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Routine Surveillance Data as a Resource for Planning Integration of NTD Case Management

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Summary

Background: There is a high burden of morbidity due to neglected tropical diseases. To help address this, the World Health Organization recommends integration of case management (CM). Here, we present a practical framework designed to identify areas that could benefit from an integrated CM strategy in Ghana. We also investigated the accessibility of primary health care (PHC) to CM cases, and the impact of this on morbidity at diagnosis.

Methods: Routinely detected cases of Buruli ulcer (BU) and leprosy, and suspected lymphedema identified through morbidity surveys during mass drug administration campaigns in Ghana in 2014 were remotely georeferenced. We estimated distances from cases' home communities to the nearest primary healthcare facility (PHC), and compared rates of reported disease, completeness of clinical information, and risk of more severe morbidity, relative to PHC accessibility.

Results: We georeferenced communities of 295/350 reported leprosy cases, 240/333 BU cases, and 1,557/2383 instances of lymphedema. Overlap of these diseases was predominantly around Accra and in the Upper East Region. Rates of

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reported disease appeared higher in populations with higher accessibility to PHC, and leprosy cases living further from PHC had a higher risk of disability at diagnosis.
Conclusions: This investigation demonstrates the feasibility and value of using routinely collected data to map CM-NTDs at low cost. The maps presented are intended to provide a resource for planning the implementation of integrated CM for NTDs in Ghana. This approach could be easily implemented by national health services in other endemic countries in the future.

Introduction

Several neglected tropical diseases (NTDs) are characterised by chronic infections associated with long-term morbidity.[1] These diseases have a considerable impact on public health as a result of their debilitating and stigmatising symptoms and sequelae, which can lead to permanent disfigurement and disability.[2] The burden of disease due to NTDs falls almost exclusively on poor communities in Africa, Asia and South America.[3]

The NTDs are often categorised by their main control strategy: the preventive chemotherapy (PC) NTDs are amenable to control through mass drug administration (MDA), whereas the intensified case management (ICM) NTDs require an individual-level approach involving early diagnosis and treatment of the infection to reduce morbidity, and the management of complications.[4] While MDA has reduced transmission of the PC-NTDs, the burden of morbidity due to NTDs remains high. Infections including Buruli ulcer (BU), leprosy, lymphatic filariasis (LF), onchocerciasis, trachoma and yaws can result in permanent disfigurement and disability, with patients requiring ongoing treatment for prevention or alleviation of morbidity (hereafter referred to as case management, CM). There is substantial overlap in the strategies for CM for different NTDs. For example, trachoma and leprosy can cause damage to the eye, resulting in vision impairment which can progress to blindness without appropriate clinical management.[5,6] Surgery is required to repair hydrocele resulting from LF and to treat severe cases of BU[7] and complications due to leprosy.[8,9] Physiotherapy can improve cases where mobility is compromised due to lymphedema, BU or leprosy.[10–12] Other common components of CM for these diseases include hygiene, skin care and wound care, which can be delivered by the patient themselves or by a care-giver, following appropriate health education.[12]

Due to the overlap in several aspects of CM, the World Health Organisation (WHO) has recommended the integration of CM interventions, to achieve a more cost-effective use of resources.[12–15] Integration of CM interventions could be implemented through integrated pre- and in-service training of health workers, the delivery of supplies such as footwear, hygiene products and medicines, integrated monitoring and integrated self-care groups in communities that are co-endemic for these diseases.[12] An additional and related aspect of integration is the inclusion of NTD services with general health services, necessary to accompany a move away from vertical programme structures as programmes integrate their activities.

Planning the integration of CM activities requires information on the distribution and burden of NTD-related morbidity, so that resources and activities can be targeted to where disease burdens are highest, and integrated where they overlap. The availability of precise and accurate data on NTD-related morbidity is extremely limited, but prevalence surveys to generate this information are often prohibitively expensive. Existing data sources include health facility case registers and morbidity surveys carried out in the context of MDA for

diseases such as LF and onchocerciasis. While it is recognised that these routine data sources do not provide a complete representation of the burden and distribution of disease, they do indicate the burden of cases already visible to the health system, which may provide a useful resource for the initial phase of integration of CM activities.

As a process within the health system, the integration of CM within NTD programmes would be informed by overlap of disease at the level at which CM activities are managed and coordinated, namely the district level in Ghana. Meanwhile, integration of CM at the point of delivery would be based upon overlap of disease at the level of local health facilities, where patients access basic care. Healthcare delivery structures play a key role in passive surveillance, representing the entry point of patients into the surveillance system as well as the health system. In the context of routine surveillance, the accessibility of services for diagnosis and treatment of NTDs is an essential consideration in planning the integration of CM, and in evaluating the quality of passive surveillance data for this purpose. Previous work has demonstrated that rates of health facility attendance are strongly influenced by the distance patients have to travel to access these facilities.[16] The accessibility of health facilities to populations at risk for NTDs may therefore be expected to impact reporting rates and diagnostic delay, and consequently influence key epidemiological indicators such as rates of reported disease and of more severe morbidity at diagnosis.

In this investigation, we mapped the distributions of routinely reported cases of leprosy, BU, and lymphedema presumably related to LF detected in Ghana in 2014, alongside the locations of health facilities expected to diagnose and treat these conditions. We aimed to investigate rates of reported disease, the completeness of key clinical data, and the risk of more severe morbidity at diagnosis, relative to the accessibility of PHC health facilities. In addition, we integrated data sources to identify co-occurrence of CM-NTD cases at district level, and co-occurrence of morbidity resulting from these diseases at health facility level. The broader goal of this analysis was to assess the potential for integration of CM activities, particularly wound management and prevention of disability for patients with leprosy, BU, and lymphedema.

Methods

STUDY DESIGN, SETTING AND DATA SOURCES

This study was a retrospective cross-sectional study of the distributions of BU, leprosy and LF-related lymphedema in the Republic of Ghana: a country with a population of approximately 28 million and a total land area of 238,537 km^2.[17] It lies on the southern coast of West Africa, bordered by Côte d'Ivoire to the west, Burkina Faso to the north and Togo to the east. The country is divided into 10 administrative regions, which are further divided into 216 districts (Figure 1).

The average population of a district is just over 100,000 people.

Primary health care (PHC) facilities in Ghana include Community-Based Health Planning and Services (CHPS), providing basic essential health services at community level, and health centres at sub-district level.[18] CHPS compounds are intended to service a maximum of 5,000 people, or 1–3 communities.[19,20] Health centres are intended to serve up to 25,000 people.[19]

The disease data mapped in this investigation was collected by the Leprosy Elimination Programme (LEP), the National Buruli Ulcer Control Programme (NBUCP) and the NTD

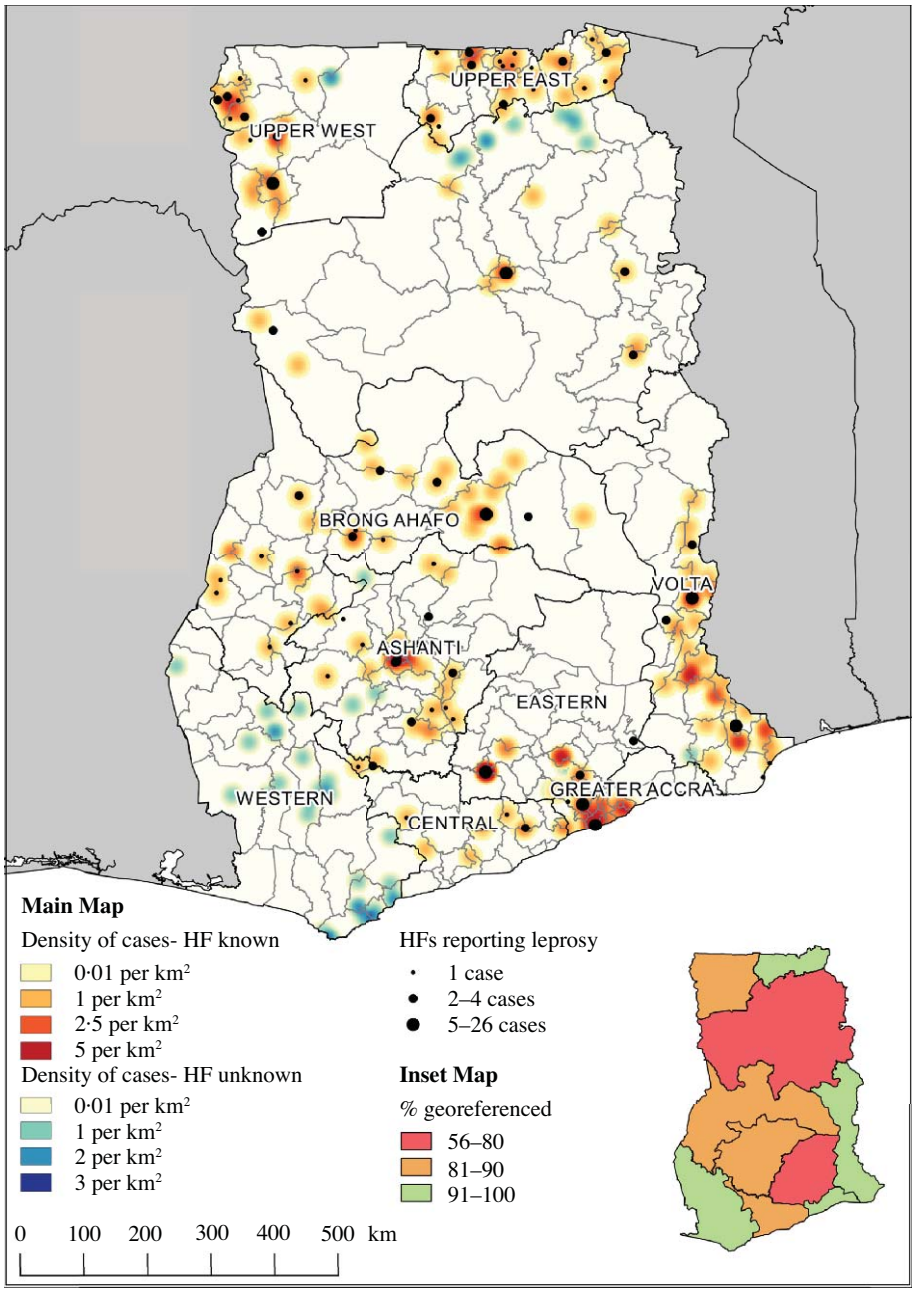

Figure 1. Density distribution of reported leprosy cases in Ghana in 2014 and the locations of the recorded reporting health facilities (HF).

programme in Ghana, as part of their routine surveillance and control activities in 2014. Reflecting the structural organisation of NTD control in Ghana, which consists of separate control programmes for each disease, the methods of primary and secondary data collection varied between datasets for the different diseases.

The Ghana LEP does not undertake active case searches, but implements community health education activities to train volunteers to suspect and refer cases. These activities were implemented in all regions in 2014. Patients who present passively or who are referred by a community volunteer (CV) or health worker (HW) are sent to a health centre or district hospital for diagnosis. Clinicians grade patients according to the WHO leprosy disability grading system[21] and record this information in hospital records. The home address of patients is recorded for case-holding purposes. Data is aggregated to regional level by district programme officers, and reported monthly to the national level. To obtain information on the home residence of cases diagnosed in 2014, all regional officers from the LEP were contacted by telephone, and provided with a standardised electronic form (Microsoft Excel 2010: Microsoft Corporation, Redmond, WA) in which to record the cases from their respective regions. The electronic forms included the district and community of each case, the health facility where treatment was given and the disability grade at diagnosis. All leprosy cases were considered to require CM and so were shown on the integrated morbidity map. The data was validated by comparison of district totals to a district level-aggregated dataset compiled separately by the LEP from routine reports from the regions.

A line-list of all BU cases reported nationally in 2014 was provided by the NBUCP. The NBUCP collects data through passive surveillance from health facilities, and conducts active case searches in known disease foci. In 2014, active case searches were implemented in Ashanti and Brong Ahafo Regions. Cases detected through active case search were not distinguished from those passively reported in the surveillance line-list, although the referral source (self/community volunteer (CV)/health worker (HW)/former patient/other) was recorded. Cases referred by CVs or HWs would include all cases detected through active surveillance, so the proportion diagnosed through these routes may indicate the relative contribution of active case searches. For each case reported, we extracted data on the place of residence (community, district and region name); clinical information including limitation of movement (LOM) at diagnosis, the category and type of lesion;[22] laboratory confirmation by Ziehl Neelsen (ZN) staining and/or polymerase chain reaction (PCR); the referral source; and if available, the health facility where treatment started. We did not restrict the investigation to confirmed cases because a substantial proportion had no laboratory test result recorded. Cases were excluded if they were negative by PCR or negative by ZN if PCR diagnosis was not available. To investigate the possible impact of active surveillance activities on case detection rates, we compared the performance of Ashanti and Brong Ahafo Regions to the country overall in terms of WHO targets for early case detection.[23] Cases with either LOM at diagnosis or category II or III lesions were considered most likely to require ongoing CM and mapped on the integrated morbidity map.

Regarding LF-related lymphedema, the NTD programme provided reporting sheets from the MDA campaigns for LF and onchocerciasis, conducted between June and August 2014. These datasets include morbidity registration data collected by community drug distributors (CDDs) during drug administration. The MDAs were conducted in a total of 141 endemic districts in all regions apart from the Volta Region, which is non-endemic for LF and onchocerciasis, and does not implement morbidity registration for hydrocele and lymphedema. From these reports, we extracted information on the number of suspected cases of lymphedema recorded in each community that had received MDA. The cases recorded are not clinically confirmed, and are only identified based on questioning and visual evidence of lower limb swelling. All suspected lymphedema cases were displayed on the

integrated map; hydrocele cases were not mapped because the main intervention for this condition is surgery, rather than ongoing management and disability prevention.

GEO-REFERENCING CASE REPORT DATA

For community-level disease mapping, we aimed to georeference all communities that reported cases of leprosy, BU, or suspected lymphedema. A range of tools was used to find coordinates, including Bing Maps,[24] Google Maps,[25] the Fuzzy Gazetteer[26] and the OpenStreetMap Project.[27] Other sources were used to estimate the geographical positions of communities that were not found using online search tools. These sources included the Geographic Names Database of the National Geospatial-Intelligence Agency,[28] maps published by the Ghana Statistical Service,[29] the Ghana National Development and Poverty Commission,[30] the Local Governance and Decentralization Program,[31] and the Millennium Development Authority.[32] Paper maps were obtained from the Headquarters of the Survey Department of the Lands Commission in Accra, Ghana. A list of settlements that could not be georeferenced was recorded.

The geo-referenced data was assembled within a geographic information system in QGIS,[33] along with the georeferenced health facilities, and other datasets including national boundary, inland water[34] and population density data.[35] We obtained a list of georeferenced health facilities in Ghana.[36] We used the QGIS Heatmap plugin[37] to map density distributions for leprosy, BU and suspected lymphedema via non-parametric Kernel Density Estimation (KDE), using a Gaussian function and a search radius of 10 km.

ESTIMATING THE ACCESSIBILITY OF PRIMARY HEALTH SERVICES

PHC facilities (including CHPS compounds, clinics and health centres in the health facility dataset) were assumed to be the first point of contact with the health system for leprosy and BU cases, which were largely recorded through passive case detection. We used Euclidean (straight-line) distance as indicator of the accessibility of these health facilities. The estimate of Euclidean distance was considered more appropriate than Manhattan distance (through a road network) for measuring distance in this context because it was assumed that journeys to local health facilities were most likely to be made on foot, so may not be well-represented by the mapped road network. This assumption is supported by evidence from household surveys and focus group discussions conducted as part of a study in a rural district of the Upper West Region of Ghana, which revealed walking to be the most common means of transport to CHPS compounds and HCs.[18]

We measured the distance of each mapped case of leprosy, BU and suspected lymphedema to the nearest PHC facility. We defined zones of good accessibility to PHC facilities across the whole country using buffers of radius 5 km around PHC facilities. This follows the approach of Agbenyo *et al.*[18] in categorising the accessibility of CHPS compounds. In each region, the population within 5 km of a PHC facility was estimated by summing pixel values of population per grid square (from a raster dataset obtained from the WorldPop project[35]) within dissolved buffer zones. These values were subtracted from regional population totals to estimate the population beyond 5 km of a PHC in each region.

ESTIMATING THE RATE OF REPORTED CASES AND THE RISK OF MORBIDITY BY DISTANCE TO PHC FACILITY

We estimated reported rates and proportions of leprosy, BU and suspected lymphedema in population zones within and beyond 5 km of a PHC facility at national and regional levels, and calculated rate ratios (RR) of cases in populations within and beyond 5 km of a PHC facility, using the calculated population estimates as denominators. We conducted a sensitivity analysis on the estimated rate ratios by calculating maximum possible rates within and beyond 5 km of a PHC facility assuming all non-georeferenced cases were more than 5 km from a health facility (to calculate the lower boundary for RR) or within 5 km (to calculate the upper boundary). As indicators of more severe morbidity at diagnosis, we calculated the proportion of leprosy cases with G1/2D at diagnosis, and the proportion of BU cases with category II or III lesions or LOM at diagnosis.

IDENTIFYING OVERLAP OF NTD MORBIDITY IN LOCAL HEALTH FACILITIES

Potential treatment facilities were those considered likely to be able to deliver basic case management for patients with leprosy, BU or lymphedema. We included facilities categorised as clinic; health centre; district hospital; hospital; metropolitan hospital; municipal hospital; polyclinic; regional hospital or training institution in this group. We linked all mapped cases of leprosy and lymphedema, and mapped cases of BU with Category II-III lesions or LOM at diagnosis to their nearest health facility, measured by Euclidean distance. We identified health facilities that were linked to at least two cases of morbidity attributable to different diseases (BU, LF or leprosy). This co-distribution was represented using proportional pie chart maps showing the total number of morbidity cases linked to each facility, and the proportion of cases caused by each of the three diseases.

ETHICS STATEMENT

Permission to conduct this work was granted by the Ghana Health Service Ethical Review Committee and the London School of Hygiene and Tropical Medicine MSc Research Ethics Committee (reference number 9798). Patient informed consent was not required because no patient-identifiable information was stored. Data were aggregated to community-level for analysis and presentation, so there was no possibility of identification of individuals.

Results

DISTRIBUTION OF REPORTED LEPROSY, BU, AND SUSPECTED FILARIAL LYMPHEDEMA

In total, 351 new cases of leprosy were reported from 306 communities in 94 districts, with cases recorded from all regions. One case reported from the Upper East Region was excluded as the case was not a resident of Ghana. The separate dataset compiled by the LEP included 317 cases in 84 districts. Precise data on new cases detected from 24 districts in 2014 was not available to the LEP; of these, four were reported by the regional programme officers to have recorded cases in 2014, with a combined total of 29 cases. Of the 192 districts with reporting data verified by the LEP, the number of cases reported was the same as the number extracted

from the district and hospital records in 123 districts (64·1%). In 43 districts, there was a discrepancy of one to two cases, while three districts showed a discrepancy of more than five cases between the datasets (Figure 1S in supplementary file).

Overall, 195 leprosy cases (55·7%) had no disability, 34 (9·7%) had G1D and 35 (10·0%) had G2D at diagnosis. Data on disability grade was missing for 86 cases (24·4%). Fifty-five of the cases (15·7%) were not georeferenced. The clinic was recorded for 310 cases, but was missing from all cases in the Western Region (Figure 1). The distribution of georeferenced leprosy cases, including those whose clinic was recorded and georeferenced ($n = 216$) and those whose clinic was not known or not georeferenced ($n = 79$), is shown on the density map in Figure 1, along with the locations of the reporting facilities. Mapped cases were sparse in the Northern and Eastern Regions, but these regions had high proportions of cases that were not georeferenced.

A total of 409 new clinical diagnoses of BU were reported from 254 communities in six regions (Ashanti, Brong Ahafo, Central, Eastern, Greater Accra and Western). A high proportion of the cases in Ashanti were referred by CVs and HWs, suggesting that active case searches made a greater contribution to case detection in this region than in Brong Ahafo Region, where a lower proportion was referred by health professionals. Table 1S (in supplementary file) shows referral routes and performance against WHO indicators for early diagnosis by region.

Samples from 321 patients (78·5%) had been tested for *M. ulcerans* using PCR, of these 250 (77·9%) had tested positive and 71 (22·1%) were negative. Of the 88 patients not analysed by PCR, 7 had been tested for the presence of mycobacteria using ZN staining; two were positive and five were negative. In total, 333 patients were positive or untested for

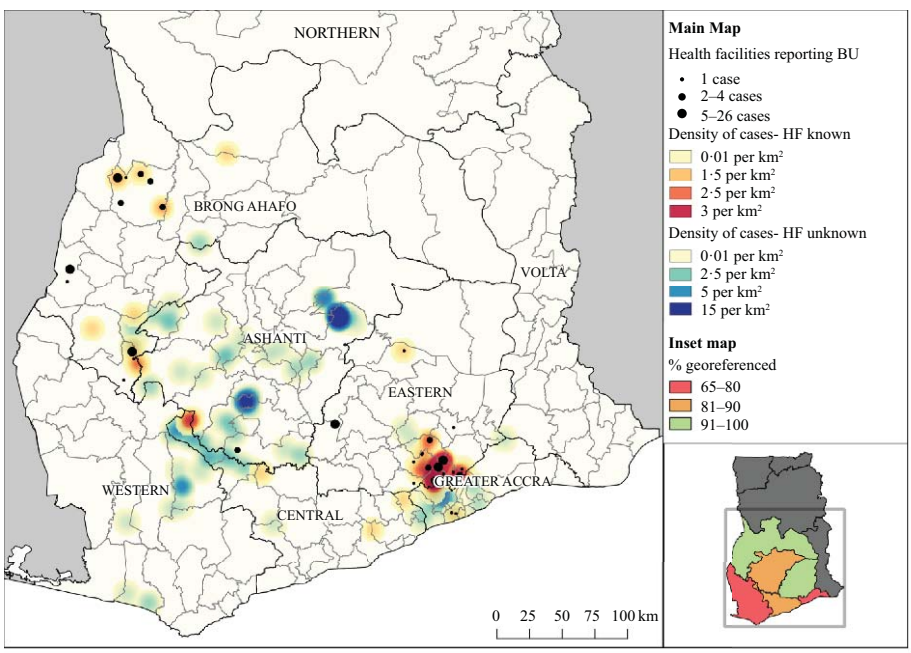

Figure 2. Density distribution of BU cases reported in Ghana in 2014 and the locations of the recorded reporting health facilities (HF).

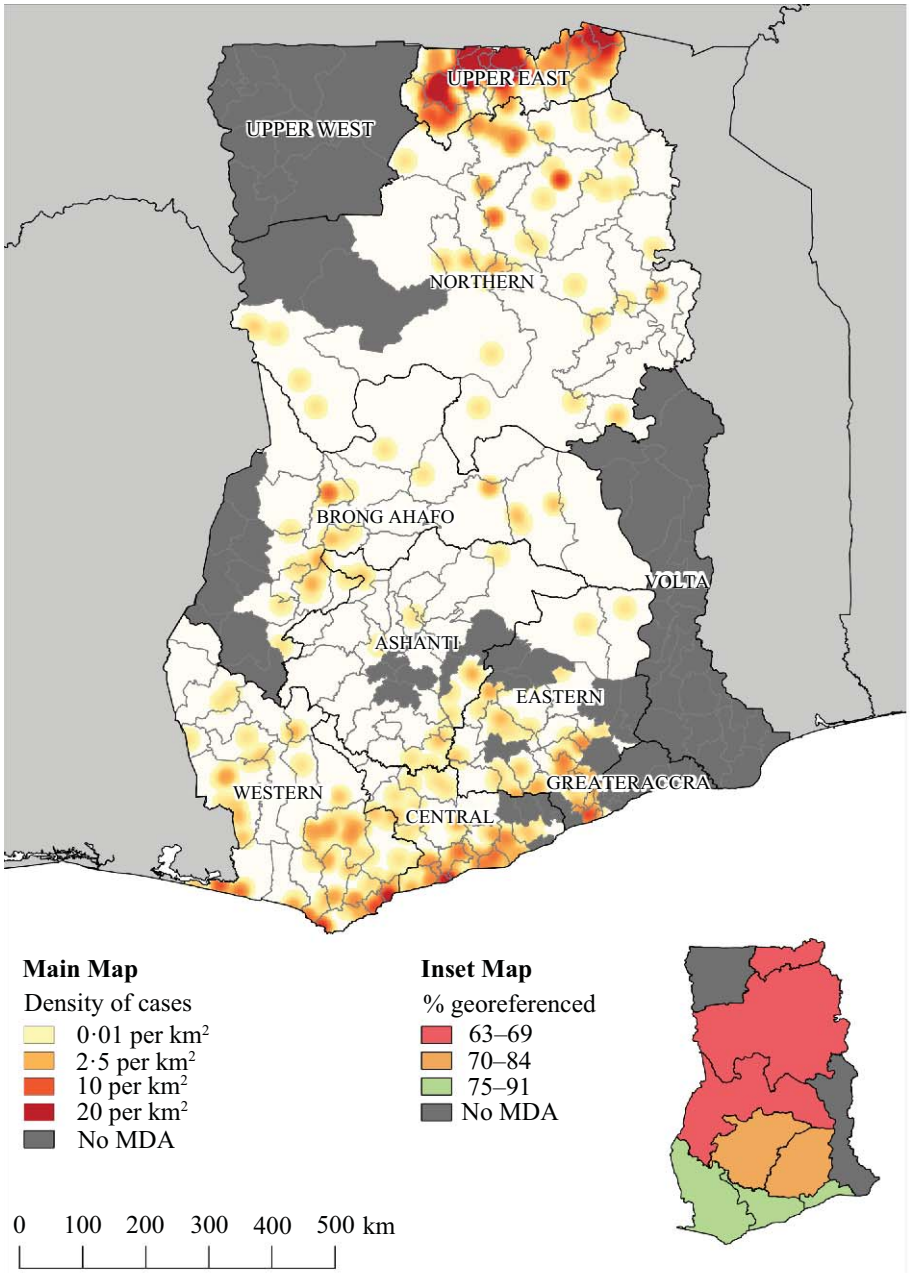

Figure 3. Density distribution of suspect cases of filarial lymphedema detected in morbidity surveys for mass drug administration campaigns (MDA) in Ghana in 2014.

M. ulcerans but considered suspicious of BU; these are hereafter referred to as 'cases'. Two hundred and fourteen cases (64·3%) had either category II or III lesions or LOM at diagnosis.

Fifty-three cases (15·6%) were not georeferenced. Health facility was recorded for 137/333 BU cases (41·1%). Thirty-three out of 43 recorded health facilities (76·7%) were

georeferenced. The distribution of georeferenced BU cases, including those whose clinic was recorded and georeferenced ($n = 82$), and those for which reporting clinic was unknown or not georeferenced (198), is shown on the density map in Figure 2, along with the reporting facilities.

Morbidity registration conducted through LF and onchocerciasis community-based MDA identified 2,383 suspect cases of lymphedema in 1,043 communities. The communities of 826 individuals (34·7%) could not be georeferenced. Cases were heavily concentrated in the Upper East Region, and the distribution was scattered throughout the rest of the country (Figure 3).

The density of mapped cases was low in the Northern and Brong Ahafo regions, and increased towards the south of the country. There were some pockets of high concentration along the coast. The proportion of communities that were georeferenced was lowest in the Upper East, Northern and Brong Ahafo Regions, and highest in the southern regions.

ACCESSIBILITY OF PHC FACILITIES

Seventy-five percent of the overall population was within 5 km of a PHC facility. This proportion varied between regions (Table 1).

At national level, rates of reported and georeferenced leprosy, BU and suspect filarial lymphedema were higher in the population within 5 km of a PHC facility. All regions had higher rates of reported and georeferenced leprosy and most had higher rates of reported and georeferenced BU in the population within 5 km of a PHC facility. This pattern was not observed for filarial lymphedema: four out of eight regions that reported data- including the two regions with the lowest access to PHC facilities- had lower rates of recorded cases in the population within 5 km of a PHC facility (Table 1). The relationship between the rate of reported cases and the accessibility of PHC was sensitive to the location of the non-georeferenced cases: when these were assumed to occur beyond 5 km of a PHC facility (rather than excluded), rates of leprosy and BU at national level and in most regions were higher in populations beyond 5 km of PHC (Table 2S, supplementary file).

Regardless of the assumed location of non-georeferenced cases, the rate of reported leprosy was higher in the population within 5 km of a PHCF in the Volta and Upper West Regions, and the rate of reported BU was higher within 5 km of a PHCF in the Eastern and Brong Ahafo Regions (Table 2S, supplementary file).

Georeferenced leprosy cases occurring more than 5 km from a PHC facility were less likely to have been graded at diagnosis than those living within 5 km of a PHC facility (Table 3S, supplementary file).

Among graded cases, the proportion with G1/2D was higher in those living further away from a PHC facility (Table 2).

The completeness of clinical indicators for BU cases was high, both in cases located within and beyond 5 km of a PHC facility (Table 3S, supplementary file). The proportion of BU cases with LOM or category II-III lesions was similar in populations within and beyond 5 km of a PHC facility, but was higher in non-georeferenced cases (Table 2).

OPPORTUNITIES FOR INTEGRATED CM

Overlap of morbidity due to leprosy and lymphedema occurred in all regions apart from the Volta Region, where LF-related morbidity was not recorded, and the Upper West, from which reporting sheets were not available. In the Upper East Region, there were high case numbers

Table 1. Regional rates of reported leprosy, Buruli ulcer (BU) and suspected filarial lymphedema, within and beyond 5 km of a primary healthcare (PHC) facility in Ghana in 2014

Area	%[1]	Reported leprosy cases				
		<5 km from PHC		>5 km from PHC		
		N	Rate (95% CIs)	N	Rate (95% CIs)	Rate Ratio[4]
All Regions	**75·4**	**251**	**1·3 (1·1–1·4)**	**44**	**0·7 (0·5–0·9)**	**1·86**
Greater Accra	**95·5**	28	0·7 (0·5–1)	0	0 (0–1·9)	–
Upper East	**93·0**	31	3 (2–4·2)	2	2·6 (0·3–9·3)	1·17
Ashanti	**83·7**	34	0·8 (0·5–1·1)	3	0·4 (0·1–1)	2·20
Central	**74·5**	6	0·3 (0·1–0·7)	2	0·3 (0–1·2)	1·03
Volta	**74·5**	46	2·7 (2–3·6)	3	0·5 (0·1–1·5)	5·24
Western	**70·0**	22	1·2 (0·8–1·9)	7	0·9 (0·4–1·9)	1·35
Eastern	**68·7**	24	1·2 (0·8–1·8)	0	0 (0–0·4)	–
Brong Ahafo	**61·6**	25	1·6 (1·1–2·4)	10	1 (0·5–1·9)	1·56
Upper West	**58·3**	23	5·3 (3·3–7·9)	7	2·3 (0·9–4·6)	2·35
Northern	**51·1**	12	0·9 (0·5–1·5)	10	0·8 (0·4–1·4)	1·15
Area	**%[1]**	**Reported BU cases**				
		< 5 km from PHC		**> 5 km from PHC**		
		N	**Rate (95% CIs)**	**N**	**Rate (95% CIs)**	**Rate Ratio[4]**
All Regions	**75·4**	**246**	**1·2 (1·1–1·4)**	**34**	**0·5 (0·4–0·7)**	**2·36**
Greater Accra	**95·5**	30	0·7 (0·5–1)	1	0·5 (0–2·9)	1·42
Ashanti	**83·7**	94	2·2 (1·8–2·7)	17	2 (1·2–3·3)	1·07
Central	**74·5**	25	1·4 (0·9–2·1)	9	1·5 (0·7–2·8)	0·95
Western	**70·0**	12	0·7 (0·3–1·2)	3	0·4 (0·1–1·1)	1·71
Eastern	**68·7**	56	2·9 (2·2–3·7)	1	0·1 (0–0·6)	25·53
Brong Ahafo	**61·6**	29	1·9 (1·3–2·7)	3	0·3 (0·1–0·9)	6·03
Area	**%[2]**	**Reported cases of suspected filarial lymphedema**				
		< 5 km from PHC		**> 5 km from PHC**		
		N	**Rate[3] (95% CIs)**	**N**	**Rate[3] (95% CIs)**	**Rate Ratio[4]**
All Regions	**72·8**	**1296**	**10·2 (9·7–10·8)**	**261**	**4·9 (4·3–5·5)**	**2·09**
Greater Accra	**99·2**	25	0·9 (0·6–1·3)	0	0 (0–2·5)	–
Upper East	**93·0**	948	91·4 (85·7–97·4)	62	80·2 (61·5–102·9)	1·14
Ashanti	**71·8**	8	0·4 (0·2–0·8)	7	0·9 (0·3–1·8)	0·49
Central	**71·2**	103	7·6 (6·2–9·2)	20	3·2 (2–5)	2·34
Western	**70·0**	117	6·5 (5·4–7·8)	61	7·9 (6–10·1)	0·83
Eastern	**67·8**	43	3·1 (2·2–4·1)	19	2·3 (1·4–3·6)	1·33
Brong Ahafo	**56·8**	12	1·2 (0·6–2·2)	27	3·1 (2–4·5)	0·40
Northern	**52·5**	40	3·1 (2·2–4·2)	65	5·4 (4·2–6·9)	0·57

[1]Proportion of population living within 5 km of a primary health facility (PHF).

[2]Proportion of population within 5 km of a PHF, in districts where LF morbidity registration was implemented in 2014.

[3]Rates of leprosy and BU were calculated from the number of newly reported cases in 2014 per 100,000 population; rates of suspected lymphedema were calculated from the number of suspect cases recorded during morbidity registration, per 100,000 population.

[4]Ratio of the rate within 5 km of PHC to that beyond 5 km of PHC.

Regional populations, populations in districts where morbidity registration was implemented, and populations within 5 km of a PHC facility were estimated using data from the WorldPop project (1).

CIs = confidence intervals, calculated using Byar's method.

Table 2. Numbers and proportions of leprosy cases with grade 1/2 disability at diagnosis, and Buruli Ulcer (BU) cases with category II/III lesions or limitation of movement (LOM) at diagnosis, by distance to nearest primary health care facility in georeferenced cases, and in non-georeferenced cases. Data are from Ghana in 2014 and are shown by region

	Reported leprosy cases											
	<5 km			>5 km			Total Mapped			Total not georeferenced		
	N. graded	With G1/2D		N. graded	With G1/2D		N. graded	With G1/2D		N. graded	With G1/2D	
		N	% (95% CIs)		N	% (95% CIs)		N	% (95% CIs)		N	% (95% CIs)
All Regions	**208**	**53**	**25·5 (20–31·8)**	**27**	**9**	**33·3 (18·6–52·2)**	**235**	**62**	**26·4 (21·2–32·4)**	**29**	**7**	**24·1 (12·2–42·1)**
Ashanti	34	14	41·2 (26·4–57·8)	3	3	100 (43·9–100)	37	17	45·9 (31–61·6)	9	3	33·3 (12·1–64·6)
Brong Ahafo	25	9	36 (20·2–55·5)	10	3	30 (10·8–60·3)	35	12	34·3 (20·8–50·8)	7	3	42·9 (15·8–75)
Central	6	1	16·7 (3–56·4)	2	0	0 (0–65·8)	8	1	12·5 (2·2–47·1)	1	1	100 (20·7–100)
Eastern	13	7	53·8 (29·1–76·8)	0	0	0	13	7	53·8 (29·1–76·8)	1	0	0 (0–79·3)
Greater Accra	28	11	39·3 (23·6–57·6)	0	0	0	28	11	39·3 (23·6–57·6)	0	0	0
Northern	2	2	100 (34·2–100)	0	0	0	2	2	100 (34·2–100)	0	0	0
Upper East	31	2	6·5 (1·8–20·7)	2	0	0 (0–65·8)	33	2	6·1 (1·7–19·6)	2	0	0 (0–65·8)
Upper West	23	6	26·1 (12·5–46·5)	7	3	42·9 (15·8–75)	30	9	30 (16·7–47·9)	7	0	0 (0–35·4)
Volta	46	1	2·2 (0·4–11·3)	3	0	0 (0–56·1)	49	1	2 (0·4–10·7)	2	0	0 (0–65·8)
Western	0	0	0	0	0	0	0	0	0	0	0	0
	Reported BU cases											
	< 5 km			> 5 km			Total Mapped			Total not georeferenced		
	N. graded	With cat II-III or LOM		N. graded	With cat II-III or LOM		N. graded	With cat II-III or LOM		N. graded	With cat II-III or LOM	
		N	% (95% CIs)		N	% (95% CIs)		N	% (95% CIs)		N	% (95% CIs)
All Regions	**216**	**156**	**72·2 (65·9–77·8)**	**29**	**20**	**69 (50·8–82·7)**	**245**	**55**	**67·9 (57·1–77·1)**	**53**	**42**	**84 (71·5–91·7)**
Ashanti	69	47	68·1 (56·4–77·9)	12	8	66·7 (39·1–86·2)	81	22	81·5 (63·3–91·8)	25	16	72·7 (51·8–86·8)
Brong Ahafo	24	20	83·3 (64·1–93·3)	3	2	66·7 (20·8–93·9)	27	26	76·5 (60–87·6)	0	0	0
Central	25	19	76 (56·6–88·5)	9	7	77·8 (45·3–93·7)	34	36	63·2 (50·2–74·5)	5	4	80 (37·6–96·4)
Eastern	56	36	64·3 (51·2–75·5)	1	0	0 (0–79·3)	57	22	71 (53·4–83·9)	5	5	100 (56·6–100)
Greater Accra	30	22	73·3 (55·6–85·8)	1	0	0 (0–79·3)	31	15	100 (79·6–100)	10	10	100 (72·2–100)
Western	12	12	100 (75·8–100)	3	3	100 (43·9–100)	15	0	0 (0–0)	8	7	87·5 (52·9–97·8)

[1]out of those with DG recorded. [2]out of cases with at least one of these indicators available.
CIs = confidence intervals, calculated using the Wilson Score method.

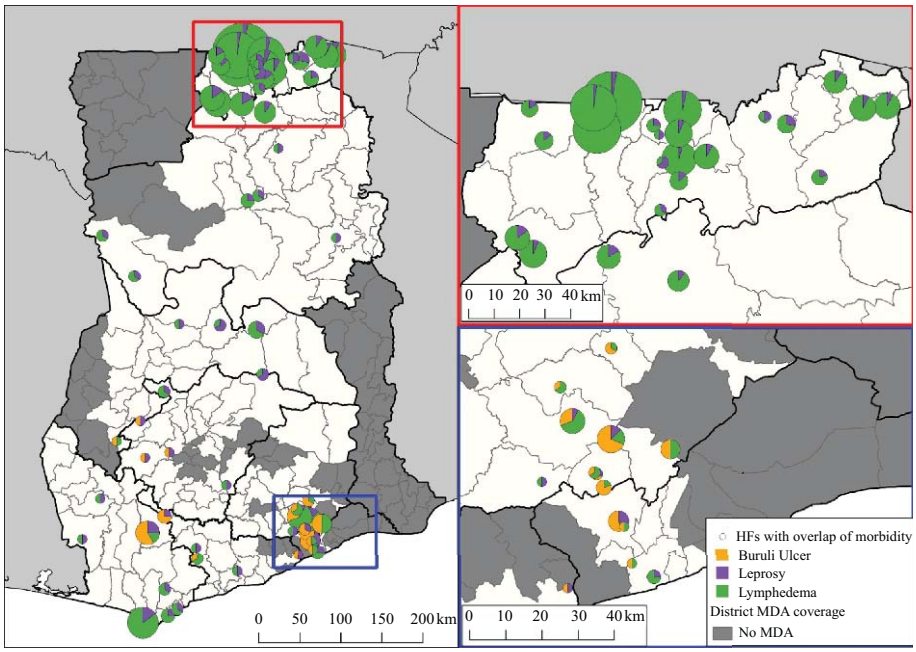

Figure 4. Overlapping morbidity caused by leprosy, BU and lymphedema in health facilities Ghana, in the Upper East Region, and in and around Accra.

of lymphedema and leprosy, and extensive overlap between these two causes of morbidity. In parts of Greater Accra and across the northern border into the Eastern Region, there was overlap of morbidity due to BU, leprosy, and lymphedema (Figure 4).

At district-level, overlap of these conditions was relatively common: 42 of 216 districts reported at least two of BU, leprosy and lymphedema (Table 3).

Discussion

The maps presented in this work show the burden of BU, leprosy and filarial lymphedema that is already visible to the health system in Ghana. We have used the mapped data to identify

Table 3. The number of districts in Ghana reporting routinely detected cases of lymphedema, leprosy and Buruli ulcer (BU) in 2014

Number of conditions recorded (BU, leprosy, lymphedema)	Number of districts	%
0	52	*24·1*
1	122	*56·5*
2	39	*18·1*
3	3	*1·4*
Total	**216**	

overlap of CM-disease within existing health care facilities that would deliver care for patients. NTD-related morbidity was primarily identified in areas where the population had a greater level of geographical access to primary healthcare. The accessibility of PHC facilities may impact the rate of recorded cases, although specific reasons for this are not clear and multiple factors are likely to be involved. Lower accessibility of PHC facilities was related to a higher risk of more advanced morbidity for leprosy, but not for BU. These results could help to inform the implementation of integrated morbidity management, in line with WHO recommendations for NTD control.

The use of routine data was a key aspect of this investigation, and we recognise that these data sources entail certain limitations, especially around under-detection and under-reporting of cases. There were some discrepancies between the numbers of leprosy cases collated by the regional programme officers from hospital and district registers, and the numbers reported by the regional programme officers to the LEP. The main cause of the discrepancy in the national totals is likely to be that four districts in which cases had been recorded did not report data to the NLP. The main cause of discrepancies in the totals at district-level is different allocation of cases to districts within this exercise and by the LEP. Within this exercise, cases were allocated to district of residence, while the LEP allocates cases to the district of the facility in which they were diagnosed.

Leprosy and BU are recognised to be under-reported globally,[38,39] with evidence of under-diagnosis and under-reporting in passive case detection systems in a range of settings.[40–42] It is also important to note that the data on LF was collected by volunteers, and is not clinically verified; a proportion of the recorded lymphedema cases included here may not be caused by LF. Validation studies would be required to assess the impact of this on our results. Meanwhile, we expect that the data used in this investigation gives an underestimate of the burden of filarial lymphedema: morbidity surveys conducted in the context of MDA campaigns are demonstrated to detect fewer cases than dedicated surveys,[43] and furthermore, cases in districts that did not implement MDA for LF in 2014 would not be detected in this system.

The impact of under-detection by passive surveillance is potentially more extreme in communities with a lower level of access to PHC, which could introduce bias due to spatial differences in availability and accessibility of health facilities to the population. We sought to assess this by mapping the distribution of reported cases alongside that of reporting health facilities, and by comparing the rates of reported disease in populations with higher and lower estimated access to health facilities. The disease distribution maps show that cases whose reporting health facility was recorded were generally close to those facilities. We also found that rates of recorded and mapped leprosy and BU were higher in the population within 5 km of a PHC facility, which may reflect higher rates of case ascertainment in populations with better access to PHC facilities. Another possibility is that cases may travel for diagnosis and treatment, and the community recorded in the clinic is not the case's permanent place of residence, but a temporary address where they are staying while under treatment. An increased rate in populations closer to PHC facilities was also observed for suspected cases of filarial lymphedema. The detection of this condition was not expected to be affected by the accessibility of health services, as the MDA campaigns through which the cases were recorded are supposed to be implemented homogeneously and massively across endemic areas. An alternative explanation is that the apparent concentration of lymphedema cases closer to PHC facilities is due to spatial differences in the availability of coordinates for remote georeferencing: cases in larger towns are presumably more likely to be georeferenced,

and more likely to be near a health facility, compared to those in smaller communities. This would apply to the other morbidity conditions as well.

We undertook a sensitivity analysis to further explore the association between the rates of detected NTD cases and the proximity of PHC facilities (results in Table 2S in supplementary file).

In most regions, the calculated rate ratios of BU and leprosy cases within and beyond 5 km of the nearest health facility were sensitive to assumptions about the distribution of non-georeferenced cases. Of the estimated upper and lower limits for the rate ratios, we expect the latter (in which all non-georeferenced cases were assumed to occur >5 km from the nearest PHC facility) to be more realistic, since non-georeferenced communities are probably small and remote, and therefore less likely to be well served by PHC. Regardless of where non-georeferenced cases were assumed to occur, calculated rates of reported leprosy were higher in populations within 5 km of PHC in the Upper West and Volta Regions. Rates of reported BU were higher in populations within 5 km of PHC in the Eastern and Brong Ahafo Regions, regardless of the assumed location of non-georeferenced BU cases. These four regions all had low or moderate levels of accessibility of PHC, implying more robust evidence for an effect of PHC accessibility on the rate of reported disease in regions lacking good access to PHC. When it was assumed that all cases of suspect filarial lymphedema occurred >5 km from the nearest PHC facility, all regions had a higher rate in this population. This implies that the entire effect of accessibility of PHC facilities on the rate of this condition may be explained by varying availability of geo-data.

Leprosy cases that occurred more than 5 km from PHC facilities or were not georeferenced were less likely to have been graded at diagnosis than cases located within 5 km of PHC facilities. This may be due to variation in data completeness between regions: most regions had no missing clinical data whereas three regions had significant numbers whose disability grading was unknown. This suggests a potentially high burden of undiagnosed or unreported morbidity among cases in these regions, which is an important consideration in terms of targeting resources for case management. Missing clinical data on BU cases occurred in only two regions, but with little variation between mapped and unmapped cases, or between cases within and beyond 5 km of primary healthcare facilities.

Six regions reported leprosy cases who were living further than 5 km from PHC facilities. Overall, cases living further from PHC showed an increased risk of more advanced morbidity at diagnosis (Table 2). This may reflect the impact of diagnostic delay on patients who have to travel further to obtain health care.

Integration of the morbidity maps for leprosy, BU and lymphedema revealed co-distribution of disease in all regions where at least two of the diseases had been reported. The extent of overlap was most common in the Upper East and the Greater Accra Regions. These regions had relatively high concentrations of both leprosy and lymphedema, and also had the highest levels of access to primary healthcare facilities. The detected disease overlap may be a result of higher rates of case detection in these areas. Forty-two instances of disease overlap were identified at district level. These districts would be considered target areas for trialling integration of NTD programme activities, including health worker training and coordination of programme management.

Although routine surveillance data entails limitations, and is recognised to underestimate true numbers of cases, the approach piloted here has many advantages that support its use in mapping NTDs and their associated morbidity in the future. For autonomy and sustainability, NTD programmes require access to internally and routinely generated data sources over

which they have full ownership. This investigation demonstrates how such datasets can be integrated and used to create a resource for the planning of interventions against NTD morbidity. The datasets were readily available, and remote geo-referencing meant there was no need for travel within country, implying a significant saving in monetary and time costs. The process could be implemented by technical staff in NTD-endemic countries with some support during the orientation of the protocol, and following basic GIS training. Overall, these advantages mean that this approach to mapping could be developed into a sustainable and routine component of NTD surveillance, implemented as part of national disease control programmes.

Management of the mapping process by national programme officers would overcome some of the limitations encountered in this pilot, in particular by reducing the impact of missing data. Firstly, local knowledge would be used as a tool to locate communities that could not be georeferenced using online or paper maps. Secondly, the use and feedback of surveillance data in the form of morbidity and disease occurrence maps to the officers responsible for reporting the data would likely lead to improvements in data collection, management and reporting. Finally, updating the maps annually with newly reported morbidity cases would provide a more complete representation of existing morbidity. The accuracy and completeness of surveillance data could be further improved through the use of modern electronic platforms such as smart phones for data collection and reporting (i.e. via SMS and electronic forms).[43] Overall, the method is likely to become more sensitive to detect community-level overlap of morbidity over time.

In Ghana, the District Health Information Management System software DHIMS II, developed and used by the GHS for reporting and analysing health data, would be an appropriate platform for integrating datasets for mapping. Investment in improving the data collection and reporting functions of this system would complement integrated data collection activities, and avoid duplication in software development and maintenance, and in training for data managers.

Achieving full population coverage of integrated CM services will require broader development of NTD surveillance, strengthening of national control programmes, and of the primary health care system.[13,44] Integrated mapping of NTD morbidity, alongside the primary healthcare system, is an essential first step in identifying population health needs, to ensure that investment in these areas is appropriately directed. We recommend the use of routine data sets in this undertaking, in order to promote in-country ownership and management of all aspects of NTD control.

Conclusions

This study has identified substantial overlap of NTD-related morbidity in Ghana. There was an apparent concentration of cases and morbidity overlap in areas which have higher levels of access to primary health facilities, although it is not clear whether this is due to differences in surveillance coverage, the availability of geo-data, or differences in disease distribution. Validation surveys would clarify this issue. In Ghana, the maps presented here are already supporting the development of a strategic plan for integrated case management of morbidity associated with NTDs. As this plan is implemented, it will be critical to update these maps with current data.

The exercise piloted here is intended to represent the start of an iterative process to provide detailed and up-to-date information to target integrated interventions against CM-NTDs. As the approach develops, parallel improvements to data collection systems will be vital to provide a more accurate and reliable representation of disease burden, in order to inform targeting of resources and activities on a national scale. It is hoped that the integration of data collection tools will lead to an overall improvement in surveillance systems for NTDs.

NTD-related morbidity affects the lives and livelihoods of millions of people worldwide, and cannot be tackled simply by interrupting transmission of NTDs. Addressing the burden of NTD-morbidity requires detailed information on the location of individuals requiring CM, which is often lacking in maps of NTD distribution. It is intended that the approach piloted here will be implemented in other countries where CM NTDs are endemic, supporting the improvement of data on the distribution of NTD-related morbidity. This would help inform investment in integrated CM and the integration of case detection activities in Africa, promoting earlier, wider, and more equitable access to care for all those affected by NTDs.

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Contributors

The idea for the work was conceived through discussion between Professor Simon Brooker, Dr. Emmy van der Grinten, Dr. Paul Saunderson and Dr. Nana-Kwadwo Biritwum. Dr Jorge Cano and Hope Simpson developed the methodological approach. The data were collected through routine surveillance via the Neglected Tropical Diseases Programme, managed by Dr Nana-Kwadwo Biritwum with Mr. Samuel Odoom as data manager; the Leprosy Elimination Programme, managed by Dr Ekow Amankrah-Otabir with Dr Benedict Quao in a deputizing role; the National Buruli Ulcer Control Programme, managed by Dr. Edwin Ampadu and the National Yaws Eradication Programme, managed by Dr. Cynthia Kwakye MacLean. Ms. Hope Simpson wrote the manuscript with input from all listed authors.

Data availability

The data mapped in this investigation are confidential and are under ownership of the Ghana Health Service in Ghana. Access to the data is at the discretion of the Director for Public Health within the Ghana Health Service, with ethical approval from the Ghana Health Service Ethical Review Committee.

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Conflict of interest

This paper was edited by Prof. W.C.S. Smith to avoid conflict of interest.

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Mapping the global distribution of Buruli ulcer: a systematic review with evidence consensus

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Summary

Background Buruli ulcer can cause disfigurement and long-term loss of function. It is underdiagnosed and under-reported, and its current distribution is unclear. We aimed to synthesise and evaluate data on Buruli ulcer prevalence and distribution.

Methods We did a systematic review of Buruli ulcer prevalence and used an evidence consensus framework to describe and evaluate evidence for Buruli ulcer distribution worldwide. We searched PubMed and Web of Science databases from inception to Aug 6, 2018, for records of Buruli ulcer and *Mycobacterium ulcerans* detection, with no limits on study type, publication date, participant population, or location. English, French, and Spanish language publications were included. We included population-based surveys presenting Buruli ulcer prevalence estimates, or data that allowed prevalence to be estimated, in the systematic review. We extracted geographical data on the occurrence of Buruli ulcer cases and *M ulcerans* detection from studies of any type for the evidence consensus framework; articles that did not report original data were excluded. For the main analysis, we extracted prevalence estimates from included surveys and calculated 95% CIs using Byar's method. We included occurrence records, reports to WHO and the Global Infectious Diseases and Epidemiology Network, and surveillance data from Buruli ulcer control programmes in the evidence consensus framework to grade the strength of evidence for Buruli ulcer endemicity. This study is registered with PROSPERO, number CRD42018116260.

Findings 2763 titles met the search criteria. We extracted prevalence estimates from ten studies and occurrence data from 208 studies and five unpublished surveillance datasets. Prevalence estimates within study areas ranged from 3·2 (95% CI 3·1–3·3) cases per 10 000 population in Côte d'Ivoire to 26·9 (23·5–30·7) cases per 10 000 population in Benin. There was evidence of Buruli ulcer in 32 countries and consensus on presence in 12.

Interpretation The global distribution of Buruli ulcer is uncertain and potentially wider than currently recognised. Our findings represent the strongest available evidence on Buruli ulcer distribution so far and have many potential applications, from directing surveillance activities to informing burden estimates.

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Introduction

Buruli ulcer is a neglected tropical disease caused by the environmental pathogen *Mycobacterium ulcerans*. This disease primarily occurs in west and central Africa, but also in parts of Asia, South America, the western Pacific, and Australasia.[1,2] It is considered an important public health problem because of the characteristic necrotic ulcers it causes, and the scarring and deformity that can persist after treatment.[3] Although the mode of transmission of *M ulcerans* is not fully understood, contact with slow-flowing, stagnant, or disturbed water bodies is an important risk factor.[4]

Buruli ulcer was reported in 34 countries between 1960 and 2015,[4] but there is no consensus on its current distribution. Ten countries reported a total of 1864 cases to WHO in 2016,[1] but this number is recognised to reflect a small proportion of the total burden. Cross-sectional surveys in endemic countries have demonstrated under-reporting of Buruli ulcer,[5–7] for reasons including the chronic, stigmatising nature of the disease, its rural distribution, patients' poor access to health care or preference for traditional healers, and lack of awareness or resources within health systems.[4,8] Misdiagnosis might also contribute to underdetection: Buruli ulcer has a range of non-specific presentations that can be confused with other skin conditions, especially in the absence of confirmatory tests.[9,10] Therefore, available data do not provide a full or accurate representation of Buruli ulcer burden and distribution. These measures are essential for targeting of active case detection, which is a key part of control,[3] and for directing resources for case management.

Estimation of the global burden and population at risk of Buruli ulcer requires detailed information on the geographical limits and prevalence of the disease. We aimed to synthesise available data on prevalence and occurrence of Buruli ulcer and environmental occurrence of *M ulcerans*, and to systematically review population-based studies reporting the prevalence of Buruli ulcer to

Research in context

Evidence before this study

We searched PubMed and Web of Science databases from inception to Aug 6, 2018, using the search terms "Buruli ulcer*" OR ("Mycob* AND ulcer*") OR "Bairnsdale ulcer". English, French, and Spanish language publications were included. We identified two systematic reviews on Buruli ulcer, neither of which was spatially focused. There were 13 non-systematic reviews, two of which included a literature search to collate evidence on the global distribution of Buruli ulcer infection, and presented the results in a map and a narrative summary, respectively. Five reviews used WHO-reported data to show the global distribution of Buruli ulcer. The Global Infectious Diseases and Epidemiology Network has mapped the Buruli ulcer distribution reports, which provides a broader evidence base, but the evidence in many countries is weak. Our understanding of global Buruli ulcer distribution is incomplete: poor access to health care and diagnostics, overburdened health systems, and weak surveillance systems and reporting capacity contribute to underdetection and under-reporting of Buruli ulcer.

Added value of this study

To our knowledge, this is the first systematic review of Buruli ulcer prevalence and distribution worldwide. We compiled data from a wide range of sources, including the peer-reviewed and grey literature, WHO reports, and previously unpublished surveillance datasets. We used a systematic framework to grade the strength of evidence for Buruli ulcer presence, based on consensus between all data sources. This approach accounted for the specificity of diagnostic case definitions and reporting dates. We found evidence of Buruli ulcer occurrence in 32 countries, of which 18 had reported cases to WHO between 2007 and 2016. We identified consensus on Buruli ulcer presence in 12 countries, which reported a total of 34 890 cases to WHO from 2007 to 2016. Given the scale of under-reporting, absence of data on Buruli ulcer cannot be assumed to reflect disease absence. We have therefore expanded on previous work by grading evidence for absence of Buruli ulcer in countries that have not previously reported the disease. Countries with weak health systems and surveillance capacity might be failing to detect Buruli ulcer cases, or misdiagnosing them as other conditions. We calculated scores to reflect these possibilities using health expenditure values as a proxy for surveillance and diagnostic capacity, and accounting for the co-endemicity of diseases sharing clinical features with Buruli ulcer.

Implications of all the available evidence

Our current understanding of Buruli ulcer distribution is incomplete: many countries that have reported data to WHO in the past decade lack published evidence of confirmed cases, whereas other countries with demonstrated evidence of Buruli ulcer transmission have not reported data to WHO. Countries with evidence of Buruli ulcer are mostly clustered in Africa. Many of these countries border countries with no evidence of cases, but with weak health systems and multiple co-endemic skin diseases, potentially masking incident Buruli ulcer cases. Further analysis, including ecological modelling, might help to further elucidate the full distribution of Buruli ulcer. Intensified active case finding should be prioritised in areas with weaker evidence, to better inform delivery of targeted interventions.

provide a descriptive analysis of Buruli ulcer epidemiology in known endemic areas. We aimed to use an evidence consensus approach[11,12] to delineate the overall distribution of previously reported cases and to quantify the strength of evidence for Buruli ulcer presence or absence in every country worldwide.

See Online for appendix

Methods

Search strategy and selection criteria

We did a systematic review of Buruli ulcer prevalence and used an evidence consensus framework to describe and evaluate evidence for Buruli ulcer distribution worldwide. Data sources included peer-reviewed scientific literature; conference proceedings, conference abstracts, and government reports (grey literature); data reported to WHO between 2007 and 2016;[1] data reported through the Global Infectious Diseases and Epidemiology Network (GIDEON);[13] and surveillance datasets from national Buruli ulcer programmes in Cameroon, Ghana, Nigeria, and Togo. Peer-reviewed literature was identified from searches of PubMed and Web of Science databases from inception to Aug 6, 2018. Additional publications were identified from reference lists of identified papers.

We used the search terms "Buruli ulcer*" OR ("Mycob* AND ulcer*") OR "Bairnsdale ulcer". There were no limits on publication date, participant population, study type, or location (details in appendix). English, French, and Spanish language publications were included. Population-based Buruli ulcer surveys were included in the systematic review if they reported the prevalence of Buruli ulcer within a defined geographical area or information that allowed prevalence to be calculated. Publications were eligible for inclusion in the evidence consensus if they reported geographical locations with evidence of *M ulcerans* infection in humans or animals, or detection of *M ulcerans* in animal and environmental samples. Articles that did not report original data were excluded.

One author (HS) screened titles to exclude non-relevant publications and screened abstracts of selected records to identify papers that apparently fulfilled selection criteria. We read full texts of selected articles to identify studies meeting the selection criteria. Studies that recruited patients from health facilities or used strains of *M ulcerans* isolated from clinical samples were included in the evidence consensus framework only if patients' home addresses were provided. Data from people with Buruli ulcer who had recorded travel history to several endemic

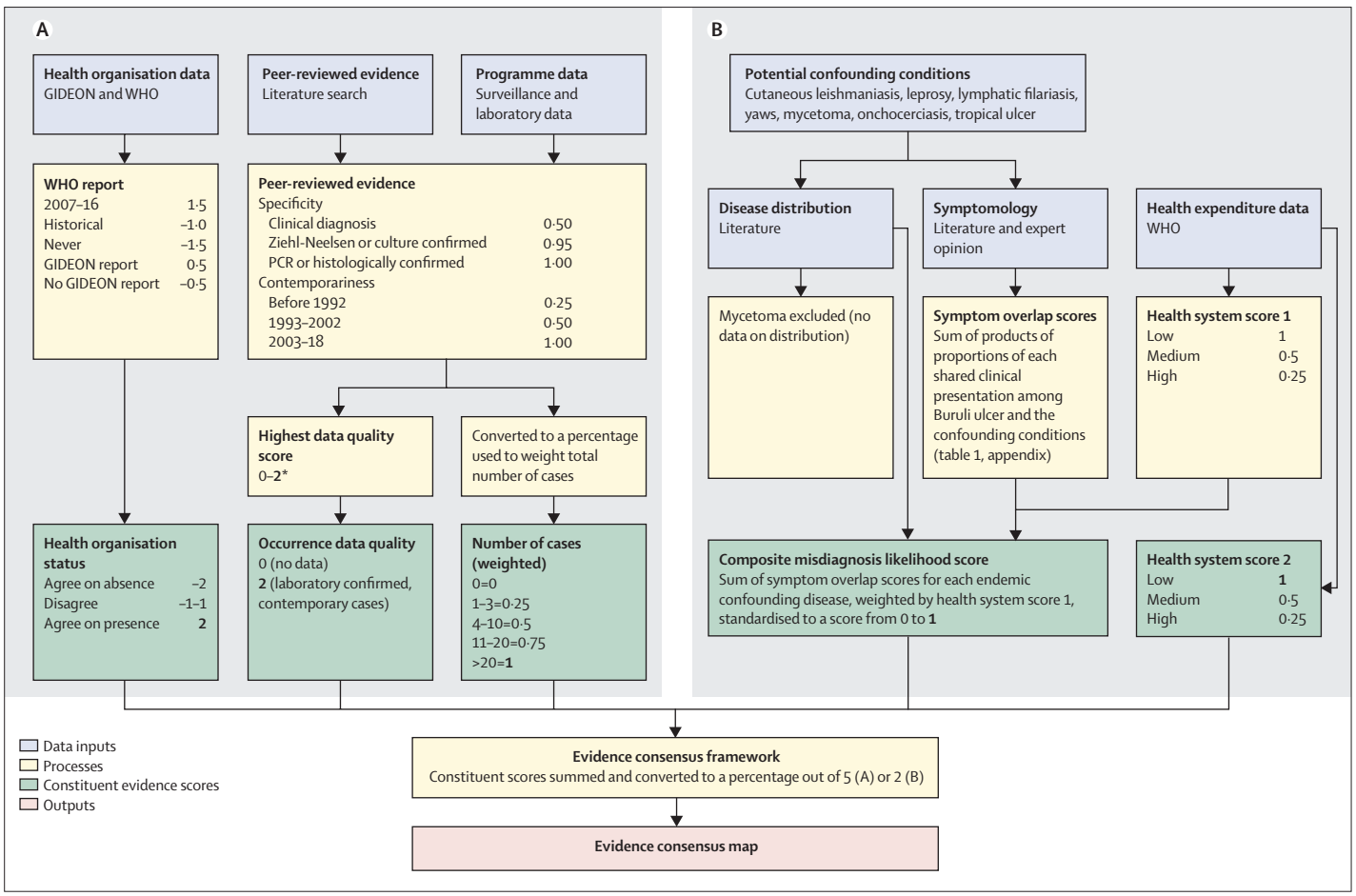

Figure 1: **Evidence consensus framework used to assess strength of evidence for Buruli ulcer presence and absence at national level**
(A) Framework for all countries. (B) Framework for countries with no evidence of reported cases. Numbers in bold show each constituent's maximum score. GIDEON=Global Infectious Diseases and Epidemiology Network. *Score was adjusted post-hoc for countries from which *Mycobacterium ulcerans* strains had been isolated, if no cases meeting inclusion criteria were identified.

regions were excluded. If a dataset was duplicated in numerous papers, the most comprehensive version was included.

Data extraction

Data from surveillance datasets and selected publications were extracted into a bespoke Microsoft Excel spreadsheet used for the Global Atlas of Helminth Infections.[14] The original spreadsheet was piloted on a subset of studies and then developed. Authors were contacted for additional data if community-level results were not presented. Data extraction was done by a single author (HS) and checked by a second one (JC). Data extracted included the number or prevalence of cases; the sample size and survey coverage (for population-based studies); the case detection method (survey, case search, or passive detection); the recording date; the diagnostic procedure, including any confirmatory tests (PCR for *M ulcerans* gene targets, Ziehl-Neelsen staining, culture for *M ulcerans*, and histopathological analysis), and their results; and the location of origin (patient residence or endemic area visited if the case originated from a non-endemic area). Areas described as endemic, with no information on case detection, were not included.

Data extracted on environmental detection of *M ulcerans* included sample date and location; sample type (water, soil, plant, or animal [clinical or faecal]); taxonomic details for animal samples; confirmatory tests; and number of samples tested and number positive.

Geographical coordinates of occurrence locations were extracted if they were provided in the publication. Otherwise, point locations were georeferenced remotely (appendix). Point locations that could not be georeferenced were linked to the lowest administrative level provided in the publication. Polygon areas corresponding to first and second administrative divisions were linked to units defined in the Database of Global Administrative Areas.

For more on the **Database of Global Administrative Areas** see http://www.gadm.org

Summary measures

The main summary measure for the systematic review was Buruli ulcer prevalence. The quality of prevalence studies was assessed with a framework based on the

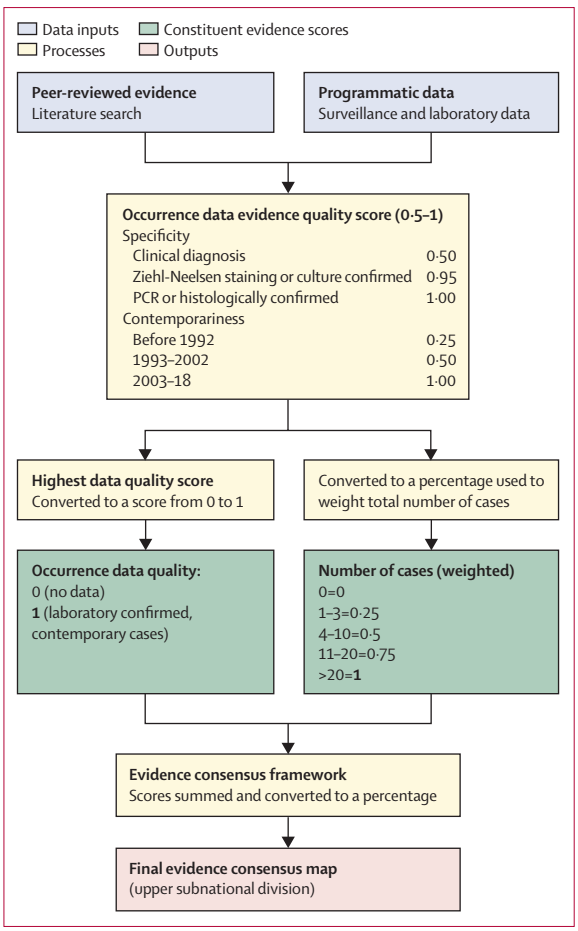

Figure 2: **Evidence consensus framework used to assess strength of evidence for Buruli ulcer presence at subnational level**
Numbers in bold show each constituent's maximum score.

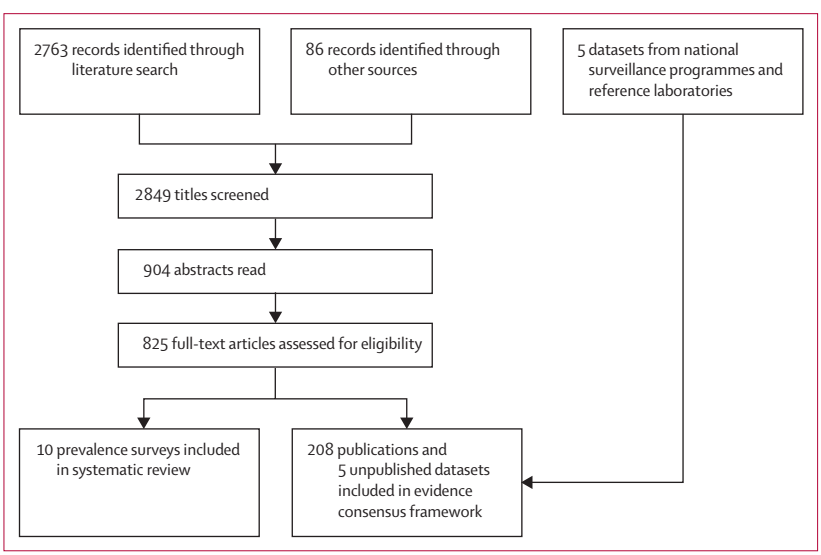

Figure 3: **Selection of eligible studies**

Newcastle-Ottawa scale,[15] adapted from a systematic review of podoconiosis prevalence[16] (appendix). This framework took account of the sampling frame, survey coverage, diagnostic specificity, and statistical analysis. The risk of outcome bias was assessed according to whether sampling was done at random or using convenience sampling within the study area. The number of studies from each country, relative to the number of cases reported to WHO, was used as an indicator of geographical bias between studies.

The main outcome measures for the evidence consensus framework were Buruli ulcer and *M ulcerans* occurrence. Occurrence locations were assigned local-level and national-level quality scores reflecting contemporariness and specificity (appendix). We used the number of studies included in the evidence consensus framework, and the number of studies reporting laboratory confirmation, as indicators of geographical bias in reporting and study quality.

Data analysis

We extracted prevalence estimates from included surveys and calculated 95% CIs using Byar's method.[17] We synthesised occurrence data through an evidence consensus approach using a weighted scoring system, following that used to determine the global distribution of other diseases.[11,12] Separate frameworks were used to assess the evidence for Buruli ulcer presence or absence at the national level (figure 1), evidence for Buruli ulcer presence at the subnational level (figure 2), and evidence for environmental occurrence of *M ulcerans* at the subnational level (appendix).

The major features for the national evidence framework were health reporting organisations (countries were assigned a score based on recent and historical reporting to WHO and reports through GIDEON); occurrence data quality (each country was assigned the highest data quality score of occurrence records within it); number of cases (the number of cases reported at each location was weighted by the local-level data quality score, and the weighted totals were aggregated to national level); and evidence for absence. In countries with no cases reported, the consensus score was designed to quantify the evidence for Buruli ulcer absence, reflecting the possibility of under-reporting due to weak surveillance capacity or misdiagnosis as known endemic diseases with similar presentations[18] (confounding diseases; figure 1B). As a proxy for surveillance and diagnostic capacity, health expenditure reported by WHO[19] was categorised as low (<US$100), medium ($100–$499), or high (≥$500), following the approach of previous authors and supported by evidence that higher health expenditure is associated with better health system performance.[20]

The confounding diseases with available evidence on their global distribution were cutaneous leishmaniasis,[12,21] leprosy,[22] lymphatic filariasis,[14] onchocerciasis,[23] tropical

	Country	Year of survey	Location	Study design	Case ascertainment	Active cases	Sample size	Prevalence per 10 000 population (95% CI)	Quality score
Johnson et al (2005)[34]	Benin	2004	Lalo commune	Exhaustive preparatory phase followed by validation of suspected cases	Clinical diagnosis following WHO guidelines	160	86 819	18·4 (15·7–21·5)	4
Sopoh et al (2010)[29]	Benin	2006	Zè district	Exhaustive preparatory phase followed by validation of suspected cases	Clinical diagnosis following WHO guidelines	222	82 450	26·9 (23·5–30·7)	4
Noeske et al (2004)[7]	Cameroon	2001	Ayos and Akonolinga health districts	Exhaustive survey in convenience sample of communities with suspect cases	Clinical diagnosis, a subset confirmed by PCR or Ziehl-Neelsen staining	202	98 500	20·5 (17·8–23·5)	2
Porten et al (2009)[8]	Cameroon	2007	Akonolinga district	Exhaustive survey in a random selection of communities	Clinical diagnosis following WHO guidelines, active and total cases reported separately	56	26 679	21·0 (15·9–27·3)	5
Bratschi et al (2013)[35]	Cameroon	2010	Bankim Health District	Exhaustive survey of health district	Clinical diagnosis, a subset confirmed by PCR	25	48 962	5·1 (3·3–7·5)	3
Kanga (2001)[36]	Côte d'Ivoire	1995	Côte d'Ivoire	Exhaustive survey of entire country	Suspect cases identified by community health workers, confirmed by clinicians	4642	14 500 000	3·2 (3·1–3·3)	2
Ecra et al (2005)[30]	Côte d'Ivoire	1998	Zoukoougbeu subprefecture	Exhaustive survey of entire subprefecture	Nodules detected clinically, *Mycobacterium ulcerans* confirmed by histopathological analysis	54	47 742	11·3* (8·5–14·8)	3
Mavinga Phanzu et al (2013)[31]	Democratic Republic of the Congo	2008	Kimpese and Nsona-Mpangu Rural Health Zones	Exhaustive preparatory phase followed by validation of suspected cases	Clinical diagnosis following WHO guidelines, a subset confirmed by PCR	259	237 418	10·9 (9·6–12·3)	6
Amofah et al (1993)[32]	Ghana	1991	Amansie West district	Exhaustive survey of entire district	Clinical diagnosis, a subset confirmed by Ziehl-Neelsen staining	90	130 000	6·9 (5·6–8·5)	4
Ampah et al (2016)[33]	Ghana	2013	Ofin River valley	Exhaustive survey in random sample (n=10) and convenience sample (n=3) of communities within 5 km of the Ofin River	Clinical diagnosis in following WHO guidelines, a subset confirmed by PCR	7	20 390	3·4 (1·4–7·1)	6

*Prevalence of nodules only, did not include other forms of Buruli ulcer.

Table 1: **Characteristics of population-based Buruli ulcer prevalence surveys included in the systematic review**

ulcer,[2] and yaws.[24] Estimates of the frequencies of the common presentations of these diseases and Buruli ulcer were obtained from literature review and expert opinion (Saunderson P, unpublished).[23,25–27] For each confounding disease, the frequency of each presentation shared with Buruli ulcer was multiplied by the frequency of the presentation among Buruli ulcer cases, and the products were summed to generate a symptom overlap score (appendix). For each country, the symptom overlap scores for its endemic confounding diseases were summed, then downweighted if health expenditure was high or medium. This score was added to an ordinal health expenditure score reflecting likelihood of under-detection or non-reporting.

For the subnational level, each upper administrative level was assigned the highest local-level evidence quality score of the occurrence records that fell within it, or within 5 km distance of its boundaries, and a score reflecting total number of cases within the unit (figure 2). Environmental detection records for *M ulcerans* were assigned to the upper administrative unit that they fell within. Each unit was assigned the highest evidence quality score of records within it, and a score reflecting the total number of detection records within it, weighted by evidence quality score (appendix).

This study is registered with PROSPERO, number CRD42018116260.

Role of the funding source

The AIM Initiative facilitated connections with disease control programmes for data transfer but neither it nor the Wellcome Trust had any role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The literature search identified 2763 records after deduplication (figure 3). Another 86 records were identified through other sources. The most common reason for exclusion was scarcity of information on patient origin. Full text was unavailable for 46 studies. Ten Buruli ulcer prevalence surveys were included in the systematic review.[7,8,28–33] Occurrence data were extracted from 208 publications (of which 190 included data on

human cases and 34 included data on *M ulcerans* in environmental or animal samples) and five unpublished surveillance datasets.

Three surveys done in Cameroon, two in each of Benin, Côte d'Ivoire, and Ghana, and one in the Democratic Republic of the Congo were included (table 1). The largest survey was done in Côte d'Ivoire, covering an estimated 14 500 000 people.[5] Seven surveys provided explicit details on the sampling frame. All surveys were community based and aimed to reach the entire population of chosen communities. Seven surveys covered the entire study area, one surveyed randomly selected communities within the study area, one surveyed a convenience sample of communities, and one used random and convenience sampling. Only one reported the survey coverage.[8] Five reported laboratory confirmation of all or a subset of cases, and five used clinical case definitions. Only one study reported prevalence with 95% CIs.[8]

Overall prevalence estimates within the study area ranged from 3·2 (95% CI 3·1–3·3) cases per 10 000 population in Côte d'Ivoire to 26·9 (23·5–30·7) cases per 10 000 in Benin (table 1). The highest reported community prevalence of Buruli ulcer was 2200 cases per 10 000 population, recorded in a village in Amansie West district in Ghana.[32]

Human cases were recorded from 32 countries and inferred for two further countries (Iran and Malaysia) from which strains were reported to have been isolated.[37,38] 33 794 (94·9%) of 35 595 cases were from the African (AFRO) region, 1740 (4·9%) cases were from the Western Pacific (WPRO) region, 60 (0·2%) were from the American (AMRO) region, and one (<0·1%) was from the Eastern Mediterranean (EMRO) region. Evidence of *M ulcerans* in environmental and animal samples was reported from nine countries. A summary of data extracted from all publications is provided in the appendix. Cases were recorded from 1952 to 2017, with the greatest number detected in 1999 (3401). From 1952 to 1998, between zero and five countries each year had evidence of Buruli ulcer based on peer-reviewed literature. The disease was identified in nine countries in 1999. Including data reported to WHO, from 2007 to 2016, between 12 and 18 countries each year had evidence of Buruli ulcer.

Laboratory confirmation of at least one case was reported by 134 (70·5%) of 190 selected studies including data on human cases, and 116 (61·1%) used PCR. However, most occurrence records (3165 [53·0%] of 5970) were categorised as clinically diagnosed only, because laboratory results were not disaggregated by unique locations.

Symptom overlap scores for the confounding diseases are shown in table 2. Tropical ulcer had the highest score, reflecting the high frequency of ulcers among Buruli ulcer and tropical ulcer.[2,33] Buruli ulcer was considered less likely to be misdiagnosed as cutaneous leishmaniasis or yaws, which present a lower frequency

	Summed score
Tropical ulcer	70·9
Cutaneous leishmaniasis	35·0
Yaws	16·3
Onchocerciasis	5·7
Leprosy	3·6
Lymphatic filariasis	0·5

Table 2: **Symptom overlap scores (0–100) for diseases whose symptoms can also be caused by Buruli ulcer**

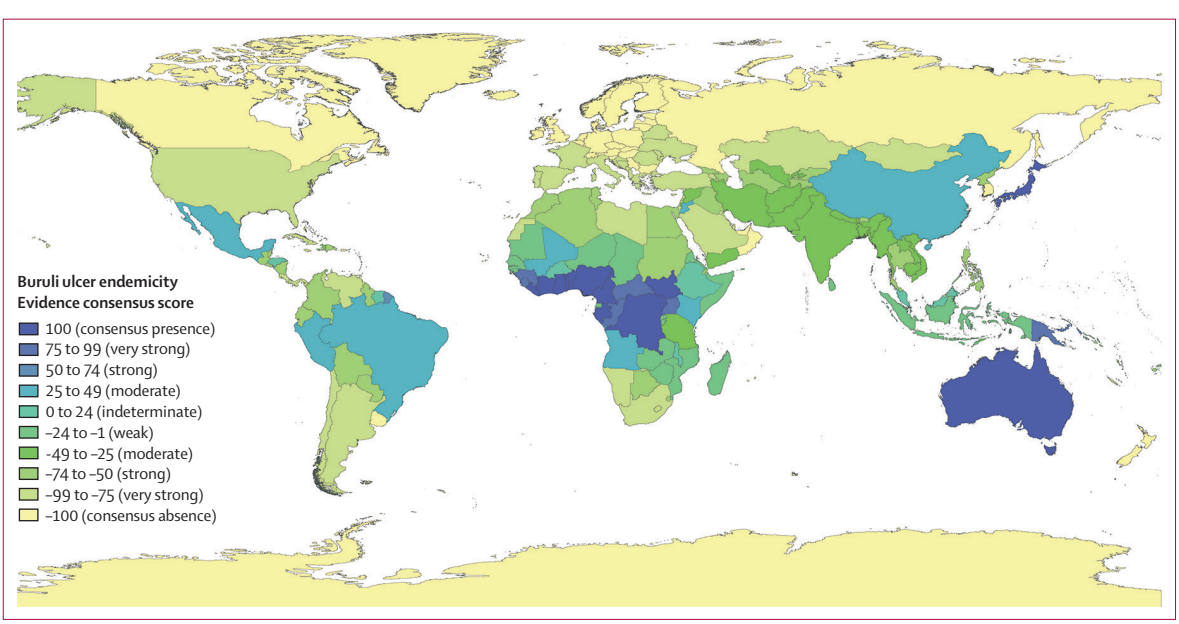

Figure 4: **Evidence consensus for Buruli ulcer presence and absence worldwide**

of ulcerous forms.[25,26] Onchocerciasis, leprosy, and lymphatic filariasis had symptom overlap scores of less than 6%.

Full results of the evidence consensus framework are provided at country level in the appendix. We identified consensus on Buruli ulcer presence in 12 countries, which collectively reported 34 890 cases to WHO from 2007 to 2016 (96·5% of all 36 164 cases reported to WHO in this period). Six countries reported cases to WHO from 2007 to 2016, but did not reach consensus of evidence for Buruli ulcer endemicity because of scarcity of information on case confirmation. Australia and Japan were the only non-African countries with consensus on presence (figure 4).

The African countries with evidence of Buruli ulcer were mostly clustered in a block covering much of central and west Africa. Countries around this block generally had weaker evidence for absence, with a higher number of endemic confounding diseases and lower health expenditure than did countries further from endemic areas. In the AMRO region, evidence of Buruli ulcer was strong in French Guiana and Peru, and moderate in Brazil, Mexico, and Suriname. Despite strong evidence of Buruli ulcer cases from French Guiana in literature reports, the disease has never been reported to WHO, so full consensus on endemicity was not reached through the framework. There was moderate evidence for Buruli ulcer in China. Endemicity status was indeterminate in Burkina Faso, Ethiopia, Honduras, Indonesia, Malawi, Malaysia, and Suriname. Niger, Eritrea, The Gambia, and Mauritania, all in the AFRO region, had the weakest evidence for absence, being endemic for cutaneous leishmaniasis and tropical ulcer, and having low health-care expenditure.

Subnational areas with evidence for endemicity were mostly clustered within equatorial, humid tropical, and tropical climate zones of west and central Africa (figure 5). Areas with evidence for Buruli ulcer in eastern, southern, and non-coastal central Africa, and other parts of the world, were more isolated (figures 5, 6).

The areas with evidence of *M ulcerans* in animal and environmental samples are shown in figure 7. Buruli ulcer disease was reported in wild and domestic animals in Australia, Benin, Cameroon, and Ghana, and *M ulcerans* DNA has been detected in faecal samples from animals in Australia (details and references in appendix). DNA from mycolactone-producing environmental bacteria has been identified in biotic and abiotic samples from bodies of water in eight countries endemic for Buruli ulcer and in the USA (details and references in the appendix). However, whether the American strains would be capable of causing Buruli ulcer disease in humans is unclear.

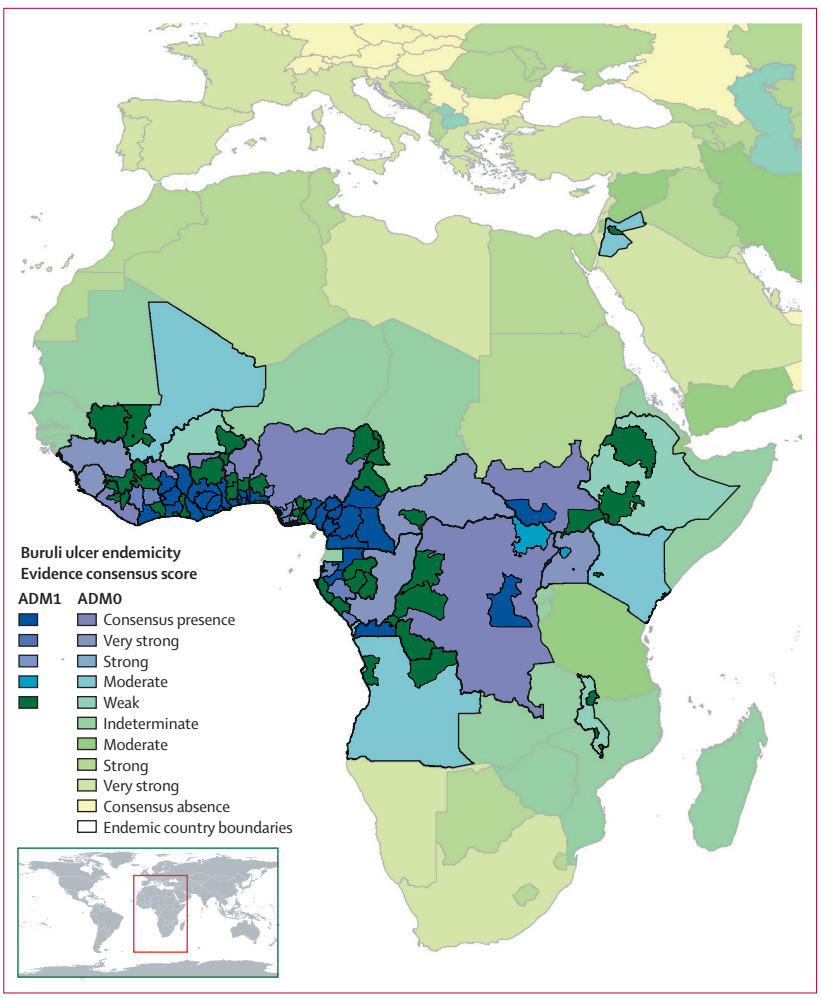

Figure 5: **Evidence for Buruli ulcer endemicity at national and upper subnational levels in Africa**
ADM0=national administrative division. ADM1=upper subnational administrative division.

Discussion

We have collated available data on Buruli ulcer prevalence and occurrence, and evidence of *M ulcerans* in animals and the environment. The evidence consensus framework applied has allowed us to expand on existing maps of Buruli ulcer distribution[2,39] in several ways. The maps presented include evidence from a wider range of sources, provide finer resolution, and quantify the strength of evidence for Buruli ulcer presence, as well as the strength of evidence of absence where Buruli ulcer has not been reported.

There have been few Buruli ulcer prevalence surveys, and most of those identified did not report detailed statistical analysis or indicators such as coverage. We did not undertake a meta-analysis because of the heterogeneous nature of compiled studies. Furthermore, most studies included were done in areas assumed to have a high local prevalence of Buruli ulcer, so a summary prevalence would probably overestimate the disease burden in the overall population.

Prevalence estimates reported by population-based studies were high relative to incidence data reported to WHO. This difference is likely to reflect under-reporting of

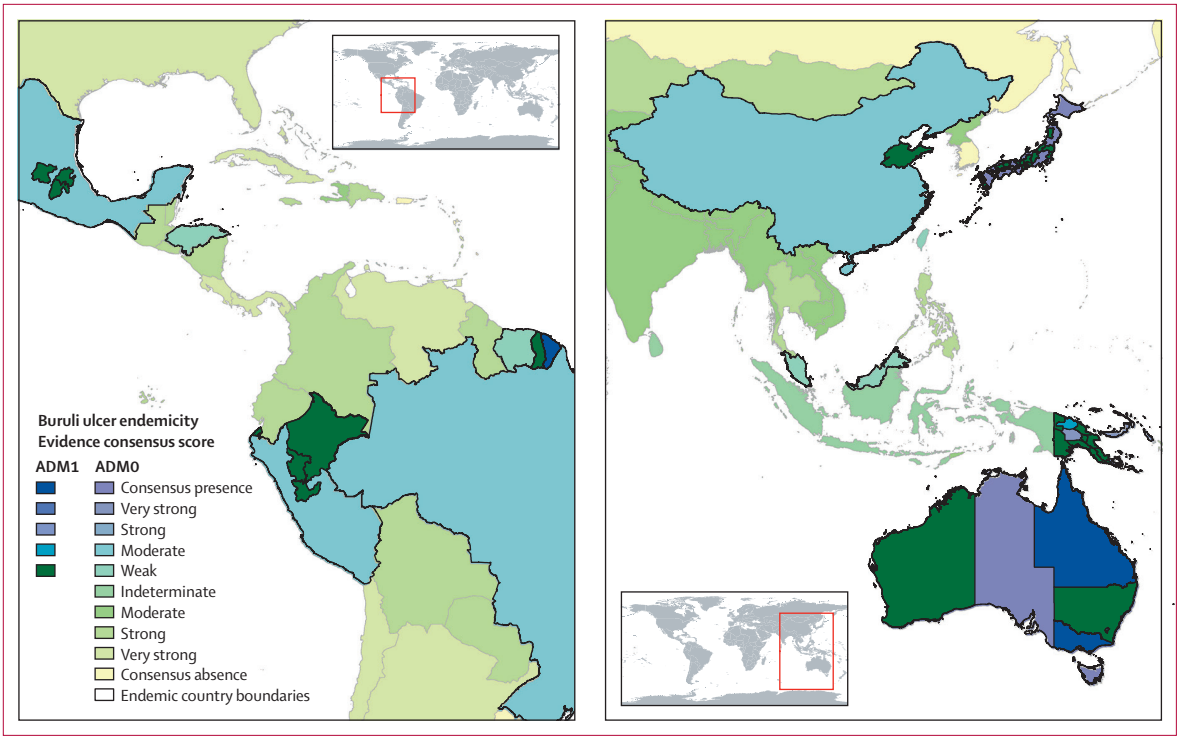

Figure 6: **Evidence for Buruli ulcer endemicity at national and upper subnational levels in Central and South America and the Pacific Region**
ADM0=national administrative division. ADM1=upper subnational administrative division.

Buruli ulcer through routine systems, but the population-based studies included might have overestimated Buruli ulcer prevalence as a result of sampling bias. Two of the ten studies included[7,33] used convenience sampling as part of the study design, which implies a risk of bias in the estimated prevalence. Five studies reported clinical diagnosis according to WHO guidelines and five used laboratory testing to confirm all or a subset of cases. There was geographical bias across the studies included, representing only five countries of the 32 identified as having evidence for Buruli ulcer.

Our investigation identified consensus on Buruli ulcer presence in 12 of 18 countries that reported Buruli ulcer cases to WHO from 2007 to 2016. However, the maps presented demonstrate remaining uncertainty on the global distribution of Buruli ulcer. There was indeterminate or moderate-quality evidence of Buruli ulcer in 15 countries that had not reported data to WHO from 2007 to 2016.

The national and subnational evidence consensus maps demonstrate large contiguous areas of potential endemicity, both within and between countries, particularly in central and west Africa. Evidence for Buruli ulcer presence was generally strongest in these contiguous areas, which is likely to be partly due to environmental similarity in terms of suitability and partly due to increased emphasis on case detection in areas established as endemic.

The area of Buruli ulcer presence defined by the subnational map of Buruli ulcer distribution in Africa (figure 5) was more restricted than that defined by the map of national-level endemicity (figure 4). This finding reflects the focal and restricted distribution of Buruli ulcer,[40] and the lower availability of data at the subnational level: in some countries, the only available data were those reported to WHO, with no information on subnational distribution. Given the recognised scale of Buruli ulcer under-reporting, it is likely that this map underestimates the scale of Buruli ulcer distribution.

Countries that had not reported Buruli ulcer cases, but were close to those that had, generally had weaker evidence for absence than countries located further from areas of Buruli ulcer endemicity. This trend was apparent in Africa, South America, and the southeast Asia and western Pacific regions, and reflects spatial clustering of countries with lower health expenditure and numerous co-endemic tropical diseases, irrespective of their evidence for Buruli ulcer. The proximity of Buruli ulcer-endemic countries to those with lowest evidence for Buruli ulcer absence adds further weight to the possibility that Buruli ulcer might occur undetected in the latter group, as a result of cross-border transmission and environmental similarity of neighbouring countries.

Although the maps provide finer detail on the distribution of Buruli ulcer than do current official maps, they still mask the underlying epidemiology of Buruli ulcer. Areas identified as endemic might in fact contain only a few localised cases of Buruli ulcer and be mostly unsuitable for the disease. Because of the focal nature

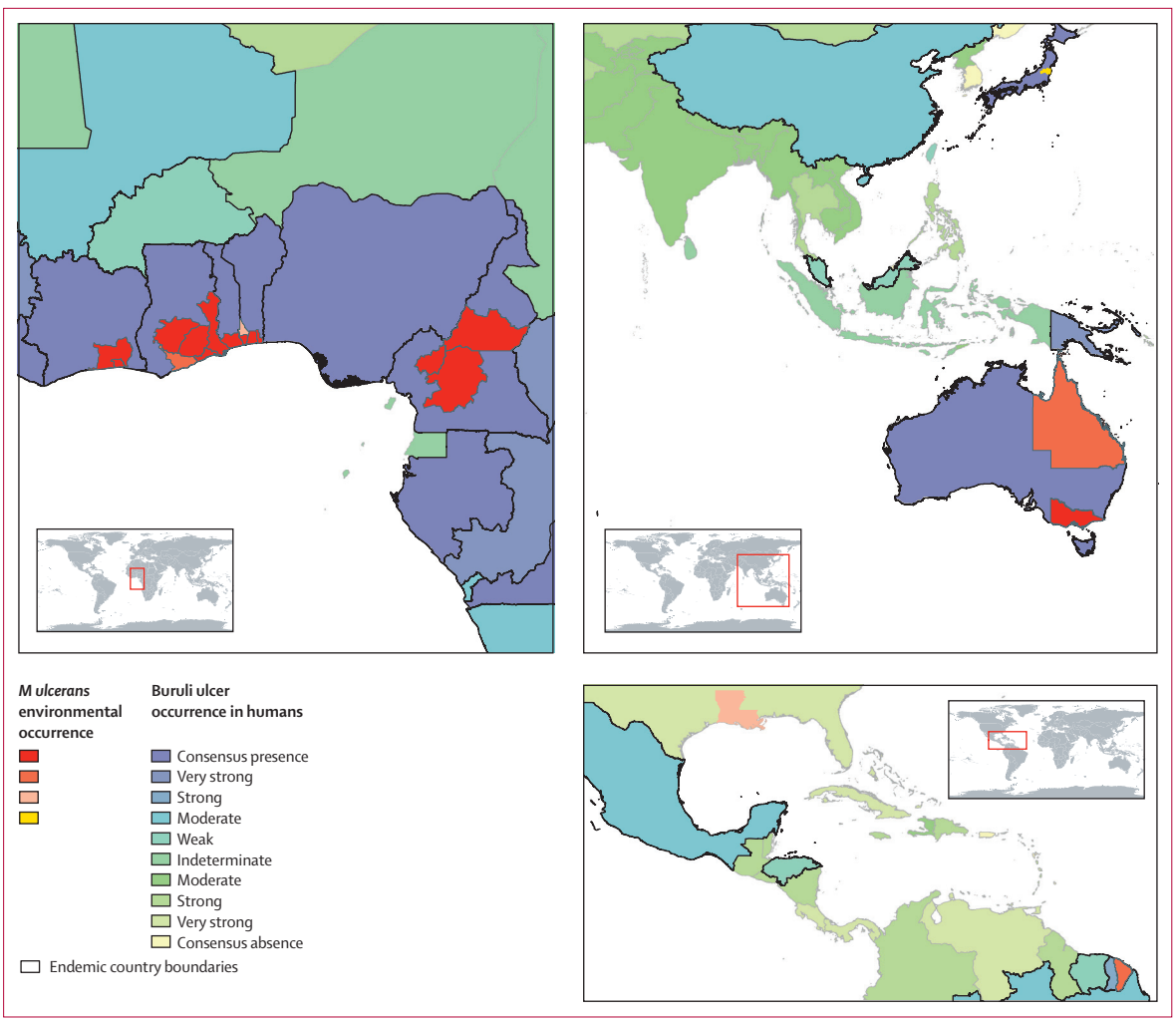

Figure 7: **Evidence for environmental occurrence of *Mycobacterium ulcerans* at upper subnational level and for Buruli ulcer endemicity at national level in west and central Africa, the western Pacific region, and South America**

of Buruli ulcer,[40] point-level data on disease occurrence are needed to support investigation into its spatial epidemiology. It is hoped that the maps and assembled geographical dataset will support such research in the future.

Studies on environmental occurrence of *M ulcerans* were limited in number, and many did not apply sufficiently specific tests to differentiate *M ulcerans* from other environmental mycobacteria. Therefore, the maps of evidence for environmental occurrence of *M ulcerans* do not provide a complete representation of environmental suitability for the bacterium. Although we assigned the maximum possible evidence quality score to clinical cases confirmed by PCR and environmental occurrences confirmed by quantitative PCR, these tests still entail a risk of false positives, as demonstrated by an external quality assessment including several reference laboratories that performed confirmatory testing in studies we included.[41]

There was substantial geographical bias in the occurrence records, reflecting different levels of research and surveillance activity between countries. Further analysis of the data underlying this work should account for this bias. In the context of this study, this bias is expected to have affected areas where there were few studies, but not areas where there were many studies, since additional studies would not change the outcome measure unless they provided higher-quality data.

The areas with highest consensus for presence are presumably most suitable for Buruli ulcer transmission and would be targets for surveillance and research since they represent known disease foci. Some countries with strong evidence for Buruli ulcer are not shown in the current WHO map of Buruli ulcer,[39] demonstrating that the disease is likely to be more widely distributed than the official map suggests. This finding has important implications for understanding and communicating the global burden of Buruli ulcer. We have also expanded

on the WHO map of Buruli ulcer distribution by qualitatively grading the strength of evidence for endemicity. In doing so, we have identified numerous countries with moderate or indeterminate evidence of Buruli ulcer, and those with weakest evidence for its absence, which might require further investigation to clarify the global distribution of Buruli ulcer. Active case finding in areas that have previously reported Buruli ulcer, and close to those currently reporting, should be prioritised. The assembled point-level dataset represents a novel resource for continent-wide exploration of environmental and biological predictors of Buruli ulcer, and estimation of the global burden and population at risk. The information provided by investigations such as these will help to target future control efforts and evaluate their impact.

Contributors

HS contributed to the design of the literature search strategy, data extraction form, evidence consensus framework, study selection, data extraction, data analysis, and map production, and drafted the manuscript. KD contributed to the design of the evidence consensus framework and revised the manuscript for important intellectual content. ENT provided access to Buruli ulcer surveillance data owned by the Cameroon Ministry of Health and revised the manuscript for important intellectual content. AP provided access to Buruli ulcer surveillance data owned by Nigeria Ministry of Health and revised the manuscript for important intellectual content. IM provided access to Buruli ulcer surveillance data owned by Togo Ministry of Health and revised the manuscript for important intellectual content. MF assembled the Buruli ulcer laboratory dataset at the Kumasi Centre for Collaborative Research in Tropical Medicine (Ghana) and revised the manuscript for important intellectual content. EA provided access to Buruli ulcer surveillance data owned by the Ghana Ministry of Health and revised the manuscript for important intellectual content. RP provided access to Buruli ulcer laboratory data owned by his own group at the Kumasi Centre for Collaborative Research in Tropical Medicine and revised the manuscript for important intellectual content. PS contributed to the design of the clinical aspect of the evidence consensus framework and revised the manuscript for important intellectual content. RLP contributed to the design of the evidence consensus framework and revised the manuscript for important intellectual content. JC contributed to the design of literature search strategy, data extraction form, and evidence consensus framework, and revised the manuscript for important intellectual content.

Declaration of interests

We declare no competing interests.

Data sharing

All occurrence data extracted and georeferenced as part of this investigation will be made publicly available through the London School of Hygiene and Tropical Medicine Data Compass repository (https://datacompass.lshtm.ac.uk/685/) upon publication of the manuscript, with the exception of the surveillance data from Cameroon. Data contributed by the programme for National Yaws, Leishmaniasis, Leprosy and Buruli ulcer Control Programme in Cameroon are under the ownership of the Ministry of Health in Cameroon and their use is subject to the approval of the Ministry of Health.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Simpson H, Deribe K, Tabah EN, et al. Mapping the global distribution of Buruli ulcer: a systematic review with evidence consensus. *Lancet Glob Health* 2019; **7:** e912–22.

Supplementary Methods

S.1. Protocol for Assembly of the Buruli Ulcer Database

Overview

The BU database was compiled through a systematic search of peer-reviewed literature and inclusion of routine surveillance data collected by control programmes responsible for BU in endemic countries. The database includes occurrence records of BU disease in humans and animals, and of evidence of Mycobacterium ulcerans detection in environmental and animal samples, each linked to a point or polygon location.

S.1.1. Peer-reviewed Literature Search

PubMed was searched using the terms:
(Buruli ulcer[Title/Abstract]) OR (Mycob*[Title/Abstract] AND ulcer*[Title/Abstract]) OR (Bairnsdale ulcer[Title/Abstract])
The Web of Science was searched using the terms:
TS=Buruli ulcer* OR TS=(Mycob* AND ulcer*) OR TS= (Bairnsdale ulcer)
The searches were updated in August 2018. There were no limits on study dates. Data were included from English, French, and Spanish language publications.
Reference lists of selected publications were screened.
Reports of relevant conferences and meetings were reviewed for relevant data.

The main outcome of interest was evidence of occurrence of Buruli ulcer or *M. ulcerans* infection in humans in any country, with no limit on detection date.
Suspect, clinical, and laboratory-confirmed cases of BU were all included, as were cases of serological evidence of *M. ulcerans* infection in the absence of clinical signs.
Imported cases were included if their place of infection was given. Imported cases with travel history to multiple BU-endemic regions were excluded.
Data extracted from publications presenting evidence of human infection with *M. ulcerans* included: i) the number or prevalence of cases identified (the minimum if a range was given), ii) the method of case ascertainment (e.g. survey, case search, passive detection), iii) the recording date (the maximum if a range was given), iv) the diagnostic procedure, including any confirmatory tests applied (PCR *M. ulcerans* gene targets; Ziehl Neelsen (ZN) staining; culture for *M. ulcerans*; histopathological analysis) and their results, and v) the location of origin (patient residence or endemic area visited if the case originated from a non-endemic area). Geographical information extracted from publications included geographical coordinates, site name, and description. If multiple cases were reported from a single geographical location, the cases were aggregated to a single occurrence location and by year.

If an area was described as 'endemic' but case numbers were not stated, the minimum number of cases was recorded as 1.
We also included occurrences of BU disease in animals, and detection of *M. ulcerans* DNA from environmental and animal samples. Data extracted from publications on environmental detection of *M. ulcerans* included: i) sample dates and location, ii) sample type (e.g. water, soil, plant, animal [faeces/clinical]), iii) taxonomic details for animal samples, iv) confirmatory tests applied (including all PCR targets tested) and their results, and v) number of samples tested and positive.
We additionally identified locations reported to be absent of or non-endemic for BU.
For these studies we identified study dates, location, and case-ascertainment strategy (e.g. passive case detection, active case search, cross-sectional survey).

S.1.2. Remote georeferencing details

Geographical information extracted from publications included geographical coordinates, site name, upper administrative unit, and any other contextual information.

Remote geo-referencing was used to link results to the study location if the coordinates were not given. If a fine scale map of occurrence locations was provided, this was converted to a raster format and georeferenced in ArcGIS Desktop 10.5 (Environmental Systems Research Institute Inc., Redlands CA, USA) to allow extraction of approximate geographic coordinates of the study locations.
Locations given as community names were georeferenced using online geodatabases. Automated georeferencing was implemented in R software through the Google Maps API Engine and Opencage Geocoder, using the ggmap and opencage packages respectively (1, 2). Locations that could not be georeferenced by these methods were manually searched in Google.

An ordinal score was assigned to reflect the reliability of the georeferenced locations (Table S.1).

Georeferenced points were mapped using ArcGIS Desktop 10.5 (Environmental Systems Research Institute Inc., Redlands CA, USA). Points falling outside of a land boundary or outside of the upper administrative unit they we assigned to in the publication were checked, and if a more reliable match could not be found, excluded.

S.1.3 Data quality score for occurrence records of BU disease in humans

All occurrence records from national programme data and selected publications were assigned local- and national-level evidence quality scores reflecting the contemporariness and specificity of the diagnosis.

Records of cases diagnosed since 2003 were given a contemporariness score of 1. Records of cases from 1990- 2002 were down-weighted by 50% and those from before 1990 were down weighted by 75%, under the assumption that historically endemic areas may no longer be endemic.

The diagnostic specificity score ranged from 0.5 to 1. The maximum score for was given for records where confirmation by PCR indicating *M. ulcerans*, or histopathological analysis indicating BU disease was reported. Although the WHO case definition for a confirmed case requires at least two positive confirmatory tests (3), we decided not to down-weight cases with only one confirmatory test result because multiple testing is uncommon due to the higher resource requirements, and comparative analysis of different confirmatory testing methods has shown the common tests to have a high specificity when used individually (4). However, records where cases were confirmed by Ziehl Neelsen (ZN) staining and/or culture alone were down-weighted by 5%, reflecting the possibility of detection of other mycobacteria by these methods (5, 6). The score was down-weighted by 50% if cases were clinically diagnosed only. If the publication reported that proportion of cases were laboratory-confirmed, but did not present the confirmation status of cases at unique locations, the record was considered unconfirmed at local-level, and confirmed at the national-level.

The contemporariness and diagnosis scores were summed to provide local- and national-level evidence quality scores for each occurrence record. Local evidence quality scores were converted to percentages, which were used as weights to adjust the total number of cases reported at each location.

For countries from which strains of *M. ulcerans* were reported to have been isolated, but with no evidence of reported cases meeting the inclusion criteria, the evidence score was adjusted *post-hoc*.

S.1.4. Data quality score for environmental detection of M. ulcerans DNA and BU disease in animals

Various PCR targeting techniques with varying sensitivities and specificities are used for *M. ulcerans* detection. The conventional PCR target for confirmation of human cases is the IS (insertion sequence) *2404*, present at high copy number in the *M. ulcerans* genome (7), and providing high sensitivity and specificity (8, 9). This target can also be used to indicate probable presence of *M. ulcerans* in the environment, but its sensitivity and specificity are reduced by the existence of PCR inhibitors and of other mycobacteria carrying the same gene within environmental samples. Other PCR targets available include the IS*2606*, and sequences encoding the enoyl reductase (ER) and ketoreductase-B (KR-B) domains, which form part of the mycolactane polyketide synthase genes [ref]. These genes are also present in other mycolactane-producing mycobacteria (MPM), but at different copy numbers (7). Recently developed multiplex qPCR assays targeting IS*2404*, IS*2606* and the KR-B domain and quantifying their respective copy numbers allow discrimination of *M. ulcerans* from other MPM (7). Variable nucleotide tandem repeat (VNTR) and mycobacterial interspersed repetitive unit (MIRU) typing can also be used to distinguish *M. ulcerans* from other MPM (10) based on the copy numbers of short repeating DNA sequences found at multiple loci within the genome (11).

According to the varying discriminatory power of these typing methods, we assigned the maximum typing score to samples confirmed as *M. ulcerans* by multiplex qPCR or VNTR analysis, a lower

score for samples typed only by conventional PCR analysis targeting IS*2404*, IS*2606*, ER or KR-B, alone or in combination. Samples confirmed as MPM other than *M. ulcerans* (by qPCR or VNTR typing) were down-weighted by 75% relative to those confirmed as *M. ulcerans*, on the assumption that these organisms may share a similar niche to *M. ulcerans*, and indeed have been considered by some authors to be part of the same species (12).

Each environmental/animal occurrence record was given a data quality score from 0-3 based on:

Typing specificity (0-2):

- confirmed as MPM other than *M. ulcerans* = 0.5
- typed only by conventional PCR analysis targeting IS2404, IS2606, ER or KR-B, alone or in combination = 1
- confirmed as *M. ulcerans* by multiplex qPCR or VNTR analysis on environmental samples (including animal faeces) or by clinical diagnosis and positive result for IS2404 PCR = 2

Contemporariness (0 -1)

- Prior to 1990 = 0.25
- 1990- 2002 = 0.5
- 2003- 2018 = 1

Each upper administrative unit {Global Administrative Areas, 2012 #14621} was assigned the highest data quality score of all environmental/ animal occurrence records within it, and a score reflecting the total number of environmental/ animal occurrence records within it

Number of occurrences (0 -1)

- 4 = 0.25
- 4- 10 = 0.5
- 10- 20 = 0.75
- >20 = 1

Within each administrative unit, the scores were summed to give a score from 0- 4, and converted to a percentage for mapping.

S.2. Evidence consensus framework

An evidence consensus framework was used to assign scores reflecting the strength of evidence for BU presence and absence at national level. A separate framework was used to assess the strength of evidence for BU presence at the highest sub-national administrative level (adm1) within countries with evidence of BU presence.

For countries with reported evidence of BU cases, four main data sources were used for the evidence consensus: i) BU data reported nationally to WHO from 2007- 2016, ii) reports of BU disease to GIDEON, iii) reports of cases in peer-reviewed literature, and iv) cases recorded by surveillance programmes or public health laboratories in BU-endemic countries. These were converted to three constituent scores: health organisation status, occurrence data quality, and case number.

The occurrence data quality score was based on the highest national data quality score assigned to each occurrence record. Countries with no occurrence data were assigned a score of 0, and those with occurrence data were assigned a score of up to 3 (if cases were recorded since 2003 and laboratory-confirmed).

The case number score was based on the total number of cases in all occurrence records, each adjusted by its local-level evidence quality score. Countries reporting more than 20 cases (post-adjustment) were given a score of 1, those reporting 11-20 were down-weighted by 25%, those reporting 4- 10 were down-weighted by 50%, and those reporting fewer than 4 cases were down-weighted by 75%.

Consensus presence was assigned if cases had been reported to WHO between 2002 and 2018; BU had been reported through GIDEON; at least one laboratory confirmed case had been recorded in peer-reviewed literature or by the national programme (for countries which had contributed surveillance data); and if a minimum number had been reported from all sources- the minimum threshold ranged from 20, if all cases were laboratory confirmed and reported since 2003, and was scaled up depending on the proportions unconfirmed and reported prior to 2003.

If there was no evidence of BU from any of the data sources included, the evidence consensus score was designed to quantify the strength of evidence for BU absence, reflecting the possibility of cases being under-reported due to weak surveillance or reporting capacity, or being masked due to misdiagnosis as known endemic diseases that share diagnostic presentations with BU (potential confounding diseases).

The potential confounding diseases with evidence available on their global distribution were cutaneous leishmaniasis (CL), leprosy, lymphatic filariasis (LF), onchocerciasis and tropical ulcer (TU), all of which have at least one possible presentation in common with BU (including nodules, plaques, oedema and ulcers) (13). The country-level endemicity of these diseases was based on

evidence consensus mapping for CL (14, 15); literature review for yaws (16), GIDEON data for TU (17); the rapid epidemiological mapping of onchocerciasis (REMO) (18); and on reporting of leprosy to WHO from 2012- 2016 (data provided on request by the WHO Leprosy team).

Estimates of the proportional frequencies of the most common presentations of BU and the potential confounding diseases were obtained from literature review (18-22) and expert opinion, using cross-sectional survey data preferentially to health facility data, as the latter would tend to overestimate the proportion of cases with more severe presentations. Prevalence of onchocerciasis in the REMO study was based only on nodule prevalence, so the frequency of nodules among onchocerciasis cases was set at 100%.

For each disease, the proportional frequencies of the presentations shared with BU were multiplied by the proportional frequency of the corresponding presentation in BU cases, and the products summed to generate a symptom overlap score, reflecting the likelihood of misdiagnosis of BU as that disease (Supplementary Figure S1, Table S.1). For each country, misdiagnosis likelihood scores for all endemic confounding diseases were summed and standardised to a percentage, representing a composite misdiagnosis likelihood score.

Health expenditure values (HE; average expenditure from 2011- 2015, from all financing sources, expressed in constant (2010) USD per capita) reported by the WHO (23) were used as a proxy for diagnostic capacity and for surveillance and reporting capacity, following the approach of previous authors (15, 24, 25) and supported by evidence that a higher level of health expenditure is associated with better health system performance (26). Countries with HE <$100 were categorised as low, those with $100≤HE<$500 were categorised as medium, and those with HE≥$500 were categorised as high.

Two separate health system scores were assigned based on HE category. The first was used to adjust composite misdiagnosis likelihood scores, reflecting lower likelihood of misdiagnosis of BU in countries with higher health expenditure, assuming a higher diagnostic capacity. The final composite misdiagnosis likelihood score was intended to indicate the likelihood of BU being misdiagnosed as any of the confounding diseases in each country. HE was also used to assign a score representing surveillance and reporting capacity. Countries with low HE were considered most likely to be under-detecting or not reporting BU so were assigned a score of 1, while those with high HE were assigned a score of 0.

Consensus absence was assigned to countries with no evidence of BU cases reported through WHO or GIDEON, or in peer-reviewed literature, no evidence of endemicity of the potential confounding diseases considered, and high health expenditure. Countries endemic for all the confounding diseases and with low HE scored 0, reflecting indeterminate BU endemicity status.

S.3. Quality assessment framework for BU prevalence surveys

This framework is adapted from Deribe et al. (27), and grades surveys on an 8 point scale using 4 quality assessment elements:

A. Definition of sampling frame

0. No information beyond overall population type (e.g. “schools” or “households”)

1. General information on sampling frame and procedures

2. Explicit details of procedures reported

B. Survey coverage

0. Not recorded/reported

1. Reported and under 65%

2. Reported and 65% or above

C. Specificity of BU diagnosis

0. No detail on diagnosis, or clinical diagnosis reported but not adequately described

1. Clinical diagnosis adequately described (e.g. WHO guidelines, or justified modification of standard diagnostic criteria)

2. Clinical diagnosis with all or a subset confirmed by laboratory tests

D. Statistical analysis

0. Only overall prevalence reported

1. Prevalence reported with 95% CIs

2. Prevalence by subgroup (e.g. age, sex, socio-demographic) reported

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Supplementary Results

Table S.1: Frequencies of shared presentations of BU and other skin diseases used to calculate symptom overlap scores for confounding diseases

Confounding disease *Reference*	**Common presentations**		**Buruli Ulcer** *Ampah et al 2016 (1); Johnson et al 2005 (2); um Boock et al 2004 (3) (pooled)*			
			Nodule	Plaque	Oedema	Ulcer
		p~ with presentation	0·057	0·007	0·025	0·709
Yaws *Coldiron et al. 2013 (4)*	Crusted ulcer	0·23				**0·1631**
Cutaneous leishmaniasis *Remadi et al. 2016 (5)*	Ulcero-crusted	0·39				**0·2744**
	Ulcerated	0·11				**0·0759**
Onchocerciasis *Zouré, 2014 (6)*	Nodules	1·00	**0·0567**			
Lymphatic filariasis *Mwingira 2017 (7)*	Oedema	0·209			**0·0052**	
Leprosy *P. Saunderson, personal communication, June 2018 (8)*	Plaques	0·05		**0·0003**		
	Ulcers	0·05				**0·0355**
Tropical Ulcer *Berger 2018 (9)*	Ulcers	1·000				**0·7091**

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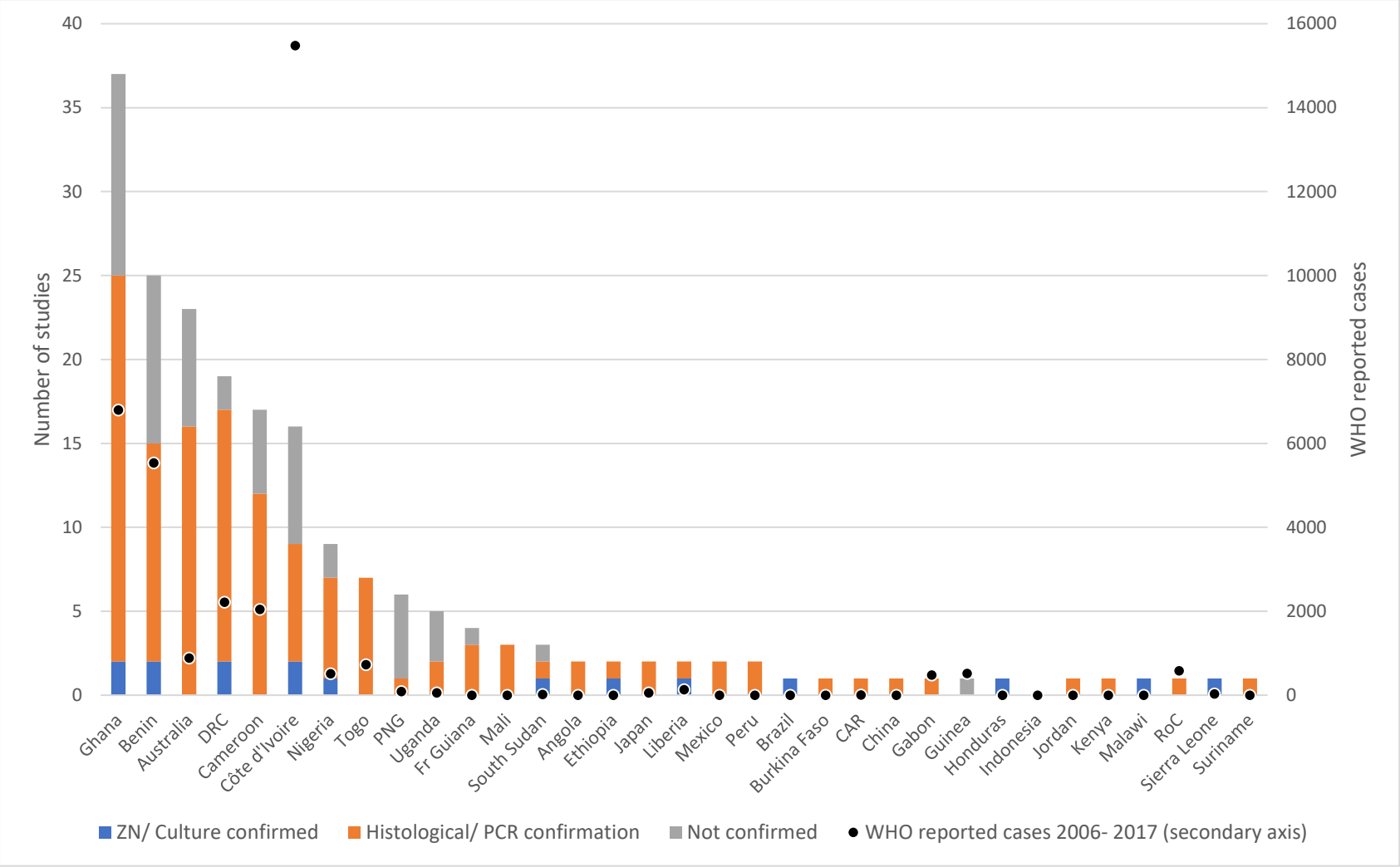
Table S.2: Scores assigned based on the number of human cases at national level and by upper administrative unit, and on positive environmental samples by upper administrative unit.

Number of human cases/ positive environmental samples	Score
1- 3	0.25
4- 10	0.5
11- 20	0.75
>20	1

Figure S.1: Number of references identified in literature review, reported case confirmation methods, and number of cases reported to WHO 2007-2016 by country



DRC = Democratic Republic of Congo, PNG = Papua New Guinea, CAR = Central African Republic

Figure S.2: Evidence consensus maps showing the distribution of occurrence points identified by systematic literature search.

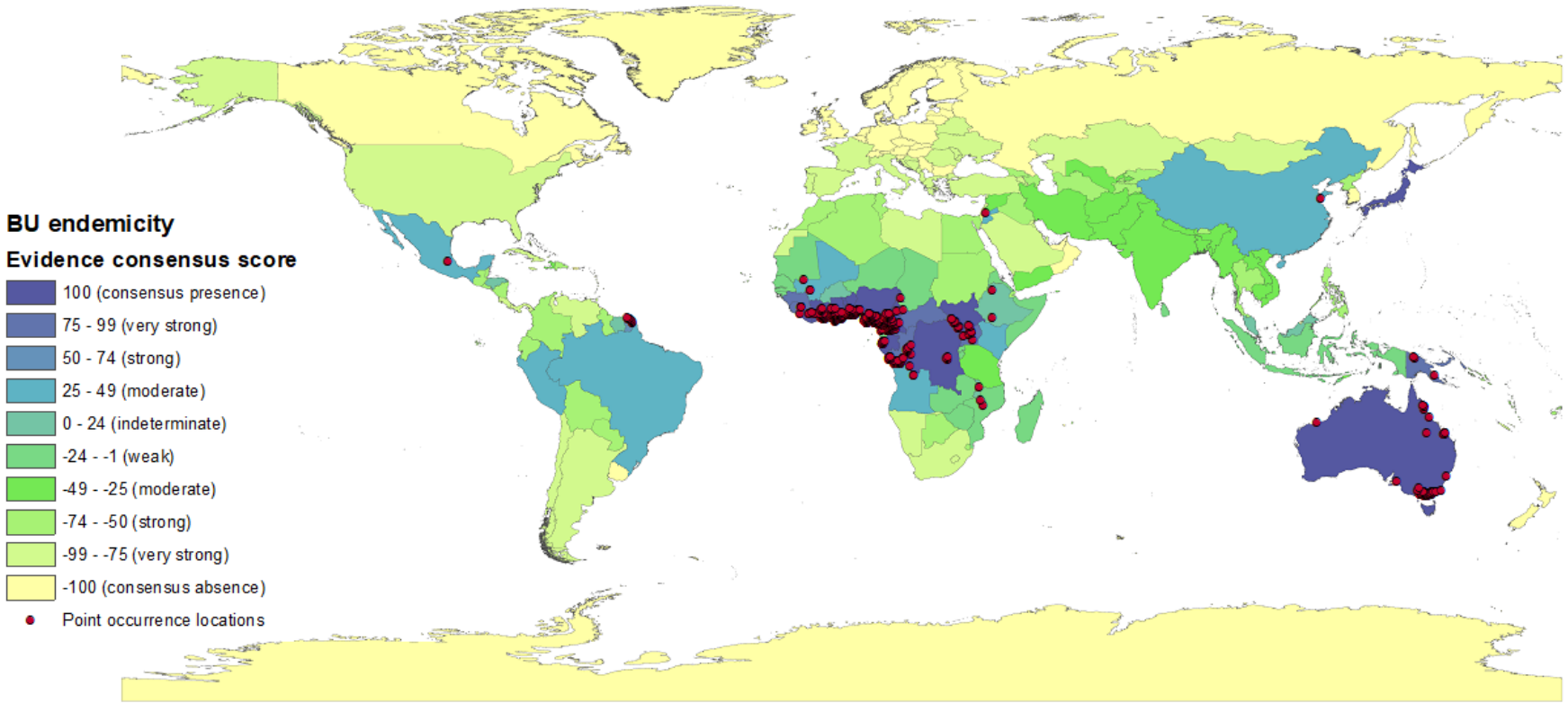


Table S.3: Data extracted from selected studies used for evidence consensus framework- human cases

Country	Reference		Recording	Confirmation method				Scores assigned			Number of cases	
	Main author (year published)	Ref	year	ZN	Culture	Histological	PCR	Diagnosis	Contemporariness	Quality	Included	Adjusted
Angola	Kibadi, K. et al. (2008)	(1)	2005	Yes			Yes	1	1	1	2	2
	Bar, W. et al. (1998)	(2)	1995	Yes		Yes	Yes	1	0.5	0.75	1	0.75
Australia	Tai, A. et al. (2018)	(3)	2017	Yes	Yes	Yes	Yes	1	1	1	434	423.15
	Boyd, S. et al. (2012)	(4)	2011	Yes			Yes	1	1	1	180	180
	Lavender, C. et al. (2011)	(5)	2009				Yes	1	1	1	81	81
	Quek, T. et al. (2007 a)	(6)	2006	Yes			Yes	1	1	1	76	76
	Quek, T. et al. (2007 b)	(7)	2005	Yes			Yes	1	1	1	42	42
	Steffen, C. et al. (2010)	(8)	2008	Yes		Yes	Yes	1	1	1	41	40.925
	WHO (Johnson) (2006)	(9)	2005		Yes		Yes	1	1	1	40	40
	O'Brien, D. et al. (2007)	(10)	2004	Yes		Yes	Yes	1	1	1	40	40
	Johnson, P. et al. (2007)	(11)	2006		Yes		Yes	1	1	1	31	29.25
	Carson, C. et al. (2014)	(12)	2013		Yes		Yes	1	1	1	6	6
	Francis, G. et al. (2006)	(13)	2009			Yes	Yes	1	1	1	4	4
	van Ravensway, J. et al. (2012)	(14)	2008					0.5	1	0.75	87	65.25
	Johnson, P. et al. (1996)	(15)	1995	Yes	Yes	Yes		1	0.5	0.75	42	28.6
	Veitch, M. et al. (1997)	(16)	1995			Yes		1	0.5	0.75	28	21
	Gooding, T. et al. (2002)	(17)	2002				Yes	1	0.5	0.75	23	17.25
	O'Brien, D. et al. (2017)	(18)	2014				Yes	0.5	1	0.75	20	16.5
	WHO (Johnson) (2001)	(19)	2001		Yes		Yes	1	0.5	0.75	14	7
	Fyfe, J. et al. (2010)	(20)	2009					0.5	1	0.75	4	3
	Taheri, T. et al. (2009)	(21)	2009					0.5	1	0.75	1	0.75
	WHO (Johnson) (2000)	(22)	1999					0.5	0.5	0.5	8	4
	WHO (2003)	(23)	2002					0.5	0.5	0.5	1	0.5
	Mitchell, P. et al. (1987)	(24)	1985					0.5	0.25	0.375	20	7.5
	Stinear, T. et al. (2000)	(25)	1987					0.5	0.25	0.375	11	4.125
Benin	Amoussouhoui, A. et al. (2018)	(26)	2016				Yes	1	1	1	137	102.75
	Sopoh, G. et al. (2010)	(27)	2008	Yes	Yes		Yes	1	1	1	104	101.4
	Nackers, F. et al. (2006)	(28)	2003	Yes	Yes	Yes	Yes	1	1	1	70	52.5
	Eddyani, M. et al. (2015)	(29)	2008				Yes	1	1	1	46	46
	Ruf, M. T. et al. (2011)	(30)	2009	Yes	Yes	Yes	Yes	1	1	1	12	12
	Andreoli, A. et al. (2014)	(31)	2009	Yes		Yes	Yes	1	1	1	8	8
	Barogui, Y. T. et al. (2018)	(32)	2016				Yes	1	1	1	6	6
Brazil	Leigheb, G. et al. (2008)	(33)	2006	Yes	Yes	Yes	Yes	1	1	1	2	2
	Sopoh, G. et al. (2010)	(34)	2007	Yes		Yes	Yes	1	1	1	1	1
	Wadagni, A. et al. (2018)	(35)	2016					0.5	1	0.75	6908	5181
	Debacker, M. et al. (2004)	(36)	2001	Yes	Yes	Yes	Yes	1	0.5	0.75	1131	848.25
	Johnson, R. et al. (2015)	(37)	2012					0.5	1	0.75	861	645.75
	Campbell, L. et al. (2015)	(38)	2005					0.5	1	0.75	558	418.5
	Sopoh, G. et al. (2010)	(39)	2006					0.5	1	0.75	425	318.75
	WHO (2001) (Guédénon)	(19)	2000	Yes	Yes	Yes	Yes	1	0.5	0.75	410	307.5
	Barogui, Y. et al. (2009)	(40)	2006					0.5	1	0.75	160	120
	Johnson, P. et al. (2005)	(41)	2004					0.5	1	0.75	160	119.25
	Sopoh, G. et al. (2011)	(42)	2009					0.5	1	0.75	125	93.75
	Durnez, L. et al. (2010)	(43)	2006					0.5	1	0.75	46	34.5

Country	Reference		Recording	Confirmation method				Scores assigned			Number of cases	
	Main author (year published)	Ref	year	ZN	Culture	Histological	PCR	Diagnosis	Contemporariness	Quality	Included	Adjusted
	Williamson, H. et al. (2012)	(44)	2009					0.5	1	0.75	12	9
	Ablordey, A. et al. (2015)	(45)	2000				Yes	1	0.5	0.75	3	2.25
	Abalos, F. et al. (2000)	(46)	2000	Yes	Yes	Yes	Yes	1	0.5	0.75	1	0.75
	Josse, R., et al. (1994)	(47)	1993	Yes				0.95	0.5	0.725	225	163.125
	Josse, R., et al. (2002)	(48)	1990	Yes				1	0.25	0.625	45	27
	Stoffel, V. et al. (2005)	(49)	2002					0.5	0.5	0.5	15	7.5
	dos Santos, J. (2007)	(50)	2004		Yes			0.95	1	0.975	1	0.975
Burkina Faso	Ouoba, K., et al. (1998)	(51)	1996	Yes	Yes	Yes		1	0.5	0.75	4	2.25
Cameroon	Cameroon MoH (2017)	(52)	2015	Yes			Yes	1	1	1	2774	2768.8
	Christenet, V (2014) [1]	(53)	2012	Yes	Yes	Yes	Yes	1	1	1	1113	1083.475
	Landier, J. et al. (2011)	(54)	2009			Yes	Yes	1	1	1	171	171
	Bratschi, M. et al. (2013)	(55)	2012				Yes	1	1	1	148	131.25
	Marion, E. et al. (2011)	(56)	2009				Yes	1	1	1	125	111.5
	Porten, K. et al. (2009)	(57)	2007					1	1	1	105	78.75
	Bratschi, M. et al. (2014)	(58)	2011	Yes			Yes	1	1	1	57	57
	Zambou, M. et al. (2011)	(59)	2010	Yes			Yes	1	1	1	54	54
	Bolz, M. et al. (2015)	(60)	2012				Yes	1	1	1	39	39
	Awah, P. K. et al. (2018)	(61)	2014					1	1	1	32	24
	Wanda, F. et al. (2014)	(62)	2013	Yes		Yes	Yes	1	1	1	1	1
	Andreoli, A. et al. (2015)	(63)	2011	Yes			Yes	1	1	1	1	1
	Landier, J. et al. (2014)	(64)	2012	Yes			Yes	0.95	1	0.975	588	541.05
	Um Boock A. (2004)	(65)	2004					0.5	1	0.75	123	92.25
	Zogo, B. et al. (2015)	(66)	2013					0.5	1	0.75	97	72.75
	Noeske, J. et al. (2004)	(67)	2001	Yes			Yes	1	0.5	0.75	68	34
	Ebong, S. M. et al. (2012)	(68)	2012					0.5	1	0.75	16	12
CAR	Minime-Lingoupou, F. et al. (2010)	(69)	2007	Yes			Yes	1	1	1	2	2
China	Faber, W. R. et al. (2000)	(70)	2000	Yes			Yes	1	0.5	0.75	1	0.75
Côte d'Ivoire	N'Krumah, R. et al. (2017)	(71)	2010				Yes	1	1	1	1145	1145
	N'Krumah R, T. et al. (2016)	(72)	2012				Yes	1	1	1	51	51
	Coulibaly-N'Golo, G. et al. (2011)	(73)	2008				Yes	1	1	1	14	14
	Kouame, K. et al. (2008)	(74)	2007	Yes		Yes		1	1	1	4	3.9
	Sangare, A. (2007)	(75)	2005	Yes		Yes		1	1	1	1	1
	Ahoua et al (2009)	(76)	2009		Yes		Yes	1	1	0.975	116	96.125
	Ecra, E., et al. (2005)	(77)	2000	Yes		Yes		1	0.5	0.75	754	390.5
	Konan, K. L. et al. (2015)	(78)	2007					0.5	1	0.75	11	8.25
	Boni, C. C., et al. (2017)	(79)	2014					0.5	1	0.75	5	3.75
	Darie, H. (1993)	(80)	1992	Yes				1	0.5	0.75	4	3
	Ablordey, A. et al. (2015)	(45)	2000				Yes	1	0.5	0.75	2	1.5
	Richard Kadio (1990)	(81)	1990	Yes				0.95	0.25	0.6	167	62.625
	Kanga et al. (2001)	(82)	1997					0.5	0.5	0.5	2409	1204.5
	WHO (2001) (Kanga)	(19)	1999					0.5	0.5	0.5	1351	675.5
	Ecra, E. J., et al. (2001)	(83)	2001					0.5	0.5	0.5	2	1
	Espey, David K. et al. (2002)	(84)	1994					0.5	0.5	0.5	2	1
	Marston, B. et al. (1995)	(85)	1991					0.5	0.5	0.5	2	1
DRC	Mavinga Phanzu et al. (2013)	(86)	2008	Yes		Yes	Yes	1	1	1	259	194.25
	Mavinga Phanzu, D. et al. (2011)	(87)	2007	Yes	Yes	Yes	Yes	1	1	1	252	189

Country	Reference		Recording	Confirmation method				Scores assigned			Number of cases	
	Main author (year published)	Ref	year	ZN	Culture	Histological	PCR	Diagnosis	Contemporariness	Quality	Included	Adjusted
	Kibadi, K. et al. (2010)	(88)	2007	Yes	Yes	Yes	Yes	1	1	1	92	92
	Suykerbuyk, P. et al. (2009)	(89)	2007				Yes	1	1	1	28	28
	Mavinga Phanzu, D. et al. (2006)	(90)	2004	Yes	Yes	Yes	Yes	1	1	1	36	27
	Kibadi, K. et al. (2009)	(91)	2007				Yes	1	1	1	19	19
	Mavinga Phanzu, D. et al. (2011)	(92)	2017	Yes	Yes	Yes	Yes	1	1	1	13	13
	Kibadi, K. et al. (2008)	(1)	2005	Yes		Yes	Yes	1	1	1	1	1
	Kibadi, K. (2009)	(93)	2007					0.5	1	0.75	1	0.75
	Mavinga Phanzu, D. et al. (2007)	(94)	2002	Yes		Yes	Yes	1	0.5	0.75	1	0.75
	Delaporte E. et al. (1994)	(95)	1992			Yes		1	0.5	0.75	1	0.75
	Meyers, M. W. (1974)	(96)	1972	Yes		Yes		1	0.25	0.625	78	33
	Smith, J. H. (1970)	(97)	1968	Yes	Yes	Yes		1	0.25	0.625	3	1.8
	Ablordey, A. et al. (2015)	(45)	1971				Yes	1	0.25	0.625	1	0.625
	Andersen, F. O. (1965)	(98)	1964	Yes		Yes		1	0.25	0.625	1	0.625
	Meyers, M. W. (1975)	(99)	1973	Yes		Yes		0.95	0.25	0.6	180	108
	Guerden, A. (1962)	(100)	1962	Yes				0.95	0.25	0.6	170	102
	Pattyn, S. R. (1965)	(101)	1965					0.95	0.25	0.6	1	0.6
	Hennebert, P. et al, (1962)	(102)	1960	Yes				0.95	0.25	0.6	1	0.6
Ethiopia	Gordon, D. et al. (2014)	(103)	2011	Yes				0.95	1	0.975	1	0.975
	Haileamlak A. et al. (2009)	(104)	2009			Yes		0.5	1	0.75	1	0.75
French Guiana	Reynaud, Y. et al. (2015)	(105)	2013				Yes	1	1	1	23	23
	Douine, M. (2017)	(106)	2013	Yes	Yes	Yes	Yes	1	1	1	12	6.5
	Ménard, A. et al. (2003)	(107)	1999	Yes	Yes	Yes	Yes	1	0.5	0.75	3	2.25
	WHO (2003)	(23)	2001					0.5	0.5	0.5	7	3.5
Gabon	Bayonne Manou, L. S. et al. (2013)	(108)	2011	Yes	Yes		Yes	1	1	1	300	294.725
Ghana	Yeboah-Manu, D. et al. (2018)	(109)	2016	Yes	Yes		Yes	1	1	1	1020	1020
	Ghana MOH (KCCR) (2017)	(110)	2039				Yes	1	1	1	628	628
	Ghana MoH (NBUCP) (2015)	(111)	2014	Yes			Yes	1	1	1	393	361.725
	Amissah, N. et al. (2014)	(112)	2011				Yes	1	1	1	245	245
	Sarfo, F. S. et al. (2010)	(113)	2007	Yes	Yes		Yes	1	1	1	160	160
	Bibert, S. et al. (2017)	(114)	2017				Yes	1	1	1	96	96
	Adu, E. J. (2013)	(115)	2012	Yes		Yes	Yes	1	1	1	65	63.375
	Roltgen, K. et al. (2010)	(116)	2006				Yes	1	1	1	63	63
	Phillips, R. O. et al. (2009)	(117)	2007	Yes			Yes	1	1	1	45	44.5
	Aboagye, S. et al. (2017)	(118)	2014				Yes	1	1	1	32	32
	Sarfo, F. S. et al. (2011)	(119)	2011	Yes	Yes		Yes	1	1	1	26	26
	Ablordey, A. et al. (2015)	(45)	2012				Yes	1	1	1	24	22.75
	Amissah, N. et al. (2015)	(120)	2013				Yes	1	1	1	19	19
	Yeboah-Manu, D. et al. (2012)	(121)	2012				Yes	1	1	1	21	16
	Narh, C. A. et al. (2015)	(122)	2015				Yes	1	1	1	14	14
	Ampah, K. A. et al. (2016)	(123)	2013				Yes	1	1	1	12	12
	Iddrisah, F. et al. (2016)	(124)	2010				Yes	1	1	1	2	2
	Sarfo, F. S. et al. (2014)	(125)	2011				Yes	1	1	1	1	1
	Hospers, I. C. et al. (2005)	(126)	2002			Yes		1	0.5	0.75	396	297
	Wu, J. et al. (2015)	(127)	2010					0.5	1	0.75	326	244.5
	Ackumey, M. M. et al. (2011)	(128)	2008					0.5	1	0.75	297	222.75

Country	Reference		Recording	Confirmation method				Scores assigned			Number of cases	
	Main author (year published)	Ref	year	ZN	Culture	Histological	PCR	Diagnosis	Contemporariness	Quality	Included	Adjusted
	Kenu, E. et al. (2014)	(129)	2011					0.5	1	0.75	118	88.5
	Raghunathan, P. L. et al. (2005)	(130)	2000	Yes	Yes	Yes	Yes	1	0.5	0.75	93	69.75
	Hamzat et al. (2011)	(131)	2011					0.5	1	0.75	84	63
	Kotey, N. K. and Ampadu, X. (2011)	(132)	2012	Yes	Yes		Yes	0.5	1	0.75	68	51
	Osei-Sarpong, F. (2015)	(133)	2005					0.5	1	0.75	62	46.5
	Tschakert, P. et al. (2016)	(134)	2009					0.5	1	0.75	47	35.25
	Williamson, H. R. et al. (2008)	(135)	2006					0.5	1	0.75	36	27
	Wu, et al. (2016)	(136)	2010					0.5	1	0.75	31	23.25
	Stienstra, Y. et al. (2006)	(137)	2000	Yes	Yes	Yes	Yes	1	0.5	0.75	3	1.5
	Amofah, G. K. et al. (1993)	(138)	1991	Yes				0.95	0.5	0.725	90	64.125
	Thangaraj, H. S., et al. (2000)	(139)	2000		Yes			0.95	0.5	0.725	14	10.15
	Aboagye, S. et al. (2017)	(140)	2015					0.25	1	0.625	3	1.5
	van der Werf, T. S. et al. (1989)	(141)	1987	Yes	Yes	Yes		0.95	0.25	0.6	5	1.875
	Amofah, G. et al. (2002)	(142)	1999					0.5	0.5	0.5	1082	541
	WHO (2001) (CDC)	(19)	2000					0.5	0.5	0.5	572	286
	Duker et al. (2004)	(143)	1999					0.5	0.5	0.5	61	30.5
Guinea	WHO (2001) (Sagno)	(19)	2000					0.5	0.5	0.5	221	110.5
Honduras	Southern, Paul M. (2016)	(144)	2015	Yes	Yes			0.95	1	0.975	1	0.975
Japan	Nakanaga, K. et al. (2013)	(145)	2012	Yes	Yes	Yes	Yes	1	1	1	35	34.625
	Ohtsuka, M. et al. (2014)	(146)	2010	Yes	Yes	Yes		1	1	1	3	3
Jordan	Al Ramahi et al. (2017)	(147)	2016	Yes		Yes	Yes	1	1	1	1	1
Kenya	Walsh, D. S. et al. (2009)	(148)	2009	Yes			Yes	1	1	1	1	1
Liberia	Kollie, K. et al. (2014)	(149)	2012				Yes	1	1	1	21	21
	Monson, MH (1984)	(150)	1981	Yes				1	0.25	0.625	6	3.65
Malawi	Komolafe, O. O. (2001)	(151)	2001	Yes				0.95	0.5	0.725	3	2.175
Mali	Bessis, D. et al (2015)	(152)	2015				Yes	1	1	1	1	1
	Vignier, N. et al. (2010)	(153)	2014				Yes	1	1	1	1	1
	Ezzedine, K. et al. (2014)	(154)	2007				Yes	1	1	1	1	1
Mexico	Coloma, J. N. et al. (2005)	(155)	1997	Yes		Yes	Yes	1	0.5	0.75	2	1.5
	Aguilar et al. (1953)	(156)	1952	Yes		Yes		1	0.25	0.625	1	0.625
Nigeria	Ayelo, G. A. et al. (2018)	(157)	2016				Yes	1	1	1	66	66
	Marion, Estelle et al. (2015)	(158)	2013				Yes	1	1	1	64	64
	Ukwaja, K. N., et al. (2016)	(159)	2013	Yes			Yes	1	1	1	36	36
	Chukwuekezie, O. et al. (2007)	(160)	2006				Yes	1	1	1	14	10.5
	Marion, E. et al. (2014 a)	(161)	2013				Yes	1	1	1	1	1
	Ablordey, A. et al. (2015)	(45)	2010				Yes	1	1	1	1	1
	Nigeria MoH (2017)	(162)	2016					0.5	1	0.75	512	384
	Otuh, P. I. et al. (2018)	(163)	2013					0.5	1	0.75	48	36
	Farber et al. (1967)	(164)	1966	Yes				0.95	0.25	0.6	1	0.62
	Gray (1967)	(165)	1966	Yes		Yes		0.95	0.25	0.6	1	0.6
PNG	Igo, J. D. et al. (1988)	(166)	1983	Yes		Yes		1	0.25	0.625	46	28.75
	Jacquemart et al. (2002)	(167)	2001					0.5	0.5	0.5	402	201
	WHO (2001) (Joseph)	(19)	2000					0.5	0.5	0.5	12	6
	WHO (2004)	(168)	2003					0.5	0.5	0.5	4	2
	WHO (Joseph) (2000)	(22)	2000					0.5	0.5	0.5	2	1
	Radford, A. J. (2009)	(169)	1966					0.5	0.5	0.5	1	0.5

Country	Reference		Recording	Confirmation method				Scores assigned			Number of cases	
	Main author (year published)	Ref	year	ZN	Culture	Histological	PCR	Diagnosis	Contemporariness	Quality	Included	Adjusted
Peru	Guerra, H. et al. (2008)	(170)	2013	Yes		Yes	Yes	1	1	1	8	7.975
	Moyano, Luz M. et al. (2008)	(171)	2008	Yes			Yes	1	1	1	1	1
Republic of Congo	Marion, E., et al. (2014 b)	(172)	2012				Yes	1	1	1	12	12
Sierra Leone	Murphy, H. E. (2013)	(173)	2003	Yes				0.95	1	0.975	17	16.575
South Sudan	South Sudan MoH (2015)	(174)	2005				Yes	1	1	1	33	24.75
	Sindani, I. S. (2006)	(175)	2005	Yes				0.95	1	0.975	30	23.625
	WHO (2003)	(23)	2003					0.5	1	0.75	960	578
Suriname	Faber, W. R. et al. (2015)	(176)	2003	Yes	Yes	Yes	Yes	1	0.25	0.625	1	0.625
Togo	Beissner, M. et al. (2015)	(177)	2013				Yes	1	1	1	199	199
	Beissner, M. et al. (2013)	(178)	2013				Yes	1	1	1	81	76.75
	Togo MoH (2017)	(179)	2017	Yes			Yes	1	1	1	62	58.75
	Maman, Issaka et al. (2018)	(180)	2015	Yes			Yes	1	1	1	46	34.5
	Beissner, M. et al. (2012)	(181)	2010	Yes			Yes	1	1	1	1	1
	Ablordey, A. et al. (2015)	(45)	2000				Yes	1	0.5	0.75	2	1.5
	Meyers, M. W. et al (1996)	(182)	1994	Yes		Yes	Yes	1	0.5	0.75	2	1.5
Uganda	Bradley, D. et al (1970)	(183)	1970	Yes		Yes		1	0.25	0.625	5	2.875
	Clancey, J. et al (1962)	(184)	1962	Yes	Yes	Yes		0.95	0.25	0.6	36	21.6
	Bradley, D. et al (1971)	(185)	1970					0.5	0.25	0.375	220	82.5
	Barker, D. J. (1973 a)	(186)	1972					0.5	0.25	0.375	42	15.75
	Barker, D. J. (1973 b)	(187)	1971					0.5	0.25	0.375	1	0.375

PCR = polymerase chain reaction. ZN = Ziehl Neelsen staining. DRC = Democratic Republic of Congo, PNG = Papua New Guinea, CAR = Central African Republic. [1] Data shared on request.

References for table S.3

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Table S.4: Data extracted from selected studies used for evidence consensus framework- detection of *M. ulcerans* in environmental and animal samples

Country	Main author (year published)	Ref	Year	Sample type	PCR targets				qPCR confirmed	VNTR/MIRU results		other results	MU confirmed	N. positive samples
					ER	KR	IS2404	IS2606		MU	other MPM			
Australia	Carson et al. (2014)	(1)	2013	terr. vert. fae.		+ve	+ve	+ve	yes				yes	23
	Elsner et al. (2008)	(2)	2006	terr. vert. clin.			+ve					Clinical diagnosis	yes	1
	Fyfe et al. (2010)	(2)	2009	terr. vert. fae.		+ve	+ve	+ve	yes			ZN +	yes	70
	Fyfe et al. (2010)	(2)	2009	terr. vert. fae.		+ve	+ve	+ve	yes				yes	82
	Johnson et al. (2007)	(3)	2007	terr. invert.			+ve				+ve		no	768
	McOrist et al. (1985)	(4)	1985	terr. vert. clin.								ZN+ and culture+	yes	2
	Mitchell et al. (1984)	(5)	1980	terr. vert. clin.								histopathology +, ZN+ and culture+	yes	7
	Mitchell et al. (1987)	(6)	1985	terr. vert. clin.								Clinical diagnosis	no	8
	O'Brien et al. (2014)	(7)	1998	terr. vert. clin.			+ve					Clinical diagnosis	yes	1
	O'Brien et al. (2014)	(7)	2000	terr. vert. clin.			+ve					Clinical diagnosis	yes	2
	O'Brien et al. (2014)	(7)	2001	terr. vert. clin.			+ve					Clinical diagnosis	yes	2
	O'Brien et al. (2014)	(7)	2002	terr. vert. clin.			+ve					Clinical diagnosis	yes	2
	O'Brien et al. (2014)	(7)	2003	terr. vert. clin.			+ve					Clinical diagnosis	yes	2
	O'Brien et al. (2014)	(7)	2005	terr. vert. clin.			+ve					Clinical diagnosis	yes	1
	O'Brien et al. (2014)	(7)	2007	terr. vert. clin.			+ve					Clinical diagnosis	yes	1
	O'Brien et al. (2014)	(7)	2008	terr. vert. clin.			+ve					Clinical diagnosis	yes	6
	O'Brien et al. (2014)	(7)	2009	terr. vert. clin.			+ve					Clinical diagnosis	yes	8
	O'Brien et al. (2014)	(7)	2010	terr. vert. clin.			+ve					Clinical diagnosis	yes	10
	O'Brien et al. (2014)	(7)	2011	terr. vert. clin.			+ve					Clinical diagnosis	yes	1
	O'Brien et al. (2014)	(7)	2012	terr. vert. clin.			+ve					Clinical diagnosis	yes	4
	Röltgen et al. (2017)	(8)	2013	terr. invert.		+ve	+ve	+ve	yes				yes	1
	Röltgen et al. (2017)	(8)	2013	terr. vert. fae.		+ve	+ve	+ve	yes				yes	2
	Röltgen et al. (2017)	(8)	2013	terr. vert. fae.			+ve						yes	1
	Ross et al. (1997)	(9)	1995	aq non-animal			+ve						no	6
	WHO (2001) (Johnson)	(10)	2001	terr. vert. clin.			+ve						yes	3
Benin	Djouaka et al. (2017)	(11)	2016	aq. animal		-ve	+ve	-ve	no				no	16
	Djouaka et al. (2017)	(11)	2016	aq. animal		-ve	+ve	+ve	no				no	34
	Djouaka et al. (2017)	(11)	2016	terr. invert.		-ve	+ve	-ve	no				no	240
	Djouaka et al. (2017)	(11)	2016	terr. invert.		+ve	+ve	-ve	no				no	120
	Djouaka et al. (2018)	(12)	2018	terr. vert. clin		-ve	+ve	-ve	yes				yes	3

Country	Main author (year published)	Ref	Year	Sample type	PCR targets				qPCR confirmed	VNTR/MIRU results		other results	MU confirmed	N. positive samples
					ER	KR	IS2404	IS2606		MU	other MPM			
Benin	Djouaka et al. (2018)	(12)	2018	terr. vert. clin		-ve	+ve	+ve	yes				yes	3
	Djouaka et al. (2018)	(12)	2018	terr. vert. clin		+ve	+ve	+ve	yes	+ve			yes	2
	Eddyani et al. (2004)*	(13)	2001	aq. animal			+ve						no	1
	Williamson et al. (2012)	(14)	2012	aq. non-animal	-ve		+ve						no	39
	Williamson et al. (2012)	(14)	2012	aq. non-animal	+ve		+ve		no				no	8
	Williamson et al. (2012)	(14)	2012	aq. non-animal	+ve		+ve		yes				yes	12
	Williamson et al. (2012)	(14)	2012	aq. non-animal	+ve		+ve						no	46
	Zogo et al. (2015)	(15)	2013	aq. animal	+ve		+ve		yes				yes	31
	Zogo et al. (2015)	(15)	2013	aq. non-animal			+ve		yes				yes	1
Cameroon	Bratschi et al. (2014)	(16)	2011	aq. non-animal		+ve	+ve	+ve	yes				yes	3
	Djouaka et al. (2018)	(12)	2018	terr. vert. clin		-ve	+ve	+ve	yes				yes	3
	Djouaka et al. (2018)	(12)	2018	terr. vert. clin			+ve		yes				yes	5
	Garchitorena et al. (2014)	(17)	2013	aq. animal		+ve	+ve		yes				yes	3084
	Marion et al. (2010)	(18)	2008	aq. animal		+ve	+ve		yes		+ve		yes	1
Côte d'Ivoire	Konan et al. (2015)	(19)	2008	aq. animal	+ve		+ve		yes				no	26
	Tano et al. (2017)	(20)	2017	aq. non-animal	+ve		+ve			-ve			no	15
French Guiana	Morris et al. (2014)	(21)	2014	aq. non-animal		-ve	+ve						no	6
	Morris et al. (2014)	(21)	2014	aq. non-animal		+ve	+ve		yes				yes	3
Ghana	Aboagye et al. (2017)	(22)	2014	aq. non-animal		+ve	+ve	+ve	yes				yes	237
	Amissah et al. (2014)	(23)	2009	aq. non-animal			+ve						no	8
	Benbow et al. (2014)	(24)	2007	aq. non-animal	+ve					+ve			yes	34
	Benbow et al. (2014)	(24)	2007	aq. non-animal	+ve						+ve		no	10
	Benbow et al. (2014)	(24)	2007	aq. non-animal	+ve								no	37
	Eddyani et al. (2004)*	(13)	2001	aq. animal			-ve						no	1
	Eddyani et al. (2004)*	(13)	2001	aq. animal			+ve						no	3
	Narh et al. (2015)	(25)	2015	aq. non-animal	+ve		+ve			+ve			no	9
	Narh et al. (2015)	(25)	2015	terr. vert. clin.	+ve		+ve						no	1

Country	Main author (year published)	Ref	Year	Sample type	PCR targets				qPCR confirmed	VNTR/MIRU results		other results	MU confirmed	N. positive samples
					ER	KR	IS2404	IS2606		MU	other MPM			
Ghana	Tobias et al. (2016)	(26)	2013	terr. vert. fae.		-ve	-ve						no	7
	Tobias et al. (2016)	(26)	2013	terr. vert. fae.			-ve						no	14
	Tobias et al. (2016)	(26)	2013	terr. vert. fae.			+ve						no	4
	Vandelannoote et al. (2010)	(27)	2010	aq. non-animal		+ve	+ve		yes				yes	1
	Vandelannoote et al. (2010)	(27)	2010	aq. non-animal			+ve		yes				yes	2
	Williamson et al. (2008)	(28)	2006	aq. non-animal	-ve								no	7
	Williamson et al. (2008)	(28)	2006	aq. non-animal	+ve					-ve	-ve		no	1
	Williamson et al. (2008)	(28)	2006	aq. non-animal	+ve					-ve			yes	5
	Williamson et al. (2008)	(28)	2006	aq. non-animal	+ve					-ve	+ve		yes	2
	Williamson et al. (2008)	(28)	2006	aq. non-animal	+ve					+ve	-ve		yes	7
	Williamson et al. (2008)	(28)	2006	aq. non-animal	+ve					+ve	+ve		yes	4
	Willson et al. (2013)	(29)	2008	aq. animal						+ve			yes	1
	Willson et al. (2013)	(29)	2008	aq. non-animal	+ve					+ve			yes	2
Japan	Ohtsuka et al. (2014)	(30)	2010	aq. animal			+ve						no	1
Togo	Maman et al. (2018)	(31)	2015	aq. non-animal	na	-ve	+ve	-ve	-ve	na			no	4
	Maman et al. (2018)	(31)	2015	aq. non-animal	na	-ve	+ve	+ve	-ve	na			no	4
	Maman et al. (2018)	(31)	2015	aq. non-animal	na	+ve	+ve	+ve	yes	na			yes	4
USA	Hennigan et al. (2013)	(32)	2011	aq. non-animal			+ve						no	66

Terr. = terrestrial; Aq. = aquatic; vert. = vertebrate; invert. = invertebrate; fae. = faeces; clin. = clinical.

References for table S.4

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Table S.5: results of evidence consensus framework showing strength of evidence for BU presence or absence worldwide.

Literature review scores D, C, and DQ show the scores assigned to the highest-scoring reference, based on diagnostic specificity (D) and contemporariness (C), combined to give a data quality (DQ) score. The total cases (TC) is the sum of the total number of cases reported in all references included in the review, each weighted according to the data quality score for the reference. Health expenditure level (HE L) was used to assign health system (HS) scores 1 and 2. Misdiagnosis scores were calculated for a range of conditions that present on the skin, based on the proportion of symptoms shared with BU. The composite misdiagnosis likelihood score (CMP) is the sum of the misdiagnosis scores for all endemic diseases in each country, weighted by HS1 which represents the quality of diagnosis. The evidence consensus score (ECS) is the sum of columns in bold. Positive values of ECS indicate evidence for presence, negative values indicate evidence for absence.

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference		D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
Australia	886	1.5	0.5	**2**	Tai, A. et al. (2018)	(1)	1.0	1	**2.0**	1138	**1**	H	0.25	**0**				0.002			**0.00**	100
Benin	5534	1.5	0.5	**2**	Sopoh, G. et al. (2010)	(2)	1.0	1	**2.0**	8629	**1**	L	1	**1**				0.002	0.005	0.71	**0.56**	100
Cameroon	2045	1.5	0.5	**2**	Landier, J. et al. (2011)	(3)	1.0	1	**2.0**	5273	**1**	L	1	**1**	0.16	0.35	0.06	0.002	0.005	0.71	**1.00**	100
Côte d'Ivoire	15481	1.5	0.5	**2**	N'Krumah, R. et al. (2017)	(4)	1.0	1	**2.0**	3664	**1**	L	1	**1**	0.16	0.35		0.002			**0.40**	100
Democratic Republic of Congo	2216	1.5	0.5	**2**	Mavinga Phanzu, D. et al. (2011)	(5)	1.0	1	**2.0**	813	**1**	L	1	**1**	0.16		0.06		0.005		**0.17**	100
Gabon	483	1.5	0.5	**2**	Bayonne Manou, L. S. et al. (2013)	(6)	1.0	1	**2.0**	295	**1**	M	0.5	**0.5**			0.06	0.002	0.005	0.71	**0.30**	100
Ghana	6797	1.5	0.5	**2**	Yeboah-Manu, D. et al. (2018)	(7)	1.0	1	**2.0**	4932	**1**	L	1	**1**	0.16	0.35		0.002	0.005	0.71	**0.96**	100
Japan	56	1.5	0.5	**2**	Nakanaga, K. et al. (2013)	(8)	1.0	1	**2.0**	38	**1**	H	0.25	**0**							**0.00**	100
Liberia	134	1.5	0.5	**2**	Kollie, K. et al. (2014)	(9)	1.0	1	**2.0**	25	**1**	L	1	**1**			0.06		0.005	0.71	**0.60**	100
Nigeria	512	1.5	0.5	**2**	Ayelo, G. A. et al. (2018)	(10)	1.0	1	**2.0**	600	**1**	L	1	**1**	0.16	0.35	0.06	0.002	0.005	0.71	**1.00**	100
Togo	726	1.5	0.5	**2**	Beissner, M. et al. (2015)	(11)	1.0	1	**2.0**	373	**1**	L	1	**1**				0.002	0.005	0.71	**0.56**	100
South Sudan	20	1.5	0.5	**2**	South Sudan MoH (2015)	(12)	1.0	1	**2.0**	626	**1**	L	1	**1**		0.35	0.06		0.005		**0.32**	100
Republic of Congo	579	1.5	0.5	**2**	Marion, E., et al. (2014 b)	(13)	1.0	1	**2.0**	12	**0.75**	M	0.5	**0.5**	0.16		0.06	0.002	0.005	0.71	**0.36**	95
Sierra Leone	29	1.5	0.5	**2**	Murphy, H. E. (2013)	(14)	1.0	1	**2.0**	17	**0.75**	L	1	**1**					0.005	0.71	**0.56**	95
CAR	3	1.5	0.5	**2**	Minime-Lingoupou, F. et al. (2010)	(15)	1.0	1	**2.0**	2	**0.25**	L	1	**1**	0.16		0.06		0.005	0.71	**0.73**	85
PNG	85	1.5	0.5	**2**	Igo, et al. (1988)	(16)	0.6	0.5	**1.1**	239	**1**	L	1	**1**	0.16				0.005	0.71	**0.68**	83
Guinea	520	1.5	0.5	**2**	WHO (2001) (Sagno)	(17)	0.5	0.5	**1.0**	111	**1**	L	1	**1**				0.002	0.005	0.71	**0.56**	80
Uganda	58	1.5	0.5	**2**	Bradley, D. et al (1970)	(18)	0.6	0.25	**0.9**	123	**1**	L	1	**1**			0.06	0.002	0.005	0.71	**0.60**	78

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference		D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
French Guiana	H	-1	0.5	**-0.5**	Reynaud, Y. et al. (2015)	(19)	1.0	1	**2.0**	35	**1**	H	0.25	**0**		0.35				0.71	**0.21**	50
Kenya	H	-1	0.5	**-0.5**	Walsh, D. S. et al. (2009)	(20)	1.0	1	**2.0**	1	**0.25**	L	1	**1**		0.35	0.06		0.005	0.71	**0.87**	35
Brazil	H	-1	0.5	**-0.5**	dos Santos, J. (2007)	(21)	1.0	1	**2.0**	1	**0.25**	H	0.25	**0**		0.35	0.06	0.002	0.005	0.71	**0.22**	35
Peru	0	-1.5	0.5	**-1**	Guerra, H. et al. (2008)	(22)	1.0	1	**2.0**	9	**0.5**	M	0.5	**0.5**		0.35		0.002		0.71	**0.41**	30
Angola	0	-1.5	0.5	**-1**	Kibadi, K. et al. (2008)	(23)	1.0	1	**2.0**	3	**0.25**	M	0.5	**0.5**			0.06		0.005	0.71	**0.30**	25
Jordan	0	-1.5	0.5	**-1**	Al Ramahi et al. (2017)	(24)	1.0	1	**2.0**	1	**0.25**	M	0.5	**0.5**		0.35					**0.14**	25
Mali	0	-1.5	0.5	**-1**	Bessis, D. et al (2015)	(25)	1.0	1	**2.0**	3	**0.25**	L	1	**1**		0.35		0.002	0.005	0.71	**0.83**	25
Mexico	H	-1	0.5	**-0.5**	Coloma, J. N. et al. (2005)	(26)	0.8	0.5	**1.3**	2	**0.25**	H	0.25	**0**		0.35		0.002			**0.07**	20
China	H	-1	0.5	**-0.5**	Faber, W. R. et al. (2000)	(27)	0.8	0.5	**1.3**	1	**0.25**	M	0.5	**0.5**		0.35		0.002			**0.14**	20
Malawi	H	-1	0.5	**-0.5**	Komolafe, O. O. (2001)	(28)	0.7	0.5	**1.2**	2	**0.25**	L	1	**1**		0.35	0.06		0.005	0.71	**0.87**	20
Suriname	H	-1	0.5	**-0.5**	Faber, W. R. et al. (2015)	(29)	0.6	0.25	**0.9**	1	**0.25**	H	0.25	**0**		0.35		0.002	0.005	0.71	**0.21**	13
Burkina Faso	0	-1.5	0.5	**-1**	Ouoba, K., et al. (1998)	(30)	0.8	0.5	**1.3**	2	**0.25**	L	1	**1**		0.35		0.002	0.005	0.71	**0.83**	10
Honduras	0	-1.5	-0.5	**-2**	Southern, Paul M. (2016)	(31)	1.0	1	**2.0**	1	**0.25**	M	0.5	**0.5**		0.35				0.71	**0.41**	5
Ethiopia	0	-1.5	-0.5	**-2**	Gordon, D. et al. (2014)	(32)	1.0	1	**2.0**	2	**0.25**	L	1	**1**		0.35	0.06	0.002	0.005	0.71	**0.87**	5
Malaysia	H	-1	0.5	**-0.5**	Stanford et al. (1973)	(33)	0.0	0	**0.5***			M	0.5	**0.5**				0.002	0.005	0.71	**0.28**	0
Niger	0	-1.5	-0.5	**-2**								L	1	**1**		0.35		0.002	0.005	0.71	**0.83**	-9
Eritrea	0	-1.5	-0.5	**-2**								L	1	**1**		0.35			0.005	0.71	**0.83**	-9
Gambia	0	-1.5	-0.5	**-2**								L	1	**1**		0.35			0.005	0.71	**0.83**	-9
Mauritania	0	-1.5	-0.5	**-2**								L	1	**1**		0.35				0.71	**0.82**	-9
Indonesia	H	-1	0.5	**-0.5**								M	0.5	**0.5**	0.16			0.002	0.005	0.71	**0.34**	-10
Equatorial Guinea	H	-1	0.5	**-0.5**								M	0.5	**0.5**			0.06	0.002	0.005	0.71	**0.30**	-10
Kiribati	H	-1	0.5	**-0.5**								M	0.5	**0.5**				0.002	0.005		**0.00**	-10
Sri Lanka	H	-1	0.5	**-0.5**								L	1	**1**		0.35		0.002	0.005		**0.28**	-10
Mozambique	0	-1.5	-0.5	**-2**								L	1	**1**			0.06	0.002	0.005	0.71	**0.60**	-20
Rwanda	0	-1.5	-0.5	**-2**								L	1	**1**			0.06	0.002	0.005	0.71	**0.60**	-20
Senegal	0	-1.5	0.5	**-1**								L	1	**1**		0.35		0.002	0.005	0.71	**0.83**	-20

NAME	Health reporting organisations				Literature review					Health expenditure			Misdiagnosis likelihood scores						ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
Burundi	0	-1.5	-0.5	**-2**							L	1	**1**			0.06		0.005	0.71	**0.60**	-20
Chad	0	-1.5	-0.5	**-2**							L	1	**1**			0.06		0.005	0.71	**0.60**	-20
Madagascar	0	-1.5	-0.5	**-2**							L	1	**1**				0.002	0.005	0.71	**0.56**	-22
Guinea-Bissau	0	-1.5	-0.5	**-2**							L	1	**1**					0.005	0.71	**0.56**	-22
Sao Tome and Principe	0	-1.5	-0.5	**-2**							L	1	**1**					0.005	0.71	**0.56**	-22
Zambia	0	-1.5	-0.5	**-2**							L	1	**1**					0.005	0.71	**0.56**	-22
Zimbabwe	0	-1.5	-0.5	**-2**							L	1	**1**					0.005	0.71	**0.56**	-22
Somalia	0	-1.5	-0.5	**-2**							L	1	**1**				0.002		0.71	**0.55**	-22
Iran, Islamic Republic of	0	-1.5	-0.5	**-2**	Behrouznasab et al. (2012) (34)			**0.5***			H	0.25	**0**		0.35					**0.07**	-29
Timor-Leste	0	-1.5	-0.5	**-2**							L	1	**1**	0.16	0.35		0.002	0.005		**0.40**	-30
India	0	-1.5	-0.5	**-2**							L	1	**1**		0.35		0.002	0.005		**0.28**	-36
Nepal	0	-1.5	-0.5	**-2**							L	1	**1**		0.35		0.002	0.005		**0.28**	-36
Yemen	0	-1.5	-0.5	**-2**							L	1	**1**		0.35		0.002	0.005		**0.28**	-36
Afghanistan	0	-1.5	-0.5	**-2**							L	1	**1**		0.35		0.002			**0.27**	-36
Pakistan	0	-1.5	-0.5	**-2**							L	1	**1**		0.35		0.002			**0.27**	-36
Syrian Arab Republic	0	-1.5	-0.5	**-2**							L	1	**1**		0.35		0.002			**0.27**	-36
Uzbekistan	0	-1.5	-0.5	**-2**							L	1	**1**		0.35					**0.27**	-36
West Bank	0	-1.5	-0.5	**-2**							L	1	**1**		0.35					**0.27**	-36
United Republic of Tanzania	0	-1.5	-0.5	**-2**							L	1	**1**			0.06		0.005		**0.05**	-48
Bangladesh	0	-1.5	-0.5	**-2**							L	1	**1**				0.002	0.005		**0.01**	-50
Comoros	0	-1.5	-0.5	**-2**							L	1	**1**				0.002	0.005		**0.01**	-50
Haiti	0	-1.5	-0.5	**-2**							L	1	**1**				0.002	0.005		**0.01**	-50
Myanmar	0	-1.5	-0.5	**-2**							L	1	**1**				0.002	0.005		**0.01**	-50
Viet Nam	0	-1.5	-0.5	**-2**							L	1	**1**				0.002	0.005		**0.01**	-50
Cambodia	0	-1.5	-0.5	**-2**							L	1	**1**					0.005		**0.00**	-50

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
Lao People's Democratic Republic	0	-1.5	-0.5	**-2**							L	1	**1**					0.005		**0.00**	-50
Bhutan	0	-1.5	-0.5	**-2**							L	1	**1**							**0.00**	-50
Dem People's Rep of Korea	0	-1.5	-0.5	**-2**							L	1	**1**							**0.00**	-50
Djibouti	0	-1.5	-0.5	**-2**							L	1	**1**							**0.00**	-50
Kyrgyzstan	0	-1.5	-0.5	**-2**							L	1	**1**							**0.00**	-50
Tajikistan	0	-1.5	-0.5	**-2**							L	1	**1**							**0.00**	-50
Guyana	0	-1.5	-0.5	**-2**							M	0.5	**0.5**	0.16	0.35		0.002	0.005	0.71	**0.48**	-51
Ecuador	0	-1.5	-0.5	**-2**							M	0.5	**0.5**	0.16	0.35				0.71	**0.48**	-51
Sudan	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35	0.06	0.002	0.005	0.71	**0.44**	-53
Thailand	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35		0.002	0.005	0.71	**0.41**	-54
Colombia	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35		0.002		0.71	**0.41**	-54
Algeria	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35				0.71	**0.41**	-54
Belize	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35				0.71	**0.41**	-54
Bolivia	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35				0.71	**0.41**	-54
El Salvador	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35				0.71	**0.41**	-54
Guatemala	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35				0.71	**0.41**	-54
Nicaragua	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35				0.71	**0.41**	-54
Philippines	0	-1.5	-0.5	**-2**							M	0.5	**0.5**				0.002	0.005	0.71	**0.28**	-61
Botswana	0	-1.5	-0.5	**-2**							M	0.5	**0.5**						0.71	**0.28**	-61
Swaziland	0	-1.5	-0.5	**-2**							M	0.5	**0.5**						0.71	**0.28**	-61
Egypt	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35		0.002	0.005		**0.14**	-68
Dominican Republic	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35			0.005		**0.14**	-68
Morocco	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35		0.002			**0.14**	-68
Paraguay	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35		0.002			**0.14**	-68
Azerbaijan	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35					**0.14**	-68
Georgia	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35					**0.14**	-68
Iraq	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35					**0.14**	-68

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
Tunisia	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35					**0.14**	-68
Turkmenistan	0	-1.5	-0.5	**-2**							M	0.5	**0.5**		0.35					**0.14**	-68
Vanuatu	0	-1.5	-0.5	**-2**							M	0.5	**0.5**	0.16				0.005		**0.07**	-72
Seychelles	0	-1.5	-0.5	**-2**							M	0.5	**0.5**				0.002	0.005		**0.00**	-75
Solomon Islands	0	-1.5	-0.5	**-2**							M	0.5	**0.5**				0.002	0.005		**0.00**	-75
Cape Verde	0	-1.5	-0.5	**-2**							M	0.5	**0.5**					0.005		**0.00**	-75
Cook Islands	0	-1.5	-0.5	**-2**							M	0.5	**0.5**					0.005		**0.00**	-75
Fiji	0	-1.5	-0.5	**-2**							M	0.5	**0.5**					0.005		**0.00**	-75
Mauritius	0	-1.5	-0.5	**-2**							M	0.5	**0.5**					0.005		**0.00**	-75
Samoa	0	-1.5	-0.5	**-2**							M	0.5	**0.5**					0.005		**0.00**	-75
Tonga	0	-1.5	-0.5	**-2**							M	0.5	**0.5**					0.005		**0.00**	-75
Tuvalu	0	-1.5	-0.5	**-2**							M	0.5	**0.5**					0.005		**0.00**	-75
Albania	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Armenia	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Belarus	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Bosnia and Herzegovina	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Dominica	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Grenada	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Jamaica	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Kazakhstan	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Kingman Reef	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Lesotho	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Mongolia	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Montenegro	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Paracel Islands	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Republic of Moldova	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Romania	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Saint Lucia	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
Saint Vincent and the Grenadines	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Spratly Islands	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Ukraine	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Western Sahara	0	-1.5	-0.5	**-2**							M	0.5	**0.5**							**0.00**	-75
Venezuela	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35	0.06		0.005	0.71	**0.22**	-89
Costa Rica	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35		0.002	0.005	0.71	**0.21**	-90
Argentina	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35		0.002		0.71	**0.21**	-90
Namibia	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35				0.71	**0.21**	-90
Panama	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35				0.71	**0.21**	-90
South Africa	0	-1.5	-0.5	**-2**							H	0.25	**0**				0.002		0.71	**0.14**	-93
Chile	0	-1.5	-0.5	**-2**							H	0.25	**0**						0.71	**0.14**	-93
Saint Helena	0	-1.5	-0.5	**-2**							H	0.25	**0**						0.71	**0.14**	-93
Croatia	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Cyprus	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
France	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Greece	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Israel	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Italy	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Kuwait	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Lebanon	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Libyan Arab Jamahiriya	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Malta	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Martinique	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Portugal	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Saudi Arabia	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Spain	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Turkey	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
USA	0	-1.5	-0.5	**-2**							H	0.25	**0**		0.35					**0.07**	-97
Marshall Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**				0.002	0.005		**0.00**	-100
New Caledonia	0	-1.5	-0.5	**-2**							H	0.25	**0**				0.002	0.005		**0.00**	-100
Trinidad and Tobago	0	-1.5	-0.5	**-2**							H	0.25	**0**				0.002	0.005		**0.00**	-100
American Samoa	0	-1.5	-0.5	**-2**							H	0.25	**0**					0.005		**0.00**	-100
French Polynesia	0	-1.5	-0.5	**-2**							H	0.25	**0**					0.005		**0.00**	-100
Maldives	0	-1.5	-0.5	**-2**							H	0.25	**0**					0.005		**0.00**	-100
Niue	0	-1.5	-0.5	**-2**							H	0.25	**0**					0.005		**0.00**	-100
Palau	0	-1.5	-0.5	**-2**							H	0.25	**0**					0.005		**0.00**	-100
Wallis and Futuna	0	-1.5	-0.5	**-2**							H	0.25	**0**					0.005		**0.00**	-100
Bahamas	0	-1.5	-0.5	**-2**							H	0.25	**0**				0.002			**0.00**	-100
Cuba	0	-1.5	-0.5	**-2**							H	0.25	**0**				0.002			**0.00**	-100
Qatar	0	-1.5	-0.5	**-2**							H	0.25	**0**				0.002			**0.00**	-100
Andorra	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Anguilla	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Antarctica	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Antigua and Barbuda	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Aruba	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Austria	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Bahrain	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Baker Island	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Barbados	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Belgium	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Bermuda	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Bouvet Island	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
British Indian Ocean Territory	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
British Virgin Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Bulgaria	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Canada	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Cayman Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Christmas Island	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Clipperton Island	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Cocos (Keeling) Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Czech Republic	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Denmark	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Estonia	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Europa Island	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Falkland Islands (Malvinas)	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Faroe Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Finland	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
French Southern and Antarctic Territories	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Germany	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Gibraltar	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Greenland	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Guadeloupe	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Guam	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Guernsey	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Heard Island and McDonald Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
Holy See	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Hong Kong	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Hungary	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Iceland	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Ireland	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Isle of Man	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Jersey	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Korea, Republic of	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Latvia	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Liechtenstein	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Lithuania	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Luxembourg	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Macau	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Mayotte	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Monaco	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Montserrat	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Nauru	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Netherlands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Netherlands Antilles	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
New Zealand	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Norfolk Island	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Northern Mariana Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Norway	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Oman	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Pitcairn	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Poland	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Puerto Rico	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Reunion	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100

NAME	Health reporting organisations				Literature review						Health expenditure			Misdiagnosis likelihood scores							ECS
	WHO rep	WHO score	GIDEON score	**HRO score**	Highest scoring reference	D	C	**DQ**	TC	**CS**	HE L	HS 1	**HS 2**	YW	CL	ONC	LPR	LF	TU	**CMP**	
Russian Federation	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Saint Kitts and Nevis	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Saint Pierre et Miquelon	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
San Marino	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Serbia	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Singapore	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Slovakia	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Slovenia	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
South Georgia and the South Sandwich Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Svalbard and Jan Mayen Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Sweden	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Switzerland	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Tokelau	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Turks and Caicos islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
U.K.	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
UAE	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
United States Virgin Islands	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100
Uruguay	0	-1.5	-0.5	**-2**							H	0.25	**0**							**0.00**	-100

WHO rep: numbers show total cases reported 2007- 16, H=historic case reporting (prior to 2007). D=diagnosis score; C=contemporariness score; DQ=data quality score; TC=total number of cases (weighted); CS=case number score. HE L = health expenditure level: L=low, M=med, H=high. HS1/2 = health system score 1/2. Misdiagnosis likelihood scores: YW=yaws, CL=cutaneous leishmaniasis, ONC=onchocerciasis, LPR=leprosy, LF=lymphatic filariasis, TU=tropical ulcer, CMP=composite. ECS= evidence consensus score. *Score adjusted *post hoc*.

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PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Mapping suitability for Buruli ulcer at fine spatial scales across Africa: A modelling study

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Data Availability Statement: We used previously compiled spatial datasets of point locations of recorded occurrences of BU disease in humans, and of detection of M. ulcerans genetic material in biotic and abiotic environmental samples (https://datacompass.lshtm.ac.uk/1143/). Data for the final models was extracted from the database on 03/01/2020. All analyses were implemented in R version 4.0.2 and scripts used are available on GitHub: https://github.com/Hope-Simpson/modelling-BU-distribution.

Abstract

Buruli ulcer (BU) is a disabling and stigmatising neglected tropical disease (NTD). Its distribution and burden are unknown because of underdiagnosis and underreporting. It is caused by *Mycobacterium ulcerans*, an environmental pathogen whose environmental niche and transmission routes are not fully understood. The main control strategy is active surveillance to promote early treatment and thus limit morbidity, but these activities are mostly restricted to well-known endemic areas. A better understanding of environmental suitability for the bacterium and disease could inform targeted surveillance, and advance understanding of the ecology and burden of BU. We used previously compiled point-level datasets of BU and *M. ulcerans* occurrence, evidence for BU occurrence within national and sub-national areas, and a suite of relevant environmental covariates in a distribution modelling framework. We fitted relationships between BU and *M. ulcerans* occurrence and environmental predictors by applying regression and machine learning based algorithms, combined in an ensemble model to characterise the optimal ecological niche for the disease and bacterium across Africa at a resolution of 5km x 5km. Proximity to waterbodies was the strongest predictor of suitability for BU, followed potential evapotranspiration. The strongest predictors of suitability for *M. ulcerans* were deforestation and potential evapotranspiration. We identified patchy foci of suitability throughout West and Central Africa, including areas with no previous evidence of the disease. Predicted suitability for *M. ulcerans* was wider but overlapping with that of BU. The estimated population living in areas predicted suitable for the bacterium and disease was 46.1 million.

These maps could be used to inform burden estimations and case searches which would generate a more complete understanding of the spatial distribution of BU in Africa, and may guide control programmes to identify cases beyond the well-known endemic areas.

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Competing interests: The authors have declared that no competing interests exist.

Author summary

Like many neglected tropical diseases primarily affecting the rural poor, Buruli ulcer (BU) is under-detected and under-reported within routine health information systems. As such, the burden and distribution are not fully known, impeding appropriate targeting of health resources, control, and care for people affected. Having previously evaluated and mapped the existing evidence for BU and its causative agent *M. ulcerans*, we concluded that the disease was likely to occur beyond the range of known endemic areas. However, we were left with the question of where exactly these undetected cases might be occurring. Answering this question required a more fine-scale approach: BU is highly focal, presumably due to local variation in the environmental factors which determine suitability for *M. ulcerans* survival and transmission to humans. We used the compiled evidence and geographical datasets to build statistical models representing the relationship between environmental factors and previously reported cases. This allowed us to define the ecological niche of BU, and subsequently to identify areas across Africa where this niche was met, providing suitable conditions for the disease. We constructed separate models of suitability for *M. ulcerans*, using locations where its DNA had been detected in environmental sources. Unsurprisingly, suitability for *M. ulcerans* was predicted to be wider than, but geographically overlapping with that for BU. This implies that beyond the conditions necessary for survival of the bacterium, additional factors are required for transmission to humans. The high-resolution suitability maps we present are intended to guide case search activities which may identify endemic areas beyond the known endemic range. Data on the true prevalence of BU from targeted case searches within predicted-suitable areas will also allow us to validate and refine the models, and potentially to predict the probability of cases occurring within predicted suitable areas.

Introduction

Buruli ulcer (BU) is a chronic necrotizing disease of the skin and soft tissue, which causes debilitating symptoms and sequelae, associated with a high burden of morbidity and stigma for patients and economic costs for affected households [1–3]. These impacts are felt particularly strongly in impoverished rural communities with poor access to health services [3,4]. The infectious agent is *Mycobacterium ulcerans*, a slow-growing environmental bacterium which appears to be transmitted from aquatic environments to humans by penetration of the skin, although the exact pathways are not fully understood and are likely to be diverse [1,5,6]. The main control strategy is active case finding in endemic areas to promote early case detection and effective treatment, which limits disease progression [7,8]. BU occurs mostly in tropical and subtropical areas of West and Central Africa, with smaller foci in parts of Asia, South America, the Western Pacific and Australasia [9]. However, the disease is recognised to be underdiagnosed and under-reported, and may occur undetected in other parts of the world [9–12].

In the 1950's and 60's, large numbers of cases occurred in Nakasongola District in Uganda, but the incidence of disease in this area then declined and has apparently not resurged since (S1 and S2 Figs) [13]. In West Africa, the highest incidence was reported in the mid 1990's and appears to have been declining since 2008 [13]. The distribution of BU is presumably linked to environmental suitability- the availability of appropriate conditions- for *M. ulcerans* survival and replication, as well as to human and environmental factors favouring transmission [14].

On a continental scale, BU appears to be limited by climatic factors: it is mostly restricted to tropical and subtropical regions and is absent from arid areas [15]. Within endemic areas, the disease shows a highly focal distribution [16–18], but reasons for this are not well understood, since the precise niche and transmission routes of *M. ulcerans* have been difficult to characterise [19]. The pathogen has only been cultured from environmental and animal samples a handful of times [20–22], although it has been detected by PCR in aquatic environments of endemic and non-endemic areas, and in a wide range of potential hosts including mammals, fish, amphibians, and aquatic and terrestrial insects [23–27]. Consistent with the ecology of an environmental pathogen, the distribution of *M. ulcerans* in the environment appears to be wider than that of BU, suggesting that factors beyond environmental suitability for *M. ulcerans* are required for transmission [14,15,28].

Our understanding of the pathways of BU infection is also limited, partly by its long and variable incubation period, which makes it difficult for patients and clinicians to attribute particular events or activities to disease acquisition [29]. Local spatial analysis has identified several environmental variables associated with increased BU incidence, primarily proximity to rivers, as well as environmental disturbance and land-use changes including deforestation, urbanisation, agriculturalization, damming of rivers and mining [30,31]. Case control studies have identified contact with unprotected waterbodies as a risk factor for disease [32], suggesting that activities which bring people into contact with water sources harbouring *M. ulcerans* increase the risk of disease acquisition [33–35].

Given the recognised scale of BU under-detection and under-reporting, it is likely that the disease occurs beyond the known range of reported cases. A better understanding of potential suitability for the pathogen in the environment and the disease in humans would help to improve its surveillance and control in countries where is known to be endemic. Furthermore, characterisation of the environmental factors linked to suitability for *M. ulcerans* and BU may reveal areas at risk of disease emergence, or harbouring unrecognised cases.

In this investigation, we aim to identify environmental factors which characterise the environmental niche of *M. ulcerans* and BU disease in humans, and to model their respective relationships with *M. ulcerans* and BU occurrence. These analyses will be used to identify areas of continental Africa which may be suitable for *M. ulcerans* or BU based on their environmental characteristics.

Methods

Data on Buruli ulcer and *M. ulcerans* distribution

We used previously compiled datasets of point locations of recorded occurrences of BU disease in humans, and of detection of *M. ulcerans* genetic material in biotic and abiotic environmental samples [9,36]. The datasets were compiled through a systematic review [9] and the BU dataset was supplemented with surveillance data from BU control programmes in Ghana, Nigeria and Cameroon. The literature search was updated in October 2020.

BU occurrence locations were restricted to those where BU infection was confirmed by a positive result for PCR targeting IS2404, or histopathology consistent with BU disease. To explore the model's sensitivity to the case definition, we repeated the analysis using all locations where clinically diagnosed BU had been reported. We hereon refer to the two datasets as '*confirmed occurrences*' and '*all occurrences*' respectively.

The environmental dataset was restricted to locations where *M. ulcerans* DNA had been identified and distinguished from that of other mycobacteria: either by multiplex qPCR assays quantifying the relative copy numbers of IS2404, IS2606 and the KR-B domain [37]; by

variable nucleotide tandem repeat (VNTR); or mycobacterial interspersed repetitive unit (MIRU) typing [38,39]. We hereon refer to this dataset as '*environmental occurrences*'.

All records were restricted to locations with reliable geographical coordinates and deduplicated by geographical location.

Environmental datasets used in ecological modelling

We assembled gridded datasets of 14 environmental variables considered relevant to the ecological niche of the bacterium or disease [19]. These included four variables considered to characterise the tropical and subtropical biomes from where the majority of BU cases in Africa have been reported [40]: minimum and maximum temperature [41,42], the aridity index, quantifying atmospheric aridity (the balance of precipitation and atmospheric water demand [43,44]) and potential evapo-transpiration (a measure of atmospheric capacity to remove water from the air through evaporation and transpiration assuming unlimited water availability) [40,43]. Tropical climates are also characterised by the amount of precipitation they experience, so we included indicators of precipitation seasonality and precipitation in the wettest and driest quarters [45], which have been linked to trends in the abundance of *M. ulcerans* in the environment and the incidence of BU cases in Cameroon, Ghana, and Uganda [46–48]. We also included indicators of topography which may identify the swampy, stagnant environments where BU is often reported in endemic countries [14,49], specifically elevation [43] and topological wetness index (derived from elevation), representing the potential for each cell to accumulate water based on its elevation relative to surrounding cells and the potential for drainage [50]. Since particular vegetation and landcover types have previously been associated with BU endemicity [31,49], we included the enhanced vegetation index (EVI) which quantifies vegetation cover [51,52]. We calculated Euclidean (straight line) to the nearest river or stream, and to the nearest waterbody recorded on Open Street Map, as contact with unprotected water is a known risk factor for BU [32,53]. Finally, we included a range of human-driven factors which have been associated with BU emergence and transmission: deforestation [54,55], agriculturalization [2,55] and damming of rivers [13,55,56,57]. We calculated Euclidean (straight line) to the nearest area of deforested land and the nearest agricultural area using landcover data [58], and to the nearest dam recorded on Open Street Map [53]. Full details of all variables and their sources are provided in S2 Text.

Variable selection

We compiled the gridded candidate predictors at a resolution of 5km x 5km within a rectangular area of West Africa from latitude -13.57195, longitude -4.11032, to lat. 16.67107, long. 14.493. This area contained 94% of all BU occurrence locations, 95% of confirmed BU occurrence locations, and all environmental occurrence locations. We extracted the values of predictor variables at the locations of BU cases (all occurrences) and environmental occurrences of *M. ulcerans* DNA. We calculated the covariance between all candidate predictors and dropped those which were correlated with another variable with a Pearson correlation coefficient of above 0.8 (or below -0.8), retaining the variable with the strongest existing evidence or biological plausibility for an association with BU or *M. ulcerans* distribution or suitability.

Pseudoabsence and background data

One major challenge in species distribution modelling is the scarcity of data on locations absent for the species or disease of interest, since absence from a given area is difficult to establish with certainty [59]. To account for this, we generated pseudo-absence points, representing the comparator class for the models, in areas where BU was assumed to be absent [60]. We

used the surface range envelope function within the *biomod2* package in R [61] to identify areas presumably suitable for the disease (containing values between the 2.5th and 97.5th percentiles of the selected predictor variables) and sampled pseudoabsence points from outside of this envelope. The selection of pseudoabsences was biased to areas with lower evidence of BU endemicity, using data from a systematic review of the geographical distribution of BU [9] to ensure higher coverage of pseudoabsence points in countries with lower evidence for BU. Further details are given in S1 Text.

Another challenge in species distribution modelling is that data from surveys and passive surveillance are often geographically biased due to variation in data collection intensity, which can lead to erroneous predictions if this bias is not accounted for [62]. We generated a separate class of model negative points which we refer to as background points. We distinguish background points from pseudoabsence points on the basis that we make no assumption about the occurrence of or suitability for BU or *M*. *ulcerans* at the background locations [60], and simply use these points to balance out the spatial bias in the occurrence points. This process has previously been termed 'background thickening' [63]. Background points were sampled at higher density around recorded occurrence points. More details are provided in S1 Text.

Human background and pseudoabsence points were restricted to a minimum distance of 10km from any BU occurrence location, and environmental background and pseudoabsence points were restricted to 10km from any environmental occurrence location. Within the models, pseudoabsence and background points were downweighted by 50% compared to occurrence points. The distributions of pseudoabsence and background points for the Buruli ulcer suitability models are shown in S3 and S4 Figs and those for the *M*. *ulcerans* suitability models in S5 and S6 Figs.

Ensemble modelling

The selected environmental covariates were used as predictor variables and the occurrence, pseudoabsence and background locations were included as the outcome. We used the *biomod2* package in R [61,64] to implement seven algorithms: generalized linear models (GLM), generalized additive models (GAM), generalized boosted regression models (GBM), artificial neural networks (ANN), multiple adaptive regression splines (MARS), maximum entropy (MaxEnt) and random forest (RF).

Individual model algorithms were each run 20 times with a random sample of 80% of data points, and evaluated with the remaining 20%. For each algorithm we calculated the mean true skill statistic (TSS), the mean percent correctly classified (PCC) and the mean area under the curve (AUC) of the receiver operation characteristic (ROC) [65]. The TSS is a prevalence-independent measure of predictive accuracy, calculated as sensitivity + specificity– 1 and ranging from -1 to 1 with a score of 1 representing perfect agreement between model predictions and data, and values from 0 to -1 representing performance no better than random. The PCC is a measure of accuracy, calculated as the proportion of points that were correctly classified. The AUC is another measure of model accuracy, measured from 0 to 1 with high values indicating better differentiation of positive and negative values. The AUC is calculated as the area under the curve of the ROC- a plot showing the true positive rate on the y-axis and the false positive rate on the x-axis.

Models with mean AUC above 0.8 were integrated in an ensemble using committee averaging to attribute higher weight to better performing models.

We plotted the importance values representing the contribution of each variable to the model and created marginal effect plots for the modelled covariates in the highest performing model ensemble.

Estimating total population living in suitable areas

We calculated the total area suitable for BU, *M. ulcerans*, and the total area suitable for both, and extracted estimates of the population living in each of these areas from a raster (gridded) dataset representing estimated number of people per 1km^2 grid square in 2020 [66].

Results

Datasets of BU occurrence in humans and *M. ulcerans* DNA detection in the environment

The modelled data included 3,700 unique point locations with reported cases of BU in Africa (Fig 1A). BU was confirmed by PCR or histopathology at 1,041 unique locations (Fig 1A). There were 79 unique locations where *M. ulcerans* DNA had been detected by MIRU, VNTR or qPCR (Fig 1B).

The dataset of clinically diagnosed human cases represented 16 countries, mostly in West and Central Africa, with a few in East and southeast Africa. The confirmed cases were restricted to 12 countries in Africa. The distribution of modelled occurrence points is shown in Fig 2. The time period of human case detection was from 1957 to 2019. The median year of diagnosis was 2010. The 91 records of environmental detection of *M. ulcerans* represented four countries: Ghana, Cameroon, Benin and Togo, and covered the period from 2006 to 2018 with a median year of detection of 2013.

Environmental covariates

Maximum temperature and elevation were excluded from the framework for BU modelling as they were collinear with minimum temperature. The aridity index was dropped as it was colinear with precipitation in the wettest quarter. The topographic wetness index was excluded after the initial modelling step as it made a very limited contribution to the models. The model predictors were therefore annual potential evapotranspiration, minimum temperature, precipitation seasonality, precipitation in the wettest quarter, precipitation in the driest quarter, enhanced vegetation index and distances to rivers and streams, water bodies, dams, deforested areas, and agricultural land.

Maximum temperature, elevation and aridity index were also dropped from the *M. ulcerans* modelling framework due to collinearity with minimum temperature. Precipitation seasonality was dropped due to collinearity with precipitation in the driest quarter, and precipitation

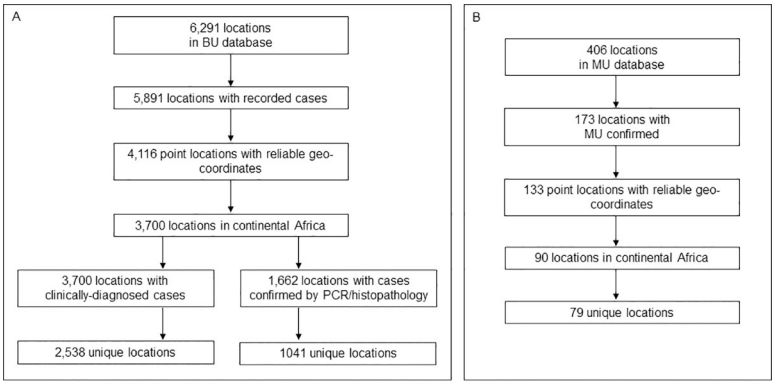

Fig 1. Selection of model occurrence points from Buruli ulcer database. Selection is shown separately for Buruli ulcer occurrences (A) and environmental occurrences of *Mycobacterium ulcerans* DNA.

https://doi.org/10.1371/journal.pntd.0009157.g001

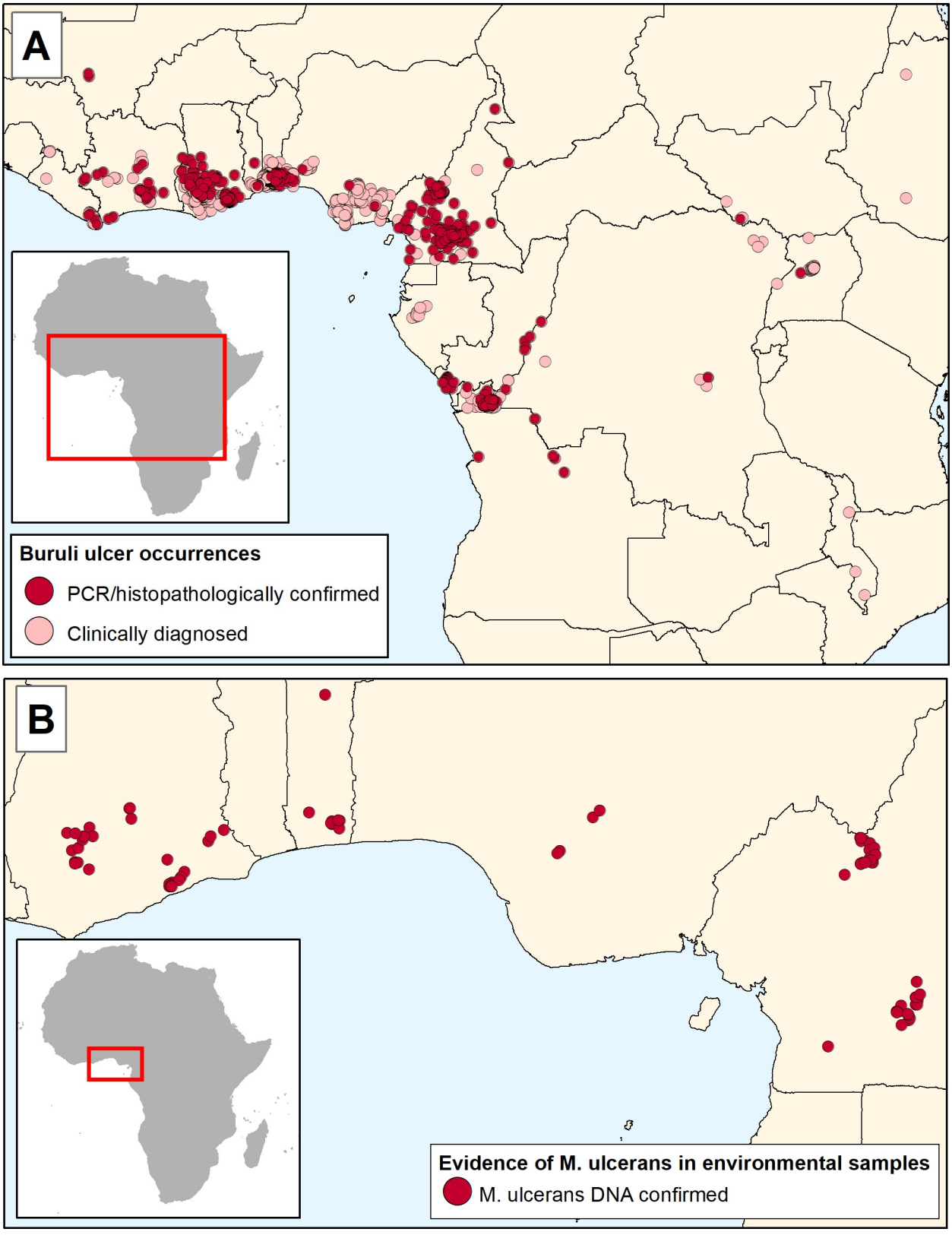

Fig 2. Distribution of occurrence records for environmental modelling of Burli ulcer (BU) and *Mycobacterium ulcerans* (MU) (A) Pink dots represent origins of clinically-diagnosed BU cases, red dots represent confirmed cases. (B) Red dots show locations where *M. ulcerans* DNA has

been isolated from environmental samples and distinguished from DNA from other mycobacteria by multiplex qPCR, or by variable nucleotide tandem repeat, or mycobacterial interspersed repetitive unit typing. All maps were produced in ArcMap 10.7 (ESRI Inc., Redlands CA, USA).

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in the wettest quarter was dropped due to collinearity with minimum temperature. The model predictors were annual potential evapotranspiration, minimum temperature, precipitation in the wettest quarter, enhanced vegetation index, topographic wetness index and distances to rivers and streams, water bodies, dams, deforested areas, and agricultural land.

Environmental suitability for BU

The overall predicted distribution was constrained to humid tropical areas and local scale variation appeared to be driven by hydrological features (Fig 3A). The total area predicted to be suitable for BU was 373,625 km^2, and the total population living in areas predicted suitable was 72.3 million (Table 2). Pockets of suitability for BU were predicted in 19 countries in Africa, including all 14 countries along the west-central African coastline from Guinea to Angola (S1 Maps and S1 Table). Democratic Republic of the Congo had the widest area predicted suitable, followed by Cameroon. Nigeria had the largest population at risk, with 25.4 million predicted to be living in areas suitable for BU, followed by the Democratic Republic of the Congo where 14.6 million were predicted to be living in suitable areas (S1 Table).

The model including all cases of BU (S7 Fig) gave similar results to the model including confirmed cases only. The Pearson coefficient of correlation between the two models was over 0.95.

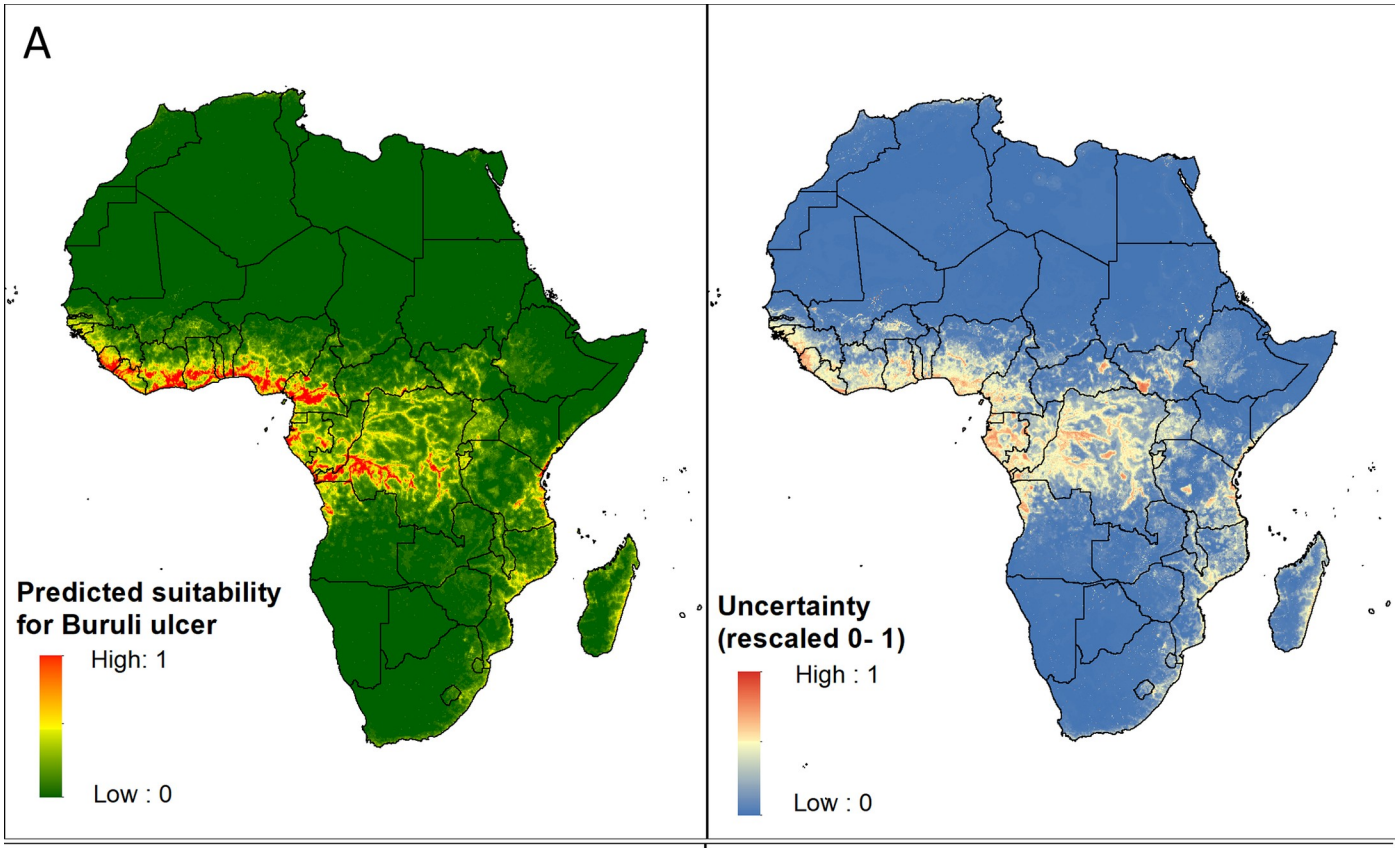
All individual distribution models performed well with AUC values above 0.8 (S8 and S9 Figs). Mean PCC scores were between 77.4 and 92.9% and mean TSS scores were between 0.57 and 0.83. RF models performed best with a mean PCC of 92.9%, a mean TSS of 0.83 and mean AUC 0.97. The final ensemble model showed an overall mean AUC of 0.96 with sensitivity of 91.0% and specificity of 88.7%. The mean TSS was 0.79 and the mean kappa score was 0.80 (Table 1).

Distance to the nearest water body was the strongest contributor to the RF models, explaining 23.8% of variance in the model, followed by potential evapotranspiration, which contributed 19.3% of the variance (S10 Fig). Suitability for BU was highest in areas within 10km of the nearest waterbody, and was limited in areas more than 30km from a waterbody (S11 Fig). Suitability was highest in environments with relatively low potential evapotranspiration (1,200–1,600 mm/month), which correlates with the tropical savanna climate zone [67,68].

Environmental suitability for *M. ulcerans*

The GAM, GBM, MARS and RF models performed well with AUC above 0.8 (S12 and S13 Figs), while the GLM, ANN and MAXENT Phillips models performed less well and were excluded from the ensemble. Mean PCC varied from 0.72–0.83 between models and mean TSS was between 0.34 and 0.66. RF outperformed other algorithms in predicting the occurrence of *M. ulcerans*. The final ensemble model had a mean TSS score of 0.87, with a sensitivity of 92.4 and specificity of 94.4% (Table 1). The mean AUC was 0.98 and the mean kappa score was 0.87.

Distance to deforested areas and potential evapotranspiration were the strongest predictors of *M. ulcerans* occurrence in the RF models, accounting for 28.4% and 28.2% of all variance in the model respectively (S14 Fig). Suitability was predicted to be low in areas more than 30km from any deforested land, and in areas with potential evapotranspiration of >1500mm/month


A
Predicted suitability
for Buruli ulcer
High: 1
Low : 0
Uncertainty
(rescaled 0- 1)
High : 1
Low : 0

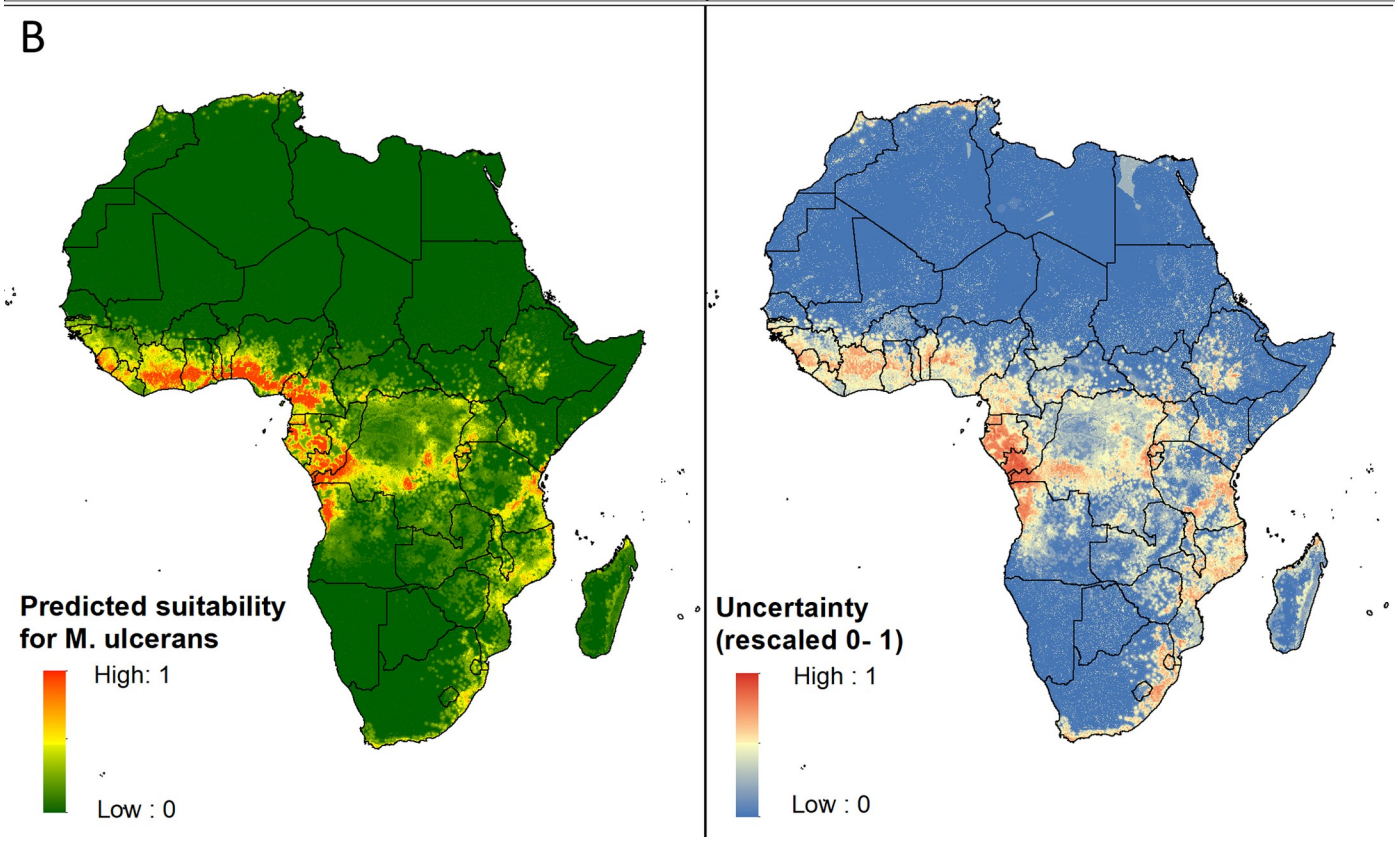

B
Predicted suitability
for M. ulcerans
High: 1
Low : 0
Uncertainty
(rescaled 0- 1)
High : 1
Low : 0

Fig 3. A.) Predicted environmental suitability for the occurrence of BU disease and associated error of prediction. B.) Predicted environmental suitability for the occurrence of *M. ulcerans* in the environment and associated error of prediction. All maps were produced in ArcMap 10.7 (ESRI Inc., Redlands CA, USA).

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(corresponding to more humid regions characterised by higher rainfall and semi-deciduous to tropical forest) (S15 Fig).

The total area predicted to be suitable for *M. ulcerans* was 388,050km^2, and the total population living in areas predicted suitable was 77.0 million (Table 2). Pockets of suitability were predicted in 17 countries (S1 Table). Nigeria had the widest area predicted suitable (85,350km^2) followed by Cameroon (66,300km^2). The highest population living in suitable areas was in Nigeria (33.1 million).

Overlap of suitability for BU and *M. ulcerans*

The total area predicted to be suitable for both BU and *M. ulcerans* was 163,225km^2, with 46.1 million people predicted to be living in areas at risk. There were some differences in the extents of the areas predicted suitable for BU disease and environmental *M. ulcerans* (Fig 4). There were wide areas predicted suitable for *M. ulcerans* but not for BU disease, mostly located around the periphery of known endemic foci in west African countries. There were patches of predicted suitability for BU but not *M. ulcerans* in DRC, Sierra Leone, Liberia and other countries in West Africa. The highest populations living in areas predicted suitable for both BU and *M. ulcerans* were in Nigeria and DRC, with 18.0 and 10.1 million respectively at risk.

Discussion

We have used ecological niche modelling to identify environmental factors associated with the occurrence of Buruli ulcer and its causative agent *M. ulcerans*, and to predict environmental suitability for the disease and bacterium across continental Africa. Incorporating existing data on BU distribution at multiple spatial levels and a set of relevant environmental covariates, the resulting maps represent evidence-based predictions which are intended to guide future surveillance for BU.

The model predictions were broadly consistent with the recognised distribution of BU in Africa [9]. We identified pockets of suitability for BU in patchy foci throughout the known-endemic range of the disease, particularly in the tropical zones of countries around the Gulf of Guinea. Suitability was also predicted in a number of regions not previously recognised as endemic, particularly in Sierra Leone, the north-west coast of Liberia, and parts of southern Nigeria. Wide areas of suitability were predicted beyond the known foci of BU in DRC, particularly along the Kasai river basin in the central-west region of the country. In Gabon, an extended focus of suitability was predicted towards the mouth of the Ogooue River. Several cases of BU have been reported from this area [69], but were not included in the main model presented here as they were not confirmed by PCR or histopathological analysis. A further

Table 1. Validation metrics for ensemble models for BU and *M. ulcerans* suitability.

		Mean	Lower CI	Upper CI
BU suitability	TSS	0.783	0.793	0.796
	AUC	0.964	0.964	0.965
	kappa	0.795	0.788	0.795
MU suitability	TSS	0.867	0.867	0.879
	AUC	0.983	0.983	0.984
	kappa	0.866	0.866	0.873

https://doi.org/10.1371/journal.pntd.0009157.t001

Table 2. Total area predicted suitable and population in areas at risk for Buruli ulcer, M. ulcerans, and both, in Africa.

	Total area suitable (km^2)	*Lower bound*	*Upper bound*	Population in suitable areas	*Lower bound*	*Upper bound*
BU	373,625	*283,275*	*498,550*	72,341,372	*55,617,280*	*90,689,787*
MU	388,050	*265,375*	*556,225*	77,026,709	*63,307,468*	*93,791,018*
BU & MU	163,225	*104,575*	*245,675*	46,120,259	*34,963,000*	*58,963,221*

Suitability for BU and *M. ulcerans* is shown by country in S1 Maps.

https://doi.org/10.1371/journal.pntd.0009157.t002

Gabonese focus was predicted in-land, in the south east of the country, which has no previous evidence of cases. Restricted foci of suitability were predicted in Equatorial Guinea, corresponding to the origin of cases diagnosed by an expert in BU between 1995 and 2005 [70,71], although the country has no evidence of cases reported in peer-reviewed literature.

There were also regions predicted unsuitable by the models where empirical evidence suggests previous cases. There are several possible reasons for these discrepancies. Some locations in northern Cameroon with evidence of PCR-confirmed BU were found to be unsuitable for the disease. Given the great volume of surveillance data collected by the well-established BU control programme in Cameroon, some patients are likely to have been diagnosed outside the region where they acquired the disease [72], and we consider it plausible that some regions where BU has been recorded are not actually suitable for transmission. The model did not predict occurrence of BU or *M. ulcerans* within the early BU foci in Uganda and northern DRC [46,73–75], or in South Sudan where cases were reported in the early 2000's [76], although moderate suitability was predicted around these areas. This discrepancy may indicate that these foci were associated with transient factors which are no longer locally prevalent, or that the model lacks sensitivity in areas with sparse occurrence points. The fact that these models

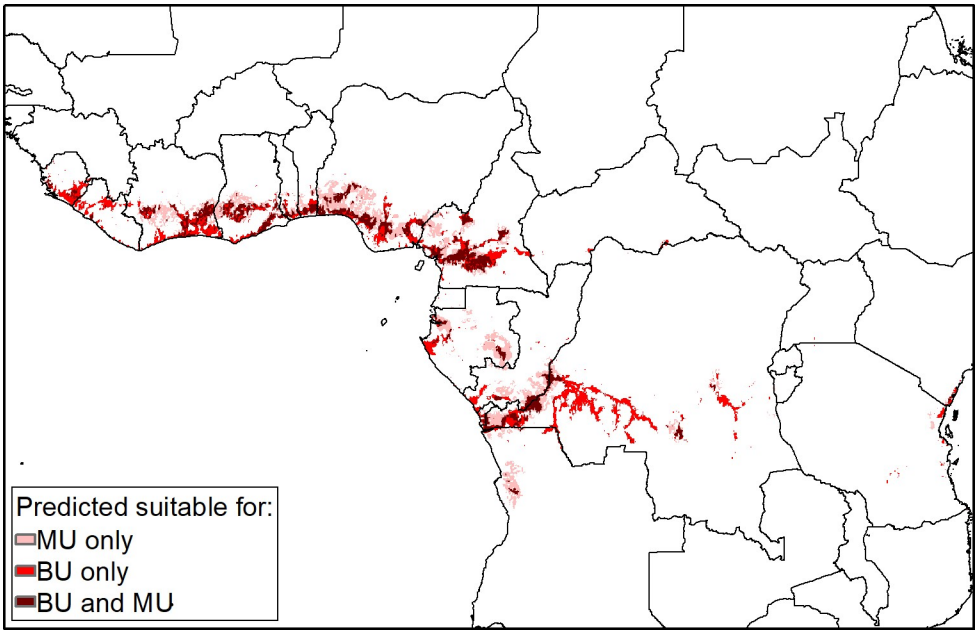

Fig 4. Predicted overlap of environmental suitability for BU and of M. ulcerans occurrence. Pink colour represents areas where Mycobacterium ulcerans (MU) is predicted to occur based on the optimal threshold of environmental suitability (0.56) but where Buruli ulcer (BU) is not predicted. Red represents areas where BU is predicted based on the optimal threshold of environmental suitability (0.51) but MU is not. Both BU and MU are predicted to occur in areas shown in dark red. All maps were produced in ArcMap 10.7 (ESRI Inc., Redlands CA, USA).

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do not include a temporal component limits their usefulness for understanding drivers of the emergence (and disappearance) of BU. Since the number of geo-located confirmed occurrences and availability of data on spatial covariates prior to 1991 was limited, we were not able to stratify the analysis by time period.

Cases of BU have recently been reported in Senegal [77,78] and Madagascar [79], where occurrence was not predicted by the model. Assuming these recent cases represent true instances of autochthonous transmission of *M*. *ulcerans*, this demonstrates a limitation of these models in their ability to predict emergent foci in regions that are environmentally distinct from known-endemic areas. Incorporating new data, particularly those originating from new-endemic or newly recognised endemic areas, will help to improve the generalisability of the models in the future.

Although we intend these models to be used as predictive rather than explanatory tools, the environmental associations we identified have relevance to understanding the ecological niche and transmission of *M*. *ulcerans*. We emphasise that the covariates we included should be viewed as associated, rather than causal factors. Both BU and *M*. *ulcerans* were constrained to tropical climate zones [68] due to sensitivity to potential evapotranspiration, temperature, and precipitation indicators. These findings fit with the current understanding of the distribution of BU in Africa and support evidence for a different epidemiology of the disease in Africa compared to endemic areas of temperate Australia and Japan [80]. Previous evidence suggests that the strain of *M*. *ulcerans* which causes BU in Japan may be adapted to cooler climates [80], while in Australia there is evidence for an important role of terrestrial mammals [81]. The existence of mammalian reservoirs may enable the disease to emerge in climates which are unfavourable for maintenance of bacterial populations in the abiotic environment. Importantly, this does not rule out the possibility of an animal reservoir for BU in [82] Africa [83], since the range of suitability predicted by these models may illustrate the ecological niche of a different reservoir taxon.

We identified a number of human-influenced variables as predictors of *M*. *ulcerans* occurrence, and to a lesser extent, BU occurrence. Variables such as distance to deforested areas, dams, and agricultural land, and the enhanced vegetation index are expected to show greater temporal variation than bioclimatic factors, and as such may be more relevant to understanding drivers of change in the distribution of BU. Environmental disturbance has been postulated as a driver of BU emergence [84], and higher rates of disease have been reported in agricultural areas on the peripheries of forests [85]. Local-scale variation in these factors resulted in a patchy distribution of predicted suitability, consistent with our understanding of the epidemiology of BU, which is recognised to be highly focal in endemic settings [86].

Although the models we developed were designed to represent the ecological niche of *M*. *ulcerans* and BU, many aspects of the ecology and transmission of the bacterium were not represented. The models we developed were 'black-box' type representations which risk oversimplifying the process of disease transmission as they do not account for ecological complexities including the behaviour and demography of hosts and interactions between host species [87]. Since these components of BU transmission are currently not well understood, we were limited to assuming that the observed occurrences of *M*. *ulcerans* and BU would adequately represent the outcomes of these interactions [87]. However, the more general prediction of suitability has practical applications in informing surveillance efforts, even if it does not enable precise estimation of transmission risk.

The available dataset of locations where *M*. *ulcerans* DNA was detected in the environment was restricted, including only 79 unique locations in four countries, and cannot be expected to represent all environmental conditions where the bacterium occurs. The limited coverage of *M*. *ulcerans* data points is a potential source of bias, since the *M*. *ulcerans* models may be less

restrictive than those for BU, potentially explaining the wider predicted occurrence of *M. ulcerans*. The scale of analysis (grid cells at 5km x 5km) may have also limited our ability to quantify the effect of predictors varying over small geographical scales and to capture fine scale variation in environmental suitability for BU. The models predicted large contiguous areas of suitability in areas with suitable conditions, particularly in West Africa. Such areas may be suitable in reality, but exhibit an uneven distribution of disease due to factors not included in our models.

Despite these limitations, the suitability maps provide a delineation of areas potentially at risk for BU beyond what is known from the distribution of reported cases, currently the basis for targeting of surveillance and control. Given the recognised scale of underreporting of BU [9], the current approach is likely to exclude cases outside of known disease foci, and we suggest that areas predicted suitable for BU and *M. ulcerans* should be considered as targets for case finding activities, with the aim of identifying unrecognised foci and patients not known to the health system. Based on the wide areas of suitability predicted by this work and existing evidence of under-reporting of BU [88], the south of Nigeria would be a key target for case finding activities. The foci predicted in Gabon, Equatorial Guinea and Sierra Leone, associated with limited evidence of previous cases, would also be targets for further investigation. We note however, that predictions in these regions (not represented by occurrences included in the model) were associated with high levels uncertainty, which should be considered in the design of any future surveys.

Using the model predictions to inform the design of cross-sectional surveys for BU could improve the efficiency of such surveys. In a nationwide survey for podoconiosis in Cameroon, the selection of survey communities was stratified according predicted suitability for the disease based on a model trained mainly using data from Ethiopia [89]. This survey identified higher rates of podoconiosis in communities that were predicted suitable, implying a benefit in terms of the cost per case identified, compared to a survey employing random selection of survey communities. Another mechanism to improve cost effectiveness may be to combine the predictions from these models with models for other diseases in order to target integrated surveys for rare outcomes [90].

In conclusion, we have identified areas of high suitability for BU and *M. ulcerans* within known endemic-areas, and in areas not currently recognised as endemic, but with evidence of possible undiagnosed or misdiagnosed BU. The population at highest risk of BU is within areas where BU and *M. ulcerans* niches overlap, comprising over 46 million people in 2020. The focal nature of BU distribution, the recognised scale of under-detection, and the impact of late diagnosis on disease severity strongly suggest a targeted approach to active case finding as a means to control this disease. The fine-scale, evidence-based predictions presented here could provide a tool to target such efforts, which will improve our understanding of the burden and distribution of the disease and help to increase the proportion of cases linked to treatment.

Supporting information

S1 Maps. Predicted environmental suitability for the occurrence of BU disease and *M. ulcerans* in the environment, in countries predicted to be suitable.
(PDF)

S1 Text. Selection of background and pseudoabsence points.
(DOCX)

S2 Text. Environmental variables used in modelling, including potential environmental predictors and their sources and the covariates that were included in the models of BU and

***M. ulcerans* suitability.**
(DOCX)

S1 Fig. Distribution of PCR and histopathologically confirmed BU cases, by year of diagnosis.
(TIF)

S2 Fig. Distribution of clinically diagnosed BU cases, by year of diagnosis.
(TIF)

S3 Fig. Selection of pseudoabsence points included in Buruli ulcer suitability models. Pseudoabsence points were selected outside of the BU surface range envelope (white; the area containing values between the 2.5th and 97.5th percentile of all predictor variables) and selection was biased according to the strength of evidence for BU at national or subnational level (yellow to blue shading) using results from Simpson et al. Lancet Glob. Health 2019.
(TIF)

S4 Fig. Selection of pseudoabsence points included in *Mycobacterium ulcerans* suitability models. Pseudoabsence points were selected outside of the MU surface range envelope (white; the area containing values between the 2.5th and 97.5th percentile of all predictor variables) and selection was biased according to the strength of evidence for BU and MU at national or subnational level (yellow to blue shading) using results from Simpson et al. Lancet Glob. Health 2019.
(TIF)

S5 Fig. Distribution of background points used in Buruli ulcer suitability models. Background points were restricted to a minimum distance of 10km from human occurrence points (not shown on the map) and were selected with probability defined by the kernel density surface representing the density of occurrence points.
(TIF)

S6 Fig. Distribution of background points used in *Mycobacterium ulcerans* suitability models. Background points were restricted to a minimum distance of 10km from human or environmental occurrence points (not shown on the map) and were selected with probability defined by the kernel density surface representing the density of occurrence points.
(TIF)

S7 Fig. Predicted environmental suitability for the occurrence of BU disease and associated error of prediction, including all clinically diagnosed cases of BU.
(TIF)

S8 Fig. Individual model performance evaluation statistics for models of environmental suitability for Buruli ulcer. Performance evaluated in terms of the mean true skill statistic (TSS) and the mean area under the curve (AUC) of the receiver operation characteristic.
(TIF)

S9 Fig. Individual model performance evaluation statistics for models of environmental suitability for Buruli ulcer. Performance evaluated in terms of accuracy (percent correctly classified) and the mean area under the curve (AUC) of the receiver operation characteristic. Individual model algorithms: ANN = artificial neural networks; GAM = generalized additive models; GBM = generalized boosted regression models; GLM = generalized linear models; MARS = multiple adaptive regression splines; MAXENT. Phillips = maximum entropy;

RF = random forest.
(TIF)

S10 Fig. Variable importance plots of the contribution of environmental covariates to random forest models of suitability. Shows contribution of variables to model for Buruli ulcer. Blue bars = variables selected as predictors of BU occurrence and *M. ulcerans* in the environment. Orange bars = variables selected as predictors of Buruli ulcer (BU) occurrence only.
(TIF)

S11 Fig. Marginal effect plots showing the relationship between environmental covariates and suitability for Buruli ulcer and *Mycobacterium ulcerans* in random forest models. Marginal Effect of Environmental Predictors on Environmental Suitability for Buruli ulcer
(TIF)

S12 Fig. Individual model performance evaluation statistics for models of environmental suitability for *Mycobacterium ulcerans*. Performance evaluated in terms of the mean true skill statistic (TSS) and the mean area under the curve (AUC) of the receiver operation characteristic.
(TIF)

S13 Fig. Individual model performance evaluation statistics for models of environmental suitability for *Mycobacterium ulcerans*. Performance evaluated in terms of accuracy (percent correctly classified) and the mean area under the curve (AUC) of the receiver operation characteristic. Individual model algorithms: ANN = artificial neural networks; GAM = generalized additive models; GBM = generalized boosted regression models; GLM = generalized linear models; MARS = multiple adaptive regression splines; MAXENT. Phillips = maximum entropy; RF = random forest.
(TIF)

S14 Fig. Variable importance plots of the contribution of environmental covariates to random forest models of suitability. Shows contribution of variables to model for *Mycobacterium ulcerans*. Blue bars = variables selected as predictors of BU occurrence and *M. ulcerans* in the environment Green bars = variables selected as predictors of *M. ulcerans* in the environment only
(TIF)

S15 Fig. Marginal effect plots showing the relationship between environmental covariates and suitability for Buruli ulcer and *Mycobacterium ulcerans* in random forest models. Marginal Effect of Environmental Predictors on Environmental Suitability for *Mycobacterium ulcerans*. Variables are plotted in order of their contribution to the random forest model. Marginal effect plots illustrate the effect of each explanatory variable on the outcome of suitability for Buruli ulcer. Variables are plotted in order of their contribution to the random forest model. *Interpretation of Enhanced Vegetation Index: low values (0.1–0.15) represent areas of barren rock or sand and built-up land; moderate values (0.15–0.3.5) may indicate shrubs, grassland or cropland; higher values (0.35–0.6) may indicate mixed wood and shrubs or open forest.
(TIF)

S1 Table. Total area predicted suitable and population living in suitable areas for Buruli ulcer, *M. ulcerans*, and both, by country in African continent. WM = weighted mean prediction across final ensemble model; LB = lower bound of prediction; UB = upper bound of prediction BU = Buruli Ulcer; MU = Mycobacterium ulcerans; CAR = Central African Republic;

DRC = Democratic Republic of the Congo
(XLSX)

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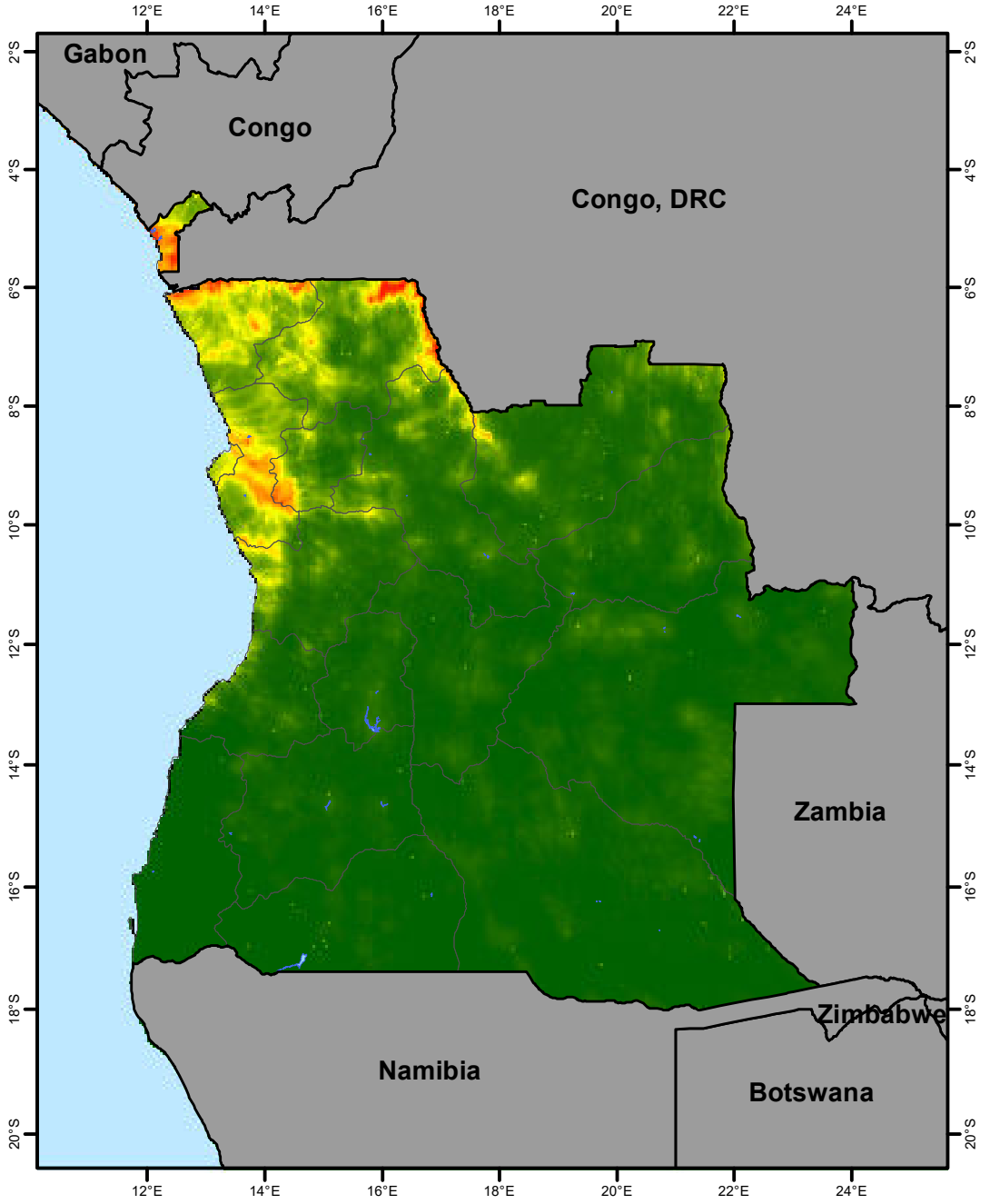
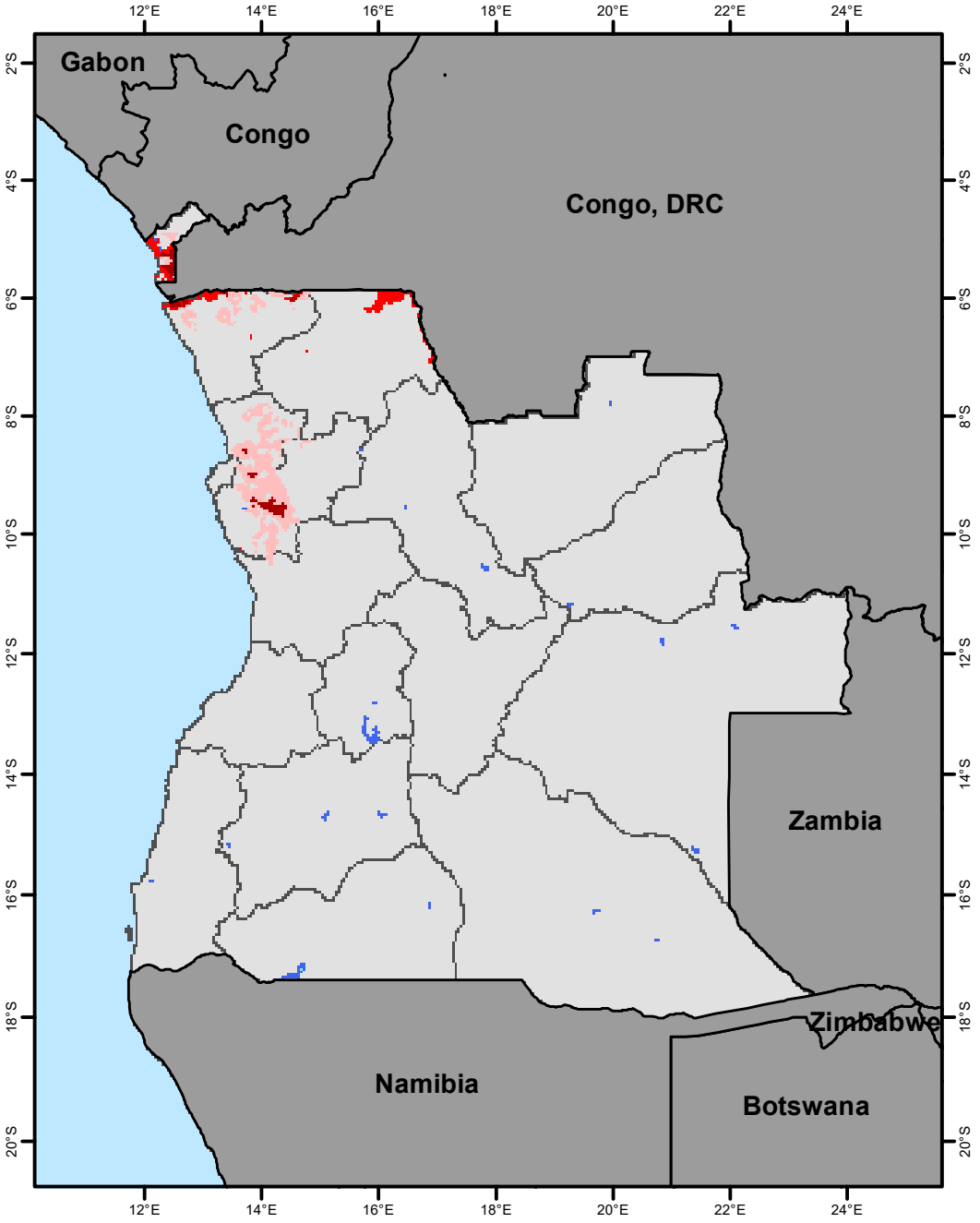
Angola





Environmental Suitability for Buruli ulcer

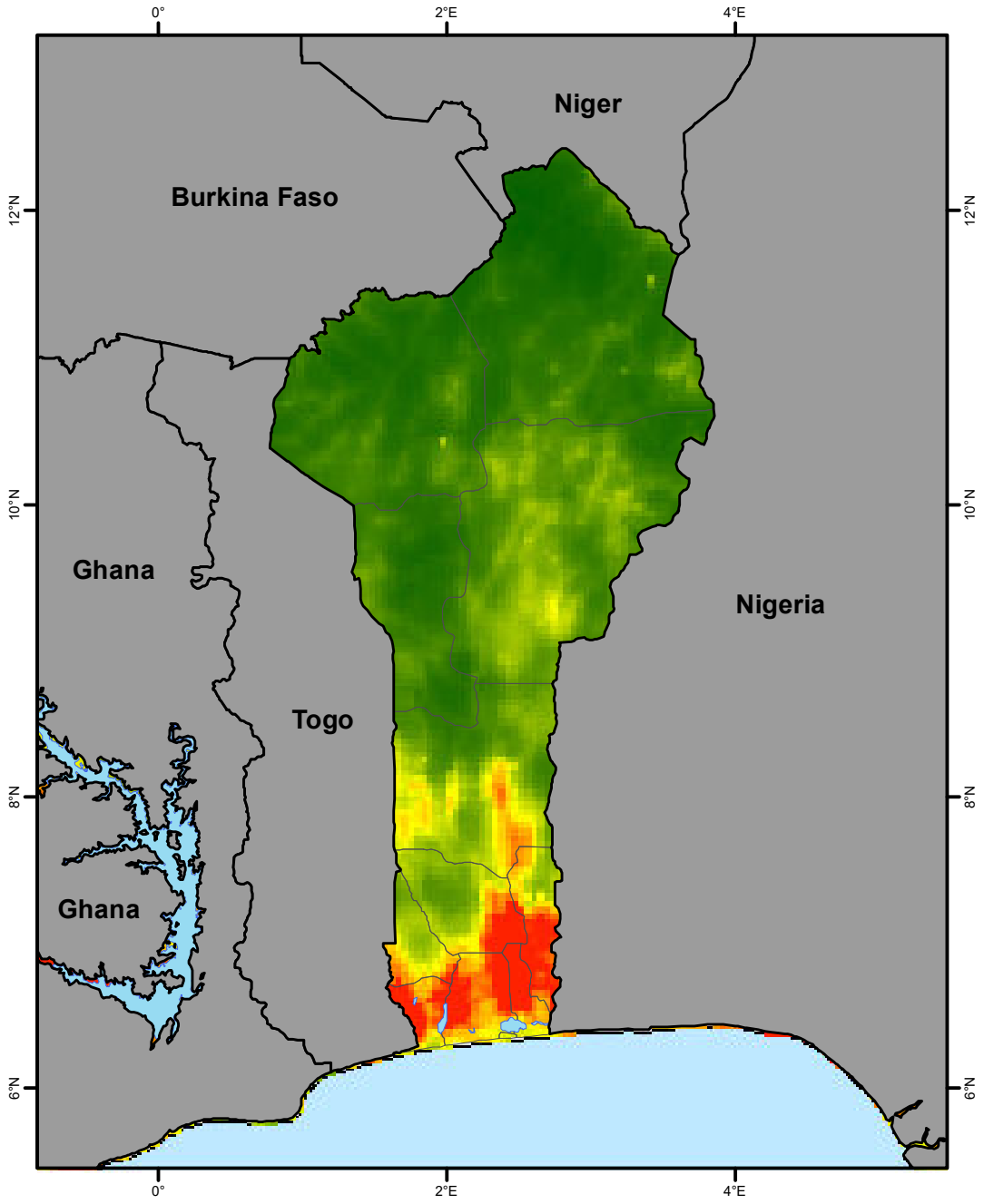
Low : 0 — High : 1

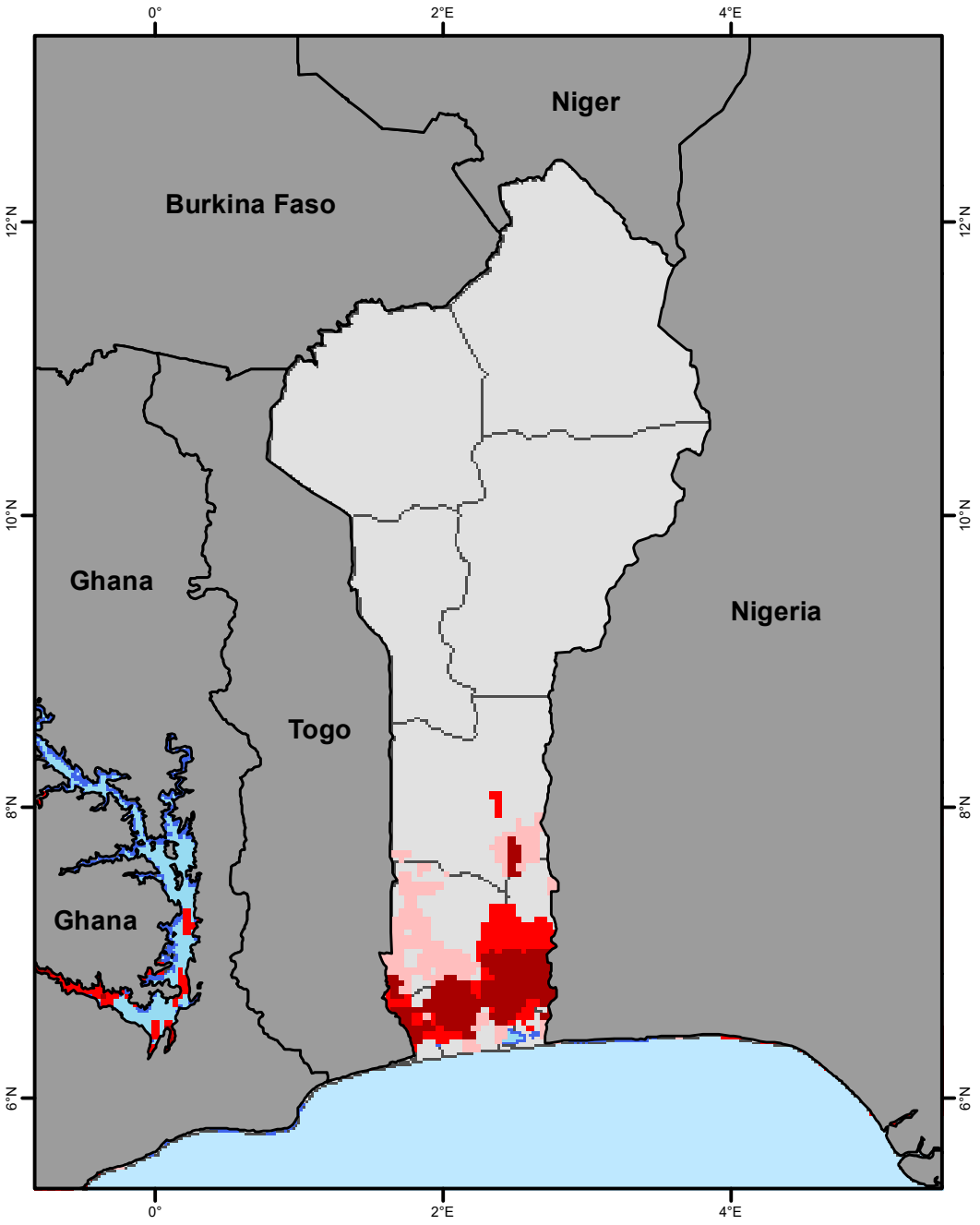
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Benin





Environmental Suitability for Buruli ulcer

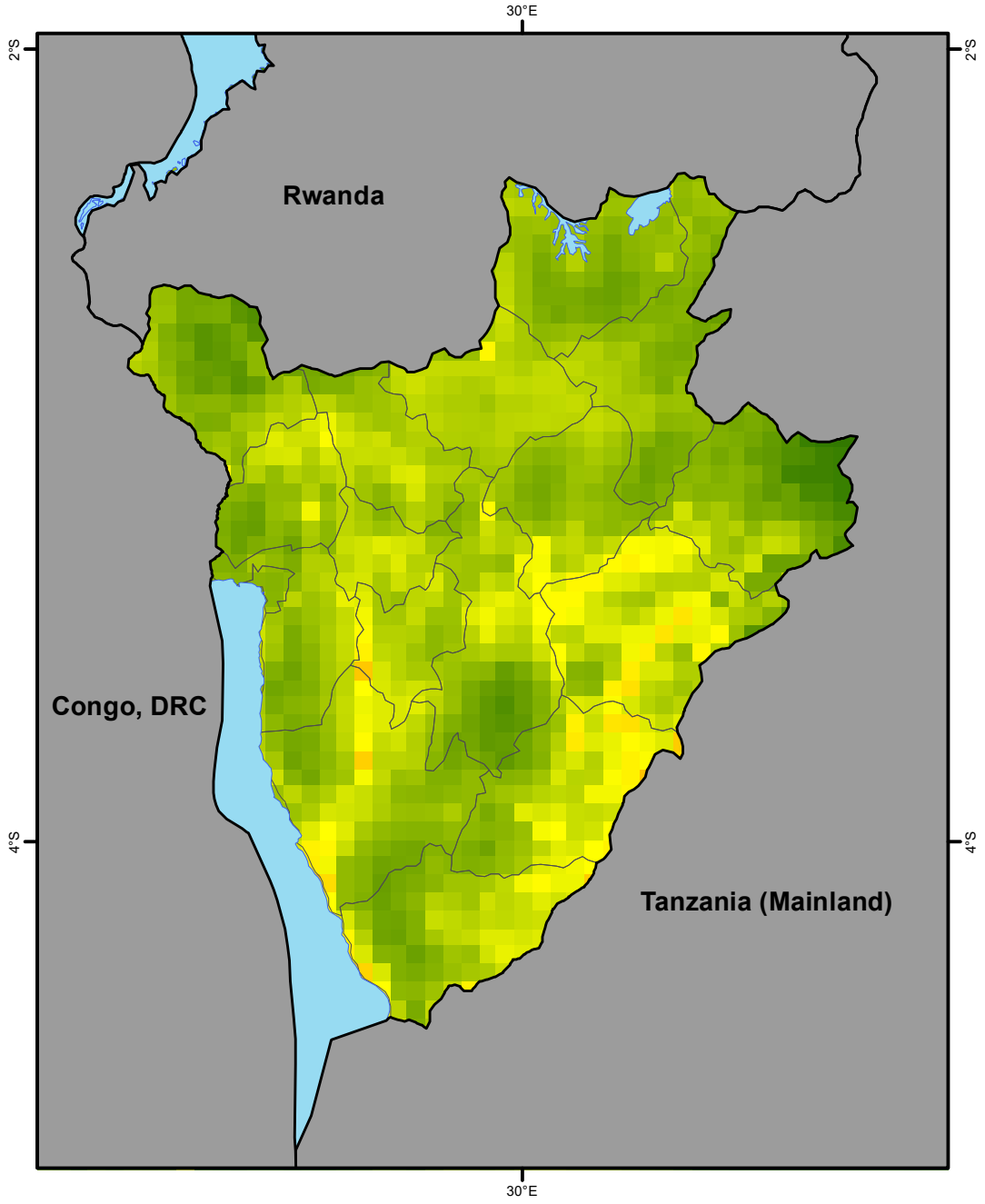
Low : 0 — High : 1

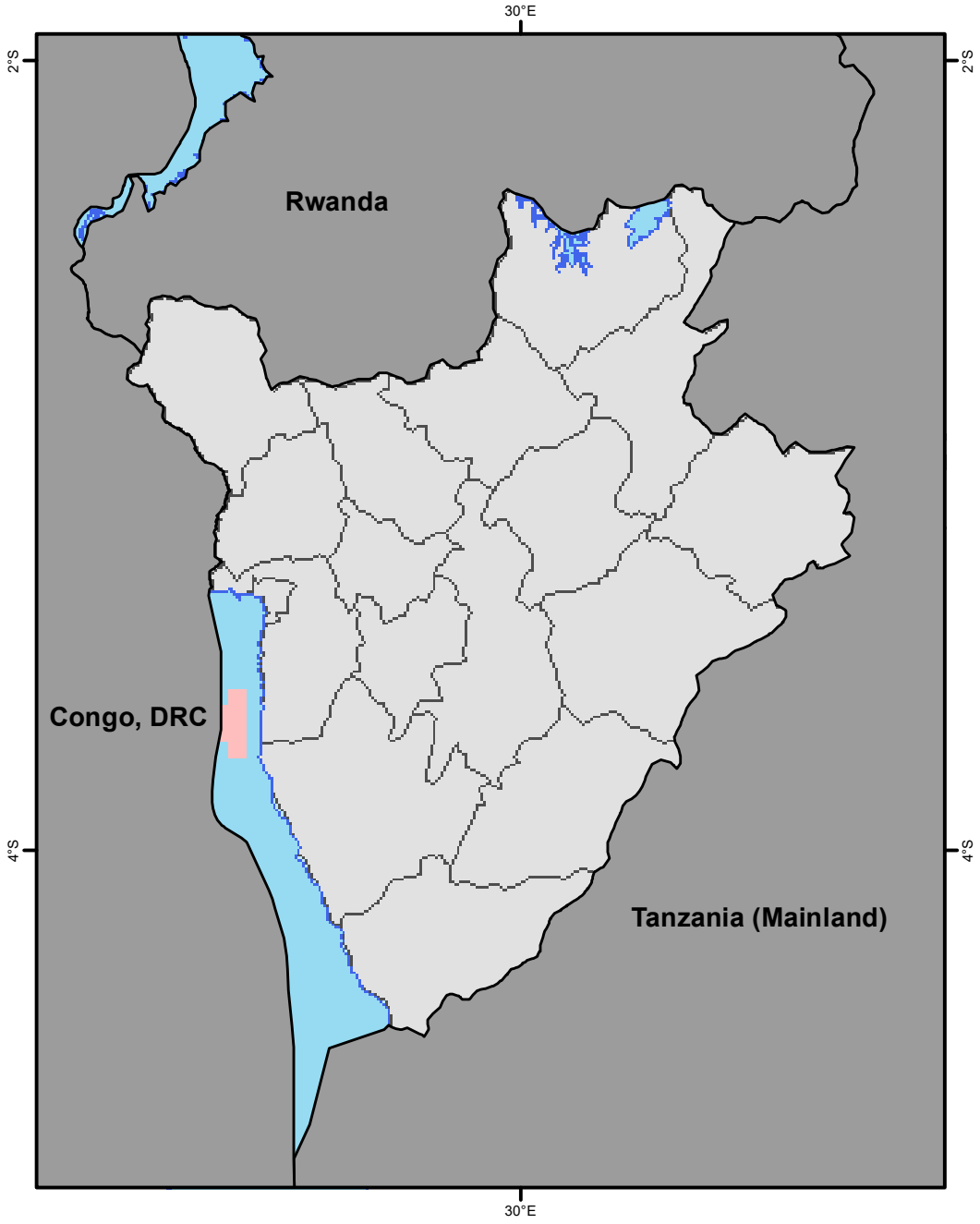
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Burundi





Environmental Suitability for Buruli ulcer

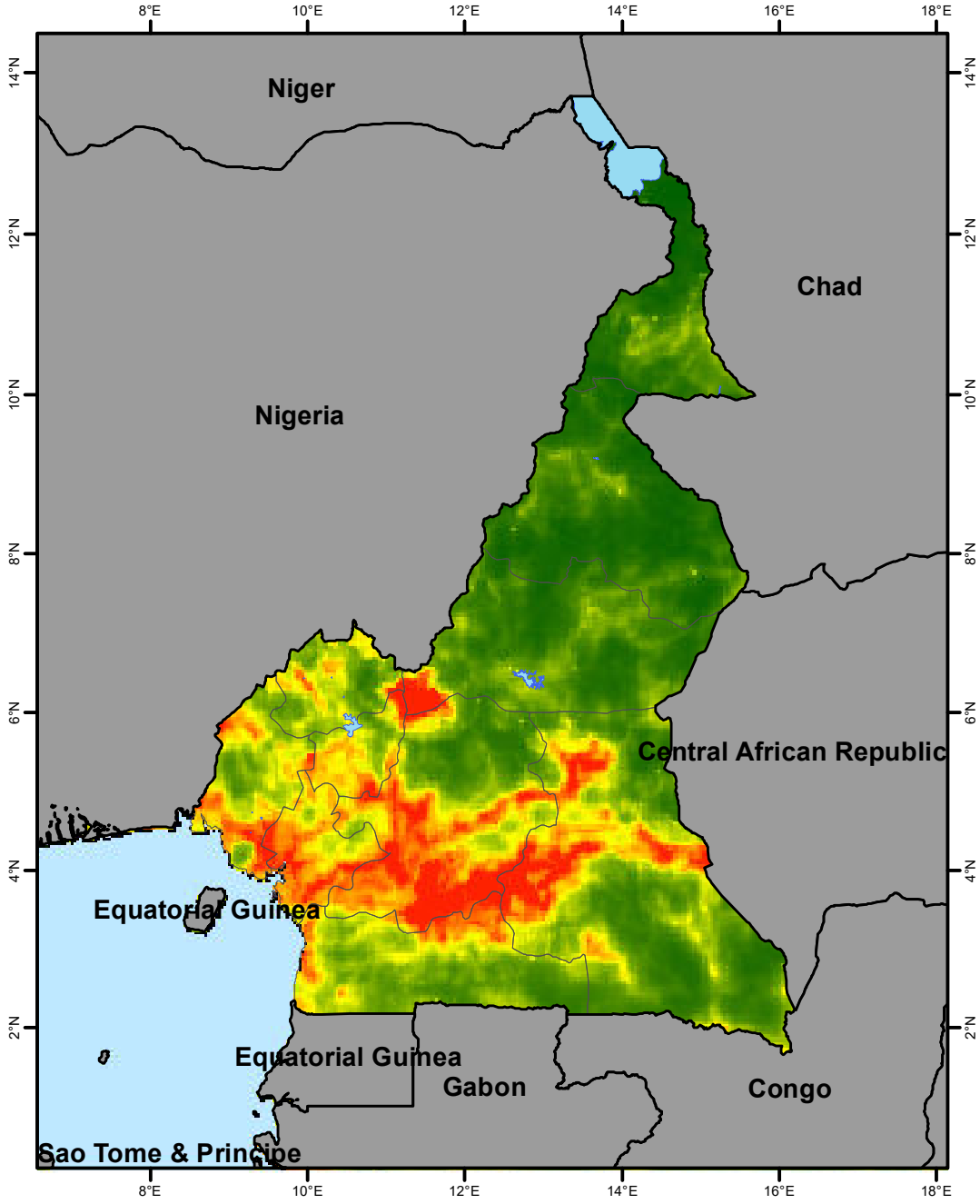
Low : 0 — High : 1

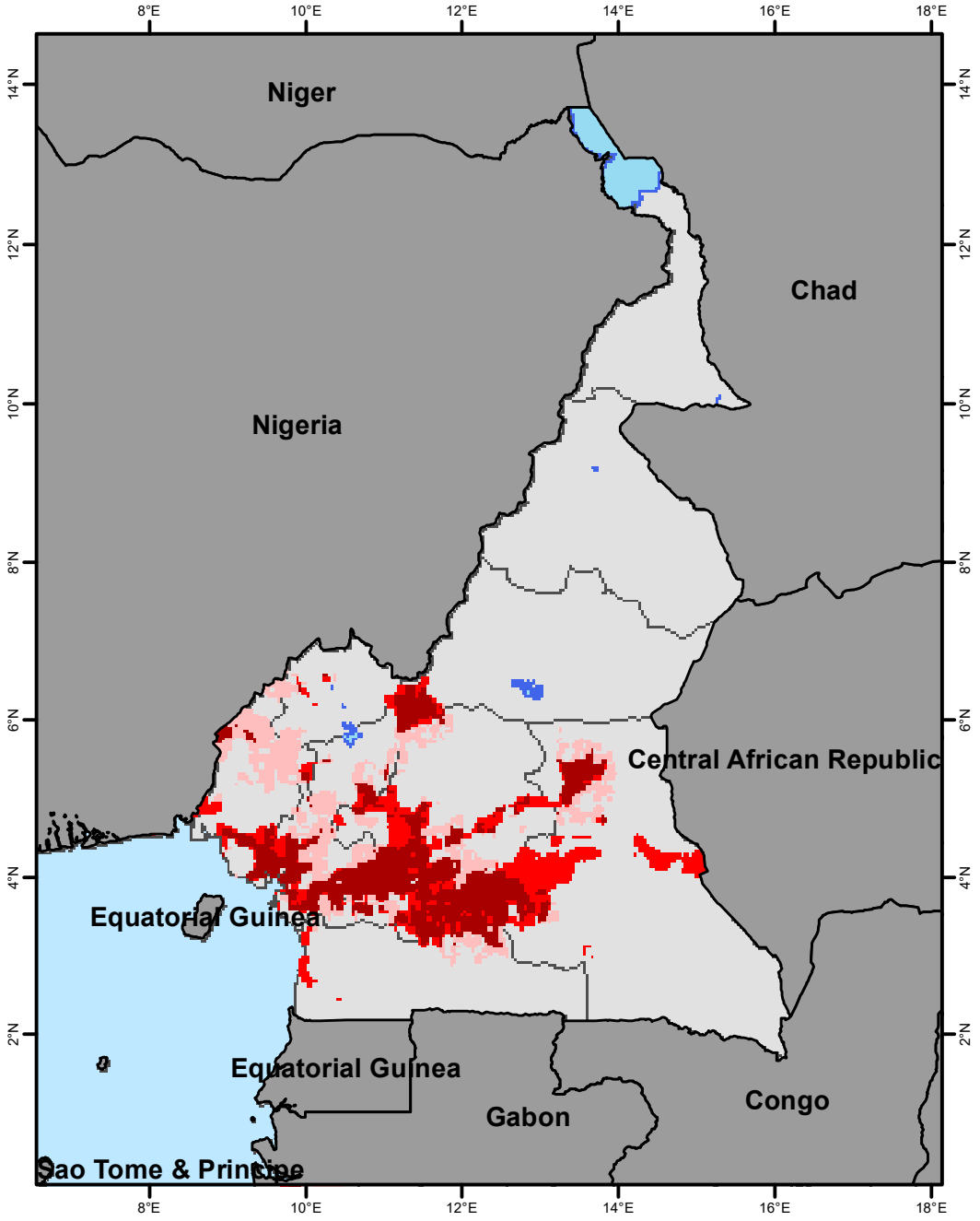
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Cameroon





Environmental Suitability for Buruli ulcer

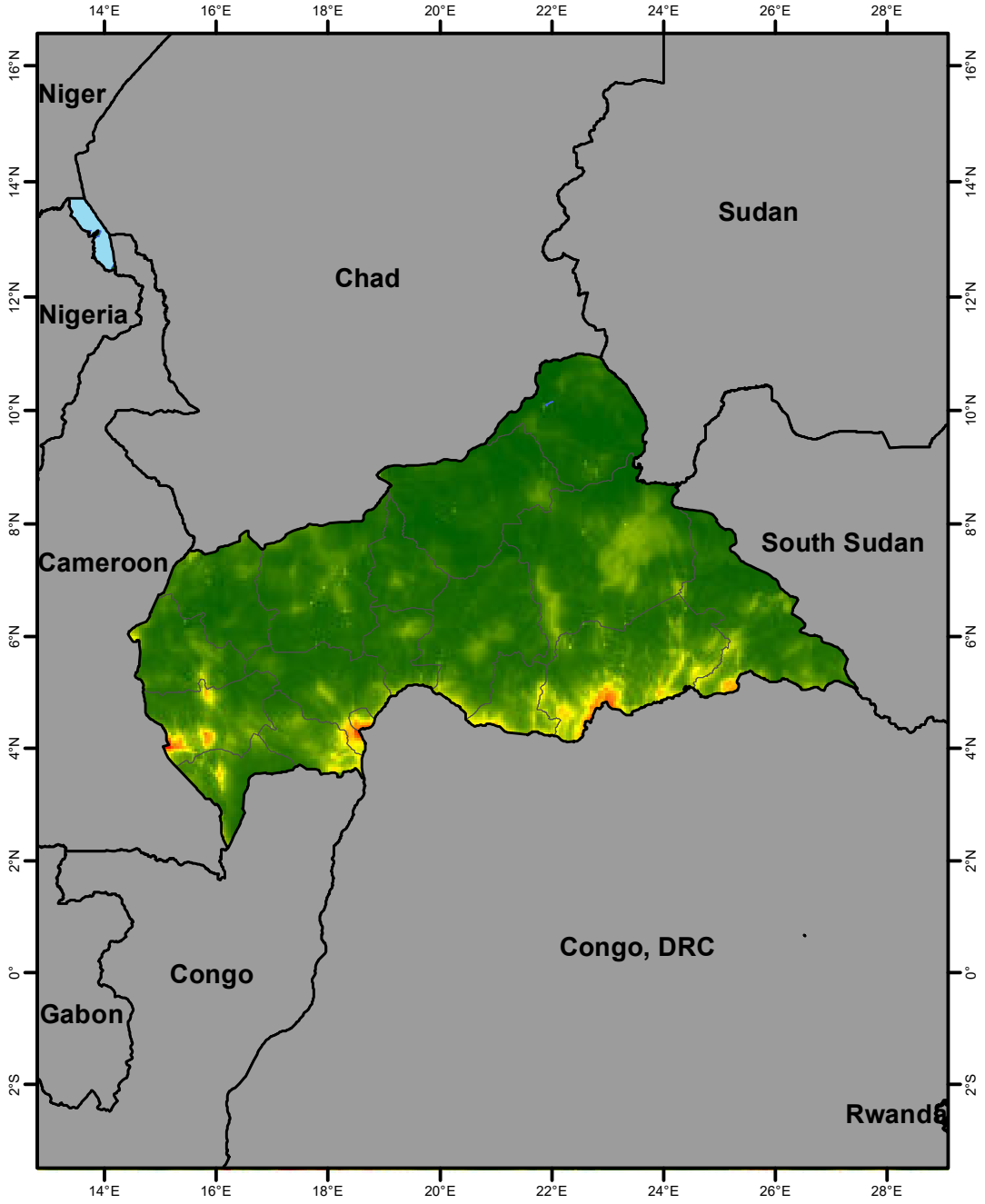
Low : 0 — High : 1

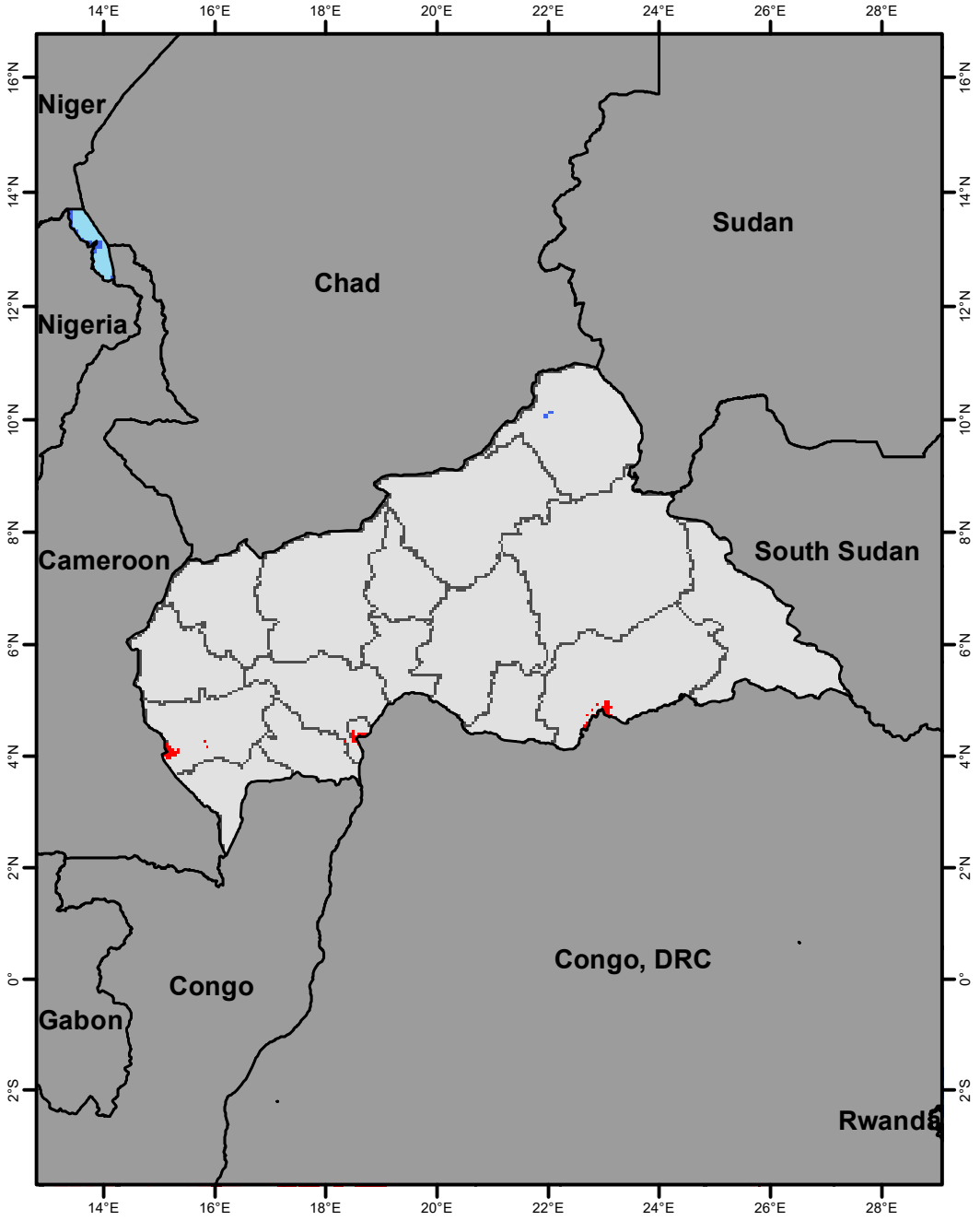
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Central African Republic





Environmental Suitability for Buruli ulcer

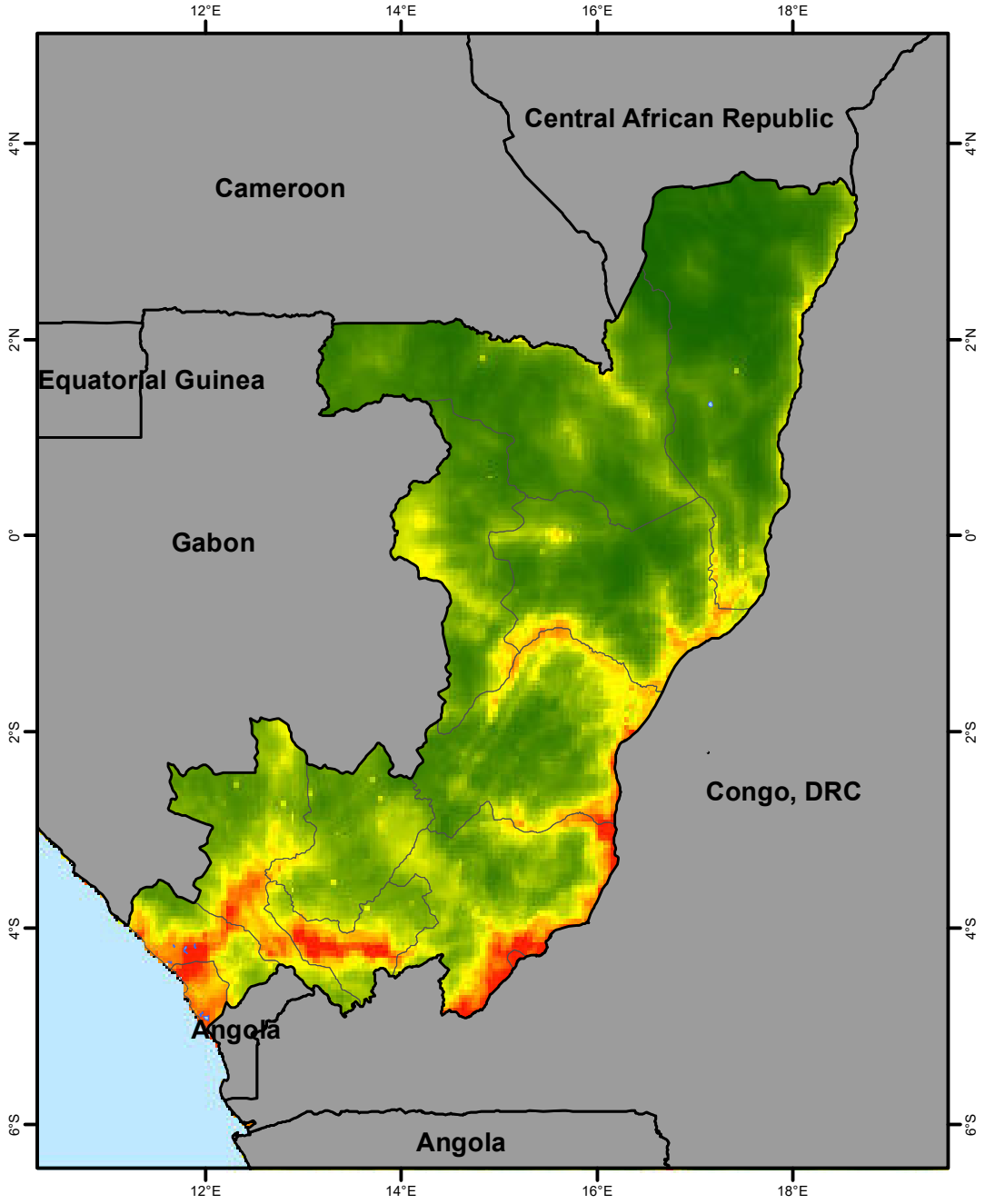
Low : 0 — High : 1

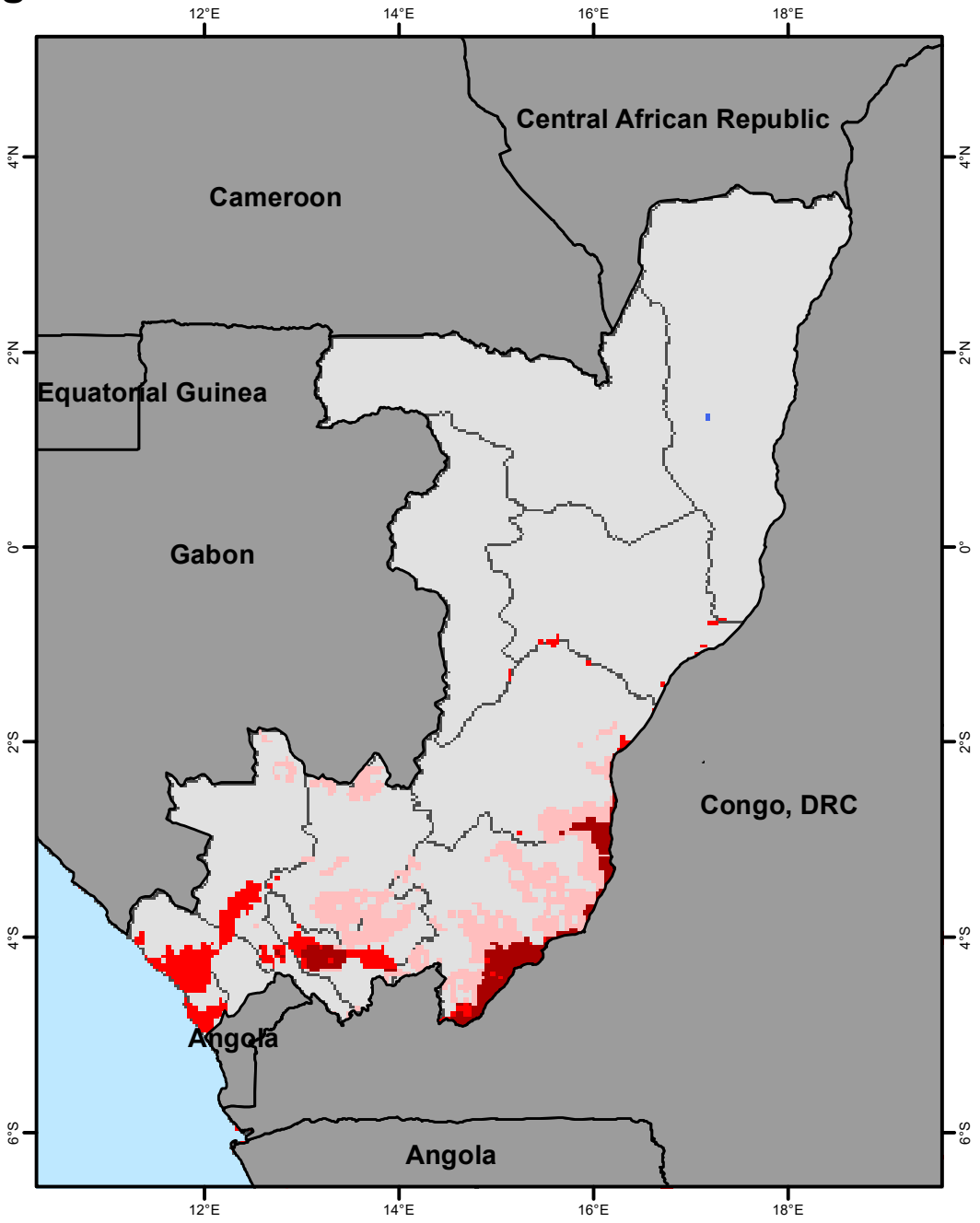
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Congo





Environmental Suitability for Buruli ulcer

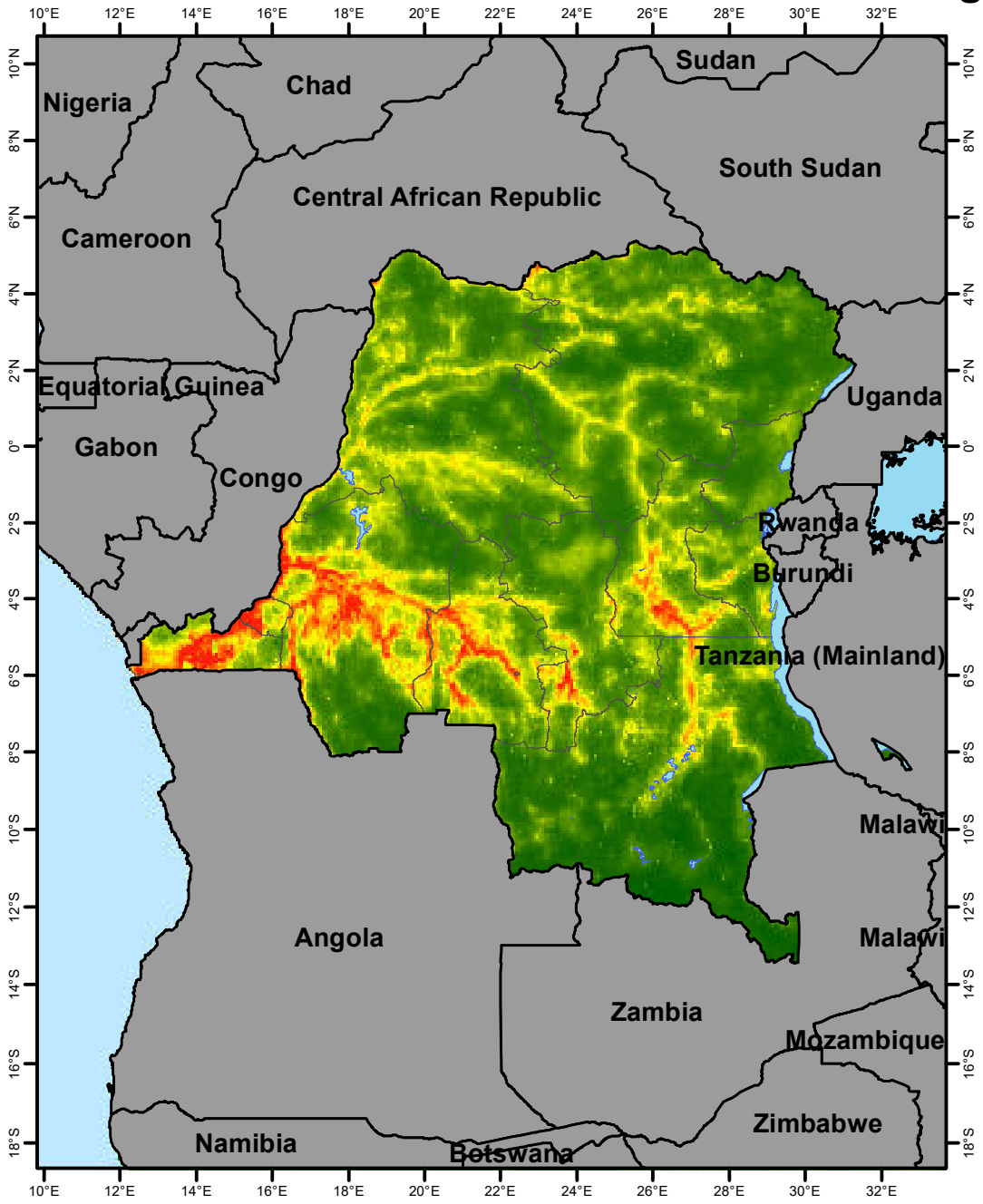
Low : 0 — High : 1

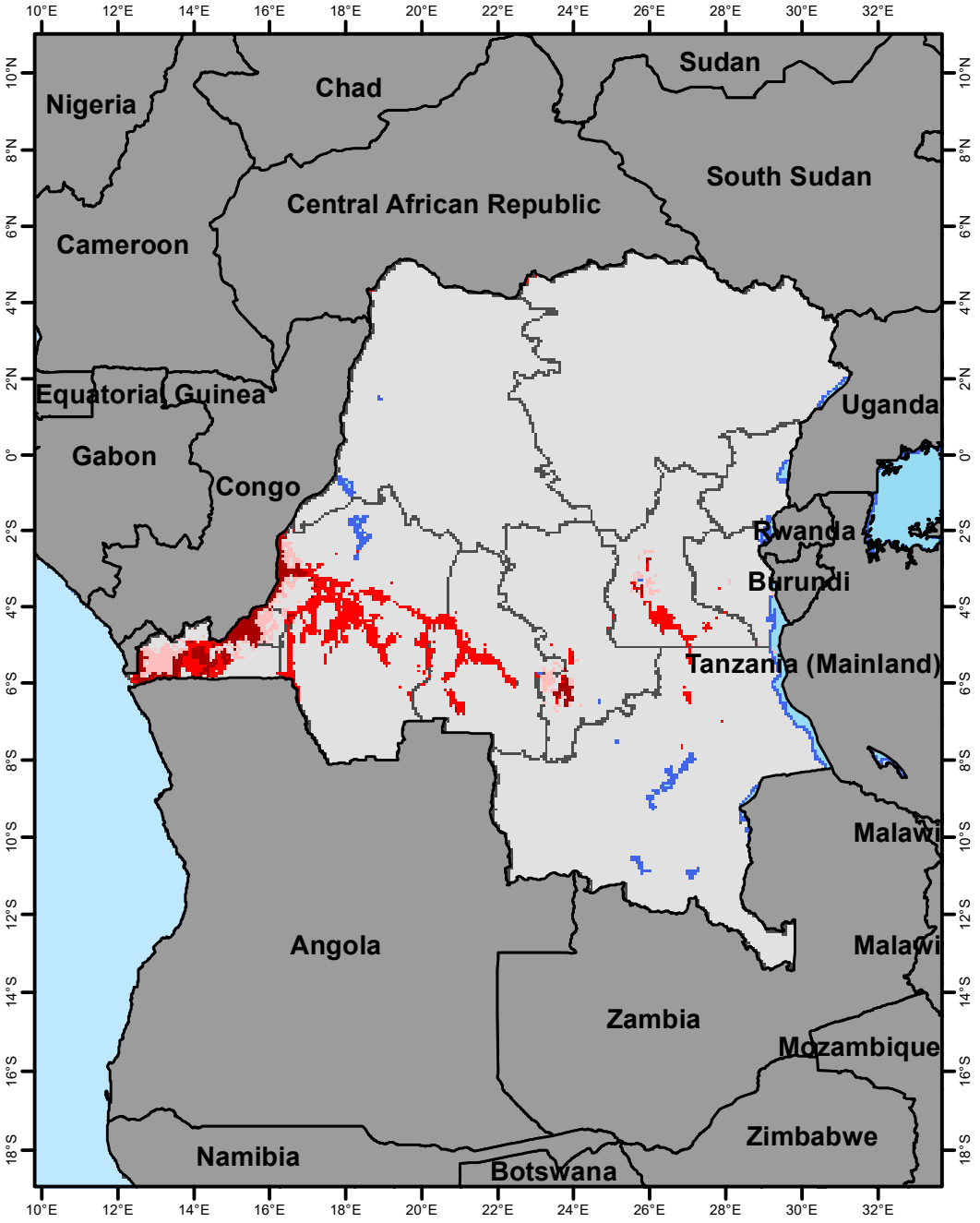
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Congo, DRC





Environmental Suitability for Buruli ulcer

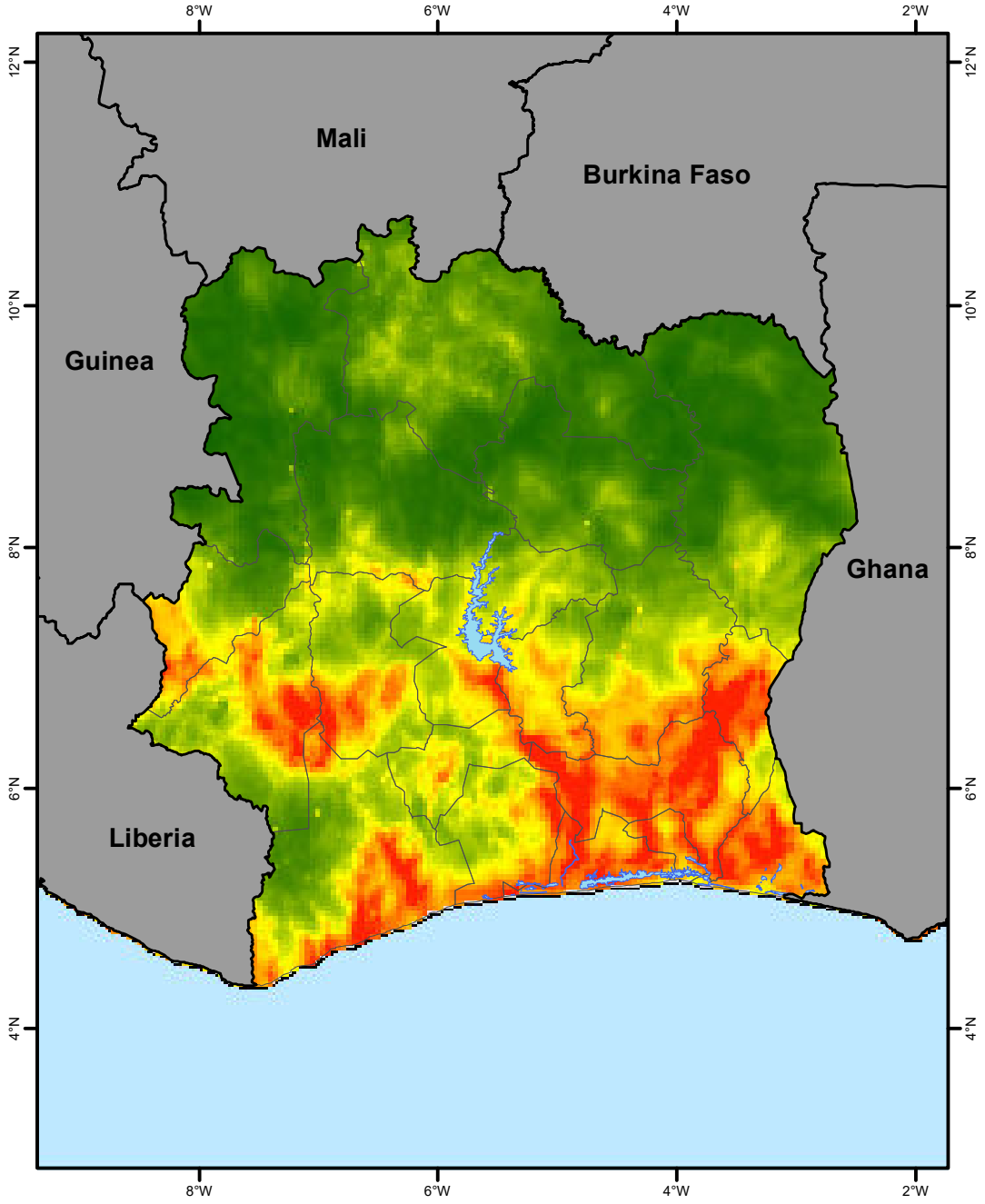
Low : 0 — High : 1

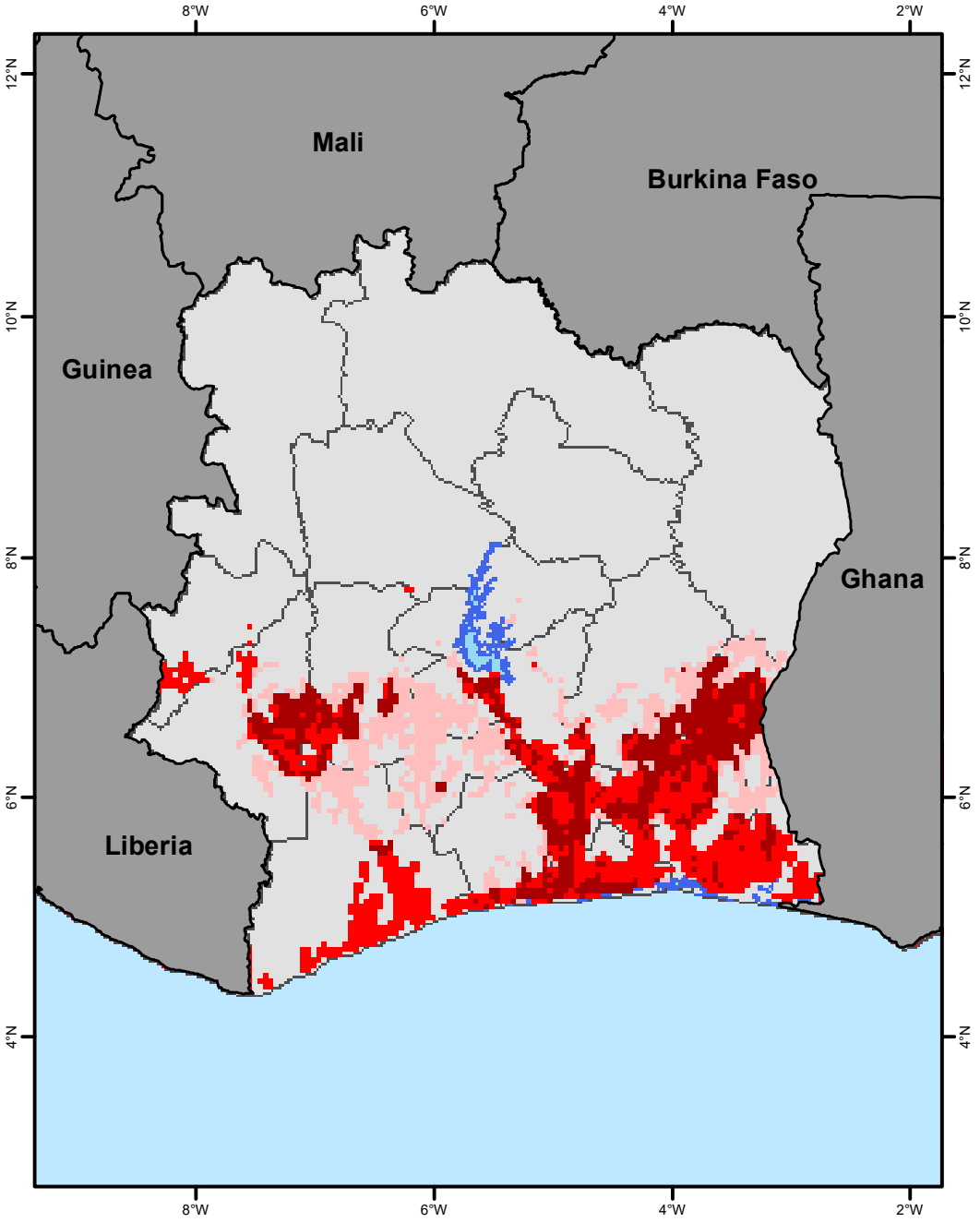
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Cote d'Ivoire





Environmental Suitability for Buruli ulcer

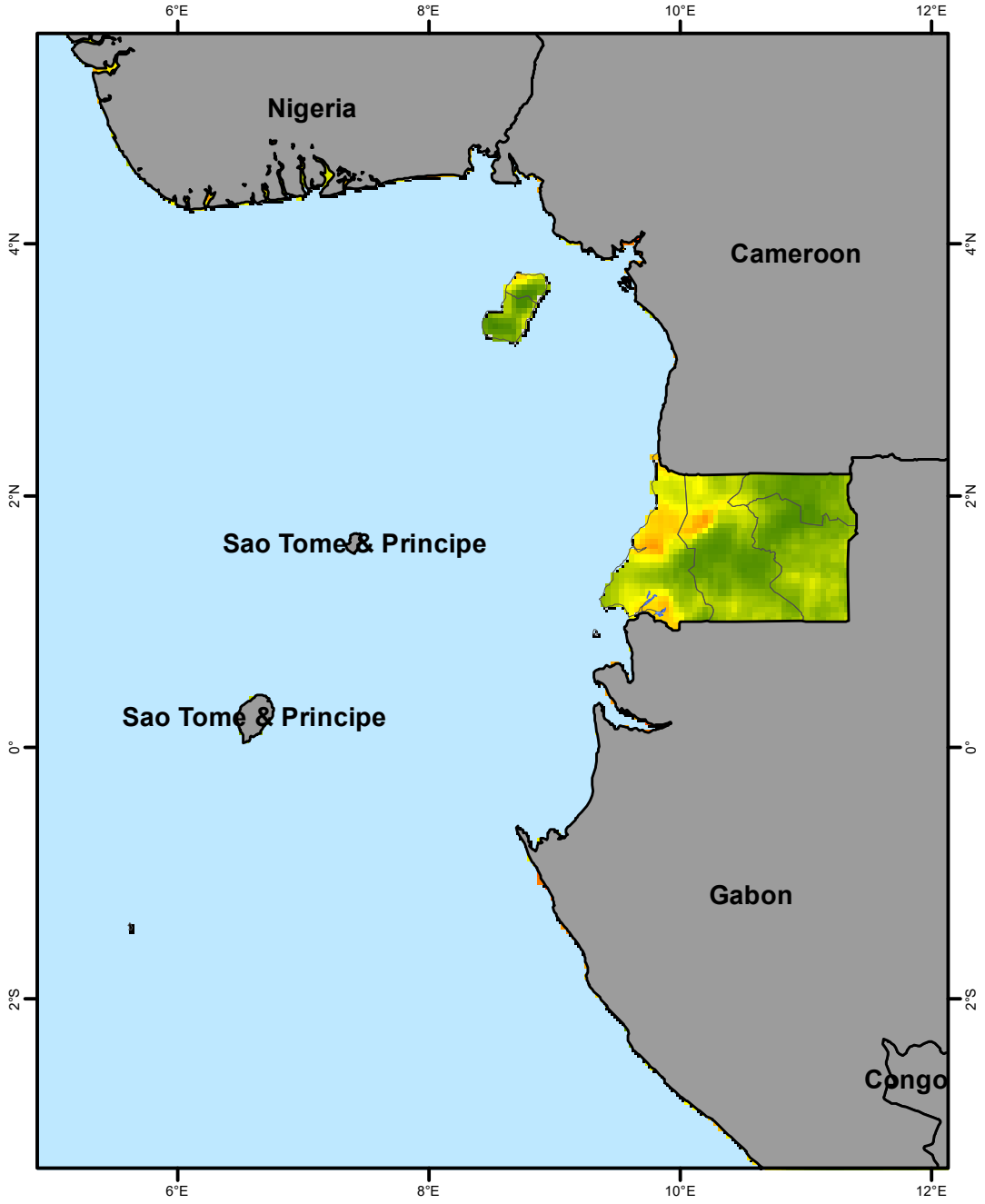
Low : 0 — High : 1

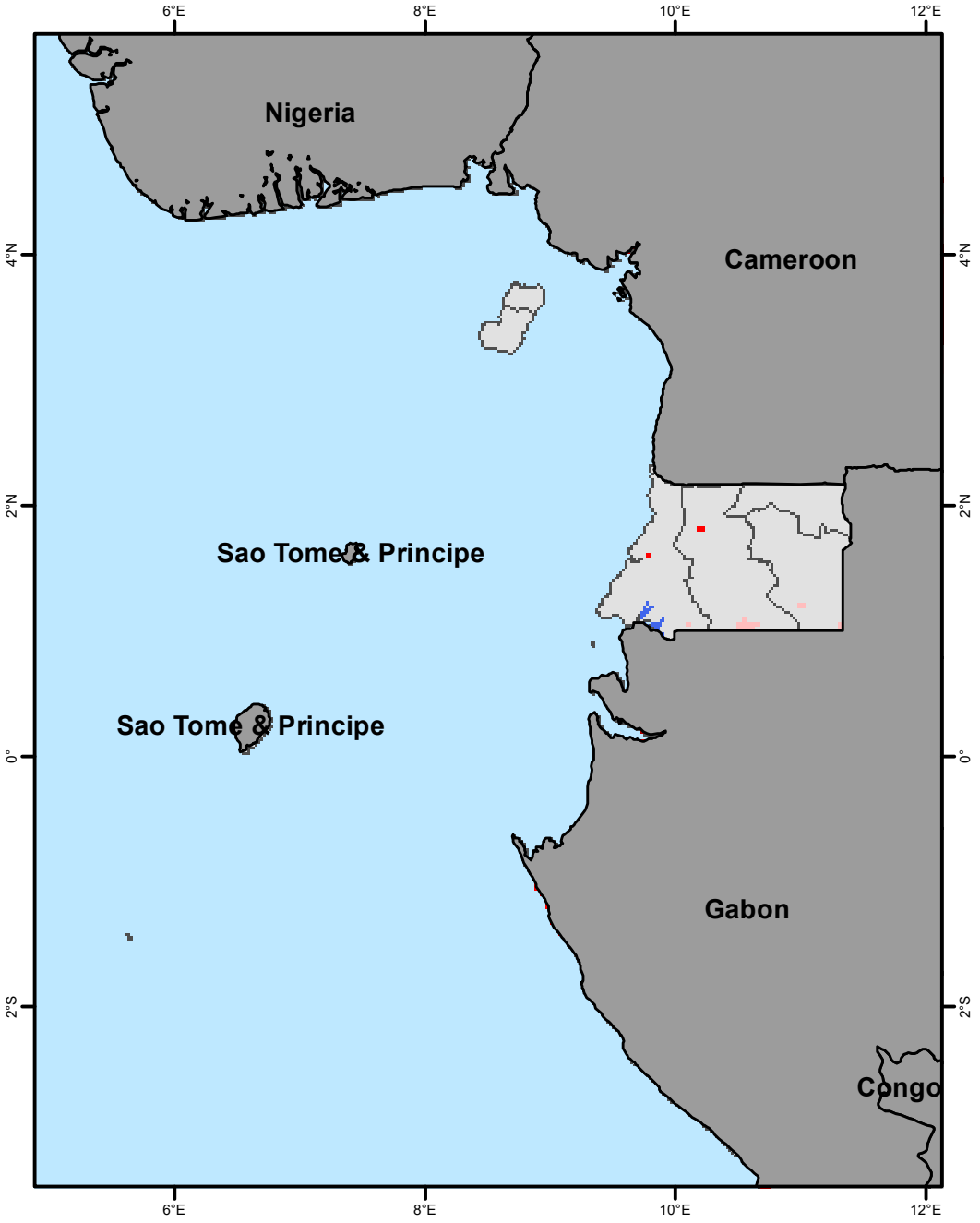
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Equatorial Guinea





Environmental Suitability for Buruli ulcer

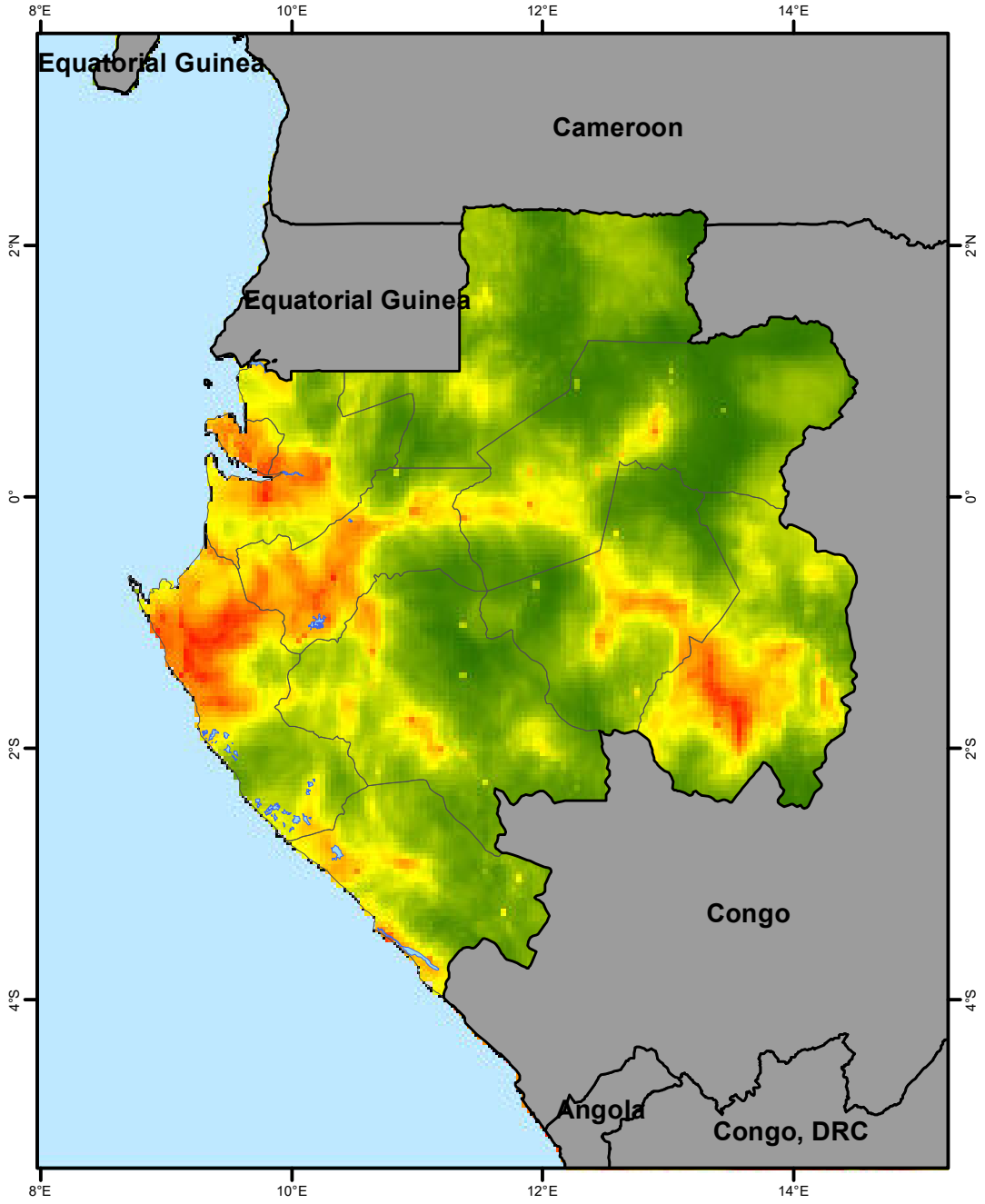
Low : 0 — High : 1

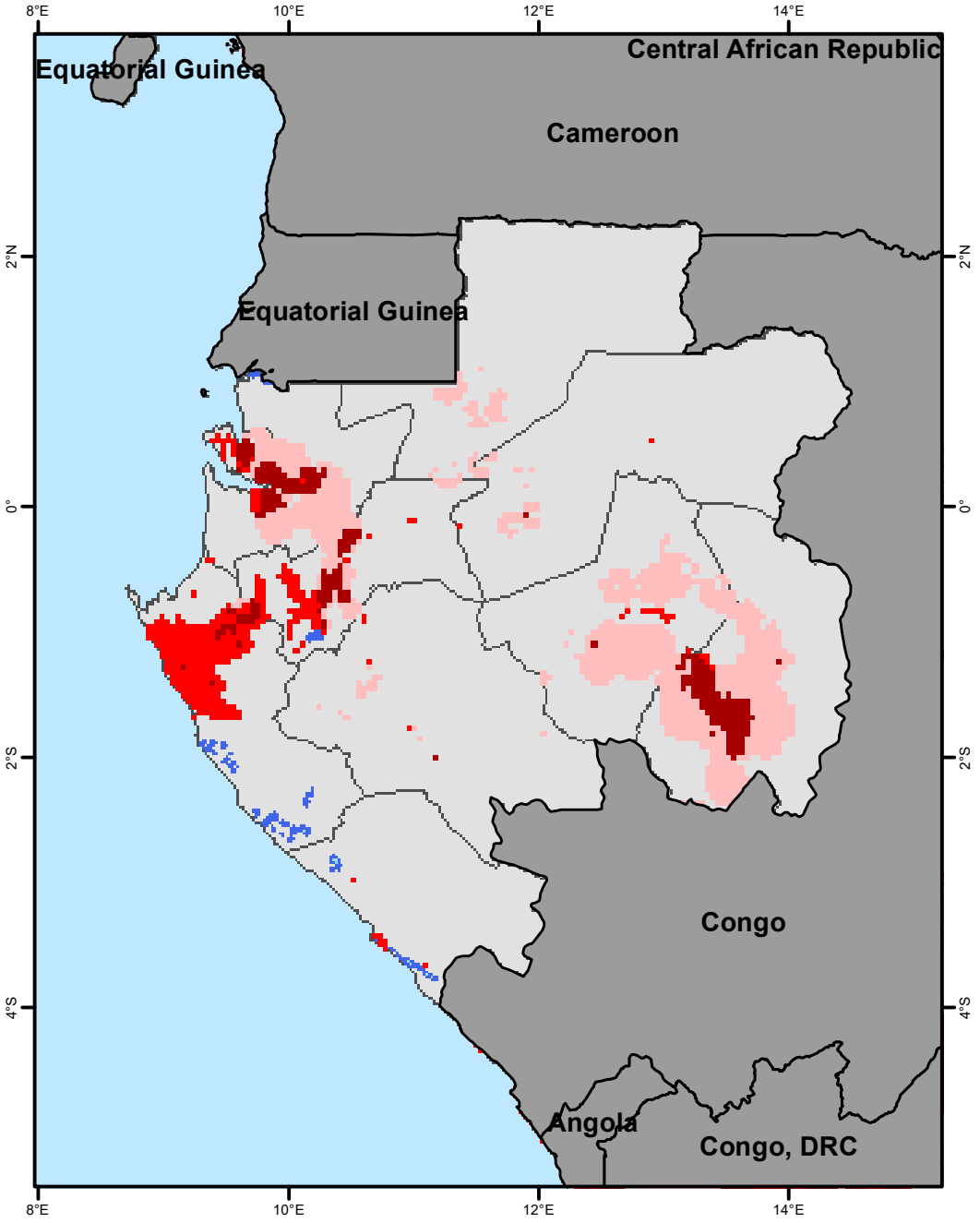
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Gabon





Environmental Suitability for Buruli ulcer

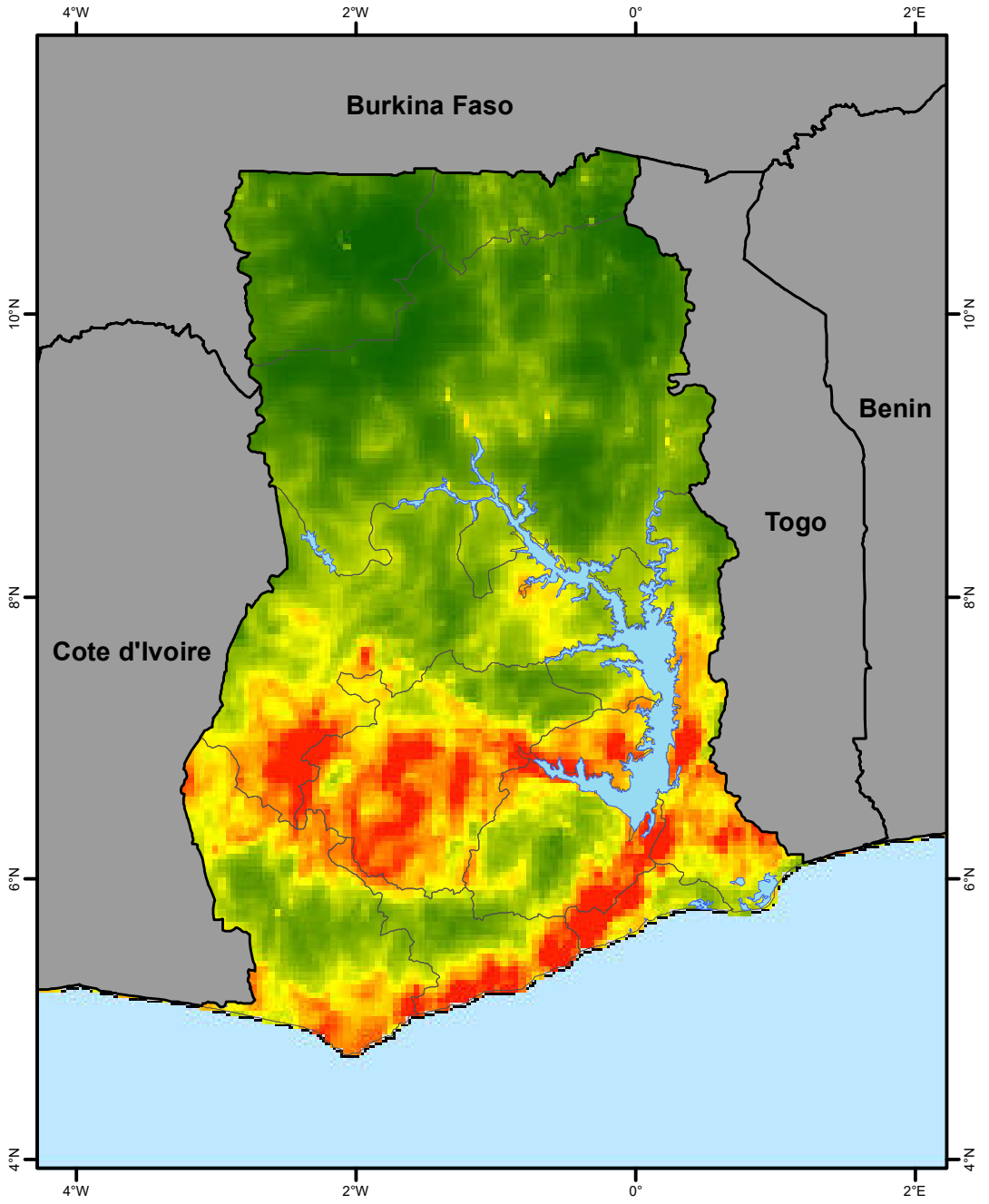
Low : 0 — High : 1

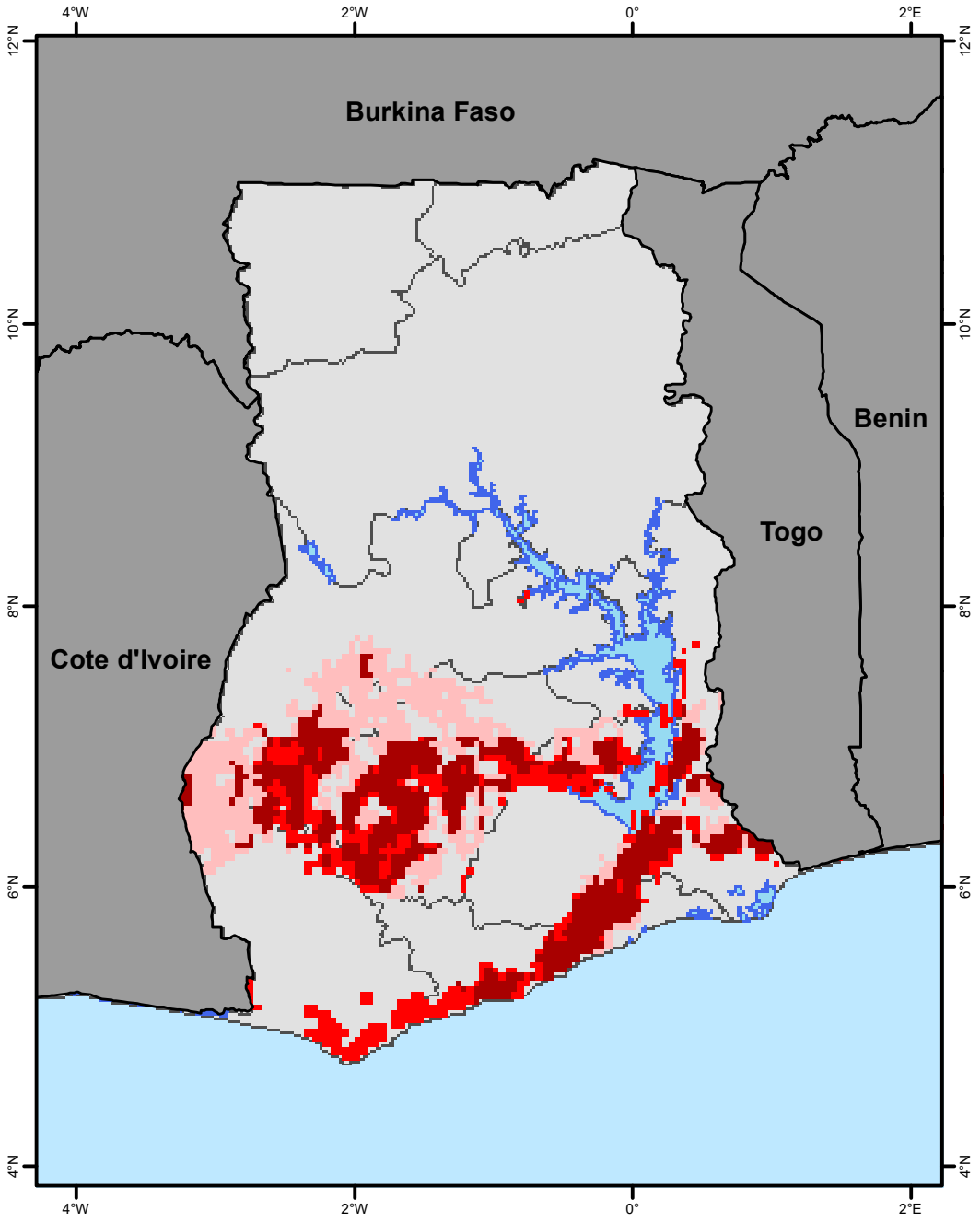
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Ghana





Environmental Suitability for Buruli ulcer

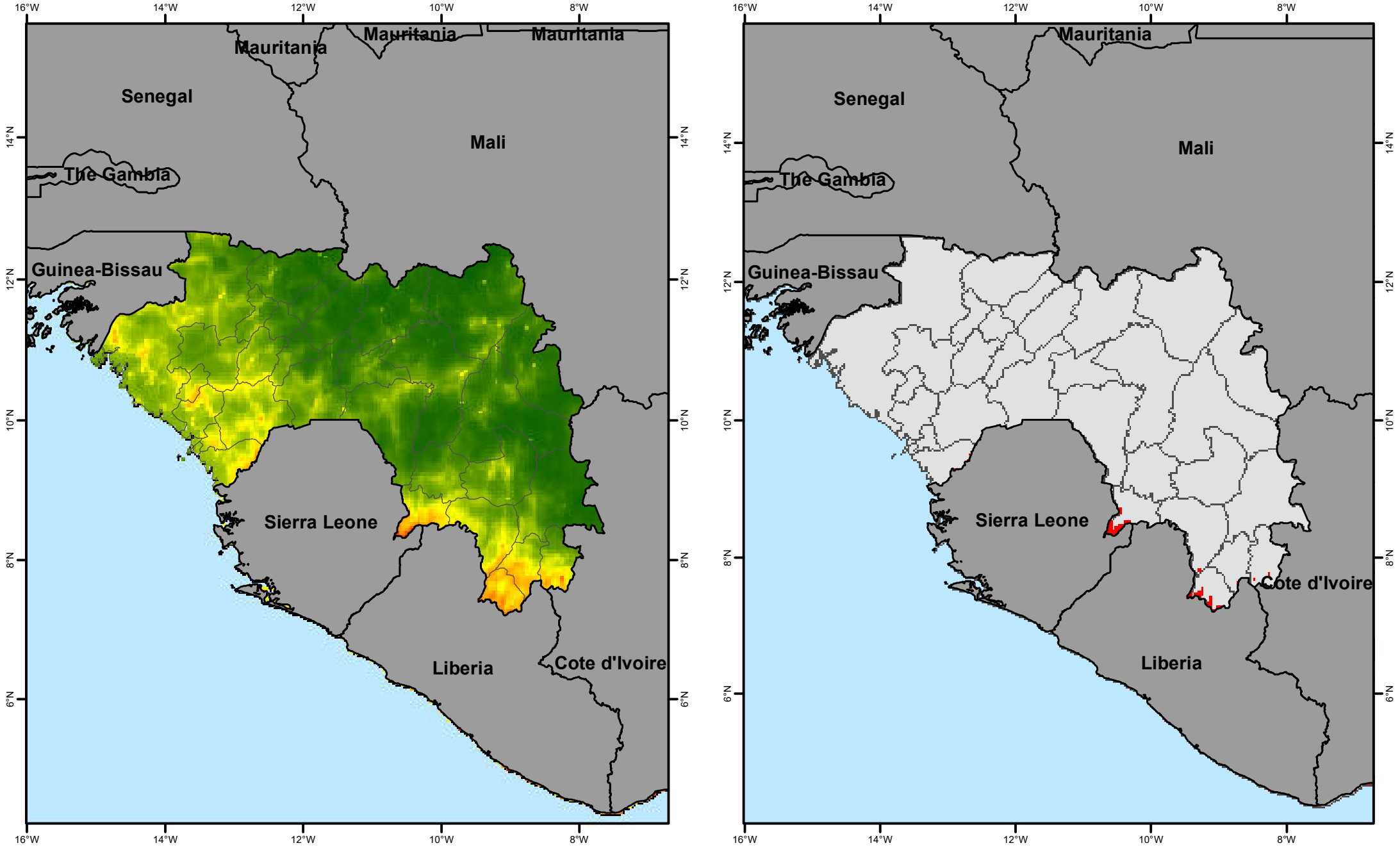
Low : 0 — High : 1

N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Guinea



Environmental Suitability for Buruli ulcer

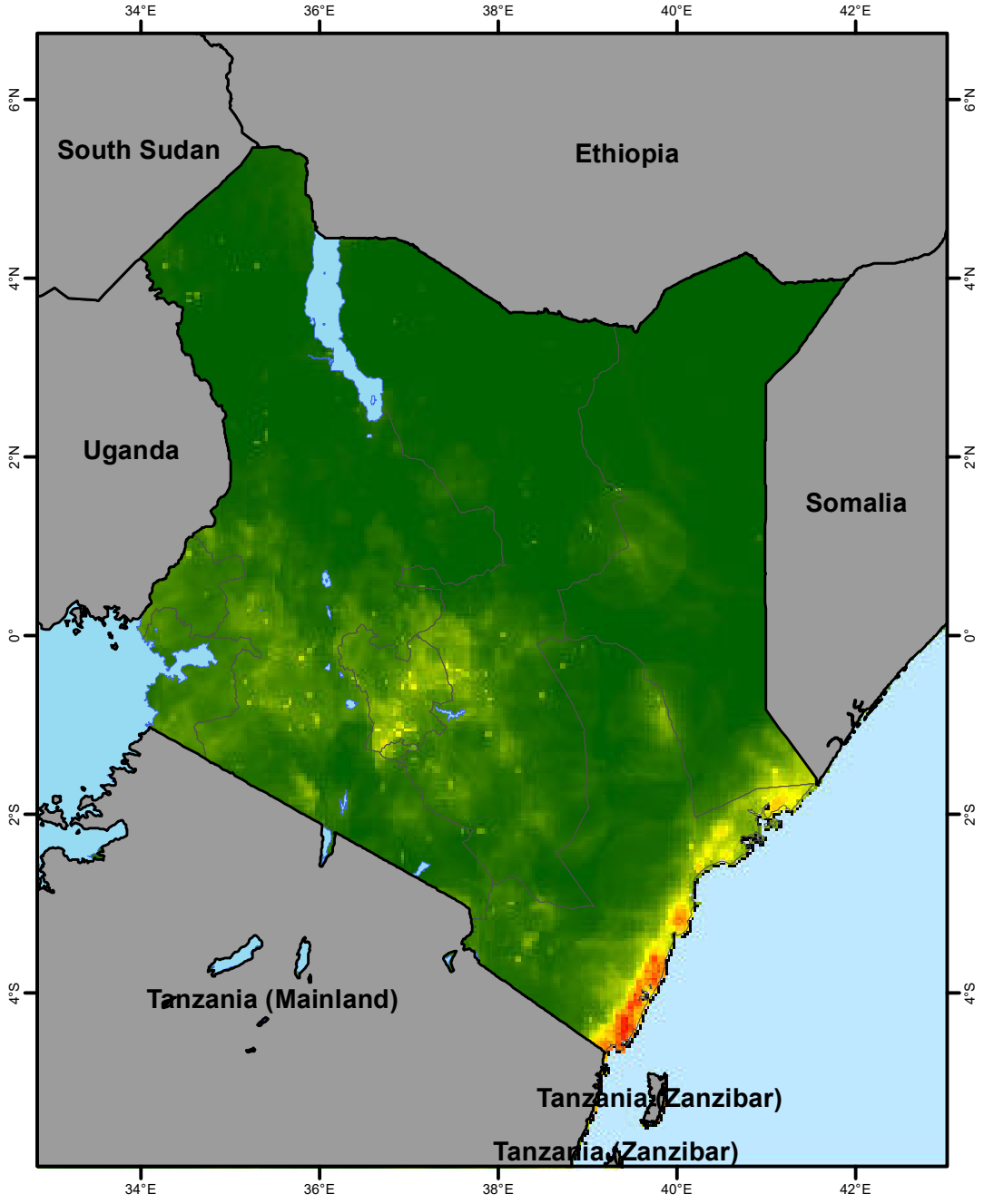
Low : 0 — High : 1

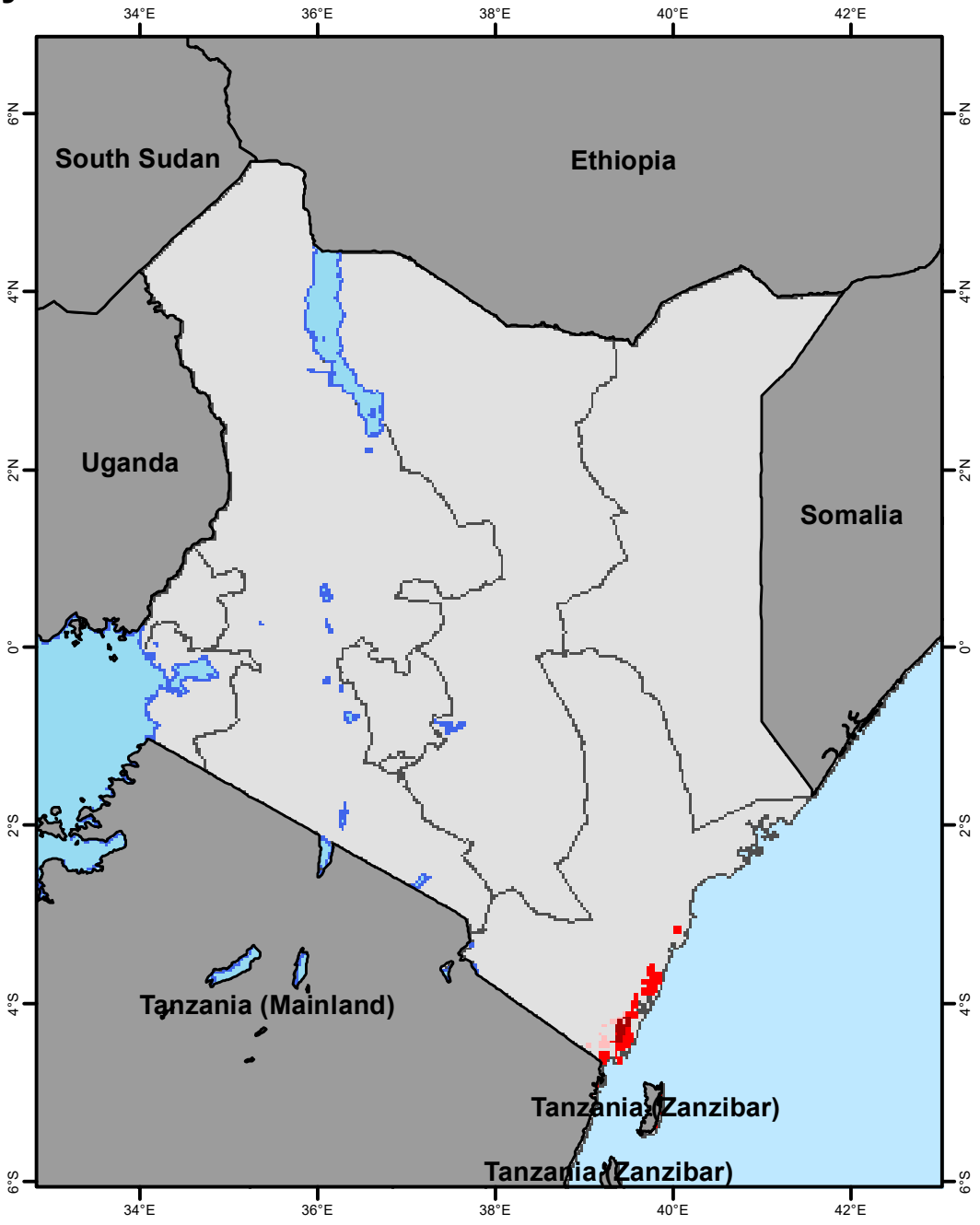
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Kenya





Environmental Suitability for Buruli ulcer

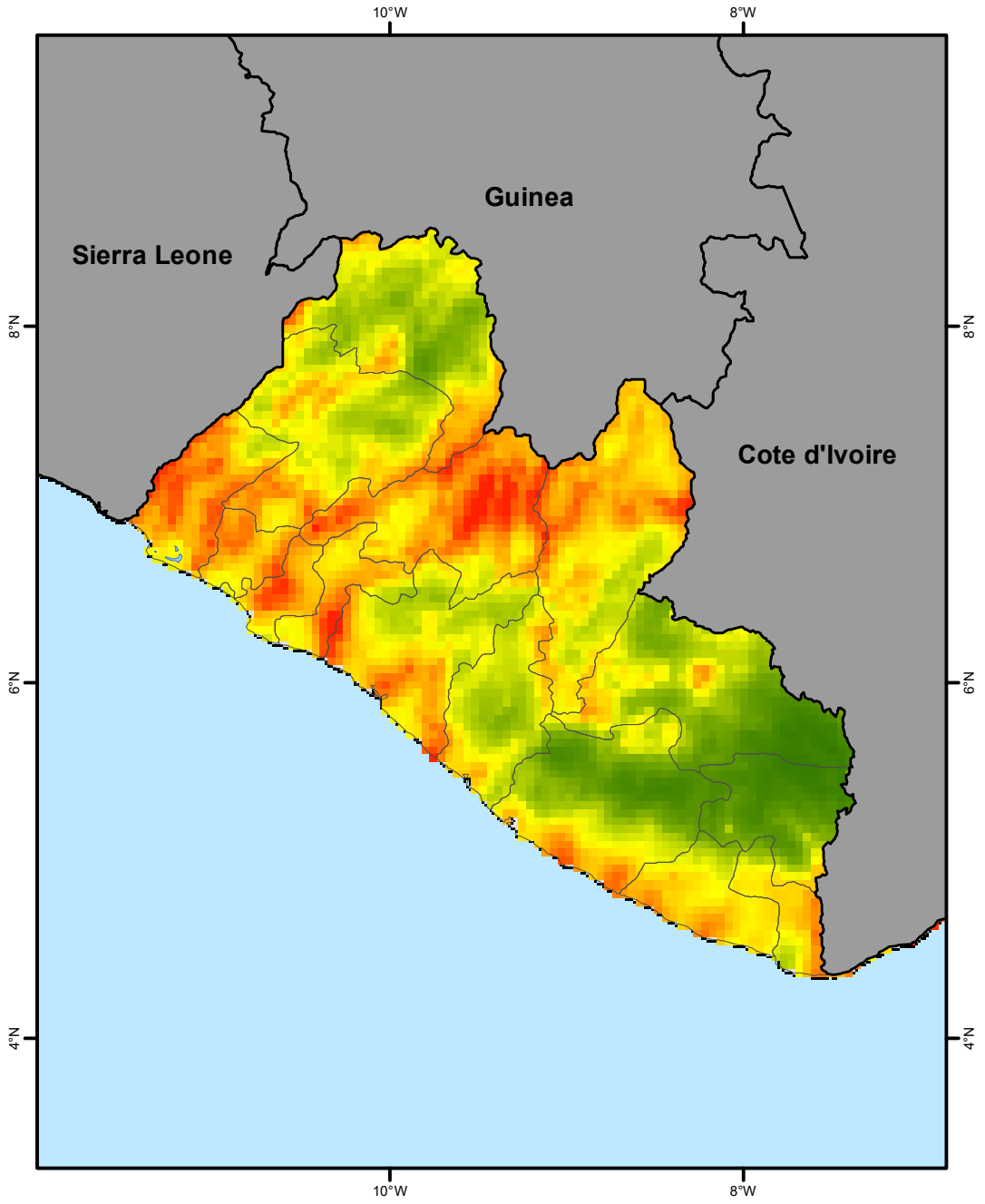
Low : 0 — High : 1

N

Predicted Occurrence Buruli ulcer + M. ulcerans

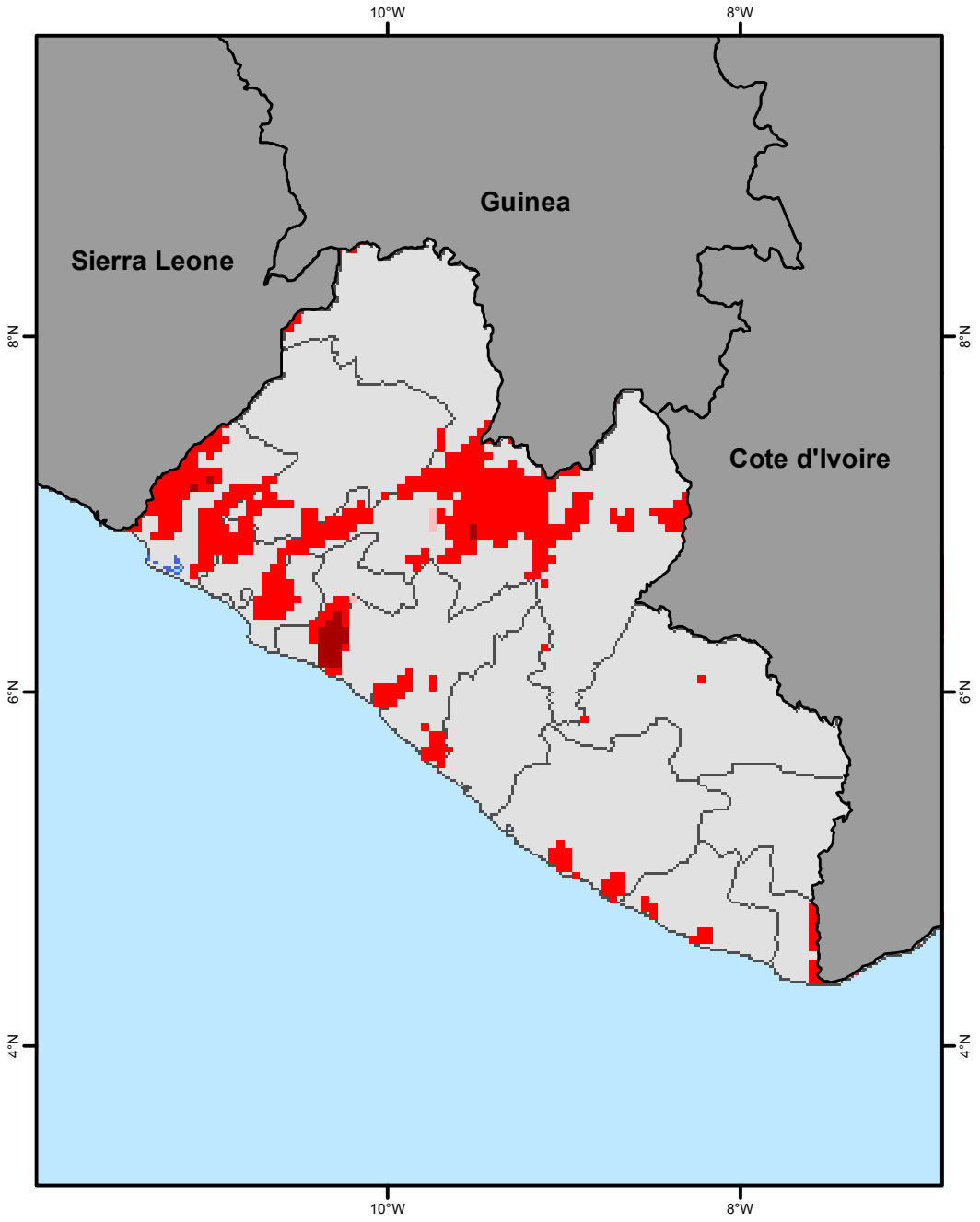
M. ulcerans | Buruli ulcer | BU + M. ulcerans

Liberia



Environmental Suitability for Buruli ulcer

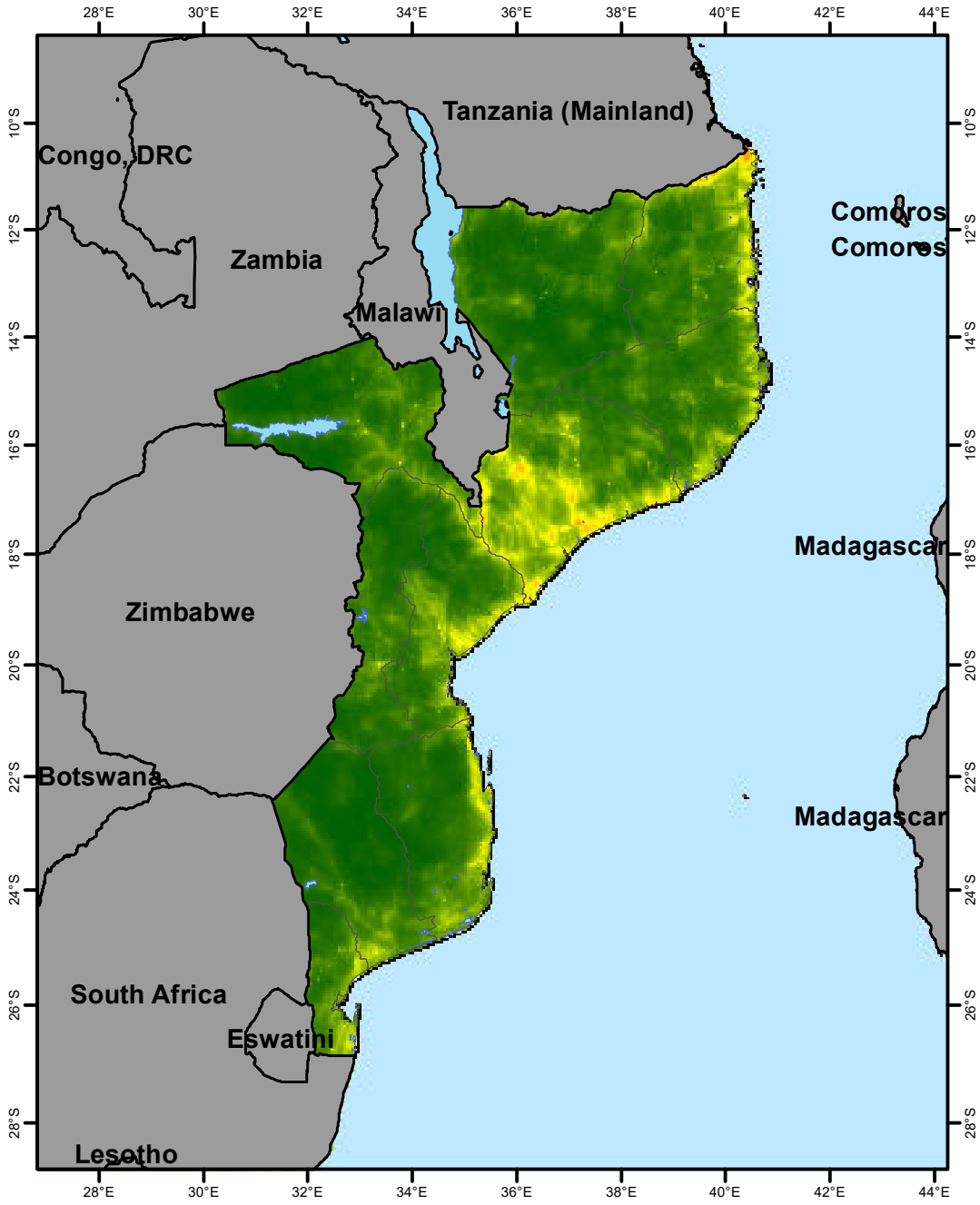
Low : 0 — High : 1

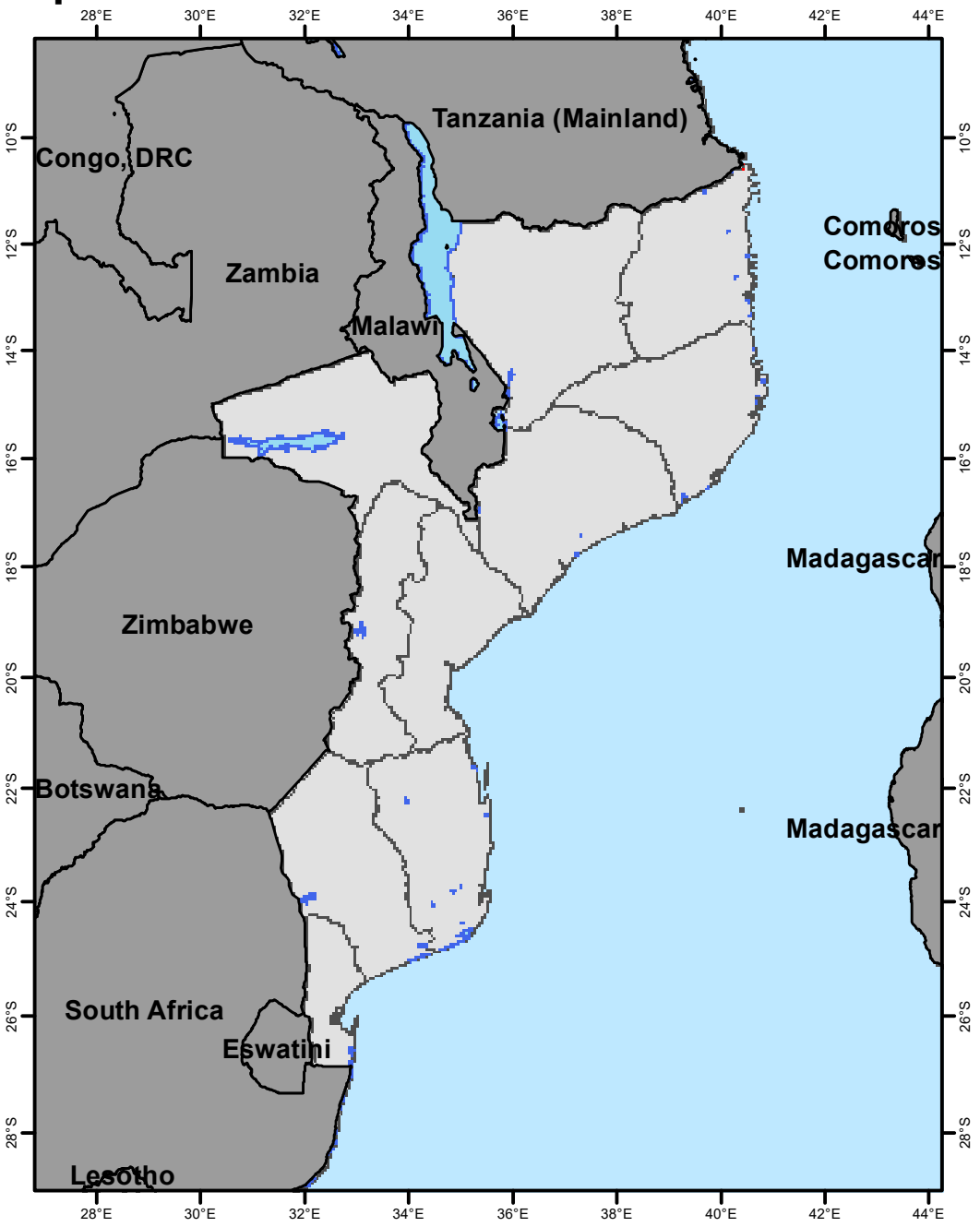


Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans — Buruli ulcer — BU + M. ulcerans

Mozambique





Environmental Suitability for Buruli ulcer

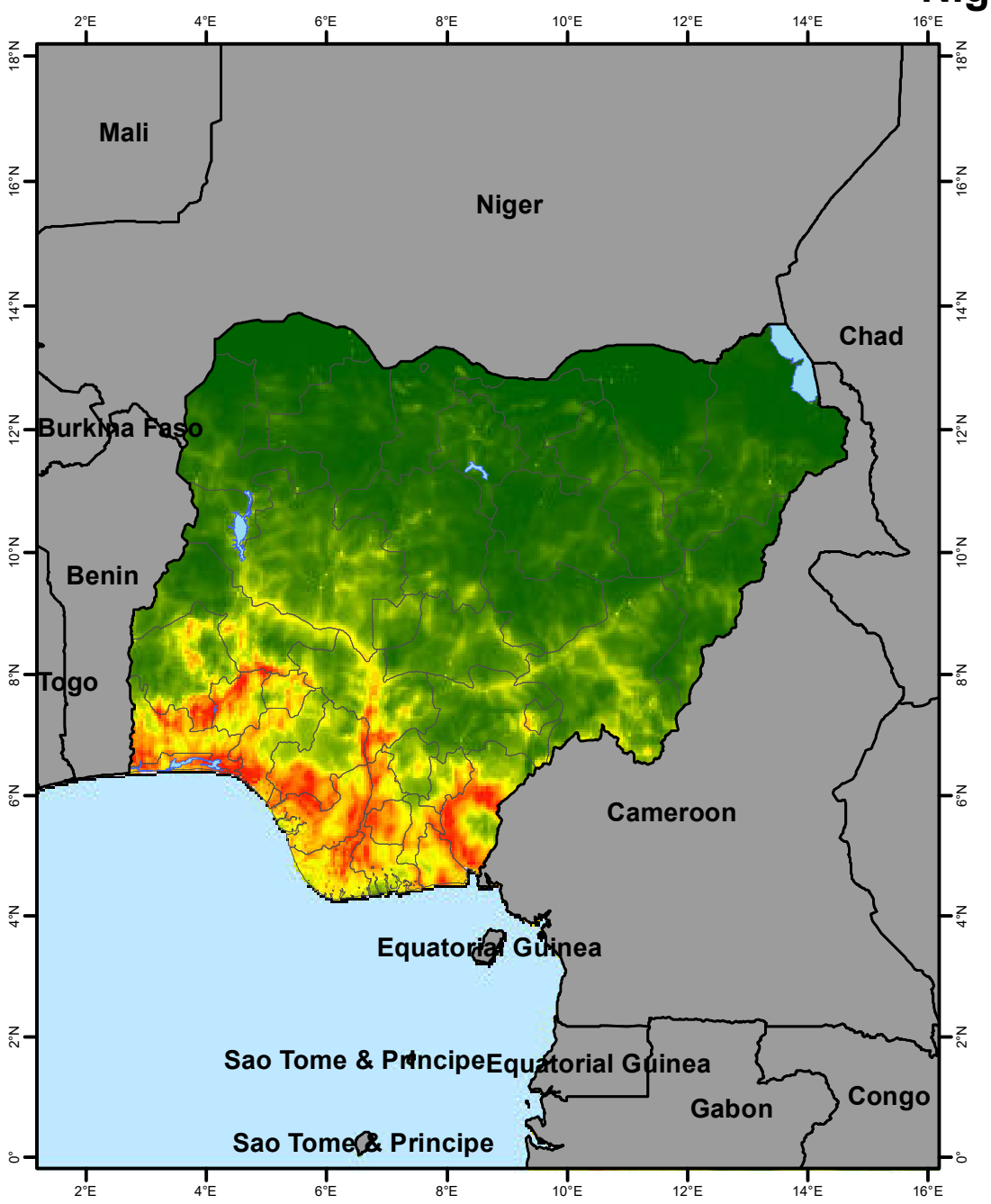
Low : 0 — High : 1

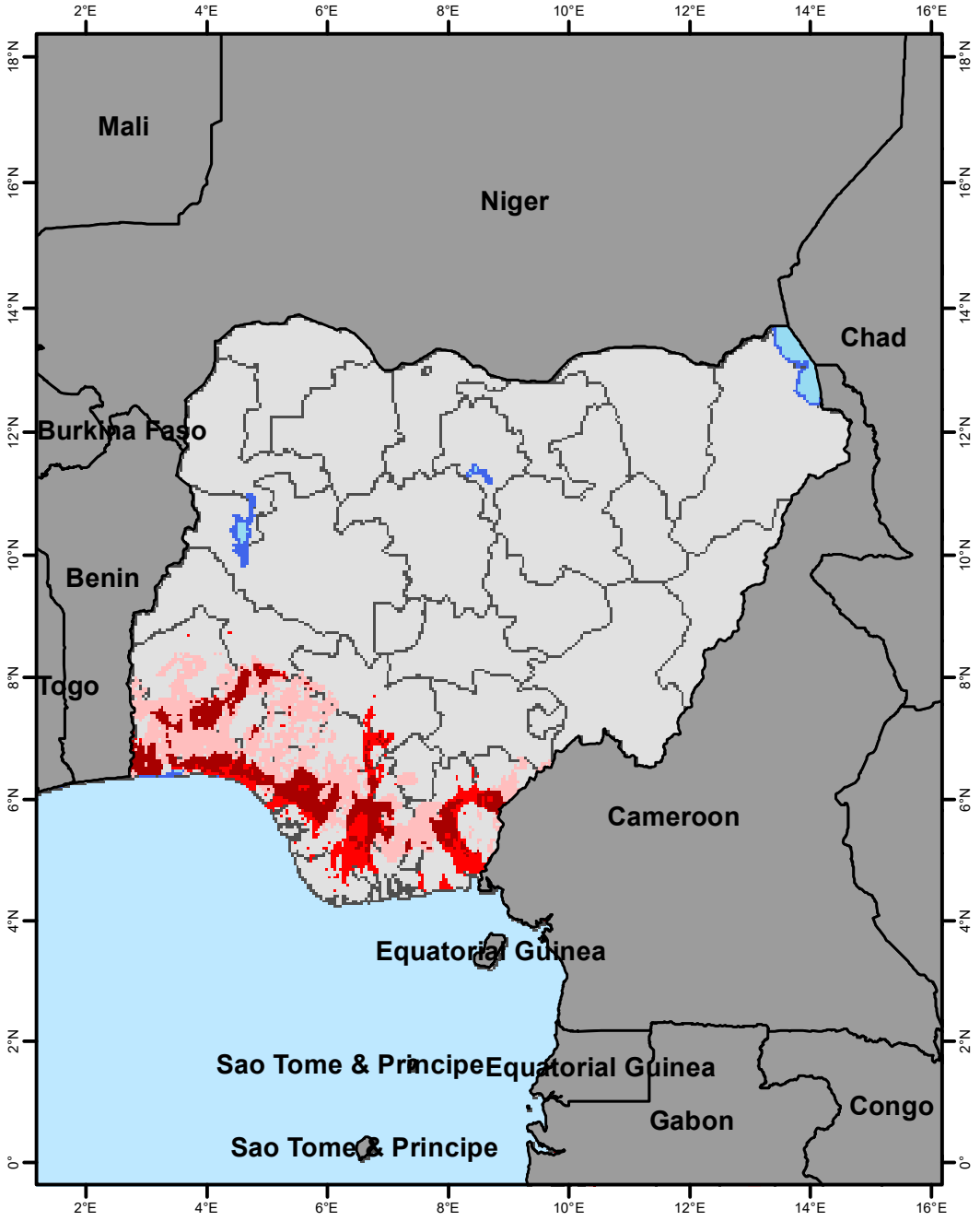
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Nigeria





Environmental Suitability for Buruli ulcer

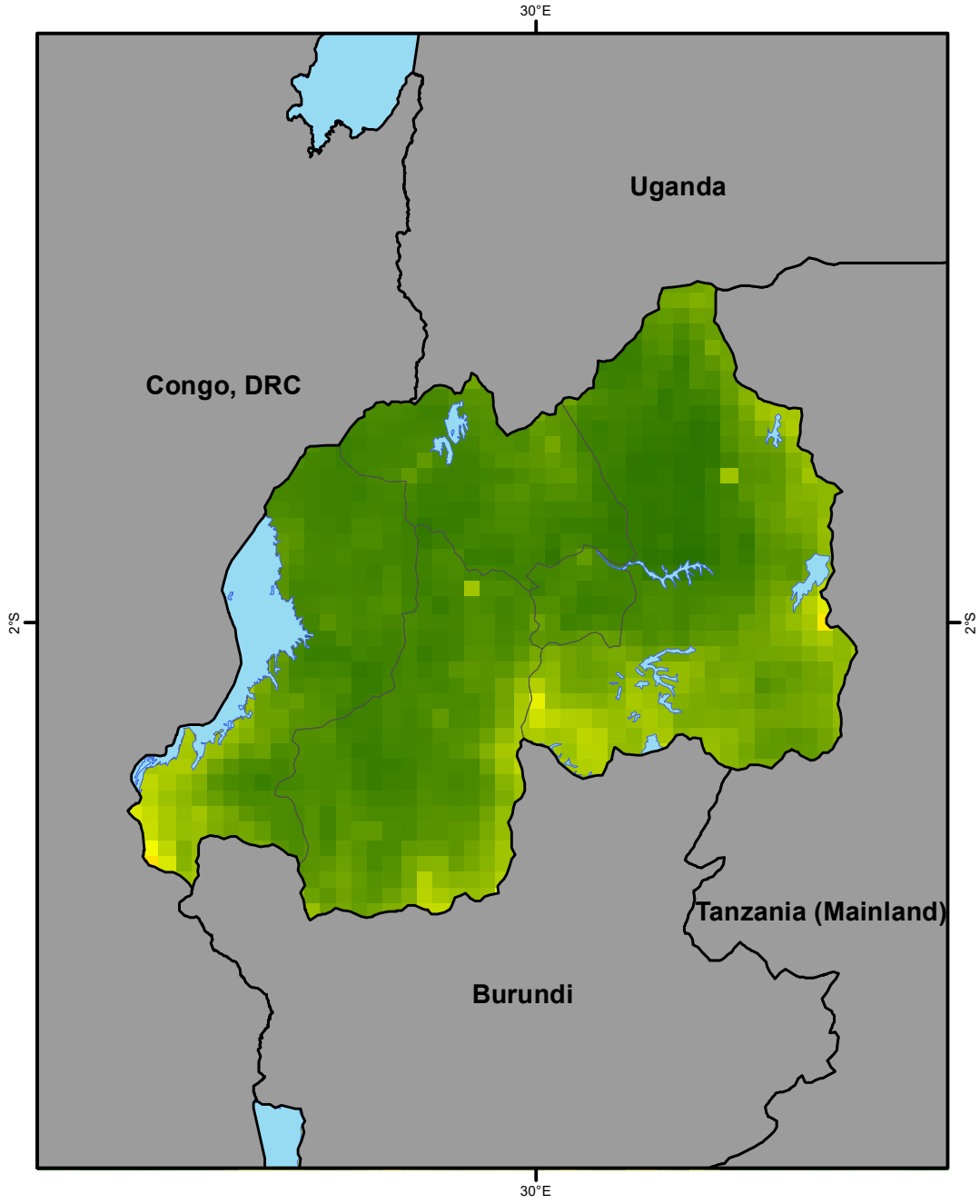
Low : 0 — High : 1

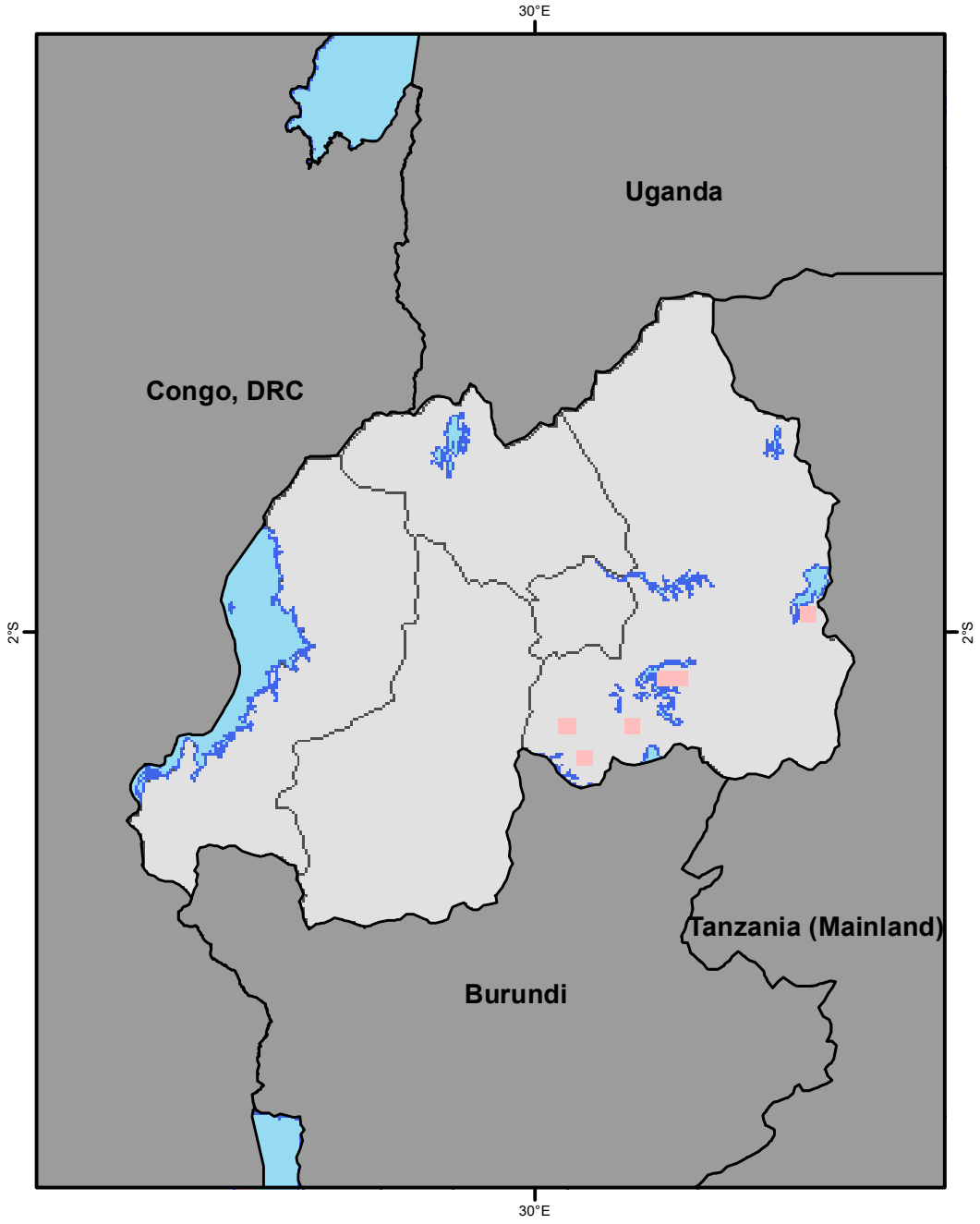
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Rwanda





Environmental Suitability for Buruli ulcer

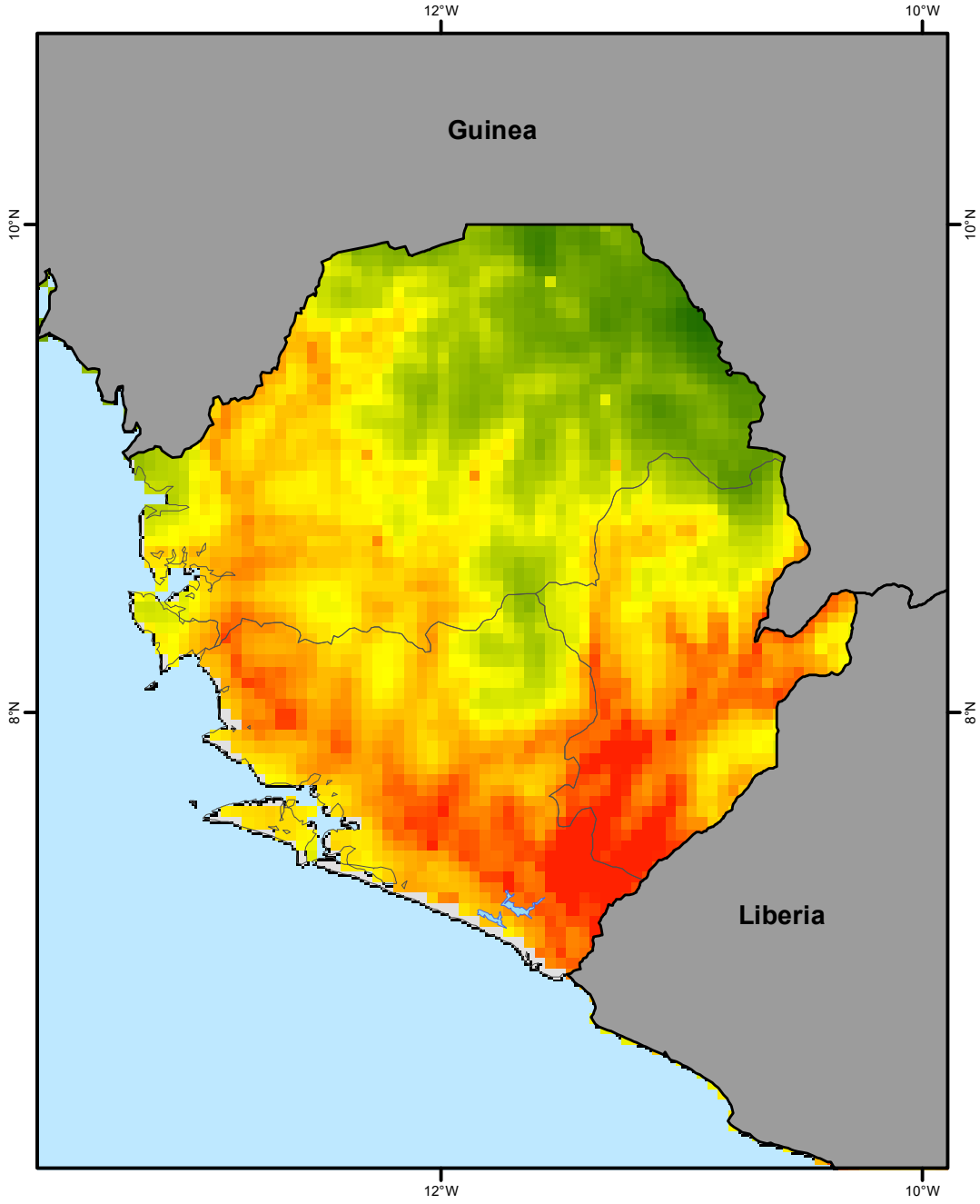
Low : 0 — High : 1

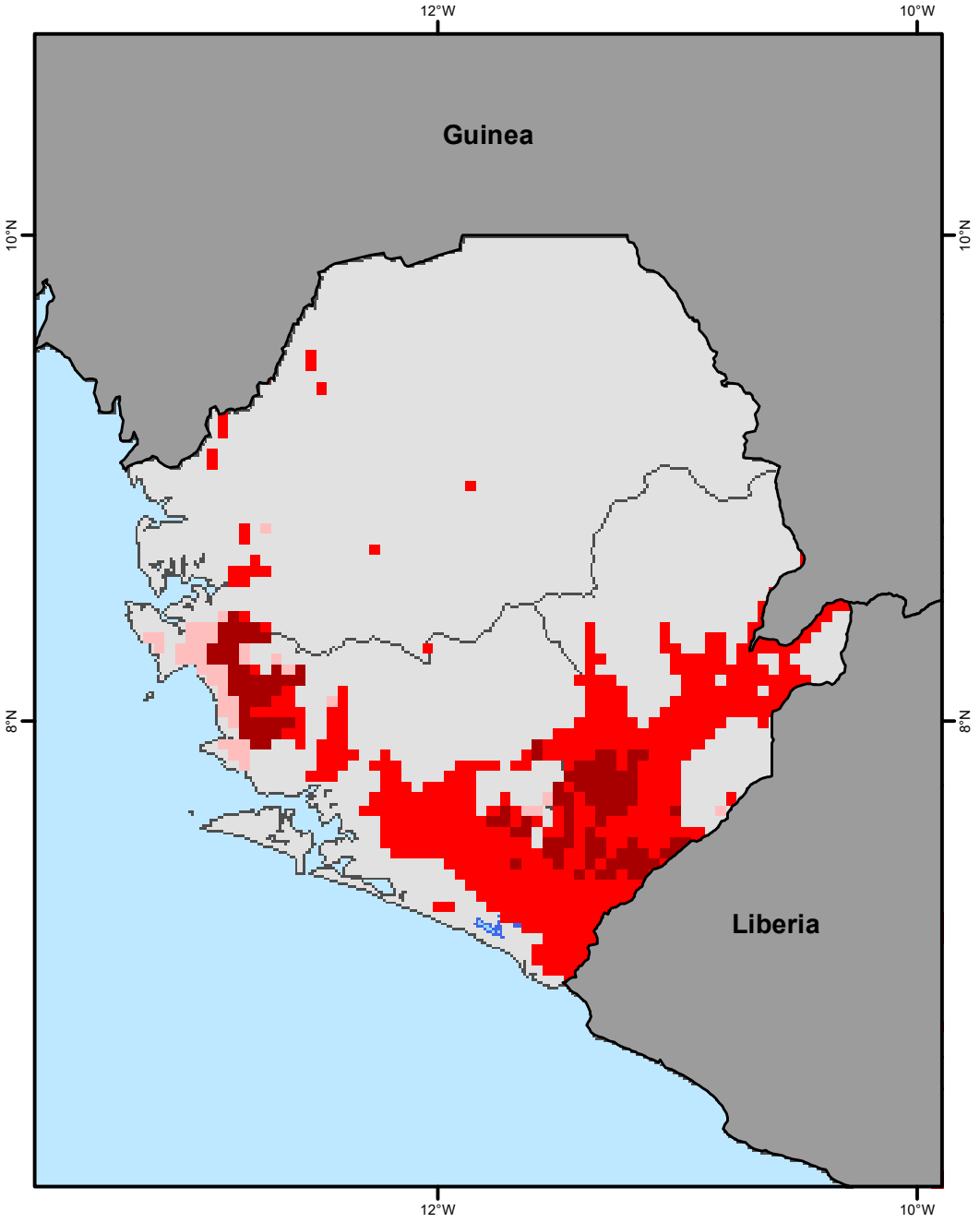
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Sierra Leone





Environmental Suitability for Buruli ulcer

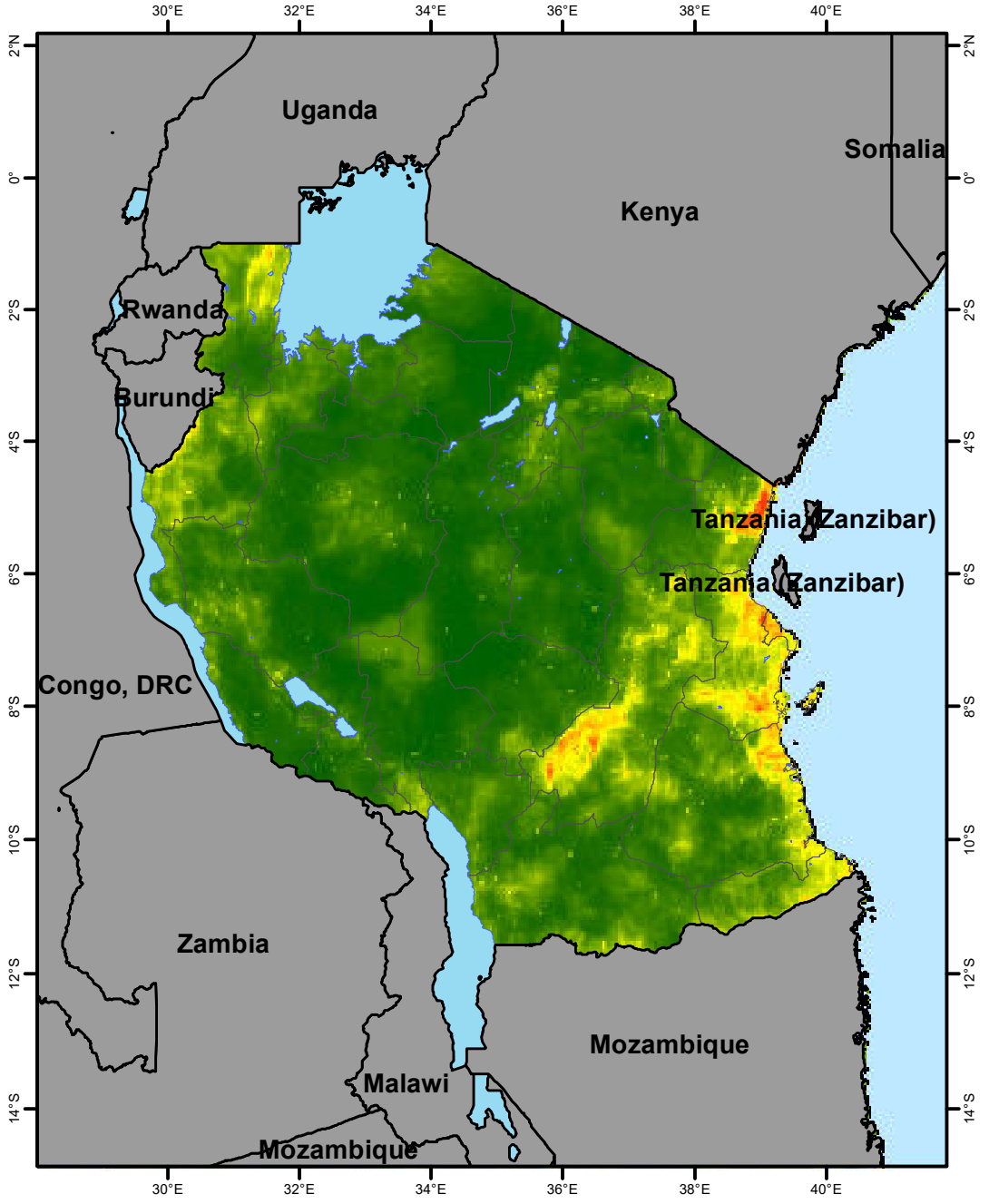
Low : 0 — High : 1

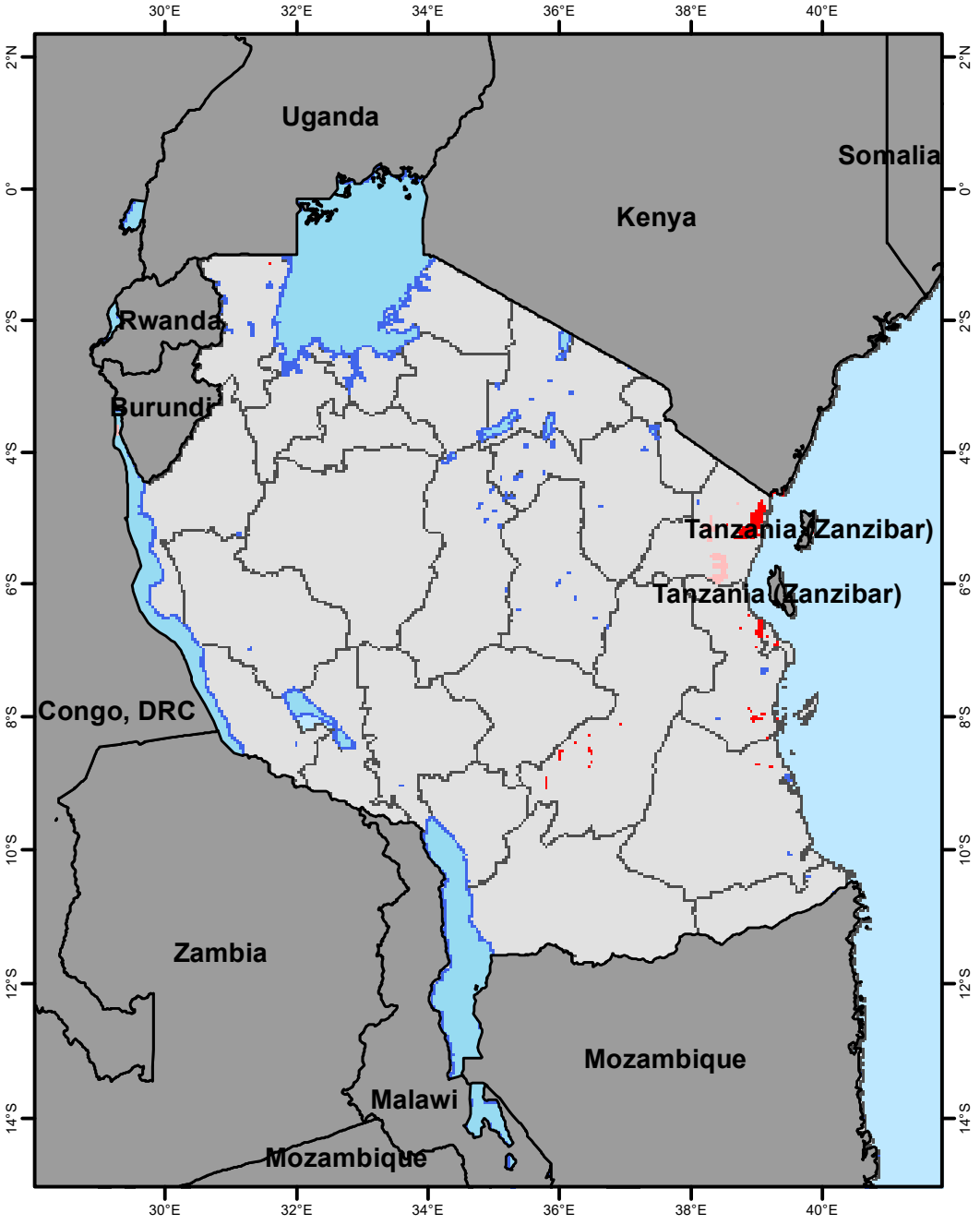
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Tanzania (Mainland)





Environmental Suitability for Buruli ulcer

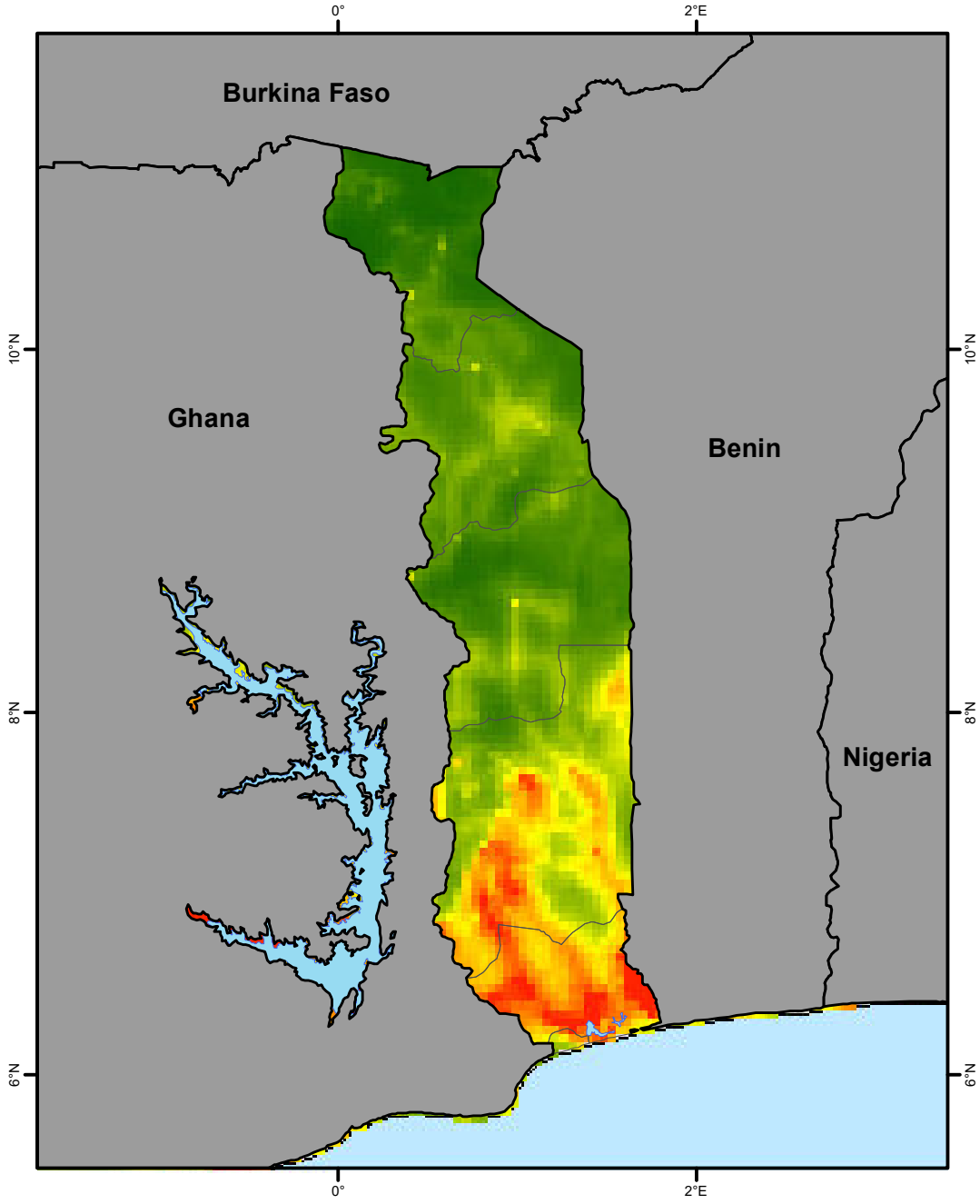
Low : 0 — High : 1

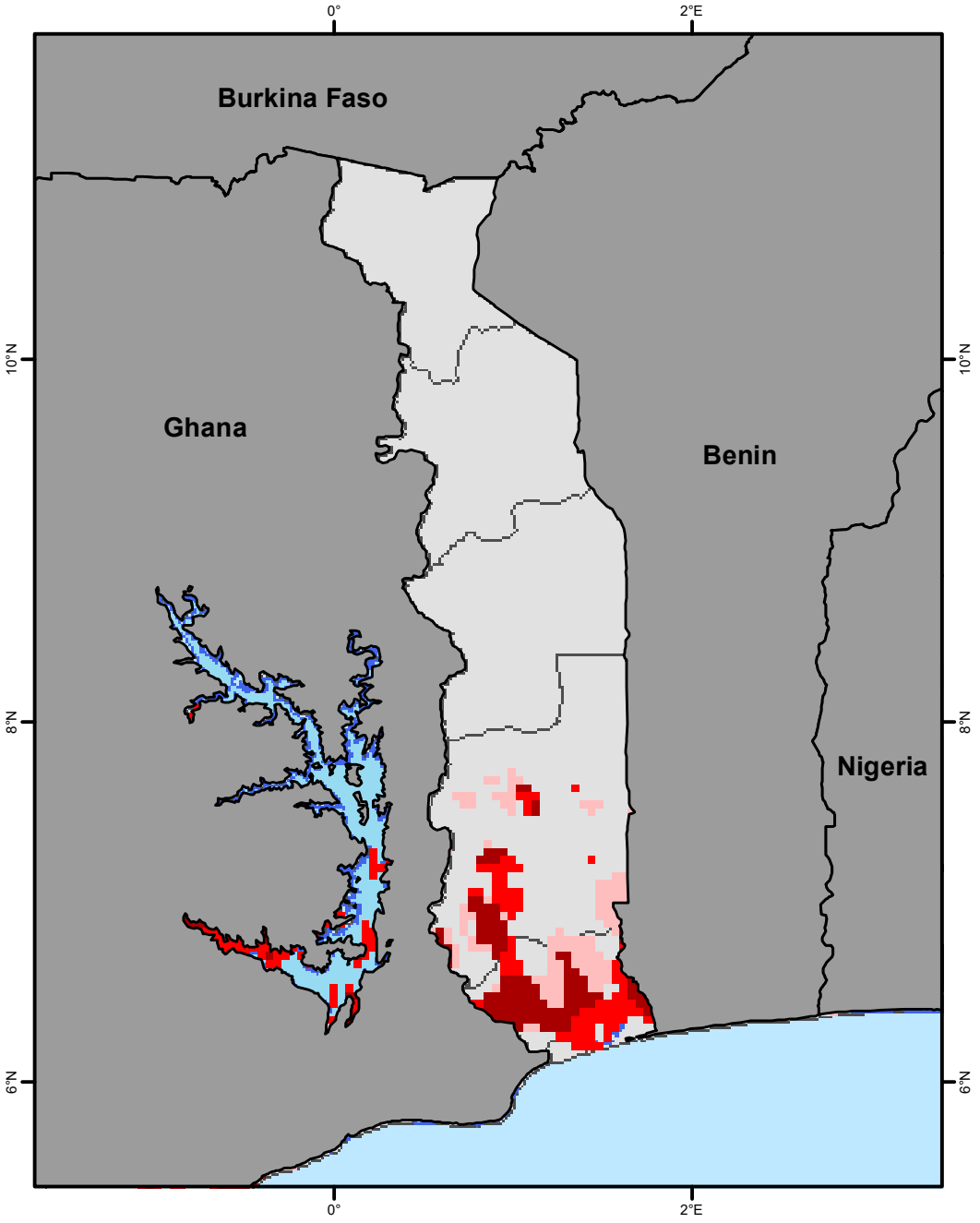
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Togo





Environmental Suitability for Buruli ulcer

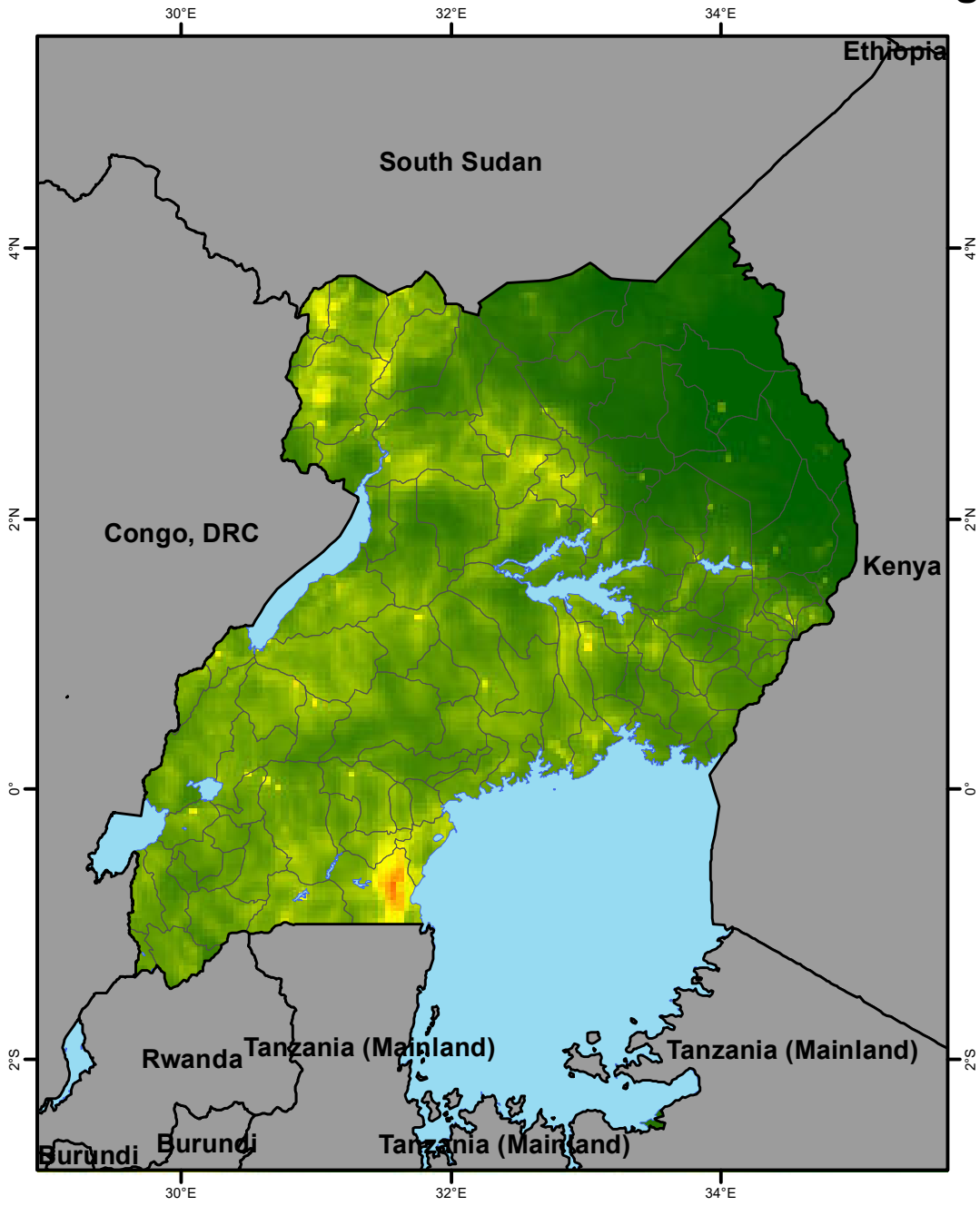
Low : 0 — High : 1

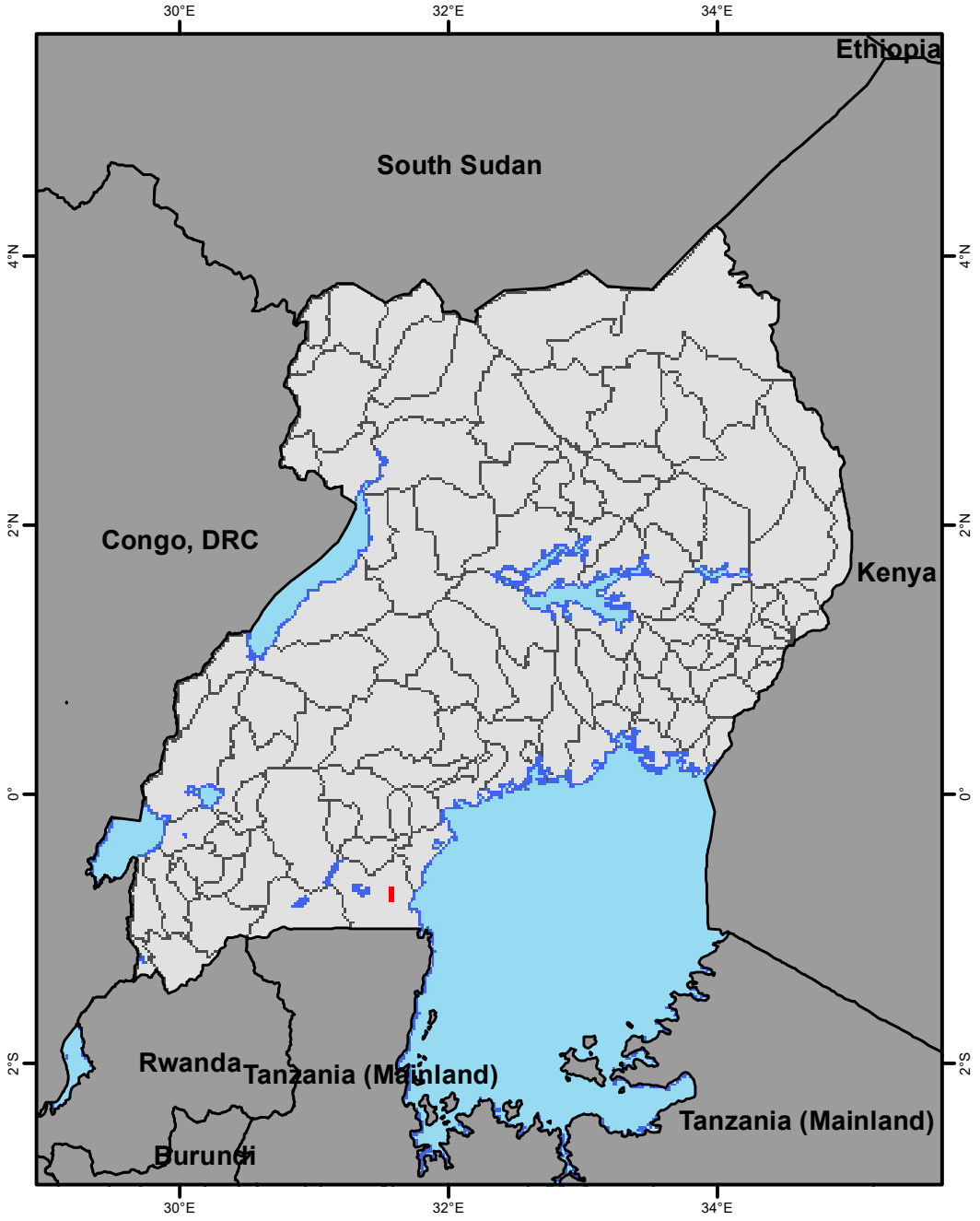
N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

Uganda





Environmental Suitability for Buruli ulcer

Low : 0 — High : 1

N

Predicted Occurrence Buruli ulcer + M. ulcerans

M. ulcerans | Buruli ulcer | BU + M. ulcerans

S1 Text: Selection of pseudoabsence and background points

Prior to building environmental models, we systematically generated pseudoabsence and background points which were integrated into the modelling framework as negative points. Pseudoabsence points, intending to represent areas where BU or *M. ulcerans* were less likely to occur [1], were sampled from areas predicted to be unsuitable for the disease or bacterium, and at higher density from areas with lower evidence for BU occurrence. The area assumed to be unsuitable was delineated using the surface range envelope (SRE) function within the *biomod2* package, with the covariates selected as model predictors used as explanatory variables and the occurrence points (all locations) used as the response variable [2]. We used a threshold of 0.025 as the tolerance value so that the envelope represented the area within the 2.5^{th} and 97.5^{th} percentile of the range of each predictor variable [2]. The area outside of the SRE and within continental Africa was used as the extent for pseudoabsence selection. To weight the selection of pseudoabsence points according to the evidence of BU, we used the results of a previous literature review of BU endemicity [3]. The review quantified the strength of evidence for BU from multiple sources and assigned each country an evidence consensus score from -100 (consensus on absence of BU) to +100 (consensus of presence of BU). Upper sub-national administrative units with evidence of cases were scored from 0- 100 based on the contemporariness and diagnostic specificity of cases.

We rescaled national and sub-national evidence consensus scores to 0- 1 and linked both to upper administrative areas from the GADM [4] to generate an evidence consensus score layer. Sub-national areas with evidence of BU were assigned the sub-national evidence consensus score, and sub-national areas with no evidence of BU were assigned the national level score scaled by a factor of 0.5. The evidence consensus score layer was converted to a raster layer at 5x5km resolution representing the strength of evidence for BU.

Within the extent of pseudoabsence selection, we generated regular spatial points datasets at a scale of 5x5km. At each point we extracted the value of the evidence consensus raster (0- 1), and assigned a random score from 0- 1. Points with evidence consensus score lower than the randomly assigned value were defined as potential pseudoabsence points [5], resulting in a higher density of pseudoabsence points in areas of lower evidence consensus. Potential pseudoabsence points within 10km of occurrence points were excluded. Model pseudoabsences were selected at random from the potential pseudoabsences. Each pseudoabsence dataset contained the same number of points as the corresponding occurrence dataset. Pseudoabsences within the model of confirmed occurrences were selected from a random sub-sample of the human pseudoabsences representing all cases.

We additionally generated samples of background points, intended to account for the spatial bias of the occurrence points [6-8]. Gaussian kernel density surfaces, representing the density of occurrence points, were generated around recorded occurrence points with a bandwidth of 150km using the *Spatial kernel density estimate* function in the *spatialEco* package [8-10]. Samples of background points, each equal in size to its corresponding occurrence dataset, were selected from the density surfaces with probability defined by the kernel value (representing the smoothed density of occurrences at that location).

References

1. Barbet-Massin M, Jiguet F, Albert CH, Thuiller W. Selecting pseudo-absences for species distribution models: how, where and how many? Methods in ecology and evolution. 2012;3(2):327-38.
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4. Global Administrative Areas. GADM database of Global Administrative Areas, version 2.0 2012 [01/06/2018]. Available from: http://www.gadm.org
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6. Fitzpatrick M, Gotelli N, Ellison A. MaxEnt versus MaxLike: empirical comparisons with ant species distributions. Ecosphere 4 (5): art 55. 2013.
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8. Evans J. spatialEco. R package version 2.0-0. 2015.
9. Fourcade Y, Engler JO, Rödder D, Secondi J. Mapping species distributions with MAXENT using a geographically biased sample of presence data: a performance assessment of methods for correcting sampling bias. PloS one. 2014;9(5):e97122.
10. Evans J. spatialEco. 2019.

S2 Text: Environmental variables used in modelling, including potential environmental predictors and their sources and the covariates that were included in the models of BU and *M. ulcerans* suitability.

Raster datasets of minimum and maximum temperature, precipitation in the wettest and driest quarters, and precipitation seasonality (representing the variation in monthly precipitation totals throughout the year) were obtained from the WorldClim v2.0 Global Climate Database [1].
Raster datasets representing annual potential evapo-transpiration (PET) and aridity, both derived from WorldClim datasets [1], were obtained from the Consortium for Spatial Information (CGIAR-CSI). PET quantifies atmospheric capacity to remove water from the air through evapotranspiration. The aridity index represents the balance of precipitation and atmospheric water demand [2]. An elevation dataset derived from data from the Shuttle Radar Topography Mission (SRTM) [3] was also obtained from CGIAR-CSI.
The topographic wetness index (TWI) raster was derived from the elevation raster as part of a previous modelling exercise [4]. The TWI represents the balance of flow accumulation (the potential to collect water) and drainage (the potential to lose water) of each cell, both based on the flow direction. Flow direction is the direction of steepest descent from each cell in the elevation dataset, calculated as: change in elevation value / distance * 100. Flow accumulation is derived by summing the flow direction value weights of all cells predicted to flow into each cell, and drainage is the sum of flow direction value weights of cells predicted to flow from each cell. Using these intermediary datasets, the TWI was generated using the algorithm

$$TWI = \ln(a/tan\beta)$$

where a is the Specific Catchment Area (SCA) for each cell, obtained from the flow accumulation layer, and β is the local slope around the cell, quantifying the potential for drainage.

Waterbodies and waterways were downloaded from the OpenStreetMap project (OSM) [5] through the platform *Geofabrik* [6]. Two separate datasets, one of rivers and streams and one of dams, were extracted from OpenStreetMap.
Raster surfaces showing tree-covered and intact forest at 250m resolution in 2015 were obtained from the Open Land Data service (LandGIS) [7,8]. These datasets were generated using data from the UNEP historic forest cover map [9], the ESA time series of land cover maps 2000–2015 [10] and data on intact forest landscape for 2000, 2013 and 2016 [11].
Land cover datasets obtained from the European Space Agency's Landcover project [12] were used to define areas of agricultural land (crops).

We used spatial analyst tools in ArcGIS 10.3 software (ESRI Inc., Redlands CA, USA) to generate continuous surfaces of straight line (Euclidean) distance to waterbodies; waterways; dams; rivers and streams; deforested areas; and agricultural land, at a spatial resolution of 5km x 5km.
A raster dataset of long-term averaged Enhanced Vegetation Index (EVI) from 2000-2015 was calculated from yearly EVI estimates obtained from the Vegetation Index and Phenology (VIPPHEN) global datasets [13]. The gridded continuous VIPPHEN data products, provided globally at 0.05-degree spatial resolution, were downloaded from the Earth Explorer NASA site (https://earthexplorer.usgs.gov/). The EVI quantifies vegetation cover based on the relative levels of different wavelengths of radiation detected by the MODIS satellite, operated by the National Aeronautics and Space Administration (NASA) [13]. The EVI was selected over other available vegetation indices as it retains higher sensitivity in densely vegetated areas, and is more robust to interference from the canopy background signal than other vegetation indices [13].

Table A: Potential environmental predictors and their sources, indicating the covariates that were included in the models of Buruli ulcer and *M. ulcerans* suitability.

Variable	Included in model		Source
	BU	MU	
Precipitation of Driest Month	✓	✓	WorldClim v2.0 Global Climate Database [1]
Precipitation Seasonality	✓		
Precipitation of Wettest Quarter	✓		
Minimum temperature	✓	✓	
Maximum temperature			
Annual potential evapotranspiration	✓	✓	CGIAR-CSI [14]
Aridity index			
Elevation			
Topographic wetness index*		✓	Derived from elevation [4]
Distance to waterbodies	✓	✓	Derived from data from Open Street Map [5]
Distance to rivers and streams	✓	✓	
Distance to dams	✓	✓	
Distance to deforested areas	✓	✓	Derived from data from LandGIS [8]
Distance to agricultural land	✓	✓	Derived from Global Land Cover 2000 [15]

BU = Buruli ulcer, MU = *M. ulcerans*

* Topographic wetness index was selected for the BU suitability model but was dropped after the initial modelling step as it made little contribution to the model.

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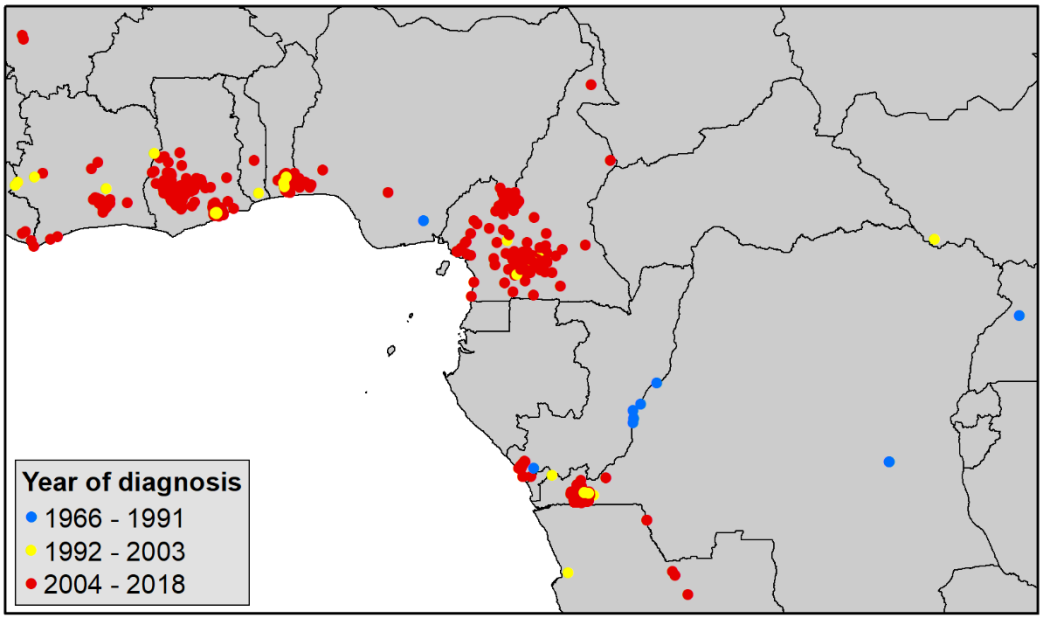
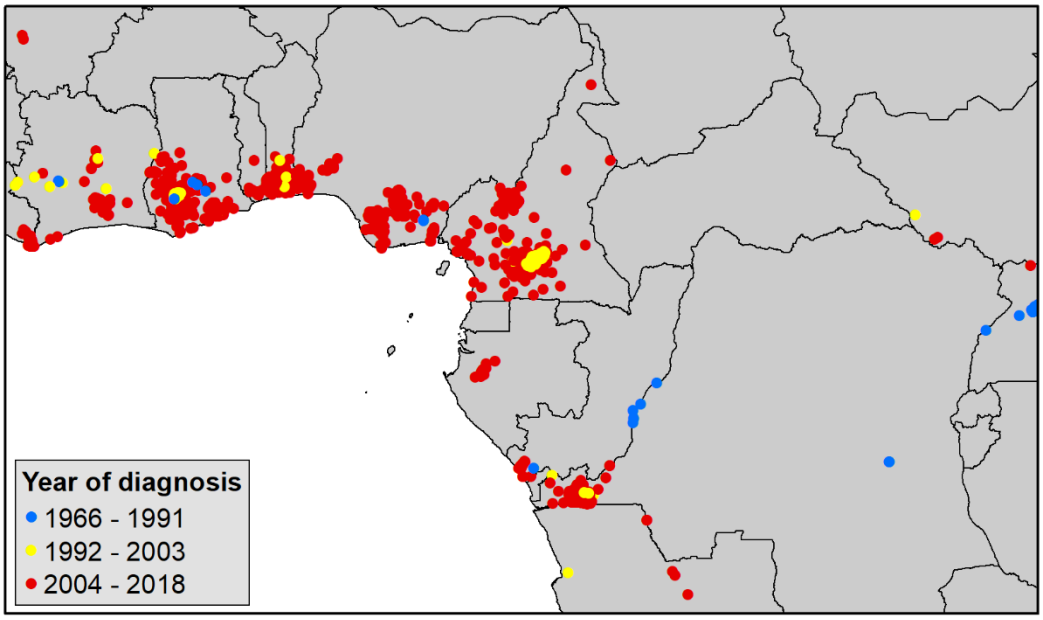
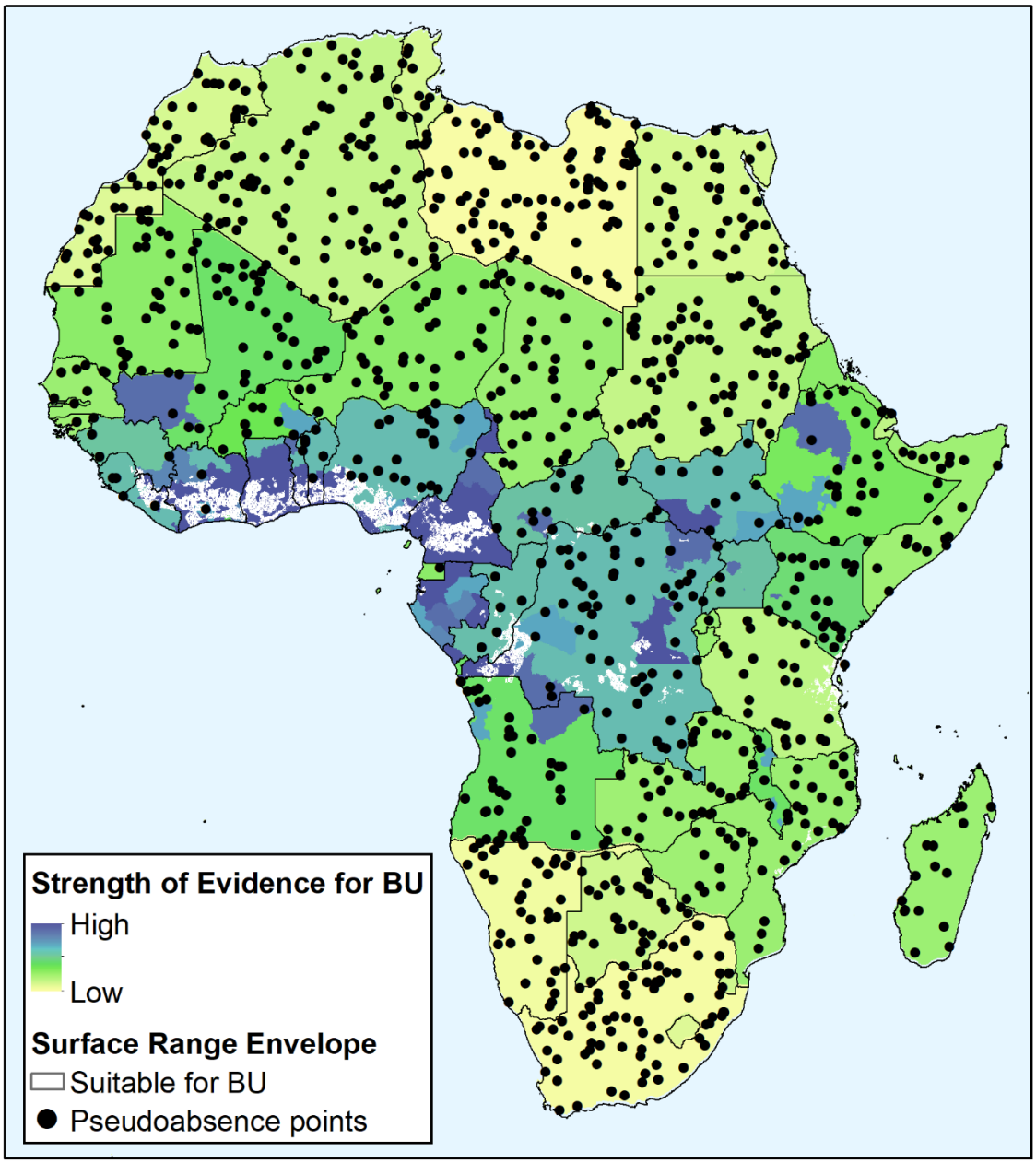
S1 Fig. Distribution of PCR and histopathologically confirmed BU cases, by year of diagnosis.
https://doi.org/10.1371/journal.pntd.0009157.s004



S2 Fig. Distribution of clinically diagnosed BU cases, by year of diagnosis.
https://doi.org/10.1371/journal.pntd.0009157.s005

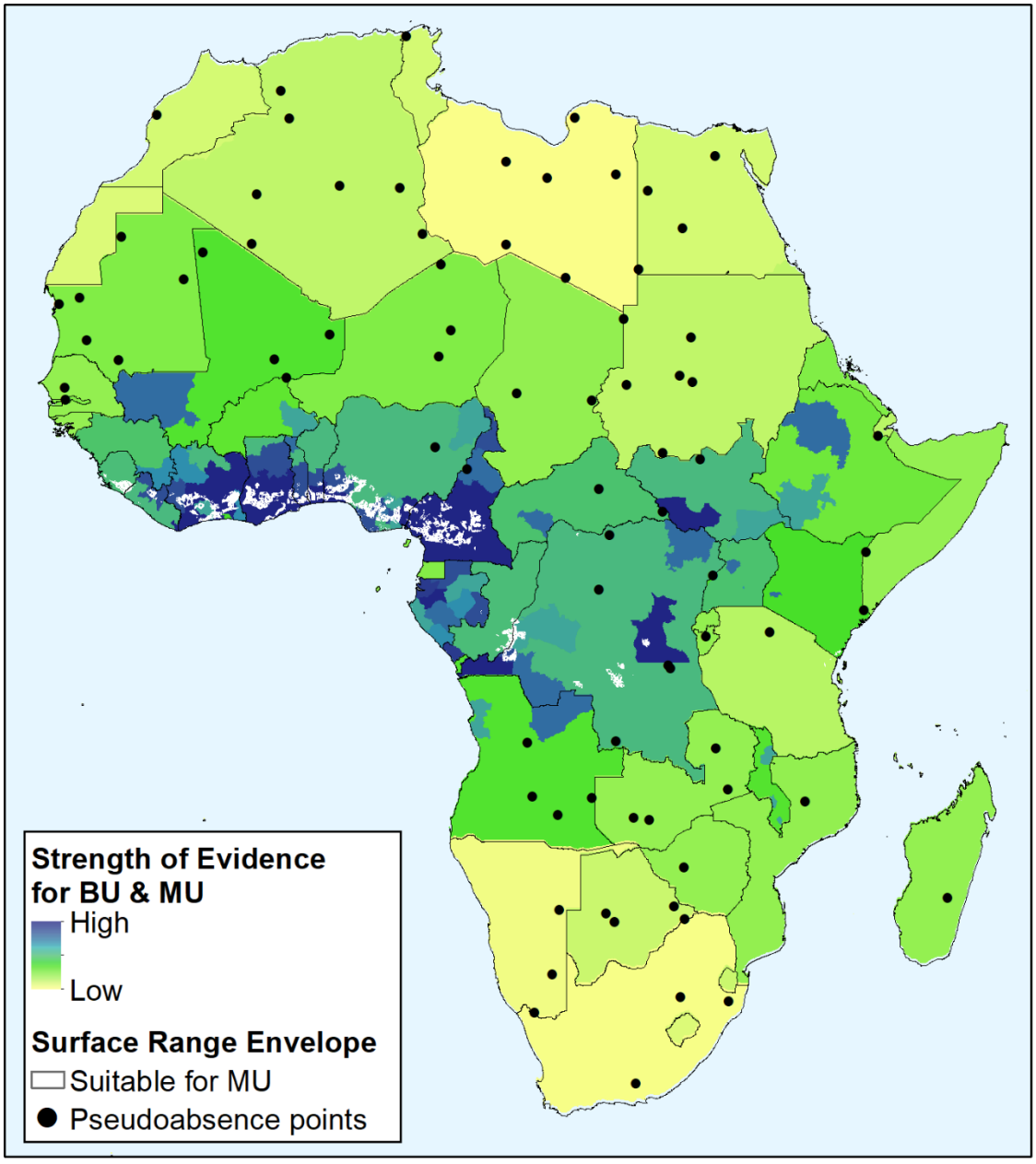


S3 Fig. Selection of pseudoabsence points included in Buruli ulcer suitability models. Pseudoabsence points were selected outside of the BU surface range envelope (white; the area containing values between the 2.5th and 97.5th percentile of all predictor variables) and selection was biased according to the strength of evidence for BU at national or subnational level (yellow to blue shading) using results from Simpson et al. Lancet Glob. Health 2019.
https://doi.org/10.1371/journal.pntd.0009157.s006

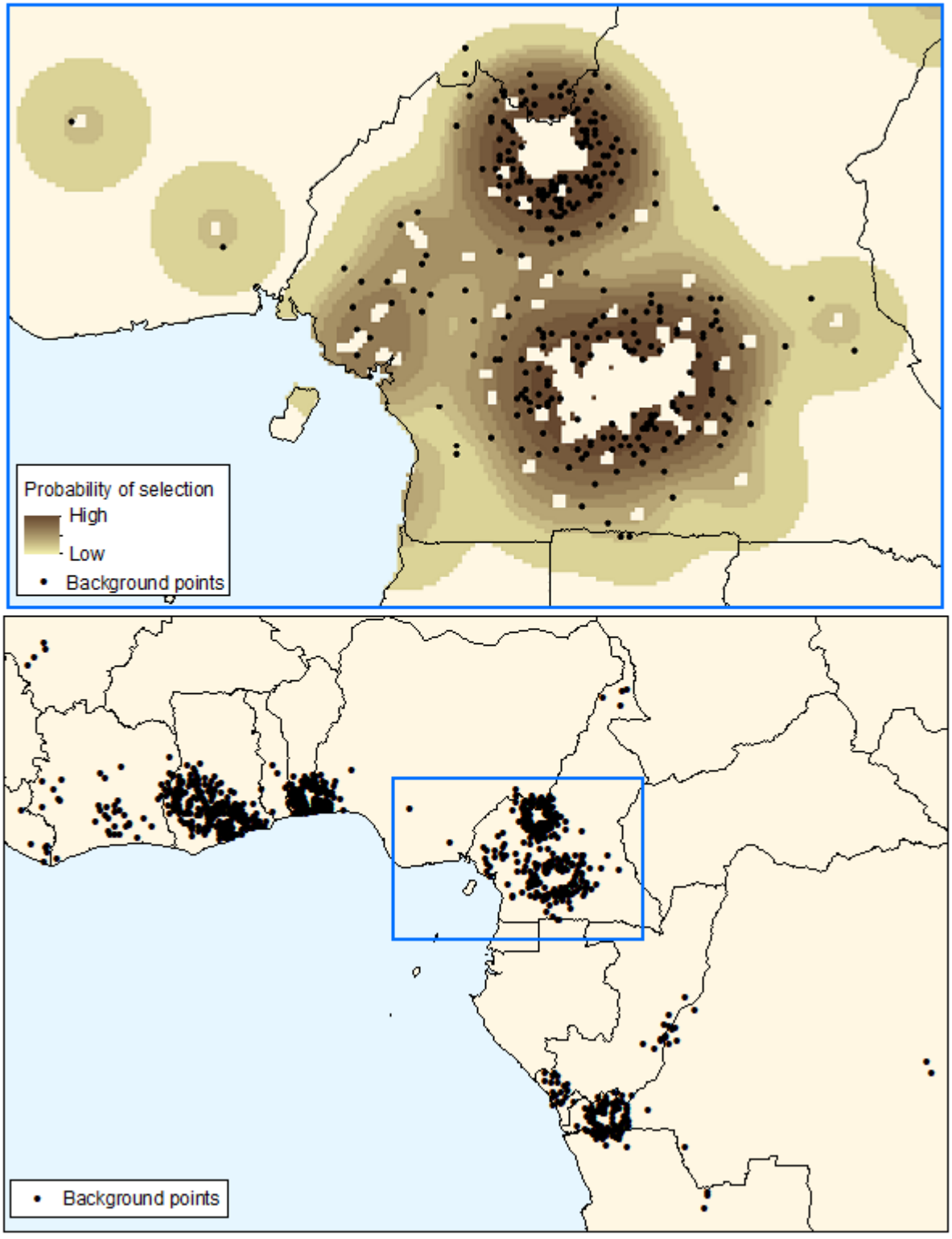


S4 Fig. Selection of pseudoabsence points included in *Mycobacterium ulcerans* suitability models.

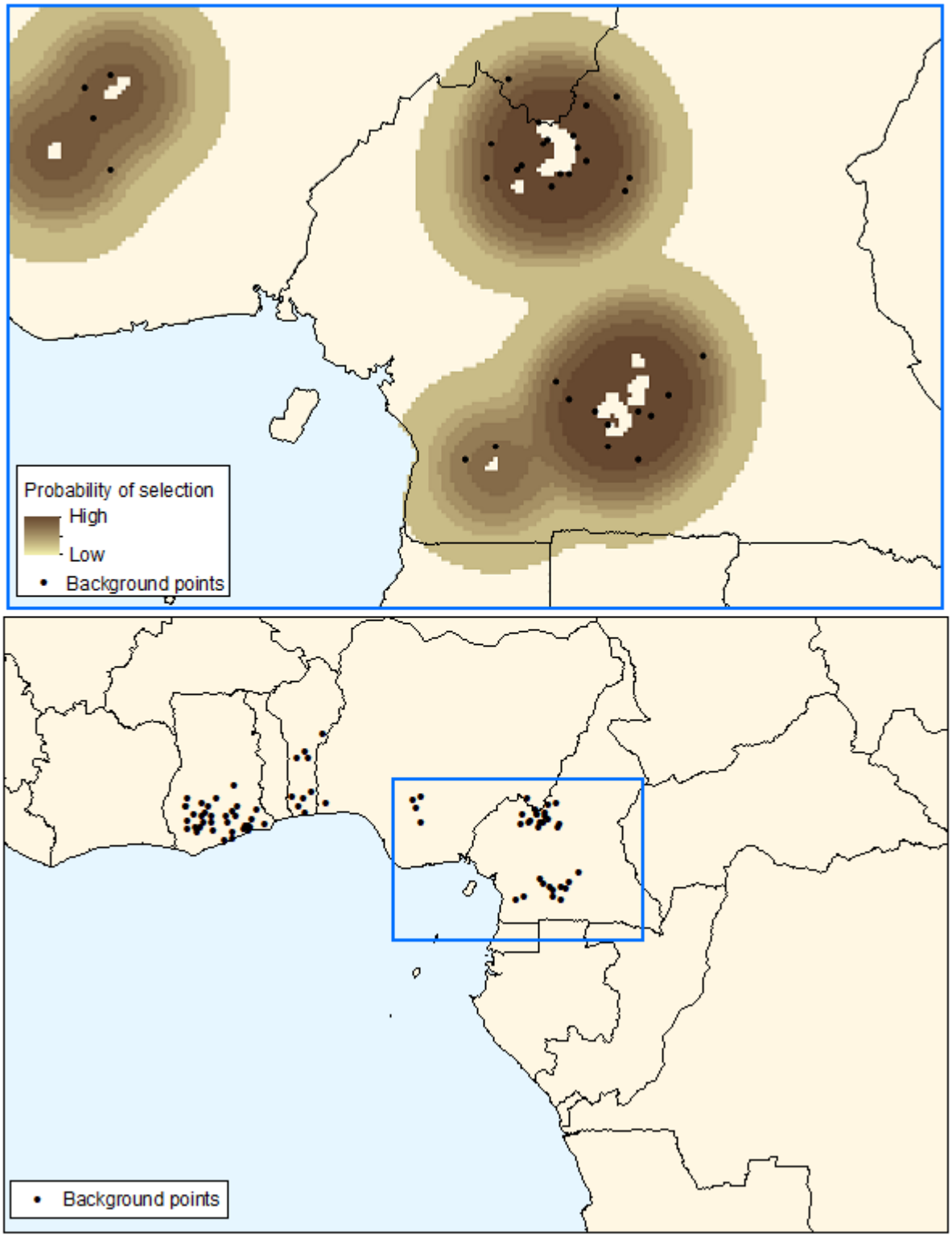
Pseudoabsence points were selected outside of the MU surface range envelope (white; the area containing values between the 2.5th and 97.5th percentile of all predictor variables) and selection was biased according to the strength of evidence for BU and MU at national or subnational level (yellow to blue shading) using results from Simpson et al. Lancet Glob. Health 2019.
https://doi.org/10.1371/journal.pntd.0009157.s007



S5 Fig. Distribution of background points used in Buruli ulcer suitability models.
Background points were restricted to a minimum distance of 10km from human occurrence points (not shown on the map) and were selected with probability defined by the kernel density surface representing the density of occurrence points.
https://doi.org/10.1371/journal.pntd.0009157.s008

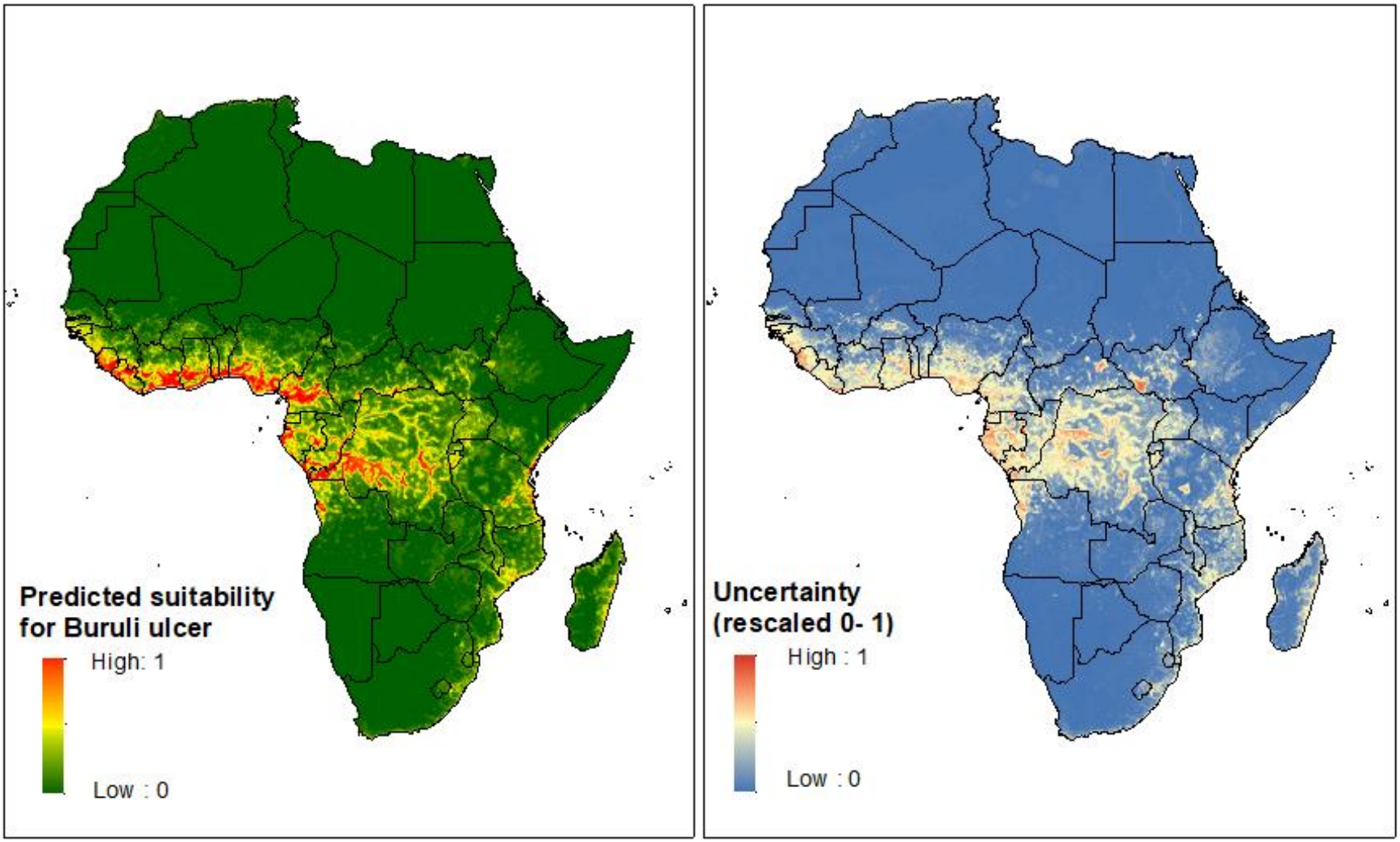


S6 Fig. Distribution of background points used in *Mycobacterium ulcerans* suitability models. Background points were restricted to a minimum distance of 10km from human or environmental occurrence points (not shown on the map) and were selected with probability defined by the kernel density surface representing the density of occurrence points.
https://doi.org/10.1371/journal.pntd.0009157.s009

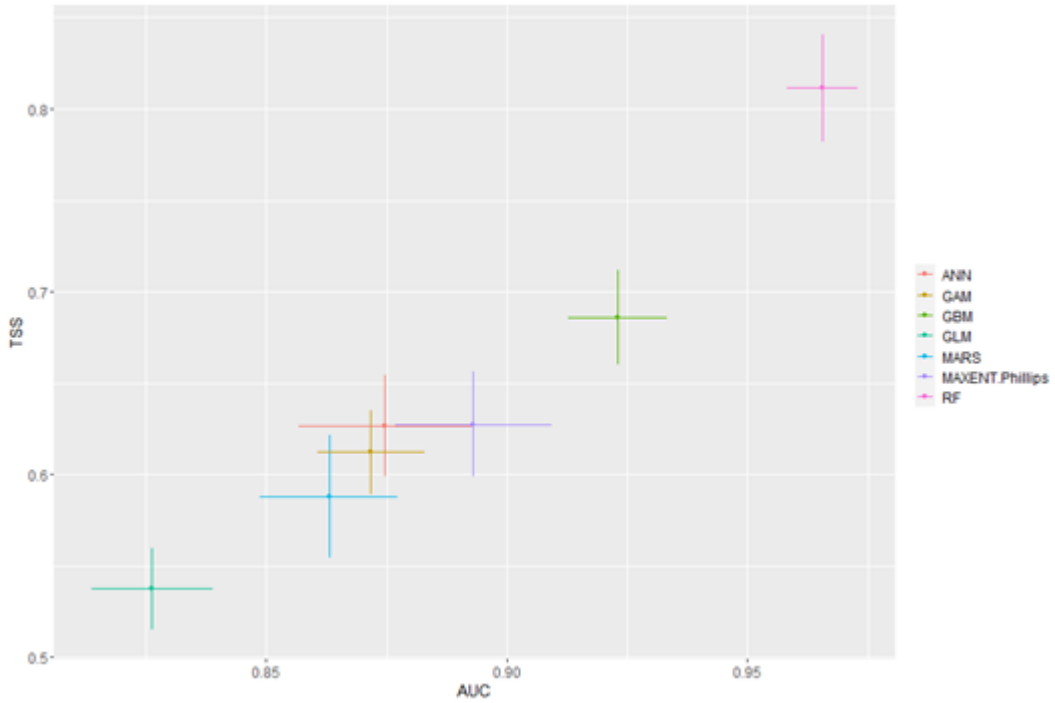


S7 Fig. Predicted environmental suitability for the occurrence of BU disease and associated error of prediction, including all clinically diagnosed cases of BU.

https://doi.org/10.1371/journal.pntd.0009157.s010



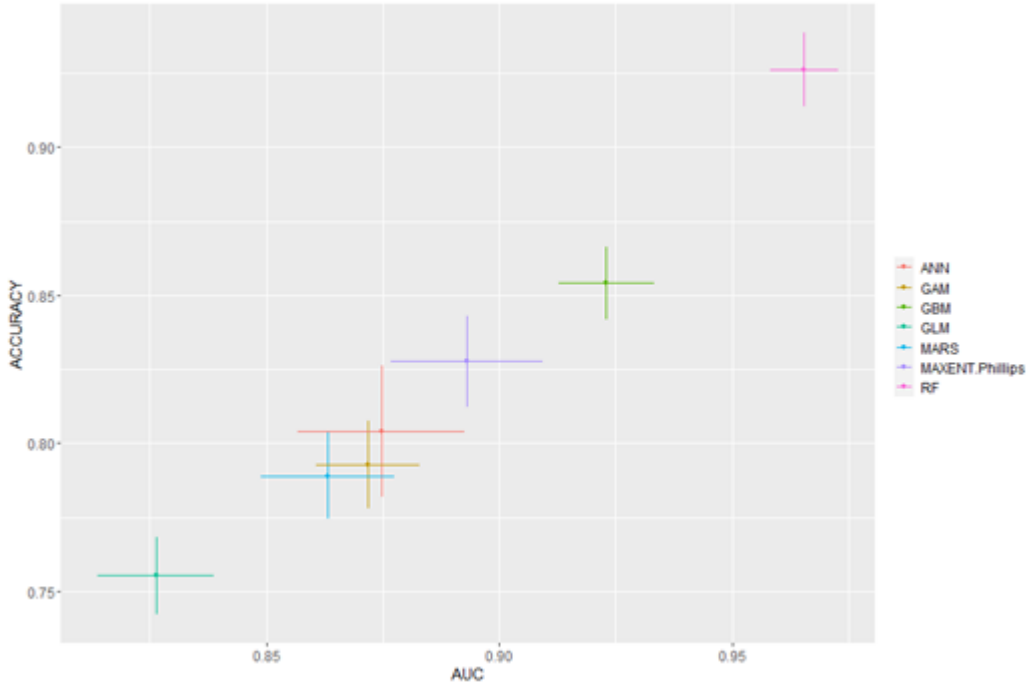
S8 Fig. Individual model performance evaluation statistics for models of environmental suitability for Buruli ulcer.
Performance evaluated in terms of the mean true skill statistic (TSS) and the mean area under the curve (AUC) of the receiver operation characteristic.
https://doi.org/10.1371/journal.pntd.0009157.s011



S9 Fig. Individual model performance evaluation statistics for models of environmental suitability for Buruli ulcer.

Performance evaluated in terms of accuracy (percent correctly classified) and the mean area under the curve (AUC) of the receiver operation characteristic. Individual model algorithms: ANN = artificial neural networks; GAM = generalized additive models; GBM = generalized boosted regression models; GLM = generalized linear models; MARS = multiple adaptive regression splines; MAXENT. Phillips = maximum entropy; RF = random forest.

https://doi.org/10.1371/journal.pntd.0009157.s012

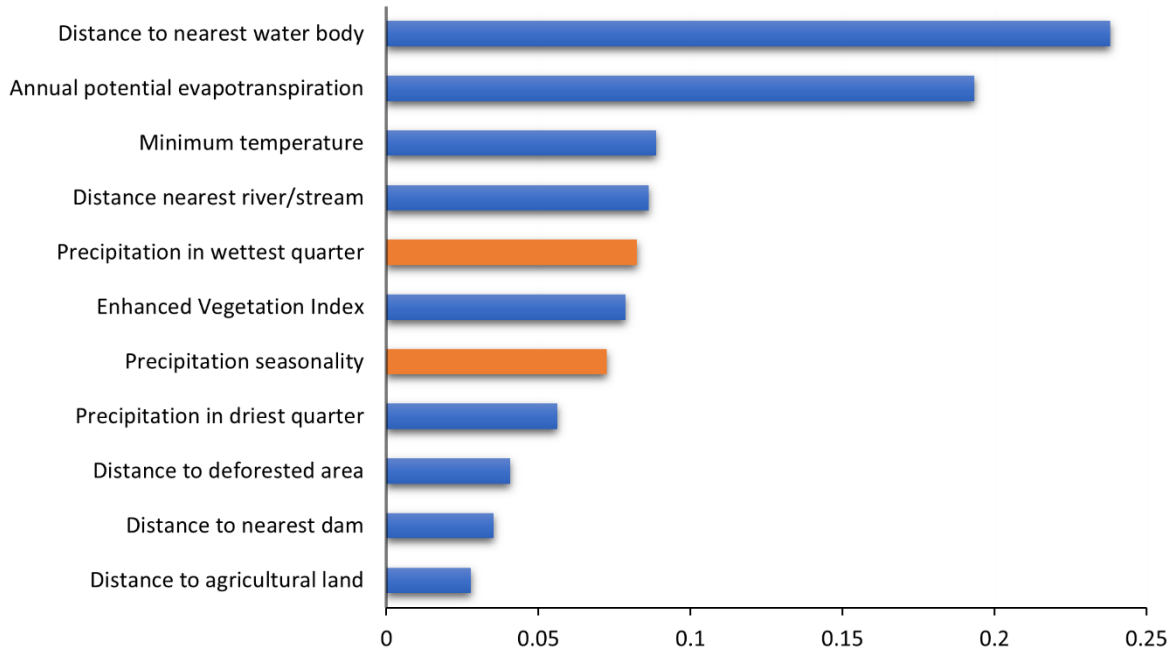


S10 Fig. Variable importance plots of the contribution of environmental covariates to random forest models of suitability.

Shows contribution of variables to model for Buruli ulcer. Blue bars = variables selected as predictors of BU occurrence and *M*. *ulcerans* in the environment. Orange bars = variables selected as predictors of Buruli ulcer (BU) occurrence only.

https://doi.org/10.1371/journal.pntd.0009157.s013

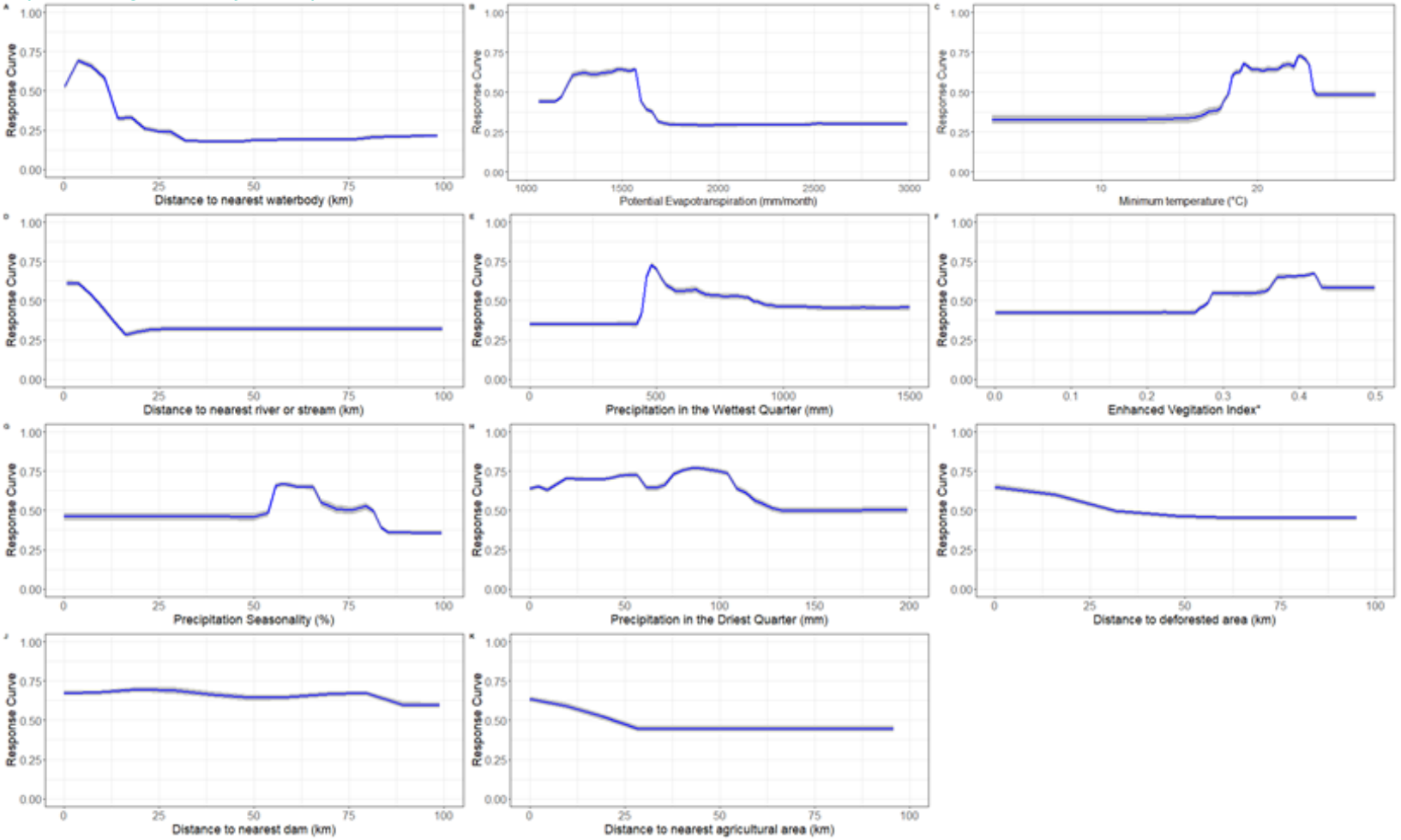
(TIF)



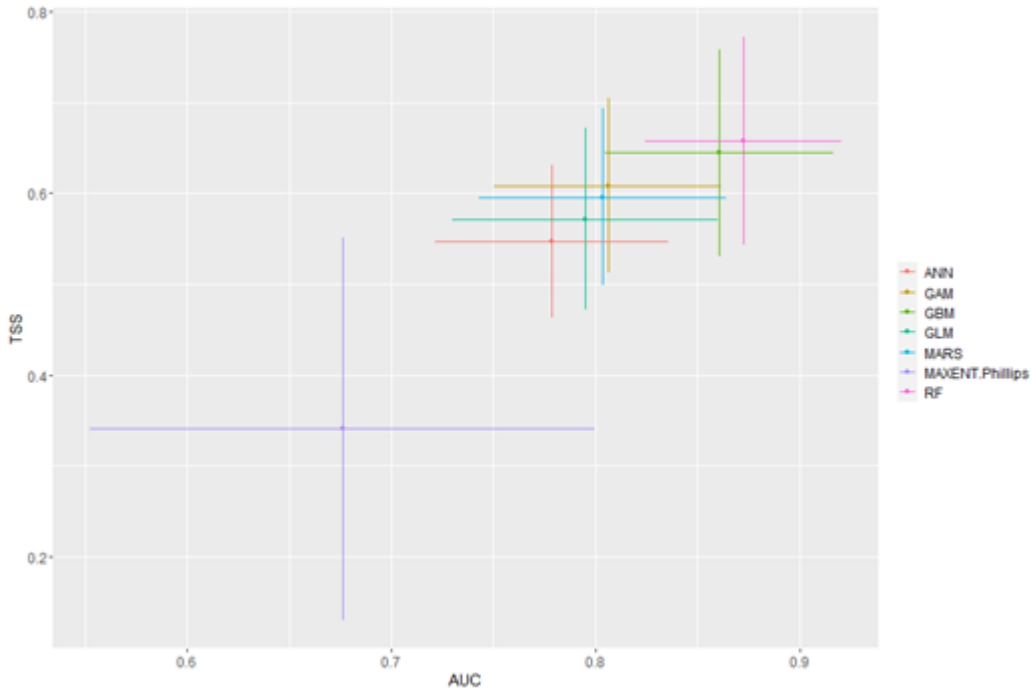
S11 Fig. Marginal effect plots showing the relationship between environmental covariates and suitability for Buruli ulcer and *Mycobacterium ulcerans* in random forest models.

Marginal Effect of Environmental Predictors on Environmental Suitability for Buruli ulcer

https://doi.org/10.1371/journal.pntd.0009157.s014



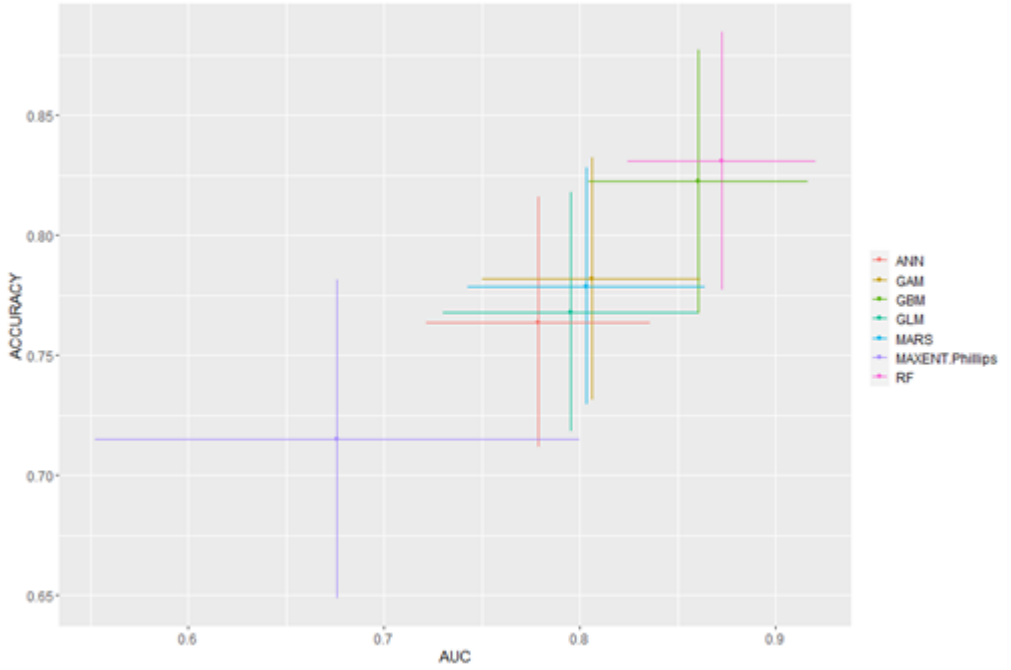
S12 Fig. Individual model performance evaluation statistics for models of environmental suitability for *Mycobacterium ulcerans*.
Performance evaluated in terms of the mean true skill statistic (TSS) and the mean area under the curve (AUC) of the receiver operation characteristic.
https://doi.org/10.1371/journal.pntd.0009157.s015



S13 Fig. Individual model performance evaluation statistics for models of environmental suitability for *Mycobacterium ulcerans*.

Performance evaluated in terms of accuracy (percent correctly classified) and the mean area under the curve (AUC) of the receiver operation characteristic. Individual model algorithms: ANN = artificial neural networks; GAM = generalized additive models; GBM = generalized boosted regression models; GLM = generalized linear models; MARS = multiple adaptive regression splines; MAXENT. Phillips = maximum entropy; RF = random forest.

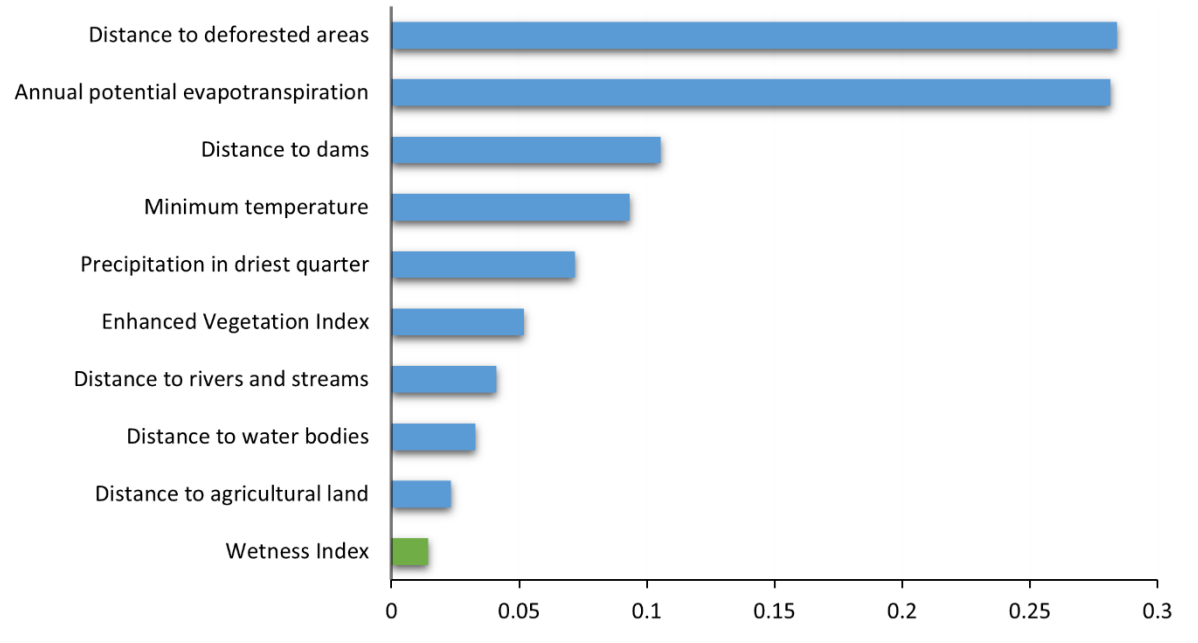
https://doi.org/10.1371/journal.pntd.0009157.s016



S14 Fig. Variable importance plots of the contribution of environmental covariates to random forest models of suitability.

Shows contribution of variables to model for *Mycobacterium ulcerans*. Blue bars = variables selected as predictors of BU occurrence and *M. ulcerans* in the environment Green bars = variables selected as predictors of *M. ulcerans* in the environment only

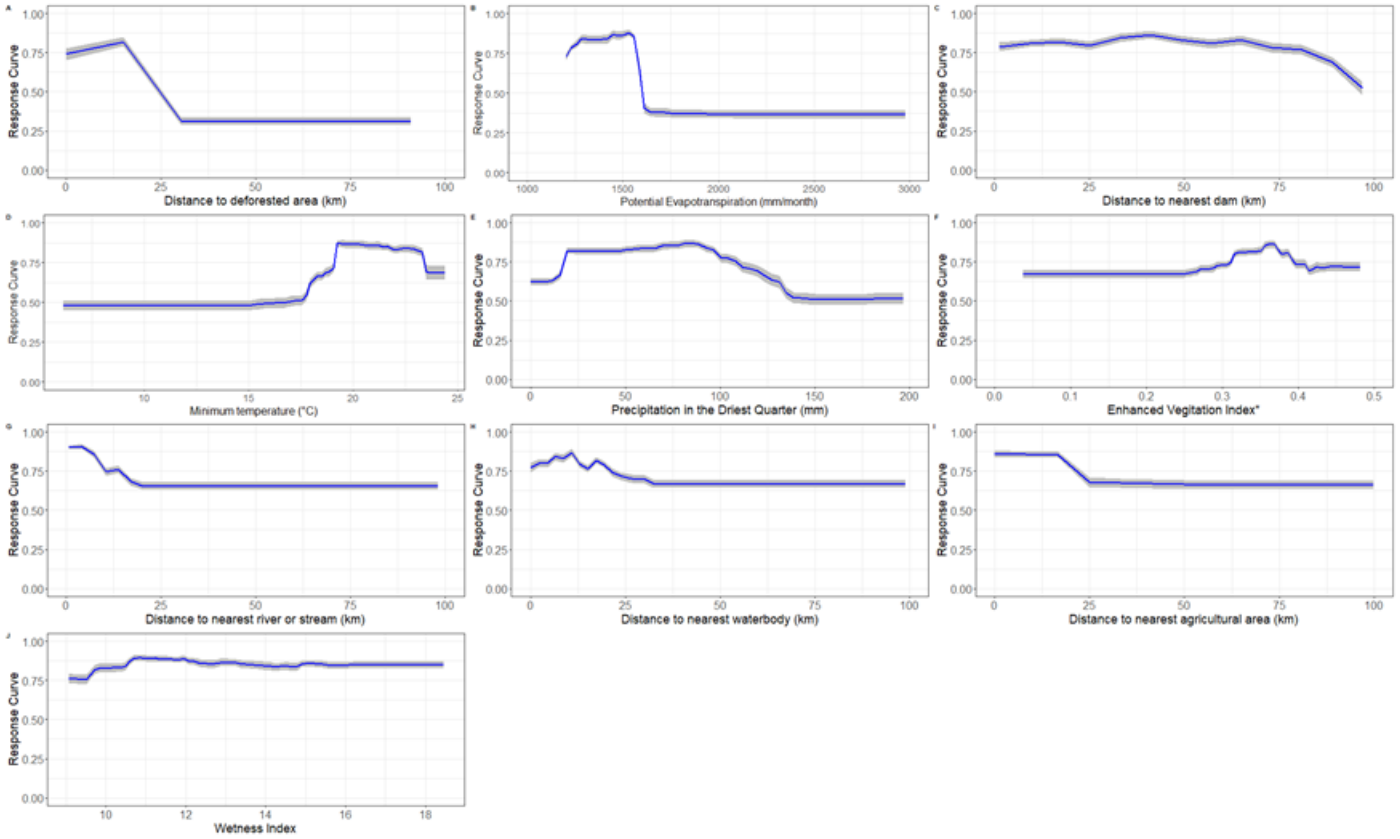
https://doi.org/10.1371/journal.pntd.0009157.s017



S15 Fig. Marginal effect plots showing the relationship between environmental covariates and suitability for Buruli ulcer and *Mycobacterium ulcerans* in random forest models.

Marginal Effect of Environmental Predictors on Environmental Suitability for *Mycobacterium ulcerans*. Variables are plotted in order of their contribution to the random forest model. Marginal effect plots illustrate the effect of each explanatory variable on the outcome of suitability for Buruli ulcer. Variables are plotted in order of their contribution to the random forest model. *Interpretation of Enhanced Vegetation Index: low values (0.1–0.15) represent areas of barren rock or sand and built-up land; moderate values (0.15–0.3.5) may indicate shrubs, grassland or cropland; higher values (0.35–0.6) may indicate mixed wood and shrubs or open forest.

https://doi.org/10.1371/journal.pntd.0009157.s018



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ORIGINAL ARTICLE

Developing consensus of evidence to target case finding surveys for podoconiosis: a potentially forgotten disease in India

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Background: Podoconiosis is a non-infectious geochemical lymphoedema of the lower legs associated with a significant burden of morbidity. There are historical reports of podoconiosis in India, but its current endemicity status is uncertain. In this investigation we aimed to prioritise the selection of districts for pilot mapping of podoconiosis in India.

Methods: Through a consultative workshop bringing together expert opinion on podoconiosis with public health and NTDs in India, we developed a framework for the prioritisation of pilot areas. The four criteria for prioritisation were predicted environmental suitability for podoconiosis, higher relative poverty, occurrence of lymphoedema cases detected by the state health authorities and absence of morbidity management and disability prevention (MMDP) services provided by the National Programme for Elimination of Lymphatic Filariasis.

Results: Environmental suitability for podoconiosis in India was predicted to be widespread, particularly in the mountainous east and hilly southwest of the country. Most of the districts with higher levels of poverty were in the central east and central west. Of 286 districts delineated by state representatives, lymphoedema was known to the health system in 189 districts and not recorded in 80. Information on MMDP services was unavailable for many districts, but 169 were known not to provide such services. We identified 35 districts across the country as high priority for mapping based on these criteria.

Conclusions: Our results indicate widespread presence of conditions associated with podoconiosis in India, including areas with known lymphoedema cases and without MMDP services. This work is intended to support a rational approach to surveying for an unrecognised, geographically focal, chronic disease in India, with a view to scaling up to inform a national strategy if required.

Keywords: ecological niche modelling, evidence consensus, lymphedema, morbidity management and disability prevention, Podoconiosis, surveillance data, targeting surveys

Introduction

Podoconiosis is a non-infectious geochemical lymphoedema of the lower legs, caused by long-term barefoot exposure to red clay soil of volcanic origin.[1,2] The disease is associated with specific environmental and climatic factors and with cultural and behavioural practices that increase the risk of contact with irritant soils.[1] The disease can be prevented by the use of footwear and the resulting lymphoedema is reversible in its early stages, while advanced lymphoedema can be managed to reduce the incidence of painful episodes of acute inflammatory attacks and prevent or slow progression.[3,4] As such, there is a strong rationale for estimating the burden of disease and identifying populations at risk so that interventions can be scaled up and targeted to areas of need.

The global burden and distribution of podoconiosis are not precisely known: like other neglected tropical diseases (NTDs) associated with chronic morbidity, the disease is recognised to be grossly underdetected and underreported due to social,

structural and epidemiological factors.[5] Podoconiosis is a highly stigmatising condition, most prevalent in poor, rural communities with low access to healthcare for diagnosis and treatment. The disease is scarcely known among healthcare workers[6] and has been considered 'the most neglected tropical disease'.[7] National policies and programmes targeting the disease are non-existent in most of the potentially endemic countries and organisations working on podoconiosis are limited to a few grassroots non-governmental organisations. Within this context, people affected by podoconiosis are unlikely to seek care; if they do, they are unlikely to be correctly diagnosed or reported.

Given the paucity of routine data on podoconiosis, population-based surveys combined with environmental modelling have become the mainstay of ongoing global efforts to estimate the burden and map the distribution of the disease.[8] Surveys in Cameroon, Ethiopia and Rwanda have found a prevalence of between 0.06 and 4.05% at the national level, and higher within barefoot populations.[9–11] Predictive models informed by empirical data from these surveys have revealed strong environmental associations, with the potential ecological niche mostly restricted to remote rural areas and characterised by annual precipitation levels and elevation and a lesser influence of vegetation, topography, hydrology and soil factors.[12] Extrapolation of this niche across the African continent suggests that 114.5 million people in Africa live in areas suitable for the disease.[8]

The risk of podoconiosis depends also on the level of exposure to irritant soils—people who lack footwear and are engaged in occupations that involve extensive contact with soil, including farming, mining, and floor loom weaving, are at highest risk.[1] In Ethiopia, sociodemographic risk factors for podoconiosis include lack of education, non-professional occupation and living in a house with mud or earth floors.[13] Since these risk factors are also indicators of general poverty,[14] we expect podoconiosis to be concentrated in deprived populations within environmentally suitable areas.

There is historical evidence of podoconiosis occurring in India,[2,15–17] although cases are not currently reported by the health system. The application of an evidence consensus framework, a method designed to evaluate the evidence for the occurrence of a disease based on multiple weighted criteria,[18,19] identified strong evidence of podoconiosis occurrence in India.[20] The evidence consensus framework took account of cases reported in published and grey literature, as well as likely causes of underreporting, including the occurrence of diseases with clinically similar presentations that might mask the incidence of podoconiosis. Despite strong evidence for podoconiosis in India, its current endemicity status is unknown. The disease may have been eliminated through socio-economic development, or it may persist in suitable environments and populations, unrecognised by the health system due to underdetection or misdiagnosis.

Lymphoedema is certainly widespread in India,[21] which bears one of the highest burdens of lymphatic filariasis (LF) globally,[22,23] with 600 million estimated to be at risk of the disease and 800 000 estimated cases of lymphoedema.[24,25] Filarial and geochemical lymphoedema show substantial clinical overlap and are both associated with acute attacks, which are painful for patients and cause further lymphatic impairment, leading to worsening of the condition.[26] Podoconiosis surveys in Africa have shown that podoconiosis is frequently misdiagnosed as LF, the latter being more widely recognised by healthcare workers.[11] This not only risks underestimation of the burden of podoconiosis, but may also confound the measurement of progress towards LF elimination.

From the perspective of case management for lymphoedema, the distinction of the cause is less important: all patients require morbidity management and disability prevention (MMDP), including frequent washing, elevation and massage, treatment of secondary infections and management of acute attacks to prevent further lymphatic impairment.[4] In India, training on self-care is provided through the National Programme to Eliminate Lymphatic Filariasis (NPELF), under the National Vector Borne Disease Control Programme (NVBDCP).[25] This implies that hypothetically, podoconiosis cases occurring within LF-endemic districts may benefit from MMDP if detected through routine channels for LF morbidity case finding. In contrast, cases of lymphoedema arising in non-LF-endemic districts are unlikely to receive MMDP through the NPELF. With this in mind, case finding activities for podoconiosis would be of most benefit to patients if targeted to districts not currently providing MMDP services through the NPELF.

In this investigation we aimed to prioritise the selection of districts for pilot mapping of podoconiosis in India according to four criteria: potential environmental suitability for podoconiosis, higher relative levels of poverty (assuming lower access to footwear and thus higher exposure to irritant soils among the poorest), occurrence of lymphoedema cases detected by the state health authorities and the absence of MMDP services provided by the LF programme. This is intended to inform a rational approach to surveying for an unrecognised, geographically focal, chronic disease in a vast and varied country, with a view to scaling up to inform a national strategy if required.

Methods

Study design

This was a consensus development exercise, applying a systematic framework to consolidate expert opinion and programmatic experience from within India with empirical evidence from other countries.

Study location

India is a South Asian country with a population of >1.3 billion and a total land area of >3 287 263 km^2.[27] It is organised into 28 administrative states and 8 union territories,[28] further divided into districts, totalling 668 in 2015.[29] State governments are responsible for the provision of healthcare and the public health system, while certain specific health programmes and initiatives are organised by the central government.[30,31]

LF programme and MMDP for lymphoedema

Government-led programmes to control LF in India have been implemented for many years, with the current NPELF in place since 2004.[32] Its key strategic pillars are the interruption of transmission through mass drug administration (MDA) and the alleviation of suffering through MMDP. The programme initially

covered 202 districts in 20 states and union territories and was subsequently scaled up to reach 256 endemic districts targeting a population of about 600 million.[32] During MDA campaigns, cases of lymphoedema are recorded at the village or subcentre level through house-to-house visits. Cases are aggregated at the primary health centre (PHC), district and state levels. People with lymphoedema are given demonstrations and training on World Health Organization–recommended hygiene-based management of lymphoedema and are encouraged to practise self-care.[32]

Development of the consensus framework

The consensus framework for the prioritisation of districts for piloting podoconiosis surveys was developed through a consultative workshop held at the Amrita Institute of Medical Sciences Ernakulam, Kerala, 10-11 December 2019. Experts in public health, community medicine, NTDs and LF from all states and union territories in India (hereafter 'state representatives') and international experts on podoconiosis were invited to this workshop in order to share their expertise for development of the framework. Those who were unable to join were engaged through remote communication after the workshop.

Following presentations on the clinical and epidemiological aspects of podoconiosis, its treatment, geographic distribution and environmental associations and LF in India, the group discussed and refined the framework to consolidate evidence that would determine priority selection of districts for pilot mapping. It was agreed that the framework should prioritise districts with suitable environmental conditions for podoconiosis, where the population was most at risk based on socio-economic indicators of poverty, where lymphoedema cases were known to the health system and where patients were less likely to be served by MMDP services (Figure 1).

When the final framework was agreed upon, state representatives formed groups to discuss the target criteria in each district within their states. On the final day of the workshop, state representatives presented the results of the consensus framework to grade the priority for mapping podoconiosis and any data gaps in each district. Data gaps were later filled through remote consultation with state health officials.

The final criteria for targeting pilot mapping surveys were district predicted to be suitable or moderately suitable for podoconiosis, district poverty higher than the median, lymphoedema cases known to the health system within the district and district does not currently implement MDA against LF and transmission interruption not recently certified.

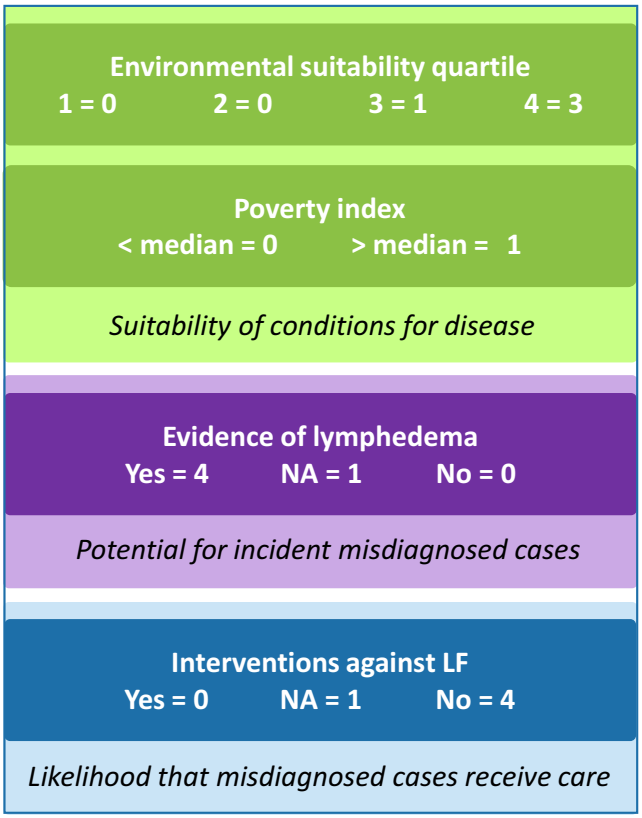

Figure 1. Weighted criteria for prioritisation of districts for pilot mapping of podoconiosis in India.

Data sources

Environmental suitability for podoconiosis was extrapolated from an ensemble model using podoconiosis occurrence data from eight countries in Africa, primarily from national surveys in Cameroon, Ethiopia and Rwanda,[9,10,13] and a suite of environmental covariates potentially associated with the disease. The data sources and development of this model have been described elsewhere.[8] Elevation and annual precipitation were the strongest predictors within the model, with the highest suitability predicted in areas with 1000– 1500 mm annual precipitation and elevation >1000 m above sea level. Other environmental predictors included soil characteristics (clay and silt fractions) and soil acidity of the topsoil, the mean land surface temperature, distance to the nearest body of water and enhanced vegetation index, a measure of vegetation cover. The mean suitability was projected at a resolution of grid cells of 5 km × 5 km and categorised into quartiles. The modal quartile of averaged suitability was calculated in each district. Districts with a modal quartile of 4 were classified as 'suitable', those with a modal quartile of 3 were classified as 'moderately suitable' and those with a modal quartile <3 were classified as 'not suitable'.

We used a multidimensional index of poverty (MDPI) produced by the Oxford Poverty and Human Development Initiative[14] to classify relative levels of poverty at the district level. The MDPI includes various indicators of health, education and living standards and takes account of the proportion of the population who are poor and the intensity of deprivation among the poor.[14] The district-level MDPI was assigned to each district defined by the GADM 2015 based on state and district names, using fuzzy logic implemented in R (R version 4.0.1 (2020-06-06), R Foundation, Vienna, Austria) to allow for variation in spellings. Districts with an MDPI above the median value were categorised as 'more deprived'.

State representatives compiled surveillance data on the incidence of lymphoedema detected through the health system in each district in their own states. Using these data, each

Table 1. Criteria for prioritising pilot mapping of podoconiosis in districts of India

	Levels of criterion		
Criteria for mapping	Number of districts in each category (N=286)		
Environmental suitability	High (MQ4)	Moderate (MQ3)	Low (MQ1 and 2)
	101	100	85
Relative poverty	Higher	Lower	
	124	162	
Evidence of lymphoedema	Recorded	Not recorded	Information NA
	189	80	17
MMDP services	Implemented	Not implemented	Information NA
	15	169	102

Numbers of districts are those described by state representatives. MQ: modal quartile (see Methods)

district was categorised according to the known occurrence of lymphoedema: 'present', 'not detected' or 'unknown'.

The state representatives also contributed programmatic information on the implementation of interventions against LF through the NPELF in each district. Districts classified as endemic or in which interruption of LF transmission had recently been certified were considered the most likely to deliver MMDP services for lymphoedema patients.

Data analysis

The units of analysis were districts defined by the state representatives. Most of these districts were represented in the dataset of second-level administrative areas in India defined by the database of Global Administrative Areas (GADM) in 2015,[29] while some were represented in the equivalent version of the dataset from 2012[28] but had been redistricted prior to 2015. The districts described by state representatives were linked to the districts defined by the GADM 2015 and the GADM 2012 using fuzzy logic, as described above. Districts that were not represented within either GADM dataset were manually linked by state representatives to districts from the 2015 shapefile.

The evidence was collated through a scoring system that attributed fixed scores to different levels of each of the target criteria (Figure 1). The component scores assigned to each district were summed to provide an overall consensus score. Districts scoring >75% of the maximum score were considered high priority for mapping.

In order to map the results, the evidence compiled in the workshop was linked to the shapefile of districts in 2015. Full details of the linkage of districts to the shapefile are provided in Supplementary Methods.

Results

Representatives from 27 states compiled data for 286 districts. The continuous extrapolated environmental suitability for podoconiosis in India is shown in Supplementary Figure 1. The modal quartile of averaged suitability was calculated in each district and linked to the district cartography. In total, 101 of 286 districts described by the state representatives and 191 of 668 from the GADM 2015 shapefile were predicted to have high suitability for podoconiosis (Table 1). Moderate suitability was predicted in 100 districts defined by the state representatives and 190 from the GADM 2015 shapefile. Twenty-three states and union territories included districts from the GADM 2015 shapefile that were predicted highly suitable.

Data on the incidence of lymphoedema was obtained for 269 districts within 24 states. The state representatives reported lymphoedema cases known to the health system in 189 districts. Information on MDA implementation was available for 184 districts, representing 19 states. These data indicated that 15 districts were LF endemic or had recently interrupted transmission, while 169 had no LF programme coverage and were thus unlikely to be implementing MMDP services (Table 1).

Figure 2 shows the levels of each component at the district level. Supplementary Table 1 shows the full results of the weighted scoring system for all of the districts identified by the state representatives. A full summary of the evidence categories assigned for all observed configurations of component scores is shown in Supplementary Figure 2. In total, 35 districts were identified as high priority for mapping and 108 were classified as medium priority (Table 2, Figure 3).

The districts listed by state representatives that were predicted highly suitable represented 17 states and union territories. Districts with higher levels of poverty were in 19 states and union territories. Lymphoedema cases were known to the health system in 12 states and union territories and 17 states and union territories were not known to implement interventions against LF.

Discussion

Through a cooperative, consultative process, we have developed and applied an evidence-based framework to prioritise the selection of districts for podoconiosis case finding surveys in India. The key criteria identified through the consensus development process were suitability for podoconiosis based on

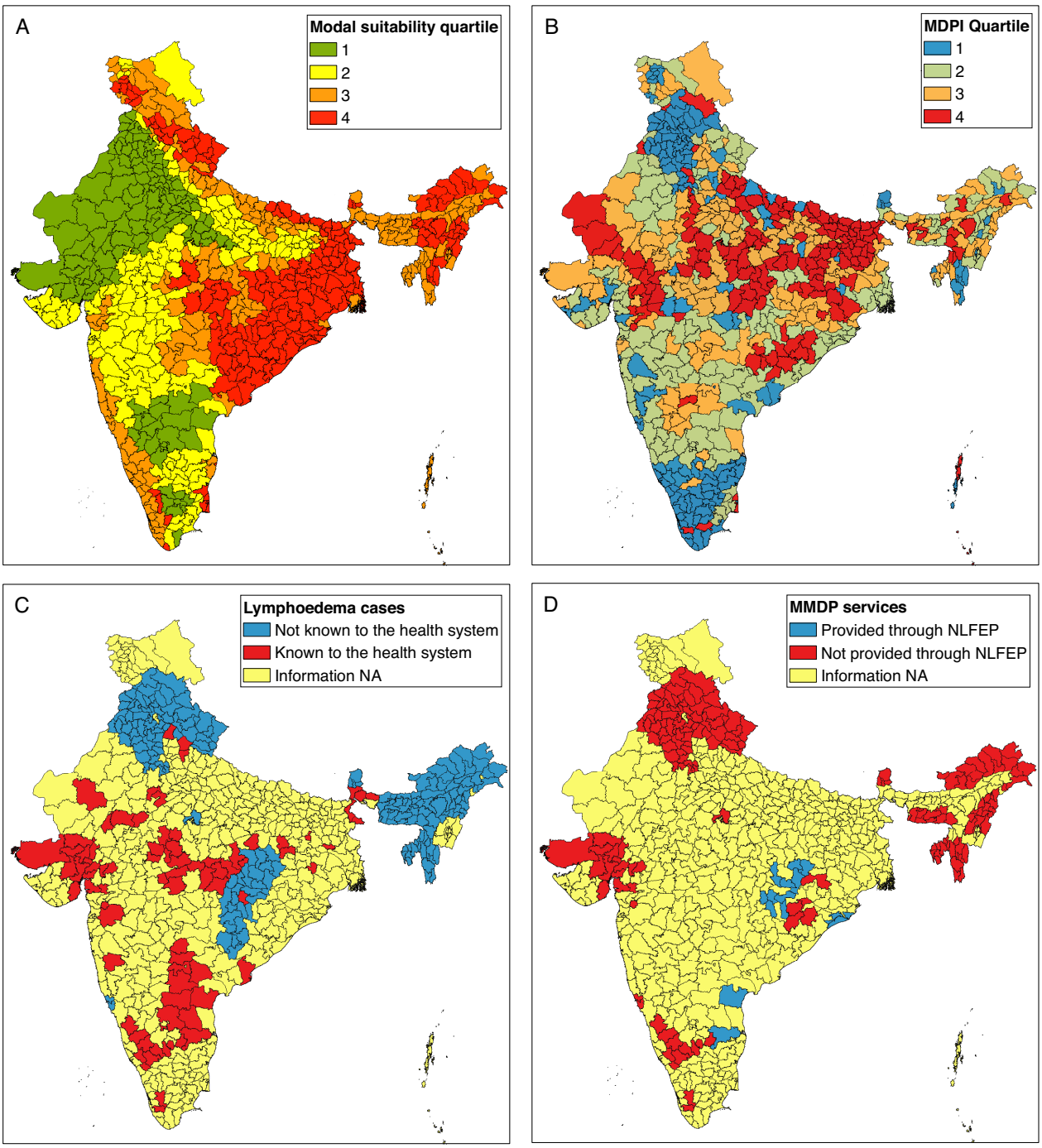

Figure 2. Component scores for prioritisation of podoconiosis mapping surveys at the district level.

evidence from environmental modelling and socio-economic indicators, the occurrence of conditions clinically consistent with the disease according to local expert opinion and the absence of case management services based on the coverage of the NPELF. This enabled the identification of 35 districts where the disease was most likely to occur and where patients were least likely to be able to access MMDP services. These districts are considered to be key targets for initial surveys to establish the endemicity status of podoconiosis in India.

The priority districts we identified are dispersed through nine states across India. None of the districts were assigned the maximum score across all of the criteria, and among those identified as being high priority mapping targets, there is variability in their suitability against different criteria. Those with the highest scores

Table 2. Total numbers of districts by level of priority for mapping

Evidence score (%)	Priority	Number of districts
75–100	High	35
50–74	Medium	108
25–49	Low	134
0–24	Very low	9

had known cases of lymphoedema and no known MMDP services but were predicted to be only moderately environmentally suitable and showed lower rates of relative poverty. Other districts identified as high priority had high environmental suitability, known cases of lymphoedema and no information on MMDP services. The framework and results are intended to provide an evidence-based tool to facilitate and inform decisions rather than to drive them. Other criteria, such as logistical feasibility of surveying, will also be considered when these decisions are made.

A key strength of this exercise was its success in consolidating a substantive knowledge base from experts of multiple relevant disciplines across most states of India. The consultative workshop enabled the sharing of knowledge and ideas among a group with a great diversity of experience and brought a varied range of perspectives to the development of the consensus framework. The outcome was a locally relevant evidence base supported by varied sources of empirical data and expert opinion. The collaborative process also built a supportive and knowledgeable local network that will be vital to the success of future efforts to map and address the burden of podoconiosis in India, if it is found to be endemic.

Throughout the consultation, there was ongoing discussion on the justification for each of the criteria within the framework. There was recognition of the need to balance rational resource allocation with sensitivity to detect a disease that might occur at very low prevalence, if at all, in a very large geographical

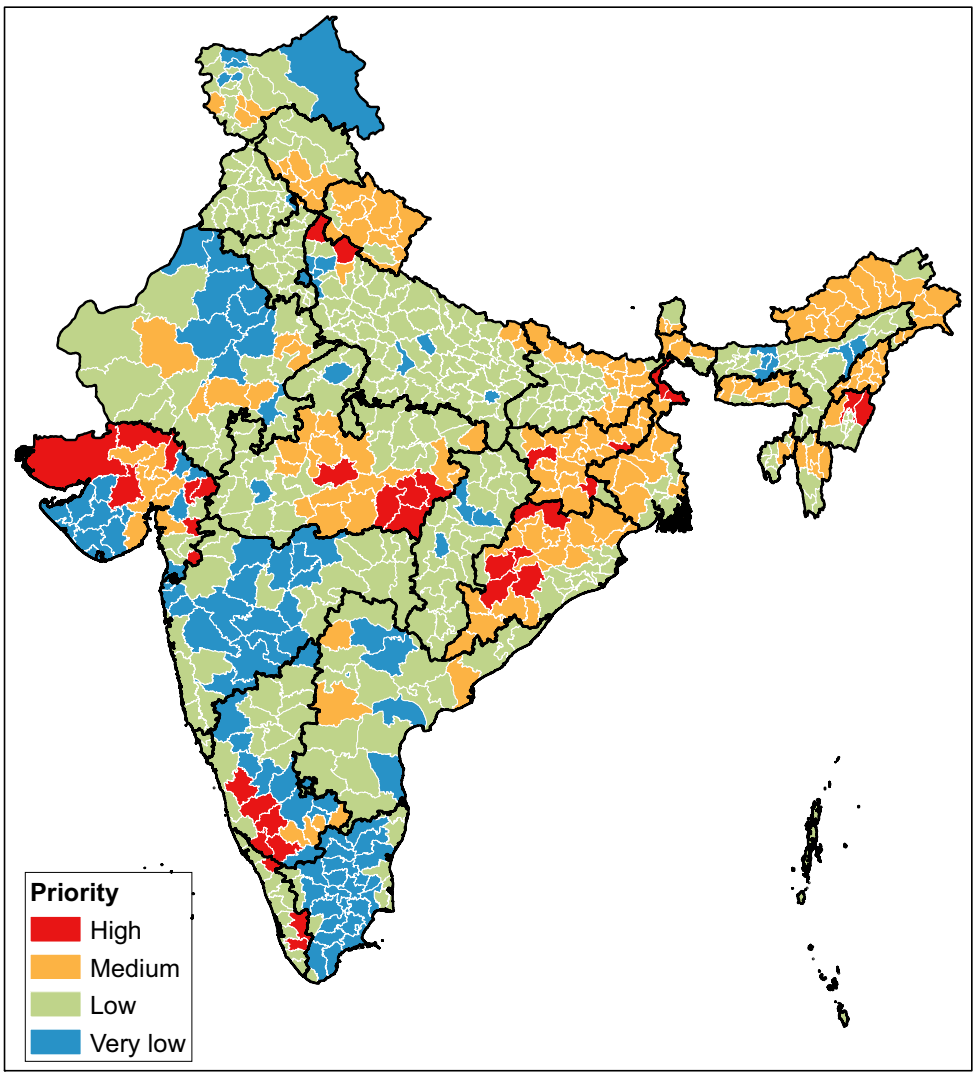

Figure 3. Level of priority for mapping surveys for podoconiosis at district level in India.

area. Due to the lack of contemporary data on podoconiosis in India, suitability for podoconiosis was extrapolated from an environmental model informed by data from Africa. It is not known whether the environmental associations of podoconiosis in Africa can be applied in India, but since podoconiosis has strong environmental drivers and is associated with specific geographic and climatic conditions, the main environmental associations are expected to be consistent across different geographical areas. This is supported by experience of podoconiosis surveys in Cameroon that identified the highest rates of the disease in areas predicted to be highly suitable by a model based mainly on data from Ethiopia.[9] In this investigation, districts were classified as highly suitable if most of the area within them was in the upper quartile of suitability based on environmental model predictions. This classification may have deprioritised districts with varied environmental conditions and focal suitability for podoconiosis. Prospective pilot surveys in India will provide an opportunity to evaluate the external validity of the existing models. Furthermore, any newly identified cases will be used to develop more specific models of environmental suitability within India, which will inform the scale-up of mapping surveys and burden estimation.

The investigation was affected by missing data, particularly on the occurrence of lymphoedema and the provision of MMDP services at the district level. The true distribution of lymphoedema in India, which may include cases of podoconiosis, is likely to be broader than that represented by existing surveillance data. This may have led to deprioritisation of potentially endemic districts lacking data. The coverage of MMDP services may also be broader than we estimated, since such services may be delivered outside of the LF elimination programme or at a small local scale. We do not consider this to be a significant limitation to the work: if surveys are implemented in districts where MMDP is already provided, it may be possible to strengthen and support these services to ensure they reach all people affected by lymphoedema.

Our results will help determine the contemporary endemicity of podoconiosis in India, refine global understanding of the epidemiology of the disease and guide future mapping strategies. We recommend a pilot study using robust sampling and diagnostic strategies be conducted in one or two districts. The aims of this study will be to establish the occurrence of podoconiosis and to investigate its social and spatial epidemiology in India. The study must be carefully designed to detect spatial and environmental variation, which are critical for future modelling of the risk of podoconiosis across India.

Conclusion

The consensus development framework we have applied constitutes an important first step in building the evidence for podoconiosis endemicity in a country where there is a strong indication of disease existence but scarce data for public health action. As a preliminary exercise, this analysis suggests that podoconiosis may occur in multiple districts across India. If true, this implies a large population at risk, some of whom would not be covered by existing services for MMDP. Case searches for podoconiosis should be planned in districts most likely to harbour cases of podoconiosis and least likely to provide MMDP to those affected. These targeted searches will help to clarify the epidemiological status of podoconiosis in India, supporting the global understanding of the burden of podoconiosis and efforts to ensure access to prevention and treatment for those at risk of or affected by the disease.

Supplementary data

Supplementary data are available at *Transactions* online.

Authors' contributions: KD conceived the study. KNP and LSG organised the consultative workshop and coordinated the contributions of the state representatives in India. JC compiled environmental data sources and extrapolated the environmental models of podoconiosis suitability. HS compiled the data sources used for the framework and finalised the framework following input from all listed authors and acknowledged contributors. HS produced all the figures. HS and KD drafted the manuscript. GD, MN, JC and LSG critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. HS and KD are guarantors of the paper.

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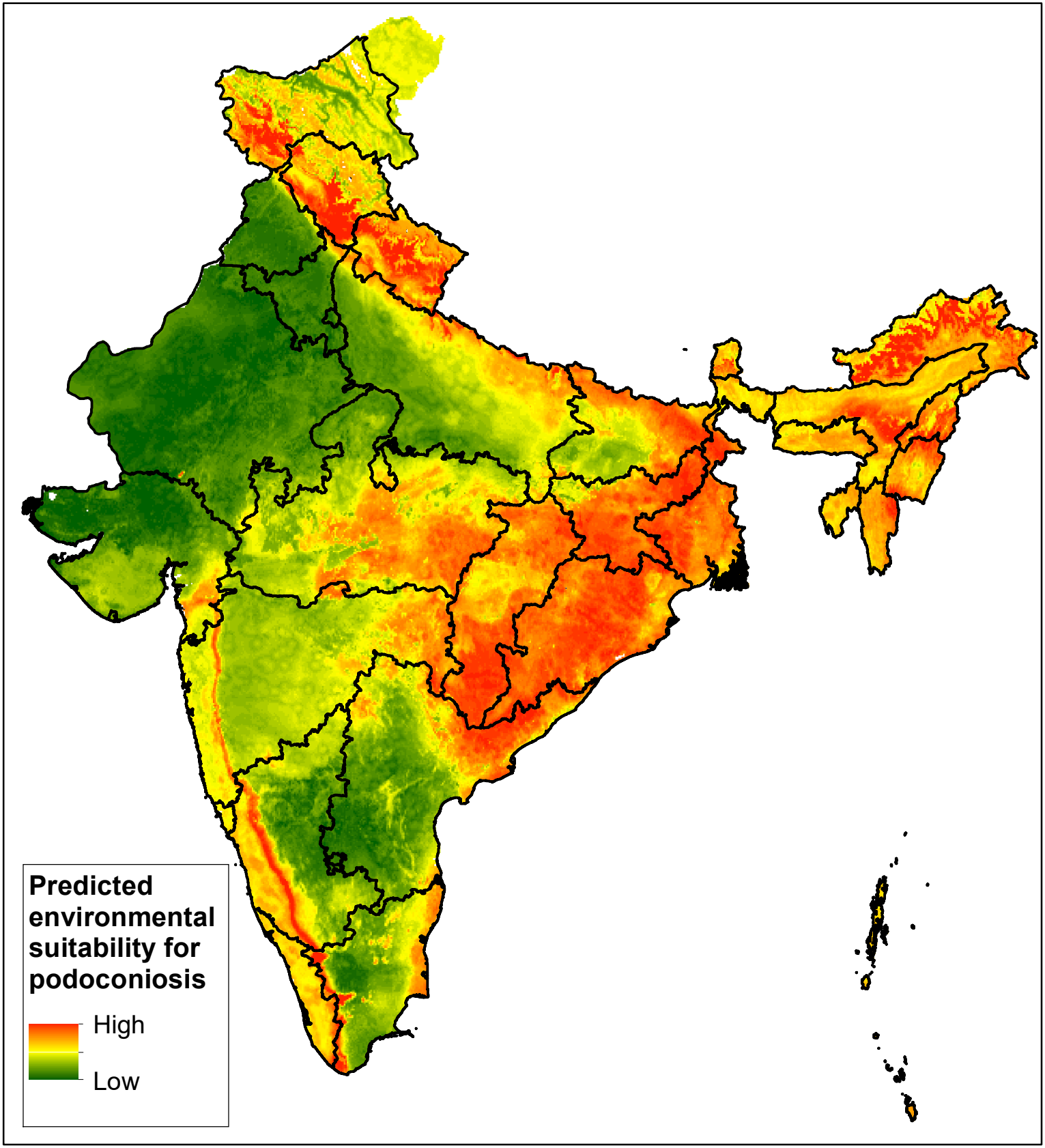
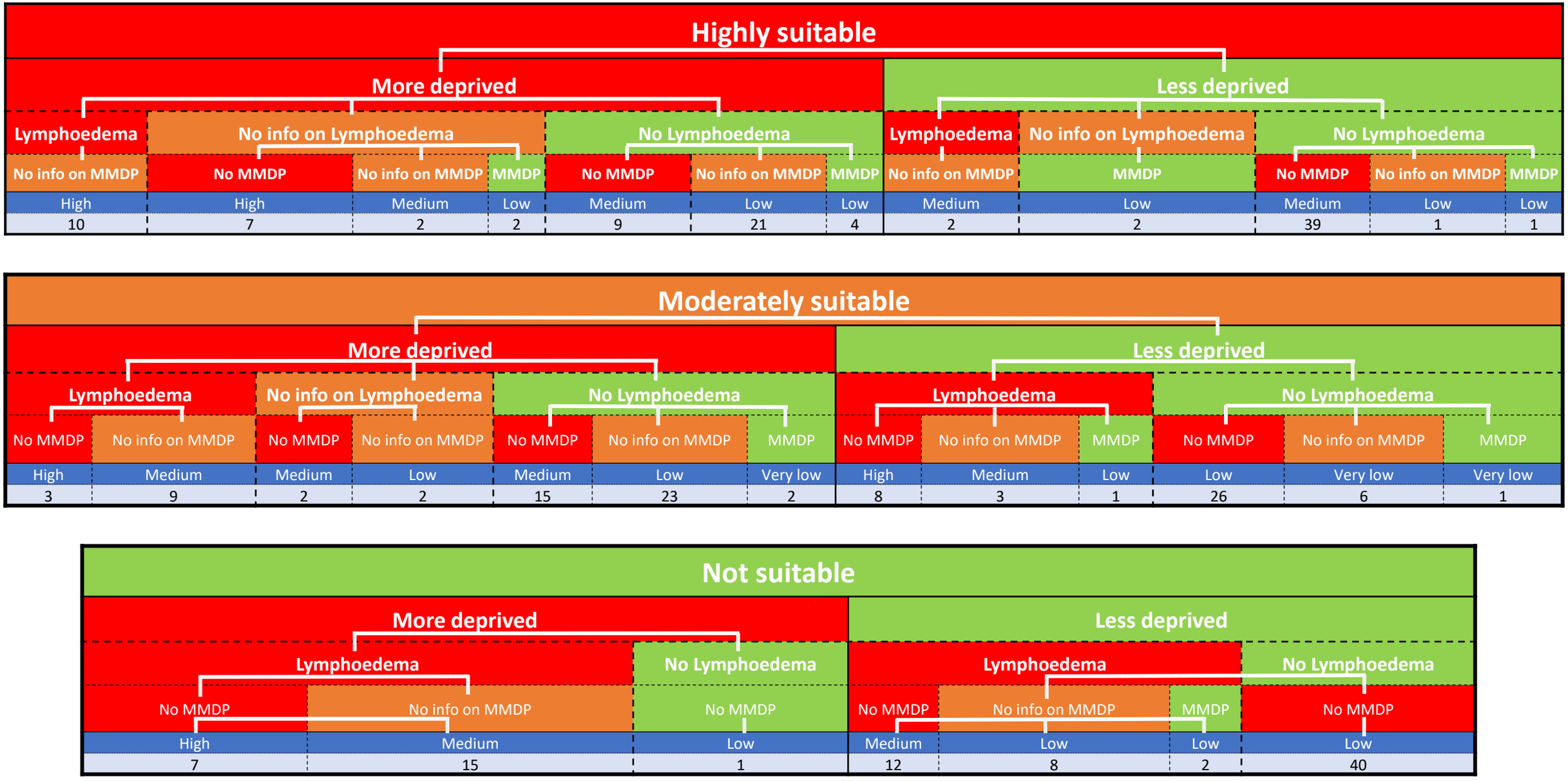

Predicted environmental suitability for podoconiosis
High
Low


Highly suitable
More deprived
Lymphoedema
No info on MMDP
High
10
No info on Lymphoedema
No MMDP
High
7
No info on MMDP
Medium
2
MMDP
Low
2
No Lymphoedema
No MMDP
Medium
9
No info on MMDP
Low
21
MMDP
Low
4
Less deprived
Lymphoedema
No info on MMDP
Medium
2
No info on Lymphoedema
MMDP
Low
2
No Lymphoedema
No MMDP
Medium
39
No info on MMDP
Low
1
MMDP
Low
1
Moderately suitable
More deprived
Lymphoedema
No MMDP
High
3
No info on MMDP
Medium
9
No info on Lymphoedema
No MMDP
Medium
2
No info on MMDP
Low
2
No Lymphoedema
No MMDP
Medium
15
No info on MMDP
Low
23
MMDP
Very low
2
Less deprived
Lymphoedema
No MMDP
High
8
No info on MMDP
Medium
3
MMDP
Low
1
No Lymphoedema
No MMDP
Low
26
No info on MMDP
Very low
6
MMDP
Very low
1
Not suitable
More deprived
Lymphoedema
No MMDP
High
7
No info on MMDP
Medium
15
No Lymphoedema
No MMDP
Low
1
Less deprived
Lymphoedema
No MMDP
Medium
12
No info on MMDP
Low
8
MMDP
Low
2
No Lymphoedema
No MMDP
Low
40
Legend
Highest level of criterion
Intermediate level of criterion
Lowest level of criterion
Evidence category
Number of districts

S1. Methods: Linkage of data to shapefile for mapping

Due to redistricting and differences in the uptake of new district configurations between states, some of the districts described by state representatives corresponded to districts in the GADM shapefile from 2015 while others corresponded to the shapefile representing districts in 2012.

Districts represented in 2015 were linked directly to the 2015 shapefile based on the state and district name while districts represented in 2012 were linked to the 2015 shapefile using spatial tools implemented in R. The two shapefiles were overlaid and the proportion of the area of each of the 2012 districts overlapping with a district from 2015 was calculated. Each of the 2012 districts was linked to the 2015 district that contained the greatest proportion of its area. This link was used to join the districts listed in the workshop to those represented by the 2015 shapefile.

In instances where districts had been merged in 2015 to create a single new district, the evidence from all constituent districts described in the workshop was combined to represent the evidence in the new district. For instance, if participants indicated evidence of lymphedema cases in a district which was merged to one that didn't, the new district was considered to have evidence of lymphedema cases. If participants indicated that MDA was done in one district which was merged with another with no MDA, the new district was considered to implement MDA.

Supplementary Table 1: Scores Assigned through the Evidence Consensus Framework for the Prioritisation of Districts for Pilot Mapping of Podoconiosis in India.

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
Uttar Pradesh	Bijnor	**3**	1	**3**	1	**1**	4	**0**	4	10	83.3	High
Gujarat	Narmada	**3**	1	**4**	1	**1**	4	**0**	4	10	83.3	High
Gujarat	The Dangs	**3**	1	**4**	1	**1**	4	**0**	4	10	83.3	High
Kerala	Pathanamthita	**3**	1	**1**	0	**1**	4	**0**	4	9	75	High
Madra Pradesh	Balaghat	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Gujarat	Banaskatha	**1**	0	**3**	1	**1**	4	**0**	4	9	75	High
Karnataka	Chikkamagaluru	**3**	1	**2**	0	**1**	4	**0**	4	9	75	High
Gujarat	Dahod	**2**	0	**4**	1	**1**	4	**0**	4	9	75	High
West Bengal	Dakshin Dinajpur	**4**	3	**3**	1	**1**	4	**NA**	1	9	75	High
Madra Pradesh	Dindori	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Karnataka	Hassan	**3**	1	**1**	0	**1**	4	**0**	4	9	75	High
Kerala	Iddukki	**3**	1	**1**	0	**1**	4	**0**	4	9	75	High
Jharkand	Jamtara	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Gujarat	Kutch	**1**	0	**3**	1	**1**	4	**0**	4	9	75	High
Odisha	Kalahandi	**4**	3	**4**	1	**NA**	1	**0**	4	9	75	High
Odisha	Kandhamal	**4**	3	**4**	1	**NA**	1	**0**	4	9	75	High
Karnataka	Kodagu	**3**	1	**1**	0	**1**	4	**0**	4	9	75	High
Jharkand	Latehar	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Madra Pradesh	Mandla	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Karnataka	Mysuru	**3**	1	**1**	0	**1**	4	**0**	4	9	75	High
Gujarat	Panchmahal	**2**	0	**4**	1	**1**	4	**0**	4	9	75	High
Madra Pradesh	Raisen	**4**	3	**3**	1	**1**	4	**NA**	1	9	75	High
Gujarat	Sabarkantha	**1**	0	**3**	1	**1**	4	**0**	4	9	75	High
Uttar Pradesh	Shaharanpur	**2**	0	**3**	1	**1**	4	**0**	4	9	75	High
Jharkand	Saraikela	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Manipur	Senapati	**4**	3	**3**	1	**NA**	1	**0**	4	9	75	High
Madra Pradesh	Seoni	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Karnataka	Shivamogga	**3**	1	**2**	0	**1**	4	**0**	4	9	75	High
Odisha	Sundergarh	**4**	3	**3**	1	**NA**	1	**0**	4	9	75	High
Gujarat	Surendranagar	**1**	0	**3**	1	**1**	4	**0**	4	9	75	High
Manipur	Ukhrul	**4**	3	**3**	1	**NA**	1	**0**	4	9	75	High
West Bengal	Uttar Dinajpur	**4**	3	**4**	1	**1**	4	**NA**	1	9	75	High
Kerala	Wayanadu	**3**	1	**1**	0	**1**	4	**0**	4	9	75	High
Odisha	Balangir	**4**	3	**3**	1	**NA**	1	**0**	4	9	75	High
Odisha	Sonepur	**4**	3	**3**	1	**NA**	1	**0**	4	9	75	High
Gujarat	Ahmedabad	**1**	0	**1**	0	**1**	4	**0**	4	8	66.7	Medium
Gujarat	Anand	**1**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
Karnataka	Bangalore Urban	**2**	0	**1**	0	**1**	4	**0**	4	8	66.7	Medium
Gujarat	Bharuch	**2**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium
Gujarat	Bhavnagar	**2**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium
Himachal Pradesh	Bilaspur	**4**	3	**3**	1	**0**	0	**0**	4	8	66.7	Medium
Arunachal Pradesh	Changlang	**4**	3	**3**	1	**0**	0	**0**	4	8	66.7	Medium
Andra Pradesh	East Godhavari	**4**	3	**1**	0	**1**	4	**NA**	1	8	66.7	Medium
Arunachal Pradesh	East Kameng	**4**	3	**4**	1	**0**	0	**0**	4	8	66.7	Medium
Gujarat	Gandhinagar	**1**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium
Madra Pradesh	Jabalpur	**4**	3	**2**	0	**1**	4	**NA**	1	8	66.7	Medium
Mehalaya	East Jaintia Hills	**4**	3	**4**	1	**0**	0	**0**	4	8	66.7	Medium
Mehalaya	West Jaintia Hills	**4**	3	**4**	1	**0**	0	**0**	4	8	66.7	Medium
Gujarat	Kheda	**1**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium
Nagaland	Kiphire	**4**	3	**3**	1	**0**	0	**0**	4	8	66.7	Medium
Karnataka	Kolar	**2**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium
Arunachal Pradesh	Kurung Kumey	**4**	3	**3**	1	**0**	0	**0**	4	8	66.7	Medium
Gujarat	Mehsana	**1**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium
Karnataka	Mandya	**2**	0	**1**	0	**1**	4	**0**	4	8	66.7	Medium
Gujarat	Patan	**1**	0	**2**	0	**1**	4	**0**	4	8	66.7	Medium
Karnataka	Bangaluru (R)	**2**	0	**1**	0	**1**	4	**0**	4	8	66.7	Medium
Nagaland	Tuensang	**4**	3	**3**	1	**0**	0	**0**	4	8	66.7	Medium
Arunachal Pradesh	Upper Subansiri	**4**	3	**3**	1	**0**	0	**0**	4	8	66.7	Medium
Uttarakhand	Pauri Garhwal	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Uttarakhand	Haridwar	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Mizoram	Aizawl	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
West Bengal	Alipurduar	**3**	1	**3**	1	**1**	4	**NA**	1	7	58.3	Medium
Uttarakhand	Almora	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	Anjaw	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Madra Pradesh	Anuppur	**3**	1	**4**	1	**1**	4	**NA**	1	7	58.3	Medium
Uttarakhand	Bageshwar	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Madra Pradesh	betul	**3**	1	**3**	1	**1**	4	**NA**	1	7	58.3	Medium
Uttarakhand	Chamoli	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Uttarakhand	Champawa	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Mizoram	Champhai	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Nagaland	Dimapur	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	Pasighat	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Sikkim	East Sikkim	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Himachal Pradesh	Hamirpur	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
West Bengal	Jalpaiguri	**3**	1	**3**	1	**1**	4	**NA**	1	7	58.3	Medium
Jharkand	Kodema	**3**	1	**3**	1	**1**	4	**NA**	1	7	58.3	Medium

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
Nagaland	Kohima	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	Lower Dibang Valley	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	Lower Subansiri	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Himachal Pradesh	Mandi	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Nagaland	Mokokchung	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Madra Pradesh	Narsinghpur	**3**	1	**3**	1	**1**	4	**NA**	1	7	58.3	Medium
Jharkand	Palamu	**3**	1	**4**	1	**1**	4	**NA**	1	7	58.3	Medium
Haryana	Panchkula	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	Papum Pare	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Nagaland	Peren	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Nagaland	Phek	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Uttarakhand	Pithoragarh	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Odisha	Raigarha	**3**	1	**3**	1	**NA**	1	**0**	4	7	58.3	Medium
Uttarakhand	Rudrapraya	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Mizoram	Serchhip	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Madra Pradesh	Shahdol	**3**	1	**4**	1	**1**	4	**NA**	1	7	58.3	Medium
Himachal Pradesh	Shimla	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Madra Pradesh	Sidhi	**3**	1	**4**	1	**1**	4	**NA**	1	7	58.3	Medium
Himachal Pradesh	Sirmaur	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Himachal Pradesh	Solan	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Sikkim	South Sikkim	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Manipur	Tamenglong	**3**	1	**3**	1	**NA**	1	**0**	4	7	58.3	Medium
Uttarakhand	Tehri Garhwal	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Uttarakhand	Udham Singh Nagar	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Himachal Pradesh	Una	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	Upper Siang	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Uttarakhand	Uttarkashi	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	West Kameng	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Arunachal Pradesh	West Siang	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Sikkim	West Sikkim	**4**	3	**1**	0	**0**	0	**0**	4	7	58.3	Medium
Nagaland	Wokha	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Nagaland	Zunheboto	**4**	3	**2**	0	**0**	0	**0**	4	7	58.3	Medium
Uttar Pradesh	Amroha	**2**	0	**4**	1	**1**	4	**NA**	1	6	50	Medium
Madra Pradesh	Ashoknagar	**2**	0	**4**	1	**1**	4	**NA**	1	6	50	Medium
Rajasthan	Bhilwara	**1**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Madra Pradesh	Bhopal	**3**	1	**2**	0	**1**	4	**NA**	1	6	50	Medium
Rajasthan	Bundi	**1**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
West Bengal	Darjeeling	**3**	1	**2**	0	**1**	4	**NA**	1	6	50	Medium
Rajasthan	Dausa	**1**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Thripura	Dhalai	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Mehalaya	East Garo Hills	**3**	1	**4**	1	**0**	0	**0**	4	6	50	Medium
Madra Pradesh	Guna	**2**	0	**4**	1	**1**	4	**NA**	1	6	50	Medium
Madra Pradesh	Harda	**2**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Madra Pradesh	Hoshangabad	**2**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Rajasthan	Jodhpur	**1**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Rajasthan	Karauli	**1**	0	**4**	1	**1**	4	**NA**	1	6	50	Medium
Arunachal Pradesh	Lohit	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Nagaland	Longleng	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Telengana	Mahbubnagar	**1**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Mizoram	Mamit	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Nagaland	Mon	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Telengana	Nizamabad	**3**	1	**2**	0	**1**	4	**NA**	1	6	50	Medium
Mehalaya	North Garo Hills	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Thripura	North Tripura	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Madra Pradesh	Rajagarh	**2**	0	**4**	1	**1**	4	**NA**	1	6	50	Medium
Rajasthan	Rajasmand	**1**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Mehalaya	Ri-Bhoi	**3**	1	**4**	1	**0**	0	**0**	4	6	50	Medium
Bihar	KOSHI	**4**	3	**4**	1	**NA**	1	**NA**	1	6	50	Medium
Madra Pradesh	Shajapur	**2**	0	**3**	1	**1**	4	**NA**	1	6	50	Medium
Mehalaya	South West Garo Hills	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Mehalaya	South West Khasi Hills	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Bihar	SUPOL	**4**	3	**4**	1	**NA**	1	**NA**	1	6	50	Medium
Arunachal Pradesh	Tawang Town	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Arunachal Pradesh	Tirap	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Madra Pradesh	Vidisha	**2**	0	**4**	1	**1**	4	**NA**	1	6	50	Medium
Mehalaya	West Garo Hills	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Mehalaya	West Khasi Hills	**3**	1	**3**	1	**0**	0	**0**	4	6	50	Medium
Uttarakhand	Dehradun	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Uttarakhand	Nainital	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Punjab	Pathankot	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Andra Pradesh	Ananthpur	**1**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Chhattisgarh	Balrampur	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Bastar	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Bijapur	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
Himachal Pradesh	Chamba	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Chhattisgarh	Dantewada	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low
Assam	Darrang	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low
Arunachal Pradesh	Upper Dibang Valley	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Assam	Dima Hasao	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Mehalaya	East Khasi Hills	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Thripura	Gomati	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Himachal Pradesh	Kangra	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Assam	Karbi Anglong	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low
Assam	West Karbi Anglong	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low
Thripura	Khowai	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Himachal Pradesh	Kinnaur	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Mizoram	Kolasib	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Chhattisgarh	Korba	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Himachal Pradesh	Kullu	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Andra Pradesh	Kurnool	**1**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Himachal Pradesh	Lahaul and Spiti	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Mizoram	Lawngtlai	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Mizoram	Lunglei	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Telengana	Medak	**2**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Haryana	Mewat	**1**	0	**4**	1	**0**	0	**0**	4	5	41.7	Low
Assam	Hojai	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Assam	Nagaon	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Telengana	Nalgonda	**1**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Chhattisgarh	Narayanpur	**4**	3	**4**	1	**0**	0	**NA**	1	5	41.7	Low
Maharashtra	Nashik	**2**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Goa	North Goa	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Sikkim	North Sikkim	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Odisha	Nuapada	**4**	3	**4**	1	**NA**	1	**1**	0	5	41.7	Low
Chhattisgarh	Raipur	**3**	1	**2**	0	**1**	4	**1**	0	5	41.7	Low
Telengana	Rangareddi	**2**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Punjab	Rupnagar	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Mizoram	Saiha	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Maharashtra	Satara	**2**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Thripura	Sipahijala	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Mehalaya	South Garo Hills	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Goa	South Goa	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
Thripura	South Tripura	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Thripura	Unakoti	**3**	1	**2**	0	**0**	0	**0**	4	5	41.7	Low
Thripura	West Tripura	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Andra Pradesh	Kadapa	**1**	0	**2**	0	**1**	4	**NA**	1	5	41.7	Low
Haryana	Yamunanagar	**3**	1	**1**	0	**0**	0	**0**	4	5	41.7	Low
Chhattisgarh	Balod	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Gariaband	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Odisha	Jagatsinghpur	**4**	3	**3**	1	**NA**	1	**1**	0	5	41.7	Low
Chhattisgarh	Kondagaon	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Koriya	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Assam	Morigaon	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Rajnandgaon	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Sukma	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Surajpur	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Chhattisgarh	Kanker	**4**	3	**3**	1	**0**	0	**NA**	1	5	41.7	Low
Punjab	Fazilka	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Ambala	**2**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Amritsar	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Barnala	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Bathinda	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Bhiwani	**1**	0	**2**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Charkhi Dadr	**1**	0	**2**	0	**0**	0	**0**	4	4	33.3	Low
Andra Pradesh	Chittoor	**2**	0	**2**	0	**1**	4	**1**	0	4	33.3	Low
Haryana	Faridabad	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Faridkot	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Fatehabad	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Fatehgarh Sahib	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Firozpur	**1**	0	**2**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Gurdaspur	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Gurgaon	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Hisar	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Hoshiarpur	**2**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Jalandhar	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Chhattisgarh	Jashpur	**4**	3	**4**	1	**0**	0	**1**	0	4	33.3	Low
Haryana	Jhajjar	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Uttar Pradesh	Jhansi	**1**	0	**2**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Jind	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Kaithal	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Assam	Kamrup Metro.	**4**	3	**2**	0	**0**	0	**NA**	1	4	33.3	Low

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
Punjab	Kapurthala	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Karnal	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Odisha	Khordha	**4**	3	**2**	0	**NA**	1	**1**	0	4	33.3	Low
Haryana	Kurukshetra	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Uttar Pradesh	Lalitpur	**3**	1	**3**	1	**NA**	1	**NA**	1	4	33.3	Low
Punjab	Ludhiana	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Chhattisgarh	Mahasamund	**4**	3	**3**	1	**0**	0	**1**	0	4	33.3	Low
Haryana	Mahendragarh	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Mansa	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Moga	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Uttar Pradesh	Moradabad	**3**	1	**3**	1	**NA**	1	**NA**	1	4	33.3	Low
Punjab	Muktsar	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Palwal	**1**	0	**2**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Panipat	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Patiala	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Andra Pradesh	Prakasam	**1**	0	**2**	0	**1**	4	**1**	0	4	33.3	Low
Odisha	Puri	**4**	3	**2**	0	**NA**	1	**1**	0	4	33.3	Low
Chhattisgarh	Raigarh	**4**	3	**3**	1	**0**	0	**1**	0	4	33.3	Low
Haryana	Rewari	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Rohtak	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Mohali	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Sangrur	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Punjab	Shahid Bhagat Singh Nagar	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Sirsa	**1**	0	**2**	0	**0**	0	**0**	4	4	33.3	Low
Haryana	Sonipat	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Chhattisgarh	Surguja	**4**	3	**4**	1	**0**	0	**1**	0	4	33.3	Low
Punjab	Tarn Taran	**1**	0	**1**	0	**0**	0	**0**	4	4	33.3	Low
Assam	Barpeta	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Bongaigaon	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Cachar	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low
Assam	Chirang	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Chhattisgarh	Dhamtari	**4**	3	**2**	0	**0**	0	**1**	0	3	25	Low
Assam	Dhemaji	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	South Salmara-Mankachar	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low
Assam	Dhubri	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low
Assam	Dibrugarh	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Goalpara	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low

State	District	Environmental suitability[1]		Poverty[2]		Lymphoedema[3]		MMDP services[4]		Consensus score[5]	Percentage	Priority
		Evidence	Score	Evidence	Score	Evidence	Score	Evidence	Score			
Assam	Hailakandi	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low
Chhattisgarh	Kabirdham	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low
Assam	Karimganj	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low
Assam	Kokrajhar	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Lakhimpur	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Biswanath	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Sonitpur	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Tinsukia	**3**	1	**4**	1	**0**	0	**NA**	1	3	25	Low
Assam	Udalguri	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Chhattisgarh	Baloda Bazar	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Chhattisgarh	Bemetara.	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Chhattisgarh	Mungeli	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Sivasagar	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Charaideo	**3**	1	**3**	1	**0**	0	**NA**	1	3	25	Low
Assam	Baksa	**3**	1	**2**	0	**0**	0	**NA**	1	2	16.7	Very low
Chhattisgarh	Bilaspur	**3**	1	**3**	1	**0**	0	**1**	0	2	16.7	Very low
Assam	Golaghat	**3**	1	**2**	0	**0**	0	**NA**	1	2	16.7	Very low
Chhattisgarh	Janjgir-Champa	**3**	1	**3**	1	**0**	0	**1**	0	2	16.7	Very low
Assam	Jorhat	**3**	1	**2**	0	**0**	0	**NA**	1	2	16.7	Very low
Assam	Majuli	**3**	1	**2**	0	**0**	0	**NA**	1	2	16.7	Very low
Assam	Kamrup	**3**	1	**2**	0	**0**	0	**NA**	1	2	16.7	Very low
Assam	Nalbari	**3**	1	**2**	0	**0**	0	**NA**	1	2	16.7	Very low
Chhattisgarh	Durg	**3**	1	**2**	0	**0**	0	**1**	0	1	8.33	Very low

Districts shown in the table are those identified by State Representatives engaged through the Consultative Workshop on Podoconiosis held in Kochi, December 2019.

1. Environmental suitability- quartiles of suitability based on extrapolation of the environmental niche of podoconiosis characterised using data from prevalence surveys in Africa.
2. Poverty- quartiles of multidimensional poverty (MDPI) modelled by the Oxford Poverty and Human Development Initiative [1].
3. Lymphoedema cases within the district known to state health authorities, according to state health representatives.
4. MMDP Services assumed to be provided based on the coverage of the National Lymphatic Filariasis Elimination Programme, according to state health representatives.
5. Consensus Score- sum of scores assigned for each of the above four components.

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PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Effectiveness of community-based burden estimation to achieve elimination of lymphatic filariasis: A comparative cross-sectional investigation in Côte d'Ivoire

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Abstract

For lymphatic filariasis (LF) elimination, endemic countries must document the burden of LF morbidity (LFM). Community-based screening (CBS) is used to collect morbidity data, but evidence demonstrating its reliability is limited. Recent pilots of CBS for LFM alongside mass drug administration (MDA) in Côte d'Ivoire suggested low LFM prevalence (2.1–2.2 per 10,000). We estimated LFM prevalence in Bongouanou District, Côte d'Ivoire, using a comparative cross-sectional design. We compared CBS implemented independently of MDA, adapted from existing Ministry of Health protocols, to a population-based prevalence survey led by formally trained nurses. We evaluated the reliability of case identification, coverage, equity, and cost of CBS. CBS identified 87.4 cases of LFM per 10,000; the survey identified 47.5 (39.4–56.3; prevalence ratio [PR] 1.84; 95% CI 1.64–2.07). CBS identified 39.7 cases of suspect lymphoedema per 10,000; the survey confirmed 35.1 (29.2–41.5) filarial lymphoedema cases per 10,000 (PR 1.13 [0.98–1.31]). CBS identified 96.5 scrotal swellings per 10,000; the survey found 91.3 (83.2–99.8; PR 1.06 [0.93–1.21]); including 33.9 (27.7–38.8) filarial hydrocoele per 10,000 (PR of suspect to confirmed hydrocele 2.93 [2.46–3.55]). Positive predictive values for case identification through CBS were 65.0% (55.8–73.5%) for filarial lymphoedema; 93.7% (89.3–96.7%) for scrotal swellings; and 34.0% (27.3–41.2%) for filarial hydrocoele. Households of lower socioeconomic status and certain minority languages were at risk of exclusion. Direct financial costs were $0.17 per individual targeted and $69.62 per case confirmed. Our community-based approach to LFM burden estimation appears scalable and provided reliable prevalence estimates for LFM, scrotal swellings and LF-lymphoedema. The results represent a step-change improvement on CBS integrated with MDA, whilst remaining at programmatically feasible costs. Filarial hydrocoele cases were overestimated, attributable to the use of case definitions suitable for

investigation in Côte d'Ivoire", https://doi.org/10.7910/DVN/K2S1R2, Harvard Dataverse, V1.

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mass-screening by informal staff. Our findings are broadly applicable to countries aiming for LF elimination using CBS. The abstract is available in French in the S1 File.

Introduction

Lymphatic filariasis (LF) is a mosquito-borne disease caused by the filarial nematodes *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* [1], estimated to infect 51 million people globally [2]. Progression of the infection to chronic disease is associated with progressive damage to the lymphatic system, which can lead to irreversible swelling and acute attacks of dermato-lymphangio-adenitis (ADLA). The two most overt manifestations of chronic LF are lymphoedema-caused by accumulation of lymph fluid in the soft tissue, generally affecting a limb or breast- and hydrocoele, caused by accumulation of lymph fluid inside the scrotal sac [3]. Although the number of people affected by lymphatic filariasis morbidity (LFM) is difficult to quantify (data being hard to collect and predictions unreliable), the burden of disease is undoubtedly substantial—estimates from 2012 suggested 19.4 million men with filarial hydrocoele and 16.7 million people with lymphoedema globally [4]. Disability-adjusted life year (DALY) estimates place LF as the second leading cause of disability due to parasitic diseases [5].

Since 1997, LF has been targeted for elimination as a public health problem, with efforts coordinated by WHO under the Global Programme to Eliminate Lymphatic Filariasis (GPELF) [6]. The elimination strategy consists of two components: interruption of transmission through mass drug administration (MDA) in endemic areas, and alleviation of suffering through morbidity management and disability prevention (MMDP) [6]. Verification of elimination depends on the sustained reduction of prevalence to below 1%, documentation of lymphoedema and hydrocoele case numbers, and the readiness and quality of MMDP services in health facilities in endemic areas [7]. While MDA has helped reduce LF infection prevalence, many people remain affected by lymphoedema and hydrocoele and require these MMDP services. However, most endemic countries lack estimates of the numbers of people affected and their distribution. There is no standardised mechanism for the collection of data on LFM, but due to resource limitations and barriers to care-seeking at health facilities [8–10], case detection in many endemic settings depends upon existing community health infrastructure [11]. Community-based interventions, particularly MDA, have been central to NTD control, enabling access to marginalised communities and higher intervention coverage [12–14], and have been successfully used for case-finding in Guinea worm eradication [15]. The suitability of these staff to identify and refer cases of more subtle, chronic NTD morbidity is less certain, however. Community-based screening (CBS) of LFM during MDA is used in Burkina Faso, Ghana and Malawi [16] and other countries, but is understood to substantially underestimate true case numbers [17].

In Côte d'Ivoire, where LF is endemic in 99 of 103 health districts and infection prevalence is predicted to exceed 1% [2], the NTD Control Programme (NTDP) plans to estimate LFM burden using CBS to guide service delivery and achieve LF elimination. The system will be scaled up gradually, providing opportunity to iteratively tailor and strengthen it. CBS through MDA piloted in 2020 identified 20 cases of lymphoedema and 9 of hydrocoele in the district of Lakota (population > = 15 years old 132,216), and 34 cases of lymphoedema and 17 of hydrocoele in the district of Divo (population > = 15 years old 248,613) [18, 19]. We aimed to improve this existing approach by de-coupling case finding from MDA, improving and strengthening the CDD training programme, and implementing simple methodological adaptations. We evaluated the effectiveness of this strengthened, standalone strategy against a

population-based prevalence survey led by nurses specially trained in LFM diagnosis. We also conducted a process evaluation during implementation to understand operational factors affecting performance including diagnostic reliability, household coverage, equity, and financial cost.

Materials and methods

Setting

The study was conducted in the health district of Bongouanou, in the Moronou Region of centre-east Côte d'Ivoire (S1 Fig). The district is LF-endemic, with evidence from geospatial and models and a community-based survey using ICT cards in 2012 suggesting high prevalence of parasitaemia [2, 20, 21], but had not previously been surveyed for LFM. The landcover is primarily Guinean forest-savanna mosaic and the main industry is cacao and coffee farming [22]. Compared to other districts in the region, the infant mortality rate is low, public and private-sector salaries are high, and there are high levels of access to piped water [22]. The district population used for health operation purposes including MDA, is 169,999, the population > = 15 years old is 94,319 and the male fraction is 0.50 [18]. The district is serviced by 24 health facilities: one general hospital, four urban health centres, eight rural health centres, and ten dispensaries. The area covered by each health facility is referred to as a health area, and populations within these health areas range from 800–26,513.

Study design and participants

We did a comparative cross-sectional study of methods to estimate LFM prevalence, and follow the STROBE guidelines for reporting of cross-sectional studies (see S1 Checklist). In the first phase of data collection, between 22nd and 26th February 2021, all LF-MDA community drug distributors (CDDs) completed a stand-alone, exhaustive door-to-door case search for leg swellings (suspect lymphoedema) and scrotal swellings (suspect hydrocoele) covering the entire district population aged 15 years and over. In the second phase of data collection, conducted immediately after (15th March- 17th June 2021), nurses specially trained in diagnosis of LFM conducted a population-based prevalence survey. Results from the CDD-led screening were compared to those from the population-based prevalence survey.

For the population-based prevalence survey, we used a stratified two-stage cluster-based design with strata based upon health areas, primary sampling units (PSUs) defined as CDD zones and secondary sampling units (SSUs) as households [23]. Total PSUs selected within strata was determined using proportional allocation. PSUs were selected using simple random sampling without replacement, due to absence of population data at CDD zone level. All individuals aged 15 years and older in selected PSUs were eligible for participation. Using a standard sample size calculation [23] assuming a prevalence of 5 cases per 1,000 population, a participation rate of 95%, design effect of 5.95, and applying a finite population correction factor for the population of Bongouanou district, we calculated that 12,217 participants needed to be examined to estimate LFM prevalence with an absolute precision of 0.003.

To assess diagnostic reliability of CBS, CDDs recruited all cases they had identified and who had not been examined through the population-based prevalence survey, for re-examination by nurses at a central location after completion of surveys within PSUs.

Procedures

Co-development of toolkit for community-based screening. The CDD toolkit, including the training of trainers guide, slide-deck, job-aid and photobook, was developed by the project

Table 1. Existing and strengthened approach to community-based screening for lymphatic filariasis morbidity (LFM) in Côte d'Ivoire.

	Existing approach (implemented 2020)	Strengthened approach (implemented 2021)
Materials	Regional team, district team and health area supervisors provided with training of trainers document. CDDs provided with job aids, photobooks and reporting forms.	Materials reviewed and revised at workshop by NTDP team and those involved in pilot screening, including district health team and CDDs. District team and health area supervisors provided with training of trainers document. CDDs provided with job aids, photobooks and reporting forms.
Training cascade	Regional team, district team and health area supervisors trained by NTDP staff; CDDs trained by health area supervisors	District team and health area supervisors trained by NTDP staff; CDDs trained by health area supervisors with oversight from NTDP and district team.
Case-finding strategy	CDDs identify cases during MDA, using a either door-to-door or fixed-post strategy (depending on how they usually distribute medicines). Using the door to door strategy, CDDs may record cases reported by family members. Using fixed-post strategy, cases must be self-reported. CDDs encouraged to examine cases if possible but this is not mandatory.	Screening decoupled from MDA. CDDs use door-to-door strategy in all areas- no fixed-post recording. CDDs may record cases reported by family members without seeing case. CDDs encouraged to examine cases if possible but this is not mandatory.
Sensitisation	Focused primarily on MDA.	Information cascaded through district health team, regional administrative leaders, traditional leaders of the sub prefectures in the district, religious leaders, representatives of men's, women's and children's groups and a communications officer. Information broadcast on district radio. Town criers informed communities about activities.
Supervision	CDD training and case identification supervised by district health team and NTDP team	CDD training and community-based screening supervised by district health team, NTDP team and/ or project team
Recording	CDDs fill patient recording forms. Patients not provided with referral ID cards.	CDDs fill patient recording forms with patient ID numbers linked to referral ID cards given to patients.

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team before being presented to a representative of the NTDP (BK) for further revisions. The draft materials were then extensively reviewed and modified at a 3-day revisions workshop held in Yamoussoukro, attended by the NTDP, members of the project team, and the team who had been involved in pilot CBS implemented by the MoH NTD programme in 2020 (members of the district health team, one CDD, and partners). The revised toolkit is available at https://doi.org/10.7910/DVN/K2S1R2.

CDD training and community-based screening. Based on feedback from the pilot, we adapted existing approaches to *community-based screening*. The main changes were that CBS was implemented as a standalone activity, separate from LF MDA, and that CDDs were instructed to exclusively use a door-to-door strategy and avoid fixed-post activities. A full list of modifications on the existing approach is shown in Table 1.

Training of CDDs was delivered through a cascade. In the first stage, health district staff and health area supervisors were trained by the head of MMDP in the NTDP (BK) using the slide deck and patient demonstrations. Health area supervisors then cascaded training to CDDs in their respective areas using the training of trainers guide, photobook and job aid, with practical demonstrations. CDDs were trained to ask to see the affected area to confirm the swelling, but were informed that they did not have to see the swelling if the person affected was unable or unwilling to show them. Following training, CDDs undertook a post-training quiz which was evaluated by the project team in order to assess the quality of the training provided.

All identified cases were provided with unique patient ID cards for re-capture during re-examination by nurses, to enable case validation. CDDs recorded cases on paper forms including patient demographic and contact details and basic clinical information and medical history. Data from these forms was entered by trained supervisors into an electronic database via electronic devices running an ODK-based application.

Population-based prevalence survey. We recruited health supervisors with nurse or midwife qualifications from Bongouanou district as clinical field surveyors. Twenty-six supervisors

underwent a 3-day training programme on the diagnosis and management of lymphoedema and hydrocoele led by specialist and experienced dermatologists from the University Hospital of Treichville in Abidjan and by the head of the MMDP unit from the NTDP. The training included didactic material on the identification of different causes of limb swellings (including pregnancy, injury, congenital lymphedema, insect bites, allergies, and other infectious diseases) and scrotal swellings (such as hernia, congenital hydrocele, varicocele, scrotal lymphedema, tumour and haematocele). There were patient demonstrations of diagnosis of scrotal swellings and of lymphoedema, and demonstrations of limb washing for lymphoedema patients. Training materials are available in the study toolkit. Participants were assessed through a post-training test, and 18 nurses were selected for implementation.

For household (SSU) selection in PSUs, teams of 3 nurses followed separate random walks beginning from randomised start points assigned by a custom built ODK-based application. An initial household census and interview was completed to collect information on sociodemographic variables, GPS location and CDD coverage using electronic devices running an ODK-based application. Each consenting individual was checked for swelling on the limbs, and males underwent a brief testicular examination. Suspect cases were defined according to the same case definitions used by CDDs, and underwent detailed examination for confirmatory diagnosis. If any eligible participants were absent, remaining eligible household members were shown pictures of LFM from a flipbook and acted as proxy respondents. Anyone identified through this screen was defined as a suspect case and targeted for follow-up examination.

Outcomes

The CDD case definition for suspect lymphoedema was *an increase in the volume of a limb or breast in a person aged 15 years or older* and that for suspect hydrocoele was *swollen testicles in a male aged 15 years or older*. The CDDs did not have to observe the swelling in order to record the case- they could record suspect cases reported by the person affected, or a family member in case the person was not present at the time of the visit.

The case definition of filarial lymphoedema was *swelling of limb or breast*, *in a patient aged 15 years older*, *present for at least a year but not since birth*, *and not due to leprosy*, *erysipelas*, *malignancy*, *surgery*, *or heart disease*. The definition of filarial hydrocoele was *a discrete*, *non-tender mass around the testes*, *not explained by an inguinal hernia or scrotal lymphoedema*, *not present since birth and present for more than 24 hours*. Lower limb lymphoedema was classified according to the Dreyer system [24]. Cases of testicular swelling were characterised according to the system proposed by Capuano and Capuano [25].

Clinically confirmed cases of filarial lymphoedema and hydrocoele were given advice on self-care, a patient identification card, and re-imbursement for travel costs to the local health facility. Confirmed hydrocoele cases were registered for inclusion in planned hydrocoele surgery within the district, which was conducted in February 2022.

Statistics and data analysis

We calculated the crude prevalence of suspect LFM detected by CDDs at district and health area levels using estimates of the district total and male population aged 15 years and older from the Côte d'Ivoire National Institute of Statistics as denominators [18]. Since PSU populations were not available from district health databases, design weights were assigned using population estimates extracted from the Facebook population density layer [12]. Further details are given in S1 Text. To enable spatial delineation of CDD zones, nurses walked the boundary of PSUs with CDDs, capturing the geographical limits of the catchment using GPS-enabled devices [26]. We calculated district-level prevalence estimates of LFM outcomes using

survey package in R (version 4.1–1) [27] with post-stratification weighting applied for age and sex [18]. Prevalence estimates of LFM outcomes from community-based screening were compared to household survey prevalence estimates using risk ratios.

To understand contextual and operational factors affecting CDD coverage, we developed a mixed-effects generalized linear model (binomial distribution), for reported visitation by CDDs. We assessed sociodemographic variables at household level, including a multi-dimensional indicator of socioeconomic status (SES) constructed using latent class analysis (LCA; full details in the S2 Text) and PSU-level indicators of CDD demographics, performance and community accessibility (All candidate predictors and sources are shown in S1 Table). Continuous variables were centred and scaled. Missing data were imputed by single imputation of PSU means or modes (for continuous and categorical variables respectively). Random intercepts were allowed for CDD zones nested within health areas. Candidate variables were subject to bivariate analysis and included within final models if $p <= 0.2$ using likelihood ratio tests, given large parameter space and absence of observed collinearity [28]. Final models were assessed for violations of assumptions.

To estimate positive predictive value (PPV; the proportion of identified cases confirmed by gold standard diagnosis [29]) of case identification by CDDs, CDD-identified LFM cases were linked to patients examined by nurses using capture re-capture of coded patient ID cards. We estimated PPV using *epiR* [30], with confirmed diagnosis by a trained nurse as gold-standard.

We estimated the direct financial costs of CDD case finding using an ingredients-based approach to estimate costs per person targeted by the screening activity and per confirmed case identified. Costs were categorised by phase of activity (sensitisation, training of trainers (first stage of cascade), training of CDDs (second stage of cascade) and community-based screening).

Ethics

Eligible participants (those aged 15 years and older) were provided with an information sheet and the study was explained. Written informed consent was obtained from individuals aged 18 years and above. Minors (aged <18 years) provided oral assent, and written informed consent was obtained from their parents or legal guardians. The study was granted ethical approval by Le Comité National d'Ethique des Sciences de la Vie et de la Santé in Côte d'Ivoire and the Ethics Committee of the London School of Hygiene and Tropical Medicine (Reference 21203).

Results

Study participants

Across 110 PSUs, nurses visited 8,247 households which were occupied and had an adult present. Of these, 58 (0.70%) refused to participate. Across 8,189 households, 12,289 people were invited to participate and 12,287 (99.99%) agreed, including 4,818 males (39.2%). Twenty participants (0.16%) refused limb examinations and 202 males (4.2%) refused scrotal examination. The median number of households visited per cluster was 75 (interquartile range [IQR] 61–86), and the median number examined per cluster was 98 (IQR 77–112).

Reliability of community-based screening

Following an exhaustive case search across the district among people >= 15 years old (population 94,319; 47,349 males), CDDs identified 824 suspect LFM cases: 374 lymphoedema, 457 hydrocoele, and 7 with both (Table 2). The prevalence of suspect LFM was 87.4 per 10,000 (95% CI 81.5–93.5 per 10,000). The prevalence of suspect lymphoedema was 39.7 per 10,000

Table 2. Number and prevalence (per 10,000) of LFM cases detected through community-based screening and population-based survey.

	Community-based screening				Re-examined by nurses			Population-based survey[1]					*Prev. ratio (screen: survey)*
	Screened (N)	Suspect cases (n)	Crude prev.	*(95% CI)*	N	Con-firmed	PPV	Examined (N)	confirmed cases (n)	Weighted			
										Estimated cases	Prev.	*(95% CI)*	
LF morbidity	94,319	824	87.4	*(81.5–93.5)*	315	150	47.1	12,267	53	475	50.3	*(43.4–57.8)*	*1.73 (1.55–1.94)*
Al leg swellings	94,319	374	39.7	*(35.7–43.9)*	120	93	77.5	12,267	49	507	53.8	*(44.6–63.7)*	*0.74 (0.65–0.84)*
LF lymphedema						78	65		36	332	35.2	*(30.3–40.5)*	*1.13 (0.97–1.31)*
All scrotum swellings	47,349	457	96.5	*(87.9–105.7)*	191	179	93.7	4,613	50	432	91.3	*(83.2–99.8)*	*1.06 (0.93–1.21)*
LF hydrocele						65	34		18	156	33.0	*(27.7–38.8)*	*2.93 (2.46–3.55)*

[1] Prevalence estimates adjusted for survey design and post-stratified on age group and gender. PPV = predicted value positive. Prev. = prevalence.

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(95% CI 35.7–43.9 per 10,000) and that of suspect hydrocoele96.5 per 10,000 males (95% CI 87.9–105.7 per 10,000) (Fig 1).

In the population-based survey, 53 cases of LFM were confirmed, giving a prevalence of 50.3 per 10,000 (95% CI 43.4–57.8) after adjusting for survey design and non-response. The prevalence ratio of CDD-identified suspect LFM to confirmed LFM was 1.73 (95% CI 1.55–1.94). Forty-nine cases of leg swellings were identified and 36 were confirmed as filarial lymphoedema. The design-adjusted prevalence estimate of confirmed filarial lymphoedema was 35.2 (95% CI 30.3–40.5) per 10,000; within confidence bounds of the CDD estimate (prevalence ratio of 1.13 [95% CI 0.97–1.31]). Fifty cases of scrotal swellings were identified and 18 confirmed as filarial hydrocoele. The adjusted prevalence of scrotal swellings was 91.3 per 10,000 males (95% CI 83.2–99.8). The prevalence ratio for scrotal swellings was 1.06 (95% CI 0.93–1.21). The prevalence of confirmed filarial hydrocoele was 33.0 per 10,000 (95% CI 27.7–38.8), with a prevalence ratio of 2.93 (95% CI 2.46–3.55). Two cases presented both filarial lymphoedema and hydrocoele.

Cases missed by CDDs

Of 36 confirmed filarial lymphoedema cases identified in the population-based prevalence survey, 11 (30.6%) had not been identified despite the household having been visited. Of 50 cases of scrotal swellings identified in the population-based survey, 15 (30.0%) had been missed despite their household being visited. The low number of missed cases limited precise comparisons between those missed and identified.

Reliability of LFM case identification by CDDs

To assess reliability of case identification, nurses examined cases identified by CDDs at post-survey clinics. Of 374 suspect lymphoedema cases, 120 (32.1%) were re-examined and leg swellings were confirmed in 93 cases, giving a PPV of 77.5% (96% CI 69.0–84.6%). Filarial lymphoedema was confirmed in 81 of the 120 cases (PPV 65.0%, 95% CI 55.8–73.5%). The 15 cases with leg swelling not diagnosed as filarial lymphoedema included 4 cases of Buruli ulcer, 3 of erysipelas, and 9 other diagnoses.

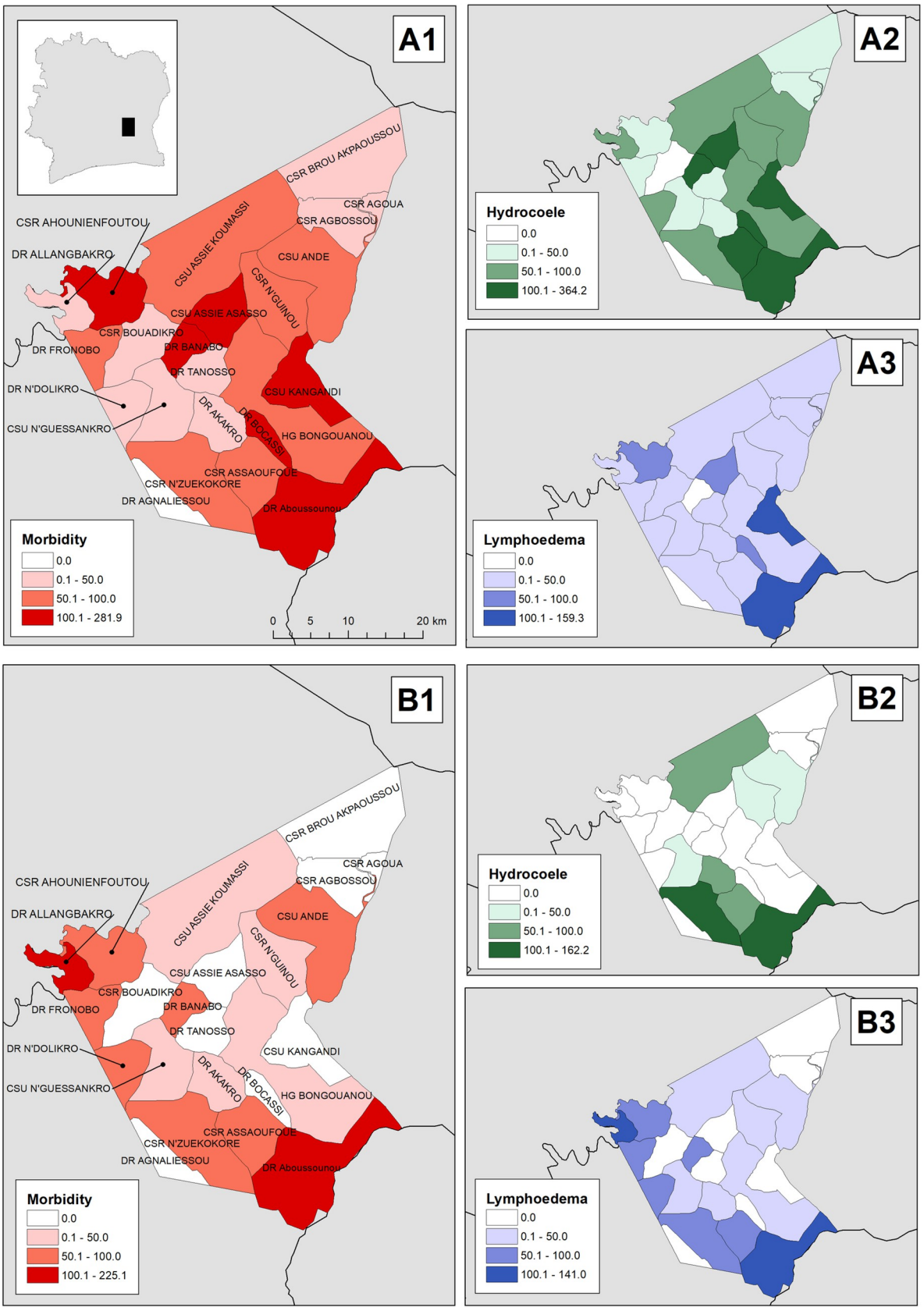
A1
CSR BROU AKPAOUSSOU
CSR AGOUA
CSR AGBOSSOU
CSR AHOUNIENFOUTOU
CSU ASSIE KOUMASSI
DR ALLANGBAKRO
CSU ANDE
CSR N'GUINOU
CSU ASSIE ASASSO
CSR BOUADIKRO
DR FRONOBO
DR BANABO
DR TANOSSO
DR N'DOLIKRO
CSU KANGANDI
DR AKAKRO
DR BOCASSI
CSU N'GUESSANKRO
HG BONGOUANOU
CSR ASSAOUFOUE
CSR N'ZUEKOKORE
DR AGNALIESSOU
DR Aboussounou
Morbidity
0.0
0.1 - 50.0
50.1 - 100.0
100.1 - 281.9
0
5
10
20 km
A2
Hydrocoele
0.0
0.1 - 50.0
50.1 - 100.0
100.1 - 364.2
A3
Lymphoedema
0.0
0.1 - 50.0
50.1 - 100.0
100.1 - 159.3
B1
Morbidity
0.0
0.1 - 50.0
50.1 - 100.0
100.1 - 225.1
B2
Hydrocoele
0.0
0.1 - 50.0
50.1 - 100.0
100.1 - 162.2
B3
Lymphoedema
0.0
0.1 - 50.0
50.1 - 100.0
100.1 - 141.0

Fig 1. Prevalence (number of cases per 10,000 population) of 1) lymphatic filariasis morbidity, 2) filarial lymphoedema, and 3) hydrocoele, detected through A) community-based screening led by volunteers and B) population-based prevalence survey led by formally trained nurses in Bongouanou, Côte d'Ivoire. Base-map contains district boundaries from the United Nations Office for the Coordination of Humanitarian Affairs (OCHA) {Affairs, 2019 #164}.

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Of 457 suspect hydrocoele cases identified by CDDs, 191 (41.8%) underwent scrotal examination by nurses. Scrotal swelling was confirmed in 179. The PPV for identification of scrotal swellings was 93.7% (95% CI 89.3–96.7%). Filarial hydrocoele was confirmed in 65 cases (PPV 34.0%, 95% CI 27.3–41.2%). Among the 126 non-filarial scrotal swellings, 103 were cases of hernia, 8 were congenital hydrocele, and 3 were other diagnoses. It is important to note that CDDs were not asked to differentiate between filarial and non-filarial aetiology for suspected case definitions (see Methods).

Household coverage and equity of community-based screening

Of 8,189 households interviewed by nurses, 5,265 (64.3%; 95% CI 63.2–65.3%) reported being visited by a CDD during CBS; 2,769 (33.8%) had not; and 154 (1.9%) did not know. Using causal modelling approaches to account for household, PSU and health-area contextual factors, household size was positively associated with inclusion in the CBS (Table 3). Households in which the primary language of the household head was Baoule, Senoufo, Dioula or other languages were less likely to have been visited than those in the predominant ethno-lingual group of Bongouanou, Agni. Households owning a basic mobile or smartphone were also more likely to have been visited than those without, independent of socioeconomic status. Crudely, households in the lowest socioeconomic class based on LCA were more likely to have been visited than those in the middle and highest classes, but after adjusting for survey design and other covariates, the middle SES class was more likely to have been visited. PSU-level fixed effects suggested higher coverage in more socioeconomically-developed clusters, with a positive association of household coverage with stable night light. A very low proportion of variance was attributable to health area levels (ICC L1 = 0.099) indicating little effect of implementation at this scale.

Patient clinical characteristics

Of the 125 confirmed cases of filarial lymphoedema, the majority (58.4%) were female and the median age was 48.0 years (interquartile range; IQR 32.4–57.0) (S2 Table). Most (60.8%) had unilateral lower limb swelling and the median duration of swelling was 7.0 years. Approximately a third (29.6%) had never experienced an acute attack, while 47.2% experienced less than one per month and 20.8% experienced at least one per month. Two thirds (66.7%) of cases were Dreyer stage one or two, and around half (47.2%) had entry lesions at the time of examination.

The median age of the 107 confirmed filarial hydrocoele cases was 52.0 years (IQR 40.5–64.0), and the median duration of swelling was 5.0 years (IQR 3.0–10.0). Around half (54.4%) said they never experienced acute attacks, 21.6% experienced at least one per month and 12.0% experienced at least one per month. By the staging and grading system proposed by Capuano and Capuano [25], most cases (72.1%) were classified beyond stage 2 (scrotum larger than a tennis ball), but few (10.4%) were beyond grade 1 (visible burial of the penis). Patient characteristics are summarised in the S2 Table.

Financial costs

The overall direct financial cost of CBS was 26,678.36 USD, of which approximately half was spent on preparation (sensitisation, training of trainers and of CDDs) and half on door-to-

Table 3. Predictors of household inclusion in community case search.

Predictors of visitation by CDDs	n visited by CDD	N in PBPS*	Risk (%)	Multivariate Analysis	
				Adjusted OR (95% CI)	LRT p-value
Household-level Fixed Effects					
Log household size				1.07 (1.06–1.09)	<0.001
Phone ownership[1]					<0.001
No phone	747	1,303	*57.33*	1 (base)	
Basic phone only	740	1,156	*64.01*	1.11 (1.07–1.15)	
Smartphone	3,645	5,419	*67.26*	1.06 (1.03–1.09)	
Language[2]					<0.001
Agni	3,998	6,022	*66.39*	1 (base)	
Baoule	322	511	*63.01*	0.94 (0.91–0.98)	
Dan	10	21	*47.62*	0.94 (0.78–1.12)	
Dioula	287	492	*58.33*	0.93 (0.90–0.97)	
French	18	33	*54.55*	1.18 (1.01–1.38)	
Malinke	110	160	*68.75*	0.96 (0.89–1.02)	
Senoufo	33	59	*55.93*	0.88 (0.79–0.98)	
Other/ Unknown	354	580	*61.03*	0.92 (0.89–0.96)	
Socioeconomic status[3]					0.001
Lowest	504	658	*76.6*	1 (base)	
Middle	2,925	4,284	*68.28*	1.06 (1.01–1.10)	
Highest	1,703	2,936	*58*	1.02 (0.98–1.07)	
Cluster/CDD-level Fixed Effects					
CDD score[4]				1.04 (1.00–1.08)	0.058
CDD gender					0.083
Female	1,722	2,474	*69.6*	1 (base)	
Male	3,410	5,404	*63.1*	0.93 (0.86–1.01)	
Mean distance to stable lights				1.06 (1.00–1.12)	0.047
Mean accessibility to HFs				1.03 (0.99–1.07)	0.123
				ICC	
				CDD zones within health areas (L1:L2)	0.099
				CDD zones (L2)	0.145

*PBPS = population-based prevalence survey.

[1] Missing for 1 household.

[2] Missing for 9 households.

[3] Multidimensional indicator constructed from: household electricity connection (missing for 5 households), education of household head (missing for 1 household), dwelling walls made from improved material (missing for 3 households), dwelling floor made from improved material (missing for 1 household), household access to improved water supply (missing for 3 households). Households missing data were assigned the cluster modal value.

[4] Missing for 3 CDDs equating to 156 households, which were not included in this model.

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door screening by CDDs (S2 Fig). The cost per suspect case identified by CDDs was $33.60, that per case confirmed was $69.62 and that per person targeted was $0.17.

Discussion

In this study, we evaluated a community-based strategy to estimate LFM burden, which can be implemented as a scalable, programmatic activity to support elimination of LF as a public health problem [7]. The strategy was programmatically feasible in terms of cost per person examined, and provided comparable prevalence estimates relative to a rigorous population-

based prevalence survey. These were 40 times higher than those obtained in recent pilots implemented during MDA in Côte d'Ivoire. Taken together, these results indicate that the strengthened, standalone strategy appears a considerably more effective approach to describe the true epidemiological situation of LFM. We also quantified the coverage and equity of our community-based strategy, and identified challenges faced by CDDs in differentiating hydrocoele from scrotal swellings of other causes. Whether this latter challenge can be overcome cost-effectively remains an open question for the GPELF and LF-endemic countries.

We made a series of simple changes to the existing programmatic strategy that was piloted during MDA in 2020 in Côte d'Ivoire. The modifications included strengthening of the training programme, increased supervision, and de-coupling of case-finding from MDA. These appear to have facilitated a step-change improvement in LFM case enumeration, resulting in prevalence estimates 40 times higher than those from initial pilots [19]. All modifications are likely to have contributed to improved reliability of case detection, though further research, including process evaluation at scale, would be needed to elucidate the contribution of each element to success at different levels of implementation. We believe the de-coupling of case-finding from MDA was a significant enabler. Previous studies have shown dedicated case searches to be more effective than those embedded in other activities, suggesting that competing demands, rather than de-centralisation *per-se*, are a more important barrier to reliable community-led LFM estimation [16, 17].

Although the estimate of LFM prevalence detected by CDDs was higher than that shown by the population-based prevalence survey, we consider the CDD-estimate reflective of the epidemiological situation in Bongouanou. CDDs appeared to face different challenges in the quantitation of suspect lymphedema and suspect hydrocele. Their identification of lymphoedema was good, though imperfect, in terms of both reliability and sensitivity: the PPV of 65% indicates that around one third of suspect cases identified by CDDs were not due to filarial lymphoedema, while the survey suggested that CDDs missed around a third of true cases (11 of 36 confirmed filarial lymphoedema cases had not been identified in the CBS). In effect, the similar magnitudes of these parameters resulted in an estimate of suspect LF-lymphoedema prevalence close to (within the confidence range of) that found in the population-based prevalence survey. This is an encouraging result in terms of obtaining accurate estimates of lymphoedema prevalence through CBS, though the sensitivity of case identification could be further improved through modifications to the CDD training materials or community education to raise awareness of early signs of lymphoedema.

The estimate of scrotal swelling prevalence by CDDs was close to (within confidence bounds of) that from the population-based prevalence survey, and the PPV of case identification for scrotal swellings was 93.7% (indicating that fewer than 7% of suspect cases were misdiagnosed). This suggests that CBS is both sensitive and specific as a tool for enumeration of scrotal swellings. It is important to emphasise that CDDs could record cases without physical examination while nurses could not confirm cases without examination. Among the 202 men who did not undergo scrotal examination during the population-based prevalence survey, there may have been cases who were willing to describe symptoms to a CDD but not to be examined by a nurse in the household setting, and thus went undetected.

The low PPV of hydrocoele identification led to an overestimation of hydrocoele prevalence by CDDs. This was not unanticipated, since CDDs were not trained to distinguish the aetiology of scrotal swellings, which was deemed unfeasible, particularly given the scale of coverage expected of them. A similarly low PPV of hydrocoele identification by CDDs has been demonstrated in Ghana, though the same study demonstrated a much higher PPV (92%) in Malawi [16]. Differentiation of hernia from hydrocoele may be possible with training [16], but given resource limitations within the GPELF, this may be unrealistic at scale. As this activity is

scaled-up, suspect hydrocoele cases would need to be confirmed by a local health worker or a pre-surgical team prior to corrective surgery. Re-examination of suspect cases would enable estimation of local PPVs, which could be used to adjust district-level estimates of hydrocoele prevalence generated by CBS. However, under current funding structures, cases are only eligible for free surgical intervention if confirmed as filarial hydrocoele, despite the fact that the repair of groin hernia, by far the most prevalent alternative diagnosis in our study, is also resolved by a simple and cost-effective surgery [31]. Our findings reinforce the clear public health and economic arguments for integration of case finding and surgery for these conditions, which should receive consideration within LF endemic countries [32]. The reliability of lymphoedema identification by CDDs was much higher, with PPV similar to estimates from other settings [16].

An important consideration for our findings is the potential scalability of the approach. This is crucial as WHO elimination dossiers for LF necessitate exhaustive enumeration of LFM across all endemic and previously endemic areas, often covering very large populations. We believe the financial cost per person screened in our study was low from an NTD programmatic perspective, being comparable to the cost per person treated through MDA in African settings in the early 2000's [33], and substantially lower than the cost per person examined in the global trachoma mapping project ($4.20 in Côte d'Ivoire in 2015) [34]. The cost per case confirmed was lower than published estimates of the cost per case found in community-based leprosy screening, varying from $72 (in Mali, 1999)- $313 (in Nigeria, 2002) [35]. The costs were also low relative to the financial burden on patients unable to work due to LFM, estimated at around $700 per individual affected [36], and costing almost $1.3 billion a year in lost productivity globally [37]. Hydrocoele surgeries are extremely cost-effective [38], and lymphoedema management costs far less than the economic benefits to patients over their lifetime [39]. Taken together, these results present a strong case for investment in community-led approaches to identify LFM cases to be linked to MMDP services. Parallel investment in universal health coverage and surveillance strengthening will be required for the sustainability of these programmes.

The level of household coverage achieved by CDDs was high, aligning to WHO coverage targets for LF MDA [40]. However, we identified factors at household and community (CDD zone) level that affected the probability of household inclusion. Within communities, households in the middle socioeconomic class were more likely to have been visited, while some minority language groups appeared at risk of exclusion. This may reflect CDD bias towards friends or those of specific social standing, which has been demonstrated in the context of MDA in Uganda [41]. To address this, the inclusion and sensitisation of minority language groups should be planned from early stages, and communications materials may need to be translated into multiple languages before implementation. There was a low level of variability at health area level, which supports the quality of the training cascade, given that CDDs were trained through supervisors at health area level.

Our study had several limitations. Both case-finding methods were fallible to ascertainment bias, as males, students, and people of working age would be less likely to be at home. Although we adjusted the survey prevalence estimate to correct this bias, it was not possible to do the same for the community-based estimate. Further, people affected by LFM may have been more likely to be at home- either because of unemployment or because they stayed intentionally for the survey. Whilst our population-based prevalence survey was conducted following specialist clinical training, outcome measures were based on clinical diagnosis made by non-physician healthcare workers, which may be imperfect. Selection bias may have been introduced by random walk procedures. While we aimed to nullify this by using multiple, random start points, random walk is more prone to selection bias than fully randomised or

segment-based sampling [42]. Another limitation is that not all suspect cases identified by CDDs presented for re-examination by nurses. This may have resulted in biased estimates of PPV if true LFM cases (potentially those with more severe symptoms) were more likely than false positives to present.

We have demonstrated the effectiveness of a scalable, community-based case-finding approach to LFM burden estimation. Together with our findings, the extensive toolkit we present can support programmes planning to implement similar activities. We believe this study transparently demonstrates how community-based infrastructure can support LF elimination, and is generalisable to other LF-endemic settings. Important advocacy points raised by our findings include the potential benefits of de-coupling LFM case-finding from MDA and the overt operational and public health benefits of integrating the detection and management of hydrocoele with scrotal hernia.

Supporting information

S1 Checklist. STROBE statement—checklist of items that should be included in reports of cross-sectional studies.
(DOCX)

S1 File.
(DOCX)

S1 Fig. Map of the study area. Population density data is from the Worldpop project: Linard C, Gilbert M, Snow RW, Noor AM, Tatem AJ. Population distribution, settlement patterns and accessibility across Africa in 2010. PloS one. 2012;7(2):e31743, www.worldpop.org [accessed 03/10/2020]. Base-map contains district and subdistrict boundaries from United Nations Office for the Coordination of Humanitarian Affairs (OCHA): (Côte d'Ivoire—Subnational Administrative Boundaries. 2019.), accessed 16/01/2022, roads from OpenStreetMap: HOTOSM Côte d'Ivoire Roads (OpenStreetMap Export), accessed via the Humanitarian Data Exchange website, and georeferenced health facility locations: Maina J, Ouma PO, Macharia PM, Alegana VA, Mitto B, Fall IS, et al. A spatial database of health facilities managed by the public health sector in sub Saharan Africa. Scientific data. 2019;6(1):1–8.
(TIF)

S2 Fig. Financial costs of CDD screening activity, per person targeted and by case confirmed (total and by phase).
(PNG)

S1 Text. Estimation of populations within survey strata and clusters.
(DOCX)

S2 Text. Constructing multidimensional indicator of socioeconomic status (SES) using latent class analysis (LCA).
(DOCX)

S1 Table. Candidate predictors and sources assessed for inclusion in mixed-effects generalized linear model of inclusion in household screening.
(DOCX)

S2 Table. Demographic and clinical characteristics of confirmed cases of lymphatic filariasis morbidity identified.
(DOCX)

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Supporting information

S1 Checklist. STROBE statement—checklist of items that should be included in reports of cross-sectional studies.
https://doi.org/10.1371/journal.pgph.0000760.s001

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4-5, 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8-9
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12, 15
		(b) Indicate number of participants with missing data for each variable of interest	S2_Table
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

S1 File.
https://doi.org/10.1371/journal.pgph.0000760.s002

English and French Abstract

Abstract

For lymphatic filariasis (LF) elimination, endemic countries must document the burden of LF morbidity (LFM). Community-based screening (CBS) is used to collect morbidity data, but evidence demonstrating its reliability is limited. Recent pilots of CBS for LFM alongside mass drug administration (MDA) in Côte d'Ivoire suggested low LFM prevalence (2.1-2.2 per 10,000).

We estimated LFM prevalence in Bongouanou District, Côte d'Ivoire, using a comparative cross-sectional design. We compared CBS implemented independently of MDA, adapted from existing Ministry of Health protocols, to a population-based prevalence survey led by formally trained nurses. We evaluated the reliability of case identification, coverage, equity, and cost of CBS.

CBS identified 87.4 cases of LFM per 10,000; the survey identified 47.5 (39.4-56.3; prevalence ratio [PR] 1.84; 95% CI 1.64-2.07). CBS identified 39.7 cases of suspect lymphoedema per 10,000; the survey confirmed 35.1 (29.2-41.5) filarial lymphoedema cases per 10,000 (PR 1.13 [0.98-1.31]). CBS identified 100.3 scrotal swellings per 10,000; the survey found 61.5 (55.5-67.8; PR 1.63 [1.41-1.88]); including 26.6 (21.5-32.4) filarial hydrocoele per 10,000 (PR of suspect to confirmed hydrocele 3.77 [3.12-4.64]). Positive predictive values for case identification through CBS were 64.0% (54.5-72.8%) for filarial lymphoedema; 93.2% (88.5-96.4%) for scrotal swellings; and 33.3% (26.4-40.8%) for filarial hydrocoele. Households of lower socioeconomic status and certain minority languages were at risk of exclusion. Direct financial costs were $0.17 per individual targeted and $69.62 per case confirmed. We provide our CBS toolkit.

Our community-based approach to LFM burden estimation appears scalable and provided reliable prevalence estimates for LFM, scrotal swellings and LF-lymphoedema. The results represent a step-change improvement on CBS integrated with MDA, whilst remaining at programmatically feasible costs. Filarial hydrocoele cases were overestimated, attributable to the use of case definitions suitable for mass-screening by informal staff. Our findings are broadly applicable to countries aiming for LF elimination using CBS.

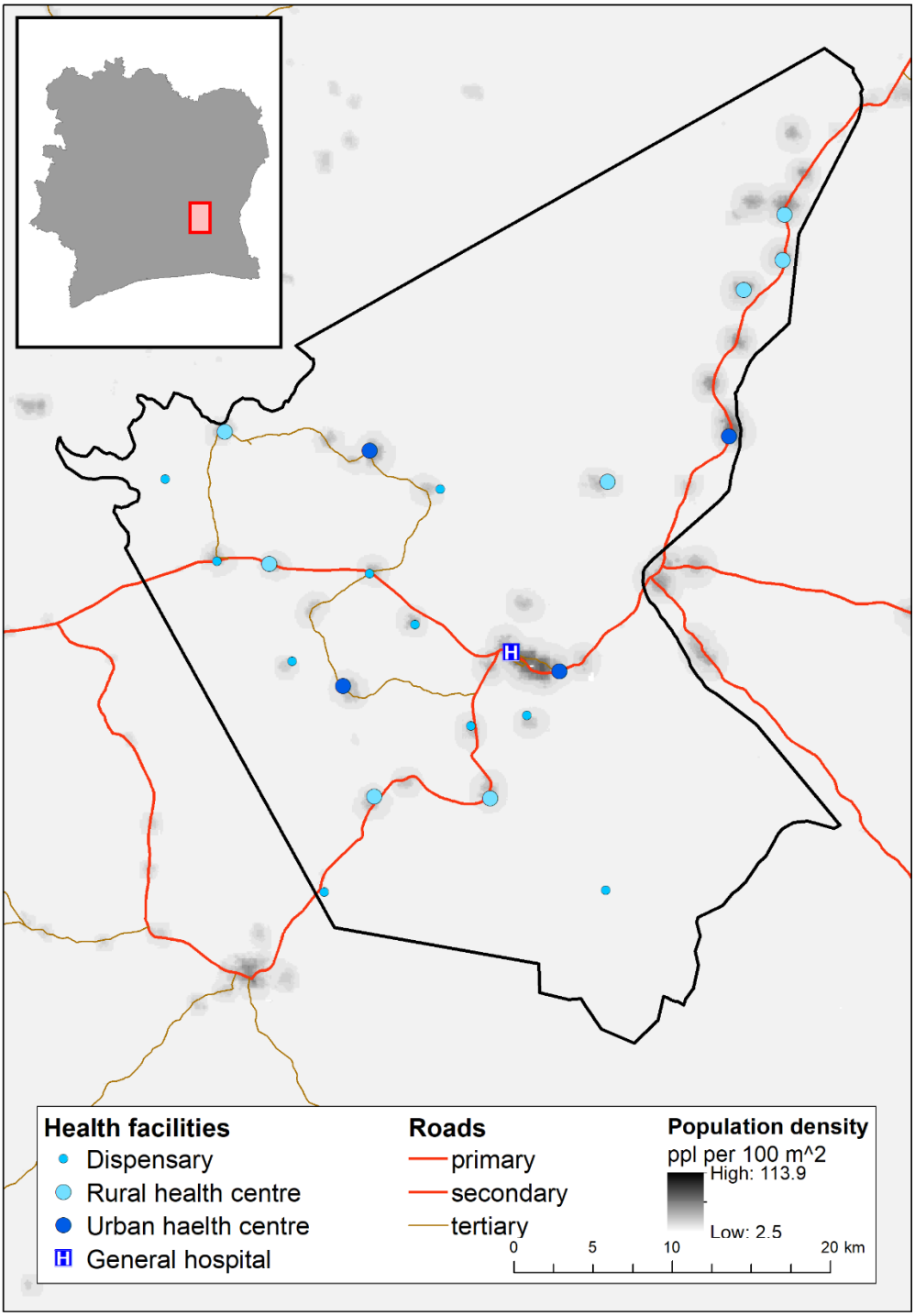
Résumé

Pour l'élimination de la filariose lymphatique (FL), les pays endémiques doivent documenter le fardeau de la morbidité due à la FL (LFM). Le dépistage communautaire (CBS) est utilisé pour recueillir des données sur la morbidité, mais les preuves démontrant sa fiabilité sont limitées. Des enquêtes pilotes récentes de dépistage communautaire pour la morbidité due à la FL parallèlement à l'administration massive de médicaments (MDA) en Côte d'Ivoire ont montré une faible prévalence de LFM (2,1-2,2 pour 10 000).

Le dépistage communautaire a identifié 87,4 cas de LFM pour 10 000 ; l'enquête a identifié 47,5 (39,4-56,3 ; ratio de prévalence [RP] 1,84 ; IC à 95% 1,64-2,07). Le dépistage communautaire a identifié 39,7 cas de lymphœdème suspect pour 10 000 ; l'enquête a confirmé 35,1 (29,2-41,5) cas de lymphœdème filarien pour 10 000 (PR 1,13 [0,98-1,31]). Le dépistage communautaire a identifié 100,3 gonflements scrotaux pour 10 000 ; l'enquête a trouvé 61,5 (55,5-67,8 ; PR 1,63 [1,41-1,88]) ; dont 26,6 (21,5-32,4) hydrocèles filaires pour 10 000 (PR de l'hydrocèle suspectée à l'hydrocèle confirmée 3,77 [3,12-4,64]). Les valeurs prédictives positives pour l'identification des cas par le dépistage communautaire étaient de 64,0 % (54,5-72,8 %) pour le lymphœdème filarien, de 93,2 % (88,5-96,4 %) pour les gonflements scrotaux et de 33,3 % (26,4-40,8 %) pour l'hydrocèle filarienne. Les ménages de statut socio-économique inférieur et certaines langues minoritaires étaient à risque d'exclusion. Les coûts financiers directs étaient de 0,17 $ par individu ciblé et de 69,62 $ par cas confirmé. Nous fournissons notre boîte à outils pour le dépistage communautaire.

Notre approche communautaire de l'estimation de la charge de la FLM (morbidité due à la FL) semble extensible et a fourni des estimations fiables de la prévalence de la FLM, des gonflements scrotaux et des lymphœdèmes. Les résultats représentent un changement radical par rapport au dépistage communautaire intégrée à la MDA, tout en restant à des coûts programmables. Les cas d'hydrocèle filarienne ont été surestimés, ce qui est attribuable à l'utilisation de définitions de cas adaptées au dépistage de masse par du personnel non formé. Nos résultats sont largement applicables aux pays visant l'élimination de la FL à l'aide du dépistage communautaire.

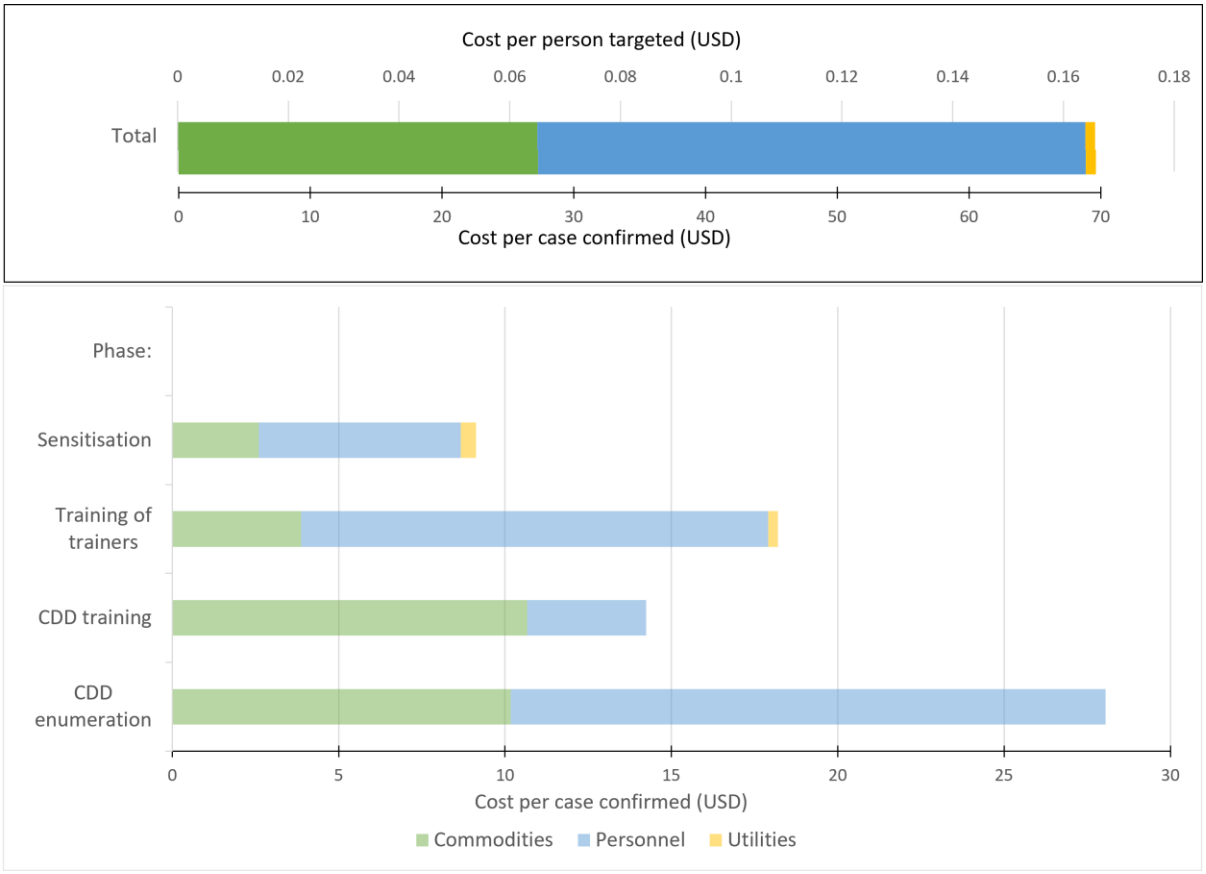
S1 Fig. Map of the study area.
https://doi.org/10.1371/journal.pgph.0000760.s003



Population density data is from the Worldpop project: Linard C, Gilbert M, Snow RW, Noor AM, Tatem AJ. Population distribution, settlement patterns and accessibility across Africa in 2010. PloS one. 2012;7(2):e31743, www.worldpop.org [accessed 03/10/2020]. Base-map contains district and subdistrict boundaries from United Nations Office for the Coordination of Humanitarian Affairs (OCHA): (Côte d'Ivoire—Subnational Administrative Boundaries. 2019.), accessed 16/01/2022, roads from OpenStreetMap: HOTOSM Côte d'Ivoire Roads (OpenStreetMap Export), accessed via the Humanitarian Data Exchange website, and georeferenced health facility locations: Maina J, Ouma PO, Macharia PM, Alegana VA, Mitto B, Fall IS, et al. A spatial database of health facilities managed by the public health sector in sub Saharan Africa. Scientific data. 2019;6(1):1–8.

S2 Fig. Financial costs of CDD screening activity, per person targeted and by case confirmed (total and by phase).

https://doi.org/10.1371/journal.pgph.0000760.s004



S1 Text. Estimation of populations within survey strata and clusters.
https://doi.org/10.1371/journal.pgph.0000760.s005

S1 Text: Supplementary Methods: Estimation of populations within survey strata and clusters

Health area boundaries were mapped based catchment areas, generated using an accessibility surface representing estimated travel time to the nearest health facility. We used the Cost Allocation tool in ArcMap to determine the most accessible health facility from each point in the district, using the precise locations of health facilities as the feature source data and the travel time surface as the input cost raster. We converted the output raster to a polygon shapefile. After the field survey, the estimated health area boundaries were manually adjusted to ensure each area encompassed the boundaries of mapped clusters within it.

We extracted the total population within mapped health area boundaries from the population density layer produced by the Facebook Connectivity Lab [1]. We compared the extracted population estimate to the reported population estimate used for operational purposes within the district and calculated a "correction factor" to re-scale health area populations to the reported populations.

Cluster boundaries were mapped by field teams accompanied by the CDD responsible for the area. Field teams recorded the limits of the zone through a "geotrace" form running from SurveyCTO software on Samsung smartphones. This automatically captured the GPS location every 20 seconds or whenever the data collector manually recorded the location. The field team were trained to pass behind houses on the boundary of the zone where possible, and to check with the CDD if any paths leading away from the main road led to houses within the zone, to ensure the full extent of the zone was captured.

Total and male populations were extracted from the mapped cluster boundaries and re-scaled by the correction factor to align the estimate to the reported population. The population estimates were multiplied by the fraction of the population aged 15 years and older in Bongouanou district [2].

References

1. Facebook Connectivity Lab and Center for International Earth Science Information Network - CIESIN - Columbia University. High Resolution Settlement Layer (HRSL). Source imagery for HRSL ©. 2016 DigitalGlobe. Accessed 10/03/2020.
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S2 Text. Constructing multidimensional indicator of socioeconomic status (SES) using latent class analysis (LCA).
https://doi.org/10.1371/journal.pgph.0000760.s006

We used the LCAvarsel package in R [1] to identify the most appropriate predictors and number of classes for LCA using the Fop et al. 2017 method which is described as a "greedy" backwards/forwards selection procedure, starting with all candidate predictors. The algorithm iteratively removes variables, tests the change in Bayesian Information Criterion (BIC) to determine whether to accept or reject the removal, adds each previously removed variable back in after successive removals and re-testing the change in BIC to determine whether to accept or reject re-addition.

The variables selected were: household electricity connection, education of household head, dwelling walls made from improved material, dwelling floor made from improved material, household access to improved water supply.

References

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S1 Table. Candidate predictors and sources assessed for inclusion in mixed-effects generalized linear model of inclusion in household screening.

https://doi.org/10.1371/journal.pgph.0000760.s007

Level	Variable	Source	Selected
Household	Log household size (scaled)	Household-level questionnaire	1
Household	Socioeconomic status (low, middle, high)	Multi-dimensional indicator generated from a combination of questions from household-level questionnaire	1
Household	Phone ownership	Household-level questionnaire	1
Household	Primary language of household head	Household-level questionnaire	1
Household	Household within a campment	Household-level questionnaire	0
Household	Any children in household	Household-level questionnaire	0
Household	Number of suspect cases in household	Household-level questionnaire	0
Cluster (CDD)	Primary language of CDD	CDD pre-post quiz	0
Cluster (CDD)	CDD age	CDD pre-post quiz	0
Cluster (CDD)	CDD gender	CDD pre-post quiz	1
Cluster (CDD)	CDD score on training quiz	CDD pre-post quiz	1
Cluster (zone)	Mean travel time to nearest health facility	Mean travel time extracted from pixels within geo-traced cluster boundary [1]	1
Cluster (zone)	Mean Euclidean distance to stable night lights	Mean Euclidean distance from pixels within geo-traced cluster boundary to the nearest stable light from National Oceanic and Atmospheric Administration (NOAA) [2]	1
Cluster (zone)	Urban-rural classification	Modal category (rural, urban, peri-urban) from Center for International Earth Science Information Network [3,4] within geo-traced cluster boundary	0
Cluster (zone)	Log CDD zone area (scaled)	Calculated from geo-traced cluster boundary	0
Cluster (zone)	Log CDD zone population (scaled)	Total population extracted from Facebook Connectivity Lab population density surface [5] within geo-traced cluster boundary	0

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S2 Table. Demographic and clinical characteristics of confirmed cases of lymphatic filariasis morbidity identified.
https://doi.org/10.1371/journal.pgph.0000760.s008

Demographic/ clinical characteristics	Confirmed filarial lymphedema (n=125) N	*% / median*	*CI/ IQR*	Demographic/ clinical characteristics	Confirmed filarial hydrocele (n=111) N	*% / median*	*CI/ IQR*
Gender							
Female	73	*58.4*	*49.2- 67.1%*				
Male	52	*41.6*	*32.4- 50.6 %*				
Age (median)		*48*	*35.0- 57.0*	**Age (median)**		*52*	*40.5- 64.0*
Years of swelling (median)		*7*	*3.0- 15.0*	**Years of swelling (median)**		*5*	*3.0-10.0*
Location of swelling				**Condition scrotal skin**			
Upper limb, unilateral	3	*2.4*	*0.5- 6.9%*	Normal	76	*60.8*	*59.0- 77.0%*
Lower limb, unilateral	76	*60.8*	*51.7- 69.4%*	Thickened	35	*28*	*23.0- 41.0%*
Lower limb, bilateral	44	*35.2*	*26.9- 44.2%*				
One upper & one lower limb	2	*1.6*	*0.00- 5.7%*				
ADLA Frequency				**ADLA Frequency**			
Never	37	*29.6*	*21.8- 38.4%*	Never	68	*54.4*	*51.0- 70.4%*
Less than once per month	59	*47.2*	*38.2- 56.3%*	Less than once per month	27	*21.6*	*16.7- 33.4%*
At least once per month	26	*20.8*	*14.1- 28.9%*	At least once per month	15	*12.0*	*7.8- 21.3%*
Unknown	3	*2.4*	*0.5- 6.9%*	Unknown	1	*0.8*	*0.02- 4.9%*
Dreyer Stage[1] (lower limb only)				**Stage**[2]			
1- 2	81	*66.4*	*55.8- 73.1%*	1	23	*18.9*	*13.6- 29.5%*
3+	41	*33.6*	*24.7- 41.8%*	2+	88	*72.1*	*70.5- 86.4%*
				Unknown	0	*0*	*0.0- 3.3%*
Entry lesions				**Grade**[2]			
Present	59	*47.2*	*22.5- 39.3*	0	97	*77.6*	*79.7- 92.9%*
None	66	*52.8*	*60.7- 77.5%*	1+	13	*10.4*	*6.4- 19.2%*
				Unknown	1	*0.8*	*0.02- 4.9%*

[1] According to the Dreyer system [1]: stage 1 = reversible lymphedema (limb may return to normal, for example at night), stage 2+ = non-reversible lymphedema.

[2] According to the staging and grading system of Capuano and Capuano [2]: Stage 1 = smaller than a tennis ball. Grade 0 = No visible burial or shortening of penis

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