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1 **On the arrival of fasciolosis to the Americas**

2

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23 **Abstract**

24 *Fasciola hepatica* is a worldwide emerging and re-emerging parasite heavily affecting

25 several regions in South America. Some lymnaeid snail species of American origin are

26 among the major hosts of *F. hepatica* worldwide. Recent paleoparasitological findings

27 detected its DNA in a 2300-year old sample in Patagonia, countering the common hypothesis

28 of a recent arrival of *F. hepatica* into the Americas during European colonization. Thus, the

29 theory of an initial introduction in the 1500s can no longer be sustained. This article discusses

30 how it was possible for *F. hepatica* to reach and spread in the Americas in relation to the

31 availability and compatibility of hosts through natural and incidental introductions. Our study

32 will serve to better understand the ongoing Neotropical scenario of fasciolosis.

33

34 ***Fasciola hepatica*: a neglected tropical worm responsible for an increasing global**
35 **burden**

36 Today no one denies the importance of understanding host-parasite relationships as the best
37 way for preventing infectious diseases and cutting off transmission quickly and efficiently.
38 The difficulty of such a task generally increases when pathogens rely on a diversified set of
39 hosts that are phylogenetically and ecologically different with contrasted patterns of
40 distribution and **compatibility** (see **Glossary**). Helminth parasites, and particularly
41 trematodes, are perhaps typical examples of not-very-loud pathogens that affect a large
42 proportion of poor people worldwide [1]. Among trematodes, the liver fluke *Fasciola*
43 *hepatica* (Linnaeus, 1758) (Digenea: Fasciolidae) was the first species whose complete life
44 cycle was resolved [2] and has the widest known global distribution [3]. According to the
45 latest estimations, nearly 50 million (range 35-72 million) people are infected every year [4],
46 and yet, it remains on the WHO's list of **Neglected Tropical Diseases** [5]. *Fasciola hepatica*
47 —as well as its sibling species *Fasciola gigantica* (Cobbold, 1855) but with a far narrower
48 distribution— causes a disease known as fasciolosis in humans, domestic animals
49 (particularly ruminants), and certain wild mammals [6]. This fluke is a food-water-borne
50 parasite that requires a freshwater snail as a host for its larval stages before reaching its
51 definitive mammalian host. The **intermediate snail hosts** belong to the family Lymnaeidae,
52 with only less than a handful of exceptions documented within the Planorbidae and
53 Succineidae, but transmission has never been proven. Not every lymnaeid snail species is,
54 however, able to transmit the parasite, and even those who do it, may display a wide
55 polymorphism of compatibility and thus differential **transmission competence** [7]. *Fasciola*
56 wide diversity of definitive and especially intermediate hosts is not common among
57 trematodes. Remarkably, the genome-wide polymorphism and the gene duplication events
58 that occurred throughout the evolutionary history of *Fasciola* have probably enabled this

59 worm to parasitize different host species and to respond rapidly to external selection
60 pressures [8].

61 In a world context marked by fasciolosis emergence and re-emergence in both human and
62 domestic animal populations [9], control and mitigation strategies must be bolstered by solid
63 knowledge of the biology, ecology, and genetic/evolutionary relationships established
64 between the parasites and their hosts. Why some intermediate hosts are more competent in
65 transmitting the liver fluke is a fundamental question for understanding the epidemiology of
66 fasciolosis. This parasitosis is greatly present worldwide, but it strikes hard in several human
67 populations from the Andean countries in South America and extensively impacts cattle
68 populations throughout the western hemisphere [9]. There are at least two native American
69 lymnaeid genera, *Galba* and *Pseudosuccinea*, which are among the most compatible
70 intermediate hosts of *F. hepatica* [10, 11]. Reconstructing the origins of these host-parasite
71 interactions may improve our understanding of such a tight partnership.

72 The origins of *F. hepatica* have long been accepted to have occurred somewhere in Eurasia
73 [12]. This hypothesis is mainly supported by the historically accepted European origins of its
74 long alleged ‘main snail host’: *Galba truncatula* (O.F. Müller, 1774) [13]. Indeed, this
75 species has been historically assigned the role as the ‘original’ and ‘main snail host’ of *F.*
76 *hepatica* worldwide [3]. This assignation may be due to the fact that this intermediate host
77 species has the largest dataset of information given its significant presence in Europe, where
78 most studies have been conducted so far. However, from the geographic extension point of
79 view, species like *Galba cubensis* (L. Pfeiffer, 1839), *Galba viator* (d’Orbigny, 1835), and
80 *Pseudosuccinea columella* (Say, 1817) may have a greater impact on the current
81 epidemiology of fasciolosis [7, 14]. Consequently, it would be difficult to accept the
82 hypothesis that places the introduction of *F. hepatica* in the Americas only as recently as the
83 1500s [3], whereas American lymnaeids are among the major vectors of fasciolosis in and out

84 of the Americas. Now that evidence finally places *F. hepatica* at least 2300 years ago in
85 South America [15], we need to at least briefly discuss two main issues: (1) its arrival in the
86 Americas before European colonization when it adapted to a whole new set of hosts, and (2)
87 the more recent introductions worldwide through human activity in the post-domestication
88 era.

89

90 **A parsimonious reconstruction of the arrival of *F. hepatica* arrival to in the Americas**

91 The question of when and how *F. hepatica* reached the Americas and secured a tight
92 relationship with native lymnaeids has been debated for many years (**Figure 1, Key Figure**).

93 To understand this issue, we need to separate the roles of both intermediate and definitive
94 hosts in spreading *F. hepatica* before human-mediated introductions: definitive hosts would
95 have spread it by passively introducing the parasites (disseminator role), while intermediate
96 hosts acted as receptors and facilitators in its establishment. The Fasciolidae family
97 comprises nine extant species belonging to five genera [13]. There are only three species
98 accepted within the genus *Fasciola*, *F. hepatica* and *F. gigantica* responsible for fasciolosis
99 worldwide [9], and *Fasciola nyanzae* (Leiper, 1910) infecting only hippos [16]. Fasciolids
100 are believed to have originated in Africa because basal species (i.e., *Protofasciola robusta*
101 (Lorenz, 1881)) use African proboscideans as definitive hosts and planorbid snails
102 (Heterobranchia: Planorbidae) as intermediate hosts [12, 13]. The origins of the family are
103 placed around 50Ma together with the origins of African proboscideans [13], but a more
104 recent study analysing the whole genome of *F. hepatica*, *F. gigantica*, and *Fasciolopsis buski*
105 (Lankester, 1857) determined a split in both genera lineages during the Cretaceous 90 Ma ago
106 [12]. With basal fasciolids using planorbid snails as intermediate hosts, both studies place the
107 switch to Lymnaeidae in Eurasia, which seems to have occurred between 65–50 Ma in the
108 lineage leading to *Fasciola* [12]. Now, this assumption raises concerns of when and where

109 such an intermediate host switch could have occurred given that Africa was separated from
110 Eurasia since the breakup of Pangea (200 Ma) remaining within Gondwana and only re-
111 assembling with Asia during the Oligocene (27–20 Ma) [17]. On the other hand, while an
112 inside-Africa switch from Planorbidae to Lymnaeidae is consistent with continental drift,
113 today's lack of lymnaeid diversity on this continent would suggest a more probable switch in
114 Eurasia where diversity in this group is much higher (several genera and species in Asia vs
115 probably only a few native sub-Saharan lymnaeids in Africa [18]). However, we cannot reject
116 the probable existence of many more, and fully aquatic *Radix*-like lymnaeid species that
117 would have later disappeared in Africa. In any case, migration out of Africa of ancient
118 fasciolids must have corresponded to the first incursions of proboscideans into Asia [13],
119 which apparently occurred only around 18 Ma during the late Oligocene [19].

120 Once in Eurasia, early forms of the subfamily Fasciolinae would have encountered a wide
121 range of both intermediate and definitive hosts and, probably, different ecological conditions
122 to which they had to adapt. Diversification and the probable emergence of today's two liver
123 fluke lineages of *Fasciola* and *Fascioloides* could very well have occurred in this region.

124 This hypothesis is based on the fact that *Fascioloides jacksoni* (Cobbold, 1869) occurs in the
125 Asian elephant [20], and the other, *Fascioloides magna* (Bassi, 1875), is native to North
126 America but ancestrally introduced from Asia [21]. The case of *Fasciola* is perhaps more
127 complicated with hypotheses suggesting allopatric divergence and speciation of *F. hepatica*
128 and *F. gigantica* around 5 Ma [12]. These authors suggest that *F. gigantica* has African
129 origins, but merely based on the fact that it is the main liver fluke on the continent. This
130 means that infected mammals would have re-entered Africa and that speciation occurred
131 there, perhaps facilitated by reduced faunal exchange during the Miocene-Pliocene transition
132 [12]. However, we should note that *F. gigantica* is also widely distributed in tropical and
133 subtropical Asia [22], and perhaps the possibility of a speciation event based on differential

134 host ecology with a later re-entry into Africa should not be disregarded. In fact, a study
135 reflecting the polymorphism of ITS-2 using samples from Asia and Africa suggests the
136 differentiation of *F. gigantica* in Asia resulting in several lineages with one eventually re-
137 entering Africa [23].

138 In the case of *F. hepatica*, its origins have long been placed somewhere in Eurasia. Some
139 authors strongly suggest its origins are in the Fertile Crescent [24], based on the arguable
140 European origins of its 'main snail host' *G. truncatula* and on the evidence of humans
141 infected during the Mesolithic and Neolithic periods in this region [3]. However,
142 diversification of the liver flukes, with the divergence of the *F. hepatica* and *F. gigantica*
143 lineages may have also been favoured by the diversification of Bovidae in Asia [25]. Each
144 bovid tribe (e.g., Bovini, Tragelaphini, Antilopini, Caprini) is characterized by conforming
145 **ecological guilds** that, according to Bibi [26], are distinguished from others by unique
146 morphological and behavioural characteristics reflecting dietary and habitat preferences.

147 Many of the lineages of these tribes, particularly Bovini, Caprini, and Antilopini, are thought
148 to have emerged in Eurasia more than 14Ma ago with some ancestral stocks later migrating
149 into Africa and diversifying there [25]. In this scenario, early liver flukes in Asia may have
150 found a high diversity of susceptible definitive hosts, but with different ecological
151 preferences. For instance, some authors accept that *F. hepatica* originated in early Caprini,
152 particularly ovicaprines, given the high infection rates observed today as well as some
153 immunocompatibility aspects [24]. However, even bovids such as goats and sheep, or other
154 like cattle that do not usually go directly into the water, but more often prefer humid
155 meadows or the surroundings of streams, rivers, and ponds for grazing, may have favoured a
156 continuous encounter between early *F. hepatica*-like flukes and amphibious lymnaeids. In
157 fact, these habitats match those preferred by today's semi-amphibious lymnaeid hosts of *F.*
158 *hepatica*, such as those of the genera *Austropeplea* and *Orientogalba* in Asia and Oceania

159 [27, 28], or even the highly amphibious *Galba* species [14]. Such an **ecological isolation**
160 rather than a drastic geographical separation (African/Asian) may have facilitated the
161 divergence between the *Fasciola* species. If the recent molecular data remains valid [12], this
162 splitting in the lineages leading to both *Fasciola* species only occurred 7.2–3.4 Ma ago,
163 meaning that both species could be relatively young. This could explain the fact that both
164 liver fluke species still hybridize, particularly in Asia [29, 30]. With bovid migration, *F.*
165 *hepatica* may have reached new regions adapting to the existing hosts (both intermediate and
166 definitive) thanks to its genome-wide polymorphism [8]. These authors suggest that, contrary
167 to most digenetic trematodes with a rather restricted host range, such genetic diversity in *F.*
168 *hepatica* provides high adaptability in genes that mediate infection and survival in the host
169 environment and thus the possibility of infecting a wide range of hosts.

170 Infected mammals could have crossed the Bering Land Bridge that was emerged episodically
171 throughout the Pleistocene (from 2.6 Ma until 15,000 years ago; [31]) and liver flukes may
172 have passively migrated in this way. *Fasciola hepatica* would have been roughly the only
173 liver fluke crossing from Asia to the Americas, and the fact that *F. magna* is native to North
174 America [21] strongly supports this hypothesis. We should note that snails serving as
175 intermediate hosts for *F. magna* in its native range in North America and in its introduced
176 European populations coincide with those of *F. hepatica* [32].

177 The Americas are a diversity hotspot for the amphibious *Galba* lymnaeids. Conditions there
178 would have facilitated the establishment of *F. hepatica* that could have already been adapted
179 to semi-aquatic snails occurring in Asia (*Austropeplea* and *Orientogalba* or other ancestral
180 forms). Species of North American *Galba* are known to effectively transmit *F. hepatica* [33,
181 34]. When exactly *F. hepatica* reached South America is debatable. However, the Great
182 American Biotic Interchange events (GABI) that occurred in waves from 2 Ma until a several
183 thousand years ago [35] would have facilitated the South American introduction of the liver

184 fluke. It is accepted that during these GABI events an uneven flow of mammals occurred
185 with considerably more North-South introductions of which we should highlight those
186 concerning the Cervidae and Camelidae lineages [36]. In any case, it is a fact that *F. hepatica*
187 already occurred in South America well before the arrival of Europeans in the 1500s, which
188 is supported by the ancient DNA (from 2300 years old) found in coprolites of endemic deer
189 in Patagonia [15]. Such common historical interaction of American lymnaeids and the liver
190 fluke, reinforced since the 1500s through intensive camelid and cattle husbandry and contact
191 with new imported European and African strains, may very well explain the vector capacity
192 displayed by the *Galba* species.

193

194 **A stowaway across the planet: *F. hepatica* during post-domestication time**

195 The natural history of *F. hepatica* must have greatly changed from the beginning of
196 domestication onward. Although it would be risky to draw a map for fasciolosis prior to the
197 Neolithic Period (10,000 years ago), its distribution would surely be scarcer and a lot less
198 prevalent than it is today. Certainly, domestication was accompanied by ecosystem
199 transformations corresponding to keeping large numbers of animals for meat, milk, or wool,
200 with grazing and drinking trough sites. Today, we understand that such conditions would
201 concomitantly facilitate the overlapping of domestic mammals and aquatic snail populations
202 resulting in increased probability of liver fluke transmission [37].

203 Human activity since early domestication times, but particularly marked in modern times, has
204 greatly altered the original genetic structure of *F. hepatica* populations. Such alterations have
205 modified the allelic and genotypic frequencies probably starting with the movement of
206 infected domestic animals, continuing with the selection of particular strains in relation to
207 new hosts (intermediate and definitive) and new environmental conditions (temperate or
208 tropical), and more recently with anthelmintic resistance [22]. In some regions, *F. hepatica*

209 populations have been more affected according to their reciprocal evolutionary history with
210 cattle husbandry compared to others found where there is no intensive farming. The Americas
211 are in fact a very interesting region to study this question. It is now a fact that *F. hepatica* was
212 present there before the arrival of Europeans [15]. However, it might be quite difficult to find
213 traces of the ancient genetic structure (prior to domestication time) of *F. hepatica* in either
214 native or introduced mammals (**Figure 2**). Europeans did not only introduce *F. hepatica* with
215 infected cattle (producing a continuous parasite spill-over of novel strains) [38, 39], but
216 shrunk many native populations of bovids through hunting, disease propagation, and habitat
217 degradation [40]. Such actions probably erased the ancient genetic footprint of American *F.*
218 *hepatica* by directly eliminating the definitive hosts, or by replacing the native flukes with
219 introduced strains through intensive cattle farming. The new strains of *F. hepatica*, although
220 probably genetically different, would have been able to interact with the native lymnaeid
221 snails, *Galba* species and *P. columella*, that had been transmitting the liver fluke long before.
222 For instance, recent *F. hepatica* populations from Peru and Brazil have been found that are
223 closely related to populations from Europe, Asia, and Africa [39, 41]. Genetic diversity in
224 such American populations is however considerably lower, and must have been the result of
225 strong genetic bottlenecks and founder effects since their introductions [41]. Other examples
226 exist that depict post-domestication introductions of *F. hepatica*, such as the recent data that
227 establish an introduction route from Afghanistan to China [42].

228

229 ***Fasciola hepatica*–Lymnaeidae: understanding a variable snail–trematode interaction**

230 Adaptation in host-parasite systems evolve from tight relationships established between
231 interacting species [43]. Such adaptation is understood as a reciprocal natural selection of
232 genotypes that provide the best outcomes in terms of survival and reproduction for both the
233 host and the parasite [44]. *Fasciola hepatica* is probably one of the most thoroughly studied

234 trematode species in relation to its interaction with its intermediate snail hosts [45, 46]. We
235 know that most phylogenetic subclades within the Lymnaeidae have species with proven
236 susceptibility to *F. hepatica* [7]. However, the infection outcome usually varies in relation to
237 some population's particular demographic traits (e.g., age, density) or prevailing ecological
238 conditions (e.g., temperature, humidity), but is usually more important as a function of the
239 prior history of interactions among them [47]. For instance, sympatric- and allopatric-tested
240 combinations show differential levels of compatibility in terms of host survival, overall
241 prevalence, and the parasite's asexual amplification inside the snail (i.e., larval intensity) [6,
242 46, 48]. These traits are the most important ones for determining the success of infection and
243 transmission, because together they affect the probability of the parasite reaching its
244 definitive host. Studies accounting for experimental infection trials are quite heterogeneous,
245 and not all of them explore these three traits. However, bibliographic records show a clear
246 pattern of higher prevalence in experimental infection trials with *F. hepatica* in lymnaeid
247 species inhabiting especially a land-water interface (i.e., amphibious lymnaeids) (see [33, 46,
248 49-51]). We should note that eggs of *F. hepatica* only develop in a certain range of
249 temperatures and humidity [52], and that most common definitive hosts (which expel eggs
250 with faeces) are ovine and bovine species that graze near the water or very humid pastures
251 but, with a few exceptions, do not commonly engage in fully aquatic behaviour. Amphibious
252 or semi-amphibious species with the highest reported prevalence belong to three clades:
253 *Galba*, *Pseudosuccinea*, and *Austropeplea/Orientogalba* according to the latest phylogenies
254 [53]. Here we stumble upon groups in which most species have native ranges outside of
255 Europe or Africa, particularly in the Americas or eastern Asia [10, 11, 54]. The
256 Amphipepleinae species, *Austropeplea tomentosa* (L. Pfeiffer, 1855) and *Orientogalba*
257 *viridis* (Quoy & Gaimard, 1833) commonly occur in eastern Asia and some Pacific islands
258 and are historically considered to be responsible for fasciolosis transmission there [49, 55].

259 On the other hand, *P. columella* is strongly suggested to have originated in North America
260 [11], and from the *Galba* clade, only the origins of *G. truncatula*, which is widely distributed
261 in the Americas and Europe, raises questions, while most remaining sibling species are native
262 or restricted to the Americas [14].

263 Thus, compatibility driven by host ecology rather than a phylogenetic inherited relationship
264 from higher clades may explain the transmission of *F. hepatica* by lymnaeid snails. As such,
265 adaptation driven by continuous host-parasite encounters might have played a key role in
266 creating a strong partnership in this host-parasite system. These facts bring us to the central
267 point of the following discussion according to which, if we follow the theory supporting the
268 observed high compatibility, we should expect a long history of species-species interactions
269 that produce this overall susceptible phenotype.

270

271 **American Lymnaeidae and *F. hepatica*: old time partners**

272 The American Lymnaeidae comprise three subfamilies: Lancinae [56], with no role in
273 fasciolosis, and the Amphipepleinae and Lymnaeinae, several species of which are proven
274 hosts of *Fasciola* flukes [7]. Within the latter resides the main snail hosts of *F. hepatica*,
275 including *Galba* and *Pseudosuccinea*, particularly relevant in fasciolosis transmission [11,
276 53]. Why both genera support an ancient interaction with *F. hepatica* will be discussed
277 hereafter.

278 Within the American Lymnaeidae, *Galba* species have been the target of several taxonomic,
279 biogeographical and phylogenetic studies [14, 53, 57, 58]. Had it not been for their role in
280 fasciolosis transmission, the fate of this genus would have probably followed those of other
281 less studied ones. Only now, after a series of studies supported by large sampling all around
282 the world, are we capable of beginning to unveil the true origins of the *Galba* species [14].

283 As already discussed, the origins of ‘the main’ *F. hepatica* snail host, *G. truncatula*, have
284 long been placed in Europe [3], including very recently introduced populations that inhabit
285 the **hyperendemic fasciolosis area** of the Bolivian Altiplano [59]. However, it is puzzling
286 that *G. truncatula* is European and the rest of its sibling *Galba* spp. are found only in the
287 Americas with just two molecularly verified exceptions with a limited distribution range in
288 the eastern hemisphere. These exceptions are *Galba schirazensis* (Küster, 1862) (with very
289 low to no transmission capacity, see [45, 46, 60]) and *Galba mweruensis* (Connolly, 1929)
290 (compatibility to be asserted, [61]). In the first case, the suggested American origins of *G.*
291 *schirazensis* are supported by a higher diversity pattern in American populations [58]. The
292 second case refers to *G. mweruensis*, which, after analysing a combination of mitochondrial
293 and nuclear markers, was assigned to a formerly described species [61]. However, this
294 species, as well as the morphologically described *Galba robusta* (Vinarski, 2018) from
295 Yemen [62] should be further analysed molecularly in order to assess its phylogenetic
296 position and possible origins. Returning to the *G. truncatula* puzzle, Burch [63] recommends
297 that Alaskan representatives should be further analysed in relation to Eurasian members,
298 which means a possible continuous Holarctic-Nearctic native distribution should not be
299 dismissed. We should note that *Galba* species are particularly resistant to desiccation and
300 thus we cannot entirely rule out human or bird-related introductions in the Americas from a
301 few million years ago to present day.

302 In the Americas, at least six molecularly confirmed species of *Galba*, i.e., *G. cubensis*, *Galba*
303 *humilis* (Say, 1822), *Galba cousini* (Jousseume, 1887), *G. schirazensis*, *G. truncatula*, and
304 *G. viator*, were reported to have been naturally or experimentally infected with *F. hepatica*
305 [7, 14]. Recent molecular data suggest that the origins of the *Galba* group are between 25-20
306 Ma [14] long before the emergence of the modern *Fasciola* species [12]. A prudent
307 hypothesis would be that of American –or Holarctic- origins of *Galba* considering the extant

308 diversity with paleo-introductions of species like *G. truncatula* in Europe and *G. mweruensis*
309 in Africa (or its ancestors meaning that speciation events occurred there). Fossil records of
310 *Galba*-like shells from the Pleistocene (as those from Austria [64]) and molecular studies
311 could help us to disentangle when and how snail introductions and speciation events took
312 place in non-American regions.

313 The monotypic genus *Pseudosuccinea* might be one of the best examples suggesting a long
314 history of interactions with *F. hepatica* in North America. Data strongly suggest that *P.*
315 *columella* has American origins and that human-mediated introduction expanded its range to
316 a worldwide distribution in the last 200 years [11]. Yet, *P. columella* acts as a suitable host of
317 *F. hepatica* in its native and introduced range [65, 66]. A common susceptible phenotype is
318 found worldwide [11]. However, until now an uncommon resistant phenotype has been
319 observed only in Cuba [67]. Resistant populations of *P. columella* are significantly
320 genetically divergent from susceptible populations from Cuba and elsewhere [11, 68]. While
321 there is still a debate on the origins of *P. columella* resistance to *F. hepatica*, the existence of
322 these resistant populations is arguably only valid in Cuba, and it is highly probable that it
323 may well also exist in North America. However, this region has been quite poorly studied in
324 relation to detecting this resistant phenotype. Since one of the hypotheses of such resistance
325 is that of a sustained parasite challenge, one might jump to the conclusion that this host-
326 parasite interaction must date from a long time ago supporting the idea of that *F. hepatica* has
327 long been present on the continent.

328

329 **Concluding Remarks**

330 The discovery of *F. hepatica* DNA in South America dating back to before the arrival of the
331 Europeans [15] is obviously sufficient to overturn the current theory that European
332 colonization is responsible for its introduction [3]. Thus, the question of whether the risks of

333 fasciolosis transmission in the Americas are just recent or ancient has now been resolved:
334 both are true. In this paper, we have tried to discuss how this might have occurred by
335 reviewing the origins, range expansion, and host compatibility in *F. hepatica*. In light of this
336 new evidence, the understanding of hyperendemic foci from the Andean countries must
337 consider the possibility that both intermediate and definitive hosts have long evolved in
338 interaction with *F. hepatica*. This interaction with native hosts should concern in particular
339 native human populations from the heavily fasciolosis-struck regions in Bolivia and Peru.
340 However, as we have discussed above, European colonization brought new and hazardous
341 challenges to the overall American scenario of fasciolosis transmission by either introducing
342 different strains of the fluke, definitive hosts, and lymnaeid snails. Further research is very
343 much needed to explore the possible existence of the ancient genetic structure of *F. hepatica*,
344 particularly from wild-native definitive hosts and its relation with sympatric and allopatric
345 lymnaeid snails (particularly in North America) as well as to answer other related questions
346 (see **Outstanding Questions**). Such research would shed light on this interesting host-
347 parasite system, which not only has implications on public and veterinary health, but also
348 from in further developing evolutionary perspectives.

349

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354

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511 *Fasciola hepatica* in Cuba. *Sci. Rep.* 9 (1), 14359

512

513 **Glossary**

514 **Compatibility:** ecological, physical, physiological, and genetic features that enable a host-
515 parasite system to function (i.e., a susceptible host is infected and transmits the parasite).

516 **Ecological guilds:** a group of species exploiting the same resources, or different resources in
517 similar ways.

518 **Ecological isolation:** separation of organisms due to a change in their ecology that may or
519 may not be the result of a change in the environment in which they live.

520 **Hyperendemic fasciolosis area:** a region where the transmission of fasciolosis is persistently
521 present with prevalence over 10% in humans and over 300 eggs per gram of faeces in
522 infected people.

523 **Intermediate snail host:** a susceptible snail that a helminth parasite is obligated to infect in
524 order to develop several larval stages before reaching the definitive (usually) vertebrate host.
525 In the case of trematodes, a clonal amplification of parasites occurs inside the intermediate
526 host snail.

527 **Neglected Tropical Disease (NTD):** a group of diseases that mostly affect around 1.7 billion
528 poor people in tropical and subtropical areas (though they may have a broader latitudinal
529 range). NTDs usually have a high burden in the economy of low- and middle-income
530 countries creating a hard to escape from poverty cycle. Financing for research in NTDs is
531 usually scarcer than for other more mediatized infections.

532 **Transmission competence:** ability of a susceptible host to sustain and discharge a different
533 amount of viable infecting pathogens to the next host in the transmission chain.

534

535 **Figure Legends**

536 **Figure 1, Key Figure. Pathways of *Fasciola hepatica* arrival in the Americas.** (A)
537 formerly accepted theory; (B) new proposed first arrival supported by ancient *F. hepatica*
538 DNA identified in the Americas, and the accepted introduction of *Fascioloides magna*
539 through the Bering Land Bridge; (C) probable migration of *F. hepatica* prior to domestication
540 time until reaching the Americas with the latest arrival of new strains introduced by European
541 colonization. References supporting each step are 1, Origins of fasciolids [13]; 2, Snail host
542 switch [12]; 3, Introduction into Asia [13, 19]; 4, definitive host switch [13, 25]; 5, Split of
543 *Fasciola* lineages [12]; 6, Crossing the Bering Land Bridge [21, 31]; 7, Spreading in the
544 Americas [36]; 8, Introduction of modern strains [39, 41].

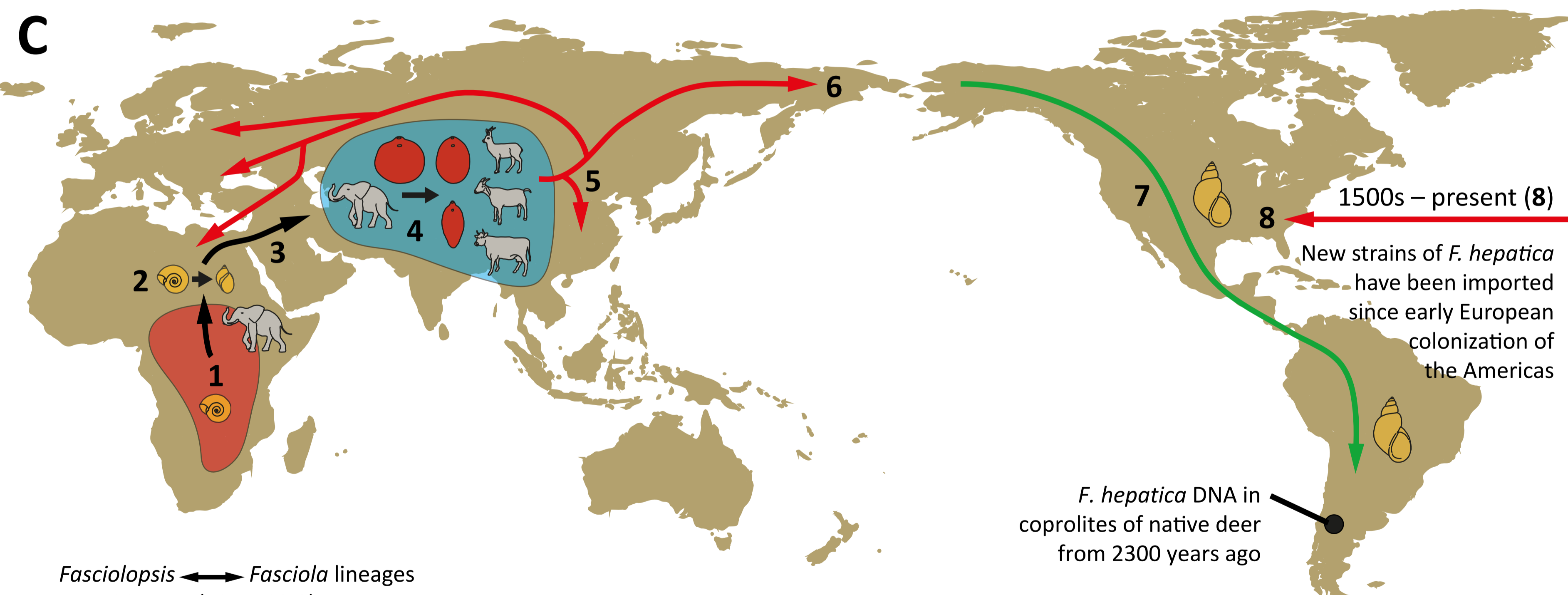
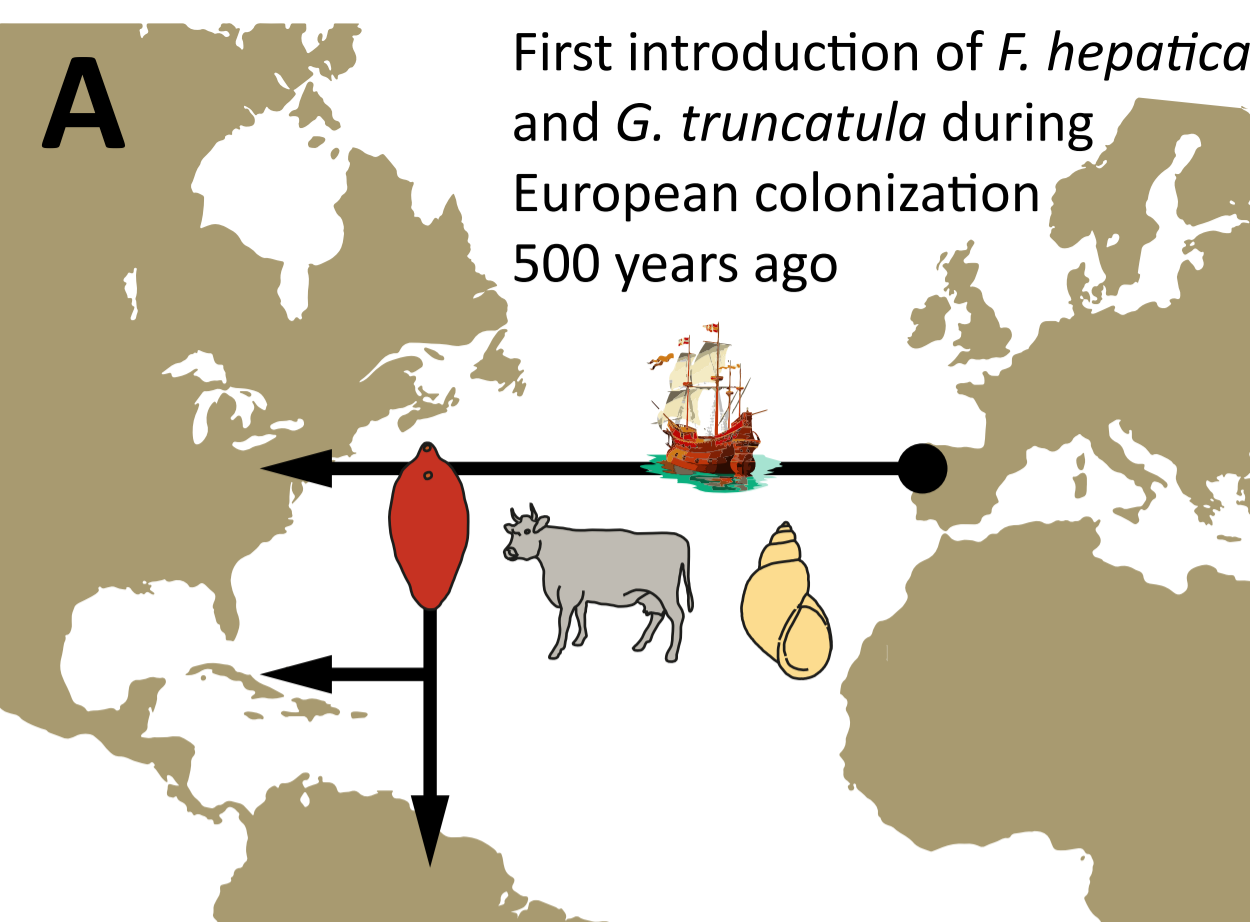
545

546 **Figure 2. *Fasciola hepatica* development in the Americas from pre-domestication to**
547 **present day due to cattle husbandry and other human-related perturbations.** First
548 incursions of mammals through the Bering Land Bridge must have carried ancient *F.*
549 *hepatica* into the Americas where it remained until the 1500s. With European colonization,
550 new strains must have continued to enter with infected cattle and introduced in the existing
551 populations of liver flukes that would have eventually restructured the genetic background of

552 American populations. Today we may encounter a scenario in which none of the ancient *F.*

553 *hepatica* genotypes persist as a result of considerable human activities.

554



Fasciolopsis ↔ *Fasciola* lineages
88.1 Ma (73 – 102.9)

Before 100 Ma (1) | 65 – 55.9 Ma (2) | 18.5 Ma (3) | 10 Ma (4) | 5.3 Ma (7.2 – 3.4) (5) | 5 – 2 Ma (6) | 2 – 0 Ma (7)

Origin of basal fasciolids in African proboscideans	Snail host switches from Planorbidae to Lymnaeidae	Migration out of Africa of ancient proboscideans	Mammal host switches in Asia matching bovid diversification	<i>F. hepatica</i> splits from <i>F. gigantica</i> and spreads with bovid migration with later reintroduction of both species into Africa	Infected bovids cross the Bering Land Bridge into the Americas	<i>F. hepatica</i> adapts to local lymnaeid snails and spreads during the GABI events through several mammal species
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