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Using model-based geostatistics for assessing the elimination of trachoma

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Abstract:	Background Trachoma is the commonest infectious cause of blindness worldwide. Efforts are being made to eliminate trachoma as a public health problem globally. However, as prevalence decreases, it becomes more challenging to precisely predict prevalence. We demonstrate how model-based geostatistics (MBG) can be used as a reliable, efficient, and widely applicable tool to assess the elimination status of trachoma.

	Methods We analysed trachoma surveillance data from Brazil, Malawi, and Niger. We developed geostatistical Binomial models to predict trachomatous inflammation—follicular (TF) and trachomatous trichiasis (TT) prevalence. We proposed a general framework to incorporate age and gender in the geostatistical models, whilst accounting for residual spatial and non-spatial variation in prevalence through the use of random effects. We also used predictive probabilities generated by the geostatistical models to quantify the likelihood of having achieved the elimination target in each evaluation unit (EU). Results TF and TT prevalence varied considerably by country, with Brazil showing the lowest prevalence and Niger the highest. Brazil and Malawi are highly likely to have met the elimination criteria for TF in each EU, but, for some EUs, there was high uncertainty in relation to the elimination of TT according to the model alone. In Niger, the predicted prevalence varied significantly across EUs, with the probability of having achieved the elimination target ranging from values close to 0% to 100%, for both TF and TT. Conclusions We demonstrated the wide applicability of MBG for trachoma programmes, using data from different epidemiological settings. Unlike the standard trachoma prevalence survey approach, MBG provides a more statistically rigorous way of quantifying uncertainty around the achievement of elimination prevalence targets, through the use of spatial correlation. In addition to the analysis of existing survey data, MBG also provides an approach to identify areas in which more sampling effort is needed to improve EU classification. We advocate MBG as the new standard method for analysing trachoma survey outputs.
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24th May 2023

Dear Alberto Novaes Ramos Jr and Elsio Wunder Jr

Re: "Using model-based geostatistical models for assessing the elimination of trachoma"

Herewith, we wish to submit the revised manuscript for consideration for publication as an original research article in the PLOS Neglected Tropical Diseases (NTDs).

Revisions were made following reviewers' comments. Point-by-point responses were submitted separately.

All authors have read and approved the final version of the manuscript. We approve this manuscript for publication, declare that the manuscript has not been considered for publication elsewhere, and that these results have never been reported. We also declare that if accepted, the paper will not be published elsewhere in the same form, in English or in any other language, without written consent of the copyright holder.

Yours sincerely

Misaki Sasanami
Lancaster University, UK

Using model-based geostatistics for assessing the elimination of trachoma

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Abstract

Background

Trachoma is the commonest infectious cause of blindness worldwide. Efforts are being made to eliminate trachoma as a public health problem globally. However, as prevalence decreases, it becomes more challenging to precisely predict prevalence. We demonstrate how model-based geostatistics (MBG) can be used as a reliable, efficient, and widely applicable tool to assess the elimination status of trachoma.

Methods

We analysed trachoma surveillance data from Brazil, Malawi, and Niger. We developed geostatistical Binomial models to predict trachomatous inflammation—follicular (TF) and trachomatous trichiasis (TT) prevalence. We proposed a general framework to incorporate age and gender in the geostatistical models, whilst accounting for residual spatial and non-spatial variation in prevalence through the use of random effects. We also used predictive probabilities generated by the geostatistical models to quantify the likelihood of having achieved the elimination target in each evaluation unit (EU).

Results

TF and TT prevalence varied considerably by country, with Brazil showing the lowest prevalence and Niger the highest. Brazil and Malawi are highly likely to have met the elimination criteria for TF in each EU, but, for some EUs, there was high uncertainty in

relation to the elimination of TT according to the model alone. In Niger, the predicted prevalence varied significantly across EUs, with the probability of having achieved the elimination target ranging from values close to 0% to 100%, for both TF and TT.

Conclusions

We demonstrated the wide applicability of MBG for trachoma programmes, using data from different epidemiological settings. Unlike the standard trachoma prevalence survey approach, MBG provides a more statistically rigorous way of quantifying uncertainty around the achievement of elimination prevalence targets, through the use of spatial correlation. In addition to the analysis of existing survey data, MBG also provides an approach to identify areas in which more sampling effort is needed to improve EU classification. We advocate MBG as the new standard method for analysing trachoma survey outputs.

Author Summary

Trachoma is the most common infectious cause of blindness worldwide. Achieving elimination in resource-limited settings requires pragmatic strategies, including for determining the likelihood that the elimination prevalence targets have been reached. Model-based geostatistics (MBG) is a branch of spatial statistics that can underpin highly efficient methods for designing surveys and analysing surveillance data for NTD programmes. Here, we illustrate the application of the MBG framework to analyse trachoma surveillance data from Brazil, Malawi, and Niger. Using the elimination criteria set by WHO, we predict the likelihood of elimination thresholds for trachomatous inflammation—follicular (TF) and trachomatous trichiasis (TT) having been achieved in each evaluation unit in each of the three countries. MBG is a statistically rigorous approach to quantify the likelihood around the

exceedance of elimination prevalence thresholds. By providing a way to identify areas where there is more uncertainty about the achievement of elimination, MBG could be used to select areas in which more intensive sampling efforts should be undertaken.

Introduction

Trachoma, one of twenty neglected tropical diseases (NTDs), remains the leading infectious cause of blindness globally [1,2]. It is caused by the bacterium *Chlamydia trachomatis,* which is transmitted from person to person by ocular and nasal secretions of infected people, during direct contact between individuals, or indirectly via flies or fomites [3–5]. Trachoma is prevalent in the most deprived and marginalised communities where crowded living conditions are common and access to clean water and sanitation is limited [2,6–9]. In endemic areas, trachomatous inflammation—follicular (TF), a sign of active trachoma, is common among children aged 1–9 years [2,10]. After years of repeated infections, some individuals develop prominent conjunctival scarring and have their upper eyelids turn inward so that the eyelashes rub against the globe. This is referred to as trachomatous trichiasis (TT), which can require surgery to prevent visual impairment and blindness [2]. TT and loss of vision are generally more common in women than in men [11,12], since the former are more likely to care for young children and therefore be exposed to more episodes of infection [2]. Although blindness caused by trachoma is generally considered irreversible, it is possible to prevent it, primarily using the surgery, antibiotics, facial cleanliness, and environmental improvement (SAFE) strategy promoted by the World Health Organization (WHO) [13,14].

In 1996, WHO launched the WHO Alliance for the Global Elimination of Trachoma by 2020 (GET2020) to eliminate trachoma as a public health problem [15]. Elimination is defined as: (i) a prevalence of TT unknown to the health system < 0.002 (0.2%) in adults aged ≥ 15

years, in each formerly endemic evaluation unit (EU) and (ii) a prevalence of TF < 0.05 (5%) in children aged 1–9 years, in each formerly endemic EU; plus (iii) the presence of a system to identify and manage incident cases of TT, which are expected to arise for many years after the prevalence thresholds (i) and (ii) are met. An EU for assessment of elimination is defined as the administrative unit for health care management, which typically contains a population of between 100,000 and 250,000 persons [16]. In the standard approach, the age- or age- and gender-specific prevalences of TF among children aged 1–9 years or TT among adults aged ≥ 15 years, respectively, are calculated. They are then standardised using the proportion of population expected to have that age or age-gender, according to the most recent census data available [17]. At the time of acceptance of this paper in May 2023, 17 countries had been validated by WHO as having eliminated trachoma as a public health problem [18].

The decision on whether a country has achieved the elimination criteria has to be informed by accurate and precise estimates of disease prevalence. This can be challenging in settings with very low prevalence and spatially sparse data, which is often the case in trachoma surveys. A possible solution to this is to sample a larger proportion of the population, however, this is usually infeasible due to resource constraints. The 4th Global Scientific Meeting on Trachoma recommended that national programmes could combine data from multiple adjacent EUs [19], which would allow improvement in estimates of disease prevalence at one location by (for example) using information from nearby EUs. Model-based geostatistics (MBG) [20] is an established set of spatial statistical methods that has been increasingly used in low-resource settings to inform disease control programmes. In a recent study of TT mapping in Ethiopia, MBG methods were used to assess the elimination status of EUs; it was shown that this approach yielded substantially more precise estimates of TT prevalence compared to the standard trachoma prevalence survey approach [21].

The objective of this paper is to demonstrate the general applicability of MBG methods to assess the elimination of trachoma in different settings. To this end, we predict TF and TT prevalence using trachoma data collected from Brazil, Malawi, and Niger. These countries were selected as they differ in their trachoma elimination status, as described in detail in the Methods section below. Through these three case studies, we demonstrate how statistically rigorous MBG methods are used for borrowing the strength of information across space and making the best possible use of spatially sparse trachoma survey data. We also provide a framework to guide the inclusion of gender and age effects in MBG for trachoma.

Methods

Country settings

Brazil: From the 18th to the early 20th century, trachoma was spread through migrant populations in Brazil's Northeast and the São Francisco Valley. The Federal Government led control campaigns from 1923 to 1998 [22], and in the 1970s, trachoma was considered eradicated in São Paulo. This belief (in eradication) became generalised across the entire country, leading to decreased engagement in surveillance and control activities. To better understand the contemporary burden of trachoma among children, school surveys were implemented in municipalities with Human Development Index (HDI) below the national mean in the early 2000s [23–25]. A nationwide study [26] found that 11 (41%) of 27 surveyed states had a prevalence of TF $\geq$ 5% (although participants included those aged $\geq$ 10 years). These results led to strengthening of national surveillance and control activities for trachoma [26,27], including antibiotic treatment of individuals with active trachoma and their contacts, identified through active case finding and contact tracing. This contributed to a marked decline in the TF prevalence between 2008 and 2016, as evidenced by the Brazil Information System for Notifiable Diseases (SINAN) [27]. A recent study showed that the prevalences of TF and TT

were below the target for elimination in eight of nine surveyed non-indigenous EUs in 2018–19 [27]. In this most recent survey series, as is traditional, prevalence was estimated using a standard statistical approach that adjusts for age for TF, and age and gender for TT [17]. The prevalence among indigenous communities has not been recently estimated; this is currently under investigation.

Malawi: Since the 1980s, Malawi has recognised trachoma as an endemic disease [29,30]. A population-based survey conducted in two districts in Central and Southern Malawi in 2008 showed a prevalence of TF ≥ 10% (a threshold prevalence defined by WHO for determining the duration of annual mass drug administration [MDA]) and TT ≥ 0.2%, indicating trachoma was a public health problem [28]. Based on these findings, the Ministry of Health launched its first national-level trachoma control programme to implement the SAFE strategy, whilst stressing the need to estimate prevalence in other regions. Through surveys conducted between 2013 and 2015 with the support of the Global Trachoma Mapping Project (GTMP), trachoma mapping was officially completed in all suspected endemic areas, showing that some EUs in Central and Southern Malawi exceeded the TF and TT elimination thresholds [29,30]. Subsequently, the country intensified its efforts to eliminate trachoma and in 2022 was validated by WHO as having eliminated the disease, based on TF and TT prevalences [31].

Niger: After identifying almost all regions as being endemic for trachoma, Niger started SAFE implementation in 1999 and expanded it nationally in 2009 [32]. In order to determine eligibility for district- or sub-district-wide SAFE implementation, 31 district-level trachoma prevalence surveys were conducted from 2009 to 2012. The prevalence of TT in ≥ 15-year-olds ranged from 0.1–5.4% and the prevalence of TF in 1–9-year-olds ranged from 0.1–42.4%, suggesting the need for continued SAFE interventions in 16 districts, primarily in eastern Niger [32]. As of June 2022, 41 out of 72 health districts were identified as having TT prevalence ≥

0.2%, and a combined population of more than three million people required the A, F and E interventions to reduce EU-level TF prevalence to < 5% [33].

Data

We obtained the data from trachoma baseline, impact and pre-validation surveillance surveys [34,35] conducted in Brazil, Malawi, and Niger. All surveys were supported by Tropical Data and used a standardised two-stage cluster sampling methodology as defined by the GTMP [17,34,36]. Briefly, the first stage involves selection of 20–30 clusters (villages) using a probability-proportional-to-size sampling method, followed by the second-stage selection of approximately 30 households within each cluster, using compact segment, systematic, or random sampling. Consenting residents had both eyes examined for TF and TT using WHO's simplified grading system for trachoma [37]. A case of TT was defined as an individual aged ≥ 15 years who had at least one eyelash touching the eyeball or showed evidence of recent epilation of in-turned eyelashes. Cases were excluded if the individuals (i) had TT post-operatively, (ii) had refused surgery, or (iii) were listed for surgery but had not yet received an operation.

Specifically, we used the data from nine Brazil EUs surveyed in 2018–19, 18 Malawi EUs surveyed in 2017–19, and 85 Niger EUs surveyed in 2017–19. The Brazil data were exclusively from baseline (i.e. pre-intervention) surveys. In Malawi and Niger, depending on the EU, impact and/or surveillance (i.e. post-intervention) surveys were available. When both impact and surveillance surveys were available in the same administrative unit, we just used the data from the most recent survey. As a result of this, only surveillance surveys were analysed in the case of Malawi. In the analysis for Brazil, we focused on the six EUs of north-eastern Brazil, namely Nordeste Paraense, Leste Maranhense, Noroeste Cearense, Sertão Pernambucano, Sertão Alagoano, and Vale São do Francisco da Bahia. We did not include the

data from the north part of Brazil, from Vale do Jurua, Sudoeste Amazonense, and Norte de Roraima, because in those EUs, only 13 TF cases were detected in 2,318 examined children, and only one TT case was detected in 5,891 examined individuals aged ≥ 15 years, making the use of any statistical model infeasible.

Geostatistical model

We developed geostatistical Binomial models for prevalence of TF and TT that account for age (for TF) or age and gender (for TT), as fixed effects, and for unexplained Binomial extra variation through the use of random effects. We express the general form of the models for TF and TT as follows.

$$log\ odds\ of\ TF\ for\ an\ individual = effects\ of\ age + spatially\ correlated\ residual\ variation + spatially\ uncorrelated\ residual\ variation$$

$$log\ odds\ of\ TT\ for\ an\ individual = effects\ of\ age + effects\ of\ gender + spatially\ correlated\ residual\ variation + spatially\ uncorrelated\ residual\ variation$$

Based on existing scientific evidence and also guided by a preliminary exploratory analysis, we have summarised our approach for the introduction of age and gender effects in Table 1. In the model for TF, we defined the trend of age effect using a linear spline with a knot at the age of 3 years, since it is expected that prevalence should increase until around age 2–4 years followed by a decline [2,10]. This expectation was supported by our data on TF for Malawi and Niger, with the highest prevalence at age 3 years. In Brazil, prevalence showed a steady increase with increasing age, hence, we introduced age as a logit linear effect. The

reason for preferring linear splines over other smoothing techniques is because of their greater interpretability for the effects of the covariates on trachoma prevalence [38]. Also, in the models for TF, we did not introduce any gender effect, since there is no strong scientific evidence to support a consistent difference in exposure to *C. trachomatis* between male and female children [2].

In the model for TT, we controlled for gender [11,12,39] regardless of statistical significance level, and introduced age as logit linear effect [2,10]. However, we did not introduce the gender effect in Brazil because it was not possible to distinguish between prevalence in males and females due to the small number of cases detected. Because differences in age trends could be observed between males and females for TT due to differences in mean exposure to *C. trachomatis* [39–41] and possibly sex-related biological phenomena [42], we decided to include an age-gender interaction in the model if this was statistically significant at the 95% confidence level. The final form of model for each sign and country is described in Table S1 (S1 Appendix).

All data analysed in this study showed evidence of residual spatial correlation for both TF and TT. To address this, the geostatistical models fitted to the data included two types of random effects. More specifically, we included a spatial random effect, modelled as a Gaussian process, and unstructured random effects, modelled as Gaussian noise. The former accounts for between-cluster variation whilst the latter accounts for within-cluster variation.

Table 1. Effects of age and gender on trachomatous inflammation—follicular (TF) and trachomatous trichiasis (TT) prevalence on logit scale

Variables	TF	TT
Age	Included as a linearly increasing trend until around age 2–4 years, followed by a linearly decreasing trend. If	Included as a linearly increasing trend

	this was not supported by data, assumed a linearly increasing trend	
Gender	Not included	Included
Age-gender interaction	Not included	Included if statistically significant

We predicted local TF and TT prevalence by first laying grid squares over the EUs and computing prevalence for each age or age-gender class within each grid. We defined the areas shown in Fig S1 (Appendix S1) as EUs for prevalence prediction in this study, and the spatial resolution was determined based on the estimated scale of the spatial correlation for each country (see Appendix S1). To allow for comparison with the standard approach [17], we then standardised prevalence for age bands of one-year for TF, and gender-specific five-year age bands for TT, using EU-specific population census data in Brazil (2010 census) [43] and national census data in Malawi (2018 census) and Niger (2012 census) [44,45]. To account for spatial heterogeneities in population density in generating the EU-wide standardised average prevalence for TF and TT, we weighted the predictions for each pixel using the population density data obtained from WorldPop [46].

Finally, we obtained 10,000 predictive samples for the EU-wide standardised average prevalence, for both TF and TT, and used the 10,000 samples to compute: the point prediction of the EU-wide standardised average prevalence, using the mean of the predictive samples; the 95% confidence-level prediction intervals; and the probability of elimination having been achieved, computed as the proportion of predictive prevalence samples that fell below the elimination threshold. We used R for all analyses, including the package “PrevMap” [47] to perform the geostatistical analysis. Technical details of the approach are provided in Appendix S1.

255 **Results**

256 Table 2 shows crude (unadjusted) TF and TT prevalence in Brazil, Malawi, and Niger.
257 For both TF and TT, Brazil had the lowest crude prevalence whilst Niger had the highest. The
258 crude TF prevalence by country, including data from all available EUs in that country, ranged
259 from 0.44% to 3.66%. For TT, prevalence was higher among females than males in Malawi
260 and Niger, although this gender difference was not observed in Brazil, where only 11 cases
261 were detected amongst 12,603 people aged ≥ 15 years examined.

262

263 Table 2. Crude prevalence of trachomatous inflammation—follicular (TF) and trachomatous
264 trichiasis (TT) in Brazil, Malawi, and Niger

Disease	Study population	Crude prevalence (%)		
		Brazil	Malawi	Niger
TF	Children aged 1–9 years	0.44% (16/3,666)	1.65% (301/18,283)	3.66% (5,369/146,790)
TT unknown to the health system	Males aged ≥ 15 years	0.12% (7/5,612)	0.06% (6/10,410)	0.16% (84/51,629)
	Females aged ≥ 15 years	0.06% (4/6,991)	0.19% (32/16,741)	0.41% (331/81,086)

265

266 According to the models, point predictions for both TF and TT prevalence in Brazil
267 were below the elimination thresholds (Fig 1). In Malawi, the predicted TF prevalences were
268 below the threshold, whereas six areas had a TT prevalence above the threshold. In Niger, the
269 North-western regions had lower predicted TF prevalence and the South-eastern had higher,
270 ranging from 0.5% to 15.7%. A similar trend was observed for TT prevalences.

271

272 Fig 1. Predicted trachomatous inflammation—follicular (TF) and trachomatous trichiasis (TT)

prevalence in Brazil, Malawi, and Niger. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the authors, or the institutions with which they are affiliated, concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

We found that in Brazil, it is highly likely that TF prevalence met the target across all EUs (Fig 2). The probability for TT being below the elimination threshold (<0.2%) was more than 90% in three EUs out of six. For Sertão Pernambucano, Vale do São Francisco da Bahia, and Noroeste Cearense, the probability was 85%, 78%, and 70%, respectively. Similarly for Malawi, models indicated that the elimination criterion for TF had been met with greater than 95% likelihood. However, results are more uncertain for TT in one EU in particular, namely Dedza East, where the likelihood of achievement of elimination was 28%. In Niger, the probability for TF and TT spanned the full range of values, from ~0% to 100%. For TF, 65 of 107 EUs had likely met the elimination target with a probability of more than 95%, although 20 EUs likely had not, with a probability of having met the elimination target of less than 50%. For TT, 8 EUs had a more than 95% likelihood, whilst 38 EUs had less than 50%.

Fig 2. Probability of having achieved the elimination target for trachomatous inflammation—follicular (TF) and trachomatous trichiasis (TT) prevalence in Brazil, Malawi, and Niger. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the authors, or the institutions with which they are affiliated, concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Discussion

We have demonstrated the use of MBG methods for assessing trachoma elimination through three case studies, involving data from Brazil, Malawi, and Niger. Our approach can be adapted to different contexts to reflect data availability and age-gender trends, which can vary substantially across countries. We also showed that MBG methods can be applied to different epidemiological settings, ranging from very low prevalence settings such as Brazil and Malawi to relatively high prevalence settings such as Niger. One crucial aspect in which our MBG framework differs from the standard approach for the analysis of trachoma prevalence survey data is that it provides a probability statement on the exceedance or not of the elimination threshold. Quantification of uncertainty is essential to better inform the decision-making process and identify areas where the data do not provide enough information on achievement of elimination. This statistical aspect is ignored by the standard approach. For this reason, we argue that the model-based geostatistical approach presented in this paper is an important methodological improvement that answers more directly the problem of achievement of elimination for TF and TT in a given EU.

As noted at the 4th Global Scientific Meeting on Trachoma, an efficient survey analysis strategy is vital for trachoma programmes [19]. As prevalence decreases, it becomes more challenging to precisely predict the prevalence without increasing sample size. MBG provides one of the most efficient solutions to this, by allowing unsampled locations to borrow information from neighbouring sampled locations [47–49]. We show here that MBG can be effectively used in different epidemiological settings, both with very low trachoma prevalence, such as Brazil and Malawi, and relatively high prevalence, such as Niger. Future extensions of the proposed MBG framework will aim to incorporate spatially referenced covariate effects to

account for well-established factors associated with trachoma, such as temperature, elevation, and precipitation [48]. However, whilst it is generally good practice to use covariates to aid spatial predictions of prevalence, it can be problematic in the context of low prevalence. This is because, as prevalence declines, the association between covariates and disease becomes more difficult to discern empirically and we would be wary of applying poorly estimated regression relationships to predict prevalence at unsampled locations. For example, in our case studies, the low levels of prevalence observed in Brazil and Malawi would likely make the use of covariates infeasible.

In the case of Brazil, the results obtained from our MBG approach are largely comparable to those generated using the standard approach (which have already been made publicly available [27]). Indeed, we observed that the 95% prediction intervals of the EU-wide standardised average prevalence from our MBG models overlap with those from the standard approach (see Appendix S1), with the only exceptions being the prevalence estimates previously reported as 0% [27] and from Vale do São Francisco da Bahia, where there was only one TF case amongst 614 examined. Using the standard approach, we would conclude that prevalence was below the elimination threshold for both TF and TT in almost all EUs. However, our MBG approach, which also considers the uncertainty in the EU-wide prevalence predictions, indicated that although all EUs achieved TF prevalence < 5% with nearly 100% confidence, there was some uncertainty that TT prevalence was < 0.2%. The highest level of uncertainty was in Noroeste Cearense, where we found a likelihood of TT elimination of 70%. More data might be collected from this EU to establish without ambiguity whether the TT elimination prevalence threshold has been reached.

Malawi's results from our analysis were mostly in accordance with WHO's validation of it having achieved the elimination goal (for which the data from the most recent surveys

were also used) [31]. The model indicated that the elimination criterion for TF was met with greater than 95% likelihood, as shown in Fig 2. For TT prevalence, however, the point predictions were above the elimination threshold of 0.2% for six EUs analysed, and it was shown that there was more uncertainty in the achievement of elimination particularly in Dedza East. The MBG analytical approach provides more tangible quantification of uncertainty in prevalence predictions, facilitating more informed discourse about exactly how much uncertainty policy makers are willing to tolerate, whilst also identifying the areas where sustained monitoring and resource allocation should be targeted even after elimination has been attained.

In all three countries, we found evidence of residual spatial correlation in the data which justified the use of MBG. However, in other settings, it is possible that the data will not show strong evidence of this, making the estimation of MBG models more difficult. In that scenario, a model-based approach for the estimation of EU-wide prevalence might still be achieved by simplifying the structure of our statistical models. More specifically, the spatial Gaussian process component which is introduced in all our models could be removed and extra-Binomial variation could be accounted for using unstructured random effects only. When using this simpler model, the generation of EU-wide standardised prevalence estimates and probabilities of elimination are obtained following the approach illustrated in this paper with only minimal technical adjustments.

When generating the EU-wide average prevalence using the illustrated model-based geostatistical approach, each pixel is weighted according to the WorldPop population density estimates. As a result of this, we should point out that the WorldPop data are based on model predictions and therefore could be uncertain if the input population data are not recent and/or not accurate due to considerable subnational variations in migration, fertility, and mortality

[49].

As shown here, the MBG process must be guided by both contextual knowledge and empirical data exploration. These were especially important when deciding how to incorporate age and gender. For example, in our analysis for Brazil, TF prevalence showed a steady increase with increasing age, which differed from the pattern observed in other settings [28,39,50]. Hence, unlike for Malawi and Niger, we decided to include age as a logit linear effect which we justify as follows. First, the data were not informative enough to allow us to estimate a more complex relationship between prevalence and age. Second, individuals diagnosed as having TF might have a conjunctivitis precipitated by a stimulus other than *C. trachomatis* infection. Scientific understanding of the diseases that cause a similar presentation to TF is currently incomplete [51–53], and disentangling them from trachoma requires further research. Finally, for the TT analysis in Brazil, we did not include gender effects. We based this decision on the fact that gender differences were so small that we could not precisely estimate them from the data. We also point out that the assumption of a logit linear trend in age for TT prevalence should be carefully assessed, especially in older ages. For example, in settings where TT surgery is offered to a population and awareness of, acceptance of and access to the service is high, age effects might be obscured.

MBG has been used for the analysis of various infectious diseases [54–61]. Recently, it was proposed as an efficient tool to determine sampling and analysis strategies for NTD elimination surveys [62]. Soil-transmitted helminths (STH) are one of several NTDs for which MBG may become widely used [63–67]; the same framework can be applied to trachoma and, more broadly, to other NTDs. We advocate MBG as the new standard method to help NTD control programmes efficiently achieve their targets worldwide.

Acknowledgments: We are grateful to all our colleagues who contributed to generating the survey data on which these secondary analyses are based, and to the residents of trachoma-endemic communities examined as part of those surveys, who remain our enduring partners in trachoma elimination.

Disclaimer: The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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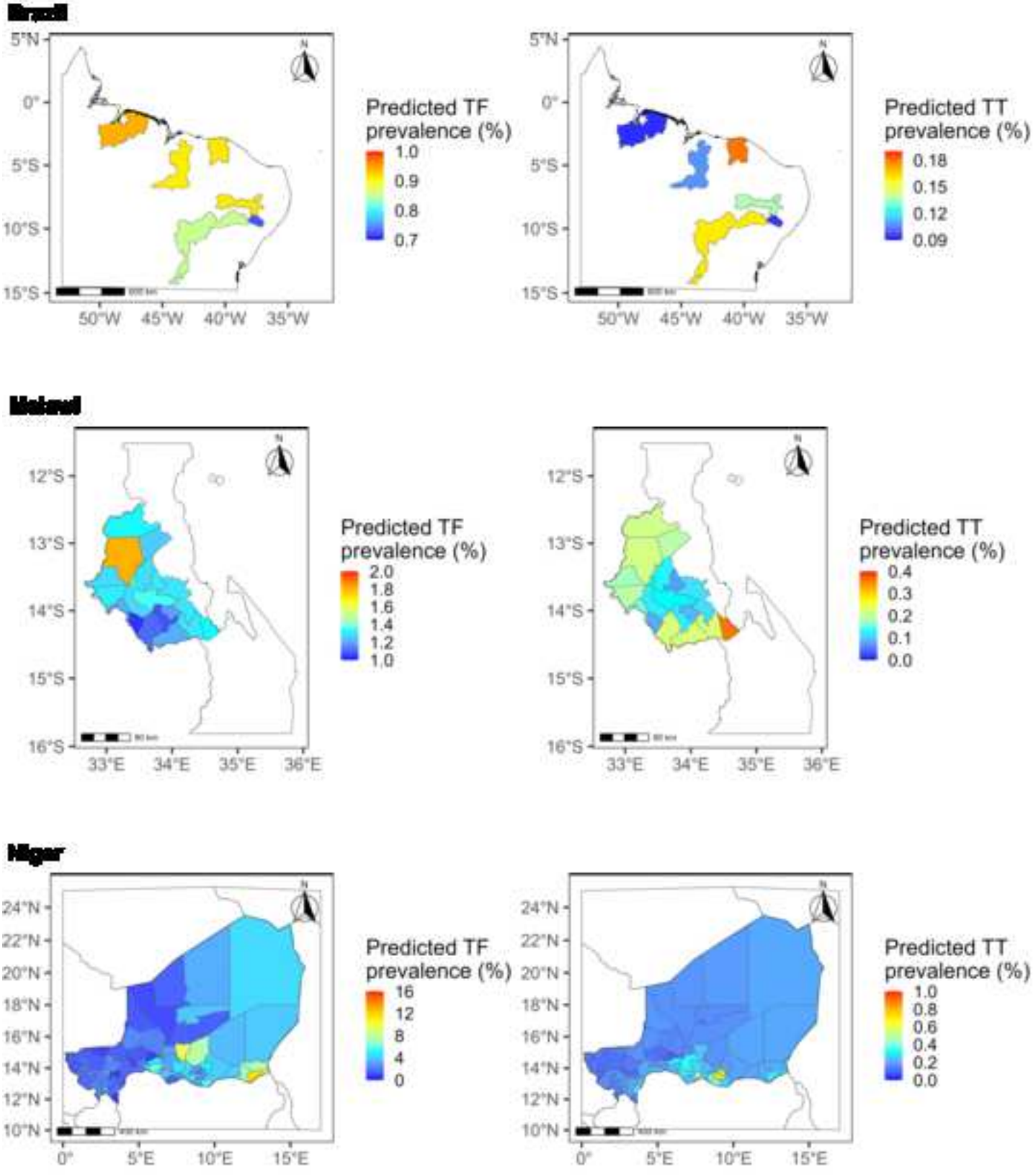
Supporting information

Appendix S1.

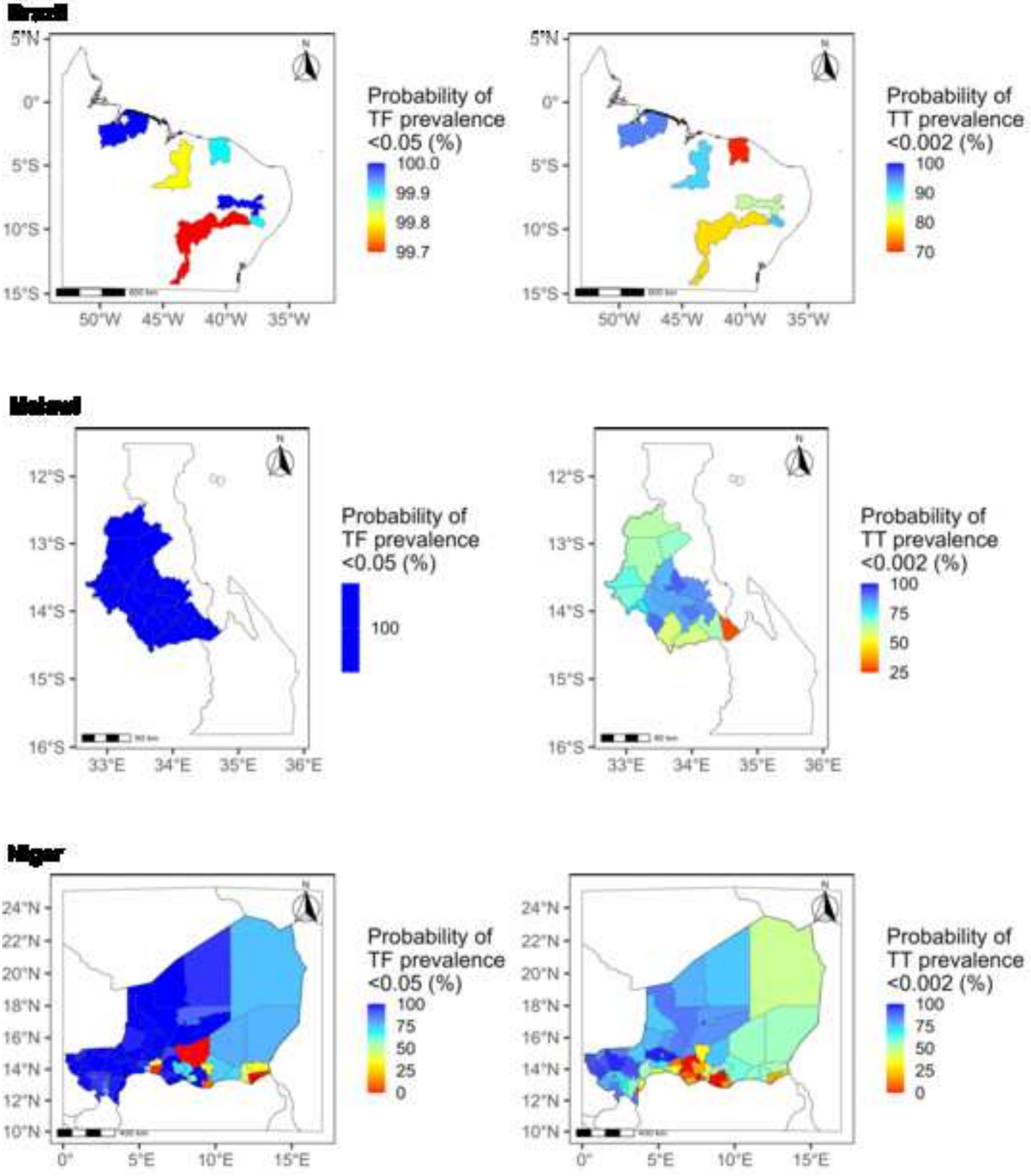
Figure

Click here to access/download;Figure;Fig_1.tiff



Figure

Click here to access/download;Figure;Fig_2.tiff



[Point-by-point responses to review comments]

Ms. No.: PNTD-D-23-00282
Title: Using model-based geostatistics for assessing the elimination of trachoma

Corresponding Author: Misaki Sasanami
Misaki Sasanami, Benjamin Amoah, Adam Nouhou Diori, Abdou Amza Abdoul Salam Youssoufou Souley, Ana Bakhtiari, Boubacar Kadri, Célia L Szwarcwald, Daniela Vaz Ferreira Gomez, Ibrahim Almou, Maria de Fátima Costa Lopes, Michael P Masika, Nassirou Beidou, Sarah Boyd, Emma M Harding-Esch, Anthony W Solomon and Emanuele Giorgi

Methods

Reviewer #1: The objectives of the study are clearly articulated with clear testable hypothesis stated. The objective was to demonstrate how model-based geostatistcs is a reliable, efficient and widely applicable tool to assess the elimination status of Trachoma. They tested their hypothesis by using survey data from three countries to show applicability of MBG in wider setting. The authors are articulated their background information and provided sufficent information on their methodology. Below are few areas that needs clarification.

>> We thank the reviewer for this positive comment and helpful suggestions below.

1. The authors indicated on line 139 that "A recent study showed that the prevalences of TF and TT were below the target for elimination in eight of nine surveyed non-indigenous EUs." Please provide the actual year.

>> We clarified the year of the survey (P7, L146-7).

2. If its possible, can the authors stick with TT or TF throughout in methodology? For example, it says Malawi eliminated trachoma in 2022 on line 156, does this mean both TT and TF?

>> Trachoma's elimination as a public health problem is defined by WHO based on three criteria, which include both TF and TT prevalences. As explained (P5, L95-102), briefly, the definition is: (i) a prevalence of TT < 0.2% in adults aged ≥ 15 years, (ii) a prevalence of TF < 5% in children aged 1–9 years, and (iii) the presence of a system to identify and manage incident cases of TT. Therefore, we aim to predict prevalence of both TF and TT in this study. We clarified the specified sentence for Malawi (P7, L162).

3. I wasn't sure if the authors were assessing prevalence or predicting prevalence? I may have read this incorrectly, but i understood the objective as an assessment of the elimination? If its predicting prevalence as indicated from line 226-227, then state that in your intro and objective?

>> Thank you for pointing this out. As clarifying (P6, L123-4), we first predict the TF and TT prevalences to assess the elimination status.

4. Were there any data quality issues with the population data (census and worldpop) used for standardization? line 228-233

>> We noted the issues with these population data (P11, L248-9 and P17, L372-7).

5. Please indicate what software, analysis package or resources used to run your analysis?

>> Thank you for pointing this out, we added a sentence (P12, L257-8).

6. any issues with uncertainty in boundaries? Authors used raster data, and would be curious to learn if they had any issues with boundary line using GIS software.

>> The boundaries used in the study are based on administrative boundaries according to Global Administrative Areas (GADM). As stated in the figure captions (P13, L278-83 and P14, L299-304), the boundaries on the maps do not imply the expression of any opinion concerning the delimitation of its frontiers or boundaries. We are not aware of any issues that might be related the use of GIS software, as we have not used it for our study.

7. Did the authors consider smoothing?

>> We clarified the reason for preferring linear splines over other smoothing techniques (P10, L216-8).

Reviewer #2: Methods were clearly described. There is consistency between objectives, study design, and analysis. No concerns about ethical aspects.

>> We appreciate this positive comment.

Reviewer #3: The objectives of the study are clearly articulated with a clear testable hypothesis stated. The study design is appropriate to address the stated objectives. There are no concerns about ethical or regulatory requirements as the study is based on secondary data. The methodology is sound and robust. I only have one question concerning the methodology for processing the survey data

>> We thank the reviewer for this positive comment and helpful suggestions made below.

- I presume that baseline, impact, and post-MDA surveillance surveys used in this study span for at least 5 or more years, and outcomes are highly impacted by treatment coverage, how did your model account for time variation and impact of treatment coverage? I presume that mapping, impact and surveillance surveys were not necessarily conducted in the same locations, but within the same area. I cannot fully comprehend how surveys conducted at the difference cycle of the trachoma control (baseline, impact and surveillance) were combined to estimate the probability of elimination.

>> Thank you for raising this important point. We clarified that our prevalence prediction was based on either pre- or post-intervention surveys, not a mixture of the two (P8, L186-91). Therefore, it was not necessary to consider treatment coverage in this paper.

- Did you produce standardized prevalence by year? You were combining prevalence data from three different survey types conducted at different stages of the elimination pathway; therefore, I must infer that you did not estimate one single prevalence by EU (aggregated prevalence from all surveys by EU), didn't you?

>> We hope our clarification above explains that we were not combining prevalence data from pre- and post-intervention surveys.

Results

Reviewer #1: The analysis presented match the analysis plan.

1. Please start the results section by stating that, "According to adjusted and unadjusted MBG models, we found that...."

>> Thank you for the suggestion. As recommended, we changed the wording (P12, L271). We did not change the first paragraph because the unadjusted prevalences are not based on the model.

2. Please refine the figures, they were hard to read.

>> We enlarged the maps and hope that they are now more readable.

3. Please try to have some kind of separation for each figure1.1 and 1.2 for TT and TF. Line 251 and 257 have the same citation (they say Fig 1.). Same with Fig 2.

>> We increased the spacing between the maps within the figures. We also changed the first sentences in each paragraph (P12, L271 and P13, L285-6).

4. Please add legend for figure_s1, so that its easier for the reader to understand what the blue dots mean in terms of the polygons in the background.

>> We added the legend.

5. If possible, please include a graph showing MBG versus traditional model estimates in your results section to validate your hypotheis regarding MBGs being efficient and reliable.

>> The objective of this paper was not to compare the results from MBG and the traditional approach. This was already done by Amoah et al. in a previously published paper (reference no. 21 in the main manuscript), we therefore kept the comparison in the Supplementary material.

Reviewer #2: Results very clear and well presented. Analysis match the analysis plan. Figures are sufficient for the study presented and clarify the results.

>> Thank you for this comment.

Reviewer #3: Revise quality of figures (maps resolution): legends and scales are unreadable.

>> We hope that the new maps are more readable.

Conclusions

Reviewer #1: Though the conclusions are supported by the data presented, I think others may argue that your results were in general the same with traditional model results. There is an important point mentioned in the discussion section regarding the precondition for MBG, which is spatial correlation. This could be included in the methods section to ensure what requirements will need to be met before you consider an MBG. Also, it will be great to learn some detail with the traditional model. This is a great work overall and just need some refinement. Overall, a great work and with minor edits, this will be an important work for estimating disease prevalence in different settings.

>> We appreciate the suggestions and encouraging comments. We further highlighted the advantage of our methods in Discussion (P14, L310-320). We have explained the precondition for MBG and standard analysis methods for trachoma surveillance in Methods (P5 L102-6, P10 L231-4, and P11 L245-8).

Reviewer #2: Conclusions are very well articulated. Limitations are listed and explained. This is a very important topic for the elimination of trachoma as well as for other neglected tropical diseases. Elimination of NTDs need innovative approaches to help countries to confirm that elimination has been reached. Knowing if elimination thresholds have been reached demand robust methodologist to help reduce uncertainty in low-endemic scenarios. This model-based geostatistic approach is a very good example of tools that can help to better understand the if elimination has been reached.

>> We thank the reviewer for this encouraging comment.

Reviewer #3: The conclusions are supported by the analysis and results. The authors have described some limitations on the analysis (not accounting for some fixed effects such as environmental data). The analytical framework and methodology is applicable to other NTDs.

>> Thank you for this comment.

Editorial and Data Presentation Modifications

Reviewer #1: Minor revision.

>> We believe that this revision has produced a better manuscript.

Reviewer #2: Lines 265 to 267: Authors said that the probability of having achieved the elimination threshold of TT was more than 90% in all EU except for two EU: 85% (Sertao Pernambucano) and 78% (Vale do Sao San Francisco da Bahia). Under the discussion section (lines 316 to 318), authors said that the likelihood of TT elimination in Noroeste Cearence was only 45% reason why authors recommend to collect more data in this EU to better understand the situation on TT. In Fig 1, the predicted TT for Brazil seems to be below 0,2% for all EU, and in Fig 2, the probability of TT prevalence to be less than 0,2% seems to be above 70% in all EU. Perhaps I am misunderstanding the results, but it would be good if authors can clarify the results for TT in Brazil. If I see the figures, it seems that the country achieved the elimination thresholds in all the studied EU, but based on what was said in the discussion, it seems that no.

>> Thank you for pointing out the mistake. We corrected it (P16, L348-9 and P13, L290).

Reviewer #3: Accept with minor editions listed under summary and general comments. Only a major comment, rather question has been included.

>> We thank the reviewer for the important major comment.

Summary and General Comments

Reviewer #1: This paper has great conceptual rationale and framework. The authors demonstrated to use this novel geostatstical approach to estimate disease prevalence where there are spatially sparse data and difference prevalence estimates. It would be great to see some refinement in the methods and results section as indicated in my feedback. I would also make a strong argument on how this easy to use approach is better compared to the status quo. Lastly, given the elimination of Trachoma in two of the three countries, how can MBG be used as a surveillance tool to monitor incidence of Trachoma, which will be important for these two countries.

>> We thank the reviewer again for all the suggestions and comments made for this review. As addressed in the previous comment, we further highlighted the advantage of MBG (P14, L310-20). Also, we mentioned the potential use of MBG as a tool to identify areas to be prioritised for monitoring after elimination has been attained, in the Discussion (P16, L359-61).

Reviewer #2: Dear authors,

Congratulations on this excellent manuscript. It is very well written and articulated. Such a complex topic is presented in a way that is understandable. The relevance for public health purposes is highlighted. MBG should be used for many other NTDs, as you said in the manuscript, so I hope this paper will contribute to accelerate its use. This is a critical paper contributing to using innovative approaches to reduce uncertainties in monitoring and evaluating elimination indicators of NTDs. Including data from 3 countries in different trachoma scenarios makes the study compelling. Using these methods broadly will contribute to improving them.

>> We thank the reviewer again for very encouraging comments throughout.

Reviewer #3: Overview: This manuscript submitted to PLOS NTD as a Research Article present the results of applying model-based geostatistics to assess the elimination status of trachoma in endemic geographical areas from three countries: Brazil, Niger and Malawi. The authors have developed binomial models to predict contemporary prevalence of trachomatous inflammation-follicular (TF) and trachomatous trichiasis (TT) in some regions of these countries. These binomials models were constructing using a collection of trachoma surveys (baseline mapping, impact assessment and post-intervention surveillance), and accounted for fixed effects (age, gender) and for residual spatial and non-spatial variation (random effects). From these models, they estimated mean prevalence by evaluation unit, with 95% credible intervals, and the probability of having brought down the TT and TF prevalence below elimination thresholds. The authors highlight the potential of applying model-based geostatistics for monitoring the control and elimination of NTDs, and the advantages of their application over standard analytical approaches (accounting for spatial autocorrelation, mitigating the impact of geographical bias, quantifying the uncertainty in the prevalence estimates, etc). Overall, the manuscript is very well-written, and the methodology is sound and robust. I only have a question concerning the methodology for processing the survey data, and minor comments.

>> We thank the reviewer again for raising the very important point to clarify.

Comments

Major:

- I presume that baseline, impact, and post-MDA surveillance surveys used in this study span for at least 5 or more years, and outcomes are highly impacted by treatment coverage, how did your model account for time variation and impact of treatment coverage? I presume that mapping, impact and surveillance surveys were not necessarily conducted in the same locations, but within the same area. I cannot fully comprehend how surveys conducted at the difference cycle of the trachoma control (baseline, impact and surveillance) were combined to estimate the probability of elimination.

>> This was addressed in response to the reviewer #3 above (P8, L186-91).

Minor:

- Page 9, Lines 133-134. I presume the authors meant “prevalence of TF > 5%” instead of >5%. I would suggest the authors revise this reference they are using here because these indicators they are providing are not included in that manuscript. In the study they are citing here, the authors presented the result of trachoma mapping conducted at municipality level in the poorest provinces of Brazil (human development index below certain value). “Cases detected in 901 municipalities (77.7% of the sample), and in 38.6% the prevalence was higher than 5%.” Study shows 7 out of 19 states (Table 4) had a prevalence of TF > 5% (36.8%)

>> The reference and the equality sign were our mistakes, and we have corrected them (P6, L139-40).

- Page 10, Line 163. I would suggest they mention here the total number of districts in Niger, so that the readers can have a reference of the trachoma burden in this country. As of June 2022, 41 districts out of 107 (…)

>> We have clarified this (P8, L169).

- Page 13, Lines 226-227. What is the spatial resolution for the laying grid? Is it 5km grid as mentioned in the title of Fig 2S? Please specify it in here.

>> We have clarified this (P11, L242-4).

- Page 13, Lines 228-229. Did you produce standardized prevalence by year? You were combining prevalence data from three different survey types conducted at different stages of the elimination pathway; therefore, I must infer that you did not estimate one single prevalence by EU (aggregated prevalence from all surveys by EU), didn't you? Please explain how prevalence estimates from different survey types were combined.

>> As addressed in response to the reviewer #3 above, we hope our clarification (P8, L186-91) explains that we did not combine prevalence data from pre- and post-intervention surveys.

- Page 15, Lines 265-266. Complete the sentence. The probability for TT to be lower than the elimination threshold (<0.2%) (…)

>> We revised the sentence as suggested (P13, L287).

- Page 17. Lines 309-310. Appendix S1. It would be beneficial for the readers to see the comparison between modelled prevalence and standard prevalence for the other two countries besides Brazil. I would suggest the authors include them in the Appendix S1 too.

>> As noted in the response to reviewer 1 above, the objective of this paper was not to compare the results from MBG and the traditional approach. This was already done by Amoah et al. in a previously published paper (reference no. 21 in the main manuscript). We therefore kept the comparison in the Appendix S1.

- Revise quality of figures (maps resolution): legends and scales are unreadable.

>> We hope maps are now more readable.

- Page 18. Line 331. (…) making the use of MBG model infeasible. I would rather say inappropriate instead. It would be inappropriate to develop a spatially-explicit model if there is not spatial structure on the data.

>> We kept the original wording "infeasible" because, in this context, geostatistical models are "appropriate" but there is not enough information from the data to fit them.