Trachoma: Ancient Scourge, Disease Elimination, and Future Research

Charles Knirsch, MD, MPH

Corresponding author
Charles Knirsch, MD, MPH
Clinical Research and Development, Pfizer Inc.,
and College of Physicians and Surgeons, Columbia University,
685 3rd Avenue, New York, NY 10017, USA.
E-mail: charles.knirsch@pfizer.com

Current Infectious Disease Reports 2007, **9:**21–28
Current Medicine Group LLC ISSN 1523-3847

Realistically, global elimination of trachoma could not have been considered until the maturation of innovation and public will that converged with the formation of both the Alliance for the Global Elimination of Trachoma by the year 2020 (GET2020) in 1997 and the public-private partnership, the International Trachoma Initiative (ITI) in 1998. Public-private partnerships are cross-sector collaborations that bring heterogeneous capabilities together to work on difficult problems for which the individual partners share common goals. The work of the ITI and partners to date demonstrates that the SAFE strategy reviewed in this article can work, and that it will revolutionize the control of blinding trachoma. Programs working to eliminate trachoma can achieve the GET2020 goals through expanded partnerships, commitment, and research on program integration into evolving health systems.

Introduction

Trachoma, recognized before Hippocrates and characterized by Galen, is the leading cause of infectious blindness in the world today [1]. In 1948, the founding of the World Health Organization (WHO), a United Nations agency devoted to healthcare, provided the opportunity for coordinated global health assessments and enhancements. Blinding trachoma, caused by repeated infections of ocular strains of *Chlamydia trachomatis*, was identified as a targeted priority at the time of the founding of WHO. Global elimination could not realistically be considered until innovation and public will matured and both converged in 1998 with a public-private partnership (PPP), the International Trachoma Initiative (ITI) (http//:www.trachoma.org). The initial 2-year assessment from the first two ITI-supported countries, Tanzania and Morocco, was presented in 2001 at the International Chlamydia Meetings [2]. Since that time, research has further defined issues relevant to field activities [3]. Speculations that secular trends may eliminate this disease of poverty are based on the correlation between improved socioeconomic conditions and the disappearance of the disease in Europe, the United States, and parts of Asia. However, a report on several proxies of poverty in a 5-year assessment of the progress of the Millennium Development Goals (http://www.unmillenniumproject.org/who/index.htm) suggested that secular improvements in socioeconomic conditions may take a long time. On the other hand, an opportunity exists now for broader alliances and further mobilization to eliminate trachoma. The research performed over the next decade to monitor progress and study the optimized delivery of services will be vital in order to achieve the goals of the Alliance for the Global Elimination of Trachoma by the year 2020 (GET2020).

Research and Institutional Organization

Trachoma is a disease caused by ocular strains of *C. trachomatis* [4]. It has been suggested that social organizations aligned across common interests are needed to catalyze action and provide global mobilization and coordination to address high-priority issues facing humanity [5]. PPPs are cross-sector collaborations designed to work on problems such as neglected diseases [6,7]. For example, a number of PPPs in health are focusing on developing new therapies, whereas others attend to the control of specific diseases [8]. From 1985 to 1998, the Edna McConnell Clark Foundation supported research on trachoma including studies on epidemiology and control, as well as immunologic research toward development of a vaccine.

Pfizer Inc. (New York, NY, USA) has been involved in treating trachoma since the 1950s, when one of the company's antibiotics was used to treat the disease. In the early 1990s, research demonstrated that Pfizer's antibiotic Zithromax (azithromycin) could treat trachoma in a single

Table 1. The International Trachoma Initiative program metrics for surgery and antibiotic components of the SAFE strategy for trachoma elimination; programs beginning before August 2006

Country	Inception	Trichiasis surgeries	Zithromax* treatments
Ethiopia	2002	61,908	5,991,390
Ghana	2001	3457	1,735,186
Mali	2000	19,573	8,005,955
Mauritania	2004	872	1,190,316
Morocco	1999	29,647	4,371,614
Nepal	2002	10,722	1,881,359
Niger	2002	24,158	6,286,376
Senegal	2004	1645	245,569
Tanzania	1999	16,852	8,041,237
Vietnam	2001	62,284	1,921,909
Egypt	2001	31	37,000
Sudan	2000	8052	1,359,823
Total		**239,201**	**41,067,734**

*Azithromycin, Pfizer Inc., New York, NY, USA.

oral dose [9–11]. Convergence of this pharmacodynamic innovation with the potential to have a humanitarian impact on people from some of the most disenfranchised parts of the world led to cross-sector collaboration. The challenge was to deliver the drug as part of a comprehensive public health program that combined treatment with prevention and strengthened the infrastructure necessary to have a sustained impact.

Confirmatory studies on a larger scale were performed in a PPP with ITI founding partners, Pfizer Inc. and the Clark Foundation, and with support from the U.S. National Institute of Allergy and Infectious Diseases. This led to a three-country trial of azithromycin in communities where trachoma was endemic [12]. The trial showed that a single dose of azithromycin was as effective as the standard treatment of 6 weeks of topical tetracycline ointment, a finding that had the potential to dramatically reduce trachoma prevalence in the community. This strategy was recommended by experts convened by WHO [13], presenting the Clark Foundation with an opportunity to move research findings into practice and offering Pfizer an opportunity to lead a large international disease elimination effort. In 1998, Pfizer and the McConnell Clark Foundation founded the ITI with the mission of advancing the WHO goal of eliminating blinding trachoma by the year 2020 [14]. Through the ITI, Pfizer is donating Zithromax, and along with ITI's other partners, the company provides technical and financial support to help eliminate this disease.

ITI-supported programming now covers 12 countries designated for priority by WHO. Program metrics on surgery and doses of Zithromax administered are outlined in Table 1. Trachoma control programs in Tanzania and Morocco were the first countries to target elimination with ITI assistance and are described in detail later in this review. Many other countries are now involved, each presenting a unique set of circumstances to address on the path to elimination. Notably, disease elimination in war-torn Sudan has been attempted by courageous people working in a partnership with the Atlanta-based Carter Centre. The results of two years of work show that clean faces can be improved and antibiotics can be delivered with a resulting decline in follicular inflammatory markers of trachoma [15•].

Implementation

The ITI's basic approach combines knowledge of trachoma control gained over the past 50 years as well as more recent studies of risk factors for disease, blindness, and the WHO-recommended SAFE strategy [16], which includes 1) S, the simplified lid surgery for the in-turned eyelashes that will halt pain and corneal damage [13,17]; 2) A, antibiotics for active infection using single-dose oral Zithromax; 3) F, clean faces especially in children through sustained behavior change [18]; 4) E, environmental improvement to increase access to water and sanitation [19].

The International Trachoma Initiative

The ITI is the lead international agency dedicated solely to the elimination of blinding trachoma. The ITI promotes the whole SAFE strategy and works with country programs to ensure that surgical services are available to patients with advanced disease, that face washing is promoted, and that communities are working to improve access to water and sanitation. To support national

Table 2. Trachoma prevalence by age in Tata, Morocco, by clinical examination in 1999 and 2000

Trachoma	0–4 years	5–9 years	10 years and older	Total
TF/TI, 1999	23.3%	26.8%	29.2%	28.0%
TF/TI, 2000	7.0%	4.9%	6.9%	6.5%
TT, 1999	0.0%	0.0%	3.3%	2.2%
TT, 2000	0.0%	0.0%	1.5%	1.0%

TF—trachomatous inflammation follicular; TI—trachomatous inflammation intense; TT—trachomatous trichiasis.

trachoma control efforts, the ITI provides technical assistance and targeted financial support and conducts health education, communications, and resource development activities. The ITI also coordinates the appropriate use of Zithromax for trachoma control. The Zithromax donation from Pfizer is a central element of the ITI's support for the SAFE strategy. The ITI builds on growing international momentum to support the GET2020 goal of eliminating this leading cause of preventable blindness by 2020, and maintains the highest scientific and management standards in the pursuit of its mission.

Tanzania and Morocco were the first countries to pilot the ITI elimination effort, because these countries possessed attributes that lent themselves to successful trachoma control programs. These attributes included viable healthcare systems with the organizational capacity and leadership necessary to implement the entire SAFE strategy. Tanzania and Morocco have active government and nongovernment organizations that are able to partner with the ITI, and their stable political systems and governments have demonstrated the interest and ability to eliminate trachoma using the SAFE strategy. The Ministry of Health in each ITI-supported country determines the regions to be targeted for trachoma control and adapts the four components of SAFE to its own country's conditions.

Tanzania

As the first country to join the ITI effort, Tanzania has proven to be a model nation for employing SAFE in the fight against trachoma in remote settings. Locally, the acronym SAFE has been translated to SAFI, the Kiswahili word for "good," "clean," or "nice." Tanzania has had a number of dedicated research teams working to assess progress. During its first phase, the Tanzania program emphasized the importance of building partnerships among government, nongovernment, and multilateral organizations to help implement SAFE and deliver Zithromax to targeted regions. The first partner organizations that worked on the Tanzania effort included the United Nations Children's Fund (UNICEF), Helen Keller International, Sight Savers International, Christoffel Blindenmission, World Vision, Tanzanian Christian Refugee Services, the Arusha Rotary Club, and the Tanzanian affiliate of Water Aid. Participating government ministries included Education and Culture; Water and Public Works; Community Development, Women, and Children; Natural Resources; and the National Environmental Council.

Community education strategies undertaken in Tanzania, which reached hundreds of thousands of children and adults, included an education campaign and pilot school curriculum. By 2001, more than 20 million people had heard radio health education messages (developed by the British Broadcasting Corporation World Service Trust for the ITI/Tanzania campaign) on facial hygiene and environmental improvement. Analysis showed that the health education campaign resulted in a greater awareness of the disease, and that knowledge of how to prevent trachoma had risen more than twofold among residents in the project area. Quite an accomplishment, given that most of the 36 villages across the first six districts for early-phase implementation are among the most remote in central Tanzania, and people live there on less than $1 per day.

Based on these first phases of success, the program has expanded to include SAFE advocacy in the 2006–2007 district health plans of 50 districts. ITI has supported baseline surveys in 10 additional districts, and senior leaders from the Tanzanian government, Pfizer, and ITI expressed support during visits to program sites to commemorate important milestones on World Sight Day.

Morocco

The ITI helped Morocco in its efforts to eliminate blinding trachoma by reinforcing and expanding trachoma control efforts already in place. Through its partnership with the ITI, Morocco completed a Zithromax distribution program, boosted surgery rates for trichiasis, and expanded its efforts to promote better hygiene practices among those at risk of infection. The ITI/Morocco Ministry of Health program conducted health education sessions on trachoma prevention. These sessions, provided from mobile vans and by video training in waiting rooms of clinics, reached more than a million people in the five provinces of Errachidia, Figuig, Ouarzazate, Zagora, and Tata. Economic development and the country's emphasis on public health had confined trachoma to these provinces bordering the desert. As shown in Table 2, rates of follicular and inflammatory disease following community treatment in Tata province declined after treatment, and this decline can remove the stimulus for inflammatory disease. Indicators of active disease have dropped dramatically after

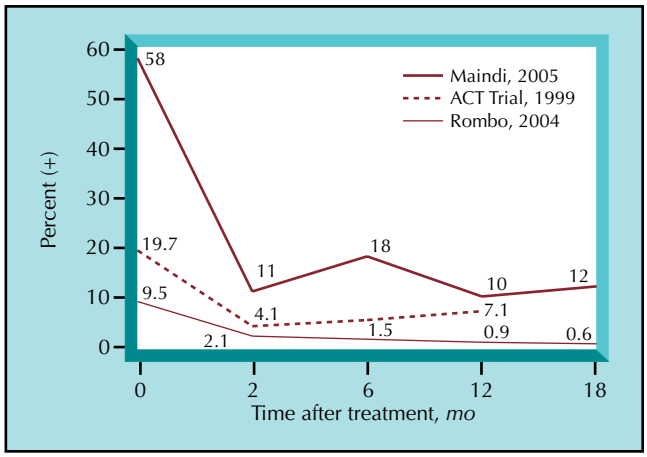

Figure 1. *Chlamydia trachomatous* infection measured by nucleic amplification tests from three sites in Tanzania, 1999–2005.

community treatment in the other provinces as well [20]. Other organizations working in partnership with the ITI and Morocco Ministry of Health include the Ministry of National Education, the National Office for Potable Water, Helen Keller International, UNICEF, and the Hassan II Foundation for Ophthalmology. The United States Agency for International Development (USAID) also provided support for health education and trachoma control.

In 2005, mass treatment of communities was completed, the Ministry of Health announced that the ultimate intervention goals were reached, and a phase of epidemiologic surveillance began to achieve certification of elimination. More research and particularly better tools may be needed to lead to WHO certification of elimination in countries, and ongoing monitoring will be needed to prevent reintroduction of infection.

Research Issues: Epidemiology

Programs to control trachoma have made significant progress over the last 50 years. Severe disease and blindness persist in the developing world where pockets of poverty, poor hygiene, and poor sanitation persist. Estimates of infectious causes of blindness have been updated with a survey of countries reporting to WHO. The number of people visually impaired due to trachoma is estimated to be 7.6 million, and an additional 84 million have active infections [21].

Since widespread surveys are not performed with diagnostic microbiology tools, rates of infection are not corroborated with an actual measure of infection and instead rely on clinical surrogates. When nucleic antigen diagnostic tests have been used, pockets of infection have been reported in previously unrecognized regions (eg, Guangxi, China) [22•]. Until we have wider-spread use of new technologies and sampling methodologies capable of definitively identifying the full burden of disease, we should accept limitations and uncertainty regarding the current measures. Comparisons over time of disease burden need to account for different reporting methods from the respective countries.

Impact and Predictors of Future Blindness

Trachoma causes blindness in the most productive years of a person's life and can ruin the economic well-being of entire families and communities. Women are two to three times more likely than men to be blinded by trachoma, largely due to repeated infection from the children in their care with high chlamydial loads in their eyes. A woman who becomes visually impaired because of the disease can no longer perform vital activities for her household such as bringing water to the home and cleaning and caring for the children. To fill this gap, an older daughter may be taken out of school to assume these responsibilities, forgoing her opportunity to break the cycle of poverty with a formal education. If many adults in a village become blind from trachoma, an entire community may be debilitated. Without intervention, trachoma perpetuates a continuous cycle of poverty, because overall vulnerability to the disease and its effects is passed from one generation to another.

It is believed that intensity and frequency of infection lead to scarring, and genetic polymorphisms may contribute to the host response to chlamydia [23]. It is not known to what degree either the community load of infection or percent of individuals infected in a community must be reduced to prevent future inflammation and scarring of individuals. Long-term follow-up is needed in regions where infection has been lowered incompletely, correlating rates of inflammation and scarring predictive of trichiasis.

Antibiotic Treatment

Topical sulfonamides were the first antibiotics used to treat conjunctivitis [24]. Topical tetracyclines were extensively studied by various investigators in Morocco to evaluate different dose frequencies and lengths of treatment. Controlled clinical trials in American Indians demonstrated the value of topical tetracyclines and the longer half life of oral sulfa preparations [25]. However, severe allergic reactions to sulfonamides and the difficult compliance of topical tetracyclines pointed out the need for an innovative compound with better attributes for treating communities with trachoma.

Mass treatment of communities is a blunt tool for the elimination of blinding trachoma; however, in hyperendemic areas, it is more cost-effective than case identification and treatment of infected individuals without overt signs of disease [26]. Researchers have performed a number of studies leading to greater understanding of the effect of community antibiotic intervention. Figure 1 shows the microbiologic results from studies performed in different regions of Tanzania: the ACT trial in 1999

[12]; Rombo trial in 2004 [27•]; and a trial in Maindi, Kongwa in 2005 [28•]. Many baseline characteristics of the communities were different including the baseline prevalence of disease, percent coverage of the community with antibiotic treatment, and the intensity of follow-up and evaluation for retreatment.

In the short term, infection levels can be reduced significantly even without 100% community coverage. In the absence of the more expensive environmental improvements and aggressive measures to treat infected migrants, though, it appears that infection rates rise after 6 months. A single round of treatment in Rombo with nearly 100% community coverage plus intermittent topical tetracycline treatment appeared to eliminate infection in one mesoendemic village [27•]. Infection was lowered by two rounds of mass treatment separated by more than 12 months, but the intervention was insufficient to sustain long-term declines in a hyperendemic village [28•]. The three weekly doses used in the ACT trial, although better than topical tetracycline, also do not completely prevent recurrence of infection at 12 months [12]. More data are required to establish the optimum frequency and time between treatments needed for communities to maximize resources when coverage does not approach 100%. Aggressive treatment of infected migrants is needed, especially in the setting of slow improvements in overall hygiene and water access, because infected migrants can lead to reinfection of a community [29•].

Data from Ethiopia are consistent with the data from Tanzania. A single dose of azithromycin lowered but did not prevent the return of infection in villages with treatment coverage below 90% [30]. The overall results from this trial led the authors to speculate about secular trends and possible beneficial herd effects on neighboring untreated villages. Remote populations present special problems in optimizing the SAFE strategy with high community antibiotic coverage rates, and full implementation of the individual components of SAFE may occur at different times. Experts at a meeting convened by WHO recommended a target of at least 80% community coverage [13], but this figure may be too low to prevent return of infection in hyperendemic regions. Even extraordinary effort by study teams in difficult-to-access geographic regions may only allow community coverage rates of antibiotic treatment approaching 90%. Further study is needed to evaluate shorter intervals between treatment (6 months) and programs to integrate trachoma control into heightened eye care in a district. Ministries of Health must consider the effect of more intense interventions on cost and resource use, because competing public health priorities exist.

It may be difficult to improve initial community coverage rates without revisiting interventions to raise the baseline treatment coverage. The treatment regimen used in the ACT study (three doses over a month) would still require intensive follow-up and intervention after the first round of treatment, given that infection begins to return at 12 months. Variations on the ACT intervention may incorporate new strategies of training regional health personnel to treat individuals with inflammatory eye disease. Trachoma control integrated into other health systems would be a mechanism to allow more frequent targeted treatment of infection or inflammatory disease upon diagnosis. Further study must evaluate optimal integration of vertical disease elimination programs into health systems that have many competing priorities with funding focus on AIDS, tuberculosis, and malaria [31•]. Communities must ultimately be taught targeted treatment, because even in areas thought to be free of trachoma, changes in migration can lead to a rapid return of infection. A case study from the Northern Territories of Australia is an example of a program that could be used as a reference and adapted in other regions [32].

Resistance to Target and Nontarget Organisms

In communities with access to antibiotics and baseline pneumococcal resistance, it has been shown that a single dose of azithromycin causes eradication of sensitive organisms, and the remaining pneumococcal organisms cultured from the nasopharynx have a resistant phenotype [33]. When surveillance studies were performed and correlated with clinical syndromes, short-term benefit in reducing diarrhea and fever was reported [34,35]. The largest surveillance study to date in a hyperendemic trachoma region with minimal access to antibiotics did not show an effect of mass community treatment with azithromycin on the prevalence of antibiotic-resistant *S. pneumoniae* [36].

Of greater importance is the effect of mass treatment on the target organism causing trachoma. *Chlamydia trachomatis* has not demonstrated a propensity to develop macrolide resistance in trachoma-endemic areas [37]. The occasional case report of suspected resistant chlamydia in patients in the developed world, where there is high antibiotic use per capita, shows the importance of continued surveillance in areas with recurrent disease [38].

Surgery and Zithromax Treatment

The S component of the SAFE strategy is designed to treat the consequences of years of inflammation that result in scarring and inturned eyelashes, which rub across the globe of the eye leading ultimately to corneal opacity. Trichiasis surgery is a technically simple procedure, yet relapse rates remain high, vary widely, and discourage people with trichiasis from having the operation. Results of studies evaluating azithromycin treatment augmenting trichiasis surgery showed a benefit in Ethiopia [39] but none in The Gambia [40]. It is unclear if this might be related to baseline prevalence

of chlamydia infection, which is high in Ethiopia and low in The Gambia. Other factors could include timing of administration of the antibiotic relative to surgery and factors related to the skill of the surgical personnel. Decreasing relapse rates following trichiasis surgery in the future will depend on enhanced training of surgeons and field-based studies continuously monitoring recurrence rates and offering feedback to surgeons.

Treating Children Younger than 6 Months

Younger children may have higher bacterial loads of *Chlamydia*. However, trachoma treatment recommendations have not included children younger than 6 months old, because safety and efficacy of azithromycin in this population has not been established. Academic reports of treatment success in young children are interesting, but additional data from studies in trachomatous regions are needed to help establish safety and efficacy for treatment of young children, given that these patients may represent an important reservoir of *Chlamydia* in a community.

Treating Pregnant Women

Reassuring data from a study in Rakai, Uganda, showed that when pregnant women were treated for genital ulcer disease in all trimesters with an azithromycin-containing regimen, their children had better birth outcomes including higher birth weights [41]. Guidelines recommend treating genital chlamydia disease in pregnant women with single-dose azithromycin [42], which supports community trachoma treatment when pregnant women are likely infected.

Knowledge of Achieved and Sustainable Elimination

Intense inflammatory signs of disease disappear soon after community infection rates are reduced after treatment, whereas the more easily measured follicular disease declines but does not disappear. Other organisms and irritants may be promoting the maintenance of follicles [43]. Rates of follicles in communities are currently a key indicator for suspecting trachoma and for determining retreatment of previous hyperendemic regions when the prevalence of follicles is above 10% in children ages 1 to 9 years old.

A diagnostic test in development provides results in the field and can supplement clinical exams. This point-of-care test has a sensitivity of 83.6% and specificity of 99.4%, which is better than the clinical exam in which presence of follicular trachoma had a 64.1% sensitivity and 80.2% specificity [44•]. Algorithms are needed to evaluate the point-of-care test in conjunction with clinical exam. A desired outcome would be to allow local programs to respond in real time to field survey data, thus focusing their efforts on high-prevalence areas. Much of the test's future use will depend on its availability and affordability. Lot quality assurance is a methodology that may help optimize and manage limited resources for surveillance work [45]. A field diagnostic may facilitate certification of trachoma elimination and enhance evaluations of suspected importation of infection. Further studies of field testing, scalability, and production costs are needed.

Chlamydia Vaccine

The first chlamydia vaccine trial was over 45 years ago and recent work is limited. An ideal chlamydia vaccine would prevent infections with both ocular and genital strains of disease. The natural and herd immunity would provide the community protection and reduce chlamydial loads contributing to inflammation, scarring, and blindness. A recent report has identified a common pan-neutralizing antigen, polymorphic membrane protein D, which may provide future leads to advance vaccine development [46].

Conclusions

PPPs, cross-sector collaborations bringing heterogeneous capabilities together to align across common goals, can address an issue that is beyond the scope of an individual partner. The number of global problems requiring urgent attention is vast. Bringing diverse organizations together requires leaders who have skill sets to facilitate collaboration and who can operate successfully in an age of polarized political positions. The political polemic seems to be a part of the human condition that unfortunately has not evolved much over the last three centuries [47]. Civil society creates the opportunity for people and organizations to speak their viewpoint honestly while respecting the contributions of parties willing to work on advancing the human condition.

With respect to efforts to eliminate trachoma, the work to date demonstrates not only that the SAFE strategy can work, but also that it will revolutionize the control of blinding trachoma. ITI partners are committed to innovation and improvement of the tools for trachoma control. Additional research will help refine the systems and interventions needed to eliminate this disease. Global economic conditions and poverty impact disease control even in the developed world [48]; a greater challenge exists to reduce poverty associated with the many diseases in the developing world that contribute disproportionately to morbidity and mortality [49]. Programs working on global elimination of trachoma cannot wait for improved socioeconomic conditions and must reach a new scale to achieve the GET2020 goals. This will require expanded partnerships, commitment, and research on program integration into evolving health systems.

Acknowledgments

The opinions and views expressed by the author in this article were developed through a decade of collaboration with talented and generous members of the chlamydia research community, colleagues working at the author's current institutional affiliations, and those at ITI and the wider trachoma elimination community. The views do not state official institutional positions and are expressed in the hope that they will stimulate further dialogue, research, and engagement in work towards the Millennium Development Goals and ultimately facilitate the elimination of blinding trachoma.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kumaresan J: **Can blinding trachoma be eliminated by 20/20?** *Eye* 2005, **19:**1067–1073.
2. Knirsch CA, Mecaskey J, Chami-Khazraji Y, et al.: **Trachoma elimination and a public private partnership: The International Trachoma Initiative (ITI).** In *Proceedings of the 10th International Symposium on Human Chlamydial Infections*. Edited by Schachter J, Christiansen G, Clarke IN, et al. San Francisco: International Chlamydia Symposium; 2002:485–494.
3. Mabey D: **Chlamydia infections.** In *Proceedings of the 11th International Symposium on Human Chlamydial Infections*. Edited by Chernesky M, Caldwell H, Christiansen G, et al. San Francisco: International Chlamydial Symposium; 2006:315–324.
4. Mabey D, Solomon A, Foster A: **Trachoma.** *Lancet* 2003, **362:** 223–229.
5. Rischard JF: *High Noon: Twenty Global Problems, Twenty Years to Solve Them*. New York: Basic Books; 2002.
6. Reich MR: **Public–private partnerships for public health.** *Nature* 2000, **6:**617–620.
7. Hripcsak G, Knirsch CA, Jain N, et al.: **A health information network for managing inner-city tuberculosis: bridging clinical care, public health, and home care.** *Comput Biomed Res* 1999 **32:**67–76.
8. Kumaresan JA, Mecaskey JW: **The global elimination of blinding trachoma: progress and promise.** *Am J Trop Med Hyg* 2003 **69(5 Suppl):**24–28.
9. Bailey RL, Arullendran P, Whittle HC, Mabey DC: **Randomised controlled trial of single-dose azithromycin in treatment of trachoma.** *Lancet* 1993, **342:**453–456.
10. Tabbara KF, Abu-el-Asrar A, al-Omar O, et al.: **Single-dose azithromycin in the treatment of trachoma. A randomized, controlled study.** *Ophthalmology* 1996, **103:**842–846.
11. Dawson CR, Schachter J, Sallam S, et al.: **A comparison of oral azithromycin with topical oxytetracycline/polymyxin for the treatment of trachoma in children.** *Clin Infect Dis* 1997, **24:**363–368.
12. Schachter J, West SK, Mabey D, et al.: **Azithromycin in control of trachoma.** *Lancet* 1999, **354:** 630–635.
13. World Health Organization: **Future approaches to trachoma control: report of a global scientific meeting, Geneva, 17-20 June, 1996.** http://whqlibdoc.who.int/hq/1996/WHO_PBL_96.56.pdf. Accessed October 10, 2006.
14. Dawson C, Schachter J: **Can blinding trachoma be eliminated worldwide?** *Arch Ophthalmol* 1999, **117:**974.
15.• Ngondi J, Onsarigo A, Matthews F, et al.: **Effect of 3 years of SAFE (surgery, antibiotics, facial cleanliness, and environmental change) strategy for trachoma control in southern Sudan: a cross-sectional study.** *Lancet* 2006, **368:**589–595.

Implementation of the SAFE strategy in war-torn Sudan.

16. Kuper H, Solomon AW, Buchan J, et al.: **A critical review of the SAFE strategy for the prevention of blinding trachoma.** *Lancet Infect Dis* 2003, **3:**372–381.
17. Reacher MH, Munoz B, Alghasany A, et al.: **A controlled trial of surgery for trachomatous trichiasis of the upper lid.** *Arch Ophthalmol* 1992, **110:**667–674.
18. West S, Munoz B, Lynch M, et al.: **Impact of face-washing on trachoma in Kongwa, Tanzania.** *Lancet* 1995, **345:**155–158.
19. Emerson PM, Cairncross S, Bailey RL, Mabey DC: **Review of the evidence base for the 'F' and 'E' components of the SAFE strategy for trachoma control.** *Trop Med Int Health* 2000, **5:**515–527.
20. Mecaskey JW, Knirsch CA, Kumaresan JA, Cook JA: **The possibility of eliminating blinding trachoma.** *Lancet Infect Dis* 2003, **3:**728–734.
21. Resnikoff S, Pascolini D, Etya'ale D, et al.: **Global data on visual impairment in the year 2002.** *Bull World Health Organ* 2004, **82:**844–851.
22.• Boost M, Cho P: **High incidence of trachoma in rural areas of Guangxi, China.** *Lancet Infect Dis* 2005, **5:**735–736.

Identification of trachoma in rural China.

23. Natividad A, Wilson J, Koch O, et al.: **Risk of trachomatous scarring and trichiasis in Gambians varies with SNP haplotypes at the interferon-gamma and interleukin-10 loc.** *Genes Immun* 2005, **6:**332–340.
24. Gradle H: **Discussion of Loe.: Sulfanilamide treatment of trachoma.** *JAMA* 1938, **111:**1371–1372.
25. Schachter J, Dawson CR: *Human Chlamydial Infections*. Littleton, MA: PSG Publishing Company; 1978.
26. Frick KD, Lietman TM, Holm SO, et al.: **Cost-effectiveness of trachoma control measures: comparing targeted household treatment and mass treatment of children.** *Bull World Health Organ* 2001, **79:**201–207.
27.• Solomon AW, Holland MJ, Alexander ND, et al.: **Mass treatment with single-dose azithromycin for trachoma.** *N Engl J Med* 2004, **351:**1962–1971.

Close to 100% community coverage with azithromycin leads to extinction of infection when ongoing cases of active disease are treated.

28.• West SK, Munoz B, Mkocha H, et al.: **Infection with Chlamydia trachomatis after mass treatment of a trachoma hyperendemic community in Tanzania: a longitudinal study.** *Lancet* 2005, **366:**1296–1300.

Eighty-six percent coverage of a community with azithromycin does not prevent infection returning after 18 months in the absence of a second round of treatment.

29.• Burton MJ, Holland MJ, Makalo P, et al.: **Re-emergence of Chlamydia trachomatis infection after mass antibiotic treatment of a trachoma-endemic Gambian community: a longitudinal study.** *Lancet* 2005, **365:**1321–1328.

Infection can be brought to communities by travel and migration.

30. Chidambaram JD, Alemayehu W, Melese M, et al.: **Effect of a single mass antibiotic distribution on the prevalence of infectious trachoma.** *JAMA* 2006, **295:**1142–1146.
31.• Hotez PJ, Molyneux DH, Fenwick A, et al.: **Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria.** *PLoS Med* 2006, **3(e102):**576–584.

Current morbidity and mortality numbers underestimate the true burden of neglected diseases.

32. Wright HR, Keeffe JE, Taylor HR: **Trachoma and the need for a coordinated community-wide response: a case-based study.** *PLoS Med* 2006, **3(e41):**186–190.
33. Leach AJ, Shelby-James TM, Mayo M, et al.: **A prospective study of the impact of community-based azithromycin treatment of trachoma on carriage and resistance of Streptococcus pneumoniae.** *Clin Infect Dis* 1997, **24:**356–362.

34. Fry AM, Jha HC, Lietman TM, et al.: **Adverse and beneficial secondary effects of mass treatment with azithromycin to eliminate blindness due to trachoma in Nepal.** *Clin Infect Dis* 2002, **35:**395–402.
35. Whitty CJ, Glasgow KW, Sadiq ST, et al.: **Impact of community-based mass treatment for trachoma with oral azithromycin on general morbidity in Gambian children.** *Pediatr Infect Dis J* 1999, **18:**955–958.
36. Batt SL, Charalambous BM, Solomon AW, et al.: **Impact of azithromycin administration for trachoma control on the carriage of antibiotic resistant Streptococcus pneumoniae.** *Antimicrob Agents Chemother* 2003, **47:**2765–2769.
37. Solomon AW, Mohammed Z, Massae PA, et al.: **Impact of mass distribution of azithromycin on the antibiotic susceptibilities of ocular Chlamydia trachomatis.** *Antimicrob Agents Chemother* 2005, **49:**4804–4806.
38. Somani J, Bhullar VB, Workowski KA, et al.: **Multiple drug-resistant Chlamydia trachomatis associated with clinical treatment failure.** *J Infect Dis* 2000, **181:**1421–1427.
39. West SK, West ES, Alemayehu W, et al.: **Single-dose azithromycin prevents trichiasis recurrence following surgery: randomized trial in Ethiopia.** *Arch Ophthalmol* 2006, **124:**309–314.
40. Burton MJ, Kinteh F, Jallow O, et al.: **A randomised controlled trial of azithromycin following surgery for trachomatous trichiasis in the Gambia.** *Br J Ophthalmol* 2005, **89:**1282–1288.
41. Gray RH, Wabwire-Mangen F, Kigozi G, et al.: **Randomized trial of presumptive sexually transmitted disease therapy during pregnancy in Rakai, Uganda.** *Am J Obstet Gynecol* 2001, **185:**1209–1217.
42. Workowski KA, Berman SM: **Sexually transmitted diseases treatment guidelines, 2006.** *MMWR Recomm Rep* 2006, **55(RR-11):**1–94.
43. Baral K, Osaki S, Shreshta B, et al.: **Reliability of clinical diagnosis in identifying infectious trachoma in a low-prevalence area of Nepal.** *Bull World Health Organ* 1999, **77:**461–466.
44.• Michel CE, Solomon AW, Magbanua JP, et al.: **Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative study.** *Lancet* 2006, **367:**1585–1590.
A new field-based diagnostic test to measure chlamydia could revolutionize community-level case identification.
45. Myatt M, Mai NP, Quynh NQ, et al.: **Using lot quality-assurance sampling and area sampling to identify priority areas for trachoma control: Viet Nam.** *Bull World Health Organ* 2005, **83:**756–763.
46. Crane DD, Carlson JH, Fischer ER, et al.: **Chlamydia trachomatis polymorphic membrane protein D is a species-common pan-neutralizing antigen.** *Proc Natl Acad Sci U S A* 2006, **103:**1894–1899.
47. Ellis JJ: *Founding Brothers: The Revolutionary Generation*. New York: Random House; 2000.
48. Barr RG, Diez-Roux AV, Knirsch CA, Pablos-Mendez A: **Neighborhood poverty and the resurgence of tuberculosis in New York City, 1984-1992.** *Am J Public Health* 2001, **91:**1487–1493.
49. Sachs J: *The End of Poverty*. New York: Penguin Books; 2005.