Spatial distribution and risk factors for foot and mouth disease virus in Uganda: Opportunities for strategic surveillance

Anna Munsey[a], Frank Norbert Mwiine[b], Sylvester Ochwo[b], Lauro Velazquez-Salinas[c], Zaheer Ahmed[d], Francois Maree[e], Luis L. Rodriguez[c], Elizabeth Rieder[c], Andres Perez[a], Kimberly VanderWaal[a*]

[a] University of Minnesota College of Veterinary Medicine, 222 Veterinary Medical Center, 1365 Gortner Avenue, St. Paul, Minnesota, 55418, USA

[b] Makerere University College of Veterinary Medicine, Animal Resources and Biosecurity (COVAB), Makerere Hill Road, P.O. Box 7062, Kampala, Uganda

[c] Agricultural Research Service (ARS), Foreign Animal Disease Research Unit, United States Department of Agriculture, Plum Island Animal Disease Center, P.O. Box 848, Greenport, NY, 11948, USA

[d] Animal and Plant Health Inspection Services (APHIS), National Veterinary Services Laboratories, Foreign Animal Disease Diagnostic Lab, United States Department of Agriculture, Plum Island Animal Disease Center, P.O. Box 848, Greenport, NY, 11948, USA

[e] Onderstepoort Veterinary Institute, 100 Soutpan Road, Pretoria, 0002, South Africa

*Corresponding Author: Kimberly VanderWaal, Ph.D.

Address: 225 Veterinary Medical Center
1365 Gortner Avenue
St. Paul, MN 55108
Phone: 612-624-9289
Fax: 612-625-1210
Email: kvw@umn.edu

Abstract

Foot-and-mouth disease virus (FMDV) has a substantial impact on cattle populations in Uganda, causing short- and long-term production losses and hampering local and international trade. Although FMDV has persisted in Uganda for at least 60 years, its epidemiology there and in other endemic settings remains poorly understood. Here, we utilized a large-scale cross-sectional study of cattle to elucidate the dynamics of FMDV spread in Uganda. Sera samples (n=14,439) from 211 herds were analyzed for non-structural protein reactivity, an indication of past FMDV exposure. Serological results were used to determine spatial patterns, and a Bayesian multivariable logistic regression mixed model was used to identify risk factors for FMDV infection. Spatial clustering of the disease was evident, with higher risk demonstrated near international borders. Additionally, high cattle density, low annual rainfall, and pastoralism were associated with increased likelihood of FMD seropositivity. These results provide insights into the complex epidemiology of FMDV in Uganda and will help inform refined control strategies in Uganda and other FMDV-endemic settings.

Keywords: Foot and mouth disease; Uganda; spatial analysis; Bayesian statistics; risk factors

Introduction

Foot-and-mouth disease (FMD) remains one of the most important livestock diseases worldwide due to its impact on animal productivity and wellbeing as well as household and national economies (James and Rushton, 2002; Perry and Rich, 2007). The causative agent of the disease is foot-and-mouth disease virus (FMDV), a single-stranded, positive-sense RNA virus in the genus *Aphthovirus*, family *Picornaviridae* (Knowles and Samuel, 2003). FMDV is genetically diverse, with seven distinct serotypes displaying high levels of antigenic variation and no immunologic cross-protection among serotypes (Bachrach, 1968; Domingo et al., 2002; Sobrino

et al., 2001). The virus affects cloven-hooved livestock including cattle, pigs, sheep, and goats and many wild ruminant species (Alexandersen and Mowat, 2005). Clinical FMD is typically characterized by fever and vesicular lesions of the feet, tongue, snout, and teats (Alexandersen et al., 2003). Mortality is low, but the debilitating effects of the disease have the potential to cause significant production losses (reviewed in Arzt et al., 2011 and Nfon et al., 2017).

FMD-related losses have the largest impact in developing countries, which contain two-thirds of the world's FMDV-susceptible livestock and where relatively more people are directly dependent on livestock production for financial and food security (Baluka, 2016; Knight-Jones et al., 2016). During the acute phase of FMD, losses are incurred through decreased milk production, lost draft power, and mortality among young stock (Bayissa et al., 2011; Perry and Rich, 2007). Additional losses are incurred through long-term decreased production, early culling, reduced fertility, and control measures such as vaccination and quarantines, which limit access to local markets (James and Rushton, 2002; Balinda et al., 2010a; Baluka, 2016). At the international level, FMDV-endemic countries have limited access to potentially lucrative markets for animal products (Dhikusooka et al., 2016; Pluimers et al., 2002; Pomeroy et al., 2015; Vosloo et al., 2002).

The epidemiology of FMDV in endemic settings, including Uganda, remains poorly understood (Di Nardo et al., 2015; Knight-Jones et al., 2016), and thus, control strategies lack evidence-based guidelines. There are at least four circulating serotypes of FMD in the country (O, A, SAT 1, and SAT 2), many of them exhibiting genetically distinct lineages (Mwiine et al., 2019; Namatovu et al., 2015a). Mwiine *et al.* (2019) demonstrated the circulation of twelve distinct

lineages among the four serotypes from 2014 to 2017 (Mwiine et al., 2019). Currently, FMD outbreaks in Uganda are controlled using ring vaccination and local restrictions on animal movements, but these strategies have had a limited impact on disease control in the country (Ayebazibwe et al., 2010a; Balinda et al., 2009, 2010b; Kasambula et al., 2012; Muleme et al., 2012). The most commonly used vaccine in Uganda during our study was a trivalent vaccine corresponding to serotypes O, SAT 1 and SAT 2 , sourced from Kenya Veterinary Vaccines Production Institute. Less commonly, vaccines from Botswana Vaccine Institute were used. Recently, a quadrivalent vaccine including serotype A has been used in some districts (World Organisation for Animal Health and Food and Agriculture Organization of the United Nations, 2018). Success of vaccination in Uganda may be limited as a result of several factors, including potential quality control issues during vaccine production and distribution resulting in vaccines of unknown potency as well as the immense genetic and antigenic variability within serotypes O, SAT 1, and SAT 2. The degree of protection against regionally circulating FMD viruses induced after vaccination is not known (Muleme et al., 2012). Additionally, factors like uncontrolled animal movements, delays in reporting of outbreaks and in implementing zoo-sanitary control measures, and incomplete vaccination coverage during outbreak response all impair FMD control in Uganda (Balinda et al., 2010b; Kasambula et al., 2012; Muleme et al., 2012; Namatovu et al., 2015b).

The Food and Agriculture Organization of the United Nations (FAO), World Organisation for Animal Health (OIE), and European Commission for the Control of Foot and Mouth Disease (EuFMD) have established the Global FMD Progressive Control Pathway (FMD-PCP), aimed at assisting endemic countries reduce the impact of FMD by progressively increasing the level of

FMD control (Sumption et al., 2012). Uganda is currently in stage 2 of the 5 FMD-PCP stages (World Organisation for Animal Health and Food and Agriculture Organization of the United Nations, 2018). In this stage, the country aims to implement risk-based control strategies, which requires an understanding of where virus circulation is greatest and which factors are drivers of viral circulation, guiding optimal utilization of resources.

Ayebaziwe *et al.* (2010a) conducted a retrospective analysis of FMD outbreak reports from 2001 to 2008 and found the distribution of reported outbreaks at least partially mirrored the geography of the cattle corridor, an area with large cattle populations and in which low rainfall has led to frequent droughts and massive seasonal movements of animals in search of pasture and water (Figure 1) (Ayebazibwe et al., 2010a). During this time frame, Central, Eastern, Western, and Southwestern Uganda had the most reported outbreaks, whereas there were few reports from Northeastern Uganda. However, underreporting of outbreaks is likely (Ayebazibwe et al., 2010a; Muleme et al., 2012).

The current study aims to use serology data to describe the spatial distribution of FMDV in Uganda and quantify associations between FMDV-seropositive herds and hypothesized risk factors using a large-scale cross-sectional study. As limited resources prevent routine mass vaccination, results presented herein will inform a tailored FMDV control plan, allow for the efficient application of resources for Uganda to progress in the FMD-PCP, and ultimately, support the control of the disease in the country.

Materials & Methods

Characteristics of the Study Area

Uganda is a land-locked country located on the East African Plateau, occupying 241,038 km^2 between latitudes 4°N and longitudes 29°35°E (Supplemental Figure 1). It is bordered by South Sudan to the north, Kenya to the east, Tanzania and Rwanda to the south, and the Democratic Republic of Congo to the west (Figure 1). Lake Victoria occupies a substantial portion of the southern part of the country. The country is divided into regions (Central, Western, Eastern, Northern, Northeastern, Northwestern, Southwestern), which are further divided into districts. Ten agroecological zones are defined by ecological conditions and farming systems (Mulumba et al., 2012). Uganda has numerous national parks and wildlife reserves, referred to as "protected areas". National parks make up 4.6% of the country's land area (11,150 km^2). Protected areas are unfenced, allowing buffalo, impala, and other ungulates to roam freely. Protected areas considered for this study are shown in Figure 1 and listed in Supplemental Table 1.

Study Design

Serum sampling of cattle herds was undertaken from 2014 to 2017. The study was approved by Uganda Institutional Animal Ethics Review Committee (SBLS/REC/13/016), Makerere University. Cattle herds in Uganda are diverse in terms of size and management practices; Ugandan district veterinary officers were contacted and asked to select cattle herds representative of the management practices within their district. A herd, considered as the unit of analysis, was defined as a group of cattle under ownership of one individual. Sampling was broadly categorized into two types: 1) random sampling, in which the infection status of the herd was not known *a priori*, and 2) purposive sampling, in which herds were sampled in a known post-outbreak area. No herd was sampled more than once (Mwiine et al., 2019).

Data Collection & Sample Testing

141 At each sampling site, the animal owner was asked a series of questions from a standardized
142 herd-level questionnaire (Table 1). Language assistance was provided by veterinary officers or
143 animal husbandry officers as needed. The herd's spatial location was also recorded. Spatial
144 locations were projected to UTM (Universal Transverse Mercator) grid 36N and displayed in
145 ArcMap v10.2.2 (ESRI®). Cattle densities were calculated using Uganda's National Livestock
146 Census (Uganda Bureau of Statistics, 2010) (Figure 2). Shapefiles for district boundaries were
147 downloaded from World Resources Institute (datasets.wri.org).
148
149 Serum samples were collected and tested for presence of antibodies against FMDV non-
150 structural proteins using a PrioCHECK ELISA test kit (Thermo Fisher Scientific, USA)
151 following the manufacturer's instructions (Mwiine et al., 2019). Percentage inhibition greater
152 than 50 percent was considered positive. Herds were classified as FMD-positive (considered
153 recently exposed to FMDV based on presence of antibodies against FMDV non-structural
154 proteins) or FMD-negative using the hypergeometric theory for demonstration of freedom from
155 disease implemented in the FreeCalc software (epitools.ausvet.com.au) (Cameron and Baldock,
156 1998). This calculation assumes a null hypothesis that the population is diseased, and accepts or
157 rejects the null using the size of the population (herd), number of animals within the population
158 tested, number of positives, and design prevalence (hypothetical prevalence of interest to be
159 detected). The calculation accounts for an imperfect test, and therefore relies on assumptions of
160 the sensitivity and specificity of the diagnostic test, which were extracted from Chung *et al.*
161 (2018) and Hosamani *et al*. (2015). Sensitivity and specificity values were subjected to a
162 sensitivity analysis to assess the robustness of results (see below). Detailed methods of the
163 freedom from disease calculations are provided in Appendix A.1.

164 **Spatial Clustering Analysis**

165 To evaluate spatial clustering of infected herds, spatial scan statistical analyses were performed
166 using the SaTScan v9.4.4 software (Kulldorff, 1997, 2009). Scans were conducted for areas with
167 high and low rates, testing for elevated or reduced cases within a window relative to the expected
168 number of cases within the window if cases are homogenously distributed. Detailed SaTScan
169 methods are provided in Appendix A.2.

170 **Regression Analysis**

171 To quantify associations between FMDV-positive herds and epidemiological factors
172 hypothesized to predict a herd's exposure to FMDV (Table 1), univariable analyses were
173 performed using generalized linear mixed effects models, with year of sampling and surveillance
174 type (random or purposive) as random effects, and hypothesized predictor variables as fixed
175 effects, using the R package lme4 v1.1-17 (Bates et al., 2015). The response variable was the
176 outcome of the freedom from disease analysis (seropositive/seronegative at the herd level).
177 Purposive samples were included with random samples in order to increase spatial
178 representativeness of the data. However, we repeated the analysis with only randomly sampled
179 herds to ensure results were not impacted by the inclusion of the purposively sampled herds.
180 All combinations of significant variables in the univariable analyses ($p < 0.2$) that were not
181 correlated (odds ratio, $OR < 8$) (Dohoo et al., 2012) were fit in a multivariable generalized linear
182 mixed effects model for model selection. Model residuals from the best-fit model, determined
183 using Akaike information criteria, were tested for spatial autocorrelation using Global Moran's I
184 in R package spdep (v0.7-7) (Bivand and Piras, 2015; Bivand et al., 2013; Cliff and Ord, 1981).
185 Model residuals displayed significant spatial autocorrelation ($z = 0.128$, $p = 0.005$). Thus, in
186 order to account for spatially structured data, we fit a model with conditional autoregressive

(CAR) priors in R using CARBayes v5.0, wherein a spatial structure component is included to account for any spatial autocorrelation that remains in the data after the covariate effects have been accounted for (Appendix A.3) (Lee, 2013). The model with the lowest deviance information criterion (DIC) using the average of three MCMC chains was considered the best fit (Spiegelhalter et al., 2002), and models with DIC within two points were considered equivalent. Model residuals were again assessed for spatial autocorrelation using Global Moran's I in R package spdep.

Sensitivity Analysis

To determine the impact of sensitivity and specificity of the PrioCHECK ELISA on our results, we conducted a sensitivity analysis in which we varied these parameters and repeated the preceding analyses. The first iteration of the sensitivity analysis was based on reducing the sensitivity and specificity, whereas the second iteration increased the sensitivity and specificity. Methods and results of the sensitivity analysis are described in detail in Appendix B.

Results

A total of 14,439 cattle within 211 herds, consisting of both purposively sampled and randomly sampled herds, were included in the analysis. After applying a freedom from disease calculation to each herd, 149 (70.6%) herds were classified as positive (within-herd seroprevalence at least ten percent) and 62 (29.4%) were classified as negative. Among randomly sampled herds, 77 (60.2%) were classified as positive, and 51 (39.8%) were classified as negative. Among purposively sampled herds, 72 (86.7%) were classified as positive, and 11 (13.3%) were classified as negative. The mean seroprevalence at the individual-level was 37.6%. The mean within-herd prevalence was 56.0% and 31.4% among purposively sampled and randomly sampled herds, respectively. Prevalence estimates reported here are slightly lower than those

reported in Mwiine *et al.* (2019) due to differences in the study populations; specifically, this study includes seroprevalence data from the most recent sampling events, adding 1146 sera samples from 25 herds. Summary statistics for hypothesized predictor variables are shown in Table 1.

Spatial Clustering Analysis

Spatial scan analyses were used to test for spatial clustering of FMDV-seropositive herds in order to identify potential high-risk zones. FMDV-positive and negative herds were spatially clustered, as indicated by the Bernoulli scan statistic model (Figure 3; Supplemental Table 2). A single low-risk cluster was identified in central Uganda (observed/expected = 0.59, $p < 0.001$). A high-risk cluster was identified in northeastern Uganda, near the Kenya border (observed/expected = 1.39, $p < 0.001$). These clusters were also identified in both iterations of the sensitivity analysis. A second high-risk cluster was identified in southwestern Uganda, near the Tanzania border (observed/expected = 1.42, $p = 0.019$). This cluster was also identified in the first iteration of the sensitivity analysis ($p = 0.011$), but was not statistically significant in the second iteration of the sensitivity analysis ($p = 0.118$). The first iteration of the sensitivity analysis identified an additional smaller high-risk cluster in southeastern Uganda, along the Kenya border (observed/expected = 1.46, $p = 0.005$), but this cluster was not found to be statistically significant in the other analyses (Supplemental Table 2).

Regression Analysis

Two CAR models best fit the data. These included (1) cattle density and proximity to international border (DIC = 163.0) and (2) cattle density, proximity to international border, and mean annual rainfall (DIC = 164.2) as explanatory variables (Table 2). The spatial distribution of mean annual rainfall is shown in Supplemental Figure 2. In the univariable analyses, pastoralism

had an OR of 19.43 (95% credible interval, CI: 3.22 – 216.3, DIC = 173.4). However, pastoralism was not included in the final models due to significant correlation (OR > 8) with the variables in models (1) and (2). In order to address the impact of including purposively sampled herds, the model fitting process was repeated using only randomly sampled herds; for this data subset, the same covariates resulted in the best fit, with similar effect sizes. The final models were confirmed to have no remaining spatial autocorrelation in residuals. Sensitivity analyses supported these results and are presented in Supplemental Tables 3 and 4. Directionality of the covariates remained constant in all but one case (Supplemental Table 4). For the first sensitivity analysis (Supplemental Table 3), the 95% credible intervals no longer encompassed one for cattle density and proximity to international border. This lends further support to the importance of these variables to FMDV exposure, whereas the contribution of rainfall is subject to more uncertainty.

Discussion

In order to establish a more complete understanding of FMD in an endemic setting, we conducted a large-scale cross-sectional study of cattle herds in Uganda. The results of our study suggest areas along the Tanzania and Kenya border are at high-risk, thus are more likely to have high numbers of seropositive cattle compared to the background risk of the country (Figure 3). These areas are characterized by high cattle density (Figure 2) and low rainfall (Supplemental Figure 2), variables which were informative in our Bayesian regression analysis. These areas have relatively more pastoral herds than other regions of Uganda, which contributes to the high level of correlation among these variables. Pastoral herds, which frequently migrate in search of water and pasture, were significantly more likely to be classified as FMDV-seropositive, relative to those which are communally grazed or graze in fenced premises.

Given the contagious nature of FMDV, disease spread follows transboundary animal movements, and animal density is expected to influence the distribution of disease in endemic settings. International borders in East Africa are relatively porous, and animals frequently cross Uganda's borders to and from other countries (Ayebazibwe et al., 2010a; Muleme et al., 2012). These findings are consistent with studies that demonstrated a close phylogenetic relationship between Ugandan FMDV isolates and those from neighboring countries (Balinda et al., 2010b; Kasambula et al., 2012; Mwiine et al., 2019; Namatovu et al., 2015b). These findings affirm the need for coordinated regional FMDV control efforts.

Given evidence that buffalo populations in Uganda are persistently infected with FMDV (Ayebazibwe et al., 2010b), national parks in Uganda are not fenced, and cattle are routinely grazed in some of the national parks, transmission of FMDV at the wildlife-cattle interface is possible. However, the frequency of those transmission events and their relative importance to the maintenance of FMDV in Ugandan cattle populations are unknown. Here, we did not find evidence of increased risk of FMDV in cattle herds located in proximity to populations of FMDV-susceptible wildlife. This difference may be explained, at least in part, because serological results here did not differentiate between infection by serotypes, and risk of transmission from wildlife populations has only been recognized for SAT serotypes (reviewed in Tekleghiorghis et al., 2016; Thomson et al., 2003). Additionally, the western region of Uganda is underrepresented in our sampling. This area is heavily pastoral and contains numerous national parks and wildlife reserves (Figure 1), so undersampling in this area could have impacted our ability to identify risk associated with wildlife contacts. Alternatively, recent reports from

elsewhere in East Africa indicate FMDV transmission events from wildlife to cattle may be less important than in southern Africa (Casey-Bryars et al., 2018; Omondi et al., 2018, 2019). Further studies on the impact of wildlife reservoirs, especially with phylogenetic analyses, are warranted. While previous studies of FMD in East Africa have identified significant associations with herd size (with large herds at higher risk) (Bayissa et al., 2011; Beyene et al., 2015; Gelaye et al., 2009), we found no significant association between herd size and FMDV seroprevalence after accounting for other hypothesized risk factors.

To begin to explore the influence of ecological factors on the occurrence of FMDV, we investigated mean annual rainfall as a hypothesized risk factor, which could potentially influence FMDV infection by impacting herd management, animal movement, and virus survivability in the environment. Our results indicate that herds which exist in areas of lower mean annual rainfall are more likely to be exposed to FMDV. This finding has less statistical support (Table 2, Supplemental Tables 3 and 4), indicating some uncertainty in the model. The importance of low rainfall as a risk factor is consistent with findings in Zambia (Hamoonga et al., 2014). Drier conditions are expected to decrease survivability outside the host (Donaldson, 1972) so this pattern is not likely a result of changes in transmissibility. Rather, it is likely that annual rainfall serves as a proxy for other management or demographic variables that were not assessed here. For example, drier conditions alter patterns of animal movement and resultant host contacts (Hamoonga et al., 2014; VanderWaal et al., 2017), as animals may move further for access to food and water and congregate around limited water resources. It is also possible that reduced body condition associated with dry conditions, or other differences in subpopulations, may impact host susceptibility to FMDV.

302

303 Although our ability to analyze temporal trends related to intra- and inter-annual variability in
304 rainfall was limited by the nature of serology data, FMD outbreaks are hypothesized to have a
305 seasonal component, with increased numbers of outbreaks seen during the two dry seasons
306 (January to March, July to September)(Ayebazibwe et al., 2010a). The occurrence of drought in
307 Uganda likely initiates a cycle which perpetuates FMDV transmission. Periods of prolonged
308 drought are characterized by increased animal movements, aggregation of cattle and wildlife at
309 communal drinking sites, and increased livestock trade as farmers anticipate losses (Hamoonga
310 et al., 2014; Muleme et al., 2012). These results suggest ecological components that potentially
311 affect both transmission and herd management (and resultant changes in contact patterns) have
312 an impact on the circulation of FMDV.

313

314 FMD control in the region would benefit from improved outbreak response, including more
315 frequent characterization of outbreak strains (Namatovu 2015), studies on vaccine potency and
316 matching, an increase in the quantity of vaccines available to veterinary services (Muleme et al.,
317 2012), and the ability to mobilize vaccines more efficiently. In our study, veterinary officers and
318 animal owners reported a median of 25 days between recognition of an FMDV outbreak and
319 deployment of vaccines. Muleme *et al.* (2012) reported 52 days between report of an outbreak
320 and onset of vaccination. These discrepancies could be attributable to the nature of different data
321 sources (official government data versus field surveys) or it may represent a true decrease in the
322 time between outbreak reporting and deployment of vaccines. However, among the herds in our
323 study which were vaccinated in response to an outbreak (77/211, 36.5%), the majority (72/77,
324 93.5%) had already experienced clinical FMDV within the herd prior to receiving vaccination.

The high seroprevalence observed in the Northeastern region of Uganda, also known as the Karamoja region, provides evidence consistent with previous suggestions that the region has historically underreported FMD outbreaks (Muleme et al., 2012). The reasons for this are many. Karamojong practice transhumance and are more likely to rely on traditional ethnoveterinary knowledge to treat FMD compared to other regions of the country (Muleme et al., 2012). Additionally, the possible occurrence of mild or subclinical infections (Miguel et al., 2013), inadequate surveillance systems, and lack of infrastructure and resources which limit timely collection and transport of samples and diagnostic capabilities may all contribute to underreporting (Muleme et al., 2012; Vosloo et al., 2002). Moreover, herders may be negatively affected by outbreak control measures (i.e., animal movement restrictions and closure of animal markets) and therefore may be reluctant to report outbreaks. A control plan which considers the impact on all stakeholders is crucial for its success.

The ecology of FMDV in East Africa is exceedingly complex and our analyses are limited by the availability of data. In particular, data on the contribution of small ruminants and animal movements to FMDV transmission may have improved our model. However, our findings represent meaningful progress toward achieving a more complete understanding of the nature and extent of factors predicting cattle herds' FMDV exposure in Uganda. Inferences from these data can help Uganda achieve the remaining objectives under FMD-PCP Stage 2 and inform potential interventions including improved surveillance, coordinated response, and outreach strategies (Dellicour et al., 2018). For example, increased active surveillance would reduce the reliance on clinical evidence of infection and reporting from areas where a lack of infrastructure

makes reporting and confirmation difficult. If pastoral herds migrate in a predictable manner, the scale of outbreaks may be limited by the implementation of strategic preventive vaccination. Capacity building among animal health professionals and paraprofessionals may result in improved outbreak control practices. Future efforts will utilize molecular data to elucidate transmission dynamics and pinpoint viral source and sink regions in East Africa. Enhanced FMDV control in Uganda would result in advancements in the health of its animals and the livelihoods of its people.

Conclusion

Elucidation of factors which promote the maintenance and circulation of FMD is essential for crafting surveillance and control plans appropriate for Uganda. Future FMDV control efforts in Uganda should aim to address endemic transmission within Uganda, areas in which cattle density is highest and opportunities for contact between herds are frequent, and high-risk zones near Tanzania and Kenya. Strategies and resources aimed at improving vaccine quality and decreasing the time between outbreak reporting and response would further reduce the impact of FMDV in Uganda. Those measures, along with strategies which would lessen negative repercussions of outbreak reporting, would help motivate cooperation among stakeholders in Uganda. These findings will help Uganda develop a risk-based FMDV control plan.

Acknowledgments

This study was funded by the Cooperative Biological Engagement Program of the United States Department of Defense Threat Reduction Agency [Agreement #8802]. Additional support was provided by the Agricultural Research Service, United States Department of Agriculture [CRIS project 1940-32000-061-00D]. AM was funded by United States Department of Agriculture [grant #2016-38420-25288]. Declarations of interest: none.

371 **Appendix A**

372 **A.1: Freedom From Disease Calculation**

373 To calculate freedom from disease within a herd, we utilized a design prevalence (expected
374 minimum within-herd prevalence) of ten percent to account for variations expected due to, for
375 example, previously infected animals being introduced to a herd. We utilized a sensitivity of 94.4
376 percent, specificity of 91.3 percent in vaccinated herds (Hosamani et al., 2015), and specificity of
377 96 percent in unvaccinated herds (Chung et al., 2018). Type I and II error rates were set to 0.05.
378 Herds in which adequate sample size was not achieved (n = 27 herds) were discarded, leaving
379 211 herds for subsequent analyses. Data for spatial variables were calculated in ArcMap using
380 the Near tool (for polygon data) or Extract Values to Points tool (for raster data) (Table 1).
381 Summary statistics for spatial and survey data were calculated using Microsoft Excel v16.10, R
382 v3.4.0 and RStudio v1.1.423.

383 **A.2: Spatial Scan Statistical Analysis**

384 The spatial scan statistic imposes a circular window of varying size upon the locations of
385 possible cases (seropositive herds). For each scan, the number of cases in the window is recorded
386 and compared to the null hypothesis of a random distribution of cases. An observed-to-expected
387 ratio is calculated as the observed number of cases within the window divided by the expected
388 number of cases within the window when the null hypothesis is true. The window with the
389 maximum log likelihood ratio (LLR) is defined as the most likely cluster. LLR is calculated by

390 $$LLR = \log\left(\frac{n}{E(n)}\right)^2 \left(\frac{N-n}{N-E(n)}\right)^{(N-n)} I' \quad (1)$$

391 where N is the total number of cases, n is the observed number of cases within the scan window,
392 $E(n)$ and $N - E(n)$ are the expected number of cases within and outside the window under the
393 null hypothesis, respectively, and I is an indicator function (equal to 1 when the window has

394 more cases than expected under the null hypothesis and zero otherwise). Sampling locations
395 were tested as potential cluster centroids. Although FMDV control measures are enforced at the
396 district level, outbreaks can sometimes encompass multiple districts, thus the maximum possible
397 spatial cluster size was set as the approximate distance between agroeconomic zone borders, 150
398 km. Monte Carlo simulation (n=999 permutations) was used to determine the significance of
399 detected clusters (Kulldorff et al., 2005).

400 **A.3: CAR Model**

401 We utilized a regression model with conditional autoregressive (CAR) priors in R using
402 CARBayes v5.0, wherein the spatial variation is modelled by a matrix of covariates X =
403 ($x_1,\ldots x_k$) and a spatial structure component $\psi = (\psi_1,\ldots, \psi_K)$ is included to account for any spatial
404 autocorrelation that remains in the data after the covariate effects have been accounted for (Lee,
405 2013) The vector of regression parameters is denoted by $\beta = (\beta_{1,\ldots,}\beta_2)$, and the CAR model fits
406 the likelihood model:

407 $$Y \sim \text{Binomial}(n_k, \theta_k) \text{ and } \ln\left(\frac{\theta_k}{(1-\theta_k)}\right) = x_k^T\beta + O_k + \psi_k \quad (2)$$

408 where n_k is the number of trials in the kth area, θ_k is the probability of success in a single trial,
409 and O is a vector of offsets. The spatial structure component ψ includes a set of random effects ϕ
410 = ($\phi_1,\ldots, \phi_k$) from a conditional autoregressive model:

411 $$\phi \sim N(0, \tau^2, Q(W, \rho)^{-1}) \quad (3)$$

412 where τ^2 is a conditional variance parameter, and Q(W,ρ) is a precision matrix which controls
413 the spatial autocorrelation structure of the random effects. The precision matrix is based on a
414 neighborhood matrix W and a spatial autocorrelation parameter ρ. Here, W is a binary
415 specification of who neighbors whom based on each herd's 20-kilometer (km) radius. (The
416 World Organisation for Animal Health guidelines recommend a 10 km radius for surveillance

around permanent premises. Thus, we assumed a 20 km radius would account for ranging behavior of Ugandan cattle herds.) This *W* specification forces (ϕ_k , ϕ_j) to be autocorrelated, where herds (S_k, S_j) are within 20 km of each other, such that their prior distribution of the random effect ϕ_k for herd S_k is conditional on the value of the response variable in S_j. Herds without a neighbor within 20 km (n = 7) were manually classified as neighbors of the nearest herd; the nearest neighbors of these herds were a mean 27.7 km away. Our model includes a CAR prior proposed by Leroux *et al*. (2000) which models varying strengths of spatial autocorrelation using a single set of random effects wherein the degree of spatial autocorrelation parameter specified by ρ follows a uniform prior (0,1) and can be estimated from the data (Leroux et al., 2000). Their model is given by

$$\phi|\phi_{-k}, \mathrm{W}, \tau^2, \rho \sim \mathrm{N}\left(\frac{\rho\Sigma_{i=1}^{K} w_{ki}\phi_i}{\rho\Sigma_{i=1}^{K} w_{ki}+1-\rho}, \frac{\tau^2}{\rho\Sigma_{i=1}^{K} w_{ki}+1-\rho}\right), \quad (4)$$

$$\tau^2 \sim \text{Inverse Gamma}(a, b).$$

The default prior distribution, inverse gamma (1, 0.01), was assumed for τ^2. For beta, we utilized non-informative vector of prior means (default Gaussian priors, vector of zeros), vector of prior variances with values equal to 10, and Markov Chain Monte Carlo (MCMC) length of 100,000 after 40,000 samples were discarded as burn-in. Convergence was assessed by visual inspection of trace files and correlation plots, effective sample size, acceptance rate for the Markov chain, and the Geweke convergence diagnostic (Geweke, 1991).

Appendix B

B.1: Sensitivity Analysis #1

For the first sensitivity analysis, specificity was decreased to 90 percent. Among cattle which were unvaccinated, or vaccinated subsequent to FMDV exposure, sensitivity was decreased to 90 percent. Among cattle which were vaccinated prior to exposure to FMDV, sensitivity was

decreased to 55 percent (Brocchi et al., 2006). Freedom from disease calculations were repeated as described in Appendix A.1. Thirty-four herds were discarded due to inadequate sample size, resulting in 64 herds (31.4%) classified as negative and 140 herds (68.6%) classified as positive. The spatial scan statistical analysis was repeated as described in Appendix A.2; results are shown in Supplemental Table 2. The regression analysis was repeated as previously described; results are shown in Supplemental Table 3.

B.2: Sensitivity Analysis #2

For the second sensitivity analysis, specificity was set to 100 percent. Among cattle which were unvaccinated, or vaccinated subsequent to FMDV exposure, sensitivity was set to 100 percent. Among cattle which were vaccinated prior to exposure to FMDV, sensitivity was set to 75 percent (Brocchi et al., 2006). Using freedom from disease calculations as described in Appendix A.1, 10 herds were discarded due to inadequate sample size, resulting in 52 herds (22.8%) classified as negative and 176 herds (77.2%) classified as positive. The spatial scan statistical analysis was repeated as described in Appendix A.2; results are shown in Supplemental Table 2. The regression analysis was repeated as described in Appendix A.3; results are shown in Supplemental Table 4.

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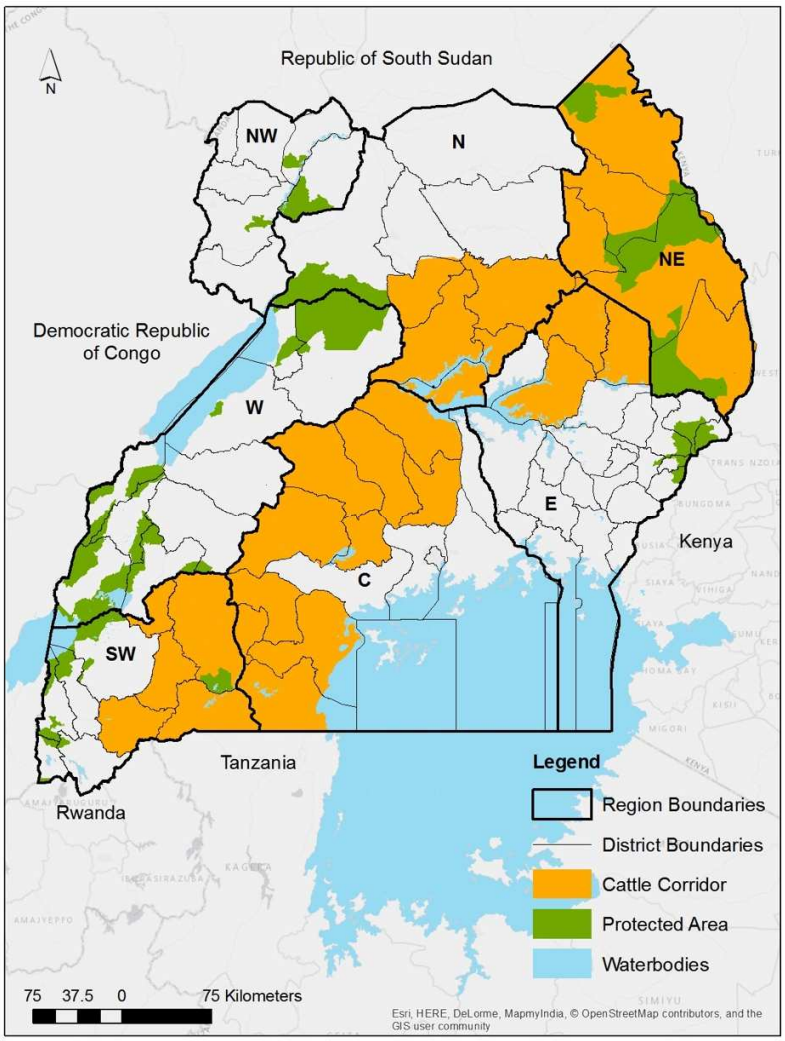

Figure 1. Map of Uganda showing protected areas (national parks and wildlife reserves), the cattle corridor, major waterbodies, and boundaries (regional/district). The regions considered for this study are Southwestern (SW), Central (C), Eastern (E), Northeastern (NE), Northern (N), Northwestern (NW), and Western (W).

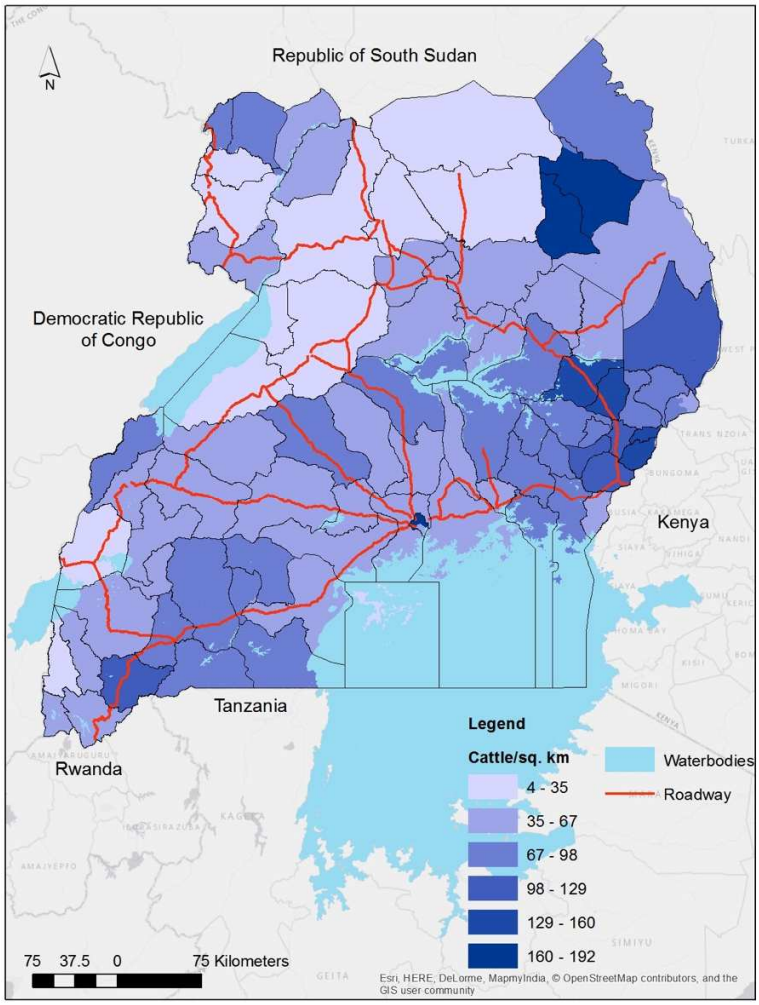

Figure 2. Map of Uganda showing cattle density (number of cattle per square kilometer, aggregated at district level), major roadways, and major waterbodies.

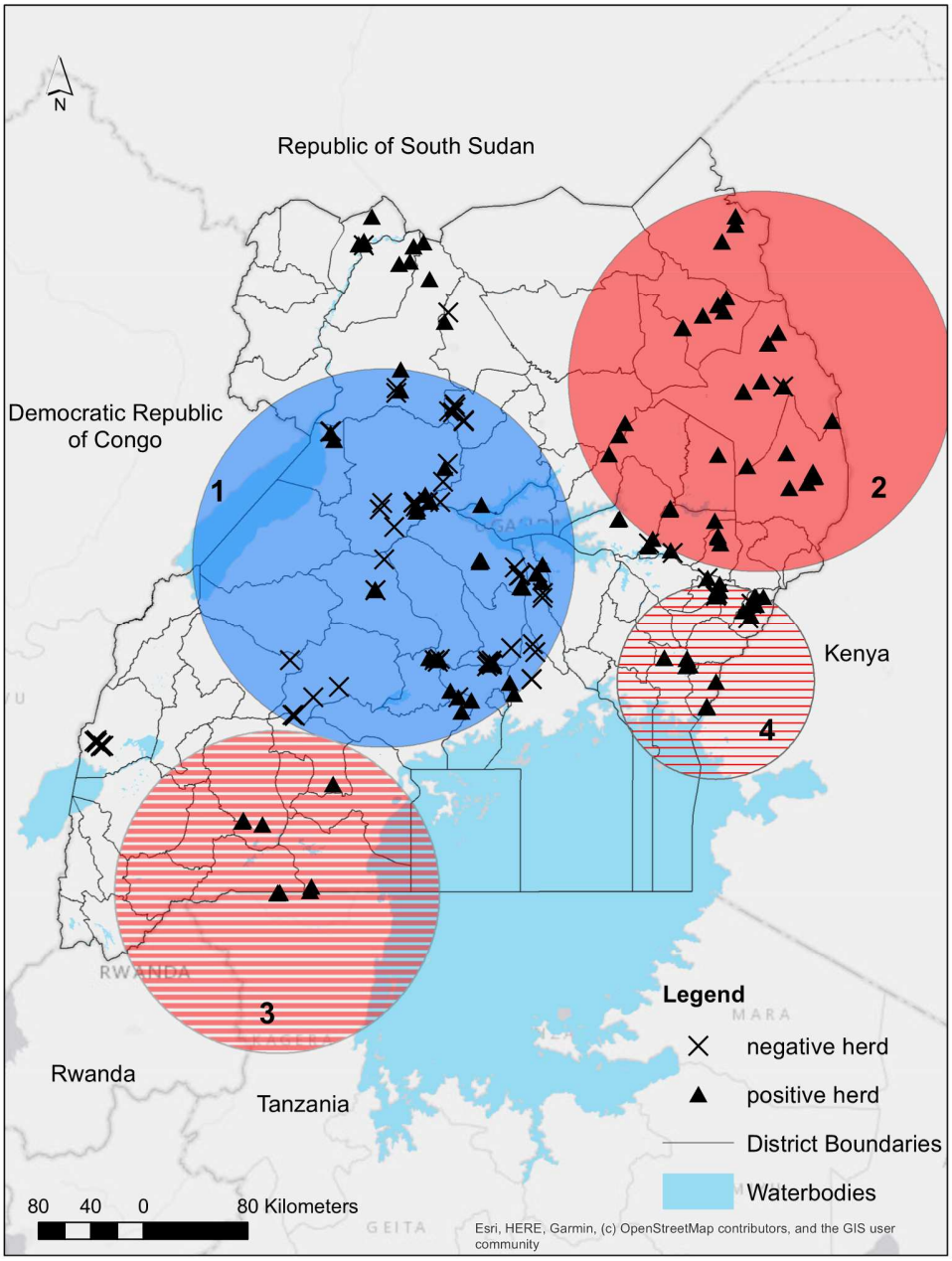

Figure 3. **Spatial clustering of FMDV in Uganda.** Locations of herds are displayed by Xs or triangles for negative herds and positive herds, respectively. SaTScan Bernoulli scan statistic clusters are shown as colored circles. High risk areas are shaded in red and low risk areas are shaded in blue. Observed/expected ratios and p-values corresponding to the three iterations of the analysis (original, sensitivity analysis #1, sensitivity analysis #2) are shown in Supplemental Table 2. Clusters 1 and 2 were identified in both versions of the sensitivity analysis. Cluster 3 was not statistically significant in the second iteration of the sensitivity analysis. Cluster 4 was statistically significant in the first iteration of the sensitivity analysis only.

Management variables	Levels	Median (min, max) or number of herds	Source
Herd size (head)	3	72 (1, 1,500)	Survey
Predominant breed	local exotic	187 24	Survey
Herd setting	pastoral communal grazing fenced	31 127 53	Survey
Spatial variables			
Distance to international border (km)	2*	73.3 (0.03, 188.5)	
Distance to protected area (km)	2*	28.4 (0.0, 185.4)	A
Distance to roadway (km)	2*	14.0 (0.09, 136.5)	B
Cattle density (cattle/square km)	2*	67.3 (4.0, 191.8)	C
Annual rainfall (cm/year)	2*	11.6 (6.9, 17.5)	D
Presence within cattle corridor	yes no	115 96	E

**codified to binomial using median*
A = Pennsylvania State University Department of Geography (psugeo.org/Africa/Africa_files/)
B = The World Bank Data Catalog (Africa Infrastructure Country Diagnostics, World Bank Group 2009)
C = 2008 National Livestock Census data (Ministry of Agriculture, Animal, Industry, and Fisheries)
D = WorldClim Global Climate Data (worldclim.org/bioclim)
E = Sempiira, 2017
(km: kilometers; cm: centimeters)

Table 1. List of hypothesized risk factors tested in the generalized linear model.

	Variable	OR Median	95% CI
Model 1	High cattle density (number of cattle/km^2)	9.18	[1.15 – 153.3]
DIC = 163.0	Proximity to international border	3.76	[0.52 – 38.0]
Model 2	High cattle density (number of cattle/km^2)	8.35	[0.93 - 186.4]
DIC = 164.2	Proximity to international border	3.01	[0.41 - 38.58]
	Low annual rainfall	2.74	[0.56 - 18.11]
	Setting (reference = communal grazing)		
DIC = 173.4	Pastoral	19.43	[3.22 - 216.3]
	Confined	1.24	[0.46 - 3.44]

Table 2. Odds ratios for the best fitting models. Mean results of three MCMC chains are reported.