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Mapping of schistosome hybrids of the *haematobium* group in West and Central Africa

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Review Article

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Abstract

Hybridization of parasitic species is an emerging health problem in the evolutionary profile of infectious disease, particularly within trematodes of the genus *Schistosoma.* Because the consequences of this hybridization are still relatively unknown, further studies are needed to clarify the epidemiology of the disease and the biology of hybrid schistosomes. In this article, we provide a detailed review of published results on schistosome hybrids of the *haematobium* group. Using a mapping approach, this review describes studies that have investigated hybridization in human (*S. haematobium, S. guineensis*, and *S. intercalatum*) and animal (*S. bovis* and *S. curassoni*) schistosome species in West Africa (Niger, Mali, Senegal, Côte d'Ivoire, Benin, Nigeria) and in Central Africa (Cameroon, Gabon, Democratic Republic of Congo), as well as their limitations linked to the underestimation of their distribution in Africa. This review provides information on studies that have highlighted hybrid species of the *haematobium* group and the regions where they have been found, notably in West and Central Africa.

Introduction

Schistosomiasis is a parasitic disease caused by digenean trematodes of the genus *Schistosoma.* Schistosomiasis is of considerable medical and veterinary importance in tropical and subtropical regions. It is estimated that nearly 779 million people live in endemic areas (Panzner & Boissier, 2021) and, as of 2019, approximately 236.6 million people were in need of preventive chemotherapy in 78 countries (Ossai *et al.*, 2014; WHO 2022). Sub-Saharan Africa alone accounts for 90% of infected cases (Dawet *et al.*, 2012). *Schistosoma* infections in domestic livestock, such as cattle, sheep, and goats, are also widespread and commonly occur in Africa, the Middle East, Asia, and in several countries bordering the Mediterranean (Boissier *et al.*, 2016; De Bont & Vercruysse, 1998). Epidemiological statistics for livestock schistosomiasis are certainly underestimated, but the number of infected animals worldwide has been estimated at 165 million (De Bont & Vercruysse, 1998). Among the 23 known species of *Schistosoma*, there are currently six major species of *Schistosoma* that infect humans: *Schistosoma mansoni (S.m), S. haematobium (S.h), S. intercalatum (S.i), S. guineensis (S.g), S. mekongi (S.me)*, and *S. japonicum (S.j).* The two latter species are recognized as zoonoses, capable of infecting a wide range of livestock and wildlife but are not currently present in Africa. Concerning animal infecting parasites, 19 species are reported to naturally infect animals (Rey *et al.*, 2021; Webster & Littlewood, 2012), for which nine of these species (*Schistosoma mattheei [S.ma], S.b, S.c, S. spindale* [*S.sp*], *S. indicum [S.ind], S. nasale [S.n], S. incognitum [S.inc], S. margrebowiei [S.mar]*, and *S.j*) have received special attention (Léger & Webster, 2017), mainly because of their veterinary importance concerning ruminants in Asian and African countries. Of these, two species (*S.b* and *S.c)* are found in West Africa, and the other seven are narrowly distributed in central and eastern Africa (Mouchet & Bremond 1989; Ndifon, Betterton & Rollinson, 1988; Rollinson *et al.*, 1990; Vera *et al.*, 1992; Vercruysse, Southgate & Rollinson, 1984). The *S.h* species group consists of nine sister species subdivided into two: *S.i* and *S.g*, which cause human schistosomiasis, and *S.b*, *S.ma*, *S.mar*, *S.leiperi (S.l)*, *S.c*, and *S. kisumuensis (S.k)*, which infect a variety of wild, ruminant, and livestock.

All species of the *haematobium* group are transmitted by snails of the family of Planorbidae and the subfamily of Bulininae. Because of the host/parasite specificity, the distribution of the disease is determined by that of the specific snail host in response to its ability to adapt to environmental conditions (pollution, drought, rainfall, etc.). Overall, the species involved in schistosomiasis transmission varies from one geographic area to another and even within the same micro-geographical area.

The schistosome transmission cycle involves two hosts, a vertebrate host where sexual reproduction occurs, and a freshwater snail host where asexual reproduction occurs. The sexual stage of these parasites promotes interactions between male and female worms inside the definitive host, whereas the asexual stage gives rise to clonal larvae that facilitates exposure

and potential infection of mammals in contact with cercarial-infested water. In the field, the sharing of the same water bodies by animals and humans promotes interspecies *Schistosoma* spp interaction within the same definitive vertebrate hosts. Consequently, coinfections can allow for heterospecific mate pairings, resulting in parthenogenesis, introgression, or whole-genome admixture through hybridization (Detwiler & Criscione, 2010; King *et al.*, 2015). In endemic areas, it is assumed that the limited distribution of schistosome species and their hosts (intermediate and/or definitive) limits the hybridization phenomenon. However, according to Platt *et al.* (2019), barriers that prevent the unspecific host/parasite couple from forming are now breaking down because of increasing economic development, human migration, global trade, and climate change. Several crosses between schistosome species have been demonstrated in the laboratory and in the field (Webster *et al.*, 2013, Léger *et al.*, 2016; Wright *et al.*, 1974). The most frequent hybrids are found within the haematobium group, most notably between *S.h* and both (*S.b* or *S.c)* livestock parasites.

The purpose of this review was to describe the presence of schistosome hybrids of the *haematobium* group in West and Central Africa from a cartographic perspective. We analyzed the presence of these hybrids with respect to the general distribution of *S.h* in the different countries of sub-Saharan Africa, with a brief description of the situation in the other regions of Africa. Using a cartographic approach to represent the well-known distribution of *S.h.* will enable information gaps in the distribution *Schistosoma* hybrids to be identified at multiple scales, whether at the regional scale, country scale, or at the scale of the African continent.

Method

Search strategy and article selection

We searched the PubMed and Google Scholar public online databases for relevant publications on human or animal schistosome hybrids by applying the following keywords: 'schistosomiasis and hybrids', '*Schistosoma*', '*haematobium*' 'bilharzia', 'Hybridization', 'introgression', 'schistosome', and 'Africa'. To limit the scope of the search, we included these search terms related to Africa or to specific regions where hybrids have been reported. Publications that identified hybrids with molecular methods (e.g., using a gene of mitochondrial cytochrome oxidase and/or nuclear ribosomal internal transcribed spacer) were the most focused, followed by other methods (e.g. enzymatic, morphological). The species *S.i*, as reported in West African countries, will be considered as *S.g*, because *S.i* is only present in the Democratic Republic of Congo (Pagès *et al.*, 2003).

Among the 216 articles selected and imported into Mendeley software, duplicates and publications for which full texts were not available were eliminated. Subsequently, 113 articles were retained for this manuscript. The final searches were performed on 15 April 2023. For each country, the review is presented in chronological order of recorded reports. All maps produced in this review are based on bibliographical reports.

Mapping

Geographical coordinates of survey locations, as reported in publications or reports from the Ministry of Health in each country, were extracted. Distribution maps of urogenital schistosomiasis and hybrids were then produced using QGIS Remote Sensing mapping software version 2.18.4 (Figs. 1–10).

Results

In Niger

The presence of eggs of typical *S.b* in the stool of 17 individuals in Niakoye in the Gaya region in the southern part of Nigeria (Fig. 1) strongly indicates that this region is a strong candidate for a possible hybridization between *S.b* species and *S.h.* (Mouchet *et al.*,1988). In 1990, Bremond *et al.*, demonstrated (using isoelectofocusing in gel) the existence of gene flow between *S.b* and *S.c* in Zinder (Niger) (Brémond *et al.*, 1990), and in 1993 the intermediate egg forms and allozyme phenotypes were observed between *S.b* and *S.h* or *S.c* in children from eastern Niger. These findings suggested a natural interaction between *S.h* and *S.b* (Bremond *et al.*, 1993). Although allozyme profiles strongly indicated a hybrid origin, the exact role of *S.c* could not be established because the allozyme markers did not distinguish between *S.h* and *S.c.* The authors proposed that *S.c* might also be involved through hybridization with *S.b* (Bremond *et al.*, 1993). Beyond the possibility of a two-species hybridization, a study by Léger *et al.*, demonstrated (using cox1 and ITS1 +2 DNA region) an interaction between three species (*S.b* × *S.h* × *S.c*) in the Tillabéri region (Léger *et al.*, 2016) (Fig 1).

An interesting genome-wide study of *S.h* miracidia exomes collected along the Niger River in northeastern Niger (Niamey) showed (through sequencing) that 3.3% to 8.2% of the nuclear genomes were derived from *S.b* (Platt *et al.*, 2019). The authors concluded that hybridization between *S.h* and *S.b* species is an ancient phenomenon and dates back from 108 to 613 generations.

The more recent molecular study (Cox1, 18S, and ITS1 + 2 DNA regions) of cercariae excreted by naturally infected *Bulinus* spp. in the Niamey district showed that of *S.b* × *S.h* and *S.b* × *S.h* × *S.c* hybrids are transmitted to humans through? *Bulinus truncatus* (Pennance *et al.*, 2020).

In Mali

Only the southern region in Mali is affected by schistosomiasis because the north is predominantly characterized by desert conditions. With the exception of reports of interactions between *S.c* and *S.b* in livestock (using isoelectofocusing in gel) in the Bamako and Mopti regions (Rollinson *et al.*, 1990), there are limited data on schistosome hybridization, despite the utilization of all existing water points by people and animals in these Sahelian regions. The study of Rollinson *et al.* (1990) was the first to focus on hybridization in Mali, revealing evidence of interactions between *S.b* and *S.c* as observed in cattle from Bamako (prevalence = 28.6%) and Mopti (prevalence = 12.5%). Observations were made on egg morphology, surface structure and enzyme profiles of *S.c* and *S.b* from Mopti and monospecific infection with *S.b* was found in 10 animals, whereas 24 animals were found to harbor only *S.c* (Rollinson *et al.*, 1990). In 2016, 10 Belgian travelers returned from Mali with an *S.h-S.b* hybrid infection, confirmed by DNA sequencing from eggs. Even if clinical symptoms and laboratory findings resembled those of classic acute schistosomiasis, the detected eggs were morphologically unusual (Soentjens *et al.*, 2016). However, to date, no reports of infection in local people from hybrids of the *haematobium* group, have yet been reported. Results of a genomic

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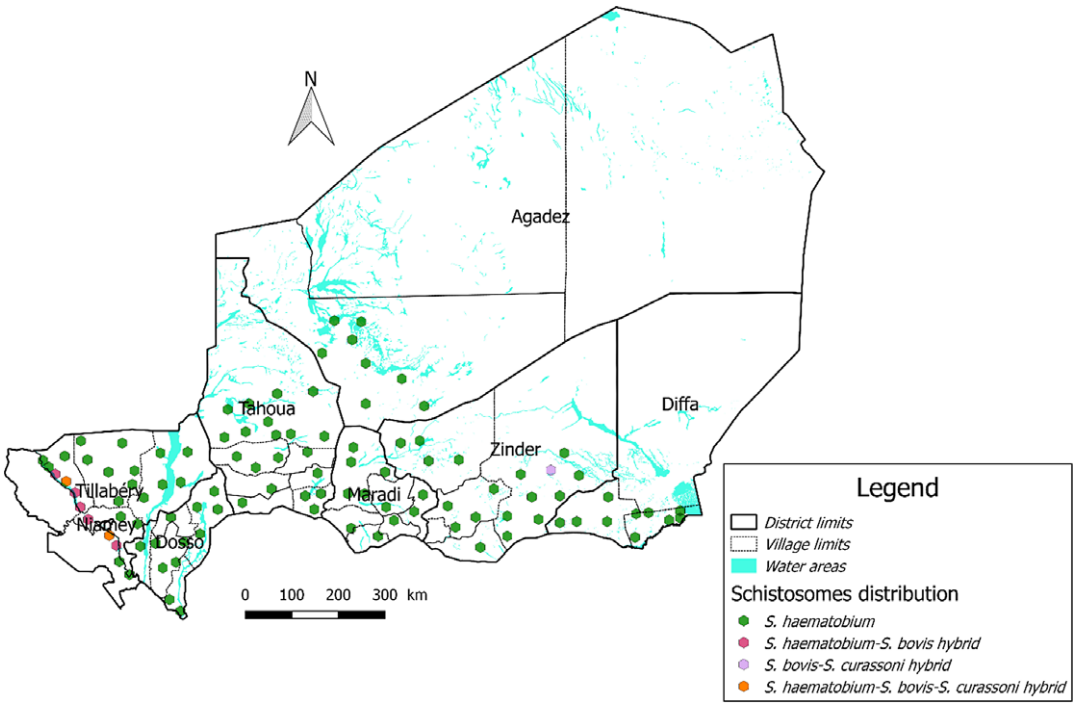

Figure 1. Distribution of *S.h* and hybrids in Niger.
S.c-S.b hybrid found in Niamey
Distribution of *S.h* (Mouchet *et al.*, 1988; Mouchet *et al.*, 1987; Vera *et al.*, 1992, Ministère de la Santé, 2017*)*
Distribution of *Schistosoma hybrids* (Brémond *et al.*, 1990; Mouchet *et al.*, 1992; Pennance *et al.*, 2020; Platt *et al.*, 2019)

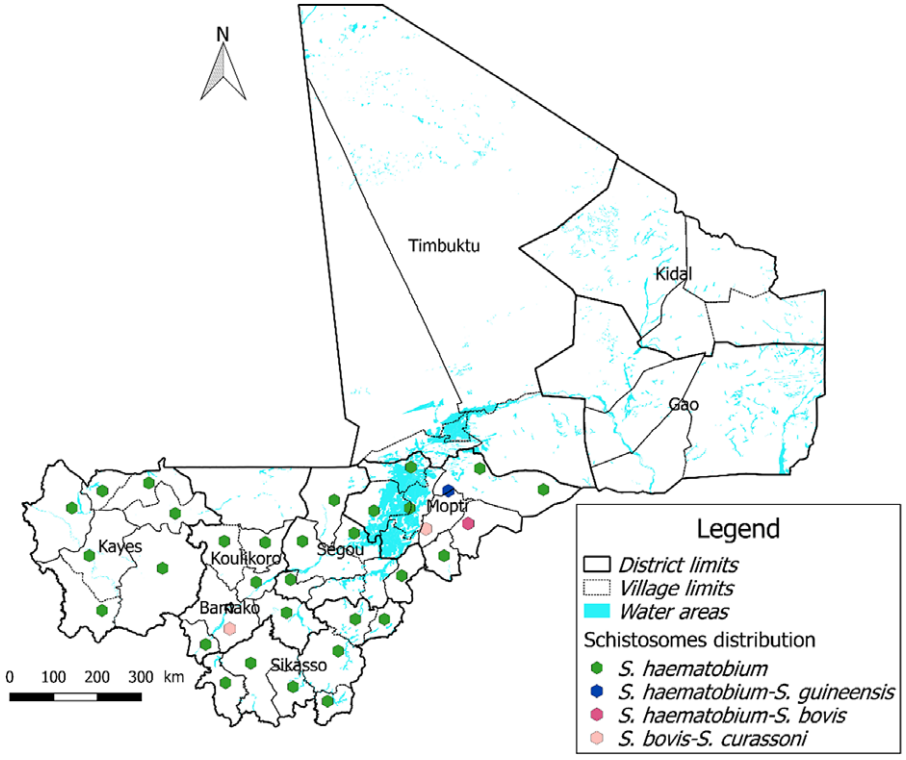

Figure 2. Distribution of *Schistosoma* hybrids in Mali.
S.c-S.b hybrid found in Bamako and Mopti. *S.h-S.b* hybrid found only in Bandiagara.
Distribution of *S.h* (Dabo *et al.*, 1997, 2011, 2013, 2015; Kouriba *et al.*, 2005; Lyke *et al.*, 2006; Clements *et al.*, 2009; Sangho *et al.*, 2009; Sissoko *et al.*, 2009; Lyke *et al.*, 2012a;Niangaly *et al.*, 2012).
Distribution of *Schistosoma* hybrids (Rollinson *et al.*, 1990; Soentjens *et al.*, 2016).

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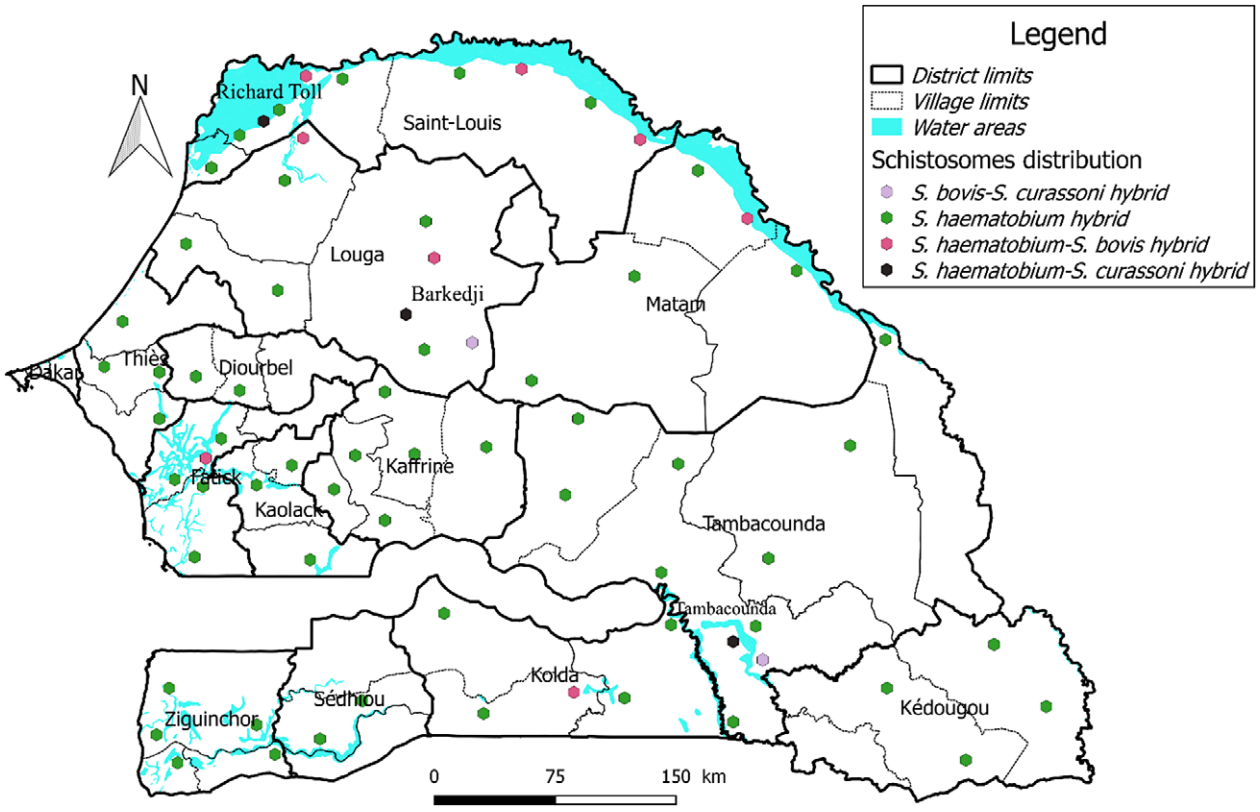

Figure 3. Distribution of S*chistosoma* hybrids in Senegal.
Distribution of *S.h* (Boon *et al.*, 2018; Briand *et al.*, 2005; De Clercq et *al.*, 1999; Ten Hove *et al.*, 2008; Meurs *et al.*, 2013; Sene-wade *et al.*, 2018; Senghor *et al.*, 2014; Webster *et al.*, 2013; Ministère de la santé, 2021)
Distribution of *Schistosoma hybrids* (Boon *et al.*, 2019; Boon *et al.*, 2018; Rollinson *et al.*, 1990; Webster *et al.*, 2013; Senghor *et al.*, 2023)

analysis (presence of invadolysin gene) of cercariae released from infected snails that were collected in 1994 led to the hypothesis that an ancient hybridization between *S.h* and *S.b* existed in Mali (Rey *et al.*, 2021). Following surveys carried out on Dogon Country (Mopti district) data based on egg morphology and Ziehl Neelsen staining of egg shells, a possible occurrence of *S.h-S.g* hybrids was detected (De Clercq *et al.*, 1994) (Fig 2).

In Senegal

In Senegal, in addition to the studies conducted by Rollinson *et al.* (1990) on *S.b* and *S.c* in West Africa, many other studies have been conducted, particularly since the construction of the Diama Dam in 1985. The habitats found in the Senegal River Basin (SRB) changed dramatically with the construction of this dam, which was intended to prevent saltwater intrusion from the sea, and thus facilitated rice and sugarcane agriculture. These new aquatic habitats allowed for the spread of *Biomphalaria pfeifferi*, the intermediate host of *S.m*, and various *Bulinus* species responsible for the transmission of *S.h* and *S.b* and *S.c.* There are now several sympatric zones between these schistosomes, and many children are found co-infected with human (urogenital and intestinal) and animal schistosomiasis. This means that with the construction of the Diama Dam, the SRB represents a hot spot of human and animal schistosomiasis transmission dynamics with the proliferation of hybridization zones (Léger *et al.*, 2020; Webster *et al.*, 2013; Boon *et al.*, 2018).

The first cases of hybridization between schistosome species under natural conditions in humans were identified in Senegal (SRB) through the work of Huyse *et al.* (2009). Hybrid schistosomes recovered from the urine and feces of children and intermediate snail hosts (*B. truncatus and B. globosus*), had a nuclear ITS rRNA sequence identical to *S.h*, whereas the partial mitochondrial sequence cox1 was identified as *S.b* (Huyse *et al.*, 2009). This study provided the first insights into the subtleties between a human and a bovine schistosome species.

In 2013, authors observed (Cox1 and ITS 1 +2 DNA region) hybrid crosses between *S.h* and *S.c* in children residing in Tambacounda and the Ferlo Valley but not in the SRB (Webster *et al.*, 2013). These findings lend support to the hypothesis that the emergence of schistosome hybrids in humans may be linked to the presence of bovine species in cattle within the same region.

Boon *et al.* (2018) conducted a study to determine and understand the spatiotemporal distribution of *S.h-S.b* hybrids in the SRB. Using 10 villages, distributed over the four main watersheds, the author genotyped miracidia and/or schistosome eggs collected from human urine samples using a partial mitochondrial Cox1 and nuclear ITS1 + 2 DNA region. Results showed that hybrid schistosomes were unevenly distributed, with significantly higher numbers in villages bordering Lake Guiers than in villages located at the Lampsar River and Senegal River valley (Boon *et al.*, 2018). Surprisingly, the frequency of hybrids per village was not related to the prevalence of urinary schistosomiasis in that village, which is one of the most common schistosome species (*S.h*) in this region

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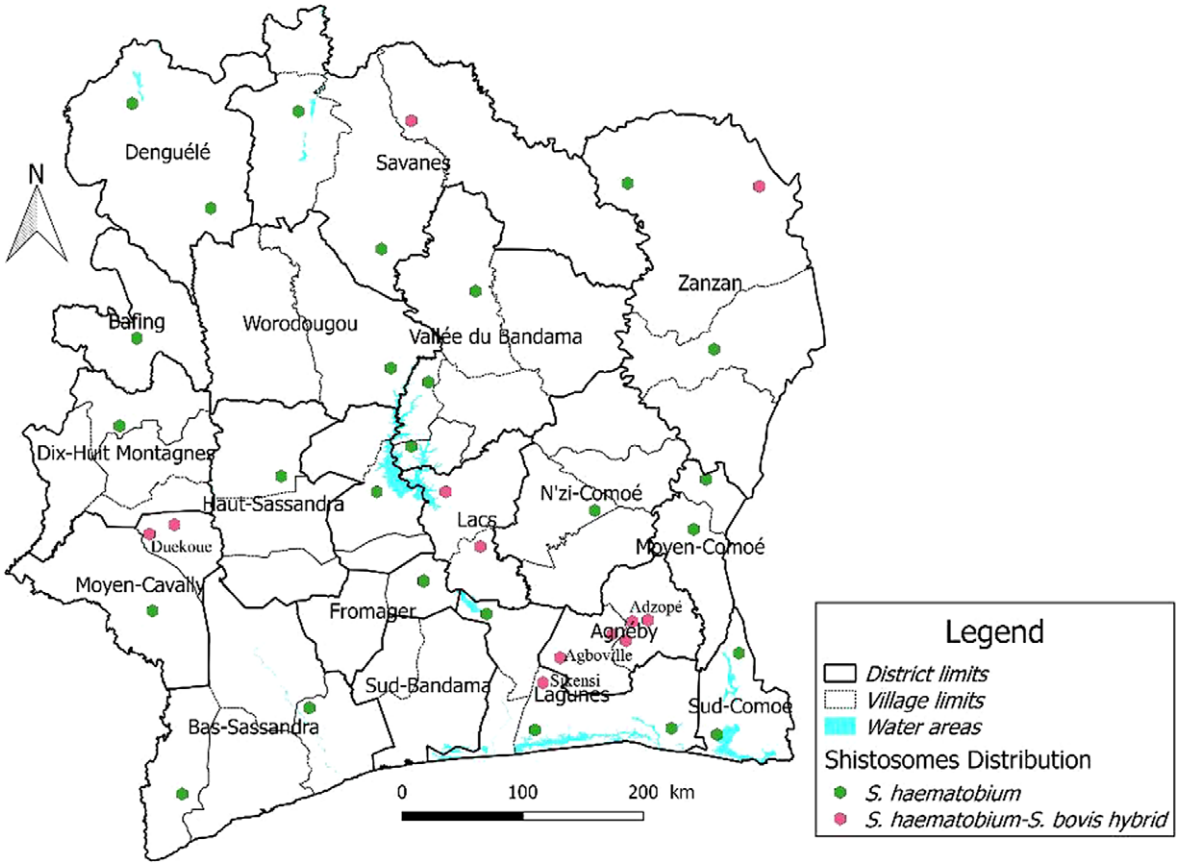

Figure 4. Distribution of *Schistosoma* hybrids in Côte d'Ivoire.
S.h-S.b hybrid found in Dekoué, Adzopé, Agboville.
Distribution of *S.h* (Coulibaly *et al., 2012;* Chammartin *et al.*, 2014; Angora *et al.*, 2019a, Ministère de la Santé, 2016)
Distribution of *Schistosoma hybrids* (Angora *et al.*, 2019b, 2022; Tian-Bi *et al.*, 2019b).

(Boon *et al.*, 2018). To explain the geographic heterogeneity of hybrids in the SRB, the authors first supported the hypothesis that in regions with high hybrid frequency, local conditions may facilitate hybridization between *S.h* and *S.b* (currently or in the past) more than in other regions. As shown in studies on other organisms, in regions with higher hybrid frequency, introgression of *S.b* mtDNA (or nuclear DNA) may be more adaptive and under positive selection (Irwin, 2002; Toews and Brelsford, 2012). The link between hybrid distribution and schistosomiasis prevalence has raised more questions than expected. One possible explanation for this link was that active immune suppression by another species (*S.m*) could make a person more susceptible to infection by schistosome species that typically are unable to infect humans (e.g., *S.b*, hybrid species), though this did not explain why *S.h* and *S.b* hybrids were not positively associated with *S.h* endemic areas (McSorley and Maizels, 2012). We agree with Boon *et al.* (2018), who suggested that individual-level studies linking within-host hybrids to intensity of single *Schistosoma* infection and co-infection with *S.m*, coupled with host-related factors (e.g., host immunology, ethnicity, water contact behavior) could improve our understanding of this hybrid heterogeneity.

Several studies (Léger *et al.*, 2020; Webster *et al.*, 2013) have shown that large-scale multiloci molecular analyses of parasite samples collected from children and domestic livestock across Senegal revealed introgressive interactions between the three closely related species of the *S.h* group ([i] *S.h*, which causes urogenital schistosomiasis in humans, and [ii] *S.b* and *S.c*, agents responsible for intestinal schistosomiasis in cows, sheep, and goats). Evidence of hybridization between *S.h-S.c* and *S.h-S.b* was commonly found throughout Senegal with an estimated 88% of children suspected of excreting hybrid schistosome eggs. These results would be the first conclusive evidence of natural hybridization between *S.h* and *S.c.* According to Boon *et al.* (2019), 25.6% of the parasites had a *S.b* cox 1 profile, whereas 74.4% had a *S.h* cox 1 profile in the same area. In the most recent study, approximately 63% to 72% of infected children carried *S.h-S.b* hybrids. In Richard Toll and Guiers Lake, 18.88% of infected urine samples contained *S.h-S.b* hybrids. In Barkedji and Linguère (Louga district), 9% to 11% of miracidia from samples tested in children were *S.h-S.b* hybrids compared to 10% in adults (Léger *et al.*, 2020). No hybrids formed with human schistosome species (i.e., *S.h-S.b*) were found in cattle. According to data recorded in Richard Toll and Guiers Lake, 35% of infected intermediate hosts of the genus *Bulinus* spp. were found to excrete cercariae of *S.h-S.b* hybrid profiles, compared to excretion rates of 68% and 17% for *S.h* and *S.b* profiles, respectively (Léger *et al.*, 2020).

Numerous studies suggest that hybridization can result in phenotypic changes that can significantly influence disease dynamics and parasite evolution (Boon *et al.*, 2018; Irwin, 2002; Webster *et al.*, 2013). Increasing the host range of hybrid

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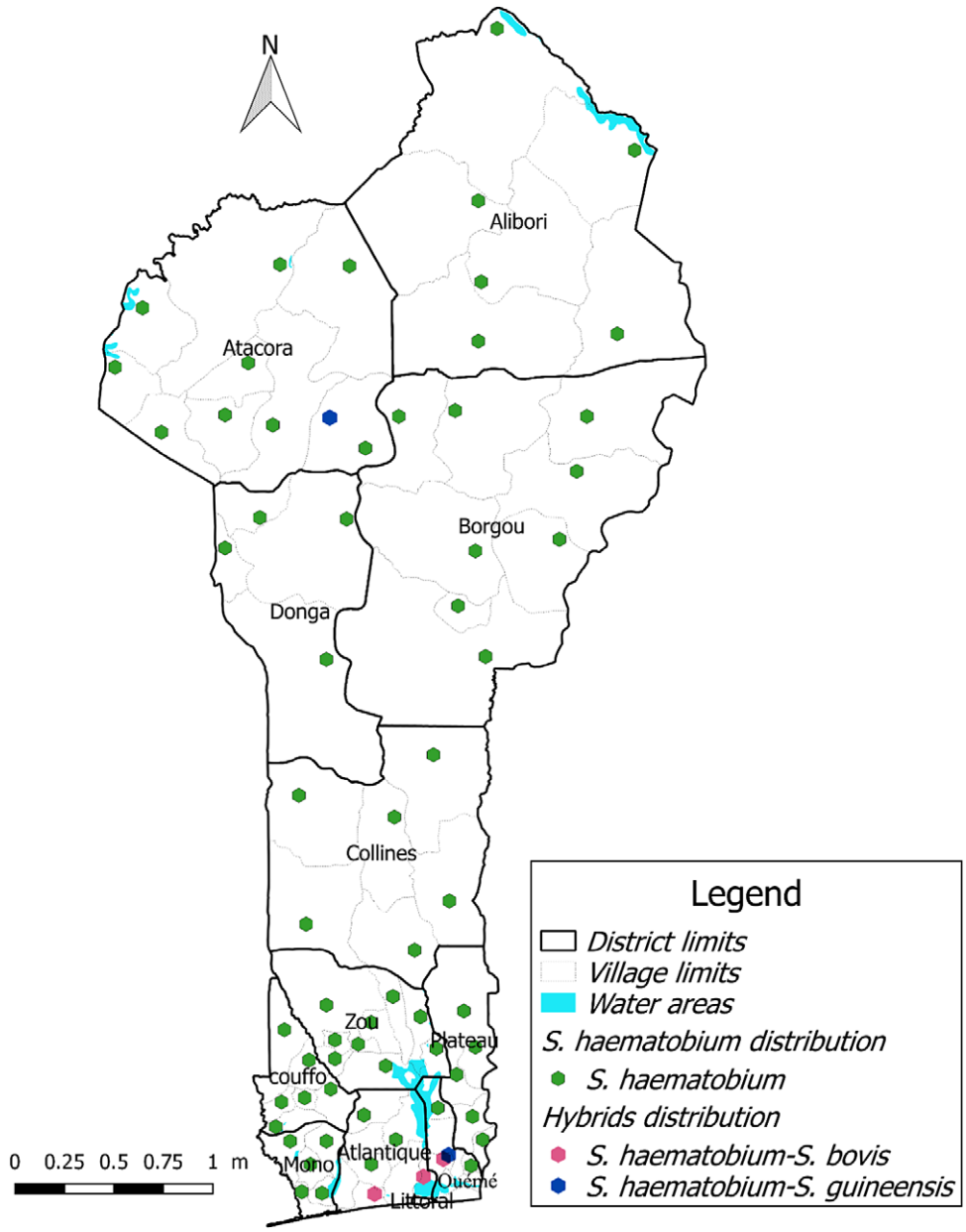

Figure 5. Distribution of *Schistosoma* hybrids in Benin.
S.h-S.b hybrid found Kessounou and Sô-tchanhoué
Distribution of *S.h* (Onzo-Aboki *et al.*, 2019).
Distribution of *Schistosoma* hybrids (Moné *et al.*, 2012; 2015; Savassi *et al.*, 2020; 2021).

parasites and changes in host distribution can directly impact the transmission of these schistosomes. Focusing on epidemiological parameters, globally, the habitat of SRB has changed significantly over the past 30 years because of the construction of the Diama (1985) and Manantali (1988) dams in Senegal and Mali, respectively. These artificial water resources have not only helped to prevent saltwater intrusion from the sea and to stabilize water flow, they have also facilitated new forms of agriculture. The successive migration of first human populations, followed by animals and snails to these resources, created areas where humans and domestic livestock were near to one another, thereby facilitating interactions between the schistosome species they carry. Very recently, authors identified hybrid cercariae (*S.h-S.b*) excreted by infected snails collected in the Fatick in Senegal, using cox1, nuclear ITS1 + 2, and partial 18S rDNA regions (Senghor *et al.*, 2023) (Fig 3).

In Côte d'Ivoire

In a molecular study on cercariae shed by naturally infected snails, Tian-Bi *et al.* (2019a) reported (using Cox1 and ITS2 DNA region analysis) transmission of *S.h-S.b* hybrids from the northern and central parts of Côte d'Ivoire with an average prevalence of 0.4% of 75 discriminated cercariae. The same survey technique yielded an

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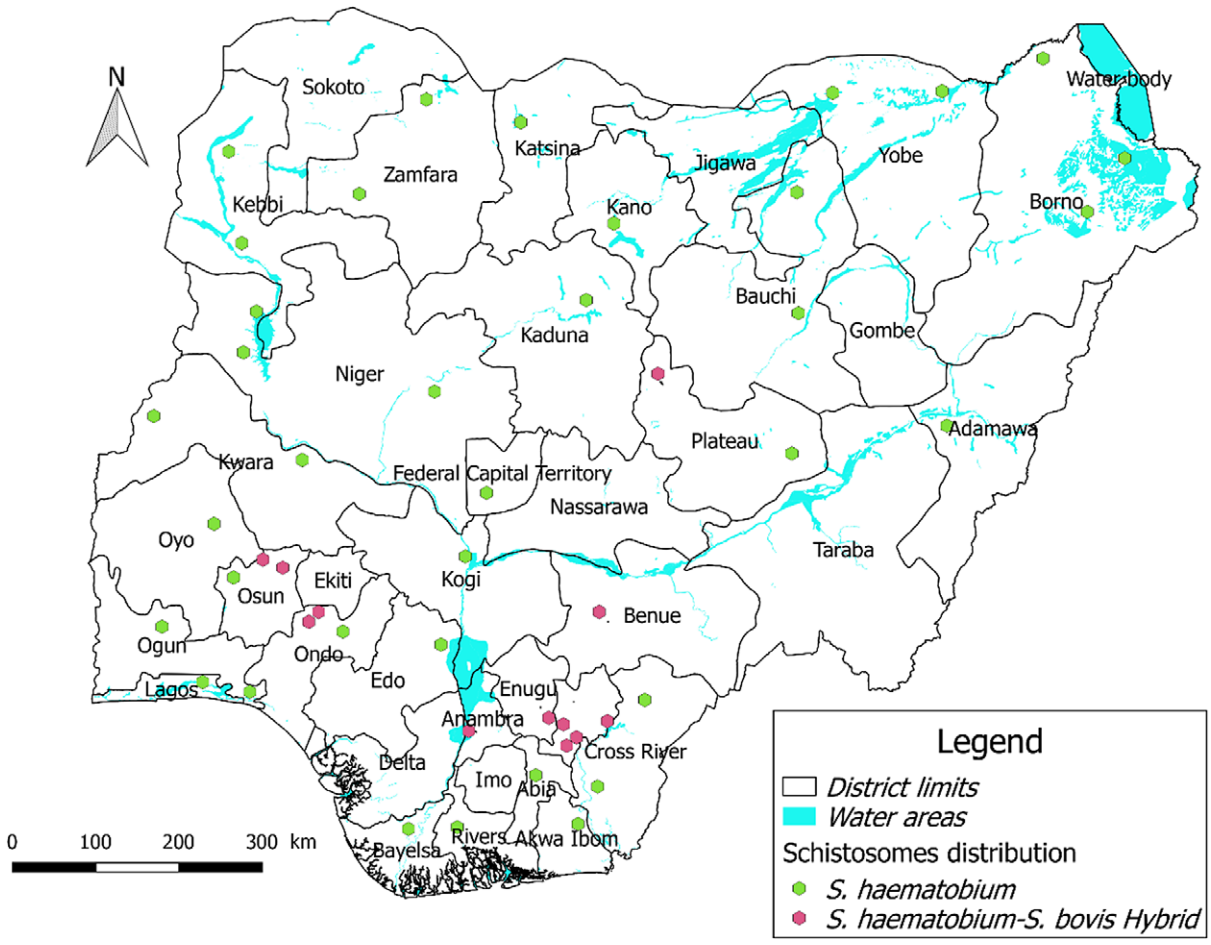

Figure 6. Distribution of *Schistosoma* hybrids in Nigeria.
S.h-S.b hybrid found in Ondo, Osun, Ebonyi, Enugu, Anambra, Benue, and Plateau.
Distribution of *S.h* (Agi & Okafor, 2005; Biu & Agbadu, 2009; Dawet *et al.*, 2012; Ekpo *et al.*, 2013; Ivoke *et al.*, 2014; Lai *et al.*, 2015; Abdulkadir *et al.*, 2017; Ezeh *et al.*, 2019; Onyekwere et al., 2022b).

average prevalence of 12.5% *S.h-S.b* hybrids in the districts of Dix-huit Montagnes, Agnéby, and Lagunes (Angora *et al.*, 2019). This technique should be considered when investigating the elimination of ectopic schistosome eggs in future studies. The LAMP test has made it possible to identify not only pure schistosome species, but also *S.h-S.b* hybrids in a urine sample (Crego-Vicente *et al.*, 2021) (Fig 4).

S.h interacts with *S.b* in the northern, southern, and western regions of Côte d'Ivoire to produce hybrids that infect humans. To identify and quantify *S.h-S.b* hybrids among schoolchildren in four sites across the Côte d'Ivoire, individual miracidia hatched from urine samples were molecularly characterized through an analysis of mitochondrial *cox1* and nuclear internal transcribed spacer 2 (*ITS 2*) DNA regions (Angora *et al.*, 2022) (Fig 4). In this study, pure *S.b* was found in some children, which indicates proof of a potential zoonotic infestation by *S.b*.

In Benin

The first study that molecularly characterized (ITS2 rDNA high-resolution melting and Cox1 sequences) *Schistosoma* from humans in Benin showed *S.h-S.g* hybrids in Dangbo, Ouemé district and Doh village, and Atacora district (Moné *et al.*, 2012) (Fig 5).

However, the authors did not identify a pure strain of *S.g.* Further studies by Moné *et al.* (2015) revealed (Cox1 and ITS2) the presence of another schistosome hybrid in additional villages in Benin (Sô-Ava and Pahoue, Atlantic District). A molecular analysis of two adult worms (one from Sô-Tchanhoué and the other from Toho) confirmed hybrids of *S.h-S.b.* More extensive molecular epidemiological studies carried out by Savassi *et al.* in 2020 and 2021 further showed that the *S.h-S.b* hybrid is most prevalent in the Ouémé and Atlantic districts (Savassi *et al.*, 2020; 2021). Although no hybrids have yet to be identified in livestock in other West African countries, zoonotic transmission has been established in Benin because Savassi *et al.* (2020; 2021) revealed that cows and rodents were infected with the same strain of hybrid found in infected humans. Although this study revealed both genetic evidence for the endemicity of *S.h* and the presence of the *S.h-S.b* hybrid, this was not the case for *S.g* and the *S.h-S.g* hybrid (Fig 5). These observations allowed us to qualify *S.g* and its hybrid as a rare schistosome species in Benin. Another of the most parsimonious hypothesis would be the replacement (Webster *et al.*, 2005) of the latter by *S.h-S.b* hybrids. Additional research is required to test these hypotheses.

In Nigeria

There is only one major molecular epidemiology study on schistosomes in Nigeria. It was performed on miracidia *Schistosoma*

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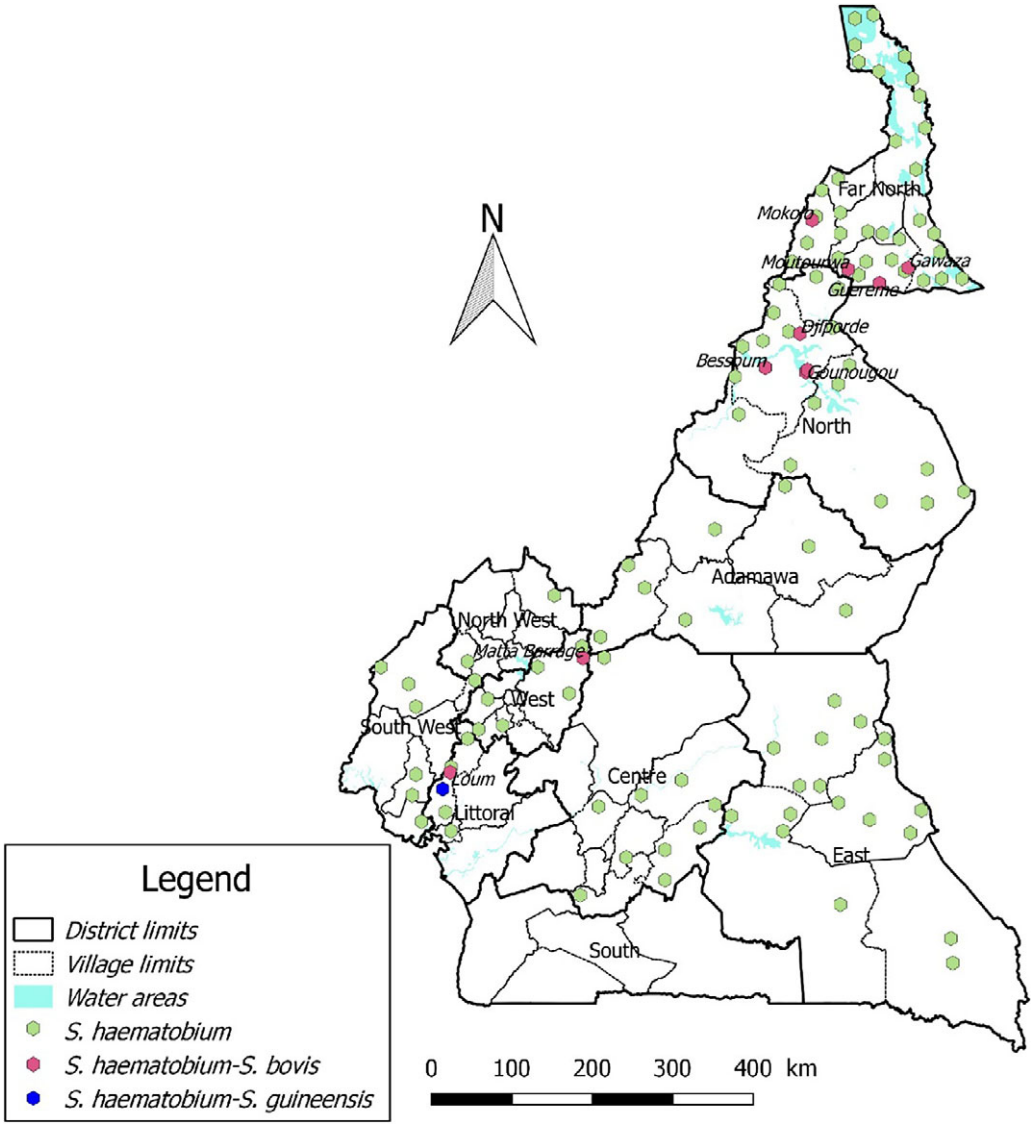

Figure 7. Distribution of *Schistosoma* hybrids in Cameroun.
S.h-S.g hybrid found in Kumba, Loum, Barombi Mbo, and Barombi Kotto. *S.h-S.b* hybrid found in Gazawa Bizili, Guereme, Mokolo and Mourtouwa, Bessoum, Djiporde, Gounougou and Ouroudoukoudje, Matta Barrage, and Loum.
Distribution of *S.h* (Ministry of Public Health of Cameroun, 2019).
Distribution *of Schistosoma* hybrids (Teukeng *et al.*, 2022; Webster *et al.*, 2003).

collected in urine from schoolchildren (Onyekwere *et al.*, 2022a). Molecular characterization by rapid diagnostic multiplex polymerase chain reaction targeting mtDNA (mtDNA Cox1) genes showed the *S.b* Cox1 profile in the sample from districts of Plateau, Benue, Enugu, Ebonyi, Anambra, Ondo, and Osun, suggesting hybridization between *S.h* and *S.b* (Onyekwere *et al.*, 2022a) (Fig 6). This study provides new insights into hybridization and population genetic structure of *S.h* in Nigeria.

Distribution of *Schistosoma* hybrids (Onyekwere *et al.*, 2022b).

The phenomenon of hybridization within the *haematobium* group has also been studied in Central Africa, such as Cameroon, Gabon, and Democratic Republic of Congo.

In Cameroun

Two hybrid profiles have been reported in the literature. The first, *S.h-S.g*, was reported initially on the morphological basis of eggs passed with human feces (Southgate, van Wijk & Wright, 1976; Tchuem Tchuenté *et al.*, 1997; Wright *et al.*, 1974) and confirmed by biochemical and molecular analyses (Ndifon *et al.*, 1988; Rollinson and Southgate, 1985; Webster *et al.* 2005; Webster, Southgate, and Tchuem Tchuenté, 2003). This hybrid pattern has remained local within in the village of Loum, Littoral district (Rollinson and Southgate, 1985; Southgate *et al.*, 1976; Tchuem Tchuenté *et al.*, 1997; Webster *et al.*, 2005, 2003; Wright *et al.*, 1974). The second hybrid profile, *S.h-S.b*, was recently reported (Cox1 and ITS) (Teukeng *et al.*, 2022) and seems to have a wider distribution than the *S.h-S.g* hybrid (Fig 7). The presence of this hybrid in all schistosomiasis-endemic regions of Cameroon should be considered because its presence was recorded in all of the areas surveyed (Teukeng *et al.*, 2022) (Fig. 7).

In Gabon

Speculation about the existence of eggs that appear to be morphological hybrids resulting from the crossing of *S.g* and *S.h.* in

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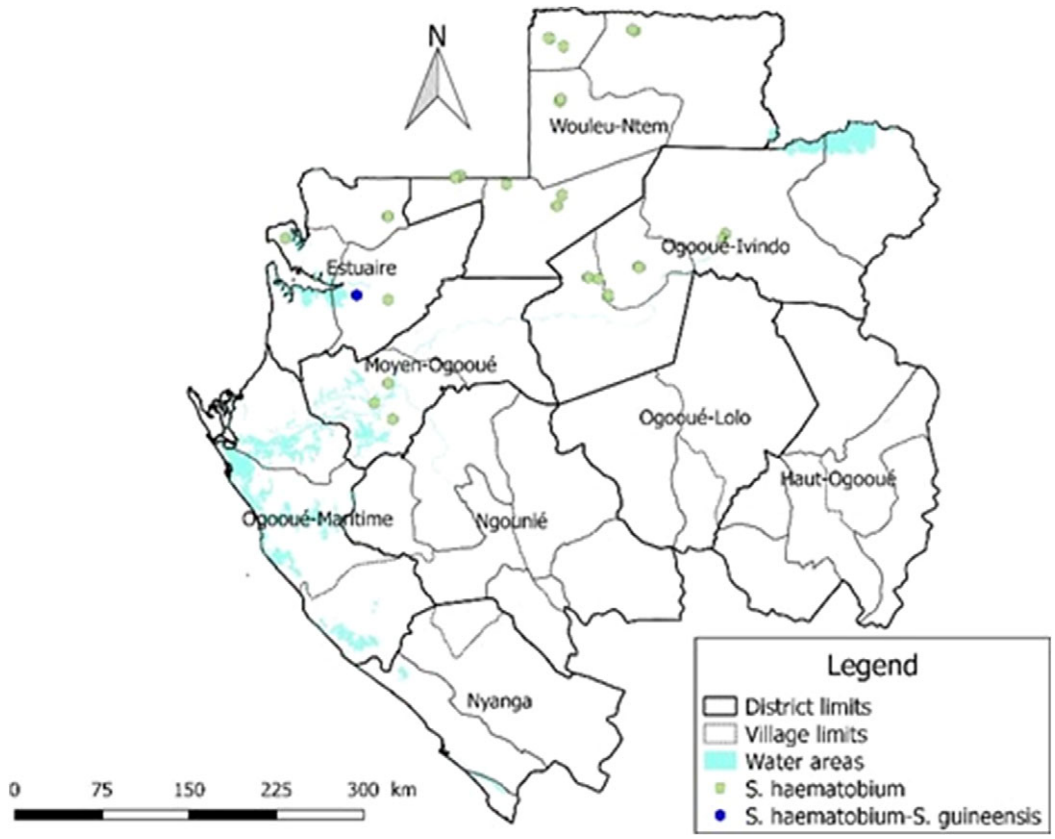

Figure 8. Distribution of *Schistosoma* hybrids in Gabon.
S.h-S.g hybrid found in Lambaréné.
Distribution of *S.h* (Dejon-Agobé *et al.*, 2022; Mintsa Nguema *et al.*, 2018).
Distribution of *Schistosoma* hybrids (Burchard & Kern, 1985).

Lambaréné dates to 1985 (Burchard & Kern, 1985). Subsequently, in 2010, the presence of hybrids between *S.h* and *S.g* was detected in Estuaire Province (western Gabon). Egg morphology showed three morphotypes: *S.h*, *S.g*, and intermediate morphotypes, using single-strand conformational polymorphism analysis on adult worms (Nguema *et al.*, 2010) (Fig. 8).

In Democratic Republic of Congo

Tchuenm Tchuenté *et al.* (1994) showed the existence of a natural hybrid species between *S.i* and *S.h* in Kinshasa. These isolates were obtained by exposing *Bulinus wrighti* to miracidia from eggs collected from two infected children and identified by biochemical (phosphoglucomutase isoenzymes), molecular (restriction fragment length polymorphism and randomly amplified polymorphic deoxyribonucleic acid analysis), and morphological (egg measurements) techniques (Tchuenté *et al.*, 1997) (Fig. 9).

Table 1 summarizes the distribution of different cases of hybridization between *Schistosoma* spp. with those of *S.h* depending on molecular or enzymatic techniques used in Africa.

Discussion

Figure 10 summarizes the presence of hybrids within the *haematobium* group at the scale of the African continent. The figure also includes information about the presence of hybrids in other parts of Africa not considered in this review (Chiti *et al.*, 2000; Cnops *et al.*, 2021; De Bont *et al.*, 1994; Kruger & Hamilton-Attwell, 1988; Pitchford RJ, 1961; Webster *et al.*, 2019; Wright & Ross, 1980; Zwingenberger *et al.*, 1990). This review shows that hybrids within the *haematobium* group are particularly common in West and Central Africa. In Africa, hybrids have been detected in a few countries where *S.h* is known to be endemic, including Senegal, Mali, Niger, Nigeria, Benin, Côte d'Ivoire, Cameroon, Tanzania, Zambia, Malawi, South Africa, Zimbabwe, Gabon, and Democratic Republic of Congo. For the remaining countries endemic to Africa (Aula *et al.*, 2021), it is therefore not possible to know whether hybrids are absent from these countries or whether they have simply not been identified. Given the current state of knowledge, discovering an area where no hybrids are found would be an exception or, perhaps, an area for further study to better understand why no hybrids are present. It is important to continue to map hybrids at different scales, whether at the country, region, or transmission site scales.

This review also highlights that *S.h* seems to be involved in most cases of hybridization. That this parasite is a human-infecting parasite certainly introduces a bias because it attracts more scientific attention than animal-infecting parasites. It is also easier to collect parasites in the urine of human patients than in animal stool or urine. It is also surprising to note that the one species (*S.h*) that lives in the veins of the perivesical plexus easily hybridizes with a variety of species that live in mesenteric veins. Where these parasites, which have very different tropisms, meet, is still unknown. It is less surprising to find hybrids that share both the same host and the same tropism, as in the case of hybrids between *S.c* and *S.b.*

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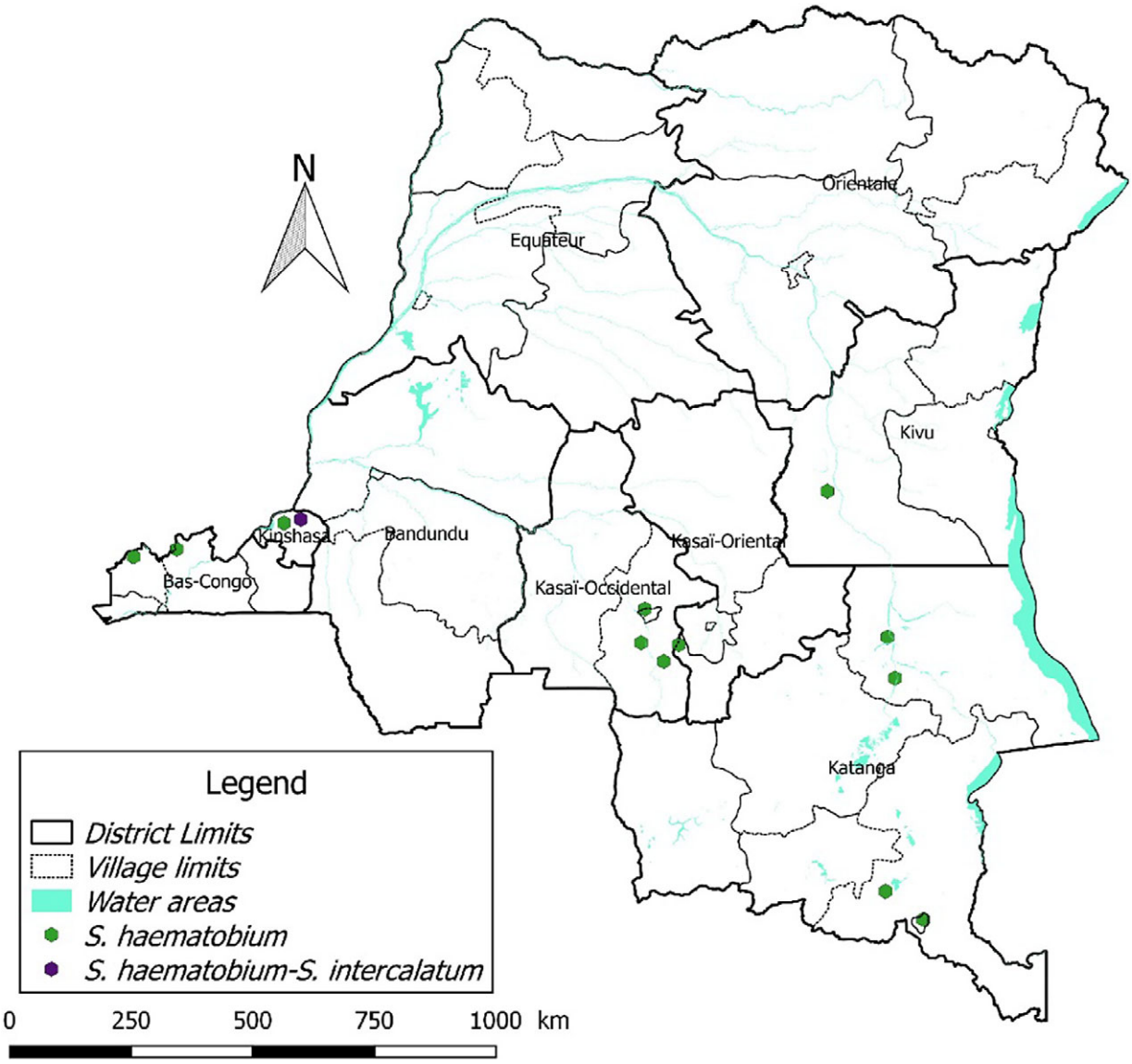

Figure 9. Distribution of *Schistosoma* hybrids in Democratic Republic of Congo.
S.h-S.i hybrid found in Kinshasa.
Distribution of *S.h* (Madinga *et al*., 2015).
Distribution *Schistosoma* hybrids (Tchuenté *et al*., 1997).

Historically, only limited data existed on hybrids, but over the past few decades this phenomenon has received a renewed interest. Even today, animal bilharziasis remains largely neglected when compared to human bilharziasis. These hybrids are of particular concern because they may be at the root of the tri-specific hybrids (*S.h-S.b-S.c*) already observed in Mali and Niger. Efforts must be made to characterize hybrids in humans as well as in animals. Today, *S.b* × *S.h* hybrids have been found in rodents in Senegal (Catalano *et al*., 2018) as well as rodents and cows in Benin (Savassi *et al*., 2020; 2021). Identifying hybrids in animals does not guarantee that they are zoonotic. To determine this, it is necessary to check that the same hybrids circulate in both humans and animals. This requires the use of molecular markers that are sufficiently polymorphic. A study carried out in Senegal (Boon *et al*., 2019) that used microsatellite markers to genotype parasites from humans and cattle showed that the animal parasites were genetically different from the human parasites, suggesting the absence of a zoonotic transmission. It is important to notice that *S.h* × *S.b* hybrids have never been identified in cows in Senegal. This kind of population genetic analysis needs to be performed in areas where hybrids have been identified in both human and in either rodents (Senegal and Benin) or cows (Benin). Today, the zoonotic nature of *S.h* × *S.b* crosses has not been confirmed. In this cross, it seems clear that humans are the key host and that the role of animals as reservoirs or as spillover hosts needs to be addressed (Webster *et al*., 2016).

Hybridization must also be analyzed in terms of transmission typology. In the Sahelian region (Burkina Faso, Niger, Mali, Senegal), all of the temporary or permanent water points attract both humans and animals (cattle, sheep, and goats) for multiple needs (drinking water for animals, and drinking water, laundry, fishing, recreational activities, and agriculture for humans). Therefore, depending on the region, there's a big difference in the type and frequency of water sources used by definitive hosts. In West Africa, it is common practice for farmers to bathe daily the local ponds. In

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Table 1. Details on detected natural hybridization between *Schistosoma* spp. with *S.h* in Africa

Schistosoma hybrids	Countries	Natural definitive hosts	Detected hosts	References
S.h–S.b	Senegal, Niger, Benin, Côte d'Ivoire, Malawi, Nigeria, Cameroon, Mali	Humans × livestock	Humans	(Bremond *et al.*, 1993; Huyse *et al.*, 2009; Webster *et al.*, 2013; Moné *et al.*, 2015; Soentjens *et al.*, 2016; Boon *et al.*, 2017, 2018; Catalano *et al.*, 2018; Boon *et al.*, 2019; Tian–Bi et al., 2019b; Webster *et al.*, 2019; Savassi *et al.*, 2020; Léger *et al.*, 2020; Angora *et al.*, 2022; Onyekwere *et al.*, 2022a; Teukeng *et al.*, 2022)
S.h–S. g	Cameroun, Benin	Humans × humans	Humans	(Webster *et al.*, 2005; Moné *et al.*, 2012)
S.h–S.ma	South Africa, Malawi	Humans × livestock	Humans	(Webster *et al.*, 2019; Wright & Ross 1980; Cnops *et al.*, 2020)
S.h–S.c	Senegal	Humans × livestock	Humans	(Webster *et al.*, 2013)

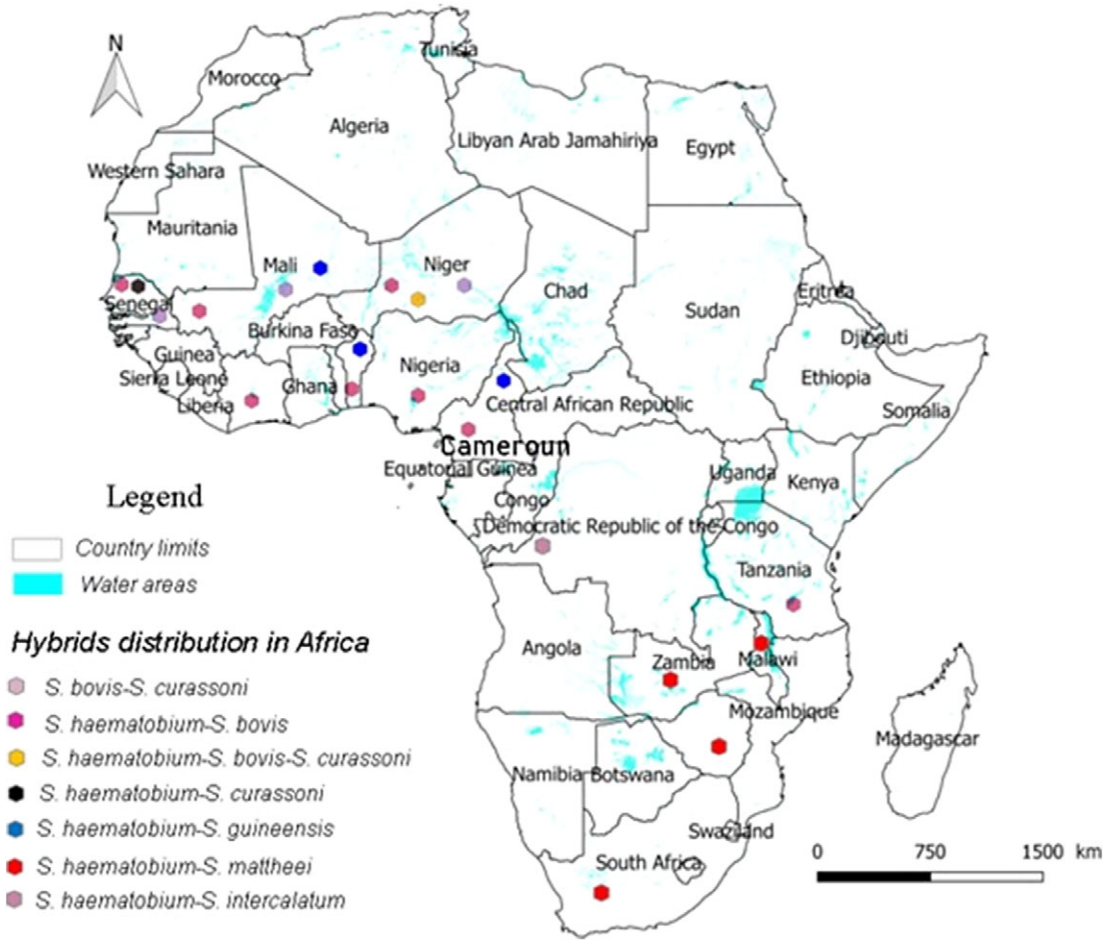

Figure 10. Distribution of schistosome hybrids of the *haematobium* group in Africa.

another example, for many parts of the world, cattle may have free access to water bodies while grazing or might be led two to three times per day to a river or canal (early morning, midday, and/or afternoon). In most areas, cattle are only in contact with water for drinking. This suggests that the type of water contact plays an important role in the transmission of schistosomiasis. It also means that within the same herd, the number of times that an animal comes into contact with water is unlikely to change with age. According to Stothard *et al.* (2020), details of the dynamics of these interactions and hybridization events in different contexts are certainly warranted, as differences are likely to occur at both micro and macro geographical scales (Stothard *et al.*, 2020).

It is also important to note that within one type of cross, there are several types of hybrids. This is particularly visible in *S.h-S.b* hybrids, which have been studied extensively. Hybrids are classically detected by mitochondrial typing, offering two possibilities (*S.b*

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or *S.h*), and nuclear typing, offering three possibilities (*S.bS.b*, *S.bS.h*, and *S.hS.h*). There are therefore six possible hybrid categories. Nuclear alleles based on ITS2 are derived predominantly from *Sh.* Most studies show *S.h* ITS2 in excess of 75% (Webster *et al.*, 2013; Teukeng *et al.*, 2022; Angora *et al.*, 2022; Savassi *et al.*, 2020; 2021). Nigeria, with only 49% *S.h* ITS2, seems to stand out. Specific variations in mitochondria are the most important. Variations in *S.b* mitochondria can range between 11% (Nigeria) and 95% (Senegal). The reasons for this variation in diversity and the expansion dynamics of these hybrids are not known. Exome capture analysis of miracidia from Niger and Zanzibar showed that hybridization is an ancient event dating back 240 years (Platt *et al.*, 2019). No first-generation hybrids were observed among the 48 miracidia of Nigerian origin. These authors concluded that if interbreeding continues to exist (e.g., the presence of F1 miracidia), it is most likely rare. In fact, some studies based on less resolutive approaches have shown that the frequency of first-generation ITS *S.b* × *S.c* heterozygotes can be low. In Senegal, this frequency can vary between 0.6% (Boon *et al.*, 2018) and 9% (Webster *et al.*, 2013). On a country scale, these variations can be significant (ratio of 15), making it difficult to generalize. This is also observable on a larger scale because the frequencies of ITS *S.b* × *S.c* heterozygotes are 7.5%, 18.8%, 29.8%, and 41.3%, in Cameroon, Cote d'Ivoire, Benin, and Nigeria, respectively (Angora *et al.*, 2020; Onyekwere *et al.*, 2022a; Savassi *et al.*, 2020; Teukeng *et al.*, 2022). As first reported in a pioneering study by Platt *et al.* (2019), who used high-throughput sequencing, it is now essential to study these hybrids at wider spatial and temporal scales, with more markers and at a higher resolution. Finally, it is important to note that hybrid identification is mainly based on molecular analyses of mitochondrial-nuclear discordance or targeting just a few single nucleotide polymorphisms. Recently, a molecular method for differentiating *S.b, S.c*, and *S.h* has made it possible to identify hybrids between these three species in a single polymerase chain reaction (Blin *et al.*, 2023). However, it would be misleading to think that the genome can be simplified to a single single nucleotide polymorphism, as this method doesn't identify backcrossing events that can mask hybridization events. The use of NSG (Next Generation Sequencing) methods has clearly shown that the frequency of hybrids is largely underestimated (Platt *et al.*, 2019). This underestimation is due to the fact that backcrossing can lead to hybrid parasites being diagnosed as pure. It is therefore important to develop more powerful tools to better characterize hybrids and to characterize the level of genetic introgression between the species concerned.

Conclusion

In conclusion, this literature review centered on the various schistosome hybridizations within the *haematobium* group shows that interactions between species continue in West and Central Africa, and involve migratory phenomena, climatic changes, and host/parasite compatibility. In the past, few studies focused on this phenomenon, but now there is a strong increase in such studies in many parasitic species, especially in schistosomes. Because of increased human population growth, anthropogenic environmental changes, and global movements of humans and animals, hybridization is a growing field of interest within the research community because of the many questions it raises, particularly in Africa. This review gives us a global idea about the foci of hybridization of urinary schistosomiasis in West and Central Africa and requires a paradigm shift that entails a multisectoral (e.g. One Health) approach to preventing zoonotic transmission of schistosomiasis.

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