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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. guineensis* (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.
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 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 subsequently 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, *Schistosoma* 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 anthelmintics 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;
Gouvas *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

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.
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REFERENCES


hybridization. Transactions of the Royal Society of Tropical Medicine and Hygiene 91, 664-665. doi: 10.1016/s0035-9203(97)90513-7


Webster, B. L. and Southgate, V. R. (2003b). Mating interactions of Schistosoma haematobium and S. intercalatum with their hybrid offspring. Parasitology 126, 327-338. doi: 10.1017/s0031182002002883


Webster, B. L., Rollinson, D., Stothard, J. R. and Huyse, T. (2010). Rapid diagnostic multiplex PCR (RD-PCR) to discriminate *Schistosoma haematobium* and *S. bovis*. *Journal of Helminthology* 84, 107-114. doi: 10.1017/s0022149x09990447


Young, N. D., Jex, A. R., Li, B., Liu, S. P., Yang, L. F., Xiong, Z. J., Li, Y. R.,
Cantacessi, C., Hall, R. S., Xu, X., Chen, F. Y., Wu, X., Zerlotini, A., Oliveira, G.,
Hofmann, A., Zhang, G. J., Fang, X. D., Kang, Y., Campbell, B. E., Loukas, A.,
Ranganathan, S., Rollinson, D., Rinaldi, G., Brindley, P. J., Yang, H. M., Wang,
*haematobium*. *Nature Genetics* **44**, 221-225. doi: 10.1038/ng.1065
*Schistosoma haematobium Schistosoma intercalatum* infection. *Annals of Tropical
### Table 1a. Reports of potential natural hybridisations.

<table>
<thead>
<tr>
<th>References (Date)</th>
<th>Species combination (Original host)</th>
<th>Methodology</th>
<th>Host species detected in</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alves (1948)</td>
<td><em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock)</td>
<td>Egg morphology</td>
<td>Human</td>
<td>Southern Rhodesia, Zimbabwe</td>
</tr>
<tr>
<td>Le Roux (1954b)</td>
<td><em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock)</td>
<td>Egg morphology</td>
<td>Human</td>
<td>Southern Rhodesia, Zimbabwe</td>
</tr>
<tr>
<td>Pitchford (1959, 1961)</td>
<td><em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock)</td>
<td>Egg morphology</td>
<td>Human</td>
<td>Eastern Transvaal, South Africa</td>
</tr>
<tr>
<td>Wright <em>et al.</em> (1974); Southgate <em>et al.</em> (1976)</td>
<td><em>S. haematobium</em> (human) x <em>S. guineensis</em> (human)</td>
<td>Egg morphology,</td>
<td>Human</td>
<td>Loum, Cameroon</td>
</tr>
<tr>
<td>Wright and Ross (1980)</td>
<td><em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock)</td>
<td>Biochemical markers</td>
<td>Human</td>
<td>South Africa</td>
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<tr>
<td>Southgate <em>et al.</em> (1985)</td>
<td><em>S. bovis</em> (livestock) x <em>S. curassoni</em> (livestock)</td>
<td>Worm morphology</td>
<td>Sheep</td>
<td>Senegal</td>
</tr>
<tr>
<td>Rollinson <em>et al.</em> (1987)</td>
<td><em>S. bovis</em> (livestock) x <em>S. curassoni</em> (livestock)</td>
<td>Worms morphology, biochemical markers</td>
<td>Cattle</td>
<td>Senegal</td>
</tr>
<tr>
<td>Authors</td>
<td>Species Combinations</td>
<td>Methods</td>
<td>Locations</td>
<td></td>
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<tr>
<td>Kruger et al. (1986a, 1986b); Kruger (1987, 1988, 1990); Kruger and Hamilton-Attwell (1988); Kruger and Evans (1990)</td>
<td>$S. \text{haematobium}$ (human) x $S. \text{mattheei}$ (livestock)</td>
<td>Egg morphology, biochemical markers</td>
<td>South Africa</td>
<td></td>
</tr>
<tr>
<td>Brémond (1990); Brémond et al. (1990)</td>
<td>$S. \text{bovis}$ (livestock) x $S. \text{curassoni}$ (livestock)</td>
<td>Biochemical markers</td>
<td>Niger</td>
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<tr>
<td>Rollinson et al. (1990a)</td>
<td>$S. \text{bovis}$ (livestock) x $S. \text{curassoni}$ (livestock)</td>
<td>Biochemical markers</td>
<td>Senegal, Mali</td>
<td></td>
</tr>
<tr>
<td>Zwingenberger et al. (1990)</td>
<td>$S. \text{haematobium}$ (human) x $S. \text{guineensis}$ (human)</td>
<td>Egg morphology</td>
<td>Gabon</td>
<td></td>
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<tr>
<td>Ratard et al. (1990); Ratard and Greer (1991)</td>
<td>$S. \text{haematobium}$ (human) x $S. \text{guineensis}$ (human)</td>
<td>Egg morphology</td>
<td>Cameroon</td>
<td></td>
</tr>
<tr>
<td>Brémond et al. (1993)</td>
<td>$S. \text{haematobium}$ (human) x $S. \text{bovis}$ (or $S. \text{curassoni}$) (livestock)</td>
<td>Egg morphology, biochemical markers</td>
<td>Niger</td>
<td></td>
</tr>
</tbody>
</table>
| De Bont et al. (1994)           | • $S. \text{haematobium}$ (human) x $S. \text{mattheei}$ (livestock)  
• $S. \text{mattheei}$ (livestock) x $S. \text{leiperi}$ (livestock) | Biochemical markers | Cattle Zambia |
<p>| Vercruysse et al. (1994)        | 1 - $S. \text{haematobium}$ (human) x $S. \text{guineensis}$ (human) | Egg morphology, biochemical markers | Human (1, 2) Mali Zambia |
|                                 | 2 - $S. \text{haematobium}$ (human) x $S. \text{mattheei}$ (livestock) |                             | Cattle (2, 3) |
|                                 | 3 - $S. \text{mattheei}$ (livestock) x $S. \text{leiperi}$ (livestock) |                             |             |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Species</th>
<th>Method</th>
<th>Species</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Añé et al. (1997)</td>
<td>(S. \text{haematobium}) (human) x (S. \text{intercalatum}) (human)</td>
<td>Egg morphology</td>
<td>Human</td>
<td>East Africa</td>
</tr>
<tr>
<td>Tchuem Tchuenté et al. (1997b)</td>
<td>(S. \text{haematobium}) (human) x (S. \text{guineensis}) (human)</td>
<td>Egg morphology</td>
<td>Human</td>
<td>Loum, Cameroon</td>
</tr>
<tr>
<td>Cunin et al. (2003)</td>
<td>(S. \text{haematobium}) (human) x (S. \text{mansoni}) (human)</td>
<td>Ectopic eggs elimination</td>
<td>Human</td>
<td>North Cameroon</td>
</tr>
<tr>
<td>Morgan et al. (2003)</td>
<td>(S. \text{mansoni}) (human) x (S. \text{rodhaini}) (wildlife)</td>
<td>Partial 16S, 12S and ITS sequencing</td>
<td>Biomphalaria sudanica</td>
<td>Tanzania</td>
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<td>Webster et al. (2003, 2005)</td>
<td>(S. \text{haematobium}) (human) x (S. \text{guineensis}) (human)</td>
<td>Biochemical markers and partial ITS2 amplification</td>
<td>Human B. truncatus, B. camerunensis</td>
<td>Loum, Cameroon</td>
</tr>
<tr>
<td>Steinauer et al. (2008)</td>
<td>(S. \text{mansoni}) (human) x (S. \text{rodhaini}) (wildlife)</td>
<td>Partial 16S, 12S and ITS sequencing</td>
<td>B. sudanica and B. pfeifferi</td>
<td>Kenya</td>
</tr>
<tr>
<td>Huyse et al. (2009)</td>
<td>(S. \text{haematobium}) (human) x (S. \text{bovis}) (livestock)</td>
<td>Partial \text{cox}1 and ITS sequencing</td>
<td>Humans B. truncatus, B. globosus</td>
<td>Senegal</td>
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<tr>
<td>Koukounari et al. (2010)</td>
<td>(S. \text{mansoni}) (human) x (S. \text{haematobium}) (human)</td>
<td>Pairings morphology</td>
<td>Humans</td>
<td>Mali</td>
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<tr>
<td>Moné et al. (2012)</td>
<td>(S. \text{haematobium}) (human) x (S. \text{guineensis}) (human)</td>
<td>Egg morphology, partial \text{cox}1 and ITS sequencing</td>
<td>Humans</td>
<td>Benin</td>
</tr>
<tr>
<td>Reference</td>
<td>Crosses</td>
<td>Methods</td>
<td>Hosts</td>
<td>Location</td>
</tr>
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</table>
| Webster et al. (2013b) | 1 - *S. haematobium* (human) x *S. bovis* (livestock)  
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
Table 1b. Reports of experimental hybridisations

<table>
<thead>
<tr>
<th>References (Date)</th>
<th>Species combination (Original host)</th>
<th>Crossing outcome</th>
</tr>
</thead>
</table>
| 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)     | 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 |
<p>| Wright and Ross (1980) | <em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock) | Viable offspring up to F1 |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Cross-Species</th>
<th>Offspring Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basch and Basch (1984)</td>
<td><em>S. haematobium</em> (human) x <em>S. mansoni</em> (human)</td>
<td>Non viable parthenogenetic offspring</td>
</tr>
<tr>
<td>Mutani et al. (1985)</td>
<td><em>S. haematobium</em> (human) x <em>S. guineensis</em> (human)</td>
<td>Viable offspring up to F7</td>
</tr>
<tr>
<td>Rollinson and Southgate (1985)</td>
<td><em>S. haematobium</em> (human) x <em>S. guineensis</em> (human)</td>
<td>Viable offspring</td>
</tr>
<tr>
<td>Kruatrachue et al. (1987)</td>
<td><em>S. japonicum</em> (wildlife) x <em>S. mekongi</em> (human)</td>
<td>Viable offspring up to F1</td>
</tr>
<tr>
<td>Brémon et al. (1989); Théron (1989)</td>
<td><em>S. mansoni</em> (human) x <em>S. rodhaini</em> (wildlife)</td>
<td>Viable offspring up to F2</td>
</tr>
<tr>
<td>Kruger and Joubert (1990)</td>
<td><em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock)</td>
<td>Viable offspring up to F1, decreased viability in F2</td>
</tr>
<tr>
<td>Pages and Theron (1990)</td>
<td><em>S. haematobium</em> (human) x <em>S. guineensis</em> (human)</td>
<td>Viable offspring up to F1</td>
</tr>
<tr>
<td>Rollinson et al. (1990b)</td>
<td><em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock)</td>
<td>Viable offspring up to F1</td>
</tr>
<tr>
<td>Rollinson et al. (1990a)</td>
<td><em>S. bovis</em> (livestock) x <em>S. curassoni</em> (livestock)</td>
<td>Viable offspring up to F4</td>
</tr>
<tr>
<td>Brémon et al. (1993)</td>
<td><em>S. haematobium</em> (human) x <em>S. bovis</em> (livestock)</td>
<td>Viable offspring up to F2</td>
</tr>
<tr>
<td></td>
<td><em>S. haematobium</em> (human) x <em>S. curassoni</em> (livestock)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. bovis</em> (livestock) x <em>S. curassoni</em> (livestock)</td>
<td></td>
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<tr>
<td>Authors</td>
<td>Crosses</td>
<td>Offspring</td>
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<td>--------------------------------</td>
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<tr>
<td>Tchuem Tchuenté et al.</td>
<td><em>S. guineensis</em> (human) x <em>S. mansoni</em> (human)</td>
<td>Low viable parthenogenetic offspring / Unknown</td>
</tr>
<tr>
<td>Imbert-Establet et al.</td>
<td><em>S. japonicum</em> (human) x <em>S. mansoni</em> (human)</td>
<td>Viable parthenogenetic offspring</td>
</tr>
<tr>
<td>Khalil and Mansour</td>
<td><em>S. mansoni</em> (human) x <em>S. haematobium</em> (human)</td>
<td>Low viable parthenogenetic offspring</td>
</tr>
<tr>
<td>Southgate et al. (1995)</td>
<td><em>S. mattheei</em> (livestock) x <em>S. haematobium</em> (human)</td>
<td>Viable offspring</td>
</tr>
<tr>
<td>Tchuem Tchuenté et al.</td>
<td><em>S. haematobium</em> (human) x <em>S. mattheei</em> (livestock)</td>
<td>Viable offspring up to F2 in hamsters Viable offspring up to F1 in sheep (carried on up to F2)</td>
</tr>
<tr>
<td>Webster et al. (1999)</td>
<td><em>S. haematobium</em> (human) x <em>S. mansoni</em> (human)</td>
<td>Non viable parthenogenetic offspring</td>
</tr>
<tr>
<td>Pages et al. (2001, 2002)</td>
<td><em>S. intercalatum</em> (human) x <em>S. guineensis</em> (human)</td>
<td>Viable offspring up to F4</td>
</tr>
<tr>
<td>Cosgrove and Southgate</td>
<td><em>S. mansoni</em> (human) x <em>S. margrebowiei</em> (livestock)</td>
<td>Non viable offspring</td>
</tr>
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<td>Cosgrove and Southgate</td>
<td><em>S. haematobium</em> (human) x <em>S. guineensis</em> (human)</td>
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<tr>
<td>Cosgrove and Southgate</td>
<td><em>S. intercalatum</em> (human) x <em>S. mansoni</em> (human)</td>
<td>Unknown</td>
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<tr>
<td>Webster and Southgate</td>
<td><em>S. haematobium</em> (human) x <em>S. guineensis</em> (human)</td>
<td>Viable offspring up to F2</td>
</tr>
<tr>
<td>(2003a, 2003b); Webster et al. (2003, 2005, 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fan and Lin (2005)</td>
<td><em>S. japonicum</em> (human) x <em>S. mansoni</em> (human)</td>
<td>Low viable (parthenogenetic?) offspring</td>
</tr>
<tr>
<td>Norton et al. (2008b)</td>
<td><em>S. mansoni</em> (human) x <em>S. rodhaini</em> (wildlife)</td>
<td>Viable offspring</td>
</tr>
</tbody>
</table>
Table:

<table>
<thead>
<tr>
<th>Webster et al. (2013b)</th>
<th>Viable offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <em>S. haematobium</em> (human) x <em>S. bovis</em> (livestock)</td>
<td></td>
</tr>
<tr>
<td>• <em>S. haematobium</em> (human) x <em>S. curassoni</em> (livestock)</td>
<td></td>
</tr>
<tr>
<td>• <em>S. bovis</em> (livestock) x <em>S. curassoni</em> (livestock)</td>
<td></td>
</tr>
</tbody>
</table>

1119 Unless stated, offspring viability has not been determined after the generation indicated.
**Figure 1.** Schematic phylogeny of the interrelationships of members of the *Schistosoma* genus and their principal vertebrate hosts (only indicated for the main schistosome species in term of human and veterinary health) (adapted from Lawton *et al.* (2011) and Webster *et al.* (2006)).
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.