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Spatial and temporal epidemiology of FMD in Bhutan (2011–2019)

Sangay Letho[1,2*] and Chris Compton[2]

Abstract

Background Foot and Mouth Disease (FMD) is an important disease in livestock in Bhutan due to its significant social and economic impacts to the farmers as well as to the government. FMD outbreaks continue to occur every year with greater frequency in some parts of the country despite the implementation of control measures. It is imperative to understand the current patterns of the disease for planning effective control programs. Therefore, this study aimed to investigate the spatial and temporal patterns of FMD in Bhutan since the most recent national survey.

Methodology Nine year's (2011–2019) of national FMD outbreak data was used for this study. An investigation of global spatial autocorrelation was undertaken using the *K* difference function statistic and local spatial clusters of FMD outbreaks using Kulldorff's spatial scan statistic. Retrospective spatio-temporal analysis was conducted using a Bernoulli probability model with monthly aggregation of data. A non-stationary cosinor model was used to examine seasonality and trend of outbreaks.

Results The *K* function statistic detected significant global spatial autocorrelation of FMD outbreaks ($p < 0.02$) and Kulldorff's spatial scan statistic identified two outbreak clusters in west Bhutan- the first primary cluster ($p < 0.002$) with relative risk (RR) of 5.22 and radius of 19.77 km in Paro and Thimphu districts and the second primary cluster ($p < 0.006$, RR = 8.44 radius: 8.98 km) in Punakha and Wangdue Phodrang districts. The spatio-temporal scan test detected a single significant ($P < 0.001$) space–time cluster of 22 FMD outbreaks centred in south-west Bhutan with a radius of 60 km over an 8-month period in 2018—2019. The temporal analysis indicated that, on an average there were 0.5 (95% CI: 0.2—0.8) additional outbreaks per month in the seasonal winter peaks at 1.9 months (95% CI: 12.55 -3.64) compared with the overall monthly average.

Conclusion The western and southern regions of Bhutan have experienced the greatest overall incidence and significant spatial and spatio-temporal clusters of outbreaks of FMD during the period 2011—2019, These findings in districts in the western medium FMD risk surveillance zone threaten progress to control of FMD in Bhutan.

Keywords FMDV, Epidemiology, Risk, Outbreak, Bhutan, Spatial, Spatio-temporal

Introduction

Foot and Mouth Disease (FMD) is a clinically acute and highly contagious viral disease of cloven-hoofed domestic and wild animals [1]. It is caused by a virus which belongs to the member of genus *Aphthovirus* of family *Picornaviridae.* The clinical disease is characterized by fever, vesicular lesions in the mouth, teats and between the hooves of infected animals. The disease severity depends upon the virus strain, the degree of exposure, the age and breed of the infected animal and the degree

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of host immunity. Although the disease is rarely fatal in adult animals, the morbidity rate is 100% [2] among in-contact animals and can be fatal in young animals [3]. FMD causes significant economic impact due to reduced production in affected animals and restrictions in trade locally as well as globally. The disease is transmitted by various routes including direct contact with the infected animals, ingestion, inhalation and movement of infected animals and animal products. Measures commonly used to control and prevent FMD are mass vaccination, quarantine and attempts to stamp out the disease [4]. The disease is estimated to cause an annual production loss in the FMD endemic regions [5] of US$ 6.5 billion and incurs an additional vaccination cost of US$ 21 billion. In the FMD free countries, losses are estimated at more than US$ 1.5 billion annually because of constant efforts to prevent disease introduction including import controls from FMD endemic countries, FMD related research and sometimes vaccination [6].

In Bhutan, FMD is reported to occur in most districts [7] but more frequently in the southern districts sharing borders with India, less frequently in west, central and eastern districts and only sporadically if at all in the alpine areas [8]. Although the geographic and temporal distribution of FMD in Bhutan has been reported up to 2008 [9], no recent studies have been conducted to update the patterns of occurrence of FMD. Foot and mouth disease is an important disease in Bhutan due to its significant economic losses to the farmers and impacts on the country's economy through lost milk production, mortality of young animals, reduced fertility, impairment of draught power and ban of livestock products and loss of the markets for livestock products [8]. However, farmers do not seem to understand the economic impacts of the disease, possibly due to the low mortality rates in the adult animals [10] and lack of data on the economic impact of the disease.

The Government of Bhutan spends considerable resources to prevent and control FMD outbreaks by carrying out vaccination, disease-monitoring and surveillance activities. However, despite these efforts, FMD outbreaks are reported to occur every year with a greater frequency in some parts of the country [11]. Bhutan, together with other South Asian Association of Regional Cooperation (SAARC) member countries is working closely with European Union (EU), Food and Agricultural Organization (FAO), World Organisation for Animal Health (WOAH) and other internal organizations to implement the global control strategy of FMD management called Progressive Control Pathway of FMD (PCP-FMD) for effective long term control [11]. The current National FMD Control Program (NFMDCP) was based on the outcomes of joint technical project between FAO and Department of Livestock (DoL) [11] and on the findings of the Post-graduate study program [9] incorporating the approach of PCP-FMD. Based on this NFMDCP, Bhutan is divided into three risk zones (high, medium and low) based on the epidemiology of the disease, sharing of a border with neighbouring countries and road connectivity to guide the surveillance, vaccination and animal movement regulation activities [11]. The PCP-FMD control activities, if implemented, should enable countries to progressively increase the level of FMD control through 6 stages on the way to achieving disease-free zone status without vaccination. Currently, it is considered that Bhutan is at stage 2 of 6 stages which involves implementing risk-based control measures such as targeted surveillance, targeted vaccination and other measures based on risk zones. The current main objective of NFMDCP is to progress to stage 3 of the PCP-FMD which requires a revised, more aggressive control strategy that has the aim of progressive reduction in outbreak incidence and development of more active contingency and emergency preparedness plans, followed by elimination of FMD virus circulation in domestic animals in at least one zone of the country.

This research aims to describe the spatial and temporal pattern of FMD outbreaks in different FMD risk zones in Bhutan and discuss whether the current control measures have been effective in progressing to stage 3 of the PCP-FMD plan. Our objective is to provide up-to-date information to inform the risk-based surveillance and control measures for FMD implemented by regulatory authorities.

Materials and methods

Study area and study population

Bhutan is a tiny Himalayan landlocked country, geopolitically located in the South Asian region bordered by India in the east, west and south and China in the north. It lies between latitudes 26°N, and 29°N, and longitudes 88°E and 93°E [12]. The total land area of Bhutan is 38,394 square kilometres and it has a total human population of 727,145 [13]. Bhutan is administratively divided into 20 districts called Dzongkhags (Fig. 1) and further subdivided into 205 Gewogs or subdistricts. The Gewogs are composed of clusters of villages. Based on the livestock census, 2019, Bhutan had a total of 434,610 FMD susceptible livestock animals which includes cattle, sheep, yaks, goats, pigs and buffaloes [14]. Cattle are the most common susceptible animals constituting 69.72% of the total susceptible population followed by yaks (11.93%), goats (10.98%), pigs (4.61%), sheep (2.63%) and buffaloes (0.13%) [14].

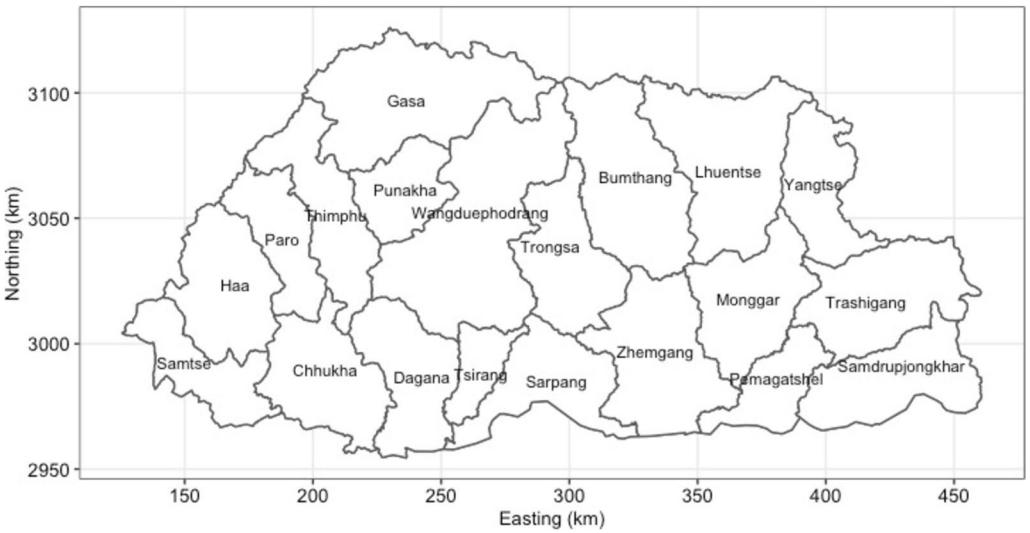

Fig. 1 Map of Bhutan depicting 20 Dzongkhags

Data sources and management

FMD is a notifiable disease in Bhutan as per the Livestock Act of Bhutan, 2001 [15] and the Livestock Rules and Regulation of Bhutan, 2017 [16]. Any suspected cases must be notified to the veterinary authorities for investigation and control measures. Both passive and active surveillance activities are conducted by a network of national, regional, district and subdistrict veterinary centres to control FMD. The detailed outbreak data are collected and maintained using the Transboundary Animal Disease Information System (TADInfo) at the National Centre for Animal Health (NCAH). When FMD is clinically diagnosed by the field veterinarians, additional data on the number and species of animals affected are recorded and geocoordinates for the affected village retrieved from a handheld device. Clinical cases are confirmed using a RT-PCR at NCAH laboratory and also at the world FMD reference laboratory, Pirbright, United Kingdom. For this study, electronic data on FMD cases in the country between the years 2011 and 2019 were obtained from NCAH.

The FMD village case data consisted of the date, month and the year, name of the affected village, district and subdistrict name, geocoordinates of the village, and number of cases and deaths by species. Data consisting of geocoordinates for 2287 villages were obtained from the Department of Forest and Park Services (DoFPS) and used as the population of villages in Bhutan. The geocoordinates of the NCAH case file were updated to those of the closest village in the DoFPS file where they differed. The shapefiles for administrative boundaries for country, districts and subdistricts of Bhutan were obtained from the Global Administrative Areas Database (http://www.gadm.org/country). The NCAH FMD village case data set was merged with the DoFPS standard village point data for spatial and temporal data analysis. All original geospatial data use the WGS84 Coordinate Reference System (EPSG:4326) and these were projected to Transverse Mercator Projection (DRUKREF 03, EPSG:5266) for distance-based analyses.

Case and outbreak definition

In the original NCAH FMD village case data set, an additional variable "outbreak" was coded as 1 or 0, with 1 indicating the village was the index case and 0 indicating the village was a secondary case related to the index case. The definition for a related case village within the same outbreak was that the next village case occurred within a time frame of 30 days. However, this definition was not applied consistently to all the outbreak records. For instance, in some records, cases occurring in the same village after 30 days from the most recent case were also considered as the same outbreak. Therefore, we created a consistent definition of an outbreak for this study based on information in published literature and knowledge of the geography of Bhutan. The FMD virus can remain infective on surfaces for up to 28 days although that is dependent on climatic conditions [7] and is known to disappear from most infected animal within 28 days, with the exception of carrier animals [17]. The windborne spread of FMD is confined to not more than 10 km [7], and local spread of the FMD can occur as close as within a two km radius [18].

Based on these information, three definitions of "village outbreaks" were created based on the Euclidean distance and time interval between any of the village cases:

two, five and ten km distance and a 30-day time interval in each combination. The index case in an outbreak was the first village case that was not preceded by the defined time and distance from another village case. Other village cases within the defined time or distance to the village index case or to another village case were denoted as part of the same outbreak. Because villages in Bhutan are mostly separated by physical barriers like rivers or streams, mountains or hills, a link between two cases beyond a radius of five km is not plausible, the five-km and 30-day cut point combination was considered the most suitable definition for Bhutan's situation.

Based on this criterion, an outbreak was defined as an occurrence of one or more cases of FMD in susceptible animals in a village within five km distance and within 30 days from any village case. If the case(s) occurred in an area beyond 5 km distance and or after 30 days from the last case of an outbreak, they were considered as part of a separate outbreak. A village outbreak could consist of one village case. An FMD case at an animal level was defined as any susceptible animal showing clinical signs with a characteristic lesions on the mouth, foot or teat, with or without a laboratory test confirmation.

Data analysis

We calculated descriptive statistics of the distributions and frequencies of village outbreaks and outbreak incidences by administrative districts and FMD surveillance risk zones. The annual and nine-year cumulative village outbreak incidences per 100 villages were calculated by dividing the number of village outbreaks by total number of villages at risk in the districts and in the three FMD risk zones between 2011 to 2019. The villages affected by FMD outbreaks were mapped and visualized by calendar year to examine the geographic pattern of outbreaks over time. We used packages in base R software (R version 4.3.3) to calculate descriptive statistics and spatial maps were created using the *sf()* and *st_sf()* functions from *sf* package [19] and *ggplot()* function from package *ggplot2* [20].

Spatial autocorrelation and clustering analysis

The geographic distribution of the FMD outbreaks may occur in different patterns such as clustered, dispersed or in a random pattern. With the null hypothesis that the outbreaks were randomly distributed against an alternate hypothesis that the outbreaks were clustered, we investigated global spatial clustering analysis using the Ripley's *K*-difference function. The *K*-function at a distance *K(s)* estimates the expected number of events of same type occurring within a distance *s* of a randomly chosen event, divided by the overall intensity of the points [21, 22]. When spatial autocorrelation is present, each event is likely to be closer to other members of the same event type and for small values of distances *s*, *K(s)* will be greater than expected [23]. *K* functions were computed for all the outbreak positive villages, $K_{case}(s)$, and for outbreak negative villages, $K_{control}(s)$. The observed difference function, defined by $D(s) = K\text{case}(s) - K\text{control}(s)$ represents the spatial aggregation of the cases over and above spatial aggregation of controls [21, 24]. Significant positive values of observed difference function, *D(s),* indicates the spatial autocorrelation. Monte Carlo permutations ($n = 499$) were used to permute the locations of cases and controls randomly, and the values of difference function *D(s)* were calculated for each permutation [23]. The upper and lower bounds of these permutations were then plotted along with the observed difference function *D(s).* Significant autocorrelation is denoted when the observed difference function deviates from the upper and the lower range of Monte Carlo simulation envelops [25]. In this statistical test, the assumption is made that point process is stationary, the direction of the neighbours does not affect the spatial process, and it reflects the second-order effect of a spatial process [26]. The observed difference function and the 95% confidence envelope were computed using the function *kdest()* from the package *smacpod* [27] in R software (R version 4.3.3).

We also undertook a Kulldorff's spatial scan statistic test based on the Bernoulli model [28] to investigate local spatial clustering of outbreaks. Each FMD outbreak positive village point was defined as case and the FMD outbreak negative village points as non-cases. This method constructs theoretical circular scan windows of varying radii around each case location throughout the study area and subsequently aggregates the next nearest neighbour to create zones [26]. Circular windows are identified within which the proportion of the cases are larger than the expected under the null hypothesis that the relative risk is equal. For each circle, the alternate hypothesis is that there is an increased risk of an outbreak in the circle compared to that of outside [23]. A circular window with the maximum spatial cluster size set to 50% of the study population was used. The risk of disease for each window was compared with the areas outside the circular window. To obtain the precise p values estimates and confidence limits, the test statistic was computed based on 499 Monte Carlo replications. Kulldorff's spatial scan statistic was performed using *spscan.test()* function from the package *spatstat* [29] in R software (R version 4.3.3).

Temporal analysis

We first visualised the temporal patterns of village FMD outbreaks over the study period with time series plots. We then used a non-stationary cosinor model to examine seasonality and trend of outbreaks during the study

period under the assumption that the seasonal patterns in the FMD outbreaks might vary over time due to seasonal changes in the exposures [30]. The non-stationary cosinor model uses a Kalman filter to decompose the time series into trend and seasonal components in order to apply to equally spaced time series data [30]. Markov chain Monte Carlo (MCMC) sampling is used in this model and the number of iterations was set to 5000, with 500 discarded as burn-in. The lambda parameter was set to 1/12 for the monthly data and cycles to 12 to evaluate an annual pattern [30]. The temporal analysis was performed using the *nscosinor(), invyrfraction()* functions from the package *season* [30] in R software (R version 4.3.3).

Spatiotemporal analysis

A data set was assembled for use in SaTScan software (v10.0 64-bit, https://www.satscan.org/). The data set consisted of villages with their Cartesian coordinates, their outbreak status over the study period and either the date of the index case for the outbreak for outbreak positive villages or a randomly selected date over the study period for outbreak negative villages. We undertook a retrospective space–time analysis of the data scanning for high rates using a Bernoulli probability model with monthly aggregation of data.

Results

Village outbreaks of FMD occurred in 19 of 20 districts (95%, Table 1) and 90 of the 205 subdistricts (44%) between the years 2011 and 2019. A total of 5492 animal cases and 138 outbreaks were reported in 124 locations (villages). Outbreaks of FMD were distributed throughout the country over the study period, with greater densities reported in southwestern regions and along the borders in 2011, 2012, 2016 and 2017, and additionally in the east in 2012 and 2014 (Fig. 2).

The greatest number of outbreaks were reported from Samtse district ($n=15$) followed by Chhukha ($n=14$) and Paro districts ($n=12$) (Table 1). Gasa district in the north did not experience any outbreaks during the study period. The greatest cumulative incidence of village outbreaks over the study period was reported from Paro Gewog (26.1%) followed by Punakha (18.2%). Paro district reported the greatest annual outbreak incidence (10.87%) in 2014. Chhukha, Paro and Samtse districts experienced FMD outbreaks almost every year during the study period. The greatest cumulative incidence of outbreaks per 100 villages from different FMD

Table 1 Cumulative (2011–2019) and annual incidence of reported foot and mouth diseases outbreaks in districts of Bhutan

Districts	Villages	Outbreaks	Cumulative incidence (2011–19%)	Annual outbreak incidence (%)								
				2011	2012	2013	2014	2015	2016	2017	2018	2019
Bumthang	86	7	8.14	0.00	0.00	0.00	1.16	3.49	0.00	0.00	1.16	2.33
Chhukha	127	14	11	0.79	0.79	1.57	0.00	0.79	2.36	1.57	1.57	3.15
Dagana	144	4	2.78	0.00	0.00	0.00	0.00	0.00	0.69	0.69	0.69	0.69
Gasa	36	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Haa	42	5	11.90	2.38	0.00	2.38	0.00	0.00	0.00	0.00	2.38	4.76
Lhuntse	143	1	0.69	0.00	0.00	0.00	0.00	0.70	0.00	0.00	0.00	0.00
Mongar	219	4	1.83	0.00	0.00	0.46	0.46	0.46	0.00	0.00	0.00	0.46
Paro	46	12	26.10	0.00	2.17	2.17	10.87	4.35	4.35	4.35	2.17	6.52
Pemagatshel	107	6	5.61	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.67	0.93
Punakha	55	10	18.20	0.00	1.82	0.00	0.00	3.64	0.00	0.00	7.27	7.27
Samdrup Jongkhar	184	10	5.43	0.00	1.09	1.09	0.54	0.00	1.63	0.54	0.54	0.00
Samtse	191	15	7.85	1.57	2.09	0.52	0.00	0.00	2.62	1.57	0.52	0.52
Sarpang	158	7	4.43	1.27	0.00	0.63	0.00	1.27	0.00	0.00	1.27	0.00
Thimphu	49	5	10.20	0.00	0.00	2.04	4.08	0.00	2.04	2.04	2.04	0.00
Trashigang	131	2	1.53	0.00	1.53	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Trashi Yangtse	68	5	7.35	1.47	0.00	0.00	2.94	1.47	0.00	0.00	0.00	1.47
Trongsa	80	2	2.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.50
Tsirang	112	1	0.89	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.89
Wangdue Phodrang	182	8	4.40	0.55	0.00	0.55	1.65	0.55	0.55	0.00	0.00	1.65
Zhemgang	127	6	4.72	0.00	0.79	0.00	0.00	2.36	0.00	0.00	0.00	1.57

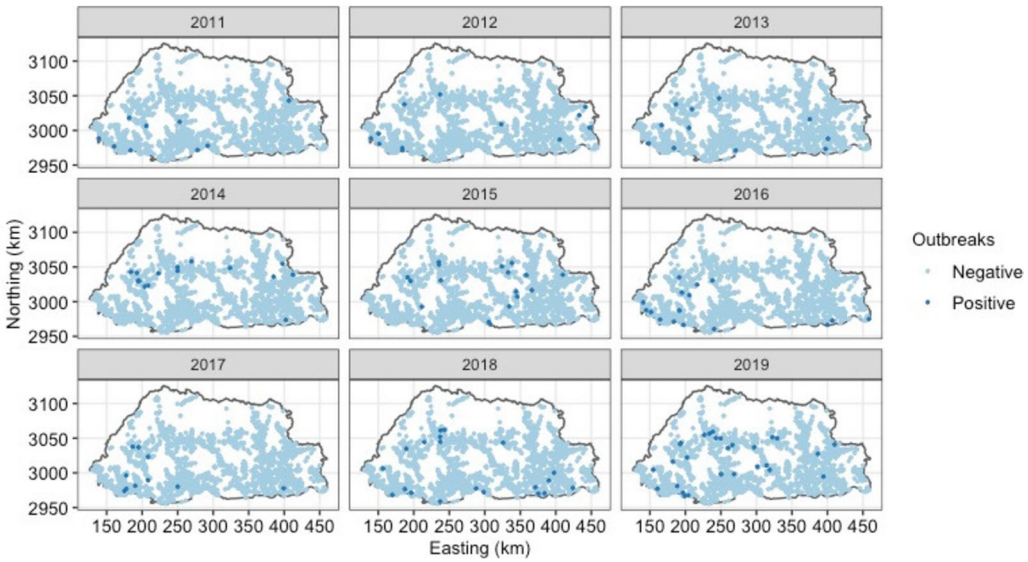

Fig. 2 Location of villages in Bhutan ($n=2287$). Dark blue dots (Positive) represent villages with reported foot and mouth disease outbreaks while light blue dots (Negative) represent villages that have not reported outbreaks between 2011–2019

risk zones was reported from the high risk zone (8.79%, Table 2).

There was significant spatial autocorrelation of FMD outbreaks at the global level indicated by a significant K function difference statistic ($p<0.02$, Fig. 3). It can be noted that, the D(s) values were above the upper limit of the approximate 95% confidence envelope beyond approximately 7 km, indicating that outbreak villages are more spatially clustered than controls over these distances. The Kulldorff spatial scan test identified two significant primary clusters of village outbreaks over the study period (Fig. 4). The first primary significant cluster ($p<0.002$) with relative risk (RR) 5.22 and radius 19.77 km was detected in the western region encompassing Paro and Thimphu districts while the second primary cluster ($p<0.006$, RR = 8.44 radius:8.98 km) was detected in the west central region encompassing Punakha and Wangdue Phodrang districts. Both the primary clusters were detected in medium risk FMD zones.

FMD outbreaks occurred throughout the year with greater numerical frequency recorded in the months of January ($n=13$), February ($n=22$), October ($n=14$) and December ($n=16$). The least number of outbreaks were reported in August ($n=5$) and the number of outbreaks varied between 10 and 11 for the remaining months. The peaks of outbreaks were observed during the end of the rainy autumn season (September to November) and the cold, dry winter season (December to February).

The estimated seasonal pattern and trend of outbreaks from a non-stationary cosinor model indicate only weak evidence of an increasing trend over the study period (Fig. 5). The mean amplitude indicated that, on an average there were 0.5 (0.2—0.8 95% CI) additional outbreaks per month in the seasonal winter peaks at 1.9 months (around February) (12.55 -3.64 95% CI) compared with the overall annual average.

The spatio-temporal test in SaTScan® detected a single significant ($P<0.001$) space–time cluster of 22 FMD outbreaks centred in south-west Bhutan including Wangdue

Table 2 Cumulative (2011–2019) and annual incidence of village outbreaks of foot and mouth disease in three FMD risk zones in Bhutan

Risk zones	Villages	Outbreaks	Cumulative incidence (2011–19%)	Annual village outbreak incidence in three risk zones(%)								
				2011	2012	2013	2014	2015	2016	2017	2018	2019
Low risk zones	473	10	2.11	0.42	0.00	0.21	0.00	0.00	0.00	0.21	0.21	1.06
Medium risk zone	1257	65	5.17	0.07	0.40	0.40	1.03	1.03	0.40	0.40	0.80	1.35
High risk zone	557	49	8.79	1.07	1.26	0.90	0.36	0.72	1.97	0.72	1.62	1.08

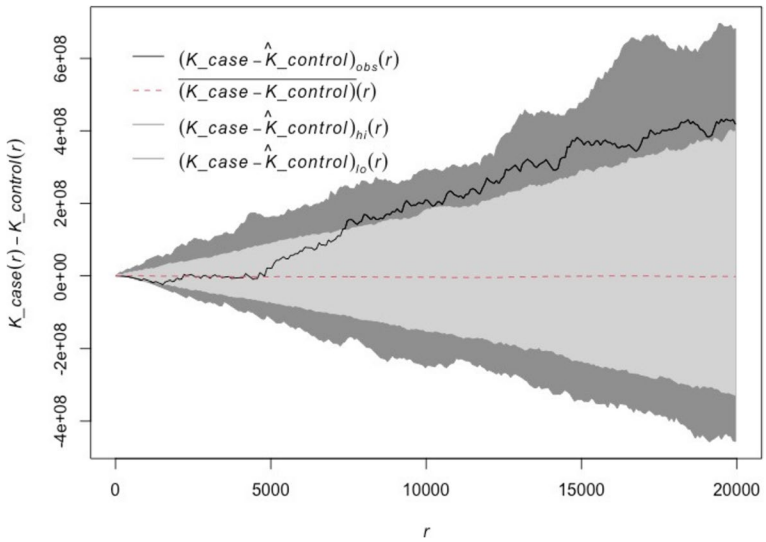

Fig. 3 K-function difference plot, *D(s)* and upper and lower range of 499 simulation envelopes based on the location of FMD outbreak positive villages (cases) and outbreak negative villages (controls) (2011–2019). The *D(s)* values are above the approximate 95% confidence envelope indicating that the outbreak positive villages are spatially clustered. The distance (r) is in metres

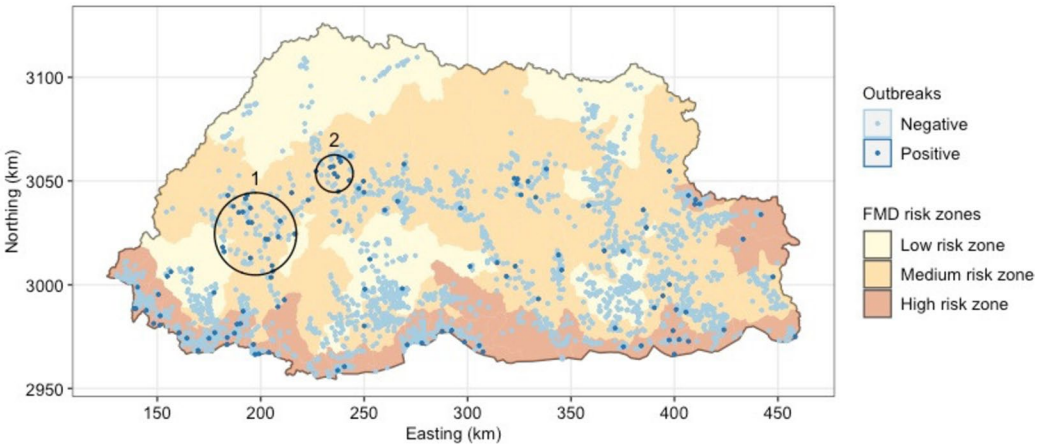

Fig. 4 Location of significant primary clusters of foot and mouth disease outbreak villages in Bhutan (2011–2019) detected by Kulldorff's spatial scan test. Dark blue dots (Positive) are villages with reported outbreaks (cases), and light blue dots (Negative) are villages with no outbreaks (non-case)

Phodrang, Punakha, Thimphu, Paro, Haa, Tsirang, Dagana, Chhukha and Samtse districts with a radius of 60 km over an 8-month period between December 2018 and Jul 2019 (Fig. 6).

Discussion

In this study, we described the spatial, temporal and spatiotemporal patterns of FMD outbreaks in Bhutan between 2011 and 2019 and discussed whether the current control measures have been effective in progressing to stage 3 of the PCP-FMD plan. We detected two statistically significant spatial clusters of FMD outbreaks and a single spatiotemporal cluster of outbreaks in the south west and west central districts of Bhutan. We did not however find strong evidence of either a seasonal pattern or increasing trend of FMD outbreaks over the study period. Since no zones or region has been declared free of FMD during the study period, this study suggest that the current control measures have been ineffective in progressing to stage 3 of the PCP-FMD plan.

Some patterns of FMD outbreaks revealed in the current study were similar to those previously reported. Districts located in proximity to the Indian border states experienced a greater frequency of outbreaks

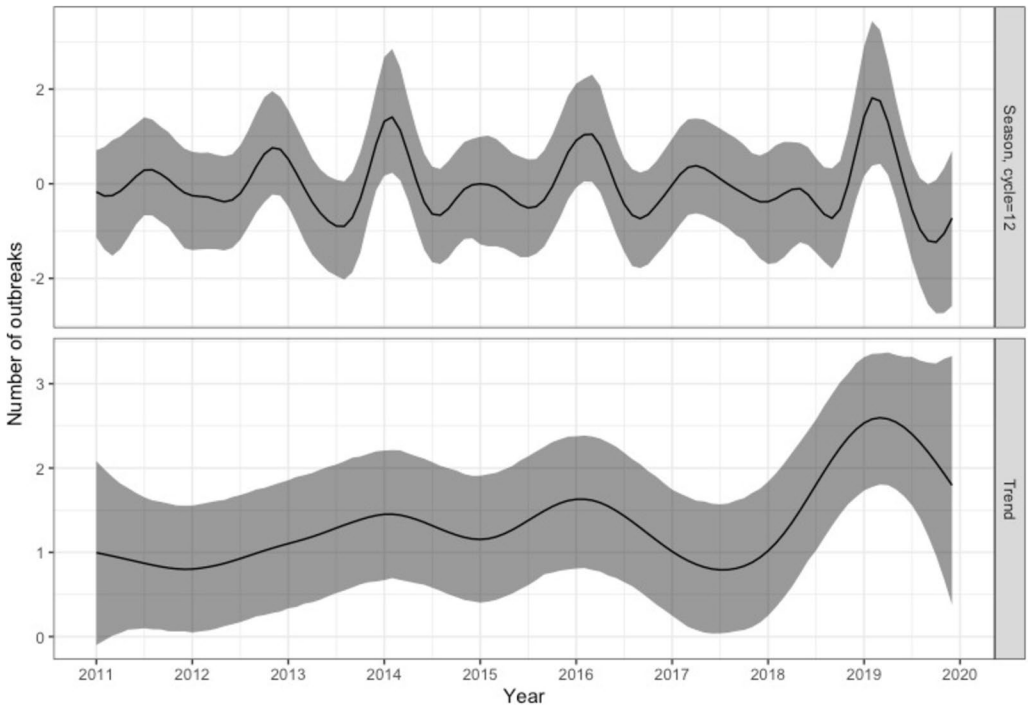

Fig. 5 Estimated number of foot and mouth disease outbreaks per month (trend) and monthly deviations of number of outbreaks per month from average (season) in Bhutan between 2009 and 2011 from a non-stationary monthly cosinor model, with mean (black lines) and 95% confidence intervals (grey shaded areas)

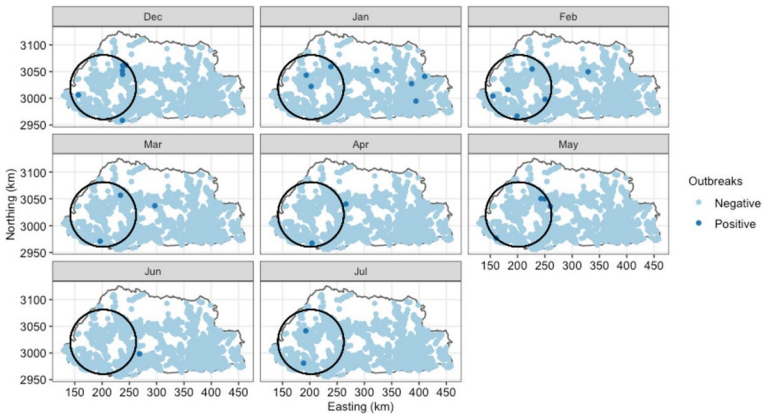

Fig. 6 Significant space–time clusters of FMD outbreaks over an 8 month period (Dec- July) between 2018–2019. Dark blue dots (Positive) are villages with reported outbreaks, and light blue dots (Negative) are villages with no outbreaks

which is consistent with the previous study [9] of data from 1996 to 2008. Among the southern districts, Chhukha had the greatest cumulative outbreak incidence of 11% among all the districts, reporting at least one outbreak every year. Most of the outbreaks in these districts occurred in the subdistricts which border Indian states in which FMD is endemic in the West Bangel [31], Assam [9, 32] and in Arunachal Pradesh [33]. The subdistricts in the south have long porous borders with India and anecdotal evidence suggests that there is congregation and mixing of animals from both the countries at common grazing and watering areas [9] which might have facilitated the cross-border transmission causing outbreaks. The frequent outbreaks in these subdistricts could also be related to the transboundary nature of the disease [10] due to movements of animals or animal products whether illegal or legal across these porous borders [9].

Districts in the eastern and central region experienced only sporadic outbreaks which is also consistent with previous reports [12]. The transhumant practices of migration of people and animals, and operation of barter trading system of animal products across the borders [34] might have played a role in the transmission of FMDV across the borders in Trashigang and Trashi Yangtse districts in the east. The low frequency of outbreaks in the districts including Trongsa, Zhemgang and Bumthang in the central Bhutan and Lhuentse, Pema Gatshel and Mongar in east could be related to their low cattle and human population densities [35]. However, the seasonal migration of cattle from Bumthang to other districts like Lhuntse, Monggar, Trongsa and Zhemgang could have contributed to the sporadic outbreaks in these districts. One of the important risks for spreading the disease over long distances is known to be the movement of animals and their products [36–39]. Movement of animals in Bhutan occurs at various levels as cattle sourcing from within and outside the country, seasonal migration, trading of draught animals and breeding bulls between villages, subdistricts and districts. Most of these informal animal movements occur without the knowledge and intervention of regulatory authorities. There is a high probability that the outbreaks could have been caused by the introduction of infected animals [40] during cattle sourcing from within the country. The cattle imported from India are also rarely tested for FMD during the quarantine period [9], and therefore, asymptomatic and or sub clinically infected animals might have played a role in the disease incursion and spread within the country. However, data were not available to investigate these hypotheses.

Gasa district in the alpine region did not report any outbreaks during the study period. Gasa, is the least populous district in the country and the presence of natural physical barriers such as snow-capped mountains and rivers in the north could have prevented the transmission and spread of FMDV via movement of animals or their products [9]. Tsirang district in the central region even though being surrounded by high FMD incidence districts, had few FMD outbreaks. Tsirang district has not reported any outbreaks since 1998 [9] and experienced only one outbreak in 2019. These findings were consistent with the findings of a previous survey [9]. On the other hand, we report a greater frequency of FMD outbreaks in the western districts, including Paro, Punakha and Wangdue Phodrang, compared with other districts. Paro had the greatest cumulative outbreak incidence (26.1%) followed by Punakha (18.2%) and Haa (11.9%) districts. The greater rate of occurrence of FMD in these regions may be associated with the greater number of susceptible species, high human population density and increased human activities [35]. Livestock rearing has become intensive in most of the subdistricts of western regions; however, the extensive system is still practised in many villages where the cattle are let out for grazing in forests. This open forest grazing practice leads to mixing of animals from villages at the common grazing areas and water points predisposing the disease transmission and spread [41]. Another reason could be the presence of road networks [35] in almost all the villages in the western region which facilitate the movement of the animals and humans via motorable networks and transmission of the disease [35].

The spatial pattern of disease outbreaks indicates both spatial heterogeneity and spatial dependence indicating both underlying long-distance and local causal factors. Ripley's *K*-function difference test identified global autocorrelation of FMD outbreaks villages from 11 km to at least 20 km. This finding is not unexpected as villages in close to one another likely share the same risk factors for incursion of the infectious pathogen FMDV. Kulldorff's spatial scan test identified significant local clusters in the western and west-central region over the study period. Additionally, a significant space–time cluster of outbreaks was identified in the same geographic region in the period between late-2018 and mid-2019. The detection of these spatial clusters of FMD over the entire study period, a space–time cluster over a limited time period and elevated frequency of FMD in the western and west-central region is a new finding of this study. Possible reasons for these patterns have been previously discussed but further cause could include the expansion of the existing FMDV or introduction of the new serotypes in the region [42, 43]. Therefore, further study is worthwhile to identify FMDV serotypes circulating in different areas in the country to ensure that the serotypes used in local vaccination programs match those of the wild virus. Also, because these regions are in the medium risk zones, they are only vaccinated annually compared with the southern regions in high-risk zone which are vaccinated twice a year as recommended for maximum immunity. However, there is a need to further investigate the potential risk factors for these changes in the epidemiological pattern of FMD to find out the potential drivers related to the shift in the endemicity of the disease in these interior and medium risk zones of Bhutan to inform disease control measures.

The evidence of a seasonal pattern of FMD occurrence from this study is not strong, but suggest that although outbreaks and cases occur throughout the year, they appear to peak in winter. This apparent pattern could be associated with migration of people and animals to the warmer areas in the south, which takes place during the winter months. Cattle-procuring activities in

most of the districts are also carried out during dry and cooler seasons to avoid stress to the animals associated with the heat of summer. These anthropogenic activities could have contributed to the increased number of FMD outbreaks during winter seasons. The study also demonstrated weak increasing trend of FMD occurrence. It was not able to demonstrate whether the increase in the trend could be linked to control measures; however, annecdotal reports suggest that an antigenic mismatch between the vaccine strain and the field virus and delayed response to outbreak through vaccination [44] could be one reason for frequent outbreaks. The scarceness of cross protection between the FMD virus serotypes and incomplete protection between some subtypes affects the potency of the vaccines and further [45], the inefficiency of existing vaccines caused by emergence of new variants of FMD virus can contribute to failure to control FMD by vaccination [5]. Besides, farmers also tend to avoid the biannual vaccination due to the temporary side effects such as temporary milk reduction and abortion [46] which also could be one of the reasons to increasing trend of FMD occurrence.

This study has several limitations related to the quality and range of variables available for analysis. First, in the FMD animal case data, there might have been underreporting of the cases. Once the outbreak has been confirmed in a village, all the follow-up animal cases might not have always been reported and recorded. This may have meant that the impacts of the FMD were underestimated, particularly in small ruminants, a well-recognised problem [9]. Second, our definition of the outbreaks based on the Euclidean distance of 5 km and time interval of 30 days between cases rather than using findings from an epidemiologic investigation might have led to errors in the calculation of the locations of some village outbreaks. However, we considered this possible error to be less problematic than use of the original data where index villages for outbreaks were inconsistently defined. Third, the spatial data set containing 2287 villages does not fully represent the actual number of villages in the country although it was the most complete data set available for this analysis, and therefore might also have led to errors in the spatial analyses. Fourth, the lack of accurate or complete data on possible risk factors for the outbreaks prevented further investigation of their causes. However, despite these limitations, we believe that it was still possible for us to describe the epidemiological patterns of FMD in Bhutan with sufficient accuracy to meet our study aims and objective.

The key objective of NFMDCP is to progress from stage 2 to stage 3 of the PCP-FMD. This requires a revised, more aggressive control strategy that aims to progressively reduce outbreak incidence, and then eliminate FMD virus circulation in domestic animals in at least one FMD risk zone in the country [47]. However, the current result reveal little progress towards that objective because there was a similar distribution pattern of FMD outbreaks to the previous survey.

This indicates that the current preventive and control measures were insufficient to achieve the objective of current NFMDCP. Therefore, we recommend that the FMD control programs in these FMD risk zones should be re-evaluated. There is also a need to build capacity to design appropriate studies to determine the relevant risk factors for FMD incursions and spread, conducting risk assessments, risk management and socio-economic studies. The data from the laboratory and epidemiological information from the field should be integrated to get a meaningful interpretation and implement appropriate control measures. Continued surveillance, timely information sharing on FMD outbreaks, inter-district cooperation, early detection and rapid response and simultaneous adoption of control measures are imperative to control the disease. Currently, NFMDCP implements the vaccine-based control policy which recommends that vaccination should be carried out bi-annually in high-risk zones and annually in medium and low-risk zones with a minimum of 80% coverage, but these are seldom achieved due to logistic challenges. The current annual vaccination protocol is reported to provide immunity for only about 4–6 months [48] which creates an opportunity for the virus to spread in the population in the remaining months of the year. Therefore a need to implement bi-annual vaccination strategy in both the high and medium risk zones ensuring more than 80% coverage. Also importantly, quality-assured FMD vaccines of matching serotypes should be used in the vaccine-based control policy. Studies [48, 49] have indicated that initial vaccine administration followed by a booster vaccine after 4–6 weeks and then subsequent boosters administered after six months allowed sufficient time to develop protection. Finally, for future FMD vaccination campaigns, it is also important to consider the transhumance practices and vaccinate the migrating herds before and after the migration. Therefore, in regions where only an annual vaccination is administered, the vaccination campaigns must be planned prior to the high-risk period of the dry and cold winter season.

In conclusion, results from this study indicated that a high frequency of FMD outbreaks occurred in the western and southern regions of Bhutan in the period 2011 to 2019 and that local spatial and spatio-temporal clusters of village outbreaks occurred in specific areas of western and west central regions. FMD outbreaks occurred throughout the year with peaks in the winter seasons and with a weak increasing trend over the years. These

epidemiologic findings and our recommendations may assist the policymakers in planning when and where the preventive and control measures should be strengthened and implemented. It is essential to further understand the factors causing the epidemiological patterns in space and time of the disease to improve the efficiency of allocation of resources for FMD control in Bhutan.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
The main manuscript and figures were prepared by Sangay Letho. Chris Comptom helped in analysing the data, reviewing the manuscript again and again with feedbacks, comments and guidance. Both the authors gave a final review before submission.

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Data availability
The dataset analysed in this study is available as supplementary file.

Declarations

Ethics approval and consent to participate
The study was conducted as part of the masters research program and no ethical approval was necessary.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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