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# GEOGRAPHIC POTENTIAL FOR OUTBREAKS OF MARBURG HEMORRHAGIC FEVER

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*Abstract.* Marburg virus represents one of the least well-known of the hemorrhagic fever-causing viruses worldwide; in particular, its geographic potential in Africa remains quite mysterious. Ecologic niche modeling was used to explore the geographic and ecologic potential of Marburg virus in Africa. Model results permitted a reinterpretation of the geographic point of infection in the initiation of the 1975 cases in Zimbabwe, and also anticipated the potential for cases in Angola, where a large outbreak recently (2004–2005) occurred. The geographic potential for additional outbreaks is outlined, including in several countries in which the virus is not known. Overall, results demonstrate that ecologic niche modeling can be a powerful tool in understanding geographic distributions of species and other biologic phenomena such as zoonotic disease transmission from natural reservoir populations.

## INTRODUCTION

Marburg virus and the Ebola viruses (family *Filoviridae,* genera *Marburgvirus* and *Ebolavirus*) have presented a series of enigmas for biologists and public health workers: complete unknowns regarding these viruses include the identity of their natural reservoir host species and the mode of transmission from the reservoir to humans or other primates.[1,2] Even the geographic distributions of filoviruses have presented challenges, with mysteries including the geographic origin of Ebola Reston virus.[3]

The known geographic distribution of outbreaks of Ebola virus–caused hemorrhagic fever in recent years has appeared to be more consistent geographically and ecologically than that of outbreaks caused by Marburg virus. Ebola viruses (Ebola Ivory Coast, Ebola Zaire, and Ebola Sudan viruses) are known principally from evergreen tropical forest regions in central Africa, and have shown few unexpected occurrences in terms of geography and ecology.[4–7] Conversely, Marburg virus has appeared only a few times, including outbreaks in regions that would appear more diverse ecologically.[8] One important commonality among known Marburg virus outbreaks is that at least three have involved caves or mines in the infection of the apparent index case.[1,2,9–13]

Few efforts have been made to map these outbreak occurrences and understand the ecologic regimen under which they occur.[6,14] The only existing spatially explicit study[6] presented maps of potential distribution of Marburg virus based on ecologic niche models derived from the four localities available at the time. The recent (ongoing) Marburg hemorrhagic fever outbreak in Angola fell within the extreme western areas predicted by our 2004 models, confirming a geographically disparate hypothesis. Since that study, however, the predictive modeling approaches have improved considerably,[15] which led us to revisit the 2004 predictions.

Hence, this contribution uses new advances in ecologic niche modeling (ENM) tools and new geographic information to improve the geographic and ecologic understanding of Marburg virus distribution. Given the uncertain geographic localization of the 1975 Marburg virus infections in Zimbabwe, we first reassess ideas as to its geographic provenance based on the three better-known outbreaks. We then continue to examine the present Angola outbreak with respect to the known ecology of Marburg virus, and conclude by presenting a state-of-knowledge prediction of the potential geographic range of this virus.

## METHODS

Ecologic niche modeling has been subjected to numerous applications and tests based on diverse analytical approaches.[16–21] The particular approach to modeling species' ecologic niches and predicting geographic distributions used herein (summarized below) is described in detail elsewhere.[22–25] Previous tests of the predictive power of this technique for diverse phenomena in various regions have been published.[25–35] The modifications described below make the approach more robust to uncertainties in spatial localization in occurrence points by incorporating uncertainty directly in the modeling process.

Distributional data for known Marburg virus hemorrhagic fever outbreaks were drawn in large part from our previous compilation.[6] However, given variation in levels of confidence regarding localization of the infection of the index case, we replaced the point-based representation in the previous study with polygons that summarize the degree of certainty with which each locality is known (Figure 1). The origin of the 1998 outbreak at Durba in the Democratic Republic of the Congo (DRC) is considered to be localized with considerable precision, and thus was represented as a circle of 5-km radius centered on Durba,[9] as was the 1987 outbreak in Kenya (5-km radius circle centered on Mount Elgon, Kenya).[13] However, the 1980 Kenya outbreak is less clear because the index case patient could have been infected at Nzoia, at Mount Elgon, or at points in between.[1] Thus, we represented that outbreak as a 25-km buffer around those two localities. Since the 1975 Zimbabwe cases involved considerable uncertainty, we initially represented the geographic origins of these cases as a 25-km buffer around the convex polygon enclosing all of the Zimbabwe points on the travelers' itinerary, which covered much of the country. Finally, the origin of the 2005 Angolan outbreak remains nebulous, and may remain so (Montgomery JM, unpublished data). Thus, we generated a polygon match-

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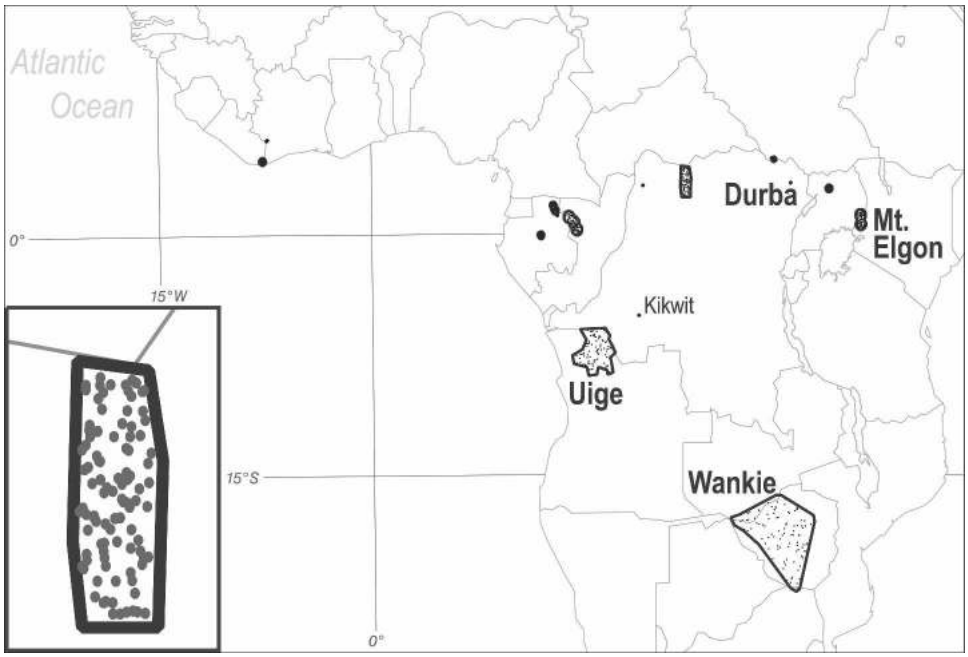


FIGURE 1. Polygons representing each of the known Marburg and Ebola hemorrhagic fever outbreak sites (Marburg virus outbreak sites labeled, plus the Kikwit Ebola Zaire site, as mentioned in the text), as outlined by Peterson and others.[6] The **inset** shows an example of random points used to represent a particular outbreak polygon.

ing the geographic limits of Uige Province, Angola. Although the exact dimensions of our polygons may be arbitrary, we believe that the relative ordering of degree of certainty is reasonable, and that it likely reflects the varying degrees of precision with which different outbreaks are localized. To incorporate the uncertainty of localization of these outbreaks in our models, we generated 100 random points within each polygon; these points were then used to represent each outbreak in our models.

Environmental data layers that were used to define the dimensions of modeled ecologic niches for Marburg virus included 23 electronic maps summarizing aspects of topography (elevation, slope, aspect, compound topographic index, from the United States Geological Survey's Hydro-1K data set;* 0.01° resolution), and aspects of climate including 19 fine-scale (0.01° resolution) bioclimatic variables developed as part of the WorldClim data set:† annual mean temperature, mean diurnal temperature range, isothermality, temperature seasonality, maximum temperature of warmest month, minimum temperature of coldest month, temperature annual range, mean temperature of wettest quarter, mean temperature of driest quarter, mean temperature of warmest quarter, mean temperature of coldest quarter, annual precipitation, precipitation of wettest month, precipitation of driest month, precipitation seasonality, precipitation of wettest quarter, precipitation of driest quarter, precipitation of warmest quarter, and precipitation of coldest quarter. All analyses were carried out using all variables at the native spatial resolution of 0.01°, or approximately 1 × 1 km, pixels.

The ecologic niche of a species can be defined as the conjunction of ecologic conditions within which it is able to maintain populations without immigration.[36,37] Several approaches have been used to approximate species' ecologic niches;[38–43] of these, one that has seen considerable testing is the genetic algorithm for rule-set prediction (GARP), which includes several inferential approaches in an iterative, evolutionary-computing environment.[23] All modeling in this study was carried out on a desktop implementation of GARP now available publicly for download.‡

In GARP, available occurrence points are divided evenly into training data sets (for rule generation) and intrinsic test data sets (for model refinement). GARP is designed to work based on presence-only data; absence information is included in the modeling via sampling of pseudoabsence points from the set of points at which the species has not been detected. GARP works in an iterative process of rule selection, evaluation, testing, and incorporation or rejection: first, a method is chosen from a set of possibilities (e.g., logistic regression, bioclimatic rules), and then is applied to the training data and a rule developed; rules may evolve by a number of means (e.g., truncation, point changes, crossing-over among rules) to maximize predictivity. Predictive accuracy (for intrinsic use in model refinement) is then evaluated based on 1,250 points resampled from the intrinsic test data and 1,250 points sampled randomly from the study region as a whole. The change in predictive accuracy from one iteration to the next is used to evaluate whether a particular rule should be incorporated into the model, and the algorithm runs either 1,000 iterations or until convergence.

Given varying levels of uncertainty in localization of the Marburg virus introduction sites (described above), we used a new approach in ENM. Within each of the polygons described above for each outbreak site, we produced 100 ran-

* http://edcdaac.usgs.gov/gtopo30/hydro/
† http://biogeo.berkley.edu/worldclim/worldclim.htm
‡ http://www.lifemapper.org/desktopgarp/

dom points. These random points were then organized into 100 occurrence data sets, each having a single representative point for each outbreak known. In this way, outbreaks for which localization is precise will have representative points that consistently fall in a very small area, whereas outbreaks for which localization is not precise will have much more variable representation, with points falling over a broader area. This approach allows a picture of the robustness of ENMs to site precision, and represents a considerable improvement over the methods used in our previous study of filoviruses.[6]

To permit visualization of patterns of Marburg virus ecologic niche variation, we combined the input environmental grids with the final Marburg virus ENM to create a new grid that has a distinct value for each unique combination of environments. We exported the attributes table associated with this grid in ASCII format. To make visualization more feasible, we reduced data density by selecting a random 10% of the table for further use; this reduced table was used for development of scatterplots for visualization.

Normally in ENM, independent test data are set aside to provide a validation of model predictions. In this application, however, so few localities were available for Marburg virus hemorrhagic fever outbreaks that we forewent this step. Because no statistical tests were possible due to small sample sizes, we validated models based on coincidence of predictions with new observations (e.g., the 2005 Angola outbreak). As such, we used the three known northern Marburg virus disease outbreaks (northern outbreaks), all reasonably well documented as to place of origin, to build models and identify suitable areas across Africa. Based on this first analysis, we reinterpreted the most likely geographic origin of the 1975 Zimbabwe cases, and explored implications for the 2005 Angola outbreak. Finally, we explored the implications of all five introductions into human populations and their ecologic characteristics for a best guess as to the potential distribution of Marburg virus across Africa. Throughout this report, we strive to avoid overinterpretation of data and results, and rather attempt to present our interpretation of what information is available.

## RESULTS

The size of the polygons representing each of the known Marburg hemorrhagic fever outbreaks (Figure 1) reflects the state of knowledge of each of the outbreaks: the initiation points for the 1980, 1987, and 1998 (northern) outbreaks (Kenya and DRC) are all known relatively precisely, whereas the origin of the two southern events (1975 in Zimbabwe and 2005 in Angola) are much less precisely known.

Our results coincided closely with Marburg potential distribution maps that we published previously,[6] which were based on analyses of points, and did not consider uncertainty in localization, as in the present analyses. Although spatial autocorrelations in environmental datasets mean that differences between the two analyses should not be great, the prediction of only part of Zimbabwe by these models is quite interesting. In general, the uncertainty-based predictions presented herein depict a somewhat more continuous potential distribution for Marburg virus in east Africa, particularly in Ethiopia and across Angola, Zambia, Zimbabwe, and Mozambique (note that the successful prediction of the potential for the 2004–2005 Marburg Virus outbreak in Angola does not depend on the uncertainty manipulation). Our original predictions published before the outbreak anticipated the potential for such an outbreak.[6] Although general patterns did not differ markedly, the potential distributional areas identified herein are suggestive of a broader distributional area than had previously been appreciated for Marburg virus. A

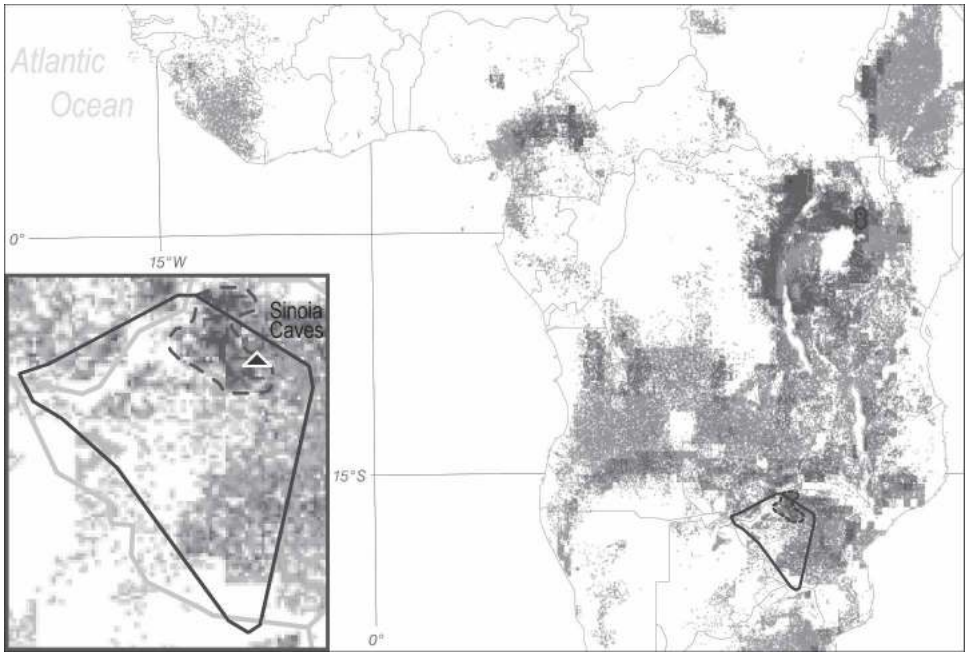


FIGURE 2. Ecologic niche modeling results based on the three northern Marburg hemorrhagic fever outbreaks projected across Africa (darker shading indicates greater model agreement in predicting presence). The **inset** shows Zimbabwe predictions in relation to the original polygon for this outbreak.

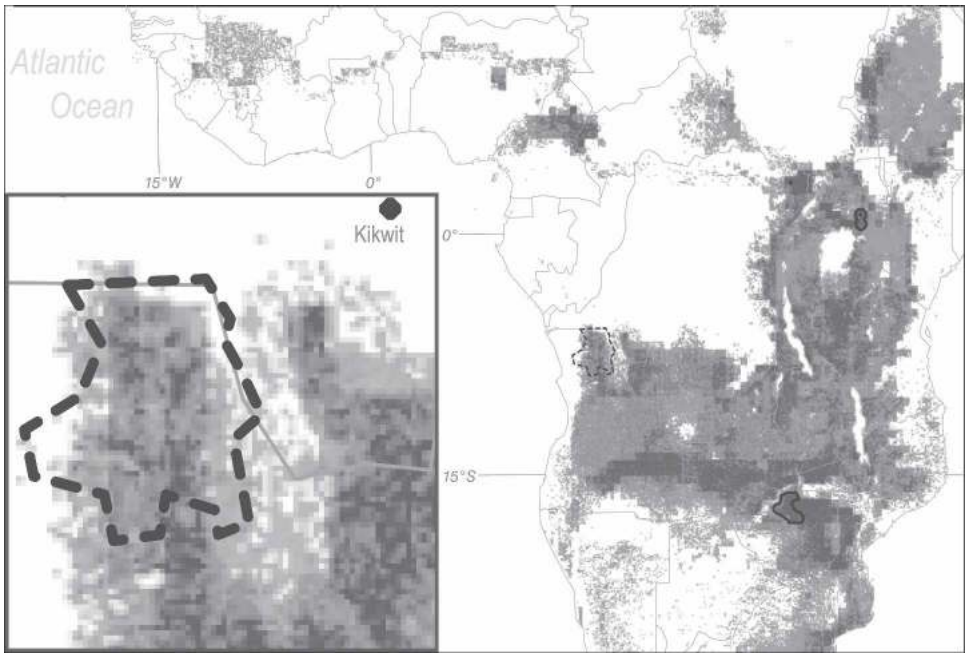


FIGURE 3. Ecologic niche modeling results based on the three northern Marburg hemorrhagic fever outbreaks and the revised knowledge of the Zimbabwe cases (darker shading indicates greater model agreement in predicting presence). The **inset** shows Angola predictions in relation to Uige Province.

first corroboration of the models' predictive power is their inclusion of Lake Kyoga, Uganda, which apparently was the source of the monkeys that started the original Marburg Virus outbreak in 1967.

**1975 Zimbabwe cases.** Our first analysis was based on the three northern outbreaks and attempted to shed light on the nebulous 1975 Zimbabwe event. In spite of the massive north-south environmental gradient that is manifested between Kenya/DRC and Zimbabwe, the ENM based on the three northern outbreaks identified areas of similar environments in Zimbabwe. Curiously, however, the areas identified were focused in northeastern Zimbabwe, and not in northwestern Zimbabwe where case investigation efforts were focused[8] (Figure 2).

With the kind assistance of J. L. Conrad, who led the original investigations of the 1975 outbreak, we traced the tour

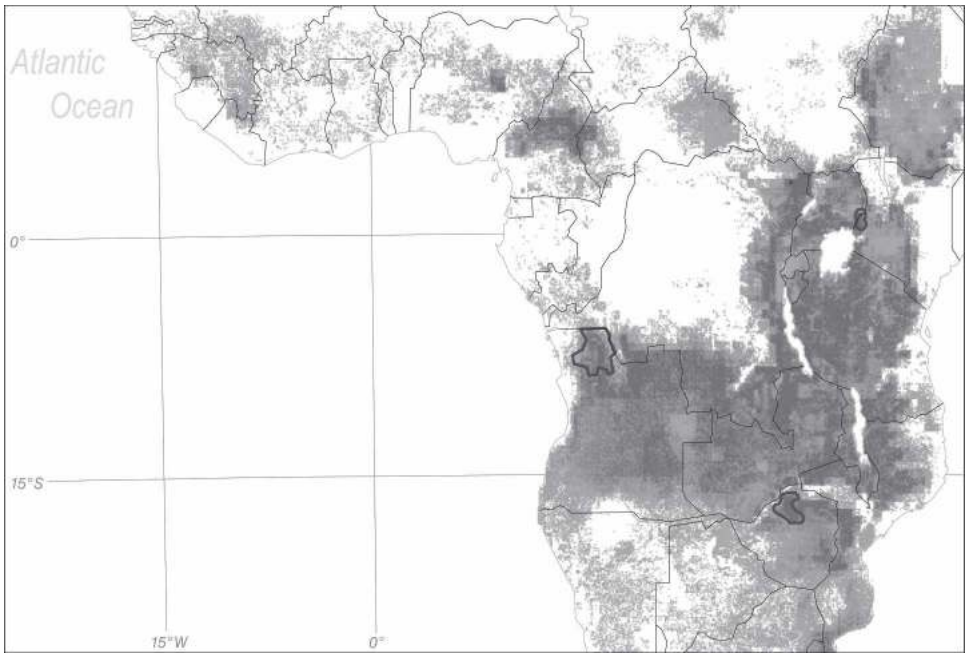


FIGURE 4. Ecologic niche modeling results based on all known African Marburg hemorrhagic fever outbreaks (darker shading indicates greater model agreement in predicting presence).

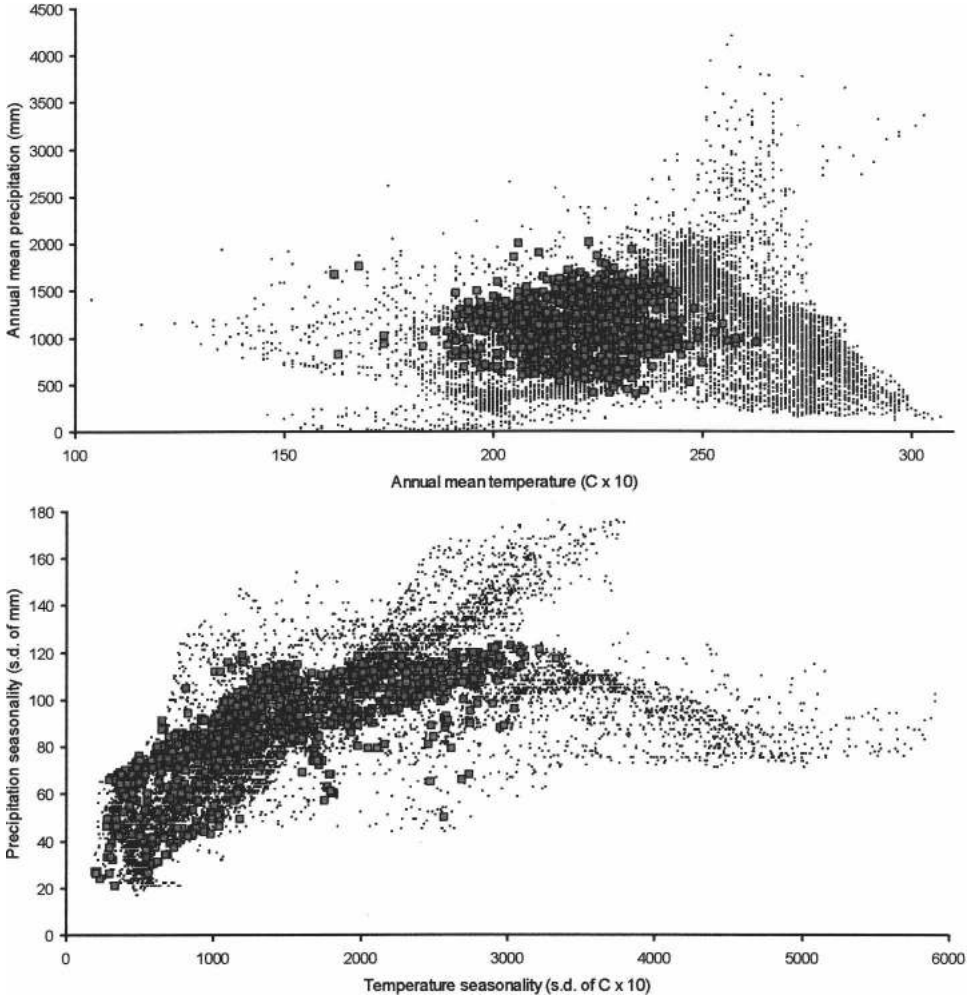


FIGURE 5. Exploratory analysis of modeled distribution of Marburg hemorrhagic fever outbreaks (map pixels falling into the modeled distributional area shown as squares) with respect to cross-Africa availability of combinations of (**top**) annual means of temperature and precipitation and (**bottom**) seasonality of temperature and precipitation (shown as black points). S.d. = standard deviation.

around Zimbabwe of the young man who became the index case patient. The Wankie roadside site that became the focus of the case investigation was not predicted as suitable by any of the best subsets models in this analysis, suggesting either that it was not the infection site, or that it would represent an extreme not otherwise appreciated in the Marburg hemorrhagic fever occurrence data set. The victim's route indeed did pass through the areas of northeastern Zimbabwe that were identified by our ENM. Most interesting is that our re-review of his itinerary showed that he visited a cave complex in that region known as Sinoia Caves (see map in Conrad and others[8]), which would fit with the known profile of the three northern outbreaks. Given that the index case patient was in Wankie on February 6, 1975 and at Sinoia Caves on February 3–4, 1975, the incubation period for virus exposure at the caves makes an almost perfect interval of 8–9 days before onset of symptoms on February 12, 1975.[8] As such, based on the ENM predictions and on the observation of a cave connection, we provisionally identify a region of northeastern Zimbabwe (Figure 2) as the likely source of the infection that gave rise to the 1975 Zimbabwe cases.

**2005 Angola outbreak.** Using the refined information regarding the 1975 Zimbabwe outbreak, we produced a second generation of ENMs for Marburg hemorrhagic fever outbreak distributions. This ENM indicated potential Marburg virus distributional areas in a crescent extending from Ethiopia south through much of east Africa, and then west to Angola (Figure 3), including Uige Province in which the 2004–2005 outbreak began. It is noteworthy that this general prediction (an area of predicted presence in northern Angola coinciding with Uige Province) was also present in our original analyses,[6] as well as in all analyses developed in this study, whether the revised or original Zimbabwe locality was used.

Uige Province is 500 km from Kikwit, DRC, where the 1995 outbreak of hemorrhagic fever caused by Ebola Zaire virus occurred,[44] whereas it is approximately 1,800 km from the nearest known Marburg hemorrhagic fever outbreak site. Nonetheless, it fits the ecologic profile of Marburg virus (Figure 3), and not that of Ebola Zaire virus.[6] This unexpected confirmation of a somewhat counterintuitive prediction of our previous ENMs[6] suggests that the models likely hold useful information regarding the geographic potential of Marburg hemorrhagic fever across Africa.

**Marburg virus geographic potential.** Under the assumption that the ENM predictions can inform regarding the geographic potential of Marburg hemorrhagic fever, we devel-

oped a final ENM based on all five available known occurrences (Figure 4). This model shows a broad potential distribution across the arid woodlands regions of Africa. In addition to countries known to harbor Marburg virus (Angola, DRC, Kenya, Zimbabwe, and likely Uganda), these models also identified Burundi, Ethiopia, Malawi, Mozambique, Rwanda, Tanzania, and Zambia as having regions of potential occurrence of the virus. Northern Cameroon holds a small area that is broadly disjunct from known distributional areas, but matches the ecologic profile of Marburg virus. We suspect that Marburg virus may actually have a broad distribution across eastern and southern Africa, and may present public health risks across a much larger area than was appreciated in the past. Note, however, that seroprevalence studies do not necessarily support this prediction, pointing to an issue for future research.[10,11]

Visualization and exploratory analyses of modeled Marburg virus distribution with respect to climatic parameters showed several interesting features (Figure 5). For example, whereas Marburg is modeled as distributed throughout precipitation regimens in Africa (except the very wettest regions), it is limited to areas of relatively low annual mean temperatures. Similarly, with respect to seasonal variation, Marburg virus is modeled as occurring in areas of low-to-moderate seasonal variation of temperature and precipitation, but not in regions of high intra-annual variation in either dimension.

## DISCUSSION

Ecologic niche modeling has great promise in interpolating into unknown or unsampled areas of species' geographic distributions.[45–47] However, its use should be cautious because it is a new tool and has only seen limited application to questions regarding disease transmission.

Of particular concern in the present study is the small sample size of localities involved. Previous sensitivity analyses have indicated that the GARP approach is relatively robust to small sample sizes.[26,27] Uncertainty regarding exact origins of outbreaks, as well as the possibility of movement of infections in primates before detection of the initial case,[8] may work to cloud the picture and reduce effective sample sizes yet further. Nonetheless, if a species has a complex ecologic niche that includes diverse environments, the sample sizes involved in the present study (3–5 sites) may prove insufficient. The usual effect of such problems, however, would be underestimation of the species' ecologic potential, suggesting that the predictions outlined herein are likely to be meaningful.

The method explored herein of using random points within polygons representing precision of localization of outbreak sites appears to be an excellent tool for dealing with such situations of variable uncertainty regarding occurrences. The method produces what is in essence a spatial bootstrap that weights occurrences known precisely more heavily than occurrences that are not known with such precision. Although the essence of the predictions did not change dramatically from our previous single-point-based predictions, our random-point approach indeed permitted the identification of subsets of Zimbabwe as particularly likely for Marburg virus occurrence. This modification to the ENM approach will offer greater robustness and reduced vulnerability to assumptions of precise localization in future applications.

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