STUDY OF THE CURRENT STATUS OF SCHISTOSOMA HAEMATOBIOUM INFECTION IN THE EUROPEAN UNION: AN APPROACH TO THE POSSIBLE RISK IN SPAIN.

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ABSTRACT

Background. In Europe, urogenital schistosomiasis was not endemic, however in 2014 the first cases of a European autochthonous infection outbreak appeared in Corsica (France). In this work a search and description of cases, both import and native urogenital schistosomiasis, published in the European Union (EU) during the last 20 years was made. In addition, a qualitative risk assessment in Spain was carried out.

Methods. A bibliographic search of European Union published cases over the last 20 years (1997-2017) was performed using PubMed. Works that evidenced the presence of intermediate hosts Bulinus truncatus and Planorbarius metidjensis in our country were searched in PubMed, ResearchGate and Google Scholar. Finally, a risk assessment of urogenital schistosomiasis in Spain using the 2011 ECDC guide was made.

Results. 481 cases in the EU were found. 328 were imported and 152 autochthonous. All from the autochthonous cases were focused in Corsica, where people from different nationalities got sick. The presence of two potential host species was documented in different locations of our geography. The result of the risk assessment in Spain was low risk.

Conclusions. Although the risk assessment in Spain was low risk, several factors as the presence of intermediate hosts in Spain, the increase on migratory flows, and the role that the S. haematobium-bovis hybrid had in the outbreak of Corsica, must alert community and health authorities about the possibility that autochthonous cases in our country appear.

Key words: Schistosoma haematobium, Genetic hybridization, Endemic disease, Spain, France, Europe, Risk assessment, Intermediate host, Planorbid, Bulinus.

RESUMEN

ESTUDIO DE LA SITUACIÓN ACTUAL DE LA INFECCIÓN POR SCHISTOSOMA HAEMATOBIOUM EN LA UNIÓN EUROPEA, UNA APROXIMACIÓN AL POSIBLE RIESGO EN ESPAÑA

Fundamentos. En Europa no era endémica la esquistosomiasis urogenital, sin embargo en 2014 aparecieron en Francia los primeros casos de un brote de infección autóctona europea. En este trabajo se hace una búsqueda y descripción de casos de esquistosomiasis urogenital, tanto importados como autóctonos, publicados en la Unión Europea (UE) durante los últimos 20 años. Además se realiza una evaluación cualitativa del riesgo en España.


Resultados. Se hallaron 481 casos en la UE, 328 eran importados y 152 autóctonos. En todos los casos autóctonos el foco se localizó en Córcega, donde enfermaron personas de diversas nacionalidades. Se documentó la presencia de dos especies hospedadores potenciales en diversas localizaciones de nuestra geografía. El resultado de la evaluación de riesgo en España fue bajo riesgo.

Conclusiones. Si bien el resultado de la evaluación de riesgo en España fue bajo riesgo, factores como la presencia de hospedadores intermedios, el aumento de los flujos migratorios, y el papel que tuvo el híbrido S. haematobium-bovis en el brote de Córcega, deben poner en sobre aviso a la comunidad médica y las autoridades sanitarias ante la posibilidad de que aparezcan casos autóctonos en nuestro país.

Palabras clave: Schistosoma haematobium, Hibridación genética, Enfermedad endémica, España, Francia, Europa, Evaluación de riesgo, Planórbito, Bulinus.
INTRODUCTION

Schistosomiasis is currently considered the second most important parasite after malaria, and it has high rates of morbidity and mortality, mainly in poor and developing countries without access to diagnosis and treatment\(^1\), \(^2\). Six species are the main agents of human schistosomiasis: on the one hand \textit{Schistosoma japonicum}, \textit{S. mansoni}, \textit{S. mekongi}, \textit{S. intercalatum} and \textit{S. guineensis} which cause intestinal schistosomiasis in Africa, the Middle East, South America and the Caribbean, China, the Philippines, Indonesia, Vietnam and Laos; and, on the other hand, \textit{S. haematobium} which produces urogenital schistosomiasis mainly in Africa, in various Middle East locations and, recently, in France\(^3\).

According to WHO data from 2017, an estimated 436 million people were at risk of contracting a \textit{S. haematobium} infection in sub-Saharan Africa, and that 112 million people develop the disease annually\(^4\).

The disease caused by this parasite is not common in the European continent. In Spain, such cases are imported by people who visit endemic areas, such as tourists on adventure trips, migrants or military personnel\(^5\),\(^6\). However, new cases of autochthonous infections caused by \textit{S. haematobium} have been reported in Europe\(^7\). The first cases of European urogenital schistosomiasis appeared in 2014, affecting several members of three French families who had not traveled to endemic areas, and who only reported having spent their summer holidays in August 2011 and 2013 in Corsica (France), where they bathed in the Cavu River\(^8\). Since then, more cases have been reported, resulting in a ban on bathing in the Cavu River\(^9\). The European Center for Disease Prevention and Control (ECDC) published a rapid risk assessment that same year evaluating the outbreak\(^7\), and it carried out an update in 2015\(^10\).

Schistosomes are flatworms of the Trematoda class with a complex life cycle. In the case of \textit{S. haematobium}, the embryonated eggs reach the external environment through the urine of infested individuals. When these eggs come into contact with fresh water, the miracidia exit the eggs and then enter some species of aquatic snails who act as their first intermediate host. The snail-parasite relationship is very specific. Only certain species of snails play a role in transmission: in the case of \textit{S. haematobium}, it would be snails of the \textit{Bulinus genus}\(^11\). In Europe, the only species found of this genus is \textit{B. truncatus}\(^12\). However, some studies have shown that snails of other species present in Europe such as \textit{Planorbarius metidjensis}, a natural host to \textit{S. bovis}, can also act as an intermediate host to \textit{S. haematobium}\(^13\). In the snail, two generations of sporocysts evolve and thus the infective forms, called furcocercous cercariae, emerge and reach the external environment where they swim actively until they find a definitive human host whom they access transcutaneously. The parasite then arrives at the portal system where it will mature until becoming an adult, when it pairs and migrates to the bladder plexuses. The laying of eggs takes place within blood vessels which irrigate the bladder walls and these eggs eventually exit the system through the urine, thereby closing the cycle\(^14\).

Clinical symptoms of schistosomiasis involve different stages which coincide with the parasite’s cycle. When the transtegumentary penetration of the furcocercous cercariae occurs, an acute pruritic dermatitis appears, called “swimmer’s dermatitis”. In the acute phase, which happens during the schistosomulum’s migration and subsequent maturation, symptoms appear several weeks after exposure, including diarrhea, vomiting, general malaise, bronchial hyperresponsiveness, and fever. During the final stage, when it’s a chronic disease, the body reacts to the eggs deposited by the helminth on the walls of the bladder and ureters, among other locations.

Initial symptoms are usually dysuria, high urinary frequency, proteinuria, and hematuria, the latter being a very suspicious indication. If the disease persists, bodily harm may evolve into fibrosis, calcification, and hydronephrosis. Without a treatment (praziquantel is the...
drug of choice \cite{15}) schistosomes parasitize humans for 3 to 10 years, and in some cases can live up to 40 \cite{16}. In addition, chronic infection in many patients leads to the appearance of bladder Squamous Cell Carcinoma, which is why \textit{S. haematobium} was classified in 1994 as a “Group 1” carcinogen by the International Agency for Research on Cancer \cite{17}.

The objective of this work was to go in-depth into the most important aspects of this parasite’s epidemiology in our environment, carrying out a search of the disease’s published cases in Europe in the last 20 years. Additionally, investigating published studies proving the presence of \textit{B. truncatus} and \textit{P. metidjensis}, potential intermediate hosts of this parasite, in our country. And, finally, performing a qualitative risk assessment of the occurrence of urogenital schistosomiasis in Spain.

**MATERIALS AND METHODS**

A bibliographic search of published articles, related to documented cases of \textit{S. haematobium} infections in all European Union member countries, was carried out individually for each country. The time interval of this search was limited to the last 20 years, from 1997 to 2017.

The search engine of choice was PubMed (https://www.ncbi.nlm.nih.gov/pubmed), because most published medical literature journals are indexed in Medline’s database. In addition, Pubmed’s advanced search made it possible to easily systematize the work methodology.

In order to find the largest possible number of published cases, three different searches were conducted for each country: the first one with the country’s name; the second one with its citizen’s nationalities; and the third with each country’s capital city.

PubMed’s advanced search system was deployed. Keywords and search fields are detailed in table 1.

After completing the search, articles were selected according to the following inclusion criteria: published works reporting one or more cases of proved infection by means of \textit{S. haematobium}, either due to the presence of eggs in urine, and/or positive serology results; articles identifying the country where the diagnosis was carried out, and when the work clearly depicted if a case was an imported disease or if it was autochthonous. Cases were classified as indigenous or imported according to what the authors reported.

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<td>Search fields and keywords used when searching for cases of \textit{S. haematobium} in EU countries.</td>
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<tr>
<th>Search field</th>
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<tr>
<td>All Fields</td>
<td>“Schistosoma haematobium”</td>
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<tr>
<td>Country</td>
<td>Germany, Britain, Portugal, Italy, France, Netherlands, Belgium, Spain, Austria, Denmark, Poland, Slovenia, Romania</td>
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<tr>
<td>Nationality</td>
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Exclusion criteria were: articles that did not report cases; articles that reported cases which had been previously selected (patients who appeared in several articles were counted as one); and articles whose object of study was a type of parasite different than *S. haematobium*.

On the other hand, a search was made for works that documented the presence in Spain of potential intermediate hosts for *S. haematobium*, gastropods (aquatic snails) of the *Bulinus truncatus* and *Planorbarius metidjensis* species\(^{(11, 12, 13)}\).

In order to range over the largest possible bibliography, the search was carried out deploying three search engines: PubMed, Google Scholar, (since this search engine covers a broad spectrum within general scientific literature), and ResearchGate (because this growing platform presently includes a large amount of published scientific literature, mainly due to its authors’ undertaking.)

The search engines and the keywords used for each snail species are detailed in table 2.

Among the articles found, the selection was based solely on those which described the presence of these possible intermediate hosts in our country.

Finally, a qualitative risk assessment was carried out related to contracting urogenital schistosomiasis in Spain, following the European Center for Disease Prevention and Control (ECDC) guidance document titled “Operational guidance on rapid risk assessment methodology” of 2011\(^{(18)}\). A combined approach methodology was carried out, which bundles, in a single algorithm, questions related to transmission probability together with questions related to the impact of the disease.

<table>
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<tr>
<th>Keywords and search engines used for snail species <em>Planorbarius metidjensis</em> and <em>Bulinus truncatus</em>.</th>
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<td>Snail</td>
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<td><em>Planorbarius metidjensis</em></td>
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<td><em>Bulinus truncatus</em></td>
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A non-combined option was ruled out since it provided a more accurate assessment for illnesses with high probability and low impact, or for diseases with low probability and high impact, and none of these assumptions took place in this case. There was also an assessment in terms of the analysis’ level of confidence based on the information’s consistency, relevance, and external validity.

**RESULTS**

Results for the search of urinary schistosomiasis cases in the European Union were as follows: a total of 69 articles were found. Out of these works, 29 were selected which met inclusion criteria, while 40 were discarded.
Table 3 shows the keywords used for the search: for each country, the number of articles found; the number of articles included in the results, indicating their bibliographic reference; and the number of cases found, indicating in separate columns the native and the imported cases. The table only includes EU countries where cases were published.

Figure 1 shows the number of cases of imported urogenital schistosomiasis that had been published, as well as the EU countries where their authors had reported them.

Figure 2 shows, on a map, the number of cases related to the European outbreak of *S. haematobium*, originating in Corsica, according to the nationality of infected patients. It should be noted that the 15 cases detected in Italy, the 5 cases in Germany, and the Belgian case, corresponded to patients who had previously traveled to the island of Corsica, where they contracted the disease\(^{(20, 23, 34)}\).
Regarding the presence in Spain of intermediate hosts, after searching and reviewing material published on *B. truncatus*, 2 articles were selected which demonstrated the presence of *B. truncatus* in El Ejido (Almería)\(^6, 47\), and in the lagoon of Villena (Alicante)\(^47\). Furthermore, Dana et al. listed other locations where this snail species had previously been depicted: Balearic Islands, Gerona, Barcelona, Tarragona, La Coruña, Pontevedra and Huelva\(^6\).

On the other hand, there were 5 articles describing the presence of *P. metidjensis* in Spain: one in Extremadura, specifically in the basins of the Guadalquivir, Guadiana and Tajo rivers (Badajoz and Cáceres)\(^48\), another one documenting the existence of this snail in the lower basin of the Guadiana River, located between the reservoir of Alqueva (Portugal) and the Atlantic Ocean\(^49\); and an article describing the presence of this snail in several rivers, streams, fountains

**Figure 1**

*Published cases of imported urogenital schistosomiasis and the EU countries where authors reported them.*

![Map showing cases of imported urogenital schistosomiasis in EU countries](source)

**Figure 2**

*Published cases related to the European indigenous outbreak and patients’ nationality.*

![Map showing cases related to the European indigenous outbreak](source)
and peatlands in the Madrid region\(^{(50)}\); and; finally, two articles which had used this species of snails for experimentation (one where the snails were collected in the province of Malaga\(^{(51)}\), and the other in the province of Salamanca\(^{(52)}\)).

Figure 3 shows, with a line pattern, Spanish provinces where the presence of *B. truncatus* specimens has been documented; and, with a dot pattern, the provinces where *P. metidjensis* has been depicted; and, in black, where both species have been found.

The result of a qualitative risk assessment, following the ECDC’s combined approximation algorithm as per its guidance document, was a “Low risk” of contracting urogenital schistosomiasis in Spain. It considered that there are no specific groups with higher risk of infection; that transmission potential within EU member states was low; that any cases would be related to an unexpected illness; dispersal ability within the European Union was low, and that urogenital schistosomiasis was a disease with a high morbidity rate but with a low mortality rate, for which there is treatment, and control measures can be carried out.

According to the ECDC’s risk analysis guide, the analysis’ result was satisfactory in terms of its level of confidence, since it was mainly based on reliable sources. Within gray literature, only consistent results were taken into account.

**DISCUSSION**

Until 2014, all cases of schistosomiasis depicted in Europe that we found were solely related to imported cases (immigrants or travelers who had visited countries where this disease is endemic.) However, this changed when reports of the first cases appeared of what became a European autochthonous outbreak located in Corsica (France). In 2014, Berry et al., described how a 4-year-old girl and her father, a French citizen, both of whom suffered from gross hematuria, were diagnosed with *S. haematobium* infection at Toulouse University Hospital. The family had not traveled to any area in which urinary schistosomiasis was endemic; they only reported having spent summer vacations in August 2011 and 2013 in Corsica, where they bathed in the Cavu River. Consequently, 4 other people were also diagnosed with schistosomiasis, concerning two French families who spent

**Figure 3**

Spanish provinces where the presence of *Bulinus truncatus* and *Planorbarius metidjensis* specimens has been documented.

Source: EuroGlobalMap of EuroGeographics website
their holidays in the same place\textsuperscript{(8)}. In 2014 Holtfreret al. depicted five infections in a German family who had also bathed in the Cavu River in 2013\textsuperscript{(34)}. In 2015, Beltrame et al. published a study carried out on 43 Italian travelers who had visited the island and had bathed in the Cavu River at least once between 2011 and 2014, of which 15 infections were reported and classified as follows: 5 confirmations, 2 likely cases, and 8 possible ones\textsuperscript{(20)}. To these episodes, we must add those of Brunet et al. who depicted 3 more cases in 2015, all of whom where members of the same French family who became ill and, as in the rest of cases, had spent a few days in August 2013 in Corsica\textsuperscript{(26)}. Another study, published in 2015, describes 11 more cases, of which only 2 were confirmed, 6 were classified as likely, and 3 as suspicious. These were travelers from different countries who had visited Corsica, of which 9 were German, 1 Canadian and 1 Belgian\textsuperscript{(23)}.

Once the issue was conclusively located, authorities banned bathing in the Cavu River for a year\textsuperscript{(9)}, and a national screening was carried out in France, which led to the diagnosis of 110 more cases\textsuperscript{(10)}. In our search, the number of depicted cases we found was 152, and confirmed cases were related to people from four different EU countries: France, Italy, Germany, and Belgium.

Subsequent published research papers on this unique episode have helped clarify the real complexity of such outbreak. One of the first works, in which an affected patient’s parasite DNA was sequenced, revealed a pattern, in the mitochondrial COI gene, which was typical of another schistosoma species: \textit{Schistosoma bovis}. In this work, Moné et al. proved with this case that the parasite involved was a hybrid between two species of schistosomes, \textit{S. haematobium} and \textit{S. bovis}, and therefore the authors suggested the possibility that a hybrid between \textit{S. haematobium} and \textit{S. bovis} was the cause of all cases of the outbreak affecting people who had become ill on the French island\textsuperscript{(41)}. However, another subsequent work by Boissier et al., conducted a molecular study of eggs and miracidia from 12 patients, and showed that the outbreak was even more complex; there were three species of parasites involved: \textit{S. haematobium}, \textit{S. bovis} and a schistosoma hybrid called \textit{S. haematobium-bovis}. They found individuals infected only by \textit{S. haematobium}, others who were infected by the hybrid species \textit{S. haematobium-bovis}, and also patients who had a coinfection involving both \textit{S. haematobium} and the hybrid schistosoma \textit{S. haematobium-bovis} specimens, and they even depicted a case of coinfection involving both \textit{S. haematobium} and \textit{S. bovis}\textsuperscript{(53)}.

Although it was proven that three species were involved in the outbreak, its origin is still un-clear. Hybridization between both species might have taken place in Corsica, and thus the hybrid would be an autochthonous species in the island. However, the most likely hypothesis is that the parasite, or parasites, would have been imported from a country in sub-Saharan Africa, such as Senegal, where these species are already endemic\textsuperscript{(54)}. In addition, a molecular analysis of the French strains showed there was a close phylogenetic relationship with schistosomes isolated in northern Senegal, which further suggests an African origin for these European parasites\textsuperscript{(53)}. If this were the case, the eggs were likely came to the island from Senegal, or another neighboring country, and contaminated urine reached the Cavu River, a habitat where the intermediate host \textit{B. truncatus} is present, and then the cycle continued until the formation of \textit{Furcocercous cercariae}. In the case of infecting types related to the hybrid species \textit{S. haematobium-bovis}, in addition to having parasitized humans, they might have also infected local livestock, which would explain why the parasite cycle remained active on the island since sick cattle would have been acting as reservoirs of the disease.

The fact that a hybrid species is involved in the outbreak is of great epidemiological importance. It has been proved that, in some instances, species hybridization can be beneficial for generations of descendants. Among other advantages, it may increase the spectrum of intermediate hosts they can infect, or the spectrum of definitive hosts, and even both. Thus, it can increase a disease’s dispersal ability, and/
or its number of reservoir species\(^{(55)}\). Amongst parasites, hybridization and in-trogression phenomena can drive the emergence and rapid evolution of new zoonotic diseases. An example of an increase in dispersal ability would be the case of hybrids between two species of protozoa: *Leishmania infantum* with *Leishmania major*. Each one uses a different vector species for transmission, but it was shown that hybrids resulting from these two species were capable of transmission using vectors from both\(^{(56)}\). As previously mentioned, schistosomes are highly specific with regards to intermediate hosts and, in Europe, *B. truncatus* is the main intermediate host for *S. haematobium*\(^{(12)}\). Nevertheless, another species called *P. metidjensis* can also act as such\(^{(8)}\). The latter is not located in Corsica but in other European countries such as Spain. In addition, as Boissier et al. mention, this species could also be harnessed by hybrid *S. haematobium-bovis*\(^{(53)}\). For all these reasons, in the event that the Corsican outbreak was actually a case of zoonosis, the issue of public health would be far greater since control and elimination measures for these diseases are much more complex than when they exclusively affect human beings.

The risk assessment concluded that, currently, the chances of contracting urogenital schistosomiasis in Spain is low for the general population, and that it would be conditioned by multiple factors. On the one hand, subjects who are most exposed to contracting the disease would be those who carry out work and/or recreational activities that involve being in contact with fresh water contaminated by furcocercous cercariae; which, in turn, depends on two other factors: that schistosoma eggs are introduced into these waters, and that intermediate hosts are present there as well.

A part of our work has focused on the search for studies revealing the presence of intermediate hosts in our country and, as results show, there are populations of *B. truncatus* and *P. metidjensis* in several locations within our country. On the other hand, the introduction of schistosoma eggs, a non-endemic species, could only take place by means of infected individuals from places where the disease is present, and it’s important to remember that, in untreated infected individuals, this parasite can live up to 40 years. In Europe, we have found documentation related to 328 imported cases (3 of them in Spain) of *S. haematobium* infection, which has been and will be the gateway for this parasite in Europe. In Spain, according to the latest data from the National Institute of Statistics (INE) for 2017, 4,424,409 of a total population of 46,528,966 were born abroad\(^{(57)}\). Monge-Maillo et al. describe in their work that foreigners from sub-Saharan Africa are mainly from Equatorial Guinea, Nigeria, and Senegal, the latter two being countries where *S. haematobium* is endemic\(^{(58)}\). According to the latest INE data for the first half of 2016, a total of 633 people born in Nigeria and 1,973 in Senegal migrated to Spain\(^{(59)}\). Neither should we forget international travelers, such as military personnel, tourists and students, who increasingly return from endemic areas where they may have contracted the disease. As examples are the cases of 8 German travelers affected by acute schistosomiasis after exposure in the waters of Lake Tanganyika\(^{(35)}\); or a group of students who contracted the disease, during an exchange program between students from Scotland and Malawi, whereby 13 of them were infected by schistosoma\(^{(60)}\), or cases related to military personnel as, for instance, a group of Belgian soldiers who returned from the Democratic Republic of the Congo, 49 of which were diagnosed with schistosomiasis\(^{(61)}\).

The main limitations that we have found in our study have been, on the one hand, that searching so widely surely downplays the real number of documented cases in each EU country; and, typically, the number of published cases tends to be significantly lower than the number of real cases. On the other hand, there’s a scarcity of published works on intermediary host species in Spain, since this subject is very specific and highly specialized.

The main conclusions of our study are that, although there’s a low risk of contracting the disease in Spain, current increasing migratory population flows, combined with the fact that
there are areas within our country where intermediate hosts are present, prevents us from ruling out the possibility of facing an indigenous outbreak scenario in the future, either by *S. haematobium* or, perhaps, by some hybrid species, similar to what occurred in Corsica. All of which coincides with conclusions by other authors mentioned in this paper\(^{(53,47,26)}\), and with those by the ECDC’s update on a risk assessment related to the European outbreak in Corsica, carried out in July 2015, alerting of a potential risk for other areas in Southern Europe\(^{(10)}\) such as Spain. Therefore, Public Health Authorities should be alert to such a risk, especially if a type of hybrid schistosoma were to be introduced, taking into account the difficulty of controlling the disease when there are animal reservoirs.

It is essential to emphasize preventive measures such as: identifying and training risk groups (military personnel, aid workers) and adequate information for international travelers (tourists). We should remember that in the case of migrants, or people who have traveled to endemic areas, hematuria may indicate that we are facing an infection by this parasite, even though it is a usually very unspecific symptom. It would also be necessary to increase surveillance and encourage studies on the presence of possible intermediate hosts in our country. We want to conclude by quoting Jean-Marie Doby, who in 1966 already predicted that there was a risk of urinary schistosomiasis cases in Corsica. Doby was almost half a century ahead of events and made his prediction based on the abundance of potential intermediate hosts *B. truncatus* that he observed on the island, and on the increase in labor population coming from Africa\(^{(62)}\).

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