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The efficacy of oral azithromycin in clearing ocular chlamydia: Mathematical modeling from a community-randomized trachoma trial

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ABSTRACT

Mass oral azithromycin distributions have dramatically reduced the prevalence of the ocular strains of chlamydia that cause trachoma. Assessing efficacy of the antibiotic in an individual is important in planning trachoma elimination. However, the efficacy is difficult to estimate, because post-treatment laboratory testing may be complicated by nonviable organisms or reinfection. Here, we monitored ocular chlamydial infection twice a year in pre-school children in 32 communities as part of a cluster-randomized clinical trial in Tanzania (prevalence in children was lowered from 22.0% to 4.7% after 3-year of annual treatment). We used a mathematical transmission model to estimate the prevalence of infection immediately after treatment, and found the effective field efficacy of antibiotic in an individual to be 67.6% (95% CI: 56.5–75.1%) in this setting. Sensitivity analyses suggested that these results were not dependent on specific assumptions about the duration of infection. We found no evidence of decreased efficacy during the course of the trial. We estimated an 89% chance of elimination after 10 years of annual treatment with 95% coverage.

Introduction

The World Health Organization (WHO) has targeted trachoma for elimination by the year 2020 (Mariotti, 2004). Repeated mass oral azithromycin distribution is a central component of the SAFE (Surgery of trichiasis, Antibiotics, Facial cleanliness and Environmental improvement) strategy endorsed by the WHO. Theoretically, repeated treatments may eventually eliminate infection from even the most severely affected areas (Lietman et al., 1999; Melese et al., 2004), and mass antibiotic distributions have, in fact, dramatically reduced the prevalence of infection in a number of locations (Burton et al., 2010; Chidambaram et al., 2006; Gaynor et al., 2003; House et al., 2009; Melese et al., 2004; Schachter et al., 1999; Solomon et al., 2004; West et al., 2005). However, concern remains that chlamydia may develop resistance to the azalides and macrolides, and that azithromycin may lose efficacy over time. *In vitro* resistance has not been observed, although it is difficult to assess and rarely tested. Small surveys after one and after four mass azithromycin distributions have failed to find drug resistance (Hong et al., 2009; Solomon et al., 2005).

The efficacy of repeated oral azithromycin distributions has been reported at the community level (Gaynor et al., 2003; Gebre et al., 2012; Melese et al., 2008; Schachter et al., 1999). However, the efficacy in an individual (probability of clearance following treatment) has been difficult to assess; treated individuals may become infected between pre-treatment and post-treatment examinations (which may be as much as 6 months) even in carefully monitored communities. Although the true probability of clearance following treatment cannot fully be assessed under field conditions because of reinfection and false positivity due to dead organisms immediately after treatment, analysis of longitudinal prevalence

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during trachoma elimination programs nevertheless reveals profound reductions in prevalence during treatment, as described elsewhere (Chidambaram et al., 2006; Melese et al., 2004; Solomon et al., 2004). Since these reductions occur because of the efficacy of the antibiotic in eliminating infection from individuals, analysis of such longitudinal prevalence curves reveals information about the efficacy. Lowered values for the individual efficacy correspond to smaller reductions in prevalence and therefore longer elimination times. It is possible to estimate an effective field efficacy, which is the value of the individual efficacy most likely to yield an observed prevalence curve given constant transmission rates over the observation period and the antibiotic coverage. The effective field efficacy can be used to estimate elimination times and program effectiveness.

Here, we apply a mathematical transmission model to laboratory infection data from the Tanzanian portion of the Partnership for the Rapid Elimination of Trachoma trial (PRET (Stare et al., 2011)) to estimate the effective field antibiotic efficacy in an individual in this setting.

Methods

Clinical and laboratory results

Villages were monitored as part of a cluster-randomized trachoma treatment trial in Tanzania (the clinical trial registration number is NCT00792922) (Harding-Esch et al., 2010; Stare et al., 2011). In brief, 32 villages in Tanzania were randomized in a factorial design (1) to high (80%) and very high (90% or more) coverage with annual mass antibiotic treatment, and (2) for the application of a discontinuation rule or no use of such a rule. None of the villages had discontinued treatment during the first three years, and thus all 32 villages received treatment at baseline, 12, and 24 months. At a mass distribution, all individuals were offered a single dose of oral azithromycin (1 g in adults, and weight-based dosing designed to provide approximately 20 mg/kg to children over age 6 months; younger children were treated with topical tetracycline). The census list of the community was used to monitor coverage, and as each resident presented for treatment, treatment was observed and recorded in the treatment log by a community treatment assistant. Reported coverage includes a small fraction of children who were offered tetracycline ointment; however, the percentage of children receiving tetracycline never exceeded 8%.

All 32 villages were censused at baseline, 12, 24, and 36 months. One hundred randomly selected children aged 0–5 years were examined at baseline, and at 6, 12, 18, 24, 30 and 36 months after baseline. A dacron swab was passed 3 times over their inverted right upper conjunctiva, and processed for the presence of chlamydial DNA as previously described (Stare et al., 2011). The estimated prevalence of infection at 6, 12, 18, 24, 30, and 36 months was used to fit parameters in the stochastic transmission model. Individual level infection data were not available for all members of the population, since only a random sample of individuals was subjected to polymerase chain reaction (PCR) testing in general.

Ethics statement

The study received ethical approval from institutional review board (IRB) of the Johns Hopkins University School of Medicine, the University of California San Francisco, and the Tanzanian National Institute for Medical Research, and was carried out in accordance with the Declaration of Helsinki. All subjects provided informed consent. The informed consent given was oral, because (1) verbal consent is the most ethical way to obtain consent, due to the high illiteracy rates in the study area, (2) IRB approved the use of the oral consent procedure for this study and (3) this oral consent is documented on the registration form for each study participant prior to examination in the field.

Modeling methods

We modeled village chlamydial positivity rates at baseline, and at 6, 12, 18, 24, 30 and 36 months in each of 32 villages. The observed data consisted of (1) the number $S_j^{(l)}$ of PCR-positive individuals in the random sample with size of $M_j^{(l)}$ at each observation time point l ($l = 0, 1, \ldots, 6$ corresponding to baseline, 6, 12, 18, 24, 30 and 36 months, respectively) for village j ($j = 1, \ldots, 32$), and (2) the number of individuals reported to have been covered by antibiotics at treatment time point k ($k = 1, 2, 3$ corresponding to baseline, 12 and 24 months).

Because reinfection may occur following treatment, we estimated the efficacy of treatment using a stochastic transmission model of transmission of *Chlamydia trachomatis* over time, similar to models previously published (Blake et al., 2009; Lietman et al., 2011; Ray et al., 2007, 2009). We fitted this mathematical model to the infection data using the maximum likelihood method. The model contains three components: (1) random sampling of individuals for PCR testing at the observation times, (2) change in the number of infected individuals over time due to transmission and recovery, and (3) change in the number of infected individuals due to mass antibiotic treatment with the reported coverage levels (at baseline, 12 and 24 months). Observations from different villages were considered independent.

Individuals were assumed to have been sampled at random. Let S_j be the number of positive individuals detected in the sample at the end of twelve months (for village j). From village j with population size N_j of which the number Y_j of infectives equals i, the probability $P(S_j = s|Y_j = i)$ that s positives are observed from a sample of size M_j is given by $\binom{i}{s}\binom{N_j - i}{M_j - s} / \binom{N_j}{M_j}$ using the hypergeometric distribution. For village j ($j = 1, \ldots, 32$), we assumed a population of size N_j, taken from the number of pre-school children found in the census at the time of treatment (at baseline, 12 or 24 months).

To model the change in prevalence between the prevalence surveys based on above assumptions, we used a classical SIS (susceptible-infective-susceptible) model structure, assuming that the force of infection is proportional to the prevalence of infection in the population with proportionality constant β. Moreover, we also assumed a constant exogenous force of infection ξ from outside the village (i.e., representing a risk which is independent of the village prevalence). Finally, we assumed a constant per-capita recovery rate γ. Between periods of treatment, we assumed that the probability $p_i^{(k)}(t)$ that there are i infectives in the population at time t after treatment time point k obeys the following equations for each village j (suppressing the subscript for clarity):

$$
\begin{aligned}
\frac{dp_0^{(k)}}{dt} &= \gamma p_1^{(k)}, \\
\frac{dp_i^{(k)}}{dt} &= \beta\frac{(i-1)(N-i+1)}{N}p_{i-1}^{(k)} + \gamma(i+1)p_{i+1}^{(k)} - \beta\frac{i(N-i)}{N}p_i^{(k)} - \gamma i p_i^{(k)} - p_i^{(k)}\xi(N-i) + p_{i-1}^{(k)}\xi(N-i+1), \quad \text{for } 1 \le i \le N-1 \\
\frac{dp_N^{(k)}}{dt} &= \beta\frac{N-1}{N}p_{N-1}^{(k)} - \gamma N p_N^{(k)} + \xi p_{N-1}^{(k)}
\end{aligned}
\tag{1}
$$