RESEARCH ARTICLE

Predicting the environmental suitability and population at risk of podoconiosis in Africa

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Abstract

Podoconiosis is a type of tropical lymphedema that causes massive swelling of the lower limbs. The disease is associated with both economic insecurity, due to long-term morbidity-related loss of productivity, and intense social stigma. The geographical distribution and burden of podoconiosis in Africa are uncertain. We applied statistical modelling to the most comprehensive database compiled to date to predict the environmental suitability of podoconiosis in the African continent. By combining climate and environmental data and overlaying population figures, we predicted the environmental suitability and human population at risk of podoconiosis in Africa. Environmental suitability for podoconiosis was predicted in 29 African countries. In the year 2020, the total population in areas suitable for podoconiosis is estimated at 114.5 million people, (95% uncertainty interval: 109.4–123.9) with 16.9 million in areas suitable for both lymphatic filariasis and podoconiosis. Of the total 5,712 implementation units (typically second administrative-level units, such as districts) defined by the World Health Organization in Africa, 1,655 (29.0%) were found to be environmentally suitable for podoconiosis. The majority of implementation units with high environmental suitability are located in Angola (80, 4.8%), Cameroon (170, 10.3%), the DRC (244, 14.7%), Ethiopia (495, 29.9%), Kenya (217, 13.1%), Uganda (116, 7.0%) and Tanzania (112, 6.8%). Of the 1,655 environmentally suitable implementation units, 960 (58.0%) require more detailed community-level mapping. Our estimates provide key evidence of the population at risk and geographical extent of podoconiosis in Africa, which will help decision-makers to better plan more integrated intervention programmes.

Author summary

Podoconiosis is one of the major causes of tropical lymphedema and results in massive swelling of the lower limbs. It is caused by exposure to mineral particle-induced inflammation among genetically susceptible individuals. People affected by the disease often suffer both physical and psychological comorbidities, which can include painful swelling, distress, depression, stigma and discrimination. In spite of its presence among some African countries, its geographical distribution and burden in Africa are uncertain. We applied statistical modelling to the most comprehensive database compiled to date to predict the environmental suitability of podoconiosis in the African continent. By combining climate and environmental data (elevation, annual precipitation, land surface temperature, vegetation index, and soil characteristics such as clay and silt fraction) and overlaying population figures, we predicted both the environmental suitability as well as the human population at risk for podoconiosis in Africa. Environmental suitability for podoconiosis was predicted in 29 African countries. Our estimates provide key evidence that will help decision-makers to better plan more integrated intervention programmes.

Introduction

Podoconiosis is a neglected tropical disease (NTD) caused by exposure to red clay soil[1] in genetically susceptible people who do not use footwear. Podoconiosis is caused by exposure to mineral particle-induced inflammation on a background of genetic susceptibility[1]. It is hypothesized that mineral particles in the soil that penetrate bare skin are engulfed by macrophages in the lower limb lymphatics and induce an inflammatory response in the lymphatic vessels. This is followed by fibrosis and obstruction of the vessel lumen leading to oedema of the lower leg, which may progress to elephantiasis[2]. It is one of the leading causes of lymphedema in Africa[2,3]. The disease is a disabling NTD which causes progressive bilateral swelling of the legs, significantly reducing quality of life[4] and productivity[5]. People affected by podoconiosis also suffer comorbid mental distress and depression[6], stigma and discrimination[7,8]. The current intervention includes prevention through consistent footwear usage starting from an early age, regular foot hygiene and covering housing floors[9]. For those with the disease, the World Health Organization (WHO) recommends simple lymphedema management consisting of foot hygiene, foot care, wound care, compression, exercises and elevation, treatment of acute attacks and use of shoes and socks to reduce further exposure to the irritant soil[10,11]. Podoconiosis is one of the diseases with the potential for elimination because it is non-infectious and there are proven prevention and treatment interventions[9]. Historical evidence shows that it has already been eliminated from northern African countries including Algeria, Morocco and Tunisia[2], through socioeconomic development, improved housing, access to water and widespread shoe wearing[2].

Although precise estimates are lacking, evidence suggests that globally, four million people are disabled by podoconiosis throughout 27 countries thought to be endemic[12,13]. In Africa, podoconiosis has been reported in 18 countries, mostly in the East and West African regions [12]. Nonetheless, most of the data originate from the 1970s[12], such that the current situation is unclear. Podoconiosis is often misdiagnosed and confused with other causes of lymphedema[14]. In a study conducted in Wolaita Zone in Ethiopia, 53.9% of 275 health workers interviewed inaccurately thought podoconiosis to be an infectious disease transmitted by mosquitoes, and of those who had treated podoconiosis, 71% prescribed diethylcarbamazine assuming that lymphatic filariasis (LF) was the cause[14]. Misdiagnosis of podoconiosis may

not only lead to underestimation of the burden of podoconiosis, but also an underestimation of the success of LF elimination programmes, by overestimating the morbidity burden due to LF [15,16].

Three countries (Cameroon, Ethiopia and Rwanda) have recently mapped the distribution of podoconiosis through nationwide mapping activities [17–20], revealing widespread distribution of the disease, constituting a considerable burden. The studies estimated the number of cases to be 41.5 thousand, 1.5 million and 6,429 in Cameron, Ethiopia and Rwanda, respectively[17,19,20]. These studies have also provided new epidemiological insights. Firstly, they identified climate and topographical factors, such as precipitation, elevation and land surface temperature; environmental factors such as enhanced vegetation index and proximity to waterways; and soil-related factors such as soil composition (i.e., clay, silt and clay content) and soil pH, as potential contributors of disease distribution. Other factors, such as night-light emissivity and distance to stable night-lights, considered indirect indicators of poverty [21–23], were also found to predict the occurrence of podoconiosis [17–20]. Although these factors cannot be considered *per se* to cause the disease, they have proven to be very informative in predicting the occurrence of podoconiosis by characterising its environmental niche.

Podoconiosis national programmes require a detailed understanding of the geographical distribution of the disease so that all endemic areas can be targeted. Previous attempts to map podoconiosis include a detailed literature review[12] and mapping at national[17,19,20] and subnational levels[24–26]. However, there are no maps outlining the potential distribution of podoconiosis at continental and global levels. To date, there are only four countries (Cameroon, Ethiopia, Rwanda and Uganda), which included podoconiosis in their national NTD masterplans. To develop national plans and investment case programmes, planners and policymakers require robust data on the geographical distribution and population at risk, and areas to be targeted for more detailed community-level mapping. Podoconiosis and lymphatic filariasis (LF) share a principal clinical manifestation—lymphedema. In endemic and co-endemic areas, these two diseases are confused. Understanding the graphical overlaps of these two diseases has clinical and programmatic benefits[9]. One of the pillars of LF elimination is morbidity management and disability prevention—i.e., providing access to basic care for LF-related diseases to every affected person in endemic areas[27]. Delineating the overlap of LF and podoconiosis will help join hands to provide access to care, which will help both programmes. In addition, the existing LF programme platform and transmission assessment surveys can be used to integrate mapping of podoconiosis and case searches.

In the current investigation, we aimed to predict the environmental limits of podoconiosis across the African continent, using available presence and absence data with clear geographical location from field surveys and other sources, and empirical evidence of its distribution [17–19,28]. Building on methods used to map the distribution of podoconiosis in known endemic countries, we developed a model to outline the environmental suitability across Africa. The present work aimed to, i) map the geographical distribution of podoconiosis in Africa, ii) estimate the population at risk of podoconiosis, iii) determine the number of WHO implementation units (IUs) where mapping is required, and iv) delineate overlapping risk of podoconiosis and LF. This work was conducted within the context of the Global Atlas of Podoconiosis, which seeks to develop a global map of podoconiosis and estimate its burden[29].

Methods

Data sources

We used data recently collected in country-wide and local surveys conducted in Ethiopia, Cameroon and Rwanda [17–20]. These datasets were supplemented with data compiled under

the Global Atlas of Podoconiosis, which comprises several relevant studies providing evidence of podoconiosis occurrence[12]. The podoconiosis database was first created in 2018, with published literature, case reports and series, and last updated 10 May, 2019. Briefly, we searched for studies that reported the epidemiology of podoconiosis. We searched databases including MEDLINE and SCOPUS from inception to 10 May, 2019 for all relevant studies that examined podoconiosis occurrence, prevalence, incidence and case reports. We used the following search terms; "podoconiosis" OR "mossy foot" OR "non-filarial elephantiasis". No time or language limits were applied. We hand-searched the reference lists of all recovered documents for additional references. Abstracts of all reports were read and full papers retrieved for those appearing to fulfil selection criteria. Publications were eligible for inclusion in the occurrence if they reported geographical locations with evidence of podoconiosis. We contacted authors of studies to further obtain data and geographic coordinates. We searched the grey literature by seeking reports not published in peer-reviewed journals through contacting experts, a search of conference abstracts and reviewing Price's monograph[2]. Further details on the development of this data repository for podoconiosis are provided elsewhere [12,28].

Geo-positioning of survey data

Geographic information extracted from publications included geographical coordinates when these were available, location names and administrative location (i.e., district, region, or state). When coordinates were not provided, we resorted to geocoders and online electronic gazetteers to identify the most accurate geographic coordinates. Briefly, automated georeferencing was implemented in R software through the Google Maps API Engine and Opencage Geocoder, using the *ggmap* and *opencage* packages, respectively[30,31]. Locations that could not be georeferenced by these methods were manually searched in Google using different gazetteers: Bing Maps[32], GeoNet Names Server[33], Fuzzy gazetteers[34] and the Open Street Map project[35]. All geographic coordinates were standardised to decimal degrees in order to be displayed in the WGS84 geographic coordinate system.

Description of covariates

Data on extrinsic determinants of podoconiosis were assembled from remotely sensed environmental datasets (S1 File). Geographic coordinates of each community were used to extract from gridded maps estimates of 1) annual precipitation, 2) land surface temperature, 3) distance to water surfaces (water bodies and streams), 4) elevation, 5) enhanced vegetation index (EVI), 6) soil composition (i.e., silt and clay soil fraction) and 7) soil pH. These climate, topographical, environmental and soil-related factors have been found to be associated with the occurrence of podoconiosis in several studies [18–20,36].

Gridded continuous maps, namely raster datasets, of averaged EVI and land surface temperature (LST) for the period 2000–2017, were generated from MODIS satellite image data downloaded from the Earth Explorer NASA site (https://earthexplorer.usgs.gov/). The MOD13Q1 product from MODIS library, which is updated every 16 days at 250m spatial resolution, includes vegetation indices such as Normalized Difference Vegetation Index (NDVI) and EVI[37]. Day and night LST data were obtained from MOD11A2 products, and have a spatial and temporal resolution of 1km and 8 days, respectively[38].

Information on rainfall was extracted from a synoptic gridded map of annual precipitation calculated from monthly total precipitation gridded datasets obtained from WorldClim v2.0 Global Climate Database[39]. This database provides a set of global climate layers obtained by interpolation of precipitation data for the period 1970–2000 collected in weather stations distributed across the world [40,41]. From the Consortium for Spatial Information (CGIAR-CSI),

we obtained a raster dataset of elevation at 1 square-km[42]. This elevation layer resulted from processing and resampling the gridded digital elevation models (DEM) derived from the original 30-arcsecond DEM produced by the Shuttle Radar Topography Mission (SRTM).

Soil data including silt and clay fraction and soil-pH of the top soil, were obtained from the ISRIC-World Soil Information project[43]. This project provides gridded maps of soil composition at 250m resolution worldwide. We also generated continuous surfaces of straight-line distance (Euclidean distance) in km to the nearest water body and permanent rivers based on data obtained from OpenStreetMap project. Waterbodies and waterways were downloaded from the OpenStreetMap project (OSM)[44] through the platform *Geofabrik*[45].

Input grids were resampled to a common spatial resolution of 5km x 5km using a bilinear interpolation and clipped to the geographic extent of a map displaying Africa limits, and eventually aligned to it. Raster manipulation and processing was undertaken using *raster* package in R v3.3.2 and final map layouts created with ArcGIS 10.5 software (ESRI Inc., Redlands CA, USA).

Data analysis and modelling

An ensemble of distribution models was generated based on the reported occurrence of podoconiosis in the surveyed communities and the environmental factors. Communities were reclassified as endemic (1) or non-endemic (0) for podoconiosis based on records of confirmed podoconiosis cases.

We used six algorithms available within the BIOMOD framework[46] to obtain ensembles of predicted distributions: generalised linear models (GLM), generalised additive models (GAM), generalised boosted regression models (GBM), artificial neural networks (ANN), multiple adaptive regression splines (MARS) and random forest (RF). These models were run using the parameters set by default in the *biomod2* R package [46], except for the GBM models. For the latter, the learning rate (*lr*) and tree complexity (*tc*) parameters in boosted regression models were set to enable up to five interactions and reducing the speed (*lr*: 0.005) to allow the model to converge without over-fitting. This tuning was undertaken using the *gbm* package in R v3.5.3.

The species distribution models we developed all require training with presence and absence points in order to predict environmental suitability. True absence is difficult to determine in surveys, as the absence of cases identified does not rule out the existence of cases when only a subsample of the total population is surveyed. The country-wide mapping surveys conducted in Cameroon, Rwanda and Ethiopia, compiled and used in the current study, targeted the total population of the communities randomly selected across all the administrative regions (i.e., regions/states, districts/zones). Health workers were trained to identify all cases of lymphedema of lower limbs within the communities, and podoconiosis was subsequently confirmed by expert clinical diagnostic teams [18–20,47]. Therefore, we considered communities not reporting cases as '*true*' absences and give them the same weight (1) as the presence records in the analysis. To represent absence locations in areas where exhaustive surveys had not been undertaken, we generated random data points, termed '*pseudo-absence*' records, in countries where the presence of the disease is considered unlikely. This approach has been used in similar modelling studies in the past and has proven to be helpful when presence and absence data are only available for restricted geographical areas [48,49]. To define the area of assumed unsuitability, we used a recently published map displaying the strength of evidence for the presence and absence of podoconiosis across Africa [28]. A sample of *pseudo-absence* points, equal to the number of compiled presence and absence records, was randomly generated from countries with an evidence score below 0 ('*weak to complete evidence of absence*') *Pseudo-*

absence records were weighted based on a rescaled version (0 to 1 scale) of the evidence score assigned for this study to each country[28].

Models were calibrated using an 80% random sample of the initial data and evaluated against the remaining 20% data using the area under the curve (AUC) of the receiver operation characteristic (ROC), the true skill statistic (TSS)[50] and the proportion correctly classified (PCC). Projections were performed 50 times per algorithm, each time selecting a different 80% random sample while verifying model accuracy against the remaining 20%. The evaluation statistics (AUC and TSS) were used to select the models to be assembled based on the matching between predictions and observations. Here, models with AUC < 0.8 or TSS values < 0.7 were disregarded when assembling the final model.

The final ensemble model was obtained by estimating the weighted mean of probabilities across the selected models per grid cell. This algorithm returns the predicted mean weighted by the selected evaluation method scores, in our case the AUC statistic score. The range of uncertainties was also calculated by estimating the confidence intervals around the mean of probabilities across the ensemble per grid cell.

The base map of the global administrative areas was downloaded from the Natural Earth (https://www.naturalearthdata.com/)[51]. All maps were produced using ArcGIS Desktop v10.5 (Environmental Systems Research Institute Inc., Redlands CA, USA).

Cross-validation and setting occurrence map

We used spatial block cross-validation to validate the environmental model. Briefly, the whole area of Africa was split into five regular squares of 2,000km by 2,000km ("folds"), which were tagged from 1 to 5 in a random order. Single models were trained using all the data (occurrences, absences and pseudo-absences) within 4 out of the 5 folds (training data) and the data in the remaining fold (test data) were used to assess the quality of the predictive performance of the trained models (S1 File). Under this approach to model evaluation, test datasets are more spatially independent from training datasets compared to those in a random internal cross-validation approach, reducing the risk of over-optimistic evaluation due to shared ecological characteristics of nearby locations. An ensemble model was constructed using the same specifications as the model run with regular cross-validation. Both models were compared using the Pearson's correlation coefficient.

The resulting predictive map quantifies the environmental suitability for podoconiosis. To convert this continuous metric into a binary map outlining the distribution limits, (i.e., ecological limits), a threshold value of suitability was determined above which podoconiosis occurrence was assumed to be possible. This cut-off represents the best trade-off between sensitivity, specificity and accuracy (fraction correctly classified). Sensitivity: a value between 0 and 1, the proportion of presences correctly identified, specificity: a value between 0 and 1, the proportion of absences correctly identified, fraction correctly classified: a value between 0 and 1 giving the proportion of presences and absences correctly classified. In addition, partial dependence functions were performed separately for two modelling approaches, GBM and RF, to visualise dependencies between the probability of podoconiosis occurrence and covariates. The partial dependence function shows the marginal effect of each covariate on the response after averaging the effects of all other covariates.

Estimation of population at-risk

We estimated the number of individuals at risk in the year 2020 by overlaying the binary raster dataset displaying the potential suitability for podoconiosis occurrence on a gridded population density map[52,53] and calculating the population in cells considered to be within the

limits of podoconiosis occurrence. The 95% uncertainty interval of the population at risk was calculated based on the uncertainty in environmental suitability, by summarising the 50 predictions by mean and 95% credible intervals.

Potential geographical overlapping with LF

Potential for overlapping with lymphatic filariasis (LF) was analysed by overlaying a gridded map of predicted LF occurrence published by Cano et al. (2014)[54] and our map of predicted occurrence for podoconiosis. Both maps were combined and the resulting map was used to estimate the population living in areas environmentally suitable for both podoconiosis and LF applying the above mentioned procedure.

Results

Characteristic of the data

The data search strategy identified 2,870 spatially unique data points from 42 studies undertaken between January, 1934, and May, 2019, in 12 countries in Africa. Of the 2,870 spatially referenced data points 1,311 (45.7%) represented podoconiosis presence. Almost all (99%) of the collected occurrences are distributed across eastern (Ethiopia, Kenya, Rwanda and Uganda) and western Africa (Cameroon, Equatorial Guinea and Sao Tomé and Principe) (Fig 1).

Environmental limits of podoconiosis suitability in Africa

Elevation, annual precipitation, soil pH-H_2O and clay fraction in the topsoil were the major contributors to the GBM and RF ensembles (S1 File). The marginal effect plots for these covariates indicates that the probability of podoconiosis occurrence increases with annual precipitation, reaching a peak between 1,000mm and 1,800mm, and then declining. For elevation, we observed an increased risk in areas located over 1,000masl ('*meters above sea level*') and sustained up to 2,500masl. Regarding soil composition, acid soils (pH H_2O<7) and soils rich in clay and silt are more likely to increase human risk of triggering podoconiosis (S1 File).

We used Global Burden of Disease (GBD) regions[55] to present the results (S1 File). In the Central Africa Region, three countries (Angola, Central African Republic and the Democratic Republic of Congo) were predicted to be suitable for the occurrence of podoconiosis. In the Democratic Republic of Congo, the suitability was predicted in the eastern mountainous part of the country, bordering with countries historically considered endemic (Uganda, Rwanda and Burundi). The mainland region of Equatorial Guinea was found to be unsuitable for the occurrence of podoconiosis, while Bioko Island- which has historically reported cases of podoconiosis, was still found to be suitable for the disease. Podoconiosis was predicted in Sao Tomé Island but not in Principe (Fig 2). For more detail, country maps displaying the predicted environmental suitability for podoconiosis and predicted overlapping with LF are provided in S1 File.

The highest suitability for podoconiosis was predicted in East Africa Region; most parts of Ethiopia, Uganda, Rwanda and Burundi were predicted to be suitable for podoconiosis occurrence. Northern and western parts of Tanzania and the western part of Kenya were also found to be suitable. Parts of the highlands of Madagascar and northern Zambia (which borders with the Democratic Republic of Congo) were also predicted to be suitable. Patchy areas in northern Mozambique, mountainous area in Niassa province, and Malawi, Nyika Plateau and Viphya mountains at the north and around Zomba Mountain and Mount Mulanje at the south, were found to be suitable for podoconiosis occurrence (S1 File and S1 Fig).
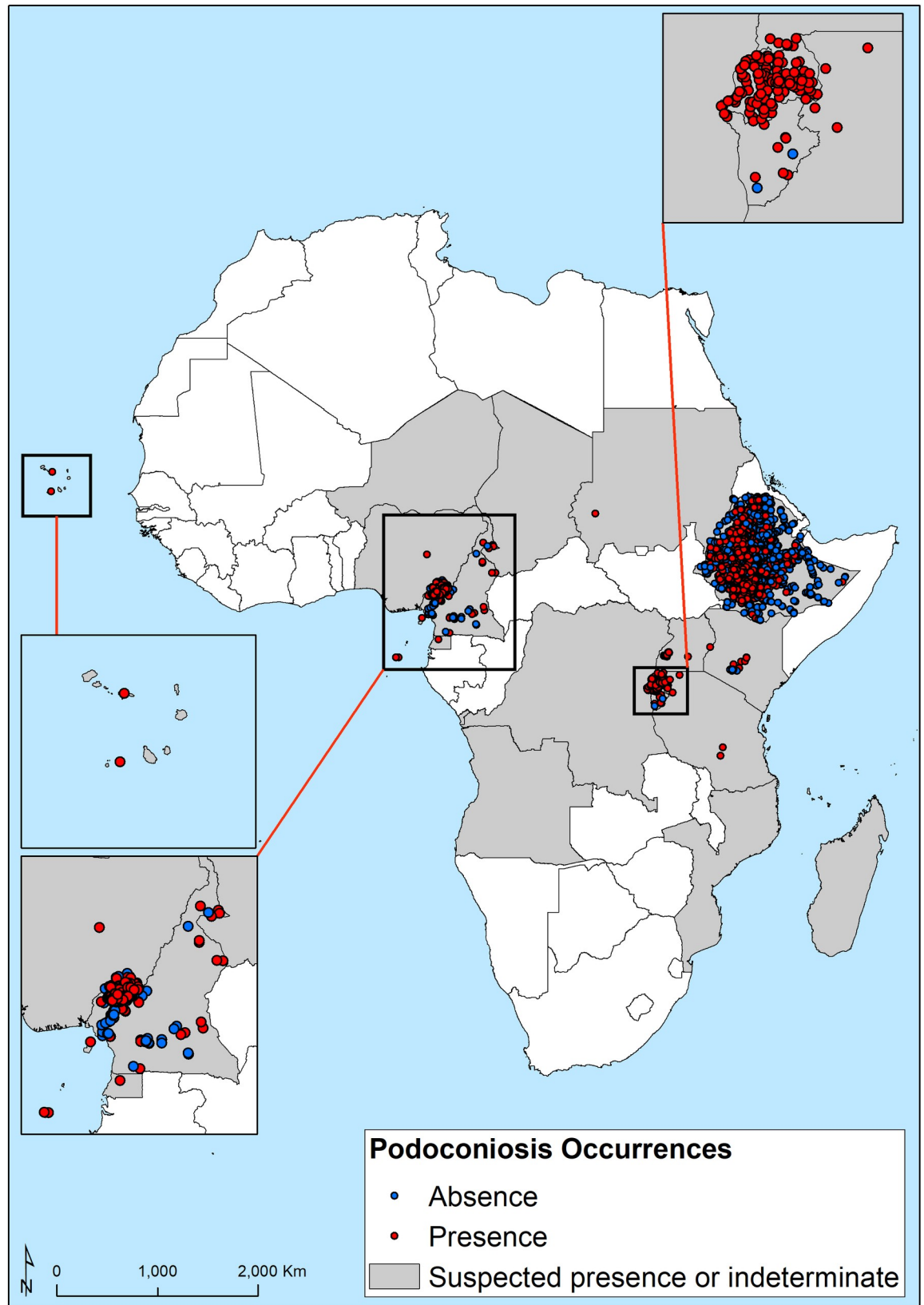
Fig 1. Geographical distribution of presence and absence surveys used in the predictive map of occurrence. Red dots correspond to survey locations where podoconiosis has been reported (n = 1,311).

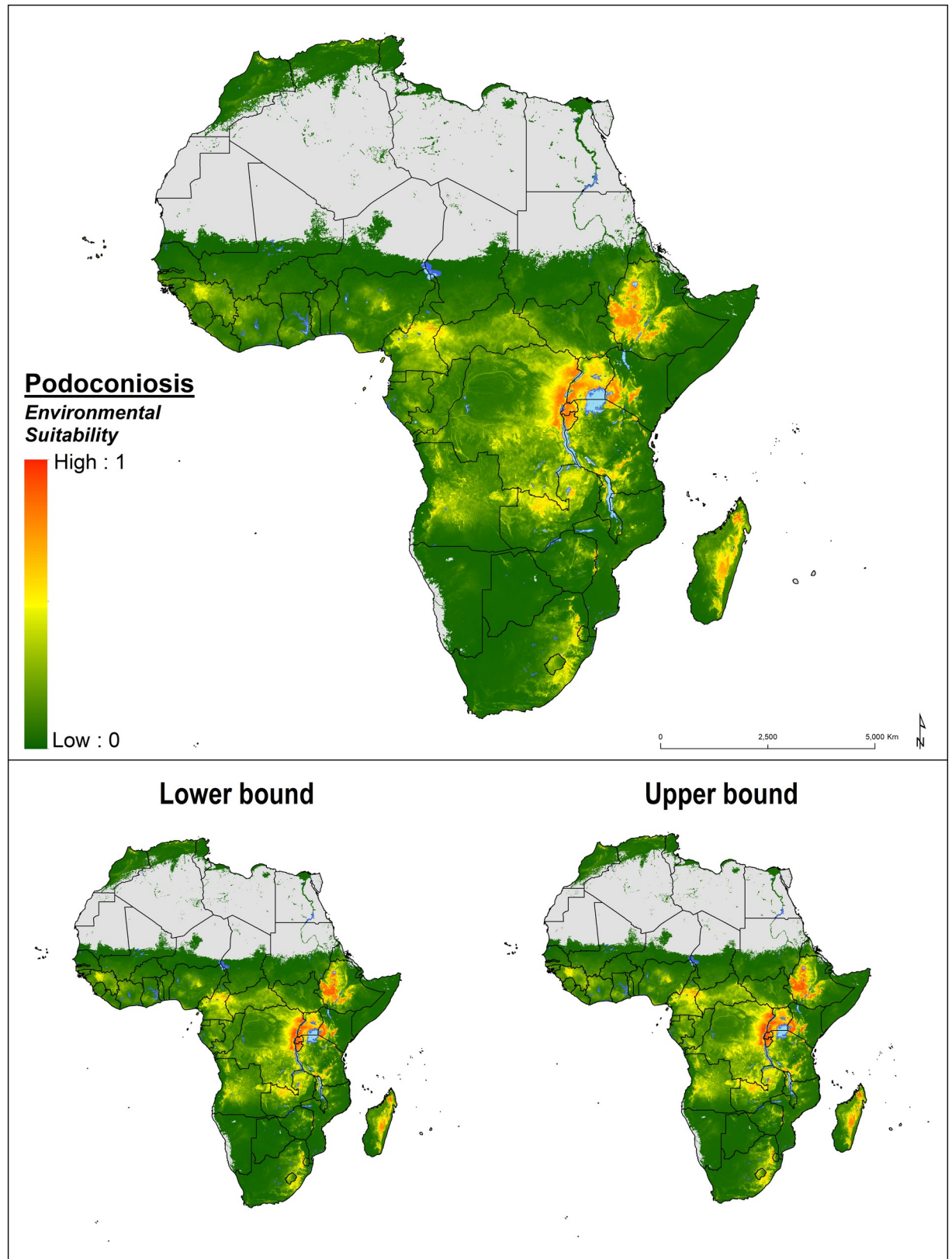https://doi.org/10.1371/journal.pntd.0008616.g001

Fig 2. Environmental suitability for the occurrence of podoconiosis across Africa. Probability of occurrence is provided in a 0 to 1 scale; orange colour indicates highest probability of occurrence (1) and green lowest probability (0). Lower (2.5%) and upper (97.5%) bound of presence limits were obtained from fitting an ensemble of 120 BRT submodels to predict sets of different risk maps.

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Most of the Southern Africa Region was not predicted to be suitable for the occurrence of podoconiosis. Pockets of environmental suitability were predicted in South Africa, along the mountain ranges of Blouberg (Blue mountains) and the Drakensberg (Dragons mountains); the Swaziland border with the Drakensberg mountains in South Africa; and the eastern highlands of Zimbabwe (S1 File and S1 Fig).

In the West Africa Region, our model predicted suitable areas in Cameroon, Cape Verde, Guinea, Nigeria and Sao Tomé Island. In Cameroon, at-risk areas were delineated in most of the central and northwest parts, whereas in Nigeria, suitability appeared to be localized in the central and eastern parts of the country, the latter bordering with Cameroon. Interestingly, the risk map reflects environmental conditions suitable for podoconiosis in countries of northern Africa where the disease is considered eliminated (Morocco and Tunisia) (Fig 2 and S1 File).

Validation statistics indicated an excellent predictive performance of all the algorithms (S1 File). However, RF and GBM outperformed the other models with AUC scores of 0.884 (95% CI: 0.881–0.901) and 0.893 (95%CI: 0.890–0.902), respectively. An environmental suitability threshold of 0.389 provided the best discrimination between presence and absence records; sensitivity 80.1%, specificity 85.5% and AUC score of 0.921, and this threshold value was used to classify the environmental suitability map into a binary map of the environmental limits of occurrence (Fig 3). The final ensemble model showed a high correlation (Pearson's correlation coefficient: 0.9902) with a model constructed using regular spatial blocks for cross-validation, indicating a high stability of the model irrespective of the method chosen for cross-validation and model selection (S1 File).

Estimating population at risk and geographical overlapping with LF

The population living in areas environmentally suitable for podoconiosis was estimated to be over 114.5 million (95% UI: 109.4–123.9) (Table 1). The largest proportion of the population at risk was found in east Africa (81.7%), followed by central Africa (10.9%). Northern, Southern and West African countries only accounted for 7.4% of the total population at-risk. Geographical overlap between podoconiosis and LF was mainly predicted in Eastern, Western and central Africa regions (Fig 4). Large areas of potential co-occurrence of podoconiosis and LF were predicted in Uganda, north of Lake Victoria, in Guinea, and in more restricted areas in Cameroon, Ethiopia and Madagascar. The population living in areas environmentally suitable for podoconiosis and LF was estimated to be 16.9 million, 14.7% of the population at risk for podoconiosis (Table 2). Eastern African countries accounted for 82.0% of the total population living in areas of potential geographic overlap for podoconiosis and LF.

Risk of podoconiosis in Implementation Units (IUs) in Africa

Based on the optimal threshold of environmental suitability (0.389), of the total 5,712 WHO implementation units (typically second administrative-level units, such as districts) in Africa 1,655 (29.0%) IUs were found to be environmentally suitable for podoconiosis. The majority of IUs with high environmental suitability are located in Angola (80 IUs), Cameroon (170 IUs), the DRC (244 IUs), Ethiopia (495 IUs), Kenya (217 IUs), Uganda (116 IUs) and Tanzania (112 IUs). Of the 1,655 environmental suitable IUs, 960 (58.0%) require more detailed community-level mapping (Fig 5).
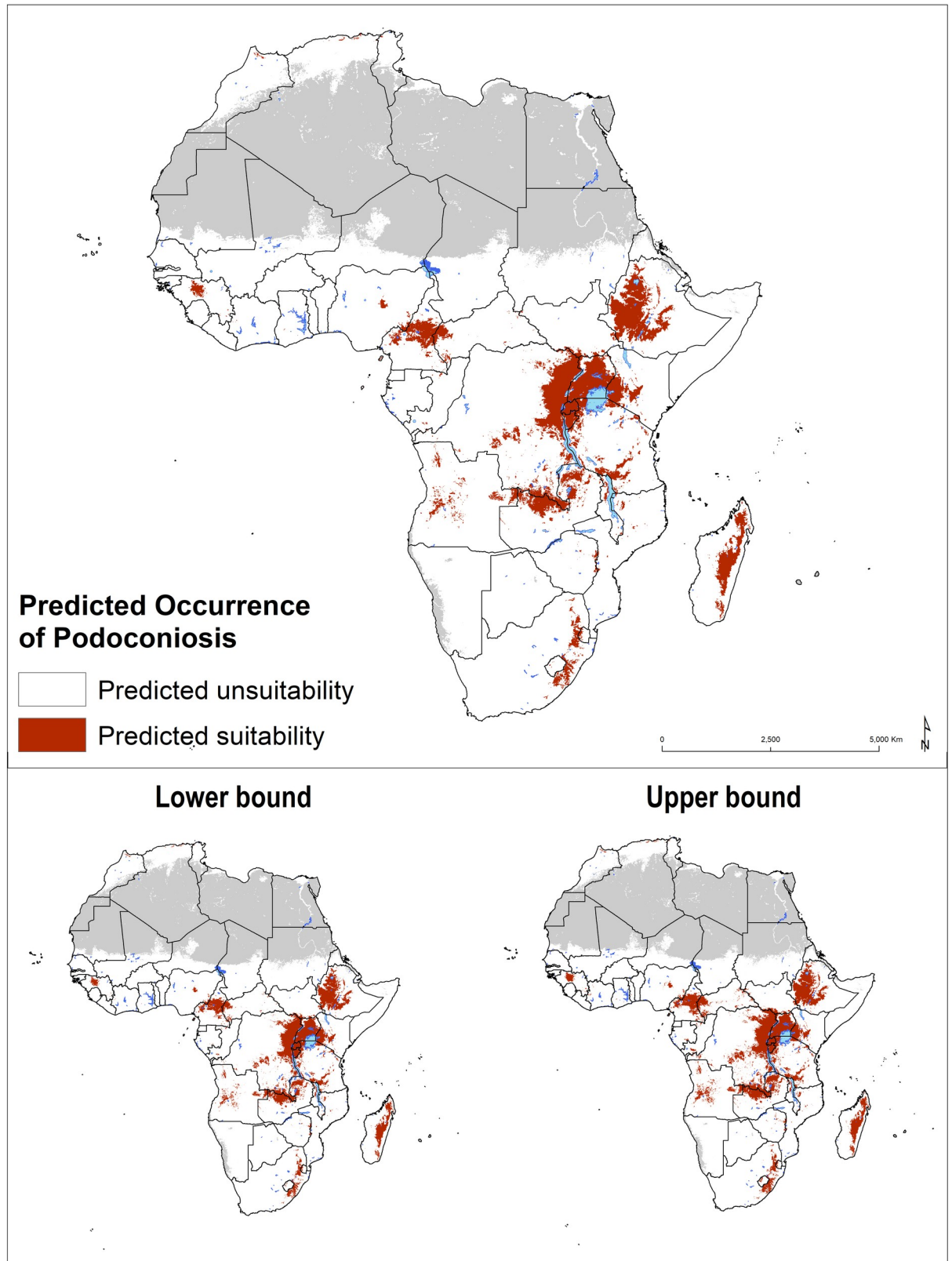
Fig 3. Predicted occurrence of podoconiosis in Africa with the lower (2.5%) and upper (97.5%) bounds of the occurrence limits based on the optimal threshold of environmental suitability (0.389).

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Table 1. Estimates of population living in areas environmentally suitable for podoconiosis in Africa. Estimates were obtained from a gridded map of population density for 2020 (www.worldpop.org).

Africa Region	Population at risk	95% Uncertainty Interval
Central	12,529,248	(11,592,258–14,413,843)
East	93,507,570	(90,335,551–98,217,585)
North	360,038	(300,847–480,627)
South	3,065,753	(2,631,172–4,458,757)
West	5,014,597	(4,517,515–6,373,689)
Total	**114,477,207**	**(109,377,342–123,944,501)**

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Discussion

Our model predicted environmental suitability for podoconiosis in many areas in Africa, with the strongest prediction largely in East, West and Central Africa Regions. In agreement with previous work, our model showed podoconiosis environmental suitability is largely influenced by annual precipitation, elevation, clay fraction and pH of the soil [17–20,36]. The novelty of
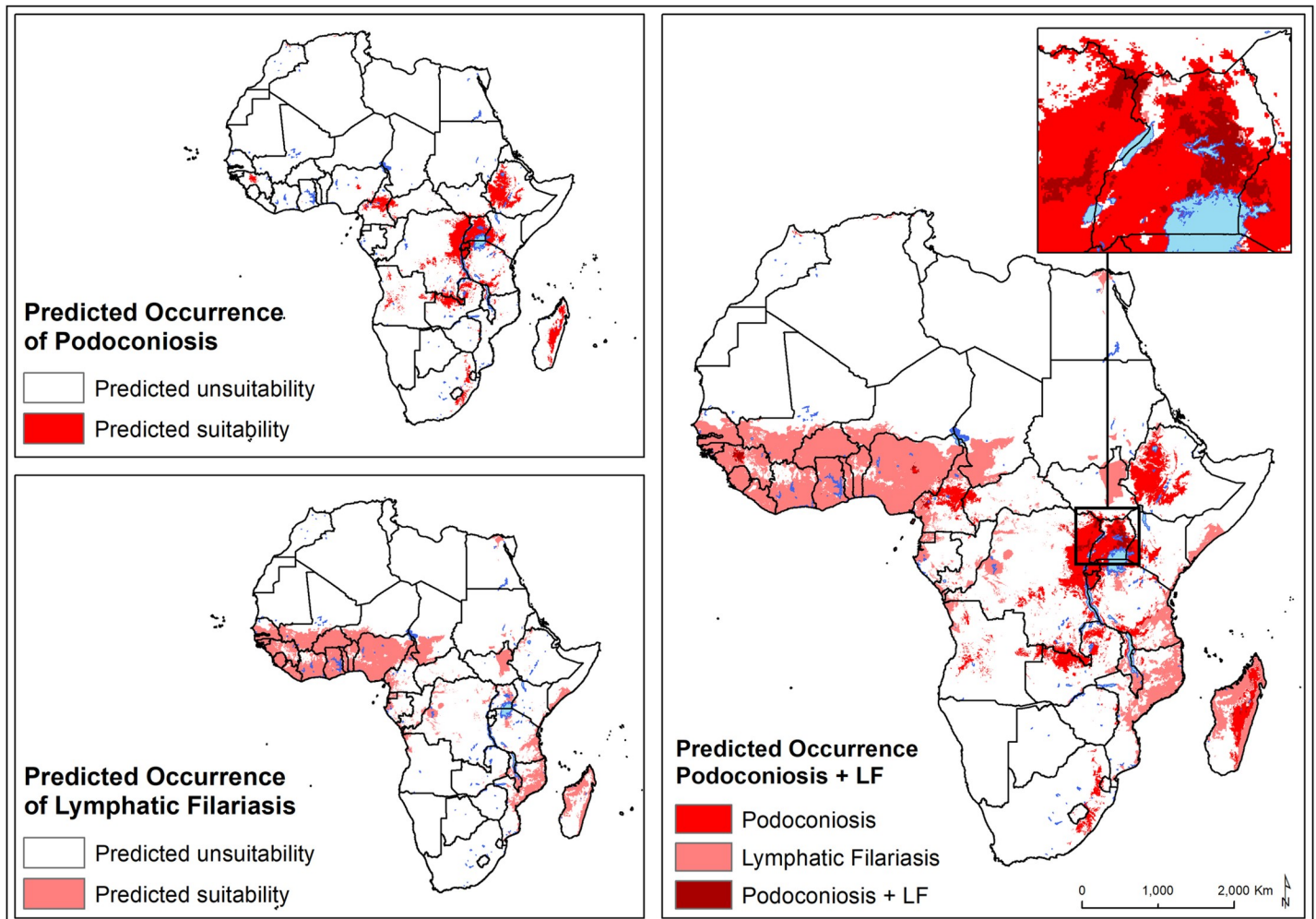

Fig 4. Predicted occurrence of podoconiosis and lymphatic filariasis in Africa. Environmental suitability for lymphatic filariasis according to the predictive map published by Cano et al. (2014) [56].

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Table 2. Estimates of population living in areas with overlapping risk of podoconiosis and lymphatic filariasis in Africa.

Africa Region	Only podoconiosis at risk population 2020	Only LF at risk population	At risk population in LF and podoconiosis overlapping areas
Central	11,660,060	15,758,872	869,188
East	79,675,440	36,548,506	13,832,130
North	360,038	42,376,960	0
South	3,063,100	36,686	2,653
West	2,856,736	182,910,848	2,157,861
Total	97,615,374	277,631,872	16,861,833

this study was in translating suitability to the IU level: aggregated risk at the IU level aids in mapping podoconiosis. These findings are not only useful in understanding the risk, population at risk, and the environmental limits of podoconiosis across Africa, but also are valuable for targeted mapping of podoconiosis in the remaining endemic countries.

Our model predicted suitability in 29 countries (Central 5, East 11, North 4, South 4 and West 5) in Africa, nonetheless we have identified 18 countries with evidence of presence of podoconiosis in Africa previously. This is a clear reflection that suitability only reflects the availability of ecological suitability for the occurrence of podoconiosis, not necessarily the presence of the disease currently. One example is that historical evidence indicates the elimination of podoconiosis from northern African countries (e.g. Algeria, Morocco and Tunisia)[2], nonetheless our model predicted suitable areas in parts of these countries. Although the disease has been eliminated due to socioeconomic development and widespread shoe wearing, the ecological characteristics which are suitable for the occurrence of podoconiosis, such as the soil characteristics, remain the same. Hence our results should be put into context. For this reason, we have restricted the list of IUs needing mapping to those 18 countries with evidence of podoconiosis presence.

Mapping podoconiosis is an important prerequisite for the initiation of data-driven national control programmes[56]. Surveying all districts in suspected endemic countries will be resource intensive and will take time. Here we provide model-based guidance to identify environmentally suitable IUs eligible for mapping activity. By focusing efforts in suitable countries and ensuring suitable IUs within those countries, resources can be targeted and used efficiently. Our prediction can also guide surveillance efforts, targeting areas predicted to be suitable. Here we are not ruling out the need to conduct mapping, our results may provide evidence in prioritizing mapping surveys and surveillance efforts to high yield areas.

Environmental suitability of podoconiosis is predicted in ten countries with no historical report of the disease (including Côte d'Ivoire, Congo, Ghana, Guinea, Malawi, Lesotho, Swaziland, South Africa, Zambia and Zimbabwe)[2,12]. As podoconiosis is a gene-environment-behaviour interaction[13,57], it is possible that it has not been reported because other elements (e.g. genetic susceptibility or lack of footwear) are not present in these countries. Several have strong health systems, making it unlikely that cases are missed without being detected [58–60]. We encourage these countries to increase their index of suspicion for podoconiosis when lymphedema cases are diagnosed and treated. We have identified areas suitable for both podoconiosis and LF. This has important implications in terms of mapping and implementation of interventions. Areas where the LF programme has already advanced, the existing platform and programme activities such as the transmission assessment surveys (TAS) can be used to integrate podoconiosis mapping. Once the mapping is completed integrated morbidity management services can be provided to all cases, as has been found to be feasible in Ethiopia[61]. The methods we applied here have been used to map the global distribution of dengue [48,62], leishmaniasis[49], and melioidosis[63]. They have also been successfully applied to map the
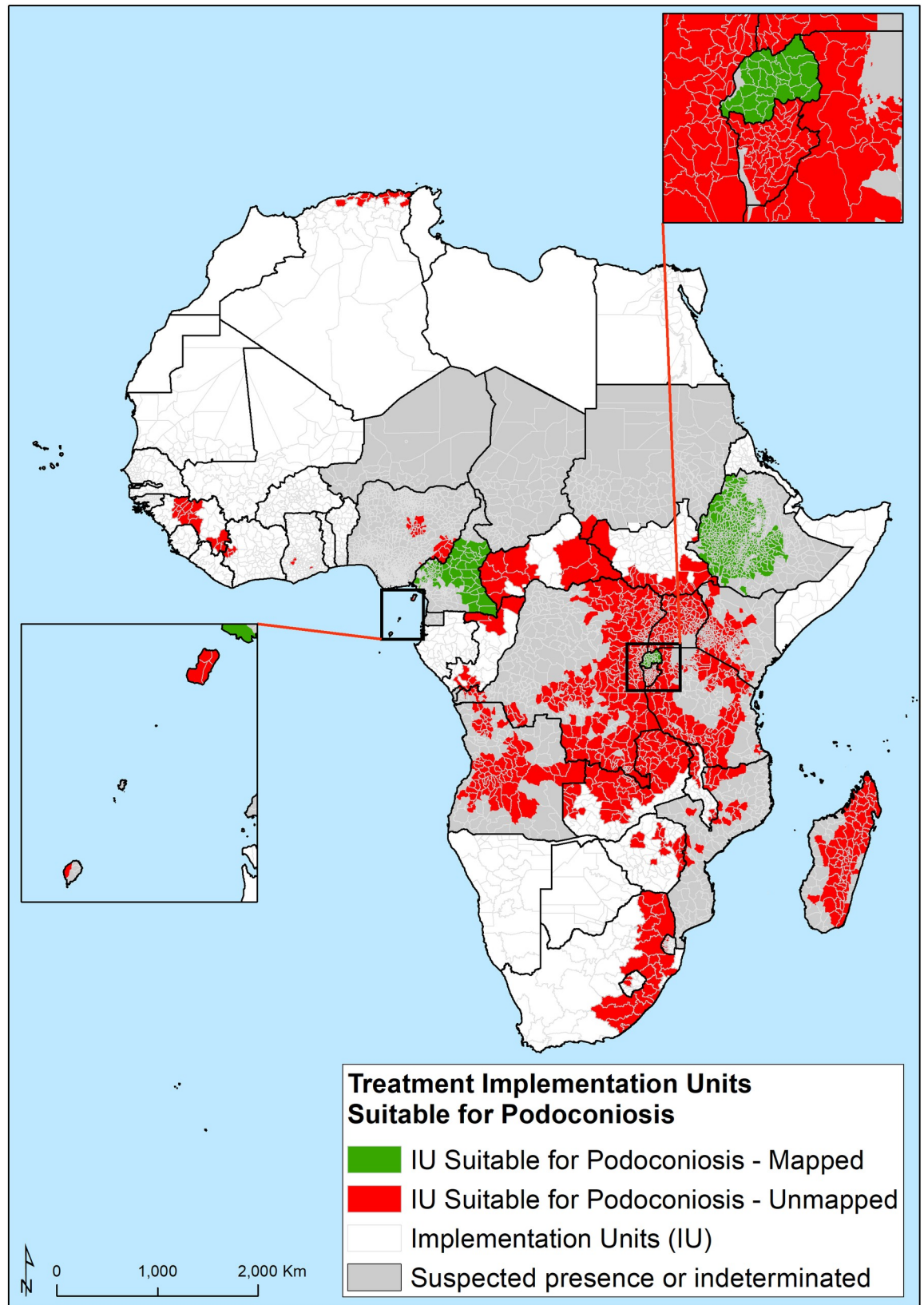
Fig 5. IU-level suitability classification based on WHO geographic units for implementation of control interventions. Red identifies suitable IUs which are not mapped and green identifies suitable IUs mapped for podoconiosis.

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environmental suitability of podoconiosis at local level in Cameroon and Ethiopia [18,63]. Delineating the potentially suitable areas for the occurrence of podoconiosis in Africa has several benefits. First, it provides a framework for targeted mapping of podoconiosis in known and suspected endemic countries by limiting this to areas suitable for the occurrence of the disease. Second, it provides a basis to stratify surveillance activities by identifying areas with different levels of risk. Thirdly, it provides an important input for estimating the burden of podoconiosis at the continent level. Finally, it can be used to guide programme development in endemic countries to strengthen surveillance and preventions strategies.

Limitations

There are some limitations of our analysis. First, our predictive mean environmental suitability is not a measure of disease prevalence or incidence. Our model characterised the similarity between locations based on covariates included with locations with confirmed cases of podoconiosis. This neither measures the magnitude of the problem nor confirms the presence of podoconiosis, it only measures the environmental suitability. Nonetheless, podoconiosis is a gene-environment disease[13,57]. To contract the disease, people must be exposed to the environment and must also be genetically susceptible. This means we might overestimate the population at risk by assuming all individuals living in areas of environmental suitability are at risk of podoconiosis. Nonetheless, our approach is stringent in identifying potential endemic areas for mapping, rather than missing potential endemic areas. Second, only a few of the surveys were conducted at the national level. Most of the surveys were conducted in potentially endemic areas, where investigators observed high prevalence of lymphedema cases. Therefore, our modelling might be characterising areas with high prevalence rather than the whole spectrum of prevalence. Third, we were not able to account for important covariates, including footwear use, which is not available for analysis.

Conclusions

In conclusion, our work has highlighted considerable environmental suitability of podoconiosis in Africa with a significant population at risk in the continent. We have identified areas suitable for podoconiosis, which needs priority both for mapping and intervention. Importantly, we have determined the number of IUs which require mapping based on the optimal cut-off point for suitability. Targeted mapping and intensified surveillance are required in areas where suitability is determined. We have also identified areas where podoconiosis and LF risk overlaps, and where it is possible to use the existing platforms to identify podoconiosis cases in LF-endemic districts, and establish a mechanism whereby podoconiosis cases can access morbidity management services in co-endemic areas. Thus, while our results and maps guide surveillance and survey activities to better define the local distribution and burden of podoconiosis in suitable areas, we encourage countries to collect primary data in pursuit of accelerating the progress towards a world without podoconiosis.

Supporting information

S1 File. Covariates, marginal effects.
(PDF)

S1 Fig. Country level risk prediction.
(PDF)

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References

1. Davey G, Tekola F, Newport MJ (2007) Podoconiosis: non-infectious geochemical elephantiasis. Trans R Soc Trop Med Hyg 101: 1175–1180. https://doi.org/10.1016/j.trstmh.2007.08.013 PMID: 17976670

2. Price E (1990) Podoconiosis:Non-filarial Elephantiasis. Oxford Medical Publications, Oxford, UK.

3. Molyneux DH (2012) Tropical lymphedemas—control and prevention. N Engl J Med 366: 1169–1171. https://doi.org/10.1056/NEJMp1202011 PMID: 22455411

4. Mousley E, Deribe K, Tamiru A, Davey G (2013) The impact of podoconiosis on quality of life in Northern Ethiopia. Health Qual Life Outcomes 11.

5. Tekola F, HaileMariam D, Davey G (2006) Economic costs of endemic non-filarial elephantiasis in Wolaita Zone, Ethiopia. Tropical Medicine & International Health 11: 1136–1144.

6. Bartlett J, Deribe K, Tamiru A, Amberbir T, Medhine G, Malik M, et al. (2015) Depression and disability in people with podoconiosis: a comparative cross-sectional study in rural northern Ethiopia. Int Health 8: 124–131. https://doi.org/10.1093/inthealth/ihv037 PMID: 26113669

7. Tora A, Davey G, Tadele G (2011) A qualitative study on stigma and coping strategies of patients with podoconiosis in Wolaita zone, Southern Ethiopia. Int Health 3: 176–181. https://doi.org/10.1016/j.inhe.2011.06.006 PMID: 24038367

8. Yakob B, Deribe K, Davey G (2008) High levels of misconceptions and stigma in a community highly endemic for podoconiosis in southern Ethiopia. Trans R Soc Trop Med Hyg 102: 439–444. https://doi.org/10.1016/j.trstmh.2008.01.023 PMID: 18339411

9. Deribe K, Wanji S, Shafi O, Tukahebwa EM, Umulisa I, Molyneux DH, et al. (2015) The feasibility of eliminating podoconiosis. Bull World Health Organ 93: 712–718. https://doi.org/10.2471/BLT.14.150276 PMID: 26600613

10. Negussie H, Kassahun MM, Fegan G, Njuguna P, Enquselassie F, McKay A, et al. (2015) Podoconiosis treatment in northern Ethiopia (GoLBet): study protocol for a randomised controlled trial. Trials 16.

11. Negussie H, Molla M, Ngari M, Berkley JA, Kivaya E, Njiguna P, et al. (2018) Lymphoedema management to prevent acute dermatolymphangioadenitis in podoconiosis in northern Ethiopia (GoLBeT): a pragmatic randomised controlled trial. Lancet Glob Health 6: e795–e803. https://doi.org/10.1016/S2214-109X(18)30124-4 PMID: 29773516

12. Deribe K, Cano J, Trueba ML, Newport MJ, Davey G (2018) Global epidemiology of podoconiosis: a systematic review. PLoS Negl Trop Dis 12: e0006324. https://doi.org/10.1371/journal.pntd.0006324 PMID: 29494642

13. Tekola Ayele F, Adeyemo A, Finan C, Hailu E, Sinnott P, Burlinson ND, et al. (2012) HLA class II locus and susceptibility to podoconiosis. N Engl J Med 366: 1200–1208. https://doi.org/10.1056/NEJMoa1108448 PMID: 22455414

14. Yakob B, Deribe K, Davey G (2010) Health professionals' attitudes and misconceptions regarding podoconiosis: potential impact on integration of care in southern Ethiopia. Trans R Soc Trop Med Hyg 104: 42–47. https://doi.org/10.1016/j.trstmh.2009.07.021 PMID: 19717176

15. Sime H, Gass KM, Mekasha S, Assefa A, Woyessa A, Shafi O, et al. (2018) Results of a confirmatory mapping tool for Lymphatic filariasis endemicity classification in areas where transmission was uncertain in Ethiopia. PLOS Neglected Tropical Diseases 12: e0006325. https://doi.org/10.1371/journal.pntd.0006325 PMID: 29579038

16. Rebollo MP, Sime H, Assefa A, Cano J, Deribe K, Gonzalez-Escalada A, et al. (2015) Shrinking the Lymphatic Filariasis Map of Ethiopia: Reassessing the Population at Risk through Nationwide Mapping. PLoS Negl Trop Dis 9: e0004172. https://doi.org/10.1371/journal.pntd.0004172 PMID: 26539700

17. Deribe K, Cano J, Giorgi E, Pigott DM, Golding N, Pullan RL, et al. (2017) Estimating the number of cases of podoconiosis in Ethiopia using geostatistical methods. Wellcome Open Res 2.

18. Deribe K, Cano J, Newport MJ, Golding N, Pullan RL,Sime H, et al. (2015) Mapping and modelling the geographical distribution and environmental limits of podoconiosis in Ethiopia. PLoS Negl Trop Dis 9: e0003946. https://doi.org/10.1371/journal.pntd.0003946 PMID: 26222887

19. Deribe K, Cano J, Njouendou AJ, Eyong ME, Beng AA, Giorgi E, et al. (2018) Predicted distribution and burden of podoconiosis in Cameroon. BMJ Glob Health 3: e000730. https://doi.org/10.1136/bmjgh-2018-000730 PMID: 29946487

20. Deribe K, Mbituyumuremyi A, Cano J, Jean Bosco M, Giorgi E, Ruberanziza E, et al. (2019) Geographical distribution and prevalence of podoconiosis in Rwanda: a cross-sectional country-wide survey. Lancet Glob Health 7: e671–e680. https://doi.org/10.1016/S2214-109X(19)30072-5 PMID: 30926303

21. Elvidge CD, Baugh KE, Kihn EA, Kroehl HW, Davis ER (1997) Mapping city lights with nighttime data from the DMSP operational linescan system. Photogrammetric Engineering and Remote Sensing 63: 727–734.

22. Doll CNH, Muller JP, Morley JG (2006) Mapping regional economic activity from night-time light satellite imagery. Ecological Economics 57: 75–92.

23. Noor AM, Alegana VA, Gething PW, Tatem AJ, Snow RW (2008) Using remotely sensed night-time light as a proxy for poverty in Africa. Popul Health Metr 6: 5. https://doi.org/10.1186/1478-7954-6-5 PMID: 18939972

24. Alemu G, Tekola Ayele F, Daniel T, Ahrens C, Davey G (2011) Burden of podoconiosis in poor rural communities in Gulliso woreda, West Ethiopia. PLoS Negl Trop Dis 5: e1184. https://doi.org/10.1371/journal.pntd.0001184 PMID: 21666795

25. Kihembo C, Masiira B, Lali WZ, Matwale GK, Matovu JKB, Kaharuza F, et al. (2017) Risk Factors for Podoconiosis: Kamwenge District, Western Uganda, September 2015. Am J Trop Med Hyg 96: 1490–1496. https://doi.org/10.4269/ajtmh.16-0932 PMID: 28719274

26. Wanji S, Tendongfor N, Esum M, Che JN, Mand S, Tanga Mbi C, et al. (2008) Elephantiasis of non-filarial origin (podoconiosis) in the highlands of north-western Cameroon. Ann Trop Med Parasitol 102: 529–540. https://doi.org/10.1179/136485908X311849 PMID: 18782492

27. WHO (2018) Global programme to eliminate lymphatic filariasis: progress report, 2017. Wkly Epidemiol Rec 91: 589–604.

28. Deribe K, Simpson H, Cano J, Pigott DM, Weaver ND, Cromwell EA, et al. (2019) Mapping the global distribution of podoconiosis: Applying an evidence consensus approach. PLoS Negl Trop Dis 13: e0007925. https://doi.org/10.1371/journal.pntd.0007925 PMID: 31790408

29. Deribe K, Cano J, Newport MJ, Pullan RL, Noor AM, Enquselassie F, et al. (2017) The global atlas of podoconiosis. Lancet Glob Health 5: e477–e479. https://doi.org/10.1016/S2214-109X(17)30140-7 PMID: 28395836

30. Kahle D, Wickham H (2013) ggmap: Spatial Visualization with ggplot2. The R Journal 5: 144–161.

31. Salmon M Opencage: Interface to the OpenCage API. R package version 0.1.2. 2017.

32. Price E (1976) The association of endemic elephantiasis of the lower legs in East Africa with soil derived from volcanic rocks. Trans R Soc Trop Med Hyg 4: 288–295.

33. Geographic Names Database NGA-GEOnet Names Server (Country Files). Avaibale at http://earth-info.nga.mil/gns/html/index.html. Accessed on July 08,2019.

34. ISODP Project Fuzzy Gazetteer. Available at http://isodp.hof-university.de/fuzzyg/query/. Accessed on August 07, 2019.

35. Open Street Map Open Street Map. Available at http://www.openstreetmap.org/. Accessed on October 7, 2019.

36. Deribe K, Brooker SJ, Pullan RL, Sime H, Gebretsadik A, Assefa A, et al. (2015) Epidemiology and individual, household and geographical risk factors of podoconiosis in Ethiopia: results from the first nationwide mapping. Am J Trop Med Hyg 92: 148–158. https://doi.org/10.4269/ajtmh.14-0446 PMID: 25404069

37. NASA LP DAAC NASA LP DAAC: MOD13Q1 Vegetation Indices 16-Day L3 Global 250m. Avaiabale at https://lpdaac.usgs.gov. Accessed on 25 Februray 2019. NASA EOSDIS Land Processes DAAC, USGS Earth Resources Observation and Science (EROS) Center, Sioux Falls, South Dakota (https://lpdaac.usgs.gov).

38. NASA LP DAAC NASA LP DAAC: MOD11A2 Land Surface Temperature and Emissivity 8-Day L3 Global 1km. Available at https://lpdaac.usgs.gov. Accessed on 23 July 2019. NASA EOSDIS Land Processes DAAC, USGS Earth Resources Observation and Science (EROS) Center, Sioux Falls, South Dakota (https://lpdaac.usgs.gov).

39. WorldClim Global Climate data. Available at https://worldclim.org/bioclim. Accessed on April 2, 2019.

40. Hijmans RJ, Cameron SE, Parra JL, Jones PG, Jarvis A (2005) Very high resolution interpolated climate surfaces for global land areas. International Journal of Climatology 25: 1965–1978.

41. Fick SE, Hijmans RJ (2017) WorldClim 2: new 1-km spatial resolution climate surfaces for global land areas. International Journal of Climatology 37: 4302–4315.

42. CGIAR-CSI Consortium for Spatial Information. Available at http://www.cgiar-csi.org/. Accessed on June 16, 2019.

43. ISRIC—World Soil Information Soil property maps of Africa at 1 km. Available for download at www.isric.org. Accessed on 14 June 2019.

44. (2015) OpenStreetMap contributors. Available at https://www.openstreetmap.org/copyright. Accessed on April 16,2019.

45. Topf J, Ramm F Geofabrik. Available at http://www.geofabrik.de/. Accessed on 10 November 2019.

46. Thuiller W, Lafourcade B, Engler R, Araujo MB (2009) BIOMOD—a platform for ensemble forecasting of species distributions. Ecography 32: 369–373.

47. Deribe K, Beng AA, Cano J, Njouendo AJ, Fru-Cho J, Awah AR,et al. (2018) Mapping the geographical distribution of podoconiosis in Cameroon using parasitological, serological, and clinical evidence to exclude other causes of lymphedema. PLoS Negl Trop Dis 12: e0006126. https://doi.org/10.1371/journal.pntd.0006126 PMID: 29324858

48. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. (2013) The global distribution and burden of dengue. Nature 496: 504–507. https://doi.org/10.1038/nature12060 PMID: 23563266

49. Pigott DM, Bhatt S, Golding N, Duda KA, Battle KE, Brady OJ, et al. (2014) Global Distribution Maps of the Leishmaniases. Elife e02851.

50. Liu CR, White M, Newell G (2011) Measuring and comparing the accuracy of species distribution models with presence-absence data. Ecography 34: 232–243.

51. Natural Earth Natural Earth. Available at https://www.naturalearthdata.com/. Accessed 02 Novemebr, 2019.

52. Linard C, Gilbert M, Snow RW, Noor AM, Tatem AJ. (2012) Population distribution, settlement patterns and accessibility across Africa in 2010. PLoS ONE 7: e31743. https://doi.org/10.1371/journal.pone.0031743 PMID: 22363717

53. WorldPop The AfriPop demography project. Available at http://www.clas.ufl.edu/users/atatem/index_files/demographydata.htm/. Accessed on Novermber 10,2019.

54. Cano J, Rebollo MP, Golding N, Pullan RL, Crellen T, Soler A, et al. (2014) The global distribution and transmission limits of lymphatic filariasis: past and present. Parasit Vectors 7: 466. https://doi.org/10.1186/s13071-014-0466-x PMID: 25303991

55. Murray CJ, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. (2012) GBD 2010: design, definitions, and metrics. Lancet 380: 2063–2066. https://doi.org/10.1016/S0140-6736(12)61899-6 PMID: 23245602

56. Marks M, Mitja O (2019) Prevalence surveys for podoconiosis and other neglected skin diseases: time for an integrated approach. Lancet Glob Health 7: e554–e555. https://doi.org/10.1016/S2214-109X(19)30158-5 PMID: 30926302

57. Davey G, GebreHanna E, Adeyemo A, Rotimi C, Newport M, Desta K. (2007) Podoconiosis: a tropical model for gene-environment interactions?. Trans R Soc Trop Med Hyg 101: 91–96. https://doi.org/10.1016/j.trstmh.2006.05.002 PMID: 16884751

58. GBD 2016 Healthcare Access and Quality Collaborators (2018) Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a systematic analysis from the Global Burden of Disease Study 2016. Lancet 391: 2236–2236. https://doi.org/10.1016/S0140-6736(18)30994-2 PMID: 29893224

59. Global Burden of Disease Collaborative Network (2016) Global Burden of Disease Study 2015 (GBD 2015) Socio-Demographic Index (SDI) 1980–2015. Seattle, United States: Institute for Health Metrics and Evaluation (IHME).

60. Global Burden of Disease Collaborative Network (2018) Global Burden of Disease Study 2017 (GBD 2017) Covariates 1980–2017. Seattle, United States: Institute for Health Metrics and Evaluation (IHME).

61. Deribe K, Kebede B, Tamiru M, Mengistu B, Kebede F, Martindale S, et al. (2017) Integrated morbidity management for lymphatic filariasis and podoconiosis, Ethiopia. Bull World Health Organ 95: 652–656. https://doi.org/10.2471/BLT.16.189399 PMID: 28867846

62. Messina JP, Brady OJ, Golding N, Kraemer MUG, Wint GRW, Ray SE, et al. (2019) The current and future global distribution and population at risk of dengue. Nat Microbiol 4: 1508–1515. https://doi.org/10.1038/s41564-019-0476-8 PMID: 31182801

63. Limmathurotsakul D, Golding N, Dance DA, Messina JP, Pigott DM, Moyes CL, et al. (2016) Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. Nat Microbiol 1: 15008.