

# Toward the Elimination of Disease: the 2019 Weisenfeld Award Lecture

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The namesake for this award was an extraordinary woman who accomplished a great deal for the prevention and treatment of visual disability, despite (one might even say because of) her own struggles with retinitis pigmentosa starting at age 15. While losing her sight, she discovered that most funding for blindness went toward care rather than new treatments or research on pathogenesis. At age 25 she founded the forerunner of Fight for Sight with \$8, and at age 28 her compelling testimony before Congress created the forerunner of the National Eye Institute; by age 30 she received the Eleanor Roosevelt award for community service. Mildred Weisenfeld would no doubt be particularly pleased if we turn our attention to the ambitious goal of eliminating diseases.

This is an exciting time for ophthalmology and vision sciences because the World Health Organization (WHO) has targeted specific diseases for elimination and two of the seven are eye diseases: onchocerciasis or river blindness caused by the *Onchocerca volvulus* worm, and trachoma, a blinding conjunctivitis caused by repeated episodes of infection with the bacterium *Chlamydia trachomatis*. The National Eye Institute's audacious goal initiative to regenerate the retina ultimately is also aiming at eliminating vision loss from retinal degeneration.

In this article, a simple framework for the elimination of disease is presented that is applicable regardless of the pathogenesis or complexity of intervention. The outline for this discussion is as follows:

- Definition of Disease Elimination
- The Roadmap
  1. What: The pathogenesis of disease
  2. How: Creating an effective intervention
  3. Who: Determining the target population or case group
  4. Where: Identifying the location of the target population
  5. When: Determining when the elimination goal has been achieved
- Conclusions

I will use trachoma as an example of how milestones have been achieved along this proposed roadmap or pathway for elimination.

## DEFINITION OF DISEASE “ELIMINATION”

The WHO has provided definitions for various levels of “elimination” and benchmarks against which progress can be measured.<sup>1</sup> While clearly relevant for infectious diseases, there is obvious crossover to noncommunicable diseases as well. The most extreme elimination endpoint is extinction, defined as

eradication of the specific pathogen so that it no longer exists in nature or the laboratory. There is no specific disease or pathogen that we are aware of that has achieved extinction. The second most extreme is eradication, defined as the permanent reduction to zero of a specific pathogen, because of deliberate efforts, with no more risk of reintroduction. The pathogen may reside in laboratories. Smallpox and rinderpest (cattle plague) are the only infections that have been eradicated; polio, Guinea worm, and recently yaws have been added to the list of diseases targeted for eradication.

Consider the history of smallpox eradication, noteworthy for the gargantuan global effort to locate the last cases and their immediate contacts in a worldwide vaccination hunt. The last known case was in 1977 in Somalia, and WHO declared eradication 3 years later when no further cases were reported.<sup>2</sup> The virus exists now only in storage in laboratories where hopefully it will remain.

The programs for the other diseases targeted for eradication have made considerable progress. In 1986, the 20 countries with Guinea worm reported 3.5 million cases per year.<sup>3</sup> In 2018, there were just 28 cases in two countries. However, elimination efforts have been set back by the recent discovery of Guinea worm infections in animals. With 1040 cases reported in dogs in Chad, likely due to their preference for eating fish entrails, researchers are scrambling to determine the extent of veterinary sources of infection and the risk of transmission to humans. Polio similarly has had a remarkable success story. In the prevaccine era, the United States reported between 13,000 and 20,000 cases of polio paralyzes each year.<sup>4</sup> In 2018 there were only 33 known cases of wild-type 1 polio, 21 in Afghanistan and the remaining in Pakistan; types 2 and 3 have been eradicated. Unfortunately, the polio elimination program has also experienced a setback. The primary vaccine used is an attenuated live vaccine. In settings where large numbers of children remain unvaccinated, the attenuated virus can circulate and mutate, becoming virulent again and leading to cases of vaccine-derived paralyzes. A large number of such cases of polio paralysis have been reported in Democratic Republic of the Congo, Nigeria, The Philippines, and Papua New Guinea. The polio elimination program has declared the year 2023 for the eradication of both wild-type and vaccine-derived polio cases, but achieving this goal will demand the same commitment from governments and funders as the smallpox eradication program commanded to achieve its goal.

The other definitions of elimination include the elimination of transmission, or the reduction to zero, of the incidence of infection caused by a specific pathogen; this is the target for the





### 1. Trachoma Follicular <5% in children ages 1-9 years in district



### 2. Trichomatous Trichiasis <1/1,000 population in district

FIGURE 1. Two criteria for elimination of trachoma as a public health problem in each endemic district.

onchocerciasis elimination program. Finally, there is elimination of disease as a public health problem, defined by achievement of a set of measurable targets for a specific disease. This last definition is the goal for the trachoma elimination program. An example of “measurable targets” is illustrated by the two for trachoma elimination, reflective of the infectious and blinding sequelae of the disease (Fig. 1). First is the reduction of follicular trachoma (TF) to less than 5% among children ages 1 to 9 years in every endemic district; the second goal is the reduction to less than 1 per 1000 population of trichomatous trichiasis in every endemic districts. Countries that have achieved both goals in all formerly endemic districts can apply for validation of elimination.

Settings targets for elimination is a process that requires deep understanding of major elements of the disease. In the next section, I review a framework for elimination of disease.

## THE ROADMAP

### 1. What: the Pathogenesis of Disease

The first essential element is to understand the pathogenesis of the disease, and it is indeed appropriate that a great deal of our scientific funding goes toward this goal because the most effective interventions are built on this foundation. For example, in ancient times trachoma was not understood as having an infectious origin. Trachoma comes from the Greek word meaning roughness, relating to the appearance of the follicles on the conjunctiva, and early treatments could involve using tweezers to squeeze the follicles. Such approaches likely did more harm than good, damaging the conjunctiva and probably accelerating transmission.

Since the 1960s, the knowledge that trachoma was caused by infection with the intracellular bacterium *Chlamydia trachomatis* was firmly established.<sup>5</sup> We also know that repeated infections over the course of childhood are necessary to result in scarring of the conjunctiva and progression to entropion and trichiasis, the blinding complications. Furthermore, the life cycle of *Chlamydia* is well described, and it is clear that trachoma has no obligate vector: there is no fly or mosquito, or other host in the life cycle responsible for transmission. The disease is spread from person to person by contact with infected secretions in an environment that favors poor hygiene practices.<sup>6</sup>

Once the pathogenesis of blinding trachoma, caused by this cycle of repeated infections from ongoing transmission, was understood, interventions could be designed to interrupt the transmission cycle that leads to progressive scarring and trichiasis.

### 2. How: Creating an Effective Intervention

With an understanding of pathogenesis, the second essential element for disease elimination is the development of an intervention strategy that is effective at the individual and at the population level. Trachoma is again a good example of the importance of assessment of the effect of the interventions at both levels. For many years, the mainstay of trachoma control programs was topical tetracycline ointment because the cure rate in infected persons was good, up to 98%, and the ointment was inexpensive. In the early 1990s, a new antibiotic, azithromycin, appeared that was highly active against *Chlamydia* and had a long intracellular half-life. One dose of azithromycin, 20 mg/kg, had a similar cure rate, 98%, as topical tetracycline used twice daily for 4 to 6 weeks against *C. trachomatis*. However, trachoma control programs provided antibiotics to entire communities, a strategy known as mass drug administration or MDA. A head-to-head comparison of the safety and efficacy of these two drugs when provided to entire communities was essential.

The first community randomized trial, with provision of either topical tetracycline or oral azithromycin to every resident in their respective communities, was conducted in Tanzania, Egypt, and The Gambia.<sup>7</sup> One year following MDA, the community rates of infection were much lower in both arms in all three countries with no adverse events reported. This first community-based trial showed similar effectiveness when both drugs were provided in the framework of MDA, and both drugs proved equally safe.

Nonetheless, at a program level there was a clear preference for use of oral azithromycin because of the ease of implementation of MDA, a single dose, and of monitoring compliance by observing the dose ingestion. Equally important was the preference at the population level for azithromycin because the ointment is messy to apply, stings, and blurs vision on application.<sup>8</sup> In addition, azithromycin has ancillary benefits as well, with activity against organisms that cause diarrheal disease and upper respiratory infection,<sup>9,10</sup> not to mention sexually transmitted *Chlamydia*, which made the provision of azithromycin quite popular in communities and helped ensure high compliance rates. Once the manufacturer committed to the free donation of azithromycin to trachoma programs, the provision of MDA became a significant component of the strategy to achieve elimination.

Although azithromycin is effective at the individual and population level, it turned out not to be a “magic bullet” for rapid elimination of trachoma as was originally hoped. For hyperendemic districts, a couple of annual MDAs was not going to be sufficient to reduce the prevalence of trachoma to <5%.<sup>11</sup> Using data from several districts in the trachoma program in Tanzania, an epidemiologic model suggested it may take up to 10 years of annual dosing for hyperendemic communities to achieve this goal.<sup>12</sup>

The slow decline in trachoma in districts providing annual MDA was a conundrum, with several possible explanations put forward. Research showed the problem was not due to the development of resistance to azithromycin by ocular *C. trachomatis*.<sup>13</sup> There were suggestions that MDA provided annually may be insufficiently frequent to achieve accelerated decline. However, in a community randomized trial, increasing the frequency of MDA from annual to twice yearly did not result in a difference in infection rates in children after 3 years.<sup>14</sup> A critical concern was that the WHO had set a target of compliance with MDA at a level too low, 80% coverage. Since research had shown that noncompliance was not at random,<sup>15</sup> there was concern that infected persons were not being covered and could lead to reemergence following MDA. A crucial, community randomized trial in two countries, Tanzania

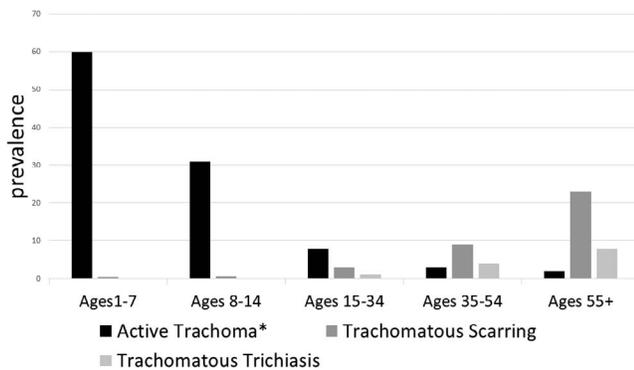


FIGURE 2. The age-specific prevalence of signs of trachoma in a hyperendemic district.<sup>21</sup> \*Active trachoma = TF and/or TI.

and Niger, demonstrated that increasing the compliance to 90% or greater did not accelerate the reduction in prevalence of infection or trachoma in children.<sup>16,17</sup>

The relatively slow decline in prevalence of trachoma was not the only concern for trachoma hyperendemic districts, but also the added uncertainty of what would happen once antibiotic pressure was removed. A study in 16 communities in Ethiopia that stopped MDA after infection was reduced to 2.6% observed a return of infection to 25% after 18 months.<sup>18</sup> Clearly, additional interventions were needed if programs were going to achieve a sustainable reduction of trachoma.

The identification of environmental factors associated with trachoma was critical to helping determine other possible strategies to add to the public health intervention. In one of the earliest studies, of almost 4000 Tanzanian children, two of the strongest factors associated with trachoma were households with low access to water and children with unclean faces.<sup>19</sup> Specifically, children whose faces had ocular and nasal secretions present were almost 2-fold likely to have trachoma. A subsequent randomized clinical trial tested the hypothesis that improving facial cleanliness with an intensive public health program would lead to a reduction in trachoma.<sup>20</sup> The intervention consisted of a series of community meetings and demonstrations over 6 weeks to improve face-washing practices. All villages were subsequently visited periodically to assess the prevalence of clean faces in the children. One year after the intervention, children were assessed for the presence of trachoma, and children in the intervention village had a lower risk of severe trachoma. A clean face at two or more follow-up visits was protective against trachoma (odds ratio = 0.58) and severe trachoma (odds ratio = 0.35).

These and other findings led to the inclusion of the “F” component in what is now the multifaceted intervention strategy adopted by trachoma elimination programs. With the acronym of “SAFE,” the strategy includes Surgery (S) to repair trichiasis, and a combination of Antibiotic mass distributions (A), improved Facial hygiene (F) and Environmental changes (E) to decrease transmission.

### 3. Who: Determining the Target Population or Case Group

The third essential element for elimination logically follows the “What” and “How.” To deploy an intervention, knowledge of the persons/populations who have the disease is critical. This question is especially relevant for diseases like trachoma where those afflicted do not routinely seek care and must be proactively identified (glaucoma is another similar example). Population-based prevalence surveys were needed and these demonstrated that active trachoma (TF and trachoma intense

[TI]) occurs primarily in young children, who are the community reservoir of infection, whilst scarring and trichiasis are mainly found in older adults and especially in women<sup>21</sup> (Fig. 2).

### 4. Where: Identifying the Location of the Target Population

In the case of genetic diseases, a concentration may be found in high-risk families. For glaucoma, persons of African descent or who claim ethnic identification as Latino are at high risk. The populations at risk of trachoma were known to be living in the poorest communities in the world, in countries with insufficient infrastructure to provide a hygienic environment. However, to deploy an intensive intervention, more precise mapping was needed. To address this need, The Global Trachoma Mapping Project was created with a truly audacious goal: using population-based surveys in every district suspected of having trachoma to determine where intervention was needed.<sup>22</sup> This massive effort required a global partnership with 53 countries, organizations, and donors and cost over £10,000,000. Ultimately, over 1500 districts were mapped and 2.6 million persons were examined by 550 trained teams.<sup>23</sup> The data were valuable because they identified not only districts in need of intervention, but also districts where trachoma was not a problem and resources could be deployed elsewhere. This project is the largest disease-mapping project ever conducted. And where is trachoma now? Figure 3, captured from the Global Trachoma Atlas,<sup>24</sup> currently shows where trachoma is still prevalent, in pockets in Latin America and the Middle East, but overwhelmingly in Africa.

### 5. When: Determining When the Elimination Goal Has Been Achieved

After the “what,” the “how,” and knowing “who” to target for intervention and “where” they are, the final essential element is the determination of when the disease has been eliminated. What criteria can be used to declare elimination success? For smallpox, success was the absence of any new case report 3 years after the last case, and elimination was announced on a global level.

For trachoma, the goal is country-by-country elimination. A country can declare elimination after every endemic district has satisfied the criteria for elimination as determined through two population-based surveys. The first survey documents that the twin goals (i.e., reduction in trichiasis cases to <1/1000 and TF to <5% in children ages 1–9 years) have been reached. MDA is stopped and the trachoma program must wait for at least 2 more years. At that point, a second population-based survey, surveillance survey, is conducted to prove there has been no reemergence of trachoma and there is the ongoing management of trichiasis. Once these twin surveys provide proof of elimination in every formerly endemic district, the country can apply to WHO for validation of elimination.

There are issues with this survey strategy as has been outlined. First, it relies on the attainment of a hard cutoff, less than 5%, without recognition that surveys are representational and there are confidence intervals around the estimates of prevalence. If the district prevalence of TF reemerges to 5.5% at the surveillance survey, is that truly a cause for concern, or is that estimate within the original WHO guidelines of powering a sample at 4% ± 2%?<sup>25</sup> Second, the outcome relies on the clinical assessment of TF. Clinical assessment of TF can be imprecise, particularly if graders have not seen trachoma for 2 years. When the prevalence is low, it is not infrequent that clinical graders tend to overcall the presence of trachoma during surveys. Moreover, other diseases can present with

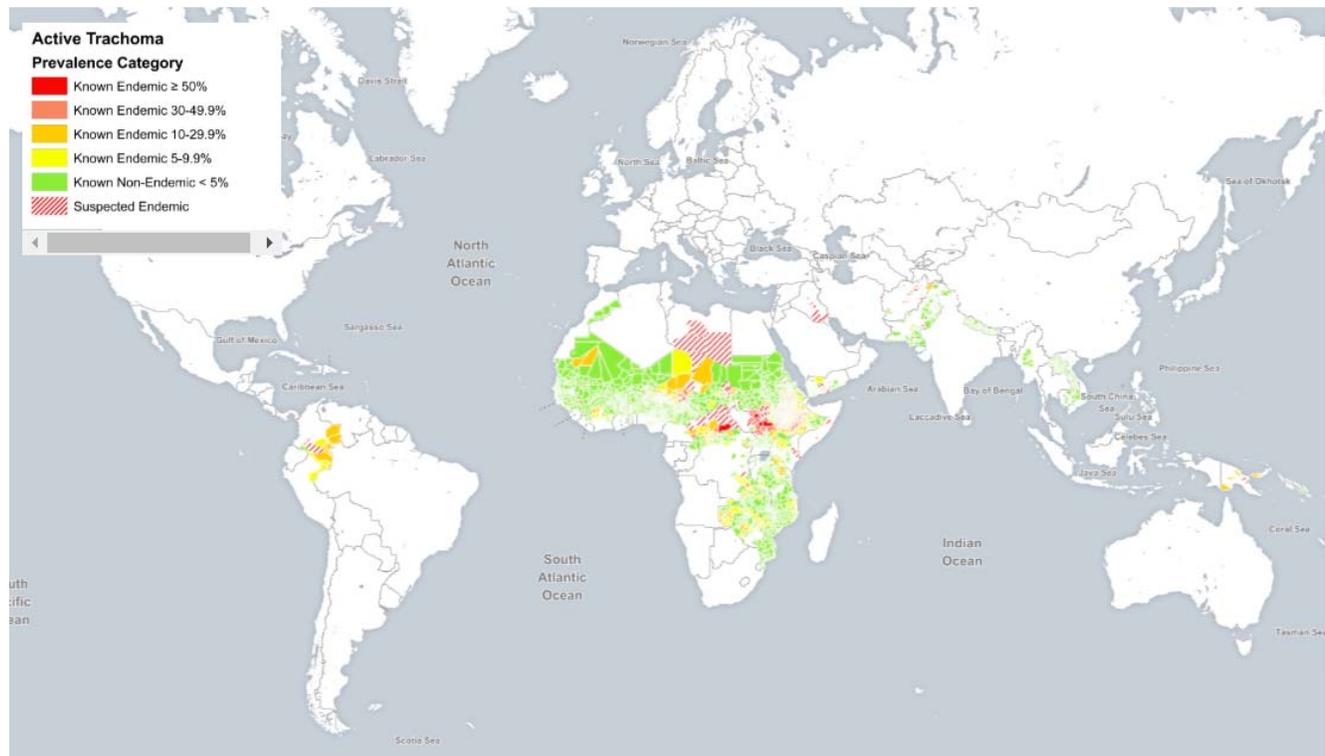


FIGURE 3. Global Trachoma Atlas as of September 24, 2019 (<http://www.trachomaatlas.org/>).<sup>24</sup>

follicles and be mistaken for trachoma. The stakes are high in such scenarios, as a country considers whether to remount a district program again and conduct another round of two surveys to document elimination.

To address this issue, research is ongoing on additional tools that may add valuable data for the determination of elimination. One such tool being considered is a test for presence of *C. trachomatis* DNA/RNA. An eye swab of the upper conjunctiva can be taken in the field and analyzed with highly sensitive and specific nucleic acid amplification tests. Currently, there is machinery for such testing that is robust, well validated, relatively inexpensive, and easy to use in field settings.<sup>26</sup> A test for infection is more precise than the assessment of clinical disease. However, these tests are expensive, and because they are so sensitive, they may detect a trivial load of infection, one not capable of transmission. The expense may be reduced if the specimens are pooled for analyses, but pooling results in loss of precision and particularly if there is a low load of infection, as would likely be the case in low-prevalence settings.

A more exciting prospect comes from research on a potential role for a serologic test to detect antibodies to *Chlamydia* antigens. Even as the prevalence of active infectious trachoma declines in children by age 7 to 9 years in endemic communities, there is a rise in the seropositivity by age.<sup>27</sup> In a steady state, this rise reflects cumulative exposure to *Chlamydia* infection, such that by age 7 years, the children have passed through the period of most intense transmission. Provided the test is reliable and the antibodies are relatively long lived, then cross-sectional data on seropositivity actually provide data on the history of exposure to trachoma in the population of children.

Hypothetically, with the introduction of antibiotics and facial hygiene/environmental programs into a district, transmission should be reduced and a lower than expected rate of seropositivity observed in those born during program activi-

ties. Ideally, if the program was effective after a certain period in lowering trachoma rates, the program could be stopped. The serologic survey after program stoppage should reveal low to no seropositivity in children born after the program ended if in fact there had been interruption of transmission.

The Centers for Disease Control and Prevention has developed such a test for antibodies to the antigen PGP3 from an ocular strain.<sup>27</sup> Using a dried blood spot obtained from a simple finger prick in the field, sera are eluted and tested by using a multiplex bead array or a simple ELISA. The test using the multiplex bead array platform is reliable, even when the same samples are tested months apart.<sup>28</sup>

However, there is evidence of seroreversion. In a longitudinal cohort of 2000 Tanzanian children in 50 communities followed up over a year, most children either retained their baseline antibody status or seroconverted. Seroreversion did occur, estimated at 6% in those seropositive at baseline.<sup>29</sup> The communities in that study were stratified according to the prevalence of trachoma and almost all the seroreversion occurred in communities that had no or very low rates of trachoma. Thus, it appears that in areas with low rates of trachoma, as would be the case where an elimination program had succeeded, the rate of seronegativity reflects both lack of exposure to trachoma and some rate of seroreversion.

This profile of seropositivity explains the data from the surveys carried out in Nepal, in districts that had stopped program activities between 2 and 10 years previously.<sup>30</sup> In all districts, the prevalence of trachoma was still far below 5%, with absence of infection. Seropositivity rates in children ages 1 to 9 years were also very low, around 2%. The age-specific prevalence of seropositivity was low, but with evidence of age-specific increase except in the district that stopped program activities 10 years ago. In that district, all the children in the survey were born after the trachoma program had stopped activities. The data suggest no ongoing transmission for at least 9 years in that district.

A more complex, dynamic scenario of changes in serostatus is emerging from formerly hyperendemic districts, where seroconversion and seroreversion appear to be ongoing. A static seropositivity rate over time may reflect ongoing transmission in some communities balanced by seroreversion in others where trachoma has been eliminated. A better understanding of how to use district serostatus as a marker for elimination is needed before this tool can be used with confidence.

In sum, for any disease for which an audacious goal of elimination has been declared, the determination of when the elimination goal has been achieved is liable to be complex and no doubt hotly debated, as is the case for trachoma.

## CONCLUSIONS

The trachoma story is one of ongoing success, albeit unlikely that global elimination will be achieved by the year 2020. Trachoma is no longer the second leading cause of blindness, and several countries have declared or are applying for validation of elimination. The current models of elimination suggest that the next decade may be a realistic target, providing conflict areas can be mapped and successful programs mounted.<sup>31</sup>

Trachoma is but an example of how an elimination roadmap can work. Whatever the disease, however sophisticated the intervention, the five steps provide a simple set of milestones that can guide the process toward elimination: *what* is the pathogenesis, *how* can we intervene, *who* is the target for the intervention and *where* are they, and *when* can we declare victory. This pathway requires a bench-to-bedside-to-population loop to be ultimately successful, and collaborative efforts among a host of disciplines must be supported to achieve what is the most audacious goal of all: elimination of disease.

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