INTRODUCTION

Plague is a highly virulent, flea-borne bacterial zoonosis caused by *Yersinia pestis*. These gram-negative bacteria are primarily maintained by rodent hosts and their flea vectors. Humans are at greatest risk of exposure to plague bacteria during epizootic periods, when susceptible hosts die in large numbers and their infected fleas are forced to seek incidental hosts, including humans. If not treated promptly with appropriate antibiotics, plague can be fatal. In the last few decades, the majority of human plague cases have been reported from eastern and southern Africa and Madagascar. In fact, greater than 95% of reported cases have been from countries in sub-Saharan Africa since 2000. The West Nile Region remains the primary epidemiologic focus for plague in Uganda and is the area of interest for this study.

In an attempt to develop tools that may aid in targeting limited plague prevention and control resources, statistical models have been developed for this region to identify areas of elevated risk. These models indicated that plague case occurrence was more likely above 1,300 m than below, and was positively associated with indices of wetness and bare soil during the dry season. The predictive variables were presumed to be associated with growth of annual agricultural crops. This assertion was supported by an observational survey study that identified growth of annual crops, such as corn, as environmental risk factors associated with areas classified as posing elevated plague risk. Together, these findings are consistent with the trophic cascade hypothesis that is predominant in the plague literature in which rainfall results in primary vegetative production that provides food and harborage for rodents, which translates to increases in the rodent populations. The increased moisture associated with rainfall also supports survival and reproduction of fleas. The combined escalation in rodent and flea abundances is believed to enhance the likelihood of plague epizootics. Although climatic variables such as temperature and rainfall are known to influence the spatial and temporal distribution of plague epizootics in many parts of the world, reliable rainfall and temperature data were lacking from this region. Thus, previous risk models were based primarily on landscape variables, such as elevation, remotely sensed correlates of vegetation, and satellite-derived snapshots of surface temperature and wetness.

Employing a 10-year meteorological dataset that was recently developed for the plague-endemic West Nile region (Monaghan et al., unpublished), we sought to identify climatic variables predictive of the spatial distribution of human plague cases. Identifying additional variables that define the geographic distribution of *Y. pestis* in this region advances our knowledge of the conditions required to maintain enzootic cycles and may ultimately be used to target limited surveillance, prevention, and control resources to areas most at risk or to predict future disease trends.

MATERIALS AND METHODS

Description of the study area. The study was conducted in the plague-endemic West Nile region, located in northwestern Uganda. This area, which focuses primarily on Okoro and Vurra counties, was described previously. However, since those studies were published, district boundaries have been redrawn, placing Okoro County in Zombo District, rather than Nebbi District; Vurra County remains within Arua District (Figure 1). The districts are roughly bisected by the Rift Valley escarpment, which results in a sudden increase in elevation moving from east to west. Low rainfall and sandy soils are typical east of the escarpment in the lower elevations, whereas fertile soil, lush vegetation, and higher elevation characterize the western portion. The majority of human plague cases are reported from the western portions of these districts, located above 1,300 m. The bimodal rainfall pattern in this region is characterized by a short, less predictable rainy season (March–May).
and a long, more predictable rainy season (late August–November). The average total annual rainfall in the West Nile region ranges from 500 mm along the lower elevation eastern boundary formed by the Albert Nile River, to 2,000 mm along the higher elevation western border with the Democratic Republic of Congo (Monaghan et al., unpublished).

Description of cases and controls. In this region of Uganda, plague is characterized clinically by sudden onset of fever, chills, malaise, headache, or prostration accompanied by either painful regional lymphadenopathy, or cough with hemotysis. To confirm *Y. pestis* infection in suspect cases, primary samples (i.e., bubo aspirates, sputum, and blood samples) were cultured for *Y. pestis* and isolates were confirmed using bacteriophage-lysis, and paired acute and convalescent sera were tested for anti-*Y. pestis*-F1 antibody titers during the 2008–2009 plague seasons, which spanned approximately from August through March. Only laboratory-confirmed cases were included in this study. Human subject involvement was reviewed and approved by Centers for Disease Control and Prevention Institutional Review Board (protocol nos. 4696 and 5301), the Uganda Virus Research Institute Scientific Ethics Committee (GC/127/08/12/22), and the Uganda National Council for Science and Technology (HS 488).

Selection and mapping of case and control locations was described previously. Briefly, the location of each case residence was recorded using a handheld global positioning system (GPS) receiver (Magellan Explorist 500; MiTAC Digital Corp., Santa Clara, CA; or Garmin GPSMap 60CSx; Garmin, Olathe, KS). Control locations were selected to maximize the likelihood they had a low probability of plague occurrence, but had similar access to health care compared with cases. To identify prospective control locations, we visited each of the seven health clinics from which our case group was derived. During these visits, clinic log books were reviewed and we extracted the names of the first villages to appear before or after the confirmed plague cases that did not report clinically diagnosed plague from 1999 to 2008. These villages served as candidate villages for inclusion in our study as controls.
For each case and control village, the perimeter was mapped using a handheld GPS device. To obtain estimates of village size and population density, human-constructed physical structures, typically round or square hut structures with thatch roofing, were digitized for each village based on QuickBird (February 16–24, 2008) or World View (2002–2009) orthorectified imagery. Control villages were selected to be similar in size and in the density of physical structures compared with case villages.11 Within control villages, a single digitized hut was randomly selected using Hawth’s Analysis Tool (version 3.27); two controls were selected for each case. A total of 36 case and 72 control points were used in our model development.

**Landscape variables.** Landscape variables that were significant in previous studies (Eisen and others11 and Winters and others12) were considered in this analysis. These previously described variables include: 1,300 m elevation cutoff, brightness, wetness, greenness, and Landsat 7 Enhanced Thematic Mapper Plus (ETM+) band 3 and band 6. A raster layer was created defining the area as above or below 1,300 m from a 90-meter digital elevation model (Shuttle Radar Topography Mission Elevation Data Set, 2008).12 Landsat ETM+ images were captured January 1, 2007 (Row/Path: 58/172) and January 10, 2007 (Row/Path 58/173) during clear atmospheric conditions and acquired through a cooperative agreement with the National Geospatial Intelligence Agency. Brightness, wetness, and greenness variables were derived from these Landsat bands using ENVI 4.5.12 All layers were projected to universal transverse Mercator (UTM) zone 36N WGS 1984.

**Climatic variables.** Because of the paucity of observational meteorological data, a climate dataset was simulated in collaboration with the National Center for Atmospheric Research, by employing the Advanced Research Weather Research and Forecasting Model (WRF) (A. Monaghan et al., unpublished). The WRF is a fully compressible conservative form nonhydrostatic atmospheric model suitable for both research and weather prediction applications, which has demonstrated ability for resolving small-scale phenomena and clouds.35 To realistically simulate the two-way land surface interactions with the atmosphere (an important consideration in the tropics) WRF was coupled to the Noah Land Surface Model (Noah LSM).36 The Noah LSM provides WRF with fluxes of energy and water from the land surface, while also maintaining stores of water and energy in four soil layers to a depth of 2 m.

The WRF simulations were constrained by a variety of observationally based datasets. The initial and boundary conditions for WRF were provided by the National Centers for Environmental Prediction-Department of Energy-Atmospheric Model Intercomparison Project Reanalysis II (NCEP-DOE-II).37 The NCEP-DOE-II was chosen because of the veracity of the results it produced in the tropics for a recent downscaling experiment.38,39 A four-domain nested WRF configuration was used for downscaling NCEP-DOE-II, with 56-, 18-, 6-, and 2-km spatial resolution domains. All four domains had 35 vertical levels spanning 0–20 km above the surface, with seven levels in the lowest 1,000 m. Daily-updated 0.25° sea surface temperatures for the oceans were specified with version 2 of the National Oceanic and Atmospheric Administration’s Optimum Interpolation (OI) sea surface temperature dataset.40 To improve rainfall simulations, inland lake surface temperatures were updated monthly with 0.05° monthly mean skin temperature data (product MOD11C3) derived from the Moderate Resolution Imaging Spectroradiometer (MODIS) instrument flown aboard the National Aeronautics and Space Administration (NASA) Terra satellite.41 Three-hourly skin temperature, soil temperature, and soil moisture fields from the 0.025° Global Land Data Assimilation System (GLDAS)42 were used to initialize the land surface and subsurface states for the Noah LSM in WRF at the beginning of each month-long simulation.

The final production simulations were performed for month-long intervals; i.e., 120 1-year simulations were performed for 1999–2008, each beginning on the last day of the previous month to allow 24 hours for spin-up of the modeled fields. The 24-hour spin-up period was subsequently thrown out. Because of computational resource constraints, we performed 1 year of simulations with all four domains turned on (year 2006); the additional 9 years of simulations were performed with only the outer two domains (56 and 18 km) turned on, and the comparatively expensive inner domains (6 and 2 km) turned off. A statistical technique known as bias correction spatial downaggregation (BCSD)43 was then used to downscale the 18-km output—monthly mean temperature (°C), maximum temperature (°C), minimum temperature (°C), relative humidity (%), specific humidity (g kg⁻¹), and total rainfall (mm)—to 2-km spatial resolution for the 9-year period in which the inner domains were turned off, by calibrating the 18-km output with the 2-km output for the overlap year of 2006. The plague model results described in this work use the climate fields from this 2-km WRF domain, which is centered over the West Nile region of Uganda.

The WRF climate fields were averaged over a 10-year period (1999–2008) for each month of the year. Note that relative humidity is defined as the percent of moisture in the air with respect to saturation—a temperature dependent variable—whereas specific humidity is an absolute measure of the amount of moisture in the air, and thus is independent of temperature. The climatic variables were projected to UTM zone 36N WGS 1984 to be consistent with other data. The model showed that the WRF-simulated climate fields compare robustly with satellite-based and in situ observations of rainfall, temperature, and humidity. For example, the WRF-simulated fields reproduce the spatial and seasonal variability of rainfall, an especially important consideration for this study.

**Model development.** Climatic and landscape variable values were extracted for each case and control point within ArcGIS version 9.3 (ESRI, Redlands, CA). To reduce the number of climate variables included in our final model, we assigned each of the monthly variables to the following “climate categories”: temperature (average, minimum, and maximum), relative humidity, specific humidity, and rainfall. For each of the four climate categories, we constructed a forward stepwise logistic regression model of the probability of case occurrence; the top five most significant variables for each climate category were retained for screening in the full model. This reduced the number of climate variables from 72 to the 20 most significant. Specific humidity variables were dropped from the model screening process because the low variation in values across case and control locations was considered too low to be biologically meaningful. Candidate models predicting case or control status were constructed by including each of the remaining three climate categories (with five monthly values
each) and the six landscape variables described previously as predictors within a forward stepwise logistic regression. Again, only variables with $P$ values $< 0.25$ were entered into the model and variables that were strongly correlated with each other were not included in the same model (Spearman correlation coefficient; $r \leq 0.85$). Whole model tests were used to assess statistical significance of each model. To determine if the variables included in the model were adequate for describing the distribution in the data, goodness of fit tests were used to compare the pure error negative log-likelihood with the fitted model log-likelihood. When the $\chi^2$ test result was not significant ($P \geq 0.05$), it was considered that sufficient explanatory variables were included in the model. To select the most parsimonious model, Akaike’s information criterion (AIC) was used to rank each of the models. The model with the lowest AIC value is considered most parsimonious but models within two AIC units of the minimum AIC ($\Delta$AIC $< 2$) are considered competing. Overall accuracy of competing models was assessed by constructing receiving operator characteristic curves and calculating the area under the curve (AUC). A receiving operator characteristic curve plots all true positive fractions obtained from the model on the vertical axis with their corresponding false positive fraction values on the horizontal axis. The AUC provides a threshold-independent measure of the overall accuracy of the model. We also compared sensitivity, specificity, and positive and negative predictive values for each candidate model based on the selected probability cutoff value that simultaneously maximized sensitivity and specificity. For the selected model, spatial dependence of model residuals was evaluated using Moran’s I statistic. A leave-one-out method was used to evaluate how sensitive the model was to any specific case or control point. Data were analyzed using the JMP version 9 statistical software (SAS Institute, Cary, NC).

RESULTS

Description of climatic variables at case and control locations. The mean annual cycles of the climatic variables averaged for all 108 case and control locations are shown in Figure 2. Rainfall exhibits a bimodal seasonal cycle with the driest season in December–February and the rainiest season in August–October (Figure 2A); average monthly total rainfall in February is 13 mm (5–19-mm range), and in August is 327 mm (162–416-mm range). Case locations consistently had greater rainfall than control locations. The mean monthly values for relative humidity were lowest in February (35% mean, 30–40% range) and highest in September (78% mean, 69–82% range), corresponding with the driest and rainiest seasons, respectively (Figure 2B). The annual cycle of maximum, mean, and minimum temperature (Figure 2C) is roughly the inverse of rainfall and relative humidity; the warmest temperatures occur during the driest months when humidity—and presumably cloud cover—are lowest, and the coolest temperatures correspond with the months leading up to and including the rainiest and most humid months. Mean monthly temperatures from 1999 to 2008 are as low as 19.4°C (17.4–22.8°C range) in August to 23.9°C (21.4–27.4°C range) in February. The mean maximum and minimum monthly temperatures (i.e., daily average maximum and minimum temperatures for each month) roughly follow the same annual cycle as the monthly mean temperatures; however, there is

![Figure 2](image-url)
less variability over the year for the monthly minimums caused by stronger nocturnal cooling in the dry months. Subsequently, the driest months also exhibit the largest diurnal temperature ranges, with a diurnal range of 11.9°C in February being the largest.

Multivariable logistic regression model. The five best predictors for each climate category that were selected based on forward stepwise logistic regression analyses are shown in Table 1. These variables were included with the landscape variables in the multivariable model selection. On the basis of AIC comparisons of forward stepwise logistic regression models, no models were considered competing based on ΔAIC values. The best model included positive associations with total rainfall in February, October, and November, and elevation above 1,300 m, and a negative association with June total rainfall (Table 2).

Model residuals were randomly distributed (Moran’s I = 0.52, \( P = 0.20 \)), and the leave-one-out evaluation showed that the model was not sensitive to any particular case or control location (AUC range = 0.932–0.946). The AUC of the model was 0.936, indicating that 93.6% of the time, randomly selected case, and control pairs will be correctly ordered by their probability scores. When the probability scores were dichotomized to simultaneously maximize sensitivity and specificity (\( P \geq 0.3726 \) was considered elevated risk), the model yielded a sensitivity of 89%, with 32 of 36 case locations being correctly classified by the model as elevated risk. Specificity was 90%, with 65 of 72 control locations classified as low risk. The positive predictive value was 82%, with 32 of the 39 hut locations expected to be within elevated risk areas identified as cases. Although the false positivity rate (18%) is fairly high, it is important to note that the model was built using only a single year of case data and plague cases are likely to occur in other localities. Plotting true and false positives and negatives on a map of incidence of suspect plague cases reported from 1999 to 2007 (Figure 3), we observed six of the seven false positives occurred in parishes reporting >5 suspect plague cases per 1,000 population, which suggests that these localities are conducive to plague activity. The negative predictive value was 94%, with 65 of the 69 points expected to be situated within low risk areas identified as controls (Figure 3).

It is noteworthy that the months for which rainfall values were included represent the driest (February) and rainiest (October and November) seasons of the year in this region of Uganda (Figure 2). Interestingly, the rainfall values during February and October were not significantly correlated with each other (Table 1) and closer examination of the spatial trends in rainfall revealed that locations further south received more rain during the month of February than locations to the north (Figure 4). The opposite was true for the months of October and November; locations further north received a greater amount of rainfall (Figure 4). Plotting the distribution of each of the variables included in our model revealed that the peak values for each of these variables is generally observed in central and southern Vurra County, but the spatial distribution of each variable is slightly offset from the others (Figure 4).

Previous models\(^{11,12}\) revealed that elevation was a strong predictor of plague risk. Elevation was included in our best model and removal of the elevation term yielded a model that was not competitive with the best model based on AIC comparison. However, although elevation was included in our best model and odds ratios indicate that in the context of rainfall patterns, location above or below the 1,300 m cut-off significantly affects the odds of case occurrence, elevation was the least significant variable included in the model (Table 2). When elevation was removed from the best model, overall accuracy remained high (AUC = 0.912); sensitivity was identical between the models (89%), but including elevation improved specificity from 82% to 90%. This is likely explained by the significant correlation between elevation and rainfall in February, June, and November (Table 1). In contrast to a previous spatial risk model for this region,\(^{12}\) temperature variables were not retained in our best model. However, elevation and temperature were found to be strongly and positively correlated (Table 1), thus temperature was captured indirectly by inclusion of elevation.

**DISCUSSION**

Using 10-year monthly averages of gridded meteorological data derived simulated by the WRF atmospheric model, we identified climatic predictors of the spatial distribution of human plague cases in the endemic West Nile region of Uganda, consistent with previous descriptive studies from Africa,\(^{56-58}\) Southeast Asia,\(^{21,51-53}\) and North America.\(^{15,16,30,47,54,55}\) Our model identified elevation and rainfall as predictors of plague epizootic activity. Specifically, areas above 1,300 m posed a greater risk of plague occurrence than areas below this threshold. Within these high elevation sites, risk was positively associated with rainfall during the months of February, October, and November and negatively associated with rainfall during the month of June. February is the driest month, and subsequently rainfall begins gradually increasing in March, until it peaks during August–October, and begins decreasing again in November (Figure 2A). Therefore, above-average rainfall during February, and again in October/November, may extend the growing season at both of its tails. June, though it is a moderately rainy month, is associated with a short, comparatively dry spell between the two rainy periods in March–May and August–October. Collectively, our model predictors suggest that areas that receive increased but not continuous rainfall provide ecologically conducive conditions for *Y. pestis* transmission in this region.

The causal relationship between rainfall, elevation, and plague case occurrence was not evaluated explicitly in this study. However, in general, warm moist conditions have been associated with higher plague incidence in Africa.\(^{17,48}\) Specifically, earlier descriptive studies\(^{48,49}\) noted that in east Africa plague was more likely to occur at higher elevations (1,200–1,800 m) and in areas that receive over 1,150 mm of annual rainfall. Several authors\(^{13,16,19,27,28,50}\) have hypothesized that increased rainfall leads to increases in primary vegetative production, which increases food and harborage for rodents. Increased rainfall may also increase survivorship of fleas.\(^{5,23}\) In general, mathematical models conclude that increases in host and vector populations should increase the likelihood of epizootic activity.\(^{2}\) Despite numerous studies citing climatic variables as conducive for *Y. pestis* transmission,\(^{15,16,19,23,24,30,31,57,58}\) very few studies have explicitly studied the relationship between temperature, rainfall, and rodent abundance or flea survival, particularly in east Africa. Notably, Roberts\(^{58}\) followed rat populations of various species (*Rattus rattus*, *Mastomys*...
TABLE 1

Spearman’s ρ correlation coefficients for variables included in each of the climate categories*

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*The climate variables shown are those that were selected by individual forward stepwise logistic regression models as the best predictors of plague case occurrence. Landscape variables include those included in previous plague risk models.11,12
†P < 0.0001.
‡P < 0.001.
§P < 0.05.
RH = relative humidity.
coucha, Arvicanthis abyssinicus, Otomys angoniensis, Rhabdomys pumilio, and Lemniscomys massicus) in plague-endemic areas of Kenya and reported that over four observational years (1931–1934), rat numbers were typically highest during the “short dry” (January–February) and “long rain” (March–May) seasons and lower during the “long dry” (June–September) and “short rain” (October–December) seasons. The seasonal and inter-annual rainfall data showed that rat abundance was positively associated with rainfall. Furthermore, flea loads on rats tended to increase with rat abundance, as has been described in other studies.27,58 In addition, although data were limited,58 plague cases tended to occur in years with higher rat abundance, and human plague incidence was highest when rat populations were increasing, but outbreaks were most common as rat densities were declining (likely a period when rats were dying from plague infection).

Interestingly, Roberts58 noted that plague cases were most common during years of “cereal abundance” (particularly corn and wheat) in part because the quantities of stored grain and wasted grain were large, grain was stored in areas accessible to rats, and therefore provided surplus food for these animals.59 He also noted, in Kenya, excessive rain in the late 1920s led to abundant harvests of grain, but prolonged heavy rains made it difficult to adequately dry the crops and delayed export of the crops, which led to surpluses of grain. In the West Nile region, farming is largely subsistence, rather than commercial. Nonetheless, it is likely that dry periods are required to adequately dry grain for long-term storage and to prevent spoilage. On the basis of the results of the present and previous models,11,12 we hypothesize that generally wet areas that receive abundant rainfall during both tails of the annual rainy season, and that experience a short dry season during June may represent areas that are conducive to growth of cereal crops and provide adequate conditions to properly dry the crops for long-term storage in the domestic and peridomestic settings. Rodent movement is often driven by food availability and appropriate habitat.60,61 Thus, properly dried grains that are stored within human habitations may increase rat abundance in the home and peridomestic setting where most human exposures are believed to occur.11,62

It is not clear if the rainfall variables for particular months emerged as significant because they affect crop production during key points in the life cycle of rodents, which in turn affects both rodent and flea abundance, or if these months provided the best fit to the data because they represent divergent distributions in rainfall over the plague risk area. It is conceivable that areas receiving increased rainfall during the dry month of February may experience a head start on the growing season for natural vegetation and crops. Drier conditions in the month of June could provide the essential increase in sunlight for photosynthetic cycles during a critical growth stage for crops or other vegetation, or could provide adequate conditions for drying crops for long-term storage. Increased

<table>
<thead>
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<th>TABLE 2</th>
<th>Parameter estimates for the multivariable logistic regression model identifying climatic predictors of the spatial distribution of human plague cases*</th>
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<td>Model covariates</td>
<td>Parameter estimate</td>
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<td>February total precipitation (mm)</td>
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<td>Elevation cutoff (1,300 m)</td>
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*Climatic variables were based on 10-year averages derived by weather research and forecasting (WRF) (1999–2008). Adjusted odds ratios and 95% confidence intervals (per unit change in regressors) for variables included in best model are shown. Model variables are listed based on the order in which they were included in the forward stepwise model.

df = degrees of freedom.

FIGURE 3. Location of inset represented in Figure 1. Spatial distribution of probability of case occurrence predicted by our best multivariable logistic regression model overlaid on incidence by parish per 1,000 populations for years 1999–2007. The overall model accuracy was 94% with a sensitivity of 89%, a specificity of 90%, a positive predictive value of 82%, and a negative predictive value of 94%.
precipitation in October and November might extend the growing season for various annual crops. This increased but non-continuous pattern of rainfall could be providing the optimal balance for plant growth.

Regardless of the exact mechanisms driving the association between rainfall, elevation, and plague risk, our climate model yielded a high overall accuracy of 93.6%. Accuracy was diminished mainly because of a relatively low positive predictive value (82%), which likely arose because only one year of laboratory-confirmed cases was used for model creation. Plotting case and control locations on historic incidence data (Figure 3) revealed that some control sites were located in parishes with high incidence. Thus, it is likely that these localities are conducive to plague activity, but not captured in our model build set. The overall accuracy of our model was higher than previously described models for this region, likely because this model was based on 10-year composite meteorological data rather than a single date snapshot. However, spatial extrapolation did not improve the resolution of elevated risk areas compared with the landscape model because pixel size of climate variables (2 km) was larger than the landscape variables (30–90 m). It is possible that as technology improves, it will be feasible to use atmospheric modeling to simulate finer resolution climate data that can be used to refine spatial risk predictions for plague or other diseases. In general, spatial and temporal

**FIGURE 4. Spatial variation among sites in mean monthly total rainfall values (1999–2008) for months included in our multivariable logistic regression model. Color variation represents quintiles in the rainfall distribution for each month. Variables are listed in the order of significance in our model: (A) October, (B) February, (C) November, and (D) June. The 1,300-m elevation threshold is shown in gray.**
distributions of vector-borne and zoonotic diseases are predictable based on climatic variables. Our study, which combines epidemiological surveillance data with moderate resolution climate model simulations could be used to predict other vector-borne and zoonotic disease distributions in areas where vector-borne and zoonotic diseases are most likely to emerge and where morbidity and mortality is greatest, but where observational meteorological networks are sparse. Such information could aid in targeting limited surveillance, prevention, and control resources.

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REFERENCES