Understanding the spatial distribution of trichiasis and its association with trachomatous inflammation—follicular

Rebecca Mann Flueckiger 1*, Emanuele Giorgi 2, Jorge Cano 1, Mariamo Abdala 3, Olga Nelson Amiel 3, Gilbert Baayenda 4, Ana Bakhtiari 5, Wilfrid Batcho 6, Kamal Hashim Bennawi 7, Michael Dejene 8, Balgesa Elkheir Elshafie 9, Aba Ange Elvis 10, Missamou François 11, André Goepogui 12, Khumbo Kalua 13, Biruck Kebede 14, Genet Kiflu 14, Michael P. Masika 15, Marilia Massangai 3, Caleb Mpyet 16, 17, Jean Ndjemba 11, Jeremiah M. Ngondi 18, Nicholas Olobio 19, Patrick Turyaguma 4, Rebecca Willis 5, Souleymane Yeo 10, Anthony W. Solomon 1 and Rachel L. Pullan 1

Abstract

Background: Whilst previous work has identified clustering of the active trachoma sign “trachomatous inflammation—follicular” (TF), there is limited understanding of the spatial structure of trachomatous trichiasis (TT), the rarer, end-stage, blinding form of disease. Here we use community-level TF prevalence, information on access to water and sanitation, and large-scale environmental and socio-economic indicators to model the spatial variation in community-level TT prevalence in Benin, Cote d’Ivoire, DRC, Guinea, Ethiopia, Malawi, Mozambique, Nigeria, Sudan and Uganda.

Methods: We fit binomial mixed models, with community-level random effects, separately for each country. In countries where spatial correlation was detected through a semi-variogram diagnostic check we then fitted a geostatistical model to the TT prevalence data including TF prevalence as an explanatory variable.

Results: The estimated regression relationship between community-level TF and TT was significant in eight countries. We estimate that a 10% increase in community-level TF prevalence leads to an increase in the odds for TT ranging from 20 to 86% when accounting for additional covariates.

Conclusion: We find evidence of an association between TF and TT in some parts of Africa. However, our results also suggest the presence of additional, country-specific, spatial risk factors which modulate the variation in TT risk.

Keywords: Trachoma, Trichiasis, Blindness, Visual impairment, Neglected tropical disease, Epidemiology, Global trachoma mapping project

Background

Trachoma is a blinding disease caused by recurrent ocular Chlamydia trachomatis infection, an organism that produces chronic inflammation of the tarsal conjunctiva. This is characterised by sub-epithelial follicles, which may meet the definition for the sign trachomatous inflammation—follicular (TF) [1]. TF is the sign whose prevalence in 1–9-year-olds is used to determine whether public health-level interventions against active (inflammatory) trachoma are needed [2]. Through repeated reinfection [3, 4], conjunctival scarring may develop, eventually causing the eyelashes to turn inward and touch the globe, a state known as trachomatous trichiasis (TT). In-turned eyelashes that abrade the cornea can result in corneal opacity and blindness [1]. Corrective surgery [5, 6] or epilation [7] are used to manage TT.

Ocular chlamydial transmission is declining in many countries [8–11] suggesting exceptional progress in interrupting the transmission cycle. Until recently TT
prevalence was only evaluated within the context of TF surveys [12]. As TT plays an essential role in trachoma elimination, it remains important to focus on areas where TT is still a public health problem, even in the absence of TF.

The pathogenesis of trachoma, implicitly conceptualized within WHO recommendations for district-level interventions, is of repeated episodes of active trachoma incrementally increasing the cumulative risk of TT. It should be noted that this may be a simplistic outlook on the complicated pathway to TT and additional elements may influence progression. However, active trachoma is a pre-requisite on TT’s causal pathway, with moderate to high prevalences of TF being a proxy for current transmission of ocular C. trachomatis, and TT a proxy for historic transmission. The prevalence levels of these signs are therefore signals for C. trachomatis transmission intensity at different times (TF is current, and TT is historic and cumulative). Even though TF prevalence and TT prevalence are markers of transmission at different time points or over different time scales, in areas where antibiotic mass drug administration (MDA) for trachoma [13] has not yet occurred, it is often assumed that ocular C. trachomatis transmission intensity has remained more or less constant over decades, and that TF prevalence and TT prevalence will therefore closely correlate. This assumption is reasonable if access to water, sanitation, hygiene and anti-chlamydial antibiotics at community level have been constant or have changed only gradually. However, such an assumption is not always valid [14, 15].

Many national programmes [8] have successfully reduced TF prevalence in children aged 1–9 years below the elimination threshold of 5% [16] in some or many districts. To eliminate trachoma as a public health problem, district-level TT prevalence must also be reduced below 0.2% in adults aged ≥15 years [16]. Whether or not active trachoma and TT are public health problems are two separate questions. In Nigeria, for example, 94 local government areas in six states mapped through the Global Trachoma Mapping Project (GTMP) yielded district-level TF prevalence estimates below the elimination threshold and district-level TT prevalence estimates above the threshold [17–23]. This is attributable to historic transmission intensity being considerably higher than the contemporary one. It is important to better understand the factors associated with high TT burden, so as to develop more targeted control interventions. Understanding where TT cases are likely to occur could help to guide strategic placement of TT intervention services.

Thanks to the GTMP, there has been an increasing availability of high quality geolocated trachoma and water, sanitation and hygiene (WASH) data. The GTMP was launched in December 2012 with the aim of mapping the global prevalence of trachoma in all suspected-endemic districts, through completion of population based prevalence surveys. It systematically collected trachoma and WASH data across 1546 districts in 29 countries, nearly exclusively in areas where control activities, including antibiotic MDA, had not yet occurred [24]. These data can be used to further our understanding of TT distribution.

In this study, we attempted to identify risk factors that, in addition to TF, might associate with variation in community-level TT prevalence. To this end we fit binomial mixed models, with random effects at community level, to GTMP baseline data from ten countries. We then test for residual spatial correlation and, in countries where this is detected, use geostatistical methods in order to model the variation in TT prevalence between countries.

Methods
Data
Ten GTMP collaborating countries provided data for this study: Benin, Cote d’Ivoire, Democratic Republic of the Congo (DRC), Ethiopia, Guinea, Malawi, Mozambique, Nigeria, Sudan and Uganda. Data provided were from 15,051 clusters (or communities) within 624 trachoma elimination intervention-naïve evaluation units (EUs) (Table 1). Individual-level information on the presence or absence of TF and TT, as well as water and sanitation access of geolocated households, were provided.

Community-level TT prevalence was calculated as the ratio between the number of adults aged ≥15 years with trichiasis in at least one eye and the number of adults aged ≥15 years examined. Community-level TF prevalence was calculated as the ratio between the number of children aged 1–9 years with TF in at least one eye and the number of children aged 1–9 years examined.

Physical and social environmental factors are hypothesized to play an important role in the natural history of trachoma. These factors could conceivably alter rate of progression to TT (Fig. 1).

Facial cleanliness is a well-established association of TF [25–30]. Access to water is necessary to facilitate personal hygiene practices. Previous studies have found an association between distance to water and risk of trachoma [25, 31–33]. There is mixed evidence on higher density populations of Musca sorbens, the fly vector for ocular C. trachomatis, being associated with a greater risk of trachoma [27, 34]. M. sorbens prefers to breed on human faeces left exposed on the soil [35, 36] and so it may be that latrine ownership has a protective association against active trachoma [37]. For this analysis, community-level WASH indicators were created...
from the GTMP household-level WASH dataset (Appendix 1). The categorization of these indicators was informed by the WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation (JMP) [38]. We calculated the prevalence of access to each categorized WASH indicator.

Previous studies have shown that lower precipitation levels and higher temperatures can lead to an increase in the risk of TF [39]. Therefore, we selected climate-related factors, including annual total precipitation, mean temperature, aridity index and potential evapo-transpiration for this analysis. Gridded maps at 1 km² resolution of annual total precipitation and mean temperature were extracted from the WorldClim database [40]. The aridity index and potential evapo-transpiration (PET) raster datasets of 1 km² resolution, were obtained from the Consortium for Spatial Information (CGIAR-CSI) [41]. CGIAR-CSI modelled aridity index and PET using the data available from WorldClim as input parameters.

It has been suggested that frequent sandstorms that occur in some areas of Sudan cause eye trauma [42]. Irritation of the eyes leads to rubbing with fingers which could potentially accelerate the progression of TT. Hence, in our analysis we consider the proportion of sand in

| Country     | No. of communities | No. examined | No. positive (%) | No. communities prevalence ≥5% | No. examined | No. positive (%) | No. communities with prevalence ≥0.2% |
|-------------|--------------------|--------------|------------------|--------------------------------|--------------|------------------|-------------------------------------|
| Benin       | 213                | 18,781       | 1594 (8.5%)      | 94 (44.1%)                     | 16,170       | 254 (1.6%)       | 89 (41.8%)                          |
| Cote d’Ivoire | 256             | 17,658       | 1829 (10.4%)     | 174 (68%)                      | 18,771       | 39 (0.2%)        | 26 (10.2%)                          |
| DRC         | 1023               | 74,142       | 7022 (9.5%)      | 610 (59.6%)                    | 52,200       | 1137 (2.2%)      | 511 (50%)                           |
| Ethiopia    | 4480               | 186,308      | 40,131 (21.5%)   | 3199 (69.6%)                   | 289,230      | 4711 (1.6%)      | 2154 (48.1%)                       |
| Guinea      | 295                | 19,488       | 832 (4.3%)       | 98 (32.2%)                     | 21,955       | 66 (0.3%)        | 53 (18%)                           |
| Malawi      | 1948               | 82,185       | 3437 (4.2%)      | 561 (28.8%)                    | 110,815      | 358 (0.3%)       | 259 (13.3%)                        |
| Mozambique  | 696                | 34,602       | 2133 (6.2%)      | 297 (42.7%)                    | 35,895       | 155 (0.4%)       | 117 (16.8%)                        |
| Nigeria     | 5364               | 337,962      | 10,070 (3%)      | 1105 (20.6%)                   | 371,928      | 4815 (1.3%)      | 2035 (37.9%)                       |
| Sudan       | 667                | 33,830       | 1394 (4.1%)      | 172 (25.8%)                    | 40,501       | 327 (0.8%)       | 197 (29.5%)                        |
| Uganda      | 109                | 6019         | 183 (3%)         | 26 (23.9%)                     | 7445         | 21 (0.3%)        | 20 (18.3%)                         |
| Total       | 15,051             | 810,975      | 68,625 (8.5%)    | 6256 (41.6%)                   | 964,910      | 11,883 (1.2%)    | 5461 (36.3%)                       |

Table 1 Summary of GTMP data included in the analysis

Fig. 1 Conceptual framework of environmental risk factors influencing progression to TT
topsoil as a potential risk factor for TT. These data were obtained from the ISRIC-World Soil Information project included in the Harmonized Soil Map of the World [43].

We speculate that access to healthcare and other services are associated with developed infrastructure, and therefore sought an infrastructure indicator. Light density at night has been shown to be correlated with local economic activity and gross production rate at different scales [44, 45]. Night light emission captured by the Operational Linescan System instrument on board a satellite of the Defence Meteorological Satellite Program was used as a proxy measure of poverty across Africa [46, 47]. A gridded map of straight line distances to stable lights, namely night light emissivity > 0, was subsequently produced from the raw night light raster for 1997. This historic year was chosen because we were interested in a measure of infrastructure during the childhood of survey participants, rather than that at the time of the surveys themselves and the mean age of participants is 36 years.

All the aforementioned environmental datasets were derived from georeferenced raster files, and converted to a standardized resolution of 5 km × 5 km. The georeferenced data were linked in ArcGIS 10.1 (ESRI, Redlands, CA, USA). When shrinkage of spatial resolution was needed for data were linked in ArcGIS 10.1 (ESRI, Redlands, CA, USA). When shrinkage of spatial resolution was needed for a 5 km × 5 km window using the aggregate tool in the Spatial Analyst toolbox of ArcGIS 10.1 (Appendix 2).

To identify collinearity among the selected variables, we used the variance inflation factor (VIF) [48], defined as

\[ VIF_j = \frac{1}{1-R_j^2} \]

where \( R_j^2 \) is the fraction of explained variance in the j-th explanatory variables by the other explanatory variables.

Model formulation
Let \( p_i \) denote the probability of having TT, \( \beta_0 \) is the intercept and \( U_i \) is community-level unstructured random effects (let i denote the i-th community). We fit the following nested binomial mixed models, where \( \gamma_{TFi} \) is the regression coefficient for the effect of TF prevalence on the log-odds of TT:

\[
M1 : \log \left( \frac{p_i}{1-p_i} \right) = \beta_0 + U_i;
\]

\[
M2 : \log \left( \frac{p_i}{1-p_i} \right) = \beta_0 + \gamma_{TF} + U_i;
\]

\[
M3 : \log \left( \frac{p_i}{1-p_i} \right) = \beta_0 + \gamma_{TF} + \sum_{j=1}^{m} \beta_j d_{ij} + U_i,
\]

where \( d_{ij} \) in \( M3 \) are the explanatory variables described in the previous section. We use the log-likelihood ratio test to select among the three models defined above.

In fitting \( M3 \), we also carried out variable selection using a backward stepwise approach, starting from the mixed effects model with all the variables included. The likelihood-ratio test was used to test for the significance of each variable, with terms removed one by one until all those remaining were significant at 5% level.

To assess the presence of residual spatial correlation, we first obtained a point estimate of the community-level unstructured random effects \( U_i \) from the best model identified in the previous step, and then computed the empirical semi-variogram. A semi-variogram provides insights into the rate of decay of spatial autocorrelation in the data. It does this by computing the mean squared difference between pairs of residuals as a function of the distance between their associated geographical locations. A flat semi-variogram is interpreted as evidence against the presence of spatial correlation. To test for spatial correlation more formally, we also generated 95% confidence intervals under the assumption of spatial independence. These intervals were obtained by computing semi-variograms on 1000 randomly permuted point estimates of \( U_i \), while holding the geographical locations fixed.

In cases where we found evidence of spatial correlation, we fitted geostatistical binomial logistic models, in which \( U_i \) was modelled as a spatial Gaussian process with a stationary and isotropic correlation function. All the geostatistical models were fitted in the PrevMap [49] package.

Results
The output for the cluster-level tests suggested that temperature, precipitation, aridity index, and PET interact with one another (Table 2). Since aridity was highly correlated with each of these indicators, we retained this variable and excluded the remainder.

The strength of association for variables in the full mixed effects model varied between countries (Table 3).

| Variable                        | VIF |
|--------------------------------|-----|
| Annual mean temperature        | 5.4 |
| Annual total precipitation     | 47.6|
| Aridity Index                  | 62.3|
| Potential evapo-transpiration  | 6.4 |
| Euclidean distance to ground water | 1.2 |
| Sand/soil fraction             | 2.0 |
| Stable Night Light (1997)      | 1.2 |
| Accessibility                  | 1.3 |
Table 3 Relative increase in odds derived from a multivariate binomial logistic model where community-level prevalence of TT in adults aged ≥15-years is dependent on a 10% increase in community-level prevalence of TF in children aged 1–9 years

| Covariate                                      | Benin OR  | p-value  | Côte d’Ivoire OR  | p-value  | DRC OR  | p-value  | Ethiopia OR  | p-value  | Guinea OR  | p-value  | Malawi OR  | p-value  | Mozambique OR  | p-value  | Nigeria OR  | p-value  | Sudan OR  | p-value  | Uganda OR  | p-value  |
|------------------------------------------------|-----------|----------|-------------------|----------|---------|----------|------------|----------|------------|----------|------------|----------|----------------|----------|-------------|----------|----------|----------|----------|----------|
| TF prevalence                                  | 1.779     | <0.001   | 1.854             | 0.010    | 1.527   | <0.001   | 1.226       | <0.001   | 1.427      | 0.311    | 1.486      | 0.001    | 1.739          | <0.001   | 1.196      | <0.001   | 1.638      | <0.001   | 2.157      | 0.163    |
| Reported use of latrines for defecation by household adults | 0.596     | 0.087    | 0.909             | 0.421    | 0.902   | <0.001   | 1.046       | <0.001   | 1.067      | 0.254    | 0.835      | 0.034    | 1.082          | 0.001    | 1.051      | <0.001   | 0.983      | 0.410    | 1.104      | 0.470    |
| Improved latrines                               | 1.664     | 0.109    | 1.153             | 0.324    | 0.961   | 0.110    | 0.990       | 0.489    | 0.950      | 0.362    | 0.830      | 0.116    | 0.973          | 0.412    | 0.976      | <0.001   | 0.998      | 0.963    | 1.259      | 0.020    |
| Improved water source                           | 0.978     | 0.554    | 0.925             | 0.280    | 0.978   | 0.067    | 1.015       | 0.005    | 1.022      | 0.683    | 1.061      | 0.111    | 1.019          | 0.285    | 1.011      | 0.078    | 1.008      | 0.644    | 0.979      | 0.883    |
| Improved water source on property               | 1.328     | 0.191    | 0.854             | 0.469    | 0.948   | 0.758    | 1.011       | 0.801    | 1.075      | 0.708    | 1.026      | 0.942    | 0.852          | 0.244    | 0.944      | <0.001   | 0.870      | 0.151    | 0.000      | 0.055    |
| Water source on property                        | 0.805     | 0.283    | 1.522             | 0.052    | 0.951   | 0.618    | 1.031       | 0.506    | 1.083      | 0.699    | 0.916      | 0.792    | 1.135          | 0.283    | 1.023      | 0.023    | 1.052      | 0.628    | 812.073    | 0.098    |
| Water source distance more than 30 min          | 0.948     | 0.105    | 1.033             | 0.688    | 1.015   | 0.224    | 1.008       | 0.170    | 1.133      | 0.031    | 0.992      | 0.844    | 1.015          | 0.446    | 0.993      | 0.406    | 0.981      | 0.318    | 1.283      | 0.263    |
| Aridity Index                                   | 0.854     | 0.402    | 0.904             | 0.729    | 0.919   | 0.006    | 0.881       | <0.001   | 0.903      | 0.121    | 0.978      | 0.779    | 0.902          | 0.070    | 0.565      | <0.001   | 2.293      | <0.001   | 2.095      | 0.400    |
| Sand/soil fraction                              | 1.962     | 0.033    | 1.444             | 0.450    | 1.002   | 0.977    | 0.798       | <0.001   | 0.973      | 0.899    | 1.112      | 0.526    | 1.047          | 0.511    | 0.977      | 0.438    | 0.950      | 0.457    | 0.540      | 0.226    |
| Stable night light (1997)                       | 0.293     | 0.200    | 10.257            | 0.371    | 1.311   | 0.003    | 0.807       | 0.008    | 0.397      | 0.414    | 1.538      | 0.640    | 2.160          | 0.001    | 2.121      | <0.001   | 1.295      | 0.265    | 16.041     | 0.259    |

Community-level household prevalence of improved sanitation and hygiene facilities as well as gridded covariates were included along with community-level prevalence of TF.
There was very strong evidence of association ($P < 0.05$) between community-level TF prevalence and TT prevalence in all countries except Guinea and Uganda. In contrast, there was evidence of association with access to latrines in 4 of 10 countries (DRC, Ethiopia, Mozambique and Nigeria ($p < 0.01$)), with access to improved latrines in 2 countries (Nigeria and Uganda ($p < 0.05$)), and with water source variables in 3 countries (Ethiopia, Nigeria and Guinea ($p < 0.05$)). Observed relationships with environmental factors were equally heterogeneous, with associations observed with aridity index in DRC, Ethiopia, Nigeria and Sudan; and with sand/soil fraction only in Benin and Ethiopia. Night light was associated in DRC, Ethiopia, Mozambique and Nigeria.

The nested mixed effects models (Table 4) show that when TF was added as a fixed effect, the proportional reduction in variance ranged from 0.06 (Nigeria) to 0.42 (Benin). When environmental risk factors were added, the proportional change in variance ranged from 0.25 (Ethiopia) to 0.79 (Cote d'Ivoire). In all countries, variance continued to decrease as TF and then environmental risk factors were added to the model.

The best models, selected using the likelihood ratio test, are shown in Table 5. DRC, Ethiopia and Nigeria maintained the largest number of variables significant at the 5% level. These three countries also had the largest quantities of data available.

Semi-variograms generated with Pearson's residuals of the best fitting non-spatial binomial models suggest presence of residual spatial correlation in Benin, DRC, Ethiopia, Mozambique and Sudan. The 95% confidence

| Table 4 | Comparison of variance explained by each mixed effects model |
|------------------------|------------------------|------------------------|
|                        | Null model | TF only model | TF prevalence + risk factors model |
| Benin                  | Variance    | 2.25         | 1.3                      | 1.09 |
| Proportional reduction | Null model | 0.42         | 0.52                     |
|                        | TF only model |          | 0.16                     |
| Cote d'Ivoire          | Variance    | 13.75        | 10.28                    | 2.92 |
| Proportional reduction | Null model | 0.79         |                          |
|                        | TF only model |          |                          |
| DRC                    | Variance    | 1.52         | 1.23                     | 1.05 |
| Proportional reduction | Null model | 0.19         | 0.31                     | 0.15 |
|                        | TF only model |          |                          |
| Ethiopia               | Variance    | 1.22         | 1.01                     | 0.92 |
| Proportional reduction | Null model | 0.17         | 0.25                     | 0.09 |
|                        | TF only model |          |                          |
| Guinea                 | Variance    | 1.88         | 1.87*                    | 1.37 |
| Proportional reduction | Null model | 0.27         |                          |
|                        | TF only model |          |                          |
| Malawi                 | Variance    | 2.17         | 1.96                     | 1.59 |
| Proportional reduction | Null model | 0.1          | 0.27                     |
|                        | TF only model |          | 0.19                     |
| Mozambique             | Variance    | 4.45         | 3.52                     | 3.06 |
| Proportional reduction | Null model | 0.21         | 0.31                     |
|                        | TF only model |          | 0.13                     |
| Nigeria                | Variance    | 1.93         | 1.82                     | 0.99 |
| Proportional reduction | Null model | 0.06         | 0.49                     |
|                        | TF only model |          | 0.46                     |
| Sudan                  | Variance    | 1.98         | 1.85                     | 1.15 |
| Proportional reduction | Null model | 0.07         | 0.42                     |
|                        | TF only model |          | 0.38                     |
Table 5 Relative increase in odds derived from a multivariate binomial logistic model where community-level prevalence of TT in adults aged ≥15-years and older is dependent on a 10% increase in community-level prevalence of TF in children aged 1–9 years. Community-level household prevalence of improved sanitation and hygiene facilities as well as gridded covariates were included along with community-level TF.

| Covariate type          | Benin | Cote d’Ivoire | DRC | Ethiopia | Guinea |
|-------------------------|-------|---------------|-----|----------|--------|
|                         | OR    | p-value       | OR  | p-value  | OR     | p-value |
| C. trachomatis transmission |      |               |     |          |        |        |
| TF prevalence           | 1.834 | < 0.001       | 1.417 | 0.187   | 1.566 | < 0.001 |
| WASH                    |       |               |     |          |        |        |
| Latrine defecation      |       |               |     |          |        |        |
| Improved latrines       |       |               |     |          |        |        |
| Improved water source   |       |               |     |          |        |        |
| Water source on property|       |               |     |          |        |        |
| Water source distance more than 30 min |     |               |     |          |        |        |
| Large scale environmental|      |               |     |          |        |        |
| Aridity Index           |       |               |     |          |        |        |
| Sand/soil fraction      |       |               |     |          |        |        |
| Poverty                 |       |               |     |          |        |        |
| Stable night light (1997)| 1.409 | < 0.001       | 0.806 | 0.003   |        |        |
intervals generated under the assumption of spatial independence demonstrate spatial correlation in these countries (Fig. 2).

The distance at which spatial correlation fell below 5% ranged from 3.0 km (in Ethiopia) (95% credible interval 1.6–6.0 km) to 14.2 km (in Mozambique) (95% credible interval 3.3–76.4 km), corresponding with a very rapid decline in spatial correlation with distance at larger scales, after accounting for covariates (Table 6).
Table 6: Scale of community-level TT prevalence spatial correlation in kilometres when accounting for covariates significant at the 5% level, by country with 95% confidence intervals

| Country       | Scale of spatial correlation | 95% confidence intervals |
|---------------|-----------------------------|--------------------------|
| Benin         | 3.2 km                      | 0.8–12.8 km              |
| DRC           | 7.7 km                      | 3.0–20.1 km              |
| Ethiopia      | 3.0 km                      | 1.6–6.0 km               |
| Mozambique    | 14.2 km                     | 3.4–48.9 km              |
| Sudan         | 2.8 km                      | 0.9–10.8 km              |

Discussion

We investigated factors associated with community-level TT prevalence after considering the community-level TF prevalence and spatial dependency, to try and understand what causes this variation. We demonstrated considerable variation in the relationship between community-level TF and TT. When accounting for other covariates, the mixed effects models demonstrated a strong association between community-level TF and TT in eight of ten countries. These models estimate that a 10% increase in community-level TF prevalence is associated with an increase in the odds for TT of 20 to 86%, varying with setting. Benin, Cote d’Ivoire and Mozambique had exceptionally high increments in odds ratios with increasing TF, whereby a 10% increase in community-level TF prevalence was associated with an increase in TT odds of 78, 86 and 74% respectively. These high increments in odds ratios for TT lead us to speculate that reductions in TF prevalence in these environments will be quickly followed by a reduction in the incidence of TT. The relatively low increments in odds ratios in Ethiopia and Nigeria, where a 10% increase in community-level TF prevalence associated with an increase in TT odds of only 23 and 20% respectively, suggest a slight disconnect between historic and current transmission. This could be a signal of (1) a change in transmission dynamics over time, (2) population movement, (3) a pointer to the fact that we are using all-trichiasis as the dependent variable, rather than only trichiasis due to trachoma or (4) other factors are influencing TT aside from C. trachomatis. Further analysis is needed to explore the influence on the relationships that we observed here of including data on the presence or absence of trachomatous conjunctival scarring in eyes with trichiasis.

Importantly, in these models, the proportion of variance explained by TF ranges from 6% (in Nigeria) to 42% (in Benin). This range highlights the complex relationship of the distribution of TT and the distribution of TF. Environmental covariates, on average, explain an additional 9% (in Ethiopia) to 46% (in Nigeria) of variance. Our models suggest that while community-level TF prevalence is generally the strongest single predictor of TT, it does not fully explain the variation in community-level TT prevalence, and implying that occasionally, high-TT-prevalence populations will be found where TF is rare. It has been widely observed that dry conditions (parameterized in our analysis as a low aridity index) is a risk factor for TF in children [31, 50–52]. We found an extension of this association in three of our countries, in the form of an association of low aridity index with increased TT prevalence. However, in Sudan we observed the phenomenon of an unexpectedly-positive association between community-level TT prevalence and aridity index. This counter-intuitive relationship may be attributed to coinfections facilitated in humid climates. It has been shown that coinfection with other bacteria [53], such as Streptococcus pneumoniae and Staphylococcus aureus [54], could influence progression of TT [55].

High levels of self-reported latrine use by adults, aridity index and 1997 night light had strongly significant associations with TT prevalence in only three of ten countries. This suggests that hygiene practices, dry climate and historic infrastructure may link to increased community-level TT prevalence in some settings, but generally they do not. Previous studies have clearly shown the association between access to WASH and risk of TT [25, 32, 39, 56] and so it is not surprising that our models, which account for TF prevalence, generally do not demonstrate significant residual associations between TT and WASH variables. The variation in direction of association may be an artefact of WASH improvements over time, or—hypothetically—existence of latrines themselves could contribute to facilitating M. sorbens breeding if the latrines are not appropriately maintained, thereby deterring some potential users whilst protecting householders from legal or peer pressure to build an adequate facility. The development of TT requires many previous C. trachomatis infections [4] and so populations that historically had poor WASH access may now have high TT burdens, even if the WASH situation has since improved.

Many other studies have identified correlates of high TF prevalence, including potential socio-economic, demographic and environmental risk factors [25, 32, 39, 56–58], and have explored TF’s spatial distribution at different geographic scales [33, 52, 59–61]. However, few studies have specifically examined TT’s environmental risk factors and spatial distribution [42, 62, 63]. These previous studies were limited by the amount of data they incorporated, and their conclusions therefore had constrained generalizability. Our models, developed using large datasets from ten countries with outcome data considered to be gold standard [64], reached similar conclusions and so provide additional validation to this previous work.

The variation between countries in directions of association of environment-related indicators and the variation in spatial structure indicate that fitting a single
model to the whole set of data is inadvisable. These variations are presumably attributable to country context.

There may be several explanations for the inconsistency of associations between large-scale indicators and community-level TT seen between countries. Studies have shown that post-operative recurrence of TT [55, 65, 66] and incidence of scarring [67, 68] may be important influence factors of TT prevention. It would be valuable for future models to further explore these elements. Our modeling approach did not capture recent or historical population movement. Migration could certainly play a role in the geographic distribution of TT. It is also important to note that different ethnic groups may have different progression rates to TT. For example, a study in the Gambia found a polymorphism in the TNF-α gene promoter was associated with scarring, and was found more frequently among Mandinkas than other ethnic groups [69].

We observed residual spatial correlation in only five countries (Benin, DRC, Ethiopia, Mozambique, and Sudan), suggesting that in the remaining countries there are no outstanding large-scale environmental factors influencing progression to TT.

In the geostatistical models, we identified a very rapid decline in spatial correlation with distance at larger scales, after accounting for covariates. This suggests that very closely adjacent communities have similar levels of TT.

Conclusion
The lack of consistent risk factors beyond community-level TF raises concerns that the models identified artefacts that are not generalizable, such as non-trachomatous trichiasis, or that the clinical history of trachoma varies substantially between settings. This underlines the importance of understanding local context when designing interventions for at-risk populations. Whilst our findings are not generalizable across countries, they can provide general direction for where to initiate case finding activities. As has been found in the Guinea Worm eradication program, active surveillance and case finding will be essential as trachoma elimination endpoints draw closer [70]; these activities become more expensive as prevalence drops [71]. This uniquely large and standardized analysis provides important insight into the variation in community-level TT distribution and identifies substantial variation in the relationship between community-level TF and TT prevalence. For some countries, important environmental risk factors were identified which can be used to inform case finding efforts, by providing insight into where TT cases are most likely to be found. Our findings suggest that in some countries it is possible to inform strategic location of TT management services, potentially improving efficiency of the end-game of trachoma elimination.

### Appendix 1

#### Table 7 GTMP Water, Sanitation, and Hygiene indicators.

| Responses are classified as improved where marked with X |
|----------------------------------------------------------|
| **S1)** Where do you and other adults in the household usually defecate? number of households reporting that adults living in the household defecate in either a shared public latrine or a private latrine / number of households enrolled in the survey |
| 1) Shared or public latrine X |
| 2) Private latrine X |
| 3) No structure, outside near the house |
| 4) No structure, in the bush or field |
| 9) Other |
| **S2)** Improved latrine: What kind of toilet facility do the adults in the household use? Observed. number of households where an improved latrine is observed / number of households enrolled in the survey |
| 1) Flush/pour flush to piped sewer system X |
| 2) Flush/pour flush to septic tank X |
| 3) Flush/pour flush to pit latrine X |
| 4) Flush/pour flush to open drains X |
| 5) Flush/pour flush to unknown place X |
| 6) Ventilated improved pit latrine (VIP) X |
| 7) Pit latrine with slab X |
| 8) Pit latrine without slab/ open pit |
| 9) Composting toilet X |
| 10) Bucket |
| 11) Hanging toilet/hanging latrine |
| 12) No facilities or bush or field |
| 99) Other |
| **S3)** Where do you and other adults in the household usually wash faces? number of households reporting that adults in the household usually wash faces / number of households enrolled in the survey |
| 1) Shared or public latrine X |
| 2) Private latrine X |
| 3) No structure, outside near the house |
| 4) No structure, in the bush or field |
| 9) Other |
| **S4)** Improved water source: In the dry season, what is the main source of water used by your household for washing faces? number of households reporting to access improved water sources / number of households enrolled in the survey |
| 1) Piped water into dwelling X |
| 2) Piped water into yard/pot X |
| 3) Public tap/standpipe X |
| 4) Tubewell/borehole X |
| 5) Protected dug well X |
| 6) Unprotected dug well X |
| 7) Protected spring X |
| 8) Unprotected spring |
| 9) Rainwater collection X |
| 10) Water vendor |
| 11) Surface water (e.g. river, dam, lake, canal) |
| 99) Other |
| **H3)** Wash near: Washing water: If you collected water there to bring back to the house, how long does it take to go there, get water, and come back? number of households reporting access to improved water sources and those water sources are on the premises / number of households enrolled in the survey |
| 0) All face washing done at the water source |
| 1) Water source in the yard X |
| 2) Less than 30 min |
| 3) Between 30 min and 1 h |
| 4) More than 1 h |
Appendix 2
Climate:

**Fig. 3** 5 km gridded climate raster maps. Data depicted in this map were obtained from the Consortium for Spatial Information (CGIAR-CSI) [41]. The georeferenced raster files were converted to a 5 km x 5 km resolution and visualized by the manuscript authors using ArcGIS 10.1 (ESRI, Redlands, CA, USA)
Water access:

**Fig. 4** 5 km gridded Euclidian distance to water raster map. The manuscript authors produced a continuous surface of distances in km to the nearest water body and permanent rivers based on data obtained from the Global Database of Lakes, Reservoirs and Wetlands [72].

Soil composition (fraction and soil properties):

**Fig. 5** 5 km gridded soil composition sand fraction raster map. Data depicted in this map were obtained from the ISRIC-World Soil Information project included in the Harmonized Soil Map of the World [43]. The georeferenced raster files were converted to a 5 km × 5 km resolution and visualized by the manuscript authors using ArcGIS 10.1 (ESRI, Redlands, CA, USA).
Remoteness:

Abbreviations
CGAAR-CSI: Consortium for spatial information; DRC: Democratic Republic of the Congo; EU: Evaluation unit; GTMP: Global trachoma mapping project; JMP: Joint monitoring programme for water supply and sanitation; MDA: Mass drug administration; PET: Potential evapo-transpiration; TF: Trachomatous inflammation — follicular; TT: Trachomatous trichiasis; VIF: Variance inflation factor; WASH: Water sanitation and hygiene

Acknowledgements
We thank the health ministries (or government-designated agencies) of Benin, Cote d’Ivoire, Democratic Republic of the Congo, Ethiopia, Guinea, Malawi, Mozambique, Nigeria, Sudan and Uganda for providing data used in this analysis.

We also thank Mathew Freeman and Josh Garn for their technical advice on questions relating to water, sanitation and hygiene.

Funding
The Global Trachoma Mapping Project (GTMP) supported collection of the data used in this study. The GTMP was funded by (1) a grant from the United Kingdom’s Department for International Development (ARES: 203145) to Sightsavers, and (2) the United States Agency for International Development (USAID), through the ENVISION project implemented by RTI International under cooperative agreement AID-OAA-A-11-00048, and the END in Asia project implemented by FHI360 under cooperative agreement number OAA-A-10-00051. AWS was a Wellcome Trust Intermediate Clinical Fellow (098521) at the London School of Hygiene & Tropical Medicine. These funders had no role in the design, analysis and interpretation of the data presented here. The funders had no role in writing the manuscript. 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.

Availability of data and materials
The data that support the findings of this study are available from the corresponding Ministry of Health but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of corresponding Ministry of Health.

Authors’ contributions
RMF, EG, JC and RLP made substantial contributions to the conception, design and analysis of the work. RMF drafted the work. AWS made substantial contributions to the conception of the work and interpretation of the data. MA, ONA, GB, AB, WB, KHB, MD, BEE, AAE, MF, AG, KK, BK, GK, MPM, MM, CM, JN, JMN, NO, PT, RW and SY made substantial contributions to the acquisition and interpretation of the data. All authors revising the draft critically for important intellectual content, had final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate
Informed verbal consent was obtained from all participants. The fundamental purpose of the data collection was to guide the implementation of trachoma elimination programmes. Consent to participate allowed survey teams to examine both eyes of the consenting individual on one occasion only. For this reason, and because local partners with whom the fieldwork protocol was discussed believe that verbal consent is more acceptable than written consent in the largely illiterate rural populations amongst whom the surveys was conducted, we obtained informed verbal consent. All data collection was electronic, using an ODQ-based Android phone application. Consent (or its refusal) was formally noted by a trained, registered data recorder, who has a unique identification number and a signature kept on file. At the conclusion of data collection for each evaluation unit, the recorder signed a statement affirming that informed verbal consent was appropriately obtained from each individual examined in the survey. The study and the verbal consent procedure was approved by the Research Ethics Committee of the London School of Hygiene & Tropical Medicine (11909).

Consent for publication
Not applicable.

Competing interests
The authors have no proprietary or commercial interest in any materials discussed in this article. 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.

Fig. 6 5 km gridded remoteness raster maps. Data depicted in this map were obtained from the Operational Linescan System instrument on board a satellite of the Defence Meteorological Satellite Program [46, 47]. The georeferenced raster files were converted to a 5 km × 5 km resolution and visualized by the manuscript authors using ArcGIS 10.1 (ESRI, Redlands, CA, USA)
References

1. Mabey DC, Solomon AW, Foster A. Trachoma. Lancet. 2003;362(9379):223–229. https://doi.org/10.1016/S0140-6736(03)13914-1. PubMed PMID: 12885486.

2. Thylefors B, Dawson CR, Jones BR, West SK, Taylor HR. A simple system for the assessment of trachoma and its complications. Bull World Health Organ 1987;65(4):477–483. PubMed PMID: 3500800; PubMed Central PMCID: PMC2491032.

3. Grayston JT, Wang SP, Yeh LJ, Kuo CC. Importance of reinfection in the pathogenesis of trachoma. Rev Infect Dis 1985;7(6):769–775. PubMed PMID: 3143415; PubMed Central PMCID: 90221117.

4. Gambhir M, Basanere MG, Burton MJ, Solomon AW, Bailey RL, Holland MJ, et al. Development of an age-structured model for trachoma transmission dynamics, pathogenesis and control. PLoS Negl Trop Dis 2009;3(6):e62. https://doi.org/10.1371/journal.pntd.0000462. PubMed PMID: 19529762; PubMed Central PMCID: PMC2691478.

5. Burton MJ, Solomon A. What’s new in trichiasis surgery? Community Eye Health 2004;17(52):52–53. PubMed PMID: 17491821; PubMed Central PMCID: PMC1705745.

6. Habtamu E, Wondie T, Aweke S, Tedesse Z, Zerihun M, Zewdie Z, et al. Posterior lamellar versus bilamellar tarsal rotation surgery for trachomatous trichiasis in Ethiopia: a randomised controlled trial. Lancet Glob Health 2016;4(3):e171–e184. https://doi.org/10.1016/S2214-109X(15)00299-5. PubMed PMID: 26774078; PubMed Central PMCID: PMC5070528.

7. Rajak SN, Habtamu E, Weiss HA, Bedir A, Gebre T, Genet A, et al. Epilation for trachomatous trichiasis and the risk of corneal opacification. Ophthalmology. 2012;119(1):84–90. https://doi.org/10.1016/j.ophtha.2011.06.045. PubMed PMID: 21975041; PubMed Central PMCID: PMC3634301.

8. World Health Organization. WHO Alliance for the global elimination of blinding trachoma by the year 2020: progress report on elimination of trachoma, 2017. Wkly Epidemiol Rec 2017;92(6):357–68.

9. Mghchelsen SJ, Sepulveda N, Martin DL, Cooley G, Gwyn S, Picking H, et al. Serology reflects a decline in the prevalence of trachoma in two regions of the Gambia. Sci Rep 2017;7(1):15080. https://doi.org/10.1038/s41598-017-15080-7. PubMed PMID: 29118442; PubMed Central PMCID: PMC5678181.

10. Martin DK, Bir D, Sandi F, Goodhew EB, Massae PA, Lawasy A, et al. Serology for trachoma surveillance after cessation of mass drug administration. PLoS Negl Trop Dis 2015;9(2):e0003555. https://doi.org/10.1371/journal.pntd.0003555. PubMed PMID: 25714363; PubMed Central PMCID: PMC4340913.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

1 London School of Hygiene and Tropical Medicine, London, UK. 2 Lancaster Medical School, Lancaster University, Lancaster, Lancashire, UK. 3 Ophthalmology Department, Ministry of Health, Maputo, Mozambique. 4 Trachoma Program, Ministry of Health, Kampala, Uganda. 5 Task Force for Global Health, Decatur, GA, USA. 6 Programmatical National de Lutte contre les Maladies Transmissibles, Ministère de la Santé, Cotonou, Benin. 7 Prevention of Blindness Program, Federal Ministry of Health, Khartoum, Sudan. 8 Michael Dejene Public Health Consultancy Services, Addis Ababa, Ethiopia. 9 National Program for Prevention of Blindness, Federal Ministry of Health, Khartoum, Sudan. 10 Programme National de la Santé Oculaire et de la lutte contre l’Oncocercose, Abidjan, Côte d’Ivoire. 11 Direction de Lutte contre la Maladie, Kinshasa, Ministère de la Santé Publique, Kinshasa, Democratic Republic of Congo. 12 Programmes National de Lutte contre l’Oncocercose et les autres Maladies Tropicales Négligées, Ministère de la Santé, Conakry, Guinea. 13 Blantyre Institute for Community Outreach, Blantyre, Malawi. 14 Ministry of Health, Lilongwe, Malawi. 15 Sightsavers Nigeria, Kaduna, Nigeria. 16 Department of Ophthalmology, Jos University, Jos, Nigeria. 17 RTI International, Dar es Salaam, United Republic of Tanzania. 18 Nigeria Trachoma Elimination Program, Federal Ministry of Health, Abuja, Nigeria.

Received: 25 July 2018 Accepted: 24 March 2019

Published online: 30 April 2019
69. Conway DJ, Holland MJ, Bailey RL, Campbell AE, Mahdi OS, Jennings R, et al. Scarring trachoma is associated with polymorphism in the tumor necrosis factor alpha (TNF-alpha) gene promoter and with elevated TNF-alpha levels in tear fluid. Infect Immun 1997;65(3):1003–1006. PubMed PMID: 9038309; PubMed Central PMCID: PMC175081.

70. Beyene HB, Bekele A, Shifara A, Ebstie YA, Desalegn Z, Kebede Z, et al. Elimination of Guinea worm disease in Ethiopia; current status of the Disease’s, eradication strategies and challenges to the end game. Ethiop Med J 2017;55(Suppl 1):15–31. PubMed PMID: 28878428; PubMed Central PMCID: PMCPMC5582630.

71. Fitzpatrick C, Sankara DP, Agua JF, Jonnalagedda L, Rumi F, Weiss A, et al. The cost-effectiveness of an eradication programme in the end game: evidence from Guinea worm disease. PLoS Negl Trop Dis 2017;11(10): e0005922. doi: https://doi.org/10.1371/journal.pntd.0005922. PubMed PMID: 28981510; PubMed Central PMCID: PMCPMC5582630.

72. Lehner B, Doll P. Development and validation of a global database of lakes, reservoirs and wetlands. J Hydrol 2004;296(1):1–22. doi: https://doi.org/10.1016/j.jhydrol.2004.03.028.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions