Received: 24 July 2020 | Revised: 6 May 2021 | Accepted: 10 May 2021

DOI: 10.1111/mec.15991

ORIGINAL ARTICLE

MOLECULAR ECOLOGY WILEY

Phylogeographic analysis of foot-and-mouth disease virus serotype O dispersal and associated drivers in East Africa

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Funding information
Cooperative Biological Engagement Program of the United States Department of Defense, Defense Threat Reduction Agency [agreement #8802]; Agricultural Research Service, United States Department of Agriculture [CRIS project #1940-32000-061-00D]; AM was supported by the National Institute of Food and Agriculture, United States Department of Agriculture [grant #2016-38420-25288]. SD is supported by the Fonds National de la Recherche Scientifique (FNRS, Belgium)

Abstract

The continued endemicity of foot and mouth disease virus (FMDV) in East Africa has significant implications for livestock production and poverty reduction, yet its complex epidemiology in endemic settings remains poorly understood. Identifying FMDV dispersal routes and drivers of transmission is key to improved control strategies. Environmental heterogeneity and anthropogenic drivers (e.g., demand for animal products) can impact viral spread by influencing host movements. Here, we utilized FMDV serotype O VP1 genetic sequences and corresponding spatiotemporal data in order to (i) infer the recent dispersal history, and (II) investigate the impact of external factors (cattle density, human population density, proximity to livestock markets, and drought) on dispersal velocity, location, and direction of FMDV serotype O in East Africa. We identified statistical evidence of long-distance transmission events, and we found that FMDV serotype O tends to remain circulating in areas of high cattle density, high human population density, and in close proximity to livestock markets. The latter two findings highlight the influence of anthropogenic factors on FMDV serotype O spread in this region. These findings contribute to the understanding of FMDV epidemiology in East Africa and can help guide improved control measures.

KEYWORDS
Bayesian inference, disease ecology, environmental factors, landscape phylogeography, molecular epidemiology, spatial analysis

1 | INTRODUCTION

Although foot-and-mouth disease (FMD) has been eradicated in most developed countries, the disease continues to have substantial impacts in developing countries, where relatively more people are dependent on livestock production for financial and food security (Knight-Jones & Rushton, 2013). Infection with foot-and-mouth disease virus (FMDV) causes vesicular lesions in cloven-hooved animals, affecting animal welfare and resulting in substantial short and long-term production losses (Perry & Rich, 2007). FMDV is transmitted primarily through direct contact via respiratory droplets but may also be indirectly transmitted via contaminated objects (Alexandersen & Mowat, 2005). Like other members of Picornaviridae, FMDV is genetically diverse, with seven distinct serotypes (O, A, C, Asia 1, and the Southern African Territories, SAT 1, 2, and 3) (Bachrach, 1968). The genetic diversity of FMDV is a result of RNA polymerase lacking proofreading ability, leading to a high nucleotide substitution rate and the ability to adapt to changing environments. The FMDV genome is comprised of positive-sense, single-stranded RNA encoding structural proteins (VP1–VP4), which form its viral capsid, and 10 nonstructural proteins. The structural protein VP1 contains an essential cell receptor recognition site in the apex of the G-H loop which, together with VP1's C-terminus, forms key neutralizing epitopes. As an important immunogenic site, the VP1 coding region has high variability and therefore is often the focus of FMDV molecular epidemiology studies (Bastos et al., 2001, 2003; Samuel & Knowles, 2001; Sobrino et al., 2001; Tekleghiorghis et al., 2016). Although the genetic diversity of FMDV presents unique challenges to its control, this diversity creates the opportunity to better understand drivers of transmission.

Recently, Bayesian phylodynamic models have become central to understanding the epidemiology of RNA viruses. Combined with spatiotemporal metadata, genetic sequences can be utilized to reconstruct pathogen transmission histories (Drummond et al., 2003). For example, Dellicour et al. (2018) demonstrated that major urban areas were crucial in dissemination of the 2014–2015 West Africa Ebola virus outbreak, Lu et al. (2017) identified geographic hot spots for diffusion of avian influenza virus in China, and Streicker et al. (2016) predicted invasion routes of vampire bat rabies in South America. As sequencing technologies become more accessible, opportunities for constructing a more comprehensive view of the epidemiology of viruses, including FMDV, are becoming more abundant (Knight-Jones et al., 2016b; Lycett et al., 2019).

Thus far, efforts to control FMD in East Africa have been informed by control strategies from outside Africa and have included vaccination and quarantine in response to outbreaks (Muleme et al., 2012). However, these approaches have not been effective in East Africa due to a number of factors. For example, significant FMDV genetic diversity exists in East Africa, including intraserotypic diversity (Balinda et al., 2010; Kasanga et al., 2015; Mwiine et al., 2019; Sangula et al., 2010). Movement of animals and animal products, which are frequent and largely unregulated in East Africa, are considered a key risk factor for transmission of FMDV (Di Nardo et al., 2011; Fèvre et al., 2006; Kasambula et al., 2012; Motta et al., 2017). Finally, difficulty accessing sufficient doses of quality vaccines means that mass vaccination is currently not feasible in East Africa (Railey & Marsh, 2019). A comprehensive understanding of the factors sustaining FMD transmission in endemic settings is needed so that tailored, strategic control measures can be devised (Knight-Jones et al., 2016a; Tekleghiorghis et al., 2016).

In Southern African, the role of wildlife as reservoirs of FMDV has been well established. However, recent studies suggest the role of wildlife in the maintenance of FMDV in East Africa is less important than in Southern Africa (Casey-Bryars et al., 2018; Omondi et al., 2020). Moreover, serotype O is responsible for most reported FMD outbreaks in East Africa, whereas buffalo have been shown to maintain and transmit SAT viruses, but not serotype O viruses, to livestock species (Vosloo et al., 2002). Previous studies have also suggested there is more long distance spread of FMDV in East Africa than in Southern Africa (Tekleghiorghis et al., 2016). More frequent long-distance transmissions have been attributed to two factors: (i) the extent of migratory animal husbandry systems such as seasonal transhumance. These migratory patterns are somewhat predictable but are also evolving in the long-term in response to climate change, and (ii) animal trade, particularly movement of animals to livestock markets to meet growing demands for animal products (Di Nardo et al., 2011; Muleme et al., 2012; Tekleghiorghis et al., 2016). Because of the porous nature of borders in East Africa and frequent movement of animals across borders, Uganda, Kenya, and Tanzania are considered a collective high-risk area, therefore a regional approach is critical to understanding FMDV in this region (Di Nardo et al., 2011). Earlier studies have supported the occurrence of transboundary FMDV transmission in East Africa (Balinda et al., 2010; Duchatel et al., 2019; Munsey et al., 2019) and confirmed serotype O as the most prevalent serotype in this region (Ayelet et al., 2009; Kasambula et al., 2012; Mwiine et al., 2019; Wekesa et al., 2015).

Identifying drivers of FMDV transmission is key to improved control strategies. Environmental heterogeneity and anthropogenic drivers (e.g., demand for animal products) can influence host movements, thereby impacting viral spread. In this study, we aimed to relate FMDV VP1 genetic sequences with corresponding spatiotemporal data in order to (i) infer the recent dispersal history, and (ii) investigate the impact of external factors on dispersal velocity, location, and direction of FMDV serotype O lineages in East Africa. Here, we use "lineage" in the generic sense, that is, sharing a common ancestor, not in reference to FMDV-specific nomenclature. A large repository of recent serotype O VP1 sequences available from our nationwide Uganda study (Mwiine et al., 2019; Velazquez-Salinas et al., 2020) offers unique opportunities to examine drivers of transmission due to the relatively fine-scale resolution of sequences, thus improving our understanding of regional transmission patterns in an endemic setting.

2 | MATERIALS AND METHODS

2.1 | Virus sampling

FMDV viral sequences were collected as part of an FMDV surveillance study in Uganda conducted from 2014 to 2017. The study was approved by Uganda Institutional Animal Ethics Review Committee (SBLS/REC/13/016), Makarere University. The cross-sectional study has been previously described in Mwiine et al. (2019), Munsey et al. (2019), and Velazquez-Salinas et al. (2020).

2.2 | Sequence analysis

Sequencing was performed at Plum Island Animal Disease Center as previously described (Mwiine et al., 2019). FMDV serotype O VP1 sequences generated as part of this study (n = 175) (Mwiine et al., 2019; Velazquez-Salinas et al., 2020) were combined with GenBank sequences (n = 386), which were selected using the NIAID Virus Pathogen Database and Analysis Resource (ViPR, http://www.viprbrc.org/) (Pickett et al., 2012). GenBank isolates which met all the following criteria were considered: (i) had a known isolation year, (ii) collected in Africa, and (iii) had a known isolation location to at least the level of subnational administrative unit. The administrative unit of collection was used to generate geographic coordinates for GenBank samples. Sequences were aligned using CLUSTALW in MEGA (v10.0.5) (Kumar et al., 2018). An initial phylogenetic tree was constructed using BOOSTER FASTTREE with 1000 bootstrap replicates (Figure S1) (Lemoine et al., 2018). Next, we selected a monophyletic clade which contained sequences generated during this study and represented clades recently circulating in East Africa (n = 231). In order to reduce the computational burden of the proceeding analyses, we performed subsampling of the monophyletic clade aimed at preserving (i) the structure of the chosen clade, and (ii) its complete spatial-temporal diversity. An example of the subsampling strategy is shown in Figure S2. Subsampling was first performed using TreeTrimmer which dereplicates trees by selecting samples closest to the median branch length while retaining the original tree topology (Maruyama et al., 2013). We utilized TreeTrimmer to select one sequence per time-location combination. This subsampling step eliminated 25 sequences. Because TreeTrimmer only dereplicates a clade if all samples in the clade are comprised of the same time-location combination, a second manual subsampling step was performed within clades with multiple time-location combinations represented. Within these clades, we retained only one sequence among those with 100% nucleotide identity which were collected from the same herd on the same date. This second subsampling step eliminated 58 sequences. The final data set contained 147 sequences with the following geographic distribution: Uganda: n = 65; Kenya: n = 64; Tanzania: n = 15; Ethiopia: n = 3. A map of isolate locations is displayed in Figure S3. Sampling data and GenBank accession numbers are summarized in Table S1.

2.3 | Phylogeographic analysis

We estimated the dispersal history of FMDV lineages using the continuous phylogeographic method implemented in BEAST (v 1.10.4) (Lemey et al., 2010; Suchard et al., 2018). First, the temporal signal of the data was evaluated using TEMPEST (v1.5) (Rambaut et al., 2016). Using a linear regression of phylogenetic root-to-tip distances against the sampling dates, a strong temporal signal was demonstrated by a positive correlation (R^2 = .73). JMODELTEST (2.1.10 v20160303) identified general time-reversible, gamma distribution (GTR+Γ) as the best nucleotide substitution model (Darriba et al., 2012). Using BEAST on the CIPRES Science Gateway (www.phylo.org), a phylogeographic model was constructed in which tree branches represent time, and tree tips and inferred internal nodes are associated with geographic locations. A Cauchy relaxed random walk model was used for inference of the spatial locations. Under this framework, the "dispersal velocity" of a branch can be estimated from the distance between spatial coordinates of the node and the tip, and the temporal duration of the branch. Dispersal velocities can vary among phylogeny branches, allowing one to test whether environmental factors correlate with branch dispersal velocity (Dellicour et al., 2016).

Combinations of molecular clock models (uncorrelated lognormal relaxed, strict) and coalescent population models (constant, exponential, GMRF Bayesian skyride, logistic) were compared using path sampling/stepping-stone sampling (Baele, Lemey, et al., 2012; Baele, Li, et al., 2012), each using default priors. Each molecular clock-population model combination was assessed by taking the mean of the log marginal likelihood of two Markov chain Monte Carlo (MCMC) runs of 500 million generations, sampling every 50,000 generations. TRACER (v 1.7.1) (Rambaut et al., 2018) was used to assess convergence of MCMC runs after excluding 10 percent of the MCMC chain as burnin, ensuring an effective sample size (ESS) of at least 200 (Drummond & Bouckaert, 2015). The best-fit model was the GTR-Γ-uncorrelated lognormal relaxed-exponential population growth combination. To reduce computational time of downstream analyses, we generated final models using an MCMC length of 200 million generations, sampling every 20,000 generations, achieving adequate ESS.

The spatiotemporal information contained in the phylogenetic trees inferred in BEAST was extracted using the seraphim package in R (Dellicour et al., 2016). We extracted the information from 1000 trees sampled from the posterior distribution after discarding burnin. seraphim was then used to estimate dispersal statistics based on phylogenetic branches, which, having duration and direction defined, can be treated as conditionally independent movement vectors (Pybus et al., 2012). Velocity was estimated using mean branch dispersal velocity, v_{branch}, and weighted branch dispersal velocity, $v_{weighted}$. Spatial diffusion of FMDV was estimated using two different metrics, $D_{original}$ and $D_{weighted}$. $D_{original}$ represents the average diffusion coefficient associated with each tree branch (Pybus et al., 2012), and $D_{weighted}$ is a weighted average across the tree (Trovão et al., 2015). Weighted calculations give less weight to branches of short duration and are more useful when comparing different epidemics. As this

study focuses on a single monophyletic clade, $D_{original}$ will be primarily discussed. $D_{original}$ and $D_{weighted}$ are calculated as follows:

$$D_{original} = \frac{1}{n}\sum_{i=1}^{n}\frac{d_i^2}{4t_i} \text{ and } D_{weighted} = \frac{\sum_{i=1}^{n} d_i^2}{\sum_{i=1}^{n} 4t_i}, \quad (1)$$

where t_i is the duration (in years) of branch i during which the lineage has moved d_i km away from its start position in two dimensions. Thus, diffusion can be thought of as similar to velocity except that it takes into account the two-dimensional nature of spread.

Next, seraphim was used to investigate the impact of underlying factors on the dispersal velocity and location of viral lineages. Due to the notable computational resources required by this analysis, we chose four factors to investigate: cattle density, human population density, geodesic distance to the nearest livestock market, and mean standard precipitation-evapotranspiration index (SPEI), which is an indicator of drought (Center for International Earth Science Information Network-Columbia University, 2017; Robinson et al., 2014; Vicente-Serrano, Beguería, & López-Moreno, 2010; Vicente-Serrano, Beguería, López-Moreno, Angulo, et al., 2010). Previous studies have demonstrated an association between low rainfall and FMD, probably resulting from increased between-herd contacts as animals gather at communal drinking sites and communal pastures (Hamoonga et al., 2014; Muleme et al., 2012; Munsey et al., 2019). We also predicted that host density would facilitate spread, and therefore areas of high cattle density would be at higher risk. Thus, we hypothesized FMDV would spread at a higher velocity in areas of high cattle density and low SPEI (corresponding to more frequent droughts/lower rainfall). Because animal movements in East Africa are not consistently documented, we utilized human population density and distance to nearest livestock market as proxies for animal movements, representing demand for animal products. We predicted a tendency of FMDV to move toward animal markets and high human population densities (Muleme et al., 2012). Sources of raster files are shown in Table S2, and correlation statistics are shown in Table S3.

2.4 | Dispersal velocity of FMDV lineages

In this analysis, we examine how environmental factors facilitate or hinder the speed with which FMDV disperses through the landscape. Each phylogenetic branch is considered a movement vector defined by a start and end location (latitude and longitude), and start and end dates; these branch-specific values are used to calculate vector velocities. Movement vectors are then assigned an associated environmental path distance between start and end locations, which is a distance weighted according to the values of an underlying raster. These values represent the environmental landscape which the virus would have to traverse when moving between the start and end locations. We used two models to compute these values: (i) the least-cost path model (Dijkstra, 1959) and (ii) the Circuitscape path model (McRae, 2006). The least-cost path model uses a least-cost algorithm to determine the route taken between locations, whereas the Circuitscape path model uses circuit theory to accommodate uncertainty in the route taken. All factors were tested as potential conductance factors (facilitating movement/increasing velocity) and potential resistance factors (impeding movement/slowing velocity). Additionally, rescaled rasters were generated by transforming original rasters with the following formula: $v_t = 1 + k \times (v_o/v_{max})$, where v_t and v_o are the transformed and original raster cell values, and v_{max} the maximum raster cell value in the raster. This rescaling step allows testing different strengths of raster cell conductance or resistance relative to the conductance/resistance of a cell, with a minimum value set to 1. For each raster, we tested three values for k: 10, 100, and 1000. Next, the statistic Q is calculated as the difference between two coefficients of determination, R^2: (i) R^2 obtained by regressing branch durations against environmental distances computed on the raster being tested as a predictor, and (ii) R^2 obtained by regressing branch durations against environmental distances computed on a null raster, which has a value of 1 assigned to all cells. Thus, the null raster represents geographic distance alone. When $Q > 0$, environmental distances weighted according to a heterogenous raster are correlated more strongly with branch duration than distances computed on a null raster. One Q is estimated per sampled tree, yielding a distribution of Q values for each environmental factor-k-path model combination. A variable was considered as potentially explanatory if at least 90% of Q values were positive ($p(Q > 0) > 0.9$) (Jacquot et al., 2017). Among these potentially explanatory variables, a Bayes factor (BF) is reported by calculating the statistical support of each positive Q distribution evaluated against a null distribution generated by a randomization procedure in which the phylogenetic node positions within the study area are randomized, keeping branch lengths (time and distance), tree topology, and root position constant) (Dellicour et al., 2017). We selected this randomization procedure as its statistical performance was assessed in the original study presenting the analytical workflow of seraphim (Dellicour et al., 2016).

2.5 | Dispersal location of FMDV lineages

We utilized methods recently added to the seraphim package to test whether lineages tend to remain in or disperse toward particular environmental conditions (Dellicour et al., 2019). Instead of branch durations, routes, and their underlying landscapes, this method analyses environmental conditions strictly at the locations of origin and destination nodes of the branch. Two metrics are tested: (i) E, the mean of environmental values extracted at the nodes' positions, which measures the tendency of lineages to remain located in lower/higher environmental values, and (ii) R, the proportion of branches for which the environmental value recorded at the oldest node position is higher than at the youngest node position, which measures the tendency of lineages to disperse toward lower/higher environmental values (Figure 1). E and R are computed for each tree in the posterior sample, yielding posterior distributions for each metric.

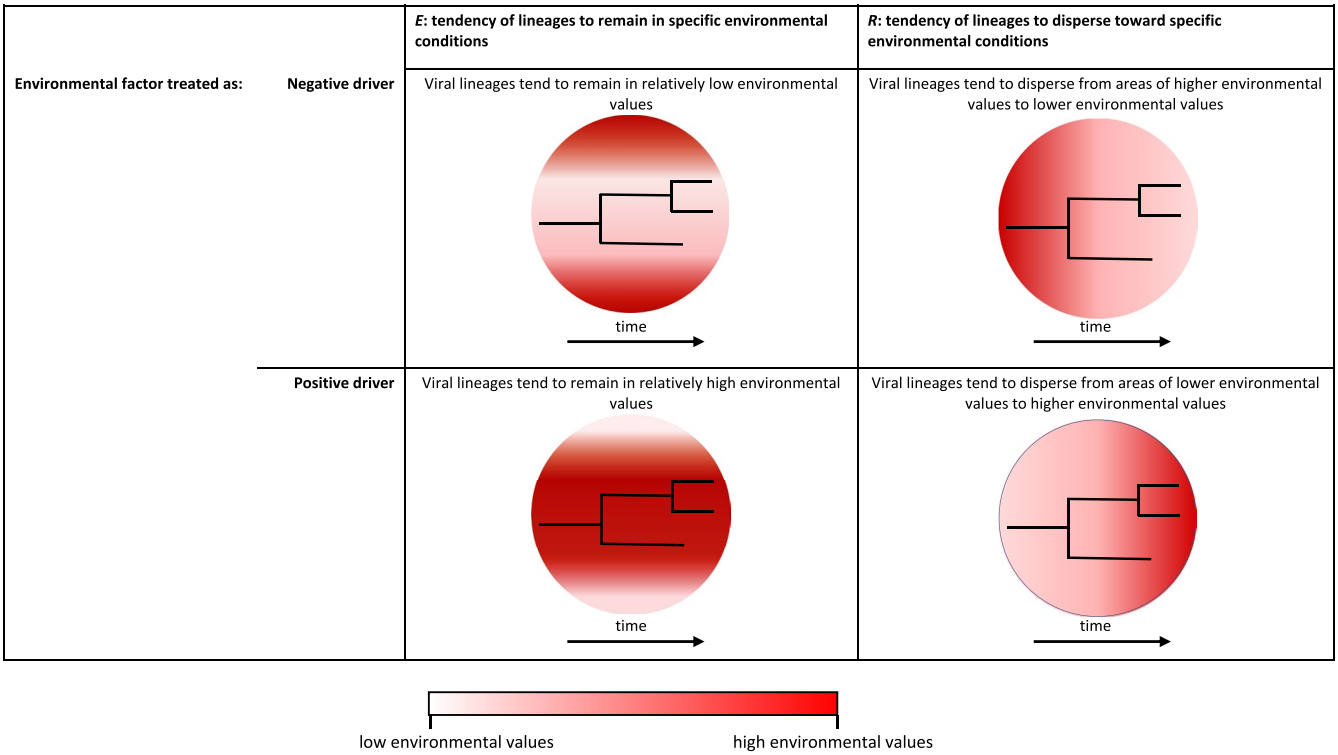

FIGURE 1 Two-by-two table representing dispersal direction analyses. The circles represent hypothetical study areas, in which darker shading indicates higher raster values [Colour figure can be viewed at wileyonlinelibrary.com]

Finally, the posterior distributions are compared to null distributions, which are computed by randomizing the phylogenetic node positions within the study area, again keeping branch lengths, tree topology, and root position constant. Each factor was tested as a potential driver and a potential impeder of virus dispersal.

3 | RESULTS

3.1 | Continuous phylogeographic inference

Results of model selection (path sampling/stepping-stone sampling) are shown in Table S4. A time-scaled phylogenetic model estimated the VP1 evolutionary rate to be 4.99×10^{-3} substitutions per site per year (95% highest posterior density, HPD: 4.10×10^{-3}–5.98×10^{-3}). The inferred phylogeny is shown in Figure S4 and corresponding spatiotemporal dispersal history of viral lineages is shown in Figure 2. The time of the most recent common ancestor for this clade was estimated to occur in 1950 (95% HPD: 1935–1964). While the majority of the contemporary sequences collected during the 2014–2017 project in Uganda cluster together, the phylogenic structure indicates transboundary transmission. Sequences collected for this project during 2014 cluster with viruses circulating in Eastern and Northern Uganda during 2008–2009, whereas sequences collected during 2015 cluster with sequences collected from both Uganda and Tanzania from 2005 to 2014 (Casey-Bryars et al., 2018; Kasambula et al., 2012). Sequences collected from northern Uganda at the end of the study period in 2017 cluster with FMDV circulating in Ethiopia and Kenya in 2005 and 2010, respectively. Details on the topotype classification of sequences collected during this study have been previously described (Mwiine et al., 2019; Velazquez-Salinas et al., 2020).

3.2 | Dispersal statistics

We estimated the mean branch dispersal velocity (v_{branch}), the weighted branch dispersal velocity ($v_{weighted}$), the mean diffusion coefficient ($D_{original}$), and the weighted diffusion coefficient ($D_{weighted}$). Dispersal statistics are shown in Table 1. Kernel density estimate of among-branch variation in mean original (unweighted) diffusion coefficient ($D_{original}$) is shown in Figure 3. The vastness of the density plot, in comparison to a more compact shape, indicates variation in diffusivity among the lineages.

3.3 | Impact of underlying factors on lineage dispersal velocity

There is considerable variability in dispersal velocity among the phylogenetic branches (coefficient of variation = 4.59). We therefore investigated the impact of several hypothesized underlying factors that could explain heterogeneity in FMDV lineage dispersal velocity. Results are shown in Table S5. We only identified weak but positive

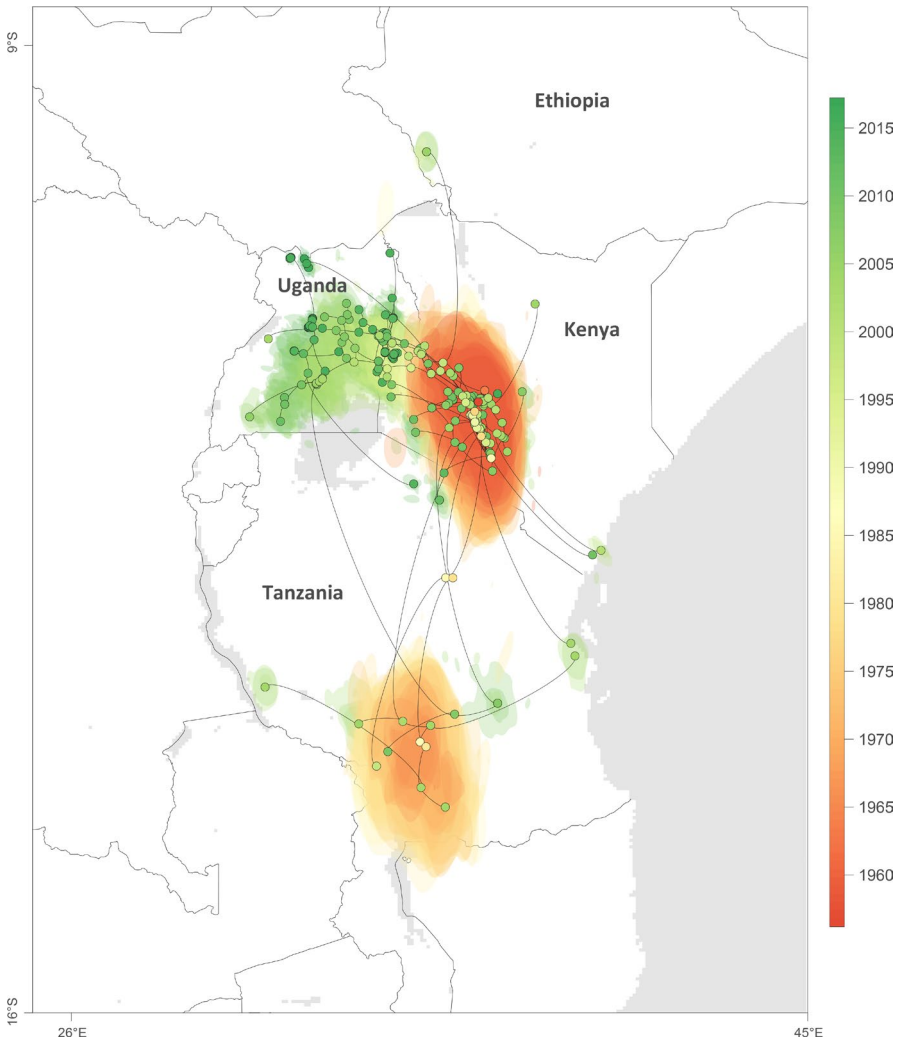

FIGURE 2 Reconstructed dispersal history of FMDV serotype O lineages in East Africa: mapped maximum clade credibility (MCC) trees and 95% highest posterior density (HPD) regions. MCC trees and 95% HPD regions are based on 100 trees subsampled from the post burnin posterior distribution. MCC tree nodes are coloured according to their time of occurrence, and 95% HPD regions were computed for successive time layers and then superimposed using the same colour scale reflecting time [Colour figure can be viewed at wileyonlinelibrary.com]

Statistic	Definition	Median value	95% HPD
v_{branch}	Mean branch dispersal velocity	195.06 km/year	128.42, 857.79
$v_{weighted}$	Weighted branch dispersal velocity	41.57 km/year	35.88, 49.32
$D_{original}$	Mean diffusion coefficient	9520.77 km^2/year	5801.04, 30,299.98
$D_{weighted}$	Weighted diffusion coefficient	4160.95 km^2/year	3570.70, 4989.62

TABLE 1 Foot and mouth disease virus serotype O dispersal statistics estimated from continuous phylogeographic inference using sequences from Uganda, Kenya, Tanzania and Ethiopia

support (BF = 4.0) when cattle density was treated as a resistance factor under the least-cost path model at a rescaling factor of 10 (i.e., higher cattle density was associated with slower lineage dispersal velocity).

3.4 | Impact of underlying factors on dispersal location

We investigated the impact of factors on FMDV dispersal location using two metrics: *E*, tendency of lineages to remain in specific environmental conditions, and *R*, tendency of lineages to disperse toward specific environmental conditions (Figure 1). The results are shown in Table 2. Under the metric *E*, we identified strong support (BF > 99) when distance to livestock market was treated as a negative driver (i.e., the viral lineages are unlikely to remain in areas far from markets). Additionally, we identified strong support (BF > 99) when human population density was treated as a positive driver, indicating that viral lineages tend to remain in areas with high human density. In order to investigate the impact of sampling bias, these analyses were repeated after removing sampled nodes (branch tips). Considering ancestral branches only, distance to livestock markets maintained support as a negative driver (BF > 99). When considering only internal tree branches (i.e., discarding branch tips), the support for human population density as a positive driver decreased (BF = 14.6). Cattle density had a weak association (BF = 15.1) when treated as a positive driver, indicating the virus tends to remain in areas of high cattle density, a finding consistent when only ancestral nodes were considered (BF = 10.1).

For the metric *R*, the only supported association (cattle density) was not repeatable when ancestral branches only were considered.

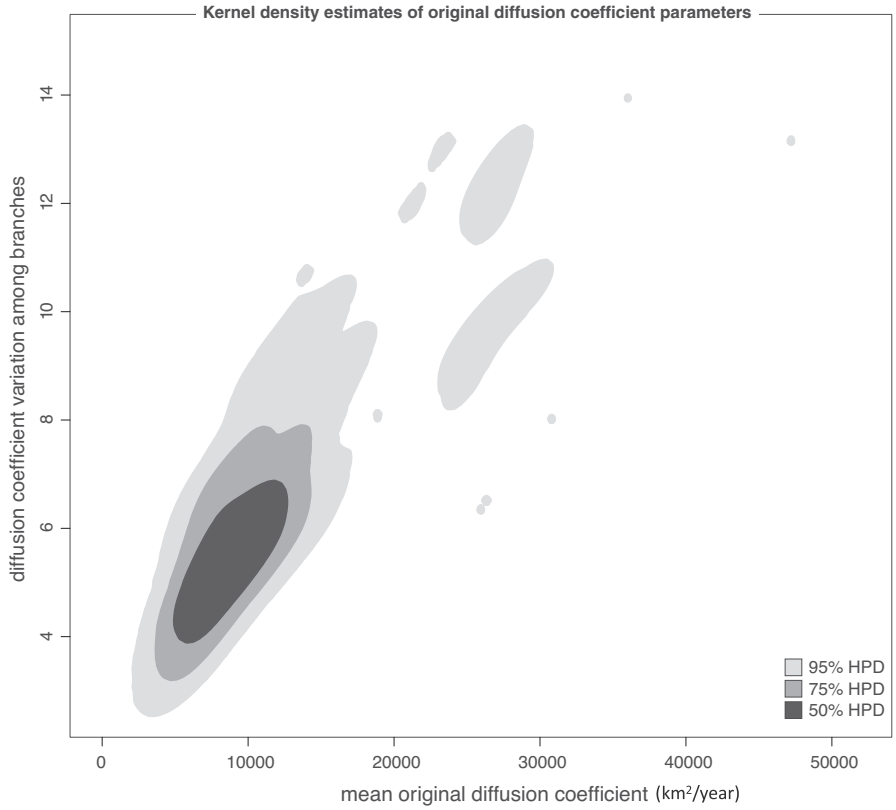

FIGURE 3 Kernel density estimates of the mean diffusion coefficient parameters. The plot shows the mean original diffusion coefficient among branches in square kilometres/year (*x*-axis) versus the coefficient of variation of that value among branches (*y*-axis)

Calculations were repeated for the logarithms of all rasters, which resulted in similar findings.

4 | DISCUSSION

This study aimed to provide insights into the complex epidemiology of FMDV in East Africa. We utilized cutting-edge Bayesian phylogeographic methods to analyse FMDV sequences, including sequences resulting from recent robust sampling in Uganda. The selected monophyletic clade, representing viruses recently circulating in Uganda, Kenya, Tanzania, and Ethiopia, provides support for regional endemicity (Mwiine et al., 2019) and transboundary transmission of serotype O. Notably, we identified heterogeneity in diffusivity across the serotype O clade examined here. Consequently, we investigated the role of hypothesized environmental factors on the velocity, location, and direction of FMDV serotype O dispersal, including anthropogenic factors. Among the environmental factors tested here, proximity to livestock markets had the most statistical support as a predictor of location of FMDV, with cattle density and human population density having positive but less supported associations.

The FMDV serotype O VP1 nucleotide substitution rate calculated in this study, 4.99×10^{-3} substitutions per site per year (95% HPD: 4.10×10^{-3}–5.98×10^{-3}), is slightly higher than rates previously reported from East Africa. Balinda et al. (2010) and Duchatel et al. (2019) reported 2.76×10^{-3} substitutions/site/year (95% HPD: 1.84×10^{-3}–3.63×10^{-3}) and 3.69×10^{-3} (95% HPD: 3.67×10^{-3}–3.71×10^{-3}), respectively. These differences may be explained in part by the choice of population model; Balinda et al. (2010), using sequences collected through 2008, utilized a constant population size model, Duchatel et al. (2019) utilized a skygrid population model, whereas our data best fit a model of exponential growth. Alternatively, it is possible that a higher substitution rate represents clade-specific epidemiology. Recent clades may be subject to more intensive selection pressure due to the use of vaccines or relatively higher levels of immunity from natural infection.

We estimated mean branch dispersal velocity (unweighted) to be 195.1 km/year (95% HPD 128.4–857.8). In one district in Tanzania that was intensively sampled over 4 years, Casey-Bryars et al. (2018) used reported cases of FMDV to estimate that the virus spread at a velocity between 2.6 and 13.1 km/month. While our phylogeny-inferred velocities are higher, the per-month confidence intervals overlap; the convergence of these estimates from two different studies utilizing different types of data provides support for the phylogenetic reconstruction methods used here. We estimated a mean diffusion coefficient (unweighted) of 9520.8 km^2/year (95% HPD 5801–30,300) with high variation in among-branch diffusion (Figure 3). Less diffusive clades are probably representative of local transmission via direct contact, whereas more diffusive clades represent long-distance displacements. These long-distance displacements suggest anthropogenic factors (i.e., movement of animals) contribute to FMDV transmission in East Africa. The impacts of human-mediated dispersal may be reflected in the higher average velocities seen across our larger study region as compared to the more localized sampling by Casey-Bryars et al. (2018).

TABLE 2 Impact of environmental factors on lineage dispersal location and direction

	***E*: Impact of environmental factors on dispersal location: tendency of lineages to remain in specific environmental conditions**		***R*: Impact of environmental factors on dispersal direction: tendency of lineages to disperse toward specific environmental conditions**	
Environmental factor	**BF for factors treated as negative drivers**	**BF for factors treated as positive drivers**	**BF for factors treated as negative drivers**	**BF for factors treated as positive drivers**
All data				
Cattle density	0.07	15.13	4.26	0.23
log (cattle density)	0.02	**54.56**	4.26	0.23
Human population density	0.002	**499**	1.77	0.55
log (human population density)	0.01	**75.92**	1.94	0.49
Distance to livestock market	**332.33**	0.003	1.64	0.54
log (distance to livestock market)	**499**	0.002	1.64	0.54
SPEI	0.65	1.53	1.24	0.69
log (SPEI)	0.64	1.56	1.24	0.69
Ancestral branches only				
Cattle density	0.1	10.11	2.79	0.30
log (cattle density)	0.31	**32.33**	2.79	0.30
Human population density	0.07	14.63	6.81	0.14
log (human population density)	0.05	**21.73**	7.20	0.13
Distance to livestock market	**141.86**	0.007	0.96	0.88
log (distance to livestock market)	**141.86**	0.007	0.96	0.88
SPEI	0.19	5.25	3.93	0.25
log (SPEI)	0.18	5.41	3.93	0.25

Note: Bolded values are BFs > 20, representing strong statistical support.

Abbreviation: BF, Bayes factor; SPEI, standard precipitation–evapotranspiration index.

We analysed four hypothesized drivers of FMDV transmission: cattle density, drought, human population density, and proximity to livestock markets. Analysis of the impact of cattle density on dispersal location (*E*, tendency of clades to remain in specific environmental conditions) revealed that FMDV tends to remain circulating in areas of high cattle density. This finding is consistent with our earlier serological studies, in which Munsey et al. (2019) demonstrated that a high relative risk of FMDV seropositivity was associated with cattle-dense areas in Uganda.

Previous studies have reported an association between FMDV and areas of low rainfall, a finding that is probably a result of increased between-herd contacts as animals gather at communal drinking sites (Ayebazibwe et al., 2010; Munsey et al., 2019). We hypothesized increased FMDV transmission would be found in areas of more frequent drought, though such an association was not supported by our analyses. Cattle herds existing in areas of extreme dryness in East Africa are typically pastoral herds, and we suspect the lack of a convincing relationship between drought and FMDV transmission is probably a result of undersampling of these areas. Our Uganda project included herds sampled both purposively (post-outbreak) and randomly (chosen for geographic representation), thus probably had an adequate representation of pastoral herds. However, publicly available sequence data are often generated from outbreak investigations, and historically there has been underreporting of FMDV outbreaks from pastoral areas (Muleme et al., 2012). Thus, the addition of publicly available sequence data here probably decreases the representativeness of pastoral areas, and thus leads to draught-prone areas being underrepresented overall.

Human population density, a proxy for demand for animal products, was hypothesized to be a driver of FMDV spread. Duchatel et al. (2019) demonstrated that the logarithm of human density was positively associated (BF = 9) with FMDV velocity. While we did not find support for a relationship between human population density and viral lineage velocity, we did find a strong association (BF > 99) when human density was tested as a positive driver under the *E* statistic, indicating that FMDV tends to remain circulating in areas of high human density. This finding was weaker when analysing only ancestral branches, though still had positive support (BF = 14.6), which indicates that this effect is robust to the moderate sampling bias existing within the data set. However, the different levels of statistical support further indicates that pastoral areas, characterized by relatively high cattle density, low rainfall, and low human population densities are probably underrepresented in publicly available FMDV isolate data sets.

In East Africa, livestock markets may ease disease transmission as animals from neighbouring areas are gathered in close proximity during transport and sale (Muleme et al., 2012). Thus, we hypothesized livestock markets to be a driver of viral transmission. Our

analysis indicates that FMDV serotype O tends to remain circulating in areas closer to livestock markets (BF > 99), a finding that remained consistent when examining ancestral branches only (BF > 99). Collectively, the results of our human density and market analyses indicate anthropogenic factors contribute to the transmission of FMDV serotype O in East Africa. These variables are surrogate markers of movement of animals and animal products, factors which are difficult to directly measure.

In this study, we chose to utilize the VP1 coding region of the FMDV genome because (i) this region codes for immunogenic sites which are crucial to antibody neutralization and (ii) the majority of publicly available sequences include only VP1. While an analysis using whole genome sequencing may be preferable (Lasecka-Dykes et al., 2018), the VP1-coding region alone may provide sufficient diversity for the relatively coarse spatial-temporal resolution of the analysis presented here. However, our analysis has several notable limitations. Seraphim is a computationally intensive tool, which limits the number of predictors which can reasonably be analysed. Additionally, the ability to incorporate a multivariable approach could provide further insights into interactions or relative importance among predictors. Finally, as with all epidemiological studies, our analyses are limited by the availability of data. Our results indicate sampling bias may play a role in our ability to infer drivers of FMDV spread, especially when using publicly available data sets which include regions from which FMDV has historically been underreported. While this probably affected our ability to identify possible associations between drought and FMDV transmission, other predictors were robust to this bias. This finding highlights the need for improved sampling in pastoral regions.

The phylogeographical analysis presented here provides valuable insights into the transmission dynamics of an important transboundary animal pathogen. The fact that our phylodynamic estimates of lineage dispersal velocity are similar to that of estimates based on intensive fine-scale outbreak monitoring (Casey-Bryars et al., 2018), suggests that Bayesian phylodynamic methods are capable of reconstructing dispersal patterns even in more sparsely sampled endemic areas. The convergence of the velocity estimates using two different methods suggest that 31.2–195.1 km/year may be a generalizable pattern for FMDV dispersal in East Africa. Our study provides support to the notion that anthropogenic activities drive FMDV transmission and areas near livestock markets may serve as transmission hotspots for FMDV serotype O. These areas, and other areas in which increased between-herd contacts are anticipated, may be prioritized in future control strategies. Further work to better understand the evolutionary dynamics of FMDV in East Africa, including improved surveillance of pastoral areas, will aid FMDV control measures in this area.

ACKNOWLEDGEMENTS

The authors thank Shinichiro Maruyama for assistance with TreeTrimmer and Ehud (Udi) Elnekave for assistance with the BEAST analysis.

AUTHOR CONTRIBUTIONS

Luis L. Rodriguez, Andres Perez, Frank Norbert Mwiine, and Kimberly VanderWaal designed research; Frank Norbert Mwiine, Sylvester Ochwo, Lauro Velazquez-Salinas, Zaheer Ahmed, Elizabeth Rieder, Francois Maree, and Anna Munsey performed research; Simon Dellicour contributed new analytical tools; Anna Munsey and Simon Dellicour analysed data; Anna Munsey wrote the manuscript.

CONFLICTS OF INTERESTS

The authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

FMDV sequences collected for this study: see Velazquez-Salinas et al. (2020) (https://doi.org/10.3389/fvets.2020.00162) and Table S1.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Munsey, A., Mwiine, F. N., Ochwo, S., Velazquez-Salinas, L., Ahmed, Z., Maree, F., Rodriguez, L. L., Rieder, E., Perez, A., Dellicour, S., & VanderWaal, K. Phylogeographic analysis of foot-and-mouth disease virus serotype O dispersal and associated drivers in East Africa. *Molecular Ecology*. 2021;30:3815–3825. https://doi.org/10.1111/mec.15991