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

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ABSTRACT

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EFFECT OF HYBRIDISATION ON CERCARIAL EMERGENCE FROM SNAIL INTERMEDIATE HOST

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

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

FACTORS POTENTIALLY FAVOURING HYBRID EVOLUTION AND ESTABLISHMENT

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

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

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

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

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

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

IMPLICATIONS FOR CONTROL

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

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

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

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

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

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

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

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

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

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

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

CONCLUSIONS AND PERSPECTIVES

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

ACKNOWLEDGEMENTS and FINANCIAL SUPPORT

The authors' current research on this topic is funded by a ZELS research grant (combined BBSRC, MRC, ESRC, NERC, DSTL and DFID: BB/L018985/1 - PI: JPW). We are also extremely grateful to our research colleagues for many fruitful discussions on the topic of multi-host parasites in general. EL and JPW are members of the London Centre for Neglected Tropical Disease Research, a collaboration between the London School of Hygiene & Tropical Medicine, the Natural History Museum, the Royal Veterinary College, and Imperial College London.

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1115 TABLES

1116 Table 1a. Reports of potential natural hybridisations.

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

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

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

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

1117

1118 Table 1b. Reports of experimental hybridisations

References (Date)	Species combination (Original host)	Crossing outcome
Vogel (1941, 1942)	• *S. mansoni* (human) x *S. haematobium* (human) • *S. mansoni* (human) x *S. japonicum* (human)	Low viable parthenogenetic eggs
Le Roux (1954a)	*S. mansoni* (human) x *S. rodhaini* (wildlife)	Viable offspring up to F1
Taylor *et al.* (1969)	*S. mansoni* (human) x *S. mattheei* (livestock)	Few parthenogenetic eggs viable up to F3
Taylor (1970) Taylor and Andrews (1973) Taylor *et al.* (1973)	1 - *S. mattheei* (livestock) x *S. mansoni* (human) 2 - *S. bovis* (livestock) x *S. mansoni* (human) 3 - *S. mattheei* (livestock) x *S. bovis* (livestock) 4 - *S. mattheei* (livestock) x *S. haematobium* (human) 5 - *S. bovis* (livestock) x *S. haematobium* (human) 6 - *S. mansoni* (human) x *S. rodhaini* (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)	*S. guineensis* (human) x *S. mattheei* (livestock)	Viable offspring up to F4
Wright *et al.* (1974); Wright and Southgate (1976); Southgate *et al.* (1976, 1982)	*S. haematobium* (human) x *S. guineensis* (human)	Viable offspring
Frandsen (1978); Bjørneboe and Frandsen (1979)	*S. guineensis* (human) x *S. intercalatum* (human)	Viable offspring up to F2
Wright and Ross (1980)	*S. haematobium* (human) x *S. mattheei* (livestock)	Viable offspring up to F1

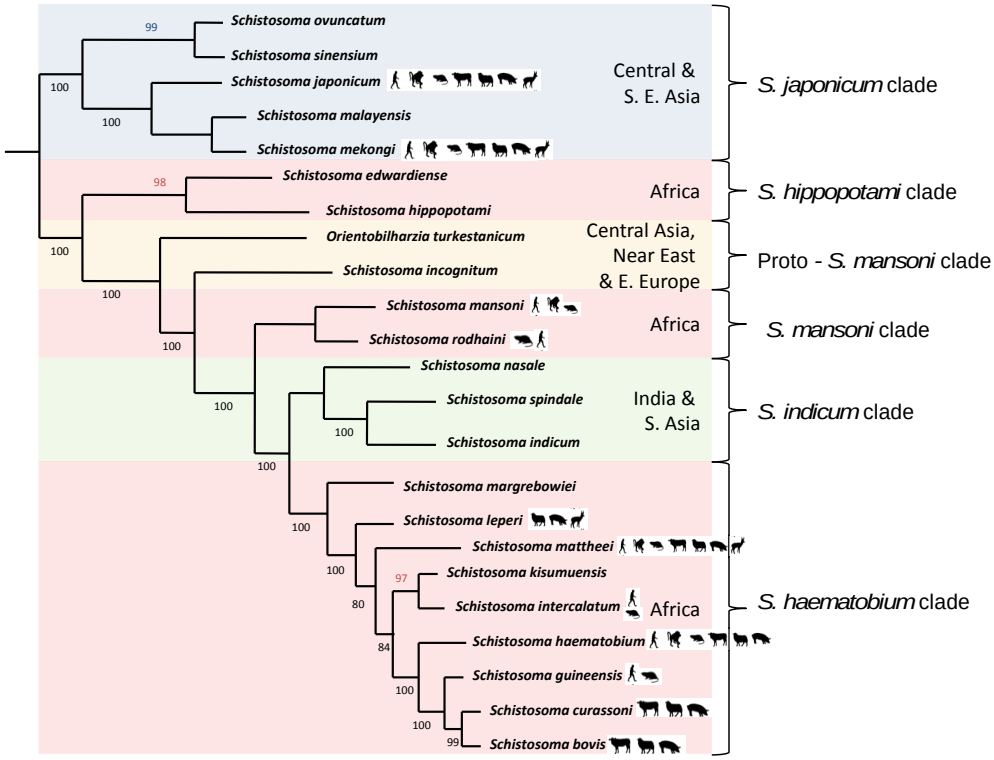
Basch and Basch (1984)	*S. haematobium* (human) x *S. mansoni* (human)	Non viable parthenogenetic offspring
Mutani *et al.* (1985)	*S. haematobium* (human) x *S. guineensis* (human)	Viable offspring up to F7
Rollinson and Southgate (1985)	*S. haematobium* (human) x *S. guineensis* (human)	Viable offspring
Kruatrachue *et al.* (1987)	*S. japonicum* (wildlife) x *S. mekongi* (human)	Viable offspring up to F1
Brémond *et al.* (1989); Théron (1989)	*S. mansoni* (human) x *S. rodhaini* (wildlife)	Viable offspring up to F2
Kruger and Joubert (1990)	*S. haematobium* (human) x *S. mattheei* (livestock)	Viable offspring up to F1, decreased viability in F2
Pages and Theron (1990)	• *S. haematobium* (human) x *S. guineensis* (human) • S. *guineensis* (human) x *S. bovis* (livestock) • *S. haematobium* (human) x S. bovis (livestock)	Viable offspring up to F1
Rollinson *et al.* (1990b)	• *S. haematobium* (human) x *S. mattheei* (livestock) • *S. mattheei* (livestock) x *S. bovis* (livestock) • *S. haematobium* (human) x *S. guineensis* (human)	Viable offspring up to F1
Rollinson *et al.* (1990a)	*S. bovis* (livestock) x *S. curassoni* (livestock)	Viable offspring up to F4
Brémond *et al.* (1993)	• *S. haematobium* (human) x *S. bovis* (livestock) • *S. haematobium* (human) x *S. curassoni* (livestock) • *S. bovis* (livestock) x *S. curassoni* (livestock)	Viable offspring up to F2

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

Webster *et al*. (2013b)	• *S. haematobium* (human) x *S. bovis* (livestock) • *S. haematobium* (human) x *S. curassoni* (livestock) • *S. bovis* (livestock) x *S. curassoni* (livestock)	Viable offspring

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)).

1126

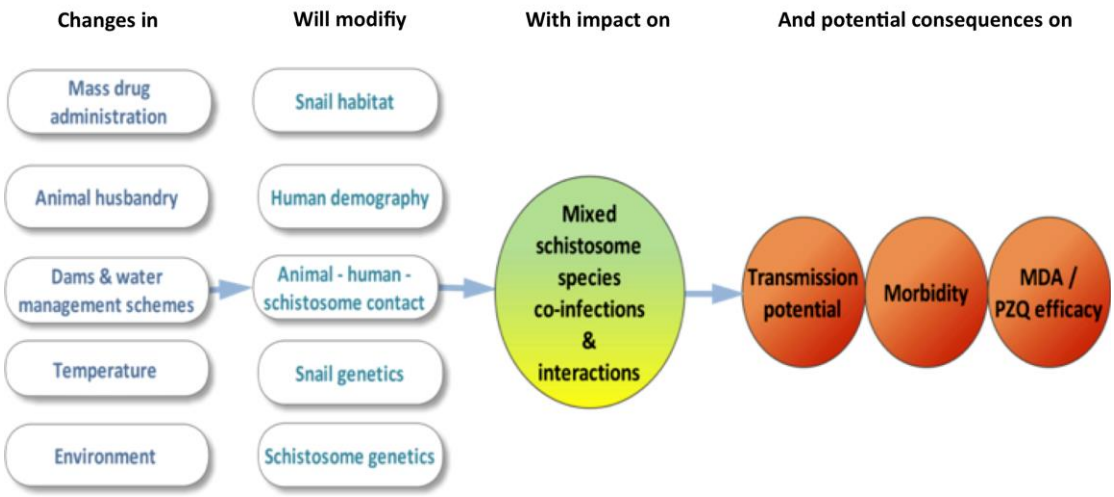


Figure 2. Schematic of causes and consequences of schistosome hybridisation. The circumstances producing increased opportunity for hybridisation are intensification of drug administration, agricultural practices and land use and modifications of environment due to human activities. This will then modify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