Global phylogeographical patterns in the spread of foot-and-mouth disease virus

Running title: Phylogeography of foot-and-mouth disease virus

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Abstract

The economic impacts of Foot-and-mouth disease virus (FMDV) have prompted most countries worldwide to embark on local, regional and national control and eradication programs. In conjunction with the global efforts to reduce further virus dissemination into free-zones and contain or eradicate circulation in endemic regions, global markets and animal trade have increased linearly in past decades facilitating virus spread to other countries. FMDV proved its potential to propagate across borders on numerous occasions, but yet details regarding how exactly the spread between countries occurred at global scale remain missing. To elucidate the FMDV global spread characteristics, we studied its spatiotemporal dynamics using Bayesian macroevolutionary analyses for serotypes O, A, Asia1, SAT1, SAT2, and SAT3, with a dataset that comprises 58 years of phylogenetic and epidemiological information. We reconstructed the evolutionary routes and historical spread of FMDV at global scale level. Our results highlight the main differences in phylogeographic patterns, dispersal rates, and the role of host species in the spread and maintenance of virus circulation. Contrary to previous studies, our results showed that four FMDV serotypes were monophyletic (O, A, Asia1 and C), while all SATs serotypes did not evidence a defined common ancestor. We also observed that FMDV diffusion was characterized by a great variability on the spatiotemporal dynamics exhibited by serotypes A and O, reflected by the wide variety of colonized countries. On the other hand, we observed that serotypes with local spread have been historically constrained into their endemic areas (Asia 1 and SATs), which in the case of SAT serotypes, may be related to a lower variety of hosts. This

study provides significant insights into the spatiotemporal dynamics of the global circulation of FMDV serotypes, by characterizing the viral routes of spread at serotype level, allowing to use the past knowledge to improve future decisions for a more efficient control and eradication of this disease.

Keywords: Disease dispersion, transboundary emerging diseases, risk factors, evolution

INTRODUCTION

The rapid growth of the global population along with the current demand for animal protein and the increasing animal trade have positively impacted the spread of a broad range of transboundary diseases. Clear examples of this phenomena are the recent emergence of African Swine Fever in China, Avian Influenza or Contagious Bovine Pleuropneumonia among others (Daszak et al., 2001; Kouba, 2003; Smith et al., 2007; Kilpatrick, 2011; Wang et al., 2018). Understanding the tempo and mode of disease evolution allows to estimate the impact of those and other factors on the evolutionary patterns exhibited by these diseases, which cannot be analyzed by classic epidemiological studies (Read et al., 1999; Trevathan, 1999; Stearns and Ebert, 2001).

Evolutionary ecology has shown to be an accurate and highly impacting approach to understand the spatiotemporal dynamics of infectious diseases, with the capacity to explain disease spread, virulence and invasion potential (Galvani, 2003; Mideo et al., 2008; Magiorkinis et al., 2009; Weaver and Forrester, 2015; Lion and Gandon, 2016; Dellicour et al., 2017; Forni et al., 2018), as well as the relationships with its underlying environment as a potential risk factor (Stephens et al., 2016; Dellicour et al., 2017; Jacquot et al., 2017). In the case of transboundary diseases, evolutionary ecology has proven to be a useful approach, providing accurate knowledge for the control of pathogens worldwide (Auguste et al., 2015; Pigeault et al., 2015; Rogalski et al., 2017; Fountain-Jones et al., 2018).

Foot-and-mouth disease virus (FMDV) is the most influential transboundary animal disease (TAD) with historical worldwide circulation reported in domestic and wildlife reservoirs (Grubman and Baxt, 2004; Brito et al., 2017). FMDV is a highly contagious disease caused by a small single-strained RNA virus of the genus *Aphthovirus*, member of the family Picornaviridae (Belsham, 1993) and classified into seven different serotypes; O, A, C, Asia 1 and Southern African Territories (SATs) 1, 2 and 3 (Sobrino et al., 2001; Brown, 2003; OIE, 2009) which affect severely the productivity of domesticated livestock, causing great economic losses (Abdul-Hamid et al., 2011; Kandeil et al., 2013; Ganji et al., 2018). The United States Department of

Agriculture has recently updated calculations suggesting that a possible introduction of FMDV could result in losses between $15 to $100 billion (Perez et al., 2004a; Knight-Jones and Rushton, 2013; Rushton and Knight-Jones, 2015; USDA-APHIS, 2017). One of the main reasons for this great impact is the wide variety of hosts known for FMDV (i.e., cattle, buffalo, swine, sheep, and deer), from which a remarkable percentage is part of the food industry.

FMDV is known to be transmitted locally and globally, often associated with infected animal products and human and animal movements (IUCN/SSC, 2018). Local transmission, on the other hand, is based on airborne spread, animal direct contact with infected individuals or carcasses and translocation of contaminated staff, equipment, and machinery (Ferguson et al., 2001; Orsel et al., 2009).

Phylogenetic relationships among FMDV serotypes have been widely studied, mostly based on individual genes (Fares and Tully, 2008; Lewis-Rogers et al., 2008; Schumann et al., 2008; Priyadarshini et al., 2009), but also, in a lower level, on whole genome sequences (WGS) (Carrillo et al., 2005; Cooke and Westover, 2008; Yoon et al., 2011). Nevertheless, most of the studies mentioned above need to be updated due to the small available number of sequences <200, and their inaccurate evolutionary analyses, which in most of the cases (excluding Yoon et al (2011)) they did not consider the Bayesian phylogenetic methods (with the robustness provided by bootstrap or Markov Chain Monte Carlo statistics), making the results less reliable.

Likewise, along with its evolution, several studies have explored the spatiotemporal evolutionary dynamics of FMDV in different parts of the world, mainly focusing on the diffusion patterns across its endemic regions: Asia and Africa (Abdul-Hamid et al., 2011; Di Nardo et al., 2011; de Carvalho et al., 2013; Brito et al., 2017; Bachanek-Bankowska et al., 2018). However, studies considering all serotypes are only available within small geographic regions, and global studies only assessed some of the viral serotypes (Di Nardo et al., 2011; Alkhamis et al., 2018; Brito et al., 2018).

In this study, we addressed the spatiotemporal dynamics of FMDV by using Bayesian macroevolutionary analyses, including a comprehensive genetic, geographical and temporal dataset regarding past and current FMDV outbreaks. The main motivation of this work was to shed light on the complex evolutionary history of FMDV via the i) reconstruction of the spatiotemporal phylogeographic history of FMDV at serotype level and ii) determine and compare the global spatial spread of each FMDV serotype.

MATERIALS AND METHODS

Data collection and curation

We built a comprehensive genetic database comprising 543 publicly available whole genome sequences from six FMDV serotypes (A, O, Asia1, SAT 1, SAT 2 and SAT 3), with sampling dates ranging from 1959 to 2017 (GenBank ID numbers in Supplementary material Table S1). Serotype C was not included in this study due to data unavailability (only 3 sequences available). Our dataset gathers information from 43 countries and 4 continents obtained from the Virus Pathogen Resource database, available at https://www.viprbrc.org (See Table S1).

To determine accurate phylogenetic relationship among FMDV reports, we combined the available genetic information along with collection date, host species (i.e., cattle, ankole cow, buffalo, swine and sheep) and location (discrete information at country level) as metadata information. Any sample lacking one of these three characteristics was discarded.

Discrete phylogeographical analysis

Sequences were aligned using Mega X, available at www.megasoftware.net/ (Kumar et al., 2008). To determine whether there was a sufficient temporal molecular evolutionary signal of the FMDV sequences used for each serotype phylogeny, we used TempEst v1.5 (Rambaut et al., 2016). To calculate the *P*-values associated with the phylogenetic signal analysis, we used the approach described by (Murray et al., 2016) based on 1,000 random permutations of the sequence sampling dates (Navascués et al., 2010). The relationship found between root-to-tip divergence and sampling dates (years) supported the use of molecular clock analysis in this study. Root-to-tip regression results for each serotype are reported in Supplementary Table S2, all the results supported a significant temporal signal (P-value<0.05).

Phylogeographic history of FMDV dispersal was recovered from the obtained spatiotemporal phylogenies for each serotype, where each tip represents the geographic centroid where the sequence was extracted. Phylogenetic trees were generated by a discrete phylogeography estimation by Bayesian inference through Markov chain Monte Carlo (MCMC), implemented in BEAST v2.5.0 (Bouckaert et al., 2014). We partitioned the coding genes into first+second and third codon positions and applied a separate Hasegawa-Kishino-Yano (HKY+G; (Hasegawa et al., 1985)) substitution model with gamma-distributed rate heterogeneity among sites to each partition (Shapiro et al., 2006). To account for evolutionary rate variation among lineages, we used an uncorrelated lognormal relaxed molecular clock (Drummond et al., 2006) using a coalescent constant population model. For each serotype, we applied an uncorrelated relaxed clock model with an underlying lognormal distribution. All analyses were developed for 200 million generations, sampling every 10,000th generation and removing 10% as chain burn-in. All the Markov chain Monte Carlo analyses for each serotype

were investigated using Tracer software v1.6 (Drummond et al., 2006) to ensure adequate effective sample sizes (ESS) (above 200) which were obtained for all parameters. Final trees were summarized and visualized via Tree Annotator v. 2.3.0 and FigTree 1.4.3 respectively (included in BEAST v2.5.0) (Rambaut and Drummond, 2016; Rambaut, 2017). Finally, to visualize the spatiotemporal diffusion of each serotype we used Spatial Phylogenetic Reconstruction of Evolutionary Dynamics using Data-Driven Documents (D3) SPREAD3 software (Bielejec et al., 2016).

RESULTS

The number of sequences per country varied from 1 to 100 samples. United Kingdom, Argentina, India, and Japan, that have experienced the most severe impacts during this century, were the countries with the highest number available genomes (Figure 1, Supplementary Table S3). Likewise, several countries have been historically affected by more than one serotype, particularly in Asia and Africa, where we observed that Uganda presented the highest virus diversity, including serotypes O, A, and all SATs (Supplementary Table S3, Supplementary Figure S1).

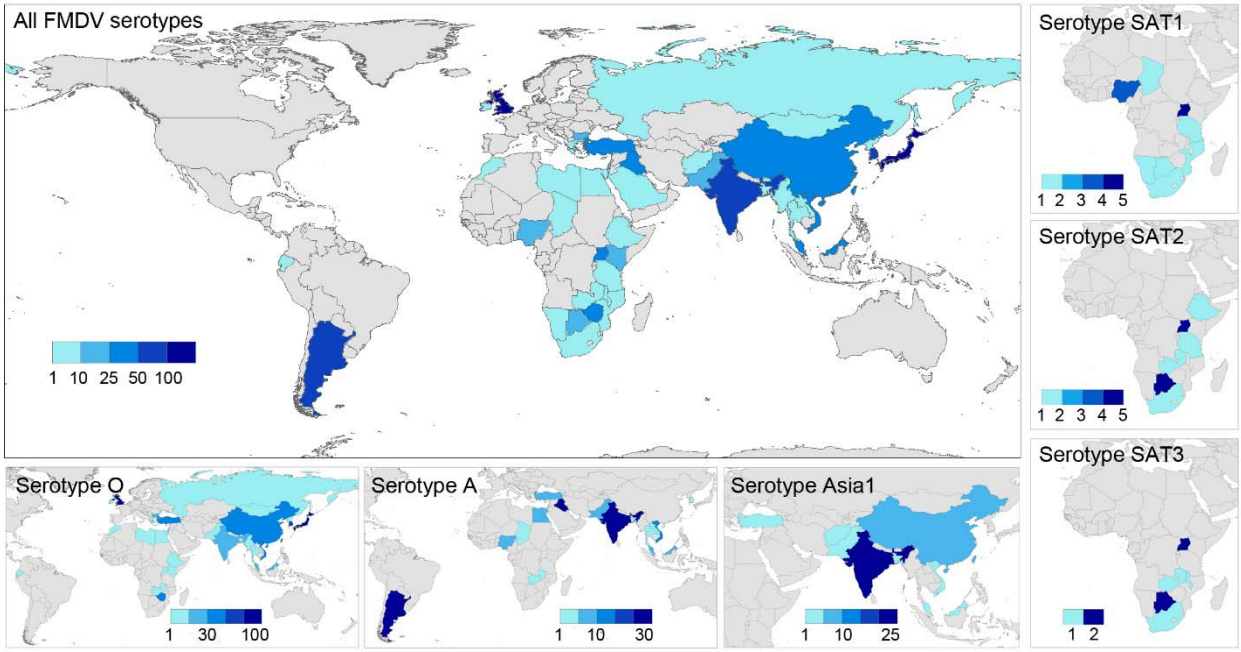

FIGURE 1. Spatial distribution of Foot-and-mouth disease virus. Blue range represents the number of sequences available at the country level.

Spatiotemporal dynamics of FMDV

The spatiotemporal dynamics obtained for all FMDV serotypes is described in Figure 2, while a more detailed explanation that shows the historical spread of each serotype in the phylogenetic and geographic space is represented in Figures 3 to 8.

Phylogeographic analyses highlighted great asymmetries in the tempo and mode of each serotype evolution (Figure 2). SAT1 appeared to be the basal clade of the entire group, originating SAT2, SAT3 and serotype A, which later diversified into serotype Asia1, O and C. Our analysis suggested O seemed to be the most recent, prolific and widespread lineage, with the higher number of sequences available worldwide. Serotype A and Asia 1 appeared second and third in the number of available sequences, followed by all SATs serotypes. The less represented lineage was Serotype C, for which only 3 available sequences were available. Maximum clade credibility phylogeny showed the monophyly of serotypes O, A, Asia 1 and C (each serotype shared a common ancestor), while SATs serotypes appeared to have multiple origins (Figure 2).

The phylogeographic analysis of FMDV was only performed at serotype level, due to the low effective sample size value obtained when we analyzed FMDV as a whole (ESS<100), which can generate a poor estimation of the posterior distributions.

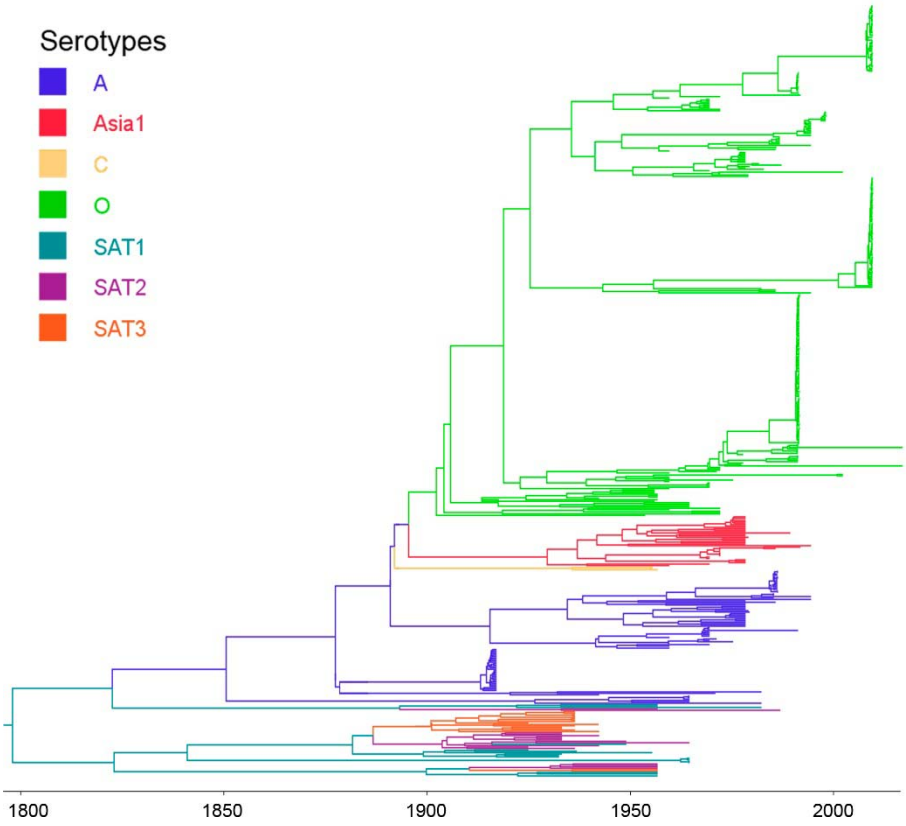

FIGURE 2. Epidemiological statistics estimated for Foot-and-mouth disease. A Maximum clade credibility phylogeny of the global FMDV epidemic, colored according to all serotypes (A, O, C, Asia1, SAT1, SAT2, and SAT3).

Spatiotemporal diffusion among serotypes

Serotype O

We analyzed 360 sequences from serotype O, which comprise 66% of the global FMDV tree (Figure 2). This serotype also presents the widest distribution of all, with records from 29 countries. Based on our analysis, its most likely center of origin was China from which it spread in all directions. Viral spread occurred both locally (30% of the cases) to the surrounding countries (the countries that are part of its international borders) and across long distances (70%) to further countries (i.e., United Kingdom, Greece, Uganda and Malaysia), spreading globally and colonizing most of Asia, Northeastern Africa and South America in less than 50 years (Figures 3a and 3b) (see Supplementary Video S1 for detailed footage). Phylogenetic reconstruction identified clusters formed by different sublineages, where the most phylogenetically distant were the group Asia, Africa and UK (outbreak in 2001) from the group conformed by the UK (outbreak in 1967-68 + 2007) and Ecuador. The biggest centers of dispersal events (geographic spread accompanied by diversification) of this serotype were China, Malaysia, Turkey, South Korea, and Uganda, which in the case of China, South Korea, and Turkey were among the countries with the highest number of sequences (see Figure 1b). Serotype O also has the highest host diversity, where the most representative were cattle (71% of the sequences) and swine (20%). Cattle were not only the most important host for this serotype but also the most likely initial host of the ancestral lineages. On the other hand, sheep, buffalo and ankole cow represented less than 10% of the total diversity (Figure 3a). Spatiotemporal diffusion map shows the serotype O global distribution with great evidence of long-range movements across countries and continents (Figure 3b).

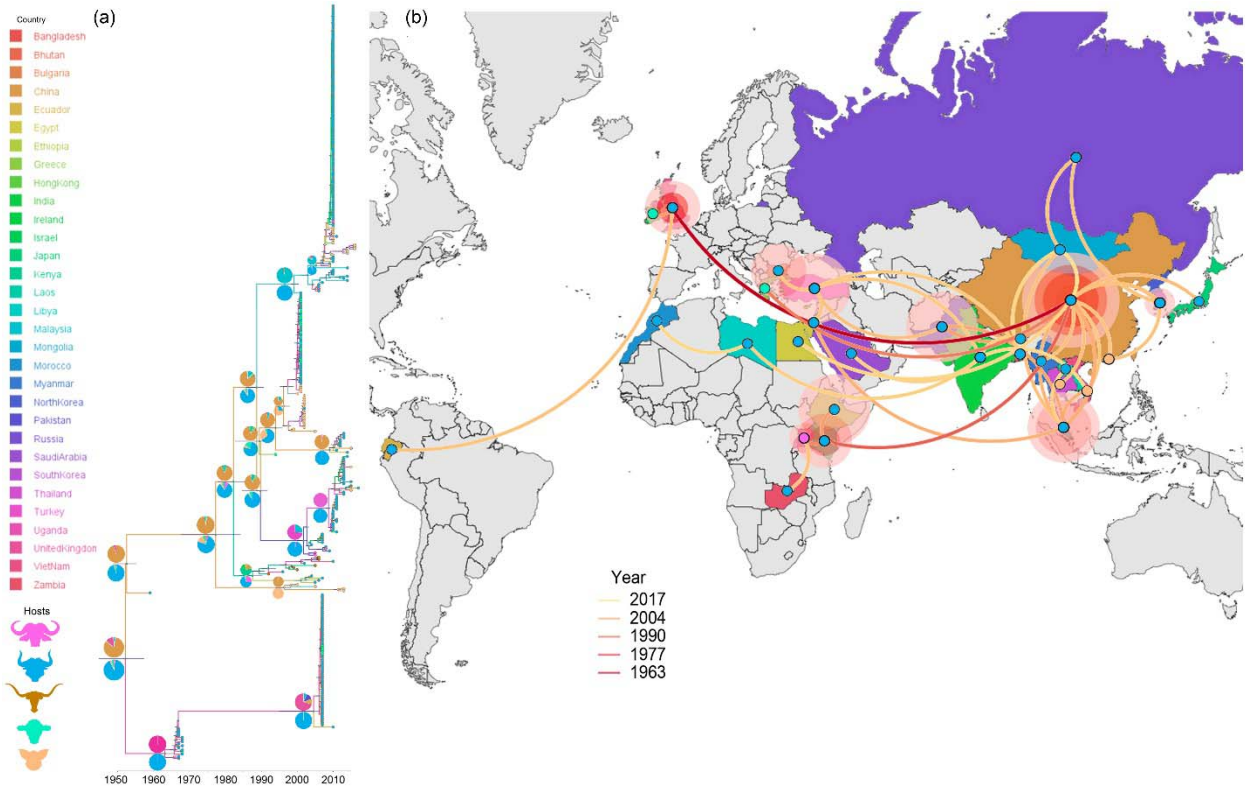

FIGURE 3. Epidemiological statistics estimated for Foot-and-mouth disease (Serotype O) epidemic. (a) Maximum clade credibility phylogeny of the FMDV epidemic colored according to the countries where the disease has been registered. Dots at the end of the branches represent the host species (buffalo, cattle, ankole cow, sheep, and swine). The probabilities of ancestral states (inferred from the Bayesian MCMC discrete traits analysis) are shown in pie charts at each node, where charts above branches represent locations and charts below branches most likely hosts. (b) Reconstructed spatiotemporal diffusion of FMD serotype O spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events.

Serotype A

Phylogeographic relationships obtained for serotype A indicated India as the most likely center of origin. Besides, India was represented as the source of the highest number of dispersal events, not only for the spread across Asia and Africa but also to South America, where we observed a high number of diversification events in a short period of time (mainly associated with the Argentina outbreak in 2001). Several phylogenetic groups were observed inside this

serotype, and the most distinguishable were the ancestral African group conformed by (Egypt, Chad, and Zambia) and the most recent group of conformed by the rest of the sublineages. We also observed that long-distance dispersal events were the most representative of the spatiotemporal dynamics of this serotype, accounting for 73% of the total spread. Another characteristic of this event was their multi-directionality, coming back to the point of origin in numerous occasions. The most recent geographic dispersal events (from 2010) also suggested India as one of the most important centers of origin for the spread of the virus and its diversification, followed by Pakistan and Malaysia. The hosts associated with serotype A were; cattle (93%), buffalo (5%), ankole cow and swine, which only represented a 2%. Viral circulation was found to be widely spread in cattle population, while infected buffalos were only registered in India, Vietnam, and Pakistan (Figures 4a and 4b; Supplementary Video S2).

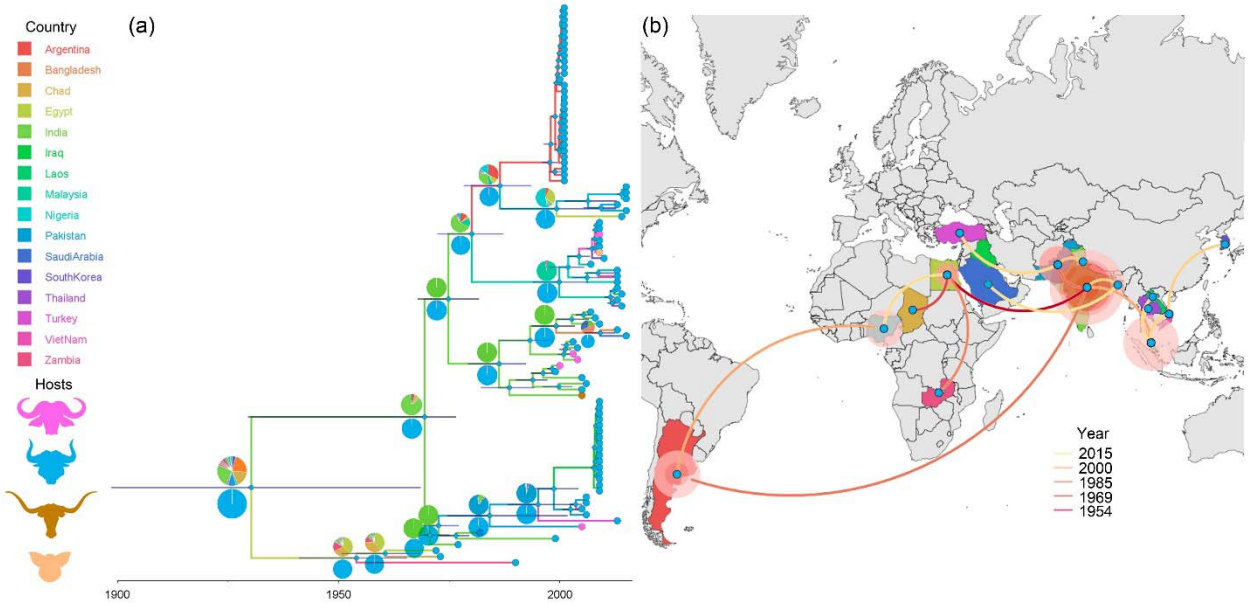

FIGURE 4. Epidemiological statistics estimated for Foot-and-mouth disease (Serotype A) epidemic. (a) Maximum clade credibility phylogeny of the FMDV epidemic colored according to the countries where the disease has been registered. Dots at the end of the branches represent the host species (buffalo, cattle, sheep, and swine). The probabilities of ancestral states (inferred from the Bayesian MCMC discrete traits analysis) are shown in pie charts at each node, where charts above branches represent locations and charts below branches most likely hosts. (b) Reconstructed spatiotemporal diffusion of FMD serotype A spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events.

Serotype Asia 1

In the case of serotype A, phylogeographic analyses also indicated India as the most likely origin, from which it diverged in all directions. Two main sublineages were identified, one of them related to India, Bangladesh and the western side (i.e., Pakistan, Afghanistan, and Turkey), while the other group gathered the dispersion through the southeastern side, including India, China, Malaysia, and Vietnam. These dispersal events occurred mainly through local movements, representing 56% of the spatiotemporal dynamics of this serotype (Figures 5a and 5b) (for detailed footage see Supplementary Video S3). The most important centers of diversification for this serotype were India, China, and Malaysia (Figure 5a). The main hosts associated to the dispersion of this serotype were cattle (representing 66% of the sequences), followed by swine (14%, exclusively in China), buffalo (6%, it was observed in India, Vietnam, and China) and sheep (~3%, also observed only in China). Its historical phylogeography also revealed a relatively constant dispersion to new places marked by a slowdown between 1930 and 1960 showing a local dispersion during that time for some lineages. However, we observed a clear increase in the diversification events related to the arrival of this serotype to Vietnam from Pakistan and its spread back to Turkey, which also corresponds to the biggest dispersion event occurring for this specific serotype.

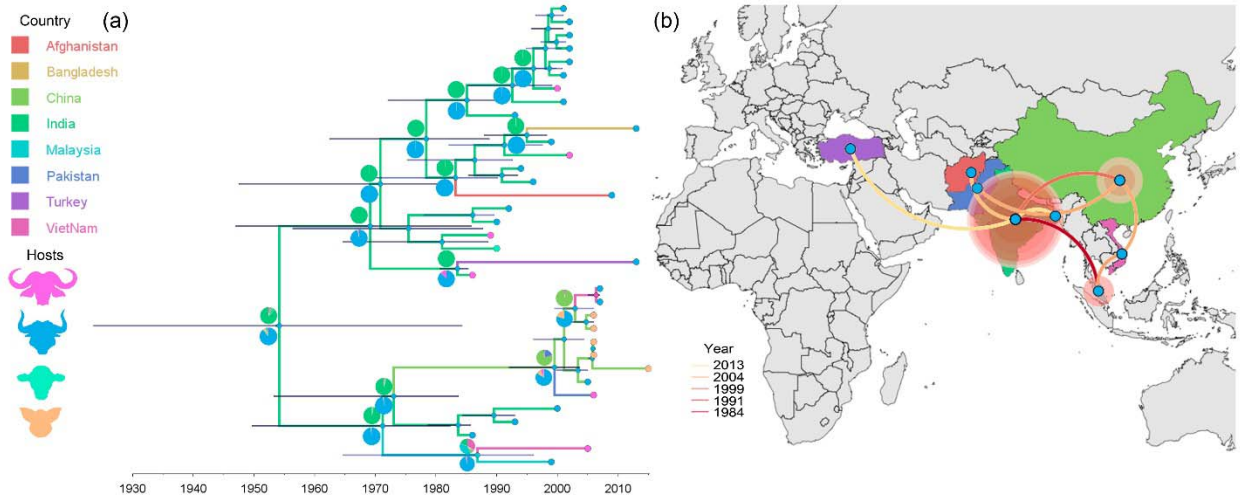

FIGURE 5. Epidemiological statistics estimated for Foot-and-mouth disease (Serotype Asia 1) epidemic. (a) Maximum clade credibility phylogeny of the FMDV epidemic, colored according to the countries where the disease has been registered. Dots at the end of the branches represent the host species (buffalo, cattle, sheep, and swine). The probabilities of ancestral states (inferred from the Bayesian MCMC discrete traits analysis) are shown in pie charts at each node, where charts above branches represent locations and charts below branches most probable hosts. (b) Reconstructed spatiotemporal diffusion of FMD serotype Asia1 spread,

where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events.

Serotype SAT1

The phylogeographic patterns of SAT1 exposed Uganda as the most likely country of origin, from where it diverged to Namibia, Nigeria, and Chad (Figures 6a and 6b). Phylogenetic relationship identified three main sublineages, one of them represented by the ancestor Uganda and Chad, other group by the countries that are part of the southern spread (i.e., Botswana, Mozambique, Namibia, South Africa and Tanzania), and the last group represented by Nigeria, which is also the sublineage with the most recent appearance. Contrary to the previous serotypes, SAT1 did not present a clear source of dispersal events, although its spread was mostly concentrated on the Eastern part of Africa (Figure 6b). Despite SATs serotypes are only distributed across Africa, in the case of SAT1, the highest proportion of its dispersal events occurred across long distance countries (63% of the cases. See Supplementary Video S4 for detailed footage). The hosts associated with the dispersion of this serotype were cattle and buffalo (Figure 6a). Cattle, with 65% of the reports, had a higher representation, mainly in the north and central Africa, while buffaloes, which represented 35% of the reports, appeared as the most common host in the southern countries (i.e., Namibia, Botswana, and South Africa). Intriguingly, the phylogenetic analysis showed cattle as the host of the ancestral lineages of SAT1, which would later adapt to infect buffalo in some regions (Figures 6a and 6b).

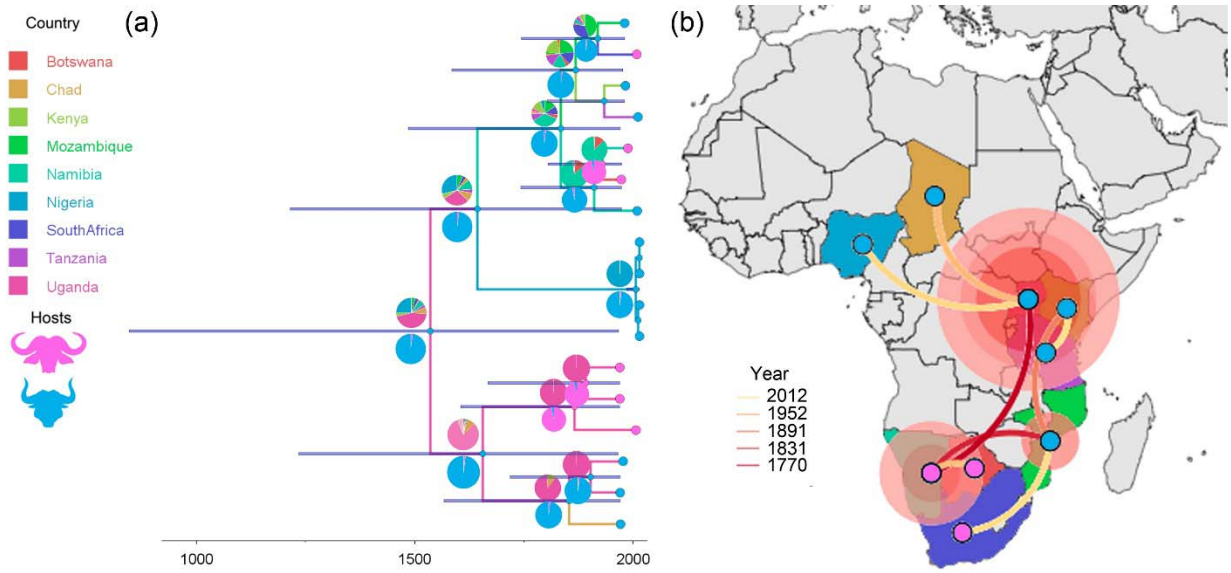

FIGURE 6. Epidemiological statistics estimated for Foot-and-mouth disease (Serotype SAT1) epidemic. (a) Maximum clade credibility phylogeny of the FMDV epidemic, colored according to the countries where the disease has been registered. Dots at the end of the branches represent the host species (buffalo, cattle, sheep, and swine). The probabilities of ancestral states (inferred from the Bayesian MCMC discrete traits analysis) are shown in pie charts at each node, where charts above branches represent locations and charts below branches most probable hosts. (b) Reconstructed spatiotemporal diffusion of FMD serotype SAT1 spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events.

Serotype SAT2

As in SAT1, phylogeographic analyses for SAT2 indicated Uganda as the most likely origin of the serotype, from which it spread to Botswana and The Gaza Strip later on time (Figures 7a and 7b). From Botswana, the serotype moved to Ethiopia, Zimbabwe, and Zambia, continuing spreading to surrounding countries also on the Eastern region of Africa (See Supplementary Video S5 for detailed footage). Phylogenetic relationships identified two main sublineages, one represented by Uganda and its further dispersion to Gaza Strip and the second group formed by countries distributed in southeastern Africa. Spatiotemporal dynamics evidenced a slightly higher proportion of long-distance movements (57%) over local dispersal events (Figure 7b). Cattle and buffalo were also the main hosts found for SAT2, but in this case, buffalo was the most representative host (65%), over 35% registered by cattle. However, cattle appeared in most of the reported locations (except in South Africa), while buffalo was only described in Uganda, Botswana and South Africa. As observed in SAT1, phylogenetic analysis showed a higher influence of cattle as the host of the ancestral lineages of this serotype (Figures 7a and 7b).

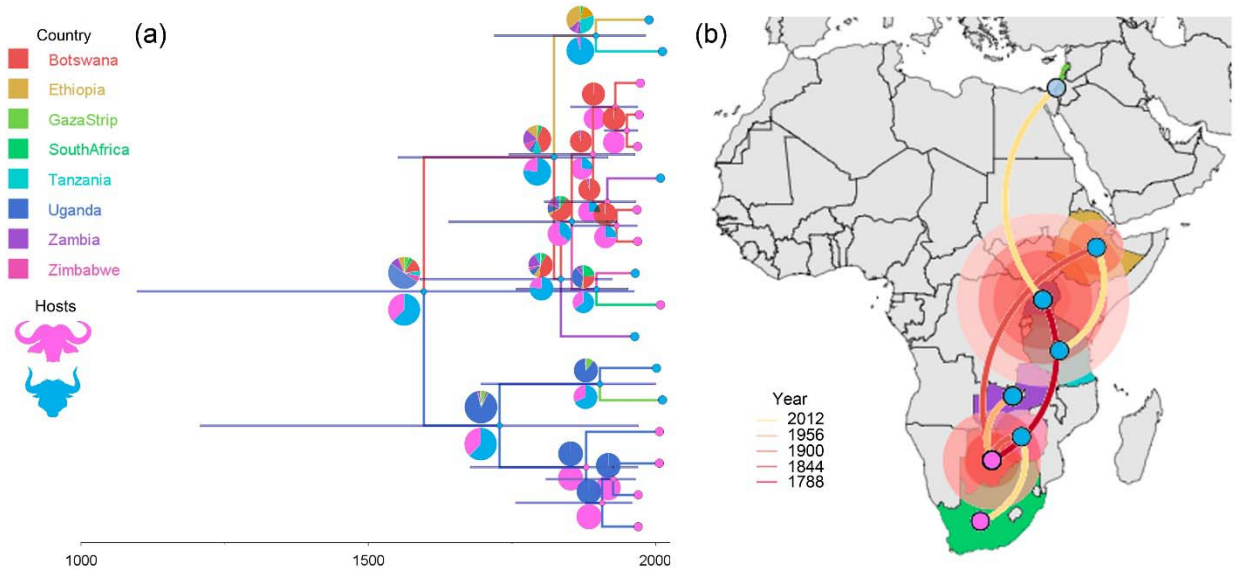

FIGURE 7. Epidemiological statistics estimated for Foot-and-mouth disease (Serotype SAT2) epidemic. (a) Maximum clade credibility phylogeny of the FMDV epidemic, colored according to the countries where the disease has been registered. Dots at the end of the branches represent the host species (buffalo, cattle, sheep, and swine). The probabilities of ancestral states (inferred from the Bayesian MCMC discrete traits analysis) are shown in pie charts at each node, where charts above branches represent locations and charts below branches most probable hosts. (b) Reconstructed spatiotemporal diffusion of FMD serotype SAT2 spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events.

Serotype SAT 3

Following the previous SATs serotypes, SAT3 also presented its ancestral origin in Uganda, from where it traveled to Zimbabwe and then spread to its neighboring countries (Figures 8a and 8b, see Supplementary Video S6). Phylogenetic analyses identified two main sublineages, one of them represented by Uganda and the second (and most diverse), by the countries that are part of the southern spread (i.e., Botswana, South Africa, Zambia, and Zimbabwe). Phylogeographic reconstruction reflected the importance of Zimbabwe for the spread of this serotype, being this country the most common center of origin for the diffusion of the disease to Zambia, Botswana and most recently to South Africa. Contrary to all the other serotypes, spatiotemporal dynamics of serotype SAT3 showed that its spread has been dominated by local

events (75%). As in the other SATs serotypes, cattle and buffalo were the main hosts reported for SAT3, appearing both in a similar proportion (cattle=59%, and buffalo=41%). Phylogeographic analyses showed that, even when cattle was determined as the most likely ancestral host, both species are almost equally responsible for the spread of the disease to most of the countries (Figures 8a and 8b).

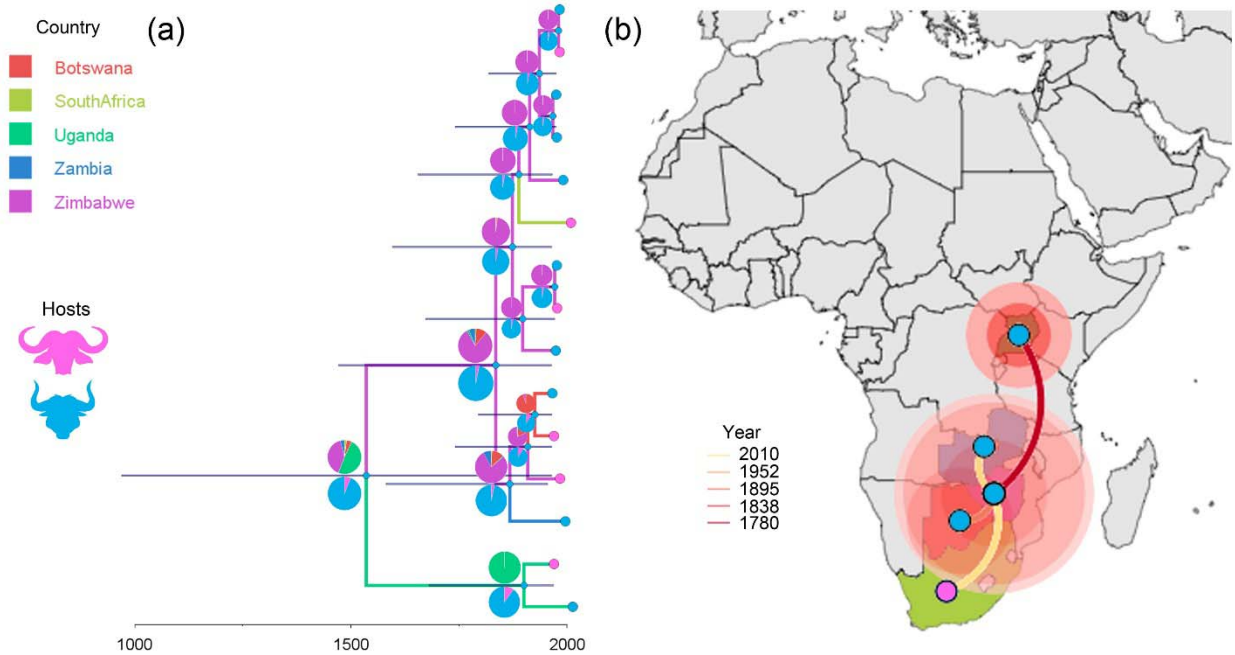

FIGURE 8. Epidemiological statistics estimated for Foot-and-mouth disease (Serotype SAT3) epidemic. (a) Maximum clade credibility phylogeny of the FMDV epidemic, colored according to the countries where the disease has been registered. Dots at the end of the branches represent the host species (buffalo, cattle, sheep, and swine). The probabilities of ancestral states (inferred from the Bayesian MCMC discrete traits analysis) are shown in pie charts at each node, where charts above branches represent locations and charts below branches most probable hosts. (b) Reconstructed spatiotemporal diffusion of FMD serotype SAT3 spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events.

DISCUSSION

Macroecological patterns in the spread of FMDV

Global patterns of FMDV spread showed considerable asymmetries in the spatiotemporal dynamics exhibited due to differences in the local and global spread showed by each serotype, these results are in concordance with the observed by Yoon et al., (2011). However, we had discrepancies with previous studies regarding the phylogenetic relationship among the FMDV serotypes, since some of them indicated that all FMDV serotypes were monophyletic (Cooke and Westover, 2008). Lewis-Rogers et al. (2008) and Yoon et al. (2011) suggested that O, A, Asia 1, C, and SAT 3 were monophyletic, while SAT 1 and SAT2 serotypes were polyphyletic. Our results indicated only four monophyletic serotypes (O, A, Asia1, and C), whilst all SATs serotypes appeared to have multiple ancestral origins which can be related to multiple points of independent introduction of the virus in the affected countries.

In this study, we followed the historical spread of FMDV, serotypes, from the ones with local distribution (Asia 1 and SATs) to the serotypes with widespread dispersion (O and A), where the lineage diversification was accompanied by colonization of new areas, which in most of the cases were considerable distant. Supporting previous studies (Sobrino et al., 2001; Fèvre et al., 2006; Di Nardo et al., 2011; Jamal and Belsham, 2013; Knight-Jones and Rushton, 2013; Brito et al., 2017) our results suggested that the success in the spread of this disease through long distances has been mainly associated with movement of commercial hosts (i.e., cattle, swine, and sheep) or/and international trade of animal products, while local movements could be more related to wild hosts (i.e., African buffalos).

Our results also showed that, even though the general spatiotemporal dynamics that characterize the spread of most serotypes is represented mostly by long distance movements across countries that are not part of their international borders, local movements are also important for some serotypes especially SATs. These results complement the observations made by (Bouslikhane, 2015), who highlighted how nomadism and transhumance play a key role in disease transmission, especially in African countries.

Long distance spread

The remarkable historical spread exhibited by serotype O was the biggest registered among all FMDV serotypes. In half of a century, this serotype colonized almost all the continents. Interestingly, this spread is characterized principally by dispersion across long geographically distant regions (to regions not sharing international borders with the origin country), instead to its neighboring countries. Our phylogeographic estimates were in agreement with the historical records of the past outbreaks (Jamal and Belsham, 2013; Brito et al., 2017) where in the case of serotype O, it was responsible for the most catastrophic economic impact of FMDV worldwide

(Knight-Jones and Rushton, 2013; Rushton and Knight-Jones, 2015). For example, the outbreak in United Kingdom in 2001 (King et al., 1981; Thompson et al., 2002; Gloster et al., 2006) Japan in 2010 (Muroga et al., 2011; Shimada et al., 2016), China 2010 (Zheng et al., 2012) and South Korea 2010 (Jeong-Nam et al., 2014). One of the reasons for the success of the evolutionary diversification of this serotype may be related to the diversity of hosts that it affects, which is the highest among all serotypes.

Following the pandemic serotype O, the next large-scale potential of diffusion was found in serotype A. This serotype has been reported in three continents, Asia, Africa and South America, where it was reported as the causing agent of one of the biggest FMDV outbreaks (Argentina, 2011), affecting a total of 2,126 herds (Perez et al., 2004b).

Local spread serotypes

Whereas our results showed that serotypes O and A have spread worldwide, serotypes Asia1 and SATs remained nonpandemic and confined in their endemic regions. The spread of the serotype Asia1 was characterized mainly by local movements across the neighboring countries surrounding India, China and Malaysia, where it is well known that free and unrestricted animal movements across country borders play a key role in the spread of FMDV (Subramaniam et al., 2013; Brito et al., 2017). The dispersion of the disease into Turkey in 2013 represents one of the most recent and longer dispersion events for this serotype, which was directly related to an Indian subgroup of the virus. Likewise, as reported by (Abdul-Hamid et al., 2011) the outbreak occurred in Malaysia during 1999 seemed to be caused also by an independent subgroup from the rest of the outbreaks observed in the region.

SAT serotypes (SAT1, SAT2, and SAT3) also exhibited a local spread, limited across their endemic areas. This spread occurred mainly in Africa, where nomadic pastoralism across international borders and animal trade in the sub-Saharan region is one of the most practiced forms of livestock movements (Di Nardo. et al., 2011), which we suggest may be the main transmission route for these serotypes. Previous studies have highlighted the importance of African buffalo (*Syncerus caffer*) as one of the main hosts described for the SATs serotypes (Vosloo et al., 1996; Thomson et al., 2003; Brito et al., 2017). Differences on phylogenetic analyses showed that for SAT2, buffalo and cattle were both present as hosts of the ancestral lineages, which could be a sign of an early crossed infection, contrary to SAT1 and SAT3, where buffalo seemed to have appeared as a host later on time, mostly on the southern countries of the continent. This could have conducted to a potential viral generalism between these host species that would later disappear due to the tendency of the virus to evolve to

narrower niches, leading to the specificity of viral-host relationships currently reported (Elena et al., 2009).

In general, considerable asymmetries in the spatiotemporal dynamics exhibited by the different serotypes were observed. Serotypes such as Asia1 and SATs presented local spread rates, mainly associated with cattle and sheep (with special importance of buffalo in the case of SATs serotypes), while serotypes O and A showed long-distance spread, covering higher extensions of territory between each outbreak. These serotypes presented the highest variety of susceptible host, although we suggest that the main reason for their successful long-distance spread relies mostly on the international movements of cattle and swine due to the intensive commerce between countries.

Final remarks

Studies considering WGS should be preferred over specific regions, mainly to ensure the detection of all informative mutations for phylogenetic analyses. FMD as a small-genome RNA virus represents an excellent candidate for this approach, due to the well-known mutation rate and the variability that RNA viruses possess (Gilchrist et al., 2015). However, for our study, the use of WGS represented a limitation since partial sequences were available in some underrepresented countries which were not included in our analysis. For that reason, here we highlight the importance of including WGS in future studies. These projects would not only increase the available information about the virus, but also have a direct impact on promoting new and more specific measures for disease control (Schrag and Wiener, 1995; Duchatel et al., 2018; Fountain-Jones et al., 2018), reducing drastically the economic impact caused by FMDV and inefficient resource allocation. One example of this would be the consideration of the most influencing host for the spread of FMDV in a given area, targeting these strategies to reduce the main source of infection. This control would not only be beneficial for the targeted region, but also for all the areas connected directly (i.e., through geographical limits) and indirectly (i.e., through commercial networks) with it. For that reason, we defend that understanding the complex evolutionary history of FMDV is not only critical for endemic countries, but also for regions in which FMDV has been eradicated and especially for countries in which vaccination will be withdrawn in the coming years, such as in Brazil (Reuters, 2018). We also encourage future efforts from regions and international organizations for the development of a better and more comprehensive archive of virus circulation by including WGS and a complete metadata repository to facilitate the understanding of the factors promoting the continual emergence and rapid spatial dispersal of new viral lineages. This will be necessary to help future vaccine design

and better-informed strategies for viral control, providing insights into viral interactions and disease control optimization based on scientific evidence.

CONCLUSION

In summary, in this study, we addressed the worldwide circulation of FMDV, by characterizing its global macroevolutionary patterns at serotype scale. The macroevolutionary approach used here relies on the principle that evolutionary processes are better understood when a broader spatiotemporal vision is available, allowing us to understand the whole evolutionary history of a given organism. Establishing the phylogeographic relationships among FMDV serotypes at the global scale will shed light on their macroevolutionary patterns by reconstructing its historical viral routes of spread, as well as the role of their major hosts. Besides, from this perspective, we can conclude that as a response to the detection of an outbreak event, closing borders with neighboring countries should not be the only measure applied, since some of the most virulent FMDV lineages spread through the long-distance transport of animals or its natural products, and therefore, control measures should take into account all the commercial network of the affected country, especially from regions that have been historically considered as centers of dispersal of the disease.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interests.

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SUPPLEMENTARY MATERIAL

TABLE S1. Sample information for all Foot and Mouth Disease virus complete genome sequences used in this study.

TABLE S2. Root-to-tip regression analyses of phylogenetic temporal signal. Correlation and determination coefficient (R2) were estimated with TempEst (Rambaut et al. 2016). P-values were calculated using the approach of Murray et al. (2016) and were based on 1,000 random permutations of the sequence sampling dates (Navascuès et al. 2010).

TABLE S3. Number of sequences and serotypes per country.

FIGURE S1. Spatial distribution of Foot-and-mouth disease virus showing the number of serotypes per country.

Video S1. Reconstructed spatiotemporal diffusion of FMD serotype O spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events, this visualization match with the main time bar on top of the video.

Video S2. Reconstructed spatiotemporal diffusion of FMD serotype A spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events, this visualization match with the main time bar on top of the video.

Video S3. Reconstructed spatiotemporal diffusion of FMD serotype Asia1 spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events, this visualization match with the main time bar on top of the video.

Video S4. Reconstructed spatiotemporal diffusion of FMD serotype SAT1 spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events, this visualization match with the main time bar on top of the video.

Video S5. Reconstructed spatiotemporal diffusion of FMD serotype SAT2 spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events, this visualization match with the main time bar on top of the video.

Video S6. Reconstructed spatiotemporal diffusion of FMD serotype SAT3 spread, where diameters of the colored circles are proportional to the square root of the number of MCC branches, maintaining a particular location state at each time period. The color of the branches represents the age of the internal nodes, where darker red colors represent older spread events, this visualization match with the main time bar on top of the video.