OPEN LETTER
Insights from mathematical modelling and quantitative analysis on the proposed 2030 goals for trachoma [version 1; peer review: 2 approved with reservations]

NTD Modelling Consortium discussion group on trachoma

Abstract
Trachoma is a neglected tropical disease and the leading infectious cause of blindness worldwide. The current World Health Organization goal for trachoma is elimination as a public health problem, defined as reaching a prevalence of trachomatous inflammation-follicular below 5% in children (1-9 years) and a prevalence of trachomatous trichiasis in adults below 0.2%. Current targets to achieve elimination were set to 2020 but are being extended to 2030. Mathematical and statistical models suggest that 2030 is a realistic timeline for elimination as a public health problem in most trachoma endemic areas. Although the goal can be achieved, it is important to develop appropriate monitoring tools for surveillance after having achieved the elimination target to check for the possibility of resurgence. For this purpose, a standardized serological approach or the use of multiple diagnostics in complement would likely be required.

Keywords
Trachoma, Elimination as a public health problem, mass drug administration, surveillance, monitoring and evaluation

This article is included in the 2030 goals for neglected tropical diseases collection.
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Background
Trachoma is a neglected tropical disease caused by infection with the bacterium Chlamydia trachomatis. During an infection episode, conjunctival inflammation occurs, which leads to the presence of follicles on the eyelids (active trachoma, Trachomatous inflammation-follicular (TF)). Repeated infection with the bacteria over time, which results in scarring of the eyelids, leading to in-turning of the eyelashes, known as trachomatous trichiasis (TT), which traumatizes the eye surface leading to superinfection and blindness.

The World Health Organization leads an Alliance that aims to achieve the elimination of trachoma as a public health problem (EPHP) in all endemic districts by 2020, this is defined by the achievement of three goals: 1) reduction of TF prevalence in 1–9 year olds to <5% 2 years after mass drug administration (MDA) interventions have halted, 2) a TT prevalence unknown to the health system in >=15-year-olds of <0.2% , and 3) the presence of a system to identify and manage incident cases of TT. In order to eliminate trachoma, the WHO endorses the implementation of the SAFE strategy which consists of four components: (S) surgery to correct trichiasis; (A) mass distribution of antibiotics to clear infection in the community (topical tetracycline is used in very young children or other individuals unable to take azithromycin), (F) promotion of facial cleanliness in order to reduce transmission via eye discharge and (E) environmental improvement to ensure that the environment no longer helps to facilitate the transmission of infection. MDA is provided to all districts where TF is >5%. A course of three annual rounds is recommended to all regions where TF is between 10–30%, after which a follow-up survey is conducted to assess whether further rounds of MDA are required. To date, 9 countries have been validated by WHO as having achieved EPHP.

Both mathematical and statistical models have been developed to gain insight into the transmission dynamics of infection. Such models have been used to try and understand the potential impact of different intervention strategies that could help to accelerate elimination efforts, as well as understanding likely elimination timelines through forecasting. In addition, a recent review on the contribution of mathematical modelling to trachoma research and elimination efforts was published by the two teams in the first iteration of the NTD modelling consortium. Furthermore, a multi-group forecast comparison was also conducted to look at the strengths and limitations of different modelling approaches for forecasting the future prevalence of TF at the district level.

Moving forward past the current 2020 goals, whilst substantial progress has been made towards achieving EPHP of trachoma, it has become apparent that a number of endemic regions will not achieve this target by 2020. Therefore, WHO is planning to revise the timeline, with the aim of achieving EPHP in all endemic districts by 2030. Using the insights that have been gained from recent modelling work on trachoma, in this article we highlight the practical implications of EPHP (the timelines required, sufficiency of current surveillance diagnostics and feasibility of achieving it) and the future considerations that may be needed following EPHP to maintain the gains (Table 1 provides a summary of the key issues).

Table 1. Executive summary.

<table>
<thead>
<tr>
<th>Current WHO Goal</th>
<th>EPHP (TF threshold &lt;5% in children, TT prevalence unknown to the health system in adults &gt;=15 years of age of 0.2%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>2030 Target</td>
<td>Validation of EPHP for all countries, including identification and management of incident TT cases</td>
</tr>
<tr>
<td>Is the new target technically feasible under the current disease strategy?</td>
<td>Yes, except in certain hyperendemic settings (&gt;40% TF prevalence) using public health-level TT surgical services + MDA alone; there are technical challenges in measuring TT prevalence with useful precision.</td>
</tr>
<tr>
<td>If not, what is required to achieve the target? (updated strategy, use of new tools, etc.)</td>
<td>Enhanced campaigns to reduce the TF prevalence.</td>
</tr>
<tr>
<td>Are current tools able to reliably measure the target?</td>
<td>No. It is currently reported to be very unreliable. Standardization of grading by using smartphone photography may help to improve reliability.</td>
</tr>
<tr>
<td>What are the biggest unknowns?</td>
<td>The best strategy to monitor the disease after EPHP has been achieved. If or how does F&amp;E contribute to the achievement and maintenance of EPHP.</td>
</tr>
<tr>
<td>What are the biggest risks?</td>
<td>Resurgence after achieving EPHP; insufficient treatment/lack of understanding about what is happening in settings where transmission persists at a moderate level despite 10 rounds of MDA.</td>
</tr>
</tbody>
</table>
against active trachoma (TF)/ocular Chlamydia trachomatis infection, and thus the article will focus on changes, modelling and monitoring of TF and infection prevalence. Limited analysis and forecasting of TT prevalence to date has occurred in part because the trajectory of changes in TT prevalence depends not only on the incidence of TT (a chronic condition and stochastic process which may not only be dependent on an individual’s past number of infections), but also due to demography and health service access – the prevalent number of TT cases is also determined by the speed and efficiency of active case finding and surgical service delivery, which are inherently more challenging and uncertain to model.

Mathematical modelling and current surveillance data suggests that EPHP is feasible, and indeed has already been achieved by a number of endemic countries. However, in areas with long-term persistence, such as a few high prevalence districts in Ethiopia (>40% baseline prevalence), MDA alone is not sufficient to achieve EPHP and must be supplemented with additional tools which helps reduce transmission of infection over the long-term\(^6\)\(^{-}\)\(^8\). More intensive facial cleanliness and environmental improvement (F&E) or more intensive antibiotics are measures that will be necessary in a select few hot spots\(^6\)\(^{-}\)\(^8\). Similarly, statistical analysis of data provided and collected by trachoma endemic countries has indicated that the vast majority of endemic evaluation units (EUs) are on track to achieve TF <5% for EPHP by 2020\(^6\)\(^{16}\). These findings are consistent across both dynamic and statistical modelling frameworks that were independently developed by the different partners of our consortium.

In areas that remain problematic, to understand how EPHP may be achieved by 2030, dynamic modelling work has explored a range of alternative and more intensive antibiotic distribution strategies that could be implemented, even in areas with the highest rates of transmission\(^15\)\(^{-}\)\(^16\). To date it has been challenging to measure the true impact of F&E and its potential role in helping to reduce transmission, and thus it has been challenging to model, however an on-going clinical trial is seeking to help try and address this gap (Stronger SAFE). Although even if annual mass antibiotic treatment is insufficient to achieve EPHP goals in certain hyperendemic areas, it may prevent resurgence of infection\(^11\).

Modelling has also been used to investigate whether targeting a residual core group of children with additional antibiotic treatment, while continuing annual MDA to the entire EU would be more effective at clearing infection from the community than implementing a single annual dose\(^15\). The study suggested that if average duration of infection per group and dominant eigenvalue of a next generation matrix of the transmission model are defined, then a sufficient core group can be determined and used to find the absolute minimum sized core group, based on a fully specified model or even from epidemiological data. A number of RCTs are currently underway in Ethiopia with the design and hypotheses under investigation informed by modelling, with the aim of assessing the potential impact of alternative and intensive treatment strategies. One RCT (KETFO) is assessing whether quarterly treatment of children alone can lead to EPHP in severely affected communities\(^13\). Mathematical modelling of a double-dose antibiotic treatment strategy where two doses of antibiotics are given two weeks apart, in combination with enhanced F&E suggested that feasibility of EPHP may be increased in high transmission settings\(^4\). This modelling suggested that sustained F&E could help maintain the gains initially achieved through intense antibiotic distribution\(^4\). Additionally, two RCTs, one looking at intensive WASH (SWIFT-WUHA)\(^11\) and the second looking at the distribution of two doses of antibiotics one week apart (TESFA)\(^10\) are due to be trialled.

What are the practical implications of the currently proposed goals?

Measuring the target of EPHP using TF prevalence

The current monitoring and evaluation survey design has been useful to predict large-scale trends and to estimate evaluation unit (EU) level prevalence of TF (as intended). However, as TF prevalence continues to decline the sensitivity and specificity of the eye examination may also decline. As fewer cases are available to train graders and the severity of the cases decreases making them harder to confirm. Equally, as prevalence decreases, noise due to sampling variation increases\(^7\). Complete cost-effective modelling work is yet to be published, but using TF surveillance for the current end goal is becoming more expensive. Additionally, recent epidemiological studies in the South Pacific have highlighted that TF is apparent within communities in the absence of being able to identify C. trachomatis through PCR\(^8\). This has led the community to start considering whether evaluation by PCR or through serology may be more appropriate as prevalence continues to decline\(^8\)\(^{20}\).

However, to date limited data with all three diagnostics where TF is ~5% have been available to understand if or how all diagnostic indicators relate to each other at low prevalence. Some recent modelling sought to evaluate the relationship between TF and serological prevalence\(^2\); however, more data are needed to test the robustness of these findings. Collectively, current modelling and surveillance data suggest that as we move towards 2030 the target (currently TF prevalence) measured may need to vary by region and be tailored to the underlying epidemiology of certain areas.

Ability to sustain achievement of the goal

Trials and longitudinal studies have found that after MDA, infection can return\(^1\)\(^11\)\(^2\), however these were locations where TF prevalence had not declined to <5%\(^1\)\(^2\). It has been suggested that infection could re-emerge due to the loss of age-specific immunity as transmission reduces\(^1\); however to date no re-emergence has been detected in districts that have eliminated trachoma. Since TF prevalence is a lagging indicator, TF-driven programmatic activities may continue long enough to frequently achieve near elimination of C. trachomatis infection. PCR as an alternative indicator for detecting resurgent infection has a number of problems, not least the short duration of infection\(^1\). Moreover, it can be fairly costly and requires specialized equipment and technicians, therefore it can be challenging to implement, albeit capacities in many trachoma-endemic countries are improving. Nevertheless, demonstrating that the causative agent of infection is absent in endemic or formally endemic communities is the key indicator of breaking transmission. In the absence of dedicated
post-elimination TF prevalence surveys, serological studies may be able to detect substantial resurgence in transmission despite imperfect antibody specificity\textsuperscript{21}.

Where are there risks that need to be mitigated to achieve and maintain the stated goals?

There are a number of practical factors that may directly impact on-going program implementation that may need to be considered and mitigated against as programmes continue. Firstly, both empirical data and dynamic modelling have suggested that in areas of high prevalence MDA alone is not sufficient to reach the goal\textsuperscript{20,24}. As previously described, a number of alternative intervention strategies are currently being evaluated within RCTs to try and mitigate against this problem. Secondly, maintaining and optimising the frequency of antibiotic use is of paramount importance in order for gains to be achieved and maintained. Coverage is often reported to be high, but in practice this can be hard to measure in the field\textsuperscript{3}. Equally, systematic non-access, particularly amongst those who are also not included in surveys, may limit progress in reducing transmission by leaving reservoir sources of infection in communities that are deemed to have been treated\textsuperscript{26}. Thirdly, to date, no resistance to azithromycin has been reported, however careful monitoring for suboptimal treatment effects is needed because if resistance does emerge, EPHP success will be severely undermined\textsuperscript{4}. Fourthly, as prevalence begins to decline in many endemic regions, movement of individuals between infected and uninfected areas may facilitate persistence of infection or re-introduction into formerly infection-free areas.

A number of risks remain for surveillance in terms of classifying and continuing to confirm elimination. First of all, it is currently uncertain whether or not TF prevalence is specific enough to classify EUs that have achieved EPHP\textsuperscript{21,27,28}. Due to the non-linearity in the relationship between PCR detectable infection and TF at low-levels understanding how the two diagnostics relate to one another and truly reflect transmission can be challenging. Additionally, TF has been detected in some areas of the world without the bacterial organism being identified, suggesting that other factors besides trachoma may also cause TF. Equally, following validation, it is currently uncertain how to conduct surveillance to ensure that EPHP is maintained. Serology has been suggested as one potential option, although post-validation sero-surveillance data are only starting to become available now. Nevertheless, the current lack of post-validation strategy is a risk for the long-term success of the programs.

There are a number of risks that we need to be mindful of with respect to modelling trachoma and also interpreting the model outputs. In all modelling to date it has been assumed that our ability to detect TF remains the same and will be so in the future. However, this is an optimistic assumption, as we expect ability to recognize TF to decrease as the disease becomes rarer. Therefore, models are likely to need refining as we begin to focus on modelling surveillance in very low transmission scenarios. Importantly, there are no high-resolution empirical studies on dynamics of infection in areas with hypo-endemic disease, which means that simulations modelling low-level prevalence are likely to have a large number of uncertainties. Therefore, further empirical studies and modelling work are needed in order to understand how to more accurately model transmission at low prevalence.

Future directions

What kind of new diagnostics could be used for post-validation surveillance?

As prevalence and transmission of trachoma declines, the specificity of TF as a diagnostic indicator of conjunctival CT infection is also reported to decline\textsuperscript{28,29}. Equally, following elimination of TF there is likely to be limited funding dedicated to TF surveillance to monitor and verify elimination. Therefore, it will be important to understand what alternative diagnostics can tell us about transmission of trachoma, one such diagnostic being the use of serology.

If serology is informative, the opportunity for trachoma post-validation surveillance increases as dried blood spots collected for other health programs have the potential to be used to also test for a response to trachoma antigens\textsuperscript{30,32}. As such, although not specifically within the 2030 targets, research into the utility of sero-surveillance for understanding and quantifying transmission is of importance for trachoma elimination. A number of individual modelling analyses have been conducted to try and estimate sero-conversion rates (SCRs) for trachoma within different settings\textsuperscript{31,33,34}. However, individual modelling analyses of datasets in isolation make it difficult to understand the global picture. A more recent modelling analysis collated datasets with TF and sero-surveillance from a number of endemic regions\textsuperscript{33} which estimated the SCRs from multiple different study sites and correlated these with the reported TF prevalence. This work was the first attempt to estimate an operational threshold for serology for trachoma programs. Modelling suggested that SCRs below 0.015 (95% confidence interval (CI): 0.0–0.049) per year corresponded to a prevalence of TF below 5%, the current threshold for elimination of active trachoma as a public health problem\textsuperscript{21}. Additionally, in terms of understanding the operational feasibility of conducting sero-surveys for trachoma, a statistical analysis suggested that sero-surveillance would require smaller sample sizes for any given level of prevalence than TF because the level of sero-prevalence that programs would be measuring is higher than the TF prevalence\textsuperscript{31}.

It is also important to highlight that results from this modelling study suggest that further work is required before serology can be recommended as a post-validation surveillance tool. One existing limitation is that current analyses are being done using both bead-based multiplex immunoassay systems, ELISA and lateral flow assays; standardization would aid comparison between sites. Additionally, it is unclear exactly what the population-level serological profile looks like in areas with sustained subcritical transmission of ocular C. trachomatis. A greater understanding of this is required before one can interpret serological data for trachoma in the context of post-validation surveillance.

What questions can modeling help address?

In discussion with WHO, a number of priority issues and questions for trachoma control programs were identified. These questions are summarized in Table 2 and describe how...
Table 2. Priorities issues and how modelling can help to address them.

<table>
<thead>
<tr>
<th>Priority issue/question identified in discussion with WHO</th>
<th>How can modelling address this?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forecasting expected timeline to reach the goals</td>
<td>Probabilistic forecasts can be developed using statistical and mechanism-based models. These forecasts must obviously be taken with caution, understanding the assumptions made and the uncertainty in the outcomes predicted.</td>
</tr>
<tr>
<td>How likely/unlikely is resurgence, how quickly is it likely to emerge and be detected and where is it more likely to emerge?</td>
<td>One approach is to analyse data from districts that return to TF prevalence &gt;5% and assess the likelihood of true resurgence versus misclassification error, and compare it with outputs from resurgence in stochastic models. Our group has been working on this, using data collected by Trachoma endemic countries and adapting the population-based deterministic model in 17 to be stochastic (unpublished). To better understand timeliness of resurgence and where it is more likely to occur, scenario-based simulations could be potentially used, but eventually a more spatially explicit model would be needed. To inform such a model, a review of empirical studies is required, which can help inform changes in endemic areas. These models would have to include diagnostics in an explicit manner, so that surveillance approaches and detection of resurgence can be appropriately assessed.</td>
</tr>
<tr>
<td>A geospatial survey design for TT</td>
<td>To produce a geospatial survey design, geostatistical models can be used that can account for both spatial and temporal uncertainty in the TT estimates. This will improve survey design and will lead to a better understanding of the needs at fine geographical scales. However, this approach requires spatially explicit data.</td>
</tr>
<tr>
<td>What is the utility of serology in Identification of current hot spots and future resurgence</td>
<td>Modelling work has been carried out to analyse whether serological data is informative of patterns of transmission and whether it could be used, as global prevalence declines, as a tool to inform programmatic decisions21. More serological data will be available in the future that can be integrated to models already developed to tackle the identification of potential hotspots.</td>
</tr>
</tbody>
</table>

mathematical and statistical modelling can potentially help address them.

Data availability
No data are associated with this article.

Acknowledgments
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RTI International, Washington, DC, USA

Rebecca Flueckiger
RTI International, Washington, DC, USA

This review describes the application of mathematical modelling and analyses in informing approaches to reach the elimination of trachoma as a public health problem. The authors focus on the “active stage of the disease”, trachomatous inflammation-follicular (TF), and the challenges around the A, F and E components of the SAFE strategy and measuring prevalence of TF in low endemic settings.

Throughout the paper acronyms are not consistently defined when they are first used and the terms district/region/evaluation unit are used interchangeably. I suggest the authors edit the review for consistency.

Background:

- The authors describe the natural pathway of progression from TF to TT. This is a key piece of information for the reader to understand and the current language in this section is unclear. I suggest rewording the sentence in the first paragraph of the background starting “Repeated infection with the bacteria...”. I also suggest changing the citation to Mabey et al. (2003).  

- In the second paragraph the authors describe the elimination targets and the intervention strategy. However, background on how the targets are measured is not included. I think it would be helpful for the reader to be provided with some background on the current clinical grading practices to set the stage for the future sections where the authors discuss challenges with the current practices in the context of low endemicity.

- Also, in the second paragraph, the authors describe three goals. We’d recommend the language of the first goal be more accurate and remove the language “2 years after MDA interventions have halted”. It is “at least 2 years” and this is not typically included in the standard WHO language.
• In the second paragraph the authors state, “MDA is provided to all districts where TF is >5%”. Is this accurate? I think it is probably more correct to say the MDA is recommended, as not all districts are able to conduct MDA for a variety of reasons. Also, the section describes MDA recommendations where TF is between 10-30%. What are the recommendations for areas where TF is >30%?

• In the fourth paragraph the authors state, “WHO is planning to revise the timeline, with the aim of achieving EPHF in all endemic districts by 2030”. The same idea is presented in Table 1 and in the abstract. This is not consistent with our understanding; the latest draft WHO NTD roadmap for 2030 is more nuanced and does not target “all endemic districts”. Is there a citation for the targets the authors are using? If not, we recommend the publicly available documents from WHO on their target revision and the new roadmap:
https://www.who.int/neglected_diseases/mediacentre/Intro_to_Roadmap_Narrative_v3.pdf

• It may also be useful to note that the original 2020 goals were political and aspirational, not based on data. Thanks to the efforts of ministries of health and countless donors and partners, the global campaign goals can now be based on data.

Section 2:
• In the fourth paragraph the authors note, “To date it has been challenging to measure the true impact of F&E...”. Why is this the case? Is there a citation that can backup this statement?

Section 3:
• In the first paragraph I suggest citing Stelmach et al. (2019).

• There is a typo in the last sentence of the first paragraph “underlying epidemiology”.

Table 2:
• In the geospatial survey design for TT section, I suggest citing “Flueckiger et al. (2019)’

References

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Yes
Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Partly

Is the Open Letter written in accessible language?
Partly

Where applicable, are recommendations and next steps explained clearly for others to follow?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** trachoma epidemiology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 09 January 2020

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Isobel M. Blake
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This is a well written review describing the insights mathematical and statistical analyses have provided on the 2030 goals of trachoma. Recent research is adequately cited, and the article outlines future work that needs to be addressed to help reach these goals.

One point which is unclear to the reader is the geographic scale of reaching the 2030 target. The abstract states that 2030 is a realistic timeline for EPHP in “most” trachoma endemic areas. It is unclear to the reader the geographical scope of how many ‘areas’ there are and what does “most” mean? Are there any countries where the prevalence of TF is unknown? Have there been any quantitative analyses showing the expected time delays on mapping, and initiating MDA to know whether EPHP is achievable if there are countries that are yet to initiate control?

The text outlines the limitations of modelling, of which a large component is the need for more empirical data to inform the analyses to hence support control guidelines. Perhaps a summary box outlining the key data needs would help strengthen this message.

There are also some minor clarifications that could be made to the text:

1. The text uses different spatial definitions: district, area, evaluation unit and it is not clear to the reader whether these refer to the same spatial unit or not.
2. Please provide a reference for which countries have achieved EPHP or state what these countries are. On page 4 last paragraph, it says no re-emergence has been detected in districts that have eliminated trachoma. Were any of these settings hyperendemic when SAFE started? Are they representative of current high prevalence settings where F&E might be low?

3. The absence of *C. trachomatis* in children with TF seems an important phenomenon to understand better for the 2030 goals. Is there data indicating the duration of TF clearance in the absence of *C. trachomatis* absence? Is the delay a few weeks or substantially longer? As there are other causes of TF as the authors state, will there be scenarios where the trachoma control will need to continue despite the absence of *C. trachomatis* or might the guidelines be revised to aim to eliminate *C. trachomatis*?

4. Page 4 last paragraph, it says the short duration of infection is a problem for PCR. Could you expand on this? Do you mean there is a shorter time window to detect infection compared to the time window to observe TF?

5. MDA coverage is touched on in one section at the top of page 5 but have there been any quantitative analyses to investigate variability in coverage across different geographies? I think there needs to be a reference to support the statement that coverage is reported to be high.

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Partly

**Is the Open Letter written in accessible language?**

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I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.