CHAPITRE 23

Which epistemological models predict the elimination of blinding trachoma by 2020? [*Quels sont les modèles épidémiologiques permettant de prédire l'élimination du trachome cécitant d'ici 2020 ?*]

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Elimination program with antibiotherapy and without an effective vaccine

If there were an effective vaccine for trachoma, the rationale for the elimination of trachoma would be clear. As long as enough people were vaccinated, then introduction of an infection in the community would die out and not lead to an epidemic because of herd immunity (Anderson et May, 1991). Unfortunately, no vaccine has shown to be effective, and in fact there has been a suggestion that vaccines increase scarring (Grayston *et al.*, 1962).

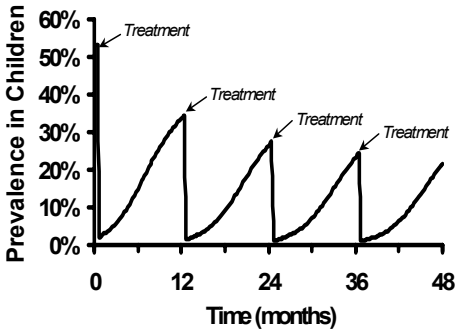
The rationale for mass periodic antibiotic treatments is less intuitive. It can be demonstrated theoretically with relatively simple mathematical models that periodic

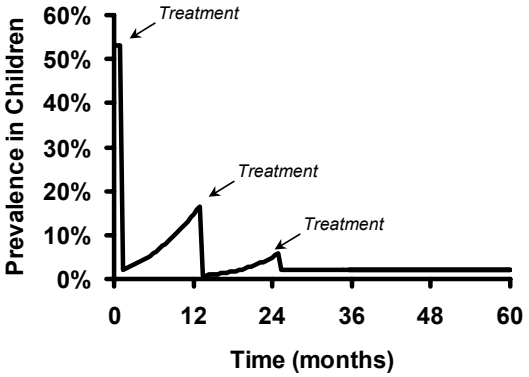
mass antibiotic distributions can eventually eliminate ocular chlamydia (Lietman *et al.*, 1999). However, according to the model, this can only be achieved if:

- coverage of the population is sufficiently high;
- distributions are frequent enough;
- the antibiotic is effective enough in an individual.

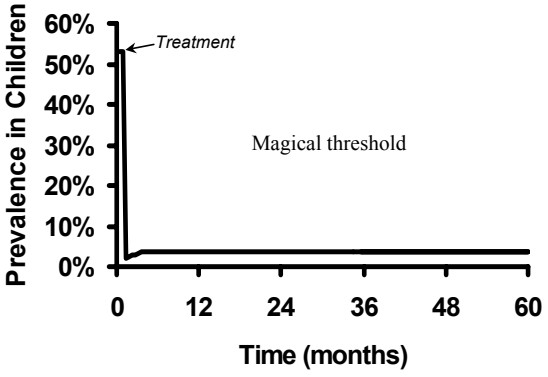
This can be demonstrated in the following scenarios. In a hypothetical population, annual treatment does not eliminate infection (Figure below left): infection will continue to return between treatments, and if treatment is discontinued, infection will return to its pre-treatment level. If treatments are performed more frequently, for example twice per year, elimination can be achieved (Figure below right).

A mathematical model suggests that in the most hyperendemic areas, biannual treatment and nearly complete coverage would be necessary for eventual elimination. In hypo-endemic areas (with a prevalence of active trachoma in children less than 20%), biennial treatment (every 2 years) may suffice (Lietman *et al.*, 1999). This mathematical model incorporated coverage, mixing between different age-groups, different degrees of immunity in different age groups, and different forces of infection in different areas. It assumed, amongst other things, that coverage is essentially random and that infection cannot persist in an individual for ever (without re-infection).





There is some hope that a single mass antibiotic treatment will reduce infection to a low level from which it cannot return (a magical threshold, Figure below left) (Gaynor *et al.*, 2002). However, if no other measures are included, presumably infection will eventually return to its pre-treatment level (Figure below right).



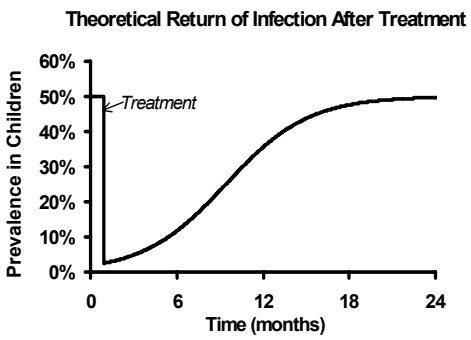


Figure 3

Thus, we are not able to predict yet the achievement of a trachoma control program. We cannot model the entire SAFE strategy, in part because there is little data about the long-term effect of mass antibiotics and over time little data about the effect of F and E on the prevalence of ocular chlamydial infection. However, a mathematical model has demonstrated several principles, including (Lietman *et al.*, 1999):

1) Infection can be eliminated from a community with repeat antibiotic distributions even without perfect coverage. We can eventually eliminate ocular chlamydia from a community as long as treatments are frequent enough and coverage is high enough. In fact, a theoretical formula has been offered to estimate the frequency necessary to eventually eliminate infection. While the efficacy of the antibiotic in an individual and the coverage of antibiotic in a population are known in some settings, the doubling time of an infection spreading through a community has proven to be a difficult parameter to estimate:

$$Necessary\ treatment\ frequency = \frac{(doubling\ time)\ \log\left(\frac{1}{(1-\ coverage \times efficacy)}\right)}{\log(2)}$$

2) Necessary treatment frequency is different in different communities. Hyperendemic communities may need more frequent treatments (i. e. biannual) and very high coverage to eliminate infection, where hypoendemic communities may require only annual or even biennial treatment and lower coverage rates.

3) Treatment of children alone may be effective. It may be possible to eliminate infection if just a core group of children are periodically treated, although such treatment would have to be offered more frequently (e. g. every 3 months) than if the entire community were treated.

Face washing.

It is difficult to include face washing in mathematical models. There is compelling anecdotal and circumstantial evidence that a clean face is associated with a lower risk of active trachoma (West *et al.*, 1996). Trachoma has been associated with poor water supply and dirty faces (Taylor *et al.*, 1989). However, evidence that face washing has a causative effect on the reduction of infection is marginal, and many studies lack controls or lack masked outcomes (Emerson *et al.*, 2000). One well-designed interventional facial cleanliness study found that an intensive facial cleanliness program added no statistical benefit to the reduction of clinically active trachoma, although it may have decreased the severity of disease (West *et al.*, 1995). This may be because trials such as this have relied on clinical activity as an outcome and chlamydia infection itself may be a more sensitive indicator, or because the full effect of such programs is not realized after only 1 year, or because face washing indeed may have only a marginal effect on the prevalence of active trachoma. Clearly, the hope is that over several years the effect of hygiene programs will become much larger. These modest estimates of the efficacy of face washing would have little effect on the above mathematical models of antibiotic treatment.

Fly control.

Likewise it is not clear to what extent fly control can reduce ocular chlamydial infection. There is circumstantial evidence that face flies (*Musca sorbens*) participate in the transmission of trachoma. Active trachoma tends to be higher in seasons with higher fly density (Emerson *et al.*, 2000). Fluoroscein dye was shown to spread from one child to another via flies (Darougar *et al.*, 1979). PCR has revealed evidence of *C. trachomatis* DNA on flies, although in less than 1% of flies tested in an endemic area. One recent pilot study offers some intriguing results (Emerson *et al.*, 1999). As said in chapter before, active trachoma was reduced more in two villages with an intensive (and perhaps unsustainable) fly control program than in two nearby villages without fly control. This is quite encouraging, although the outcome was unmasked, and it is difficult to compare such small numbers of villages statistically. A well-designed fly control study involving multiple villages has recently finished in the Gambia and has shown encouraging results at 6 months (Emerson *et al.*, 2002).

Inclusion of face washing and environmental measures in a mathematical model.

If any hygiene or environmental were to offer a demonstrable effect, then mathematical models could be used to estimate how much less often mass antibiotic treatments could be used. In other words, if hygiene could reduce the prevalence of clinically active trachoma in children from 30% to 15%, then a program might be able to reduce mass antibiotic treatments from annual to every other year.

Trachoma clearly can disappear as economic conditions improve, even in the absence of a program dedicated to trachoma eradication. Trachoma disappeared from much of Western Europe before the widespread use of antibiotics (Taylor, 1999). Recent reports have indicated that this secular trend continues in other areas now affected by trachoma. One study found that active trachoma had decreased from 66% to 4% from 1959 to 1987 in a single Gambian village. As there had been only a modest antibiotic program from 1959-1961, the authors attributed the decline to trends outside of an active trachoma program. Similarly, another recent report found that the average prevalence of active trachoma in children in a district in Malawi had decreased from 37% to 14% from 1983 to 1999, in the absence of organized antibiotic distributions (Hoechsmann *et al.*, 2001; Dolin *et al.*, 1997). A report from Nepal revealed a dramatic decrease in prevalence of trachoma not attributable to a trachoma program, an approximately 20% decrease every 6 months (Jha *et al.*, 2002). It is difficult to determine the exact cause of this decline in trachoma, however many investigators attribute the decrease to socioeconomic factors including hygiene, sanitation, fly control, and water supply. If the decrease in Nepal, the Gambia, and Malawi could be reproduced by hygiene and environmental programs, then a mathematical model would clearly validate their use. However, modelling such an effect given current data would be premature.

Elimination of blinding trachoma before 2020

Even if infection were eliminated, many of the existing cases of scarring and trichiasis may still progress to blindness. A generation will have to pass before blindness from trachoma is eliminated. There has been little work on modelling how long incident blindness will continue even after chlamydial infection has been eliminated. While we can estimate the progression rates from scarring to trichiasis and from trichiasis to corneal opacity, no one knows how cicatricial trachoma will progress in the absence of recurrent chlamydial infections. As infection in a community is reduced, the progression of the existing pool of scarred conjunctivae to trichiasis and blindness may slow down. On the other hand, as ophthalmologists who have treated Stephens-Johnson syndrome know, it is possible for cicatricial conjunctival disease to progress even after the inciting agent has been removed. If persistent and repeated episodes of infection are eliminated, does scarring still progress at the same rate? How often will trichiasis recur after surgery in the absence of chlamydia?

A recent longitudinal study in the Gambia provides estimates of the progression rates from conjunctival scarring to trichiasis and from trichiasis to corneal opacity (Bowman *et al.*, 2001). Interestingly, these estimates are somewhat lower than those derived from data in Tanzania, where the prevalence of active, infectious trachoma is much higher (Munoz *et al.*, 1997; Munoz *et al.*, 1999). Direct comparison between the two studies is difficult, but this trend is encouraging. Although cicatricial trachoma is clearly progressing, even at the lower levels of infection found in the Gambia, it may be doing so at a slower rate than hyper-endemic areas of Tanzania. This would bode well for trachoma programs. Perhaps decreasing the infectious burden in a community will not only prevent children from ever developing scarring, but also slow down the progression of those with existing scarring to trichiasis and blinding corneal ulcers. At least two clinical trials are now addressing whether or not the absence of chlamydia can reduce the progression rate of cicatricial trachoma (personnel communications with Matthew Burton and Sheila West).

Trichiasis can clearly recur even after surgery. Studies have shown that the bilamellar tarsal rotation procedure is as good or better than several other procedures but still had a failure rate of about 20% over an average of 18 months (Reacher *et al.*, 1990; Reacher *et al.*, 1992). Longer follow-ups may reveal even more failure. Bowman et al. document 30% failure from surgeries performed at various times between 1986 and 1999 (Bowman *et al.*, 2001). In fact, their 12-year follow-up survey revealed trichiasis cases that went untreated, surgical cases in which trichiasis recurred, and surgical cases which successfully prevented trichiasis but not corneal opacities. In fact, a history of trichiasis surgery was actually associated with corneal opacity, perhaps because surgery was often performed too late, after opacities were already present.

Better estimates of long-term scarring progression rates and surgical failure rates, in both the presence and absence of chlamydial infections, should become available soon. With these rates, a mathematical model of how long it will take to eliminate blinding trachoma will be possible.

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