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Mass Drug Administration for Trachoma:

How Long Is Not Long Enough?

by

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Master of Public Health

Hubert Department of Global Health

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Mass Drug Administration for Trachoma:

How Long Is Not Long Enough?

by

Violeta Jimenez

B.A., Columbia University, 2007

Thesis Committee Chair: Danny Haddad, MD, MPH

An abstract of

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Abstract

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Background: Blinding trachoma is targeted for elimination by 2020 through global intervention with the SAFE strategy. Although annual mass drug administration (MDA) to curb transmission is a cornerstone of this strategy, its effect on different baseline trachoma prevalence levels is poorly characterized. In order to achieve elimination goals, the World Health Organization (WHO) recommends an increase from a minimum of 3 treatment rounds to 5 prior to re-survey if prevalence exceeds 30%, these recommendations are based on expert opinion and grounded in a relatively small evidence base. Assessment of the effectiveness of these recommendations in practice is necessary to guide programming such that elimination by 2020 is ensured.

Methodology/Principal Findings: Data on prevalence and treatment was drawn from cross-sectional surveys in the International Trachoma Initiative's database and matched on location. Of three hundred and eighty one pairs representing baseline and follow-up surveys, MDA was applied in 186, while 113 represented a change in prevalence in the absence of MDA. Regression modeling showed that as baseline prevalence increased, the likelihood that treatment would reduce prevalence decreased significantly. Treatment rounds, skipped years, and length of time before and after treatment started were also significant predictors in

multivariate models. Logistic models predicted that even with perfect programmatic continuity, the probability of achieving successful reduction was low for high endemic areas, even with increasing rounds of treatment.

Conclusions:

In addition to treatment rounds, quality of treatment cycles and the context in which they occur are important predictors of trachoma prevalence reduction. In particular, care should be taken to ensure uninterrupted treatment. Programmatic recommendations must be strengthened to emphasize uninterrupted treatment, and greater effort must be made to change the underlying conditions in which transmission occurs. There are six years before the 2020 elimination deadline. There is a very low probability of achieving sufficient prevalence reduction in high endemic settings under the current treatment paradigm. More intense treatment strategies are needed in order to guarantee elimination by 2020.

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Chapter 1: Introduction

Context

Though trachoma has been afflicting humanity since before history was recorded, it is today classified as a neglected tropical disease, which affects the world's poorest and most marginalized. It is also a disease which many hope will soon be consigned to the history books, added to a very short list of diseases we expect will never again inflict suffering on the human race. To rid the world of this disease, which is the world's foremost cause of infectious blindness, would indeed be a monumental achievement.

It is useful to emphasize what "neglected" means in the context of trachoma. As advances in sanitation caused the disappearance of trachoma from most of the developed world, it is likely that in time trachoma will disappear on its own from many of the places where it is remains endemic. However, according to the most current estimates from the World Health Organization (WHO), about 21.4 million suffer from active trachoma, while 7 million have trichiasis, the more advanced scarring stage of the disease, and 1.2 million are irreversibly blind [1]. Moreover, significant benefit has been associated with averting the economic consequences of trachoma: in Africa, where much of the current trachoma cases remain, doing so would cause 0.19-0.38% growth in GDP for the continent as a whole [2]. Ignoring this burden of disease would indeed constitute neglect.

Fortunately, the global community has not ignored trachoma. The estimates above are in fact significantly reduced from those of the past. This is due in large part to the formation in 1997 of the Global Alliance for the Elimination of Trachoma by 2020 (GET2020), bolstered by the institution of a drug donation program through Pfizer. GET2020 was endorsed by the World Health Assembly one year later [3], and the SAFE strategy was adopted as a means for elimination of both active trachoma and trachomatous blindness. This consists of **S**urgery for trichiasis, **A**ntibiotics for active disease, **F**acial cleanliness, and **E**nvironmental improvements. Given the reduction observed from pre-GET2020 numbers—146 million active disease cases and 10.6 million trichiasis cases [4]—to the numbers cited above, implementation of the SAFE strategy has so far been quite effective. Now, six years from the elimination deadline, the essential question has become: is it effective enough?

Problem Statement

Elimination of blinding trachoma is a realistic possibility given its natural history and dynamics, in which blinding effects are not caused by a single infection. In fact, disease modeling has generated an estimate of at least 88 single episodes of infection required to cause the scarring that begins progression to blindness [5]. Thus, if infection can be suppressed below a crucial threshold, currently defined as 5% active trachoma prevalence, this should interrupt transmission and guarantee that no individual acquires enough repeated infections to progress to the severe stages of disease.

While all components of the SAFE strategy are crucial, the “A” component is being relied upon as a means of immediately breaking the cycle of trachoma infection and transmission. Despite a weight of evidence for azithromycin’s effectiveness at treating active infection in an individual, the best practices for treatment in the field remain unclear. These are complicated by a number of factors, which include uncertainties about everything from azithromycin’s field efficacy, to the capability of trachoma to persist in the environment, to diagnostic tools for assessing prevalence, and to the underlying factors that drive transmission and reinfection after treatment. Given these uncertainties, it is difficult to provide clear, evidence-based guidelines for operational questions such as how often MDA should take place, for how long, and at what coverage. At present, these questions are the subject of much debate in the literature. The WHO recommendations regarding them were decided by expert opinion, and have not been updated since 2006 [6].

Before now, sufficient evidence to address these issues has not been available. While various types of studies have investigated them, often with great rigor, such studies are by nature setting-specific, limiting the conclusions that may be drawn from them. Only recently have efforts to quantify and map trachoma prevalence worldwide rendered a standardized, extensive global database available [7]. Evaluation of this data, collected in the context of programmatic implementation, would allow evidence-based assessment and modification of current recommendations. It also allows assessment of progress towards the 2020 elimination goal, with the aim of application of better-targeted efforts to achieve this.

Purpose Statement

Thus, the purpose of this study is to investigate the effect of mass distribution of antibiotics, in the context of the SAFE strategy, on the prevalence of trachoma. We aim to answer the following questions through analysis of the International Trachoma Initiative's prevalence database:

- What is the overall relationship between baseline trachoma prevalence and prevalence after MDA, given the contribution of variables such as number of treatment rounds, skipped years of treatment, and coverage levels?
- Does the relationship between baseline and follow-up prevalence differ at different initial levels of endemicity?
- What is the overall pattern in trachoma prevalence over time in the absence of treatment?

Further, we will quantify these effects in programmatically useful terms, such as:

- What is the likelihood of reduction from one threshold prevalence level to a lower threshold level?
- What is the relative contribution of each of the above variables to reduction from one threshold level to a lower one?
- How many treatment rounds are required, at different baseline prevalence levels, to achieve reduction below 5%?

Answering these questions, and quantifying the effect of MDA in this dataset, will provide a means for assessment of the "A" component of the SAFE strategy in practice. This study can also inform evaluation of current progress towards GET2020 goals, as well as, crucially, informing the development of evidence-based practices to ensure achievement of these goals. Although many GET2020 partners have committed significant resources towards trachoma elimination, these resources are not unlimited, and appropriate resource targeting will facilitate swifter and more certain progress towards the ultimate intervention goals.

Chapter 2: Literature Review

A Brief History of Trachoma

Trachoma, like malaria, tuberculosis, or leprosy, has been part of human history since before it began to be recorded. The specific serotypes of *Chlamydia trachomatis* that infect the eye appear to have diverged from their ancestors around the same time that early hominids did, suggesting close coevolution [8]. But the blinding side effects of ocular chlamydial infection, which constitute what we today call trachoma, likely did not play a major role in human health until people began collecting in communities, thus facilitating better transmission of a multitude of infectious diseases. Then trachoma began to appear in records from a variety of civilizations. The earliest mention may be of an early Chinese emperor who apparently had surgery for trichiasis in 2700 BCE. Epilation forceps were found in excavations of Ur from 2000 BCE, and references to "opaque spots" on the eye and lashes growing towards the eye have been found in Mesopotamian tablets describing medicine [9]. Surgery and treatments were also described in Egyptian and Indian medical texts [10,11]. Plato and Aristotle, among others, theorized that trachoma is contagious. Later texts coined the term trachoma, which comes from *trachus,* Greek for rough; and the physician Galen came up with possibly the first grading scheme for trachoma progression, including the term trichiasis [12].

Trachoma became important in more recent history with the advent of large cities, poor sanitation, and various military campaigns, especially the Egyptian Campaign of 1798-1802. Poor conditions in army camps helped spread the infection, at that time called ophthalmia,

among the troops, who then brought it home to the civilian population. Probably as a result of the rapid spread of the disease, ophthalmology came to prominence as a specialty [13]. However, as trachoma began to be recognized as contagious, quarantine measures were taken to prevent its spread, perhaps the most notable being the United States' medical detention of immigrants with clinical signs of trachoma [14]. Sanitation also improved in many parts of the world, and as a result trachoma disappeared from most of the developed world by the 1950s, excepting some Native American communities in the U.S. Southwest and Aboriginal communities in Australia [15]. To this day it has a foothold in parts of Australia [16].

The presence of trachoma-endemic communities within nominally developed countries illustrates an important point about the disease: its presence today is associated with poverty and neglect. With sufficient time, development, and patience, it is likely that trachoma would disappear from most parts of the world on its own, along with the poverty and poor sanitation that facilitate its transmission. Allowing this would also require enormous negligence, since trachoma and its underlying causes account for a staggering amount of human suffering, which is not just costly but easily preventable. Notably, the improvements in water, sanitation, and hygiene which facilitate the disappearance of trachoma are an integral part of the Millennium Development Goals [17]. The reduction in disease related to their improvement will by no means be limited to trachoma.

The cost, both human and financial, of doing nothing has in fact been quantified: globally, trachoma remains the leading infectious cause of blindness. Today, 1.2 million people are

irreversibly blind from trachoma, while 7 million have trichiasis [1], an advanced stage of the disease, and 21.4 million suffer from active trachoma infection [2]. Fifty-three countries are known to be trachoma endemic, while six more are suspected endemic. In total, 229 million people are currently known to live in these endemic areas [1], thus putting them at risk for trachoma, while 320 million people are suspected to be at risk. These estimates, however, exclude several large countries for which data is incomplete: Brazil, China, and India. Given the sizes of their populations, determination of pockets of endemicity could significantly contribute to the at-risk population globally [2].

Estimates of the disability-adjusted life year (DALY) costs of trachoma vary substantially. The Global Burden of Disease (GBD) study, which originated the idea of DALYs, assessed trachoma to cost about 1 million DALYs each year in 1996, but information on the global burden of trachoma was limited at that time [18]. In 2000, while the GBD estimate had increased to 2.2 million DALYs, another assessment, which excluded years of life lost due to inadequate data, counted 3.6 annual DALYs due to trachoma [19]. Further analysis correlated this to productivity loss of $5.3 billion per year ($5.8 billion adjusted for inflation) [19]. Including trichiasis in this estimate increases it to $8 billion annually. If this loss could be averted, it would result in 0.19-0.38% growth in GDP for the continent of Africa as a whole [2]. Varying conclusions exist regarding the cost effectiveness of implementing interventions to avert the consequences of trachoma. Trichiasis surgery in particular, however, is found to be very cost effective [18,20].

Importantly, the statistics regarding trachoma have changed over time, and not only due to improved disease surveillance. Estimates from 2002-2003 counted between 40-84 million with active trachoma, and 7.6-8.2 million thought to have trichiasis [21,22]. Estimates of people living at risk for active trachoma have been reduced from 314 million in 2011 to 229 million in 2013 [1]. What has changed between then and now is due in large part to the 1997 establishment of GET2020, WHO Alliance for the Global Elimination of Trachoma by 2020 [4], which was endorsed by the World Health Assembly one year later [3]. These resolutions proposed the global elimination of trachoma by the year 2020 through the SAFE strategy: **S**urgery for trichiasis, **A**ntibiotics for active disease, **F**acial cleanliness, and **E**nvironmental improvements. Although now, six years from the deadline, it is clear that much work still remains, substantial global commitment and significant resources are available to address the particular challenges of the disease. In the minds of many, trachoma is already consigned to history.

Assessing Trachoma in an Individual

Clinical Progression of Disease

Trachoma is a keratoconjunctivitis—an inflammation of the cornea and conjunctiva of the eye—caused by recurrent infection of *Chlamydia trachomatis* serotypes A, B, Ba, and C. While recombination between these serovars and types D-K, which cause genital infection, has been documented, each set of subtypes appears to have functional genetic differences which cause them to selectively localize to the ocular or genital epithelial surfaces [23-26]. Ocular infection with serotypes D-K or L1-L3 (lymphgranuloma venereum) has been documented to cause non-

persistent adult inclusion conjunctivitis [27,28]. Genital infection with ocular subtypes also causes self-limiting infection [26].

C. trachomatis is an obligate intracellular bacterium, meaning it relies upon the metabolytes from other cells to replicate. It is able to switch between two functional forms: the elementary body, an inert extracellular form which can persist in the environment (the amount of time this form can persist in or on different media is unknown) and which is taken up very efficiently by epithelial cells; and the reticulate body, which becomes active once inside a host cell [28]. Reticulate bodies multiply within vacuole inclusions in the host cells during an exponential growth phase, culminating in re-differentiation into elementary bodies, which are released when the host cell lyses [27].

The process of infection, replication of reticulate bodies, and host cell lysis takes 3-4 days in tissue culture; this corresponds to an incubation period of 5-10 days in human hosts [27]. Some infections are sub-clinical, while in others symptoms include irritation, redness, discharge, and photophobia. The classic sign of active trachoma infection is called a tarsal follicle, a whitish-yellow raised spot on the conjunctiva of the upper eyelid. In more severe infections red papillae, thickened conjunctiva, and edema (swelling) of the eyelid may be noticeable [29].

A single infection, however, is self-limiting and does not constitute trachoma. The effects of repeated infections produce the damage associated with the disease [30]: as the follicles from repeated infection heal, they resolve into scarring which begins to change the architecture of

the eyelid. In the cicatricial stage of trachoma, this inflexible scar tissue thickens and contracts over a period of years such that the eyelids begin to turn in towards the eye (entropion). This eventually leads to the eyelashes rubbing against the globe of the eye, an intensely painful condition called trichiasis. In addition to the direct damage to the cornea caused by mechanical abrasion by the lashes, secondary infections are often introduced, and scarring of the glands of the eye may impede their function. As scars begin to cover the cornea, a condition known as corneal opacification, the trachoma sufferer eventually goes blind [28].

Importantly, autoimmune response is thought to contribute significantly to the progression of trachoma. Infection seems to result in a state of immune hypersensitivity, in which re-challenge with *C. trachomatis* results in a higher state of inflammation but faster infection clearance [28,31]. Thus, significantly higher titers of antibody have been found in individuals experiencing advanced stages of the disease [32]. The frequency of reinfection may play a role in mediating this response: in a cynomolgus monkey model, a single infection resolved after approximately 4 weeks, and while subsequent infection at 15 and 30 weeks produced mild clinical response (immune hypersensitivity having presumably abated), weekly reinfections caused the development of pannus and scarring similar to that seen in human disease [33]. Studies in humans have also demonstrated that individuals with constant, severe trachoma are more likely to develop scarring than those without (OR = 4.85, 95% CI = 2.05, 11.40) [34]. It seems that genetics play a role in determining susceptibility to persistent infection and disease sequelae [35]. Those possessing certain genotypes of Human Leucocyte Antigen (HLA) may be particularly prone to scarring [36].

Diagnosis and Grading of Trachoma

Clinical examination for trachoma is relatively simple, requiring only a simple magnifying loupe and good light. However, agreement is necessary among graders in order to ensure consistency in results. Given the long history of trachoma as a global public health concern, the existence of over ten distinct clinical grading systems [28] is not surprising. The simplified WHO system, which is currently in use, was developed in order to address the complexity and lack of reproducibility of the grading systems extant at that time [37]. One of its aims was facilitating increased use by "non-specialist health personnel working at the community level" [38] in mind. It uses five key signs to grade trachoma severity (see Figure 1):

- **Trachomatous inflammation, follicular (TF)** – defined as the presence of five or more follicles over 0.5mm on the upper tarsal conjunctiva.
- **Trachomatous inflammation, intense (TI)** – characterized by conjunctival thickening that obscures over half the normal blood vessels.
- **Trachomatous scarring (TS)** –characterized by visible scarring of the tarsal conjunctiva.
- **Trachomatous trichiasis (TT)** – at least one lash touches the eye.
- **Corneal opacity (CO)** – is visible over the pupil of the eye.

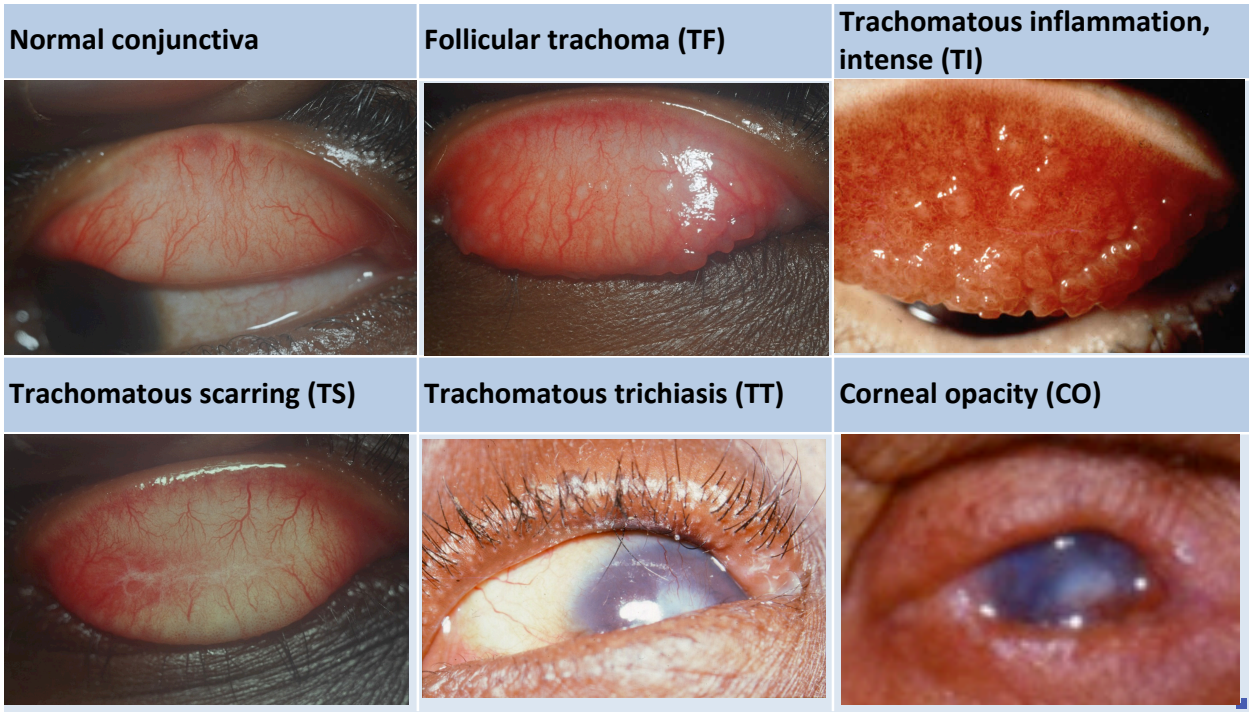

Figure 1. Clinical grading system for trachoma.

This system recommends the assessment of TF among children aged 1-9 as an indicator of active disease in a community, and assessment of TT among those among those 15 or older as a measure of severity of disease and surgical needs [6]. This is based in large part in the well-recognized gradient in infection as it relates to age, which will be discussed later.

This system has proven to be relatively easy to use and reproducible, with good inter- and intra-user agreement, which improves with further training [39,40]. Some concerns include its tendency to under-call mild TF [41], since it disregards less than five follicles, as well as those not present on the middle upper eyelid [27,28]. Some also worry that graders may not wish to ignore less than five follicles and may thus class mild infection as TF [28]. In fact, this lack of sensitivity was intentionally built into the system in order to prevent overdiagnosis of active

trachoma [38]. Additionally, the system disregards certain pathognomic signs of trachoma, such as Herbert's pits (which form as limbal follicles heal, and indicate past trachoma) and pannus (transient vascularization of the peripheral cornea) [29]. Despite these imperfections—which are to a certain degree inevitable in any grading system—the system is now considered standard for trachoma grading worldwide.

Importantly from an epidemiological standpoint, clinical signs of trachoma interact in a relatively complex way with actual presence of infection, regardless of the grading system used. In theory, infection is followed by an incubation period, then a period in which clinical signs and infection are both present, and then a recovery period in which infection has been cleared but clinical signs are still present [42]. The length and dynamics of each of these phases are, unfortunately, quite variable and not easy to quantify, though mathematical modeling fitted to cohort study data has estimated the following parameters: a median incubation period of about 17 days (95% CI = 11-28), median infection of 17 weeks (95% CI = 12-24), and median duration of infection without disease of 5 weeks (95% CI = 3-8) [43]. These parameters, even if accurate, vary based on a number of factors, especially age. The practical result that some individuals may be infected without showing clinical signs of infection, while others have clinical signs without actually being infected [44]. This has led to concerns that clinical signs may not always accurately estimate active disease, and thus the actual likelihood of transmission within a community [28,42,45].

Laboratory testing is thus often used in research to better understand what is signified by clinical grading. Unfortunately, many laboratory assays lack sensitivity and specificity, and present logistical challenges in under-resourced areas. By nature, various tests also answer different questions. Cell culture, for example, relies on the ability to culture *C. trachomatis* cells isolated from an individual sample, and its success at achieving a positive result thus depends on the level of bacteria present in a sample. While this was long considered a gold standard for laboratory assessment of trachoma, it is technically difficult and requires maintenance of a cold chain in order to ensure sample integrity [28]. Direct fluorescent antibody (DFA) tests, which measure the level of antibodies in sera, and thus the immune response of the individual, were found to have similar sensitivity but were technically easier to perform [46]. However, if immune response is suppressed for some reason, or at a low level due to the timeframe of the infection, DFA testing would be unlikely to yield a positive result.

The results of many tests also depend on infection level: a variety of studies have demonstrated that those with TI are more likely than those with TF to test positive using either cell culture, DFA, or PCR [42,47]. This is likely due to the fact that—as demonstrated by quantitative PCR, which measures the amount of chlamydial DNA in a sample—those with TI are on average more highly infected than those with TF [48]. Additionally, TI generally responds even more strongly to antibiotic treatment than does TF [49-51]. These findings have led to the suggestion by some that measuring TI as well as TF (rather than just TF) would increase the sensitivity of clinical grading as a measure for active infection [52,53]. It may also serve as a good proxy for sustained transmission after treatment [54].

Today, nucleic acid amplification tests (NAATs) are considered most sensitive and have a fairly high specificity, but the presence of nucleic acids from *C. trachomatis* does not necessarily imply the presence of active, replicating organisms or established (as opposed to transient) infection. There are a number of NAATs in use, all with slightly different sensitivities [55]. Given the uncertainty as to whether NAATs detect chlamydial infection of epidemiological significance, some have proposed that specific forms of NAAT testing, such as 16S rRNA amplification, should be used to measure infection [56,57]. This particular gene is expressed during differentiation of reticulate from elementary bodies during the process of host cell infection, and thus it is thought that 16S rRNA levels are a good proxy for measuring active infection [57]. Once again, though, sensitivity varies between rRNA-based NAATs. Some tests are found to have lower sensitivity (determine fewer positives) than DNA-based PCR, which is interpreted to mean that they are not detecting inactive or non-chlamydial nucleic acids [57]. Others are found to be more sensitive [58,59]. The major point of agreement is that these tests are useful, but must be modified in order to be practical and affordable for wide-scale field use.

So far, efforts to create a field assay for trachoma have met with varied success. A point-of-care (POC) dipstick immunoassay showed great promise during field testing in Tanzania. Using PCR testing as a gold standard for presence of infection, the POC assay showed a significantly better performance than clinical assessment for TF in terms of sensitivity, specificity, and positive predictive value [60]. However, subsequent testing in Senegal and The Gambia found great

variation in these values. In particular, at high temperatures and low humidities, in which conditions trachoma is most often found, the test specificity decreased significantly [61].

The lack of a diagnostic test or set of criteria that is sensitive, specific, cheap, and practical for field use—whether microbiological or clinical—is lamentable. Despite this, laboratory assays may play a role in the final determination of whether an area has successfully suppressed transmission, given that they are more specific (thus reliably differentiating negatives from positives) than is clinical grading in low-endemic settings. Some promising tests are being developed, including multiplex assays which would allow evaluation of trachoma alongside other diseases. Antibody level should correlate to level of past infection, such that a lower titer would be found in those who had experienced fewer infections. By evaluating antibody titers in young children, who usually bear the highest burden of active disease and thus serve as sentinels, one could determine whether or not transmission in a community was ongoing [62]. Such confirmatory testing may provide crucial information to allow program managers to decide whether a given area has reached its targets or requires further treatment [63].

Although laboratory tests are not presently in wide use in the field, it is important to take into account how the limitations of existing tools have shaped our understanding of trachoma. In high-prevalence settings, correspondence between active disease (TF) and some kind of NAAT testing (e.g. PCR or ligase chain reaction, LCR) tends to be highest. However, studies note that correlation between clinical and laboratory detection of infection even in hyperendemic communities is only “modest” [64], with a kappa value of 0.26-0.34. Latent Markov modeling,

which uses unobserved random variables to make inferences about diagnostic parameters, was applied to data from endemic communities in Tanzania and The Gambia and also demonstrated significant differences, varying by site, in the sensitivity, specificity, and positive predictive value of TF, TI, and DNA-PCR [65].

In hypoendemic communities, where clinical signs of trachoma without infection are more common [47,66], clinical grading may in particular overestimate prevalence [42]. This is also true after mass distribution of antibiotics: while community prevalence of ocular chlamydia, measured by PCR or a similar test, may fall dramatically after mass treatment, clinical signs decrease far less [67,68]. However, laboratory tests for trachoma, such as PCR or direct fluorescent antibody (DFA), also become less sensitive as trachoma prevalence drops [42,44].

Given the limited resources available to address trachoma, overestimation in these circumstances may lead to superfluous treatment and waste. Here especially, a better-performing test would be of great value to allow for a better understanding of the distribution of the disease, and thus better targeting of resources.

Assessing Trachoma Prevalence at the Community Level

Transmission and Risk Factors

Trachoma is highly contagious and focal, with various means of transmission whose relative importance varies by community. Direct transmission may occur during close contact, or through infectious secretions from the eyes or nose. Indirect transmission can also occur by

means of fomites such as clothing, bedding, or washcloths that have infectious secretions on them. The relative importance of true nasopharyngeal versus nasolacrimal secretions is unclear. Though chlamydial DNA was detectable in nasal secretions from about one third of children in a longitudinal study carried out in Tanzania and The Gambia, it is not clear whether these secretions were from nasal epithelial cells or from nasolacrimal drip [69]. There was a high correlation between positive ocular and positive nasal swabs. Children with active trachoma in this study were significantly more likely to have nasal discharge than those without active disease, and having positive nasal discharge was associated with more severe infection of longer duration [69]. Other studies also demonstrated significant association between ocular or nasal discharge and greater severity of active trachoma [70-72]. However, no correlation between infected nasal secretions and self reinfection has been demonstrated [73].

Generally, unclean faces are known to be strongly associated with active infection in a variety of studies [74,75]. A recent systematic review and meta-analysis of trachoma risk factors calculated that having a clean face was associated with reduced odds of TI or TI (OR 0.42, 95% CI 0.32–0.52), as well as infection with *C. trachomatis* (OR 0.67, 95% CI 0.55–0.78). Intermediate indicators such as lack of ocular or nasal discharge, soap use, towel use were also associated with significantly reduced odds of TF/TI and infection. Face-washing itself was also associated with reduced odds of clinical signs [76].

Regardless of the precise means of infection, modeling studies that assume a relationship between individual disease burden and likelihood of transmission demonstrate good

concordance with observed disease incidence [77]. Thus, “high-positive” individuals are likely to contribute significantly to the spread of disease within a community. Moreover, though clustering of trachoma has been shown at many levels—from the bedroom, to the household, to the village and sub-village—intra-household transmission seems to be the most important contributing factor to reinfection within a household as well as to generation of new infections in the community [78]. Essentially, households appear to act as incubators: most transmission occurs at the household level; and the larger the household size, the greater the relative contribution of the infected individual to overall community incidence of infection.

Finally, *Musca sorbens* flies, which are attracted to the eyes, act as important vectors of trachoma in certain areas. As might be expected, flies contribute little to transmission in areas where they are less common [79]. In areas where eye-seeking flies are common, other factors such as poor sanitation and personal hygiene are likely to increase their importance as vectors. Lack of a latrine in the compound has been shown to be a significant risk factor for active trachoma in several settings [71,80]. In the systematic review and meta-analysis referenced above, access to sanitation (defined as presence of a household latrine or toilet) was associated with lower odds of both clinical signs of disease (OR 0.85, 95% CI 0.75–0.95) and confirmed infection (OR 0.67, 95% CI 0.55–0.78) [76]. This association is presumably due to the fact that human feces are a preferred breeding medium for muscid flies [81]. Perhaps the best proof that flies contribute to transmission may be demonstrated by the success of fly control methods in reducing incidence of trachoma, as will be discussed later. Although few fly samples showed evidence of chlamydial DNA in a study in the Gambia, fly-eye contacts on children were

frequent: approximately 3 per 15 minutes [82]. Flies on eyes are associated with significantly increased odds of active infection in a variety of studies [72,83]. This suggests that where muscid flies are common, they can play a significant role in transmitting infection in a community.

Other risk factors for trachoma can be classed generally as personal or environmental. The relationship between younger age and active trachoma, as well as the possibility of greater genetic susceptibility to severe sequelae, has been mentioned above. However, the most significant personal risk factor is female sex. Although the ratio of trichiasis in women versus men appears to vary based on location, a variety of surveys and projections show that the burden of severe disease is more likely to fall, to varying degrees, on women [75,84,85]. Recently, meta-analysis of data from 12 countries quantified this: overall, the odds of trichiasis were significantly increased for women as opposed to men (OR 1.82, 95% CI 1.61—2.07) [86]. It is possible that there is some genetic basis for this, given the demonstrated association between trichiasis in a female patient and history of trichiasis in that woman's mother [87]. Some studies also show higher infection loads and longer duration of infection in girls [34]. However, generally this increased risk among women is thought to be due not to genetics but to their role of women as caretakers in most societies, which exposes them repeatedly to the individuals with highest infection burden in the community: infants and very young children.

In terms of environmental risk factors, climate and altitude are known to relate to trachoma prevalence. Modeling studies have confirmed the generally-accepted belief that trachoma is

more prevalent in hot, arid areas [88]. Geospatial modeling has also found negative correlation between rainfall and active trachoma [89]. Given this, trachoma is believed to show seasonal variation as well [90,91]. Altitude tends to show an inverse correlation to trachoma prevalence, with a variety of studies exhibiting a statistically significant reduction in trachoma prevalence with increase in altitude [92-94]. In some settings the reverse trend is observed, with increasing trachoma prevalence at higher altitudes [70]. It is likely that this gradient may be underpinned by interactions between fly density [92] and population density [93], which tend to increase at lower altitudes.

Additionally, trachoma is generally related to poor sanitation. Latrines are known to be a protective factor, as discussed. Attempts to parse other contributing risk factors have resulted in the conclusion that water use, consequent to water availability, affects spread and prevalence. Although the systematic review and meta-analysis did not find that either latrine use or location within 1km of a water source correlated with trachoma indicators, this lack of evidence may be to due to the difficulty of measuring the significant underlying exposure in each case. In other studies, household use of less water for washing children was found to be significantly associated with unclean faces, as well as with trachoma in a household [95]. Accessibility of the nearest water supply in terms of time and distance also tends to relate inversely to active trachoma prevalence, such that the longer the time required to collect water, the higher the prevalence per household [93,96]. Again, though water availability is important factor, it is mediated by water use. Attitudes towards face washing seem to have been modified by health education efforts in some areas, with the majority of women reporting

that they made decisions regarding household water use and washed their childrens' faces at least once a day [97].

The Interaction Between Age, Incidence, and Prevalence

As stated above, infection within a community is heterogeneous. In order to facilitate control attempts, it is therefore important to identify and target those members of a community who contribute most to transmission. In fact, the interaction between age, infection, and disease progression has been documented in a number of studies [31,47,98,99]. Especially in highly endemic communities, it appears that up to half of the burden of chlamydial DNA—representing active trachoma infection—may be in infants under 1 year of age [99]. In the same study, carried out in Tanzania, 90% of chlamydial DNA was found in children younger than 9 years. Once again, if one assumes that individual disease burden is strongly correlated to transmission, this means that the most highly infected individuals are also the most important contributors to disease transmission [77].

It is therefore noteworthy that infection and active disease seems to last longer in children. This is likely contingent on the development of incomplete immunity with age. While one is never completely immune, past infection lessens the likelihood and duration of active disease. This is evident in a study in The Gambia: although the percentage of subjects with any level of infection did not vary significantly with age, the prevalence of active disease declined starkly as age increased, indicating that infection is less likely to lead to active disease among older subjects [47]. Even among children aged 5-9 versus 1-4 years, older age was associated with

significantly reduced odds of having any signs of active trachoma, whether TF or TI (OR 0.7, 95% CI 0.6-0.8) [100].

Generally, the duration of disease phases varies by age. Survival analysis in a Gambian cohort indicated that median duration of active disease decreased from 36 weeks in children under four years to 7 weeks in those over fifteen; while median duration of infection varied between 15 weeks in under-fours and 7.6 weeks in over-fifteens [43]. Recovery time also decreased with age: whereas in subjects 0-4 years old, time to recovery was 13.2 weeks, this decreased to 5.3 weeks among subjects aged 4-14, and 1.7 weeks among those over 15 years old [31]. Stratifying by sex or village had no effect on these recovery times. Additionally, it is worth noting that while some of the lag between resolution of infection and resolution of clinical signs of trachoma likely relates to the sequelae of *C. trachomatis* infection, some of this lag time may be attributable to secondary infection or other irritation [101]. It is not clear whether either of these factors interacts with age.

While incidence and prevalence of active trachoma may decrease with age, the opposite relationship is seen with more advanced stages of disease. As age increases, the levels of TS, TT, and CO tend to increase in a community. Even in areas with low prevalence of infection, progression to trichiasis, and progression of severity of cicatricial disease, may be observed [101]. As described, the significant sequelae associated with blinding trachoma are related to repeated reinfections. In a model fitted to transmission parameters estimated from data from hypo- (<10% TF), meso- (10-20% TF), and hyperendemic settings (>20% TF), and using maximum

likelihood estimates for age-dependent prevalence of serious disease sequelae in a hyperendemic setting [102], it was estimated that at least 88 infections were required to cause TS, and 130 to cause TT [5]. Using modeling to create disease sequelae curves, these threshold numbers were estimated as at least 102 infections were required to cause TS, and at least 151 for TT [98]. While these numbers would vary given different model parameters, they give a general idea of the high level of incidence and prevalence necessary to generate severe disease in communities.

Assessing Trachoma Globally

Survey Methodology

Just as different methods for assessing trachoma in an individual vary in terms of what they measure, and to what standard, various survey methodologies provide diverse kinds and qualities of information. Although cross-sectional population-based prevalence surveys (PBPS) are considered the gold standard for trachoma prevalence assessment [7,52], surveys vary in terms of sampling methods (e.g. cluster random sampling, systematic, simple random), sampling units (e.g. administrative level), location of survey (school- or community-based), and populations sampled (e.g. school-aged children, children 1-9 years). The use of techniques such as cluster random sampling (CRS) and probability proportional to size (PPS) methods allow sampling of a fixed number of geographically-defined clusters, such that surveying entire populations is unnecessary. These techniques can also be used to accurately assess several indicators of trachoma at once (usually TF and TT). Of concern is that not all surveyers adjust for

design effect—which necessitates a change in variance due to correlation between clusters—and few provide precision estimates related to their prevalence figures.

CRS, the sampling method endorsed by WHO, consists of identification of population clusters of similar sizes (PPS) within suspected endemic districts. Clusters are then randomly selected for surveying, such that the total sample size is sufficient to estimate population prevalence [6]. Households are selected next, either at random or using household lists to inform multistage sampling within clusters. WHO recommends that in addition to collecting data on TF and TT prevalence, surveyers should collect data on water and latrine access to facilitate targeted application of the SAFE strategy [6]. The use of community-based sampling for children with active trachoma is important: analysis of data from four countries demonstrates that by using schools as convenience sampling sites, surveyers may inadvertently underestimate trachoma prevalence [103]. The exception to this rule is likely to be in areas where school attendance is high and prevalence peaks among school-aged children [104].

Another frequently-used survey method is Trachoma Rapid Assessment (TRA), which was developed as a means to quickly and relatively cheaply determining whether trachoma prevalence is high enough to warrant follow-up, and which strategies might be most effective [105]. It uses convenience samples in order to highlight and rank areas needing intervention, and thus it may be particularly useful where trachoma prevalence is expected to be very heterogeneous [106]. By nature, it is unable to measure prevalence, and trials of TRA methodology have exhibited low consistency and accuracy [107]. Often TRA must be followed

by PBPS in order to better understand where and how to implement interventions [108]. In particular, TRA may overestimate active trachoma [109].

Lot-quality assurance sampling (LQAS) methods, such as Acceptance Sampling Trachoma Rapid Assessment (ASTRA), have also grown somewhat in popularity, as they usually require less time and investment of resources than PBPS. In this method, sampling is carried out until a threshold number of cases or a maximum sample size is reached, and then a given area is assigned according to a pre-determined classification method and "acceptable" levels of error. In field trials, ASTRA showed good sensitivity in classifying community prevalence of active trachoma [110], and this method allows for finer spatial resolution than multistage cluster sampling [104]. Although in theory, ASTRA may be adjusted to provide prevalence estimates by sampling until maximum sample size is reached (rather than a case threshold), recent comparison of LQAS to CRS demonstrated lack of agreement in terms of coverage estimates, casting doubt on the utility of ASTRA in practice [111]. Even if adjustments can be performed on ASTRA results, estimates may still be biased due to the small sample sizes used. Unbiased sampling would also be next to impossible in areas where good population censuses are not extant [112]. Additionally, ASTRA guidelines presently recommend assessing children 2-5 years old for active trachoma and do not include assessment of TT; this too would have to be modified in order to provide data comparable to the standard estimates recommended by WHO.

In sum, PBPS using CRS methodology remains the recommended technique for assessment of trachoma prevalence. The higher costs associated with PBPS are foreseeable and to a certain

extent reducible [113]. However, many suggest that current practices could be improved upon [52,53]. Consistently providing estimates of design effect and precision would ensure greater understanding of the study design used and its results. Surveys ought to be carried out using WHO standards, which recommend that the district be taken as the administrative implementation unit, 1-9 years as the acceptable age range for estimation of active trachoma, and over 15 years as the age range for estimation of trichiasis. In addition to reporting TF, reporting TI may improve understanding of the susceptibility of the community to intervention. Given the age-dependence of prevalence, and the sometimes-poor correlation between TF and actual presence of infection, these recommendations could improve our understanding of the disease burden of trachoma at the population level.

The Size of the Problem

By use of standardized, methodologically robust techniques to assess population prevalence of trachoma, we can achieve understanding of trachoma globally. This became a priority especially upon establishment of GET2020 and trachoma elimination goals, as allocation of limited resources requires grasp of the size of the problem needing to be addressed [88,89,114]. This need led to the development of the Global Trachoma Mapping Project (GTMP), which actively aggregates, standardizes, and updates available data on trachoma prevalence and indicators in map form and provides open-source access to these data through the Global Atlas of Trachoma (GAT) [7].

The first stage of the atlas, expected to be completed by March 2015, entails mapping trachoma baseline prevalence worldwide. As of February 2014, the mapping target consists of 1746 districts in 33 countries have been mapped; 952 of these surveys took place in the last 14 months. Now, 792 districts in 21 countries remain to be mapped, and plans for mapping are unconfirmed in eight countries, some due to internal conflicts [115]. Although scale-up of mapping efforts has been rapid, the urgency of carrying out baseline assessments in these countries cannot be overestimated. Six years remain until the 2020 deadline, and time to elimination depends on a number of factors. Furthermore, resources to control trachoma are not unlimited, and addressing the potential burden in suspected areas necessitates reallocation.

As there is great heterogeneity in trachoma at the community level, there is also heterogeneity in the distribution of trachoma globally. High burden countries—such as Ethiopia, Niger, Nigeria, and Uganda—represent a disproportionate amount of total global prevalence (see Figure 2). In total, the endemic populations in 14 high burden countries represent 83% of remaining TF burden, and 71% of the remaining TT burden [2]. On the other hand, some countries have already reported achievement of their ultimate intervention goals (UIGs): Ghana, Iran, Morocco, Myanmar, and Oman have achieved all UIGs related to interruption of active disease as well as surgical needs. Others, such as Algeria, The Gambia, Libya, Mexico, and Vietnam, have partially achieved these or are waiting for certification [1]. While cause for celebration, this data, too, can be used to inform elimination efforts in other areas.

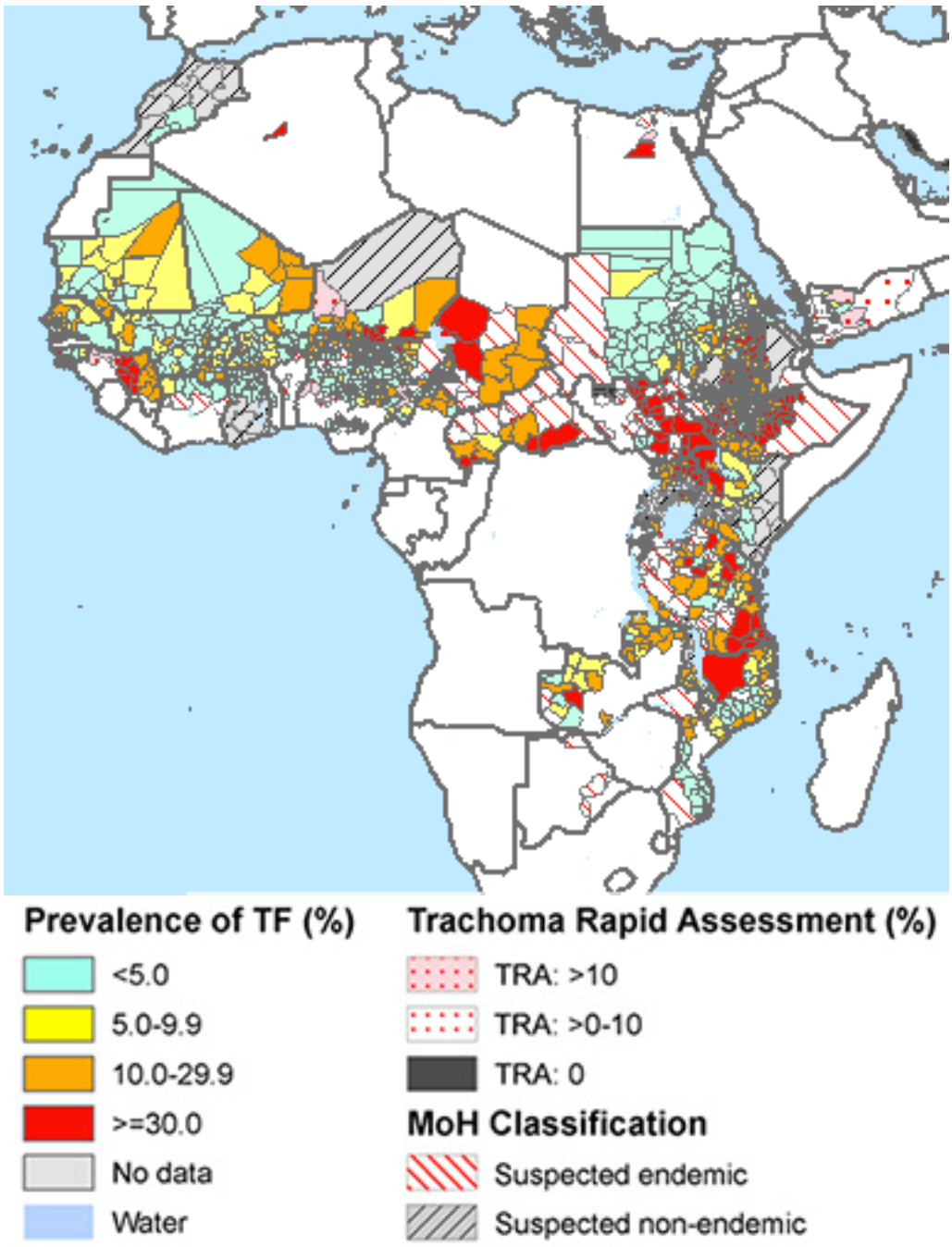

Figure 2. Current prevalence of active trachoma (TF) in Africa.

Addressing Trachoma Globally: The SAFE Strategy

The SAFE strategy (**S**urgery, **A**ntibiotics distribution, **F**acial cleanliness, and **E**nvironmental improvements) is the cornerstone of trachoma elimination efforts. Elimination of blinding trachoma is to be achieved primarily through reduction of active trachoma prevalence to below 5%, such that no individual accrues sufficient lifetime infections to reach the blinding end stages of the disease [5]. The idea that reduction below a certain threshold beyond which transmission cannot sustain itself, is known in population biology as the Allee effect and supported by theoretical and empirical evidence regarding trachoma (to be discussed later in this section) [68,116,117]. Reduction of active trachoma will ensure that generations to come do not suffer blindness. However, the GET2020 goals are unique in that they address present morbidity as well: they call for surgical interventions to reduce TT prevalence to below 0.1% [4].

The SAFE strategy has been in use for almost 20 years, and over that period of time a variety of studies have demonstrated its efficacy in reducing prevalence of trachoma [49,118,119]. Lack of success has been attributable to failing to follow WHO recommendations regarding study design and SAFE implementation [120,121], or failing to apply each component sensitively according to the needs of a specific community or region [16]. Each component was chosen for its efficacy towards the end goal of elimination. Each, properly executed, is vital to trachoma elimination.

Surgery

A variety of options exist to delay or prevent complications of advanced trachoma [122-124]. Informal methods attempt to address the irritation and trauma caused by rubbing of the lashes against the cornea include epilation and binding or taping the eyes to keep them open. Epilation, or plucking of the lashes, is common among those with TT, and likely has been used for millennia [9,12]. Cross-sectional evidence from Ethiopia shows that epilated eyes are significantly less likely to have CO if inturning (entropion) is moderate or severe, but no association is evident when entropion is mild [125]. However, in a small randomized trial in China, patients treated with a sticky plaster which pulls the eyelids away from the eyeball were significantly less likely than patients with a single round of epilation to show disease progression at 6 months [126].

Although non-surgical alternatives may be helpful, surgical methods can actively address entropion itself. Bilamellar tarsal rotation (BLTR) has been found to best resolve the effects of trichiasis and improve visual acuity [124], and thus is recommended by WHO. Although surgery improves vision and increases perceived comfort [127], post-surgical recurrence of trichiasis is common [128-131]. This likely depends on a number of factors, from initial severity of disease to the quality of the surgery and post-operative infection. Attempts to correct for infection have met with mixed success, with provision of azithromycin being associated with reduced recurrence in two studies [132,133], but with increased recurrence in a third [134]. But it is not clear whether, in fact, reinfection with *C. trachomatis* plays a large role in trichiasis recurrence. While recurrence was associated with chlamydial infection in one Tanzianian cohort [135],

other studies have found chlamydial infection to be relatively infrequent in trichiasis patients. About 1% of patients in Gambian cohort with trichiasis had *C. trachomatis* infection, but 23% had other bacterial infections [101]. Similarly, in a Tanzanian cohort in an endemic area, just 6% were currently infected with *C. trachomatis* [130]. However, as conjunctival inflammation—likely consequent to some kind of infection—is associated with more severe stages of disease, addressing it may help reduce trichiasis recurrence.

Also of concern is that surgical uptake rates tend to be low due to factors like inconvenience, cost of travel, and fear of surgery. This can be addressed in part by conducting surgery at the village level, which saves time and money and reduces patient fear. A trial in the Gambia found over 20% higher uptake when surgeries were conducted in villages rather than at health centers [136]. Promotion of surgery by community leaders, especially school teachers, may help educate people about the benefits of surgery and reduce their fear [137]. Studies show that nurses can be trained to perform BLTR surgery for trichiasis as well as ophthalmologists, with no significant difference in probability of recurrence at 6-month followup [138]. With adequate support, outreach, and supervision, it is possible to ensure quality of surgical care, productivity, and retention of trained surgeons [129,139,140].

Support and encouragement of existing surgeons is crucial in addressing the global backlog of needed trichiasis surgeries. At the rate of about 170,000 surgeries reported worldwide in 2012 (over a fourfold increase from 2005) [1], all the needed surgeries would not conclude until

2032. Clearly, scaleup is necessary in order to meet this portion of the GET2020 goals [2], which addresses the chronic blinding stages of the disease.

Face-Washing and Health Education

As described, poor facial hygiene is well-known to be associated with active trachoma. In particular, it is thought that unclean faces—generally defined as faces with visible evidence of ocular or nasal discharge [83,141]–promote transmission of trachoma, whether through direct transmission, indirect spread via fomites, or transmission by fly vectors. Despite the presence of many studies showing association between active trachoma and unclean faces [71,72,74,80,95,142], only a few demonstrate efficacy of face-washing through randomization [141].

While in an Australian trial there was no significant difference in development of active trachoma when comparing groups randomized to no treatment and face-washing, a marginal protective effect was found among those randomized to eye washing and tetracycline eye drops, versus just eye drops [143]. Similarly, odds of active trachoma were reduced in three pairs of villages randomized to antibiotic treatment plus face-washing versus antibiotics alone, though this effect was not statistically significant. The same study did find a statistically significant reduction in the odds of more severe active trachoma (defined as TI) [144]. However, both studies were subject to some confounding due to varying baseline prevalences and lack of diagnostic standardization between graders [143], as well as potential unintended uptake of face-washing in control villages [144]. Moreover, the short time frame in which these studies

were conducted may not be sufficient to demonstrate the effect of an intervention meant to slow disease transmission [141].

Generalized health education programs, which tend to focus on latrine use, sanitation and garbage, and personal hygiene (including face-washing) have also shown mixed effects. While health education showed a modest decrease in TF incidence as compared to no intervention, addition of health education to antibiotic provision did not demonstrate significant impact. The authors concluded that "the efficacy of [health education] depends essentially on the capacity of the community to modify its hygiene behavior" [145]. Provision of clean water interventions and health education compared to no intervention also showed no change in trachoma incidence, and a decrease in prevalence which was not statistically significant. However, in both the intervention and control group, tetracycline ointment was provided to children showing signs of trachoma. This may have confounded a relatively modest effect from the intervention [146].

The lack of randomized trials showing direct benefit of face-washing is partly due to the difficulty of separating this component of the SAFE strategy from the others to which it is related. Some observational studies attempt to parse the effects of each component, though their conclusions are limited by study design. For example, investigators in Sudan assessed the independent effects of the A, F, and E components of the SAFE strategy and found that clean face and washing childrens' faces three or more times daily were associated with significantly reduced odds of TI [147]. In Ethiopia, clean face was associated with significantly reduced signs

of TF or TI [148]. As discussed above, meta-analysis demonstrated that a clean face was associated with significantly reduced odds, across 25 studies, of active disease and infection. This was true for other facial hygiene indicators, such as nasal and ocular discharge, frequency of washing, and washing with soap and towels [76].

Other difficulties of assessing the independent effects of face-washing include the fact that increases in health education and promotion regarding hygiene may occur without being well-reported or standardized. Also, given the proven immediate benefit of antibiotic treatment (to be discussed) and the approaching 2020 elimination goals, many would consider it unethical and impractical to conduct a strictly controlled trial in which face-washing or health education was provided separately from other interventions. As non-chlamydial bacteria may contribute to active trachoma in low-prevalence settings [149], it is especially important not to neglect the promotion of basic hygiene measures which can prevent unnecessary morbidity even when *C. trachomatis* itself is not present.

Finally, as discussed previously, attitudes and practices regarding face-washing are also subject to empowerment of women as decision makers in the household [97], as well as to water availability and use.

Environmental Interventions

It is likewise well-known that trachoma prevalence declines with the development of water and sanitation measures. This is evident from the historical disappearance of trachoma from most

parts of the developed world by the mid-twentieth century, but has also been demonstrated in developing countries in the recent past. In the Gambia, for example, comparison of cluster randomized sampling results from 1986 and 1996 demonstrated a reduction in active trachoma prevalence of 54% [150]. No specific trachoma control program was implemented, but education about trachoma and face-washing was reportedly widespread, and adequate toilets or latrines were available in 79% of rural communities and 99% of urban communities. Similarly, approximately 50% reduction of active trachoma between 1983 and 1999 in Malawi was observed in the absence of targeted control efforts [151]. These illustrate a well-known point in the trachoma community: over time, with improvements in health education and sanitation, trachoma will disappear on its own.

However, various studies have aimed to actively address the “E” component of the SAFE strategy. Given its breadth, this component is less well-defined than others, but generally, interventions aim to reduce transmission and thus disease incidence. They can be roughly categorized as improving safe water availability and utilization and controlling fly populations through measures such as latrine provision and insecticide use [152,153].

The association between active trachoma and low water availability, which leads to reduced use of water for washing, is well-recognized [93,95]. As a result, many have provided water improvements alongside other interventions, but few have investigated the effect of providing better access to water separately from other components of the SAFE strategy. A study in

Niger, discussed above, randomized communities to no intervention or health education and provision of a clean water well, but showed a non-statistically-significant decline in TF [146].

There is better evidence for the effect of fly control through insecticide spraying. Insecticide was effective at reducing muscid populations [154,155], and studies which randomized areas to just insecticide spraying versus no intervention achieved 56% [156] and 61% [154] mean reduction in TF prevalence. Where areas were randomized to insecticide spraying or control, but both also received antibiotics, spraying demonstrated no effect on trachoma prevalence [155]. It is important, of course, to consider the side effects of repeated insecticide spraying, as well as how such an intervention might be sustained in the long term.

Latrine provision is also associated with active trachoma reduction, including in meta-analysis [71,76,80], and some observational studies showed independent association between active trachoma reduction and presence of a pit latrine [147,148]. Randomized trials have shown success at achieving some intermediate effects of latrine provision, such as greater latrine use and reduction of fly populations, but evidence for the effect of latrine provision on trachoma prevalence is less clear. Whether latrines are used consistently is important, as communities may resist change due to cultural norms, and thus lessen the impact of this intervention [157]. In fact, true latrine coverage and usage is very heterogeneous at the landscape and population levels [158,159]. Though a study in The Gambia found high latrine utilization and reduction in muscid fly populations, reduction of active trachoma among intervention villages receiving latrines was not statistically significant [156]. Another study demonstrated increase in latrine

utilization with promotion efforts, but likewise could not show reduction in active trachoma prevalence [160].

Once again, environmental interventions meant to reduce fly populations will only have an impact in areas where flies are a significant vector for trachoma. Usage of latrines or water sources will also clearly impact their effects, and it is doubtful whether usage patterns during relatively short study patterns accurately reflect long term use, and thus intervention impact. As stated, concerns also exist regarding the use of insecticides for trachoma control, as well as for other diseases. Combinations of the "F" and "E" components of the SAFE strategy, if sensitive to the particular norms and situations of the communities where they are implemented, can have a great impact on peoples' lives in terms of trachoma and beyond.

Antibiotics

Mass distribution of antibiotics (MDA) is considered the cornerstone of the SAFE strategy, as it has been conclusively demonstrated to clear active infection and thus help achieve reduction of transmission. Several important issues will be discussed here: which antibiotic to use, side benefits and risks of antibiotic use, the appropriate dosing schedule in terms of how often the drug should be given and for how many rounds, the population coverage level that should be achieved, and evidence for efficacy of the current WHO recommendations.

A number of antibiotics have shown efficacy in clearing *C. trachomatis* infection. Historically, oral sulfonamides were used and were reported to have successfully reduced trachoma

prevalence on Indian reservations in the United States, among Aboriginal communities in Australia, and in Malta and Ethiopia [11]. Erythromycin has also been used topically and systemically to clear trachoma infection—especially among pregnant women, in whom azithromycin is contraindicated—but it is not widely used due to side effects and the necessity of a two-week regimen [51,161]. Tetracycline and doxycycline are also effective, but cannot be taken orally by children, which is an obvious drawback when control of active infection is desired. As a topical ointment, they must be applied once or twice daily for six weeks [51]. Again, compliance with this regimen is a concern, though tetracycline is cheap and effective when used properly [162].

Azithromycin, which carries the brand name Zithromax, is and will likely remain the main antibiotic used for the elimination of trachoma, for reasons practical and biological. Both tetracycline ointment and oral azithromycin are recommended by WHO, and have demonstrated equal cure rates in most studies [51,163]. In practice, azithromycin is far more commonly used, though tetracycline is an important complementary treatment among people in whom azithromycin is contraindicated. Compliance with tetracycline application is known to be poor due to the long regimen required, and it also has unpleasant side effects such as stinging and blurred vision [6]. Probably due to these factors, azithromycin demonstrates higher efficacy in practice [162]. Perhaps most importantly from an operational standpoint, Pfizer committed, at the time the GET2020 alliance was formed, to donating as much Zithromax as was necessary to achieve elimination goals. Having a donation program for a safe and effective drug has rendered the use of other antibiotics for trachoma elimination virtually nonexistent.

To this point, azithromycin is particularly well-suited to treat active trachoma, and it is safe. It is part of the macrolide drug class, which have a longer half-life in tissues than in plasma and tend to concentrate in phagocytes, such that they reach intracellular bacteria (such as *C. trachomatis)*. Animal studies demonstrate high concentrations in eye tissues [164], while serum studies demonstrate that the concentration of the drug in tears remains within the minimum inhibitory concentration for *C. trachomatis* for over 6 days [165]. Long persistence in ocular tissues is important in treating a slow growing organism which localizes in the tissues, such as *C. trachomatis.* Although macrolides are bacteriostatic, meaning that they inhibit bacterial growth rather than killing bacteria immediately, they have shown quasi-bactericidal activity in vitro [166].

Importantly, azithromycin is safe in children as young as 1 month, though it is not recommended in pregnant women. Systemic dosage (usually 20-30mg/kg) can be reliably assessed using height as a proxy for weight [167,168]. Given that young, very highly-infected children still show presence of *C. trachomatis* in eye swabs after treatment, a higher dose may sometimes be requisite [50]. Although 1.5% azithromycin eye drops, given twice a day for three days, are also effective [169], they are not widely used due to their dosage schedule as well as the lack of donated azithromycin in eye drop form.

Side effects of azithromycin tend to be minor and mostly gastrointestinal in nature [170]. In fact, several studies of side effects demonstrate significant benefits to taking azithromycin, as it

also clears other infections. In The Gambia, children randomized to azithromycin rather than tetracycline had significantly fewer episodes of fever, headache, diarrhea, and vomiting [171]. In Nepal, significant reductions in odds of impetigo and diarrhea were observed [172]. While the mechanism for this rather astonishing finding is not clear, a year after MDA, 50% reduction in all-cause mortality was observed among children who had received azithromycin versus those who had not [173].

Although azithromycin's bacteriostatic mode of action and long elimination half-life have raised concerns about the cultivation of antibiotic resistance [174], *C. trachomatis* resistance to azithromycin has not been detected [175,176]. Some increased resistance on the part of genital serovars of *C. trachomatis* has been demonstrated among recurrently infected patients in India [177], but the greatest concerns have surrounded pneumococcal resistance to the macrolide drug family, to which azithromycin belongs. Although communities randomized to intensive (four yearly) mass distributions had significantly increased pneumococcal resistance to macrolides as compared to communities received no MDA, resistance to penicillin, which remains the first-line drug for pneumococcal infections, was not observed [178]. Additionally, significant decrease in the prevalence of resistant pneumococcal strains has been shown at 12 and 24 months post-MDA, demonstrating that resistance begins to disappear once antibiotic pressure eases [179].

The best dosing and distribution schedule for oral azithromycin remains a subject of debate. Currently no recommendations exist regarding timing of dose; though hypothetically, if setting-

specific seasonality could be identified, treatment would be most successful if applied between the high and low seasons, when transmission is lowest [91]. Frequency of distribution and dosing has been better studied. Due in part to its bacteriostatic action, the first trials of mass distribution of azithromycin provided a single dose weekly for three weeks [51]. This was not adopted. Instead, WHO recommends a single oral dose given during yearly distributions. Now, some evidence suggests that efficacy of azithromycin treatment for chlamydia species may be partially dependent on a longer exposure to a high dose of azithromycin, at which level it acts chlamydicidal [180]. This has been suggested by *in vitro* studies as well [166]. As a result, many estimate that azithromycin is approximately 95% effective at clearing a single infection in an individual [91,181]. However, field studies support evidence for a much lower individual treatment efficacy (67.6%, 95% CI 56.5–75.1%), which has serious implications for the number of rounds necessary for successful elimination [182].

Some evidence supports the effectiveness of a one-time dose. A single dose reduced community chlamydial load from 9.5% to nearly zero; a second dose in the same community eliminated infection. However, extraordinarily high coverage rates (97.8% and 93.1%, respectively) were achieved [68,183]. In other communities with TF prevalence below 10%, both communities randomized to 80-89% coverage and those that received over 90% coverage achieved elimination [63]. Elimination was also expected to be achievable with a single round of treatment in other low-prevalence settings, but this was complicated in practice due to reinfection caused by travel and importation from neighboring communities [184]. Still other

areas with relatively low starting prevalence (10-20%) found that at least three rounds were requisite to eliminate trachoma [185].

In settings with higher baseline prevalences, it seems clear that a single round of treatment is insufficient. In a hyperendemic community, with baseline TF prevalences between 57-71%, two rounds of treatment reduced prevalence to just 17-28%. Coverage at baseline was good, ranging from 80-90%, but second-round coverage was below 70% [186]. Other studies document similar effects of a single round of treatment, in which prevalence is reduced but not completely [50,117,187]. Even after three treatment rounds in a high-endemic area suppressed prevalence to below 5%, six of seven districts demonstrated a recurrence above 5% when re-surveyed three years later [188].

These findings likely have to do with the phenomenon of reemergence, in which a single round of treatment suppresses temporarily transmission, but cannot completely eliminate it given insufficient coverage and the waning effects of the drug. This manifests as a transient reduction in prevalence within the first few months of treatment, which is followed by a rise in prevalence measured after a year [54], though not to pre-treatment levels. One study in Ethiopia measured the rate of infection reemergence to be 12.3% per month, but this is likely to be somewhat setting specific [117].

Many have recommended biannual treatment in hyperendemic communities. Among hyperendemic communities in Ethiopia, villages randomized to biannual rather than annual

treatment had a significantly lower prevalence at 24 months; however, coverage was high (90.8%) overall [189]. This was confirmed with NAAT testing at 42 months [190]. Several mathematical modeling efforts also demonstrate the theoretical underpinnings of this recommendation, and project the success of biannual treatments in high-prevalence settings [181,191]. However, this is not currently in practice or in WHO recommendations.

Whatever the distribution schedule, coverage plays a substantial role in determining efficacy at the population level. WHO recommends that coverage be above 80%, and certainly the higher the coverage, the more effective the treatment round. However, several important issues must be clarified with respect to coverage: first, coverage within a community does not prevent against reinfection due to population movement. In a study previously mentioned, while most intervention communities achieved suppression of infection load after a single round of treatment, two experienced increased infection due to mass contact with other untreated communities [184]. Population movement and reinfection from reservoirs of higher prevalence reduces the effects of even excellent coverage; thus, treatment and coverage must be ensured on a large geographic scale.

Regarding who should receive treatment in order that MDA is effective, compelling evidence exists to suggest that the paradigm of treating children to suppress transmission is effective. A randomized trial in Ethiopia showed that treating children resulted in herd protection: it reduced the prevalence in untreated age groups by up to 47% [192]. However, given that distribution of infection within a community is uneven, pooling at the individual and household

level [47], coverage must be high and even in order to ensure that children who are high-burden, and thus high-risk, are reached. Unfortunately, “persistent” non-participation—in which a child repeatedly fails to participate in treatment—is more likely among large households living far from community health workers [193], and non-participation is likely to cluster at the household level rather than being random [194]. Again, these are non-trivial concerns due to the importance of households as incubators of disease [78]. They may be addressed by using motivated community volunteers to assist with MDA, which has been shown to help achieve higher population coverage [195].

Additionally, the level of reported coverage is likely much higher than actual coverage. Many survey administrators report coverage quite simply: as number of doses distributed divided by estimated population. However, estimated population may or may not be current or accurate. CRS for evaluation of various methods of MDA distribution in Sudan measured coverage between 20.9% to 61.5% [196]; and results of independent coverage estimation in Nigeria reported MDA coverage as 60.3% compared to a program estimate of 75.8% [197]. The study’s authors concluded that the difference in the coverage estimates was due in large part to entire communities missed during distribution. In light of trachoma’s nature as a focal disease, and the reported problems with reemergence of infection due to importation from untreated communities, this poses a large problem for trachoma control programs.

Finally, other factors may play a strong role in reemergence of active trachoma after MDA. While level of baseline endemicity is strongly associated with infection post-treatment,

coverage ceases to be a predictor after 6 months post-treatment [198]. Moreover, though very high coverage (over 90%) was achieved during four biannual treatments in one trial in a high-endemic area, leading to suppression of active disease below 2.6%, prevalence returned an average of tenfold after two years without treatment [199]. This suggests that unmeasured factors underlying transmission drive reemergence, and that sustainable changes to the community's environment must be made in order to break the cycle of transmission.

Given the various issues that affect the efficacy of a given treatment round, and given the heterogeneity that often exists in trachoma distribution, WHO recommends that reduction in active trachoma prevalence below 5% be verified at the sub-district level, and that sustained reduction should be demonstrated for three years. This is, however, challenging in practice given the number of clusters that may have to be surveyed as a result [200]. Given these baseline levels, the following treatment scheme is recommended [6]:

- **TF ≥ 30%** - begin 5 years of A, F, E. Conduct follow-up survey at 5 years.
- **TF 10-29%** - begin 3 years of A, F, E. Conduct follow-up survey at 3 years.
- **TF 10%** - conduct sub-district surveys (sub-districts being defined as geographically-appropriate subdivisions of 3+ villages within a district).
    - **TF ≥ 10%** - begin 3 years of A, F, E. Conduct follow-up survey at 3 years.
    - **TF 5-9.9%** - conduct targeted MDA, and consider F and E.
    - **TF < 5%** - consider supplementary F and E to sustain local elimination.

These guidelines were developed using expert opinion, and they have not been updated since 2006. Their relative success in achieving elimination has not been verified, and questions have been raised about virtually all pieces of the above scheme. As the 2020 elimination target nears, reactive reassessment of the "A" component is necessary. In particular, the dosing schedule should be rigorously reevaluated at all levels: from frequency of doses per distribution, to number of rounds of distribution per year, to total years of treatment required in various settings. Innovative approaches, such as using motivated community volunteers to achieve higher population coverage [195], ought also be considered.

The SAFE Strategy as a Holistic Approach

Although the SAFE strategy is meant to be implemented in its entirety in each country where distribution takes place, this is not always the case. In 2012, surgical interventions have been implemented in only 5% of endemic districts, face-washing programs have been implemented in 40%, and environmental improvements in just 24% [201]. Few would argue that this is appropriate.

We observe a significant reduction in trachoma prevalence when implementing multiple components of the SAFE strategy [49,119,148,202], though the literature supports distribution of antibiotics as the most immediately and strongly efficacious component. This is not a sufficient argument for ignoring three of the four strategic pieces. First, although prevention of future blindness is crucial, the surgical component is the only portion which will address the need of those currently suffering from trichiasis. Second, to promote biomedical intervention

for a disease while failing to address the basic sanitation and hygiene practices which promote it is short-sighted. There is much we know about trachoma, and much we do not (and perhaps will never) understand, including what "endemicity" truly means in terms of facilitating transmission. As has been discussed, reemergence of active trachoma seems to depend on some of these unknown factors, which are likely mediated through the environment in which people live. These factors cannot be addressed by antibiotics, but improving peoples' environment and hygiene standards has proven, on a historical scale, to effectively eliminate trachoma.

Addressing Trachoma: The End in Sight?

Six years from the 2020 elimination deadline, the GET2020 alliance is conducting rigorous assessment of its progress towards its ultimate intervention goals [2]. The basic questions of whether we are on track for elimination—and if not, what course corrections must be made—are crucial. The necessity of addressing certain issues, such as assessing the status of suspected endemic countries and addressing the surgical backlog, is undeniable. Others are subject to more uncertainty. While few argue that face-washing and environmental interventions are important parts of the SAFE strategy, there is no single clear way implement these in all communities. Perhaps most importantly, there is a weight of evidence suggesting that a one-size-fits-all approach to antibiotic distribution is inadequate to address the needs of all communities. Moreover, there is simply little basis for certainty as to whether our current strategy will be effective for *any* communities in which we are attempting elimination.

There have been considerable attempts to extrapolate from extant data in order to better understand the natural history and dynamics of trachoma. As discussed, mathematical modeling has been used to describe the duration of various stages of disease [43], as well as disease progression and the levels of infection and prevalence necessary to achieve cicatricial disease [5,98]. It has also demonstrated the importance of coverage to address heterogeneity in infection and prevalence, from diversity in terms of infection susceptibility and clearance in individuals [77] to clustering of infection in households [78]. It has helped confirm the paradigm of treating children in order to confer herd protection to the population at large [192]. Models have been fit to investigate the field efficacy of azithromycin, and the consequent probability of disease elimination over time. Given 95% coverage and the calculated field efficacy, elimination was estimated to be 89% probable after 10 annual treatment rounds [182].

Modeling has also helped explain and predict some of the changes in prevalence seen after treatment. For example, modeling that addressed the feasibility of “graduating” areas that attained suppression below 5% found that using this benchmark, infection could be eliminated in most communities. However, these models did not investigate reemergence after the 5% target was achieved, and it was noted that hyperendemic areas were far more vulnerable to reinfection [203]. The relative contribution from level of infection and level of transmission to reinfection was described in other modeling efforts: reduction of infection without reduction of transmission leads to slow reemergence in the community, while reduction of transmission (a function of the basic reproductive number, increased in higher-endemic settings) leads to a gradual decrease in infection prevalence [204].

Finally, modeling has been used to project the effectiveness of various strategies for elimination. In particular, models have investigated the necessity and utility of biannual treatment. Some models considering the return of infection after treatment in a high-endemic inferred that at 80% coverage, treatment is only necessary annually. These did not, however, explicitly investigate reemergence after achievement of the 5% elimination target [117]. Most other studies find that biannual treatment may indeed be necessary in hyperendemic settings. Given the dependence of epidemic initial doubling time (IDT) on setting-specific conditions before treatment, one set of models showed that regardless of coverage, a single annual distribution was appropriate for settings with initial prevalence under 35%, but that biannual treatment was necessary in hyperendemic conditions [181]. This is supported by the age-prevalence models previously mentioned, in which correlation between endemicity levels and necessary treatment frequency is suggested [77]. A final study projected that biannual treatment for five years would eliminate trachoma in 95% of communities. Generally, it found that antibiotic distribution at high frequency and coverage suppresses infection, but that where infection is not successfully eliminated, it returns to pre-treatment levels [191].

While informative, models are only as good as the information and parameters included in them, and thus the information that can be drawn from each is by nature limited. One limitation of many of the models described herein is that they are setting-specific. They are fitted to data from a limited number of sites, and many of their parameters are drawn from a relatively small number of studies. Thus, for example, azithromycin treatment efficacy of 95% is

assumed in many of the models discussed above, while it may in fact be much lower in the field. Modifying an important parameter is likely to change the conclusions of the model; and a model fitted to data from a specific setting may have limited applicability to other environments.

These setting-specific limitations have been inevitable, as an extensive global dataset has not existed heretofore. However, with the advent of GTMP, which collects data on global prevalence of trachoma for elimination, a growing database of information on prevalence before and after MDA is now available. This database is becoming progressively more comprehensive as data from each country conducting MDA is continually appended. While limited in terms of data types collected—for example, only clinical grading and not laboratory confirmation of infection is included–the database contains standardized data which are generally comparable to each other.

This makes possible an extraordinary opportunity to investigate and characterize patterns of response to antibiotic treatment in a global dataset, assess progress towards elimination goals, and make recommendations regarding programmatic changes that could ensure success in the achievement of these goals. The manuscript that follows details the process of fitting models to these data, interpreting the models, and drawing operable conclusions to inform recommendations for trachoma control programs.

Chapter 3: Manuscript

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Mass Drug Administration for Trachoma:

How Long Is Not Long Enough?

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Data assembly and database management was carried out by RMF and ITI staff. VJ performed data cleaning and data analysis with guidance from DH, HG, and PME. VJ completed the literature search, wrote the first manuscript draft, and developed figures and tables, with revisions and guidance from DH, HG, PME, and DM. All authors approved the final version herein.

Abstract

Background: Blinding trachoma is targeted for elimination by 2020 through global intervention with the SAFE strategy. Although annual mass drug administration (MDA) to curb transmission is a cornerstone of this strategy, its effect on different baseline trachoma prevalence levels is poorly characterized. In order to achieve elimination goals, the World Health Organization (WHO) recommends an increase from a minimum of 3 treatment rounds to 5 prior to re-survey if prevalence exceeds 30%, these recommendations are based on expert opinion and grounded in a relatively small evidence base. Assessment of the effectiveness of these recommendations in practice is necessary to guide programming such that elimination by 2020 is ensured.

Methodology/Principal Findings: Data on prevalence and treatment was drawn from cross-sectional surveys in the International Trachoma Initiative's database and matched on location. Of three hundred and eighty one pairs representing baseline and follow-up surveys, MDA was applied in 186, while 113 represented a change in prevalence in the absence of MDA. Regression modeling showed that as baseline prevalence increased, the likelihood that treatment would reduce prevalence decreased significantly. Treatment rounds, skipped years, and length of time before and after treatment started were also significant predictors in multivariate models. Logistic models predicted that even with perfect programmatic continuity, the probability of achieving successful reduction was low for high endemic areas, even with increasing rounds of treatment.

Conclusions:

In addition to treatment rounds, quality of treatment cycles and the context in which they occur are important predictors of trachoma prevalence reduction. In particular, care should be taken to ensure uninterrupted treatment. Programmatic recommendations must be strengthened to emphasize uninterrupted treatment, and greater effort must be made to change the underlying conditions in which transmission occurs. There are six years before the 2020 elimination deadline. There is a very low probability of achieving sufficient prevalence reduction in high endemic settings under the current treatment paradigm. More intense treatment strategies are needed in order to guarantee elimination by 2020.

Keywords

Trachoma, Chlamydia trachomatis, Mass Drug Administration, Neglected tropical diseases, Mathematical modeling, Prevalence, Transmission

Author Summary

Trachoma, the world's leading infectious cause of blindness, is scheduled for elimination by 2020. Reaching this elimination target depends on successful implementation of the SAFE strategy (surgery, antibiotics, face-washing, and environmental improvements). Repeated annual mass antibiotic distribution is key to breaking the cycle of transmission in a community. However, it is not clear how many rounds of treatment need to be distributed in order to achieve elimination. Our study analyzes the effect of mass antibiotic distribution on different baseline prevalence levels of trachoma, in order to assess factors that affect the success of reaching elimination goals. We find that the prevailing belief, which suggests that 3 rounds of

treatment can achieve local elimination of trachoma at prevalences between 10-30%, and 5 rounds for districts above this benchmark, is likely incorrect. In fact, much longer intervals may be required with “business as usual” programmatic strategies, which often include skipped years of treatment. Districts with high prevalence levels require more intense treatment strategies to eliminate trachoma. Intensified recommendations must be implemented without delay in order to reach the 2020 elimination deadline.

Introduction

Though trachoma has disappeared from much of the developed world due to advances in hygiene and sanitation, it remains the world's leading infectious cause of blindness. Its classification as a neglected tropical disease (NTD) is apt: where it remains, it is concentrated among the world's poorest, who live beyond the reach of development infrastructure and lack access to the basic sanitation measures that prevent disease transmission. Importantly, trachoma is highly focal, and repeated reinfections are necessary to cause blindness [1]. Thus, it is thought that reduction in local prevalence of active disease, measured as trachomatous inflammation—follicular (TF), to below 5% among children aged 1-9 years will ensure that no individual accrues sufficient lifetime infections to progress to the blinding end stages of the disease, thus accomplishing functional elimination. Global achievement of this goal is expected by 2020 through implementation of a comprehensive approach, the SAFE strategy (Surgery, Antibiotics, Face-washing, and Environmental improvements). This will be no small feat. Though great reductions in active disease and long-term morbidity have been made since the formation of the Alliance for the Global Elimination of Blinding Trachoma by 2020 (GET 2020) in 1997, the World Health Organization (WHO) estimated that in 2012, 21.4 million people have active trachoma, while 8 million suffer from trachomatous trichiasis (TT), and are at risk of becoming blind [2].

In order to achieve elimination on this scale, effective implementation of each component of the SAFE strategy is essential. Antibiotics very successfully clear individual infections [3,4], and Pfizer's commitment to donate azithromycin to achieve elimination ensures a sufficient supply

of the drug to realize elimination. However, many factors affect the success of mass drug administration (MDA) at the population level. To address these, the WHO recommendations for trachoma control programs specify that MDA should occur within the context of the full SAFE strategy, though good indicators for F and E implementation are lacking. Antibiotic treatment coverage should near 100%, and additional rounds of treatment should be provided at higher baseline prevalence levels. Current guidelines are that at least three annual rounds should be accomplished prior to an impact survey at baseline prevalence between 10-29%, and at least five annual rounds should be conducted before an impact survey where prevalence is greater than or equal to 30% [5]. These benchmarks were instituted to inform programmatic assessment, such that planning and budgeting for sufficient implementation of SAFE components can be conducted. These guidelines have been in place since 2010, but may need refinement based on the large amount of data that has since been generated by ongoing monitoring and assessment.

This data suggests that many more rounds are actually necessary to reach elimination of blinding trachoma in highly endemic areas, and that revision of the current treatment paradigm is therefore necessary. In the past, many believed that one round of treatment could accomplish elimination, and some studies in relatively low-endemic regions, with 10-15% prevalence, appeared to prove this [6,7]. Still others have found that elimination in such settings may take more than three treatment rounds [8,9]. However, in higher-prevalence settings, reemergence several years after “elimination” has been demonstrated: one round of treatment at over 40% baseline prevalence was not sufficient for sustained elimination, nor

were three rounds at roughly 30% baseline prevalence [10]. In hyperendemic settings, with prevalences exceeding 50%, these problems are compounded. Two rounds are evidently insufficient to achieve elimination [11], and indeed 7-10 rounds may be necessary [12]. Reemergence was documented even after four rounds applied over two years [13]. Modeling efforts also demonstrate that in hyperendemic areas, five years of annual treatment is likely insufficient [14,15]. Many of these studies demonstrated relatively high treatment coverage (>80%), but low coverage is believed to strongly affect efficacy of treatment rounds [12,13].

These studies suggest that a paradigm in which a certain number of years of treatment "guarantee" elimination may be misleading. Moreover, with the increase in available data, the current treatment recommendations can be refined. An overall assessment of the effects of factors like treatment rounds, calculated across a broad evidence base, is essential to assess and inform programmatic guidelines. Metrics describing the contribution of factors such as treatment rounds and years skipped between treatment rounds would allow trachoma control programs, donors, and other partners to appropriately plan and budget for elimination.

In this study, we use a global dataset of baseline and impact surveys to assess the evidence base for the effect of MDA on trachoma prevalence, with the goal of determining whether improved recommendations can be developed in order to achieve elimination.

Methods

Database

In order to effectively implement its role in the coordination of the Zithromax® donation for Pfizer, The International Trachoma Initiative (ITI) maintains a comprehensive database of trachoma prevalence and Zithromax treatments performed around the world. This database allows ITI to effectively allocate drugs, and conduct forecasting and planning of programmatic scale-up [16,17]. Data sources include published literature reports and annual applications for Zithromax submitted to ITI, personal communication with program staff and researchers, and targeted review of other sources. Much of this data has been collected for the Global Atlas of Trachoma [16]. This study includes database updates through February 2014.

Each observation in the database includes the following information, where available: active trachoma prevalence and the clinical sign used as an active indicator (TF or TF/TI), trachomatous trichiasis (TT) prevalence, age range of individuals surveyed for TF and TT, survey location, survey year, survey design and sampling methodology, and data source. Where multiple surveys were conducted at a given location, they were coded to indicate whether they were current or historical estimates, and if they prompted or followed treatment. Where treatment was conducted, some entries include estimates of district population, reported antibiotic distribution, and coverage (estimated as doses distributed divided by total population).

There is substantial variation between some of the metrics used in the surveys represented in the database, as well as in the surveys themselves. For example, the indicator used for active trachoma is a measure of circulating disease in a community. WHO recommends measuring TF in children aged 1-9 years. Departure from this standard results in a different prevalence estimate, as there is a well-recognized change in prevalence of various trachoma stages with age [22-25]. All surveys included in the database used the simplified clinical grading system for trachoma [18], but some measured TF as an indicator for active trachoma and others used TI (trachomatous inflammation, intense). Additionally, some assessed TF among children aged 1-9 years, while others used school-aged children or children less than 6 years.

While cross-sectional population-based prevalence surveys (PBPS) are considered the gold standard for assessing trachoma prevalence at a given location [16,19], alternate methods such as trachoma rapid assessments (TRAs) and acceptance sampling trachoma rapid assessments (ASTRA) were used in some locations, as the trachoma community had experimented over several years with simpler methods for providing evidence to start programmatic implementation. However, neither provided a good estimate of prevalence [19]. TRAs in particular are known to provide biased prevalence estimates, as they prioritize finding trachoma where it exists [20,21]. In most cases, these TRAs represented baseline data and were followed by PBPS. Although prevalence surveys are intended to take place using the district as the implementation unit (where district is defined as an administrative unit of 100,000-250,000 people), prevalence was sometimes measured at a larger geographic area, such as the zonal

level, when trachoma was expected to be endemic [5]. Sub-district analyses are also required if TF prevalence is below 10% at district level [5].

Data Cleaning and Abstraction

We aimed to assess the factors affecting change in prevalence over time in pairs of surveys collected at the same location. The database initially contained 2369 surveys representing 29 countries. Of these, 156 were TRAs, and 45 were ASTRAs. These were censored. Of the remaining, 353 were surveys remaining coded as representing follow-up after treatment, while 1317 were coded as representing baseline that prompted treatment. All were assigned unique IDs by location and matched. Matches were parsed into pairs corresponding to two prevalences surveyed in the same location and ordered by time such that one represented baseline and the other follow-up. Matched pairs were merged with data on treatment and coverage which used the same unique IDs by location. In areas where follow-up assessment was conducted at a smaller implementation level than the baseline survey (e.g. district surveys following a zonal survey), the follow-up data was averaged across the original unit of implementation to allow comparison.

Where TF was not measured among children aged 1-9 years, prevalence was adjusted if surveys had been conducted at TF prevalences exceeding 20%. In these settings, the age-prevalence peak shifts such that younger individuals are more likely to have a greater share of disease burden [22-25]. If TF prevalence was assessed among children under six rather than those aged 1-9 years, it was adjusted by a factor of 0.85, calculated based on the average differences in

prevalence between these age groups in published studies [23,26]. As the only surveys in the dataset that sampled children aged 6-15 were conducted in Vietnam, where school attendance is high and prevalence peaks among school-aged children [27], no adjustment was applied. If TF/TI was used as an active indicator rather than TF alone, it was adjusted by a factor of 0.87. This was calculated as an average of the relative difference between TF and TF/TI prevalences in published studies [28-31]. Finally, among surveys for which a year range was specified, the survey year was coded as the median of that range or the most recent year of a two-year range.

Pairs were identified as representing MDA if any treatment was recorded between the survey dates, or if ITI coding indicated that MDA had taken place. All other pairs were considered to represent "background" prevalence change. Variables were created representing rounds between treatment (number of rounds that took place between baseline and follow-up surveys), years between surveys, total rounds (number of rounds before the follow-up survey, regardless of whether they took place after the baseline survey), skips between ("treatment holiday," or skipped years between rounds of treatment), and total skipped years (any years without treatment before the follow-up survey and after the beginning of treatment). See Figure 4 for a representation of this coding scheme.

As all temporal information in the dataset is based on calendar years, discrimination between time intervals smaller than a year was not possible. Coding proceeded on the assumption that baseline surveys would be followed by treatment, while impact surveys followed treatment. Instances of anomalous code were manually inspected and cleaned. The final dataset had 170

pairs of surveys corresponding to baseline and follow-up after MDA, and 113 pairs that did not correspond to MDA.

TF categories were specified based on the thresholds that define current WHO recommendations for treatment [5]. An additional category, in which prevalence exceeded 50%, was added to represent hyperendemic settings where trachoma is entrenched (see Figure 1). Coverage data, only measured in 2010-2012, was available for 34 pairs in the treatment dataset.

Data Analysis

We used SAS 9.3 (SAS Institute, Cary, NC) to produce descriptive statistics of the dataset (Table 1). The outcome variable for each was defined as TF prevalence at follow-up. Simple linear regressions were used to analyze the relationships between exposure variables and outcome. Variables that were significant in bivariate analysis were used in regression to fit generalized linear models to the full dataset of prevalence pairs; the "background" dataset, which represented change in prevalence in the absence of MDA; the "treatment" dataset representing MDA; and the "reduction" dataset, which represented all pairs in which MDA showed a reductive effect on prevalence. Stepwise selection and backwards elimination strategies, with entry and stay criteria of α=0.10, respectively, were used for model building. Outliers were assessed based on high jackknife residuals, leverage, and influence (expressed through Cook's distance). Univariate and multivariate logistic regression models were fitted to banded TF prevalence at follow-up (see Figure 1 for categories) to demonstrate the odds of

reduction to a lower category of follow-up TF prevalence, as well as the odds of reduction below 5%. Where ordinal logistic regression demonstrated violation of the proportional odds assumption, polytomous logistic regression was used. Maximum likelihood was used to estimate the coefficients for model predictors [32].

Of the treatment dataset, 28 observations coded as representing MDA but missing data on treatment were dropped from the linear and logistic models due to missing predictor values. These represented data from Ghana, Nigeria, Tanzania, The Gambia, and Vietnam.

Results

In the full dataset, simple linear regressions showed significant linear associations between outcome (follow-up TF prevalence) and exposure variables (baseline TF prevalence, years between surveys, years since treatment began). A generalized linear model fit to these variables included rounds of treatment between survey years, baseline TF prevalence, years since treatment, skipped years of treatment, and the interaction between rounds of treatment and baseline prevalence. These variables, significant at the 0.05 level, accounted for approximately 25% of the variation in the data:

$$\widehat{\boldsymbol{TFPr2}} = \mathbf{6.05} + \mathbf{0.21} * \boldsymbol{TFPr1} - \mathbf{2.38} * \boldsymbol{Rounds\ Between} + \mathbf{0.967} * \boldsymbol{Years\ Since\ Treatment\ Start} - \mathbf{0.922} * \boldsymbol{Years\ Before\ Treatment} + \mathbf{0.91} * \boldsymbol{Skipped\ Treatment\ Years} + \mathbf{0.050} * (\boldsymbol{TFPr1} * \boldsymbol{Rounds\ Between})$$

The best model fit to the background dataset accounted for only about 8% of the variation in the data, demonstrating that these model parameters do not do a good job of accounting for prevalence change in the absence of treatment. The above model for the full dataset does not discriminate well when MDA is not applied. One can see the difference in TF prevalence change for those areas where MDA was applied versus where it was not in Figure 5.

In the treatment dataset, baseline TF prevalence, years between surveys, rounds of treatment, skipped years between treatment rounds, and total skipped years since the beginning of treatment showed significant positive linear association with increasing follow-up TF prevalence. Each of these variables was significant at the 0.05 level in multiple linear

regression; the model with TT prevalence was missing data for 53 observations, so it was not selected. The final multivariate model, specified below, was missing 25 observations and had an r^2 value of 0.40.

$$\widehat{\boldsymbol{TFPr2}} = \mathbf{3.29} + \mathbf{0.11} * \boldsymbol{TFPr1} - \mathbf{2.60} * \boldsymbol{Rounds\ Between} + \mathbf{1.81} * \boldsymbol{Years\ Since\ Treatment\ Start} - \mathbf{0.91} * \boldsymbol{Years\ Before\ Treatment} + \mathbf{0.064} * (\boldsymbol{TFPr1} * \boldsymbol{Rounds\ Between})$$

Both full and treatment models were used to generate predicted probabilities for TF prevalence, but they were unable to produce plausible estimates of prevalence reduction if modeling an ideal treatment interval (in which variables describing years prior to treatment and skipped treatment years were omitted). However, both demonstrated the importance of continuity of treatment, as skipping a year of treatment made reduction less likely. This effect was approximately equal whether a skipped year occurred during the treatment interval or after it.

Univariate ordinal logistic regression results (Table 2) demonstrated that increased baseline TF prevalence was associated with reduced likelihood of achieving lower categories of follow-up TF prevalence in the full, treatment, and background datasets. However, in the treatment model, baseline prevalence and years since treatment began remained significant. Several measures of skipped years (years skipped between treatment rounds, and total skipped years) were also significantly associated with decreased likelihood of reduction. In the treatment model, increased number of treatment rounds also showed a non-significant trend towards

association with reduced likelihood of reduction. Increased coverage also seemed to be associated with reduced odds, but this relationship was not significant, likely due to sparse data available.

A multivariate ordinal regression model fitted to the treatment dataset was used to model the odds of reduction to a lower category of follow-up TF prevalence. An increase in the following was associated with significantly lower odds of TF prevalence reduction: increased baseline prevalence (OR=0.92, 95% CI 0.89-0.94), and years since treatment began (0.77, 95% CI=0.61-0.97). However, an increase in rounds between (OR 2.28, 95% CI 1.42, 3.78) and years before treatment (OR 1.53, 95% CI=1.08, 1.56) were associated with significantly increased odds of prevalence reduction.

This model demonstrated a significantly increased probability of reduction at lower prevalence levels. While it predicted a 76% probability of reduction to below 10% given 3 treatment rounds at 20% ($p<0.0001$), this probability was only estimated to be 67% given 3 rounds at 20% baseline prevalence ($p=0.043$). At higher baseline endemicities, the point estimate for probabilities became lower, and the error increased. So while a 56% probability of reduction was predicted for a baseline prevalence of 30% given 3 rounds of treatment, this was not significant ($p=0.494$). As rounds were increased, the confidence interval narrowed, such that a 64% chance of reduction from 30% baseline was predicted for 5 treatment rounds ($p=0.09$). Even if the number of treatment rounds was increased to 10 for an area at 50% endemicity, the probability of reduction (estimated at 42%) was non-significant.

Skipping a year during the treatment interval led to about a 5% reduction in the probability of success achieving reduction below 10% using this model (this is significant at 10% and 20% endemicity). The model also predicts increasing success with a waiting period before implementing treatment.

Discussion

In this study, we aimed to investigate the effect of different variables with programmatic relevance for trachoma control on the prevalence at follow-up survey. We used a dataset representing surveys conducted in the context of program implementation and monitoring over the 15-year history of ITI. Several modeling strategies applied to this dataset demonstrated the importance of not just rounds of treatment, but the context in which they are implemented. Figure 2 shows the logic behind the coding scheme. For example, it is generally recognized that in many contexts, trachoma declines slowly on its own, probably due to the effects of gradual environmental improvements and non-trachoma specific development [33,34]. This is represented by the variable for years before treatment, which predicts that in the absence of treatment (or before treatment occurs), there is a modest decrease in prevalence at follow-up. Furthermore, trachoma prevalence seems to exhibit an equilibrium dependent on baseline endemicity, such that it its more likely to reemerge after treatment in higher prevalence settings [13,15,35,36], while in lower prevalence settings it disappears after treatment [7,37]. In the model, we see that effect of treatment rounds differs at different levels of endemicity (shown by the variable for baseline TF prevalence, as well as the interaction term in the linear

models). Skipping a year after treatment begins also increases the prevalence at follow-up, demonstrating reemergence.

Importantly, interruptions in treatment may serve as a proxy for general programmatic quality, and may be due to difficult implementation context. In situations where endemic areas are large and difficult to access, continuous treatment is more difficult. As described, trachoma also tends to remain prevalent in areas “beyond the end of the road,” where sanitation infrastructure is poor or missing. Thus, we may see a confounding association between these variables and the effect of treatment on follow-up prevalence. This warrants further investigation.

We used the multivariate logistic model to generate predictions for treatment schemes. This model predicted that while increasing treatment rounds leads to higher probability of success at achieving TF reduction, this reduction becomes more and more difficult as baseline prevalence increases. Additionally, as in the linear models, interruptions in the treatment cycle significantly decrease the probability of prevalence reduction. However, the model had poor discriminatory ability above 30% baseline prevalence. This is likely due to the lack of data showing successful reduction at higher prevalences. As is visible in Figure 6, of the ten districts in the treatment dataset which had baseline prevalences over 50%, none showed reduction to below 5%, and only one achieved reduction to below 10%, despite the application of up to 7 treatment rounds. Even at prevalences from 30-50%, only about half showed reduction below 10%. However, most of these hyperendemic districts experienced discontinuous treatment.

While this failure to achieve reduction lends credence to the importance of terms in the model regarding treatment continuity, it also means that the model is extrapolative for hyperendemic districts.

These results must be interpreted with caution given the sparse data available, as well as the lack of predictors for treatment quality. However, in a large dataset which inevitably contains a high degree of actual variability in programmatic quality, it seems clear that the context in which treatment occurs is crucial. Implementing a treatment round, without regard to the degree to which it is implemented, the baseline endemicity, and the years during which treatment was not implemented, does not in itself guarantee a decline in prevalence.

These findings are supported by other studies. Seven to ten years of annual treatment were suggested by a research study in a hyperendemic setting in Tanzania [12], while in a programmatic context in Mali, three rounds were not sufficient at baseline prevalences of close to 30% [10]. Our conclusions are also strengthened by the associations we find in a dataset of surveys conducted in very different contexts, with varying qualities of data, and without several significant predictors that are known to affect prevalence. For example, successful prevalence reduction with antibiotics is dependent on treatment coverage [13]. However, coverage data was available in such a small subset of surveys that it was impossible to include it in any of the models. Even if more programs provided these estimates, the quality of coverage data currently collected by trachoma control programs is known to vary greatly [38]. In the ITI database it is

calculated as a measure of doses distributed over total population, which sometimes leads to implausible estimates when census measures are incorrect.

We also lack measures of hygiene and environmental factors, the F and E components of the SAFE strategy. Reduction in trachoma has been associated with clean faces and hygiene indicators [39], latrine provision [23,40], and insecticide spraying to control flies, which act as trachoma vectors where they are prevalent [41] [42]. However, direct causative evidence is lacking to guide the development of metrics that could be used by control programs. Nonetheless, the endemic equilibrium which leads to reemergence of trachoma, suggested by this and other studies, is likely dependent on environmental factors. If the setting in which antibiotic treatment is applied is unchanged, “elimination” will be transient at best.

This study adds significantly to the evidence base regarding the effect of MDA on trachoma. While many other studies have investigated the number of rounds necessary for trachoma elimination, most have been conducted in research settings. None have represented as wide a range of contexts and timelines as has this one. These data show the effect of treatment as it is applied programmatically, with inevitably great variation in quality. Under such circumstances, additional treatment rounds help suppress prevalence at higher endemicities, but do not guarantee elimination. That is, if a program adds treatment rounds but has poor programmatic continuity, it is unlikely to achieve elimination goals.

With additional data, as well as additional indicators for coverage and environmental factors, we likely could quantify treatment rounds necessary at different endemicities. However, while we can explain much of the variation we see in this dataset based on the context of treatment, we cannot provide a rigorous prediction of the effect of treatment without better indicators of treatment quality. It does appear that under the programmatic circumstances investigated here, high endemic areas are very unlikely to achieve elimination without intensified treatment strategies.

Given that less that six years remain before the 2020 elimination deadline must be achieved, the question becomes, how should these results be applied in a programmatic context? They argue strongly for continuity of treatment in any context, but may be especially relevant for programs facing the need to implement treatment in areas with prevalences exceeding 30%. In these cases, intensified treatment appears essential. Programs facing this challenge have several alternatives to consider. One is population-based distribution, in which initial treatment rounds are given to the entire population of a trachoma-endemic area rather than just children. Little evidence is available to support the effectiveness of this strategy [43]. Increased frequency of treatment is also a possibility. As reemergence may occur after high-coverage biannual treatment [13], distribution at more frequent intervals might be considered, though evidence for efficacy of this approach is scant. Moreover, in areas for which long, intensive efforts may be required to achieve elimination, reconsideration of the role of trachoma control programs in the broader context of health systems may be warranted. Integration of efforts to survey and distribute treatment with programs for other NTDs has been proposed [44,45], but

little action has been taken. Given the resources that will be required of donors, program managers, and other stakeholders, there may be substantial cost savings associated with such integration, or with incorporation of trachoma control into existing health system infrastructure.

Moreover, though this study can only quantify the “A” component of the SAFE strategy, this holistic approach was chosen for a reason. Trachoma serves as an object lesson that biochemical interventions can only go so far in the context of poor development. With additional rounds of treatment, we may reduce prevalence to below 5%, but antibiotics alone will not ensure that it stays there. For a program seeking real and sustainable elimination, it may be that no amount of time is long enough to achieve trachoma elimination without lasting change of the environment in which it persists.

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Tables and Figures

	TF Prevalence	Treatment Guidelines
Category 0	<5%	Elimination goal achieved
Category 1	5-9.9%	Targeted SAFE
Category 2	10-29%	3 years of SAFE
Category 3	30-49%	5 years of SAFE
Category 4	≥50%	5 years of SAFE

Figure 3. Categories of TF prevalence based on WHO recommendations for elimination.

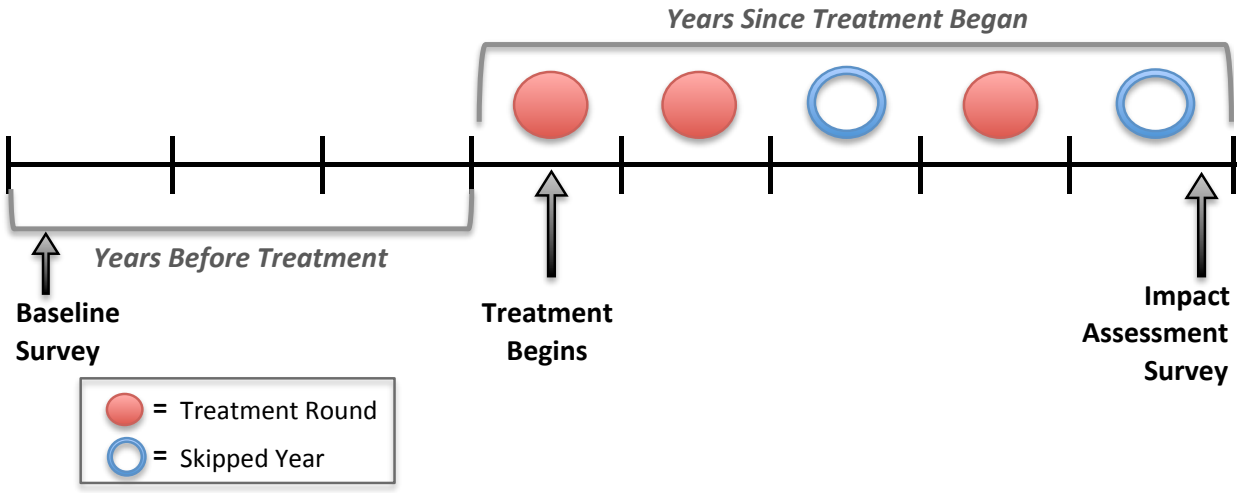

Figure 4. Sample treatment schedule illustrating the rationale behind the coding of variables Rounds Between (number rounds between survey years), Years Before (years before treatment), and Years Since (years since treatment began).

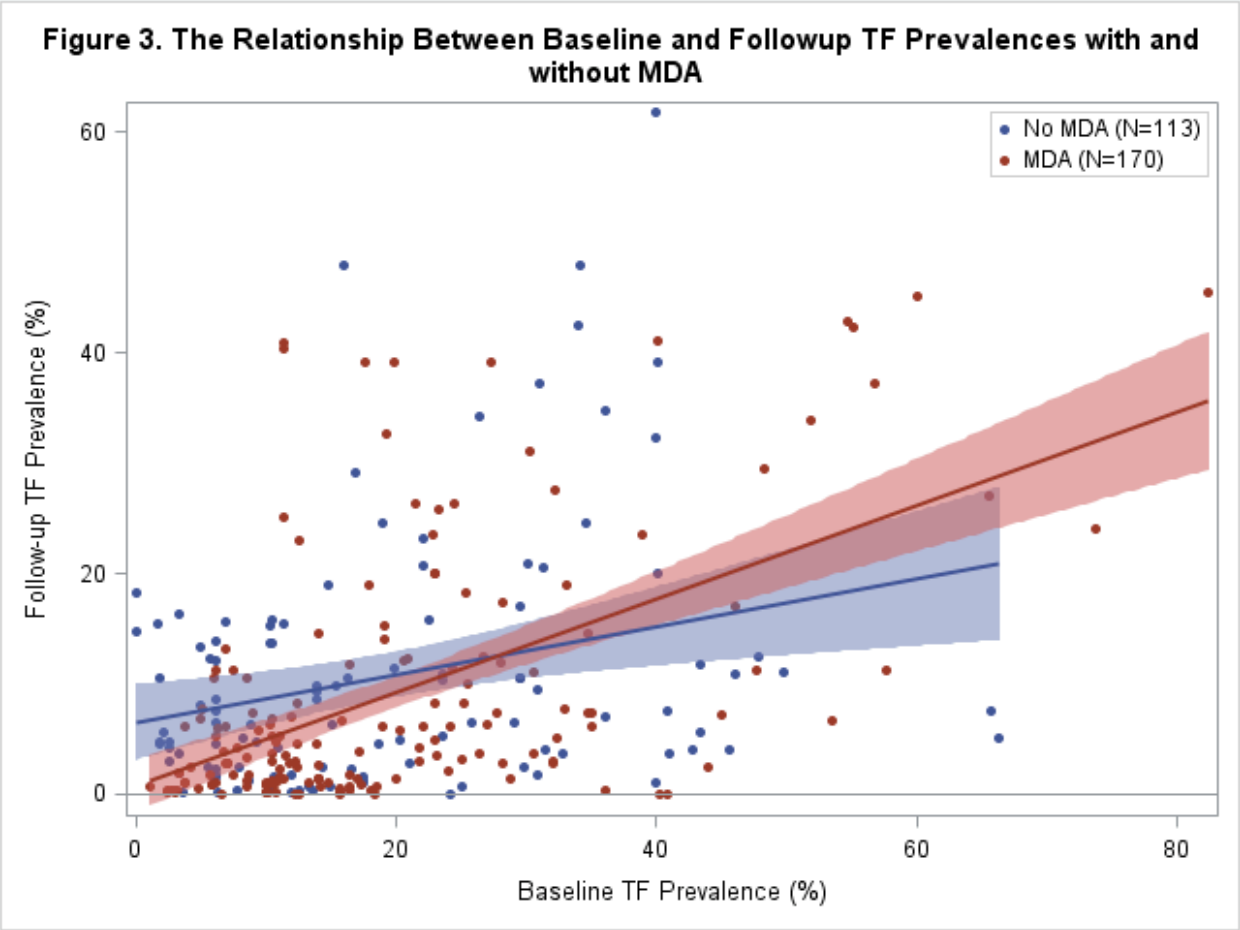
Figure 3. The Relationship Between Baseline and Followup TF Prevalences with and without MDA
No MDA (N=113)
MDA (N=170)
Follow-up TF Prevalence (%)
Baseline TF Prevalence (%)
0
20
40
60
80

Figure 5

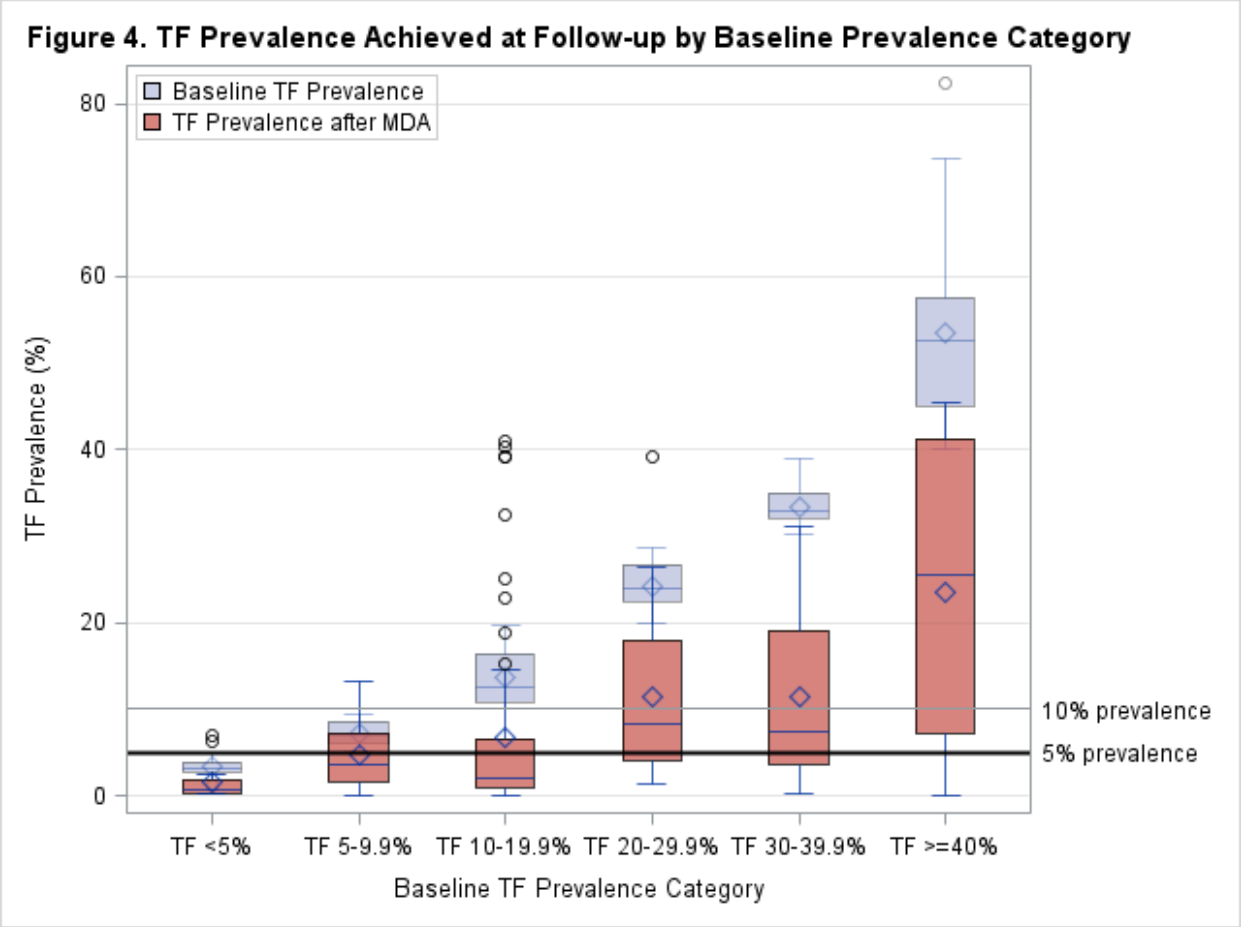
Figure 4. TF Prevalence Achieved at Follow-up by Baseline Prevalence Category
Baseline TF Prevalence
TF Prevalence after MDA
TF Prevalence (%)
80
60
40
20
0
10% prevalence
5% prevalence
TF <5%
TF 5-9.9%
TF 10-19.9%
TF 20-29.9%
TF 30-39.9%
TF >=40%
Baseline TF Prevalence Category

Figure 6

Table 1

Table 1. Characteristics of survey data, matched on location, from the ITI global trachoma prevalence database[a]

	All Pairs (n=283)		"Treatment" (with MDA)[a] (n=170)		"Background" (no MDA)[b] (n=113)	
	No.	%	No.	%	No.	%
Countries represented						
Burkina Faso	55	19.4	18	10.8	37	32.7
Ethiopia	35	12.4	25	15.0	10	8.8
Ghana	23	8.1	23	13.8	0	0.0
Mauritania	20	7.1	20	12.0	0	0.0
Nigeria	54	19.1	4	2.4	50	44.2
Vietnam	25	8.8	25	13.2	0	0.0
Burundi, Guinea, Guinea Bissau, Kenya, Malawi, Mali, Morocco, Mozambique, Nepal, Niger, Sudan, Tanzania, The Gambia	71	25.1	55	32.4	16	14.2
Baseline TF Prevalence						
Category 0: <5%	29	10.2	15	8.8	14	12.4
Category 1: 5-9.9%	48	17.0	26	15.3	22	19.5
Category 2: 10-29.9%	145	51.2	96	56.5	49	43.4
Category 3: 30-49.9%	49	17.3	23	13.5	26	23.0
Category 4: >50%	12	4.2	10	5.9	2	10.0
Follow-up TF Prevalence						
Category 0: <5%	137	48.4	91	53.5	46	40.7
Category 1: 5-9.9%	50	17.7	29	17.1	21	18.6
Category 2: 10-29.9%	73	25.8	36	21.2	37	32.7
Category 3: 30-49.9%	22	7.8	14	8.2	8	7.1
Category 4: >50%	1	0.4	--	--	1	0.9
Years Between Surveys						
1-2 years	26	9.2	25	14.7	1	0.9
3-4 years	64	22.6	51	30.0	13	11.5
5-6 years	79	27.9	43	25.3	36	31.9
7-9 years	49	17.3	35	20.6	14	12.4
>10 years	65	23.0	16	9.4	49	43.4
Rounds Between Surveys						
0 Rounds	113	39.9	--	--	113	100
1-3 Rounds	99	35.0	99	58.2	--	--
4-5 Rounds	33	11.7	33	19.4	--	--
>5 Rounds	13	4.6	13	7.6	--	--
Missing	*25*	*8.8*	*25*	*14.7*		
Years Before Start of Treatment[d]						
0 Years	46	48.6	46	27.1	--	--
1-2 Years	58	11.2	57	33.5	--	--
3-7 Years	76	1.6	31	18.2	--	--
Missing	*36*		*36*	*21.2*	--	--
Years Since Start of Treatment						
1-3 Years	57	33.5	51	30.0	--	--
4-5 Years	94	55.3	54	31.8	--	--
6+ Years	96	56.5	29	17.1	--	--
Missing[c]	36	21.2	36	22.4	--	--
Coverage Data						
Any data, 2010-2012	34	20.0	34	20.0	--	--
Missing	*249*	146.5	*149*	87.6	--	--

[a]Including database updates through February 2014.

[b]Pairs were sorted into the "impact" dataset if any MDA had occurred in the interval between them.

[c]41 pairs in the treatment dataset were missing data on treatment.

[e]These values represent treatment outside of the survey interval.

Table 2. Univariate ordinal regression analysis demonstrating the likelihood of an increased TF prevalence at follow-up given an increase in continuous predictors.[a]

	All Pairs (n=283)				"Impact" (with MDA)[a] (n=170)				"Background" (no MDA)[b] (n=113)			
	No. (%)	OR	95% CI	*p*-value	**No. (%)**	OR	95% CI	*p*-value	**No. (%)**	OR	95% CI	*p*-value
Baseline TF Prevalence	**283 (100%)**	**0.93**	**(0.91,0.95)**	**<0.0001**	**183 (100%)**	**0.93**	**(0.91,0.95)**	**<0.0001**	**113 (100%)**	**0.968**	**(0.95,0.99)**	**0.008**
Years Between Surveys	283 (100%)	0.96	(0.90,1.03)	0.253	183 (100%)	1.02	(0.94,1.11)	0.642	113 (100%)	0.91	(0.81,1.03)	0.142
Years Since Last Treatment	283 (100%)	0.99	(0.92,1.07)	0.853	**158 (86%)**	**0.78**	**(0.66,0.91)**	**0.002**	--	--	--	--
Rounds Between Surveys	258 (91%)	1.05	(0.94,1.17)	0.381	142 (78%)	0.91	(0.76,1.10)	0.320	--	--	--	--
Years Skipped During Treatment Interval	--	--	--	--	142 (78%)	0.81	(0.64,1.03)	0.0870	--	--	--	--
Total Skipped Years Since Treatment Began	--	--	--	--	142 (78%)	0.83	(0.69,1.00)	0.052	--	--	--	--

[a]TF prevalence at follow-up is measured in five ordered categories (<5%, 5-9.9%, 10-29.9%, 30-39.9%, 40-49.9%, and >50%).

Conclusions

In this study, we aimed to investigate the effect of different variables with programmatic relevance for trachoma control on the prevalence at follow-up survey. We used a dataset representing surveys conducted in the context of program implementation and monitoring over the 15-year history of ITI. Several modeling strategies applied to this dataset demonstrated the importance of not just rounds of treatment, but the context in which they are implemented. Figure 2 shows the logic behind the coding scheme. For example, it is generally recognized that in many contexts, trachoma declines slowly on its own, probably due to the effects of gradual environmental improvements and non-trachoma specific development [33,34]. This is represented by the variable for years before treatment, which predicts that in the absence of treatment (or before treatment occurs), there is a modest decrease in prevalence at follow-up. Furthermore, trachoma prevalence seems to exhibit an equilibrium dependent on baseline endemicity, such that it its more likely to reemerge after treatment in higher prevalence settings [13,15,35,36], while in lower prevalence settings it disappears after treatment [7,37]. In the model, we see that effect of treatment rounds differs at different levels of endemicity (shown by the variable for baseline TF prevalence, as well as the interaction term in the linear models).

Importantly, interruptions in treatment may serve as a proxy for general programmatic quality, and may be due to difficult implementation context. In situations where endemic areas are large and difficult to access, continuous treatment is more difficult. As described, trachoma also tends to remain prevalent in areas “beyond the end of the road,” where sanitation

infrastructure is poor or missing. Thus, we may see a confounding association between these variables and the effect of treatment on follow-up prevalence. This warrants further investigation.

We used the multivariate logistic model to generate predictions for treatment schemes. This model predicted that while increasing treatment rounds leads to higher probability of success at achieving TF reduction, this reduction becomes more and more difficult as baseline prevalence increases. Additionally, as in the linear models, interruptions in the treatment cycle significantly decrease the probability of prevalence reduction. However, the model had poor discriminatory ability above 30% baseline prevalence. This is likely due to the lack of data showing successful reduction at higher prevalences. As is visible in Figure 6, of the ten districts in the treatment dataset which had baseline prevalences over 50%, none showed reduction to below 5%, and only one achieved reduction to below 10%, despite the application of up to 7 treatment rounds. Even at prevalences from 30-50%, only about half showed reduction below 10%. However, most of these hyperendemic districts experienced discontinuous treatment. While this failure to achieve reduction lends credence to the importance of terms in the model regarding treatment continuity, it also means that the model is extrapolative for hyperendemic districts.

These results must be interpreted with caution given the sparse data available, as well as the lack of predictors for treatment quality. However, in a large dataset which inevitably contains a high degree of actual variability in programmatic quality, it seems clear that the context in

which treatment occurs is crucial. Implementing a treatment round, without regard to the degree to which it is implemented, the baseline endemicity, and the years during which treatment was implemented, does not in itself guarantee a decline in prevalence.

These findings are supported by other studies. Seven to ten years of annual treatment were suggested by a research study in a hyperendemic setting in Tanzania [12], while in a programmatic context in Mali, three rounds were not sufficient at baseline prevalences of close to 30% [10]. Our conclusions are also strengthened by the associations we find in a dataset of surveys conducted in very different contexts, with varying qualities of data, and without several significant predictors that are known to affect prevalence. For example, successful prevalence reduction with antibiotics is dependent on treatment coverage [13]. However, coverage data was available in such a small subset of surveys that it was impossible to include it in any of the models. Even if more programs provided these estimates, the quality of coverage data currently collected by trachoma control programs is known to vary greatly [38]. In the ITI database it is calculated as a measure of doses distributed over total population, which sometimes leads to implausible estimates when census measures are incorrect.

We also lack measures of hygiene and environmental factors, the F and E components of the SAFE strategy. Reduction in trachoma has been associated with clean faces and hygiene indicators [39], latrine provision [23,40], and insecticide spraying to control flies, which act as trachoma vectors where they are prevalent [41] [42]. However, direct causative evidence is lacking to guide the development of metrics that could be used by control programs.

Nonetheless, the endemic equilibrium which leads to reemergence of trachoma, suggested by this and other studies, is likely dependent on environmental factors. If the setting in which antibiotic treatment is applied is unchanged, “elimination” will be transient at best.

This study adds significantly to the evidence base regarding the effect of MDA on trachoma. While many other studies which have investigated the number of rounds necessary for trachoma elimination, most have been conducted in research settings. None have represented as wide a range of contexts and timelines as has this one. This data shows the effect of treatment as it is applied programmatically: with inevitably great variation in quality. Under such circumstances, additional treatment rounds help suppress prevalence at higher endemicities, but do not guarantee elimination. That is, if a program adds treatment rounds but has poor programmatic continuity, it is unlikely to achieve elimination goals.

With additional data, as well as additional indicators for coverage and environmental factors, we likely could quantify treatment rounds necessary at different endemicities. However, while we can explain much of the variation we see in this dataset based on the context of treatment, we cannot provide a rigorous prediction of the effect of treatment without better indicators of treatment quality. It does appear that under the programmatic circumstances investigated here, high endemic areas are very unlikely to achieve elimination without intensified treatment strategies.

Further analysis of this dataset may add value to the conclusions demonstrated herein. We have created very good associative models, which have acceptable predictive power when applied to this dataset. They explain why elimination has *not* been achieved in many areas, especially those which are very highly endemic. Conditioning on some of these intervening variables, which may confound the association between treatment and follow-up prevalence, may allow better analysis of the effect of treatment in their absence.

Given that less that six years remain before the 2020 elimination deadline must be achieved, the question becomes, how should these results be applied in a programmatic context? They argue strongly for continuity of treatment in any context, but may be especially relevant for programs facing the need to implement treatment in areas with prevalences exceeding 30%. In these cases, intensified treatment appears essential. Programs facing this challenge have several alternatives to consider. One is population-based distribution, in which initial treatment rounds are given to the entire population of a trachoma-endemic area rather than just children. Little evidence supports the effectiveness of this strategy, though [43]. Increased frequency of treatment is also a possibility. As reemergence may occur after high-coverage biannual treatment [13], distribution at more frequent intervals might be considered, though evidence for efficacy of this approach is scant. Moreover, in areas for which long, intensive efforts may be required to achieve elimination, reconsideration of the role of trachoma control programs in the broader context of health systems may be warranted. Integration of efforts to survey and distribute treatment with programs for other NTDs has been proposed [44,45], but little action has been taken. Given the resources that will be required of donors, program managers, and

other stakeholders, there may be substantial cost savings associated with such integration, or with incorporation of trachoma control into existing health system infrastructure.

Moreover, though this study can only quantify the “A” component of the SAFE strategy, this holistic approach was chosen for a reason. Trachoma serves as an object lesson that biochemical interventions can only go so far in the context of poor development. With additional rounds of treatment, we may reduce prevalence to below 5%, but antibiotics alone will not ensure that it stays there. For a program seeking real and sustainable elimination, it may be that no amount of time is long enough to achieve trachoma elimination without lasting change of the environment in which it persists.

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