UNIVERSITAT DE VALÈNCIA

FACULTAT DE FARMÀCIA

TESIS DOCTORAL

DEPARTAMENT DE PARASITOLOGÍA I TECNOLOGIA FARMACÈUTICA

FACULTAT DE FARMÀCIA, UNIVERSITAT DE VALÈNCIA

Programa de Doctorado en Parasitología Humana y Animal

HUMAN SCHISTOSOMIASIS: AN EPIDEMIOLOGICAL AND PUBLIC HEALTH APPROACH

Por:

RAQUEL SÁNCHEZ MARQUÉS

Directora:

Prof. Dra. María Dolores Bargues Castelló

Catedrática de Parasitología

Departament de Parasitología y Tecnologia Farmacèutica

Valencia, marzo de 2023

DEPARTAMENT DE PARASITOLOGÍA I TECNOLOGIA FARMACÈUTICA
FACULTAT DE FARMÀCIA, UNIVERSITAT DE VALÈNCIA

La abajo firmante Prof. Dra. MARÍA DOLORES BARGUES CASTELLÓ, Catedrática del Área de Parasitología del Departament de Parasitología i Tecnología Farmacèutica de la Facultat de Farmàcia de la Universitat de València, por la presente:

CERTIFICA:

que RAQUEL SÁNCHEZ MARQUÉS ha realizado íntegramente el trabajo titulado "HUMAN SCHISTOSOMIASIS: AN EPIDEMIOLOGICAL AND PUBLIC HEALTH APPROACH" en el Departament de Parasitologia i Tecnología Farmacèutica de la Facultat de Farmàcia de la Universitat de València con el fin de optar al Grado de Doctora por la Universitat de València.

Y para que así conste, a los efectos oportunos, firma el presente informe en Valencia, a 22 de febrero de 2023.

MARIA DOLORES| BARGUES| CASTELLO

Firmado digitalmente por MARIA DOLORES| BARGUES|CASTELLO
Fecha: 2023.02.22 15:01:20 +01'00'

Fdo: Prof. Dra. María Dolores Bargues Castelló

Of all the forms of inequality, injustice in health care is the most shocking and inhumane.

Rev. Dr. Martin Luther King, Jr. (March 25, 1966).

Acknowledgments

Nada es más honorable que un corazón agradecido.

Lucius Annaeus Seneca (4 BC – 65 AD).

Esta tesis no hubiese sido posible sin el apoyo de numerosas personas y su contribución directa o indirecta. Por eso, me siento afortunada de poder agradecérselo públicamente y que quede aquí por escrito.

Primero de todo, quiero agradecer a la Prof. Dra. MARÍA DOLORES BARGUES CASTELLÓ, Catedrática de Parasitología del Departamento de Parasitología y Tecnología Farmacéutica de la Universitat de València, por aceptar ser mi directora de tesis y confiar en mí. Me abriste las puertas del laboratorio, me acogiste en el equipo y me has guiado desde que empecé, y lo sigues haciendo. Gracias por estar siempre disponible, por impulsarme en mi carrera y por ayudarme a hacer mi estancia doctoral en un país endémico y hacer los proyectos que me gustan. En definitiva, gracias por todo tu apoyo.

Al Prof. Dr. Dr. Honoris Causa SANTIAGO MAS COMA, Catedrático de Parasitología del Departamento de Parasitología y Tecnología Farmacéutica de la Universitat de València, por ser una fuente de inspiración. Gracias por la oportunidad de formar parte de un gran equipo, por los consejos que me ayudan a mejorar y por contar conmigo para la expedición a Bolivia, la cual será sin duda, una gran experiencia.

A la Dra. MARÍA ADELA VALERO ALEXANDER, Catedrática de Parasitología del Departamento de Parasitología y Tecnología Farmacéutica de la Universitat de València por su infinita positividad. Durante la última parte de mi doctorado he tenido la oportunidad de trabajar contigo, gracias por confiar en mi en este proyecto. La semana de intenso trabajo en A Coruña fue más divertida y agradable gracias a ti.

Al Dr. ISRAEL MOLINA, por hacer posible mi estancia en Angola y apoyar los proyectos. Al Dr. FERNANDO SALVADOR y la Dra. CRISTINA BOCANEGRA, por haberme aceptado en el equipo Schisto. Confiasteis en mi desde el principio y desde la distancia, me habéis acompañado en todo el proceso. Me siento muy afortunada de poder compartir con vosotros ideas, proyectos y la fascinación por esta enfermedad. Gràcies Joan i Sandra per la vostra acollida al quintal i per facilitar els projectes. Gràcies per tot el que vau fer per mi, especialment com a metges, que ho vaig necessitar més d'un cop. Però sense cap dubte, el millor ha sigut la vostra amistat, perquè a més de treballar, sempre vam tenir temps per paelles, excursions i xarrades interminables.

Obrigada a todos os meus colegas do HOSPITAL NOSSA SENHORA DA PAZ em Cubal, especialmente Arlette, Zeferino, Pesela, Pedro, Eva, Moises, Armindo e as irmãs que tornaram o dia-a-dia no hospital inesquecível. Todos eles me ajudaram a adaptar-me e a desfrutar do meu trabalho. Todos os dias com um grande sorriso, não importa o que aconteceu dentro ou fora do hospital. Mesmo tivéssemos muito trabalho no laboratório, havia sempre espaço para o riso. Ensinaram-me muitas coisas que nada têm a ver com o conhecimento e estarei sempre grata por me terem acolhida na sua família.

A mis compañeros de laboratorio (el Dr. PATRICIO ARTIGAS, el Dr. ALBERTO MARTÍNEZ, el Dr. PABLO CUERVO y la Dra. MARÍA CECILIA FANTOZZI) con los que tantas horas he compartido, tanto dentro del laboratorio como en las expediciones. Gracias por vuestros consejos, por el compañerismo, por todas las charlas y, por supuesto, por los cafés.

A mi compañera de doctorado, ALEJANDRA DE ELÍAS. Que digo "compañera de doctorado" por el contexto, pero que es más amiga que compañera. A ti, gracias simplemente por estar. Empezamos este camino a la vez y lo hemos recorrido juntas. Contigo las partes duras se han hecho más llevaderas y las partes buenas, mucho más buenas. Después de nuestros viajes y escapadas, cervezas, conversaciones interminables, fiestas, inmersiones, risas dentro y fuera del laboratorio, habitaciones aguantando mi desorden, queserías, y, en resumen, todo lo que hemos vivido, puedo decir que eres lo mejor que he sacado de esta etapa. Siempre podrás usar mi flor.

Al área de Parasitología del Departamento de Parasitología y Tecnología Farmacéutica de la Universitat de València con los que he compartido no sólo el espacio sino muchos buenos momentos tanto en el laboratorio como en congresos. Incluyo a todas las secretarias que siempre han estado dispuestas a ayudarme con las gestiones y a Marina que siempre aparece con una sonrisa. En especial, a la Dra. ALBA CORTÉS y la Dra. MARÍA ÁLVAREZ que se han convertido en amigas entre cafés, comidas y charlas.

Als meus pares pel seu suport incondicional. Mama, aquesta tesis és el resultat d'un llarg camí que vaig començar amb les meves primeres petjades a l'Àfrica i que va ser possible gràcies al teu suport i al teu esforç per ajudar-me a complir els meus somnis. Tu sempre vas entendre la meva passió i em vas animar a seguir el meu propi camí encara que aquest no fos el que s'esperava de mi. La decisió que l'esquistosomiasi fos la malaltia estudiada a la meva tesi la vaig prendre amb tu, i tant de bo haguessis pogut compartir amb mi tot el que he viscut des de llavors. Tant de bo em poguessis veure defensar aquesta tesi. Espero que estiguis orgullosa de mi, del que he fet i del que encara em queda per fer. Papa, gràcies per estar sempre al meu costat i donar-me suport encara que no sempre ho hagis entès. Han estat gairebé quatre anys durs i intensos, però tu m'has acompanyat en tot i m'has animat a tirar endavant i treure el millor de mi. Gràcies perquè sé que sempre puc comptar amb tu i gràcies per ajudar-me a volar, encara que això signifiqui que estigui lluny de tu. Gràcies a la resta de la meva família per les seves paraules de suport, i especialment a Gala, pel seu amor infinit.

A mis Guarpas (Ana, Belén, Carmen, Claudia, Elena, Marina, Natalia, Paula, Raquel Rosa y Sara) por haber sido muralla en los momentos complicados y trampolín para los buenos. Hemos crecido juntas, y me siento tremendamente afortunada de que podamos ver como todas vamos cumpliendo nuestros sueños y metas. Por eso, me encanta poder compartir esto con vosotras. Sin duda, habéis contribuido a que sea capaz de hacer esto, sobre todo al principio, porque la verdadera amistad siempre está en los peores momentos. Por otro lado, no puedo olvidarme de Gemma. Desde hace tres años, eres prácticamente la única persona que me conoce y me entiende de verdad. Vemos el mundo desde los mismos ojos, por eso, de entre los millones de cosas que hemos hecho juntas, la que me hace más feliz es la de poder cambiar contigo "mi Gambia" por "nuestra Gambia". Gracias por todo, porque si tengo que mencionar cada cosa, no me cabe. No importa donde estemos cada una, tú eres casa para mí.

A mis chicas de Angola (Aina, Cuca, María, Sheila y Silvia) que estuvieron presentes en una parte muy especial de mi doctorado, la estancia en Angola. Sé perfectamente la suerte que tuve con vosotras. Me acompañasteis a buscar caracoles, a hacer encuestas y al matadero. Juntas, cada una desde su campo, hicimos un gran equipo, para la UEN y la promoción de la salud entre otras cosas. Gracias por apoyarme en todos mis proyectos y compartir mi motivación. Gracias a todas porque cada una de vosotras sois inspiración para mí, y me enseñasteis cosas que no se aprenden en una universidad. Pero, sobre todo, gracias por todo lo que vivimos allí, que llevaré siempre tatuado en mi piel. Espero que siempre podamos ficar a vontade, juntas. I a Lubis, que avui ja no està, però que estarà sempre a la nostra memòria, perquè a més de robar menjar, sabates i globus, també ens va robar el cor a totes.

A mi gente de Valencia (Alba, Alejandro, Koky, Manu y Migue), que son mi zona de confort. Han sido mi espacio seguro para desahogarme, despejarme y reírme durante todo el tiempo de mi doctorado. Gracias por adoptarme en vuestra familia, secarme las lágrimas con patatas, venir a conocer mi segunda casa y llevarme a la vuestra, celebrarlo todo conmigo y, en resumen, gracias por formar parte de mi vida. Que quede claro que me habéis ayudado a tener la energía necesaria para mi día a día de trabajo. Y gracias a mis compañeros de piso por aguantar que esta tesis se haya escrito en nuestro salón.

Esta tesis ha sido posible gracias a diferentes proyectos que han permitido financiar tanto el trabajo de laboratorio como el trabajo de campo. Por eso, quiero agradecer a las siguientes fuentes de financiación:

- Red de Investigación de Centros de Enfermedades Tropicales—RICET (RD16/0027/0023 y RD16/0027/0013) del Plan Nacional de I+D+I, ISCIII-Subdirección General de Redes y Centros de Investigación Cooperativa RETICS, Ministerio de Salud, Madrid
- CIBER de Enfermedades Infecciosas (CB21/13/00056), ISCIII, Ministerio de Ciencia y Educación, Madrid, Spain
- PROMETEO, Programa de Ayudas para Grupos de Investigación de Excelencia (2021/004), Generalitat Valenciana, Valencia, Spain

- Proyecto de Investigación en Salud PI-0001-2019 (Cofundado FEDER, Una forma de hacer Europa/Invertir en tu futuro), Consejería de Salud y Familias de la Junta de Andalucía, Sevilla, Spain
- CIBER de Enfermedades Infecciosas (CB21/13/00029), ISCIII, Ministerio de Ciencia y Educación, Madrid, Spain

Abstract

Schistosomiasis is a parasitic disease caused by species of genus *Schistosoma*, with millions of people infected and thousands of deaths each year. According to the World Health Organization, it is one of the Neglected Tropical Diseases, which are characterised by being endemic to tropical and subtropical areas and linked to poverty. The main objective of this thesis is to carry out an epidemiological study about Schistosomiasis with a public health approach. To this end, a bibliometric study with 1,988 scientific articles was carried out analysing publications on human Schistosomiasis during the acute phase of the COVID-19 pandemic to determine the impact it had on the research. It was concluded that during the years when the pandemic hit hardest, the scientific production increased compared to the two previous years, may be because the confinement made field work impossible, favouring writing tasks. In addition, a high degree of collaboration between institutions from endemic and non-endemic countries was observed. We also wanted to know the current situation of Schistosomiasis among pre-school children in an endemic area of Angola, so a study of prevalence and associated morbidity was carried out among 245 children under 5 years of age. Infection was determined based on the detection of eggs in urine by filtration and subsequent microscopic analysis. The prevalence of urogenital Schistosomiasis in this age group was 30.2% and 54.5% of those infected had urinary tract damage. It should be noted that the thickening of the bladder wall was found in 100% of children with lesions. In addition, 91% of all participants were anaemic and 50% suffered from some form of malnutrition. Another study was carried out to find out the knowledge, attitudes and practices regarding urogenital Schistosomiasis and their socioeconomic situation with 250 participants. It turned out that 94% of the people surveyed were aware of the existence of the disease, although only a quarter knew the mode of infection. Overall, the level of information about Schistosomiasis was low, with only 0.4% scoring high in the knowledge section. However, 79% showed a high attitude towards improving their health situation. A large proportion of the participants reported risky practices, bathing in the river being the most common. Regarding the socioeconomic situation, almost 70% live in overcrowded conditions, with metal sheets and mud being the most common materials used to build their houses. Finally, an analysis was conducted to determine if the different aspects of the caregivers analysed had any influence on the Schistosomiasis infection and morbidity of the pre-school children in their care, which resulted in a low level of knowledge about the disease and not knowing how to prevent it were the main risk factors for the infection and morbidity in children, respectively.

Key words: Schistosomiasis research; *Schistosoma haematobium*; Urogenital Schistosomiasis; Urine examination; Pre-school children; Prevalence; Morbidity; KAP survey; Angola.

Resumen

La Esquistosomiasis es una enfermedad parasitaria provocada por especies del género *Schistosoma*, con millones de personas infectadas y miles de muertes cada año. De acuerdo con la Organización Mundial de la Salud, forma parte de las Enfermedades Tropicales Desatendidas, las cuales se caracterizan por ser endémicas de zonas tropicales y subtropicales y por estar ligadas a la pobreza. El objetivo principal de esta tesis es realizar un estudio epidemiológico sobre esquistosomiasis con un enfoque de salud pública. Con este fin, se realizó un estudio bibliométrico con 1.988 artículos científicos analizando las publicaciones sobre Esquistosomiasis humana durante la fase aguda de la pandemia por COVID-19 para determinar el impacto que tuvo en su investigación. Se concluyó que durante los años en los que la pandemia golpeó más duro, la producción científica aumentó respecto a los dos años anteriores, quizás porque el confinamiento imposibilitó el trabajo de campo, favoreciendo las tareas de escritura. Además, se observó una fuerte colaboración entre instituciones de países endémicos y no endémicos. También se quiso conocer la situación epidemiológica actual de la Esquistosomiasis entre los niños de edad preescolar en una zona endémica de Angola, para lo que se realizó un estudio de prevalencia y su morbilidad asociada entre 245 niños y niñas menores de 5 años. La infección de los niños se determinó en base a la detección de huevos en orina mediante su filtración y posterior análisis microscópico. La prevalencia de Esquistosomiasis urogenital en este grupo de edad resultó ser de un 30,2% y un 54,5% de los infectados tenían daños en el tracto urinario. Cabe destacar que el engrosamiento de la pared de la vejiga fue encontrado en el 100% de los niños con lesiones. Además, de todos los participantes, un 91% tenían anemia y un 50% sufrían de algún tipo de desnutrición. Se realizó un estudio para saber los conocimientos, actitudes y prácticas respecto a la Esquistosomiasis urogenital y su situación socio-económica con 250 participantes. Resultó que el 94% de las personas encuestadas estaban al tanto de la existencia de la enfermedad, aunque sólo un cuarto conocía el modo de infección. En general, el nivel de información sobre la Esquistosomiasis era bajo, ya que solo un 0,4% obtuvo una puntuación alta en la sección del conocimiento. Sin embargo, un 79% demostró tener una gran actitud para mejorar su situación sanitaria. Una gran parte de los participantes declaró llevar a cabo prácticas de riesgo, siendo la de bañarse en el río la más común. Respecto a la situación socio-económica, casi un 70% vive en condiciones de hacinamiento, siendo las chapas metálicas y el barro los materiales más comunes para la construcción de sus casas. Por último, se hizo un análisis para determinar si los diferentes aspectos de los cuidadores analizados tenían alguna influencia en la infección y morbilidad de los niños de edad preescolar a su cargo, lo que resultó en que los principales factores de riesgo para la infección y morbilidad de los niños eran un nivel bajo de conocimiento sobre la enfermedad y no saber cómo prevenirla, respectivamente.

Palabras clave: Investigación de esquistosomiasis; *Schistosoma haematobium*; Esquistosomiasis urogenital; Examen de orina; Niños preescolares; Prevalencia; Morbilidad; Encuesta KAP; Angola.

Resum

L'Esquistosomiasi és una malaltia parasitària provocada per espècies del gènere *Schistosoma*, amb milions de persones infectades i milers de morts cada any. D'acord amb l'Organització Mundial de la Salut, forma part de les Malalties Tropicals Desateses, que es caracteritzen per ser endèmiques de zones tropicals i subtropicals i per estar lligades a la pobresa. L'objectiu principal d'aquesta tesi és fer un estudi epidemiològic sobre esquistosomiasi amb un enfocament de salut pública. A aquest efecte, es va realitzar un estudi bibliomètric amb 1.988 articles científics analitzant les publicacions sobre Esquistosomiasi humana durant la fase aguda de la pandèmia per COVID-19 per determinar l'impacte que va tenir en la seva investigació. Es va concloure que durant els anys en què la pandèmia va copejar més dur, la producció científica va augmentar respecte als dos anys anteriors, potser perquè el confinament va impossibilitar el treball de camp i va afavorir les tasques d'escriptura. A més, es va observar una forta col·laboració entre institucions de països endèmics i no endèmics. També es va voler conèixer la situació epidemiològica actual de l'Esquistosomiasi entre els nens d'edat preescolar en una zona endèmica d'Angola, per a la qual cosa es va fer un estudi de prevalença i la seva morbiditat associada entre 245 nens i nenes menors de 5 anys. La infecció dels nens es va determinar sobre la base de la detecció d'ous en orina mitjançant la seva filtració i posterior anàlisi microscòpica. La prevalença d'esquistosomiasi urogenital en aquest grup d'edat va ser d'un 30,2% i un 54,5% dels infectats tenien danys al tracte urinari. Cal destacar que l'engruiximent de la paret de la bufeta va ser trobat al 100% dels nens amb lesions. A més, de tots els participants, un 91% tenien anèmia i un 50% patien algun tipus de desnutrició. Es va realitzar un estudi per saber els coneixements, les actituds i les pràctiques respecte a l'Esquistosomiasi urogenital i la seva situació socioeconòmica amb 250 participants. Va resultar que el 94% de les persones enquestades estaven al corrent de l'existència de la malaltia, encara que només un quart coneixia la manera d'infecció. En general, el nivell d'informació sobre l'esquistosomiasi era baix, ja que només un 0,4% va obtenir una puntuació alta a la secció del coneixement. Tot i això, un 79% va demostrar tenir una gran actitud per millorar la seva situació sanitària. Una gran part dels participants va declarar dur a terme pràctiques de risc, sent la de banyar-se al riu la més comuna. Pel que fa a la situació socioeconòmica, gairebé un 70% viu en condicions d'amuntegament, sent les xapes metàl·liques i el fang els materials més comuns per a la construcció de casa seva. Finalment, es va fer una anàlisi per determinar si els diferents aspectes dels cuidadors analitzats tenien alguna influència en la infecció i morbiditat dels nens d'edat preescolar al seu càrrec, cosa que va resultar que els principals factors de risc per a la infecció i morbiditat dels nens eren un nivell baix de coneixement sobre la malaltia i no saber com prevenir-la, respectivament.

Paraules clau: Investigació d'esquistosomiasi; *Schistosoma haematobium*; Esquistosomiasi urogenital; Examen d'orina; Nens preescolars; Prevalença; Morbiditat; Enquesta KAP; Angola.

Contents

List of figures

List of tables

Abbreviations and acronyms

DALY	Disability-adjusted life-year
FGS	Female Genital Schistosomiasis
FWCI	Field-weighted citation impact
GDP	Gross domestic product
GERD	Gross domestic expenditure on R&D
HNSP	Hospital Nossa Senhora da Paz
JCR	Journal Citation Reports
KAP	Knowledge, attitude and practices
MDA	Mass drug administration
MICS	Multiple indicator cluster surveys
MPM	Multidimensional poverty measure
MUAC	Mid-upper arm circumference
NTD	Neglected tropical diseases
PSAC	Preschool-age children
PZQ	Praziquantel
SAC	School-age children
SCORE	Schistosomiasis Consortium for Operational Research and Evaluation
SDG	Sustainable development goals
STI	Sexually transmitted infections
UNICEF	United Nations Children's Fund
UT	Urinary tract
WASH	Water, sanitation and hygiene
WHO	World Health Organization

Chapter 1
Introduction

1.1. Neglected tropical diseases

The neglected tropical diseases (NTD) refer to a group of diseases mainly present in the tropical and subtropical regions of the planet. In the early 2000s, this group comprised a total of 17 bacterial, parasitic, viral, and fungal diseases: blinding trachoma, Buruli ulcer, Chagas disease, dengue and chikungunya, dracunculiasis (Guinea-worm disease), echinococcosis, foodborne trematodiases (clonorchiasis, fascioliasis, paragonimiasis and opisthorchiasis), human African trypanosomiasis (sleeping sickness), leishmaniasis cutaneous and visceral, leprosy (Hansen's disease), lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), rabies, Schistosomiasis (bilharziasis), soil-transmitted helminthiasis (ascariasis, hookworm disease, strongyloidiasis and trichuriasis), taeniasis/cysticercosis, and yaws (WHO, 2010). Recently, the World Health Organization (WHO) increased the number of NTDs to 20, including snakebite envenoming, scabies and other ectoparasites, and deep mycoses (mycetoma and chromoblastomycosis) (WHO, 2020).

Figure 1.1. Global distribution of the NTDs burden by DALYs. From: WHO (2020).

NTDs are present on all five continents, but they particularly affect the regions where the most impoverished population lives. Figure 1.1 shows the geographical distribution of the NTDs worldwide in terms of disability-adjusted life-year (DALY), which is a time-based epidemiological indicator that encompasses mortality, morbidity, impairment and disability and represents the loss of a single life-year lived in optimal health. Since NTDs cause more disability due to chronic infections than death, DALY has become the standard metric to quantify the burden of these diseases (Vanderelst and Speybroeck, 2010; Murray et al., 2012; Fisher and Fukuda-Parr, 2019).

NTDs can lead to death, but these diseases also affect physical and cognitive development, and cause social and economic consequences for the weakest communities, creating a cycle of poverty. They thrive in communities with poor hygiene and sanitation conditions along with limited access to clean water and healthcare, cohabiting with animals or vectors, and often living in remote rural communities. Figure 1.2 illustrates the geographical distribution of the NTDs by gross domestic product (GDP) per capita, clearly showing how the lowest GDP overlaps with the highest DALY regions in Figure 1.1.

Figure 1.2. Global distribution of the NTDs burden by GDP per capita. From: WHO (2020).

With nearly 63 million DALYs, NTDs become the second group of diseases with highest burden, only behind HIV/AIDS (Paul et al., 2021; Lin et al., 2022). Seven of these neglected diseases are the most prevalent, affecting more than 1.4 billion people worldwide: three soil-transmitted helminthiases (ascariasis, hookworm, and trichuriasis), lymphatic filariasis, onchocerciasis, trachoma, and Schistosomiasis. In addition, of the people affected by some of these seven diseases, an estimated 500 million are children.

Defeating NTDs is part of the 2030 Agenda for Sustainable Development, which was adopted by all United Nations Member States in 2015 with the aim of working together for reaching 17 sustainable development goals (SDGs) and 169 targets. More specifically, the eradication of NTDs is one of the targets of SDG 3 (good health and well-being). Since the vast majority of countries organize their programs around the SDGs, including the destination of funding, the fact that the fight against these diseases is explicitly included in the 2030 Agenda is an important help to improve their control. In addition, NTDs activities are usually multidisciplinary tasks that contribute indirectly to many other SDGs:

- SDG 2 (zero hunger): fascioliasis, food security.
- SDG 4 (quality education): disability caused by NTDs causes learning difficulties.
- SDG 5 (gender equality): most NTDs can create stigma in society, which is always more aggravated in women, especially if it has to do with genitalia, such as female genital Schistosomiasis (FGS).

- SDG 6 (clean water and sanitation): Schistosomiasis, waterborne disease.
- SDG 8 (decent work and economic growth): any NTD creates disability and hinders the ability to work.
- SDG 10 (reduced inequalities): NTDs are strongly associated with population inequalities and have a detrimental impact on health and productivity.
- SDG 13 (climate action): climate change can affect the transmission dynamics and geographic spread vector-borne NTDs.
- SDG 15 (life on land): rabies, contact with animals.

This is intended to be just a sample of the multiple dimensions of NTDs, which could surely be eradicated if SDG 1 (no poverty) were achieved. In fact, poverty is the dominant determinant for NTDs (Fazal and Hotez, 2020).

1.2. Schistosomiasis

Schistosomiasis, also known as bilharziasis, was first described in 1851 in Egypt by a German physician (McManus et al., 2018) and is classified by the WHO as a parasitic NTD. It is a disease closely linked with poverty, common in tropical and subtropical areas without access to clean water and proper sanitation, poor hygiene and lack of adequate healthcare systems. An estimated 780 million people are at risk of being infected with Schistosomiasis. Globally, this disease affects approximately 250 million people (including 24 million pre-school children and 65 million school-age children), more than 200 million of whom live in sub-Saharan Africa. This parasitosis causes 200,000 deaths a year so, although it does not have a high mortality rate, the main problem with Schistosomiasis is its high morbidity. After malaria, Schistosomiasis is the second most prevalent disease in African children (Skopp, 2014). In 2019, Schistosomiasis was found to be the cause of 1.9 million DALYs, which can result in loss of family income due to inability to work for infected family members, learning difficulties in children, or social exclusion of women diagnosed with FGS (McManus et al., 2018; IHME, 2019). Despite notable efforts to control Schistosomiasis, the disease remains a major public health problem in sub-Saharan Africa.

Schistosomiasis is caused by a blood-fluke of the genus *Schistosoma*. There are two major forms of Schistosomiasis depending on the specie: intestinal (caused by *S. mansoni*, *S. japonicum*, *S. guineensi*s, *S. intercalatum* and *S. mekongi*) and urogenital (caused by *S. haematobium*). Of these six species that affect humans, *S. mansoni*, *S. haematobium*, and *S. japonicum* are of major public health importance as it accounts for the majority of Schistosomiasis infections. Schistosomes require a species-specific intermediate host to continue their cycle to the infective form. *S. mansoni* and *S. haematobium* require the freshwater snails *Biomphalaria spp.* and *Bulinus spp.* respectively, while *S. japonicum* uses the amphibian freshwater snail *Oncomelania spp.* as vector. Since the parasite needs the snail, the geographical distribution of the vectors defines the endemicity of the disease. Therefore, the distribution of each species varies between the tropical and subtropical regions of the world, although they overlap in several countries, especially in Africa. Because the vectors need certain environmental conditions, climate change creates favourable conditions for disease transmission and threatens to increase the endemic areas of the disease (Mas-Coma et al., 2009). It should be noted that the mere presence of the vector is a risk for the introduction of Schistosomiasis, especially in the era of globalization in which we live. In fact, France entered the list of countries with Schistosomiasis when an outbreak of urogenital Schistosomiasis was detected in 2013, representing the first European country to report autochthonous transmission (de Laval, et al., 2014; Boissier et al., 2016). A suspicious of Schistosomiasis infection was also recently reported in southern Spain (Salas-Coronas et al., 2021). The emergence of Schistosomiasis in southern Europe highlights the risk that climate change and other factors such as globalization and migration pose to the widening of the geographical distribution of the vectors enabling the spread of this disease in non-endemic areas (Chala and Hamde, 2021; Martínez-Ortí et al., 2022).

The fact that Schistosomiasis is a vector-borne disease present in freshwater means that people become infected by coming into contact with these waters. It should be borne in mind that most of the endemic areas belong to low- and middle-income countries, with a high rate of poverty and a low percentage of people with access to safe drinking water. That Schistosomiasis is a disease closely linked to poverty is evident when looking at the 2013 outbreak in Corsica where, by prohibiting bathing in the waters that were identified as a source of infection, its transmission has been almost halted. However, a measure as simple as this cannot be implemented in the countries most affected by the disease, since people at risk need access to freshwater sources to wash their clothes, bathe or even fish and irrigate crops.

1.3. Urogenital Schistosomiasis

S. haematobium is the main species of genus *Schistosoma* causing urogenital Schistosomiasis. It has been described in 54 countries, notably in sub-Saharan Africa, although it is also found in some countries in the Middle East and southern Europe and appears to be the most prevalent form of Schistosomiasis affecting humans worldwide (McManus et al., 2018; WHO, 2022a). The most common symptom of urogenital Schistosomiasis is haematuria, which is generalized in some endemic regions due to its high burden. It can be diagnosed by detecting the presence of eggs in the urine through microscopic visualization and its treatment consists of a single dose (40 mg/kg) of praziquantel (PZQ), which is currently the only available antischistosomal drug (Cioli et al., 2014). PZQ is an anthelmintic drug, which is classified as a Class II drug (low solubility, high permeability) according to the Biopharmaceutics Classification System (Lindenberg et al., 2004). Since PZQ does not prevent schistosome reinfections, other activities such as health promotion, vector control, mass drug administration (MDA) campaigns, and water, sanitation and hygiene (WASH) measures are required for an effective control of the disease (WHO, 2020, Oluwole et al., 2022)).

1.3.1. *Schistosoma haematobium*

S. haematobium lives in the vessels around the urogenital system. It has a complex life cycle that includes the freshwater snail of the genus *Bulinus spp.* as intermediate host and humans (and other mammals) as definitive host. Figure 1.3 graphically represents the stages of *S. haematobium* and indicates where each stage takes place.

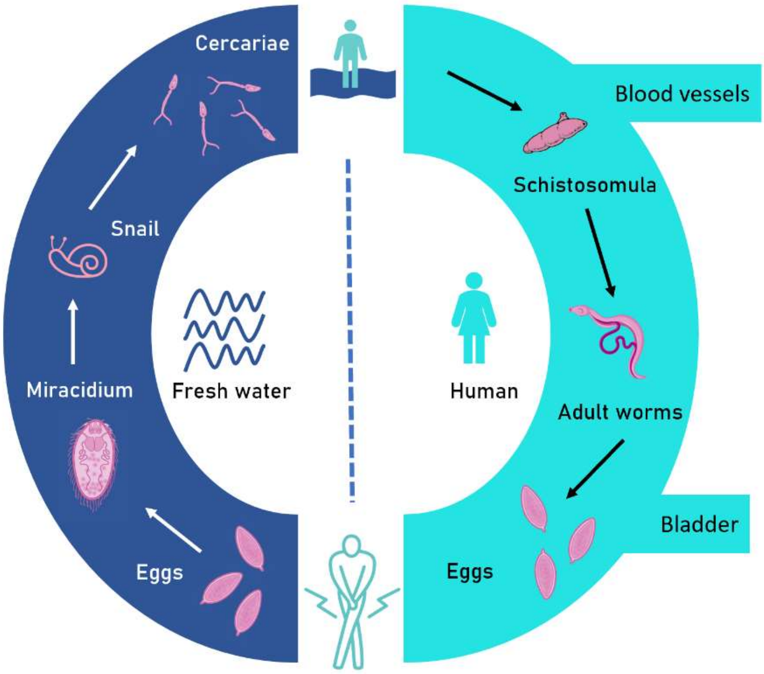


Figure 1.3. Life cycle of the *S. haematobium* parasite (made with Biorender).

Adults schistosomes are white or greyish worms of 7–20 mm in length with a flat body that features two terminal suckers, a complex tegument, a blind digestive tract, and reproductive organs (Figure 1.4(a)). Schistosomes have separate sexes (female and male) and live within the perivesical venous plexus during an average of 3–10 years, although they can live up to 40 years (McManus et al., 2018). Adult males have a gynaecophoric channel, in which it holds the female. The adult female produces between hundreds and thousands of eggs a day (Gryseels et al., 2006). They live almost their entire lives in copulation. The ova contain a ciliated miracidium larva (Figure 1.4(b)), which secretes proteolytic enzymes that help the eggs to migrate into the lumen of the bladder and will be excreted through the urine. If the eggs are in contact with water with the right light and salinity conditions, they will hatch, releasing the ciliated miracidium that is capable of swimming to find its intermediate host. The freshwater snails *Bulinus* spp. (Figure 1.4(c)) are their natural intermediate host and act as a vector. The miracidia penetrate the snail and transform into multicellular sporocysts to undergo asexual replication. The resulting sporocysts produce cercarial larvaes with embryonic suckers (called furcocercariae due to the biforked tail) (Figure 1.4(d)). A snail infected by one miracidium can produce thousands of cercariae every day for months (Colley et al., 2014). The cercariae penetrate the skin of the snail to emerge and adopt their free-swimming form, which is the infective schistosomal form and can spin around in the water for up to 72 hours before finding an appropriate definitive host (a human). The larvae penetrate the skin of the host and migrate to the perivesical destination through the portal veins where they lose the tail, adopting the form called schistosomula, then mature and develop into an adult form and restart their cycle (Gryseels et al., 2006).

a) Adult *schistosoma* worms in *copula*

b) *S. haematobium* egg

c) *Bulinus truncatus*

d) *S. haematobium* furcocercariae

Figure 1.4. Different stages of *S. haematobium* and its vector.

1.3.2. Pathogenesis and morbidity

There is a broad consensus that the pathogenicity of Schistosomiasis is caused by the eggs and not by the adult worms. The eggs that are not excreted remain in the bladder or urogenital system, inducing an immune response that causes inflammation, leading to the clinical manifestations of Schistosomiasis (McManus et al., 2018).

When infective cercariae penetrate the skin, migration through the blood is not always successful and consequently, some die on the skin. The immune response to these larvae can lead to cercarial dermatitis due to a hypersensitive reaction. Nonetheless, this is common only in those people exposed to the parasite for the first time.

Once the cercariae penetrate the skin and migrate to their destination and carry out their cycle successfully, the disease can be divided in three overlapping stages, which may overlap, depending on the progression of the infection (McManus et al., 2018): acute, established active and late chronic infection. The acute form, also known as Katayama fever or Katayama syndrome, starts suddenly with fever, fatigue, myalgia, headache, eosinophilia, and malaise. Abdominal pain may appear later due to the migration of the mature worms. This stage can last between 2 and 10 weeks. The symptoms are caused by systemic reactions and formation of immune complexes due to the deposition of eggs. It occurs between 2 weeks and 3 months after the first exposure, so it is common to find it in travellers or immigrants. Katayama fever is rarely seen in endemic areas, suggesting that it is due to desensitization in utero (Colley et al., 2014).

The second stage is the established active infection which is characterized by excretion of live eggs in urine. Intensity can be assessed by egg count (egg/10 mL) (WHO, 2011). The characteristic symptoms of urogenital Schistosomiasis begin at this stage: haematuria, pelvic pain, abnormal vaginal discharge, itch and burning with urination. If left untreated, the disease can progress to the chronic infection stage. Severe urogenital Schistosomiasis is due to poor immunoregulation of antischistosome-egg responses, which can lead to chronic fibrosis of the urinary tract and cause different types of lesions in the bladder, ureters and pelvis (Cimini et al., 2021). It is known and studied for many years that people with chronic *S. haematobium infection* can develop bladder cancer (squamous cell carcinoma of the bladder), which occurs at an earlier age than transitional cell carcinomas of the bladder in endemic regions (Colley et al., 2014; Ishida, 2018).

In women, a chronic infection can cause FGS. The eggs migrate to the genital tract causing damage in the ovaries, cervix, vagina and fallopian tubes. Between 33% and 77% of females infected with *S. haematobium* are thought to suffer from FGS, with yellow genital spots of schistosome eggs and eosinophilic inflammatory in host tissue (Christinet et al., 2016; Ekpo et al., 2017). The condition has a wide range of affections throughout the lower and upper genital tract with symptoms ranging from vaginal discharge, postcoital bleeding, genital itching, burning sensation or abdominal pain to ectopic pregnancies, abortions, or cervical cancer in the most advanced cases. In addition, it may lead to infertility and higher risk of human immunodeficiency virus. Ectopic pregnancies can potentially lead to death and have been related to FGS due to Schistosomiasis granulomata and/or salpingitis and tubal submucosa alteration (Christinet et al., 2016). Women who suffer from this type of parasitism are often subject to social stigmatization due to matching of symptoms of FGS and sexually transmitted infections (STIs) and the social impact of infertility. The WHO and the Joint United Nations Programme on HIV/AIDS have classified it as the most neglected gynaecological condition in Africa (WHO, 2015).

1.3.3. Control activities

For non-parasitic diseases, the path to eradication lies through the development of a vaccine. Unfortunately, no parasitosis currently has an effective vaccine and therefore, the road towards eradication of diseases such as Schistosomiasis focuses on interrupting the parasite cycle with a One Health approach and a special focus on prevention. In 2022, the WHO has launched a new guideline for the control of Schistosomiasis in endemic countries, updating some issues such as eligibility for MDA or increasing the focus on One Health activities (WHO, 2022b). It should be noted that no single intervention is recommended: while all are useful, their effectiveness is significantly increased when combined with other interventions.

1.3.3.1 Mass drug administration

MDA campaigns are based on mass distribution of PZQ to at-risk groups living in endemic areas. This action aims to treat those who are infected but have not searched for treatment, either because they were unaware of the infection or because they do not have access to medical care. These campaigns prevent the disease from progressing to a chronic mode that causes morbidity and also avoid the release of eggs into the water allowing the parasite cycle to continue. Although annual prevalence surveys are not required, a survey prior to the first intervention is necessary to determine whether or not the area is eligible for this type of campaigns. The WHO also recommends regular surveillance to assess the effectiveness of MDA campaigns (WHO, 2022b).

PZQ is the only existing treatment against all species of schistosome infections. The WHO recommends annual MDA campaigns with the administration of a single dose of 40 mg/kg in endemic countries with a prevalence greater than 10% in 75% of at-risk groups, including children from 2 years of age, pregnant women and adults (WHO, 2022b). Although PZQ was already included in the WHO Model list of Essential Medicines for Children in 2011, the eligibility of the aforementioned groups is one of the most notable updates in the new WHO guidelines (WHO, 2021a). This responds to the evidence that these groups are also at risk, especially preschool-age children (PSAC) and adults with occupations directly related to freshwater such as fishermen, farmers, and housewives. In addition, PZQ has shown high cure rates and egg reduction rates in infected children and pregnant women (Siqueira et al., 2017; Kabuyaya et al., 2020; Tesfie et al., 2020; Spangenberg, 2021). On the other hand, studies on the safety of PZQ in children under 5 years of age and in pregnant women have been a key point to include them in the groups recommended for MDA (Olveda et al., 2016; Jin et al., 2020; Webb et al., 2021). Although PZQ is safe for children, the fact that the most common dosage forms are tablets of 500 mg makes it difficult to administer the correct dose according to their weight, as well as the administration itself in very young children (Zajicek et al., 2013). For this reason, the Pediatric Praziquantel Consortium[1], an international alliance between public and private institutions, was created with the aim of reducing the global disease burden of Schistosomiasis by developing, registering and providing access to a suitable paediatric PZQ formulation for the treatment of Schistosomiasis in PSAC. Nonetheless, it is worthy to bear in mind that mass administration to PSAC has the difficulty that they do not attend school and therefore, the PZQ delivery should be done door-to-door.

1.3.3.2 Water, sanitation and hygiene

Since people become infected when they come in contact with infected water, WASH intervention plays an essential role in both preventing transmission and avoiding exposure. It is widely known that lack of access to clean water is the main risk factor for Schistosomiasis, far above all other risk factors (WHO, 2020). Ideally, ensuring that all

[1] https://www.pediatricpraziquantelconsortium.org/

communities living in risk areas have constant access to clean water would be the ultimate measure to eradicate the disease, but unfortunately this is a utopia in low- and middle-income countries. WASH interventions are resource intensive. Often this entails a high economic cost because it requires the construction of large infrastructures, which involves difficulties in logistics and in finding the necessary materials, training people in the maintenance of the facilities to ensure their sustainability, and joining forces with local and national authorities. In addition to the viability of the project, its sustainability and its maintenance are a key point to consider in this type of actions since a lot of money is invested, and both the suitability and acceptability of the beneficiary communities will define the success of the intervention (WHO, 2022b)

As argued by the SCI Foundation[2], WASH actions aimed at reducing the prevalence of Schistosomiasis are based on strengthening local authorities with the ability to improve water access infrastructures, create wells or other devices that allow access to safe water, create sustainable forms of water sanitation and provide facilities for urination.

1.3.3.3 Vector control

Snail vector is the backbone to ensure the continuity of schistosome cycle, so interventions focused on vector control aim to interrupt the cycle by preventing human exposure. The main advantages of this type of actions are not having to act directly on individuals, avoiding the problem of not reaching everyone, and the fact that if the intervention is successful, re-infections and new infections are eliminated. Vector control interventions can be divided in two phases: vector surveillance and vector elimination.

a) Vector surveillance is based on monitoring the presence of snails in their natural habitat. Its purpose is to determine infection hotspots and assess the risk of a water body, which is extremely useful for defining target areas for MDA. Historically, it has been done by expert malacologists who search for host snails in suspicious water bodies and, if found, bring them to the laboratory for cercariae shedding test. This surveillance technique has numerous drawbacks: (i) it is highly time-consuming, (ii) there are few expert malacologists capable of carrying out this work, (iii) the natural characteristics of the target water body may be an obstacle to assess the presence of the vector, and (iv) the cercariae shedding test could be negative as not all snails are infected at the same time, which may lead to an underestimation of the risk of infection for humans. Recently, new molecular techniques have been developed in order to carry out the vector surveillance leaving behind the tedious work of malacological surveillance, thus reducing human errors and allowing to map extensive areas of endemic countries (Kamel et al., 2021).

b) Vector elimination: Erasing the presence of the snails can be done by chemical or biological methods. Both have a slow mechanism of action, so their effectiveness

[2] https://Schistosomiasiscontrolinitiative.org/

depends on the parallel implementation of annual MDA campaigns. The chemical strategy works by adding molluscicide (niclosamide is the chemical molluscicide recommended by the WHO) to water bodies where there is continuous transmission. It is not toxic to humans and is not harmful to livestock in the long term, but it damages the environment within 24 hours of its application (WHO, 2022b). Moreover, evidence shows the development of resistance to this molluscicide by snail vectors of Schistosomiasis (Dai et al., 2015). On the other hand, the biological strategy aims to control the presence of the vector using natural predators of snails. This type of intervention must be carried out without altering the ecosystem in order to avoid further problems. An example of biological vector control is the introduction of *Macrobrachium* prawns, which feed on molluscs and have a special preference for infected snails. It is also important to note that these prawns are capable of eating other types of snails as those intermediate host for *Fasciola spp*., which are also of public health importance as the parasite affects both humans and cattle causing food insecurity (Sokolow et al., 2015).

1.3.3.4 Health promotion

Health promotion interventions in Schistosomiasis are based on boosting the knowledge of people at risk about the disease and its management, empowering them to better control their health. This intervention aims to improve their decision-making about daily practices that could compromise their health regarding Schistosomiasis through the full participation of the communities involved. The success of the intervention is strongly related to a proper design and performing it from a horizontal position.

To design a set of appropriate activities, it is essential to determine the prior knowledge of the target community, to identify their most common risk practices related to the disease, and know their attitude towards a change in behaviour to prevent the disease. In order to meet that baseline, a knowledge, attitude and practice (KAP) survey is commonly used. The WHO has recommended carrying out health education as a prevention tool against Schistosomiasis since 1990 (WHO, 1990) and continues to recommend it after observing success in different countries (WHO, 2022b). The evidence shows that the increase in knowledge about how Schistosomiasis is transmitted and how to prevent it, has an implication in individual decision-making as far as their conditions allow it (Hu et al., 2005; Adie et al., 2015). A well understood and developed health education can even motivate action by and for the community, as is the case in Nigeria, where people who received training on how to prevent Schistosomiasis created an initiative to inform the rest of the population and try to reduce the prevalence of the disease (Olaseha et al., 2005).

1.3.3.5 Research

Although research is not part of the four key interventions for the control of Schistosomiasis, it is a necessary and cross-cutting activity in the control of any disease.

In order to combat a disease, it is necessary to have methods of prevention, diagnosis techniques and a suitable treatment. This is not possible without carrying out proper research. The main challenge for this purpose is that biomedical research requires a high level of time and human and material resources, which can be translated into a large financial investment. The impact on a disease that increased research can have has been witnessed worldwide with the COVID-19 pandemic, where the speed with which an effective vaccine was developed in record time was possible thanks to the involvement of a large part of the scientific community. In fact, neglected diseases are so named because of the scarce attention they receive from the research organisations and pharmaceutical companies, as well as the limited funding devoted to their research compared to other diseases. This importance is reflected in the WHO guideline for Schistosomiasis, which has been developed on the basis of previous research to produce an evidence-based protocol. On the other hand, the document concludes with some priority research objectives in relation to the disease to encourage the scientific community to work on it (WHO, 2022b).

There are several research groups in the world that are interested in this parasitosis and are willing to investigate it. Within this field, some non-profit organizations have been created made up of different research groups with the aim of eradicating Schistosomiasis. The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE)[3], funded by the Bill & Melinda Gates Foundation, aims to find answers to the obstacles to the control and elimination of Schistosomiasis. Similarly, the aforementioned Pediatric Praziquantel Consortium was created to find a suitable pharmaceutical formulation of PZQ for this age group. These are only two of the most famous examples, but each effort by every group working on this disease contributes enormously to the path towards the elimination of Schistosomiasis as a public health problem.

1.4. Urogenital Schistosomiasis in Angola

Angola is a country located on the southwestern coast of Africa, bordered by Namibia, the Democratic Republic of the Congo, Zambia, and the Atlantic Ocean (Figure 1.5). With an extension of 1,246,700 km^2 and an estimated population of 34.8 million (based on the latest United Nations data), 47.8% of whom are under 15 years of age (the median age is 15.9 years), Angola is the seventh largest country in Africa. The population density in Angola is 26 per Km^2, but the major urban areas account for the highest concentrations of people (68.1% of the population is urban).

[3] https://score.uga.edu/

In 2002, Angola ended a devastating 27-year civil war that left a seriously deteriorated health system. Health care is currently free and universal, but there is a huge shortage of health workers, medicines and diagnostic devices, which makes real access to minimum quality health care very limited. This situation is especially aggravated in rural areas, where there are hardly any doctors and resources are even scarcer. Access to clean water sources and sanitation facilities differs greatly from urban to rural areas. Thus, while access to drinking water in urban areas is 81.3% of the population, it falls to 36.5% in rural areas; these inequalities are even greater in the case of access to sanitation facilities, with 93.7% and 30.3% respectively (CIA, 2021).

With a national poverty rate of 41% rising to more than 90% for almost half of the Angolan municipalities (INE, 2019), the diseases associated with this condition represent a major public health problem, especially considering the high number in the risk group of school-age children (SAC).

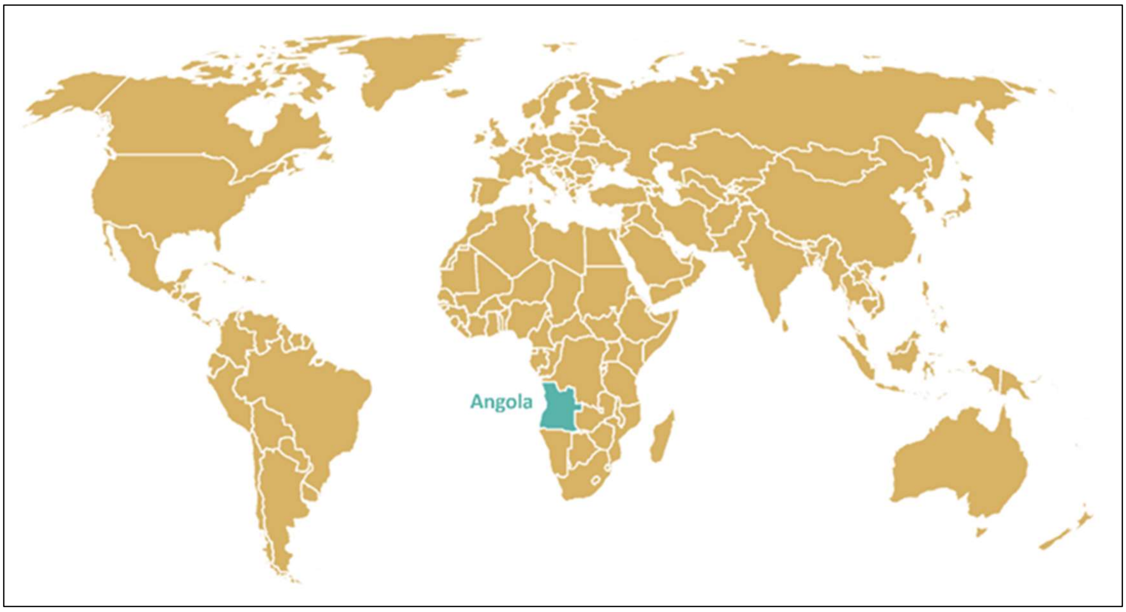


Figure 1.5. Geographical location of Angola (map created with MapChart[4]).

Angola was classified as a hyperendemic Schistosomiasis country according to WHO standards with a prevalence threshold above 50% (WHO, 2002). Numerous investigations carried out in the country support this classification with a SAC prevalence that ranges between 61% and 70% in the provinces of Benguela and Bengo (Sousa-Figueiredo et al., 2012; Bocanegra et al., 2015; Lemos et al., 2020a; Lemos et al., 2020b,). The prevalence in the country might seem overestimated because SAC is a high-risk group, but other studies also revealed a prevalence of 71% in adults (Botelho et al., 2015). However, a recent study on the prevalence of Schistosomiasis in SAC conducted in the 18 provinces of Angola found the highest prevalence per province was only 32.3% (Mendes et al., 2022). The National Sanitary Development Plan for 2012–2025 of the Angolan Ministry of Health established MDA with PZQ and albendazole as a priority

[4] https://www.mapchart.net/

intervention for mass deworming in SAC. Even so, many hyperendemic communities are not benefiting from these measures. Nevertheless, Mendes et al (2022) determined that at least 50% of the municipalities in each province need to be subject to MDA according to the WHO guidelines.

Benguela is one of the 18 Angolan provinces and has been ranked by Mendes et al. (2022) as the second province with the highest prevalence in the country. It should be borne in mind that this province is made up by 10 municipalities, 3 of which are coastal, which are the most populated and also have the highest GDP (INE, 2019). Cubal is one of the 10 municipalities that constitute the province of Benguela with a population of 322,000 inhabitants, 47% of whom are under 15 years of age and an estimated 58,000 are children under 5 years of age (INE, 2014). The main source of income of its population is agriculture and livestock farming.

As shown in Figure 1.6(a), it is an inland municipality far enough away from the coast to be free of brackish water. It is a rural area with a poverty rate of 87.3% (INE, 2019) that has several waterbodies used for human activities such as bathing or washing. It counts with a lake and a river that surrounds the entire southern part of the municipality, as can be seen in Figure 1.6(b). In addition, these are also waterbodies where children often play and bathe for recreational purposes. The only study carried out in Cubal shows a prevalence of urinary Schistosomiasis among SAC of 61% and an associated morbidity of 85.4% (Bocanegra et al., 2015, 2018).

a) Geographical location of Cubal, Angola (map created with MapChart) b) Cubal city map

Figure 1.6. The municipality of Cubal in the province of Benguela.

1.5. Research objectives

Schistosomiasis is a disease that affects millions of people a year, mainly in the tropical and subtropical regions of the planet, where the most frequent is caused by *S. haematobium*. The main objective of this Ph.D. thesis is to gain a comprehensive understanding of the current situation of this parasitic disease through an epidemiological and public health approach. From this general goal, the following specific objectives were formulated:

1. To determine the impact of the COVID-19 pandemic on Schistosomiasis research.
2. To analyse the prevalence and associated morbidity of urogenital Schistosomiasis in PSAC in endemic areas.
3. To assess the knowledge, attitudes and practices of endemic societies regarding urogenital Schistosomiasis.

1.6. Thesis outline

This thesis has been organized in such a way that each of the aforementioned objectives is developed in a different chapter. Thus, Chapter 2 addresses the first specific objective by providing a post-pandemic bibliometric analysis of scientific articles on human Schistosomiasis published during the most acute phase of the COVID-19 pandemic. The purpose of this chapter is to assess the effect of the global lockdown on research activities on this neglected disease.

The rest of the thesis focuses on urogenital Schistosomiasis caused by *S. haematobium*. Chapter 3 develops the second specific objective, which has been addressed through a cross-sectional study on 245 children under 5 years of age from the endemic municipality of Cubal, Angola. The prevalence of urogenital Schistosomiasis and its associated morbidity in this age group were analysed to determine their situation as they are not included in deworming campaigns. The third objective is developed in Chapter 4 based on another study also carried out in the municipality of Cubal. Through a survey of knowledge, attitudes and practices, the level of understanding of the population regarding urogenital Schistosomiasis has been determined and the most common actions and habits that expose them to the parasite and possible infection have been established. In addition, the study design has allowed us to depict the profile of the population both demographically and socioeconomically. On the other hand, this chapter also presents an analysis of the risk factors for infection and associated morbidity of urogenital Schistosomiasis in PSAC, based on the results of the survey and the study described in the previous chapter. Finally, in Chapter 5 the global conclusions reached in this thesis are outlined, which are presented classified according to the objectives.

Chapter 2

Effect of the COVID-19 pandemic on Schistosomiasis research

2.1. Introduction

This chapter is based on the article published in the *International Journal of Environmental Research and Public Health* (see Appendix A). The COVID-19 disease caused by a strain of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was officially declared as a global pandemic by the WHO on March 11, 2020 due to its high rates of viral transmission and mortality, putting additional pressure on health systems around the world. As of November 7, 2022, more than 629.37 million confirmed cases and 6.58 million deaths were globally registered since the first patient detected in Wuhan, China in December 2019. Table 2.1 shows the important differences in cases and deaths that exist between regions, suggesting that Africa has been moderately affected by COVID-19 compared to other areas, with a number of about 9.36 million cases and 175,000 deaths so far. However, these reported figures may be underestimated due to the limitations of local health systems in accurately diagnosing the disease on a large scale. Based on Spearman's correlation coefficient (r), it was found that the number of deaths was not significantly associated with the number of cases (r = 0.77143, p-value = 0.0724) at a significance level of 0.05.

Table 2.1. COVID-19 situation by WHO region (as of November 7, 2022)[5].

Region	Cases	Deaths	%Deaths/Cases
Europe	261,751,184	2,120,778	0,8102
Americas	180,074,239	2,856,069	1,5861
Western Pacific	94,517,918	277,282	0,2934
South-East Asia	60,493,265	800,555	1,3234
Eastern Mediterranean	23,165,118	348,751	1,5055
Africa	9,368,401	174,797	1,8659

The main transmission pathway of COVID-19 is airborne, that is, human-to-human transmission via droplets nuclei or aerosols produced by infected individuals during all expiratory activities, such as coughing, sneezing, talking, singing, shouting or breathing, especially at a distance of less than 1.5 to 2 meters (Wang et al., 2021). To mitigate the

[5] https://covid19.who.int

risk of viral infection and limit the spread of COVID-19, health authorities around the world strongly recommended basic preventive measures, such as hand hygiene, social distancing and the use of face masks (Chu et al., 2020; Colomer et al., 2021). However, mass vaccination is the most important and the only really effective tool to halt any pandemic.

Given the high number of lives lost due to the COVID-19 pandemic, several effective vaccines were rapidly developed to provide protection against serious illness, hospitalization and death from COVID-19. As of April 8, 2022, ten vaccines obtained the WHO Emergency Use Listing, which determines whether a product can be recommended for use based on all available data on quality, safety, and efficacy and on its suitability in low- and middle-income countries. In addition, some national regulators also assessed other vaccines for use in their countries.

However, despite the COVAX initiative[6] created by the Global Alliance for Vaccines and Immunization, the WHO, the United Nations Children's Fund (UNICEF) and the Coalition for Epidemic Preparedness Innovations to share vaccines against COVID-19 worldwide, vaccines have not reached all regions equally due to dose hoarding by European Union and G7 (the grouping of the world's most advanced economies) countries. For instance, the European Union purchased 4.5 billion doses for 450 million citizens, which supposes that each people should receive ten doses of the vaccine. Similarly, Australia purchased 280 million doses for a population of 25 million, that is, 11 vaccines per person. As reported in Table 2.2, there exist significant differences in the total vaccine doses administered between wealthy and developing/poor countries. In fact, as of November 7, 2022, of the more than 12.9 billion doses distributed worldwide, only 489.57 million doses were administered in Africa. In addition, 74.63% of the population in high income countries and 75.12% in upper middle-income countries were fully vaccinated with last dose of primary series in November 2022, but only 20.42% of people in low-income countries and 58.23% in lower middle-income countries (Mathieu, 2020).

Table 2.2. COVID-19 situation by World Bank income group (as of November 7, 2022)[7].

Group	Total vaccine doses administered per 100 population	Persons vaccinated with at least one dose per 100 population
High-income	214.59	79,795
Upper middle-income	202.27	80,348
Lower middle income	138.25	65,143
Lower-income	33.83	25,041

[6] https://www.who.int/initiatives/act-accelerator/covax
[7] https://covid19.who.int

On the other hand, it is also worth noting that, during the first months of the COVID-19 pandemic, more diagnostic tests were developed for SARS-CoV-2 than for all NTDs in the last 100 years (de Souza et al., 2020). As shown, the pandemic heightened inequalities between high- and low-income countries. However, these differences are not only related to the availability of doses of the COVID-19 vaccine and adequate testing policies or to social and economic conditions, but also to interventions for other diseases, and most especially for many diseases closely linked to poverty. Thus, the health policies implemented by governments in order to control the transmission of the coronavirus caused the research and treatment of various diseases to be suddenly stopped, which caused serious damage to those affected by these diseases and set back the progress achieved. For instance, some studies have concluded that neglecting care for cancer and certain chronic diseases, such as cardiovascular and non-infectious respiratory diseases, could lead to preventable deaths or late diagnoses (Morris et al., 2021; Wadhera et al., 2021). This could prove especially fatal for the prevention, control and eradication of NTDs because in April 2020, the WHO issued a general recommendation to temporarily suspend population-based surveys, mass drug administration, and active case-finding to minimize the potential risk that NTD programs could facilitate SARS-CoV-2 transmission. As of early 2021, disruption of NTDs programs occurred in 44% of countries, primarily in South-East Asian, the Americas, the Eastern Mediterranean, and Africa. Unfortunately, this situation did not change during the second half of 2021, in which many countries either cancelled or postponed MDA campaigns (WHO, 2022c).

In light of this bleak scenario, it is possible to find some studies pointing to the serious threat that syndemic malaria and NTDs can pose in low- and middle-income countries (Gutman et al., 2020; Mantica et al., 2021). Delays in MDA and active case-finding due to the COVID-19 pandemic may have caused a resurgence of some NTDs, with Schistosomiasis, trachoma and visceral leishmaniasis (in high transmission settings for each) appearing as most likely to require several corrective strategies (WHO, 2021b). A study conducted by the NTD Modelling Consortium concluded that postponing MDA will result in a delay of up to two years to the 2030 goal of eliminating Schistosomiasis as a public health problem (NTDMC, 2020).

Holen (2021) warned that the important advance in the fight against Schistosomiasis is at risk of being reversed in most countries due to the measures adopted to face the COVID-19 emergency. Similarly, Ehrenberg et al. (2020) pointed out that COVID-19 could have a short-term impact on the prevention and control of NTDs because financial and human resources would be diverted. Kura et al. (2021) showed that the interruption of MDA campaigns because of the COVID-19 pandemic would cause an increase in *S. mansoni* and *S. haematobium* infection. Olamiju et al. (2022) reported an outbreak of Schistosomiasis in northeast Nigeria during the pandemic, suggesting that it might be due to the disruption of MDA campaigns. Guo et al. (2020) observed a significant reduction in gross funds allocated to Schistosomiasis prevention and control programs from January to March 2020 in 12 endemic provinces of China. Adepoju (2020) drew attention to the case of a village in Ogun state (Nigeria), where its regular supply of PZQ was abruptly cut off by movement restriction measures during the pandemic, leaving the local community unprotected against Schistosomiasis. Hollingsworth et al. (2021) evaluated the potential impact of disruptions to NTD programs caused by the COVID-19 pandemic and found that visceral leishmaniasis, trachoma, and Schistosomiasis could have faster epidemic growth rates and a significant increase in morbidity or even mortality, especially in areas of high transmission. Toor et al. (2021) also drew similar conclusions that Schistosomiasis, soil-transmitted helminthiases and trachoma were likely to experience a more rapid resurgence.

Li et al. (2022) noted that the risk of Schistosomiasis increased during the COVID-19 outbreak due to an increase in snail colonies in Wuhan (China). Hotez et al. (2021) forewarned that COVID-19 could spoil control and elimination efforts for Schistosomiasis, river blindness and lymphatic filariasis in Africa or lymphatic filariasis in India. Kura et al. (2021) indicated that for both *S. mansoni* and *S. haematobium* in moderate- and high-prevalence settings, the interruption of programs might delay the goal of eliminating Schistosomiasis as a public health problem by up to 2 years. Similarly, Borlase et al. (2022) also stated that a 1-year interruption of NTD programs could lead to an average delay of 2 to 3 years in settings with a high prevalence of Schistosomiasis and other NTDs. Dantas et al. (2023) assessed the impact of COVID-19 pandemic on the actions of the Schistosomiasis control program in endemic municipalities of Alagoas (Brazil).

The Global Schistosomiasis Alliance[8] launched a brief questionnaire to some of its partners to know how the COVID-19 crisis impact on their research activities, revealing that the pandemic and associated restrictions affected clinical studies, field surveillance and scheduled basic and preclinical laboratory work (GSA, 2020). This chapter presents a review of the scientific publications on Schistosomiasis disease during the most acute phase of the COVID-19 pandemic by means of a comprehensive bibliometric study (Donthu et al., 2021), in order to analyse, measure, and visualize the impact of the pandemic on Schistosomiasis research and how it affected its development. Ultimately, this study may shed some light on whether the pandemic had a short- and medium-term negative effect not only on prevention, diagnosis and treatment activities, but also on global Schistosomiasis research.

2.2. Materials and methods

This study was carried out following the PRISMA statement (Page et al., 2021) by conducting a systematic literature search using the Scopus database for the period from January 1, 2020 to March 26, 2022. The cross-searching was based on a set of terms (*Schistosoma*, Schistosomiasis, snail fever, bilharzia, bilharziasis) in the title, abstract or keywords of a document to generate the initial outputs.

[8] https://www.eliminateschisto.org/

Of all the documents retrieved, those that met any of the following exclusion criteria were eliminated from any further analysis.: (i) written in any language other than English; (ii) documents published in any format other than journal articles or letters; and (iii) articles in press. Therefore, according to the second exclusion criterion, documents such as editorials, reviews, surveys, opinion articles, commentaries, notes, conference papers and book chapters were left out of this study. Subsequently, the title and abstracts of all selected documents were screened to ensure that they did indeed addressed Schistosomiasis. Both the literature search process and the application of the exclusion criteria were carried out on March 27, 2022. Figure 2.1 shows the PRISMA diagram of the selection process of documents.

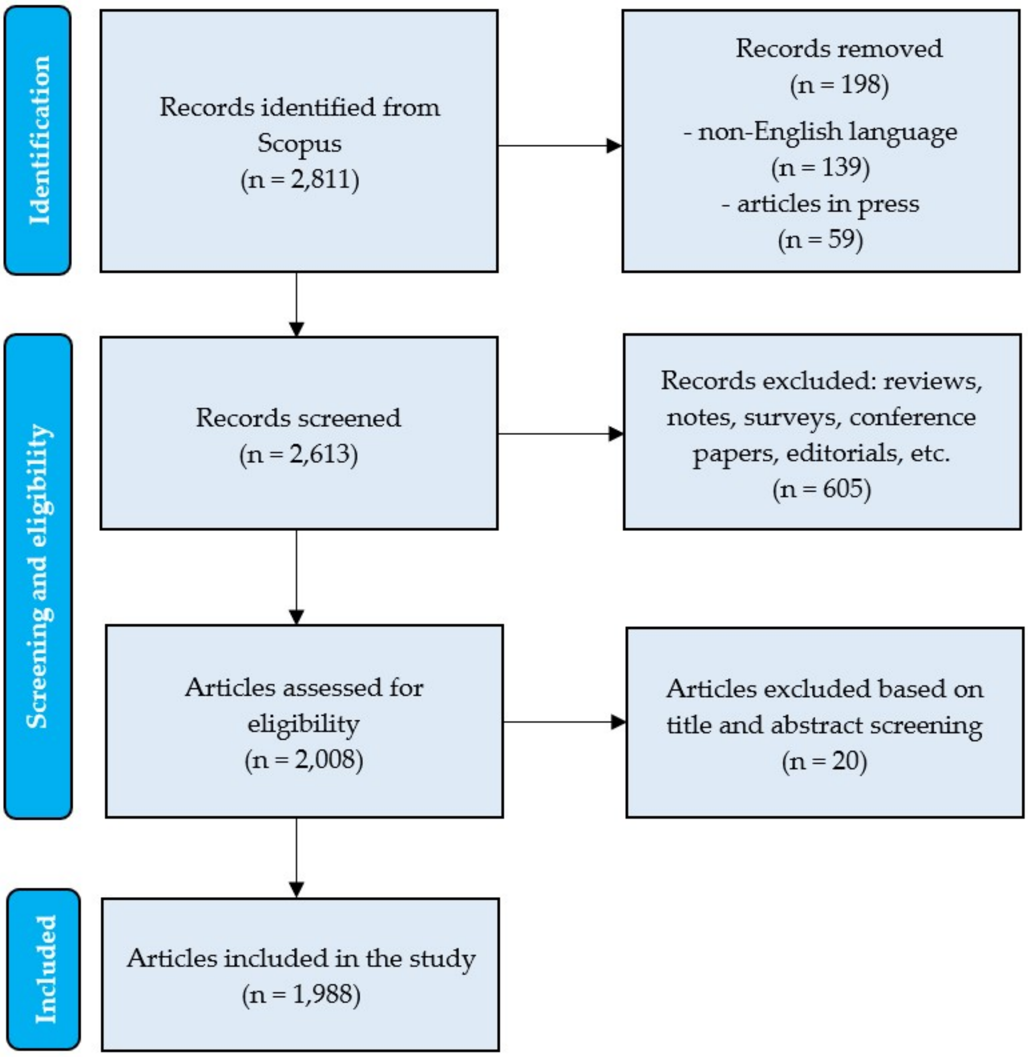


Figure 2.1. PRISMA diagram.

2.2.1. Data retrieval and collection

We retrieved a total of 2,811 records from the Scopus database, which offers an extensive coverage of biomedical literature (Falagas et al., 2008). After removal of 139 non-English documents and 59 articles in press, 2,613 were selected for eligibility. Of these, 605 records were excluded based on the types of documents not considered for this study (i.e. the second exclusion criterion), leaving 2,008 documents for the title-and-abstract verification stage. After screening the title and abstract, 20 documents were excluded as not being directly related to research on Schistosomiasis. At the end of the entire PRISMA process, a final pool of 1,988 documents was considered in the study.

For each of the 1,988 documents definitely included in the study, relevant data elements were collected: authors names, publication year, title, journal, affiliations, country, keywords, funding institution, research category, and number of citations. The number of authors and the country of the corresponding author were also extracted. Then, all this data was organized in standardized tables to make their analysis easier. In addition, we also recorded the journal impact factor taken from the 2020 Journal Citation Reports (JCR), which was the latest published at the time of conducting this study.

2.2.2. Data analysis

Spearman's rank correlation coefficient (r) was applied to explore any relationship between standard bibliometric indices. In addition, we also checked the association between the number of publications per country and important demographic and socioeconomic indicators: population, GDP per capita, gross domestic expenditure on R&D (GERD), multidimensional poverty measure (MPM), and researchers per million inhabitants (i.e. number of professionals dedicated to the conception or creation of new knowledge during a given year expressed as a proportion of a population of one million). All these demographic and socioeconomic measures were obtained from the websites of the Organisation for Economic Co-operation and Development[9], the International Monetary Fund[10] and the World Bank[11]. GERD is an indicator of the total expenditure (current and capital) on R&D made by all resident companies, research institutes, university and government laboratories, etc., in a country expressed as a percentage of GDP (OECD, 2022). MPM is a measure of poverty that captures deprivations in education (attainment and enrolment) and access to basic infrastructure (electricity, sanitation and drinking water) in addition to the extreme poverty threshold of USD 1.90 (World Bank, 2022).

In this chapter, two variables are considered significantly correlated when the p-value is lower than 0.05 (i.e. a significance level of 5%). We used IBM SPSS Statistics to carry out the statistical analysis, the VOSviewer program (van Eck and Waltman, 2010) to map bibliometric networks and perform co-authorship and keyword co-occurrence analysis, and *Paintmaps.com* to generate a world map of the number of publications by country.

[9] https://www.oecd.org/
[10] https://www.imf.org/en/home
[11] https://www.worldbank.org/en/home

2.3. Results

Of the 1,988 publications selected for the study, 1,948 corresponded to articles and the remaining 40 to letters. These documents were published in 160 different journals and cited 4,711 times (as of March 27, 2022). From the total documents analysed, 1,143 papers were cited at least once and showed an h-index of 19. The documents were authored by 159 researchers from 132 countries across five continents. The vast majority of articles were multi-authored, since only 1.86% of the total papers were from a single author, which gives a collaboration coefficient of 0.98. The average productivity per year (i.e. average number of publications per year) was 662.66 and the average number of citations per year was 1,570.33. Figure 2.2 depicts a histogram with the number of citations versus the number of publications inn logarithmic scale.

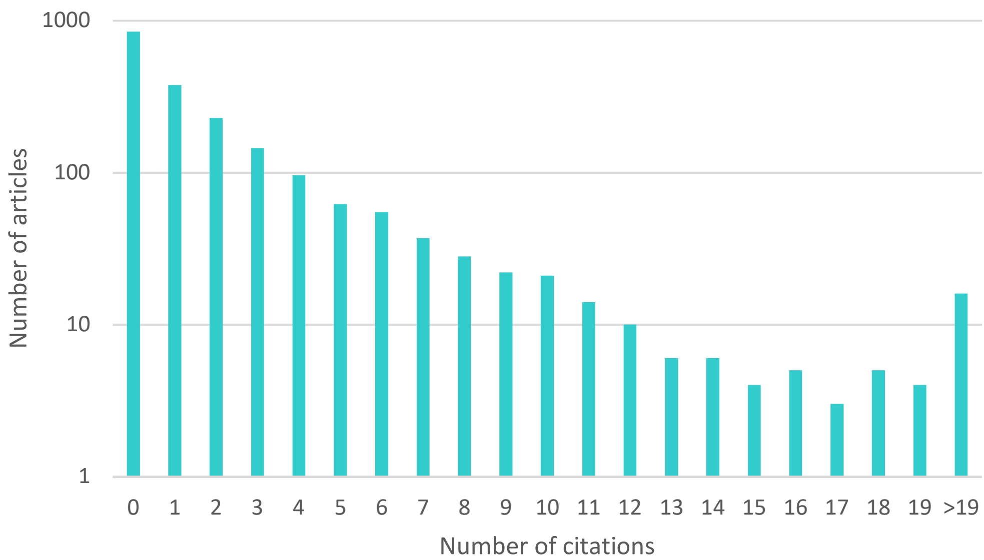


Figure 2.2. Number of publications vs number of citations in logarithmic scale.

2.3.1. Year-wise distribution of publications

To analyse the evolution of publications over time, Figure 2.3 shows a bar chart with the number of documents published between 2018 and 2022. We also included the values for the two years prior to the pandemic (2018 and 2019) in order to test whether the pandemic led to a decrease in research publications on Schistosomiasis. Surprisingly, visual examination of this plot allowed us to detect a moderate increase in the number of scientific publications during the acute phase of the pandemic (2020 and 2021), which could suggest that research on Schistosomiasis was not disrupted due to the global emergency situation. However, looking at the trend for the first quarter of 2022, a quite probable estimate of the number of publications at the end of 2022 would indicate the possibility of a slight decrease in scientific production, which could respond to the fact that the resources traditionally allocated to certain lines of medical and biomedical research have now been redirected to research on COVID-19, most especially for vaccine design and development.

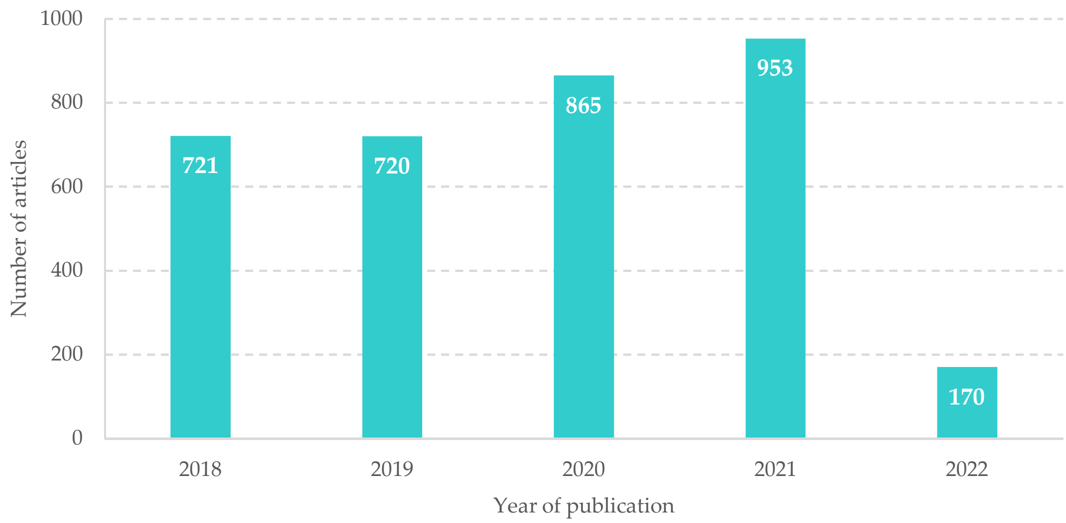


Figure 2.3. Number of publications peer year.

In order to determine if there is any different trend between systematic-review-type publications and the two types of documents considered in this study (articles and letters), we also conducted a cross-search for reviews published between 2018 and the first quarter of 2022. This process gave a total of 744 review-type articles: 141, 155, 184, 219 and 45, respectively. Spearman's correlation analysis found a significant association between research articles and systematic reviews (r = 0.9, p-value = 0.03739). These results indicate that, despite the confinement of people and the possible lack of some supplies (for instance, lack of reagents) during the acute phase of the pandemic, the rate of production of research articles was comparable to that of review-type articles. A plausible explanation for this could be that most of the research articles published during the pandemic were based on data and/or results of studies and experiments conducted in previous years.

2.3.2. Distribution of publications by journals and research categories

Figure 2.4 shows a treemap with the 10 journals with the largest number of articles along with three simple bibliometric indices, which allows revealing the journals that have been most productive and influential during the period analysed. From this, it can be seen that PLoS Neglected Tropical Diseases was by far the most frequently publishing journal, having 225 articles published (11.32%) and receiving 524 citations. Acta Tropica ranks second, although quite far from PLoS Neglected Tropical Diseases, with 73 articles (3.67%) and a total of 183 citations. Overall, the top 10 journals published 618 papers (31.09%) and received 1,601 citations, representing 31.09% of the articles selected and approximately 34% of the citations. All of these journals, with the exception of Scientific Reports, are ranked in the top quartiles (Q1 or Q2) of the 2020 JCR.

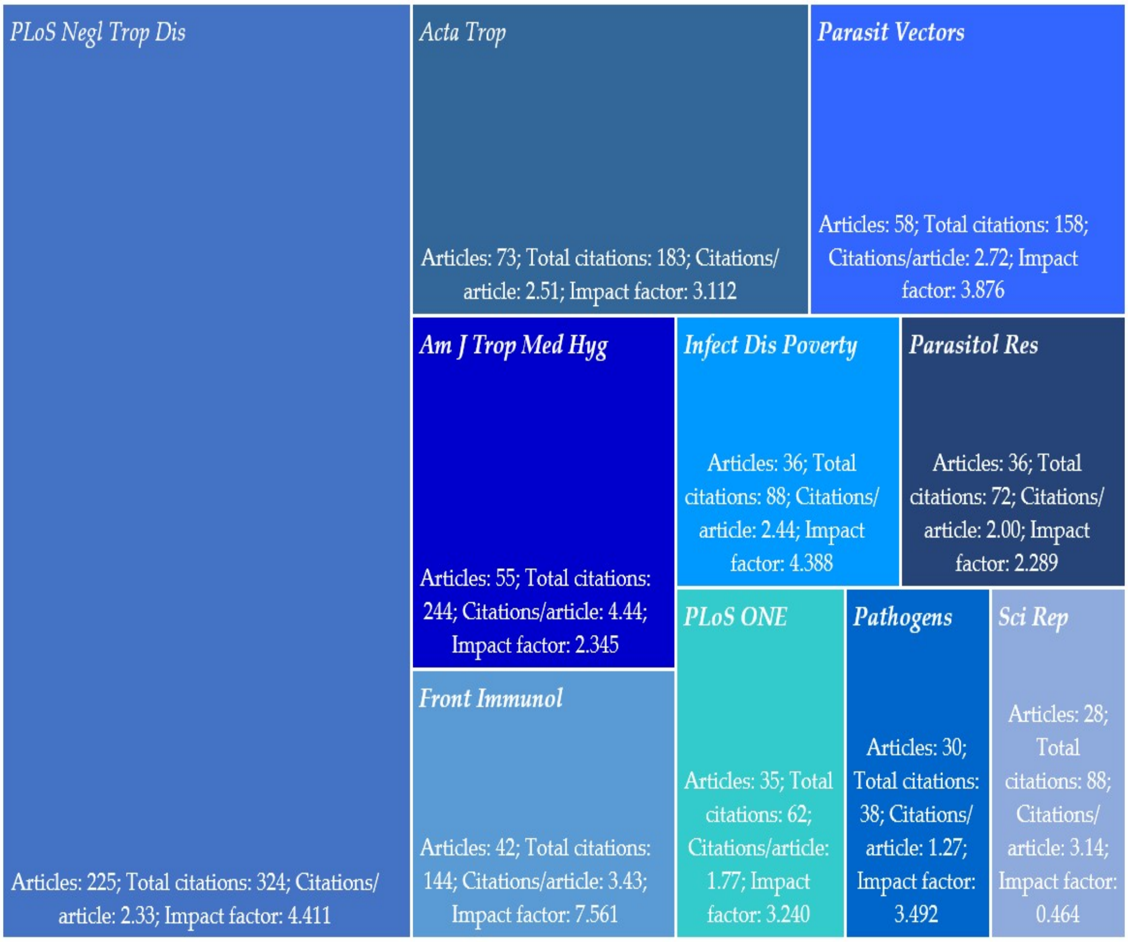


Figure 2.4. The 10 journals with the most publications.

Spearman's correlation analysis revealed significantly correlated data between the number of publications and the number of citations (r = 0.8628, p-value = 0.00131), but not between the number of publications and the journal impact factor (r = 0.4073, p-value = 0.24271).

Focusing on the research categories, we find a total of 25 categories from very different areas, from Health Sciences to Finance or Computer Science. Figure 2.5 shows that most of the publications fell into various categories belonging to Health Sciences, such as Medicine (n = 1,397, 70.27%), Immunology and Microbiology (n = 732, 36.82%) or Biochemistry, Genetics and Molecular Biology (n = 348, 17.51%). It is worth mentioning that 15 research categories (e.g. Computer Science, Social Sciences, Nursing, Dentistry, Psychology, Economics, Econometrics and Finance, or Energy) were found with fewer than 30 documents each. It should be noted that the sum of percentages exceeds 100% because publications may fall into more than one research category.

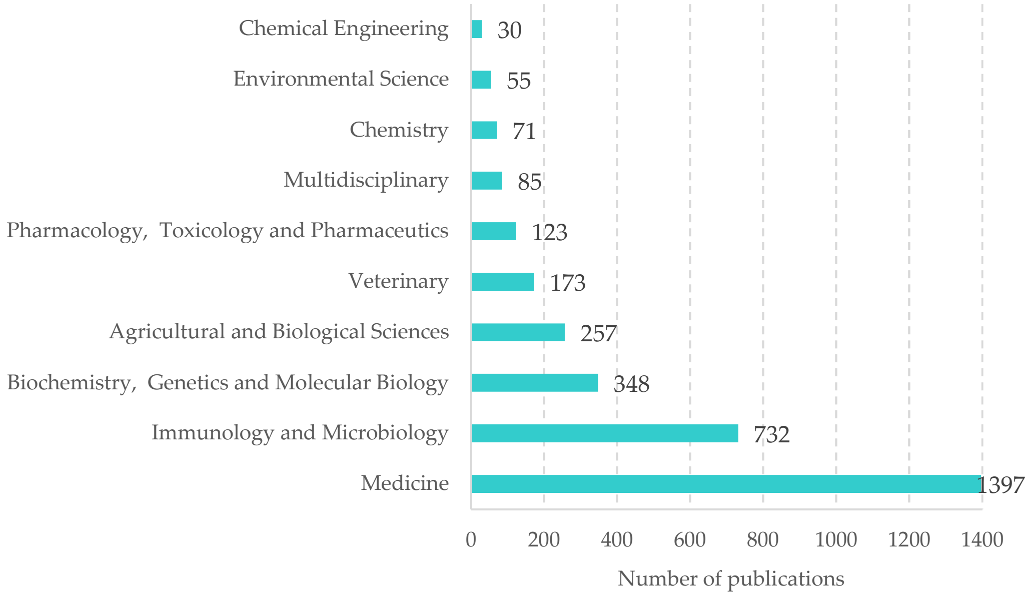


Figure 2.5. Top 10 research categories.

2.3.3. Distribution of publications by countries

Figure 2.6 shows a world map to reflect the geographical distribution of retrieved documents by the country affiliation of the authors. The United States of America with a total of 436 documents (21.93%) was the country with the highest number of publications, followed by the United Kingdom (n = 343, 17.25%), China (n = 309, 15.54%), Brazil (n = 245, 12.32%), Egypt and Switzerland (n = 139, 6.99% each), Germany (n = 130, 6.54%), and the Netherlands (n = 106, 5.33%). On the other hand, authors from 39 countries, mostly low- and middle-income countries (Algeria, Bolivia, Peru, Guatemala, Honduras, Liberia, Paraguay, Belarus, Burundi, Namibia, Chad, Sierra Leone, Lebanon, Swaziland, Kazakhstan, Armenia, Papua New Guinea, Eritrea, Iraq, Yemen, Cambodia, among others), contributed only one or two publications.

Regarding two of the regions with highest burden of Schistosomiasis worldwide, we found that the Sub-Saharan African countries that published the most were South Africa (n = 83, 4.18%), Tanzania (n = 80, 4.02%), Ethiopia (n = 73, 7.30%), Nigeria (n = 65, 3.27%), Kenya (n = 62, 3.12%) and Uganda (n = 41, 2.06%), whereas Thailand (n = 35, 1.76%) and the Philippines (n = 30, 1.51%) were by far the Southeast Asian countries with the highest number of publications.

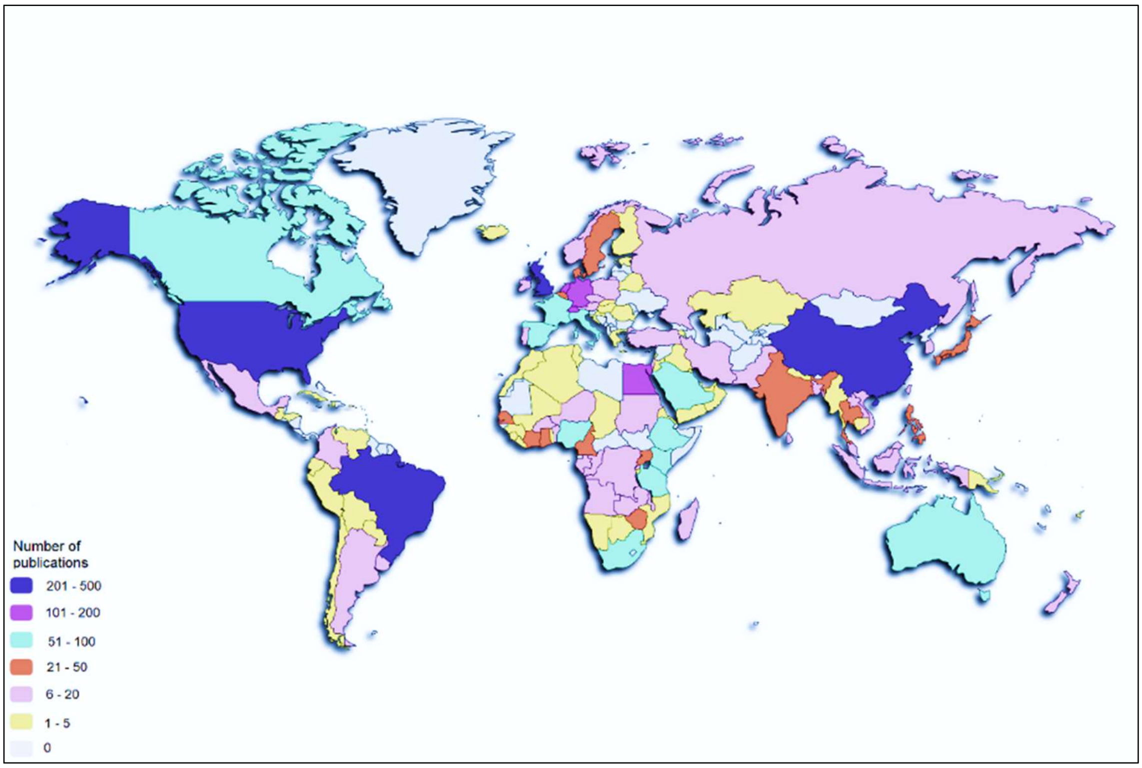


Figure 2.6. Geographical distribution of publications (map created with paintmaps[12]).

2.3.4. Co-authorship analysis

Co-authorship network was employed to visualize and explore collaboration patterns between authors. A co-authorship network is a two-dimensional map where the nodes represent authors and the links connecting two nodes (authors) indicate that there is at least one co-authored publication between them (Morel et al., 2009). The size of the nodes reflects the number of publications, colours indicate clusters, and line length represents the strength of the relationship.

For the sake of easier visualization of the network, Figure 2.7 only shows authors with a minimum of 10 co-authored papers. The analysis of the network revealed the presence of nine clusters that include a total of 83 authors with some type of collaboration between subgroups of them. It was also observed that the densest cluster consisted of 29 authors, but the level of international collaboration was very low since most of these authors were affiliated with Chinese institutions. On the other hand, it can be seen that there are two clusters made up of only two authors each and one cluster with three authors, indicating that there was some type of non-international inter-institutional cooperation. A thorough exploration of the network allowed us to detect some strong international collaborations at the level of co-authored publications between researchers belonging to different clusters. An example of this finding is the collaborations between researchers from the Swiss Tropical and Public Health Institute with researchers from the Natural History Museum of London, the Université de

[12] https://paintmaps.com/

Perpignan via Domitia (France) and the University Félix Houphouët-Boigny (Côte d'Ivoire).

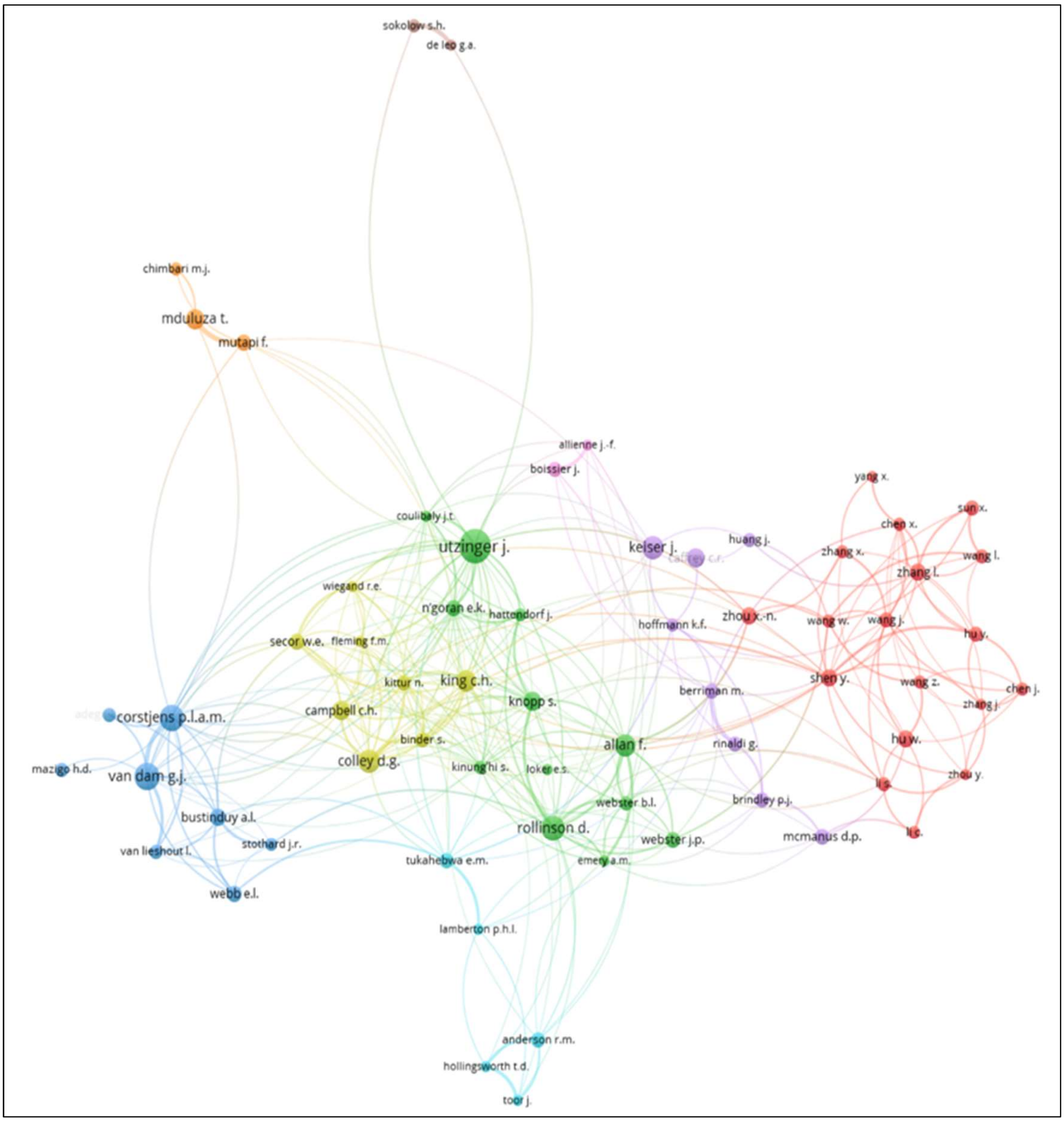


Figure 2.7. Network for co-authorship analysis.

2.3.5. Funding institutions

Figure 2.8 shows the 10 most common funding institutions for Schistosomiasis research during the COVID-19 pandemic, which accounted for more than half of all documents (54.17%). As can be seen, various government agencies, foundations and private organisations funded the research conducted for the publications included in this study. The National Natural Science Foundation of China (n = 161, 8.10%), the US National Institutes of Health (n = 138, 6.94%), the Bill & Melinda Gates Foundation (n = 114, 5.73%), the European Commission (n = 113, 5.68%), and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazil) (n = 113, 5.68%) were the five institutions with the highest number of publications in which they appear as funders.

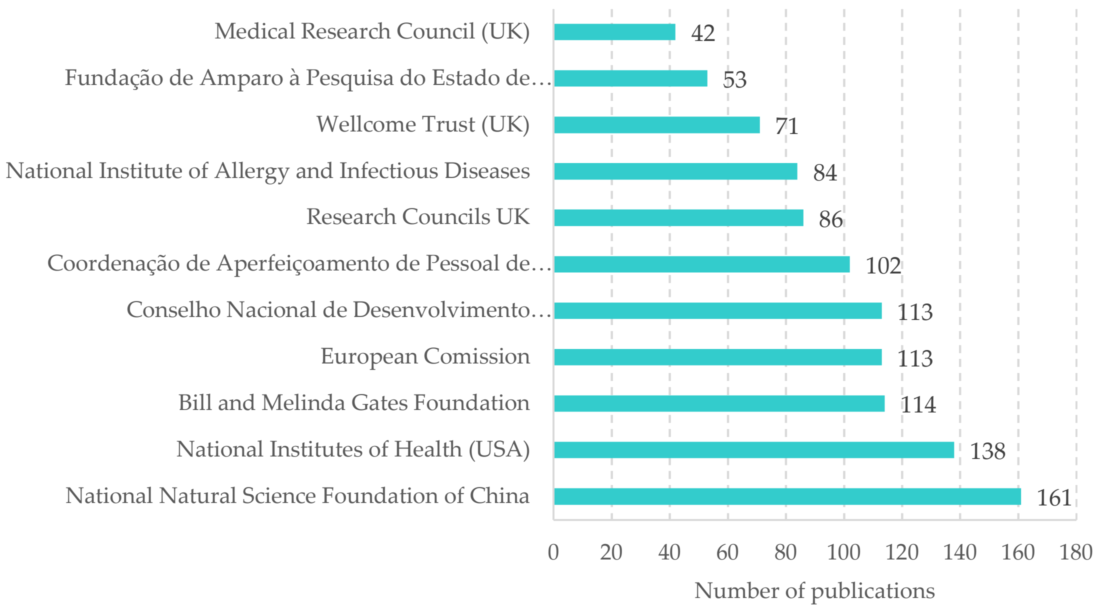


Figure 2.8. Top 10 funding institutions.

2.3.6. Keyword co-occurrence analysis

Co-occurrence analysis of keywords makes it possible to estimate how often a set of keywords appear together in publications, reflecting research hotspots in a field. The common way to represent this is by means of a co-occurrence network, which is a two-dimensional map where the nodes represent the keywords and the links correspond to their relationships (Liu et al., 2022). The size of the nodes is proportional to the frequency with which the keywords appear in the documents, while the distance between two nodes indicates the strength of their relationship: the closer two nodes are in the map, the stronger the relationship between them.

For this study, the co-occurrence network was built from the keywords that appeared at least five times in the sample. As shown in Figure 2.9, a total of 14 clusters and 135 items were obtained by co-occurrence analysis. The most represented keyword with a total of 360 occurrences was "Schistosomiasis", followed by "*schistosoma mansoni*" with 218 occurrences, "*schistosoma japonicum*" with 108 occurrences, "praziquantel" with 85 occurrences, and "*schistosoma haematobium*" with 57 occurrences. Other represented keywords, such as "real-time pcr", "ultrasonography", "immune modulation", "transcriptome" or "biomarkers", refer to the most commonly used methods for the diagnosis of the disease.

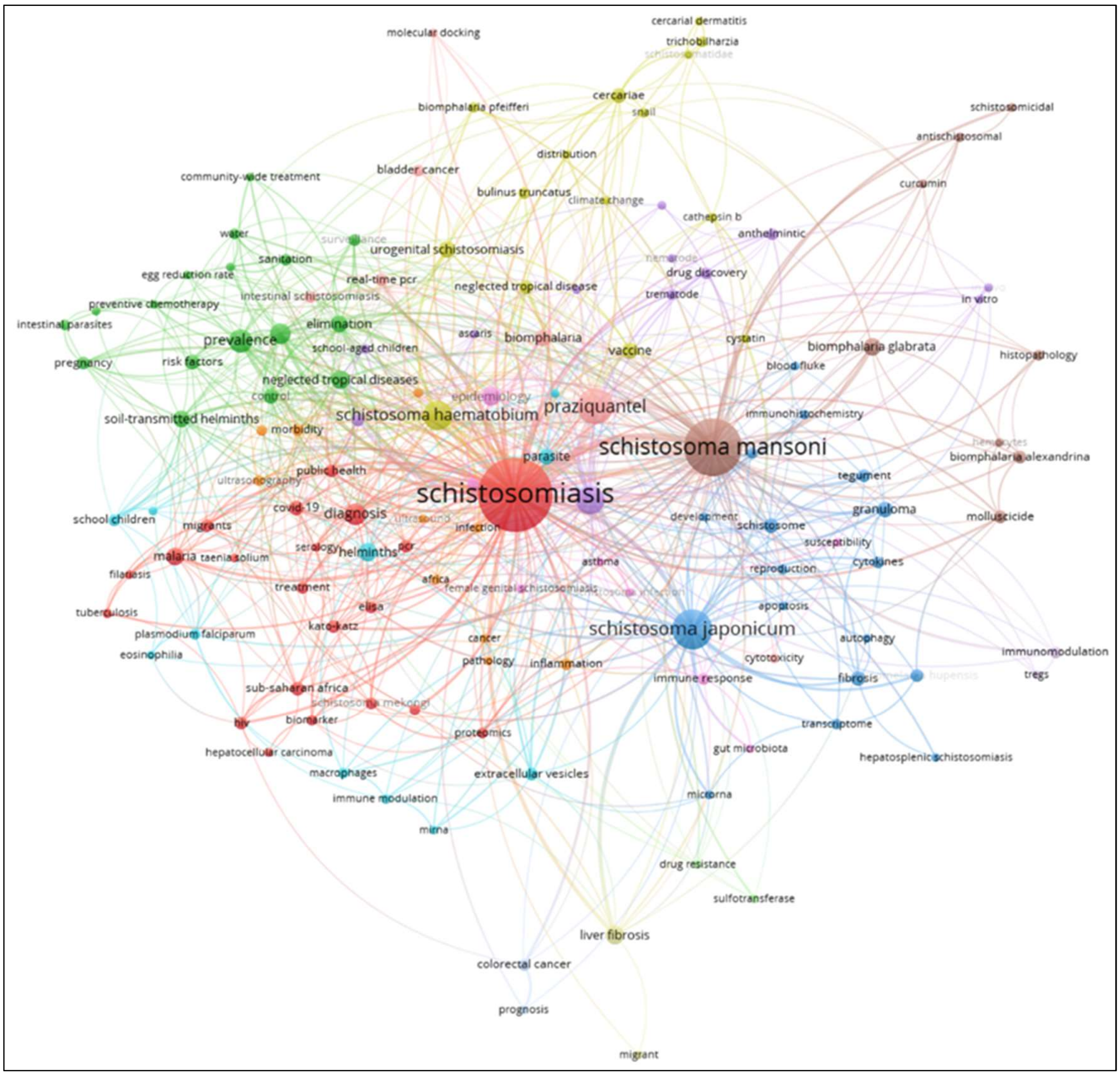


Figure 2.9. Network for keyword co-occurrence analysis.

2.3.7. Publications with the most citations

Table 2.3 reports the most cited articles ranked by total citations (TC) and by field-weighted citation impact (FWCI). The FWCI is the ratio of the total number of citations actually received by an article and the average number of citations received by all other similar documents in the same year and field of research over the previous three years (Elsevier, 2019): a value equal to 1.00 means that the article performs just as expected for the average, while a value greater (lower) than 1.00 indicates that it is more (less) cited than expected based on the average for similar publications. The advantage of FWCI over the total number of citations is that it is a normalized index, which means that it considers differences in research and citation behaviour between disciplines. It also controls for article age, removing bias towards older articles and between more or less frequently cited document types.

For each article in Table 2.3, the international collaboration (IntC) and the number of citations per year (CYear) are also shown. The number of citations per year for a given article was calculated as follows:

$$CYear = \frac{TC}{year_{study} - year_{publication} + 1}, \tag{2.1}$$

where $year_{study}$ denotes the year in which the study was conducted (for this thesis, it was 2022) and $year_{publication}$ refers to the year of publication of the article.

The 10 most cited articles received 590 citations, which represents 12.52% of the total number of citations (4711). However, it should be noted that the publication that ranked first accumulated 335 citations, which represents 7.11% of the total. When looking at the remaining nine articles, the average citation was 28.33 per publication.

The two publications that received most citation attention also had the highest FWCI value. However, some important differences can be observed in the rankings reported in Table 2.3; thus, for example, the article "A controlled human *Schistosoma mansoni* infection model to advance novel drugs, vaccines and diagnostics" (Langenberg et al., 2020) ranked third in total citations, but ranked tenth when used the FWCI.

Six of the 10 most cited articles were written by authors affiliated with institutions from different countries, standing out two of these articles in which authors from nine different countries collaborated. For example, the authors of the paper entitled "Circulating anodic antigen (CAA): A highly sensitive diagnostic biomarker to detect active *schistosoma* infections—improvement and use during SCORE" (Corstjens et al., 2020) were from the Netherlands, Switzerland, the United Kingdom, France, Rwanda, Tanzania, Kenya, the United States of America and St. Lucia. Analogously, the article "Impact of different mass drug administration strategies for gaining and sustaining control of *Schistosoma mansoni* and *Schistosoma haematobium* infection in Africa" (King et al., 2020) was the result of a collaboration between researchers from the United States of America, Switzerland, Kenya, Cote d'Ivoire, Denmark, the United Kingdom, Tanzania, Mozambique and Niger.

Apart from these two articles co-authored by people belonging to various institutions from nine countries, there are two other papers with authors from four countries and two with the collaboration of authors from three countries. In addition, it should be noted that the authors of these articles are both from countries where Schistosomiasis is endemic (e.g. Senegal and China) and from European or North American countries (especially the United Kingdom, the United States of America, Switzerland, and Germany) with many more resources devoted to research on NTDs.

2.3.7.1. An overview of the publications with the most citations

Using the list of publications given in Table 2.3, this section gives a general overview of each article. The estimated number of squamous cell carcinomas of the bladder attributable to *S. haematobium* was showed by de Martel et al. (2020) in 2018. Veeresha et al. (2020) proposed a fractional Schistosomiasis model to symbolize a parasitic disease caused by trematode flukes of the genus *Schistosoma*. Langenberg et al. (2020) conducted a dose-escalating safety clinical trial in 17 volunteers with male *S. mansoni* cercariae and found a dose-related increase in adverse events related to acute Schistosomiasis (18% of volunteers showed severe adverse events and high rates of infection); all volunteers healed with PZQ administered 12 weeks after exposure.

Wendt et al. (2020) described a comprehensive single cell atlas of the adult schistosome and identified regulators of gut biology using single-cell RNA sequencing. Toor et al. (2021) used a mathematical model to predict the impact of the COVID-19 pandemic on various NTDs, showing that the risk of resurgence of Schistosomiasis, soil-transmitted helminthiases, and trachoma could be faster, especially in high-transmission areas. Meningher et al. (2020) showed that, during chronic stage of infection, *S. mansoni* downregulates Th2 differentiation in an antigen-presenting cell-independent manner, by modulating the Th2-specific transcriptional program. Parkin et al. (2020) estimated that the number of urinary bladder cancer cases in persons infected with *S. haematobium* in Africa to be 10,500, representing 1% of all cancers detected in Africa in 2018.

King et al. (2020) summarised the results of the seven largest projects of the SCORE, which were large-scale, randomized trials of different approaches to MDA using PZQ for control of either *S. mansoni* or of *S. haematobium* in endemic areas of Sub-Saharan Africa, comparing the relative effectiveness of community-based treatment against school-based treatment, and the relative efficacy of annual PZQ administration versus administration in skipped years.

Léger et al. (2020) conducted an epidemiological study and molecular analyses to investigate the prevalence, distribution, multi-host, and multi-parasite transmission cycle of *S. haematobium* in two areas of northern Senegal (one where transmission is perennial and one where it is seasonal) during the period 2016-2018. Corstjens et al. (2020) reviewed the evolution of the upconverting particle-lateral flow circulating anodic antigen assay format for the detection of *S. mansoni* and *S. haematobium* infections, demonstrating that it is a highly sensitive and specific tool to figure out the prevalence of active infection at all levels, indirectly estimate the worm burdens, and evaluate treatment programs.

Table 2.3. The 10 publications with the most citations.

Rank TC	Rank FWCI	Article	IntC*	TC	CYear	FWCI
1	1	Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis (de Martel et al., 2020)	N	335	111.66	53.09
2	2	Regarding new numerical solution of fractional Schistosomiasis disease arising in biological phenomena (Veeresha et al., 2020)	Y(3)	45	15.00	12.52
3	10	A controlled human *Schistosoma mansoni* infection model to advance novel drugs, vaccines and diagnostics (Langenberg et al., 2020)	N	34	11.33	1.45
4	8	A single-cell RNA-seq atlas of *Schistosoma mansoni* identifies a key regulator of blood feeding (Wendt et al., 2020)	N	30	10.00	3.08
5	3	Predicted impact of COVID-19 on neglected tropical disease programs and the opportunity for innovation (Toor et al., 2021)	Y(4)	28	14.00	12.20
6	5	Schistosomal extracellular vesicle-enclosed miRNAs modulate host T helper cell differentiation (Meningher et al., 2020)	N	27	9.00	4.00
7	6	Cancer in Africa 2018: The role of infections (Parkin et al., 2020)	Y(3)	26	8.66	3.74
8	7	Impact of different mass drug administration strategies for gaining and sustaining control *of Schistosoma mansoni* and *Schistosoma haematobium* infection in Africa (King et al., 2020)	Y(9)	23	7.66	3.33
9	4	Prevalence and distribution of Schistosomiasis in human, livestock, and snail populations in northern Senegal: A one health epidemiological study of a multi-host system (Léger et al., 2020)	Y(4)	21	7.00	4.88
10	9	Circulating anodic antigen (CAA): A highly sensitive diagnostic biomarker to detect active *schistosoma* infections - improvement and use during SCORE (Corstjens et al., 2020)	Y(9)	21	7.00	3.04

*Y(n): international collaboration (number of countries); N: w/o international collaboration.

2.4. Correlation analysis between number of publications and socioeconomic and demographic indicators

To understand any possible relationship between the productivity of a country (measured by the total number of publications) and some socioeconomic and demographic indicators, a statistical correlation analysis was applied.

Based on the Spearman's rank correlation test, we observed that the productivity measured by the number of publications was significantly associated with the size of the population (r = 0.61196, p-value = 0), with GERD (r = 0.4629, p-value = 0) and with researchers per million inhabitants (r = 0.26755, p-value = 0.00952) at the significance level of 5%.

According to the 2021 World Bank estimates (World Bank, 2021), the GDP per capita for low-income countries was USD 749.8, for middle-income countries was USD 6,102.0, and for high-income countries was USD 4,7886.8, showing that very important inequalities persist between nations around the world. From these data, a strong correlation could be expected between the total number of publications and GDP per capita of a country. However, it was found that the association between these two variables (r = 0.09659, p-value = 0.27059) was not statistically significant. Similarly, the total number of publications was also not significantly correlated with MPM (r = 0.08238, p-value = 0.44018) at a significance level of 0.05.

Not surprisingly, these results suggest that research on Schistosomiasis depends to a large extent on the human and material resources that a country allocates to undertake it, and yet the level of wealth of its population appears as a less decisive factor. In the case of human resources, it can be seen that the countries with the highest productivity in terms of articles are also the countries with the highest number of researchers per million inhabitants. Unfortunately, the density of researchers continues to be unevenly distributed, leading to significant differences in scientific production in the form of publications and patents. For instance, in 2018, Sub-Saharan Africa was home to 14% of the world's population, but only 0.7% of the world's researchers (UNESCO, 2021). On the other hand, the 2017 averages for the percentage of GDP devoted to R&D activities was 2.5% in North America and Western Europe and 2.1% in East Asia and the Pacific, while it was only 0.4% in Sub-Saharan Africa or 0.2% in Central Asia (UNESCO, 2020)

2.5. Discussion

Bibliometric analysis is an important tool for exploring the state of research on a particular area and provides meaningful information for researchers to assess the trends and impact of the research. This chapter has addressed the research on Schistosomiasis, which constitutes one of the most widespread NTDs worldwide, during the COVID-19 pandemic. Our bibliometric analysis found that the number of publications increased during the acute phase of the pandemic (2020 and 2021), which could be explained because the social confinement gave authors more time to write scientific papers on research conducted in the years prior to the pandemic. However, the data for the first quarter of 2022 point to a slight decrease in the number of publications; a possible explanation for this drop could be that most of the resources were for research on COVID-19.

The countries that contributed the greatest number of articles were the United States of America, the United Kingdom, China and Brazil. Regarding the productivity of the Schistosomiasis-endemic regions, this study has shown that some Sub-Saharan countries contributed a remarkable number of articles that should be highlighted considering their socioeconomic situation. South Africa, Tanzania, Ethiopia, Nigeria, Kenya and Uganda are the countries that have most clearly been concerned with carrying out some research on the disease. By contrast, looking at countries in Southeast Asia, Thailand and the Philippines were the only countries that contributed a similar number of articles to Sub-Saharan Africa. Paradoxically, the fact that most Sub-Saharan African countries have lower GDP per capita and fewer researchers than countries in Southeast Asia does not appear to have hindered research on Schistosomiasis.

The journals with the highest number of publications during the pandemic period analysed here were PLoS Neglected Tropical Diseases, Acta Tropica, and Parasites & Vectors. It should be noted that almost all the journals most used to publish research on Schistosomiasis occupy very relevant positions in the 2020 JCR, although the correlation between the number of articles and the impact factor of the journals did not turn out to be significant. As expected, the journals with the most publications were in the subject categories of Tropical Medicine, Parasitology and Infectious Diseases of the Web of Science.

The co-authorship network allowed us to guess that there is a high degree of international collaboration, which is also proven by the fact that six of the 10 most cited articles consist of authors from various countries. It is also noteworthy that there were collaborations between institutions from countries with high research productivity (e.g. the United Kingdom or Switzerland) and countries with lower productivity but with many cases of Schistosomiasis (e.g. Rwanda or Tanzania).

The keyword co-occurrence network showed that *S. mansoni*, *S. japonicum* and *S. haematobium* are currently the most investigated blood fluke species. The keyword "praziquantel", which is a tetrahydroisoquinoline and the drug of choice for the treatment and control of Schistosomiasis in many endemic countries due to its efficacy and low cost (Vale et al., 2017; Zwang and Olliaro, 2017), also appeared a high number of times in the documents in our sample. A series of terms associated with diagnosis and development of immunotherapy, such as "biomarkers", "real-time pcr", "ultrasonography" and "immune modulation", were also other keywords with a significant number of occurrences in the articles.

The most cited article was "Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis" (de Martel et al., 2020) with 335 citations and 111.66 citations per year, which was co-authored by de Martel et al. and published in The Lancet

Global Health. The FWCI for this article was 53.09, well above the other most cited articles.

This study also presents some limitations. Firstly, since the analysis was carried out shortly after the end of the acute phase of the pandemic, it would be interesting to repeat this same study after a few years with the aim of obtaining a larger sample and thus having a broader view of the effect of the pandemic on Schistosomiasis research. Second, this bibliometric analysis was carried out with the exclusive use of the Scopus database, but it could be complemented with other bibliographic databases (e.g. Web of Science and Google Scholar) to cover a greater number of sources.

Another weakness of this study refers to the exclusion of articles written in a language other than English. Although the number of publications written in other languages was low, the use of this exclusion criterion could give a biased view of the true situation of Schistosomiasis research at the level of the distribution of articles by country. On the other hand, the elimination of meta-analyses constitutes an insignificant limitation because it does not affect any of the items studied here, considering that this type of publication does not provide new research.

Finally, an interesting avenue to further complement our study would consist of also analysing the impact of the COVID-19 pandemic on prevention, diagnosis, and MDA tasks for Schistosomiasis. In this sense, a broader perspective and a better understanding of the real situation of control and research programs could be achieved through a cross-sectional study consisting of a well-structured survey questionnaire aimed at institutions that work against this parasitosis.

2.6. Conclusions

The objective of this chapter was to review the scientific literature on Schistosomiasis during the acute phase of the COVID-19 pandemic in a holistic manner to find out from a series of widely used bibliometric indices the effect of the pandemic on research in this disease. In addition, we also tested whether there is a significant correlation between research (measured by the total number of publications) and some demographic (population and researchers per million inhabitants) and socioeconomic (GERD, GDP per capita and MPM) indicators of the countries.

Our analysis was based on a total number of 1,988 articles, which were published in 160 different journals and cited 4,711 times. Of the total number of documents included in the study, only 1,143 received at least one citation, obtaining an h-index of 19. The geographical distribution of the 159 authors of these publications covers a total of 132 countries across five continents. Regarding the Spearman's correlation analysis, it was observed that the total number of publications per country was significantly associated with population, GERD, and researchers per million inhabitants, while no significant correlation was found with GDP per capita and MPM.

As Hillyer (2020) pointed out, the main difference between COVID-19 and parasitic diseases is that many of the countries most affected by the global pandemic have vast economic resources, while NTDs mainly affect the most impoverished countries. It is therefore necessary that the scientific community and public health authorities fight against COVID-19 or any other global pandemic that may appear in the future, but not at the cost of neglecting research on acute and chronic parasitic diseases and their control and prevention programs. In fact, the resumption of preventive chemotherapy for Schistosomiasis should be done immediately because it has also been shown that the administration of PZQ could reduce active cases of COVID-19 and improve the recovery rate (Oyeyemi et al., 2020).

Chapter 3
Urogenital Schistosomiasis in preschool-age children in rural Angola: prevalence and morbidity

3.1 Introduction

Children aged under 5 years of age have historically been excluded from MDA programmes with PZQ for control of Schistosomiasis infection and morbidity. The main reasons have been the paucity of studies on the prevalence of the disease among pre-schoolers, the lack of evidence on the efficacy and safety of PZQ in this age group and ultimately, the difficulty of accessing them during an MDA campaign because they do not have a place to meet, such as the school in the case of SAC. The earliest evidence of morbidity caused by Schistosomiasis during childhood dates back to colonial times, specifically to 1893 when The British Colonial Office recommended that English children living in tropical areas be sent back to England due to the risk of suffering physical and cognitive impairment because of this disease (Farley, 1991). At the time, little was known about the effect of the disease for both children and adults, and the first study on Schistosomiasis-related childhood morbidity was conducted in schools of what is now known as Zimbabwe in the late 1960s, describing fatigue, delay in schooling and decreased physical ability of children when playing as the main effects on this age group (Gelfand, 1968). In addition, this study showed that about half of the two-year-old children had *S. haematobium* eggs in their urine. However, the only treatment available at the time was an injectable dose of potassium antimony tartrate, which was extremely expensive and had several side effects, so treatment for these children was not even considered.

Since that first study, knowledge has increased significantly, but little has been done about it. Unlike now, it used to be believed that it was not possible to become infected and not excrete eggs, as well as that morbidity was directly related to the number of eggs in the urine, leading to many not being diagnosed or the extent of their infection was underestimated (Mott, 2004). This misclassification delayed the consideration of paediatric Schistosomiasis as a major public health problem in endemic countries, which is concerning as modern seroprevalence studies have established that the vast majority of children in hyperendemic areas are infected at puberty (Colley et al., 2014). It was not until 2010 that the first WHO meeting focused on discussing the situation of PSAC in Schistosomiasis control programmes was held (WHO, 2011b). The report resulting from this meeting highlights the reasons mentioned above as the main obstacles and discusses the first studies on prevalence carried out in PSAC, which prompted this debate and documented cases where crushed PZQ mixed with water or juice had been used as a method of administering the drug. However, it was not until the 2022 guide that PSAC were included in the recommended target groups for MDA campaigns (WHO, 2022b). As is often the case, the WHO reports have a major impact on the scientific community, which focused its efforts on reversing the aforementioned obstacles by increasing the studies on the prevalence and morbidity of Schistosomiasis in PSAC and demonstrating the efficacy and safety of PZQ, and what is the best way to administer the drug to this age group.

Studies on the prevalence of Schistosomiasis (Figure 3.1) and on efficacy and on safety of PZQ (Figure 3.2) in PSAC increased significantly after the publication of the WHO report. In the new millennium, only 14 studies on the epidemiological situation of Schistosomiasis in this age group were published before the 2010 WHO meeting, while in the second decade of the millennium and following the interest of WHO in increasing knowledge on this topic, the number of studies has increased to 91 (50 related to the prevalence and 41 to efficacy and on safety of PZQ).

Figure 3.1. Number of articles on the prevalence of Schistosomiasis among PSAC.

Figure 3.2. Number of articles on efficacy and safety of PZQ in PSAC.

Despite the increase in publications on Schistosomiasis in PSAC since 2010, Table 3.1 shows that these studies have analysed its situation in only 19 of the 78 Schistosomiasis-endemic countries, which means that although knowledge about the behaviour of this parasitosis in PSAC has increased, we still do not have a complete portrait of the epidemiological situation of children under 5 years for the vast majority of endemic countries (note that there are no studies for approximately 75% of these countries).

Table 3.1. Distribution of studies on Schistosomiasis in endemic countries by year.

Country	2000-2010	2011-2013	2014-2016	2017-2019	2020-2022	Total
Brazil					1	1
Cameroon	1			1		2
Côte d'Ivoire	1	2		4		7
Ethiopia			4	1		5
Ghana					1	1
Kenya		1		2	1	4
Madagascar					1	1
Malawi			2			2
Mali		1				1
Niger	1			1		2
Nigeria	2	3	3	1		9
Rwanda				2	1	3
Senegal					1	1
Sierra Leone		1				1
South Africa				1	1	2
Sudan		1				1
Tanzania	1		3	1	3	8
Uganda	3	6	1	5	1	16
Zimbabwe		2	2	3	2	9

Prevalence studies in PSAC have numerous complications compared to studies in SAC. On the one hand, the aforementioned problem that recruitment must be door-to-door, since in low- and middle-income countries there are no kindergarten and those that do exist are generally private, so households at risk of Schistosomiasis with low income do not have access. On the other hand, poor urination control at younger ages makes sampling difficult, and children under 1 year of age often require a urine collection bag due to the difficulty of collecting urine with the typical urine collection bottle. All these difficulties make the amount of studies with a large number of PSAC (especially under two years of age) very small compared to studies in SAC groups (Kalinda et al., 2020).

Studies of the prevalence of urinary Schistosomiasis in areas classified as highly endemic according to the prevalence in the SAC groups showed a prevalence among PSAC greater than 25% (Mafiana et al., 2003; Bosompem et al., 2004; Garba et al., 2010; Poole et al., 2014; Kimani et al., 2018). Early infection by Schistosomiasis is a risk factor for the chronification of the disease and the development of severe morbidity (Stothard et al, 2013); in fact, it is presumed that the high morbidity values found in SAC are due to early infection in pre-school age (Stothard et al., 2013; Bocanegra et al., 2018). To assess the true impact of Schistosomiasis-associated morbidity in children, it is important to consider the cumulative factor of Schistosomiasis, not only at the level of the affected organs, but of the performance of the whole body. Infections at that early age create inflammation that predisposes to organ fibrosis, which will then last for decades. Furthermore, stunted growth and low cognitive performance create a disability that can be fatal in settings where there are no resources and programmes for children with disabilities. Most of these cognitive delays are irreversible even if the child receives treatment, especially when the disease has already become chronic. Therefore, it is too risky for children living in endemic areas to receive their first treatment at the age of five (Colley et al., 2014).

In 2000, the WHO refined its protocol for assessing Schistosomiasis-associated morbidity, creating what is known as the "Niamey practical guide", which is still in use today (Richter et al., 1997). In this protocol, ultrasonographic examination is defined as the gold standard technique to determine the degree of morbidity associated with infection of the different human schistosomes. According to these guidelines, the UT abnormalities that should be considered in the evaluation of morbidity associated with *S. haematobium* infection are the shape of the bladder and the thickness of its wall, the presence of masses and pseudopolyps, and dilatation of the ureters and renal pelvis. This protocol not only establishes how to assess morbidity, but also provides a scale that allows damage to be quantified, resulting in what could be called a "severity index". Also, as mentioned above, the upper UT (ureters and renal pelvis) is examined, which is injured at later stages of the infection than the bladder, and is also the one that takes the longest to reverse after treatment. Although its use is widely accepted and its efficacy has been demonstrated (Akpata et al., 2015), it has the limitation that it is difficult to detect calcifications caused by this infection with this device.

Radiology is recommended to determine the presence of urinary calculi as it has been shown to be more effective than ultrasound in this case (Salas-Coronas et al., 2013). Its importance lies in the fact that its occurrence can be an indicative factor of bladder cancer; however, this is a post-treatment test for Schistosomiasis, so it does not pose a major problem for the assessment of morbidity due to *S. haematobium* itself. Since its publication, it has been the guide for studies of morbidity caused by urinary Schistosomiasis in all target groups, including studies in PSAC (Akpata et al., 2015). It is true that a major drawback of this technique is the small number of radiologists capable of recognising the damage in endemic countries. However, it is an easy technique to learn and in fact, there is a documented case of a local radiologist in Senegal who in just 8 days was able to match the diagnoses of a radiologist experienced in this type of lesions (Bonnard et al., 2011). Nonetheless, the lesions that can be assessed by ultrasound are the tip of the iceberg, since the incipient morbidity of the disease, such as anaemia or micro-haematuria, cannot be detected with this device.

Figure 3.3. Prevalence in children under 5 years of age. From: WHO (2021c).

Anaemia is a disorder in which the number of red blood cells or the concentration of haemoglobin is lower than normal, with haemoglobin values less than 11g/dL being considered mild anaemia and haemoglobin values less than 7g/dL being considered severe anaemia (WHO, 2011a). As haemoglobin is responsible for transporting oxygen, its deficiency results in a reduced capacity to transport oxygen to the tissues of the organs. Anaemia in PSAC is associated with physical impairment, delayed cognitive development, immune system dysfunction, and even death. In addition, the percentage of children with anaemia is a WHO indicator for evaluating the level of child nutrition and general health (Magalhães et al., 2011).

The most up-to-date estimates of the WHO on the prevalence of anaemia in children under 5 years determine that in 2019, about 269 million children (39.8%) worldwide suffer from anaemia and, as shown in Figure 3.3, Africa is the continent with the highest burden, reaching a prevalence of 60.2% (WHO, 2021c). This is not surprising since the main factors involved in the acquisition of anaemia in this age group are malnutrition, thalassaemia and infectious diseases, especially malaria, HIV, bacteraemia caused by *Streptococcus pneumoniae*, salmonellosis, hookworm and *S. haematobium*. The association between anaemia and *S. haematobium* infection is widely investigated; although there is no consensus on how the parasite causes the decrease in haemoglobin, it is assumed to occur due to the extracorporeal loss of iron caused by haematuria typical of *S. haematobium* infection and by the so-called anaemia of inflammation, which is due to chronic inflammation that is a characteristic symptom of chronic Urogenital Schistosomiasis. Although studies on the association of anaemia and *S. haematobium* infection in PSAC are scarce compared to other age groups, probably because the high number of children at that age with anaemia in sub-Saharan Africa makes their evaluation difficult, there are different investigations that give evidences of anaemia caused by *S. haematobium* in PSAC (Sousa-Figueiredo et al., 2008; Magalhães et al., 2011; Kinung'hi et al., 2014; Weze et al., 2021).

Another condition triggered in children by Urogenital Schistosomiasis is malnutrition. This association was first described in the late 1980s when an epidemiologic study of *S. haematobium* in children showed increased appetite and improved nutritional status after receiving treatment for the infection (Latham et al., 1990). Malnutrition is also a disorder involving many factors, such as infections (e.g. Schistosomiasis), the nutritional status of the mother during pregnancy, lack of breast milk intake during the first months of life (common in children with malnourished mothers) and low food intake or lack of nutrient-dense foods after 12 months of age.

In 2006, the WHO together with UNICEF launched their latest protocol for the assessment of severe malnutrition in children. In this guide, they establish two ways of classifying malnutrition: (1) a proxy measure using the mid-upper arm circumference (MUAC) strip in which values below 110 mm indicate severe malnutrition and between 110 and 130 mm mild malnutrition and (2) the *z*-score, a more refined measure, which measures the weight-for-height ratio that determines the level of wasting relative to when a child is too thin for his/her height and that classifies severe malnutrition with a maximum ratio of -3 and mild malnutrition with a ratio ranging between -1 and -2. The latest data on malnutrition show that by 2020, around 13.6 million PSAC were affected by severe wasting. As can be seen in Figure 3.4, almost all of the world's wasted children under 5 are found in Asia and Africa, with the African continent accounting for 41% of severely malnourished children (WHO, 2021d).

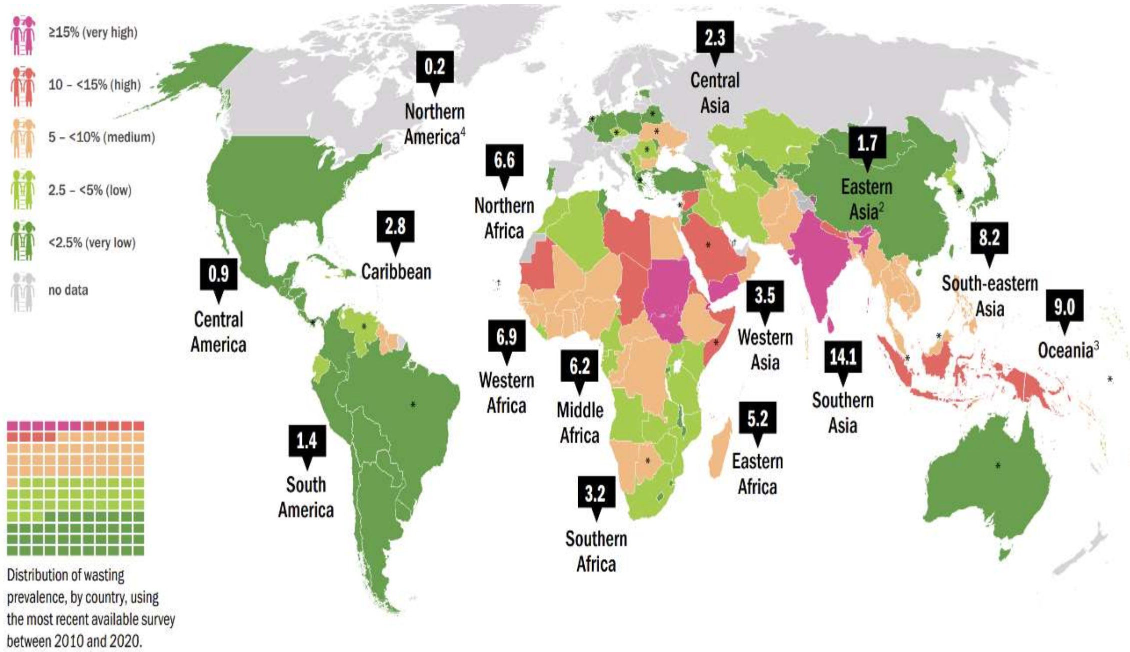


Figure 3.4. Global wasting levels among children under 5 years of age. From: Levels and trends in child malnutrition (WHO, 2021d).

This chapter addresses the study carried out in Cubal (Angola) on the prevalence and morbidity of Urogenital Schistosomiasis in PSAC. Aspects such as malnutrition and anaemia are also assessed to determine their association with infection. Our aim is to establish the epidemiological situation of PSAC in this African rural area with regard to *S. haematobium* infection and to increase the available literature on this topic to motivate further interest in this age group.

3.2 Material and methods

A cross-sectional study was carried out between February and May 2022 in Cubal (Angola). The study was carried out in the facilities of Hospital Nossa Senhora da Paz (HNSP) in Cubal, shown in Figure 3.5. This one, together with the Municipal Hospital, are the health centres of the entire municipality of Cubal, serving not only the population of the city of Cubal but also the three communes belonging to the municipality (Yambala, Tumbulu and Capupa). The Municipal Hospital is publicly managed, and therefore free and universal, but since it is a rural hospital it receives minimal funding, so it lacks resources and has an extraordinary deficit of health professionals and equipment, unlike hospitals in the big cities that are highly financed, and even in the capital city there are hospitals with high technology comparable to the best hospitals in high-income countries.

The HNSP, unlike the Municipal Hospital, is a private, non-profit hospital included in the country's public network, founded by the Mission of the Teresian Sisters of Jesus. It also has a close collaboration with the Spanish Hospital Vall d'Hebron of Barcelona and its research centre, which means that its resources, although limited, are far superior to those of the Municipal Hospital. This hospital has a laboratory equipped and trained for the diagnosis of different parasitological, bacterial and viral diseases, an important child malnutrition unit, X-ray and ultrasound devices, a consultation specialised in monitoring and supporting people living with HIV and a large tuberculosis unit famous throughout the country for its treatment of multi-resistant tuberculosis. These characteristics make the HNSP very frequented and attract people not only from the municipality of Cubal but also from other relatively close municipalities such as Caimbambo. Medical visits, hospitalisation, and diagnostic tests are financed through patient co-payment, with the exception of families admitted for malnutrition. However, the hospital has many deficiencies: there is only electricity from 8:00 a.m. to 12:30 p.m. and from 6:00 p.m. to 11:00 p.m., they often have difficulties covering the demand for oxygen, there is a lack of palliative medicines, the malnutrition unit is overcrowded, part of the tuberculosis unit was damaged by heavy storms and is unusable, the laboratory is often short of reagents and they do not have the capacity to feed the hospitalised people. Furthermore, the hospital has only three medical doctors.

a) Entrance of the HNSP

b) Hospital water source for families of hospitalised patients

c) Laboratory of the HNSP

d) Cooking area for families of children admitted due to malnutrition

Figure 3.5. Hospital Nossa Senhora da Paz (Cubal, Angola).

3.2.1 Study population and data collection

The municipality of Cubal is located in the province of Benguela, with a population of 322,000 inhabitants, 47% of whom are under 15 years of age and an estimated 58,000 children under 5 years-old (INE, 2014). It is a rural area that has several waterbodies used for human activities such as bathing or washing clothes. We identified three main freshwater hotspots with human activity. Two of them were part of the Cubal river that crosses the municipality and the other was a lake next to the town.

As the target population was PSAC, traditional school recruitment was not possible and therefore a call out was made in churches and markets to inform about the ongoing study without mentioning that the study was on urinary Schistosomiasis to avoid receiving only children with symptoms compatible with the disease and thus get a representative sample of the community. The inclusion criteria were children under five years of age without symptoms identified by their parents as being typical of Schistosomiasis. As shown in Figure 3.6, children arrived at the hospital to participate in the study accompanied by their caregivers, and parents often brought more than one child. Once it was verified that the children met the inclusion criteria, the purpose of the study, the tests that would be carried out, and what would be done with the resulting data were explained to their caregivers. This explanation was also given in the local language (Umbundu) if necessary. After the explanation, they were asked to sign the informed consent form in order to include the children in the study. The results of all tests were given to the parents.

Figure 3.6. Course of the study at Hospital Nossa Senhora da Paz (Cubal, Angola).

Epidemiological and clinical data were collected, including gender, age, neighbourhood, height, weight, weight-for-height-for-age *z*-score, mid-upper arm circumference (MUAC) and haemoglobin level (Appendix B). The malnutrition degrees were determined according to WHO standards: children with *z*-score values lower than -3 were classified as severe malnutrition and admitted directly to the child malnutrition area, values of -2 were classified as moderate malnutrition and -1 as mild malnutrition (WHO, 2006). A urine sample was then collected and a urine dipstick test (Abbonn) was performed to describe the characteristics of the urine. In addition, an evaluation of the capillary haemoglobin (Hb) level was performed using the Haemocheck Kit TM (Remedy Healthcare). Anaemia was defined as haemoglobin values lower than 11 g/dL and severe anaemia for values less than 7 g/dL (WHO, 2011a). Children with haemoglobin values equal to or less than 5g/dL were referred directly to the haemotherapy service for blood transfusion. Finally, each participant was sent for a urological ultrasound examination.

Given the high prevalence of Schistosomiasis previously described in the municipality, the single dose of PZQ was given after evidence of haematuria on the dipstick test. Those who were diagnosed by the presence of *schistosoma* eggs on the subsequent urine microscopic analysis received the drug after the ultrasound test. Those children with low values of haemoglobin or *z*-score were referred for further medical examination.

3.2.2 Sample size calculation

The sample size was calculated based on the estimation of 58,000 PSAC, a 61% prevalence of Schistosomiasis, and 85% urinary affectation, according to a previous study by Bocanegra et al. (2018). Considering 95% confidence, 7% precision and 10% loss, the sample size resulted in 186 children. Due to the fact that at the time of carrying out the study we found an ultrasound dropout rate of 22.4%, the sample was increased to 245 children.

3.2.3 Urine examination

A preliminary assessment of macroscopic haematuria was performed by visual examination of the researchers (Figure 3.7), followed by a urine dipstick test (Abbonn) to assess for the presence of leukocytes (trace for 15 cells/μl, one cross for 70 cells/μl, two crosses for 125 cells/μl and three crosses for 500 cells/μl or more), proteins (one cross for 0.3 g/L, two crosses for 1 g/L, three crosses for 3 g/L and four crosses for 20 g/L or more) and erythrocytes (trace for less than 25 cells/μl, one cross for 25 cells/μl, two crosses for 80 cells/μl and three crosses for 80 cells/μl or more).

The presence of the eggs was evaluated with a laboratory stereomicroscope after filtering the urine through 40 μm nylon filters (Thermo Fisher). The total number of eggs was also recorded to classify the intensity of the infection according to WHO standards, where less than 50 eggs/10 mL is considered to be of low intensity and more than 50 eggs/10 mL is a high intensity infection (WHO, 2022b).

Figure 3.7. Preliminary macroscopic haematuria assessment.

3.2.4 Urologic ultrasound

All children were scheduled for urinary ultrasound regardless of urine results; children were given water prior to the ultrasonography examination to properly assess the bladder status. It was performed with a portable ultrasound machine (myLab 25; ESAOTE, Genova, Italy) at Hospital Nossa Senhora da Paz (Cubal) by a trained clinician who was unaware of the prior analysis and in the presence of the child's caregiver.

Urinary pathology abnormalities were evaluated following the WHO guidelines for assessment of *S. haematobium* infection known as "Niamey practical guide" (Richter, 1997). The shape of the urinary bladder, the lesions detected in the bladder wall, and the degree of dilatation of the ureters and renal pelvis were recorded. The severity of the morbidity observed in the ultrasound was categorised by means of the global score based on each one of the pathological changes found according to the WHO score, which classifies the affectation in scores from 0 to 32, with 0 being normal ultrasound and 1 in forward ultrasounds with abnormalities that increase the score according to severity. This is the same methodology that was used in a previous study of urinary disorders caused by *S. haematobium* in SAC of Cubal (Bocanegra et al., 2018).

3.2.5 Statistical analysis

Normally distributed quantitative variables were compared using the Student's t-test and expressed as the mean standard deviation (SD). Categorical variables were compared using the chi-squared or Fisher's exact test when the frequencies were less than 5%, and were expressed as frequencies and percentages. Both Pearson's correlation analysis and point-biserial correlation analysis were applied to check for any relationship between some pairs of variables. The correlation coefficient (r) was considered significant if the p-value was less than 0.05. All statistical analyses were performed using IBM SPSS Statistics.

3.2.6 Ethical aspects

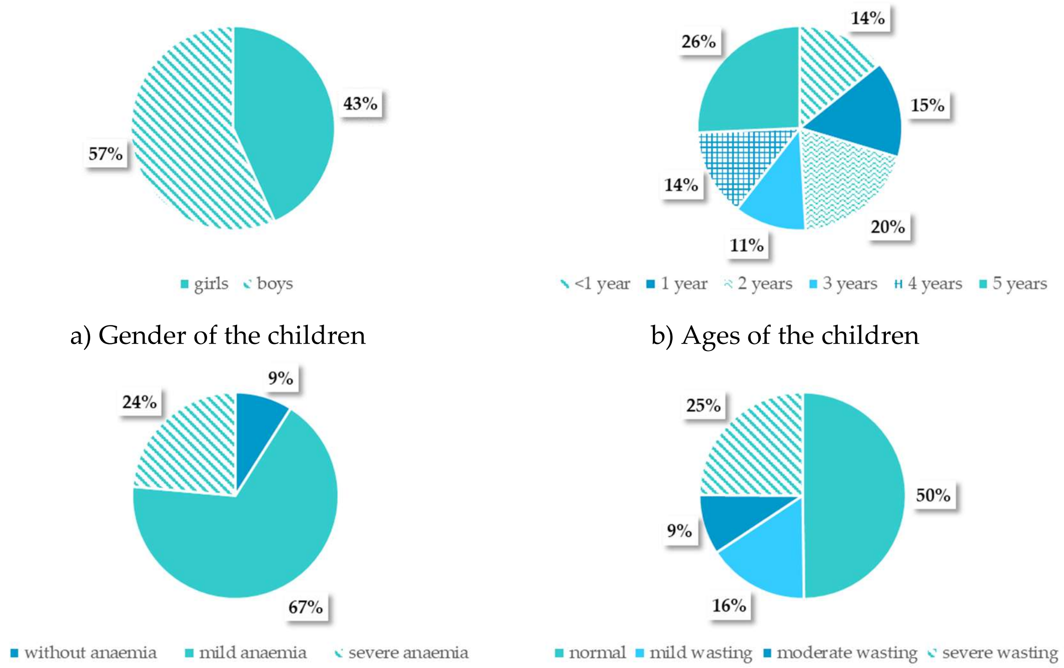
This study was approved by the Ethics Committee of the Ministério de Saúde de Angola and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements (see Appendix C). The legal tutors of each child involved in the study were informed in Portuguese or Umbundu (local language) and gave written informed consent to participate. All data were anonymized and the study has no costs for the participants. In addition, PZQ was given free of charge to children with ongoing infection.

3.3 Results

The results of this study are divided into four blocks: study population, urogenital Schistosomiasis prevalence, indirect test analysis, and ultrasound examination.

3.3.1 Study population

A total of 245 children aged 5 years or younger were enrolled to participate in the study. All of the children lived in the Cubal district, except for 18 children (7.3%) who lived in Caimbambo, a nearby rural village whose population often travels to Cubal for medical care. The demographic and epidemiological data of participants are shown in Figure 3.8. A total of 106 girls (43%) and 139 boys (57%) participated in the study. Their ages ranged from one month to 5 years, with a mean age of 3.3 (SD = 1.6) years. Haemoglobin values varied between 4 g/dL and 14 g/dL, with a mean value of 9.4 g/dL (SD = 2.07). Overall, 223 children (91%) presented anaemia (between 11g/dL and 7g/dL); of these, 57 children (246%) had severe anaemia (below 7g/dL). Regarding the nutritional status of the participants, only 122 (50%) did not present malnutrition, 39 (16%) had mild malnutrition, 23 (9%) moderate malnutrition, and 61 (25%) severe wasting (z-score ≤ -3).



a) Gender of the children

b) Ages of the children

c) Anaemia status of the children

d) Nutritional status of the children

Figure 3.8. Demographic and epidemiological data of participants.

3.3.2 Urogenital Schistosomiasis prevalence

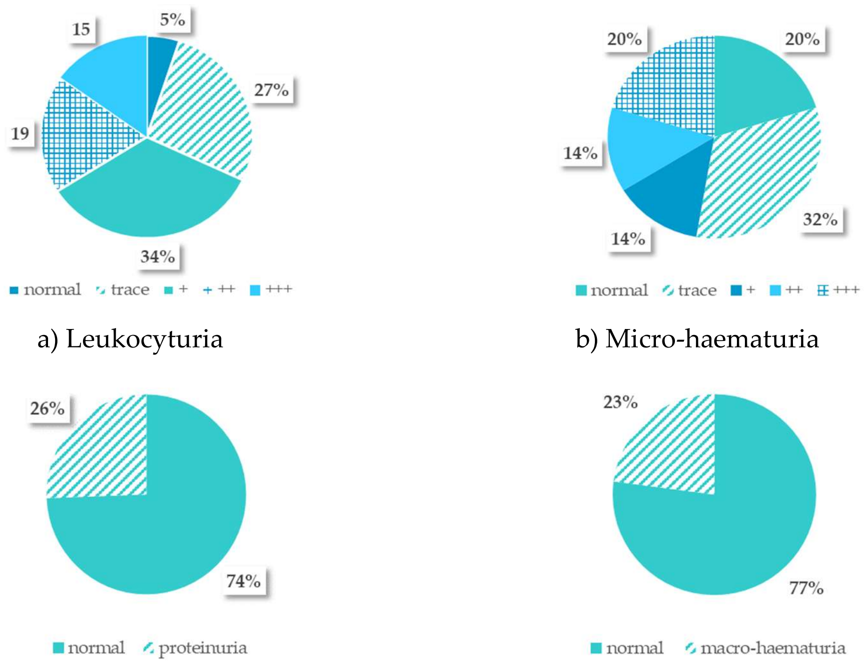
The presence of *S. haematobium* eggs was detected by microscopic examination in 74 children, which represents 30.2% of the total showing eggs in the microscopic examination, among whom 59 children presented low-intensity infection (79.7%) and 15 (20.3%) had high-intensity infection. Their mean age was 3.1 years (SD = 1.59), and older age was found to be related to infection (r = 0.14419, p-value < 0.05). Furthermore, as can be seen in Table 3.2, height and weight proved to be significantly associated with *S. haematobium* infection.

Table 3.2. Demographic and clinical data for infected and non-infected children. Data are reported as mean and (standard deviation). The *p*-value for each item in relation to *S. haematobium* infection is given and significant associations are highlighted in bold.

	Infected (N = 74)	**Non-infected (N = 171)**	***p*-value**
Age (years)	3.1 (1.5)	2.8 (1.7)	**0.024**
Weight (kg)	13.3 (4.5)	11.3 (4.6)	**0.00235**
Height (cm)	91.7 (15.5)	85.2 (15.2)	**0.0258**
Z-score	-1.2 (1.5)	-1.4 (1.6)	0.35136
Haemoglobin	8.9 (1.9)	8.6 (2.1)	0.26749

3.3.3 Indirect test analysis

As can be seen in Figure 3.9, among the *S. haematobium* egg-positive samples, leukocytes were detected in 70 samples (94.5%): 20 (27%) with traces, 25 (34%) with one cross, 14 (19%) with two crosses and 11 (15%) with three crosses. For erythrocytes (so-called micro-haematuria), 59 (79.7%) samples were positive, 24 (32%) with traces, 10 (14%) with one and two crosses, and 15 (20%) with three crosses. On the other hand, dipstick urinalysis showed that leukocytes and erythrocytes were found to be statistically significant for infection (r = 0.36313, p-value < 0.01). Regarding proteinuria, it was positive in 19 (26%) samples, of which 6 (0.08%) presented traces, 8 (0.1%) one cross, 3 (0.04%) two crosses and 2 (0.02%) three crosses. Macro-haematuria was present in 17 (23%) of the urines with *S. haematobium* eggs.



a) Leukocyturia b) Micro-haematuria

c) Proteinuria d) Macro haematuria

Figure 3.9. Results of the indirect analysis of *S. haematobium* of egg-positive urines.

3.3.4 Ultrasound examination

As can be seen in Figure 3.10, urologic ultrasound examination was performed on 190 children (77.5%), since the rest of the children missed the ultrasound appointment. Among the children infected with *S. haematobium* eggs, 30 (54.5%) presented at least one abnormality, with a mean score of 5.8 (SD =5.43). Regarding the ultrasound of the children without any type of active infection, only 4 (2.9%) presented some abnormality, with a mean score of 1.75 (SD = 0.43).

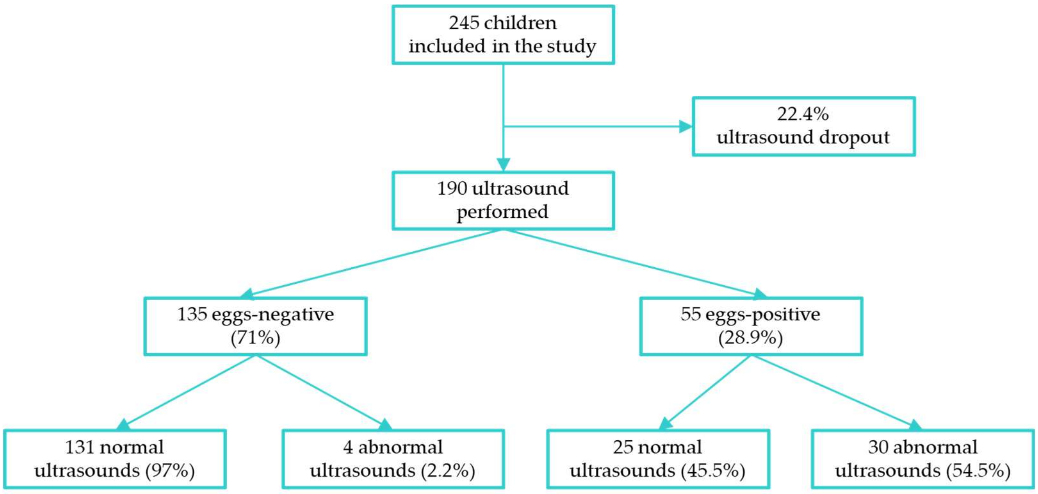


Figure 3.10. Distribution of children included in the current study.

Table 3.3 reports the results for the 30 children who presented an abnormal ultrasound and had ongoing *S. haematobium* infection by age group. As can be seen, among the different types of UT lesions, bladder wall thickening was the most common finding (100% of abnormal ultrasound scans). On the other hand, 8 (26.7%) children with abnormal ultrasound had ureteral lesions, whereas 7 (23.4%) presented pelvic morbidity.

Table 3.3. Types of UT lesions in PSAC with active urogenital Schistosomiasis. The number of children (N) with each affectation and their mean overall score (OS) stratified by age group are shown. The number of children is reported under the age heading. The percentage (%) was calculated over the total of same age children with ongoing *S. haematobium* and abnormal ultrasound.

	≤ 1 year old (N = 7)		2-3 years old (N = 7)		4-5 years old (N = 16)		Total (N = 30)	
Lesion	**N (%)**	**OS**	**N (%)**	**OS**	**N (%)**	**OS**	**N (%)**	**OS**
Bladder wall								
Wall irregularity	3 (42.9)	2	7 (100)	2	11 (68.8)	2	21 (70.0)	2
Wall thickening	7 (100)	2	7 (100)	2	16 (100)	2	30 (100)	2
Bladder masses	1 (14.3)	2	0 (0)	0	0 (0)	0	1 (3.3)	2
Pseudopolyp	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0
Ureters								
Right ureter	1 (14.3)	4	1 (14.3)	3	1 (6.3)	3	3 (10.0)	3.3
Left ureter	2 (28.6)	3.5	0 (0)	0	3 (18.7)	3	5 (16.7)	3.2
Pelvis								
Right pelvis	1 (14.3)	8	0 (0)	0	1 (6.8)	8	2 (6.7)	8
Left pelvis	2 (28.6)	7	0 (0)	0	3 (18.8)	7.3	5 (16.7)	7.2
Mean score	7.8		4.1		5.8		5.8	

The mean morbidity score for the bladder wall, ureter, and kidneys, as well as the overall mean score, are shown in Figure 3.11. UT morbidity score was shown to be significantly related to Schistosomiasis infection ($r = 0.47673$, p-value ≤ 0.05).

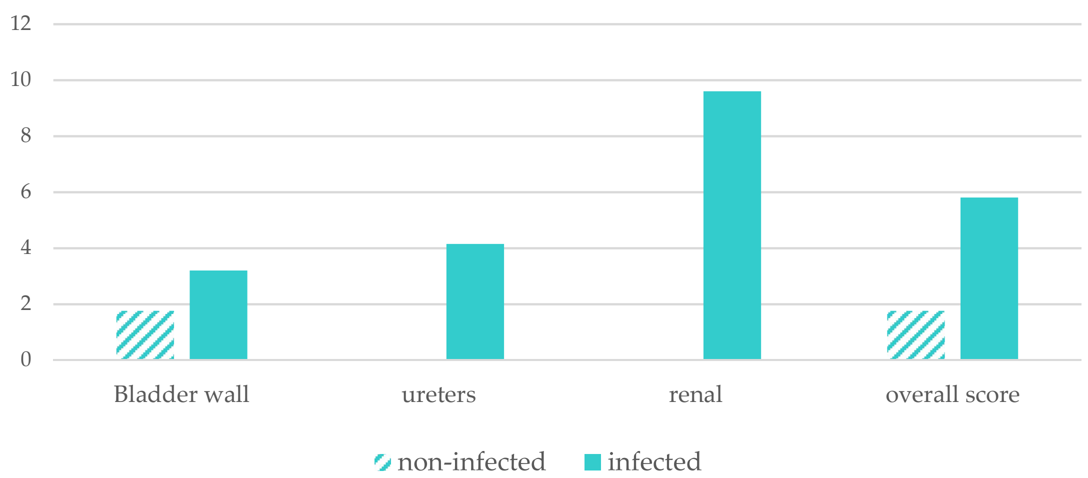


Figure 3.11. Mean morbidity score for infected and non-infected children.

The number of eggs found in the urine was significantly higher in those children with abnormal ultrasound scans ($r = 0.6541$, p-value < 0.05). Table 3.4 shows that macro-haematuria, micro-haematuria and proteinuria were correlated with UT morbidity ($r = 0.161$, p-value ≤ 0.05; $r = 0.262$, p-value ≤ 0.01; $r = 0.249$, p-value ≤ 0.01; respectively). In addition, the development of UT lesions seemed to be related to anaemia and severe malnutrition ($r = 0.238$, p-value < 0.01; r = 0.160, p-value ≤ 0.05).

Table 3.4. Prevalence of indirect morbidity assessment criteria in children with UT morbidity and children with normal UT observed in ultrasound examination. The number and (percentage) are reported. The *p*-value of indirect test urinalysis and its correlation with UT morbidity are shown. Significant associations are highlighted in bold.

	Abnormal ultrasound (N = 34)	**Normal ultrasound (N = 156)**	***p*-value**
Macro-haematuria	4 (11.7)	6 (3.8)	**0.012**
Micro-haematuria	15 (44.1)	40 (25.6)	**0.001**
Leukocyturia	17 (50.0)	25 (16.0)	0.377
Proteinuria	5 (14.7)	4 (2.5)	**0.002**

3.4 Discussion

Historically, Schistosomiasis control and eradication programmes have been focussed on SAC deworming in endemic countries. Targeting this age group leaves children under the age of 5 behind not only in MDA campaigns but also in research. Thus, little is known about schistosome-related morbidity among pre-school-age population. However, in recent years, some studies have been carried out to determine the prevalence of *S. haematobium* infection among PSAC, showing data that range from 0.83% to 74.9% (Mafiana et al., 2003; Bosompem et al., 2004; Dabo et al., 2011; Mazigo et al., 2021) depending on the degree of endemicity of the studied area. As a consequence, different research groups demonstrated the efficacy and safety of praziquantel in PSAC and claimed for its inclusion in MDA campaigns (WHO, 2011b). It is now in 2022 when the WHO has modified its guide for MDA against Schistosomiasis and recommends applying it to children from 2 years of age and above (WHO, 2022b). Children under two years of age are also candidates for treatment on individual basis, mainly due to the difficulty of adjusting PZQ doses in this particular group. However, with the support of the Pediatric Praziquantel Consortium[13], research for a suitable paediatric PZQ version for PSAC administration is currently ongoing.

Our study confirms that the high prevalence in PSAC also extends to Angolan endemic areas with a prevalence of Urogenital Schistosomiasis of 30.2% in Cubal. It is within the expected values considering other studies on PSAC prevalence and previous research in the SAC group that was carried out in Cubal in 2014, where a prevalence of 61% was found (Bocanegra et al., 2015). The likelihood of infection increases with age as older children have been in contact with infested water for longer. In fact, we found that age was correlated with the risk of infection (r = 0.14419, p-value < 0.05). However, it is known that children from endemic areas are exposed to the parasite since they are one

[13] https://www.pediatricpraziquantelconsortium.org/

year old or less, considering that their mothers bathe them with river water (Kibira et al., 2019).

An overwhelming 91% of children had anaemia, what is considerably higher than other anaemia burden studies among African pre-school children (Turawa et al., 2021; Weze et al., 2021) and a 23.3% of severe anaemia. Although we found a significant relation between anaemia and UT morbidity (p-value <0.01), we did not find it with the Schistosomiasis infection, which could mean that these lesions are due to chronic inflammation. This is understandable since anaemia is a multifactorial condition with a great impact in low and middle countries where malnutrition, bacterial and parasitic infections (especially malaria), poor access to water and the use of unsanitary toilets had been related to low values of haemoglobin (Valero et al., 2008; Gujo and Kare, 2021; Balis et al., 2022). Severe anaemia can cause impermeant in physical and cognitive growth (Lynch et al., 2018). Regarding the malnutrition status of participants, 50.2% had malnutrition which is also above nutritional studies of other African countries that ranges between 12 and 47.1% (Abdulahi et al., 2017).

Detection of haematuria and proteinuria is commonly used as a criterion to assess the severity of UT morbidity in *S. haematobium* infections. However, it is nonspecific and may not correspond to reality (Table 3.3) and so its exclusive use can be misleading. As an accurate assessment of morbidity, the use of ultrasonographic imaging is widely accepted (Akpata et al., 2015). The need of using ultrasound for the assessment of UT lesions gain importance since it remains asymptomatic until the disease progresses (King et al, 2015). Our study revealed 54.5% of UT lesions in infected children, which is consistent with other studies of Schistosomiasis morbidity (Wami et al., 2015; Barda et al., 2017) where PSAC shows a prevalence of UT morbidity associated with Schistosomiasis around 50%. According to our findings, we can state that children are affected with severe morbidity since 73.5% of the abnormal ultrasounds had an overall score higher than 4. Surprisingly the highest score was obtained by a participant of only 10 months of age, with a score of 26. However, no precursor lesions of neoplasia such as pseudopolyp (0%) or masses in the bladder (2.9%) were found in line with the study by Barda et al. (2017).

In our study, UT morbidity showed a significant association with Schistosomiasis infection ($r = 0.47673$, p-value = < 0.05) as only four abnormal ultrasounds were found in children with no *S. haematobium* eggs in the urine (2.5%) (Fig. 3.6). Nonetheless, it may be necessary to collect more than one sample in children with low egg excretion in order to be detected. Likewise, it has been noted that the absence of eggs in the urine may be because they are trapped in the bladder wall as a result of the inflammatory reaction, thus avoiding its excretion (Kihara et al., 2009).

MDA campaigns are the only available tool to prevent the cumulative morbidity caused by *S. haematobium* infection in endemic settings where access to health facilities may be a problem. Barda et al. (2017) observed progression of UT pathology in 40% of children in just 6 months. This rapid morbidity evolution raises the need to include

PSAC in MDA campaigns. Although this is already contemplated in the new WHO guide for Schistosomiasis MDA programs (WHO, 2022b), its recommendation is to cover children from two years of age in advance, which excludes younger children who, as our study shows, counts with serious pathologies at the UT. The neglection of these children and their non-treatment can lead to serious damage to the entire UT as well as irreversible damage to their integral development.

Chapter 4

Knowledge, attitudes and practices survey concerning Schistosomiasis

4.1 Introduction

NTDs, by their nature, are diseases that involve different dimensions and need to be addressed from a multidisciplinary perspective. Figure 4.1 represents the four main areas that involve control interventions to defeat these diseases: (1) environment, they are generally vector-borne diseases that require people to be in contact with certain animals or with other aspects of the environment such as water or soil for their transmission; (2) poverty and equity, social inequality and poverty are the main barriers to eradicating these diseases since most risk practices for infection are related to limited resources; (3) access to health care, as with any disease, access to diagnosis and treatment is crucial to combat it, including mass deworming and formulation of appropriate drugs for all age groups, as well as more complicated interventions such as surgery; and (4) behaviour, individual behaviour is a critical point of NTDs since their transmission is usually related to practices that expose humans to the pathogen or that reduce the possibilities of prevention, in addition to attitudes towards seeking health care. Moreover, the behaviour of institutions in terms of social awareness and health promotion is also a backbone, as well as the availability of health care and the improvement of the population's living conditions (UCNTD, 2017).

Figure 4.1. Main areas of control interventions to defeat NTDs. From: UCNTD (2017).

In the case of Schistosomiasis, control and eradication projects also follow these four lines. At the environmental level, snail vector controls are carried out through surveillance and application of molluscicides. Inequity and inequality are addressed through WASH interventions, improving hygiene and trying to overcome barriers related to access to clean water for target communities. Regarding access to health care, the WHO urges endemic countries to carry out massive deworming with PZQ annually in risk groups of high-endemic areas, and more appropriate ways of administering the drug to children under two years of age are being developed. Finally, health promotion and awareness campaigns are carried out to create behaviour change. However, changing entrenched behaviours in a community is a challenging endeavour. For this, effective health promotion campaigns are necessary, which requires a detailed analysis of their risk practices and current preventive practices. In addition, it is important to analyse why these practices are carried out, what vision they have of health interventions and their predisposition to adopt new habits. To collect all this information, cross-sectional surveys are used, among which the surveys called Knowledge, Attitudes and Practices (KAP) are the most popular and widely used (Launiala, 2009). Its relevance in public health is based on the fact that its characteristics include ease of administration, access to quantitative data, cross-cultural comparability, easy-to-interpret information, results that can be extrapolated to society as a whole, rapid implementation and results, and a design that allows to discover unplanned points.

KAP surveys allow you to collect quantitative information about a community. The use of KAP surveys began in the 1950s in the study area of family planning and population studies. In the field of tropical medicine, it rapidly gained popularity because projects in this area often involve different cultures, so biomedical knowledge about diseases must be complemented by the socio-cultural reality of the target population (Launiala, 2009). This has intensified since the planning of public health interventions in low- and middle-income countries shifted from a paternalistic approach to a cooperative one, in which the target population must be part of the intervention and the right to patient autonomy must be respected. Since most of the target diseases in African public health are closely related to behavioural habits, this type of survey is widely used on the continent. According to the WHO, KAP surveys serve to identify knowledge gaps about endemic diseases, cultural beliefs, and risk behaviour patterns for these diseases in low- and middle-income countries. The importance of this information lies in the fact that the success of a disease prevention and/or control campaign depends to a large extent on the behaviour, acceptance and adherence of the target community (WHO, 2008). In addition, these surveys require a very low budget, so having them available before designing a prevention or control campaign, which usually requires a large budget and logistical deployment, is extremely useful and increases the chances of success in a cost-effective manner. In summary, the KAP surveys in public health ultimately aim to serve as a starting point for the design of intervention campaigns for the prevention, control and eradication of diseases associated with behavioural patterns.

This type of survey evaluates the knowledge of the population about the disease and the extent to which it corresponds to reality, as well as identifying the myths and legends that may be present in society, especially with regard to the symptoms and mode of transmission or infection (Hausmann-Muela et al., 2003). Myths and legends often prevail in diseases that have been endemic for a long time and are linked to social behaviour or cultural habits. Identifying these false beliefs is crucial in projects that focus on behaviour change and health empowerment of the population. The second aspect that the surveys include is attitude, which is understood as the predisposition to think or act towards someone or something (Launiala, 2009). Understanding the attitudes towards the disease in particular and towards the state of health in general, towards the health system and about its active participation in the improvement of the community is essential for the design of health promotion activities and the strategy of interventions. Population attitudes largely depend on individual knowledge and social beliefs, as well as cultural views about certain practices, such as blood collection or the collection of genital fluid samples. Their attitude is also influenced by their previous experience with the disease or other similar illnesses, as well as their experiences with previous similar projects, especially in cases involving white people. The attitude of participants will define their adherence to the project. The last block of the survey focuses on practices against the disease. It is usually bounded to a time limit, such as one or two years. It includes both risk practices for infection as well as positive practices regarding the use of preventive measures and treatment-seeking practices. In this part, it is essential to design the questions in such a way that information is obtained not only on the frequency of the practice, but also on the logic behind the practices evaluated, such as the economic cost or the related environmental conditions.

All these data are usually complemented with demographic information of the people surveyed and their socioeconomic level. The demographic part is important since it manages to personalize health promotion campaigns to different groups (age groups, gender, professions, etc.). Religious beliefs or ethnic cultures usually have a great influence on human behaviour, therefore in societies where different ethnic groups and/or religions coexist, being able to identify their influences on the knowledge, attitudes and practices of their population allows a more precise design of the interventions. The inclusion of the socioeconomic part in the survey depends on the nature of the disease. In NTDs it has a double relevance: on the one hand, it makes it possible to denounce the poverty nature of the diseases and on the other hand, it allows to adapt the efforts of the project to the socioeconomic reality of the target community, knowing the obstacles and strengths that must be considered or behavioural changes that are feasible. The main obstacle to analysing this item was the cultural difference between the evaluated community and the society from which it is designed. For example, in Spain, the emancipation rate of young people is an indicator of youth poverty (CJE, 2022), which cannot be used in Africa because, due to its extended family culture, different generations live together in the same household even for the wealthiest families. To avoid these gaps, the UNICEF developed the Multiple Indicator Cluster Surveys (MICS) in the mid-1990s to monitor different key issues that affect the situation of children and women worldwide. It was accomplished by standardising the surveys and making it possible for everyone to use them in different countries, regardless of their cultural reality, and for their data to be comparable between countries and used in higher institutions that can shape national policies (UNICEF, 2015). The surveys are designed to be conducted face-to-face to assess the household situation. Since their inception, the surveys have been reviewed and updated until reaching the sixth round (MICS6) launched in 2016, which provides a comprehensive set of tools to analyse and assess various aspects and covers a large number of the survey-based SDG indicators of the 2030 Agenda (UNICEF, 2015).

Since KAP surveys should always be carried out prior to the implementation of the aforementioned intervention, there is numerous literature available on the knowledge, attitudes and practices of people living in Schistosomiasis-endemic areas. Awareness of the existence of Schistosomiasis differs between studies at both extremes, with studies showing either numbers above 90% and others below 30%. The most prevalent knowledge among responders is in relation to the symptoms, with haematuria standing out. Knowledge about preventive measures obtained the lowest scores in all published surveys. On the other hand, all the reported misconceptions are related to the mode of transmission of the parasite; among the most popular are urinating in corners, especially if a dog has urinated before, drinking dirty water, eating uncooked food or certain types of food, witchcraft and sexual transmission or even haematuria as a typical sign of puberty. Regarding attitudes, several manuscripts report that the main obstacles for seeking health care are the distance from their residence to a healthcare centre and the price of medical consultation or medicines. Furthermore, self-medication and preference of traditional medicine is common among endemic societies. Nonetheless, acceptance of the MDA is generally high among the communities surveyed. In relation to the practices, all the studies agree on the large number of risk practices that are carried out weekly or daily by at-risk groups. Laundry is the most common risk practice among women and fishing is the prominent practice among men while having bath is the most frequent habit that exposes both sexes to Schistosomiasis infection since urinating near the waterbodies is usually reported in all studies (Onyeneho et al., 2010; Dawaki et al., 2015; Mwai et al., 2016; Folefac et al., 2018; Anyanwu et al., 2020; Angora et al. 2019).

In African culture, women bear the burden of domestic work, they are the ones who cook, wash clothes, collect water for household chores, clean the house and take care of the children, among many other tasks (note that most of these tasks require contact with water). Due to this lifestyle, most women do any kind of work or housework taking care of the youngest children. This means that, as can be seen in Figure 4.2, women who usually go to waterbodies for daily tasks must take their children under five years of age with them, since they still do not attend school. This causes children to be exposed to Schistosomes from a very early age and with recurrence (Kibira et al., 2019). Different studies relate the Schistosomiasis infection of PSAC with the risk practices of their caregivers. Children in the care of people who bathe in the river are twice as likely to be infected as those in the care of people who use tap water for bathing. In addition, lack of knowledge about the disease and its prevention methods also appears to pose a risk for infection (Moyo et al., 2016; Mutsaka-Makuvaza et al., 2019; Sacolo-Webu et al., 2019a).

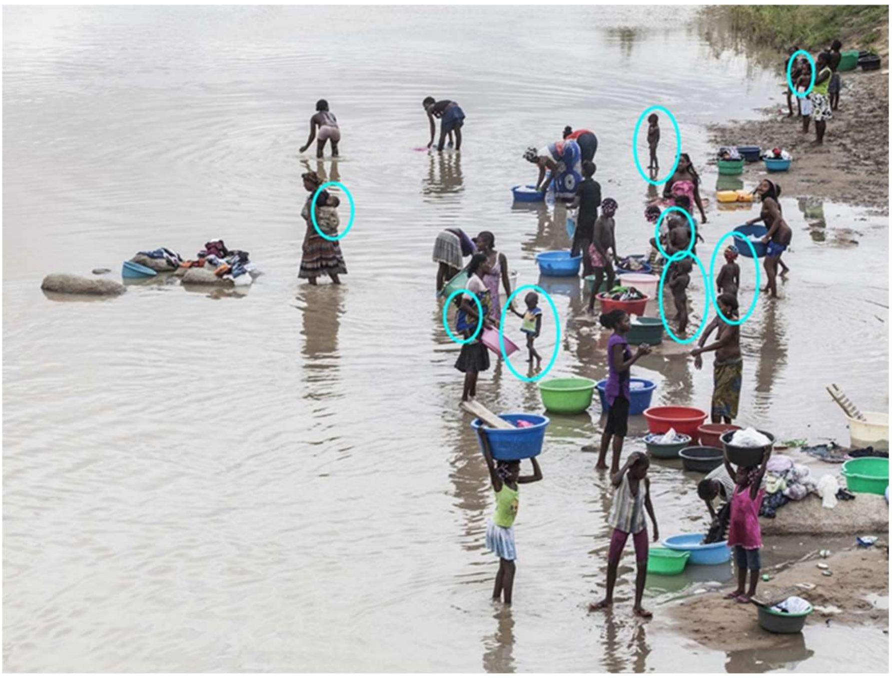


Figure 4.2. Women performing daily tasks in Cubal River.

4.2 Methodology

4.2.1 Study design

This study was a quantitative, cross-sectional household survey that assessed knowledge, attitude and practices toward urogenital Schistosomiasis and behavioural risk factors for PSAC infection and morbidity in their caregivers. It was held between February and May 2022 in Cubal, Angola.

4.2.2 Study site and sample size

Benguela covers 10 municipalities, of which six has a poverty rate above 80%. One of them is the rural municipality of Cubal with an estimated population of 322,000 inhabitants and a poverty rate of 87.3%. It has a lake and a river that surrounds the entire southern part of the municipality used for fishing, bathing and laundry. Participants were recruited in the course of a parallel study aiming to assess the prevalence and morbidity associated with urogenital Schistosomiasis in children under 5 years of age, where we found a prevalence of urogenital Schistosomiasis of 30.2% in PSAC and a 54.5% UT morbidity among infected PSAC. All caregivers of children in the previous study were offered to participate in the surveys. In addition, an active recruitment was carried out throughout the neighbourhoods of Cubal.

4.2.3 Survey questionnaire

The questionnaire was designed in order to quantitatively assess the knowledge, attitudes and practices towards Schistosomiasis as well as the socioeconomic situation of the household. Since there is no template of KAP survey for Schistosomiasis, we designed it based on WHO guidelines for KAP surveys (WHO, 2008). To assess the socioeconomic situation of the household, the MICS6 was included (UNICEF, 2015) and the overcrowding index was defined as houses where there are more than three people per habitable room (UN, 2007). Table 4.1 provides the survey scoring and its interpretation, showing that it consisted of four blocks, plus a series of demographic data (e.g. gender, age, marital status, literacy level, etc.) (see Appendix B for the survey questionnaire): (i) knowledge, which included three sub-blocks (disease, prevention and treatment); (ii) attitude; (iii) practice; and (iv) socioeconomic situation of the household (e.g. number of people contributing to household income, house facilities, type of floor, walls and roof, etc.). Most of the survey items were open-ended questions to ensure that participants expressed their real thoughts without being influenced by the possible answers proposed. However, the attitude block included a question on a Likert scale (from 0 to 5) about trust in doctors. On the other hand, the practice block had a nominal scale design ranging from "never" to "everyday", whose answers were later transformed to a binary scale by grouping all those different from "never" into a single value. It should be noted that the word "Schistosomiasis" was replaced by "tchitokoto" (the name by which the disease is known in this region of Angola) and "haematuria" by "blood in the urine" or "red urine" to facilitate the understanding of the respondents.

Figure 4.3. Ongoing implementation of the KAP survey.

4.2.4 Data analysis

The total scores were divided into thirds to classify the responses as low, medium and high (Table 4.1). Results of the survey were described using descriptive statistics, while Pearson's Chi-square test was used to analyse the correlation between variables. Odds Ratio with a 95% confidence interval was used to assess the risk factors for PSAC. The prevalence and morbidity results of the previous study on PSAC were integrated to evaluate the risk factors of their caregivers. All statistical analyses were carried out using IBM SPSS Statistics.

Table 4.1. Scoring and classification of survey responses. The disease sub-block refers to knowledge about transmission and symptoms.

	Knowledge				Attitudes	Practices	Socio-economic
	Disease	Prevention	Treatment	Schistosomiasis knowledge			
Scoring	Correct answer = 1 Incorrect answer = 0	Correct answer = 1 Incorrect answer = 0	Correct answer = 1 Incorrect answer = 0	Disease score + Prevention score + Treatment score	Yes = 1 No = 0 Likert ≤ 3 = 0 Likert > 3 = 1	Yes = 0 No = 1	(*)
Range	0-14	0-5	0-3	0-22	0-6	0-10	0-26
Classif.	0-5: low 6-10: medium 11-14: high	0-1: low 2-3: medium 4-5: high	0-1: low 2: medium 3: high	0-6: low 7-14: medium 15-22: high	0-2: low 3-4: medium 5-6: high	0-3: low 4-6: medium 7-10: high	0-8: low 9-17: medium 18-26: high

(*) Scoring was based on the MICS6 tool (UNICEF, 2015).

4.2.5 Ethical consideration

This study was approved by the Ethics Committee of the Ministério de Saúde de Angola (MINSA) (No. 41/2021) and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. Every participant was informed about the type of study and the purpose of its outcomes. The participants (or caregivers in the case of children) signed an informed consent for the inclusion of their children in the study. The informed consent and the survey were provided in both Portuguese and the local language (Umbundu).

4.3 Results

This section is divided into seven blocks to show the results of the study on knowledge, attitudes and practices related to Schistosomiasis: demographic characteristics, knowledge, attitudes, practices, Schistosomiasis history, household socioeconomic status and risk factors for PSAC with respect to their caregivers.

4.3.1 Demographic characteristics

Table 4.2 reports the demographic data of the survey participants. 250 people were participated in the study, aged between 15 and 61 years with a mean age of 31.2 (SD = 10.08), most of whom were female (62.4%). Most of the participants were married (61.2%) and slightly more than half knew how to read and write in Portuguese (59.6%). Regarding the education level, 23.6% never went to school, while only 3.2% had studied at the university. The most common nearby water body was the river, since 33.6% stated that they lived less than 15 minutes from the river. while only 9.2% lived at the same distance from the lake. Figure 4.4 shows the distribution of respondents by neighbourhood, with Kimbos (the local name for isolated rural villages) being the most frequent. Out of the total, 183 (73.2%) were caregivers who agreed to include their children under 5 years old in the aforementioned parallel study on the prevalence and morbidity of urogenital Schistosomiasis.

Table 4.2. Demographic characteristics of the participants.

	Number of participants (N=250)	**%**
Gender		
Female	156	62.4
Male	94	37.6
Age		
<40	206	82.4
≥40	44	17.6
Marital status		
Married	153	61.2
Single	83	33.2
Widow	14	5.6
Literacy level		
Can write and read	149	59.6
Cannot write and read	101	40.4
Higher educational level		
None	59	23.6
Primary	64	25.6
Secondary	69	27.6
College preparatory	18	7.2
Professional training	32	12.8
University	8	3.2
Distance to the river		
<5 min	28	11.2
5-15 min	56	22.4
16-30 min	106	42.4
≤30 min	60	24.0
Distance to the lake		
<5 min	4	1.6
5-15 min	19	7.6
16-30 min	13	5.2
≤30 min	214	85.6
Caregivers	183	73.2

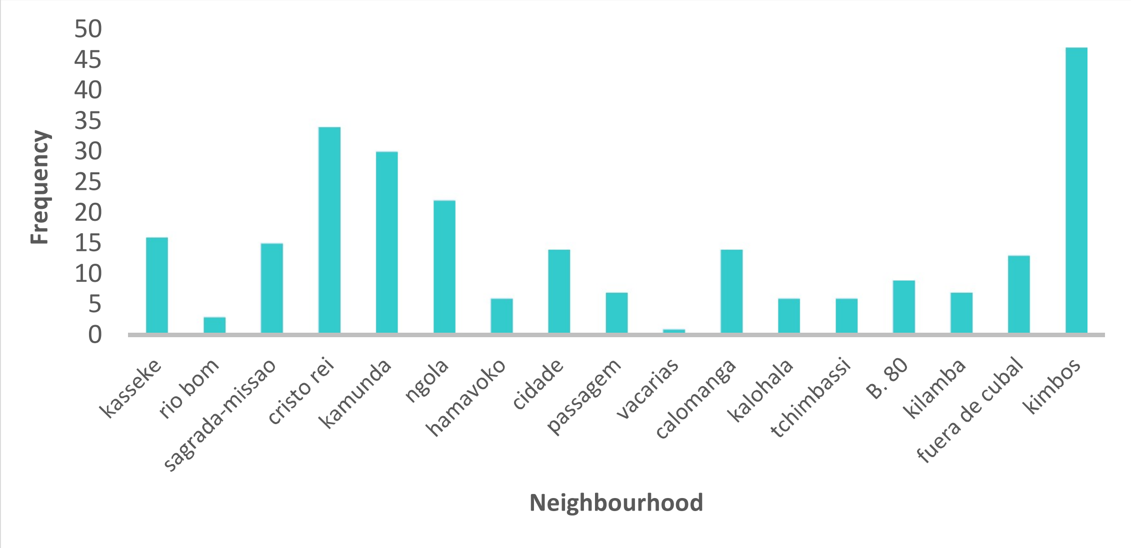


Figure. 4.4. Distribution of respondents by neighbourhood.

4.3.2 Knowledge

Table 4.3 summarizes the knowledge of urogenital Schistosomiasis among the population. 235 people (94%) declared knowing that Schistosomiasis is a disease. The majority indicated the street (47.6%) and the hospital (38%) as their main source of information about it. Blood in urine was the most widely known symptom (54.4%), followed by abdominal pain (30.4%), while 58% of them believed it is a dangerous disease that can cause death. 32.8% of the participants identified activities in river water as the main source of infection and only 2.8% identified a freshwater snail as a vector of the disease. On the other hand, there is a popular belief among the community that people become infected by eating sugar cane, which reaches up to 20.8% of responses in the survey. Regarding prevention, 72.4% stated that Schistosomiasis infection can be avoided. The most popular prevention measure among those surveyed was taking prophylactic medication (35.6%), followed by refraining from entering the river (20.4%). The greatest knowledge about Schistosomiasis among the respondents referred to the treatment. Almost all of them (91.8%) assured it can be cured either with modern medicine tablets (80%) or traditional medicine (16.8%). The overall mean knowledge score was 7.09 (SD = 3.25), with the majority (57.6%) having medium knowledge score and 42% a low knowledge score.

Table 4.3. Knowledge about Schistosomiasis, prevention and treatment.

Variable	Female (N=156) N (%)	Male (N=94) N (%)	Total (N=250) N (%)
DISEASE			
Heard about	144 (92.3)	90 (95.7)	235 (94.0)
Source of information			
School	16 (10.3)	17 (18.1)	33 (13.2)
Hospital	59 (37.8)	36 (38.3)	95 (38.0)
Street	76 (48.7)	43 (45.7)	119 (47.6)
Church	12 (7.7)	20 (21.3)	32 (12.8)
Home	22 (14.1)	27 (28.7)	49 (19.6)
Media	-	2 (2.1)	2 (0.8)
Symptoms			
Abdominal pain	50 (32.1)	26 (27.7)	76 (30.4)
Blood in urine	66 (42.3)	70 (74.5)	136 (54.4)
Fever	11 (7.1)	9 (9.6)	20 (8.0)
General discomfort	3 (1.9)	2 (2.1)	5 (2.0)
Cause of death	84 (53.8)	61 (64.8)	145 (58.0)
How to get infected			
River bath	44 (28.2)	38 (40.4)	82 (32.8)
Laundry	5 (3.2)	2 (2.1)	7 (2.8)
Drink water	9 (5.8)	10 (10.6)	19 (7.6)
Fishing	1 (0.6)	2 (2.1)	3 (1.2)
Eating sugar cane	25 (16.0)	27 (28.7)	52 (20.8)
Snail as the vector	2 (1.3)	5 (5.3)	7 (2.8)
Who can get infected			
Everyone	107 (68.6)	72 (76.6)	179 (71.6)
Only boys	3 (1.9)	2 (2.1)	5 (2.0)
Only children	11 (7.1)	10 (10.6)	21 (8.4)
It can be prevented	104 (66.6)	77 (81.9)	181 (72.4)
How to prevent it			
Avoid the river	25 (16.0)	26 (27.7)	51 (20.4)
To boil water	15 (9.6)	8 (8.5)	23 (9.2)
Medication	51 (32.7)	38 (40.4)	89 (35.6)
Not to eat sugar cane	11 (7.1)	18 (19.1)	29 (11.6)
TREATMENT			
It can be cured	139 (89.1)	89 (94.7)	228 (91.2)
How can it be cured			
Traditional medicine	23 (14.7)	19 (20.2)	42 (16.8)
Modern medicine pills	123 (78.8)	77 (81.9)	200 (80.0)
KNOWLEDGE SCORE			
Low score	77 (49.4)	28 (29.8)	105 (42.0)
Medium score	78 (50.0)	66 (70.2)	144 (57.6)
High score	1 (0.6)	0 (0.0)	1 (0.4)
MEAN SCORE	6.6 (SD=3.2)	7.9 (SD=3.2)	7.1 (SD=3.2)

4.3.3 Attitudes

Most of the participants (87.2%) believe that blood in the urine and abdominal pain are compelling reasons to seek medical care (Table 4.4). Nonetheless, only 58.8% declared going to the hospital whenever they feel sick. An overwhelming 31.6% stated that the hospital is not their first choice because it is too expensive or too far from their residence. However, 96% expressed their willingness to participate in an MDA campaign against Schistosomiasis. The mean attitude score among the participants was 5.17 (SD = 0.93) and 79.2% obtained a high attitude score.

Table 4.4. Attitudes towards Schistosomiasis.

Variable	Female (N=156) N (%)	Male (N=94) N (%)	Total (N=250) N (%)
Willing to participate in MDA	150 (96.2)	90 (95.7)	240 (96.0)
Trust in doctors	122 (78.2)	79 (84.0)	201 (80.4)
Worried if found blood in urine	138 (88.5)	80 (85.1)	218 (87.2)
Worried if abdominal pain	136 (87.2)	82 (87.2)	218 (87.2)
Hospital as first choice	93 (59.6)	54 (57.4)	147 (58.8)
Why not?			
Hospital is too far or too expensive	57 (36.5)	27 (28.7)	84 (33.6)
Prefers traditional medicine	6 (3.8)	13 (13.8)	19 (7.6)
ATTITUDE SCORE			
Low score	1 (0.6)	2 (2.1)	3 (1.2)
Medium score	32 (20.5)	17 (18.1)	49 (19.6)
High score	123 (78.8)	75 (79.8)	198 (79.2)
MEAN SCORE	5.1 (SD=0.8)	5.2 (SD=1.0)	5.1 (SD=0.93)

4.3.4 Practices

Laundry in the river was the most popular practice during the last year, with 61.2% of participants doing it (Table 4.5), of which which 52.2% said they only did it during the dry season due to the lack of another source of water (32% of the total). The same situation occurs with bathing in the river (58.8%), where 52.4% of them do so it only in the dry season, representing 30.8% of the total. Fishing is not a common practice in the community, so only 15.6% had been in contact with the river during the last year because of this practice, being significantly higher among men (χ^2 = 15.7, *p*-value <0.01). Regarding fetching water from the river to irrigate the crops, only 8% of the surveyed do it frequently, but 21.6% need it to continue with their gardening work during the dry season. Only 58 people (23.2%) claimed to carry out a prevention activity towards Schistosomiasis, but 17 of them said that not eating sugar cane is the prevention activity they carry out. The mean practice score was 3.5 (SD = 2.24) with 55.2% having a low practice score.

Table 4.5. Practices related to Schistosomiasis.

Variable	Female (N=156) N (%)	Male (N=94) N (%)	Total (N=250) N (%)
To urinate into the river	75 (48.1)	50 (53.2)	125 (50.0)
To perform Schistosomiasis prevention	17 (10.9)	31 (32.9)	58 (23.2)
To have bath at the river	90 (57.7)	57 (60.6)	147 (58.8)
Only during dry season	50 (32.0)	27 (28.7)	77 (30.8)
Frequently	40 (25.6)	30 (31.9)	70 (28.0)
To laundry at the river	103 (66.0)	50 (53.2)	153 (61.2)
Only during dry season	57 (36.5)	23 (24.5)	80 (32.0)
Frequently	46 (29.5)	27 (28.7)	73 (29.2)
To fetch river water for daily tasks	80 (51.3)	49 (52.1)	129 (51.6)
Only during dry season	42 (26.9)	23 (24.5)	65 (26.0)
Frequently	38 (24.3)	26 (27.6)	62 (24.8)
To fetch river water for irrigation	40 (25.6)	34 (36.2)	74 (29.6)
Only during dry season	25 (16.0)	29 (30.8)	54 (21.6)
Frequently	15 (9.6)	5 (5.3)	20 (8.0)
To fish	16 (10.3)	23 (24.5)	39 (15.6)
PRACTICE SCORE			
Low score	86 (55.1)	52 (55.3)	138 (55.2)
Medium score	59 (37.8)	27 (28.7)	86 (34.4)
High score	11 (7.1)	15 (16.0)	26 (10.4)
MEAN SCORE	3.5 (SD=2.1)	3.4 (SD=2.4)	3.5 (SD=2.2)

4.3.5 Schistosomiasis history

All participants were asked if they had ever received PZQ prophylaxis, 28 of whom said they had received it at some time in their lives (17 at hospital, 10 at school, and one at church). Among all the participants, 80 of them (32%) reported a history of urogenital Schistosomiasis having been diagnosed at least once in their lifetime and only 18 of them were informed about how to prevent future reinfections. As can be seen in Table 4.6, most of them (60%) claimed to have had the disease once, while only two people had the infection more than three times. The age range in which most infections occurred was between 10 and 20 years old and 83.7% of the cases were diagnosed by medical consultation in the hospital or in a primary care centre. Blood in urine and abdominal pain were the main reasons for health seeking (62.5% and 56.2%, respectively). Only 25 of the 69 people who took PZQ when diagnosed with Schistosomiasis (the remaining 11 were treated with traditional medicine) reported no side effects. Dizziness was the most frequent side effect among respondents, followed by headache and nausea.

Table 4.6. History of Schistosomiasis in participants.

Variable	Female (N=40) N (%)	Male (N=40) N (%)	Total (N=80) N (%)
How many times have been diagnosed with Schistosomiasis			
Once	25 (62.5)	23 (57.5)	48 (60.0)
Twice	13 (32.5)	13 (32.5)	26 (32.5)
Three times	2 (5.0)	2 (5.0)	4 (5.0)
More than three times	-	2 (5.0)	2 (2.5)
Age at diagnosis of Schistosomiasis			
Between 5 and 10 years	8 (20.0)	14 (35.0)	22 (27.5)
Between 10 and 20 years	25 (62.5)	28 (70.0)	53 (66.2)
More than 20 years	8 (20.0)	6 (15.0)	14 (17.5)
How Schistosomiasis was diagnosed			
Tracking campaigns	2 (5.0)	-	2 (2.5)
Medical consultation	34 (85.0)	33 (82.5)	67 (83.7)
Traditional Medicine	4 (10.0)	7 (17.5)	11 (13.7)
Symptoms			
Abdominal pain	24 (60.0)	21 (52.5)	45 (56.2)
Haematuria	18 (45.0)	32 (80.0)	50 (62.5)
Fever	7 (17.5)	2 (5.0)	9 (11.2)
General discomfort	4 (10.0)	1 (2.5)	5 (6.2)
Side effects of praziquantel			
Headache	6 (15.0)	6 (15.0)	12 (15.0)
Dizziness	7 (17.5)	17 (42.5)	24 (30.0)
Stomach-ache	5 (12.5)	-	5 (6.2)
Nausea	2 (5.0)	9 (22.5)	11 (13.7)
Fever	4 (10.0)	-	4 (5.0)
Polyuria	2 (5.0)	1 (2.5)	3 (3.7)
No side effects	15 (37.5)	10 (25.0)	25 (31.2)
Cannot remember	1 (2.5)	4 (10.0)	5 (6.2)

As shown in Figure 4.5, of those who experienced adverse effects, the majority suffered only one effect and no one had more than four. Nevertheless, they all stated that the effects lasted only one day and that the symptoms of the disease disappeared after the side effects ceased.

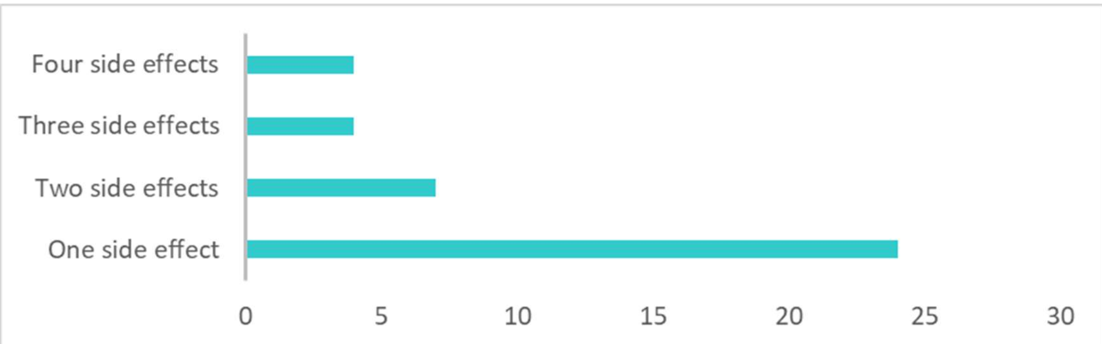


Figure 4.5. Number of PZQ side effects experimented by participants.

4.3.6 Household socioeconomic status

Most of the participants (53.2%) obtained a medium socioeconomic score, while 31.6% live in a low socioeconomic situation and 174 (69.6%) households meet the overcrowded condition (Table 4.7). The majority of the respondents must walk between 1 and 15 minutes to access a water source (71.2%) and only 44 people (17.6%) have a piped water supply at their residence. The most common environment to live in was urban areas (66.8%), and most of the construction materials for the houses are sheet metal for the roof, mud for the walls, and cement for the floor (69.6%, 47.2% and 57.6%, respectively).

Table 4.7. Socioeconomic characteristics of participants.

Variable	Female (N=156) N (%)	Male (N=94) N (%)	Total (N=250) N (%)
Number of people contributing to household income			
None	23 (14.7)	7 (7.4)	30 (12.0)
One	94 (60.3)	69 (73.4)	163 (65.2)
Two	32 (20.5)	2 (2.1)	46 (18.4)
Three or more	7 (4.5)	4 (4.3)	11 (4.4)
House items			
Overcrowding	108 (69.2)	66 (70.2)	174 (69.6)
Electricity	52 (33.3)	36 (38.3)	88 (35.2)
Tap water	25 (16.0)	19 (20.2)	44 (17.6)
Radio	51 (32.7)	64 (68.1)	115 (46.0)
TV	42 (26.9)	30 (31.9)	72 (28.8)
House environment			
Swampy area	22 (14.1)	8 (8.5)	30 (12.0)
Rural	18 (11.5)	18 (19.1)	36 (14.4)
Urban area	108 (69.2)	59 (62.8)	167 (66.8)
Paved urban area	8 (5.1)	9 (9.6)	17 (6.8)
Roof			
Sticks	20 (12.8)	14 (14.9)	89 (35.6)
Sheet metal	114 (73.1)	60 (63.8)	144 (57.6)
Cement	22 (14.1)	20 (21.3)	17 (6.8)
Walls			
Sticks	5 (3.2)	7 (7.4)	12 (4.8)
Mud	87 (55.8)	31 (33.0)	118 (47.2)
Blocks	27 (17.3)	29 (30.9)	56 (22.4)
Cement	37 (23.7)	27 (28.7)	64 (25.6)
Cooking material			
Firewood	33 (21.2)	23 (24.5)	58 (23.2)
Charcoal	42 (26.9)	16 (17.0)	56 (22.4)
Gas	81 (51.9)	54 (57.4)	135 (54.0)
Electricity	0 (0.0)	1 (1.1)	1 (0.4)
Wash			
No place to urine	29 (18.6)	26 (27.6)	55 (22.0)
Latrine	75 (48.1)	47 (50.0)	122 (48.8)

Variable	Female (N=156) N (%)	Male (N=94) N (%)	Total (N=250) N (%)
Toilet	52 (33.3)	21 (22.3)	73 (29.2)
Walking time to closest tap water			
0 min	25 (16.0)	19 (20.2)	44 (17.6)
1-5 min	82 (52.5)	41 (43.6)	123 (49.2)
6-15 min	31 (19.8)	24 (25.5)	55 (22.0)
16-30 min	11 (7.1)	9 (9.6)	20 (8.0)
> 30 min	7 (4.5)	1 (1.1)	8 (3.2)
SOCIOECONOMIC SCORE			
Low score	51 (32.7)	28 (29.8)	79 (31.6)
Medium score	82 (52.6)	51 (54.3)	133 (53.2)
High score	23 (14.7)	15 (16.0)	38 (15.2)
MEAN SCORE	11.3 (SD=5.6)	11.6 (SD=6.5)	11.4 (SD=5.9)

As can be seen in Table 4.8, statistical analyses showed that a low socioeconomic score is correlated with engaging in practices at risk of Schistosomiasis infection.

Table 4.8. Statistical relationship between low socioeconomic situation and Schistosomiasis risk practices.

Variable	χ^2 value	*p*-value
Low practice score	24.10	<0.01
River bath	26.06	<0.01
River laundry	12.35	<0.01
To fetch river water for daily tasks	25.39	<0.01
To fetch river water for irrigation	10.06	<0.01
To urinate into the river	31.74	<0.01

4.3.7 Risk factors for PSAC regarding their caregivers

Risk factors for PSAC infection are summarized in Table 4.9. Low knowledge of caregivers about Schistosomiasis was a risk factor for PSAC Schistosomiasis infection (OR=7.45, 95%CI: 3.72-14.91). In more detail, poor knowledge about the disease (how it is transmitted and its symptoms) represents the greatest risk factor (OR=16.93, 95%CI: 3.93-72.82). In fact, the overall knowledge score was higher in those caregivers who do not had infected PSAC, as was the knowledge score broken down by blocks (Figure 4.6). Bathing and washing clothes at the river also turned out to be a risk factor for PSAC infection (OR= 2.2, 95%CI: 1.16-4.16 and OR= 2.5, 95%CI: 1.28-4.89, respectively). In addition, not having prior knowledge about Schistosomiasis also appeared as an important risk factor (OR=2.47, 95%CI: 1.79-3.39).

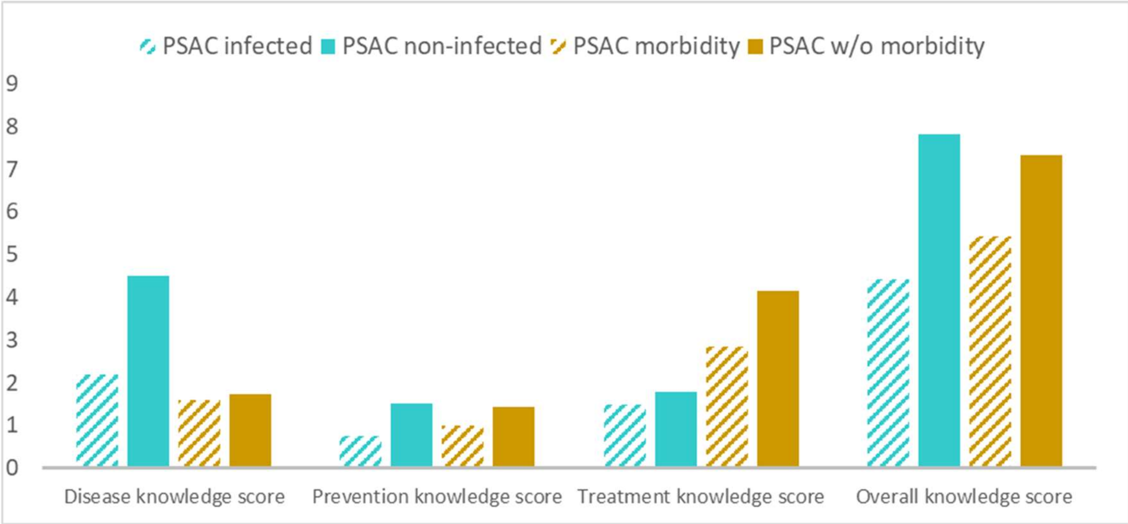


Figure 4.6. Knowledge scores among caregivers.

In addition, we found that those with low knowledge about Schistosomiasis (OR=2.24,95%CI: 1.05-4.47) have never heard of this disease (OR=2.7, 95%CI: 1.2-6.1), not recognizing its symptoms (OR=2.22, 95%CI: 1.12-4.41), believe that you can get infected by eating sugar cane (OR=2.78, 95%CI: 1.44-5.39), and not knowing how to prevent it (OR=8.14, 95%CI: 1.14-58.25) are also, among others (Table 4.10), risk factors for the development of UT morbidity among PSAC.

Table 4.9. Risk factors associated with infection by *S. haematobium* in PSAC.

Caregiver variable	**Infected (N=68) N (%)**	**Non-infected (N=115) N (%)**	**OR [CI 95%]**
Risk factor for *S. haematobium* infection			
Not knowing about Schistosomiasis	13 (19.1)	3 (2.6)	2.47 [1.79-3.39]
Not recognising any symptom	32 (47.1)	32 (27.8)	2.17 [1.41-3.32]
Haematuria is not a symptom	50 (73.5)	49 (42.6)	2.36 [1.50-3.71]
Abdominal pain is not a symptom	58 (85.3)	68 (59.1)	2.62 [1.45-4.75]
It cannot cause death	30 (44.1)	37 (32.1)	1.80 [1.16-2.76]
Not knowing source of infection	43 (63.2)	54 (46.9)	3.27 [1.6-6.67]
Believe it cannot be prevented	27 (39.7)	21 (18.8)	2.27 [1.52-3.38]
Avoid river bathing does not prevent it	65 (95.6)	85 (73.9)	4.76 [1.60-14.24]
Believe it cannot be cured	5 (7.3)	3 (2.7)	1.91 [1.10-3.41]
Medicines are not the treatment	22 (32.4)	18 (15.7)	1.7 [1.20-2.47]
Never had Schistosomiasis	56 (82.4)	77 (67.0)	1.75 [1.03-2.98]
River bathing	48 (70.6)	60 (52.2)	2.2 [1.16-4.16]
River laundry	52 (76.5)	65 (56.5)	2.5 [1.28-4.89]
Low disease knowledge	66 (97.1)	76 (66.1)	16.93 [3.93-72.82]
Low prevention knowledge	47 (69.1)	46 (40.0)	3.35 [1.77-6.33]
Low treatment knowledge	21 (30.9)	18 (15.7)	2.4 [1.17-4.94]
Low Schistosomiasis knowledge	53 (77.9)	37 (32.2)	7.45 [3.72-14.91]

Table 4.10. Risk factors associated with morbidity due to *S. haematobium* in PSAC.

Caregiver variable	Morbidity (N=32) N (%)	w/o morbidity (N=151) N (%)	OR [CI 95%]
Risk factor for *S. haematobium* associated UT morbidity			
Not knowing about Schistosomiasis	5 (15.6)	10 (6.6)	2.7 [1.20-6.10]
Not recognising any symptom	19 (59.4)	41 (27.1)	2.22 [1.12-4.41]
Haematuria is not a symptom	20 (62.5)	66 (43.7)	1.98 [1.02-3.90]
Sugar cane as source of infection	6 (18.7)	15 (9.9)	2.78 [1.44-5.39]
Avoid river bathing does not prevent it	31 (96.9)	94 (62.2)	8.14 [1.14-58.25]
MDA refusal	4 (12.5)	0 (0.0)	1.27 [1.17-1.39]
River bathing	22 (68.7)	67 (44.3)	2.33 [1.04-5.26]
River laundry	27 (84.4)	68 (45.0)	3.9 [1.46-10.63]
Low disease knowledge	30 (93.7)	92 (60.9)	1.16 [1.10-1.25]
Low prevention knowledge	20 (62.5)	62 (41.1)	2.2 [1.02-4.72]
Low Schistosomiasis knowledge	19 (59.4)	61 (40.4)	2.24 [1.05-4.77]

4.4 Discussion

As far as we know, this is the first study of knowledge, attitude and practice regarding urinary Schistosomiasis conducted in Angola.

Knowledge about urogenital Schistosomiasis is generally poor, as most respondents were not able to answer half of the survey correctly. However, 94% had prior knowledge about the existence of Schistosomiasis. This huge percentage is probably due to the high prevalence of the disease in the area of this study (Bocanegra et al., 2015), which makes people familiar with it. While only one person (0.4%) scored high knowledge, 105 (42%) were classified as having low knowledge. Knowledge in endemic areas varies considerably between published studies, however low scores are the most common results (Odhiambo et al., 2014; Dawaki et al., 2015; Folefac et al., 2018). Higher knowledge scores showed to be correlated with having passed a Schistosomiasis infection (◎2 = 10.18, p-value < 0.01), which supports the hypothesis that it is due to the fact that it is a common disease in this population. Furthermore, the low knowledge score is statistically related to a low socio-economic level (◎2 = 29.57, p-value < 0.01), which is alarming considering the close link between the disease and poverty. Only two people declared the radio as a source of information on Schistosomiasis. Taking into account that 115 households (46%) have a radio, and that it is a device that does not require an electrical installation, so lower-income families can have it at home, the radio is a tool that could be used to raise awareness of this disease and that it is not being exploited. The fact of carrying out the methodology without a self-administrated survey and with open questions allowed us to consider cultural myths that were not planned, as well as eating sugar cane as a source of infection. 52 people (20.8%) had this belief which supposes a double negative repercussion; on the one hand, people who have this belief are not aware of the real source of infection, which makes proper prevention practice impossible. On the other hand, efforts to prevent the disease can cause an economic impact on sugar cane farmers. Nevertheless, sugar cane is commonly being stripped by Africans with their teeth and has been highlighted to be a potential source for human fascioliasis when grown in swampy areas of Africa (Mas-Coma et al., 2018). Indeed, *Fasciola gigantica* is widespread in all this part of Africa (Mas-Coma et al., 2022), it is known to be highly pathogenic (Valero et al., 2016), induce evident symptomatology (Mas-Coma et al., 2014), and its infection in humans has already been reported (although referred to as F. hepatica, which is absent throughout this part of the continent) in the Cubal municipality (De Alegria et al., 2017). This suggests that people may confuse the symptoms caused by the liver fluke with those due to *S. haematobium* and consequently confuse one trematodiasis with the other.

However, it is worth highlighting the high level of knowledge about the treatment of Schistosomiasis (80%). Respondents scored highest in their attitude towards Schistosomiasis, with 198 people (79.2%) scoring high in attitude. In fact, 87.2% of people would seek for health care if they detected blood in urine or felt abdominal pain, and the average score that the participants gave to their doctors in terms of trust was 3.58 out of 5. Nonetheless, this positive attitude, is left behind when infected people cannot attend healthcare facilities due to the price of the medical consultation or the distance from their residence to healthcare centres or hospitals (31.4% of cases). In fact, the socio-economic level was strongly associated with attending at the medical consultation (χ^2 = 44.395, p-value <0.01). On the other hand, traditional medicine is the only option for 7.6% of people and 4% expressed that would not participate in an MDA campaign because they did not trust modern pills. Although this should not be a problem, they could avoid their children to benefit from MDA campaigns. However, 96% acceptance of MDA campaigns is a very important figure that can ensure adherence to future prevention campaigns. MDA strategies seem to be unusual in the area of this study, since only 11.2% stated that they have received PZQ prophylactically, mainly in hospital. One person who reported receiving PZQ at church, suggesting that churches may be a suitable venue to conduct MDA campaigns for adult populations.

Regarding the practices, laundry and bathing in the river were the most common risky activities, which is consistent with other studies (Dawaki et al., 2015; Sady et al., 2015; Folefac et al., 2018; Anyolitho et al., 2022), and 50% of the respondents stated that they urinate in the river, which is a major concern since this makes it difficult to interrupt the transmission of *S. haematobium* and matches the conclusions of studies carried out in other countries (Folefac et al., 2018; Anyanwu et al., 2020). Although in most KAP surveys, fishing is one of the highest risk activities (Anyolitho et al., 2022), this is not the case in our study. The professional activity of cultivating represented twice as many contacts with water as fishing, and this considering that most farmers only cultivate during the rainy season and therefore do not come into contact with the river for their professional activity. This is not surprising considering that only 6% of the country is dedicated to fishing, while 46.7% of Angolan population works in the fields (IFDA, 2018). On the other hand, only 23.2% stated that they carry out prevention activities. Prevention actions and knowledge on Schistosomiasis are significantly associated (◎2 = 22.59, p-value < 0.01), which means that being aware of the disease transmission increases the number of people who carry out prevention activities, raising high hopes in health promotion and awareness campaigns.

With reference to the history of Schistosomiasis of the participants, only 32% claimed to have been diagnosed with it at least once in their lifetime. It should be noted that no one claimed to have been infected before the age of 5, which could mean that the real percentage is higher since most people develop their memories from the age of 3 or 4 (Robinson-Riegler and Robinson-Riegler, 2021). Haematuria was the symptom that most led to medical consultation, which would explained why it is the most widely known symptom by the population (Table 4.3). Unfortunately, side effects are common when taking PZQ, which are thought to be due to the killing of the schistosomes and the relief of its products. There is evidence that the appearance of side effects of PZQ is directly related to the number of pre-treatment eggs, therefore, with the intensity of the infestation, and it occurs in 30–60% of people (Cioli and Pica-Mattoccia., 2003). In our study, 44 of the 69 people who had taken PZQ reported side effects, representing 63.7%; dizziness appeared as the most common effect, which is consistent with other studies (Cioli and Pica-Mattoccia, 2003; Raso et al.; 2004; Reta and Erko, 2013; Timson, 2020; Torres-Vitolas et al., 2021; Kabatende et al., 2022).

The results of the analyses to determine risk factors for *S. haematobium* infection among PSAC with respect to their caregivers have revealed that it is related in many aspects (Table 4.9). Bathing and laundry in the river are common risk factors for studies on the association between PSAC infection and their caregivers (Kibira et al., 2019; Mutsaka-Makuvaza et al., 2019; Sacolo-Gwebu et al., 2019a). In our study, children under caregivers with little knowledge about Schistosomiasis are 2.2 times more likely to be infected than those with medium knowledge. This is consistent with previous studies (Mutsaka-Makuvaza et al., 2019; Sacolo-Gwebu et al., 2019a), but differs from the conclusions of a study conducted in Malawi (Moyo et al., 2016) where it was not possible to find significant differences in PSAC infection between caregivers with high and low knowledge scores.

To the best of our knowledge, there is no other studies on the association between UT morbidity due to *S. haematobium* in PSAC and their caregivers. Lack of knowledge on how to prevent the disease resulted in the strongest risk factor for the development of UT morbidity in PSAC. Although caregivers' attitude towards MDA campaigns and river contact was associated with their morbidity, the majority of risk factors were related to their knowledge (Table 4.10). This evidence that health promotion among caregivers not only protects PSAC from contracting the infection, as is already known (Sacolo-Gwebu, et al., 2019b), but also protects them against developing the disease in an acute mode. The results obtained by this study can be used for the design of a health promotion strategy that eliminates the gap between knowledge and practice, providing the environment to achieve a behaviour change that can have a high protection impact among PSAC.

In conclusion, Cubal population has a medium knowledge about Schistosomiasis and a high number of risk practices; however, their attitude towards the prevention and treatment of the disease is a promising starting point to improve on the aforementioned deficiencies. In addition, poor knowledge and risk practices may represent a risk factor both for the infection of the children in their care and for the development of the disease and its associated morbidity.

Chapter 5

Conclusions and future work

5.1. Conclusions

This chapter outlines the main conclusions of this thesis, which is the result of original studies. In addition, some promising ideas and possible directions for future research are also discussed. The research work presented in the previous chapters of this document has fulfilled the specific objectives that were proposed for this thesis (see Section 1.5). The conclusions and main contributions on each of these objectives are summarized below.

At the time of submitting this thesis, the bibliometric study on the influence of the COVID-19 pandemic on human Schistosomiasis research, presented in Chapter 2, has already been published in the International Journal of Environmental Research and Public Health. Chapter 3 develops one of the few studies on morbidity associated to urogenital Schistosomiasis in pre-school children, which is the first conducted in Angola. Finally, Chapter 4 presents the first study in Angola on knowledge, attitudes and practices regarding urogenital Schistosomiasis. In addition, this chapter also provides for the first time an analysis of the risk factors that knowledge and practices of caregivers pose for the morbidity caused by *S. haematobium* infection in pre-school children.

Regarding the **bibliometric analysis of research on Schistosomiasis during the acute phase of the COVID-19 pandemic** (Chapter 2), the main conclusion is that the global health emergency declared by the WHO did not affect the production of scientific articles on human Schistosomiasis. From this, some more specific conclusions can be drawn as follows:

- The number of publications during the most difficult years of the pandemic, when there were even mass lockdowns, increased compared to the previous two years.
- Large inequalities have been observed in the distribution of publications by country between high-income countries and low-and middle-income countries.
- Despite these differences, some endemic countries such as South Africa, Tanzania or Ethiopia reached significant levels of scientific production considering some of their socioeconomic indicators.
- The correlation analyses carried out have demonstrated that research on Schistosomiasis depended more on the resources allocated by each country than on the wealth of its population; for instance, the number of publications resulted significantly associated with the size of the country’s population and with

researchers per million inhabitants, but not with the GDP per capita nor with MPM.

- The vast majority of journals in which articles were published during this period of the pandemic were journals with relevant positions in the JCR, among which it is worth mentioning PLoS Neglected Tropical Diseases, Acta Tropica, and Parasites & Vectors.
- There was a fairly high degree of international collaboration and this cooperation did not occur only between institutions from countries with high scientific productivity, but also with others from less productive countries.
- The FCWI of all the most cited publication was greater than 1.00, meaning that they were cited more than expected based on the average of similar publications. This demonstrates the relevance of Schistosomiasis research even during a global health emergency.

Concerning the **prevalence of *S. haematobium* infection and its morbidity associated in PSAC of Cubal, Angola** (Chapter 3), a number of interesting conclusions can be drawn. Undoubtedly the most important thing is that children in Cubal are exposed to Schistosomiasis infection from a very early age and therefore, it is urgent to include the PSAC group in MDA campaigns with PZQ. Apart from this fundamental question, the following conclusions should also be pointed out:

- It was estimated a urogenital Schistosomiasis prevalence of 30.2% in children under 5 years of age caused by *S. haematobium*.
- The probability of acquiring a *S. haematobium* infection increases with age.
- Macrohaematuria, a common sign of urogenital Schistosomiasis infection, is present in only one quarter of PSAC releasing *S. haematobium* eggs, while half of pre-schoolers experience some level of wasting and almost all PSAC have anaemia and a quarter of them have severe anaemia.
- Among PSAC infected with *S. haematobium*, 54.5% of them have developed UT morbidity and all of these show thickening of the bladder wall.
- Pseudopolyps are the only lesion not found in any pre-schooler with UT morbidity caused by urogenital Schistosomiasis.
- Macrohaematuria, microhaematuria and proteinuria could be used as an indirect indicator of morbidity in PSAC, since their presence in urine is correlated with UT morbidity caused by *S. haematobium* infection.
- PSAC infected with *S. haematobium* have a great potential to develop UT morbidity, which would lead them to reach school age with high cumulative morbidity.

In reference to the **study on knowledge, attitudes and practices in regarding urogenital Schistosomiasis in Cubal, Angola** (Chapter 4), the main conclusions that can be extracted from the survey respondents are poor knowledge about the disease, good attitude towards it and the presence of a high number of risky practices. In more detail, the following concluding remarks can be highlighted:

- Almost half of the respondents scored low on knowledge about Schistosomiasis, but practically all of them were aware of its existence and approximately half believe that this is a serious disease that can cause death.
- The most common source of information for the little knowledge they have was friends and neighbours and through what is said on the street.
- Among the various symptoms of urogenital Schistosomiasis, haematuria was the best known.
- The most widespread misbelief among the community was the possibility of becoming infected by eating sugar cane. By contrast, just over a quarter of those surveyed were aware that bathing in the river is the most common manner of infection. Hardly anyone either knew that a river snail is part of the *S. haematobium* infection cycle.
- Taking medication was the most common response for proper Schistosomiasis prevention activities and virtually all respondents knew that the disease can be cured, with modern pills being the main form of treatment.
- On attitude, most of the people surveyed scored high. Thus, for example, almost all of them were willing to participate in an MDA campaign and a high level of trust in doctors was observed.
- Slightly more than half of those surveyed regularly carried out risk practices for Schistosomiasis infection, being bathing in the river the most common risk practice among the community.
- The scarcity of water during the dry season forces many people to resort to the river to supply water to their households because they do not have other water source. However, not a quarter of those respondents carried out any prevention activity. In fact, half claimed to urinate in the river water regularly.
- Only 30.2% of those surveyed declared having been diagnosed with urogenital Schistosomiasis at least once in their lives.
- Most people who had been treated with PZQ at least once in their lives reported having experienced side effects, with dizziness being the most widespread.
- People may be confusing Fascioliasis symptoms with those caused by *S. haematobium.*

In relation to **caregivers and risk factors for *S. haematobium* infection and morbidity in PSAC in Cubal, Angola** (Chapter 4), it has been possible to conclude that poor knowledge of caregivers about the disease constitutes a very important risk factor for *S. haematobium* infection and UT morbidity in PSAC. In particular, we can mention a couple of interesting findings:

- Caregivers are unaware that development of UT morbidity caused by *S. haematobium* infection can be prevented by avoiding bathing in the river.
- Washing clothes in the river is the greatest risk factor in the practices of caregivers for urogenital Schistosomiasis infection in pre-schoolers.

5.2. Future research avenues

The bibliometric analysis on the impact of the COVID-19 pandemic on research in human Schistosomiasis revealed that scientific production increased during this period, but our hypothesis is that this is due to the fact that researchers had more time to prepare articles based on studies carried out before the declaration of the pandemic. On the other hand, the survey launched by The Global Schistosomiasis Alliance concluded that the pandemic has affected previously planned laboratory work, clinical trials and field surveillance and therefore, it is expected that post-pandemic scientific production will decrease. Bearing these two issues in mind, a particularly interesting extension of this work would consist of conducting a similar analysis in the coming years with the aim of having a larger sample that more accurately reflects the impact of the pandemic and that allows for a classification of the articles according to the type of study carried out (laboratory work, clinical trials, field surveillance, and others).

Another interesting way to further deepen our understanding of the impact of the COVID-19 pandemic could consist of analysing its consequences not only on research but also on the activities of prevention, diagnosis and MDA of Schistosomiasis. To this purpose, a cross-sectional study aimed at a large number of public health institutions, foundations and non-profit organizations involved in the control and management of this disease should be carried out.

Regarding the studies carried out in Cubal, Angola, there is still a lot of room to extend the work carried out so far and, very particularly, in the epidemiological investigation related to children. In fact, as stated by Rees et al. (2019), there is still a very important gap between the burden of NTDs in children and the research directed towards this population group. Thus, on the one hand, the dissemination among policy makers of the results of the prevalence of urogenital Schistosomiasis and its associated morbidity among PSAC should be undertaken to raise awareness about the damage that the disease is causing in this age group. This would urge to ensure the mass administration of PZQ in this hyperendemic area, also including pre-schoolers within the target population. At the same time, this could also highlight the importance of improving access to clean water throughout the year for the population. Moreover, research studies must be undertaken in many other directions to reduce the risk factors associated with Schistosomiasis infection, which widely affects people in this area.

Once the epidemiological situation in pre-schoolers and school-age children is known (as a result of the study presented in Chapter 3 and the previous study carried out by Bocanegra et al. (2014)), the condition in adults should be determined. Within this study in adults, the genital form in which Schistosomiasis caused by *S. haematobium* can develop should be considered, analysing not only the prevalence but also its effect on fertility and on their social life. In this line, consideration should be given to training health professionals to understand this form of the disease, its symptoms and how to diagnose it. On the other hand, it is important to establish the hotspots with the highest risk of infection in all water bodies of the municipality based on mass vector surveillance.

Based on these data, possible vector control measures should be explored to interrupt the *Schistosoma* cycle.

In addition, the results obtained from the survey presented in Chapter 4 could be used to design and implement a comprehensive and large-scale awareness campaign. Thanks to these results, it would be possible to consider not only the typical campaigns where activities are carried out directly to the groups, but also communication tools such as radio to reach the maximum number of people at risk. Also, the campaign could focus on the misconceptions and gaps detected, as well as create a behaviour change in the population.

Appendix A

Article in the *International Journal of Environmental Research and Public Health*

This appendix provides the full text of the article "Research on Schistosomiasis in the Era of the COVID-19 Pandemic: A Bibliometric Analysis", published in the International Journal of Environmental Research and Public Health:

Sánchez-Marqués, R.; Mas-Coma, S.; Salas-Coronas, J.; Boissier, J.; Bargues, M.D. (2022) Research on Schistosomiasis in the era of the COVID-19 pandemic: a bibliometric analysis. *Int J Environ Res Public Health* 19, 8051. https://doi.org/10.3390/ijerph19138051

International Journal of
Environmental Research and Public Health

MDPI

Review

Research on Schistosomiasis in the Era of the COVID-19 Pandemic: A Bibliometric Analysis

Raquel Sánchez-Marqués [1,*], Santiago Mas-Coma [1,2], Joaquín Salas-Coronas [3], Jerôme Boissier [4] and María Dolores Bargues [1,2]

[1] Departmento de Parasitología, Facultad de Farmacia, Universidad de Valencia, Av. Vicent Andres Estellés s/n, Burjassot, 46100 Valencia, Spain; s.mas.coma@uv.es (S.M.-C.); m.d.bargues@uv.es (M.D.B.)
[2] CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos IIII, C/Monforte de Lemos 3-5, Pabellón 11. Planta 0, 28029 Madrid, Spain
[3] Tropical Medicine Unit, Hospital del Poniente, Ctra. de Almerimar 31, El Ejido, 04700 Almería, Spain; joaquin.salas.sspa@juntadeandalucia.es
[4] IHPE, University Montpellier, CNRS, Ifremer, University Perpignan Via Domitia, F-66000 Perpignan, France; boissier@univ-perp.fr
* Correspondence: raquelsanmarques22@gmail.com

Abstract: The objectives of this work are to check whether the COVID-19 pandemic affected the research on schistosomiasis, to provide an insight into the most productive countries and journals and the most cited publications, and to analyse any association between the total publications of countries and a set of socio-economic and demographic factors. Based on PRISMA methodology, we used the Scopus database to search for articles published between 1 January 2020 and 26 March 2022. VOSviewer was used to generate the co-authorship and the co-occurrence networks, and Spearman's rank correlation was applied to study associations. A total of 1988 articles were included in the study. Although we found that the year-wise distribution of publications suggests no impact on schistosomiasis research, many resources have been devoted to research on COVID-19, and the Global Schistosomiasis Alliance revealed the main activities for eradication of schistosomiasis had been affected. The most productive country was the United States of America. The articles were mainly published in *PLoS Neglected Tropical Diseases*. The most prolific funding institution was the National Natural Science Foundation of China. The total publications per country were significantly correlated with population, GERD, and researchers per million inhabitants, but not with GDP per capita and MPM.

Keywords: schistosomiasis; COVID-19; bibliometric analysis; socio-economic indicators; correlation analysis; PRISMA

Citation: Sánchez-Marqués, R.; Mas-Coma, S.; Salas-Coronas, J.; Boissier, J.; Bargues, M.D. Research on Schistosomiasis in the Era of the COVID-19 Pandemic: A Bibliometric Analysis. *Int. J. Environ. Res. Public Health* **2022**, *19*, 8051. https://doi.org/10.3390/ijerph19138051

Academic Editor: Richard Paul

Received: 21 May 2022
Accepted: 28 June 2022
Published: 30 June 2022

1. Introduction

The COVID-19, caused by a newly identified strain of the SARS-CoV-2, was officially declared as a pandemic by 11 March 2020 and put additional pressure on health systems around the world. The pandemic heightened inequalities and set back many diseases due to the health policies adopted by governments to prevent the coronavirus transmission. Many studies in high-income countries have claimed that paying less attention to cancer and several chronic diseases, such as cardiovascular and non-infectious respiratory diseases, might lead to avoidable deaths or late diagnostic of lethal diseases [1,2]. This could be especially dramatic for the neglected tropical diseases (NTDs), a diverse group of about 20 diseases endemic in tropical and sub-tropical regions of the globe, affecting more than one billion people, mainly associated with poor hygienic conditions and sanitation facilities and the absence of safe drinking water.

Among the parasitic NTDs, schistosomiasis (also known as snail fever or bilharziasis) is one of the most widespread and the most common parasite transmitted through contact of skin with freshwater contaminated by *Schistosoma* larvae. There are two main forms of schistosomiasis that affect human caused by six main species of blood flukes: intestinal (*S. mansoni*, *S. japonicum*, *S. mekongi*, *S. guineensis*, *S. intercalatum*) or urogenital (*S. haematobium*). The World Health Organization estimates that overall schistosomal infections affect about 240 million people worldwide, of which over 85% live in the sub-Saharan Africa region and nearly 200,000 die every year [3]. Though schistosomiasis is endemic in 52 low-income countries in Africa, Asia, South America, the Middle East, and several Caribbean islands, high-income countries have suffered an increase in imported cases mainly due to migration and international travels and commerce [4–6]. For instance, Boissier et al. reported an outbreak of urogenital schistosomiasis in Europe, in Corsica Island (France), produced by parasites imported from Senegal, and alerted the potential risk of schistosomiasis outbreaks in other European areas [7]. European schistosomes had previously been identified as hybrids between the livestock- and the human-infective species *Schistosoma bovis* and *Schistosoma haematobium*, respectively [8,9]. Recently, after an in-depth clinical and epidemiological study of several cases, evidence of autochthonous transmission of urogenital schistosomiasis in Almería (Spain) was demonstrated [10], and new cases of acute schistosomiasis have been reported in people from Antwerp, Belgium after staying in South Africa [11].

The high number of people at risk of getting infected with schistosomiasis makes the need for attention evident. As the best strategy to control and eliminate human schistosomiasis, the World Health Assembly urged State Members to ensure access to regular administration of preventive chemotherapy for the treatment of clinical cases and groups at high risk of morbidity (especially, women and school-aged children) [3]. However, the World Health Organization advised that NTD surveys, active case detection activities, and mass drug administration campaigns should be postponed due to the COVID-19 pandemic, whereas prompt diagnosis should continue if possible. Given this scenario, several studies have pointed up the serious threat of syndemic malaria, NTDs, and COVID-19 in low and middle-income countries [12,13]. In fact, there are warnings that the great advances in the fight against schistosomiasis are at risk of being reversed in many countries due to the measures adopted in the face of the COVID-19 pandemic [14]. It was also evidenced that the interruption of mass drug administration campaigns due to the COVID-19 pandemic would lead to an increase in *S. mansoni* and *S. haematobium* infection [15]. Similarly, the recent outbreak of schistosomiasis reported in northeast Nigeria suggests that one of the possible reasons was the interruption of mass drug administration programs [16]. On the contrary, the number of imported cases of schistosomiasis in non-endemic countries have most likely been affected by the reduced international travel capacity during the COVID-19 pandemic as well as other international travel-related diseases [17,18].

The Global Schistosomiasis Alliance launched a brief questionnaire to some of its partners to know how the COVID-19 pandemic impact on their research activities, revealing that the pandemic and associated restrictions affected clinical studies, field surveillance, and planned basic and preclinical lab work [19]. The purpose of this work is to analyse the scientific literature on schistosomiasis during the COVID-19 pandemic through a comprehensive bibliometric analysis, which may allow us to quantify, measure and visualize the development, potential trends and impact of research on schistosomiasis. This will also shed light on whether the pandemic has affected not only the activities for the prevention, diagnosis and treatment, but also the global research on schistosomiasis.

2. Materials and Methods

This study was carried out based on the PRISMA statement [20] by cross-searching a comprehensive set of terms (schistosoma, schistosomiasis, snail fever, bilharzia, bilharziasis) in the title, abstract or keywords of an article using the Scopus electronic database for the period from 1 January 2020 to 26 March 2022. Articles were excluded if they met one or more of the following criteria: (i) written in a language other than English, because the impact of publications written in non-English language is usually very low; (ii) reported in conference papers, books, book chapters, editorial material, reviews, conference reviews, short surveys, notes, or errata; and (iii) articles in press. The main reason for excluding these types of publications was that some of them are not usually peer-reviewed, whereas others do not contribute new research (laboratory investigations, clinical studies, etc.). In addition, the abstracts of all identified papers were checked to verify that they were really related to schistosomiasis. The search process was conducted on 27 March 2022. The PRISMA flowchart of the research protocol is shown in Figure 1.

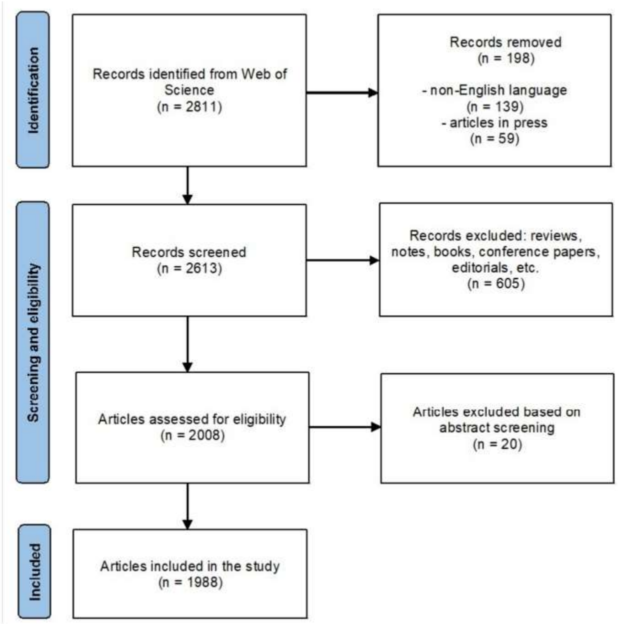


Figure 1. PRISMA flow diagram.

2.1. Data Retrieval and Collection

The search strategy identified 2811 records from the Scopus database as it offers an extensive coverage of medical literature [21]. After removing 198 records, 2613 were included for screening. We excluded 605 records based on the document types not considered in this work, leaving 2008 articles to be checked for eligibility. After abstract reading, 20 records were eliminated because they did not meet the inclusion criteria. Finally, a total of 1988 documents were put in the study.

For each paper, meaningful data were collated: Authors, year of publication, title, journal, authors' affiliation, country, title, keywords, funding/sponsor agency, subject area, and citation count. In addition, we recorded for each paper the number of authors and the country of the corresponding author. These data were then organized in the form of standardized tables to facilitate the analysis of outputs. The impact factor (IF) of journals was gathered from the 2020 Journal Citation Reports, which was the most recent one published by Clarivate Analytics at the moment of preparing this work.

2.2. Data Analysis

Spearman's rank correlation was applied to check for correlation between some bibliometric indices and also between total publications per country and several socio-economic and demographic indicators: population, gross domestic product (GDP) per capita, gross domestic expenditure on R&D (GERD), multidimensional poverty measure (MPM), and researchers per million inhabitants. All these indicators were taken from the websites of the Organisation for Economic Co-operation and Development, the International Monetary Fund, and the World Bank. GERD provides an indication of the level of financial resources devoted to R&D as a percentage of the GDP [22]. MPM is a measure of poverty that captures deprivations in education (attainment and enrolment) and access to basic infrastructure (electricity, sanitation, and drinking water) in addition to the extreme poverty threshold of $1.90 [23].

The Spearman's correlation coefficient (ρ_s) was considered significant if the *p*-value was less than 0.05. In addition, we employed VOSviewer [24] tool to perform the analysis of co-authorship and the analysis of co-occurrence of keywords, and *paintmaps.com* to generate a geographical mapping of publications per country.

3. Results

Out of the 1988 documents included in the study, 1948 were articles and 40 corresponded to letters. These documents were published in 160 different journals and cited 4711 times (as of 27 March 2022). The number of cited documents was 1143 with an h-index of 19. The 159 authors of these publications were from 132 countries on five continents. The overwhelming majority of publications were conducted by multiple authors as only 1.86% of the 1988 documents were sole-authored, leading to a collaboration coefficient of 0.98. The average productivity per year was 662.66 and the average citations per year was 1570.33. The histogram in Figure 2 represents the number of citations against the number of publications in logarithmic scale. The use of a logarithmic scale was to avoid skewing towards large values since the number of publications ranged from 3 (for publications with 17 citations) to 845 (for the case of 0 citations).

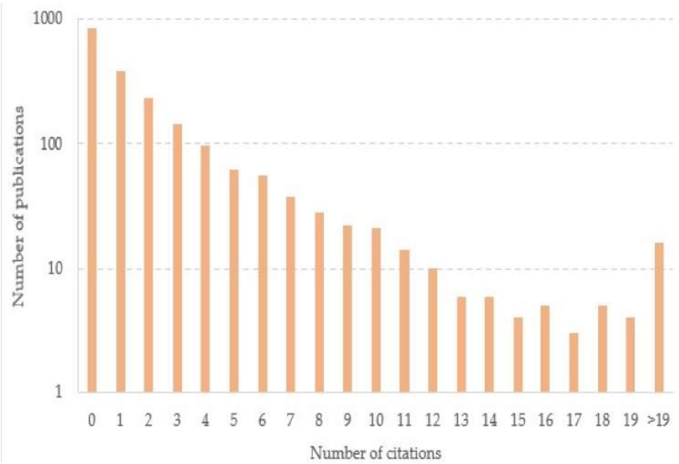


Figure 2. Logarithmic number of publications vs. number of citations.

3.1. Chronological Evolution of Publications

To examine the trend of publications over time, Figure 3 depicts a distribution bar chart with the number of papers published per year. Here we also included the scores of 2018 and 2019, the two years previous to the pandemic, with the aim of checking whether or not the pandemic caused a decrease in research publications. Surprisingly, visual inspection of this picture revealed that there was a slight increase in the annual number of publications during the acute phase of the COVID-19 pandemic (2020 and 2021), which could suggest that research on schistosomiasis was not dropped out due to the pandemic. However, following the trend of the first three months of 2022, a fairly probable estimate of the number of publications at the end of the year indicates that there could be a certain decrease, probably due to the fact that the resources have been allocated mainly to research on COVID-19 to the detriment of other research lines.

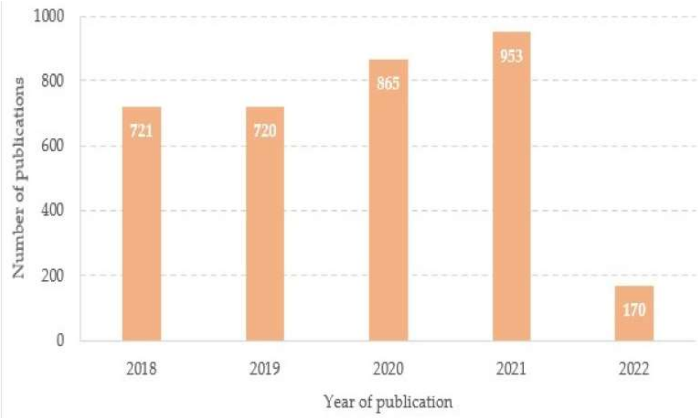


Figure 3. Year-wise distribution of publications.

To investigate whether there exists any different trends between systematic reviews and the type of publications included in our study (i.e., those based on experimentation), we also performed a search for reviews published in the period 2018–2022. Thus, the number of reviews from 2018 to 2022 were 141, 155, 184, 219, and 45, respectively. By normal standards, the association between the two variables (research articles versus reviews) should be considered statistically significant ($\rho_s = 0.9$, p-value = 0.03739). This suggests that there were no more reviews than experimental articles during the acute phase of the pandemic due to the lockdown and the possible lack of some supplies (e.g., lack of reagents). This could probably be because the experimental articles are based on data and results of experiments carried out during the years prior to the pandemic.

3.2. Geographical Distribution of Publications

Figure 4 shows a global mapping of the retrieved documents according to the country of all contributing authors. The most active country was the United States of America with 436 publications (21.93%), followed by the United Kingdom (n = 343, 17.25%), China (n = 309, 15.54%), Brazil (n = 245, 12.32%), Egypt and Switzerland (n = 139, 6.99% each), Germany (n = 130, 6.54%), and the Netherlands (n = 106, 5.33%). Authors from 39 countries contributed to the production of only one or two articles.

Focusing on two of the regions most affected by schistosomiasis, we found that the sub-Saharan African countries with the highest number of publications were South Africa (n = 83, 4.18%), Tanzania (n = 80, 4.02%), Ethiopia (n = 73, 7.30%), Nigeria (n = 65, 3.27%), Kenya (n = 62, 3.12%), and Uganda (n = 41, 2.06%), whereas in Southeast Asia, the most productive countries were Thailand (n = 35, 1.76%) and the Philippines (n = 30, 1.51%).

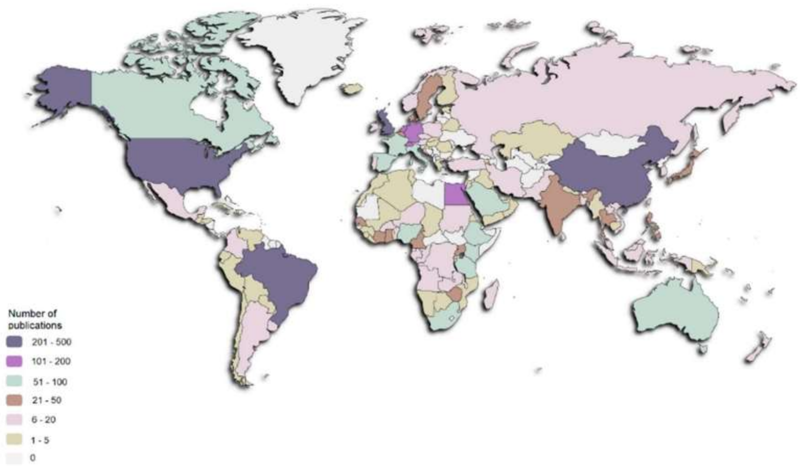


Figure 4. Global mapping of publications on schistosomiasis.

3.3. Distribution of Publications by Journals and Research Areas

To analyse the journals that could be considered as the most influential, Table 1 reports the 10 most productive journals together with some bibliometric indices. *PLoS Neglected Tropical Diseases*, with 225 publications (11.32%) and 524 citations, was by far the most used journal in our sample, followed by *Acta Tropica*, with 73 publications (3.67%) and 183 citations. In total, the top 10 journals published 618 documents (31.09%) and received 1601 citations, which accounted for 31.09% of all publications and 33.98% of the total citations. All these journals are ranked in the first quartiles of the 2020 Journal Citation Reports.

Table 1. Top 10 most prolific journals.

Journal	Articles	Total Citations	Citations per Article	IF
PLoS Negl. Trop. Dis.	225	524	2.33	4.411
Acta Trop.	73	183	2.51	3.112
Parasites Vectors	58	158	2.72	3.876
Am. J. Trop. Med. Hyg.	55	244	4.44	2.345
Front. Immunol.	42	144	3.43	7.561
Infect. Dis. Pover.	36	88	2.44	4.388
Parasitol. Res.	36	72	2.00	2.289
PLoS ONE	35	62	1.77	3.240
Pathogens	30	38	1.27	3.492
Sci. Rep.	28	88	3.14	4.380

The study showed that the number of publications and the number of citations were significantly correlated (ρ_s = 0.8628, *p*-value = 0.00131), whereas the number of publications was not significantly correlated with the impact factor (ρ_s = 0.4073, *p*-value = 0.24271).

Regarding the distribution of articles by research areas, we identified a total of 25 different domains. As can be observed in Figure 5, the vast majority of publications belonged to health sciences, such as Medicine (n = 1397, 70.27%), Immunology and Microbiology (n = 732, 36.82%), and Biochemistry, Genetics and Molecular Biology (n = 348, 17.51%).

There were less than 30 publications in 15 research fields (e.g., Computer Science, Social Sciences, Nursing, Dentistry, Psychology, Economics, Econometrics and Finance, and Energy). Note that the sum of percentages exceeds 100% because articles could be classified into more than one research area.

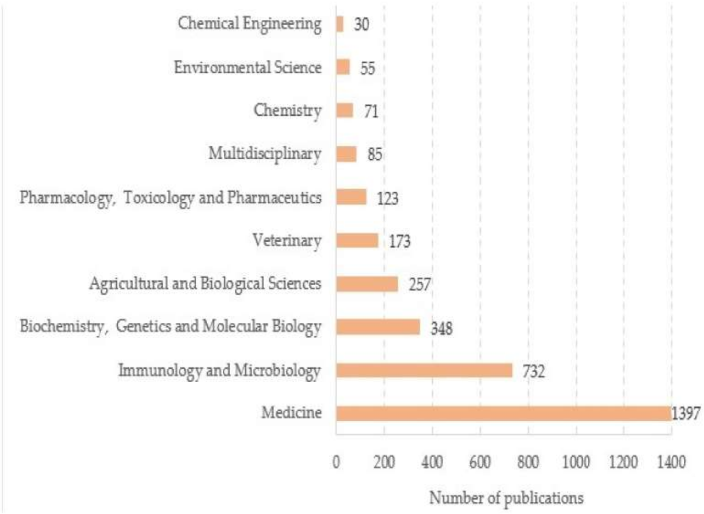


Figure 5. The top 10 research areas.

3.4. Co-Authorship Analysis

In Figure 6, the co-authorship network highlights the research collaborations between authors. Each node of the network represents an author, and the links between the nodes represent the collaborative relationships between authors. For the sake of a better visualization of the network, only authors with at least 10 documents were selected for this analysis. As can be observed, nine clusters including 83 authors were identified as collaborations in the production of articles. The densest cluster included a total of 29 authors, but with little international collaboration since most of them were from China. There were two clusters formed by only two authors each and one cluster with three authors, showing some kind of inter-institution cooperation. A more exhaustive exploration of the network allowed for finding strong international collaborations between the authors of the different clusters. For instance, we found collaborations between authors from the Swiss Tropical and Public Health Institute with authors from the Natural History Museum of London, the Université de Perpignan via Domitia (France), and the University Félix Houphouët-Boigny (Côte d'Ivoire).

3.5. Funding Sources

A great variety of public and private agencies and institutions were involved in funding the research for the articles included in this study. The most prolific were the National Natural Science Foundation of China (n = 161, 8.10%), the National Institutes of Health USA (n = 134, 6.74%) and the Bill and Melinda Gates Foundation (n = 114, 5.73%). Figure 7 displays the top 10 most common funding sources, which accounted for 45.93% of all retrieved documents.

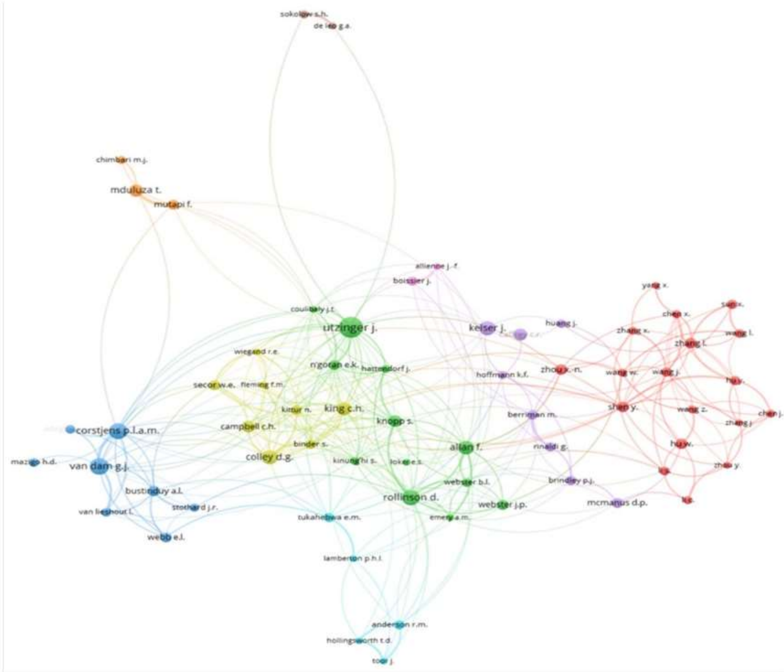


Figure 6. Co-authorship network.

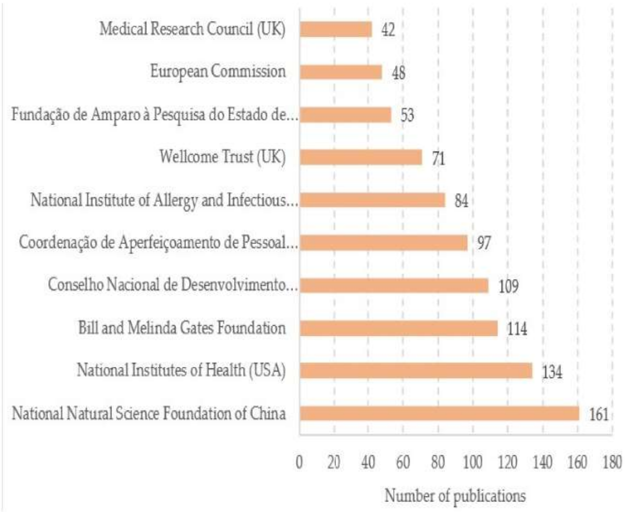


Figure 7. The top 10 funding sources.

3.6. Co-Occurrence Analysis of Keywords

A co-occurrence network allows for identifying how often a set of keywords appeared together in the publications. In this kind of network, keywords are represented by nodes and their relationships are represented by links; the bigger is the size of a node, the more often the occurrence of a keyword. In addition, the shorter is the distance between two nodes, the stronger their relation.

Figure 8 shows the co-occurrence network of the retrieved documents in this study. We selected keywords that occurred at least five times to build the co-occurrence network. A total of 14 clusters and 135 items were identified. As expected, "schistosomiasis" was the most representative keyword (360 occurrences), followed by "schistosoma mansoni" (218 occurrences), "schistosoma japonicum" (108 occurrences), "praziquantel" (85 occurrences) and "schistosoma haematobium" (57 occurrences). We also observed the occurrence of other keywords, such as "real-time pcr", "ultrasonography", "immune modulation", "transcriptome" or "biomarkers", that reveal the current research trends to diagnose the disease.

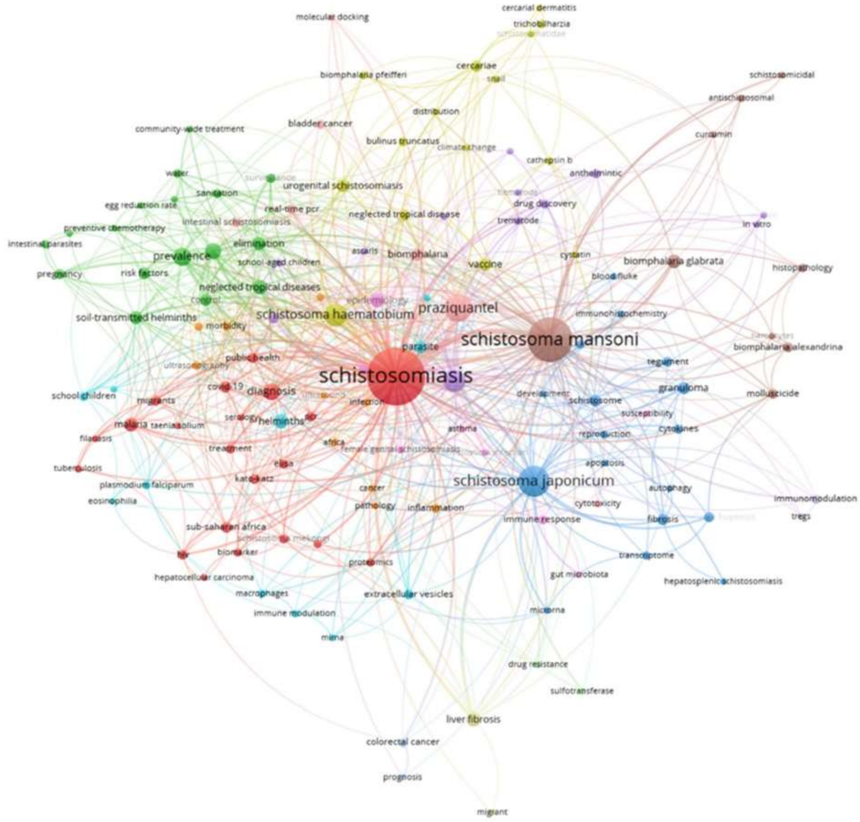


Figure 8. Co-occurrence network of keywords.

3.7. Most Cited Publications

Table 2 reports the most cited articles ranked by the total citations (TC) and by the field-weighted citation impact (FWCI). The FWCI proposed in Scopus denotes the ratio of the total citations actually received by an article to the average number of citations received by all similar documents over a three-year window; a value equal to 1.00 indicates that the article performs just as expected for the average, whereas a value greater than 1.00 means that the article is more cited than expected according to the average. In addition, this table also shows whether or not an article involves international collaboration (Col) and the number of citations per year (C-Year), which was calculated as: Total citations / (Year of the study—Year of publication + 1).

Table 2. The top 10 most cited documents (ranked by total citations and by FWCI).

Rank TC	Rank FWCI	Article	Col [1]	TC	C-Year	FWCI
1	1	Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis [25]	N	335	111.66	53.09
2	2	Regarding new numerical solution of fractional Schistosomiasis disease arising in biological phenomena [26]	Y(4)	45	15.00	12.52
3	10	A controlled human Schistosoma mansoni infection model to advance novel drugs, vaccines, and diagnostics [27]	N	34	11.33	1.45
4	8	A single-cell RNA-seq atlas of Schistosoma mansoni identifies a key regulator of blood feeding [28]	N	30	10.00	3.08
5	3	Predicted impact of COVID-19 on neglected tropical disease programs and the opportunity for innovation [29]	Y(4)	28	14.00	12.20
6	5	Schistosomal extracellular vesicle-enclosed miRNAs modulate host T helper cell differentiation [30]	N	27	9.00	4.00
7	6	Cancer in Africa 2018: The role of infections [31]	Y(3)	26	8.66	3.74
8	7	Impact of different mass drug administration strategies for gaining and sustaining control of Schistosoma mansoni and Schistosoma haematobium infection in Africa [32]	Y(9)	23	7.66	3.33
9	4	Prevalence and distribution of schistosomiasis in human, livestock, and snail populations in northern Senegal: A one health epidemiological study of a multi-host system [33]	Y(4)	21	7.00	4.88
10	9	Circulating anodic antigen (CAA): A highly sensitive diagnostic biomarker to detect active schistosoma infections—improvement and use during SCORE [34]	Y(9)	21	7.00	3.04

[1] Y(n): international collaboration (number of countries); N: no international collaboration.

The top 10 most cited articles by total citations received 590 citations, accounting for 12.52% of the total number of citations (4711). However, it is worth noting that the work ranked as the first accumulated 335 citations, which represents 7.11% of the total. By considering only the remaining top 9 articles, the average number of citations was 28.33 per publication.

The two publications with the highest total citations also received the highest FWCI. However, some important differences were found in these two indices; for instance, the article ranked the third by total citations was the tenth when using the FWCI metric.

Six out of the top 10 most cited articles were performed by authors from different countries. Two articles showed the highest level of international collaboration with authors from nine countries. For instance, the authors of the paper entitled "Circulating anodic antigen (CAA): A highly sensitive diagnostic biomarker to detect active schistosoma infections—improvement and use during SCORE" [34] were from the Netherlands, Switzerland, the United Kingdom, France, Rwanda, Tanzania, Kenya, the United States of America, and St. Lucia.

4. Correlation between Total Publications and Country Indicators

According to the Spearman's correlation coefficient, we found that the total number of publications was significantly correlated with population (ρ_s = 0.61196, *p*-value = 0), GERD (ρ_s = 0.4629, *p*-value = 0) and researchers per million inhabitants (ρ_s = 0.26755, *p*-value = 0.00952). Conversely, the association between total publications and GDP per capita (ρ_s = 0.09659, *p*-value = 0.27059) and MPM (ρ_s = 0.08238, *p*-value = 0.44018) could not be considered statistically significant. As expected, these results show that research depends mainly on the resources that a country allocates to carry it out, but not so much on the level of wealth of its population. However, more interestingly, this analysis has made it possible to verify that research on schistosomiasis has maintained the same correlations during the COVID-19 pandemic.

5. Discussion

Bibliometric analysis constitutes an important tool for exploring the situation on a particular field and offers meaningful information for researchers to evaluate the trends and impact of the research. This work addressed the research on schistosomiasis, which is one of the most widespread neglected tropical diseases, during the COVID-19 pandemic. To the best of our knowledge, this is the first bibliometric analysis with a focus on schistosomiasis research during the pandemic. The bibliometric analysis found that the number of publications increased during the first two years of the pandemic (2020 and 2021), which could be explained because the social lockdown allowed authors more time to write scientific papers in expectation. However, the data for the first months of 2022 suggest a slight slowdown; this change in trend could be due to the fact that many resources have been devoted to research on COVID-19, so that the 2020 and 2021 publications actually refer to research carried out in the pre-pandemic years.

The country with most studies was the United States of America, followed by the United Kingdom, China, and Brazil. Regarding the productivity of regions where schistosomiasis is endemic, the bibliometric analysis revealed that several Sub-Saharan African countries, such as South Africa, Tanzania, Ethiopia, Nigeria, Kenya, and Uganda, contributed significantly to research with a reasonable number of publications. However, when focusing on the Southeast Asia countries, only Thailand and the Philippines had a similar number of articles as those in Africa. Interestingly, most Sub-Saharan African countries have a lower GDP per capita and number of researchers than the Southeast Asian countries, but this does not seem to have been a hinderance for conducting research.

PLoS Neglected Tropical Diseases, *Acta Tropica*, and *Parasites and Vectors* were identified as the journals with the largest number of articles on schistosomiasis research in the period analysed. All the most used journals are located in relevant positions in the JCR, although no significant correlation was found between the number of publications and the impact factor. Not surprisingly, the journals with the highest number of articles were in the Tropical Medicine, Parasitology and Infectious Diseases categories of the Journal Citation Reports.

The co-authorship network showed international collaborations and in fact, six out of the top 10 most cited articles were performed by authors from different countries. It is also worth noting that we found collaborations between institutions from countries with high research productivity (e.g., the United Kingdom or Switzerland) and countries with less productivity and high disease prevalence (e.g., Rwanda or Tanzania).

Visualization of the co-occurrence network of keywords highlighted the currently most studied species of blood flukes: *S. mansoni*, *S. japonicum*, and *S. haematobium*. The keyword "praziquantel", which is a tetrahydroisoquinoline and the drug of choice for the treatment and control of schistosomiasis in many endemic countries because it is effective and its cost is low [35,36], also appeared a high number of times in the documents of our sample. A series of terms associated with diagnosis and immunotherapy development, such as "biomarkers", "real-time pcr", "ultrasonography", and "immune modulation", were among the most used keywords.

The most cited article was "Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis", with 335 citations and 111.66 citations per year, which was co-authored by de Martel et al. from France. The field-weighted citation impact of the article was 53.09, demonstrating a significant advantage over the rest of highly cited publications.

Several limitations to this study can be mentioned. First, our analysis was carried out shortly after the end of the acute phase of the pandemic. To have a broader view of the possible impact of the pandemic on schistosomiasis research, this study should probably be repeated when a longer period of time has elapsed from the end of the critical phase of the pandemic in order to have a larger sample of articles. Second, the bibliometric analysis was based on using only the Scopus database and, therefore, some relevant information sources from other bibliographical databases might be omitted from our study.

Another limitation was the exclusion of publications that were not written in the English language. Although there were not many articles written in other languages, this limitation might not reflect the true situation of research on schistosomiasis, especially with regard to the analysis of the geographical distribution of publications. We also excluded meta-analysis because these types of publications were considered not to provide new investigations.

Our study could be further complemented by analysing how the COVID-19 pandemic affected schistosomiasis prevention, diagnosis, and mass drug administration. To this end, a cross-sectional study based on a well-designed structured questionnaire addressed to organizations and institutions that fight against this parasitic disease could provide a more complete perspective and a better understanding of the current situation of control programmes and research on schistosomiasis.

6. Conclusions

The aim of this study was to examine the research on schistosomiasis during the COVID-19 pandemic in a holistic manner to discover which are the most active countries, the most widely-used journals and research areas, the main funding sources, and the hot keywords. In addition, we also investigated whether there exists any association between the total number of publications and some socio-economic and demographic factors of the countries.

A total of 1988 documents were included in our analysis. These were published in 160 different journals and cited 4711 times. The number of cited documents was 1143 with an h-index of 19. The 159 authors of these publications were from 132 countries on five continents. The total publications per country were significantly correlated with population, GERD, and researchers per million inhabitants, but not with GDP per capita and MPM.

As pointed out by Hillyer, the main difference between COVID-19 and parasitic diseases is that many of the countries most affected by the current global pandemic have vast economic resources [37]. Therefore, it is essential that the scientific and public health communities fight COVID-19, but not at the cost of neglecting the research on acute and chronic parasitic diseases and their control and prevention programs. In fact, resumption of preventive chemotherapy for schistosomiasis should be carried out immediately because it has also been shown that the administration of praziquantel could reduce active cases of COVID-19 and improve the recovery rate [38].

Author Contributions: Conceptualization, R.S.-M. and M.D.B.; methodology, R.S.-M.; validation, S.M.-C., J.S.-C., J.B. and M.D.B.; formal analysis, R.S.-M. and S.M.-C.; investigation, R.S.-M. and M.D.B.; resources, R.S.-M.; data curation, M.D.B.; writing—original draft preparation, R.S.-M.; writing—review and editing, S.M.-C., J.S.-C., J.B. and M.D.B.; visualization, R.S.-M.; supervision, S.M.-C. and M.D.B.; and funding acquisition, J.S.-C. and M.D.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Red de Investigación de Centros de Enfermedades Tropicales—RICET (RD16/0027/0023 and RD16/0027/0013) of the PN de I+D+I, ISCIII-Subdirección General de Redes y Centros de Investigación Cooperativa RETICS, Ministry of Health and Consumption, Madrid; by CIBER de Enfermedades Infecciosas (CB21/13/00056), ISCIII, Ministry of Science and Education, Madrid, Spain; by the PROMETEO Program, Programa de Ayudas para Grupos de Investigación de Excelencia (2021/004), Generalitat Valenciana, Valencia, Spain; and by Proyecto de Investigación en Salud PI-0001-2019 (Cofunded FEDER, A way to make Europe/Investing in your future), Consejería de Salud y Familias de la Junta de Andalucía, Sevilla, Spain.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Morris, E.J.A.; Goldacre, R.; Spata, E.; Mafham, M.; Finan, P.J.; Shelton, J.; Richards, M.; Spencer, K.; Emberson, J.; Hollings, S.; et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: A population-based study. *Lancet Gastroenterol. Hepatol.* **2021**, *6*, 199–208. [CrossRef]
2. Wadhera, R.K.; Shen, C.; Gondi, S.; Chen, S.; Kazi, D.S.; Yeh, R.W. Cardiovascular deaths during the COVID-19 pandemic in the United States. *J. Am. Coll. Cardiol.* **2021**, *77*, 159–169. [CrossRef] [PubMed]
3. World Health Organization. WHO Guideline on Control and Elimination of Human Schistosomiasis. 2022. Available online: https://www.who.int/health-topics/schistosomiasis#tab=tab_1 (accessed on 31 March 2022).
4. Kärki, T.; Napoli, C.; Riccardo, F.; Fabiani, M.; Dente, M.G.; Carballo, M.; Noori, T.; Declich, S. Screening for infectious diseases among newly arrived migrants in EU/EEA countries—Varying practices but consensus on the utility of screening. *Int. J. Environ. Res. Public Health* **2014**, *11*, 11004–11014. [CrossRef]
5. Mavridou, A.; Pappa, O.; Papatzitze, O.; Dioli, C.; Kefala, A.M.; Drossos, P.; Beloukas, A. Exotic tourist destinations and transmission of infections by swimming pools and hot springs—A literature review. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2730. [CrossRef]
6. Tilli, M.; Olliaro, P.; Gobbi, F.; Bisoffi, Z.; Bartoloni, A.; Zammarchi, L. Neglected tropical diseases in non-endemic countries in the era of COVID-19 pandemic: The great forgotten. *J. Travel Med.* **2021**, *28*, taaa179. [CrossRef]
7. Boissier, J.; Grech-Angelini, S.; Webster, B.L.; Allienne, J.-F.; Huyse, T.; Mas-Coma, S.; Toulza, E.; Barré-Cardi, H.; Rollinson, D.; Kincaid-Smith, J.; et al. Outbreak of urogenital schistosomiasis in Corsica (France): An epidemiological case study. *Lancet Infect. Dis.* **2016**, *16*, 971–979. [CrossRef]
8. Kincaid-Smith, J.; Tracey, A.; de Carvalho Augusto, R.; Bulla, I.; Holroyd, N.; Rognon, A.; Rey, O.; Chaparro, C.; Oleaga, A.; Mas-Coma, S.; et al. Morphological and genomic characterisation of the *Schistosoma* hybrid infecting humans in Europe reveals admixture between *Schistosoma haematobium* and *Schistosoma bovis*. *PLoS Negl. Trop. Dis.* **2021**, *15*, e0010062. [CrossRef]
9. Moné, H.; Holtfreter, M.C.; Allienne, J.-F.; Mintsa-Nguéma, R.; Ibikounle, M.; Boissier, J.; Berry, A.; Mitta, G.; Richter, J.; Mouahid, G. Introgressive hybridizations of *Schistosoma haematobium* by *Schistosoma bovis* at the origin of the first case report of schistosomiasis in Corsica (France, Europe). *Parasitol. Res.* **2015**, *114*, 4127–4133. [CrossRef]
10. Salas-Coronas, J.; Bargues, M.D.; Lozano-Serrano, A.B.; Artigas, P.; Martínez-Ortí, A.; Mas-Coma, S.; Merino-Salas, S.; Vivas-Pérez, J.I.A. Evidence of autochthonous transmission of urinary schistosomiasis in Almeria (Southeast Spain): An outbreak analysis. *Travel Med. Infect. Dis.* **2021**, *44*, 102165. [CrossRef]
11. Cnops, L.; Huyse, T.; Maniewski, U.; Soentjens, P.; Bottieau, E.; Van Esbroeck, M.; Clerinx, J. Acute schistosomiasis with a *Schistosoma mattheei* × *Schistosoma haematobium* hybrid species in a cluster of 34 travelers infected in South Africa. *Clin. Infect. Dis.* **2021**, *72*, 1693–1698. [CrossRef]
12. Gutman, J.R.; Lucchi, N.W.; Cantey, P.T.; Steinhardt, L.C.; Samuels, A.M.; Kamb, M.L.; Kapella, B.K.; McElroy, P.D.; Udhayakumar, V.; Lindblade, K.A. Malaria and parasitic neglected tropical diseases: Potential syndemics with COVID-19? *Am. J. Trop. Med. Hyg.* **2020**, *103*, 572–577. [CrossRef] [PubMed]
13. Mantica, G.; Martini, M.; Riccardi, N. The possible impact of SARS-COV-2 on neglected tropical diseases in Europe: The out of spotlights emerging of schistosomiasis. *J. Prev. Med. Hyg.* **2021**, *62*, E3–E4. [CrossRef] [PubMed]
14. Holen, Ø. Schistosomiasis in the shadow of COVID-19. *Tidsskr. Nor. Laegeforen.* **2021**, 141. [CrossRef]
15. Kura, K.; Ayabina, D.; Toor, J.; Hollingsworth, T.D.; Anderson, R.M. Disruptions to schistosomiasis programmes due to COVID-19: An analysis of potential impact and mitigation strategies. *Trans. R. Soc. Trop. Med. Hyg.* **2021**, *115*, 236–244. [CrossRef]
16. Olamiju, F.; Nebe, O.J.; Mogaji, H.; Marcus, A.; Amodu–Agbi, P.; Urude, R.O.; Apake, E.; Olamiju, O.; Okoronkwo, C.; Achu, I.; et al. Schistosomiasis outbreak during COVID-19 pandemic in Takum, Northeast Nigeria: Analysis of infection status and associated risk factors. *PLoS ONE* **2022**, *17*, e0262524. [CrossRef]
17. European Centre for Disease Prevention and Control. Dengue—Annual Epidemiological Report for 2020. Available online: https://www.ecdc.europa.eu/en/publications-data/dengue-annual-epidemiological-report-2020 (accessed on 5 May 2022).
18. European Centre for Disease Prevention and Control. Chikungunya Virus Disease—Annual Epidemiological Report for 2020. Available online: https://www.ecdc.europa.eu/en/publications-data/chikungunya-virus-disease-annual-epidemiological-report-2020 (accessed on 5 May 2022).

19. Global Schistosomiasis Alliance. Special Schisto Bulletin—Impact of COVID-19 on Schistosomiasis Activities. Available online: https://www.eliminateschisto.org/news/special-schisto-bulletin-impact-of-covid-19-on-schistosomiasis-activities (accessed on 29 April 2022).
20. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
21. Falagas, M.E.; Pitsouni, E.I.; Malietzis, G.; Pappas, G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: Strengths and weaknesses. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2008**, *22*, 338–342. [CrossRef]
22. Organisation for Economic Cooperation and Development. Gross Domestic Spending on R&D. Available online: https://data.oecd.org/rd/gross-domestic-spending-on-r-d.htm (accessed on 8 April 2022).
23. The World Bank. Measuring Poverty. Available online: https://www.worldbank.org/en/topic/measuringpoverty (accessed on 8 April 2022).
24. Van Eck, N.J.; Waltman, L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* **2010**, *84*, 523–538. [CrossRef]
25. De Martel, C.; Georges, D.; Bray, F.; Ferlay, J.; Clifford, G.M. Global burden of cancer attributable to infections in 2018: A worldwide incidence analysis. *Lancet Glob. Health* **2020**, *8*, e180–e190. [CrossRef]
26. Veeresha, P.; Baskonus, H.M.; Prakasha, D.; Gao, W.; Yel, G. Regarding new numerical solution of fractional Schistosomiasis disease arising in biological phenomena. *Chaos Soliton. Fract.* **2020**, *133*, 109661. [CrossRef]
27. Langenberg, M.C.C.; Hoogerwerf, M.-A.; Koopman, J.P.R.; Janse, J.J.; Oosterhoud, J.K.-V.; Feijt, C.; Jochems, S.P.; De Dood, C.J.; Van Schuijlenburg, R.; Ozir-Fazalalikhan, A.; et al. A controlled human Schistosoma mansoni infection model to advance novel drugs, vaccines and diagnostics. *Nat. Med.* **2020**, *26*, 326–332. [CrossRef] [PubMed]
28. Wendt, G.; Zhao, L.; Chen, R.; Liu, C.; O'Donoghue, A.J.; Caffrey, C.R.; Reese, M.L.; Collins, J.J. A single-cell RNA-seq atlas of Schistosoma mansoni identifies a key regulator of blood feeding. *Science* **2020**, *369*, 1644–1649. [CrossRef] [PubMed]
29. Toor, J.; Adams, E.R.; Aliee, M.; Amoah, B.; Anderson, R.M.; Ayabina, D.; Bailey, R.; Basáñez, M.-G.; Blok, D.J.; Blumberg, S.; et al. Predicted impact of COVID-19 on neglected tropical disease programs and the opportunity for innovation. *Clin. Infect. Dis.* **2021**, *72*, 1463–1466. [CrossRef] [PubMed]
30. Meningher, T.; Barsheshet, Y.; Ofir-Birin, Y.; Gold, D.; Brant, B.; Dekel, E.; Sidi, Y.; Schwartz, E.; Regev-Rudzki, N.; Avni, O.; et al. Schistosomal extracellular vesicle-enclosed miRNAs modulate host T helper cell differentiation. *EMBO Rep.* **2020**, *21*, e47882. [CrossRef] [PubMed]
31. Parkin, D.M.; Hämmerl, L.; Ferlay, J.; Kantelhardt, E.J. Cancer in Africa 2018: The role of infections. *Int. J. Cancer* **2020**, *146*, 2089–2103. [CrossRef] [PubMed]
32. King, C.H.H.; Kittur, N.; Binder, S.; Campbell, C.H., Jr.; N'Goran, E.K.; Meite, A.; Utzinger, J.; Olsen, A.; Magnussen, P.; Kinung'Hi, S.; et al. Impact of different mass drug administration strategies for gaining and sustaining control of Schistosoma mansoni and Schistosoma haematobium infection in Africa. *Am. J. Trop. Med. Hyg.* **2020**, *103*, 14–23. [CrossRef]
33. Léger, E.; Borlase, A.; Fall, C.B.; Diouf, N.D.; Diop, S.D.; Yasenev, L.; Catalano, S.; Thiam, C.T.; Ndiaye, A.; Emery, A.; et al. Prevalence and distribution of schistosomiasis in human, livestock, and snail populations in northern Senegal: A one health epidemiological study of a multi-host system. *Lancet Planet Health* **2020**, *4*, e330–e342. [CrossRef]
34. Corstjens, P.L.A.M.; De Dood, C.J.; Knopp, S.; Clements, M.N.; Ortu, G.; Umulisa, I.; Ruberanziza, E.; Wittmann, U.; Kariuki, T.; LoVerde, P.; et al. Circulating anodic antigen (CAA): A highly sensitive diagnostic biomarker to detect active Schistosoma infections—Improvement and use during SCORE. *Am. J. Trop. Med. Hyg.* **2020**, *103*, 50–57. [CrossRef]
35. Vale, N.; Gouveia, M.J.; Rinaldi, G.; Brindley, P.J.; Gärtner, F.; Correia da Costa, J.M. Praziquantel for schistosomiasis: Single-drug metabolism revisited, mode of action, and resistance. *Antimicrob. Agents Chemother.* **2017**, *61*, e02582-16. [CrossRef]
36. Zwang, J.; Olliaro, P. Efficacy and safety of praziquantel 40 mg/kg in preschool-aged and school-aged children: A meta-analysis. *Parasites Vectors* **2017**, *10*, 47. [CrossRef]
37. Hillyer, J.F. Parasites and parasitology in this SARS-CoV-2, COVID-19 world: An American Society of Parasitologists Presidential Address. *J. Parasitol.* **2020**, *106*, 859–868. [CrossRef] [PubMed]
38. Oyeyemi, O.T.; Okunlola, O.A.; Adebayo, A.D. Assessment of schistosomiasis endemicity and preventive treatment on coronavirus disease 2019 outcomes in Africa. *New Microbes New Infect.* **2020**, *38*, 100821. [CrossRef] [PubMed]

Appendix B

Epidemiological and clinical data of urogenital Schistosomiasis in PSAC

CODE________

Pediatric Schistosomiasis epidemiological data

Personal data			
Name		Neighbourhood	
Age	Sex	Macrohaematuria	Haemoglobin
Weight	Height	Z score	PB
Caregiver Contact	KAP code	Recruitment Date	

Urine						
Leucocytes	Negative	trace	+70		+125	+500
Proteins	Negative	trace	30	100	300	1000
Blood	Negative	trace	25		80	200
Urine volume						
Eggs count						

Ultrasound	
Bladder	
Form Normal =0 Deformed =1	
Bladder wall	
Wall irregularity (thickness < 5 mm) No =0 Focal =1 Multifocal =2	
Wall thickness (>5 mm < 10 mm) No (<5 mm) =0 Focal =1 Multifocal =2	
Mass (>10 mm) No =0 One =2 Multiple (nº) + 2	
Pseudopolyp No =0 One =2 Multiple (nº) + 2	
Bladder score	
Ureters	
Right Ureter Not visualized = 0 Dilated in the proximal and/or distal third =3 Severely dilated and/or fully dilated =4	
Left Ureter Not visualized = 0 Dilated in the proximal and/or distal third =3 Severely dilated and/or fully dilated =4	
Renal Pelvis	
Right Pelvis Not dilated =0 Moderate dilation (thickness of the parenchyma >1 cm =6) Marked hydronephrosis (parenchyma < 1 cm) =8	
Left Pelvis Not dilated =0 Moderate dilation (thickness of the parenchyma >1 cm =6) Marked hydronephrosis (parenchyma < 1 cm) =8	
Upper urinary tract score	
Total score for *Schistosoma haematobium* morbidity	
Comments	

Appendix C

Approval by the ethics committee

REPÚBLICA DE ANGOLA
MINISTÉRIO DA SAÚDE
COMITÉ DE ÉTICA

PARECER N.º 41 C.E/MINSA.INIS/2022

Sobre o projecto de pesquisa intitulado "AVALIAÇÃO DA MORBILIDADE ASSOCIADA À ESQUISTOSSOMOSE URINÁRIA NA POPULAÇÃO PRÉ-ESCOLAR DO MUNICÍPIO DE CUBAL-ANGOLA", submetido a este Comité pelo investigador **Fernando Salvador**

Após apreciação do protocolo do projecto de investigação supracitado, somos a tecer o seguinte parecer:

- Consideramos o protocolo de grande relevância para o pais, contudo, constatamos incongruências e que se faça as seguintes alterações: revisão do texto e correcção autográfica, falta de justificativa e ausência de dados anteriores. Estando acautelados os princípios fundamentais éticos, observando-se a conformidade na elaboração do respectivo projecto, este Comité não se opõe à sua realização.

Decisão: Este Comité recomenda que devam proceder revisões sobre os aspectos acima descritos e submeter no prazo de 15 dias. Pelo que somos de parecer **FAVORÁVEL.**

LUANDA, AOS 10 DE NOVEMBRO DE 2022.

A COORDENADORA
JOANA DE MORAIS, PHD.

O COORDENADOR ADJUNTO
NGIAMBUDULU FRANCISCO, PHD

Rua Amilcar Cabral, Nº. 96, por tras do Hospital Josina Machel, Maianga. Luanda – Angola
E-mail: comiteetica91@gmail.com

minsa.gov.ao

Appendix D
KAP survey questionnaire

DATE_____________ CODE _________________

UROGENITAL SCHISTOSOMIASIS KAP SURVEY

A. Demographic data

A.1 Name:

A.2 Age:

A.3 Sex:

1. Feminine 2. Masculine

A.4 Civil status:

1. Married 2. Single 3. Widow/er

A.5 Neighbourhood:

1. Kasseke 2. Rio bom 3. Sagrada – Missão 4. Cristo Rei – Benfica

5. Kiskeroff – La Salette 6. Kamunda 7. Ngola 8. Hamavoko

9. Cidade 10. Passagem 11. Vacarias 12. Calomanga

13. Kaloha 14. Tchimbassi 15. Bairo 80 16. Kimbos

17. Out of Cubal 18. Other________

A.6 Ethnicity:

1. Umbundu 2. Kimbundu 3. Bakongo 4. Lwenea

5. Other______

A.7 Literacy level:

1. Cannot read and write 2. Can read 3. Can write 4. Can read and write

A.8 Educational level:

1. None 2. Primary 3. Secondary 3. Grade 12

4. Professional training 5. University

A.9 Job: _______________

B. Urogenital Schistosomiasis Knowledge

B1. Have you ever heard about Tchitokoto?

1. No 2. Yes

B2. Where?

1. School 2. Hospital 3. Church 4. Home / Family 5. Street / Friends

6. Radio 7. Other_________

B3. Do you know the Tchitokoto symptoms?

1. No (B5) 2. Yes (B4)

B4. Which are the Tchitokoto symptoms?

1. Abdominal pain 2. Blood in urine 3. Fever 4. General discomfort

5. DK/DA 6. Other_____________

B5. Do you believe Tchitokoto is a disease than can cause death?

1. No 2. Yes

B6. Do you know how can you get infected by Tchitokoto?

1. No (B11) 2. Yes (B7)

B7. How can you get infected by Tchitokoto?

1. Drink water (B8) 2. Having bath (B8) 3. Laundry (B8)

4. Fishing (B8) 5. Eating sugar cane (B11) 6. Other (B11) _______

B8. Which kind of water?

1. Sea water 2. River/Lake water 3. Well water

4. Tap water 5. Other__________

B9. Do you know how Tchitokoto parasite arrives to the water?

1. No (B11) 2. Yes (B10)

B10. How? ________________________

B11. Do you believe Tchitokoto can be prevented?

1. No 2. Yes

B12. How can it be prevented?

1. To avoid going into the river/lake 2. To use clean water for daily tasks

3. To boil water before using it 4. To take medicines

5. To avoid eating sugarcane 6. DK/DA 7. Other____________

B13. Do you carry out any preventive activity?

1. No 2. Yes

B14. Which?

1. To avoid going into the river/lake 2. To use clean water for daily tasks

3. To boil water before using it 4. To take medicines

5. To avoid eating sugarcane 6. DK/DA 7. Other____________

B15. Do you believe Tchitokoto can be cured?

1. No 2. Yes

B16. How?

1. Traditional Medicine 2. Modern Medicines 3.Cirugy 4. DK/DA

5. Other__________

C. Urogenital Schistosomiasis background

C1. Have you ever been diagnosed with Tchitokoto?

1. No 2. Yes

C2. How many times?

1. Once 2. Twice 3. Three or more

C3. How old were you?

1. Less than 5 years old 2. Between 5 and 10 years old

3. Between 10 and 20 years old 4. More than 20 years old

C4. How were you diagnosed?

1. Tracking campaigns/Research projects 2. Medical consultation

3. Traditional medicine consultation

C5. Which symptoms did you have?

1. Abdominal pain 2. Blood in urine 3. Fever 4. General discomfort

5. Cannot remember 6. DK/DA 7. Other_____________

C6. Did you take modern medication to treat Tchitokoto?

1. No 2. Yes

C7. Did you experience side effects?

1. No 2. Yes

C8. Which?

1. Headache 2. Dizziness 3. Stomachache 4. Nausea

5. Fever 6. Polyuria 7. Cannot remember 8. Other_____________

C9. Did the symptoms disappear after the treatment?

1. No 2. Yes

C10. After receiving the treatment, did you receive any information about how to prevent future infections?

1. No 2. Yes

C11. Who gave you that information?

1. Health professionals 2. Teachers 3. Other________

C12. Have you ever been involved in a deworming campaign?

1. No 2. Yes

C13. Where?

1. Hospital 2. School 3. Other_________

C14. During the deworming campaign, did you receive information about how to prevent Tchitokoto?

1. No 2. Yes

C15. Who gave you that information?

1. Health professionals 2. Teachers 3. Other________

D. Attitudes and Beliefs

D1. Do you believe reed urine is normal?

1. No 2. Yes

D2. Do you believe abdomen al pain is normal?

1. No 2. Yes

D3. Do you go to the doctor when you feel sick?

1. No 2. Yes 3. Some times

D4. Why?

1. It is too far 2. It is too expensive 3. I am afraid

4. I prefer traditional medicine for certain diseases

5. I prefer traditional medicine

D5. What do you do when you feel sick?

1. Wait for it to pass on its own 2. Ask for advice to a family member

3. Self-medication 4. Seek for traditional medicine

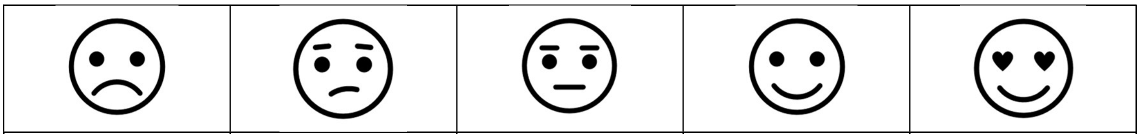
D6. Are you willing to participate in a deworming campaign?

1. No 2. Yes

D7. When you go to medical consultation, do you understand what doctor tells you?

1. No 2. Yes 3. Somehow

D8. How would you score your trust in doctors?



1	2	3	4	5

E. Risk practices for urogenital schistosomiasis exposure

Please tell me how often you do the following practices

E1. To bath in the river/lake

Never	Some times	Only during dry season	Almost everyday	Everyday

E2. To laundry in the river/lake

Never	Some times	Only during dry season	Almost everyday	Everyday

E3. To fetch river/lake water for watering their crops

Never	Some times	Only during dry season	Almost everyday	Everyday

E4. To fetch river/lake water for housework

Never	Some times	Only during dry season	Almost everyday	Everyday

E5. To urinate in the river/lake or on the shores

Never	Some times	Only during dry season	Almost everyday	Everyday

F. Socioeconomic situation

F1. People living in your household

1. One 2. Two 3. Three 4. Four 5. Five 6. Six

7. Seven 8. Eight 9. Nine 10. Ten or more

F2. How many beds do you have at home?

1. Zero 2. One 3. Two 4. Three 5. Four 6. Five

7. Six 8. Seven 9. Eight 10. Nine 11. Ten or more

F3. How many people have income in your household?

1. Zero 2. One 3. Two 4. Three or more

F4. Do you have electricity at home?

1. No 2. Yes

F5. Do you have tap water at home?

1. No 2. Yes

F6. How much do you have to walk to get to the nearest water source?

1. Less than 5 minutes 2. Between 5 and 15 minutes

3. Between 15 and 30 minutes 4. More than 30 minutes

F7. Do you have a radio at home?

1. No 2. Yes

F8. Do you have a TV at home?

1. No 2. Yes

F9. House environment

1. Swampy area 2. Area with ponds 3. Urban area

4. Paved urban area 5. Rural area

F10. Roof material

1. Sheet metal 2. Cement 3. Sticks

F11. Walls material

1. Adobe 2. Sticks 3. Bricks 4. Cement

F12. Floor material

1. Ground 2. Cement 3. Tiles

F13. Where is the kitchen?

1. Fully open exterior 2. Partially open exterior

3. Fully enclosed exterior 4. Inside

F14. What do you use for cooking?

1. Charcoal 2. Wood 3. Gas 4. Electricity

F15. Do you have a toilet?

1. No 2. Yes

F16. Where is it?

1. Fully open exterior 2. Partially open exterior

3. Fully enclosed exterior 4. Inside

F17. Do you have a latrine?

1. No 2. Yes

F18. Where?

1. Fully open exterior 2. Partially open exterior

3. Fully enclosed exterior 4. Inside

F19. How much do you have to walk to get to the river?

1. Less than 5 minutes 2. Between 5 and 15 minutes

3. Between 15 and 30 minutes 4. More than 30 minutes

F20. How much do you have to walk to get to the lake?

1. Less than 5 minutes 2. Between 5 and 15 minutes

3. Between 15 and 30 minutes 4. More than 30 minutes

CODE of the child or children under his or her responsibility who participate in the parallel prevalence and morbidity study: ______________________

Bibliography

A

Abdulahi, A.; Shab-Bidar, S.; Rezaei, S.; Djafarian, K. (2017) Nutritional status of under five children in Ethiopia: a systematic review and meta-analysis. *Ethiop J Health Sci*

Adepoju, P. (2020) NTDs in the time of COVID-19. *Lancet Microbe* 1, 6, e244. https://doi.org/10.1016/s2666-5247(20)30153-1

Adie, H. A.; Oyo-Ita, A.; Okon, O.E.; Arong, G.A.; Atting, I.A.; Braide, E.I. et al. (2015) Evaluation of intensity of urinary schistosomiasis in Biase and Yakurr local government areas of cross river state, Nigeria after two years of integrated control measures. *Res J Parasitol* 10, 2, 58–65. http://dx.doi.org/10.3923/jp.2015.58.65

Akpata, R.; Neumayr, A.; Holtfreter, M.C.; Krantz, I.; Singh, D.D.; Mota, R. et al. (2015) The WHO ultrasonography protocol for assessing morbidity due to *Schistosoma haematobium*. Acceptance and evolution over 14 years. Systematic review. *Parasitol Res* 114, 4, 1279–1289. https://doi.org/10.1007/s00436-015-4389-z

Angora, E.K.; Boissier, J.; Menan, H.; Rey, O.; Tuo, K.; Touré, A.O. et al. (2019) Prevalence and Risk Factors for Schistosomiasis among Schoolchildren in two Settings of Côte d'Ivoire. *Trop Med Infect Dis* 4, 3, 110. https://doi.org/10.3390/tropicalmed4030110

Anyanwu, F.C.; Ramoteme, M.; Mabunda, J.; Henry, A.; Kwabena, K.; Nenzhelele, F. (2020) A quantitative assessment of the level of knowledge, attitude and practices of farmworkers regarding schistosomiasis in a rural community in South Africa. *Afr J Prim Health Care Fam Med* 12, 1, e1–e8. https://doi.org/10.4102/phcfm.v12i1.2098

Anyolitho, M.K.; Poels, K.; Huyse, T.; Tumusiime, J.; Mugabi, F.; Tolo, C.U. et al. (2022) Knowledge, attitudes, and practices regarding schistosomiasis infection and prevention: A mixed-methods study among endemic communities of western Uganda. *PLoS Negl Trop Dis* 16, 2, e0010190. https://doi.org/10.1371/journal.pntd.0010190

B

Balis, B.; Dessie, Y.; Debella, A.; Alemu, A.; Tamiru, D.; Negash, B. et al. (2022) Magnitude of anemia and its associated factors among pregnant women attending antenatal care in Hiwot Fana Specialized University Hospital in Eastern Ethiopia. *Front Public Health* 10, 867888. doi:10.3389/fpubh.2022.867888

Barda, B.; Coulibaly, J.T.; Hatz, C.; Keiser. J. (2017) Ultrasonographic evaluation of urinary tract morbidity in school-aged and preschool-aged children infected with *Schistosoma haematobium* and its evolution after praziquantel treatment: a randomized controlled trial. *PLoS Negl Trop Dis* 11, 2, e0005400. https://doi.org/10.1371/journal.pntd.0005400

Bocanegra, C.; Gallego, S.; Mendioroz, J.; Moreno, M.; Sulleiro, E.; Salvador, F. et al. (2015) Epidemiology of schistosomiasis and usefulness of indirect diagnostic tests in school-age children in Cubal, Central Angola. *PLoS Negl Trop Dis* 9, 10, e0004055. https://doi.org/10.1371/journal.pntd.0004055

Bocanegra, C.; Pintar, Z.; Serres, X.; Mendioroz, J.; Moreno, M.; Gallego, S. et al. (2018) Ultrasound findings and associated factors to morbidity in *Schistosoma haematobium* infection in a highly endemic setting. *Trop Med Int Health* 23, 2, 221–228. https://doi.org/10.1111/tmi.13020

Boissier, J.; Grech-Angelini, S.; Webster, B. L.; Allienne, J. F.; Huyse, T.; Mas-Coma, S. et al. (2016) Outbreak of urogenital schistosomiasis in Corsica (France): an epidemiological case study. *Lancet Infect Dis* 16, 8, 971–979. https://doi.org/10.1016/s1473-3099(16)00175-4

Bonnard, P.; Boutouaba, S.; Diakhate, I.; Seck, M.; Dompnier, J.P.; Riveau, G. (2011) Learning curve of vesico-urinary ultrasonography in *Schistosoma haematobium* infection with WHO practical guide: a "simple to learn" examination. *Am J Trop Med Hyg* 85, 6, 1071–1074. https://doi.org/10.4269/ajtmh.2011.11-0282

Borlase, A.; Le Rutte, E.A.; Castaño, S.; Blok, D.J.; Toor, J.; Giardina, F. et al. (2022) Evaluating and mitigating the potential indirect effect of COVID-19 on control programmes for seven neglected tropical diseases: a modelling study. *Lancet Glob Health* 10, 11, e1600–e1611. https://doi.org/10.1016/S2214-109X(22)00360-6

Borrego-Sánchez, A.; Sánchez-Espejo, R.; García-Villén, F.; Viseras, C.; Sainz-Díaz, C.I. (2020) Praziquantel-clays as accelerated release systems to enhance the low solubility of the drug. *Pharmaceutics* 12, 10, 914. https://doi.org/10.3390/pharmaceutics12100914

Bosompem, K.M.; Bentum, I.A.; Otchere, J.; Anyan, W.K.; Brown, C.A.; Osada, Y. et al. (2004) Infant schistosomiasis in Ghana: a survey in an irrigation community. *Trop Med Int Health* 9, 8, 917–922. https://doi.org/10.1111/j.1365-3156.2004.01282.x

Botelho, M C.; Figueiredo, J.; Alves, H. (2015) Bladder cancer and urinary schistosomiasis in Angola. *J Nephrol Res* 1, 1, 22. https://doi.org/10.17554/j.issn.2410-0579.2015.01.4

C

Chala, B.; Hamde, F. (2021) Emerging and re-emerging vector-borne infectious diseases and the challenges for control: a review. Front Public Health 9, 715759. https://doi.org/10.3389/fpubh.2021.715759

Christinet V.; Lazdins-Helds J.K.; Stothard J.R.; Reinhard-Rupp J. (2016) Female genital schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease. *Int J Parasitol* 46, 395–404. https://doi.org/10.1016/j.ijpara.2016.02.006

Chu, D.K.; Akl, E.A.; Duda, S.; Solo, K.; Yaacoub, S.; Schünemann, H.J. et al. (2020) Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet* 395, 1973–1987. https://doi.org/10.1016/s0140-6736(20)31142-9

CIA (Central Intelligence Agency) (2021) The World Factbook 2021. Washington, DC: Central Intelligence Agency. Available online: https://www.cia.gov/the-world-factbook/countries/angola/ (accessed on 18 Nov 2022)

Cimini, A.; Ricci, M.; Gigliotti, P.E.; Pugliese, L.; Chiaravalloti, A.; Danieli, R. et al. (2021) Medical imaging in the diagnosis of schistosomiasis: A review. *Pathogens* 10, 8, 1058. https://doi.org/10.3390/pathogens10081058

Cioli, D.; Pica-Mattoccia, L. (2003) Praziquantel. *Parasitol Res* 90, Suppl 1, S3–S9. https://doi.org/10.1007/s00436-002-0751-z

Cioli, D.; Pica-Mattoccia, L.; Basso, A.; Guidi, A. (2014) Schistosomiasis control: praziquantel forever?. *Mol Biochem Parasitol* 195, 1, 23–29. https://doi.org/10.1016/j.molbiopara.2014.06.002

CJE (Consejo de la Juventud de España) (2022) Balance General 1er. Semestre 2022. Madrid, Spain: Consejo de la Juventud de España, Observatorio de Emancipación. Available online: http://www.cje.org/es/publicaciones/novedades/observatorio-de-emancipacion-primer-semestre-2022/ (accessed on 18 Dec 2022) (in Spanish)

Colley, D.G.; Bustinduy, A.L.; Secor, W.E.; King, C.H. (2014) Human schistosomiasis. *Lancet* 383, 9936, 2253–2264. https://doi.org/10.1016/s0140-6736(13)61949-2

Colomer, M.A.; Margalida, A.; Al`os, F.; Oliva-Vidal, P.; Vilella, A.; Fraile, L. (2021) Modelling the SARS-CoV-2 outbreak: Assessing the usefulness of protective measures to reduce the pandemic at population level. *Sci Total Environ* 789, 147816. https://doi.org/10.1016/j.scitotenv.2021.147816

Corstjens, P.L.A.M.; de Dood, C.J.; Knopp, S.; Clements, M.N.; Ortu, G.; Umulisa, U. et al. (2020) Circulating anodic antigen (CAA): A highly sensitive diagnostic biomarker to detect active *Schistosoma* infections-improvement and use during SCORE. *Am J Trop Med Hyg* 103, 50–57. https://doi.org/10.4269/ajtmh.19-0819

D

Dabo, A.; Badawi, H.M.; Bary, B.; Doumbo, O.K. (2011) Urinary schistosomiasis among preschool-aged children in Sahelian rural communities in Mali. *Parasit Vectors* 4, 21. https://doi.org/10.1186%2F1756-3305-4-21

Dai, J.R.; Li, Y.Z.; Wang, W.E.I.; Xing, Y.T.; Qu, G.L.; Liang, Y.S. (2015) Resistance to niclosamide in *Oncomelania hupensis*, the intermediate host of *Schistosoma japonicum*: should we be worried? *Parasitology* 142, 2, 332–340. https://doi.org/10.1017/s0031182014000870

Dantas, N.M.; Andrade, L.A.; da Paz W.S.; Borges, W.N.; Barbosa, V.G.B.; da Hora, D.P.G. et al. (2023) Impact of the COVID-19 pandemic on the actions of the Schistosomiasis Control Program in an endemic area in Northeastern Brazil. *Acta Trop* 106859. https://doi.org/10.1016/j.actatropica.2023.106859

Dawaki, S.; Al-Mekhlafi, H.M.; Ithoi, I.; Ibrahim, J.; Abdulsalam, A.M.; Ahmed, A. et al. (2015) The menace of schistosomiasis in Nigeria: knowledge, attitude, and practices regarding schistosomiasis among rural communities in Kano state. *PLoS One* 10, e0143667. https://doi.org/10.1371/journal.pone.0143667

De Alegria M.L.A.R.; Colmenares, K.; Espasa, M.; Amor, A.; Lopez, I.; Nindia, A. et al. (2017) Prevalence of *Strongyloides stercoralis* and other intestinal parasite infections in school children in a rural area of Angola: a cross-sectional study. *Am J Trop Med Hyg* 97, 1226–1231. https://doi.org/10.4269/ajtmh.17-0159

de Laval, F.; Savini, H.; Biance-Valero, E.; Simon, F. (2014) Human schistosomiasis: an emerging threat for Europe. Lancet 384, 9948, 1094–1095. https://doi.org/10.1016/s0140-6736(14)61669-x

de Martel, C.; Georges, D.; Bray, F.; Ferlay, J.; Clifford, G.M. (2020) Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health* 8, e180-e190. https://doi.org/10.1016/S2214-109X(19)30488-7

de Souza, D.K.; Picado, A.; Biéler, S.; Nogaro, S.; Ndung'u, J.M. (2020) Diagnosis of neglected tropical diseases during and after the COVID-19 pandemic. *PLoS Negl Trop Dis* 14, 8, e0008587. https://doi.org/10.1371/journal.pntd.0008587

Donthu, N.; Kumar, S.; Mukherjee, D.; Pandey, N.; Lim, W.M. (2021) How to conduct a bibliometric analysis: An overview and guidelines. *J Bus Res* 133, 285–296. https://doi.org/10.1016/j.jbusres.2021.04.070

E

Ehrenberg, J.P.; Zhou, X.N.; Fontes, G.; Rocha, E.M.M.; Tanner, M.; Utzinger, J. (2020) Strategies supporting the prevention and control of neglected tropical diseases during and beyond the COVID-19 pandemic. *Infect Dis Poverty* 9, 1, 86. https://doi.org/10.1186/s40249-020-00701-7

Ekpo, U.; Odeyemi, O.; Sam-Wobo, S.; Onunkwor, O.; Mogaji, H.; Oluwole, A. et al. (2017) Female genital schistosomiasis (FGS) in Ogun State, Nigeria: a pilot survey on genital symptoms and clinical findings. *Parasitol Open* 3, e10. https://doi.org/10.1017/pao.2017.11

Elsevier (2019) *Research Metrics Guidebook*. Amsterdam, The Netherlands: Elsevier B.V. https://www.elsevier.com/research-intelligence/resource-library/research-metrics-guidebook

F

Falagas, M.E.; Pitsouni, E.I.; Malietzis, G.A.; Pappas, G. (2008) Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. *FASEB J Publ Fed Am Soc Exp Biol* 22, 338–342. https://doi.org/10.1096/fj.07-9492LSF

Farley, J. (1991) *Bilharzia: A History of Imperial Tropical Medicine*. Cambridge, MA: Cambridge University Press

Fazal, O.; Hotez, P.J. (2020) NTDs in the age of urbanization, climate change, and conflict: Karachi, Pakistan as a case study. *PLoS Negl Trop Dis* 14, 11, e0008791. https://doi.org/10.1371/journal.pntd.0008791

Fisher, A.; Fukuda-Parr, S. (2019) Introduction—Data, Knowledge, Politics and Localizing the SDGs, J Hum Dev Capab 20, 4, 375–385. https://doi.org/10.1080/19452829.2019.1669144

Folefac, L.N.; Nde-Fon, P.; Verla, V.S.; Tangye, M.N.; Njunda, A.L.; Luma, H.N. (2018) Knowledge, attitudes and practices regarding urinary schistosomiasis among adults in the Ekombe Bonji Health Area, Cameroon. *Pan Afr Med J* 29, 161. https://doi.org/10.11604/pamj.2018.29.161.14980

G

Garba, A.; Barkiré, N.; Djibo, A.; Lamine, M.S.; Sofo, B.; Gouvras, A.N. et al. (2010) Schistosomiasis in infants and preschool-aged children: infection in a single *Schistosoma haematobium* and a mixed *S. haematobium–S. mansoni* foci of Niger. *Acta Trop* 115, 3, 212–219. https://doi.org/10.1016/j.actatropica.2010.03.005

Gelfand, M. (1968) A clinical study of intestinal bilharziasis (*Schistosoma mansoni*) in Africa. *Proc R Soc Med* 61, 8, 849–849. https://doi.org/10.1177/003591576806100847

Gryseels, B.; Polman, K.; Clerinx, J.; Kestens, L. (2006) Human schistosomiasis. *Lancet* 368, 9541, 1106 –1118. https://doi.org/10.1016/s0140-6736(06)69440-3

GSA (Global Schistosomiasis Alliance) (2020) Special Schisto Bulletin - impact of Covid-19 on schistosomiasis activities. Available online: https://www.eliminateschisto.org/news/special-schisto-bulletin-impact-of-covid-19-on-schistosomiasis-activities (accessed on 29 Apr 2022)

Gujo, A.B.; Kare, A.P. (2021) Prevalence of intestinal parasite infection and its association with anemia among children aged 6 to 59 months in Sidama National Regional State, Southern Ethiopia. *Clin Med Insights: Pediatr* 15. https://doi.org/10.1177/11795565211029259

Guo, J.Y.; Zhang, L.J.; Cao, C.L.; Lü, S.; Xu, J.; Li, S.Z.; Zhou, X.N. (2020) Challenges of schistosomiasis control in China during the coronavirus disease 2019 (COVID-19) epidemic. *Chin J Schistosomiasis Control* 32, 511–516. https://doi.org/10.16250/j.32.1374.2020198

Gutman, J.R.; Lucchi, N.W.; Cantey, P.T. ; Steinhardt, L.C. ; Samuels, A.M. ; Kamb, M.L. et al. (2020) Malaria and parasitic neglected tropical diseases: potential syndemics with COVID-19? *Am J Trop Med Hyg* 103, 572–577. https://doi.org/10.4269/ajtmh.20-0516

H

Hausmann-Muela, S.; Ribera, J.; Nyamongo, I.K. (2003) Health-seeking behaviour and the health system response. Disease Control Priorities Project working paper No. 14

Hillyer, J.F. (2020) Parasites and parasitology in this SARS-CoV-2, COVID-19 world: An American Society of parasitologists presidential address. *J Parasitol* 106, 859–868. https://doi.org/10.1645/20-158

Holen, Ø. (2021) Schistosomiasis in the shadow of COVID-19. *Tidsskr Nor Laegeforen* 141 https://doi.org/10.4045/tidsskr.21.0057

Hollingsworth, T.D.; Mwinzi, P.; Vasconcelos, A.; de Vlas, S.J. (2021) Evaluating the potential impact of interruptions to neglected tropical disease programmes due to COVID-19. *Trans R Soc Trop Med Hyg* 115, 3, 201–204, https://doi.org/10.1093/trstmh/trab023

Hotez, P.J.; Fenwick, A.; Molyneux, D. (2021) The new COVID-19 poor and the neglected tropical diseases resurgence. *Infect Dis Poverty* 10, 1, 10. https://doi.org/10.1186/s40249-020-00784-2

Hu, G.H.; Jia, H.; Song, K.Y.; Lin, D.D.; Zhang, J.; Cao, C.L. et al. (2005) The role of health education and health promotion in the control of schistosomiasis: experiences from a 12-year intervention study in the Poyang Lake area. *Acta Trop* 96, 2-3, 232–241. https://doi.org/10.1016/j.actatropica.2005.07.016

I

IFDA (International Fund for Agricultural Development) (2018) República da Angola. Avaliação da Estratégia e do Programa do País. Rome, Italy: International Fund for Agricultural Development. Available online: https://ioe.ifad.org/documents/38714182/40296310/Full+document+-+Portuguese.pdf (accessed on 5 Dec 2022)

IHME (Institute for Health Metrics and Evaluation) (2019) Global Burden of Disease Study 2019. Seattle, WA: Institute for Health Metrics and Evaluation. Available online: https://www.thelancet.com/pb-assets/Lancet/gbd/summaries/diseases/neglected-tropical-diseases.pdf (accessed on Aug 31 2022)

INE (Instituto Nacional de Estatística) (2014) Resultados Definitivos do Recenseamento Geral da População e da Habitação 2014. Luanda, Angola: Instituto Nacional de Estatística, Gabinete Central do Censo, Subcomissão de Difusão de Resultados. Available online: https://archive.org/details/PublicacaoResultadosDefinitivosCensoGeral2014Versao22032016DEFINITIVA18H17CENSOG/mode/2up (accessed on Nov 14 2022)

INE (Instituto Nacional de Estatística) (2019) Pobreza multidimensional nos municípios de Angola. Luanda, Angola: Instituto Nacional de Estatística, Departamento de Informação e de Difusão. Available online: https://fdocumentos.tips/document/pobreza-multidimensional-nos-municpios-de-angola-inedepartamento-de-informao.html?page=3 (accessed on 12 Nov 2022)

Ishida, K; Hsieh, M.H. (2018) Understanding urogenital schistosomiasis-related bladder cancer: An update. *Front Med* 5, 223. https://doi.org/10.3389/fmed.2018.00223

J

Jin, Y.; Cha, S.; Lee, J.; Elhag, M.S.; Hong, S.T.; Lee, Y.H. (2020) Parasitological observation in schoolchildren with urogenital schistosomiasis following treatment with three different brands of praziquantel. *J Korean Med Sci* 35, 46, e394. https://doi.org/10.3346/jkms.2020.35.e394

K

Kabatende, J.; Barry, A.; Mugisha, M.; Ntirenganya, L.; Bergman, U.; Bienvenu, E. et al. (2022) Safety of praziquantel and albendazole coadministration for the control and elimination of schistosomiasis and soil-transmitted helminths among children in Rwanda: An active surveillance study. *Drug Saf* 45, 909–922. https://doi.org/10.1007/s40264-022-01201-3

Kabuyaya, M.; Chimbari, M.J.; Mukaratirwa, S. (2020) Comparison of praziquantel efficacy at 40 mg/kg and 60 mg/kg in treating *Schistosoma haematobium* infection among schoolchildren in the Ingwavuma area, KwaZulu-Natal, South Africa. *S Afr Med J* 110, 7, 657–660. https://doi.org/10.7196/samj.2020.v110i7.13926

Kalinda, C.; Mindu, T.; Chimbari, M.J. (2020) A systematic review and meta-analysis quantifying schistosomiasis infection burden in pre-school aged children (PreSAC) in sub-Saharan Africa for the period 2000-2020. *PloS ONE* 15, 12, e0244695. https://doi.org/10.1371/journal.pone.0244695

Kamel, B.; Laidemitt, M.R.; Lu, L.; Babbitt, C.; Weinbaum, O.L.; Mkoji, G.M. et al. (2021) Detecting and identifying Schistosoma infections in snails and aquatic habitats: A systematic review. *PLoS Negl Trop Dis* 15, 3, e0009175. https://doi.org/10.1371/journal.pntd.0009175

Kibira, S.P.S.; Ssempebwa, J.C.; Ssenyonga, R.; Radloff, S.; Makumbi, F.E. (2019) Schistosomiasis infection in pre-school aged children in Uganda: a qualitative descriptive study to identify routes of exposure. *BMC Infect Dis* 19, 1, 165. https://doi.org/10.1186/s12879-019-3803-z

Kihara, J.H.; Njagi, E.N.; Kenya, E.U.; Mwanje, M.T.; Odek, A.E.; van Dam, G. et al. (2009) Urinary soluble egg antigen levels in *Schistosoma haematobium* infection in relation to sex and age of Kenyan schoolchildren following praziquantel treatment. *Trans R Soc Trop Med Hyg* 103, 10, 1024–1030. https://doi.org/10.1016/j.trstmh.2009.04.021

Kimani, B.W.; Mbugua, A.K.; Kihara, J.H.; Ng'ang'a, M.; Njomo, D.W. (2018) Safety, efficacy and acceptability of praziquantel in the treatment of *Schistosoma haematobium* in pre-school children of Kwale County, Kenya. *PLoS Negl Trop Dis* 12, 10, e0006852. https://doi.org/10.1371/journal.pntd.0006852

King, C.H.; Kittur, N.; Binder, S.; Campbell, C.; N'Goran, E.; Méité, A. et al. (2020) Impact of different mass drug administration strategies for gaining and sustaining control of *Schistosoma mansoni* and *Schistosoma haematobium* infection in Africa. *Am J Trop Med Hyg* 103, 14–23. https://doi.org/10.4269/ajtmh.19-0829

Kinung'hi, S.M.; Magnussen, P.; Kaatano, G.M.; Kishamawe, C.; Vennervald, B.J. (2014) Malaria and helminth co-infections in school and preschool children: a cross-sectional study in Magu district, north-western Tanzania. *PloS ONE* 9, 1, e86510. https://doi.org/10.1371/journal.pone.0086510

Kura, K.; Ayabina, D.; Toor, J.; Hollingsworth, T.D.; Anderson, R.M. (2021) Disruptions to Schistosomiasis programmes due to COVID-19: an analysis of potential impact and mitigation strategies. *Trans R Soc Trop Med Hyg* 115, 236–244. https://doi.org/10.1093/trstmh/traa202

L

Langenberg, M.C.C.; Hoogerwerf, M.-A.; Koopman, J.P.R.; Janse, J.J.; Kos-van Oosterhoud, J.; Feijt, C. et al. (2020) A controlled human *Schistosoma mansoni* infection model to advance novel drugs, vaccines and diagnostics. *Nat Med* 26, 326–332. https://doi.org/10.1038/s41591-020-0759-x

Latham, M.C.; Stephenson, L.S.; Kurz, K.M.; Kinoti, S.N. (1990) Metrifonate or praziquantel treatment improves physical fitness and appetite of Kenyan schoolboys with *Schistosoma haematobium* and hookworm infections. *Am J Trop Med Hyg* 43, 170–179. https://doi.org/10.4269/ajtmh.1990.43.170

Launiala, A. (2009) How much can a KAP survey tell us about people's knowledge, attitudes and practices? Some observations from medical anthropology research on malaria in pregnancy in Malawi. *Anthropol Matters* 11, 1. https://doi.org/10.22582/am.v11i1.31

Léger, E.; Borlase, A.; Fall, C.B.; Diouf, N.D.; Diop, S.D.; Yasenev, L. et al. (2020) Prevalence and distribution of schistosomiasis in human, livestock, and snail populations in northern Senegal: a one health epidemiological study of a multi-host system. *Lancet Planet Health* 4, e330–e342. https://doi.org/10.1016/S2542-5196(20)30129-7

Lemos, M.; Pedro, J.M.; Fançony, C.; Moura, S.; Brito, M.; Vaz Nery, S. et al. (2020a) Schistosomiasis and soil-transmitted helminthiasis preventive chemotherapy: Adverse events in children from 2 to 15 years in Bengo province, Angola. *PLoS ONE* 15, 3, e0229247. https://doi.org/10.1371/journal.pone.0229247

Lemos, M.; Fançony, C.; Moura, S.; Mirante, C.; de Sousa, P.; Barros, H. et al. (2020b) Integrated community-based intervention for urinary schistosomiasis and soil-transmitted helminthiasis in children from Caxito, Angola. *Int Health* 12, 2, 86–94. https://doi.org/10.1093/inthealth/ihz055

Li, G.; Xu, D.; Hu, Y.; Xu, M.; Zhang, L.; Du, X. et al. Impact of the coronavirus disease 2019 lockdown on *Schistosoma* host *Oncomelania hupensis* density in Wuhan. *Acta Trop* 226, 106224. https://doi.org/10.1016/j.actatropica.2021.106224

Lin, Y.; Fang, K.; Zheng, Y.; Wang, H.-l.; Wu, J. (2022) Global burden and trends of neglected tropical diseases from 1990 to 2019. *J Travel Med* 29, 3, taac031. https://doi.org/10.1093/jtm/taac031

Lindenberg, M.; Kopp, S.; Dressman, J.B. (2004) Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *Eur J Pharm Biopharm* 58, 2, 265–278. https://doi.org/10.1016/j.ejpb.2004.03.001

Liu, Y.L.; Yuan, W.J., Zhu, S.H. (2022) The state of social science research on COVID-19. *Scientometrics* 127, 369–383. https://doi.org/10.1007/s11192-021-04206-4

M

Mafiana, C.F.; Ekpo, U.F.; Ojo, D.A. (2003) Urinary schistosomiasis in preschool children in settlements around Oyan Reservoir in Ogun State, Nigeria: implications for control. *Trop Med Int Health* 8, 1, 78–82. https://doi.org/10.1046/j.1365-3156.2003.00988.x

Magalhães, R.J.; Clements, A.C.A. (2011) Mapping the risk of anaemia in preschool-age children: the contribution of malnutrition, malaria, and helminth infections in West Africa. *PLoS Med* 8. 6, e1000438. https://doi.org/10.1371/journal.pmed.1000438

Mantica, G.; Martini, M.; Riccardi, N. (2021) The possible impact of SARS-COV-2 on neglected tropical diseases in Europe: the out of spotlights emerging of schistosomiasis. *J Prev Med Hyg* 62, E3–E4. https://doi.org/10.15167/2421-4248/jpmh2021.62.1.1867

Martínez-Ortí, A.; Adam, S.; Garippa, G.; Boissier, J.; Bargues, M.D.; Mas-Coma, S. (2022) Morpho-anatomical characterization of the urogenital schistosmiasis vector *Bulinus truncatus* (Audouin, 1827) (Heterobranchia: Bulinidae) from Southwestern Europe. arXiv preprint arXiv:2210.02451. https://doi.org/10.48550/arXiv.2210.02451

Mas-Coma, S.; Valero, M.A.; Bargues, M.D. (2009) Climate change effects on trematodiases, with emphasis on zoonotic fascioliasis and schistosomiasis. *Vet Parasitol* 163, 4, 264–280. https://doi.org/10.1016/j.vetpar.2009.03.024

Mas-Coma, S.; Agramunt, V.H.; Valero, M.A. (2014) Neurological and ocular fascioliasis in humans. *Adv Parasitol* 84, 27–149. https://doi.org/10.1016/b978-0-12-800099-1.00002-8

Mas-Coma, S.; Bargues, M.D.; Valero, M.A. (2018) Human fascioliasis infection sources, their diversity, incidence factors, analytical methods and prevention measures. *Parasitol* 145, Special Issue 13, 1665–1699. https://doi.org/10.1017/S0031182018000914

Mas-Coma, S.; Valero, M.A.; Bargues, M.D. (2022) Human and animal fascioliasis: Origins and worldwide evolving scenario. *Clin Microbiol Rev* 35, 4, e0008819. http://dx.doi.org/10.1128/cmr.00088-19

Mathieu, E.; Ritchie, H.; Rodés-Guirao, L.; Appel, C.; Giattino, C.; Hasell, J. et al. (2020) Coronavirus Pandemic (COVID-19). OurWorldInData.org. Available online: https://ourworldindata.org/coronavirus (accessed 18 Oct 2022)

Mazigo, H.D.; Uisso, C.; Kazyoba, P.; Nshala, A.; Mwingira, U.J. (2021) Prevalence, infection intensity and geographical distribution of schistosomiasis among preschool and school aged children in villages surrounding Lake Nyasa, Tanzania. *Sci Rep* 11, 1, 295. https://doi.org/10.1038/s41598-020-80317-x

McManus, D.P.; Dunne, D.W.; Sacko, M.; Utzinger, J.; Vennervald, B.J.; Zhou, X.N. (2018) Schistosomiasis. *Nat Rev Dis Primers* 4, 1, 13. https://doi.org/10.1038/s41572-018-0013-8

Mendes, E.P.; Okhai, H.; Cristóvão, R.E.; Almeida, M.C.; Katondi, N.; Thompson, R. et al. (2022) Mapping of schistosomiasis and soil-transmitted helminthiases across 15 provinces of Angola. *PLoS Negl Trop Dis* 16, 6, e0010458. https://doi.org/10.1371/journal.pntd.0010458

Meningher, T.; Barsheshet, Y.; Ofir-Birin, Y.; Gold, D.; Brant, B.; Dekel, E. et al. (2020) Schistosomal extracellular vesicle-enclosed miRNAs modulate host T helper cell differentiation. *EMBO Rep* 21, e47882. https://doi.org/10.15252/embr.201947882

Morel, C.M.; Serruya,S.J.; Penna, G.O.; Guimarães, R. (2009) Co-authorship network analysis: A powerful tool for strategic planning of research, development and capacity building programs on neglected diseases. *PLoS Negl Trop Dis* 3, 8, e501. https://doi.org/10.1371/journal.pntd.0000501

Morris, E.J.A.; Goldacre, R.; Spata, E.; Mafham, M.; Finan, P.J.; Shelton, J. et al. (2021) Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. *Lancet Gastroenterol Hepatol* 6, 199–208. https://doi.org/10.1016/S2468-1253(21)00005-4

Mott, K.E. (2004) Schistosomiasis. In C.J.L. Murray, A.D. Lopez, C.D. Mathers (Eds.), *Global Epidemiology of Infectious Diseases* (pp. 341–391). Geneva, Switzerland: World Health Organisation. https://apps.who.int/iris/handle/10665/43048

Moyo, V.B.; Changadeya, W.; Chiotha, S.; Sikawa, D. (2016) Urinary schistosomiasis among preschool children in Malengachanzi, Nkhotakota District, Malawi: Prevalence and risk factors. *Malawi Med J* 28, 1, 10–14. https://doi.org/10.4314/mmj.v28i1.3

Murray, C.J.; Vos, T.; Lozano, R.; Naghavi, M.; Flaxman, A.D.; Michaud, C. et al. (2012) Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 9859, 219–2223. https://doi.org/10.1016/S0140-6736(12)61689-4

Mutsaka-Makuvaza, M.J.; Matsena-Zingoni, Z.; Katsidzira, A.; Tshuma, C.; Chin'ombe, N., Zhou, X.N. et al. (2019) Urogenital schistosomiasis and risk factors of infection in mothers and preschool children in an endemic district in Zimbabwe. *Parasit Vectors* 12, 1, 427. https://doi.org/10.1186/s13071-019-3667-5

Mwai, J.; Njenga, S.; Barasa, M. (2016) Knowledge, attitude and practices in relation to prevention and control of schistosomiasis infection in Mwea Kirinyaga county, Kenya. *BMC Public Health* 16, 1, 819. https://doi.org/10.1186/s12889-016-3494-y

// N

NTDMC (NTD Modelling Consortium) (2020) The potential impact of programmes interruptions due to COVID-19 on 7 neglected tropical diseases: a modelling-based analysis. Oxford, UK: NTD Modelling Consortium. Available online: https://gatesopenresearch.org/documents/4-115 (accessed on 28 Sep 2022)

O

Odhiambo, G.O.; Musuva, R.M.; Atuncha, V.O.; Mutete, E.T.; Odiere, M.R.; Onyango, R.O. et al. (2014) Low levels of awareness despite high prevalence of schistosomiasis among communities in Nyalenda informal settlement, Kisumu city, western Kenya. *PLoS Negl Trop Dis* 8, 4, e2784. https://doi.org/10.1371/journal.pntd.0002784

OECD (Organisation for Economic Co-operation and Development) (2022) Gross domestic spending on R&D. Organisation for Economic Co-operation and Development. Available online: https://data.oecd.org/rd/gross-domestic-spending-on-r-d.htm (accessed on 8 May 2022)

Olamiju, F.; Nebe, O.J.; Mogaji, H.; Marcus, A.; Amodu–Agbi, P.; Urude, R.O. et al. (2022) Schistosomiasis outbreak during COVID-19 pandemic in Takum, Northeast Nigeria: Analysis of infection status and associated risk factors. *PLoS ONE* 17, e0262524. https://doi.org/10.1371/journal.pone.0262524

Olaseha, I.O.; Sridhar, M.K. (2005) Participatory action research: community diagnosis and intervention in controlling urinary schistosomiasis in an urban community in Ibadan, Nigeria. *Int Q Community Health Educa* 24, 2, 153–160. https://doi.org/10.2190/cbym-94n2-e7dh-qral

Oluwole, A.S.; Ekpo, U.F.; Nebe, O.J.; Akpan, N.M.; Jacob, S.M.; Amazigo, U.V. et al. (2022) The new WHO guideline for control and elimination of human schistosomiasis: implications for the Schistosomiasis Elimination Programme in Nigeria. *Infect Dis Poverty* 11, 1, 111. https://doi.org/10.1186/s40249-022-01034-3

Olveda, R.M.; Acosta, L.P.; Tallo, V.; Baltazar, P.I.; Lesiguez, J.L.S.; Estanislao, G.G. et al. (2016) Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis* 16, 2, 199–208. https://doi.org/10.1016/S1473-3099(15)00345-X

Onyeneho, N.G.; Yinkore. P.; Egwuage, J.; Emukah, E. (2010) Perceptions, attitudes and practices on schistosomiasis in Delta state, Nigeria. *Tanzan J Health Res* 12, 4, 287–98. https://doi.org/10.4314/thrb.v12i4.60123

Oyeyemi, O.T.; Okunlola, O.A.; Adebayo, A.D. (2020) Assessment of schistosomiasis endemicity and preventive treatment on coronavirus disease 2019 outcomes in

Africa. *New Microbes New Infect* 38, 100821. https://doi.org/10.1016/j.nmni.2020.100821

P

Page, M.J.; McKenzie, J.E.; Bossuyt, P.M. ; Boutron, I. ; Hoffmann, T.C. ; Mulrow, C.D. et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71. https://doi.org/10.1136/bmj.n71

Parkin, D.M.; Hämmerl, L.; Ferlay, J.; Kantelhardt, E.J. (2020) Cancer in Africa 2018: The role of infections. *Int J Cancer* 146, 2089–2103. https://doi.org/10.1002/ijc.32538

Paul, P.; Podder, D.; Kumar, A.; Rahman, A.; Rahman, H.; Purba, N.H. et al. (2021) Neglected tropical diseases (NTDs) - A snapshot of research. *Recent Res Sci Technol* 6, 12. https://doi.org/10.25081/RRST.2021.13.6927

Poole, H.; Terlouw, D.J.; Naunje, A.; Mzembe, K.; Stanton, M.; Betson, M. et al. (2014) Schistosomiasis in pre-school-age children and their mothers in Chikhwawa district, Malawi with notes on characterization of schistosomes and snails. *Parasit Vectors* 7, 1, 1–12. https://doi.org/10.1186/1756-3305-7-153

R

Raso, G.; N'Goran, E.K.; Toty, A.; Luginbühl, A.; Adjoua, C.A.; Tian-Bi, N.T. et al. (2004) Efficacy and side effects of praziquantel against *Schistosoma mansoni* in a community of western Côte d'Ivoire. *Trans R Soc Trop Med Hyg* 98, 1, 18–27. https://doi.org/10.1016/s0035-9203(03)00003-8

Rees, C.A.; Hotez, P.J.; Monuteaux, M.C.; Niescierenko, M.; Bourgeois, F.T. (2019) Neglected tropical diseases in children: An assessment of gaps in research prioritization. *PLoS Negl Trop Dis* 13, 1, e0007111. https://doi.org/10.1371/journal.pntd.0007111

Reta, B.; Erko, B. (2013) Efficacy and side effects of praziquantel in the treatment for *Schistosoma mansoni* infection in school children in Senbete Town, northeastern Ethiopia. *Trop Med Int Health* 18, 11, 1338–1343. https://doi.org/10.1111/tmi.12187

Richter, J.; Hatz, C.; Campagne, G.; Bergquist, N.R.; Jenkins, J.M. (Eds.) (1997, October 19-24) *Ultrasound in schistosomiasis: A practical guide to the standard use of ultrasonography for assessment of schistosomiasis-related morbidity*. Satellite Symposium on Ultrasound Methodology in *Schistosoma mansoni* Infection, Belo Horizonte, Brazil (WHO No. TDR/STR/SCH/00.1). https://www.who.int/publications/i/item/TDR-STR-SCH-00.1 (accessed on 28 Nov 2022)

Robinson-Riegler, B.; Robinson-Riegler, G.L. (2021) *Cognitive Psychology: Applying the Science of the Mind, 4th edition*. London, UK: Pearson

S

Sacolo-Gwebu, H.; Chimbari, M.; Kalinda, C. (2019a) Prevalence and risk factors of schistosomiasis and soil-transmitted helminthiases among preschool aged children (1-5 years) in rural KwaZulu-Natal, South Africa: a cross-sectional study. *Infect Dis Poverty* 8, 1, 47. https://doi.org/10.1186/s40249-019-0561-5

Sacolo-Gwebu, H.; Kabuyaya, M.; Chimbari, M. (2019b) Knowledge, attitudes and practices on schistosomiasis and soil-transmitted helminths among caregivers in Ingwavuma area in uMkhanyakude district, South Africa. *BMC Infect Dis* 19, 1, 1–11. https://doi.org/10.1186/s12879-019-4253-3

Sady, H.; Al-Mekhlafi, H.M.; Atroosh, W.M.; Al-Delaimy, A.K.; Nasr, N.A.; Dawaki, S. et al. (2015) Knowledge, attitude, and practices towards schistosomiasis among rural population in Yemen. *Parasit Vectors* 8, 1, 1–13. https://doi.org/10.1186/s13071-015-1050-8

Salas-Coronas, J.; Vázquez-Villegas, J.; Villarejo-Ordóñez, A.; Sánchez-Sánchez, J.C.; Espada-Chavarría, J.; Soriano-Pérez, M.J. et al. (2013) Hallazgos radiológicos en pacientes con esquistosomiasis importada [Radiological findings in patients with imported schistosomiasis]. *Enferm Infecc Microbiol Clin* 31, 4, 205–209. https://doi.org/10.1016/j.eimc.2012.04.003

Salas-Coronas, J.; Bargues, M.D.; Lozano-Serrano, A.B.; Artigas, P.; Martínez-Ortí, A.; Mas-Coma, S. et al. (2021) Evidence of autochthonous transmission of urinary schistosomiasis in Almeria (southeast Spain): an outbreak analysis. *Travel Med Infect Dis* 44, 102165. https://doi.org/10.1016/j.tmaid.2021.102165

Siqueira, L.D.P.; Fontes, D.A.F.; Aguilera, C.S.B.; Timóteo, T.R.R.; Ângelos, M.A.; Barros Silva, L.C.P.B. et al. (2017) Schistosomiasis: Drugs used and treatment strategies. *Acta Trop* 176, 179–187. https://doi.org/10.1016/j.actatropica.2017.08.002

Sokolow, S.H.; Huttinger, E.; Jouanard, N.; Hsieh, M.H.; Lafferty, K.D.; Kuris, A.M. et al. (2015) Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host. *Proc Nat Acad Sci U S A* 112, 31, 9650–9655. https://doi.org/10.1073/pnas.1502651112

Sousa-Figueiredo, J.C.; Basáñez, M.G.; Mgeni, A.F.; Khamis, I.S.; Rollinson, D.; Stothard, J.R. (2008) A parasitological survey, in rural Zanzibar, of pre-school children and their mothers for urinary schistosomiasis, soil-transmitted helminthiases and malaria, with observations on the prevalence of anaemia. *Ann Trop Med Parasitol* 102, 8, 679–692. https://doi.org/10.1179/136485908X337607

Sousa-Figueiredo, J.C.; Gamboa, D.; Pedro, J.M.; Fançony, C.; Langa, A.J.; Soares Magalhães, R.J. et al. (2012) Epidemiology of malaria, schistosomiasis, geohelminths, anemia and malnutrition in the context of a demographic surveillance system in northern Angola. *PloS One* 7, 4, e33189. https://doi.org/10.1371/journal.pone.0033189

Spangenberg, T. (2021) Alternatives to praziquantel for the prevention and control of schistosomiasis. *ACS Infect Dis* 7, 5, 939–942. https://doi.org/10.1021/acsinfecdis.0c00542

Stothard, J.R.; Sousa-Figueiredo, J.C.; Betson, M.; Bustinduy, A.; Reinhard-Rupp, J. (2013) Schistosomiasis in African infants and preschool children: let them now be treated!. *Trends Parasitol* 29, 4, 197–205. https://doi.org/10.1016/j.pt.2013.02.001

T

Tesfie, A.; Getnet, G.; Abere, A.; Yihenew, G.; Belete, Y.; Kassa, M.et al. (2020) Praziquantel is an effective drug for the treatment of *Schistosoma mansoni* infection among school-aged children in Northwest Ethiopia. *Trop Med Health* 48, 28. https://doi.org/10.1186/s41182-020-00204-z

Timson D.J. (2020) Praziquantel: An enigmatic, yet effective, drug. *Methods Mol Biol* 2151, 1–8. https://doi.org/10.1007/978-1-0716-0635-3_1

Toor, J.; Adams, E.R.; Aliee, M.; Amoah, B.; Anderson, R.M.; Ayabina, D. et al. (2021) Predicted impact of COVID-19 on neglected tropical disease programs and the opportunity for innovation. *Clin infect Dis* 72, 1463–1466. https://doi.org/10.1093/cid/ciaa933

Torres-Vitolas, C.A.; Dhanani, N.; Fleming, F.M. (2021) Factors affecting the uptake of preventive chemotherapy treatment for schistosomiasis in Sub-Saharan Africa: A systematic review. *PLoS Negl Trop Dis* 15, 1, e0009017. https://doi.org/10.1371/journal.pntd.0009017

Turawa, E.; Awotiwon, O.; Dhansay, M.A.; Cois, A.; Labadarios, D.; Bradshaw, D. et al. (2021) Prevalence of anaemia, iron deficiency, and iron deficiency anaemia in women of reproductive age and children under 5 years of age in South Africa (1997–2021): a systematic review. *Int J Environ Res Public Health* 18, 23, 12799. https://doi.org/10.3390/ijerph182312799

U

UCNTD (Uniting to Combat Neglected Tropical Diseases) (2017) Reaching a Billion. Ending Neglected Tropical Diseases: A gateway to Universal Health Coverage, 5th progress report on the London Declaration on NTDs. Uniting to Combat Neglected Tropical Diseases. Available online: https://unitingtocombatntds.org/reports/5th-report/ (accessed on 7 Jan 2023)

UNESCO (United Nations Educational, Scientific and Cultural Organization) (2020) Global investments in R&D – 2020. Fact Sheet No. 59, S/2020/SCI/59. New York, USA: United Nations Educational, Scientific and Cultural Organization. Available online:

http://uis.unesco.org/sites/default/files/documents/fs59-global-investments-rd-2020-en.pdf (accessed on 7 Nov 2022)

UNESCO (United Nations Educational, Scientific and Cultural Organization) (2021) Researchers per million inhabitants by country, 1996–2018 (in full-time equivalents). New York, USA: United Nations Educational, Scientific and Cultural Organization. Available online: https://www.unesco.org/reports/science/2021/en/dataviz/researchers-million-habitants (accessed on 7 Nov 2022)

UNICEF (United Nations Children's Fund) (2015) The Multiple Indicator Cluster Surveys (MICS) 1995-2015: Monitoring the Situation of Children and Women for 20 Years. New York, USA: United Nations Children's Fund, Data and Analytics Section. Available online: http://54.92.12.252/publications/reports-and-methodological-papers (accessed on 23 Dec 2022)

V

Vale, N.; Gouveia, M.J.; Rinaldi, G.; Brindley, P.J.; Gärtner, F.; Correia da Costa, J.M. (2017) Praziquantel for schistosomiasis: single-drug metabolism revisited, mode of action, and resistance. *Antimicrob Agents Chemother* 61, e02582–16. https://doi.org/10.1128/AAC.02582-16

Valero, M.A.; Gironès, N.; García-Bodelón, M.A.; Periago, M.V.; Chico-Calero, I.; Khoubbane, M. et al. (2008) Anaemia in advanced chronic fasciolosis. *Acta Tropic* 108, 1, 35–43. https://doi.org/10.1016/j.actatropica.2008.08.007

Valero, M.A.; Bargues, M.D.; Khoubbane, M.; Artigas, P.; Quesada, C.; Berinde, L. et al. (2016) Higher physiopathogenicity by Fasciola gigantica than by the genetically close F. hepatica: experimental long-term follow-up of biochemical markers. Trans R Soc Trop Med Hyg 110, 1, 55–66. https://doi.org/10.1093/trstmh/trv110

Vanderelst, D.; Speybroeck, N. (2010) Quantifying the Lack of Scientific Interest in Neglected Tropical Diseases. *PLoS Negl Trop Dis* 4, 1, e576. https://doi.org/10.1371/journal.pntd.0000576

van Eck, N.J.; Waltman, L. (2010) Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 84, 523–538. https://doi.org/10.1007/s11192-009-0146-3

Veeresha, P. ; Mehmet Baskonus, H.; Prakasha, D.G. ; Gao, W. ; Yel, G. (2020) Regarding new numerical solution of fractional Schistosomiasis disease arising in biological phenomena. *Chaos Soliton Fract* 133, 109661. https://doi.org/10.1016/j.chaos.2020.109661

W

Wadhera, R.K.; Shen, C.; Gondi, S. ; Chen, S. ; Kazi, D.S. ; Yeh, R.W. (2021) Cardiovascular deaths during the COVID-19 pandemic in the United States. *J Am Coll Cardiol* 77, 159–169. https://doi.org/10.1016/j.jacc.2020.10.055

Wami. W.M.; Nausch, N.; Midzi, N.; Gwisai, R.; Mduluza, T.; Woolhouse, M. et al. (2015) Identifying and evaluating field indicators of urogenital schistosomiasis-related morbidity in preschool-aged children. *PLoS Negl Trop Dis* 9, 3, e0003649. https://doi.org/10.1371/journal.pntd.0003649

Wang, C.C.; Prather, K.A.; J. Sznitman, J.; Jimenez, J.L.; Lakdawala, S.S.; Tufekci, Z. et al. (2021) Airborne transmission of respiratory viruses. *Science* 373, 6558, eabd9149. https://doi.org/10.1126/science.abd9149

Webb, E.L.; Edielu, A.; Wu, H.W.; Kabatereine, N.B.; Tukahebwa, E.M.; Mubangizi, A. et al. (2021) The praziquantel in preschoolers (PIP) trial: study protocol for a phase II PK/PD-driven randomised controlled trial of praziquantel in children under 4 years of age. *Trials* 22, 1, 601. https://doi.org/10.1186/s13063-021-05558-1

Wendt, G.; Zhao, L.; Chen, R.; Liu, C.; O'Donoghue, A.J.; Caffrey, C.R. et al. (2020) A single-cell RNA-seq atlas of *Schistosoma mansoni* identifies a key regulator of blood feeding. *Science* 369, 1644–1649. https://doi.org/10.1126/science.abb7709

Weze, K.; Abioye, A.I.; Obiajunwa, C.; Omotayo, M. (2021) Spatio-temporal trends in anaemia among pregnant women, adolescents and preschool children in sub-Saharan Africa. *Public Health Nutr* 24,12, 3648–3661. https://doi.org/10.1017/S1368980020004620

WHO (World Health Organization) (2002) Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO expert committee (No. WHO-TRS-912). Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/WHO-TRS-912 (accessed on 18 Nov 2022)

WHO (World Health Organization) (2008). Advocacy, communication and social mobilization for TB control: a guide to developing knowledge, attitude and practice surveys (No. WHO/HTM/STB/2008.46). Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789241596176 (accessed on 21 Dec 2022)

WHO (World Health Organization) (2010) Working to overcome the global impact of neglected tropical diseases: first WHO report on neglected tropical diseases (No. WHO/HTM/NTD/2010.1). Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789241564090 (accessed on 16 Sep 2022)

WHO (World Health Organization) (2011a) Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity (No. WHO/NMH/NHD/MNM/11.1). Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1 (accessed on 2 Oct 2022)

WHO (World Health Organization) (2011b) Report of a meeting to review the results of studies on the treatment of schistosomiasis in preschool-age children (No. WHO/NMH/NHD/MNM/11.1). Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/schistosomiasis/resources/9789241501880/en/ (accessed on 16 Nov 2022)

WHO (World Health Organization) (2015) Female genital schistosomiasis: a pocket atlas for clinical health-care professionals (No. WHO/HTM/NTD/2015.4). Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789241509299 (accessed on 10 Oct 2022)

WHO (World Health Organization) (2020) Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789240010352 (accessed on 27 Sep 2022)

WHO (World Health Organization) (2021a) The Selection and Use of Essential Medicines (2021) – TRS 1035. Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789240041134 (accessed on 4 Nov 2022)

WHO (World Health Organization) (2021b) Impact of the COVID-19 pandemic on seven neglected tropical diseases: a model-based analysis (Licence: CC BY-NC-SA 3.0 IGO). Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789240027671 (accessed on 14 Oct 2022)

WHO (World Health Organization) (2021c) WHO Global Anaemia estimates, 2021 Edition. Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children (accessed on 24 Nov 2022)

WHO (World Health Organization) (2021d) Levels and trends in child malnutrition: UNICEF/WHO/The World Bank Group joint child malnutrition estimates: key findings of the 2021 edition. Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789240025257 (accessed on 4 Dec 2022)

WHO (World Health Organization) (2022a) Schistosomiasis. Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/news-room/fact-sheets/detail/schistosomiasis (accessed on 2 Oct 2022)

WHO (World Health Organization) (2022b) WHO guideline on control and elimination of human schistosomiasis. Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/publications/i/item/9789240041608 (accessed on 28 Sep 2022)

WHO (World Health Organization) (2022c) Neglected tropical diseases: progress towards recovery from COVID-19 – 2022 update. Geneva, Switzerland: World Health Organization. Available online: https://www.who.int/teams/control-of-neglected-tropical-diseases/overview/ntds-and-covid-19 (accessed on 14 Oct 2022)

World Bank (2021) Open Data. Available online: https://data.worldbank.org/ (accessed on 14 May 2022)

World Bank (2022) Measuring Poverty. Available online: https://www.worldbank.org/en/topic/measuringpoverty (accessed on 28 Apr 2022)

Z

Zajicek, A.; Fossler, M.J.; Barrett, J.S.; Worthington, J.H.; Ternik, R.; Charkoftaki, G. et al. (2013) A report from the pediatric formulations task force: perspectives on the state of child-friendly oral dosage forms. *Am Assoc Pharm Sci J* 15, 4, 1072–1081. https://doi.org/10.1208/s12248-013-9511-5

Zwang, J.; Olliaro, P. (2017) Efficacy and safety of praziquantel 40 mg/kg in preschool-aged and school-aged children: A meta-analysis. *Parasit Vectors* 10, 47. https://doi.org/10.1186/s13071-016-1958-7