Am. J. Trop. Med. Hyg., 105(1), 2021, pp. 18–23
doi:10.4269/ajtmh.20-1381

Review Article

Epidemiology, Ecology and Prevention of Plague in the West Nile Region of Uganda: The Value of Long-Term Field Studies

Rebecca J. Eisen,[1]* Linda A. Atiku,[2] Russell E. Enscore,[1] Joseph T. Mpanga,[2] Sarah Acayo,[2] Paul S. Mead,[1] Titus Apangu,[2] Brook M. Yockey,[1] Jeff N. Borchert,[1] Charles B. Beard,[1] and Kenneth L. Gage[1]

[1]*Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado;* [2]*Plague Unit, Uganda Virus Research Institute, Entebbe, Uganda*

Abstract. Plague, a fleaborne rodent-associated zoonosis, is a neglected disease with most recent cases reported from east and central Africa and Madagascar. Because of its low incidence and sporadic occurrence, most of our knowledge of plague ecology, prevention, and control derives from investigations conducted in response to human cases. Long-term studies (which are uncommon) are required to generate data to support plague surveillance, prevention, and control recommendations. Here we describe a 15-year, multidisciplinary commitment to plague in the West Nile region of Uganda that led to significant advances in our understanding of where and when persons are at risk for plague infection and how to reduce morbidity and mortality. These findings provide data-driven support for several existing recommendations on plague surveillance and prevention and may be generalizable to other plague foci.

INTRODUCTION

Plague is arguably among the most significant diseases in human history, having caused three major pandemics that claimed millions of human lives, transformed public health policy, and had a notable impact on commerce and social structure.[1–3] Although improvements in sanitation and treatment have reduced morbidity and mortality, the disease has not been eradicated and continues to cause panic and international concern when outbreaks occur.[4,5] In modern times, plague has a nearly global distribution, but in recent decades, the majority of plague cases have been reported from east and central Africa and Madagascar.[6]

Plague is characterized by long periods of apparent quiescence that are disrupted by epizootic periods in which rodents often die in large numbers, forcing their potentially infectious fleas to seek alternative hosts, including humans. Human plague outbreaks are typically associated with these epizootic periods. Where and when threatening epizootics will occur remain largely unpredictable. Field investigations conducted in response to plague cases have contributed significantly to our knowledge of plague ecology and epidemiology, and these findings suggest rational recommendations for early detection of plague outbreaks (surveillance), prevention, and control. Unfortunately, data-driven evidence to support them is limited. Although many themes are generalizable across global plague foci (e.g., reducing human contact with rodents and their fleas reduces plague cases), understanding the local ecology is paramount to successful early detection and timely implementation of effective prevention programs.

For 15 years that spanned interepizootic and epizootic periods, the U.S. CDC has partnered with the Uganda Virus Research Institute (UVRI) in the plague-endemic West Nile region (WNR) of Uganda to 1) improve plague diagnostics and epidemiological surveillance; 2) understand when and where persons are at elevated risk for acquiring plague infection; and 3) identify key hosts and vectors involved in local transmission, which was ultimately used to 4) develop, evaluate, and implement effective and locally acceptable environmental surveillance and prevention strategies. To emphasize the value of long-term applied public health field studies, we concisely synthesize the main findings and key lessons learned from a decade and a half of plague research in Uganda.

Description of the study area. The CDC-UVRI plague studies were conducted primarily in Vurra and Okoro counties, located within the Arua and Zombo (formerly Nebbi) districts, respectively, of the WNR in northwestern Uganda (Figure 1). The counties border the well-established plague focus in Ituri District within Orientale Provence in the Democratic Republic of Congo (DRC).[7] Arua and Zombo districts are roughly bisected by the Rift Valley escarpment with elevation ranging from 626 to 1,668 m; plague cases occur most commonly at higher elevations, which are typically wetter and cooler compared with lower elevation sites. Within these districts, approximately 90% of the population reside in rural areas, and nearly 60% live in Ugandan government–defined poverty. A majority of the population relies on subsistence farming to make a living.[8]

The study area is situated in a climatic transition zone between the drier East African plateau and the wetter Congo Basin. Rainfall patterns are between the unimodal and bimodal distributions characteristic of the Sahel and of equatorial East Africa, respectively. Variation in average monthly temperature is fairly minor ranging from 21.8°C in August to 25.4°C in February. The primary rainy season spans from approximately August through November and is followed by the dry season that spans December through February. The secondary, less predictable rainy season typically spans March through May.[9–11]

Human plague case occurrence in the WNR. Until recently, plague cases were diagnosed clinically and seldom with support of laboratory diagnostics, yielding a high degree of uncertainty in the distribution and occurrence of cases. As a result, when the first autochthonous cases of plague occurred in the WNR is poorly defined. As of 1949, plague cases were reported mainly from southern Uganda. Although occasional cases were reported as far north as Masindi, those were likely acquired in southern Uganda.[12] On the basis of oral histories,

* Address correspondence to Rebecca J. Eisen, Centers for Disease Control and Prevention, 3156 Rampart Road, Fort Collins, CO 80521. E-mail: dyn2@cdc.gov

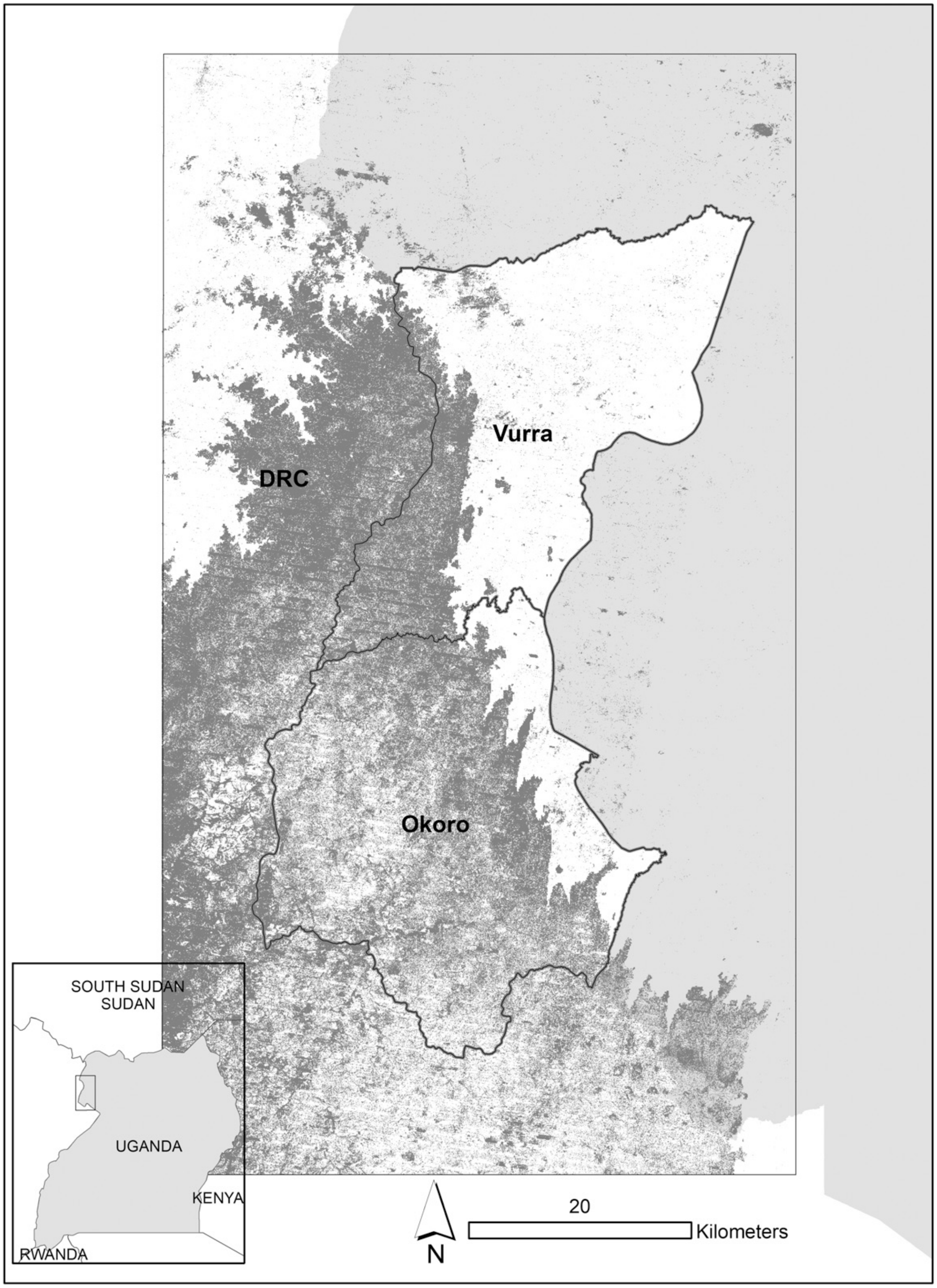

FIGURE 1. Predicted areas of elevated risk for plague (gray stippling)[18] in the West Nile region of Uganda and neighboring Democratic Republic of Congo (DRC). Location of the area of interest within East Africa is shown in the inset.

it is estimated that plague cases have been reported in what was then Nebbi district since at least the 1960s. Reportedly, cases in this district often followed those in the neighboring DRC. Soon after being recognized in Nebbi district, cases appeared in adjoining Arua district.[13]

Beginning in 1999 in Arua and Nebbi districts, a uniform reporting system was initiated that required clinics to record all consults and presumptive diagnoses. Retrospective review of records from 31 health facilities revealed 1,859 locally acquired plague cases reported from January 1999 through

December 2007, of which 1,783 (96%) were considered suspect and 76 (4%) probable. Interannual variability in case occurrence was considerable with a mean of 199 cases per year and a range from 11 to 445 cases.[14] When in 2008 the UVRI Arua laboratory began routinely confirming suspect plague cases using standard diagnostics,[15] accuracy in estimating the true burden of disease in the WNR was improved. From 2008 to 2016 in Arua and Zombo districts, 255 plague cases were reported, of which 140 (55%) were classified as suspected, 37 (15%) as probable, and 78 (31%) as confirmed. Interannual variation was considerable during this time period with nearly 60 confirmed cases reported in 2008 and none in 2010, 2014, and 2016–2018.[16,17]

Despite a high degree of interannual variability in plague case counts, each of the published epidemiological studies from the WNR reported seasonal consistency in case occurrence.[11,13,14,16,17] Plague cases were most common during the longer of two rainy seasons, with most reported in October and November. Also consistent among studies, plague patients often observed rat die-offs near their presumed exposure site before onset of illness.[13,14,17]

Assessing where and when persons are at greatest risk for exposure to *Yersenia pestis.* Understanding predictors of when and where humans are at greatest risk for exposure to *Y. pestis* can aid in targeting limited public health resources allocated for plague surveillance and prevention. When coupled with other ecological and epidemiological data, such information can provide insights into which local host and vector species play significant roles in epizootics and contribute to elevated human risk. These data can also identify behaviors and seasonal activities that put persons at elevated risk.

A series of models were developed to identify environmental predictors of where plague cases were most likely to occur in the WNR.[9,14,18,19] Implementation of routine laboratory confirmation of plague cases, improvements in mapping potential exposure sites, and development of a regional climate model[10] aided in improving spatial precision, reliability, and the area of interest of the models. From this series of models, several consistent trends emerged. Specifically, plague cases 1) were more common in western parishes, suggesting that the West Nile focus represents the eastern edge of a larger focus centered in the DRC (Figure 1), 2) were more common at higher elevation sites that are typically cooler and wetter than lower elevation sites, and 3) were associated with predictors consistent with areas where growth of annual crops, as opposed to perennials, is common.

A single study that sought to explain interannual variability in plague case counts showed that the number of annual suspect plague cases was negatively associated with dry season rainfall (December–February) and positively associated with rainfall before the plague season (June and July).[11] These same predictors were later found to correlate with seasonal abundance of potentially important *Y. pestis* reservoirs, *Arvicanthis niloticus* and *Crocidura* spp.[20] Together, these findings suggest that changes in host abundance likely linked to climatic variables may contribute significantly to seasonal and interannual differences in plague occurrence.

In general, the findings of these models were consistent with those from other plague foci, such that rainfall patterns were found to influence spatial, seasonal, and interannual occurrence of plague cases.[12,21–24] However, given the global variability in whether rainfall is positively or negatively associated with case occurrence and at what time scale emphasizes the need for long-term studies within regional plague foci that aim to understand how climatic factors affect local transmission of *Y. pestis*. In the WNR, higher elevation sites that were associated with elevated risk for plague exposure had similar vertebrate host abundance and diversity as well as similar numbers of fleas infesting hosts compared with lower elevation sites where plague cases have not been reported. However, flea diversity, which is likely associated with temperature and humidity, was significantly higher at the cooler and wetter high elevation sites. The presence of multiple vector species that have different environmental tolerances may serve to create a more connected vector–host network to facilitate *Y. pestis* persistence during interepizootic periods.[25] Thus, while changes in host abundance appear to contribute to seasonal and interannual differences in plague occurrence, flea diversity may play an important mechanistic role in defining the plague focus.

The spatial risk models also suggested that agricultural practices, which likely also correlate with food storage practices, influence plague risk, and this was further elucidated in a series of studies focused on vector and host ecology and human behavior.[19,26–28] In theory, availability of food crops could increase rodent abundance in these areas, and if crops are later stored in homes, they could draw field rodents and their fleas into homes increasing the risk of human encounters with fleas and rodents.[13] Supporting this theory, later studies in the WNR showed that growth of annual crops, such as maize, and storage of food crops in huts were associated with elevated plague risk.[19,27] Moreover, food storage inside huts where persons sleep is common practice in the region, owing in part to concerns about food theft when stored in outdoor granaries.[26,27]

In addition to identifying environmental correlates of when and where persons are at elevated risk for plague infection, additional potential risk factors were identified in a village-level case-control study.[27] Although rat abundance was similar inside huts within case and control villages (villages where plague cases were or were not reported, respectively), contact rates between rats and humans (as measured by rat bites), and host-seeking flea abundance were higher in case villages. Compared with controls, cases more often reported sleeping on reed or straw mats, storing food in huts where people sleep, owning dogs and allowing them into huts where people sleep, storing garbage inside or near huts, and cooking in huts where people sleep. Compared with cases, controls more commonly reported replacing thatch roofing and growing coffee, tomatoes, onions, and melons in agricultural plots adjacent to their homesteads. Rodent and flea control practices, knowledge of plague, distance to clinics, and most care-seeking practices were similar between cases and controls.

Small mammals and fleas collected in and around homes. Changing host composition might explain why plague cases are now reported in the WNR where they were apparently absent nearly a century ago. Surveys conducted in the late 1930s in the WNR showed that two common and effective *Y. pestis* vectors, *Xenopsylla cheopis* and *Xenopsylla brasiliensis*,[3] were established in the region, but the roof rat, *Rattus rattus*, was absent at that time.[12] Although we cannot rule out the possibility that *Y. pestis* was circulating in sylvatic cycles before recognition of human cases, the introduction of *R. rattus* and its establishment as the primary hut-dwelling species, replacing *Mastomys* sp., might explain changes in human risk of exposure to *Y. pestis*.[29]

Recent field surveys revealed that *R. rattus* is the predominant small mammal captured within huts.[16,25,27–34] *R. rattus* is known to be susceptible to *Y. pestis* and is often viewed as an important amplifying host.[3] Indeed, *Y. pestis* has been isolated from numerous *R. rattus* carcasses from the WNR,[35] but serological evidence to suggest they survive plague infection in this region is lacking. These rats are commonly infested with *X. cheopis* or *X. brasiliensis*, which are known *Y. pestis* vectors.[3,36] Inside huts, cat fleas are the predominant host-seeking flea,[27,28,37] however, laboratory studies have demonstrated that cat fleas are largely nuisance biters.[38] Because they seldom take blood meals from rodents, and are inefficient vectors of *Y. pestis*, they are not believed to be important bridging vectors from zoonotic hosts to humans, thus emphasizing the need to continue to focus control efforts on rat fleas.[37,38]

How *Y. pestis* is maintained during interepizootic periods and what ecological changes trigger transitions to epizootics has been debated for decades and remains poorly defined; it is likely that several mechanisms are important and may vary by location and time.[39] In the WNR, host and flea diversity increase with distance away from huts, supporting the prevailing hypothesis that in east Africa, *Y. pestis* is maintained in enzootic cycles in the bush and that the bacteria occasionally spill over to rats in the hut environment.[27–29] Seroprevalence is typically low (< 1%) in small mammals. However, positive results from *Arvicanthis niloticus* and *Crocidura* spp. showing previous exposure to *Y. pestis* suggest the involvement of these hosts in the perpetuation of the transmission cycles.[28] In addition, the heavy flea infestation and diversity of fleas infesting *A. niloticus*, as well as the observation that their abundance increases seasonally inside the plague focus, but not outside, provides support for the assumption that it is a key host in *Y. pestis* transmission outside of homes.[20,27–29]

Environmental surveillance and plague prevention. Plague occurs sporadically and at low incidence, and resources for surveillance and prevention often compete with other diseases of greater incidence, stressing the need for environmental surveillance and control approaches to be low cost or provide additional collateral public health benefits. Similar to other global plague foci, human exposure to *Y. pestis* in the WNR likely occurs most commonly in the home environment. A series of studies sought to evaluate hut-based prevention strategies focusing on control of vector fleas or rodents (Table 1).[30–34]

Rodents negatively affect human health and economics, particularly in developing countries where they pose a dual threat by damaging crops and stored foods and act as reservoirs of human pathogens including those causing plague, rat bite fever, leptospirosis, Lassa fever, murine typhus, salmonellosis, and campylobacteriosis. As described earlier, rodents are common inside of homes in the WNR. Recent surveys have revealed that villagers commonly see rats in their homes, rat bites are not uncommon, and villagers often practice some form of rodent control (e.g., poisons or traps, hanging food so it is out of reach of rodents), demonstrating a willingness to invest limited resources into rodent control; however, rodent abundance is similar between households that reportedly practice some form of rodent control and those that do not, suggesting current practices are insufficient.[26,27,40]

A plague prevention strategy that effectively reduces rodent abundance in and around homes could yield positive impacts beyond plague risk mitigation. However, such strategies have generally proven to be unaffordable or labor-intensive and likely unsustainable. A pilot study from the WNR showed that food storage modification practices could reduce rodent abundance in homes, but the quantity of food stored and cost of the storage devices severely limited the benefits and feasibility of the approach. Another study showed that intensive use of relatively inexpensive and reusable lethal rodent traps effectively reduced rodent abundance in homes. However, use of multiple trap types was needed to achieve success, and control was short-lived after trapping efforts ceased.[34]

Vector control, specifically indoor residual spraying (IRS) of long-lasting insecticides following protocols developed for malaria control, significantly reduced flea loads on hut-dwelling

Table 1
Strengths and weaknesses of environmental surveillance and plague prevention strategies evaluated in the West Nile region of Uganda

	Strategy	Strengths	Weaknesses
Surveillance			
	Flea index[16]	Reasonable predictor of plague risk season	Labor-intensive, poor predictor of plague activity at spatial and temporal scales feasible for implementation
	Rat fall[35]	Directly detects *Yersinia pestis*, rather than a proxy, broad spatial coverage, timely results, engages community members; good spatial precision	Requires access to sensitive and specific *Y. pestis* diagnostics
Prevention			
	Rodent-proof food storage	Reduces rodent abundance in homes, potential to reduce food insecurity and contamination	May be cost-prohibitive, labor-intensive
	Rodent removal[34]	Collateral benefits of food protection, reduction in human–rat encounters	Multiple-trap types, consistent implementation needed; control is short-lived after trapping efforts ceased
	Indoor residual insecticide spraying[31]	Reduces abundance of fleas and other biting arthropods for at least 100 days	Costly; requires specialized training to apply; for widespread use, need to consider chemical rotation to prevent evolution of insecticide resistance
	Flea control on rodents[30,33]	Low cost, if commercially available likely marketed to homeowners not requiring special pest management training	Short duration flea control, few collateral health benefits

rodents for at least 100 days postapplication.[31] Such a strategy should effectively reduce flea abundance in homes throughout the duration of the plague season and provide added benefits of reducing abundance of other nuisance arthropods and diseases vectors. Widespread preventive indoor residual spraying is not likely to be economically feasible in this setting, cannot be implemented by residents due to the restricted nature and hazards of the chemicals used, and, if not managed effectively, could contribute to the evolution of insecticide resistance, which could undermine emergency control efforts. Nonetheless, IRS has been recommended and adopted by district Ministry of Health authorities on a limited basis as an emergency control strategy after recognition of plague in humans or rats. Alternative strategies that focused on ridding rodents of fleas either through delivery of insecticidal compounds via oral baits or spot-on applications were also shown to be effective, although with varying durations of residual activity.[30,33] As an advantage, these approaches use alternative modes of action in the insecticides delivered compared with those used in IRS and therefore should not impose selection pressures to fix resistance to compounds used for emergency vector control. These practices might be attractive locally because they are relatively low cost, and do not require specialized training to apply, but they convey fewer synergistic health or quality-of-life benefits compared with IRS or rodent control.

When plague epizootics are recognized early, preventive measures including vector control, healthcare provider awareness, and community sensitization can be deployed to reduce human morbidity and mortality. Despite a long-standing belief that elevated flea loads, specifically a flea index > 1, are indicative of elevated risk for plague epizootics and human exposure, in the WNR, this labor-intensive surveillance strategy had limited spatial coverage and poor predictive power.[16] Compared with surveillance focused on the flea index, community-based surveillance focused on recognizing and reporting dead rats (rat fall surveillance, RFS) had broader spatial coverage, was less labor-intensive, yielded more timely results, and directly detected plague bacteria, rather than focusing on a proxy.[16,35]

Built on the observations that most plague patients reported seeing dead rats before the onset of plague symptoms,[14,17] in 2012, a trial RFS program was implemented in the WNR in an effort to identify plague activity before reports of human cases and to rapidly mobilize prevention and control activities. The program engaged the community to report sightings of dead rats that were tested for *Y. pestis* by the UVRI Arua laboratory. In response to plague-positive submissions, IRS was implemented in affected villages to reduce flea abundance in homes, healthcare provider awareness and training were implemented, and community education was initiated to raise awareness of ongoing risk, prevention, and the importance of seeking care rapidly if symptoms consistent with plague occur. Recent surveys suggest variability across the WNR regarding the percentage of villagers who understand accurately how the infection is spread and signs and symptoms of infection, and surveys revealed that although the majority of respondents seek care at local health clinics, others also use drug shops and traditional healers, underscoring the need for continued community sensitization and training of a wide variety of providers.[27,40] Local enthusiasm for the program, which has continued for more than 6 years, is evident as indicated by village participation expanding significantly through word of mouth to villages not initially recruited for participation. Among the villages where plague activity was detected and IRS conducted, no additional *Y. pestis*–infected carcasses were submitted within 2 months of IRS applications, and no human cases were reported from affected villages.[35] Sustainability of this program, or successful adaptation of the concept in other plague endemic areas where *R. rattus* is a key amplifying host should be possible but is dependent on generating and sustaining community engagement, access to accurate diagnostics, effective insecticides, and a network of healthcare providers trained in the diagnosis and treatment of plague.

CONCLUSIONS

This long-term, multidisciplinary commitment to plague in the WNR led to significant advances in our understanding of where and when persons are at risk for plague infection and how to reduce morbidity and mortality. These advances provide data-driven support for several existing recommendations on plague surveillance, control, and prevention; have guided efforts away from less effective or less economical interventions; and may be generalizable to other plague foci. This long-term multidisciplinary collaboration greatly enhanced national and local public health infrastructure by developing a broadly trained public health workforce at UVRI as well as many individuals at all health center levels, including the community village health teams. The benefits of this program are more far-reaching than can be gleaned from the few published studies reviewed here. Specifically, improvements in laboratory capacity resulted in improved accuracy and availability of diagnostic testing and enabled accurate detection of *Y. pestis* in rodent carcasses that guided prevention activities. Clinician and community education efforts raised awareness of signs and symptoms of plague, the importance of early care-seeking, and appropriate evidence-based treatment of plague infections. Knowledge gained from studies on plague ecology, environmental risk, and control have enabled CDC, UVRI, and the Uganda Ministry of Health to improve efficiency of surveillance and control efforts and to target them to populations at elevated risk. As plague was designated a priority zoonotic disease by the Uganda Ministry of Health, the suites of studies described herein built capacity to assist Uganda in achieving their Global Health Security goals and improving WHO Joint External Evaluation scores.[41] This program represents a model for capacity-building for other priority zoonotic diseases in Uganda and elsewhere.

Received October 23, 2020. Accepted for publication March 5, 2021.

Published online May 3, 2021.

Acknowledgments: We thank the numerous community members for allowing us to work in their homes, the village health teams for serving as a bridge to the communities, and the UVRI plague team for their assistance in the field and in the laboratory. We also thank the CDC Division of Vector-Borne Diseases (DVBD) Bacterial Disease Branch participants who contributed to the studies reviewed here.

Financial support: Funding for this review was provided by the CDC DVBD. The findings and conclusions of this study are by the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Authors' addresses: Rebecca J. Eisen, Russell E. Enscore, Paul S. Mead, Brook M. Yockey, Jeff N. Borchert, Charles B. Beard, and Kenneth L. Gage, Division of Vector-Borne Infectious Diseases, CDC, Ft. Collins, CO, E-mails: dyn2@cdc.gov, renscore@cdc.gov, pfm0@cdc.gov, bmy0@cdc.gov, gqx1@cdc.gov, cbb0@cdc.gov, and klg0@cdc.gov. Linda A. Atiku, Joseph T. Mpanga,Sarah Acayo, and Titus Apangu, Plague Unit, Uganda Virus Research Institute, Entebbe, Uganda, E-mails: l_atikupraise@yahoo.com, socakabrown@yahoo.ca, joe1ug@msn.com, and apangu26@gmail.com.

REFERENCES

1. Gage KL, Kosoy MY, 2005. Natural history of plague: perspectives from more than a century of research. *Annu Rev Entomol 50:* 505–528.
2. Hirst LF, 1953. *The Conquest of Plague*. London, UK: Oxford University Press.
3. Pollitzer R, 1954. *Plague*. World Health Organization Monograph Series No. 22. Geneva, Switzerland: World Health Organization.
4. Mead PS, 2018. Plague in Madagascar—a tragic opportunity for improving public health. *N Engl J Med 378:* 106–108.
5. Ramalingaswami V, 2001. Psychosocial effects of the 1994 plague outbreak in Surat, India. *Mil Med 166:* 29–30.
6. Neerinckx S, Bertherat E, Leirs H, 2010. Human plague occurrences in Africa: an overview from 1877 to 2008. *Trans R Soc Trop Med Hyg 104:* 97–103.
7. Abedi AA et al., 2018. Ecologic features of plague outbreak areas, Democratic Republic of the Congo, 2004–2014. *Emerg Infect Dis 24:* 210–220.
8. Lakwo A, Cwinyaai W, Abdallay O, 2008. *West Nile Profiling*. Nebbi, Uganda: Agency for Accelerated Regional Development.
9. MacMillan K et al., 2012. Climate predictors of the spatial distribution of human plague cases in the West Nile region of Uganda. *Am J Trop Med Hyg 86:* 514–523.
10. Monaghan AJ, MacMillan K, Moore SM, Mead PS, Hayden MH, Eisen RJ, 2012. A regional climatography of West Nile, Uganda, to support human plague modeling. *J Appl Meteorol Climatol 51:* 1201–1221.
11. Moore SM, Monaghan A, Griffith KS, Apangu T, Mead PS, Eisen RJ, 2012. Improvement of disease prediction and modeling through the use of meteorological ensembles: human plague in Uganda. *PLoS One 7:* e44431.
12. Hopkins GHE, 1949. *Report on Rats, Fleas and Plague in Uganda*. Kampala, Uganda: East African Standard, Ltd., 52.
13. Orochi-Orach S, 2003. Plague outbreaks: the gender and age perspective in Okoro Counti, Nebbi District, Uganda. Nebbi, Uganda: Agency for Accelerated Regional Development, 51.
14. Winters AM et al., 2009. Spatial risk models for human plague in the West Nile region of Uganda. *Am J Trop Med Hyg 80:* 1014–1022.
15. Chu MC, 2000. *Laboratory Manual of Plague Diagnostics*. Atlanta, GA and Geneva, Switzerland: Centers for Disease Control and Prevention and World Health Organization.
16. Eisen RJ, Atiku LA, Mpanga JT, Enscore RE, Acayo S, Kaggwa J, Yockey BM, Apangu T, Kugeler KJ, Mead PS, 2020. An evaluation of the flea index as a predictor of plague epizootics in the West Nile region of Uganda. *J Med Entomol 57:* 893–900.
17. Forrester JD et al., 2017. Patterns of human plague in Uganda, 2008–2016. *Emerg Infect Dis 23:* 1517–1521.
18. Eisen RJ et al., 2010. Assessing human risk of exposure to plague bacteria in northwestern Uganda based on remotely sensed predictors. *Am J Trop Med Hyg 82:* 904–911.
19. MacMillan K, Enscore RE, Ogen-Odoi A, Borchert JN, Babi N, Amatre G, Atiku LA, Mead PS, Gage KL, Eisen RJ, 2011. Landscape and residential variables associated with plague-endemic villages in the West Nile region of Uganda. *Am J Trop Med Hyg 84:* 435–442.
20. Moore SM, Monaghan A, Borchert JN, Mpanga JT, Atiku LA, Boegler KA, Montenieri J, MacMillan K, Gage KL, Eisen RJ, 2015. Seasonal fluctuations of small mammal and flea communities in a Ugandan plague focus: evidence to implicate *Arvicanthis niloticus* and *Crocidura* spp. as key hosts in *Yersinia pestis* transmission. *Parasit Vectors 8:* 11.
21. Davis DH, 1949. Current methods of controlling rodents and fleas in the campaign against bubonic plague and murine typhus. *J R Sanit Inst 69:* 170–175.
22. Davis DH, 1953. Plague in Africa from 1935 to 1949; a survey of wild rodents in African territories. *Bull World Health Organ 9:* 665–700.
23. Gage KL, Burkot TR, Eisen RJ, Hayes EB, 2008. Climate and vectorborne diseases. *Am J Prev Med 35:* 436–450.
24. Neerinckx SB, Peterson AT, Gulinck H, Deckers J, Leirs H, 2008. Geographic distribution and ecological niche of plague in sub-Saharan Africa. *Int J Health Geogr 23:* 7.
25. Eisen RJ, Borchert JN, Mpanga JT, Atiku LA, MacMillan K, Boegler KA, Montenieri JA, Monaghan A, Gage KL, 2012. Flea diversity as an element for persistence of plague bacteria in an East African plague focus. *PLoS One 7:* e35598.
26. Eisen RJ et al., 2013. Evidence that rodent control strategies ought to be improved to enhance food security and reduce the risk of rodent-borne illnesses within subsistence farming villages in the plague-endemic West Nile region, Uganda. *Int J Pest Manage 59:* 259–270.
27. Eisen RJ, MacMillan K, Atiku LA, Mpanga JT, Zielinski-Gutierrez E, Graham CB, Boegler KA, Enscore RE, Gage KL, 2014. Identification of risk factors for plague in the West Nile Region of Uganda. *Am J Trop Med Hyg 90:* 1047–1058.
28. Amatre G, Babi N, Enscore RE, Ogen-Odoi A, Atiku LA, Akol A, Gage KL, Eisen RJ, 2009. Flea diversity and infestation prevalence on rodents in a plague-endemic region of Uganda. *Am J Trop Med Hyg 81:* 718–724.
29. Enscore RE, Babi N, Amatre G, Atiku L, Eisen RJ, Pepin KM, Vera-Tudela R, Sexton C, Gage KL, 2020. The changing triad of plague in Uganda: invasive black rats (*Rattus rattus*), indigenous small mammals, and their fleas. *J Vector Ecol 45:* 333–355.
30. Boegler KA, Atiku LA, Mpanga JT, Clark RJ, Delorey MJ, Gage KL, Eisen RJ, 2014. Use of insecticide delivery tubes for controlling rodent-associated fleas in a plague endemic region of West Nile, Uganda. *J Med Entomol 51:* 1254–1263.
31. Borchert JN, Eisen RJ, Atiku LA, Delorey MJ, Mpanga JT, Babi N, Enscore RE, Gage KL, 2012. Efficacy of indoor residual spraying using lambda-cyhalothrin for controlling nontarget vector fleas (Siphonaptera) on commensal rats in a plague endemic region of northwestern Uganda. *J Med Entomol 49:* 1027–1034.
32. Borchert JN et al., 2012. Evaluation and modification of off-host flea collection techniques used in northwest Uganda: laboratory and field studies. *J Med Entomol 49:* 210–214.
33. Borchert JN, Enscore RE, Eisen RJ, Atiku LA, Owor N, Acayo S, Babi N, Montenieri JA, Gage KL, 2010. Evaluation of rodent bait containing imidacloprid for the control of fleas on commensal rodents in a plague-endemic region of northwest Uganda. *J Med Entomol 47:* 842–850.
34. Eisen RJ, Atiku LA, Boegler KA, Mpanga JT, Enscore RE, MacMillan K, Gage KL, 2018. An evaluation of removal trapping to control rodents inside homes in a plague-endemic region of rural northwestern Uganda. *Vector Borne Zoonotic Dis 18:* 458–463.
35. Boegler KA et al., 2018. Rat fall surveillance coupled with vector control and community education as a plague prevention strategy in the West Nile Region, Uganda. *Am J Trop Med Hyg 98:* 238–247.
36. Eisen RJ, Wilder AP, Bearden SW, Montenieri JA, Gage KL, 2007. Early-phase transmission of *Yersinia pestis* by unblocked *Xenopsylla cheopis* (Siphonaptera: Pulicidae) is as efficient as transmission by blocked fleas. *J Med Entomol 44:* 678–682.
37. Graham CB, Borchert JN, Black WCt, Atiku LA, Mpanga JT, Boegler KA, Moore SM, Gage KL, Eisen RJ, 2013. Blood meal identification in off-host cat fleas (Ctenocephalides felis) from a plague-endemic region of Uganda. *Am J Trop Med Hyg 88:* 381–389.
38. Eisen RJ et al., 2008. Early-phase transmission of *Yersinia pestis* by cat fleas (*Ctenocephalides felis*) and their potential role as vectors in a plague-endemic region of Uganda. *Am J Trop Med Hyg 78:* 949–956.
39. Eisen RJ, Gage KL, 2009. Adaptive strategies of *Yersinia pestis* to persist during inter-epizootic and epizootic periods. *Vet Res 40:* 1.
40. Kugeler KJ et al., 2017. Knowledge and practices related to plague in an endemic area of Uganda. *Int J Infect Dis 64:* 80–84.
41. Uganda Ministry of Health, 2019. Zoonotic diseases: In: *National Action Plan for Health Security 2019–2023*. Kampala, Uganda: Uganda Ministry of Health, 34–36.