



OPEN LETTER

REVISED **Insights from mathematical modelling and quantitative analysis on the proposed 2030 goals for trachoma [version 2; peer review: 2 approved]**

NTD Modelling Consortium discussion group on trachoma

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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.

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

In response to reviewer comments, we have updated and clarified the wording of the manuscript throughout, including amendments to the tables. The language used has been aligned more with WHO policy and a number of additional references have been added.

Any further responses from the reviewers can be found at the end of the article

Disclaimer

The views and opinions expressed in this article are those of the author(s) and do not necessarily reflect the views of the World Health Organization. Publication in Gates Open Research does not imply endorsement by the Gates Foundation.

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 (Trachomatous inflammation-follicular (TF))¹. Repeated infection with the bacteria over time, which results in scarring of the eyelids, leads to in-turning of the eyelashes. This is known as trachomatous trichiasis (TT), which traumatizes the eye surface leading to superinfection and blindness^{1,2}.

The World Health Organization leads an Alliance that aims to achieve the elimination of trachoma as a public health problem (EHP) in all endemic districts by 2020¹. This is defined by the achievement of three goals: 1) reduction of TF prevalence in 1–9 year olds to <5% in each formerly endemic district, 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. Currently, the prevalence of clinically active trachoma is assessed by trained graders’ clinical examination. In the context of low endemicity, other methods are being considered, including photographic and laboratory assessment. MDA is recommended to all districts where TF is >5%. A course of one, three, or five annual rounds is recommended where TF is between 5–10%, 10–30%, and over 30% respectively. Following completion of the prescribed MDA, a follow-up survey is conducted to assess whether further rounds of MDA are required. To date, ten countries have been validated by WHO as having achieved EHP³.

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 efforts⁴, 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 consortium⁵. 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 level⁶.

Moving forward past the current 2020 goals, whilst substantial progress has been made towards achieving EHP of trachoma, it has become apparent that a number of endemic regions will not achieve this target by 2020. It is important to note that the original 2020 goals were political and aspirational, and thanks to the effort of ministries of health and countless donors and partners over the years can now be formally assessed with data. Therefore, WHO has revised the timeline, with the aim of validating EHP in all endemic countries by 2030. Using the insights that have been gained from recent modelling work on trachoma, in this article we highlight the practical considerations of EHP (the timelines required, sufficiency of current surveillance diagnostics and feasibility of achieving it) and the future considerations that may be needed following EHP to maintain the gains (Table 1 provides a summary of the key issues).

What have we learned from the past 10 years that we can apply for the next 10 years?

There has been a substantial amount of programmatic success in trachoma elimination over the last 10 years, with global prevalence falling dramatically as a result of successful intervention programs. Whilst EHP includes both TF and TT, most research focuses 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 observed TT prevalence depends not only on the incidence of TT (a chronic condition and stochastic process related to an individual’s past number of infections⁷), but also due to demography and health service access. Thus the observed prevalent number of TT cases is partly 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 EHP is feasible, and indeed has already been achieved by a number of endemic countries³. However, in health districts with long-term persistence, such as a few high prevalence districts in Ethiopia (>40% baseline prevalence), annual MDA alone is not sufficient to achieve EHP and must be supplemented with additional tools to reduce transmission^{6,8–10}.

Table 1. Executive summary.

Current WHO Goal	Validation of EPHP (TF threshold <5% in children, TT prevalence unknown to the health system in adults ≥ 15 years of age of 0.2%).
2030 Target	Validation of EPHP for all countries, including identification and management of incident TT cases.
Is the new target technically feasible under the current disease strategy?	Except in certain hyperendemic settings (>40% TF prevalence) EPHP is achievable using public health-level TT surgical services + annual MDA alone.
If not, what is required to achieve the target? (updated strategy, use of new tools, etc.)	Enhanced MDA campaigns to reduce the TF prevalence.
Are current tools able to reliably measure the target?	No. It is currently reported to be very unreliable. Standardization of grading by using smartphone photography may help to improve reliability. There are also technical challenges in measuring TT prevalence with useful precision.
What are the biggest unknowns?	1) The best strategy to monitor the disease after EPHP has been achieved. 2) If or how does F&E contribute to the achievement and maintenance of EPHP.
What are the biggest risks?	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.

In particular, more intensive facial cleanliness and environmental improvement (F&E) or more intensive antibiotics are measures that may be necessary in a select few hot spots^{4,8,11}. Similarly, statistical analysis of data provided and collected by trachoma endemic countries has indicated that the vast majority of endemic health districts are on track to achieve TF <5% for EPHP by 2020^{6,8}. These findings are consistent across both dynamic and statistical modelling frameworks that were independently developed by the different partners of our consortium.

In health districts 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^{4,12}. 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. A few field studies that have assessed F&E were unable to find a significant effect^{13–15}. However, an on-going clinical trial is seeking to help address this gap in knowledge (Stronger SAFE). Even if annual mass antibiotic treatment is insufficient to achieve EPHP goals in certain hyperendemic areas, it may prevent resurgence of infection¹⁶.

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 population would be more effective at clearing infection from the community¹⁷. 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 separate mathematical model 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 settings¹⁸. This modelling suggested that sustained F&E could help maintain the gains initially achieved through intense antibiotic distribution¹⁸.

A number of RCTs informed by modelling are currently underway in Ethiopia, 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 communities¹⁹. Additionally, an RCT looking at intensive WASH (SWIFT-WUHA)²⁰ and an RCT looking at the distribution of two doses of antibiotics one week apart (TESFA²¹) are in progress.

What are the practical considerations of the currently proposed goals?

Measuring the target of EPHP using TF prevalence

The current monitoring and TF survey design has been useful to predict large-scale trends and to estimate health district level prevalence of TF¹. However, as TF prevalence continues to decline, fewer cases are available to train graders and the decreasing severity of cases decreases make them harder to confirm. Thus, the sensitivity and specificity of the eye examination may decline. Equally important, noise due to sampling variation increases as prevalence decreases²².

Complete cost-effective modelling work is yet to be published, but using TF surveillance for the current end goal is becoming more expensive²³. 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 PCR²⁴. This could be due to the fact that at the community level, TF resolves slowly²⁵. This has led the community to start considering whether evaluation by PCR or through serology may be more appropriate as prevalence continues to decline^{26,27}. However, limited data with all three diagnostics where TF is ~5% have been available to understand how all diagnostic indicators relate to each other at low prevalence. Some recent modelling sought to evaluate the relationship between TF and serological prevalence²⁸; 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 TF prevalence target may need to vary by health district 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^{9,16,29} in locations where TF prevalence had not declined to <5%^{16,29}. It has been suggested that infection could re-emerge due to the loss of age-specific immunity as transmission reduces³⁰, however to date re-emergence has not been detected in districts that have eliminated trachoma (TF < 5%), that cannot be explained by misclassification error³¹. Since TF prevalence is a lagging indicator, TF-driven programmatic activities may continue long enough to frequently achieve near elimination of *C. trachomatis* infection.

Demonstrating that the causative agent of infection is absent in endemic or formally endemic communities is the key indicator of breaking transmission. PCR as an alternative indicator for detecting resurgent infection has a number of problems, not least the short duration of infection, which limits the time-window it can be detected²². Modelling work has shown that including PCR data does not significantly improve forecasts of TF³². Moreover, it can be fairly costly and requires specialized equipment and technicians. However, capacities in many trachoma-endemic countries are improving. In the absence of dedicated post-elimination TF or PCR prevalence surveys, serological studies may be able to detect resurgence in transmission despite imperfect antibody specificity²⁸.

What risks need to be mitigated to achieve and maintain the 2030 goals?

There are a number of practical factors that may directly impact on-going program implementation. Firstly, both empirical data and dynamic modelling have suggested that in areas of high prevalence, annual MDA alone is not sufficient to reach the goal^{5,11,33}. As previously described, a number of alternative intervention strategies are currently being evaluated within RCTs

to identify solutions to 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 high³⁴, but in practice this can be hard to measure in the field³⁵. Equally, systematic variation within Health districts leading to local pockets of undelivered MDA and exclusion from TF surveys, may limit progress by leaving reservoir sources of infection in communities that are deemed to have been treated³⁶. Thirdly, no resistance to azithromycin has been reported, however careful monitoring for suboptimal treatment effects is needed. If resistance does emerge, EPHP success will be severely undermined⁵. 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 alone is sufficient to classify health districts that have achieved EPHP^{28,37,38}. Meanwhile, the non-linear relationship between viral load and TF complicates our understanding of how PCR detection and TF relate to one another. In fact, 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. In short, following EPHP, it is unclear how to conduct surveillance to ensure that EPHP is maintained. Serology has been suggested as one potential option, although sero-surveillance data in EPHP settings are only starting to become available.

There are a number of risks that we need to be mindful of with respect to modelling trachoma and interpreting model outputs. It is typically assumed that the accuracy of TF detection will remain constant. However, this is an optimistic assumption, as we expect the ability to recognize TF to decrease as the disease becomes rarer. This issue will become particularly important as modelling surveillance in very low transmission scenarios receives greater attention. Importantly, there are no high-resolution empirical studies on dynamics of infection in areas with hypo-endemic disease, which means that simulations and models of low-level prevalence are likely to have a large number of uncertainties. Further empirical studies 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^{38,39}. 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, such as serology, can tell us about the prevalence and transmission of trachoma.

If serology is informative, the opportunity for trachoma post-validation surveillance increases as dried blood spots collected for other health programs might be screened for trachoma antibodies^{40–42}. As such, although not specifically within the 2030 targets, research into the utility of sero-surveillance for understanding and quantifying transmission is important 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^{40,41,43}. However, individual modelling analyses of datasets in isolation make it difficult to understand the global picture. A more recent modelling analysed TF prevalence and serology data from a number of endemic regions²⁸ to estimate the SCRs and correlate 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%²⁸. Additionally, a statistical analysis suggested that sero-surveillance would require smaller sample sizes than TF surveillance because sero-prevalence is higher than the TF prevalence²⁸.

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 bead-based multiplex immunoassay systems, ELISA and lateral flow assays; standardization would aid comparison between sites. Additionally, it is unclear exactly what the quantitative population-level serological profile is expected to be in areas with sustained EPHP. A greater understanding of this is required before one can interpret serological data for trachoma in the context of post-EPHP 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 mathematical and statistical modelling can help address them.

What are the data needs?

From a modelling perspective, additional high quality data never hurts. However, since data can be so challenging to acquire, modelling techniques need to be adjusted for the limitations of data. When parameterization is challenging, models can highlight the specific type of data that would be particularly useful. A key challenge will be to maintain the advances in the reproducibility and reliability of TF prevalence surveys. Meanwhile, as new data elements such as serology are incorporated into models, it will be important to understand the measurement process so that relevant observation bias can be incorporated.

Table 2. Priorities issues and how modelling can help to address them.

Priority issue/question identified in discussion with WHO	How can modelling help?
Forecasting expected timeline to reach the goals	Probabilistic forecasts can be developed using statistical and mechanism-based models. However, these forecasts must be taken with caution by understanding the assumptions made and the uncertainty in the predicted outcomes.
How likely/unlikely is resurgence, how quickly is it likely to emerge and be detected and where is it more likely to emerge?	One approach is to analyze data from districts that return to TF prevalence >5% and compare it with outputs from resurgence in stochastic models. Our group has been working on assessing the likelihood of true resurgence versus misclassification error, using data collected by Trachoma endemic countries and adapting a stochastic version of the population-based model in 22,32 . To better understand timeliness of resurgence and where it is more likely to occur, scenario-based simulations could be potentially used. To inform such a model, a review of empirical studies is required, which can help inform the spatial variability. These models would benefit from including diagnostics in an explicit manner, so that surveillance approaches and detection of resurgence can be appropriately assessed.
A geospatial survey design for TT	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 ⁴⁴ . However, this approach requires spatially explicit data.
What is the utility of serology in Identification of current hot spots and future resurgence	Modelling work has been carried out to analyze whether serological data is informative of patterns of transmission and whether it could be used to inform programmatic decisions ²⁸ . More serological data will be available in the future that can be integrated to models already developed to tackle the identification of potential hotspots and post-EPHP monitoring.

Data availability

No data are associated with this article.

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Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 10 May 2021

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 **Isobel M. Blake** 

Department of Infectious Disease Epidemiology, Imperial College London, London, UK

I have reviewed this new version and the authors have responded to my original comments sufficiently. I would like to thank the authors for taking the time to do this and for their response. I am happy for the status to be amended to 'Approved'.


Competing Interests: No competing interests were disclosed.

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.

Reviewer Report 06 April 2021

<https://doi.org/10.21956/gatesopenres.14449.r30502>

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 **Lisa A. Rotondo**
RTI International, Washington, DC, USA

Rebecca Flueckiger 
RTI International, Washington, DC, USA

It does appear that the authors have addressed all concerns.

Competing Interests: No competing interests were disclosed.

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.

Version 1

Reviewer Report 10 February 2020

<https://doi.org/10.21956/gatesopenres.14228.r28446>

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**Lisa A. Rotondo**

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.* (2003¹).
- 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 EPHP 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.* (2019²).
- 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.* (2019³).

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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.

Author Response 02 Feb 2021

Joaquin M. Prada, University of Surrey, UK

We thank the reviewers for their insightful comments and suggestions. We have addressed all suggestions, as well as updated the text for additional clarity. Our response below in italics.

Reviewers 2:

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.

We have updated throughout to “health district” 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.* (20031).

We have updated the text to clarify the pathway of progression, as suggested, and added the reference.

- 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.

Added: "Currently, the prevalence of clinically active trachoma is assessed by trained graders' clinical examination. In the context of low endemicity, other methods are being considered, including photographic and laboratory assessment."

- 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.

We have clarified the text and aligned it with 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%?

We have updated and clarified the text.

- In the fourth paragraph the authors state, "WHO is planning to revise the timeline, with the aim of achieving EPHP 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

We have clarified that the aim is validation of EPHP throughout the text.

- 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.

We have added this in the fourth paragraph.

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?

*We have clarified that field studies that have assessed F&E have been unable to find a significant effect and added three references (Lockwood *et al.*, 2014; Stoller *et al.* 2011, Ejere *et al.* 2015).*

Section 3:

- In the first paragraph I suggest citing Stelmach *et al.* (20192).

Added the reference.

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

Corrected.

Table 2:

- In the geospatial survey design for TT section, I suggest citing “Flueckiger *et al.* (20193).

Reference added

Competing Interests: None

Reviewer Report 09 January 2020

<https://doi.org/10.21956/gatesopenres.14228.r28315>

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Isobel M. Blake

Department of Infectious Disease Epidemiology, Imperial College London, London, UK

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?

Yes

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

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious Disease Epidemiology

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.

Author Response 29 Jan 2021

Joaquin M. Prada, University of Surrey, UK

We thank both reviewers for their insightful comments and feedback. We have clarified and addressed all their comments, as well as updated the text to add additional clarity where needed. We have added our response in italics below.

Reviewer 1:

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?

We have clarified in the abstract that elimination as a public health problem is for all endemic health districts (in all endemic countries). Current goal set by WHO is to validate 64 countries by 2030. We have also updated the text throughout to clarify the spatial units we refer to are health districts (which are the practical implementation units of the interventions).

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.

We apologize if we came across as requesting more and more data! That's the perennial excuse of modellers. More data is always nice. However, since data can be so challenging to acquire, we need to adjust our modelling techniques for the limitations of data. Such models could also highlight which data would be particularly useful. We have added a section at the end of the manuscript to this effect.

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

- 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.

We have now for consistency used the term health district throughout (as mentioned above, these are the implementation units) or alternatively countries.

- 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?

We have reworded this to clarify that there is no evidence that re-emergence can't be explained by

misclassification error (Godwin et al 2020). We have also added a web citation for the number of countries achieving EPHP.

- 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*?

We have clarified in the text that at the community level, TF resolves slowly (Keenan et al, 2011).

Moreover, the non-linear relationship between viral load and TF makes understanding the relationship between PCR and TF challenging.

- 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?

We have clarified this in the text, indeed, the time window for detect positive individuals by PCR is smaller. Moreover, modelling work has shown that including PCR data does not significantly improve forecasts of TF (Liu et al. 2015).

- 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.

We have added a reference for this statement (Astale et al. 2018).

Competing Interests: No competing interests were disclosed.