

Regular article

Spatial distribution of foot-and-mouth disease (FMD) outbreaks in South Africa (2005-2016)

M.M. Sirdar ^{a,b*}, G.T. Fosgate ^a, B. Blignaut ^{a,b}, R.L. Mampane ^c, O. Rikhotso ^d, B. Du Plessis ^d, B. Gummow ^{a,e}

^a Epidemiology Section, Department of Production Animal Studies, Faculty of Veterinary Sciences, University of Pretoria, Onderstepoort, 0110, South Africa

^b Onderstepoort Veterinary Research, Agricultural Research Council, Onderstepoort, 0110, South Africa

^c Limpopo Veterinary Services, Department of Agriculture and Rural Development, Polokwane, Limpopo, South Africa

^d Mpumalanga Veterinary Services, Department of Agriculture, Rural Development, Land and Environmental Affairs, Mpumalanga, South Africa

^e College of Public Health, Medical and Veterinary Sciences, James Cook University, Townsville, 4811, Queensland Australia

* Corresponding author at: Onderstepoort Veterinary Research, Agricultural Research Council, South Africa. Tel.: +27735985122. [ORCID: 0000-0003-1830-702X](https://orcid.org/0000-0003-1830-702X)

Email address: SirdarM@arc.agric.za; sirdar44@hotmail.com (M.M. Sirdar)

Abstract

Foot-and-mouth disease (FMD) is a transboundary animal disease that has negative socio-economic consequences including impacts on food security. In South Africa, FMD outbreaks in communal farming communities cause major livestock and human livelihood concerns; they raise apprehensions about the effectiveness of FMD control measures within the FMD protection areas. This study aimed to identify high-risk areas for FMD outbreaks at the human/domestic animal/wildlife interface of South Africa. Cuzick-Edwards tests and Kulldorff scan statistics were used to detect spatial autocorrelation and spatial-temporal clusters of FMD outbreaks for the years 2005 - 2016.

Four high-risk clusters were identified and the spatial distribution of outbreaks in cattle were closer to game reserve fences and consistent with wildlife contacts as a main contributor of FMD occurrence. Strategic allocation of resources, focused control measures and cooperation between the affected provinces are recommended to reduce future outbreaks. Further research is necessary to design cost-effective control strategies for FMD.

Keywords: Cluster; Dip-tank; Human/domestic animals/wildlife interface; Kruger National Park

Declarations

Funding

This work was supported in part by the National Research Foundation of South Africa (grant numbers 90578, 7673) and the University of Pretoria.

Conflicts of interest/Competing interests (include appropriate disclosures)

None of the authors has any financial or personal relationship that could inappropriately influence or bias the content of this paper.

Availability of data and material (data transparency)

Not applicable

Code availability (software application or custom code)

Not applicable

Ethics approval (include appropriate approvals or waivers)

Ethical approval was obtained from the Animal Ethics Committees of the University of Pretoria (No. v005-15).

Consent to participate

Not applicable

Consent for publication (include appropriate statements)

Not applicable

Introduction

Foot-and-mouth-disease (FMD) is a contagious trans-boundary animal disease that affects cloven-hoofed animals and reduces productivity of livestock (Grubman and Baxt 2004). The disease is caused by infection with FMD virus (FMDV), which belongs to the genus *Aphthovirus* within the family *Picornaviridae* (Kitching et al. 2005). There are seven serotypes of FMDV: O, A, C, Asia 1 and Southern African Territories (SAT) 1, 2 and 3 (Larska et al. 2009).

Wildlife play an important role in the transmission of FMDV in southern Africa due to African buffalo (*Syncerus caffer*) being a carrier of SAT serotypes and the principal reservoir of infection for domestic livestock (Brahmbhatt et al. 2012; Vosloo et al. 2002). However, other wildlife species, including impala (*Aepyceros melampus melampus*), can be a source of infection for domestic livestock (Hunter 1998).

In South Africa, FMD is a controlled disease in accordance with the South African Animal Diseases Act (Act 35 of 1984) and the country is classified by the World Organisation for Animal Health (OIE) as having an FMD free zone without vaccination (Bruckner et al. 2002). However, South Africa lost its FMD free status in January 2019 due to an outbreak outside the protection zone of Limpopo Province (DAFF 2019). FMD control in South Africa includes animal movement restrictions placed on cloven-hoofed species and products, prophylactic vaccination of cattle, clinical surveillance and disease control fencing to separate livestock from wildlife reservoirs (DAFF 2014).

FMD control areas are divided into three primary FMD control zones: infected, protection and free zones. The majority of the infected zone is the Kruger National Park (KNP) and adjacent wildlife conservation areas with the Ndumo Nature Reserve and the Tembe Elephant Park in

KwaZulu-Natal Province also considered infected. The KNP and adjacent wildlife reserves are separated from communal farming areas by a 1.80 - 2.45-metre high fence (Ferguson and Jori 2010). The protection zone (approximately 480 km long and 10 - 20 km wide) is situated adjacent to the infected zone and falls within the three provinces of Mpumalanga, Limpopo, and KwaZulu Natal (DAFF 2014). The FMD protection zone is subdivided into two areas: the protection zone with vaccination and the protection zone without vaccination. Cattle within the protection zone with vaccination are inspected for FMD at designated dip-tanks (animal assembly points) every seven days and small stock (i.e. goats, sheep and pigs) are inspected every 28 days. In this zone, cattle of all ages are routinely vaccinated (every four months) using a commercially available trivalent vaccine (containing SAT serotypes 1, 2 and 3) (DAFF 2014). The protection zone without vaccination is situated to the west and south of the protection zone with vaccination and all cattle in this area are inspected every 14 days. FMD vaccination is not permitted in the protection zone without vaccination or the free zone.

Spatial mapping is performed to assist in developing risk management policies and strategies (Pfeiffer et al. 2008). Spatial analysis of FMD data can be performed to describe the geographical patterns and to ultimately understand the epidemiology of disease spread. Furthermore, the spatial distribution can also be used to visualize the progression of disease epidemics including disease introduction with local or long-distance spread. Cluster detection methods assist in identifying high-risk areas for virus introduction or transmission (Premasithira et al. 2011). Kriging, a spatial geostatistical interpolation technique, has been used to investigate previous FMD reports (Perez et al. 2006; Yasrebi et al. 2009).

Spatial autocorrelation is a measure of whether observations from nearby locations are similar in magnitude. The magnitude, intensity, as well as the extent of spatial autocorrelation can be quantified using spatial statistics (Fortin et al. 2013). Techniques available for assessing spatial

autocorrelation include Moran's I, Cuzick and Edwards' k-nearest neighbouring test and Kulldorff's spatial scan statistic. FMD in Tanzania has been studied using Moran's I to assess spatial autocorrelation in the model residual (Allepuz et al. 2015; Besag and Newell 1991) and Moran's I has also been used to study FMD in Great Britain (Bessell et al. 2010). The Cuzick and Edwards test has been used to assess FMD clustering in Mongolia (Shiilegdamba et al. 2008).

FMD control measures limited the occurrence of disease to less than one outbreak per decade in South Africa up until the mid 20th century. However, from 2000, the number of FMD outbreaks in cattle within the protection zone increased by more than one outbreak a year (Baipoledi et al. 2004; Jori et al. 2009; Thomson et al. 2013). Prior to 2000, the most recent FMD outbreak in the free zone was during 1957 and the last outbreak in domestic animals within the FMD protection zone was in 1983 (Bruckner et al. 2002). All outbreaks in South Africa have been caused by SAT serotypes except a single serotype O outbreak that occurred in the free zone of KwaZulu-Natal Province during 2000 (Bruckner et al. 2002).

FMD outbreaks in southern Africa and other endemic areas support the need for the collection of qualitative and quantitative data in an effort to strengthen FMD control measures. The objectives of this study were to identify and describe high-risk areas for FMD outbreaks in the protection zone of South Africa in effort to inform FMD control policy. It was hypothesized that high-risk areas would be close to wildlife areas and areas within KNP with high densities of African buffaloes.

Material and methods

Study area

The study was performed in the FMD protection zone with vaccination (PZV) in the South African provinces of Mpumalanga and Limpopo (Figure 1). The FMD PZV of Mpumalanga and Limpopo Provinces includes four and six local municipalities, respectively. These study areas are regarded as the KNP human/wildlife/livestock interface adjacent to the FMD infected zone. The study excluded the Protection zone of KwaZulu-Natal Province since this is a relatively recently designated protection area (2014) and FMD outbreaks have not been recorded since its establishment.

Data collection and management

All reported FMD cases in domestic cattle from 1 January 2005 to 31 December 2016 in the PZV communal farming areas for both Limpopo and Mpumalanga Provinces of South Africa were identified. This time period was chosen due to the availability of data from the World Animal Health Information Database (WAHIS). Total susceptible cattle numbers from affected dip-tanks were extracted from WAHIS database. The unit of analysis (case) was defined as any dip-tank where at least one domestic bovine showed FMD clinical signs. Liquid-phase blocking ELISA was used to investigate clinical suspects and laboratory confirmation of at least one animal was performed using either PCR or virus isolation.

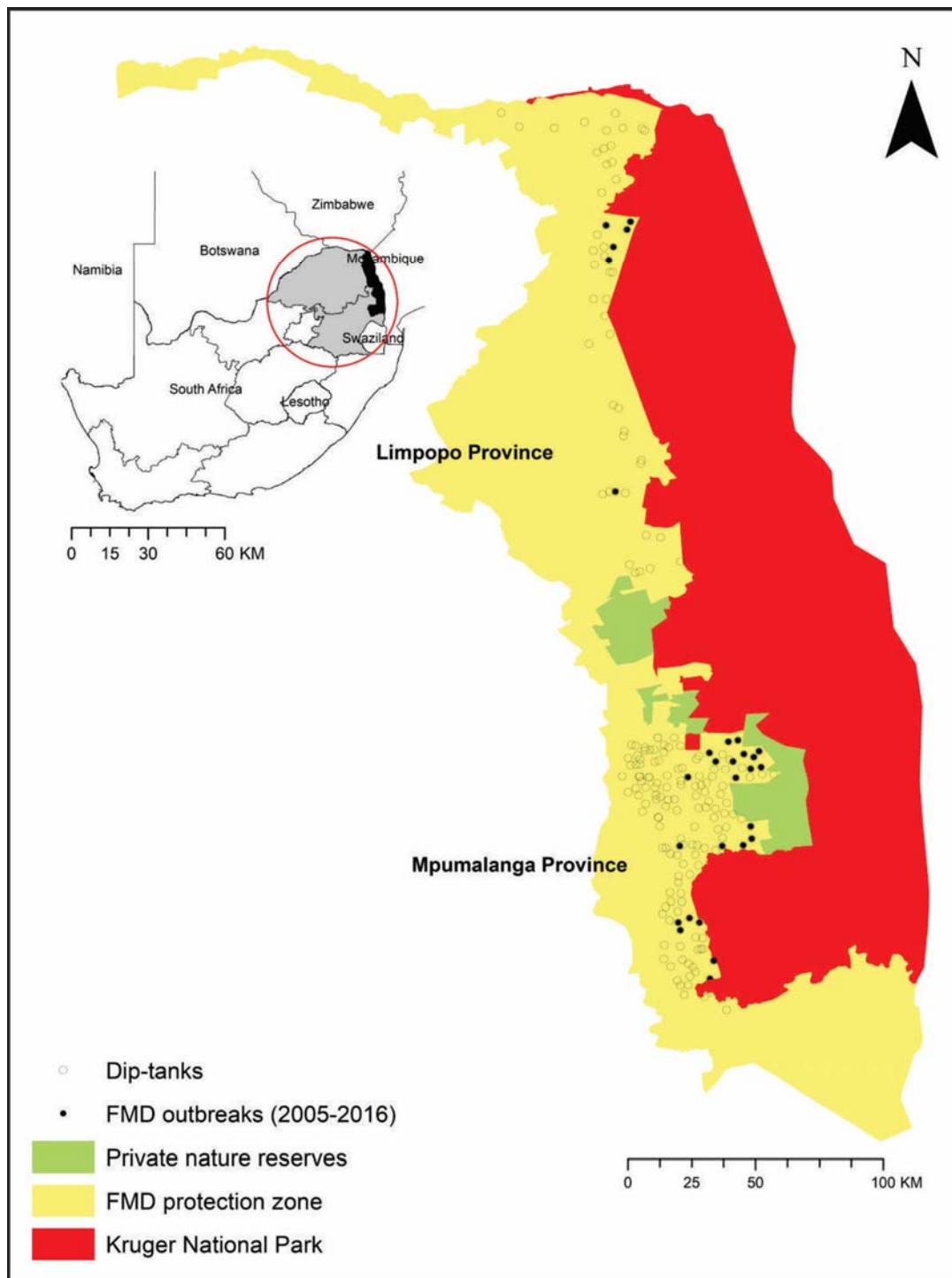


Figure 1: Study area including foot-and-mouth disease (FMD) control zones (infected and protection) within Limpopo and Mpumalanga Provinces of South Africa including all cattle dip-tanks and FMD outbreaks for 2006-2016 (no outbreaks occurred during 2005)

Dip-tanks are livestock assembly points used for routine inspection and disease control and these were the statistical unit of analysis. A dip-tank serves at least one village within an average area of five km². Commercial farms (large scale and industry driven organised farming) within the PZV were excluded from analysis. Commercial farms accounted for less than 5% and 10% in Mpumalanga and Limpopo Provinces respectively. The Department of Agriculture and Rural Development, Veterinary Services of both Mpumalanga and Limpopo Provinces provided information on all registered dip-tanks including georeferenced locations, total susceptible animals and animal-specific demographics. Animal demographics were extracted from monthly FMD inspection reports. These reports included information on the total number of cattle per dip-tank at the beginning of each month as well as increases (births and in-movement) and decreases (death, out-movement and slaughter) of the population.

FMD cases in domestic cattle were aggregated per dip-tank and summed for the total time length of each outbreak. The length of an outbreak was defined as the elapsed days between first and last reported cases based on the OIE database (<http://www.oie.int/animal-health-in-the-world/the-world-animal-health-information-system/data-after-2004-wahis-interface/>).

Coordinates for dip-tanks were converted to the Universal Transverse Mercator (UTM) zone 36S World Geodetic System (WGS) 1984 format and plotted using ArcGIS version 10.4 (ESRI, Redlands, California, USA).

Descriptive analyses

The cumulative incidence (CI) of affected cattle at the dip-tank level was used as the dependent variable for some statistical analyses. The cumulative incidence was calculated as the total number of reported FMD cases occurring within each dip-tank for a specific outbreak divided by the total number of susceptible cattle reported in the WAHIS reports. Data were assessed

for normality by plotting histograms, calculating descriptive statistics, and performing the Anderson-Darling test for normality. Data violating the normality assumption were \log_{10} transformed prior to statistical analysis.

The distance from each dip-tank to the nearest fence of a wildlife reserve was estimated using the measuring tool in the GIS software. All dip-tanks were divided into two groups; either affected at some time or never experiencing a FMD outbreak during the study period. These distances were compared between outbreak and non-outbreak dip-tank groups using a Mann-Whitney U test. Statistical analysis was performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and results were interpreted at $p < 0.05$.

Spatial interpolation

The average number of cattle for January and December 2009 (year corresponding to a middle point of the study period) was used to describe the spatial distribution of the susceptible cattle population. The average cattle population was then modeled using a point density approach, which calculates a magnitude-per-unit area from point features that fall within a neighborhood around each cell (<http://pro.arcgis.com/en/pro-app/tool-reference/spatial-analyst/point-density.htm>). The FMD CI was interpolated using ordinary kriging (Waller and Gotway 2004; Stevens et al. 2009). The CI were analysed per serotype and a combined analysis of all SAT serotypes was also performed. All maps were produced in ArcGIS 10.4.

Spatial cluster analyses

Cuzick and Edwards tests (Cuzick and Edwards 1990; Selvin et al. 2004) were used to estimate global spatial autocorrelation. The Euclidean distances between all dip-tanks were calculated using the easting-northing UTM coordinates (eq. 1). The nearest neighbouring dip-tank was identified, and each neighbouring pair was classified based on the presence/absence of reported

FMD outbreaks during the study period. For example, a case/case pair was defined as a dip-tank and its nearest neighbor when both dip-tanks experienced FMD outbreaks at any time during the study period. The observed frequency of case/case pairs of nearest neighbors (m) was then compared to the expected frequency ($E [m]$) (eq. 2). In Eq.2, p represents the probability of the occurrence of a case/case pair, n_1 represent the total number of cases and n represents the total number of dip-tanks (controls + cases = $n_0 + n_1 = n$). The test statistic (eq. 3) was calculated for the null hypothesis assuming a hypergeometric distribution.

$$\sqrt{(E1 - E2)^2 + (N1 - N2)^2} \dots\dots\dots(\text{eq.1})$$

$$\text{Expected frequency} = E [m] = np = n \frac{\binom{2^{n_1}}{\binom{2^n}} = \frac{n_1 (n_1 - 1)}{n(n-1)} \dots\dots\dots (\text{eq. 2})$$

$$z = \frac{m + 0.5 - E [m]}{\sqrt{np (1-p)}} \dots\dots\dots(\text{eq. 3})$$

Clustering of FMD outbreaks in the PZV was evaluated using purely spatial, purely temporal and space-time scan statistics. Tests were performed using SaTScan v9.4 software [<http://www.satscan.org/>] based on a Bernoulli probability model (dip-tank affected yes/no) following the method described by Kulldorff and Nagarwalla (Estrada et al. 2008; Kulldorff and Nagarwalla 1995). The spatial range of the space-time scan analysis included all dip-tanks in the FMD PZV and the time range was the 12 years from 2005 to 2016. The null hypotheses were that the distribution of affected dip-tanks and the time frame of infection were random. Statistical significance for the identification of clusters was set as $p < 0.05$.

Spatial distribution of African Buffalo in KNP

The distribution of African buffalo within KNP were described based on the results of a previous study (Hughes et al. 2017) in which data were collected during both the dry (August 2012) and wet (January 2013) seasons using a random walk design. A predicted spatial distribution model was developed using a zero-inflated Poisson model built using 1 km² grid map of KNP (Hughes et al. 2017).

Results

There were a total of 201 dip-tanks within the PZV during the study period. In Mpumalanga Province, an estimated 91 329 cattle were distributed among 151 dip-tanks and in Limpopo Province, 42 417 cattle were distributed among 50 dip-tanks based on data from 2009. The highest cattle densities were observed in the northern part of Mpumalanga Province (Figure 2).

A total of 1040 cattle FMD cases were reported during the study period. These cases occurred within seven outbreaks and all outbreaks were due to infection with SAT serotypes (Table 1). In total, thirty-one dip-tanks were affected from a total of 201 dip-tanks in both provinces (151 Mpumalanga/50 Limpopo). Two dip-tanks within Limpopo Province experienced two independent FMD outbreaks each during the study. Four outbreaks and almost 75% (23/31) of the affected dip-tanks were in Mpumalanga Province.

SAT2 FMD outbreaks were more common in Mpumalanga and all SAT3 FMD outbreaks occurred in Limpopo Province. Descriptively, outbreaks in Mpumalanga Province took longer to resolve (range 210-540 days and 120-180 days for Mpumalanga and Limpopo respectively) and a higher proportion of affected cattle were reported (Table 1).

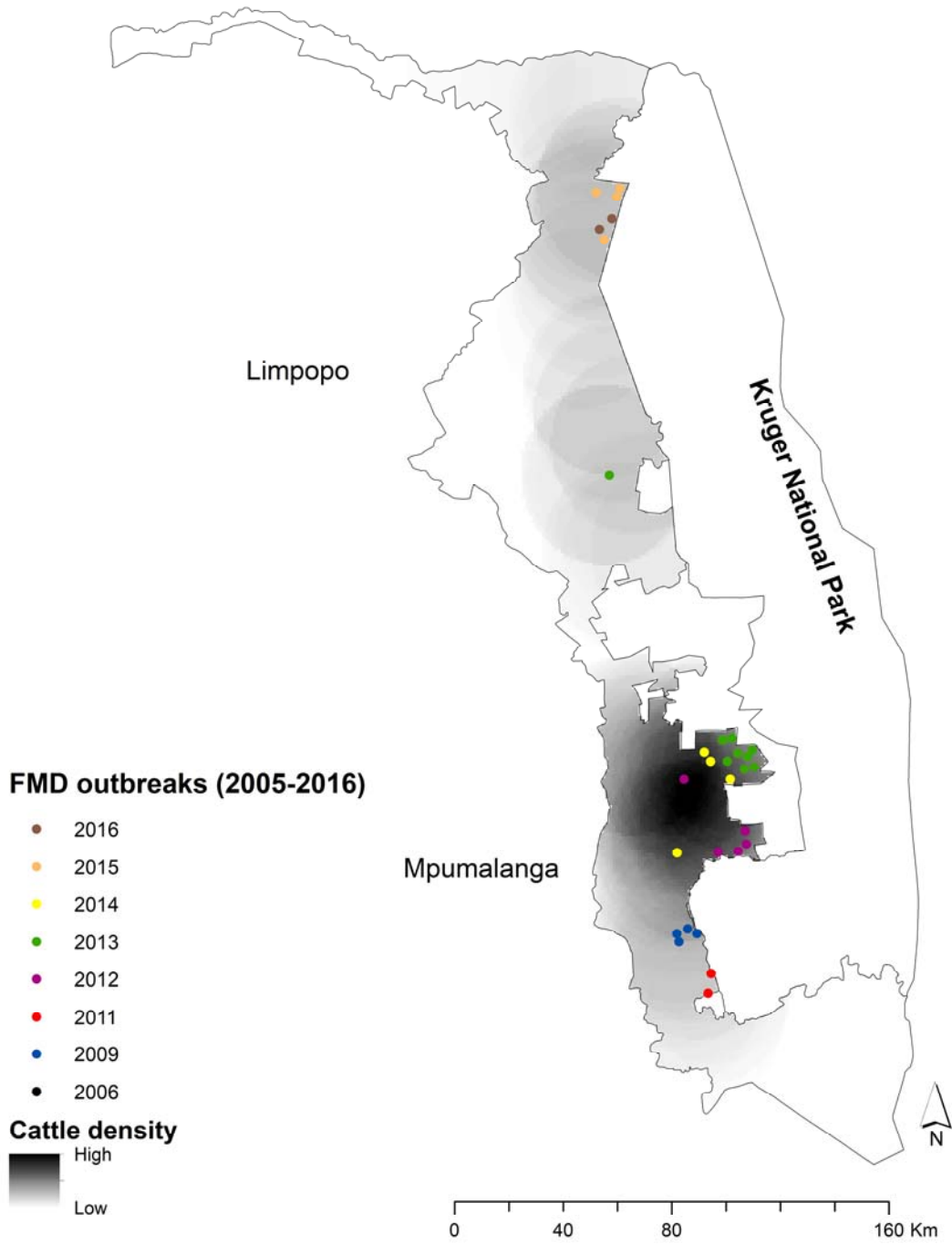


Figure 2: Point density estimation of 2009 cattle population in the protection zone with vaccination of South Africa in relation to 2006-2016 FMD outbreak locations (no outbreaks occurred during 2005)

In all the outbreaks that were recorded in this study, the first dip-tank to be infected was the closest dip-tank to the disease control fence; subsequently affected dip-tanks were always further away. The distance from a dip-tank to a wildlife reserve fence was shorter for the dip-tanks that experienced FMD outbreaks. The median (range) distances for FMD outbreak and non-outbreak dip-tanks were 2.5 km (0.1-10.9) and 8.4 km (0.1-57.9) respectively ($p < 0.001$). The interpolated CI were higher in Mpumalanga Province and the northern area of Limpopo Province (Supplemental Figure 1).

The spatial distribution of FMD affected dip-tanks appeared different based on FMDV serotype. SAT1 and SAT2 outbreaks tended to occur in southern and northern Mpumalanga respectively, while SAT3 was in the northern part of Limpopo Province (Supplemental Figure 2).

There was significant global spatial autocorrelation ($p < 0.001$) and the study identified two spatial and four spatiotemporal clusters of FMD outbreaks (Supplemental Figure 3). Three of these clusters were detected in Mpumalanga Province with the other being in the northern part of Limpopo. Three of the four high-rate clusters were close to a major road, while rivers crossed two high-rate areas (Figure 3). Most of the outbreaks occurred during the period 2012-2015 and the temporal model identified a single high-rate cluster for the years 2012-2015 (Supplemental Table 1).

During the wet season (August), a higher number of African buffalo were observed in close proximity to two spatiotemporal high-rate clusters in the southern part of KNP (Mpumalanga Province). In contrast, higher numbers of African buffalo were observed in the far north of Limpopo Province during the dry season (Figure 4). The index case of 2009, 2012 and 2013 spatiotemporal high-rate clusters were reported in the dry season, while the index case of the fourth spatiotemporal high-rate cluster (2015) was reported during the wet season

(Supplemental Table 1; Figure 4). The predicted African buffalo distribution suggested moderately higher numbers of African buffalo in the southern part of KNP close to two-high rate spatiotemporal FMD outbreak clusters (Figure 5).

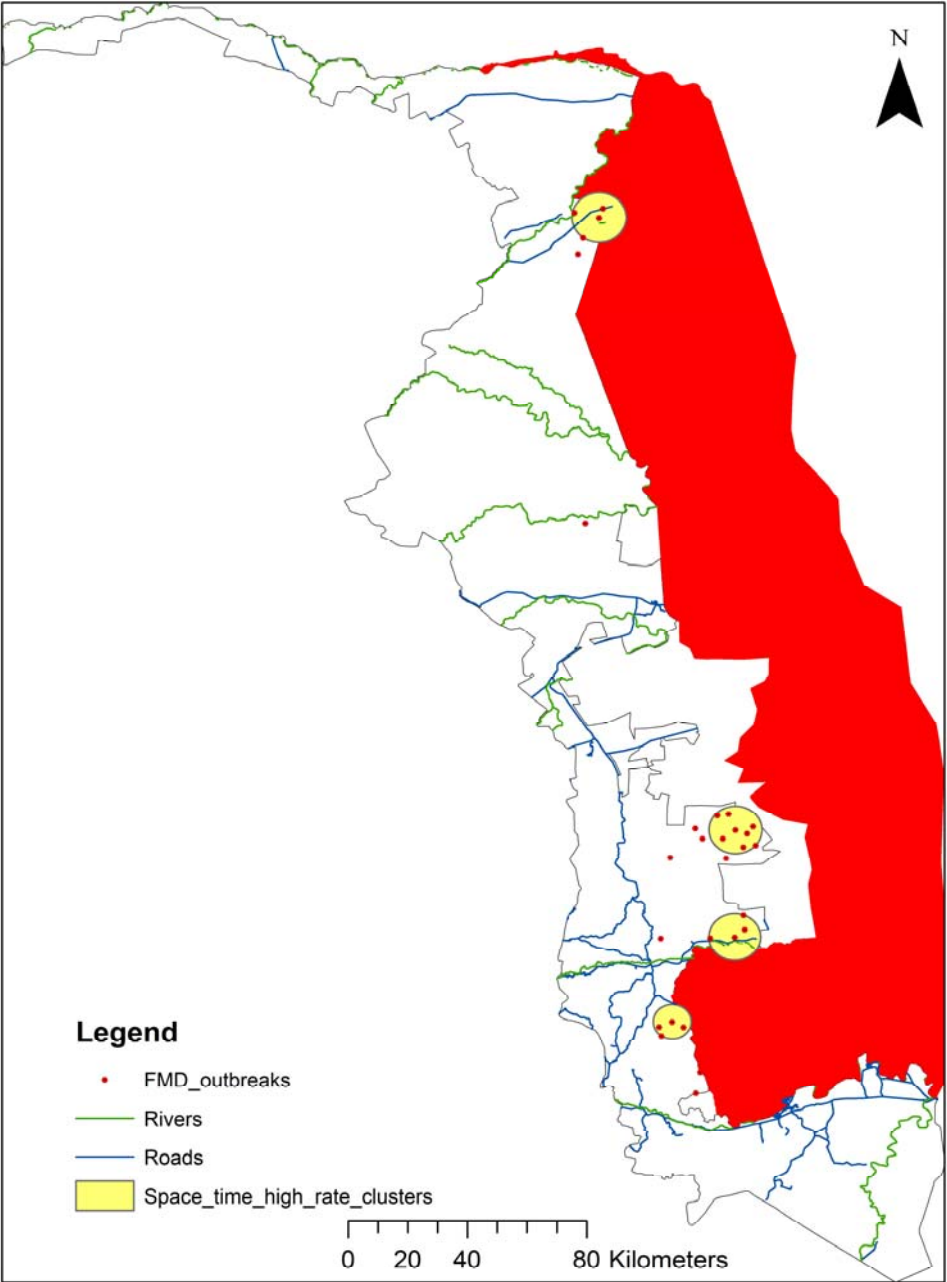


Figure 3: Space-time high-rate clusters of foot-and-mouth disease outbreaks in cattle (2006-2016) including roads and rivers in the protection zone with vaccination of South Africa

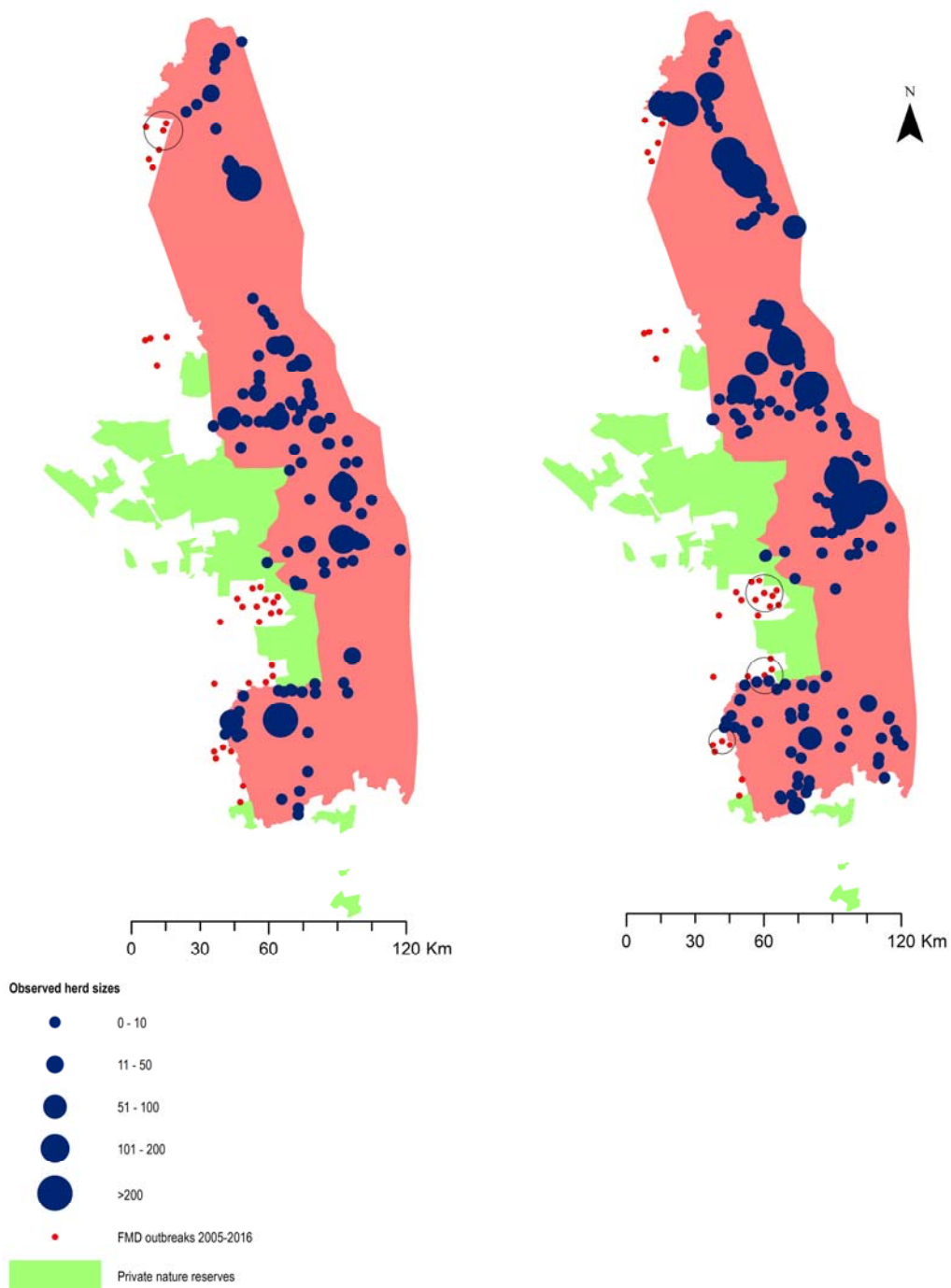


Figure 4: Space-time high-rate clusters of foot-and-mouth disease outbreaks in cattle (2006-2016) in relation to the observed African buffalo numbers within the Kruger National Park of South Africa during the wet season (January 2013, left pane) and dry season (August 2012; right pane)

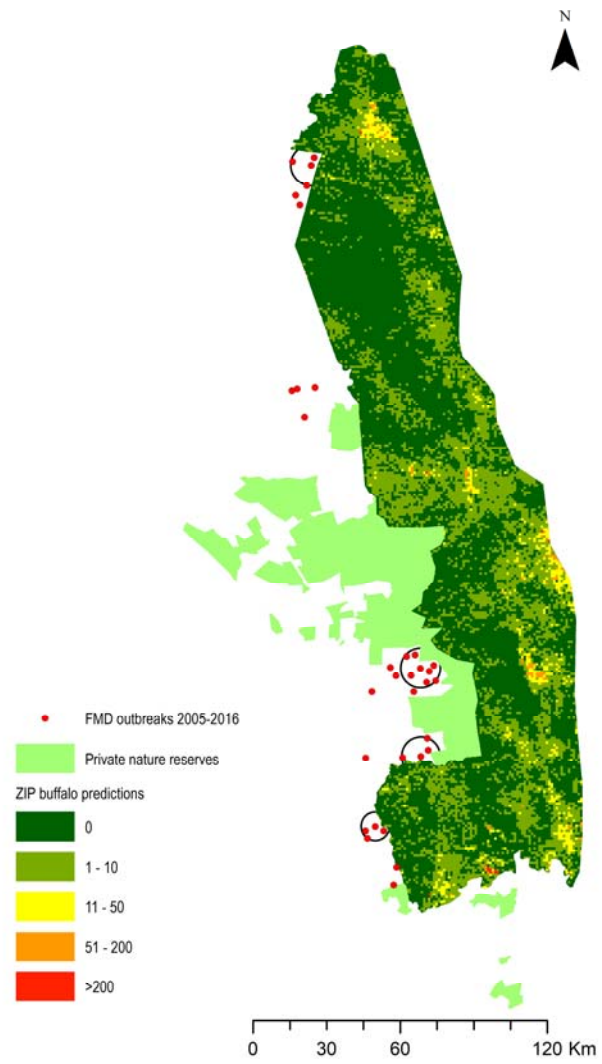


Figure 5: Space-time high-rate clusters of foot-and-mouth disease outbreaks in cattle (2006-2016) in relation to the predicted African buffalo density within the Kruger National Park of South Africa

Table 1: Foot-and-mouth disease (FMD) outbreaks within the South Africa FMD protection zone with vaccination, duration and seasonal comparisons (2005-2016)

Outbreak ID	Province	Duration (days)	Start of outbreak	End of outbreak	Total dip-tanks in province	Dip-tanks affected (n)	Serotype (SAT ¹)	Total susceptible animals (cattle) within affected dip-tanks	Total cases	Proportion of affected animals
1	Limpopo	150	07/2006	11/2006	50	2	SAT3	1300	42	0.03
2	Mpumalanga	270	09/2009	05/2010	151	4	SAT1	9505	757	0.08
3	Mpumalanga	240	12/2011	07/2012	151	2	SAT2	5510	38	0.007
4	Mpumalanga	120	04/2012	07/2012	151	5	SAT2	1750	16	0.009
5	Limpopo	180	07/2013	12/2013	50	1	SAT1 ²	1141	1	0.0008
6	Mpumalanga	570	08/2013	02/2015	151	12	SAT2	42903	131	0.003
7	Limpopo	210	12/2015	06/2016	50	5	SAT3	6060	55	0.009
						31		68169	1040	0.015

¹Southern African Territories.

²This outbreak affected other dip-tanks located in the FMD protection zone without vaccination (not part of the study area).

Discussion

Foot-and-mouth disease control in South Africa includes animal movement restrictions placed on cloven-hoofed species and products, prophylactic vaccination of cattle, clinical surveillance, and disease control fencing to separate livestock from wildlife reservoirs. Foot-and-mouth disease outbreaks in South Africa between 1970 and 2009 have been previously described (Dyason 2010). In the 34 years prior to our study period (1970-2004), seven SAT1, 14 SAT2 and one SAT3 FMD outbreaks were detected in cattle. No FMD outbreaks were identified in the protection zone between 1983 and 2000. However, six outbreaks occurred in cattle between 2000 and 2008. Five of these outbreaks were epidemiologically linked to contact with African buffalo (van Schalkwyk et al. 2016). During our 12-year study period, three SAT2 outbreaks and two outbreaks for SAT1 and SAT3 serotypes occurred within Limpopo and Mpumalanga Provinces. The proportion of affected cattle was lower in Limpopo Province compared to Mpumalanga and this might be due to a lower cattle density in affected dip-tanks of Limpopo. Sixteen percent (8/50) of Limpopo dip-tanks were affected compared to 21% (31/151) in Mpumalanga during the study period arguing against a difference in risk between provinces. The typical duration of a South African outbreak was descriptively longer than reports in Northern Hemisphere countries. The median duration of FMD epidemics in cattle herds was 67 days in FMD-free countries that applied depopulation with or without vaccination (Halasa et al. 2015). This should be compared to seven months for South Africa. The longer duration of FMD outbreaks might be attributable to the unrestricted movement of livestock within the disease management area (village/dip-tank; 3-6 km²), which typically constitutes 50-200 livestock owners. Also in contrast to control measures in Europe, stamping-out is not practiced during an outbreak.

The total number of outbreaks in our study was too small to formally test for seasonal effects. However, 57% (4/7) of outbreaks were reported during the dry season (April - September), which is when there is an increased occurrence of stray African buffalo from KNP (Jori and Etter 2016; van Schalkwyk et al. 2016). This finding is also consistent with the previous report (Dyason 2010) where the majority (70%) of outbreaks from 1970 - 2009 occurred between June and October. Contact between cattle and African buffalo has also been estimated to be higher during April - September (Brahmbhatt et al. 2012). During the dry season, villagers might graze their livestock in KNP increasing the chance of wildlife and domestic animal contact (Brahmbhatt et al. 2012).

There was a non-random distribution of FMD outbreaks in the PZV during 2005 - 2016. The cumulative incidence, duration of each outbreak and the total number of affected dip-tanks was higher in Mpumalanga compared to Limpopo. Mpumalanga had a high density of dip-tanks in close proximity to each other with high numbers of cattle in the province. The highest number of cattle were in the northern and southern area of Mpumalanga and the far north east of Limpopo. Descriptive results suggest a link between cattle densities and FMD outbreaks with higher cattle densities increasing the chance of FMD outbreak detection (Figure 2). This finding is consistent with previous research suggesting that cattle population density is positively associated with the risk of FMD outbreaks (Allepuz et al. 2015).

In the study area, the majority of private game reserves are either inside or adjacent to the PZV, increasing the chance of wildlife/domestic animal contact. FMD affected dip-tanks being closer to wildlife game reserve fences provides circumstantial evidence that outbreaks were a consequence of wildlife/cattle contacts possibly due to fence permeability. Proximity to national parks and potential wildlife reservoirs have been reported to increase the risk of FMD in other African countries (Allepuz et al. 2015). The western fence of the KNP has different

structural types, and thus susceptible to different degrees and causes of damage (Bengis et al. 2003). A section of KNP fence was damaged by a flood in 2000 and was without functional electrification (Ferguson and Jori 2010) for much of its length. This section was highly permeable to cattle and African buffalo in certain areas (Jori et al. 2011). Effective separation of wildlife and cattle is important to reduce risk of FMDV transmission (Dion and Lambin 2012).

Mpumalanga Province appeared to have higher risk for SAT1 and SAT2 outbreaks while SAT3 only occurred in Limpopo Province (Supplemental Figure 2). Historically, SAT3 was detected in cattle of Limpopo Province in 1979 and again in 2002 within an African buffalo herd outside KNP (Dyason 2010). SAT3 has not been reported in Mpumalanga suggesting that it is circulating within a reservoir restricted to Limpopo Province.

The areas of high-rate clustering (Supplemental Figure 3) occurred at the same locations as high cattle densities. In addition, dip-tanks in these areas were close to each other and in close proximity to game reserve fences. The only cluster that was identified in Limpopo Province included the two dip-tanks that experienced FMD outbreaks twice during the study period. Three of the high-risk areas contained a road network that could influence the control of animal movements, while another two included rivers (Figure 3).

In Tanzania, the risk of FMD is associated with proximity to main roads (Allepuz et al. 2015). Also, the movement of livestock along major roads contributed to the persistence of FMD during epidemic phases in Iran (Perez et al. 2005). Disease control fences that are near or crossed by rivers can be damaged during floods or not provide a secure barrier during times of extreme drought. The spatiotemporal dynamics of cattle/African buffalo contacts are influenced by animal interaction, landscape and fence breakage (Dion et al. 2011). Severe drought and animal congregation increase the risk of FMD outbreaks and spread within similar

endemic settings (Shiilegdamba et al. 2008). High-risk areas require intensive monitoring and maintenance of the disease control fence to reduce contact between wildlife and livestock.

The higher numbers of observed and predicted buffalo herds were descriptively associated with identified high-rate clusters, although they differed based on the season (Figure 4 and 5). Higher numbers of buffaloes were observed in the far north of Limpopo Province during the dry season within the area identified as a high-rate cluster. This finding is consistent with the reporting date of the first case (31 July 2006) during the 2006 FMD outbreak in the same area. A similar situation was observed in the far south during the wet season and one of the outbreaks located in the high-rate cluster in this area was reported on the 30th of December 2011. However, these findings were not consistent across all reported FMD outbreaks and causal associations cannot be identified by the current study design.

A limitation of this study was the use of maps based on spatial interpolation to identify high-risk areas. Spatial distances were calculated using straight line or Euclidean distances, which failed to capture the biological realism of disease spread. Spatial interpolation and cluster analyses are also data-driven approaches and prone to sampling bias. Such analyses might miss areas of high-risk because of non-homogenous surveillance efforts (Escobar and Craft 2016).

Although the middle point data for cattle populations in the study area does not fall in the midpoint of the analysis, these numbers were only utilized for cattle density mapping (Figure 2). The year 2009 was selected due to the availability of a complete dataset to avoid interpolating missing data for subsequent years.

The relatively small sample size was a limiting factor for further assessment of the global spatial autocorrelation. FMD outbreak clustering might have occurred due to areas being at high-risk for FMD introductions or dip-tank aggregation and local disease spread after

introduction. All animals within a dip-tank are seldom examined during an outbreak. Despite this fact, the identified cases were used to calculate cumulative incidences using the total number of animals in the population rather than the total number of animals examined (data are not recorded or reported). Another potential bias is that surveillance efforts might not have been uniform and FMD detection might have been biased towards dip-tanks with more cattle.

Commercial (intensive production) farms were excluded from this study. These farms typically follow strict biosecurity measures, with control of animal movements and unlikely contact with African buffalos. During the study period, only one FMD outbreak was reported on a commercial dairy farm in August 2010 and the farm was located in the FMD protection zone without vaccination (outside the study area). In addition, commercial farms within the FMD protection zone accounted for only 10% of the total cattle population in Limpopo Province and less than 5% in Mpumalanga Province (2012 census). Strict FMD control measures applied in these areas limit marketing of livestock and livestock products outside the FMD control areas and this discourages commercialized production in the area.

The identification of high-rate clusters can be used to support the implementation of risk-based surveillance and help mitigate the risk of FMD outbreaks at the wildlife interfaces of southern Africa. Wildlife-livestock contact, cattle density and road networks appear to play a role in FMD occurrence suggesting that animal movement and human activities might be drivers of FMD transmission and these require further study. The development of quantitative models could further assist with targeted FMD surveillance and control. Improved control is expected to lead to a more robust rural economy that would contribute to poverty alleviation in endemic countries.

Acknowledgments

The authors would like to thank all veterinarians and animal health technicians in Mpumalanga and Limpopo Veterinary Services for their support assisting with data collection.

This work was supported in part by the National Research Foundation of South Africa [grant numbers 90578, 76734] and the University of Pretoria.

Author's contributions

MM, GF, BB and BG conceived and designed study. MM, RL, OR and BB performed the research. MM and GF analyzed the data. GF contributed new methods or models. MM and GF wrote the paper. All authors read and approved the manuscript.

Statement of animal rights

Ethical approval was obtained from the Animal Ethics Committees of the University of Pretoria (No. v005-15).

Conflict of interest statement

None of the authors has any financial or personal relationship that could inappropriately influence or bias the content of this paper.

The South African National Research Foundation (NRF) provided partial funding for this study. NRF played no role in the study design nor in the collection, analysis and interpretation of data, nor in the decision to submit the manuscript for publication.

References

- Allepuz, A, Stevenson, M, Kivaria, F, et al (2015) Risk factors for foot-and-mouth disease in Tanzania, 2001-2006, *Transbound Emerg Dis*, 62, 127-136
- Baipoledi, EK, Matlho, G, Letshwenyo, M, et al (2004) Re-emergence of foot-and-mouth disease in Botswana, *Vet J*, 168, 93-99
- Bengis, RG, Grant, R, de Vos, V (2003) *Wildlife diseases and veterinary controls: a savanna ecosystem perspective. The Kruger experience: ecology and management of savanna heterogeneity*, (Island Press, Washington)
- Besag, J, Newell, J (1991) The detection of clusters in rare diseases, *J R Stat Soc Ser A Stat Soc*, 154, 143-155
- Bessell, PR, Shaw, DJ, Savill, NJ, et al (2010) Statistical modeling of holding level susceptibility to infection during the 2001 foot and mouth disease epidemic in Great Britain, *Int J Infect Dis*, 14, e210-215
- Brahmbhatt, DP, Fosgate, GT, Dyason, E, et al (2012) Contacts between domestic livestock and wildlife at the Kruger National Park Interface of the Republic of South Africa, *Prev Vet Med*, 103, 16-21
- Bruckner, G, Vosloo, W, Plessis, B, et al (2002) Foot and mouth disease: the experience of South Africa, *Rev Sci Tech*, 21, 751-761
- Cuzick, J, Edwards, R (1990) Spatial clustering for inhomogeneous populations, *J R Stat Soc Series B Stat Methodol*, 52, 73-104

- DAFF, 2014. Veterinary Procedural Notice for Foot-and-mouth Disease control in South Africa. In: FaF Department of Agriculture, Republic of South Africa (ed), 2014, (Department of Agriculture, Forestry and Fisheries, Republic of South Africa, Pretoria),
- DAFF, 2019. Positive Foot-and-mouth disease result in the Vhembe District of Limpopo. In: FaF Department of Agriculture (ed), 2019, (Department of Agriculture, Forestry and Fisheries, <https://www.daff.gov.za/docs/media/FMD%20media%20statement.pdf>),
- Dion, E, Lambin, E (2012) Scenarios of transmission risk of foot-and-mouth with climatic, social and landscape changes in Southern Africa, *Appl Geogr*, 35, 32-42
- Dion, E, vanSchalkwyk, L, Lambin, E (2011) The landscape epidemiology of foot-and-mouth disease in South Africa: A spatially explicit multi-agent simulation, *Ecol Model*, 222, 2059-2072
- Dyason, E (2010) Summary of foot-and-mouth disease outbreaks reported in and around the Kruger National Park, South Africa, between 1970 and 2009, *J S Afr Vet Assoc*, 81, 201-206
- Escobar, LE, Craft, ME (2016) Advances and Limitations of Disease Biogeography Using Ecological Niche Modeling, *Front Microbiol*, 7, 1174
- Estrada, C, Perez, AM, Turmond, MC (2008) Herd reproduction ratio and time-space analysis of a foot-and-mouth disease epidemic in Peru in 2004, *Transbound Emerg Dis*, 55, 284-292
- Fortin, M-J, Dale, MRT, ver Hoef, J (2013) *Spatial Analysis in Ecology*, Encyclopedia of Environmetrics, John Wiley & Sons, Ltd

- Ferguson, K, Jori, F (2010) Monitoring fence permeability along the western boundary fence of Kruger National Park, South Africa. In: HJ Ferguson K. (ed), *Fencing Impacts: A review of the environmental, social and economic impacts of game and veterinary fencing in Africa with particular reference to the Great Limpopo and Kavango-Zambezi Transfrontier Conservation Areas*, 2010, (Mammal Research Institute, Pretoria),
- Grubman, MJ, Baxt, B (2004) Foot-and-mouth disease, *Clin Microbiol Rev*, 17, 465-493
- Halasa, T, Toft, N, Boklund, A (2015) Improving the Effect and Efficiency of FMD Control by Enlarging Protection or Surveillance Zones, *Front Vet Sci*, 2, 70
- Hughes, K, Fosgate, GT, Budke, CM, et al (2017) Modeling the spatial distribution of African buffalo (*Syncerus caffer*) in the Kruger National Park, South Africa, *PLoS One*, 12, e0182903
- Hunter, P (1998) Vaccination as a means of control of foot-and-mouth disease in sub-saharan Africa, *Vaccine*, 16, 261-264
- Jori, F, Brahmabhatt, D, Fosgate, GT, et al (2011) A questionnaire-based evaluation of the veterinary cordon fence separating wildlife and livestock along the boundary of the Kruger National Park, South Africa, *Prev Vet Med*, 100, 210-220
- Jori, F, Etter, E (2016) Transmission of foot and mouth disease at the wildlife/livestock interface of the Kruger National Park, South Africa: Can the risk be mitigated?, *Prev Vet Med*, 126, 19-29
- Jori, F, Vosloo, W, Du Plessis, B, et al (2009) A qualitative risk assessment of factors contributing to foot and mouth disease outbreaks in cattle along the western boundary of the Kruger National Park, *Rev Sci Tech*, 28, 917-931

- Kitching, RP, Hutber, AM, Thrusfield, MV (2005) A review of foot-and-mouth disease with special consideration for the clinical and epidemiological factors relevant to predictive modelling of the disease, *Vet J*, 169, 197-209
- Kulldorff, M, Nagarwalla, N (1995) Spatial disease clusters: detection and inference, *Stat Med*, 14, 799-810
- Larska, M, Wernery, U, Kinne, J, et al (2009) Differences in the susceptibility of dromedary and Bactrian camels to foot-and-mouth disease virus, *Epidemiol Infect*, 137, 549-554
- Perez, AM, Thurmond, MC, Carpenter, TE (2006) Spatial distribution of foot-and-mouth disease in Pakistan estimated using imperfect data, *Prev Vet Med*, 76, 280-289
- Perez, AM, Thurmond, MC, Grant, PW, et al (2005) Use of the scan statistic on disaggregated province-based data: foot-and-mouth disease in Iran, *Prev Vet Med*, 71, 197-207
- Pfeiffer, DU, Robinson, T, Stevenson, M, et al (2008) *Spatial analysis of epidemiology*, (Oxford University Press)
- Premashthira, S, Salman, MD, Hill, AE, et al (2011) Epidemiological simulation modeling and spatial analysis for foot-and-mouth disease control strategies: a comprehensive review, *Anim Health Res Rev*, 12, 225-234
- Selvin, S, Ragland, KE, Chien, EY, et al (2004) Spatial analysis of childhood leukemia in a case/control study, *Int J Hyg Environ Health*, 207, 555-562
- Shiilegdamba, E, Carpenter, TE, Perez, AM, et al (2008) Temporal-spatial epidemiology of foot-and-mouth disease outbreaks in Mongolia, 2000 - 2002, *Vet Res Commun*, 32, 201-207

- Thomson, GR, Penrith, ML, Atkinson, MW, et al (2013) Balancing livestock production and wildlife conservation in and around southern Africa's transfrontier conservation areas, *Transbound Emerg Dis*, 60, 492-506
- van Schalkwyk, OL, Knobel, DL, De Clercq, EM, et al (2016) Description of Events Where African Buffaloes (*Syncerus caffer*) Strayed from the Endemic Foot-and-Mouth Disease Zone in South Africa, 1998-2008, *Transbound Emerg Dis*, 63, 333-347
- Vosloo, W, Bastos, AD, Sangare, O, et al (2002) Review of the status and control of foot and mouth disease in sub-Saharan Africa, *Rev Sci Tech*, 21, 437-449
- Yasrebi, H, Sperisen, P, Praz, V, et al (2009) Can survival prediction be improved by merging gene expression data sets?, *PLoS One*, 4, e7431