ECOLOGY AND GEOGRAPHY OF HUMAN MONKEYPOX CASE OCCURRENCES ACROSS AFRICA

Christine K. Ellis,[1] Darin S. Carroll,[2] Ryan R. Lash,[2] A. Townsend Peterson,[3,6] Inger K. Damon,[2] Jean Malekani,[4] and Pierre Formenty[5]

[1] United States Department of Agriculture–Animal and Plant Health Inspection Service, Wildlife Services, National Wildlife Research Center, 4101 W Laporte Ave., Fort Collins, Colorado 80521, USA
[2] Poxvirus and Rabies Branch, United States Centers for Disease Control and Prevention, Atlanta, Georgia 30329, USA
[3] Biodiversity Institute, University of Kansas, Lawrence, Kansas 66045, USA
[4] Department of Biology, University of Kinshasa, Kinshasa, Democratic Republic of Congo
[5] World Health Organization, Avenue Appia 20, 1202 Geneva, Switzerland
[6] Corresponding author (email: town@ku.edu)

ABSTRACT: As ecologic niche modeling (ENM) evolves as a tool in spatial epidemiology and public health, selection of the most appropriate and informative environmental data sets becomes increasingly important. Here, we build on a previous ENM analysis of the potential distribution of human monkeypox in Africa by refining georeferencing criteria and using more-diverse environmental data to identify environmental parameters contributing to monkeypox distributional ecology. Significant environmental variables include annual precipitation, several temperature-related variables, primary productivity, evapotranspiration, soil moisture, and pH. The potential distribution identified with this set of variables was broader than that identified in previous analyses but does not include areas recently found to hold monkeypox in southern Sudan. Our results emphasize the importance of selecting the most appropriate and informative environmental data sets for ENM analyses in pathogen transmission mapping.

Key words: Ecologic niche modeling, epidemiology, georeferencing, monkeypox, point-radius method.

INTRODUCTION

Human monkeypox is a severe febrile rash illness occurring in humans infected with monkeypox virus, a double-stranded DNA virus found in the genus *Orthopoxvirus* (family *Poxviridae*, subfamily Chordopoxvirinae) along with camelpox, cowpox, ectromelia, variola, vaccinia, and others (Breman, 2000). Monkeypox virus was identified as an agent of disease in 1959 when an outbreak occurred in a colony of cynomolgus monkeys (*Macaca fascicularis*) in Denmark (Sale et al., 2006). Human monkeypox was identified as a distinct disease in the 1970s when smallpox eradication efforts in rural areas of western and central Africa and present-day Democratic Republic of Congo (DRC) revealed a smallpox-like illness (Arita et al., 1985; Huhn et al., 2005). Since smallpox eradication, monkeypox has proven troublesome to diagnose and combat and is currently included in the select list of biologic agents considered potentially serious human health threats (CDC, 2005; USDA, 2005).

The natural history of monkeypox has remained opaque to detailed understanding. Much remains unknown about its geographic distribution and ecology, although it appears endemic to West Africa and the Congo Basin of Central Africa, with most human cases occurring in the latter region (Huhn et al., 2005; Reynolds et al., 2006). Natural reservoir host(s) or intermediate host(s) remain unidentified, although rodents have been implicated (monkeys are incidental hosts; Khodakevich et al., 1988). Monkeypox virus has been isolated only once from a wild animal: a rope squirrel (*Funisciurus anerythrus*) trapped in the DRC in 1986 (Khodakevich et al., 1986). Human infection is thought to occur via contact with infected animals (72% of cases) and to a lesser extent by human-to-human contact, respiratory aerosol, or contact with body fluids (Jezek et al., 1988; Sale et al., 2006).

Significant differences have been noted in the epidemiologic and clinical features of human monkeypox in Central versus West Africa. In the Congo Basin, monkeypox is

associated with higher case numbers and increased morbidity, mortality, viremia, and transmission via human-to-human contact when compared with cases in West Africa (Chen et al., 2005; Likos et al., 2005). Initial molecular genetic studies and whole-genome analyses of monkeypox isolates indicate the presence of two distinct strains (Mackett and Archard, 1979; Esposito and Knight, 1985; Likos et al., 2005). Isolates from outbreaks in Cameroon, Republic of the Congo, Gabon, and the DRC comprise the Congo Basin clade, whereas isolates from Nigeria, Liberia, and those imported from Ghana into the United States constitute the West African clade (Reed et al., 2004; Likos et al., 2005; Sale et al., 2006).

Here, we analyze ecologic factors relevant to the environmental, phytogeographic, and geographic distribution of human monkeypox in Africa. We build on previous analyses, in which the ecologic niche of the virus was modeled preliminarily and its potential distribution reconstructed and explored, with the interesting result that the monkeypox occurrences from West and Central Africa do not appear to occur under different environmental circumstances (Levine et al., 2007). We analyze a more-refined occurrence data set, utilizing more-diverse environmental parameters, in an attempt to shed additional light on monkeypox ecology and, particularly, on the recent records of monkeypox of the Congo Basin clade from southern Sudan (Formenty et al., 2010).

MATERIALS AND METHODS

Human monkeypox occurrence data

Locations of known case occurrences of human monkeypox in endemic regions of West and Central Africa were compiled from outbreak investigation and surveillance data provided by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). A human monkeypox case was defined as a published reported case or a nonredundant unpublished case confirmed by laboratory evidence of disease. Laboratory detection methods used to classify

human monkeypox cases recorded by the WHO between 1970–1986 included electron microscopy (EM), virus culture, and serology; whereas PCR, EM, and tissue culture were used for case definition by the CDC (Learned et al., 2005; Levine et al., 2007).

Overall, 404 human monkeypox cases were available and were referenced geographically with variable degrees of specificity (i.e., to country, region, district-zone, municipality, or specific locality). Geographic coordinates were assigned to cases based on municipality and specific locality using the Alexandria Digital Library Gazetter (www.alexandria.ucsb.edu), the National Geospatial Intelligence Agency Geographic Names Database (www.gnswww.nga.mil/geonames/GNS/index), and electronic data published with the Rand McNally New Millennium World Atlas (Rand McNally and Company, 1988). The Mammal Networked Information System (MaNIS) point-radius georeferencing method was used to assess spatial uncertainty in the geographic referencing of each occurrence point to account for the spatial extent of the named place, uncertainty of directions, and uncertainty of distances (Wieczorek et al., 2004). We restricted our analyses to sites that could be georeferenced with a spatial precision finer than 10 km. Because most cases were poorly described geographically, only 216 occurrence localities could be used. Redundant case occurrences (cases with identical geographic coordinates) were then removed, leaving 127 occurrences available for analysis. West African and Central African cases were all included in the occurrence data set because a previous study (Levine et al., 2007) found that their respective niches were not differentiated from one another. The human monkeypox cases recently reported from Sudan (Formenty et al., 2010) were excluded from this data set owing to doubt regarding the provenance of these infections.

Environmental data sets

Environmental data were drawn from four principal sources: 1) Climatic data were drawn from the WorldClim archive (WorldClim 2005), a database containing global climate data interpolated from weather station data from 1950–2000 at 10′ (arc minutes; ~344 km^2) spatial resolution (Hijmans et al., 2005). Nineteen 'bioclimatic' variables were initially explored, including: annual mean temperature; annual precipitation; isothermality; maximum temperature of the warmest month; minimum temperature of the coldest month; mean diurnal temperature range; mean temperature and

precipitation of the coldest, driest, warmest, and wettest quarters; precipitation of the driest and wettest months; precipitation seasonality, temperature annual range, and temperature seasonality. 2) Data sets summarizing soil and vegetation characteristics were obtained from the GeoData Portal (United Nations Environment Programme, 2006) at 30′ (~1,000 km^2) including data layers summarizing net primary productivity (NPP), potential evapotranspiration (pevap), soil carbon, soil moisture, and soil pH. 3) Topographic data were obtained from the United States Geological Survey's Hydro-1K digital elevation model (USGS, 1955) at 0.5′ (~1 km^2) including aspect, compound topographic index, flow accumulation, and slope. 4) Finally, we used composite Normalized Difference Vegetation Index (NDVI) data layers derived from the Advanced Very High Resolution Radiometer satellite (University of Maryland, 2010) at 0.5′ (~1 km^2) to summarize monthly photosynthetic mass during April 1992–March 1993 as an exemplar year. All datasets were resampled to 10 km^2 spatial resolution for analysis in order to match the approximate spatial precision of the case occurrences.

Ecologic niche modeling

The ecologic niche of a species can be defined as the set of environmental conditions under which it is able to maintain populations without immigrational subsidy (Grinnell, 1917). Ecologic niches can be estimated by integrating information on spatial occurrences of the species with relevant raster data layers summarizing aspects of the environment (Araújo and Guisan, 2006). Once developed, niche models can be used to identify suitable areas for populations of the species, effectively creating potential distribution maps (Austin et al., 1990; Peterson, 2003).

We used Maxent (version 3.0, www.cs. princeton.edu/~schapire/maxent) for generating the ENMs in this study. Maxent is a general-purpose, maximum entropy–based, evolutionary computing tool for inferring niche dimensions (Phillips et al., 2004). Maxent is used to estimate the probability distribution for species' occurrences by identifying the distribution of maximum entropy (i.e., a probability distribution closest to uniform), subject to the constraint that the expected value of each environmental variable within the estimated distribution should match its empirical average (Phillips et al., 2006). Maxent builds niche models based on environmental characteristics of presence-only occurrence data and 10,000 randomly chosen background points representing areas of nonoccurrence (pseudoabsence) across the study area (Elith et al., 2006).

Predictions generated for each grid cell are initially raw probabilities that sum to unity and, thus, are low when the extent of analysis is broad. Maxent results are more commonly presented as cumulative values (i.e., each cell receives a value equal to its assigned probability plus the sum of all lower probabilities), wherein a value of 100 indicates highest suitability and values close to zero would be unsuitable (Phillips et al., 2004; Peterson et al., 2007). To avoid overfitting, Maxent employs a smoothing feature called regularization to constrain estimated distributions, such that the average value for a given predictor remains within the empirical error boundaries and close to the empirical average (Phillips et al., 2004; Hernandez et al., 2006). Maxent output is in the form of floating-point ASCII raster grids which are then imported into GIS programs and reclassified into integer grids for analysis.

Identification of key environmental factors

To assess the importance of individual ecologic variables, we used two approaches, based on jackknife analyses, in which we omitted layers systematically to assess their importance in determining model quality. As such, for N layers, we developed N niche models, each omitting one of the N parameters (Peterson and Cohoon, 1999). The first analysis grouped the environmental parameters into 10 sets including land cover, precipitation, productivity (NPP), seasonal NDVI data, soils, temperature, and topography to obtain a broad overview of the importance of general classes of ecologic variables. After initial testing and reduction on groups of variables, a second analysis assessed the importance of individual variables within the remaining groups. We measured Maxent model performance as unregularized test gain (random 50% of occurrences used for testing) and developed analyses for each variable or suite of variables and analyses omitting each variable or suite of variables (Peterson and Cohoon, 1999; Phillips et al., 2006). Variables were ranked in order of significance based on these analyses, and variables appearing important were selected for final model construction. In sum, 19 bioclimatic variables, 12 NDVI variables, five soil and vegetation variables, and five topographic variables were used.

Characterization of distributions and ecologic niches

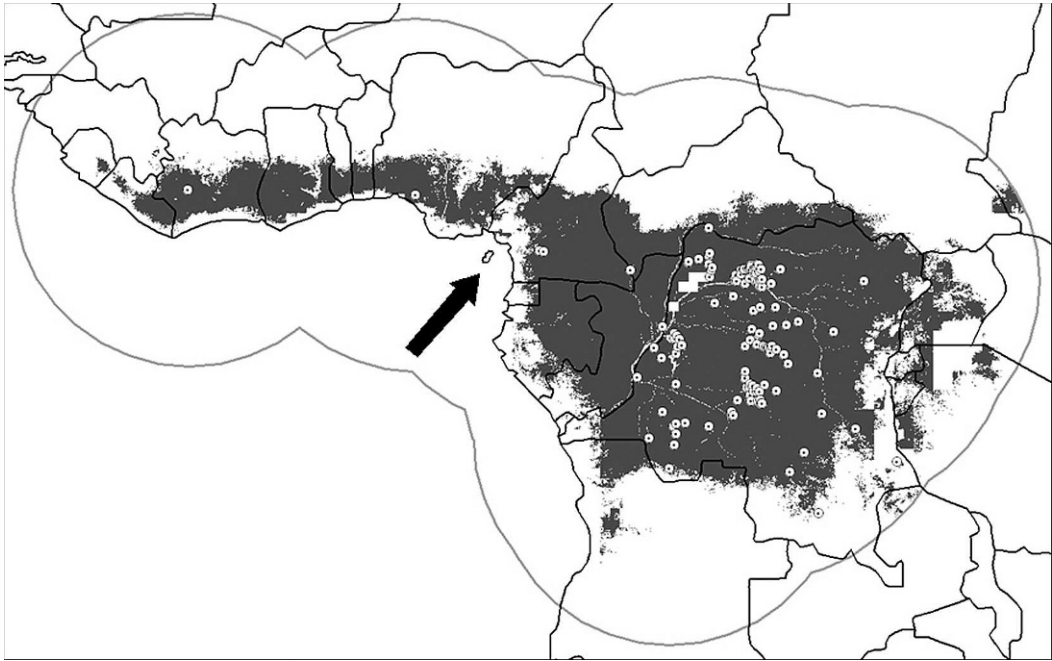Model results were initially compared with the phytogeographic regions proposed for

FIGURE 1. Summary of monkeypox geography showing known occurrence points (dotted circles), predicted potential geographic distribution (gray shading), and the 1,000-km buffer within which analyses were developed (gray line). Arrow indicates a geographic gap in the potential distribution of the disease and, potentially, the division between the two monkeypox virus clades. White areas are identified as unsuitable.

Africa based on biodiversity considerations (Habiyaremye, 1997). To explore these points in greater detail, we developed a Maxent ENM based on all available occurrence data and all environmental dimensions proven informative in the jackknife tests. This model was converted from continuous to binary based on the least training presence threshold approach of Pearson et al. (2007). This model prediction was then combined (Grid Combine option, ArcGIS, version 9.2, ESRI, Redlands, California, USA) with the environmental coverages on which it was based to create a raster GIS coverage with an associated attributes table summarizing the predictions and all combinations of environmental conditions. This table was then exported for visualization as bivariate plots.

To assess the degree to which the Sudan monkeypox cases fit into the environmental profile of the remaining cases, we performed a principal components analysis of the entire suite of raster environmental coverages identified in the jackknifing exercises as having significant explanatory power, retaining the first three components for visualization (analyses conducted in ArcGIS 10). We then plotted occurrences in three dimensions for visual comparison.

RESULTS

The human monkeypox occurrence data set used to develop the ENMs, once refined and reduced appropriately, consisted of 127 localities including two from West Africa and 125 from Central Africa (Fig. 1). The ENMs based on this occurrence information predicted a potential distribution extending across most of the humid tropical evergreen forest areas of Africa. Favorable habitat was identified in 18 African countries (Angola, Benin, Burundi, Cameroon, Central African Republic, Côte d'Ivoire, DRC, Equatorial Guinea, Gabon, Ghana, Liberia, Nigeria, Republic of the Congo, Rwanda, Sierra Leone, Togo, Tanzania, and Uganda). The distribution outlined in this study coincides with the Guineo-Congolese region for all the previous cases and with the Sudano-Zambezian region for the recent case reported in southern Sudan. A geographic break in the potential
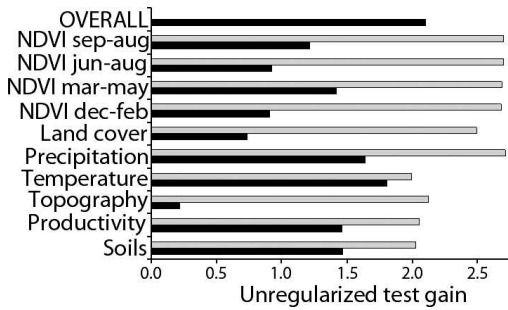
FIGURE 2. Summary of influences of major sets of environmental variables on predictivity (measured by the unregularized test gain) of monkeypox occurrences across Africa based on Maxent models of the monkeypox ecologic niche. Longer bars represent higher predictivity of models built using the indicated variable (black) or all variables except the indicated variable (light gray). NDVI=normalized difference vegetation index; sep=September; aug=August; mar=March; may=May; dec=December; feb=February.
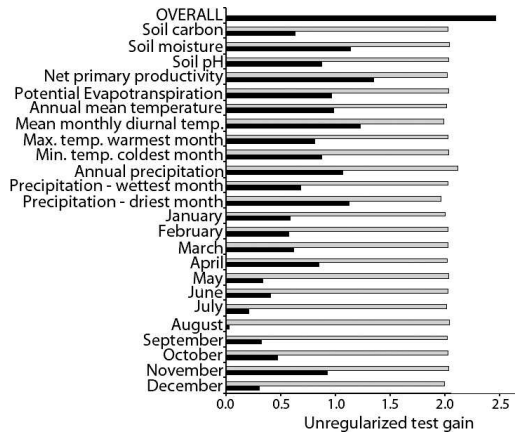

FIGURE 3. Summary of influences of individual environmental variables on predictivity (measured by the unregularized test gain) of monkeypox occurrences across Africa based on Maxent models of the monkeypox ecologic niche. Normalized difference vegetation index variables designated by month. Gray bars=variable excluded; black bar=variable alone; max=maximum; min=minimum.

distribution of the disease was noted between western Cameroon and eastern Nigeria (Fig. 1, arrow).

In the jackknife analyses, temperature variables consistently had the best explanatory power, producing the best predictions when used alone and having the most negative effects when omitted from analysis; precipitation, productivity, and soil information also had some explanatory power (Fig. 2). Land cover, seasonal NDVI, and topographic variables had little explanatory power, and topographic variables as a group had the lowest predictive power when analyzed in isolation.

Removing topographic variables from consideration, we used the second jackknife manipulation to analyze contributions of individual variables to model predictivity (Fig. 3). Monthly NDVI variables had the lowest explanatory ability, whereas a suite of climatic variables (annual precipitation, mean precipitation of the driest month, annual mean temperature, mean monthly diurnal temperature, maximum temperature of the warmest month, minimum temperature of the warmest month), productivity information (April NDVI, NPP, November NDVI, pevap),

and soil characteristics (soil moisture and pH) had better explanatory ability.

Finally, we developed an overall model and derived visualizations of areas and conditions modeled as suitable and unsuitable for monkeypox occurrence. Monkeypox occurrence is focused in areas of low soil pH combined with high soil moisture and concentrates in areas of moderate-to-high annual mean temperatures combined with high precipitation values (Fig. 4). These visualizations of conditions of predicted presence and absence can also be restricted to specific zones to characterize barriers of dispersal potentially limiting a species' distribution in a particular area. For instance, across three transects crossing different portions of the monkeypox range boundary (Fig. 5), the limitation of monkeypox to areas of moderate temperature and high precipitation is consistent whereas distribution relative to November NDVI and soil moisture is variable or inseparable from one transect to the next.

The principal components analyses of environments across the range of monkeypox showed a coherent scatter for all of
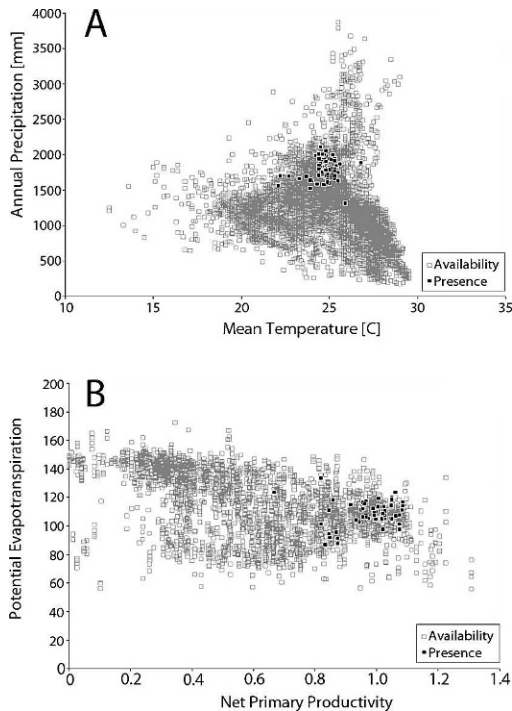
FIGURE 4.   Visualizations of the distribution of monkeypox in pairs of environmental variables: (A) Annual mean temperature versus annual precipitation; and (B) net primary productivity versus potential evapotranspiration. Gray squares represent availability across Africa. Black squares represent areas modeled as appropriate for monkeypox.

the Congo Basin and West African cases (Fig. 6). The Sudan cases fall in very different environments compared to the other known monkeypox cases; they are outliers environmentally and fall well off the main axis of covariation among inhabited environments, such that these cases represent an entirely distinct environmental regime for monkeypox.

DISCUSSION

This study illustrates the utility of a suite of methodologies that, while not new to disease mapping (Peterson, 2006), have not been fully applied to the challenge. In the simplest sense, we have used ENMs to outline a potential distribution for monkeypox occurrence across Africa, which coincides closely with the limits of the

Guineo-Congolese phytogeographic region except for the newly documented occurrence in Sudan, which falls in the Sudano-Zambezian region. However, we have gone beyond the relatively straight-forward task of describing distributions to characterize the relevant dimensions of the ecologic "niche" associated with monkeypox occurrence as well as to hypothesis testing regarding the consistency of certain occurrence sites with the ecologic niche of the bulk of the known sites.

Comparison with previous studies

Our goal was to identify ecologic factors relevant to understanding the geographic distribution of human monkeypox occurrence in Africa using ecologic niche modeling. We were building upon, and revisiting, the results of a previous study via improved occurrence data georeferencing methodologies and via more-detailed exploration of diverse environmental parameters (Levine et al., 2007). The ENMs produced, as in the previous analysis, identified areas of potential monkeypox distribution in Central and West Africa focused in areas consistent with humid lowland tropical forests (Levine et al., 2007).

We identified favorable habitat in 18 African countries. By comparison, the previous study identified suitable habitat in 13 African countries, the most dramatic differences being the inclusion of Angola, Benin, Burundi, Rwanda, and Uganda, and the exclusion of Madagascar and Mozambique, from the newer models. The fact that the models developed in the present study are more realistic is perhaps supported by recent reports of an unknown orthopoxvirus in red colobus monkeys (*Piliocolobus* spp.) that is similar to other known orthopoxviruses in Uganda (Goldberg et al., 2008). A geographic break in the potential distribution of human monkeypox, located along the border of eastern Nigeria and western Cameroon in an area characterized by a chain of mountain ranges and volcanoes known as the Cameroon Range, was noted
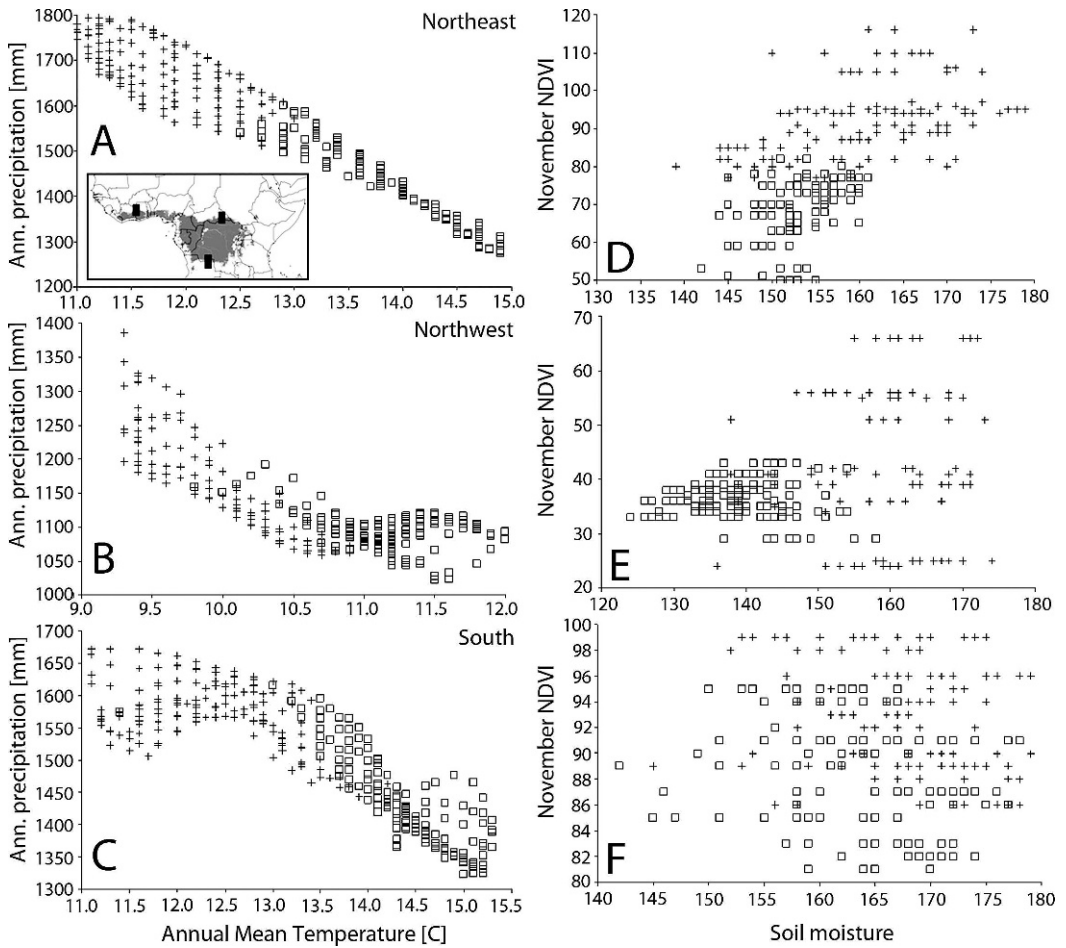
FIGURE 5. Summary of conditions of predicted presence versus absence within three transects crossing different sectors of the monkeypox range boundary (black rectangles in map): Northeast (A and D), Northwest (B and E), and South (C and F). Plus signs indicate presence of suitable conditions for monkeypox transmission and open boxes indicate absence. Predictions appear to be highly and consistently dependent on temperature and precipitation, whereas normalized difference vegetation index (NDVI) and soil moisture do not show consistent relationships in separating areas of presence and absence.

in both studies and may correspond to the distributional gap between the two major monkeypox clades (Chen et al., 2005; Likos et al., 2005).

One reason for the differences between the two studies may be the environmental variables used. Here, we used a more-diverse suite of climatic variables reflecting annual, seasonal, and monthly patterns; this allowed a more refined view of climate dimensions. The WorldClim data set is resolved spatially to 10′ (Hijmans et al., 2005; WorldClim www.worldclim.org), a

ninefold improvement in spatial resolution over the data sets used in the previous study. We also included aspects of land surface reflectance, soil features, and vegetation characteristics, all of which offer additional information by means of summarizing aspects of land cover. Descriptors such as NPP, pevap, soil carbon, pH, and moisture were included in our final models and proved highly informative in model development. Hence, we took advantage of a much richer base of environmental data.
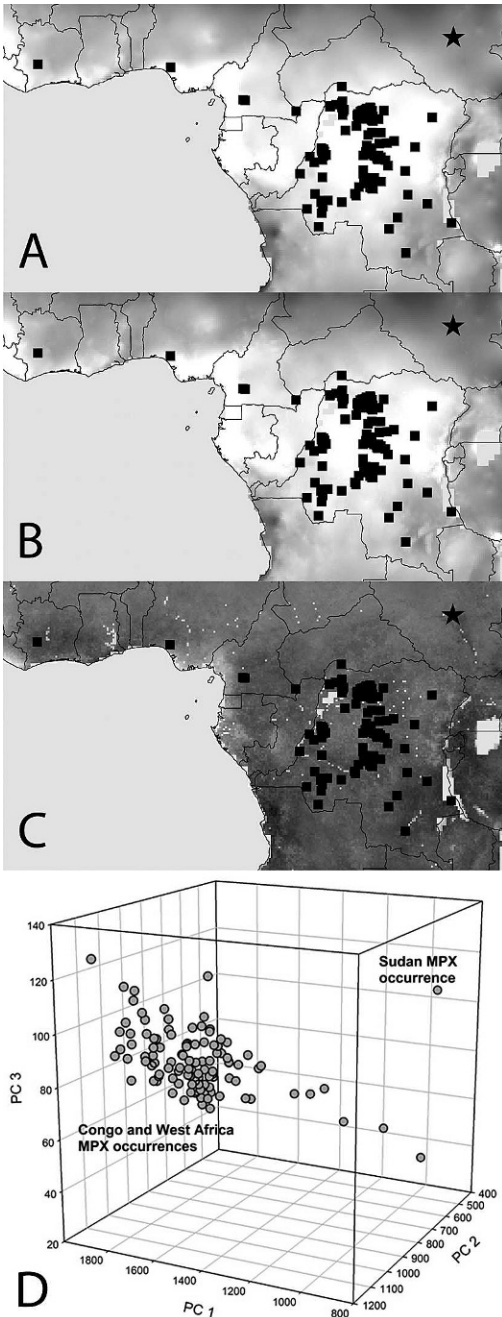
FIGURE 6.   Visualization of environments associated with monkeypox case occurrences with regard to the recently documented Sudan cases (Formenty et al., 2010). Geographic visualization of the first three principal components extracted from the environmental data sets. Higher values in lighter tones (A=PC1, B=PC2, and C=PC3; Sudan occurrence shown as star; other monkeypox occurrences shown as squares). D=three-dimensional scatter plot of the

Our ENMs are based on human case occurrence data collected by the CDC and WHO during 1970–1987. Biases in raw case data are well known and include sampling bias, detection and reporting biases, and other factors that may distort the picture of actual distributions of species with respect to ecologic and environmental factors (Elith et al., 2006). In this respect, the niche modeling step employed in both studies—to some degree—allows a less-biased and more-objective view of the environmental distributions of species. Even given the niche modeling inferences, however, some adjustments must be made to determine which occurrence points are suitable for analysis (Peterson, 2008a, b). Our case occurrence data set consisted of 404 laboratory confirmed cases of human monkeypox in Africa, but only 127 were both unique spatially and sufficiently precise for inclusion in the model. The previous analysis used 156 occurrences but did not filter case occurrences based on spatial precision—as such, occurrences may have been included that referred to broader regions or that were nebulous regarding precise location; this imprecision can produce overly broad estimates of ecologic niches (Levine et al., 2007). The point-radius method we employed considers a "locality" as a geographic point combined with a radius that encompasses any associated uncertainties (Wieczorek et al., 2004). This approach has recently been recommended for broader application to reporting of disease occurrence (Peterson, 2008b).

The previous study concluded that informative model layers included aspect, elevation, flow accumulation, flow direction, land cover, and topographic index (among others), none of which was an important contribution to our models.

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same data, showing that the Sudan occurrence falls into very different environmental conditions than all other known monkeypox occurrences.

Possible explanations for these differences may be associated with data sources or spatial resolution, but are most likely a consequence of the different statistical analyses used in the two studies. Although both studies utilized jackknife approaches, final statistical analyses in the previous study were performed using *t*-tests and the Kappa statistic, both of which are easily confounded by pseudoreplication of points (creating artificially large sample sizes), by prevalence of the phenomenon across the landscape, and by correlations among environmental variables (Fleiss, 1971; Press et al., 1992; Viera and Garrett, 2005).

Another previous study of monkeypox occurrence based on ecologic niche modeling focused on a restricted region of the Congo Basin (Sankuru District; Fuller et al., 2010). Those authors provided an interesting perspective on monkeypox case distributions across a restricted area of the Congo Basin and speculated on virus-host relationships in a preliminary fashion. However, as that study was cast across a local landscape, it is not directly relevant to the broad climatic and coarse-grained environmental picture that we develop in this contribution.

Recent work with monkeypox isolates from Unity State, in what is now South Sudan, indicate that they represent an endemic novel virus nested phylogenetically within the Congo Basin clade (Formenty et al. 2010); their study establishes quantitatively that the Sudan occurrence of monkeypox falls very clearly outside of the environmental range in which all other known monkeypox cases are distributed. Although Formenty et al. (2010) pointed out that possible reservoirs of the virus (e.g., *Cricetomys* spp., *Heliosciurus* spp.) are present in the region, our study shows that the Sudan isolates occur under an entirely distinct environmental regime, indicating the need for a much more detailed understanding of the ecology of the virus in this new region. This result is particularly striking because our occurrence data set included records from across West and Central Africa, thereby covering an impressive diversity of environments in which monkeypox virus has infected humans.

Formenty et al. (2010) discussed a set of explanations for the presence of monkeypox virus in Sudan, most prominently the possibility of endemic Sudan monkeypox versus importation from adjacent sectors of the DRC. The 2005 Sudanese strain is nestled phylogenetically among isolates from the Congo (Formenty et al., 2010). Our results offer a second concrete point—the Sudan occurrences represent a distant outlier from the ecologic circumstances under which all other monkeypox isolates have been found. Hence, our results suggest the possibility of importation (i.e., nonendemicity) of the virus into Sudan; this possibility is facilitated by the occurrence of large-scale human movements during this precise period (Saeed and Badri, 2010). These possibilities can be explored further by means of detailed sampling of potential monkeypox hosts in the Sudan area.

Diseases and niche modeling

Incidences of infectious disease emergence appear to be increasing: from 1940–2004, ~335 newly emerging or re-emerging infectious disease events occurred (Jones et al., 2008). During that period, zoonotic pathogens were responsible for the majority of emerging disease (60.3%), of which most (72%) were caused by pathogens of wildlife origin (Jones et al., 2008). From 1990–2000, the number of emerging disease events caused by wildlife pathogens increased by 52% over previous periods, and incidence of emerging disease caused by vector-borne pathogens also increased by 28.8% (Jones et al., 2008). The resulting scenario is one in which emerging zoonotic diseases will have significant impacts on local and global public health and economies (Jones et al., 2008).

The niche modeling methodologies demonstrated here may be used to summarize spatial and environmental patterns of pathogen transmission and risk, offering

several advantages over commonly used spatial and landscape epidemiology methodologies (Peterson, 2008a). The customary spatial analyses often identify broad trends and, as such, are not fully applicable to characterizing the fine details of pathogen transmission that may be highly dependent on local conditions. Because the spatial resolution of ENMs is limited only by the spatial precision of the occurrence and environmental data, the resulting picture is much more refined (Peterson, 2007). Niche modeling approaches are applicable even when sample sizes are relatively small (Pearson et al., 2007) as demonstrated in analyses of the geography of Marburg virus transmission to humans (Peterson et al., 2006a). Niche models also permit exploration of the potential geography and ecology of pathogen transmission across novel landscapes (Peterson, 2003).

Several issues must be addressed before ecologic niche modeling methods can be applied fully to emerging disease and pathogen transmission systems. As exemplified in the present analysis, identification and selection of key environmental datasets is particularly significant in building maximally accurate models; for example, climate data may provide longer temporal applicability but remotely sensed data provide a finer spatial resolution view of ecologic landscapes (Peterson et al., 2006b). Analyzing these two data resources in tandem, as we have done, may offer advantages regarding identification of key environmental factors that could provide important insights into the transmission biology of diseases (Press et al., 1992).

The two-level jackknife analysis used in this paper offers a means of identifying the environmental variables most informative for model development. Variables were first evaluated in suites to understand the significance of general classes of variables (Fig. 2). The most significant suites included temperature and precipitation and aspects of soils and surface reflectance. Individual variables were then assessed:

the most informative climate variables we identified included annual precipitation, annual mean temperature, maximum temperature of the warmest month, mean monthly diurnal temperature, minimum temperature of the coldest month, and precipitation of the driest month (Fig. 3). Significant individual, nonclimatic variables included April NDVI and NPP, November NDVI, pevap, soil moisture, and soil pH. Hence, our exploratory approach to environmental variable selection identified diverse informative variables but still allowed a reduction of the dimensionality important to avoid overfitting (Sweeney et al., 2006).

Inspecting the NDVI variables through the year (Fig. 3) suggests possible seasonal trends. The importance of NDVI is minimal in August, increases rapidly through November, remains high through April (note that November and April were the most informative months from among the year-round NDVI data layers), and then declines. The cause of this trend is unclear, given that little is known of the natural history of monkeypox; however, the pattern is clear: Surface reflectance in the Austral summer months offers the best discrimination of suitable versus unsuitable sites. Further field studies of monkeypox may help to illuminate this association.

Our purpose was to build upon and improve insights from a previous ecologic niche modeling analysis of the potential distribution of monkeypox in Africa. Our results emphasize the importance of selecting the most appropriate and informative environmental data for ecologic niche modeling. Models based on simple environmental data sets may be overly general and lacking detail, owing to the broad interpolation and smoothing inherent in the process of generating the climate coverages (Nakazawa et al., 2007). Refinements such as filtering occurrence localities based on spatial precision can avoid imprecision resulting from an uncertain geolocation (Wieczorek et al., 2004; Peterson, 2008b). As ecologic niche modeling continues to

evolve as a tool in spatial epidemiology and public health, focused studies evaluating these points may prove useful.

ACKNOWLEDGMENTS

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