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Original Contribution

A Landscape-based Model for Predicting *Mycobacterium ulcerans* Infection (Buruli Ulcer Disease) Presence in Benin, West Africa

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Abstract: *Mycobacterium ulcerans* infection (Buruli ulcer [BU] disease) is an emerging tropical disease that causes severe morbidity in many communities, especially those in close proximity to aquatic environments. Research and control efforts are severely hampered by the paucity of data regarding the ecology of this disease; for example, the vectors and modes of transmission remain unknown. It is hypothesized that BU presence is associated with altered landscapes that perturb aquatic ecosystems; however, this has yet to be quantified over large spatial scales. We quantified relationships between land use/land cover (LULC) characteristics surrounding individual villages and BU presence in Benin, West Africa. We also examined the effects of other village-level characteristics which we hypothesized to affect BU presence, such as village distance to the nearest river. We found that as the percent urban land use in a 50-km buffer surrounding a village increased, the probability of BU presence decreased. Conversely, as the percent agricultural land use in a 20-km buffer surrounding a village increased, the probability of BU presence increased. Landscape-based models had predictive ability when predicting BU presence using validation data sets from Benin and Ghana, West Africa. Our analyses suggest that relatively small amounts of urbanization are associated with a decrease in the probability of BU presence, and we hypothesize that this is due to the increased availability of pumped water in urban environments. Our models provide an initial approach to predicting the probability of BU presence over large spatial scales in Benin and Ghana, using readily available land use data.

Keywords: *Mycobacterium ulcerans*, Buruli ulcer, infectious disease, West Africa, land use/cover, landscape-based model

INTRODUCTION

Human-induced landscape alterations are widespread and can have large effects on the structure and function of ecosystems, including habitat loss, species extinction, altered nutrient dynamics, invasive species colonization, and

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other ecosystem processes (Forman, 1995; Moloney and Levin, 1996; Ceballos and Ehrlich, 2002; King et al., 2005; Linderman et al., 2006). In addition, it is becoming increasingly apparent that the spatial pattern of land use/land cover (LULC) plays a role in the dynamics of infectious diseases in both wildlife and human populations (Farnsworth et al., 2005; Smith et al., 2005). This link between LULC and disease dynamics is documented for several well-studied vector-borne diseases where landscape alterations, such as residential development or agricultural land use, results in higher contact rates between humans and disease vectors. Furthermore, changes in LULC can create favorable conditions for vectors and hosts leading to an increase in disease incidence rates (e.g., Jackson et al., 2006). For newly emerging yet neglected diseases, the identification of large-scale patterns in disease presence and their associations with LULC types can provide valuable information used to prioritize and target geographic areas for surveillance and intervention programs. For emerging diseases where little is known about vectors or modes of transmission, the quantification of large-scale patterns and associations with LULC types can also provide insight into potential vectors, because vector dynamics are often closely linked to environmental gradients (Hakre et al., 2004).

One such neglected disease is Buruli ulcer (BU), the more common name of *Mycobacterium ulcerans* infection, a debilitating skin affliction recently recognized by the World Health Organization and the 57th World Health Assembly as a rapidly emerging disease of tropical and sub-tropical regions of the world (WHO, 2000a; Johnson et al., 1999, 2005a; Thangaraj et al., 1999; Merritt et al., 2005). Unlike other mycobacterial infections such as tuberculosis and leprosy, BU transmission is poorly understood but is reported to be associated with disturbed aquatic habitats (Barker, 1973; Barker and Carswell, 1973; Portaels, 1989; Johnson et al., 1999; WHO, 2000a; for more on the epidemiology and clinical features of this disease, see Portaels et al., 1999; Marsollier et al., 2003; Johnson et al., 2005a). Further, although there has been some research targeted at identifying environmental reservoirs and potential vectors, these aspects of the disease still remain speculative, with most reservoirs identified using PCR (Merritt et al., 2005).

Research on the distribution of *M. ulcerans* has received intense interest since the disease was first described, but studies on the ecology of the disease have lagged behind. However, nearly all epidemiological studies have associated disease outbreaks with proximity to human-disturbed freshwater habitats, including marshes, impoundments, wetlands, and slow moving riverine environments (Barker and Carswell, 1973; Radford, 1975; Hayman, 1991; Horsburgh and Meyers, 1997; Thangaraj et al., 1999; Hayman and Asiedu, 2000; WHO, 2000b; Aiga et al., 2004; Duker et al., 2004; Johnson et al., 2005b; Merritt et al., 2005; Raghunathan et al., 2005). This ecological association with aquatic habitats is generally reported and described as part of the distribution and/or determinants of the disease, but it has never been quantified (Merritt et al., 2005). Rather, the association is most often anecdotal related to specific human activities (e.g., wading), or developed from case-control studies, which are often limited in spatial extent and thus prevents the identification of large-scale spatial patterns in disease occurrence (Johnson et al., 2005b; van der Werf et al., 2005; Debacker et al., 2006). To our knowledge, there have been no large-scale studies focused on quantifying relationship between LULC and BU presence. Thus, the objectives of this study were: (1) to identify, using landscape-based models, LULC types useful in predicting the probability of BU presence; and (2) to test the landscape-based models' ability to predict the probability of disease presence in villages in Benin, West Africa.

Hypotheses

Based on our current understanding of BU, we developed hypotheses for the covariates we included in our statistical analyses (Table 1). The association between agricultural activities and BU remains unclear. For example, studies have demonstrated that agricultural activity near rivers is a risk factor for BU (Marston et al., 1995), and that wearing a shirt while farming reduces the risk of BU (Raghunathan et al., 2005). However, others have demonstrated that being engaged in agricultural activities does not represent a risk factor for BU (Aiga et al., 2004). We hypothesized that outdoor agricultural activity increases the risk of exposure to *M. ulcerans* in the environment, and therefore expected a positive correlation between BU presence and the proportion of agricultural land use surrounding a village.

The presence of BU is also hypothesized to be associated with disturbed environments (Merritt et al., 2005), such as deforested areas. Therefore, we predicted that the probability of BU presence would decrease as the percent of land cover types that represented less-disturbed habitats increased around a village. Land cover types which we considered to represent less-disturbed habitats included percent forest and shrub land cover. Debacker et al. (2006) suggested that the

Table 1. List of Covariates Used in Multilevel Logistic Regression Models to Predict the Probability of Buruli Ulcer Presence in Villages in Benin, West Africa[a]

Covariate	Unit of measurement	Range
Latitude	Decimal degrees	6.383–9.476
Longitude	Decimal degrees	1.551–2.730
Distance to nearest river	m	22.5–12,157
Mean elevation	m	0.73–400
Total population	No. of inhabitants	217–801,683
Urban land use	%	0.0–6.0; 0.0–6.0
Agricultural land use	%	0.0–61.0; 0.0–42.0
Forest land cover	%	0.0–69.0; 0.0–52.0
Water land cover	%	0.0–23.0; 0.0–7.0
Agricultural and urban land use	%	0.0–14.0; 0.0–6.0
Wetland land cover	%	0.0–2.0; 0.0–11.0
Shrub land cover	%	3.0–42.0; 3.0–28.0

[a]Ranges for land use/land cover variables are given for the 20- and 50-km buffers, respectively.

availability of pumped water is an important factor in reducing the risk for BU. We therefore hypothesized that the percent urban land use surrounding a village would be associated with an increased availability of pumped water and thus would lower the probability of BU presence. We included the percent agricultural plus urban land use surrounding a village to represent a measure of the total human alteration to the landscape, and the covariates of latitude and longitude to account for any spatial gradients in BU presence.

Past research also suggests that *M. ulcerans* is associated with aquatic habitats. These studies have determined that certain activities, such as swimming or other activities in or near rivers, are risk factors for BU (Aiga et al., 2004; Raghunathan et al., 2005; Debacker et al., 2006). Thus, we hypothesized that individuals living in villages surrounded by large amounts of water, and those living in villages in close proximity to water would have high contact rates with aquatic habitats. Specifically, we predicted that the probability of BU presence would decrease with increasing village distance to the nearest river and with increasing elevation, and increase as the percent water and wetland cover surrounding a village increased. We included village elevation because we expected that villages at higher elevations would be further removed from low land areas where rivers and standing water are more abundant. We also hypothesized that exposure rates to *M. ulcerans* at the village level would be a function of population size, with villages with larger populations having a higher probability of BU compared to villages with smaller populations.

Materials and Methods

Study Area

The Republic of Benin is located in West Africa, with a population of nearly eight million and encompassing 112, 622 km^2 of land. Benin is bordered by Burkina Faso and the Republic of Niger to the north, by the Federal Republic of Nigeria to the east, and by the Republic of Togo to the west. The southern portion on Benin comprises coastline of the Gulf of Guinea (Fig. 1). The main agricultural activities (by land area) in Benin include maize (480,000 ha), representing the largest area, followed by sorghum, cassava, and yams (all > 100,000 ha), and rice (representing 7777 ha; Rapport de l'Enquête, 2003).

Buruli Ulcer Data

In Benin, BU 02 surveillance forms were used through routine community-based surveillance to collect data about BU patients during 2004 and 2005 (Sopoh et al., 2007). These forms were proposed by the World Health Organization in early 2000 to allow for the standardization of the reporting of the disease within and across countries (WHO, 2000b). This form allowed us to collected suitable information about BU presence/absence for 335 villages in Benin (Fig. 1). For our analysis, we considered BU present in a village if one or more cases were reported from that village on BU surveillance forms.

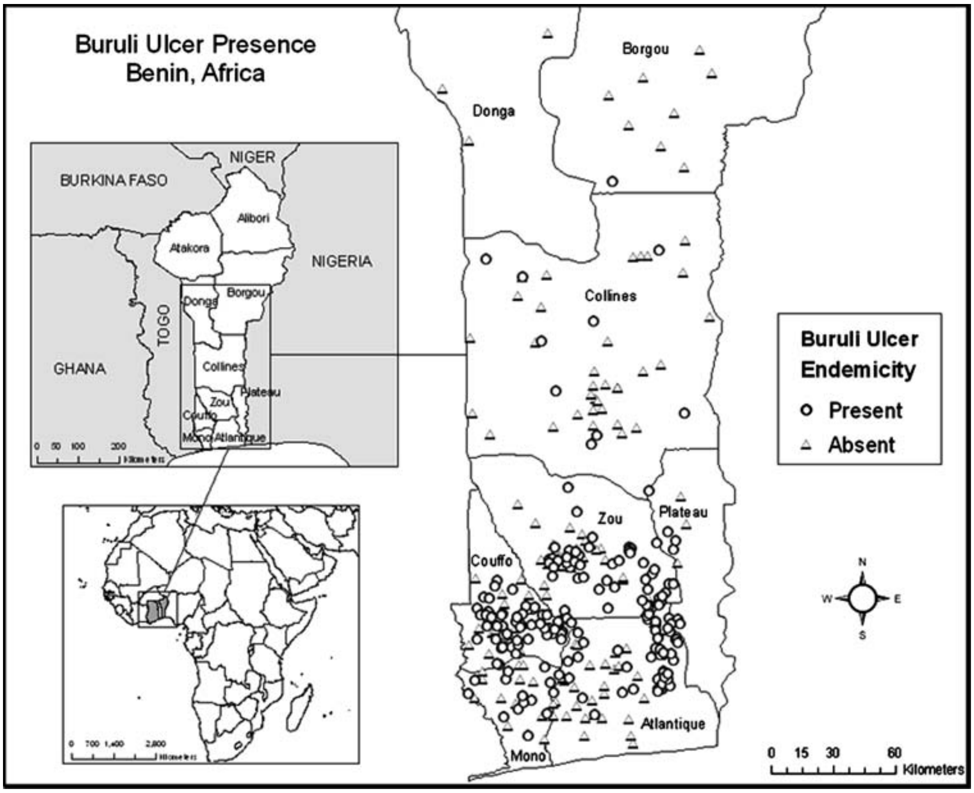

Figure 1. Location of villages and political districts in Benin, West Africa. Circles represent villages where Buruli ulcer (BU) is present, and triangles represent villages where BU is absent.

Land Use/Land Cover Data

Land use/land cover data were obtained from Landsat ETM+ imagery. The Landsat ETM+ imagery data were obtained from the University of Maryland Global Land Cover Facility (http://glcf.umiacs.umd.edu/index.shtml), December 13, 2000. Once the imagery was geometrically rectified and projected (UTM Zone 30), an unsupervised classification was performed (Lillesand and Kiefer, 2000). The unsupervised classification was run in Erdas IMAGINE with 100 initial classes on the principal axis with pseudocolor for 10 iterations or a 0.95 convergence. The initial classes were then narrowed to 22 unique LULC categories.

Each of the villages in Benin was buffered in ArcGIS (ESRI, 2005). The buffers around the villages were centered on latitude and longitude coordinates representing village centroids. Because we were interested in LULC at multiple spatial scales, seven buffers were created around each village at distances of 100 m, 500 m, 1000 m, 5000 m, 10 km, 20 km, and 50 km. The percent of each LULC class was calculated for each buffer distance by dividing the number of pixels for each individual LULC class within a buffer by the total number of pixels within that buffer. Prior to analyses, the 22 LULC categories were reduced to seven (Table 1) because we eliminated those LULC categories that consisted of more than two LULC types. For example, the LULC category "evergreen forest/agriculture/shrub" was not included in the analysis due to uncertainties regarding the actual LULC. Furthermore, we combined LULC types that were similar, such as combining LULC categories "forest" and "evergreen forest" into a single category called "forest." We also calculated the distance of each village to the nearest river (Table 1). The distance to the nearest river was calculated using the Benin river coverage at a 1:1,000,000 scale, and was calculated using the entire coverage which included streams, rivers, and channelized rivers.

Statistical Analyses

We used multilevel Bayesian logistic regression models to examine the effects of LULC and other village characteristics on BU presence in villages in Benin (Table 1). Multilevel models are appropriate for modeling covariate information at different levels of variation and for data with a nested data structure (Gelman et al., 2004; Wagner et al., 2006a, 2006b). Similar models have been developed to examine relationships between *Wuchereria bancrofti* infection and geographic, socioeconomic, and demographic risk factors in Haiti (Boyd et al., 2004), and malaria risk factors for children in Ghana, West Africa (Klinkenberg et al., 2005). In our analysis, villages are nested within regional districts of Benin. Specifically, the model consisted of a district-specific random effect to account for correlation between villages in the same district, while all slopes of the landscape-based covariates were constrained to be the same for all districts. Although we did not include district-level covariates in this model (i.e., the model was unconditional at the second level), we included the random district effect because we hypothesized that the probability of disease presence would be more similar within a district compared to between districts. Although data were not available to include in the model, we hypothesized that villages within districts would be more similar due to districts differing, on average, in characteristics such as rainfall and other environmental attributes, and the degree of public health education. In addition, the inclusion of the district-level random effect improved model fit substantially (i.e., including the random effect resulted in a lower DIC value, a decrease in the DIC of >50 units. See methods below for explanation of DIC). The general form of the model is as follows:

$$\text{logit}P(Y_{ij} = 1) = \beta_0 + \sum_{q=1}^{Q} \beta_q X_{qij} + \rho_i \qquad (1)$$

Where Y_{ij} equals 1 if BU is present at village j in district i and 0 otherwise, $j = 1,\ldots n_i$, with n_i being the number of villages in district i, and $i = 1,\ldots 9$. The parameter β_0 is the intercept, and β_q is the effect of covariate X_{qij} on the log odds of BU presence, where Q is the total number of covariates. The district-specific random effect is defined as $\rho_i \sim N(0, \tau)$, where τ is a hyperparameter representing the variance between districts in district-average log odds of BU presence. We used uninformative normally distributed priors for β_0 and β_q (*i.e.*, $\beta \sim N(0,1.0E6)$), and an uninformative gamma distributed prior for the hyperparameter τ (*i.e.*, $\tau \sim \Gamma(0.001,0.001)$). All analyses were performed using WinBUGS version 1.4 (Spiegelhalter et al., 2004).

Because estimating model parameters in WinBUGS is computationally intensive, and because we were interested in examining the effects of several LULC covariates at multiple spatial scales (7 land use/cover covariates × 7 buffer widths = 49 land use/cover covariates), we initially examined the effects of each LULC covariate separately by running univariate generalized linear mixed models in the statistical software SAS (PROC GLIMMIX; SAS Institute, 2000). After we identified those covariates that affected the probability of BU presence, we fit a series of models using Equation 1 that contained those covariates we hypothesized to be associated with the presence of BU (Table 1). We used the deviance information criteria (DIC) as a model selection criterion (Spiegelhalter et al., 2002). As a rule of thumb, a difference of greater than three units in the DIC values between two models suggests that the model with the lower DIC is preferred. A difference of less than three suggests that the models are indistinguishable. The model with the lowest DIC value indicates a better model. WinBUGS was used to generate 500,000 samples from the posterior distributions for each of the analyses after discarding the first 50,000 samples. We retained every 5th sample for a total of 100,000 samples. The mean, standard deviation (SD), and 95% Bayesian credible intervals were calculated. We examined the Gelman-Rubin convergence statistic, chain histories, and posterior density plots to assess convergence, and we assessed model sensitivity to different initial starting values for all parameters. Although using uninformative priors in our Bayesian analyses provided numerically similar estimates to those using a maximum likelihood approach, the interpretation of the parameters and credible intervals are different. For example, a 95% Bayesian credibility interval represents a 95% probability that the parameter of interest is contained within that interval. Whereas, frequentist 95% confidence intervals do not mean that there is a 95% chance that the parameter of interest will occur within the interval. Rather a 95% confidence interval "asserts that in n hypothetical runs of an experiment, the parameter of interest (e.g., the true population mean) is expected to occur in the computed interval 95% of the experimental runs" (Ellison, 2004).

Our analysis allowed us to identify landscape-based covariates associated with BU presence. However, we were also interested in evaluating the "best" model's ability to predict the probability of BU presence in other villages. To accomplish this goal, prior to fitting models, we randomly divided the data set into training (n = 233) and validation data sets (n = 112). The models were constructed using the training data set and we assessed the predictive ability using the validation data set. To further test the model, we used data from 70 villages in Ghana, Africa for which we had GIS and BU presence/absence data (similar methods described for the acquisition of Benin LULC were employed for the Ghana villages). There are few BU data available for Ghana, so the ability to predict villages that have a high probability of BU presence is highly desirable. We plotted histograms of the mean posterior estimates of the probability of BU presence on the x-axis and number of villages

Table 2. Deviance Information Criteria (DIC) Estimates for the Multilevel Logistic Regression Models Used to Predict the Presence of Buruli Ulcer (BU) in Villages in Benin, West Africa[a]

Model no.	Covariates			DIC
1	Distance to river			241.92
2	Longitude			238.67
3	Latitude			237.07
4	Urban50			233.88
5	Mean elevation			233.63
6	Latitude	Longitude		233.48
7	Ag20			231.54
8	Latitude	Longitude	Urban50	229.17
9	Longitude	Ag20		228.47
10	Latitude	Urban50		227.89
11	Ag20	Urban50		226.97

[a]Ag20, percent agricultural land use in a 20-km buffer; Urban50, percent urban land use in a 50-km buffer. Models are listed in descending order based on DIC values.

on the y-axis as a way to visualize predictive performance. If the model predicted well, we would expect a bimodal distribution of the posterior means, with the BU positive sites being predicted closer to one and the BU negative sites clustering near zero.

Results

The models we considered for predicting the presence of BU along with DIC values are shown in Table 2. The probability of BU presence increased with increasing longitude and percent agricultural land use in a 20-km buffer surrounding a village, and decreased as latitude and the percent urban land use in a 50-km buffer surrounding a village increased. Furthermore, latitude and percent agriculture were negatively correlated ($r^2 = -0.67$), with the percent agricultural land use decreasing as latitude increased. Thus, latitude and percent agriculture in a 20-km buffer were never entered into the same model together. Three models had DIC values within three units of the model with the lowest DIC value, suggesting that those models were essentially indistinguishable when taking into account model fit and complexity. However, we will focus on the two models with the lowest DIC values and explore their abilities to predict the validation data set.

For the two best models, the posterior means, standard deviations, and 95% credible intervals for the parameters are shown in Table 3. Both models demonstrated predictive ability when predicting the Benin validation data set. The distributions of the posterior mean probability of BU presence for BU positive and negative villages demonstrated moderate separation (Fig. 2). For example, when using model 10 (see Table 2), the average of the mean posterior probabilities of BU presence for BU negative villages was 0.41 (standard deviation [SD] = 0.29) while the average of the mean posterior probabilities of BU presence for BU positive villages was 0.67 (SD = 0.25). For model 11, the average of the mean posterior probabilities of BU presence for BU negative villages was 0.43 (SD = 0.28), while the average of the mean posterior probabilities of BU presence for BU positive villages was 0.65 (SD = 0.26). For the Ghana validation data set, we used model 10 (latitude and percent urban land use in a 50-km buffer) because we did not have a comparable agricultural land use category from the Landsat ETM+ data to use model 11. Model 10 performed quite well when predicting sites in Ghana. The average of the mean posterior probabilities of BU presence for BU negative villages was 0.45 (SD = 0.19), while the average of the mean posterior probabilities of BU presence for BU positive villages was 0.80 (SD = 0.12). Both validation data sets suggest that the models are better able to predict BU positive villages correctly compared to BU negative villages, as indicated by the distributions of the mean posterior probabilities (Fig. 2).

Discussion

Land Use/Land Cover Associated with Buruli Ulcer

Because BU has been associated with aquatic ecosystems and human activities near water bodies (Portaels, 1989; Marsollier et al., 2003; Merritt et al., 2005), it was unexpected that the percent water land cover in a buffer around villages and the distance of a village to the nearest river were not important predictors of the probability of BU presence. Previous studies that have found associations between water and BU, however, were performed over smaller spatial scales. For instance, Debacker et al. (2006), in an unmatched case-control study in Benin, found that individuals that used unprotected water sources (i.e., water that was not pumped) had an increased risk of BU. Another case-control study performed in Ghana by Aiga et al. (2004) determined that individuals swimming in rivers on a habitual basis were at a greater risk for BU. Both of these case-control studies considered much smaller spatial areas

Table 3. Posterior Means, Standard Deviations (SD), and 95% Credible Intervals (CI) for Parameters Estimated Using Multilevel Logistic Models Used to Predict Buruli Ulcer Presence in Benin, West Africa[a]

Parameter	Model					
	Latitude $(\hat{\beta}_1)$ Urban50 $(\hat{\beta}_2)$			Ag20 $(\hat{\beta}_1)$ Urban50 $(\hat{\beta}_2)$		
	Mean	SD	95% CI	Mean	SD	95% CI
$\hat{\beta}_0$	16.80	5.11	7.34, 27.24	−0.89	1.34	−3.50, 1.82
$\hat{\beta}_1$	−2.02	0.67	−3.37, −0.78	4.65	1.53	1.76, 7.76
$\hat{\beta}_2$	−27.11	9.07	−45.51, −9.96	−20.09	8.49	−37.29, −3.98
$\hat{\tau}$	5.80	6.30	0.98, 21.43	5.60	5.43	1.14, 19.01

[a]Ag20, percent agricultural land use in a 20-km buffer; Urban50, percent urban land use in a 50-km buffer. $\hat{\beta}_0$ is the intercept, $\hat{\beta}_1$ and $\hat{\beta}_2$ are coefficients for covariates one and two, respectively, and $\hat{\tau}$ is the between-district variance estimate.

compared to our study. For instance, Debacker et al. (2006) used patients from a single clinic in Zou, Benin, although about 30% of the patients were from other regions (Debacker et al., 2006). Similarly, only one district (Amansie West District) of Ghana was used in the Aiga et al. (2004) study. In a slightly larger study in Ghana that included three districts, it was found that wading in a river or stream was a significant risk factor in a multivariate model, but the source of drinking water was not (Raghunathan et al., 2005). Lastly, Johnson et al. (2005b) found an inverse relationship between BU prevalence and distance to the Couffo River in Benin, with BU prevalence increasing as the distance to the river decreased from 10 to 1 km. This study was also limited to villages within one district (Gnizounmé).

Taken together, these more locally-focused studies suggest that human activity near aquatic habitats is a risk factor at the individual level; however, our analysis suggests that percent of water land cover surrounding villages and the distance to the nearest river are not associated with an increased probability of BU presence at the village level. This apparent discrepancy between our study and those previously cited may be in part due to the large spatial extent and coarse resolution of our LULC data (30 m^2). Our models were not able to take into account water body type (e.g., wetland vs. pond) or whether it was disturbed. Small water bodies that may be important water sources were likely missed in the calculation of percent water in a surrounding buffer. In addition, our calculation of distance to nearest river was limited to relatively large rivers due to data resolution limitations. Distance to smaller water bodies (e.g., smaller ponds or wetlands) may be an important factor in determining BU presence (Aiga et al., 2004). Our experience in both Ghana and Benin indicates that there are small water sources (both streams and wetlands) that could go undetected using the LandSat images employed in this study. Indeed, most communities have some type of water source, which can range in size from large rivers and lakes to small streams (or wetlands) only 2-m wide. Furthermore some of these water bodies are ephemeral and highly variable, drying up during periods of low rainfall and flooding extensively during periods of high rainfall.

Our analyses suggest that it is the percent of agricultural and urban land use surrounding a village (or villages) that influences the probability of BU presence. Furthermore, our analysis suggests that it is large-scale patterns in urban land use (i.e., in a 50-km buffer surrounding a village) that are important, rather than localized urban land use patterns. We speculate that this lower probability of BU presence with increasing urban land use is due to an increase in the availability of pumped water (i.e., protected water sources) with increasing urbanization. If this is the case, then our results support those by Debacker et al. (2006) and suggest that the availability of pumped water is an important factor in reducing the risk for BU at the individual level (Debacker et al., 2006) and the probability of BU presence at the village level. However, the availability of pumped water is likely not the only factor. This is because in some places, due to local beliefs, populations do not use the pumped water and prefer to use non-protected water sources. Although our results show that urban land use is important, it also demonstrates that very little urban land use, as a percentage of total LULC surrounding a village, is adequate to reflect a decrease in the probability of BU presence. In Benin, urban land use does not comprise a large proportion of total land use. In fact in the 50-km buffer used in this analysis, percent urban land use ranged

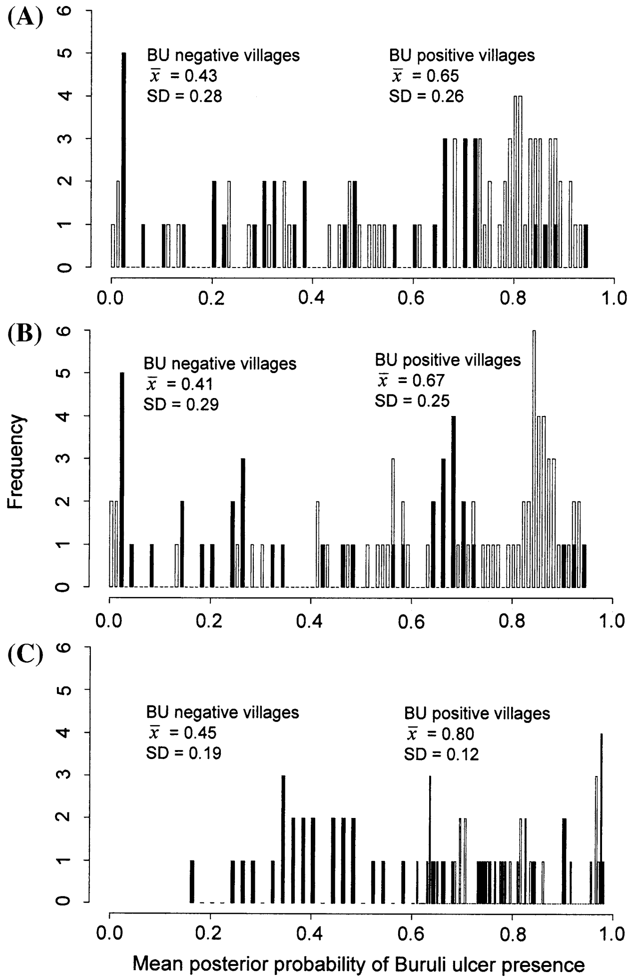

Figure 2. Mean posterior probabilities of Buruli ulcer (BU) presence in villages in Benin, West Africa **(A, B),** and in Ghana, West Africa **(C)** for villages with reported BU presence (light bars) and without reported BU presence (dark bars) in validation data sets. Predictions in (A) (Benin validation data set) were made with a model using percent agricultural land use in a 20-km buffer and percent urban land use in a 50-km buffer around villages as covariates. Predictions in (B) (Benin validation data set) and (C) (Ghana validation data set) were made using latitude and percent urban land use in a 50-km buffer around villages as covariates. The means ($\bar{x}$) and standard deviations (SD) for the distributions of predicted values for BU-positive villages and BU-negative villages are shown.

from 0–6% of the total LULC. An additional hypothesis as to why BU presence is negatively associated with urban land use is that, in urban areas, contact with "risk ecosystems" is low compared to rural areas, and that agricultural activities in rural areas increases the intensity of contact. Another explanation may be that a small urban center provides additional employment opportunities that replace the need for subsistence or other types of farming.

Percent agricultural land use and latitude were confounded in our study. Because BU has been associated with disturbed aquatic environments, such as those impacted by agricultural activities (Marston et al., 1995; Merritt et al., 2005), we wanted to further discern the effects of agriculture and latitude. To this end, we performed an analysis that excluded the northern three districts. By focusing the analysis on southern Benin, we were able to decrease the correlation between agriculture and latitude ($r^2 = -0.52$). This analysis showed that the percent agriculture land use in a 20-km buffer around villages still had a positive effect on BU presence, and the magnitude of the effect was similar to that in the original analysis that considered all districts. This suggests that agricultural land use may be associated with BU presence in villages in Benin, but it is still not possible to completely separate the effects of agricultural land use and latitude. The significance of latitude in our model also suggests a north–south gradient in the probability of BU presence. This gradient may reflect the effects of climate on the availability of suitable aquatic habitats for *M. ulcerans*, with semiarid conditions in the north resulting in a lower probability of BU presence. Alternatively, the gradient may also constrain the arable land available for certain crops. Our satellite images were not able to differentiate between different types of agriculture, but this could be important, as certain crops require more or less irrigation, fertilizer, or other alterations to the landscape. Additional studies are warranted to test for specific agricultural practices related to BU presence (Raghunathan et al., 2005).

There may also be an interaction between agricultural land use and proximity of agricultural activities to water. For instance, in a case-control study, Marston et al. (1995) found that decreased walking distance between agricultural fields and a main river in Côte d'Ivoire was a risk factor for BU. However, additional research on the ecology of *M. ulcerans* is necessary to determine the mechanisms involved in the transmission of BU. Once reservoirs and vectors are identified and the processes that link human activities and disease dynamics are quantified, the creation of mechanistic models that incorporate LULC should provide a powerful tool to understanding the ecology of BU.

It should be noted, however, that an accuracy assessment of the LULC data used in this study was not conducted because ground-truth data were not available. An accuracy assessment was not possible because of a combination of the cost and time involved in quantifying LULC classification error for nearly the entire country of Benin.

However, we did take steps to minimize the potential for classification errors to influence our results. For example, we used only easily distinguished LULC classes in our study (e.g., forest vs. urban vs. water), which have fewer propensities for errors during the classification process given that the spatial coverage in our study was large (Cunningham, 2006). In addition, we did not consider LULC categories that were comprised of more than two LULC types in an effort to reduce the amount of classification error potentially introduced into our analyses. Furthermore, the results of this study provide a preliminary evaluation of the spatial distribution of BU as it relates to LULC. From this study using spectral signatures and general classes, we can expand to field-based studies and a more specific land cover classification with an accuracy assessment. Thus, although LULC classification error is an important concern, in light of this uncertainty, we feel that the results and interpretations presented in this current study are valid.

Predicting Buruli Ulcer Presence

Our landscape-based models demonstrated predictive ability when tested using validation data sets from Benin and Ghana. Our two best models performed similarly when predicting the validation data set from Benin. This is not surprising given the high correlation between agricultural land use and latitude used as covariates in the two models. The ability to predict BU presence using widely available landscape-based data provides an important step towards prioritizing research and control efforts, especially when primary prevention strategies are not possible due to the lack of knowledge regarding modes of transmission. The high socioeconomic costs associate with this disease (Asiedu and Etuaful, 1998), along with the increasing number of cases makes the quantification of disease presence a critical first step to disease control and education efforts. For example, targeting education efforts in villages that have a high probability of BU presence may help reduce the stigma associated with this disease (Stienstra et al., 2002). Furthermore, we were better able to predict villages where BU was present compared to those villages where BU was absent. Those villages where BU was absent and were predicted as having a high probability of BU presence may represent villages where an increase in surveillance is warranted. One hypothesis as to why it was difficult to predict BU absence is that the bacteria may be widespread in the environment, but particular human activities, both adjacent to and within the water, are required for transmission. Thus, there may be an important human behavioral component involved in the presence of BU in certain villages.

Our analyses indicated that the large-scale patterns in LULC play a role in determining the presence of BU in Benin, West Africa. Our study is unique as being the first large-scale analysis to demonstrate that the probability of BU presence increases with increasing agricultural land use and decreases with increasing urbanization surrounding villages. To our knowledge, there have been no other studies of this spatial extent that have addressed land use and cover in relation to patterns in BU occurrence. For diseases such as BU, where uncertainty exists with regards to reservoirs, vectors, and modes of transmission, the affirmation of associations from vastly different data sets and approaches (e.g., case-control studies and landscape-based models) is necessary to guide future research. Furthermore, interdisciplinary research programs that include collaborative efforts between ecologists and epidemiologists are fundamental to understanding the ecology of BU in West Africa and in other countries. This collaborative approach is necessary to link large-scale factors such as LULC patterns with local vector and disease dynamics. Fortunately, these interdisciplinary efforts are currently underway and promise to provide the much needed data and insight that is necessary to reduce the impacts of this disease.

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