using standard methods, and 10,000 iterations were used following a burn-in period. Restricted models were fit in which any or all of the three parameters ν_1, ν_2, or ϕ were set to zero, effectively removing them from the model (note that setting ν_2 to zero renders the value of ϕ moot). Model selection was performed using the sample size-corrected Akaike information criterion (AIC_c), a goodness-of-fit measure that penalizes for inclusion of each additional parameter (Burnham and Anderson, 1998). The confidence set was defined as those models which had an AIC_c of within 4 AIC_c-units of the optimal model (Burnham and Anderson, 1998). The quasi-stationary distributions in Fig. 3 were obtained by constructing an $N \times N$ matrix, representing the N Kolmogorov forward equations without the zero state; the eigenvector associated with the largest eigenvalue of this matrix was taken as the quasi-stationary distribution (Brauer et al., 2008; Ray et al., 2007; Nasell, 1999). Note that external infection from other communities was specifically not considered in these scenarios.

We used simulated data to validate the model selection procedure. On 24 simulated communities generated by the stochastic version of Model 5 (mass action model), the model which included only parameters β and γ correctly had the best AIC_c of the 6 possible models. Likewise on 24 simulated communities generated by the stochastic version of the other 5 models, the model with the optimum AIC_c included the correct subset of β, ν_1, ν_2, γ, and ϕ. These findings support the use of model selection to identify the optimal model using longitudinal data from 24 communities.

In this analysis, we allowed transmission to be a polynomial function of the prevalence, but other dependence structures could have been implemented (van den Driessche and Watmough, 2000; Moghadas and Alexander, 2006). The per-capita recovery rate could also depend on the prevalence; the transmission parameter β in Eq. (1) could vary between communities as a random effect (Ray et al., 2009), or the model could assume that the laboratory test did not detect all infections (by estimating test sensitivity). All of these models were fit to the Ethiopian data, and none provided a better AIC_c than Model 1.

Results

We fit this 5-parameter model by maximizing the likelihood of observing the results from the 24 TANA communities (Fig. 1), estimating ν_2 as $+2.673$ (95% CI $+1.238$ to $+6.127$, Table 1). In addition, we fit restricted 2-, 3-, and 4-parameter versions of these equations, performing model selection using AIC_c (Table 1). The top 4 models all retained a positive, non-linear transmission term, ν_2. The two mass-action models, in which infection hazard was proportional to prevalence, had poor AIC_cs and were not included in the 95% confidence set (Table 1) (Burnham and Anderson, 1998). For the full 5-parameter model, the same optimum was reached from 25 separate, randomly chosen starting points. For the preferred Model 1 (Table 1), we estimated the correlation between parameter estimates. The value of β was correlated with γ ($r = 0.79$), ν_2 ($r = -0.52$), and ν_1 ($r = -0.51$); the estimated correlation between ν_1 and ν_2 was $r = 0.75$.

Predictions obtained by weighting the 6 possible models by AIC_c-score (Table 1) (Burnham and Anderson, 1998) suggest that three annual antibiotic distributions with coverage of 80% of the population (the WHO target) should eliminate infection in most communities (Fig. 2a). A single reintroduced infection may fade away or repopulate the community. In the latter case, model averaging suggests that return would occur slowly, giving surveillance systems an opportunity to detect recrudescence before a new epidemic emerges (Fig. 2b).

The behavior of the optimal model (the 4 parameter Model 1 in Table 1) is different in communities with more, or less, transmission than found in the communities analyzed here. If we vary the transmission parameters β (relative to the recovery parameter γ) and ν_2 in the deterministic Eq. (1) above, the equilibrium prevalence of infection behaves as the well-studied cusp catastrophe (Cobb,

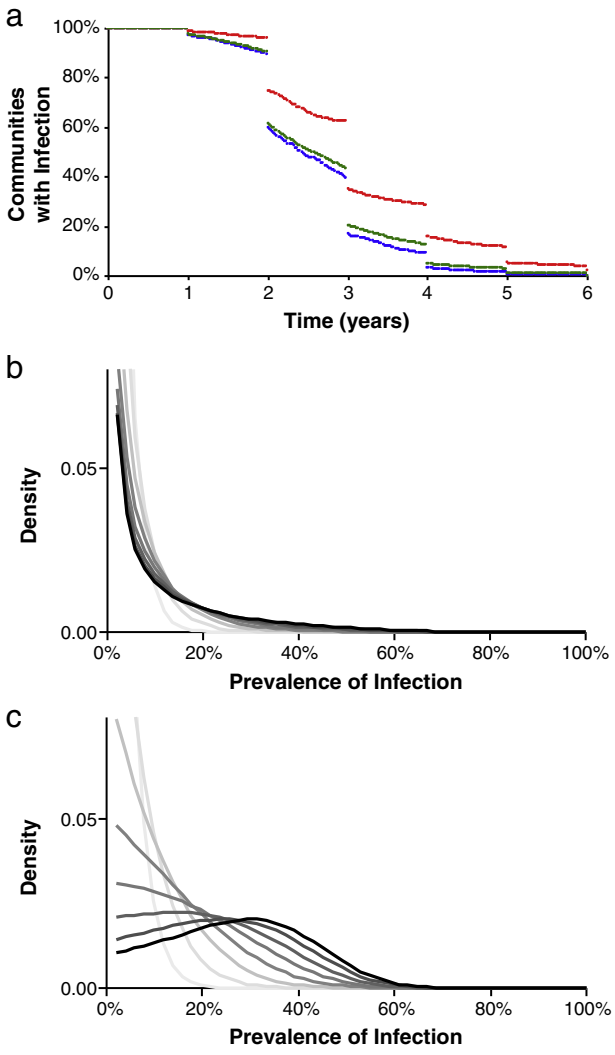

Fig. 2. a. A survival curve of infection in hypothetical communities. All communities have infection at baseline, but this decreases with each annual antibiotic treatment with 80% coverage. The prediction of the preferred model (Model 1 in Table 1) is in blue, the prediction of the previously analyzed, mass action model (Model 5) in red, and the prediction from model averaging of the 6 possible models in Table 1 by their AIC_c score is in green. Although all models were fit to the same data (Fig. 1), both Model 1 and the model average have far more encouraging results than the previously studied mass action model. b. The expected distribution of infection after a single infection is reintroduced into hypothetical communities of 50 children. The expected distribution at yearly intervals, from 1 year (lightest gray) to 8 years (black) are displayed for a model average of the 6 models in Table 1 (b); infection disappears in some communities and slowly returns in others. With the mass-action model (c), infection returns in most communities (Ray et al., 2007, 2009). Note that external infection from other communities has not been considered in these scenarios.

1978). Fig. 3 reveals a cross-section of this phase diagram in which we increase $R_0 = \beta/\gamma$ (while keeping ν_2 constant), yielding three qualitatively different behaviors (Brauer et al., 2008). In areas with low transmission, the model predicts that infection gradually disappears, as was seen in Western Nepal (Gaynor et al., 2003). The only stable equilibrium is zero prevalence (Zone I in Fig. 3). The stochastic version of this model (Eq. (2) above) estimates the expected distribution of prevalence seen in these low transmission communities prior to treatment (the quasi-stationary distribution, conditioned on non-elimination, Fig. 3b) (Brauer et al., 2008; Nasell, 1999). In areas with more transmission than seen in this report, such as those previously studied in Southern Ethiopia (Lakew et al., 2009), the only deterministic equilibrium is at a high prevalence (Zone III in Fig. 3), with the expected distribution in the stochastic model shown in Fig. 3d.

The distributions expected in Zones I and III in Fig. 3 are qualitatively similar to what has been found previously for stochastic versions of the mass-action model (Model 5 in Table 1) (Brauer et al., 2008; Ray et al., 2007; Nasell, 1999). In a mid-range of transmission, as seen in the Northern Ethiopian communities in this report, positive feedback allows for two stable equilibria in the deterministic model: one with zero prevalence and another with a higher prevalence (Zone II). The quasi-stationary distribution for the prevalence in communities which still have infection is now bimodal (Fig. 3c) (Cobb, 1978).

In the deterministic version of Model 1 (Eq. (1), with ν_2 set to zero), whether infection returns are dependent on whether the prevalence of infection post-treatment is above or below the unstable equilibrium of ~16%. This suggests that a level of coverage that is sufficient to reduce infection below a critical threshold may have a lasting effect by nudging infection from the higher equilibrium to the lower equilibrium. However, when the prevalence of infection is brought below 25% in the stochastic model, expected incidence is very close to expected recovery; thus whether the prevalence tends towards the higher or lower equilibrium in any particular community is due more to chance, at least over the timescale of several years.

Discussion

This analysis suggests that the transmission of trachoma exhibits positive feedback—that is, the hazard of a susceptible individual becoming infected per infectious case goes up as the prevalence in the community increases. This has several ramifications for trachoma programs. If infection returns slowly after being brought to a low level, then elimination may be easier than previous models had suggested. Earlier mass-action models had predicted that infection could only be eliminated with multiple treatments with high coverage, and that once reintroduced, infection would rapidly repopulate the community (Fig. 2c) (Lietman et al., 1999; Ray et al.,

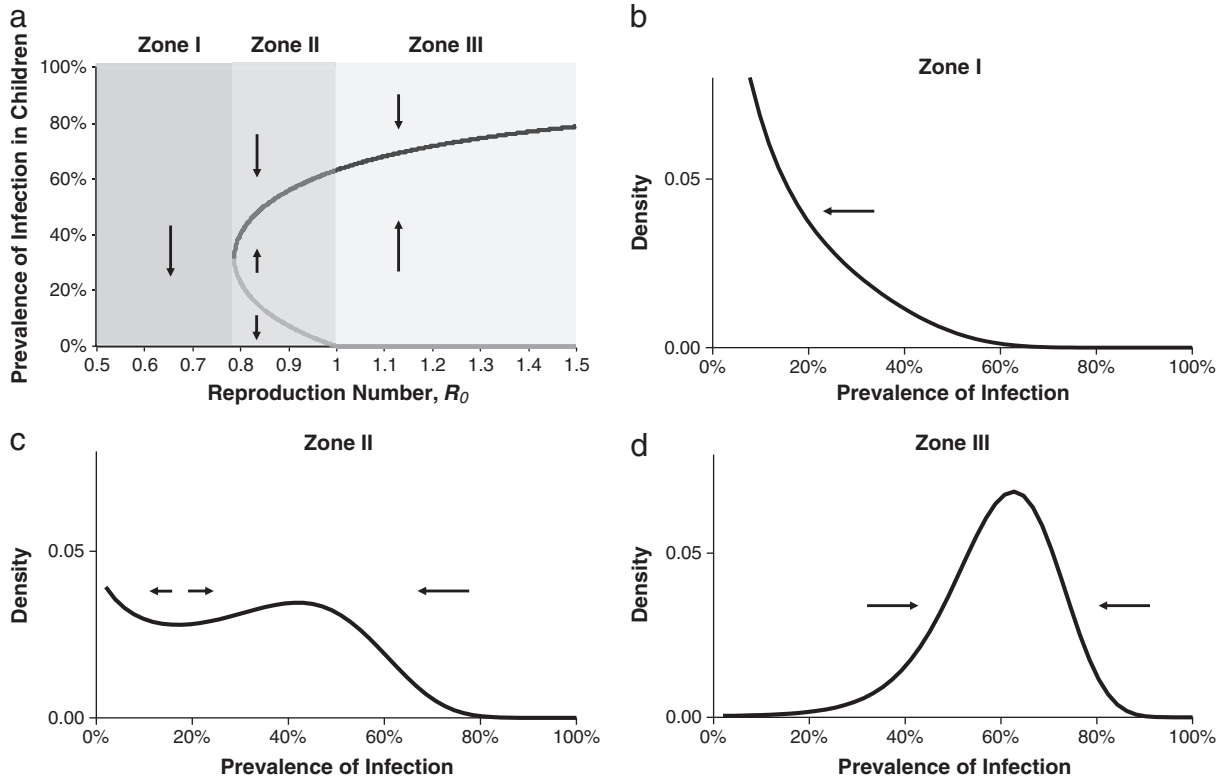

Fig. 3. a) Bifurcation diagram for the preferred model (Model 1 in Table 1). In Eq. (1), varying the transmission parameters β and ϕ vary the equilibrium prevalence of infection as a cusp catastrophe. A cross section through this cusp is shown, varying the initial reproduction number, R_0 (defined here as β/γ), keeping ν_2 constant, and not including transmission from outside of the community (i.e. $\nu_1 = 0$). At low levels of R_0 (Zone I), the only equilibrium is that with no disease (black curve representing a stable equilibrium at 0 prevalence); the prevalence of infection should drift towards zero (arrow). At a high R_0 (Zone III), the endemic equilibrium prevalence of infection is >60% (black curve representing a stable equilibrium), and the no-infection equilibrium is unstable (gray curve at 0 prevalence). At values of R_0 between 0.79 and 1.00 (Zone II), there is an additional unstable equilibrium represented by the gray curve; if infection is above this gray curve, levels should move to the higher, stable equilibrium of 30–60%, while those below the gray curve will move to the stable, no-infection prevalence of zero (arrows) (van den Driessche and Watmough, 2000; Moghadas and Alexander, 2006). The stochastic version of the model (Eq. (2)) was fit to data from three locations, allowing estimation of the expected pre-treatment (quasi-stationary (Brauer et al., 2008; Nasell, 1999) distribution of infection: a) Zone I, an area of Western Nepal with low transmission and $R_0 = 0.65$(Gaynor et al., 2003), with the arrow indicating the direction of drift, b) Zone 2, the areas studied in this report from Amhara, Ethiopia with $R_0 = 0.83$, and c) Zone III, a more severely affected region of Gurage, Ethiopia, with $R_0 = 1.12$ (Lakew et al., 2009). Note that external infection from other communities has not been considered in these scenarios.

Table 2
Implications in areas of varying endemicity. Model 1 (Table 2) suggests that the epidemiology of trachoma infection may differ depending on the ease of transmission in a particular region. The pre-treatment endemicity in a community may reveal the response to a single mass azithromycin distribution. The models predictions are consistent with results from communities in Nepal, Tanzania, and Ethiopia.

	Zone I	Zone II	Zone III
Pre-treatment endemicity from deterministic version of the preferred model (Model 1, Table 1)	Low (0 to 30%)	Medium (either 0% or 30% to 60%)*	High (>60%)
Expected pre-treatment distribution from stochastic version of the preferred model (Model 1, Table 1)	Unimodal Fig. 3b	Bimodal Fig. 3c	Unimodal Fig. 3d
Response to a single mass treatment	Infection tends not to return	Infection tends not to return if brought to a low enough level	Infection tends to return unless completely eliminated
Examples	Nepal (Gaynor et al., 2003) Tanzania (Solomon et al., 2004; Ray et al., 2009)	Ethiopia (House et al., 2009) Tanzania (West et al., 2005)	Ethiopia (Lakew et al., 2009; Ray et al., 2009)

*Here, there are two stable equilibria, no infection (prevalence = 0) and a second equilibrium with a prevalence from 30% to 60%, depending on the R_0 (see Fig. 3).

2007, 2009). The positive feedback allows three qualitatively different behaviors. As with the mass-action SIS model, infection may gradually disappear without treatment in hypo-endemic areas, or infection may return to baseline even after treatment in hyper-endemic areas. However with positive feedback, a third behavior is possible; infection may be endemic, but if brought to a low level may tend not to return. These results are consistent with the phenomena observed in trachoma programs (Table 2). In hypo-endemic areas of Nepal and the Gambia, infection tended to decline when brought to a low level, even before subsequent treatments were given (Gaynor et al., 2003; Solomon et al., 2004). In a hyper-endemic region in Ethiopia, infection returned on average after mass treatment, although this return still took several years (Lakew et al., 2009). In a meso-endemic setting in Tanzania, the prevalence after treatment wandered at a modest level of 5–20% for 18 months (West et al., 2005).

The positive feedback in Model 1 results in a form of stochastic hysteresis. If the transmission parameter is decreased, then the prevalence of infection decreases slowly at first due to positive feedback from existing cases. Thus hygiene programs and latrine construction designed to reduce transmission may have little effect in the short term, even if eventually successful (Emerson et al., 2000). In contrast, if infection is reduced markedly without altering transmission, infection will take time to repopulate the community with little positive feedback initially. This is consistent with infection returning slowly, if at all, after mass treatment (Chidambaram et al., 2006; Solomon et al., 2004; West et al., 2005).

A feature present in all models in the 95% confidence set (Models 1–4 in Table 1) is that the hazard of infection for each susceptible case increases as the prevalence of infection increases. While the models themselves do not reveal the mechanism for this positive feedback, ample literature exists on assumptions that could lead to this behavior. For example, treatment programs might saturate with too many cases, social groups might have different susceptibilities, or multiple infections could overwhelm the immune system (van den Driessche and Watmough, 2000; Moghadas and Alexander, 2006; Dushoff et al., 1998; Liu et al., 1987). Strain diversity might also lead to a form of positive feedback; if heterogeneity exists in part to evade the human immune system, then elimination of many, but not all strains might prevent infection from returning to pre-treatment levels. This is supported by the observation that the diversity of strains correlates with pre-treatment endemicity (Zhang et al., 2004).

It is possible that extrinsic factors may have played a role in the lack of return after treatment. In particular, any difference in transmission conditions from baseline to 12–24 months, could be misinterpreted as evidence for positive feedback. In fact, the disappearance of trachoma in the absence of a trachoma program is a well recognized phenomenon (Dolin et al., 1997; Hoechsmann et al., 2001; Jha et al., 2002; Chidambaram et al., 2004). Control communities which did not initially receive treatment, but were randomized from the same pool as the communities studied in this report, had the same prevalence of infection at 12 months as these communities did at baseline, suggesting that transmission conditions did not change dramatically during the course of the monitoring (House et al., 2009).

Others have fit semi-mechanistic models, in which the states are defined as in transmission models, but the transition between these states is not assumed to be mass-action; for both measles and cholera, saturation was found (suggesting negative feedback rather than positive feedback) and attributed to spatial clustering of infectious cases (Koelle and Pascual, 2004; Ellner et al., 1998; Finkenstädt et al., 2002; Finkenstädt and Grenfell, 1998).

Regardless of the mechanism of the observed positive feedback, its existence suggests that large-scale elimination may be an achievable goal. Both herd protection and local elimination have been documented empirically (Gaynor et al., 2003; Solomon et al., 2004; House et al., 2009; Biebesheimer et al., 2009; Harding-Esch et al., 2009). If infectious trachoma can be eliminated from the most severely affected areas, then global eradication may be feasible as well. This would be the first example of a bacterial disease eliminated by antibiotic treatment alone, and one which might encourage mass treatment strategies against other bacterial pathogens whose only host is humans and for which effective vaccines are unavailable.

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References

Alexander, M.E., Moghadas, S.M., 2004. Periodicity in an epidemic model with a generalized non-linear incidence. Mathematical Biosciences 189 (1), 75–96 May.
Bailey, R.L., Arullendran, P., Whittle, H.C., Mabey, D.C., 1993. Randomised controlled trial of single-dose azithromycin in treatment of trachoma. Lancet 342 (8869), 453–456.

Biebesheimer, J.B., House, J., Hong, K.C., et al., 2009. Complete local elimination of infectious trachoma from severely affected communities after six biannual mass azithromycin distributions. Ophthalmology 116 (11), 2047–2050.
Blake, I.M., Burton, M.J., Bailey, R.L., et al., 2009. Estimating household and community transmission of ocular *Chlamydia trachomatis*. PLoS Neglected Tropical Diseases 3 (3), e401.
Brauer, F., van den Driessche, P., Wu, J., 2008. Mathematical Epidemiology. Springer-Verlag, Berlin.
Burnham, K.P., Anderson, D.R., 1998. Model Selection and Inference: A Practical Information-Theoretic Approach. Springer, New York.
Chidambaram, J.D., Bird, M., Schiedler, V., et al., 2004. Trachoma decline and widespread use of antimicrobial drugs. Emerging Infectious Diseases 10 (11), 1895–1899 Nov.
Chidambaram, J.D., Alemayehu, W., Melese, M., et al., 2006. Effect of a single mass antibiotic distribution on the prevalence of infectious trachoma. JAMA 295 (10), 1142–1146 Mar 8.
Cobb, L., 1978. Stochastic catastrophe models and multimodal distribution. Behavioral Science 23, 360–374.
Dolin, P.J., Faal, H., Johnson, G.J., et al., 1997. Reduction of trachoma in a sub-Saharan village in absence of a disease control programme. Lancet 349 (9064), 1511–1512.
Dushoff, J., Huang, W., Castillo-Chavez, C., 1998. Backwards bifurcations and catastrophe in simple models of fatal diseases. Journal of Mathematical Biology 36 (3), 227–248.
Ellner, S.P., Bailey, B.A., Bobashev, G.V., Gallant, A.R., Grenfell, B.T., Nychka, D.W., 1998. Noise and nonlinearity in measles epidemics: combining mechanistic and statistical approaches to population modeling. The American Naturalist 151 (5), 425–440 May.
Emerson, P.M., Cairncross, S., Bailey, R.L., Mabey, D.C., 2000. Review of the evidence base for the 'F' and 'E' components of the SAFE strategy for trachoma control. Tropical Medicine & International Health 5 (8), 515–527.
Finkenstädt, B., Grenfell, B., 1998. Empirical determinants of measles metapopulation dynamics in England and Wales. Proceedings of the Royal Society of London, Series B 265 (1392), 211–220 Feb 7.
Finkenstädt, B.F., Bjornstad, O.N., Grenfell, B.T., 2002. A stochastic model for extinction and recurrence of epidemics: estimation and inference for measles outbreaks. Biostatistics (Oxford, England) 3 (4), 493–510 Dec.
Gambhir, M., Basanez, M.G., Burton, M.J., et al., 2009. The development of an age-structured model for trachoma transmission dynamics, pathogenesis and control. PLoS Neglected Tropical Diseases 3 (6), e462.
Gaynor, B.D., Miao, Y., Cevallos, V., et al., 2003. Eliminating trachoma in areas with limited disease. Emerging Infectious Diseases 9 (5), 596–598 May.
Grassly, N.C., Ward, M.E., Ferris, S., Mabey, D.C., Bailey, R.L., 2008. The natural history of trachoma infection and disease in a Gambian cohort with frequent follow-up. PLoS Neglected Tropical Diseases 2 (12), e341 Gaynor.
Harding-Esch, E.M., Edwards, T., Sillah, A., et al., 2009. Active trachoma and ocular *Chlamydia trachomatis* infection in two Gambian regions: on course for elimination by 2020? PLoS Neglected Tropical Diseases 3 (12), e573.
Hoechsmann, A., Metcalfe, N., Kanjaloti, S., et al., 2001. Reduction of trachoma in the absence of antibiotic treatment: evidence from a population-based survey in Malawi. Ophthalmic Epidemiology 8 (2–3), 145–153.
House, J.I., Ayele, B., Porco, T.C., et al., 2009. Assessment of herd protection against trachoma due to repeated mass antibiotic distributions: a cluster-randomised trial. Lancet 373 (9669), 1111–1118 Mar 28.
Jha, H., Chaudary, J., Bhatta, R., et al., 2002. Disappearance of trachoma in Western Nepal. Clinical Infectious Diseases 35 (6), 765–768.
Koelle, K., Pascual, M., 2004. Disentangling extrinsic from intrinsic factors in disease dynamics: a nonlinear time series approach with an application to cholera. The American Naturalist 163 (6), 901–913 Jun.
Lakew, T., House, J., Hong, K.C., et al., 2009. Reduction and return of infectious trachoma in severely affected communities in Ethiopia. PLoS Neglected Tropical Diseases 3 (2), e376.
Lietman, T., Porco, T., Dawson, C., Blower, S., 1999. Global elimination of trachoma: how frequently should we administer mass chemotherapy? Nature Medicine 5 (5), 572–576.
Liu, W.M., Hethcote, H.W., Levin, S.A., 1987. Dynamical behavior of epidemiological models with nonlinear incidence rates. Journal of Mathematical Biology 25 (4), 359–380.
Melese, M., Alemayehu, W., Lakew, T., et al., 2008. Comparison of annual and biannual mass antibiotic administration for elimination of infectious trachoma. JAMA 299 (7), 778–784 Feb 20.
Moghadas, S.M., Alexander, M.E., 2006. Bifurcations of an epidemic model with non-linear incidence and infection-dependent removal rate. Mathematical Medicine and Biology 23 (3), 231–254 Sep.
Nasell, I., 1999. On the quasi-stationary distribution of the stochastic logistic epidemic. Mathematical Biosciences 156 (1–2), 21–40 Mar 1.
O'Neill, P.D., 2002. A tutorial introduction to Bayesian inference for stochastic epidemic models using Markov chain Monte Carlo methods. Mathematical Biosciences 180, 103–114 Nov-Dec.
Ray, K.J., Porco, T.C., Hong, K.C., et al., 2007. A rationale for continuing mass antibiotic distributions for trachoma. BMC Infectious Diseases 7 (1), 91 Aug 7.
Ray, K.J., Lietman, T.M., Porco, T.C., et al., 2009. When can antibiotic treatments for trachoma be discontinued? Graduating communities in three African countries. PLoS neglected tropical diseases 3 (6), e458.
Resnikoff, S., Pascolini, D., Etya'ale, D., et al., 2004. Global data on visual impairment in the year 2002. Bulletin of the World Health Organization 82 (11), 844–851 Nov.
Schachter, J., West, S.K., Mabey, D., et al., 1999. Azithromycin in control of trachoma. Lancet 354 (9179), 630–635.
Solomon, A.W., Holland, M.J., Alexander, N.D., et al., 2004. Mass treatment with single-dose azithromycin for trachoma. The New England Journal of Medicine 351 (19), 1962–1971 Nov 4.
van den Driessche, P., Watmough, J., 2000. A simple SIS epidemic model with a backward bifurcation. Journal of Mathematical Biology 40 (6), 525–540.
West, S.K., Munoz, B., Mkocha, H., et al., 2005. Infection with *Chlamydia trachomatis* after mass treatment of a trachoma hyperendemic community in Tanzania: a longitudinal study. Lancet 366 (9493), 1296–1300 Oct 8.
Zhang, J., Lietman, T., Olinger, L., Miao, Y., Stephens, R.S., 2004. Genetic diversity of *Chlamydia trachomatis* and the prevalence of trachoma. The Pediatric Infectious Disease Journal 23 (3), 217–220 Mar.