

1 **Tracing foot-and-mouth disease virus phylogeographical patterns and transmission**
2 **dynamics.**

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

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15

16 **Abstract**

17 Foot-and-mouth disease virus (FMDV) has proven its potential to propagate across local and
18 international borders on numerous occasions, but yet details about the directionality of the
19 spread along with the role of the different host in transmission remain unexplored. To elucidate
20 FMDV global spread characteristics, we studied the spatiotemporal phylodynamics of serotypes
21 O, A, Asia1, SAT1, SAT2, and SAT3, based on more than 50 years of phylogenetic and
22 epidemiological information. Our results revealed phylogeographic patterns, dispersal rates, and
23 the role of host species in the dispersal and maintenance of virus circulation. Contrary to
24 previous studies, our results showed that three serotypes were monophyletic (O, A, and Asia1),
25 while all SATs serotypes did not evidence a defined common ancestor. Root state posterior
26 probability (RSPP) analysis suggested Belgium as the country of origin for serotype O (RSPP=

27 0.27). India was the ancestral country for serotypes A (RSPP= 0.28), and Asia-1 (RSPP= 0.34),
28 while Uganda appeared as the most likely origin country of all SAT serotypes (RSPP> 0.45).
29 Furthermore, we identified the key centers of dispersal of the virus, being China, India and
30 Uganda the most important ones. Bayes factor analysis revealed cattle as the major source of
31 the virus for most of the serotypes (RSPP> 0.63), where the most important host-species
32 transition route for serotypes O, A, and Asia1 was from cattle *Bos taurus* to swine *Sus scrofa*
33 *domesticus* (BF>500), while, for SAT serotypes was from *B. taurus* to African buffalo *Syncerus*
34 *caffer*. This study provides significant insights into the spatiotemporal dynamics of the global
35 circulation of FMDV serotypes, by characterizing the viral routes of spread at serotype level,
36 especially uncovering the importance of host species for each serotype in the evolution and
37 spread of FMDV which further improve future decisions for more efficient control and
38 eradication.

39

40 **Keywords:** molecular epidemiology, transboundary emerging diseases, virus dispersal.

41

42 INTRODUCTION

43 The rapid growth of global population along with the current demand for animal protein and the
44 increasing animal trade have increased the spread of a broad range of transboundary animal
45 diseases (TADs) [1, 2]. Clear examples of this phenomenon are the recent emergence of
46 African Swine Fever in Asia, Avian Influenza or Contagious Bovine Pleuropneumonia and the
47 return of Foot-and-mouth disease virus (FMDV) to Korea and other countries which successfully
48 eliminated the virus for several years [3–7]. Understanding the tempo and mode of disease
49 evolution allows to estimate the impact of external factors influencing these diseases and
50 assess the evolutionary patterns followed over time, which can be better studied by considering
51 the most recent advances in virus sequencing and phylogenetics [8–10].

52 Molecular phylogenetics has shown to be an accurate and highly impacting approach in
53 the understanding of the spatiotemporal dynamics of infectious diseases, with the capacity to
54 explain disease spread, virulence and invasion potential [11–20]. In the case of TADs,
55 molecular phylogenetics has also proven to be a useful approach, providing accurate
56 knowledge for the control of pathogens worldwide [21–24], however, it remains underused.

57 FMDV causes the most influential transboundary animal disease with historical
58 worldwide circulation reported in domestic and wildlife reservoirs [25, 26]. FMD is a highly
59 contagious disease caused by a small single-stranded RNA virus of the genus *Aphthovirus*,
60 member of the family Picornaviridae [27] and classified into seven different serotypes; O, A, C,
61 Asia1 and Southern African Territories (SATs) 1, 2 and 3 [25, 28–30] which severely affect the
62 productivity of domesticated livestock, causing great economic losses [31–33]. The United
63 States Department of Agriculture has estimated that the introduction of FMDV could result in
64 losses between \$15 to \$100 billion [34–37]. One of the main reasons for this great impact is the
65 wide variety of hosts known for FMDV (i.e., cattle, buffalo, swine, sheep, and deer), altogether it
66 affects more than 70 species of cloven-hoofed animals [38]. FMDV is known to be transmitted
67 locally and globally, often associated with infected animal products and human and animal
68 movements [39, 40]. Transmission is also facilitated by airborne spread, direct animal contact
69 with infected individuals or carcasses and translocation of contaminated staff, equipment, and
70 machinery [41, 42].

71 Individual genes have been widely used to study the phylogenetic relationships among
72 FMD serotypes [43–50], however, little has been done using whole genome sequences (WGS)
73 [26, 51–53]. Nevertheless, these studies have been often based on a limited number of
74 sequences (<200), or on phylogenetic methods that do not have the ability to accommodate
75 uncertainty (i.e., Bayesian phylodynamic methods) [54]. Although these methods have been
76 widely used, they present certain degree of evolutionary inaccuracy since in most cases
77 (excluding Yoon et al (2011) and Omondi et al (2019)) the Bayesian phylogenetic and

78 phylodynamic methods were not considered. Thus, their inherent ability to accommodate
79 uncertainty, and therefore to assess the level of error of the predictions obtained, was often
80 neglected.

81 Several studies have explored the spatiotemporal evolutionary dynamics of FMDV in
82 different parts of the world, mainly focusing on the diffusion patterns across its endemic regions:
83 Asia and Africa [31, 48, 55–59] However, studies considering all serotypes are only available
84 within small geographic regions, and global studies only assessed some of the viral serotypes
85 [56, 60].

86 In this study, we investigated the spatiotemporal dynamics of FMDV by using Bayesian
87 phylodynamic analyses of comprehensive genetic, geographical and temporal data regarding
88 past FMDV occurrences. The objectives of this work were to reconstruct the global evolutionary
89 epidemiology of FMDV serotypes O, A, Asia1, and SATs, to make comparisons among the
90 global spatiotemporal spread of each FMDV serotype, identify ancestral countries and provide
91 inferences about the evolutionary patterns and the transmission between host species.

92

93 **MATERIALS AND METHODS**

94 **Data collection and curation**

95 We built a comprehensive genetic database comprising 249 publicly available whole genome
96 sequences from six FMDV serotypes (A, O, Asia1, SAT 1, SAT 2 and SAT 3), with collection
97 dates ranging from 1959 to 2017 (GenBank ID numbers in Supplementary material Table S1).
98 Serotype C was not included in this study due to data unavailability (only 3 sequences were
99 available). Our dataset gathers information from 43 countries and 4 continents obtained from
100 the Virus Pathogen Resource database, available at <https://www.viprbrc.org> (See Table S1). To
101 determine accurate phylogenetic relationships among FMDV reports, we combined the available
102 genetic information along with collection date, host species (i.e., *Bos taurus*= cattle, *Syncerus*
103 *caffer*= African buffalo, *Bubalus bubalis*= Water buffalo, *Sus scrofa domesticus*= swine, *Sus*

104 *scrofa*= boar, and *Ovis aries*= sheep) and location (discrete information at country level) as
105 metadata information. Any sample lacking one of these three characteristics was discarded.

106

107 **Discrete phylogeographical analysis**

108 Sequences were aligned using Mega X, available at www.megasoftware.net [61]. The
109 recombination detection program (RDP) v5.3 was used to search for evidence of recombination
110 within our dataset [62]. Each serotype was screened using five different methods (BootScan,
111 Chimaera, MaxChi, RDP, and SiScan). After removing all the duplicated sequences (i.e.,
112 representing the same outbreak), no evidence of recombinant sequences was observed in any
113 FMDV serotypes analyzed. To determine whether there was a sufficient temporal molecular
114 evolutionary signal of the FMDV sequences used for each serotype phylogeny, we used
115 TempEst v1.5 [63]. To calculate the *P*-values associated with the phylogenetic signal analysis,
116 we used the approach described by [64] based on 1,000 random permutations of the sequence
117 sampling dates [65]. The relationship found between root-to-tip divergence and sampling dates
118 (years) supported the use of molecular clock analysis in this study for all serotypes. Root-to-tip
119 regression results for each serotype are reported in Supplementary Table S2, all the results
120 supported a significant temporal signal (*P*-value<0.05). Phylogeographic history of FMDV
121 dispersal was recovered from the obtained spatiotemporal phylogenies for each serotype.
122 Phylogenetic trees were generated by a discrete phylogeography estimation by Bayesian
123 inference through Markov chain Monte Carlo (MCMC), implemented in BEAST v2.5.0 [66]. We
124 partitioned the coding genes into first+second and third codon positions and applied a separate
125 Hasegawa-Kishino-Yano (HKY+G; [67]) substitution model with gamma-distributed rate
126 heterogeneity among sites to each partition [68].

127 By using Nested Sampling Beast package v1.0.4 [69] we compared different molecular
128 clock models to find the one that showed the best fit for the data related to each serotype. The
129 marginal likelihood value supported the use of uncorrelated lognormal relaxed molecular clock

130 [70]. To infer the epidemic demographic histories of FMDV per each serotype we estimated the
131 effective number of infections through time by using the Bayesian skyline plot approach [71]. All
132 analyses were developed for 200 million generations, sampling every 10,000th generation and
133 removing 10% as chain burn-in. All the Markov chain Monte Carlo analyses for each serotype
134 were investigated using Tracer software v1.7 [72] to ensure adequate effective sample sizes
135 (ESS) (above 200), which were obtained for all parameters. Final trees were summarized and
136 visualized via Tree Annotator v. 2.3.0 and FigTree 1.4.3 respectively (included in BEAST v2.5.0)
137 [66, 73].

138 To reconstruct the ancestral-state phylogeographic transmission across countries and
139 hosts, we used the discrete-trait extension implemented in BEASTv2.5.0 [66]. In addition, to
140 explore the most important historical dispersal routes for the spread FMDV across countries, as
141 well as most probable host-species transition, we used a Bayesian stochastic search variable
142 selection (BSSVS) [74]. Using BSSVS approach, we identified and eliminated the nonzero rates
143 of change between each pair of discrete traits (countries and hosts species) based on its Bayes
144 factor value obtained (lower than 3). To perform this analysis, a symmetric rate matrix was
145 assumed. To infer the intensity of directional transitions (forward and backward) within a matrix
146 of the discrete traits mentioned above, we used a Markov jumps approach. To interpret the
147 Bayes factors, a value of <3 , as mentioned above, is not significant (hardly worth mentioning),
148 $BF= 3.1-20$ represents positive support, $BF= 20.1-150$ represents strong support, while >150.1
149 represents an overwhelming support [75].

150 Finally, we visualized the spatiotemporal viral diffusion of each serotype by using Spatial
151 Phylogenetic Reconstruction of Evolutionary Dynamics using Data-Driven Documents (D3)
152 SPREAD3 software [76] considering the whole transmission and also the most significant
153 connections between localities following the Bayesian stochastic search variable selection
154 (BSSVS) method, with each country used as a discrete variable with a cutoff $BF > 3$ [75]. In
155 addition, we classified the viral spread of each serotype in two categories: local, if the

156 transmission occurs through neighboring countries, and long distance, if the dispersion jumps
157 beyond adjacent neighboring countries.

158

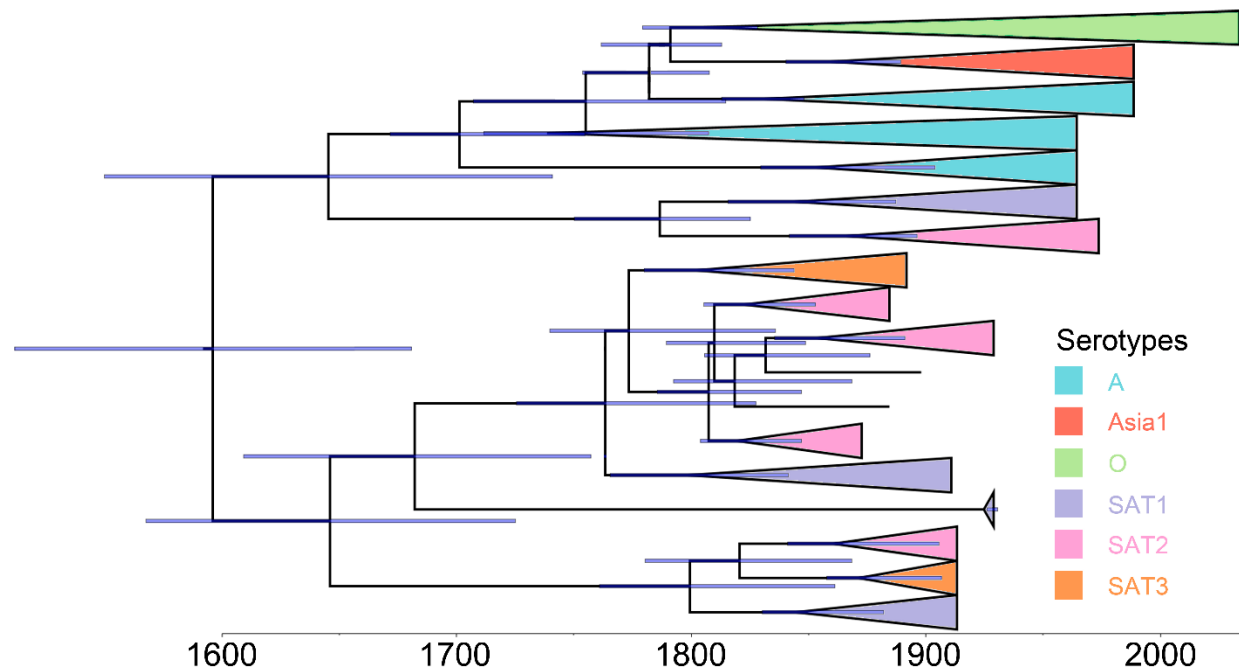
159 **RESULTS**

160 The number of available sequences per country varied from 1 to 18 whole genome sequences
161 (WGS). Our results showed that India, China, Uganda, Argentina, and Zimbabwe were the
162 countries with the highest number of available genomes (Supplementary Table S3). Likewise,
163 several countries have been historically affected by more than one serotype, particularly in
164 Africa and Asia, where we observed that Uganda presented the highest virus diversity as it has
165 been subjected to the spread of serotypes O, and all SATs (Supplementary Table S3,
166 Supplementary Fig. S1).

167

168 **Spatiotemporal dynamics of FMDV**

169 Phylogeographic analyses highlighted great asymmetries in the tempo and mode of each
170 serotype evolution (Fig. 1). SAT1 appeared to be the basal clade of the entire lineage,
171 originating SAT2, SAT3 and serotype A, which later diversified into serotype Asia1, and O. Our
172 analysis suggested O as the most recent, prolific and widespread lineage, with the highest
173 number of sequences available worldwide. Serotype A and Asia1 appeared second and third in
174 the number of available sequences, followed by all SAT serotypes. Maximum clade credibility
175 phylogeny showed the monophyly of serotypes O, A, and Asia1 (each serotype shared a
176 common ancestor), while SAT serotypes appeared to have multiple origins (Fig. 1).



177

178 **Fig. 1** Condensed phylogenetic tree showing the overall evolutionary history of FMDV
179 representing the relationships between all serotypes. The tree is based on a maximum clade
180 credibility phylogeny inferred from 249 whole genome sequences. Branch bars represent
181 posterior probabilities of branching events ($P > 0.95$).

182

183 **Spatiotemporal diffusion among serotypes**

184 We investigated and compared the historical spreads of FMDV at serotype level, from the ones
185 with local distribution (Asia1 and SATs) to the serotypes with widespread dispersal (O and A)
186 (Sobrino et al., 2001; Fèvre et al., 2006; Di Nardo et al., 2011; Jamal and Belsham, 2013;
187 Knight-Jones and Rushton, 2013; Brito et al., 2017).

188

189 **Serotype O**

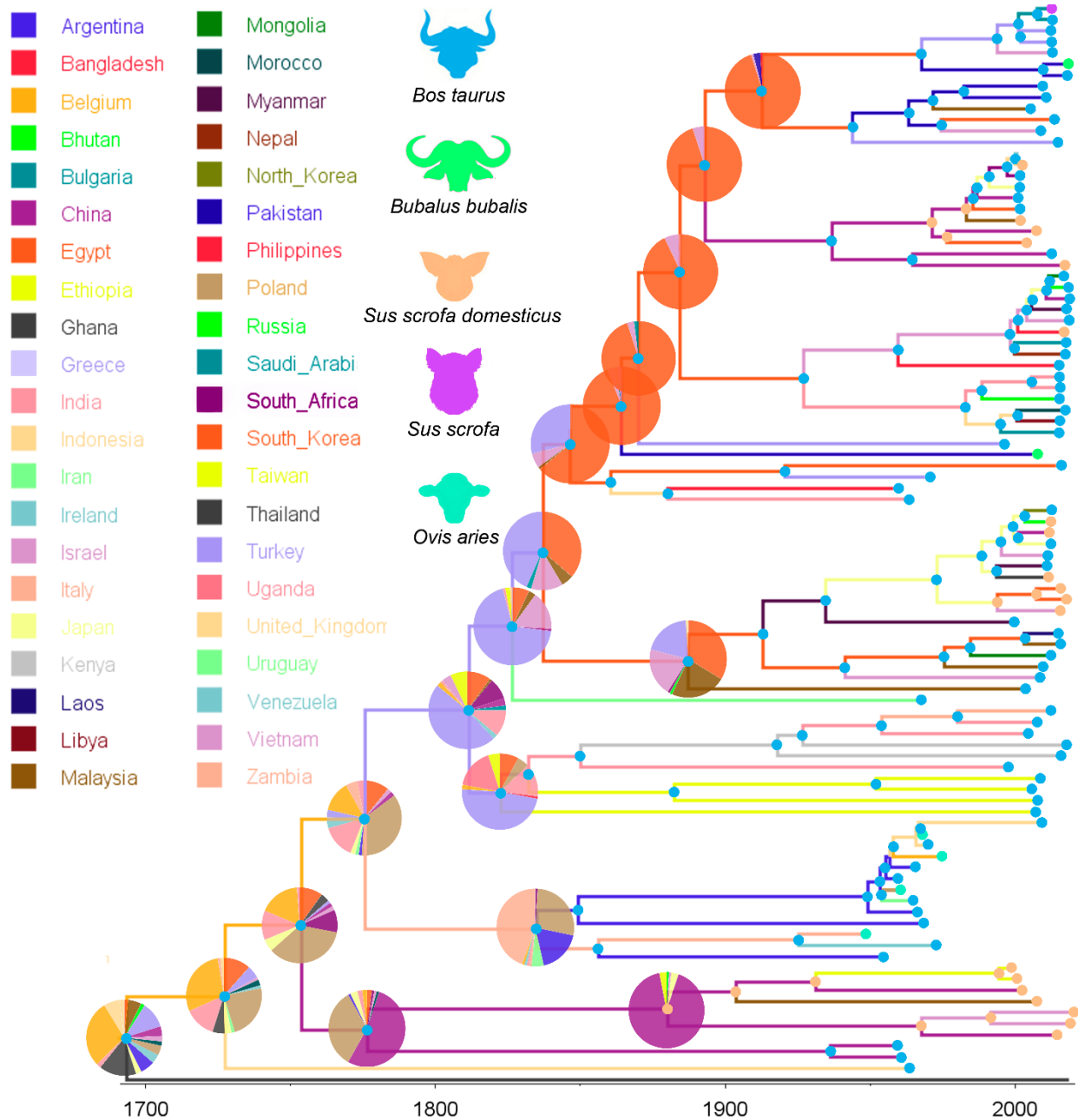
190 We analyzed 97 WGS from serotype O, which comprises 39% of the global FMDV tree (Fig. 1).
191 This serotype also presents the widest distribution of all serotypes, with records from 42
192 countries (Fig. 2). Based on our phylogeographic analysis, the most likely center of origin for

193 this serotype was Belgium (root state posterior probability [RSPP] = 0.27) from which it spread
194 globally across long distances to several countries through Europe, Asia, Africa and South
195 America. A remarkable aspect of this global spread is that most of it has occurred in less than
196 50 years (Fig. 3A) (see Supplementary Video S1 for detailed footage). These patterns have also
197 appeared in our spatiotemporal diffusion map, which shows that the global distribution of this
198 serotype is highly represented by long-range movements across countries and continents (Fig.
199 3A). Phylogenetic reconstruction identified clusters formed by different sub-lineages, where the
200 most representative centers of dispersal events (geographic spread accompanied by
201 diversification) for this serotype were Poland and the United Kingdom in Europe, China, Japan,
202 and Indonesia in Asia, Egypt in Africa and Argentina in South America. Likewise, we observed
203 that China, South Korea, and Turkey were also among the countries with the highest number of
204 sequences (see Fig. 1A). In addition, BSSVS-BF results showed the most significant viral
205 transmission routes for serotype O, where the most intense were represented from Turkey to
206 Egypt, from Egypt to Indonesia and from Myanmar to Japan ($BF > 1038.7$) (Fig. 3B).

207 Serotype O also showed the highest host diversity among all FMDV serotypes, which is
208 represented by cattle (*Bos taurus*), swine (*Sus scrofa domesticus*), boar (*Sus scrofa*), sheep
209 (*Ovis aries*), and the water buffalo (*Bubalus bubalis*), where the most representative were *B.*
210 *taurus* (71% of the sequences) and *S. scrofa domesticus* (20%). *B. taurus* was not only the
211 most important host for this serotype but also the most likely initial host of the ancestral lineages
212 (RSPP= 0.95), followed by *S. scrofa domesticus* (RSPP= 0.03) and *O. aries* (RSPP= 0.032)
213 respectively (Fig. 2). Bayes factor analysis showed that the most significant transmission routes
214 occurred from *B. taurus* to *S. scrofa domesticus* (BF= 635.3), followed by from *B. taurus* to *O.*
215 *aries* (BF=73.6), and in a minor scale, from *S. scrofa domesticus* to *B. taurus* (BF= 9.7), as well
216 as from *B. taurus* to *B. bubalis* (BF=9.1) (Fig. 3C).

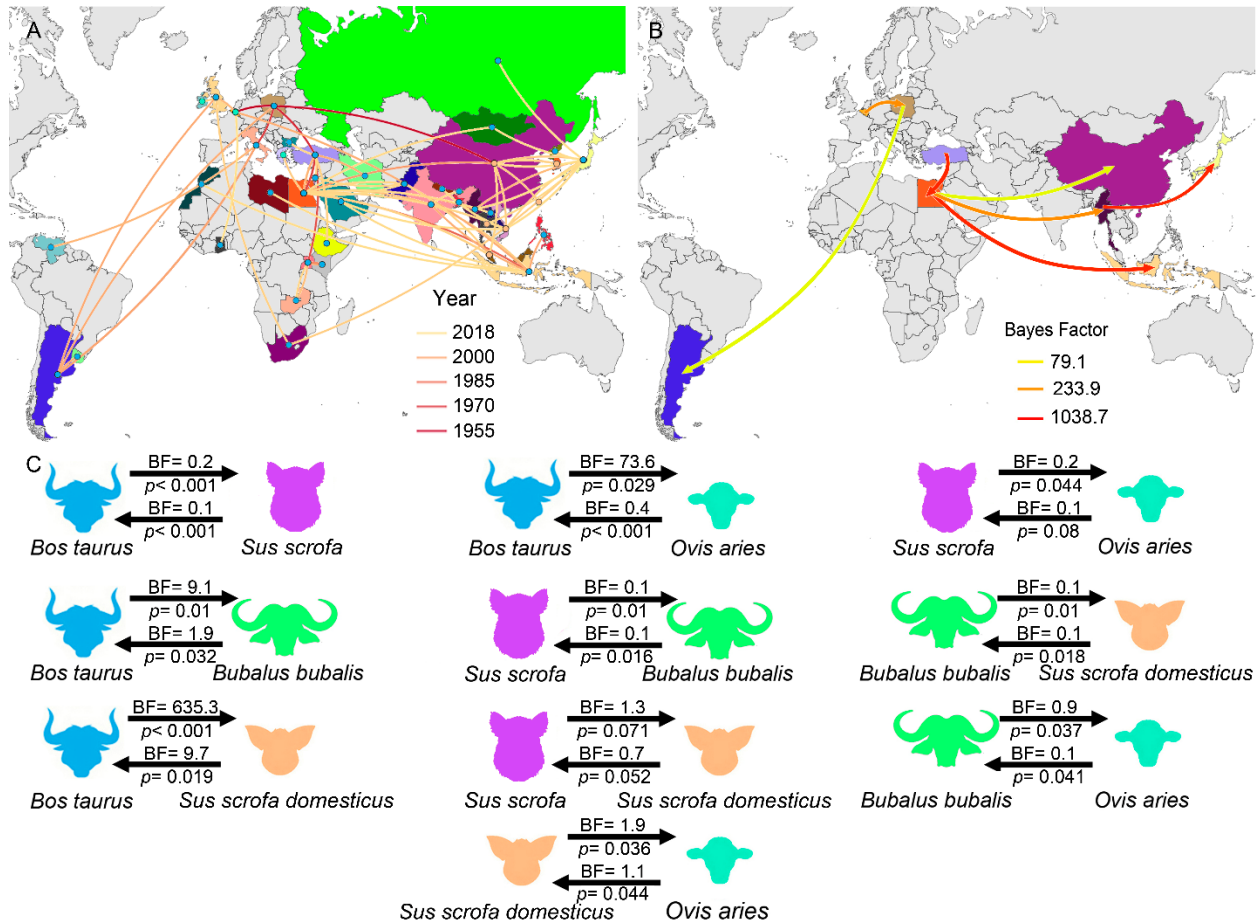
217 The Bayesian skyline plot (BSP) was used to describe the observed changes in genetic
218 diversity (population size) through time, showing a steady pattern in this serotype, with a sharp

219 decrease in its effective population size occurred ~2000, which returned to previous rates years
220 later (Fig. S2).



221
222 **Fig. 2** Dispersal history of FMDV lineages of Serotype O, as inferred by discrete
223 phylogeographic analysis. Maximum clade credibility phylogeny colored according to the
224 countries of origin. Branch bars represent posterior probabilities of branching events ($P > 0.95$).
225 Colored dots at the end of the branches represent the host species (*Bos taurus*= cattle, *Sus*

226 *scrofa domesticus*= swine, *Ovis aries*= sheep, *Bubalus bubalis*= water buffalo, and *Sus scrofa*=
 227 *boar*). The probabilities of ancestral states (inferred from the Bayesian discrete trait analysis)
 228 are shown in pie charts at each node, while circles on each branch and tips represent the most
 229 likely hosts.



230
 231 **Fig. 3** (A) Reconstructed spatiotemporal diffusion of FMDV serotype O spread, the color of the
 232 branches represents the age of the internal nodes, where darker red colors represent older
 233 spread events. (B) Representation of the most significant location transitions events for FMDV
 234 serotype O spread based on only the rates supported by a BF greater than 3 are indicated,
 235 where the color of the branches represent the relative strength by which the rates are
 236 supported. (C) Transmission rates between hosts (*Bos taurus*= cattle, *Sus scrofa domesticus*=
 237 swine, *Ovis aries*= sheep, *Bubalus bubalis*= water buffalo, and *Sus scrofa*= boar). based on

238 BSSVS-BF values are represented on the top of the black arrows, while the root state posterior
239 probability for the host-species transition are given on its bottom.

240

241 **Serotype A**

242 Phylogeographic relationships obtained for serotype A indicated India as its most likely center of
243 origin (RSPP= 0.28, Fig. 4). Besides, several centers of diversification have been identified for
244 this serotype, where the most important have been India and Malaysia in Asia, Netherlands and
245 Germany in Europe, Chad in Africa and Brazil in South America (Fig. 4). Our phylogeographic
246 analysis also highlighted the importance of Brazil as a center of origin for a wide variety of
247 European and South American lineages (Fig. 4). As in serotype O, we observed that long-
248 distance dispersal events were the most representative of the spatiotemporal dynamics of this
249 serotype, evidencing a global distribution, with records from 33 countries (Fig. 5B), which
250 represents 33% of the total FMDV sequences.

251 BSSVS-BF analysis evidenced that the most significant transmission routes for this
252 serotype come from India. Bayesian Factor analysis describing the most important viral
253 transmission routes highlighted the importance of India in different directions, mainly to
254 Netherlands (BF= 173.2), to Chad (BF= 162.9), and to Malaysia (BF= 28.3). Likewise, some
255 European, such as Germany appeared to be important for the spread of this serotype into South
256 America (BF=81.6, Fig. 5B).

257 The host species that showed highest number of serotype A sequences comes from *B.*
258 *taurus* (82%), followed by *O. aries* (10%), *S. scrofa domesticus* (6%), and *B. bubalis* (2%)
259 (Supplementary Table S1). Thus, the most important host behind the origin of the analyzed
260 sequences of serotype A was *B. taurus* (RSPP= 0.98, Fig. 4). Furthermore, Bayes factor
261 analysis indicated that the most significant transmission routes for the spread of this serotype
262 occurred from *B. taurus* to all the other host. In order of significance, we can observe: to *S.*
263 *scrofa domesticus* (BF= 1256.8), to *B. bubalis* (BF= 628.5), and to *O. aries* (BF= 74.1, Fig. 5C).

264 The BSP for this serotype showed a constant lineage diversity with a slight increase in
265 1980. The biggest variations between the years 2000 -2017, showed a sharp decrease followed
266 by a rapid increase in lineage diversity that was maintained until 2010 when these values mostly
267 returned to the original values (Fig. S2).

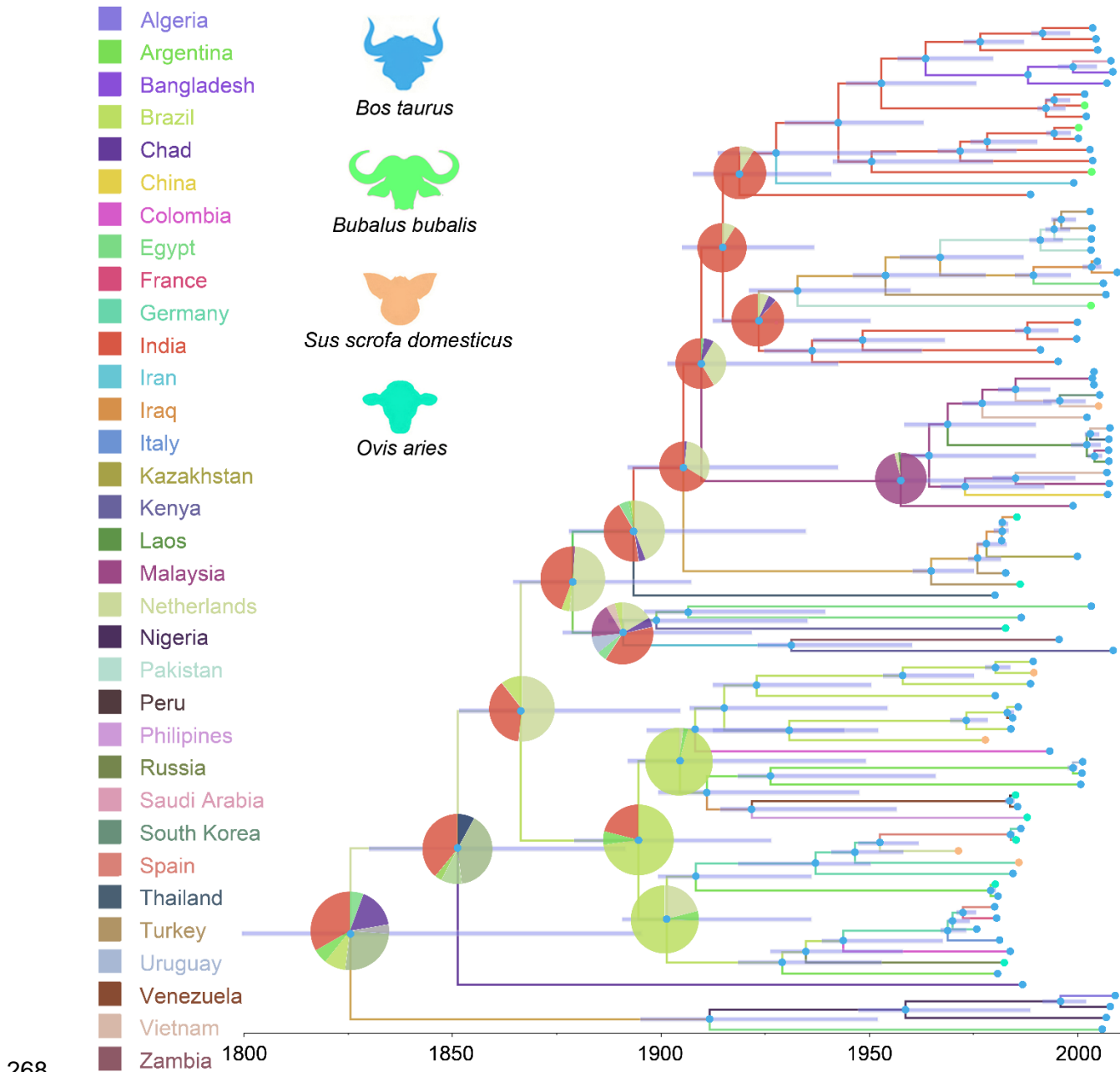
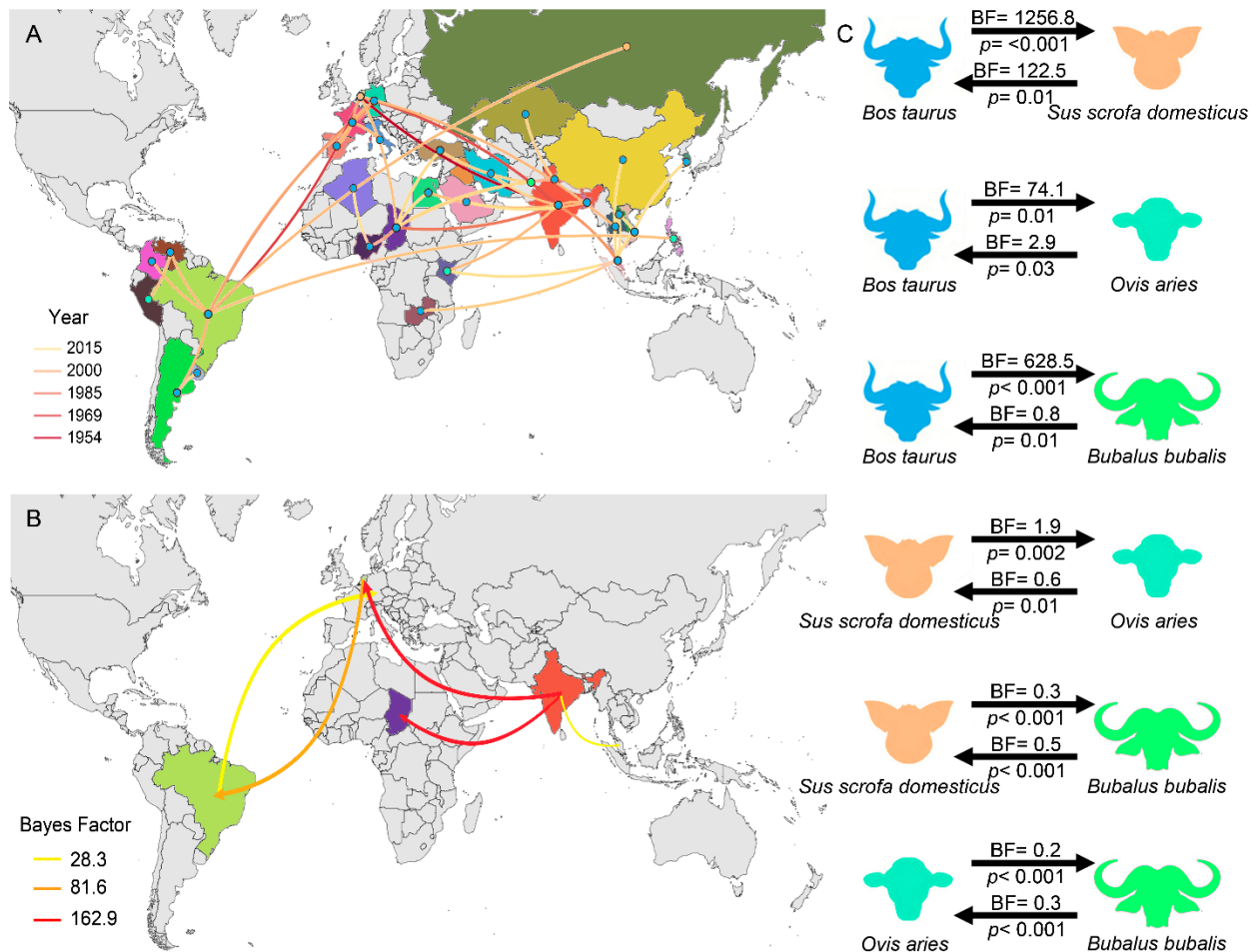


Fig. 4 Dispersal history of FMDV lineages of Serotype A, as inferred by discrete
phylogeographic analysis. Maximum clade credibility phylogeny colored according to the

271 countries of origin. Branch bars represent posterior probabilities of branching events ($P > 0.95$).
 272 Colored dots at the end of the branches represent the host species (*Bos taurus*= cattle, *Sus*
 273 *scrofa domesticus*= swine, *Ovis aries*= sheep, and *Bubalus bubalis*= water buffalo. The
 274 probabilities of ancestral states (inferred from the Bayesian discrete trait analysis) are shown in
 275 pie charts at each node, while circles on each branch and tips represent the most likely hosts.
 276



277
 278 **Fig. 5** (A) Reconstructed spatiotemporal diffusion of FMDV serotype A spread, the color of the
 279 branches represents the age of the internal nodes, where darker red colors represent older
 280 spread events. (B) Representation of the most significant location transitions events for FMDV
 281 serotype A spread based on only the rates supported by a BF greater than 3 are indicated,
 282 where the color of the branches represent the relative strength by which the rates are

283 supported. (C) Transmission rates between hosts (*Bos taurus*= cattle, *Sus scrofa domesticus*=
284 swine, *Ovis aries*= sheep, and *Bubalus bubalis*= water buffalo) based on BSSVS-BF values are
285 represented on the top of the black arrows, while the root state posterior probability for the host-
286 species transition are given on its bottom.

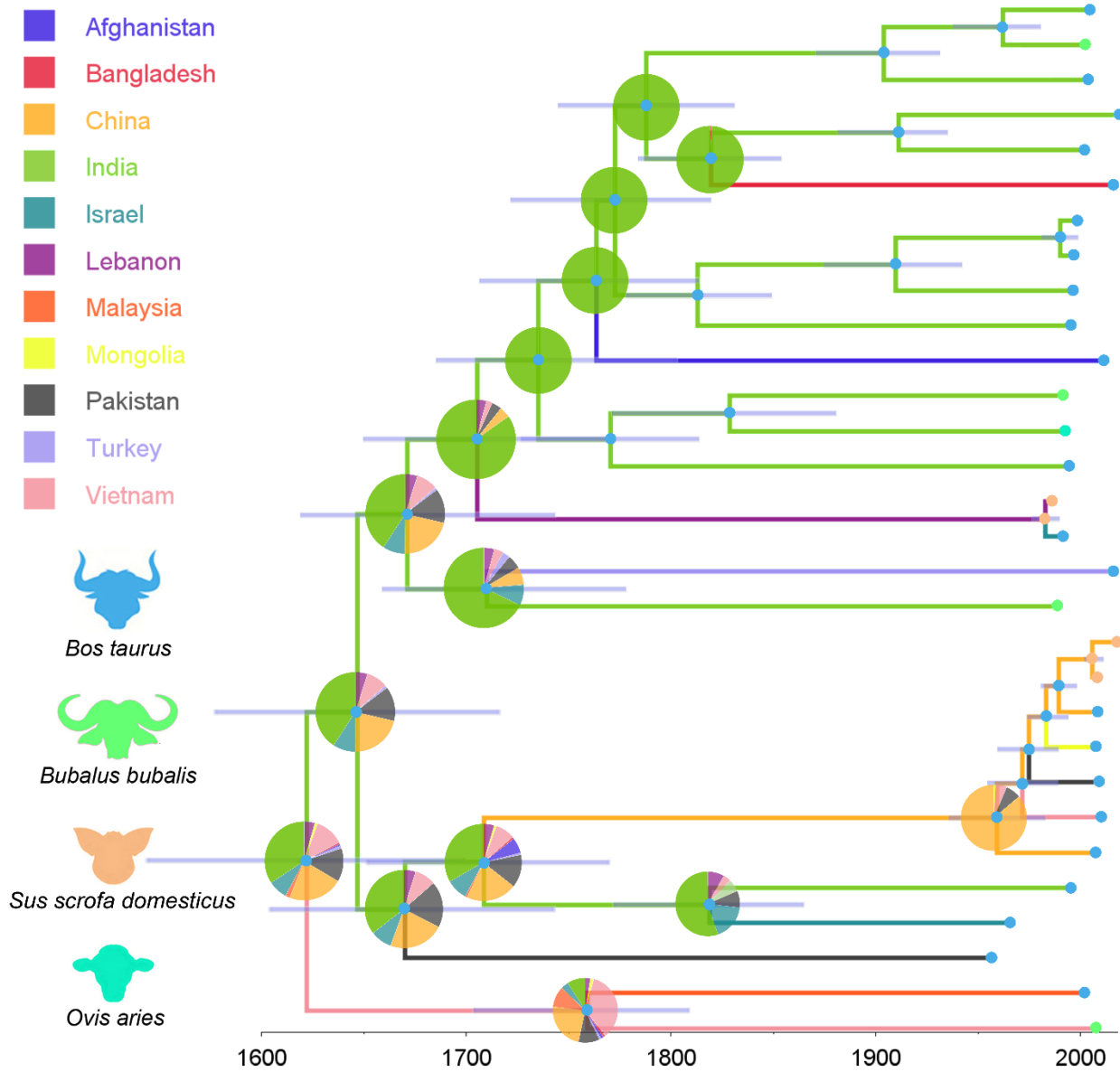
287

288 **Serotype Asia1**

289 This serotypes represented 12% of the entire FMDV sequences. Similarly to serotype A,
290 phylogeographic analyses indicated India as the most likely origin of this serotype (RSPP=
291 0.34), from which it diverged in all directions (Fig. 6, Supplementary Video S3). The
292 phylogenetic relationships seen in this serotype show a clear disparity between the lineages
293 found in countries from western Asia (i.e., Israel, Lebanon, Afghanistan, and Turkey) and
294 eastern Asia (i.e., China, Mongolia, Malaysia, and Vietnam) (Fig. 7A). Phylodynamic analysis
295 shows that the most important centers of diversification for this serotype are India, China,
296 Pakistan and Vietnam (Fig. 7A). BSSVS-BF analysis showed similar results as the observed in
297 serotype A, where the most significant transmission routes are related to India. In order of
298 intensity, the most important routes are the ones from India to China (BF= 182.8) and from India
299 to Vietnam (BF= 61.5) (Fig. 7B).

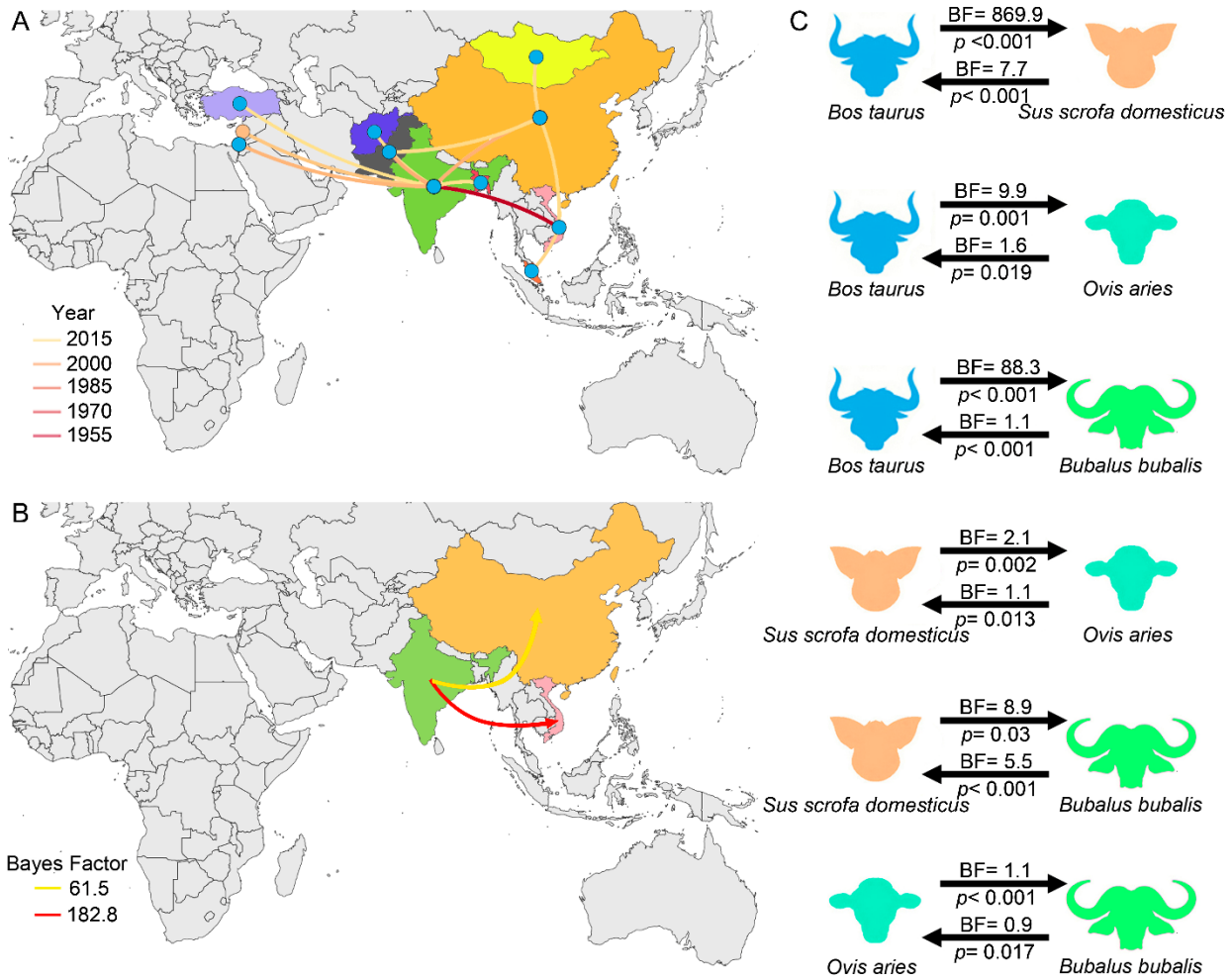
300 In relation to the number of available sequences, the most representative hosts for this
301 serotype were *B. taurus* (66% of the sequences), followed by *S. scrofa* (14%, exclusively in
302 China), *Bubalus bubalis* (6%, observed in India, Vietnam, and China) and *Ovis aries* (~3%,
303 observed only in China). Phylogenetic analysis showed that the hosts responsible for the spread
304 of this serotype were *B. taurus* (RSPP= 0.98), followed by *S. scrofa* (RSPP= 0.2). In addition,
305 Bayes factor analysis indicated that the most strongly supported transmission routes for the
306 spread of this serotype occurred from *B. taurus* to *B. bubalis* (BF= 1405.6), followed by from *B.*
307 *taurus* to *S. scrofa* (BF= 401.3), and from *B. taurus* to *O. aries* (BF= 134.1) (Fig. 7C).

308 Phylodynamic patterns of serotype Asia1 spread through BSP approach showed a
309 constant lineage diversity over time, with a very slight variation around the year 2000 (Fig. S2).
310



312 **Fig. 6** Dispersal history of FMDV lineages of Serotype Asia1, as inferred by discrete
313 phylogeographic analysis. Maximum clade credibility phylogeny colored according to the
314 countries of origin. Branch bars represent posterior probabilities of branching events ($P > 0.95$).
315 Colored dots at the end of the branches represent the host species (*Bos taurus*= cattle, *Sus*

316 *scrofa domestica*= swine, *Ovis aries*= sheep, and *Bubalus bubalis*= water buffalo. The
 317 probabilities of ancestral states (inferred from the Bayesian discrete trait analysis) are shown in
 318 pie charts at each node, while circles on each branch and tips represent the most likely hosts.
 319



320
 321 **Fig. 7** (A) Reconstructed spatiotemporal diffusion of FMDV serotype Asia1 spread, the color of
 322 the branches represents the age of the internal nodes, where darker red colors represent older
 323 spread events. (B) Representation of the most significant location transitions events for FMDV
 324 serotype Asia1 spread based on only the rates supported by a BF greater than 3 are indicated,
 325 where the color of the branches represent the relative strength by which the rates are
 326 supported. (C) Transmission rates between hosts (*Bos taurus*= cattle, *Sus scrofa domestica*=

327 swine, *Ovis aries*= sheep, and *Bubalus bubalis*= water buffalo) based on BSSVS-BF values are
328 represented on the top of the black arrows, while the root state posterior probability for the host-
329 species transition are given on its bottom.

330

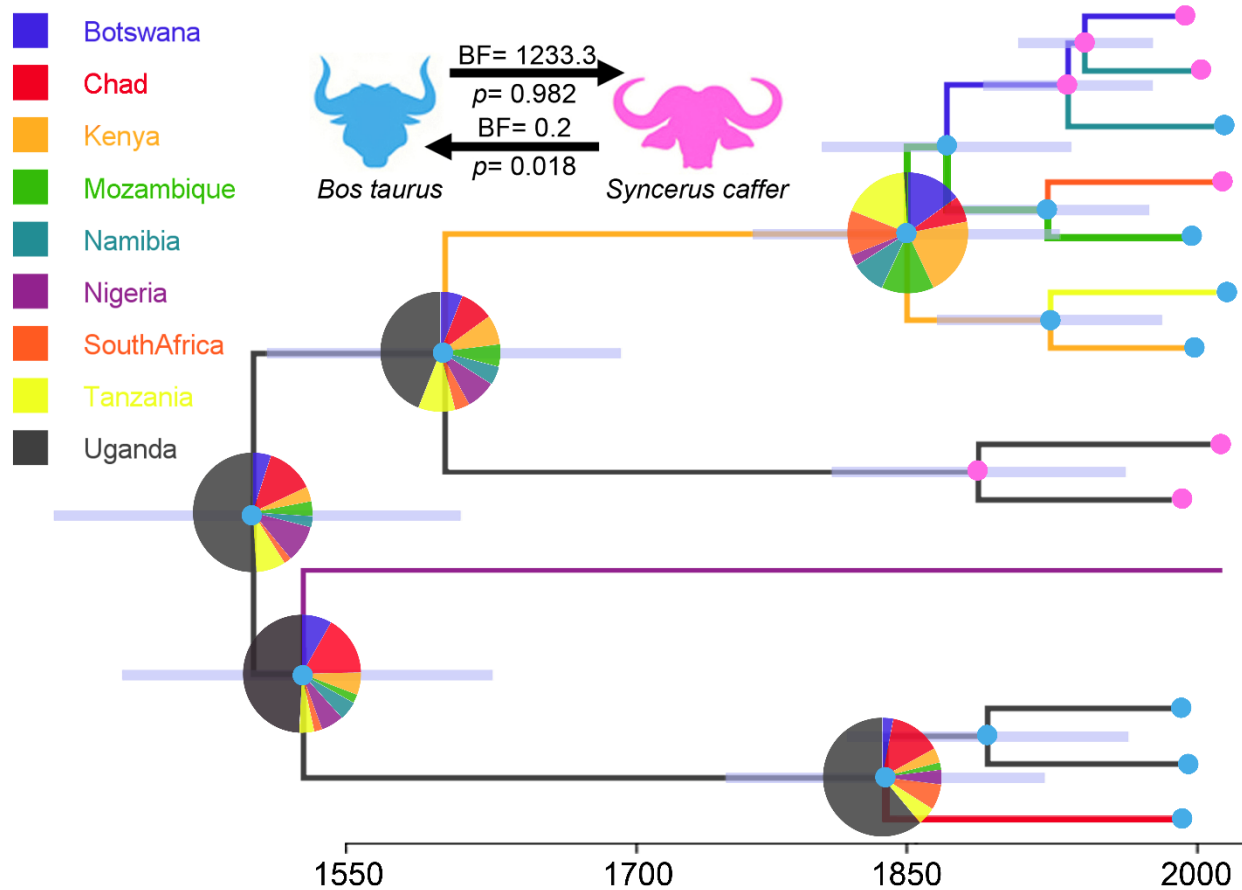
331 **Serotype SAT1**

332 The phylogeographic patterns of SAT1 exposed Uganda as its most likely country of origin
333 (RSPP= 0.45), from where it spread to Namibia, Nigeria, and Chad (Fig. 8). The phylogenetic
334 relationships identified three main clusters, one of them represented by the ancestor of the
335 lineages found in Uganda and Chad, other by the lineages located in the countries that are part
336 of the southern area of spread (i.e., Botswana, Mozambique, Namibia, South Africa and
337 Tanzania), and the last cluster represented by the lineages found in Nigeria, which also
338 presented the sub-lineage with the most recent appearance. Contrary to the previous serotypes,
339 SAT1 did not present a clear source (country) of dispersal events, although its spread was
340 mostly concentrated on Eastern Africa (Fig. 9A). Our results showed that the highest proportion
341 of its dispersal events occurred across long distance countries (representing 63% of the cases,
342 See Supplementary Video S4 for detailed footage). The most significant dispersal routes were
343 strongly related to Uganda, which in order of intensity, were seen to happen from Uganda to
344 Nigeria (BF= 35.2), which seemed the most significant, followed by the transition from Kenya to
345 Tanzania (BF= 26.5) (Fig. 9B).

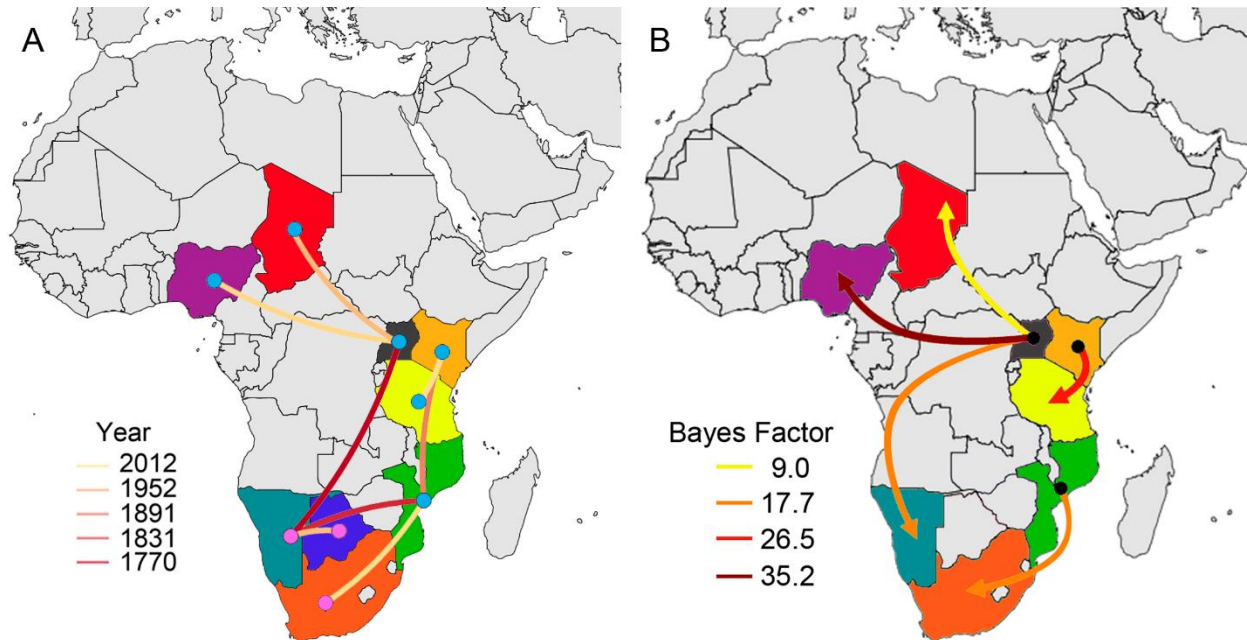
346 The host species associated with the dispersal of this serotype were *Bos taurus* and
347 *Syncerus caffer* (Fig. 8). *B. taurus*, with the majority of the number of sequences (58.3%), is
348 mostly distributed in the north and central Africa, while *S. caffer* (41.7%, appeared as the most
349 common host species in the southern countries (i.e., Namibia, Botswana, and South Africa).
350 Phylogenetic analysis suggested *B. taurus* as the most important host species for the origin of
351 this serotype (RSPP= 0.98). Strongly supported transmission routes were inferred from *B.*

352 *taurus* to *S. caffer* (BF= 1233.3). However, the reverse transmission was not significant (BF<3)
353 (Fig. 8).

354 Intriguingly, SAT1 BSP showed the most variable lineage diversity between all SATs,
355 with an early increased in 1860 that was maintained until 1970, where this diversity increased
356 again, reaching the values observed today (Fig. S2).



365 values) are represented on the top of the black arrows, while the root state posterior probability
366 for the host-species transition are given on its bottom.
367



368
369 **Fig. 9** (A) Reconstructed spatiotemporal diffusion of FMDV serotype SAT1 spread, the color of
370 the branches represents the age of the internal nodes, where darker red colors represent older
371 spread events. (B) Representation of the most significant location transitions events for FMDV
372 serotype SAT1 spread based on only the rates supported by a BF greater than 3 are indicated,
373 where the color of the branches represent the relative strength by which the rates are
374 supported.

375

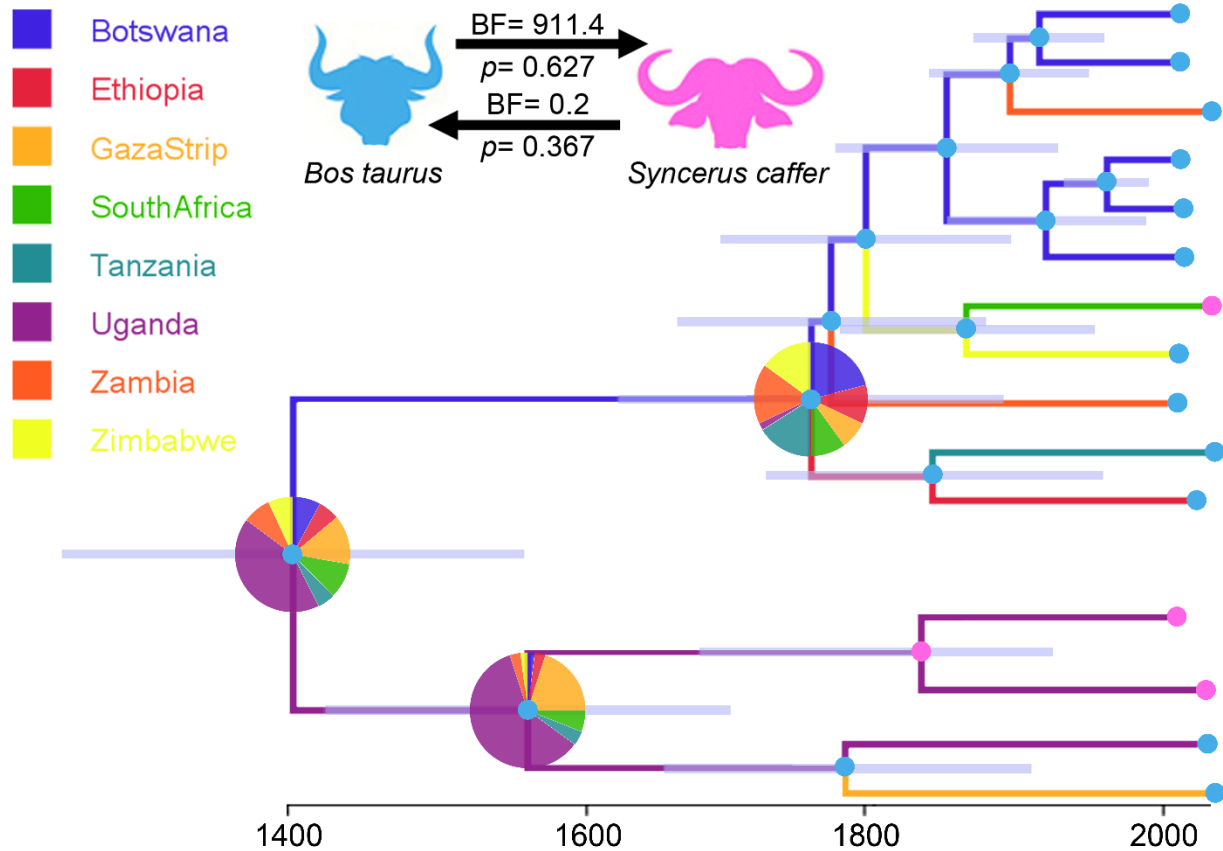
376 Serotype SAT2

377 Phylogeographic analyses for SAT2 indicated Uganda as the most likely origin of the serotype
378 (RSPP= 0.51), from which it spread to Botswana and The Gaza Strip later on time (Fig. 10).
379 Later, from Botswana, this serotype expanded its distribution to Ethiopia, Zimbabwe, and
380 Zambia, continuing spreading to surrounding countries also on the Eastern region of Africa (see
381 Supplementary Video S5 for detailed footage). Phylogenetic analysis identified two main sub-

382 lineages, one found between Uganda and Gaza Strip and the second cluster formed by the
383 lineages found in countries distributed in southeastern Africa (Fig. 10). Likewise, our results also
384 evidenced that serotype SAT2 spread is mostly characterized by a higher proportion of long-
385 distance movements (57%) over local dispersal events (Fig. 11A). Our phylodynamic model
386 suggested that the strongest geographic transition routes occurred from Uganda to Gaza Strip
387 (BF= 34.6), and from Botswana to Zambia (BF= 23.2) (Fig. 11B).

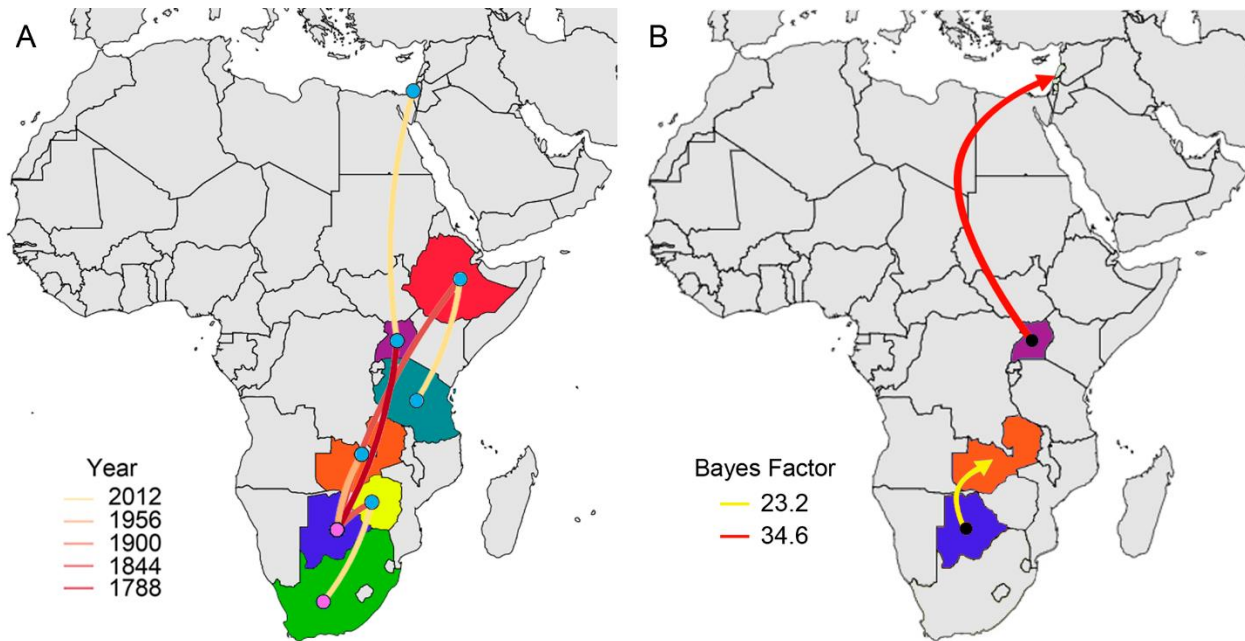
388 *B. taurus* and *S. caffer* were also the main host associated with SAT2 sequences, but in
389 this case, *S. caffer* was the most representative (53.9%), over *B. taurus* (46.1%). However, *B.*
390 *taurus* appeared in most of the reported locations (except in South Africa), while *S. caffer* was
391 only described in Uganda, Botswana and South Africa. As observed in SAT1, phylogenetic
392 analysis showed a higher influence of *B. taurus* as the host of the ancestral lineages of this
393 serotype (RSPP= 0.63) (Fig. 10). Transmission dynamics between host species suggested that
394 transmission from *B. taurus* to *S. caffer* was the most important (BF= 911.4), while transmission
395 from *S. caffer* to *B. taurus* was not significant (BF<3) (Fig. 7D). Finally, BSP showed no variation
396 in the lineage diversity found over time (Fig. S2).

397



398

399 **Fig. 10** Dispersal history of FMDV lineages of Serotype SAT2, as inferred by discrete
400 phylogeographic analysis. Maximum clade credibility phylogeny colored according to the
401 countries of origin. Branch bars represent posterior probabilities of branching events ($P > 0.95$).
402 Colored dots at the end of the branches represent the host species (*Bos taurus*= cattle, and
403 *Syncerus caffer*= African buffalo). The probabilities of ancestral states (inferred from the
404 Bayesian discrete trait analysis) are shown in pie charts at each node, while circles on each
405 branch and tips represent the most likely hosts. Transmission rates between hosts (BSSVS-BF
406 values) are represented on the top of the black arrows, while the root state posterior probability
407 for the host-species transition are given on its bottom.



408

409 **Fig. 11** (A) Reconstructed spatiotemporal diffusion of FMDV serotype SAT2 spread, the color of
410 the branches represents the age of the internal nodes, where darker red colors represent older
411 spread events. (B) Representation of the most significant location transitions events for FMDV
412 serotype SAT2 spread based on only the rates supported by a BF greater than 3 are indicated,
413 where the color of the branches represent the relative strength by which the rates are
414 supported.

415

416 **Serotype SAT3**

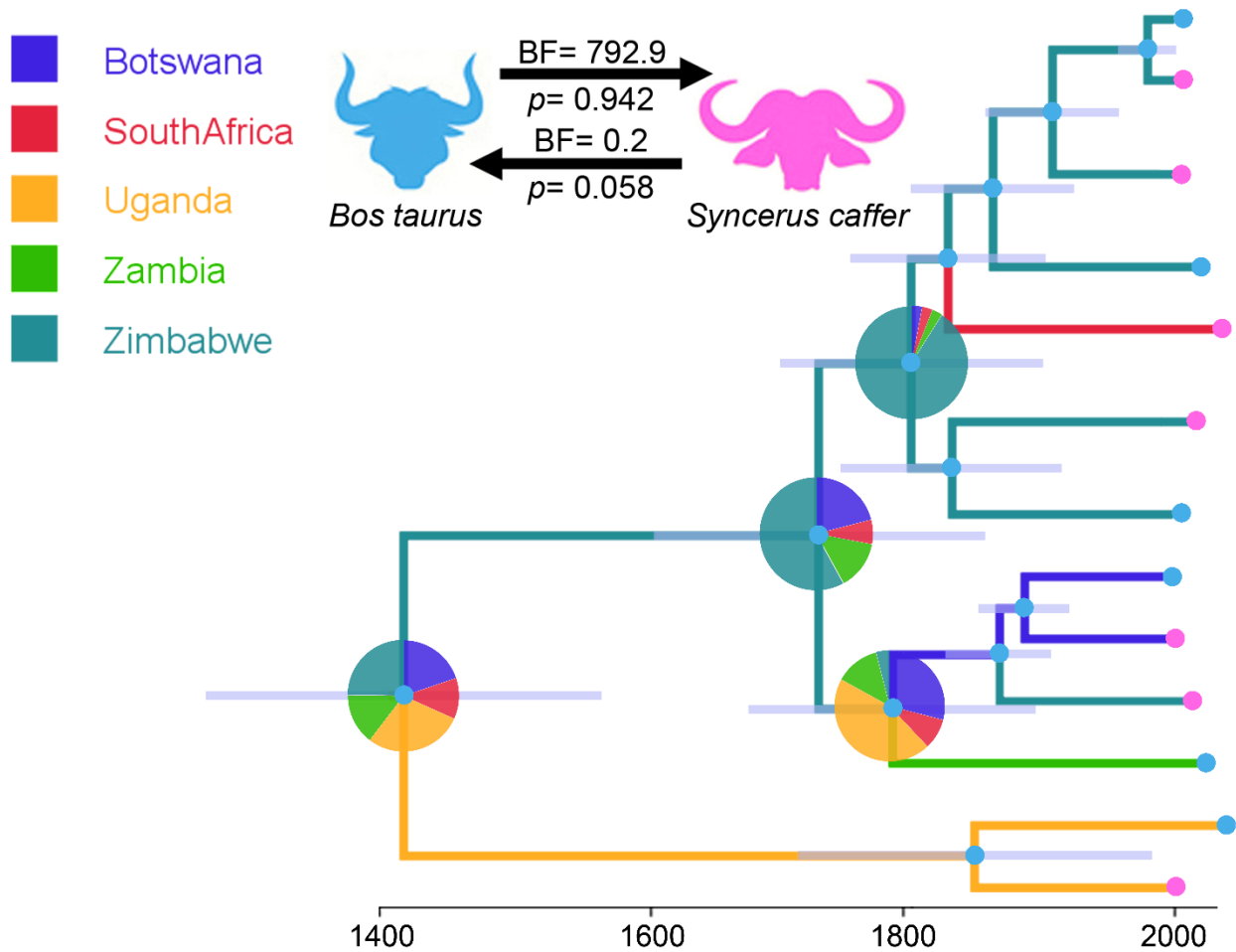
417 Similar to the previous SAT serotypes, SAT3 also had its ancestral origin in Uganda (RSPP=
418 0.49), from where it traveled to Zimbabwe and then spread to its neighboring countries (Fig. 12,
419 see Supplementary Video S6). Phylogenetic analyses identified two main sub-lineages, one of
420 them found in Uganda and the second (and most diverse), present in the countries that are part
421 of southern Africa (i.e., Botswana, South Africa, Zambia, and Zimbabwe). Phylogeographic
422 reconstruction reflected the importance of Zimbabwe for the spread of this serotype, being this
423 country the most common center of origin for the diffusion of the disease to Zambia, Botswana
424 and most recently to South Africa. Contrary to all the other serotypes (except for Asia1),

425 spatiotemporal dynamics of serotype SAT3 showed that its spread has been dominated by local
426 events (75%, Fig. 13A). Based on BSSVS-BF results, the most significant viral transmission
427 routes for serotype SAT3 were represented by the dispersion from Zimbabwe to Botswana (BF=
428 15.9) and from Zimbabwe to South Africa (BF= 12.1) (Fig. 13B).

429 *B. taurus* and *S. caffer* were also the main hosts reported for SAT3, appearing both in a
430 similar proportion (*B. taurus*= 62.5%, and *S. caffer*= 37.5%). Similarly to all the serotypes above
431 mentioned, cattle was the likely ancestral host species for this serotype (RSPP= 0.94).
432 Furthermore, we found that most significant transmission routes for its spread occurred from *B.*
433 *taurus* to *S. caffer* (BF= 792.9), while the transmission in the opposite direction was not
434 significant (Fig. 12).

435 Like in the case of SAT2, the BSP obtained for this serotype showed no variation in the
436 lineage diversity over time (Fig. S2).

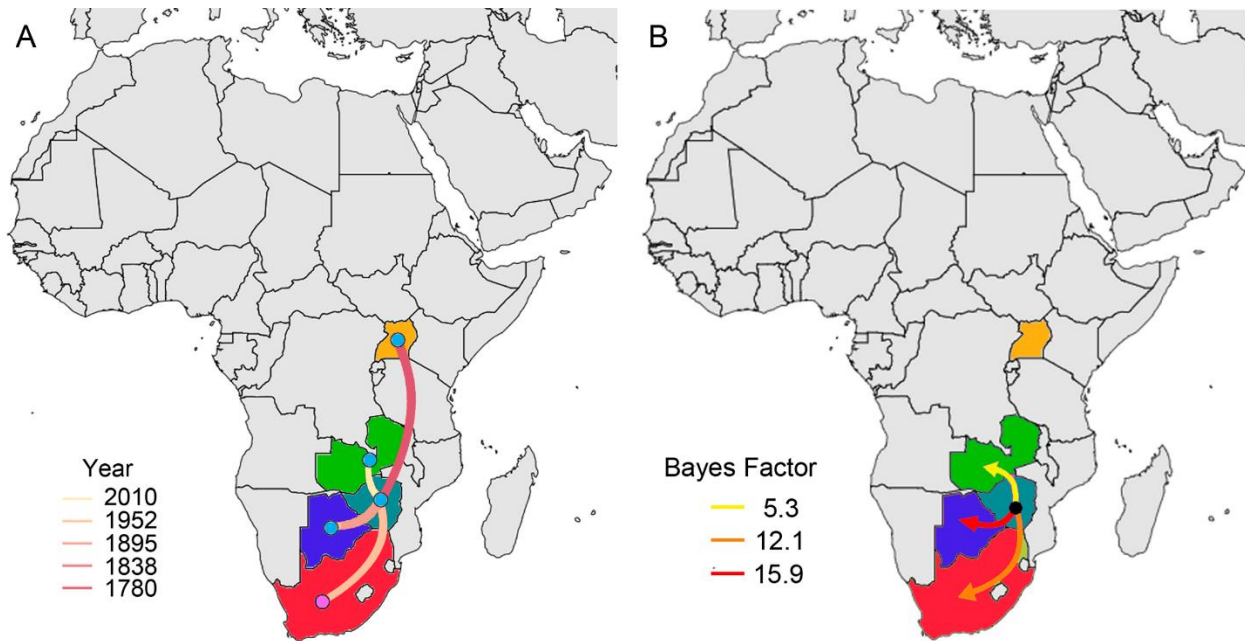
437



438

439 **Fig. 12** Dispersal history of FMDV lineages of Serotype SAT3, as inferred by discrete
440 phylogeographic analysis. Maximum clade credibility phylogeny colored according to the
441 countries of origin. Branch bars represent posterior probabilities of branching events ($P > 0.95$).
442 Colored dots at the end of the branches represent the host species (*Bos taurus*= cattle, and
443 *Syncerus caffer*= African buffalo). The probabilities of ancestral states (inferred from the
444 Bayesian discrete trait analysis) are shown in pie charts at each node, while circles on each
445 branch and tips represent the most likely hosts. Transmission rates between hosts (BSSVS-BF
446 values) are represented on the top of the black arrows, while the root state posterior probability
447 for the host-species transition are given on its bottom.

448



449

450 **Fig. 13** (A) Reconstructed spatiotemporal diffusion of FMDV serotype SAT3 spread, the color of
451 the branches represents the age of the internal nodes, where darker red colors represent older
452 spread events. (B) Representation of the most significant location transitions events for FMDV
453 serotype SAT3 spread based on only the rates supported by a BF greater than 3 are indicated,
454 where the color of the branches represent the relative strength by which the rates are
455 supported.

456

457 **DISCUSSION**

458 This study revealed new insights about the evolutionary dynamics of the FMDV's global
459 transmission dynamics at serotype level. The most likely country of origin for each serotype was
460 identified, along with its historical spread characteristics, and divergence patterns across its
461 historical dispersal. Finally, we assessed the impact of each host interaction in the spread of
462 FMDV, providing a comprehensive characterization of transmission dynamics between host
463 species.

464

465 **Phylogeographic patterns of FMDV spread**

466 Global patterns of FMDV spread were considerably asymmetric in its spatiotemporal
467 arrangement, showing important variation among all serotypes, as previously observed by Yoon
468 et al., (2011) and Brito et al., (2015). On the other hand, our results yielded discrepancies
469 regarding the phylogenetic relationships of FMDV serotypes due to the disagreements observed
470 in the cladistic characterization of FMDV serotypes (monophyletic or polyphyletic origin) [52].
471 Lewis-Rogers et al. (2008) and Yoon et al. (2011) suggested that O, A, Asia1, C, and SAT3
472 were monophyletic, while SAT1 and SAT2 serotypes were polyphyletic. However, our results
473 indicated the presence of only three monophyletic serotypes (O, A, and Asia1), whilst all SAT
474 serotypes appeared to have multiple ancestral origins which can be related to multiple points of
475 independent introduction of the virus.

476

477 *Serotypes with global distribution (O and A)*

478 Serotype O has shown a remarkable widespread distribution across the globe. In half of a
479 century, this serotype reached almost all continents, causing dramatic economic losses [58, 77,
480 78]. Root state posterior probability analysis inferred Belgium as the most likely center of origin
481 for this serotype, which, as a result of being responsible for the majority of outbreaks worldwide
482 [79], we can observe multiple centers of diversification in most of the continents. Our
483 phylogeographic analysis showed that this spread has been characterized by lineage dispersal
484 events between distant regions (i.e. to regions not sharing international dry borders with the
485 origin country), instead of dispersal events between neighboring countries, which may be one of
486 the keys for its successful global spread. Bayesian skyline plot showed a severe decline in the
487 genetic diversity around early 21th century, this interesting pattern also observed by Yoon et al.,
488 (2011). This decline and recover in the effective population size could be directly related to the
489 increase in the FMDV outbreaks that occurred worldwide, which was followed by an intensive
490 control and prevention strategies. The intense wave of outbreaks occurred during that period
491 worldwide included countries such as, Argentina (Perez et al., 2004; Perez et al., 2004), the

492 United Kingdom [82, 83], Brazil [84], India [85], and Taiwan [86, 87]. As we observed in our
493 phylogeographic visualization, there is strong evidence that most of these outbreaks were
494 strongly interconnected [25, 88–90], evidencing local and long-distance spread of serotype.

495 One of the reasons for the success of the evolutionary diversification of this serotype
496 may also be related to the diversity of hosts that it affects, which is the highest among all
497 serotypes. Globally, *B. taurus* represented the most important host species for the spread of
498 serotype O, while *S. scrofa* was mostly related to the spread of this serotype in southeastern
499 Asia. Thus, phylodynamic analysis suggested that viral transition rate between these two
500 livestock was the strongest reported between all the reported hosts.

501 Following the pandemic patterns showed by serotype O, the next large-scale potential of
502 diffusion was exhibited by serotype A. Phylogeographic analysis suggested India as the most
503 likely center of origin of the current circulating serotype A strains. Supporting previous studies
504 [26, 60], we observed that India was also a key source of dispersal events for this serotype
505 since most of the current strains are strongly related to India. Whole genome sequences of this
506 serotype have been recorded in three continents, Asia, Africa, and South America, where it was
507 reported as the causing agent of one of the biggest FMDV outbreaks, which occurred in
508 Argentina in 2011, affecting a total of 2,126 herds [81]. It is important to note, that there is
509 evidence of a posterior spread of these serotypes (O and A) to other countries, mainly in South
510 America, since both of them are currently found in nearly every country of the continent [26, 79].
511 However, due to the lack of whole-genome data, we were unable to further assess this spread.

512 As expected, the main host affected by serotype A was *B. taurus*. This species had an
513 important role in its viral spread [56], especially in this globalized era, where the continuous
514 increase in livestock trading markets facilitates the spread of transboundary animal diseases
515 [91]. Likewise, our phylodynamic analysis showed that the most intense host species
516 transmission route occurred from *B. taurus* to *S. caffer*, and apparently, the reverse
517 transmission is an infrequent event.

518

519 *Asia1 and SAT serotypes*

520 Whereas our results showed that serotypes O and A have spread worldwide, serotypes Asia1
521 and SATs remained non-pandemic and confined in their endemic regions [79, 92]. Since there
522 is a lack of detailed sequences data available, especially for African countries, it is important to
523 note that these results may vary with a better representation of the currently circulating virus,
524 although they support what has been previously described [59, 79, 93, 94].

525 Undoubtedly, India has been historically considered as one of the most important
526 countries for the spread and maintenance of FMDV, especially for serotypes A, and Asia1 [26,
527 55, 79, 94] Indeed, our phylogeographic analyses showed India as the most likely origin country
528 for Asia1 serotype [26, 94]. The spread of this serotype was mainly restricted to Asia [53, 55,
529 93], and characterized by local movements across the neighboring countries surrounding India,
530 China and Malaysia, where it is well known that free and unrestricted animal movements across
531 country borders may play a key role in the spread of FMDV [55, 95]. We also observed India as
532 a key center of dispersal for this serotype, which coincides with previously reported results [55].
533 The arrival of Asia1 into Turkey in 2013 represents one of the most recent and longer dispersal
534 events reported for this serotype, which was directly related to an Indian sub-lineage of the virus
535 [96]. Likewise, there have been sporadic incursions into other countries such as Greece in 1984
536 and 2000 [93], Malaysia in 1999 [31] or Turkey in 2017 [55], whose outbreaks seemed to be
537 caused also by independent sub-lineages from the rest of the outbreaks observed in these
538 regions.

539 Despite a previous study described multiple potential origins for SAT serotypes, (i.e.,
540 SAT1 in Zimbabwe and SAT2 in Kenya [48]), our root state posterior probability results
541 suggested Uganda as the most likely origin for all of them. Likewise, our phylogeographic
542 analysis also highlighted the importance of Uganda as a primary source of dispersal events to

543 different countries, where the most strongly significant routes were found from Uganda to
544 Nigeria (SAT1), from Uganda to Gaza strip (SAT2) and from Zimbabwe to Botswana (SAT3).

545 SAT serotypes (SAT1, SAT2, and SAT3) are characterized by a higher proportion of
546 local spread, limited across their endemic areas. This spread occurred mainly in southeastern
547 Africa, where nomadic pastoralism across international borders and animal trade in the sub-
548 Saharan region is one of the most practiced forms of livestock movements [48, 56, 93, 94].
549 These results complement the observations made by Bouslikhane (2015), who highlighted how
550 nomadism and transhumance play a key role in disease transmission, especially in African
551 countries.

552 Previous studies have highlighted the importance of African buffalo (*Syncerus caffer*),
553 hypothesizing that current FMDV genotypes may emerge in domesticated host species from
554 viral reservoirs maintained by this species [49, 53, 59, 94, 98–104] However, the uncertainty
555 over the involvement of African buffalo arose the need for deeper research to confirm its
556 influence in livestock outbreaks [94]. Our results coincide with the evidence mentioned in a
557 recent study by Omondi et al (2019), where cattle appeared as the most important host species
558 for the spread of FMDV, while buffalo played a secondary role. This pattern was observed not
559 only in SATs but in all serotypes studied.

560 In general, we observed considerable differences in the spatiotemporal dynamics
561 exhibited by the different serotypes. Where the serotypes with global distribution (O and A)
562 presented the most asymmetrical pattern in the annual genetic diversity in comparison with
563 (SAT and Asia1 serotypes). Cattle was observed to play a key role in the historical spread of all
564 serotypes of FMDV. Likewise, our phylodynamic analysis inferred that the transmission route
565 from cattle to buffalo was the most highly supported, pattern that was also observed for all
566 serotypes, independently of its spread potential.

567 Serotypes such as Asia1 and SATs presented local spread rates, mainly associated
568 with cattle and sheep (with special importance of buffalo in the case of SATs serotypes)

569 supporting previously described results (Brito et al., 2015; Omondi et al., 2019), while serotypes
570 O and A showed long-distance spread, covering higher extensions of territory between each
571 outbreak, which also confirms previously described information [59]. These serotypes presented
572 the highest variety of susceptible hosts, although we speculate that the main reason for their
573 successful long-distance spread relies mostly on the international movement of cattle and swine
574 due to the intensive commerce between countries.

575 Finally, important limitations related to the use of whole genome relay in the lack of good
576 global data, especially in African countries which remains endemically affected by five different
577 serotypes, therefore some countries with known FMDV circulation are not part of this study.
578 However, to reduce the bias generated by the strong unbalance of the available data in both
579 dimensions (i.e., number of samples per country and uneven number of samples per host
580 species), we removed all the sequences that where duplicated (i.e., represented the same
581 outbreak multiple times), which, in the case of big outbreaks such as United Kingdom
582 2001/2007, Argentina 2001, and Japan 2010, accounted for hundreds of sequences
583 representing each event. This limitation is common among phylogenic studies with no yet best
584 alternative, this is true mainly because sample that are available hosted in public databases or
585 from diagnostic laboratories [105]. Although whole genome sequences are increasingly proving
586 to be a more accurate tool for phylogenetic analyses [106, 107], its high cost in comparison to
587 studies considering partial genome results in lower availability of WGS, which became the major
588 limitation for the construction of our dataset, resulting several countries with known reports of
589 FMDV but lacking genetic data. Finally, it is important to highlight that, despite the nucleotide
590 sequences encoding the capsid protein VP1, VP2, and VP3 are sufficient to identify FMDV at
591 serotype level, we preferred using WGS because of its higher accuracy in the determination of
592 the genetic relationship between the reported cases [108].

593

594 **Final remarks**

595 Studies considering whole genome sequences should be preferred over partial sequence
596 research to ensure the importance of considering virus spread in its overall context
597 [53, 106, 107]. Besides, the growing awareness of the importance of using whole genome
598 sequences to assess the evolution of infectious diseases, and more specifically for RNA viruses
599 as FMDV plays a key role on the future ability to analyze the ever-increasing volume of data
600 accurately, getting closer to a real-time assessing of disease outbreaks [106]. However, the use
601 of whole genome sequences represented a limitation in our study since the lack of FMDV
602 sequences in a given country does not mean that the virus has not been circulating in that
603 country but maybe associated with technical or economic constraints, therefore interpretation
604 requires caution due to the possible introduction of sampling bias. The popularization of whole
605 genome sequencing will help not only to increase the available information about the virus, but
606 also have a direct impact on promoting new and more specific measures for disease control [24,
607 59, 109]. The result of such improvement in disease surveillance would not only be beneficial for
608 the targeted region, but also for all the areas that are directly connected (i.e., through
609 geographical limits) and indirectly (i.e., through commercial networks), including countries
610 currently considered as free zones [110].

611

612 **CONCLUSION**

613 In summary, we have seen how FMDV evolved and diversified in five species among 64
614 countries, by using a comprehensive phylodynamic approach, we characterized and compared
615 its global phylogeographic distribution at serotype scale. The phylogeographic approach used
616 here relies on the principle that evolutionary processes are better understood when a broader
617 spatiotemporal vision is available. Our results shed light on FMDV's macroevolutionary patterns
618 and spread, allowing to unravel the ancestral country of origin for each serotype as well as the
619 most important historical routes of viral dispersal, the role that the main host species played in
620 its spatial diffusion and how likely the disease is transmitted between them. The use of whole

621 genome sequences allowed us to clarify past discrepancies related to the polyphyletic nature of
622 some serotypes (i.e., SATs), previously described as monophyletic.

623 Based on our findings, we corroborate with recent advancements that have been
624 undertaken to control global distribution of major arbovirus (i.e., Dengue, yellow fever and Zika)
625 [111–113], with the need to also implement real-time genome-scale sequencing to food-animal
626 epidemics, in which metagenomics and phylogeography approaches inform epidemic responses
627 and improve control intervention strategies.

628

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635

636 **CONFLICT OF INTEREST**

637 The authors declare that there are no conflict of interests.

638

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969

970 **SUPPLEMENTARY MATERIAL**

971

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

974

975 **TABLE S2.** Root-to-tip regression analyses of phylogenetic temporal signal. Correlation and
976 determination coefficient (R^2) were estimated with TempEst (Rambaut et al. 2016). P-values
977 were calculated using the approach of Murray et al. (2016) and were based on 1,000 random
978 permutations of the sequence sampling dates (Navascuès et al. 2010).

979

980 **TABLE S3.** Number of sequences and serotypes per country.

981

982 **Fig. S1** Spatial distribution of Foot-and-mouth disease virus showing the number of serotypes
983 per country.

984

985 **Fig. S2** Reconstructed Bayesian Coalescent Skyline plots (BSP) of FMDV serotypes. The
986 median estimated of the effective population size through time are represented by the dark blue.
987 The 95% highest posterior density confidence intervals are marked in blue.

988

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

994

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

1000

1001 **Video S3.** Reconstructed spatiotemporal diffusion of FMD serotype Asia1 spread, where
1002 diameters of the colored circles are proportional to the square root of the number of MCC
1003 branches, maintaining a particular location state at each time period. The color of the branches
1004 represents the age of the internal nodes, where darker red colors represent older spread
1005 events, this visualization match with the main time bar on top of the video.

1006

1007 **Video S4.** Reconstructed spatiotemporal diffusion of FMD serotype SAT1 spread, where
1008 diameters of the colored circles are proportional to the square root of the number of MCC
1009 branches, maintaining a particular location state at each time period. The color of the branches

1010 represents the age of the internal nodes, where darker red colors represent older spread
1011 events, this visualization match with the main time bar on top of the video.

1012

1013 **Video S5.** Reconstructed spatiotemporal diffusion of FMD serotype SAT2 spread, where
1014 diameters of the colored circles are proportional to the square root of the number of MCC
1015 branches, maintaining a particular location state at each time period. The color of the branches
1016 represents the age of the internal nodes, where darker red colors represent older spread
1017 events, this visualization match with the main time bar on top of the video.

1018

1019 **Video S6.** Reconstructed spatiotemporal diffusion of FMD serotype SAT3 spread, where
1020 diameters of the colored circles are proportional to the square root of the number of MCC
1021 branches, maintaining a particular location state at each time period. The color of the branches
1022 represents the age of the internal nodes, where darker red colors represent older spread
1023 events, this visualization match with the main time bar on top of the video.