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Hybridisations within the genus *Schistosoma*: implications for evolution, epidemiology and control.

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21 ABSTRACT

22

23 Hybridisation of parasites is an emerging public health concern in our changing world.
24 Hybridisation and introgression in parasites and pathogens can have major impacts on the host
25 and the epidemiology and evolution of disease. Schistosomiasis is a Neglected Tropical Disease
26 (NTD) of profound medical and veterinary importance across many parts of the world, with the
27 greatest human burden within sub-Saharan Africa (SSA). Here we review how early phenotypic
28 identification and recent confirmation through molecular studies on naturally occurring
29 infections, combined with experimental manipulations, have revealed evidence of viable
30 hybridisation and introgressions within and between human and animal schistosome species.
31 Environmental and anthropogenic changes in selective pressures following, for instance, new
32 dam constructions, altered agricultural practices, together with mass drug administration
33 (MDA) programs, may all be predicted to further impact the availability of suitable definitive
34 and intermediate hosts for schistosomes. It is therefore imperative to understand the distribution
35 and role of such novel zoonotic hybrid schistosomes on host range, drug efficacy, and hence
36 ultimately transmission potential, if we are to achieve and maintain sustainable control.

37

38 Key words: *Schistosoma* spp.; Hybridisation; Introgression; Epidemiology; Evolution; Control;
39 Anthropogenic changes.

40

41 INTRODUCTION

42

43 The evolution and impact of introgressive hybridisation is now well recognized in
44 plants and certain animal species, although examples from within parasitic organisms
45 remain rare (Barton 2001; Arnold 2004; Baack and Rieseberg 2007; King *et al.* 2015).
46 Hybridisation (i.e. interbreeding between two species) and introgression (i.e. the
47 introduction of single genes or chromosomal regions from one species into that of
48 another through repeated backcrossing of an interspecific hybrid with one of its parent
49 species) in parasites and pathogens can have a major impact on the host and the
50 epidemiology and evolution of disease. The acquisition of new genes may affect
51 virulence, resistance, pathology and host use and potentially ultimately lead to the
52 evolution and emergence of new parasitic organisms and new diseases (Arnold 2004;
53 Detwiler and Criscione 2010; King *et al.* 2015). Today, in a changing world,
54 hybridisation of parasites is an emerging public health concern as the geographic
55 distribution of human, domestic animals and wildlife is altering and novel infectious
56 agents and infectious agent combinations may occur more frequently, including those
57 involving co-infections by parasites from different lineages or species within individual
58 hosts (Patz *et al.* 2000; Slingenbergh *et al.* 2004; Lafferty 2009; Shuman 2010; Nichols
59 *et al.* 2014).

60

61 Schistosomiasis (or bilharzia) is a chronic and debilitating disease caused by parasitic
62 trematodes, inducing a range of morbidities including, but not exclusive to, severe
63 anaemia, hypertension and organ damage, sometimes causing death. It affects more
64 than 240 million people, mainly in tropical and sub-tropical regions, and with the
65 greatest burden within sub-Saharan Africa (Steinmann *et al.* 2006; Colley *et al.* 2014).
66 There are currently six main species of schistosome infecting humans: *Schistosoma*
67 *mansoni*, *S. haematobium*, *S. intercalatum*, *S. guineensis*, *S. mekongi* and *S. japonicum*,
68 the latter two species being acknowledged zoonoses (diseases that are naturally
69 transmitted between vertebrate animals and humans), able to infect a broad range of
70 livestock and wildlife. Schistosomiasis is also a disease of substantial veterinary
71 importance (see Fig. 1). It has been estimated that, for instance, about 165 million cattle
72 are infected with schistosomiasis worldwide, with chronic infections resulting in a
73 range of pathologies depending on the infecting species, including haemorrhagic
74 enteritis, anaemia, emaciation and death (De Bont and Vercruyssen 1997, 1998). Of the

75 19 species reported to naturally infect animals, nine have received particular attention,
76 mainly because of their recognized veterinary significance for ruminants in Asia and
77 Africa: *S. mattheei*, *S. bovis*, *S. curassoni*, *S. spindale*, *S. indicum*, *S. nasale*, *S.*
78 *incognitum*, *S. margrebowiei* and *S. japonicum*. Finally, wild animals also represent
79 significant hosts for schistosomes with, for example, *S. rodhaini*, *S. ovuncatum* and *S.*
80 *kisumuensis* being schistosome species of rodents. Moreover, rodents and non-human
81 primates can also act as important zoonotic reservoirs, as demonstrated for *S. japonicum*
82 in Asia (He *et al.* 2001; Rudge *et al.* 2009, 2013; Lu *et al.* 2010b, 2011) and for *S.*
83 *mansoni* in Africa (Fenwick 1969; Muller-Graf *et al.* 1997; Duplantier and Sene 2000)
84 and the Caribbean (Théron *et al.* 1992; Théron and Pointier 1995).

85
86 *Schistosoma* spp. have an asexual stage occurring in an invertebrate intermediate host,
87 a freshwater snail, and a sexual stage within the vascular system of a definitive
88 vertebrate host; parasite eggs are voided with the definitive host's urine or faeces,
89 depending on the infecting parasite species. One exception being *S. nasale*, where adult
90 pairs are located in the blood vessels of the nasal mucosa and eggs are excreted through
91 nasal discharge. Schistosomes are dioecious, rather than hermaphroditic as it is the case
92 for most other trematodes. This potentially creates enhanced opportunities for
93 interactions between male and female schistosomes within their definitive host. Several
94 schistosome species also overlap in their geographical and host range, which allows
95 males and female schistosomes of different species to pair within their definitive
96 hosts. It was traditionally believed that the combination of host specificity and
97 physiological barriers (i.e. intestinal schistosomes being located around the mesenteric
98 system as adults, urogenital schistosomes are nearby the bladder) would prevent
99 heterospecific interactions or pairings to occur (Jourdane and Southgate 1992;
100 Southgate *et al.* 1998). However, subsequent evidence revealed that closely-related
101 species, in particular *S. haematobium* with *S. mattheei* and *S. haematobium* with *S.*
102 *guineensis* (previously known as *S. intercalatum*) have the potential, and the propensity,
103 to pair and hybridise both in the wild and experimentally in the laboratory (Taylor 1970;
104 Morgan *et al.* 2003; Webster and Southgate 2003b; Webster *et al.* 2013b). Even
105 distantly related schistosome species such as *S. mansoni* and *S. haematobium* often pair
106 (Khalil and Mansour 1995; Cunin *et al.* 2003; Koukounari *et al.* 2010). Whilst such
107 pairings are likely to result predominantly in parthenogenetic egg production, recent

108 molecular evidence suggests that under certain conditions, such distance pairings may
109 also result in introgression and the production of viable offspring (Huysse *et al.* 2009).

110

111 Here we review studies performed on natural and experimental schistosome hybrids
112 and discuss how new molecular tools have improved our understanding of the evolution
113 and epidemiology of these hybrids. We consider the factors that may be predicted to
114 further influence the potential for novel zoonotic hybrid parasites to emerge and
115 establish and present the theoretical and applied implications and applications for both
116 schistosomiasis and other important host-parasite associations that impact humans,
117 livestock and wildlife today and in the future.

118

119

120 HISTORY OF THE SCIENTIFIC WORK UNCOVERING THE EVOLUTION AND 121 ESTABLISHMENT OF *SCHISTOSOMA* HYBRIDS

122

123 From some of the earliest scientific literature on schistosomes, evidence of potential
124 crosses and hybridisations between different species of schistosomes have been
125 reported. These first identifications were mainly based on phenotypic eggs
126 observations. For example, Alves in 1948 reported potential *S. haematobium*-*S.*
127 *mattheei* hybrids amongst cases of human urogenital schistosomiasis in Southern
128 Rhodesia, Zimbabwe (Alves 1948). This observation was followed by several others
129 proposing the existence of the same hybrids occurring in both Zimbabwe and South
130 Africa (Le Roux 1954b; Pitchford 1959, 1961; Kruger *et al.* 1986a, 1986b; Kruger and
131 Hamilton-Attwell 1988), as well as other potential hybridised pairings, predominantly
132 between *S. haematobium* with *S. guineensis* in Cameroon (Wright *et al.* 1974;
133 Southgate *et al.* 1976; Rollinson and Southgate 1985; Ratard *et al.* 1990; Ratard and
134 Greer 1991; Tchuem Tchuente *et al.* 1997b) and Gabon (Burchard and Kern 1985;
135 Zwingenberger *et al.* 1990) (see Table 1a). However, the viability of these eggs were
136 rarely, if ever, assessed and these early phenotypic observations have often been
137 considered, or even dismissed, as misleading identifications (Teesdale 1976; Kinoti and
138 Mumo 1988). Likewise, early reports of apparent human infections with pure animal
139 *Schistosoma* spp., such as *S. bovis*, *S. curassoni* or *S. mattheei* (Raper 1951; Grétilat
140 1962; Albaret *et al.* 1985; Chungue *et al.* 1986; Mouchet *et al.* 1988), as were based
141 primarily on egg morphologies, were again subsequently dismissed as misdiagnoses

142 (Capron *et al.* 1965; Vercruyssen *et al.* 1984; Rollinson *et al.* 1987; Kruger and Evans
143 1990; Brémond *et al.* 1993). The use of biochemical markers confirmed, however, some
144 of the earlier phenotypic observations made on schistosome hybrids, albeit not of any
145 apparent cases of pure animal schistosome species infecting humans, and furthermore
146 revealed new hybridisation between different species. The first study on hybrid
147 schistosomes using isoelectric-focusing of enzymes was made by Wright and Ross
148 (1980), which confirmed hybridisation between *S. haematobium* with *S. mattheei* in
149 Eastern Transvaal, South Africa. By the 1990s, studies reported hybridisation between
150 *S. bovis* with *S. curassoni* in cattle, sheep and goats through the identification of gene
151 flow using biochemical markers (Brémond 1990; Brémond *et al.* 1990; Rollinson *et al.*
152 1990a). Likewise, by 1993, Brémond *et al.* (1993) used both morphological and
153 biochemical markers to assess, for the first time, natural introgression of *S.*
154 *haematobium* by genes from *S. bovis* in Niger.

155

156 The increasing use of molecular techniques available for parasitological research
157 resulted in a growing number of reports on hybridisation and introgression in
158 schistosomes. Furthermore, these are providing new insights for understanding the
159 evolution and epidemiology of the disease. For instance, new methods have been
160 developed which can discriminate between different schistosomes species and their
161 hybrids, in particular multi-locus approaches, combining both nuclear and
162 mitochondrial DNA markers, as single-locus approaches are not appropriate to detect
163 hybridisation or introgression events (Norton *et al.* 2008b; Huyse *et al.* 2009; Webster
164 B.L. *et al.* 2010). The internal transcribed spacer (ITS) is a particularly powerful marker
165 to detect introgression. This region can retain both parental copies for several
166 generations before they are homogenised by concerted evolution, the nuclear DNA
167 profiles resulting in double chromatogram peaks at the species-specific mutation sites
168 (Dover 1986; Sang *et al.* 1995; Aguilar *et al.* 1999; Kane *et al.* 2002; Huyse *et al.* 2009,
169 2013; Webster *et al.* 2013b; Moné *et al.* 2015). The ITS marker has therefore repeatedly
170 been used to detect hybridisation events across the *Schistosoma* genera. Webster *et al.*
171 (2007) used a single-strand conformation polymorphism analysis of the second internal
172 transcribed spacer (ITS2) of nuclear ribosomal DNA for the identification of *S.*
173 *haematobium*, *S. guineensis* and their hybrids in Loum, Cameroon. This analysis
174 revealed that some individuals previously considered to be *S. haematobium*, based on
175 egg morphology and sequence data alone, were actually hybrids and this would not

176 have been detected without employing such high resolution analysis. Recent studies in
177 Senegal, using sequence data of nuclear (ITS1+2) and mitochondrial (*cox1*) loci,
178 reported the bidirectional hybridisation between *S. haematobium* with *S. bovis* and *S.*
179 *haematobium* with *S. curassoni* in school children and also in both *Bulinus* snails and
180 between *S. bovis* with *S. curassoni* in cattle (Huyse *et al.* 2009; Webster *et al.* 2013b).
181 Molecular analyses on cercariae from infected snails in Kenya and Tanzania have also
182 observed hybrids between the human schistosome *S. mansoni* and its sister species, *S.*
183 *rodhaini*, from rodents (Morgan *et al.* 2003; Steinauer *et al.* 2008). Furthermore, these
184 authors, using microsatellite markers, demonstrated that the hybrids produce viable
185 offspring through first or successive generation backcrosses with *S. mansoni* (Steinauer
186 *et al.* 2008). More recently, studies combining epidemiological molecular and nuclear
187 data have also revealed potential rare introgressions between the two major human
188 schistosome species in Africa, *S. haematobium* with *S. mansoni* (Meurs *et al.* 2012;
189 Huyse *et al.* 2013), a phylogenetically distant pairing previously believed to result in
190 unviable eggs exclusively through parthenogenesis (Khalil and Mansour 1995; Webster
191 *et al.* 1999; Cunin *et al.* 2003; Koukounari *et al.* 2010). The use of molecular tools also
192 allows identification of the direction of introgression. For example, Steinauer *et al.*
193 (2008) observed unidirectional gene flow from the rodent schistosome *S. rodhaini* to
194 the human *S. mansoni*, whereas there appears to be bidirectional hybridisation between
195 the *S. haematobium* with *S. bovis* or *S. curassoni* hybrids described above.

196

197 There is, to date, no evidences of hybrids in Asia where *S. japonicum* and *S. mekongi*
198 overlap, although experimental crossing of these two species has been achieved
199 (Kruatrachue *et al.* 1987). Reports of potential schistosome hybrids are distributed
200 across much of Africa, but it appears with predominance within West Africa (Table 1).
201 This is a region both with multiple species of schistosomes, of humans and animals,
202 naturally circulating, and of profound poverty.

203

204 Thus, through the use of either molecular or biochemical tools or phenotypic analyses,
205 various combinations of *Schistosoma* spp. hybrids have been documented repeatedly
206 within snails, livestock, wildlife, and within humans. Moreover, these heterospecific
207 crosses are between animal schistosome species (e.g. *S. bovis* with *S. curassoni*); human
208 schistosome species (e.g. *S. guineensis* with *S. haematobium*); and perhaps most
209 importantly and interestingly epidemiologically and clinically, between human

210 schistosome species with animal schistosome species (e.g. *S. mansoni* with *S. rodhaini*
211 or *S. haematobium* with *S. bovis* or *S. curassoni* or *S. mattheei*). However, to date,
212 zoonotic hybrids between *S. haematobium* with *S. bovis* or *S. curassoni* have been
213 reported in humans and snails but never from livestock, although past attempts at
214 research therein have been rare and sporadic and bladder and urine from livestock have
215 never been inspected (e.g. Vercruysse *et al.* 1984; Webster *et al.* 2013). This is
216 particularly important as *S. haematobium* males have been shown to be dominant over
217 other species such as *S. mansoni*, *S. mattheei* or *S. guineensis*, and to take females to
218 the urogenital tract (Southgate *et al.* 1976, 1982, 1995; Webster *et al.* 1999; Cunin *et al.*
219 2003; Cosgrove and Southgate 2003a; Webster and Southgate 2003b; Koukounari *et*
220 *al.* 2010; Gouvras *et al.* 2013).

221

222 Concurrent with research under field conditions, hybridisation experiments in the
223 laboratory began in the 1940s. Some were conducted between schistosome species that
224 are unlikely to hybridise in the wild, because they have not shared the same
225 geographical range (e.g. *S. mansoni* with *S. japonicum* (Vogel 1941, 1942; Imbert-
226 Establet *et al.* 1994; Fan and Lin 2005)). These distant pairings were reported to result
227 in the production of non-viable or apparently parthenogenetic eggs. Likewise, the
228 experimental crosses conducted between the two phylogenetically distant species *S.*
229 *mansoni* and *S. haematobium*, *S. guineensis* or *S. mattheei* also resulted in non-viable
230 or parthenogenetic eggs (Taylor *et al.* 1969; Tchuem Tchuente *et al.* 1994; Khalil and
231 Mansour 1995; Webster *et al.* 1999). Several experimental studies in laboratory have,
232 however confirmed that certain closely-related schistosome species can successfully
233 hybridise for several generations. Most of experimental research on interspecies crosses
234 has been conducted within the *S. haematobium* group species (see the list of all
235 crossings in Table 1b). In the *S. mansoni* group, successful experimental crossings have
236 been repeatedly performed only between *S. mansoni* with *S. rodhaini* (Le Roux 1954a;
237 Taylor 1970; Brémond *et al.* 1989; Théron 1989; Norton *et al.* 2008b). It appears that
238 the successfully hybridization, or not, of these pairings will vary in part with the
239 geographical origin as well as the strain of the parasite. For example, Taylor (1970)
240 observed that the cross between a *S. haematobium* from Nigeria and *S. bovis* from Iran
241 was viable, while the cross between *S. haematobium* and *S. bovis* both from Iran was
242 of very low viability. Also, Wright and Ross (1980) showed that F1 hybrids issued from
243 the cross between *S. haematobium* from Durban and female *S. mattheei* from Transvaal

244 presented heterosis (i.e. hybrid vigour) whereas the same crossing with *S. mattheei* from
245 Zambia with *S. haematobium* from the Ivory Coast did not (Tchuem Tchuente *et al.*
246 1997a). More importantly, even viable crosses of the same species are not always
247 reciprocal. For example, crossing only produces viable and fertile hybrid descendants
248 between male *S. haematobium* and female *S. guineensis* or female *S. mattheei* (Wright
249 *et al.* 1974; Wright and Ross 1980; Tchuem Tchuente *et al.* 1997a; Southgate *et al.*
250 1998). However, crossings between *S. haematobium* and *S. bovis* or *S. curassoni* appear
251 bidirectional and involve both male and female of each species (Huyse *et al.* 2009;
252 Webster *et al.* 2013). One hypothesis could be that laboratory studies will mainly be on
253 F1 crosses whereas molecular analyses on parasites from natural population in the field
254 will detect repeated backcrossing and hence more evidences of bidirectional
255 introgression.

256

257 Further experimental infections and crossings are required to study the mating
258 behaviour of different schistosome species and to study the biological characteristics of
259 the hybrid lines such as fecundity, infectivity, longevity, cercariae production and
260 response to praziquantel, the drug routinely used to control human schistosomiasis, and,
261 in some parts of the world, in Asia for example, animal schistosomiasis too. However,
262 we must keep in mind that the laboratory system might bias studies on hybridisation
263 due to selection and genetic bottleneck events because of less compatible rodent or snail
264 hosts in experimental infections. Most of the crossings performed to date have been
265 obtained in rodents and we do not know yet how hybrids would develop in other
266 mammalian hosts, in particular domestic livestock other than sheep, which may be
267 predicted to be potentially more relevant to ongoing natural transmission cycles.

268

269 There also remains a great deal to elucidate concerning the genetics and genomics of
270 hybridisation and introgression across the *Schistosoma* genus and in parasites in
271 general, such as, for example, how hybridisation may affect spread and pathogenicity.
272 Genetic introgression could occur in areas of the genome affecting the evolution of
273 virulence, transmission and host specificity, among others characteristics. Modern
274 molecular techniques can expose the signature of hybridisation in the genome more
275 rapidly and accurately and the recent whole genome sequencing of the three main
276 human schistosome species *S. japonicum*, *S. mansoni* and *S. haematobium* (Berriman
277 *et al.* 2009; Zhou *et al.* 2009; Young *et al.* 2012) will undoubtedly provide new insights

278 into the study of schistosomes' hybridisation and NTDs research in general (Webster
279 J. P. *et al.* 2010).

280

281

282 EFFECT OF HYBRIDISATION ON CERCARIAL EMERGENCE FROM SNAIL 283 INTERMEDIATE HOST

284

285 Cercarial emergence is a heritable trait shaped by the definitive hosts' behaviour and
286 this can vary within species, as Lu *et al.* (2009) observed within *S. japonicum* with two
287 different emergence peaks, one in late afternoon emergence compatible with a
288 nocturnal rodent reservoir, and one early emergence consistent with a diurnal cattle
289 reservoir. Norton *et al.* (2008a) also showed that co-infection and therefore competition
290 between *S. mansoni* and *S. rodhaini* was influencing cercarial chronobiology resulting
291 in a slight shift in the *S. mansoni* shedding pattern and a reduction of the *S. rodhaini*
292 shedding period. In hybrids with different definitive host species, one could predict
293 different chronobiology of cercariae shedding emergence depending on their relative
294 parental species. Evidence in support of this has been provided by Théron (1989) with
295 hybrids between *S. mansoni* with *S. rodhaini* showing two unequal emergence peaks,
296 one diurnal (characteristic of *S. mansoni* for human infection) and the other nocturnal
297 (characteristic of *S. rodhaini* for rodents' infection). Depending on the
298 chronobiological strain of *S. mansoni* used in the cross-breeding it was either the diurnal
299 peak (when the early strain of *S. mansoni* was used), or the nocturnal peak (when the
300 late strain of *S. mansoni* was used), that is preponderant. This could also explain some
301 patterns of excretion observed by Norton *et al.* (2008a) as some of the *S. rodhaini* and
302 *S. mansoni* are likely to have hybridised. Finally, experimental crosses conducted
303 between *S. haematobium*, *S. guineensis* and *S. bovis*, revealed a cercarial emission
304 pattern amongst F1 hybrids with only one emergence peak, but with a mean shedding
305 time always in advance (from one hour to five hour depending on the crossing) of those
306 of the respective parental species, except for *S. bovis* from which no difference was
307 observed (Pages and Theron 1990). The authors explained this modification by a
308 greater sensibility of the hybrids to synchronisation with photoperiod. Also, as cercariae
309 can survive in the environment for several hours, one could proposed that an earlier
310 shedding time would allow them to infect all the potential definitive host of their
311 parental species, and hence give them a selective transmission advantage relative to

312 their later shedding counterparts. These studies to date were, however, all performed
313 using experimental laboratory infections and crossings. The only monitoring of hybrids
314 cercarial emergence from natural infections to date was performed by Steinauer *et al.*
315 (2008) on *S. mansoni* with *S. rodhaini* hybrids collected from *B. sudanica* and *B.*
316 *pfeifferi* in Western Kenya. Species were subsequently identified using
317 microsatellites, rDNA and mtDNA markers. They observed that most of the hybrids
318 showed an emergence pattern similar to that of *S. mansoni*, except for one individual,
319 that presented a bimodal emergence pattern that was characteristic of both parental
320 species.

321

322

323 FACTORS POTENTIALLY FAVOURING HYBRID EVOLUTION AND 324 ESTABLISHMENT

325

326 Environmental and/or anthropogenic changes, through natural phenomena (e.g. climate
327 change) or human activities, such as dam constructions, changes in agricultural
328 practices or drug treatments, can substantially impact the dynamics and distribution of
329 schistosomiasis and infectious diseases in general, with potential positive and negative
330 effects upon human and animal health (King *et al.* 2015). These environmental and
331 anthropogenic changes place selective pressures on human and animal schistosomes
332 and increase the opportunities for mixing of different species. This mixing within the
333 human or animal hosts may be predicted to further influence the potential for novel
334 zoonotic hybrid parasites, which may impact their potential for disease transmission
335 and morbidity (Fig. 2). For example, it has been suggested that local deforestation may
336 have altered the environment in Loum area (Cameroon) and allowed *B. truncatus*
337 (previously named *B. rohfsi*), the intermediate host for *S. haematobium*, to become
338 established, and, the increase of human exchanges through the introductions of the
339 railways created areas of sympatry between *S. guineensis* and *S. haematobium*, leading
340 to the formation of hybrids (Southgate *et al.* 1976; Southgate 1978).

341

342 In the north of Senegal, the rehabilitation of the Lac de Guiers area (Mbaye 2013)
343 provided new accesses to freshwater. These new contact areas are used both by people
344 and livestock and are important sites where mixing of animals and humans schistosome
345 species can happen. Likewise in Senegal, the construction of Diama dam on the Senegal

346 river, for the creation of irrigation canals and development and extension of rice culture
347 in the Senegal River Basin, resulted in a reduction in salinity and more stable water
348 flow, with a subsequent occurrence of new outbreaks of schistosomiasis, as well as
349 other trematodiasis, in humans and livestock in this region (Vercruysse *et al.* 1994;
350 Diaw *et al.* 1998). N'Goran *et al.* (1997) also observed a strong increase in human
351 urogenital schistosomiasis prevalence around the Kossou and Taabo Lakes in Côte
352 d'Ivoire between 1970 and 1992 after the construction of the two Dams of Kossou and
353 Taabo.

354

355 The recent deliberate crossing/hybridisation of local cattle breeds with European cattle,
356 in an effort to increase milk and meat yield (Nicolas Diouf, personal communications),
357 in Senegal may also be predicted to have consequences on the spreading of zoonotic
358 hybrid schistosomes. These new hybrid cattle may be predicted to have different
359 susceptibilities for schistosome establishments and infection. The introduction of exotic
360 cattle has already proved to accelerate the spread of several parasitic organisms. For
361 example the southern cattle tick *Rhipicephalus (Boophilus) microplus*, initially a
362 parasite of Asian bovid species, has spread over the tropical and subtropical belts to
363 become a major invasive pest in many agrosystems (Barré and Uilenberg 2010). Its
364 current geographic distribution and its dramatic expansion over the last century can
365 primarily be explained by the introduction of highly susceptible European cattle (*Bos*
366 *taurus*) breeds to tropical areas (Chevillon *et al.* 2013; Léger *et al.* 2013). In contrast to
367 both wild and domestic tropical Bovidae, these introduced hosts of European origin are
368 almost incapable of mounting efficient immune responses to *R. microplus* infestations
369 (Frisch 1999).

370

371 Temperature, among other factors, can also have a significant effect on the schistosome
372 life-cycle and the survival of its intermediate snail host (Mas-Coma *et al.* 2009).
373 Climate change (e.g. desertification) taking place in West Africa has also been argued
374 to be responsible for important changes in the movement of domestic livestock, where
375 animals may have to moved long distance for food and water and may be in contact
376 with multiple potential transmission sites. Indeed such livestock movement changes
377 have been proposed to have brought *S. bovis* and *S. curassoni* into contact and may
378 have led to hybridisation between them (Rollinson *et al.* 1990a). In addition to human
379 and animal movements, the current climate of global warming may also offer the

380 potential to novel zoonotic hybrids to be a global disease. Many schistosome species
381 infecting livestock could have a broader geographical range beyond Asia and Africa if
382 compatible snail intermediate hosts are present. This appears now the case in parts of
383 Europe, where novel introgressed hybrids between human *S. haematobium* with the
384 livestock *S. bovis* have recently been identified in Corsica (France), and sporadically in
385 Spain and Portugal, with substantial ongoing transmission amongst both local Corsican
386 residents and tourists (de Laval *et al.* 2014; Boissier *et al.* 2015; Moné *et al.* 2015;
387 Berry *et al.* 2016; Webster *et al.* 2016).

388

389

390 IMPLICATIONS FOR CONTROL

391

392 The recurrent hybridisation between schistosome species in nature may have major
393 implications in light of the current global push and shift from controlling morbidity to
394 interrupting transmission (Webster *et al.* 2014). How such introgression may alter host
395 range and transmission dynamic is perhaps the most pressing area for future research
396 (King *et al.* 2015) (Fig. 2).

397

398 Since the first observations of hybridisation of animal and human schistosomes, the
399 main concern has been the possible complication of control measures occasioned by
400 the existence of an animal reservoir infection (Wright and Southgate 1976; Wright and
401 Ross 1980). Indeed, schistosomiasis control has focused almost exclusively on
402 treatment of humans with mass drug administration using praziquantel. However, the
403 extent to which hybridisation may increase the role of wild mammals and livestock as
404 reservoir hosts for infection, due to hybrid vigour for example, is poorly understood,
405 although it is widely accepted that zoonotic diseases may be harder to eliminate due to
406 the presence of animal reservoirs driving ongoing transmission (Webster *et al.* 2016).
407 It has been shown that *S. haematobium* alone is incapable of developing in sheep
408 (Vercruysse *et al.* 1984), but *S. haematobium* with *S. mattheei* hybrids have that ability
409 (Tchuem Tchuente *et al.* 1997a). Similarly, Taylor *et al.* (1973) and Vercruysse *et al.*
410 (1984) showed experimentally that *S. bovis* or *S. curassoni* cannot infect baboons as a
411 single species but they can when hybridised with *S. haematobium*. Hybrids between *S.*
412 *mansoni* with *S. rodhaini* in Kenya may also be predicted to prove problematic,
413 particularly in the elimination era. Rodents are reservoirs for several schistosome single

414 species (*S. mansoni*, *S. bovis*, *S. rodhaini* and *S. kisumuensis*. *S. mansoni* and *S.*
415 *rodhaini*), and co-infections in a single host individual has been observed, suggesting
416 that this host species could be responsible for the production of hybrid schistosomes
417 found in the area (Hanelt *et al.* 2010). In a worst case scenario, one could predict that
418 this could lead to a comparable situation as observed in China today, where after over
419 fifty years of concerted and multi-faceted interventions (including chemotherapy, snail
420 control, health education, sanitation and environmental improvement), *S. japonicum*
421 remains endemic among humans and transmission has even re-emerged in some areas
422 where schistosomiasis was thought to have been eliminated. It has been demonstrated,
423 by combining field data with novel mathematical modelling, that spillover from animal
424 zoonotic transmission is maintaining such human schistosomiasis in China (Lu *et al.*
425 2009, 2010a, b, 2011; Rudge *et al.* 2009, 2013).

426

427 There are also other potential serious implications of wide-scale hybridisation events
428 in nature. For instance, introgressive hybridisation may lead to phenotypic changes that
429 can dramatically influence disease dynamics and evolution of the parasites.
430 Hybridisation between different *Schistosoma* species have already been suggested to
431 affect the success of drug treatment; Pitchford and Lewis (1978) have suggested that
432 the poor response of *S. mattheei* to oxamniquine treatment in children, in a trial they
433 conducted in Eastern Transvaal, may be due to hybridisation with *S. haematobium*,
434 which is not susceptible to the drug. Although the efficacy of praziquantel, which is
435 currently the only anti-schistosome drug in wide-scale use, is not well documented in
436 terms of livestock, as distinct from human, *Schistosoma* species, changes in MDA
437 pressures could be predicted to play an important role in the evolution of hybrid
438 schistosomes. Drug resistance or decreased sensitivity of *S. mansoni* to praziquantel
439 has been documented under both field and laboratory conditions (Cioli *et al.* 1993;
440 Fallon and Doenhoff 1994; Bonesso-Sabadini and de Souza Dias 2002; Botros *et al.*
441 2005; Alonso *et al.* 2006; Melman *et al.* 2009; Pica-Mattoccia *et al.* 2009; Lamberton
442 *et al.* 2010; Valentim *et al.* 2013; Webster *et al.* 2013a). To which extent hybrid
443 schistosomes may differ in terms of praziquantel efficacy, and how MDA could
444 differentially select for hybrids, is not known but should be considered in the control
445 of schistosomiasis (Fenwick and Webster 2006; Webster *et al.* 2008, 2014).
446 Hybridisation and the occurrence of large animal reservoirs may, however, also have a
447 positive role in the context of reducing the risk of drug resistance emergence or

448 establishment by increasing the proportion of untreated worms, and hence *Refugia*,
449 through the untreated animal host populations. Human infection could also be reduced
450 as selection imposed by drug treatment in humans may be predicted to lead to a shift in
451 host preference, favouring strains that prefer nonhuman hosts. Conversely, if livestock,
452 particularly in Africa, were to also be intensively treated with praziquantel in the future,
453 then the risk of drug resistance emerging would be exacerbated. This could be due both
454 to the relative loss of *Refugia*, but also the increased risk of resistance developing in
455 the veterinary field through treatment mismanagement, as has been the case with all the
456 current veterinary anthelmintics to date, and its subsequent impact for human
457 treatment, particularly critical for zoonotic hybrids (Webster *et al.* 2016).

458

459 Hybrid infections may also be predicted to result in a differential morbidity profile in
460 both humans and livestock, relative to their single species infection counterparts.
461 Schistosomiasis morbidity is caused primarily by parasite eggs being trapped within
462 the host tissues. Previous studies have reported higher bladder morbidity in mixed *S.*
463 *haematobium*-*S. mansoni* mixed infections compared to single *S. haematobium*
464 infections. They suggested that *S. haematobium* males were mating with *S. mansoni*
465 females and deviating the eggs to the urinogenital tract, thereby reducing the amount
466 of egg granulomas in liver tissues whilst increasing the egg output at the vesicle venous
467 plexus and therefore aggravating urogenital schistosomiasis in co-infected individuals
468 (Koukounari *et al.* 2010; Gouvras *et al.* 2013). To date there has been no such morbidity
469 surveys performed related to introgressed schistosomes within the *S. haematobium*
470 group. Any Such differential morbidity in hybrid infections may have major
471 implications for current methods of monitoring and evaluation of human morbidity
472 levels and control programme efficacy.

473

474 Hybrid vigour is also a potential issue for successful disease control. As it has already
475 been observed for hybrids between *Leishmania major* and *Leishmania infantum*, with
476 hybrids having enhanced transmission potential and fitness (Volf *et al.* 2007),
477 schistosome hybrids may exhibit heterosis. Laboratory experiments have shown that
478 F1 and F2 hybrids between *S. haematobium* and *S. guineensis* exhibited greater
479 infectivity for snail intermediate hosts and for hamsters, as well as an increased
480 longevity, growth rate and reproductive potential (i.e. females produced more eggs and
481 larger numbers of eggs were passed in hamster faeces relative to single-species

482 infections) (Southgate *et al.* 1976; Wright and Southgate 1976; Webster and Southgate
483 2003a). Similar results were observed by Wright and Ross (1980) and Taylor (1970)
484 on F1 hybrids between *S. haematobium* males with *S. mattheei* females showing
485 increased infectivity for snails and hamsters infected experimentally. Work has also
486 been done on hybrid vigour in term of extended intermediate host range. Due to the
487 potential inheritance of a snail infectivity factor by hybrid schistosomes, *Schistosoma*
488 hybrids might be predicted to be able to break down the host specificity barrier and
489 develop in both the intermediate snail hosts of the parental species, as it has already
490 been observed. For example, Huyse *et al.* (2013) identified *S. haematobium* with *S.*
491 *bovis* hybrids within both *B. globosus* and *B. truncatus* which are the intermediate snail
492 hosts of *S. haematobium* and *S. bovis* respectively. In other experimental studies,
493 hybrids of *S. haematobium* and *S. guineensis* were found to be able to infect both *B.*
494 *forskalii* and *B. truncatus* (Southgate *et al.* 1976; Wright and Southgate 1976; Wright
495 and Ross 1980; Webster and Southgate 2003a), but also *B. globosus* and *B. wrighti*
496 (Mutani *et al.* 1985). And finally, hybrids of *S. haematobium* and *S. mattheei* have been
497 shown to be able to develop in both *B. globosus* and *B. forskalii* (Wright 1974).

498

499 The excretory route of certain *Schistosoma* hybrids may also have substantial
500 implications for their control. Hybrids between *S. haematobium* and *S. guineensis* are,
501 for instance, predominantly passed with the host urine and not the faeces, akin to pure
502 *S. haematobium*. In humans, prevention of environmental contamination from urine
503 might be harder to achieve relative to that from stool, and least in terms of human
504 behavioural practices, and this could be of some importance in term of transmission
505 where some level of local sanitation has been achieved (Southgate *et al.* 1976).

506

507 Finally, in Cameroon it has been suggested that hybridisation between *S. haematobium*
508 and *S. guineensis* has caused disease outbreaks and that, rapidly after the establishment
509 of *S. haematobium*, *S. guineensis* had been replaced by the hybrid and *S. haematobium*;
510 *S. haematobium* and the hybrids offspring being more competitive than *S. guineensis*
511 (Wright *et al.* 1974; Southgate *et al.* 1976, 1982; Southgate 1978; Tchuem Tchuente *et al.*
512 1997b; Morand *et al.* 2002; Cosgrove and Southgate 2003a; Webster and Southgate
513 2003b). Other studies have also observed competitive exclusion of one species by the
514 other, *S. mansoni* males being more competitive than *S. intercalatum* and *S. guineensis*
515 males at pairing with their respective females (Tchuem Tchuente *et al.* 1993, 1995,

516 1996; Cosgrove and Southgate 2003b), *S. haematobium* being more competitive than
517 *S. mansoni* males (Webster *et al.* 1999; Cunin *et al.* 2003; Koukounari *et al.* 2010;
518 Gouvras *et al.* 2013) or than *S. mattheei* males (Southgate *et al.* 1995), and *S. rodhaini*
519 males over *S. mansoni* counterparts (Norton *et al.* 2008b). Hybrids may therefore be
520 predicted to outcompete current single species as these inter-specific interactions would
521 affect parasite establishment, growth, maturation, reproductive success and drug
522 sensitivity (Norton *et al.* 2008; Webster *et al.* 2008).

523

524

525 CONCLUSIONS AND PERSPECTIVES

526

527 There is a gathering and convincing body of evidence for the natural hybridisation
528 between human and animal schistosome species. These raise a number of critical
529 questions regarding evolution, epidemiology, health impact and ultimate control of
530 schistosomiasis. The implications of hybrids in terms of human health remains unclear,
531 but the emergence and spread of hybrid schistosomes, and in particular zoonotic
532 hybrids, could prove problematic in terms of maintaining transmission in our current
533 era of control/elimination, particularly if they can replace existing species and parasite
534 strains, extend intermediate and definitive host ranges or present an increased
535 infectivity and virulence. In term of future work, it is necessary to accurately identify
536 these species. In particular, are the evolution and expansion of these hybrids a recent
537 phenomenon, in response to new anthropogenic changes and pressures, or are they
538 simply better detected now due to improvements in molecular diagnostics? This will
539 allow us to understand the populations at risk and the transmission dynamics of
540 infection with novel zoonotic hybrid schistosomes and will help to elucidate their role
541 on host range, praziquantel efficacy, host morbidity and hence ultimately transmission
542 potential, with a view to informing control programmes. This is especially important in
543 today's era of 'elimination of schistosomiasis as a public health problem' implemented
544 in the WHO roadmap (WHO 2012) whereas schistosome zoonotic hybrids have the
545 potential to become a global disease (de Laval *et al.* 2014; Boissier *et al.* 2015; Moné
546 *et al.* 2015; Berry *et al.* 2016). More generally, these research these questions could
547 enhance our understanding of a wide spectrum of multi-host parasitic diseases of
548 humans and animals, and in particular the role of hybridisations within major
549 taxonomic groups in our rapidly changing world.

550

551

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1114

1116 Table 1a. Reports of potential natural hybridisations.

References (Date)	Species combination (Original host)	Methodology	Host species detected in	Country
Alves (1948)	<i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock)	Egg morphology	Human	Southern Rhodesia, Zimbabwe
Le Roux (1954b)	<i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock)	Egg morphology	Human	Southern Rhodesia, Zimbabwe
Pitchford (1959, 1961)	<i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock)	Egg morphology	Human	Eastern Transvaal, South Africa
Wright <i>et al.</i> (1974); Southgate <i>et al.</i> (1976)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Egg morphology,	Human	Loum, Cameroon
Wright and Ross (1980)	<i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock)	Biochemical markers	Human	South Africa
Burchard and Kern (1985)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Egg morphology	Human	Palmevas, Gabon
Rollinson and Southgate (1985)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Biochemical markers	Human, <i>Bulinus forskalii</i>	Loum, Cameroon
Southgate <i>et al.</i> (1985)	<i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock)	Worm morphology	Sheep	Senegal
Rollinson <i>et al.</i> (1987)	<i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock)	Worms morphology, biochemical markers	Cattle	Senegal

Kruger <i>et al.</i> (1986a, 1986b); Kruger (1987, 1988, 1990); Kruger and Hamilton-Attwell (1988); Kruger and Evans (1990)	<i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock)	Egg morphology, biochemical markers	Human, multimammate mouse (<i>Mastomys coucha</i>)	South Africa
Brémond (1990); Brémond <i>et al.</i> (1990)	<i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock)	Biochemical markers	Cattle, sheep, goats	Niger
Rollinson <i>et al.</i> (1990a)	<i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock)	Biochemical markers	Cattle	Senegal, Mali
Zwingenberger <i>et al.</i> (1990)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Egg morphology	Human	Gabon
Ratard <i>et al.</i> (1990); Ratard and Greer (1991)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Egg morphology	Human	Cameroon
Brémond <i>et al.</i> (1993)	<i>S. haematobium</i> (human) x <i>S. bovis</i> (or <i>S. curassoni</i>) (livestock)	Egg morphology, biochemical markers	Human	Niger
De Bont <i>et al.</i> (1994)	• <i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock) • <i>S. mattheei</i> (livestock) x <i>S. leiperi</i> (livestock)	Biochemical markers	Cattle	Zambia
Vercruysse <i>et al.</i> (1994)	1 - <i>S. haematobium</i> (human) x <i>S. guineensis</i> (human) 2 - <i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock) 3 - <i>S. mattheei</i> (livestock) x <i>S. leiperi</i> (livestock)	Egg morphology, biochemical markers	Human (1, 2) Cattle (2, 3)	Mali Zambia

Añé <i>et al.</i> (1997)	<i>S. haematobium</i> (human) x <i>S. intercalatum</i> (human)	Egg morphology	Human	East Africa
Tchuem Tchuente <i>et al.</i> (1997b)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Egg morphology	Human	Loum, Cameroon
Cunin <i>et al.</i> (2003)	<i>S. haematobium</i> (human) x <i>S. mansoni</i> (human)	Ectopic eggs elimination	Human	North Cameroon
Morgan <i>et al.</i> (2003)	<i>S. mansoni</i> (human) x <i>S. rodhaini</i> (wildlife)	Partial <i>16S</i> , <i>12S</i> and <i>ITS</i> sequencing	<i>Biomphalaria sudanica</i>	Tanzania
Webster <i>et al.</i> (2003, 2005)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Biochemical markers and partial <i>ITS2</i> amplification	Human <i>B. truncatus</i> , <i>B. camerunensis</i>	Loum, Cameroon
Steinauer <i>et al.</i> (2008)	<i>S. mansoni</i> (human) x <i>S. rodhaini</i> (wildlife)	Partial <i>16S</i> , <i>12S</i> and <i>ITS</i> sequencing	<i>B. sudanica</i> and <i>B. pfeifferi</i>	Kenya
Huyse <i>et al.</i> (2009)	<i>S. haematobium</i> (human) x <i>S. bovis</i> (livestock)	Partial <i>cox1</i> and <i>ITS</i> sequencing	Humans <i>B. truncatus</i> , <i>B. globosus</i>	Senegal
Koukounari <i>et al.</i> (2010)	<i>S. mansoni</i> (human) x <i>S. haematobium</i> (human)	Pairings morphology	Humans	Mali
Moné <i>et al.</i> (2012)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Egg morphology, partial <i>cox1</i> and <i>ITS</i> sequencing	Humans	Benin

Webster <i>et al.</i> (2013b)	1 - <i>S. haematobium</i> (human) x <i>S. bovis</i> (livestock) 2 - <i>S. haematobium</i> (human) x <i>S. curassoni</i> (livestock) 3 - <i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock)	Partial <i>cox1</i> and <i>ITS1+2</i> sequencing	Humans (1, 2) Cattle (3)	Senegal
Huyse <i>et al.</i> (2013)	<i>S. mansoni</i> (human) x <i>S. haematobium</i> (human)	Partial <i>cox1</i> and <i>ITS</i> sequencing	Humans	Senegal
Gouvras <i>et al.</i> (2013)	<i>S. mansoni</i> (human) x <i>S. haematobium</i> (human)	Morbidity assessment	Humans	Kenya
Boissier <i>et al.</i> (2015)	<i>S. haematobium</i> (human) x <i>S. bovis</i> (livestock)	Egg morphology, partial <i>cox1</i> and <i>ITS</i> sequencing	Humans	Corsica, France
Moné <i>et al.</i> (2015)	1 - <i>S. haematobium</i> (human) x <i>S. bovis</i> (livestock) 2 - <i>S. haematobium</i> (human) x unknown	Partial <i>cox1</i> and <i>ITS</i> sequencing	Humans	Corsica (France) (1) Benin (1, 2)

1118 Table 1b. Reports of experimental hybridisations

References (Date)	Species combination (Original host)	Crossing outcome
Vogel (1941, 1942)	<ul style="list-style-type: none"> • <i>S. mansoni</i> (human) x <i>S. haematobium</i> (human) • <i>S. mansoni</i> (human) x <i>S. japonicum</i> (human) 	Low viable parthenogenetic eggs
Le Roux (1954a)	<i>S. mansoni</i> (human) x <i>S. rodhaini</i> (wildlife)	Viable offspring up to F1
Taylor <i>et al.</i> (1969)	<i>S. mansoni</i> (human) x <i>S. mattheei</i> (livestock)	Few parthenogenetic eggs viable up to F3
Taylor (1970) Taylor and Andrews (1973) Taylor <i>et al.</i> (1973)	1 - <i>S. mattheei</i> (livestock) x <i>S. mansoni</i> (human) 2 - <i>S. bovis</i> (livestock) x <i>S. mansoni</i> (human) 3 - <i>S. mattheei</i> (livestock) x <i>S. bovis</i> (livestock) 4 - <i>S. mattheei</i> (livestock) x <i>S. haematobium</i> (human) 5 - <i>S. bovis</i> (livestock) x <i>S. haematobium</i> (human) 6 - <i>S. mansoni</i> (human) x <i>S. rodhaini</i> (wildlife)	1 - Parthenogenetic offspring, viable up to F3 2 - Non viable offspring 3 - Very low viable offspring up to F3 4 - Fully viable offspring up to F4 5 - Fully viable offspring up to F3 6 - Fully viable offspring up to F4
Wright (1974)	<i>S. guineensis</i> (human) x <i>S. mattheei</i> (livestock)	Viable offspring up to F4
Wright <i>et al.</i> (1974); Wright and Southgate (1976); Southgate <i>et al.</i> (1976, 1982)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Viable offspring
Frandsen (1978); Bjørneboe and Frandsen (1979)	<i>S. guineensis</i> (human) x <i>S. intercalatum</i> (human)	Viable offspring up to F2
Wright and Ross (1980)	<i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock)	Viable offspring up to F1

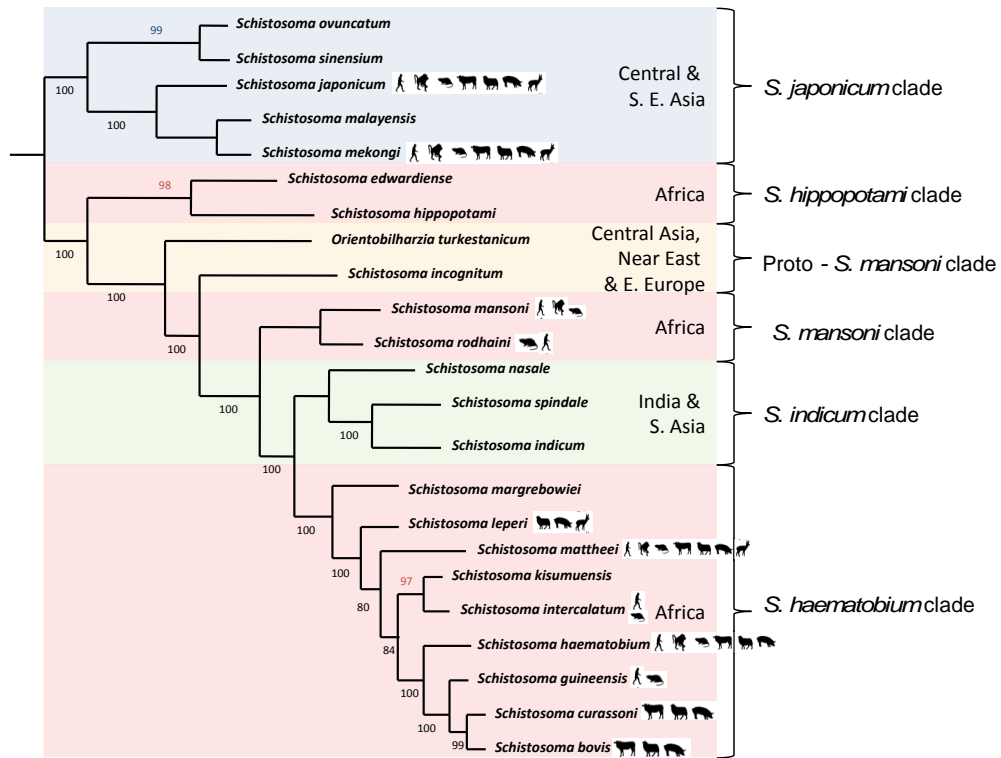
Basch and Basch (1984)	<i>S. haematobium</i> (human) x <i>S. mansoni</i> (human)	Non viable parthenogenetic offspring
Mutani <i>et al.</i> (1985)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Viable offspring up to F7
Rollinson and Southgate (1985)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Viable offspring
Kruatrachue <i>et al.</i> (1987)	<i>S. japonicum</i> (wildlife) x <i>S. mekongi</i> (human)	Viable offspring up to F1
Brémond <i>et al.</i> (1989); Théron (1989)	<i>S. mansoni</i> (human) x <i>S. rodhaini</i> (wildlife)	Viable offspring up to F2
Kruger and Joubert (1990)	<i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock)	Viable offspring up to F1, decreased viability in F2
Pages and Theron (1990)	<ul style="list-style-type: none"> • <i>S. haematobium</i> (human) x <i>S. guineensis</i> (human) • <i>S. guineensis</i> (human) x <i>S. bovis</i> (livestock) • <i>S. haematobium</i> (human) x <i>S. bovis</i> (livestock) 	Viable offspring up to F1
Rollinson <i>et al.</i> (1990b)	<ul style="list-style-type: none"> • <i>S. haematobium</i> (human) x <i>S. mattheei</i> (livestock) • <i>S. mattheei</i> (livestock) x <i>S. bovis</i> (livestock) • <i>S. haematobium</i> (human) x <i>S. guineensis</i> (human) 	Viable offspring up to F1
Rollinson <i>et al.</i> (1990a)	<i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock)	Viable offspring up to F4
Brémond <i>et al.</i> (1993)	<ul style="list-style-type: none"> • <i>S. haematobium</i> (human) x <i>S. bovis</i> (livestock) • <i>S. haematobium</i> (human) x <i>S. curassoni</i> (livestock) • <i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock) 	Viable offspring up to F2

Tchuem Tchuente <i>et al.</i> (1993, 1994, 1995, 1996)	<i>S. guineensis</i> (human) x <i>S. mansoni</i> (human)	Low viable parthenogenetic offspring / Unknown
Imbert-Establet <i>et al.</i> (1994)	<i>S. japonicum</i> (human) x <i>S. mansoni</i> (human)	Viable parthenogenetic offspring
Khalil and Mansour (1995)	<i>S. mansoni</i> (human) x <i>S. haematobium</i> (human)	Low viable parthenogenetic offspring
Southgate <i>et al.</i> (1995)	<i>S. matthei</i> (livestock) x <i>S. haematobium</i> (human)	Viable offspring
Tchuem Tchuente <i>et al.</i> (1997a)	<i>S. haematobium</i> (human) x <i>S. matthei</i> (livestock)	Viable offspring up to F2 in hamsters Viable offspring up to F1 in sheep (carried on up to F2)
Webster <i>et al.</i> (1999)	<i>S. haematobium</i> (human) x <i>S. mansoni</i> (human)	Non viable parthenogenetic offspring
Pages <i>et al.</i> (2001, 2002)	<i>S. intercalatum</i> (human) x <i>S. guineensis</i> (human)	Viable offspring up to F4
Cosgrove and Southgate (2002)	<i>S. mansoni</i> (human) x <i>S. margrebowiei</i> (livestock)	Non viable offspring
Cosgrove and Southgate (2003a)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Unknown
Cosgrove and Southgate (2003b)	<i>S. intercalatum</i> (human) x <i>S. mansoni</i> (human)	Unknown
Webster and Southgate (2003a, 2003b); Webster <i>et al.</i> (2003, 2005, 2007)	<i>S. haematobium</i> (human) x <i>S. guineensis</i> (human)	Viable offspring up to F2
Fan and Lin (2005)	<i>S. japonicum</i> (human) x <i>S. mansoni</i> (human)	Low viable (parthenogenetic?) offspring
Norton <i>et al.</i> (2008b)	<i>S. mansoni</i> (human) x <i>S. rodhaini</i> (wildlife)	Viable offspring

Webster <i>et al.</i> (2013b)	<ul style="list-style-type: none"> • <i>S. haematobium</i> (human) x <i>S. bovis</i> (livestock) • <i>S. haematobium</i> (human) x <i>S. curassoni</i> (livestock) • <i>S. bovis</i> (livestock) x <i>S. curassoni</i> (livestock) 	Viable offspring
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1119 Unless stated, offspring viability has not been determined after the generation indicated.

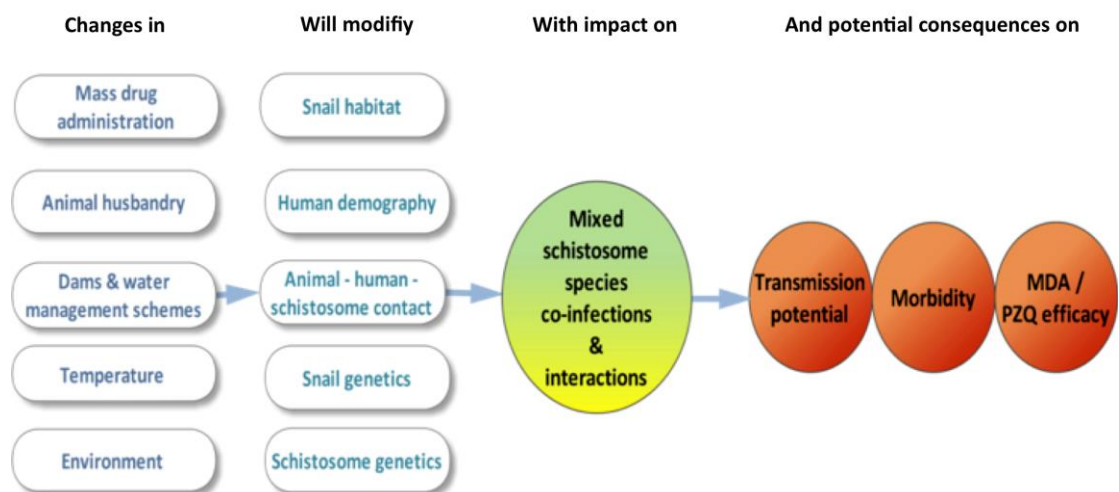
1120 FIGURE LEGENDS



1121

1122 **Figure 1.** Schematic phylogeny of the interrelationships of members of the *Schistosoma*
 1123 genus and their principal vertebrate hosts (only indicated for the main schistosome
 1124 species in term of human and veterinary health) (adapted from Lawton *et al.* (2011) and
 1125 Webster *et al.* (2006)).

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1128 **Figure 2.** Schematic of causes and consequences of schistosome hybridisation. The
 1129 circumstances producing increased opportunity for hybridisation are intensification of
 1130 drug administration, agricultural practices and land use and modifications of
 1131 environment due to human activities. This will then modify the ecology of both
 1132 schistosomes' intermediate and definitive host but also biology of the parasites. We
 1133 outline what we think would be the most important and/or potentially dangerous effects
 1134 of hybridisation: an increase in transmission potential and morbidity and an altered
 1135 response to drug therapy.

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