Consensus definitions in imported human schistosomiasis: a GeoSentinel and TropNet Delphi study

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Terminology in schistosomiasis is not harmonised, generating misunderstanding in data interpretation and clinical descriptions. This study aimed to achieve consensus on definitions of clinical aspects of schistosomiasis in migrants and returning travellers. We applied the Delphi method. Experts from institutions affiliated with GeoSentinel and TropNet, identified through clinical and scientific criteria, were invited to participate. Five external reviewers revised and pilot-tested the statements. Statements focusing on the definitions of acute or chronic; possible, probable, or confirmed; active; and complicated schistosomiasis were managed through REDCap and replies managed in a blinded manner. Round 1 mapped the definitions used by experts; subsequent rounds were done to reach consensus, or quantify disagreement, on the proposed statements. Data were analysed with percentages, medians, and IQRs of a 5-point Likert scale. The study was terminated on the basis of consensus or stability-related and time-related criteria. 28 clinicians and scientists met the criteria for experts. 25 (89%) of 28 experts replied to Round 1, 18 (64%) of 28 to Round 2, 19 (68%) of 28 to Round 3, and 21 (75%) of 28 to at least two rounds. High-level consensus (79–100% agreement and IQRs ≤1) was reached for all definitions. Consensus definitions will foster harmonised scientific and clinical communication and support future research and development of management guidelines for schistosomiasis.

Introduction

Schistosomiasis is a neglected tropical disease caused by infection with trematodes of the genus *Schistosoma*. An estimated 250 million people are infected in tropical and subtropical areas, mostly in sub-Saharan Africa.[1] Infection is acquired through contact with freshwater containing cercariae, the parasite infective larval stage of trematodes, that are released by snails—the intermediate hosts. After infection, parasites reach visceral venous plexuses where adults mature and females produce eggs. These eggs penetrate the bladder or intestinal walls and are excreted in urine or faeces. In freshwater environments, eggs hatch first-stage larvae, which infect the snail intermediate host.

In the clinical context, schistosomiasis is usually classified into acute and chronic disease.[2] A transitory allergic acute dermatitis, named swimmer's itch or cercarial dermatitis, can be observed soon after contact with cercariae-containing freshwater; this can also occur after contact with cercariae from *Schistosoma* species not able to infect humans. When symptomatic, acute schistosomiasis is usually called Katayama fever or Katayama syndrome, which occurs in individuals exposed to the infection for the first time; in practice it is observed in non-immune travellers. The pathophysiology is unclear; acute schistosomiasis has been variably attributed to hypersensitivity triggered by the start of egg production or against migrating juvenile parasites.[3] Experimental infections with single-sex worms revealed that egg production is not required for the disease's clinical occurrence, which is induced by the sole presence of juvenile worms.[4] Pathology in chronic schistosomiasis is universally accepted to be caused by the inflammatory and fibrotic reaction to parasite eggs trapped in tissues.[1] *Schistosoma haematobium*, residing in the pelvic plexus, cause urogenital schistosomiasis, whereas *Schistosoma mansoni*, *Schistosoma japonicum*, and other less prevalent species that reside in the mesenteric plexus cause intestinal and hepatosplenic schistosomiasis.[1]

Schistosomiasis is frequently observed in travellers and migrants from endemic areas, although diagnosis

Key messages

- Consensus definitions in clinical medicine are pivotal for scientific communications, research and clinical descriptions, and decision making. The lack of harmonisation in the terminology and definition of clinical aspects of schistosomiasis generates misunderstanding and hampers further development of treatment and follow-up recommendations, which are still in need.
- Since biological and clinical features of schistosomiasis are a continuum throughout the evolution of the infection, clear-cut classifications can only be a convention deriving from agreement among the scientific community.
- We achieved consensus on the definitions of clinical aspects of schistosomiasis in migrants and travellers, including acute or chronic; possible, probable, or confirmed; active; and complicated schistosomiasis through a rigorous Delphi study involving experts from international GeoSentinel and TropNet networks of travel and tropical medicine.
- The definitions of chronic schistosomiasis could possibly also be applied in the endemic setting, after considering the specific conditions and practical applications.
- These case definitions could represent a shared ground for a broader consensus among physicians of other disciplines.

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might be overlooked outside specialised centres.[5–7] Katayama syndrome is typically reported in single travellers or in small clusters of people with shared freshwater exposure, affecting less than 2% of travellers who travelled to and returned from endemic areas.[5] Urogenital, intestinal, and hepatosplenic schistosomiasis are observed mainly in migrants from endemic areas, with an estimated 20% having active infection (ie, presence of living adult worms producing eggs) when diagnosed.[6,8]

The diagnostic approach and treatment of acute and chronic schistosomiasis are not standardised at the international, and often at national, level. The diagnosis of schistosomiasis in returning travellers with symptoms compatible with Katayama syndrome can be particularly difficult due to the poor sensitivity of common diagnostic tests during early infection (eg, serology and microscopy). Routinely available diagnostic assays also have poor performance for the identification of patients with active infection, both at diagnosis and after treatment.[9,10] Uncertainty regarding treatment persists, including the optimal timing of administration of corticosteroids and praziquantel in acute schistosomiasis and the optimal dosing of praziquantel to achieve parasitological cure in patients with chronic active schistosomiasis.[5,11,12]

The terminology defining the biological and clinical evolution of infection and disease is not harmonised. Furthermore, multiple other questions remain unresolved, including the case definitions of the disease's clinical manifestations (eg, which features define schistosomiasis as complicated?) and their timing (eg, how long after infection can schistosomiasis be considered chronic?).[3,13] This discrepancy generates misunderstanding in clinical descriptions, interpretation of research data, and clinical management of cases.

We carried out the first rigorous Delphi study among centres belonging to two international networks (GeoSentinel and TropNet), represented by academic and clinical specialists in the diagnosis, surveillance, and clinical management of infectious diseases in travellers and migrants. The aim was to achieve expert consensus, or quantify disagreement, on the definitions of clinical aspects of imported schistosomiasis.

Methods

Project aim and consensus method

The aim of this project was to reach consensus on the following case definitions, in patients travelling from schistosomiasis-endemic areas: (1) possible, probable, or confirmed acute schistosomiasis; (2) possible, probable, or confirmed chronic schistosomiasis; (3) active schistosomiasis; and (4) complicated schistosomiasis.

We applied the Delphi method as a recognised, structured consensus-building process used when the available knowledge is incomplete or subject to uncertainty.[14] This method was used since biological and clinical features of schistosomiasis are a continuum throughout the evolution of the infection; therefore, clear-cut classifications can only be a convention deriving from agreement in the scientific community. The study performance was adapted from the methods detailed by Beiderbeck and colleagues[15] and is reported according to the CREDES criteria for conducting and reporting of Delphi studies.[16] The study flowchart is shown in figure 1. The study was implemented with the REDCap tool for online surveys.

Preparatory phase: literature review and expert panel selection

A PubMed search was carried out before the study start to evaluate the literature published over the past 20 years on this topic and inform the framing of initial case definitions proposed in Round 1. We searched PubMed using the keywords "acute schistosomiasis" OR "chronic schistosomiasis", without language restriction, for case reports or series, clinical studies, observational studies, clinical trials, comparative studies, reviews, and practice guidelines reporting a clinical definition of acute or chronic schistosomiasis, published between Jan 1, 2003, and Oct 15, 2023. We retrieved 106 records. After exclusion of 22 records that were off-topic (n=9) or for failure to access the full text (n=13), 84 records were evaluated for their definitions of acute or chronic schistosomiasis (or both). 54 (64·3%) of 84 included publications did not report any case definitions or timespan from possible infection event for defining acute or chronic schistosomiasis. When timespan was mentioned (in 18 case reports or series, ten reviews, and two clinical trials), it was extremely heterogeneous: 27 (90%) of 30 papers referred to different timespans (range 1–12 weeks for acute schistosomiasis); only three (10%) of 30 referred to the same timespan (3–6 weeks after infection) for acute schistosomiasis. Three papers indicated the classification of schistosomiasis into acute, chronic, and advanced without specifying their case definitions.

The directors of all centres (n=116) affiliated with GeoSentinel and TropNet networks were contacted to enquire about the involvement of their centres in the clinical management of imported schistosomiasis; their interest in participating in the study; and the name of a reference person most involved in the clinical or diagnostic management of schistosomiasis in their centres. The publication records of the reference people indicated by the centres' directors were searched in PubMed to define the final list of potential experts. Experts were defined as those who attended patients with schistosomiasis and authored at least one publication on schistosomiasis in a peer-reviewed journal in the past 10 years or authored at least five publications on schistosomiasis in a peer-reviewed journal in the past 10 years. Experts were invited to take part in the study through individual emails containing details of the

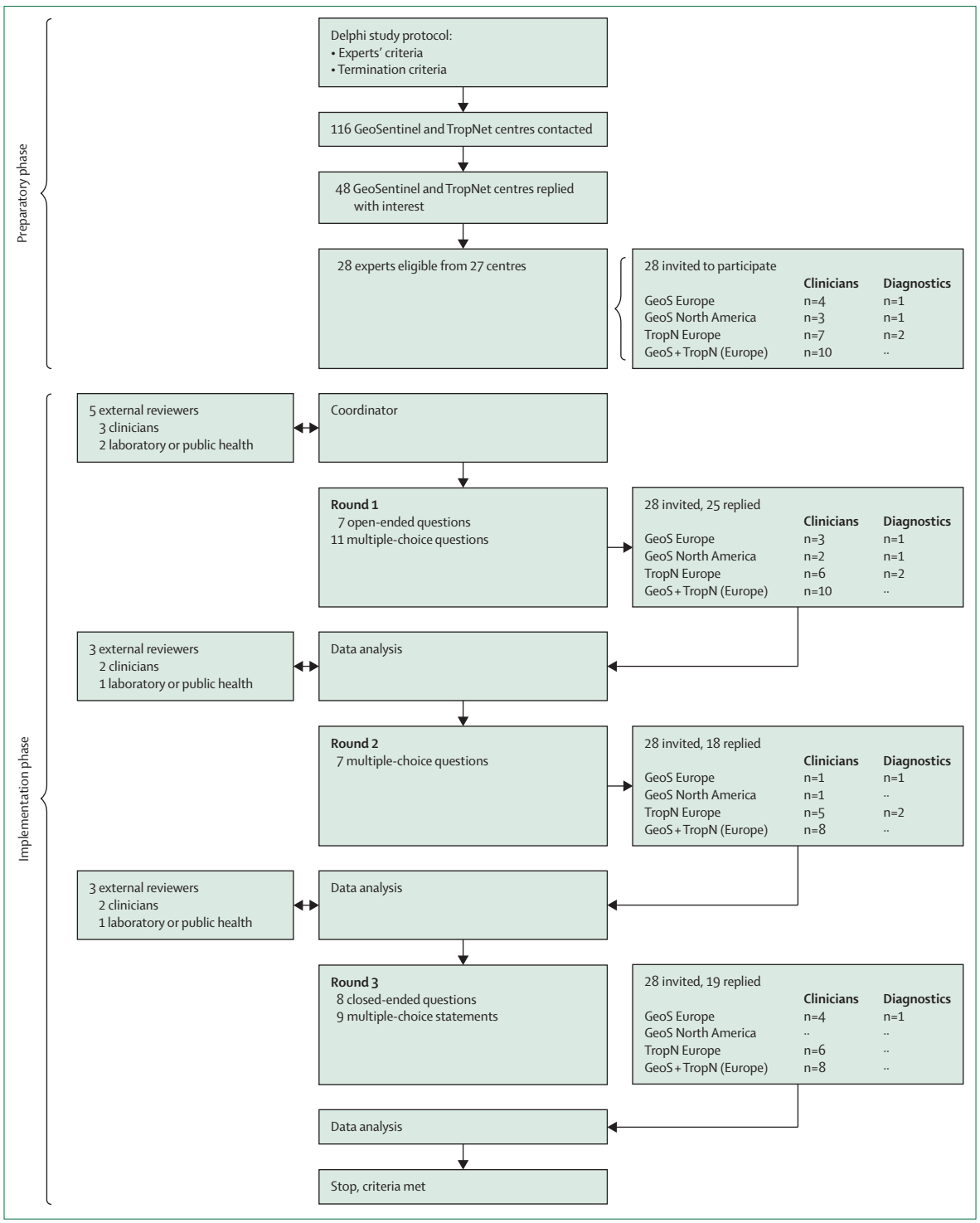

Figure 1: **Study flowchart and panellists' details**
GeoS=GeoSentinel. TropN=TropNet.

study aim and objectives, procedures, funding, and publication criteria.

Five external reviewers, with different expertise (ie, clinical, diagnostic, and methodological) in schistosomiasis were also invited to revise and pilot-test the questionnaires before each round.

This study was blind. The data manager (CM) set up the REDCap platform and invited experts individually through

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For the **GeoSentinel website** see https://geosentinel.org/

For the **TropNet website** see http://tropnet.eu/

For the **REDCap tool** see https://www.project-redcap.org/

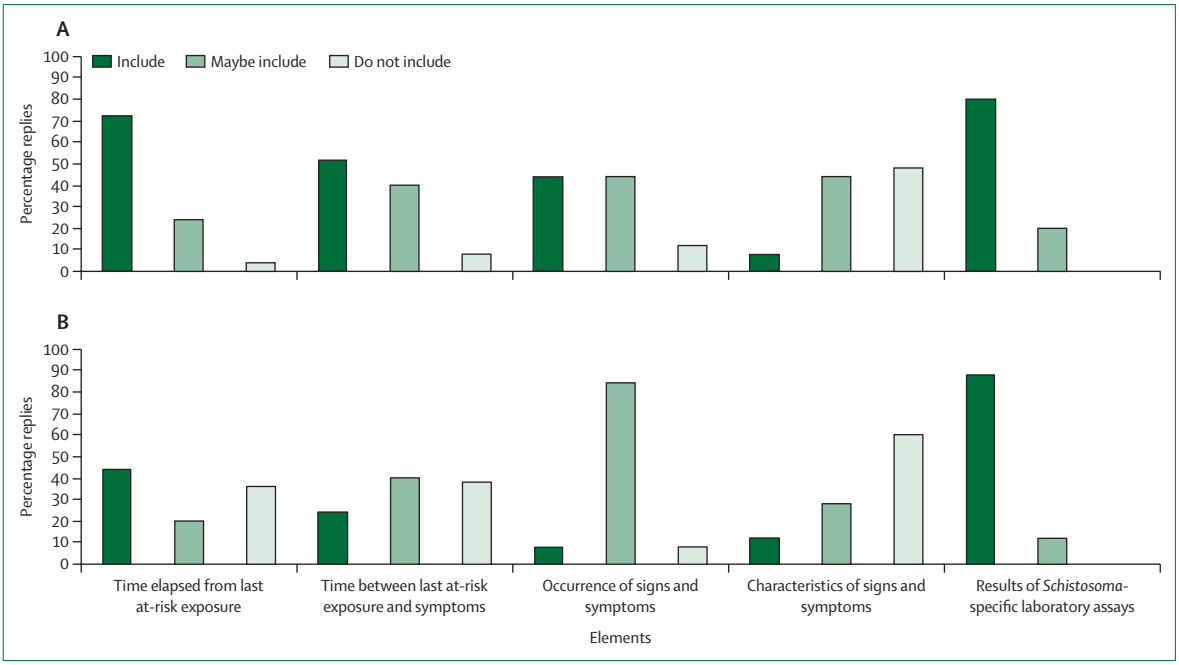

Figure 2: **Summary of elements to be included in definitions of schistosomiasis**
Based on expert panel's replies to Round 1 of the Delphi method for defining acute (A) and chronic (B) schistosomiasis.

the platform. Each expert was assigned an identification number by which their replies were identified for analysis. The study coordinator (FT) was masked to the identity of the experts' replies. Experts and external reviewers were masked to the identity of the other participants.

Implementation phase: survey rounds and study termination criteria

The study questions and statements presented to the experts at each round, and the replies to all rounds, are available online.

For the **statements and replies in all rounds of this study** see https://zenodo.org/records/10351269

Round 1 aimed to map the range of definitions used by the experts and the elements (eg, timing from infection, signs and symptoms, and tests results) deemed most important for each case definition through a survey containing both open-ended and closed-ended questions. Experts had the opportunity to suggest additional elements if missed from the proposed questionnaire and reference to the guidance or recommendation documents they use to guide diagnosis and clinical management of patients with schistosomiasis in their centres.

Replies were summarised, with definitions sharing similar elements grouped and used to develop a closed-ended questionnaire for Round 2. This subsequent round presented to the experts the range of elements to be included in each definition that had emerged from Round 1. Definitions included in Round 2 and subsequent rounds were formulated by summarising the most frequent replies from the previous rounds and experts were asked to provide yes or no replies or their agreement with the tentative definitions on a 5-point Likert scale.

Throughout the study, experts were required to provide explanation and support with published material when their agreement with the statements was less than complete (ie, <5 [Likert scale] or a response of no [yes or no]) and were given the option to reply "I do not know" and "I do not feel qualified to answer this question". Experts were reminded once a week about answering the questions. Each round was available for 4 weeks.

After each round, results were shared with the experts through summary results (percentage distribution of responses to each question or statement). Each expert was provided personalised feedback about their own replies in relation to the summary panel's replies. Thus, participants could compare their responses with group results and possibly adjust their subsequent replies, while preserving the anonymity of their responses.

We used a cascade decision system to define consensus and to terminate the survey. The consensus-related criterion was at least 70% of the experts participating in the round gave feedback on the statement and, of these responders, at least 75% gave a score 5 or at least 80% gave a score 4 or 5 (ie, agree or completely agree) on the Likert scale. The stability-related criterion was that the statement could not be modified further to accommodate for discordant opinions and time-related criterion was that the study would be terminated after five rounds in any case.

Data analysis

Data were analysed quantitatively with percentages, medians, and IQRs. For Round 1, when elements to be

	"Always defining the condition"	"Defining the condition only in untreated person"	"Not defining the condition"	"Don't know"
Presence of viable eggs in biological materials, alone*	15 (83%)	3 (17%)	0	0
Presence of any eggs† in biological materials, alone*	2 (11%)	7 (39%)	9 (50%)	0
Positive CAA antigen test, alone*	10 (56%)	4 (22%)	2 (11%)	2 (11%)
Positive CCA antigen test, alone*	5 (28%)	5 (28%)	5 (28%)	3 (17%)
Positive PCR on biological materials, alone*	3 (17%)	9 (50%)	6 (33%)	0
Positive serology, alone*	0	3 (17%)	15 (83%)	0
Signs or symptoms of Katayama syndrome; laboratory tests negative or not done	0	2 (11%)	15 (83%)	1 (6%)
Presence of any egg† in biological materials and signs or symptoms	6 (33%)	6 (33%)	6 (33%)	0
Positive CAA and signs or symptoms	13 (72%)	2 (11%)	2 (11%)	1 (6%)
Positive CCA and signs or symptoms	6 (33%)	2 (11%)	6 (33%)	3 (17%)
Positive PCR on biological materials and signs or symptoms	6 (33%)	6 (33%)	5 (28%)	1 (6%)
Positive serology and signs or symptoms	3 (17%)	3 (17%)	11 (61%)	1 (6%)
Presence of any eggs† in biological materials and positive serology	3 (17%)	8 (44%)	7 (39%)	0
Positive PCR on biological materials and positive serology	4 (22%)	9 (50%)	5 (28%)	0
Positive PCR on biological materials and any positive antigen test	10 (56%)	2 (11%)	4 (22%)	2 (11%)
Presence of any eggs† in biological materials and positive serology and signs or symptoms	8 (44%)	5 (28%)	5 (28%)	0
Presence of any eggs† in biological materials and any positive antigen test and signs or symptoms	12 (67%)	2 (11%)	3 (17%)	1 (6%)
Presence of any eggs† in biological materials and any positive PCR on biological materials and signs or symptoms	6 (33%)	8 (44%)	4 (22%)	0

Data are n (%). The total number of experts who responded to this questionnaire is 18. CAA=circulating anodic antigen. CCA=circulating cathodic antigen. *Asymptomatic person and other tests not performed or negative. †*Schistosoma* spp eggs' viability not assessed.

Table 1: **Panel's opinion on elements defining active schistosomiasis**

included in case definitions indicated in open-ended questions did not match elements indicated by the same expert in multiple-choice closed-ended format questions, a conservative approach was applied and all definition elements were included for evaluation by the panel in Round 2. Definitions included in Round 3 were formulated on the basis of the most frequent replies to Round 2 questions.

A threshold of a maximum 25% IQR (ie, 1·25 on a scale from 1 to 5) also served as an indicator of consensus. Histograms were visually inspected for outliers and conflicting replies.

Results

Of the 116 centres affiliated with GeoSentinel (n=56), TropNet (n=45), or both (n=15) networks, the directors of 48 centres replied with interest to the invitation and gave the name of one reference person in their centre. After checking their eligibility, 28 experts were selected from 27 centres (n=24 in Europe; n=2 in Canada; n=1 in the USA; in only one case, two experts were selected from the same centre because they represented two different departments with distinct and independent roles and expertise) and invited to participate in the Delphi study. Of the five external reviewers, four were from Europe and one from the USA; three had clinical expertise and two had laboratory expertise. Panel members' details are summarised in figure 1.

The Round 1 questionnaire was revised and pilot-tested by the five external reviewers and answered by 25 (89%) of the 28 experts. A summary of opinions related to the elements to be included in the definitions of acute and chronic schistosomiasis is shown in figure 2. Time from last at-risk exposure and laboratory diagnosis were indicated as relevant information to include in the definitions of acute and chronic schistosomiasis. The range of timespans indicated by the experts was heterogeneous; however, 15 (68%) of the 22 experts who provided an actual timespan indicated less than 3 months for acute schistosomiasis, and 14 (88%) of 16 indicated more than 3 months for chronic schistosomiasis. The time between last at-risk exposure and onset of symptoms was also indicated as relevant information, and the timespans were concordant for most experts (ie, 16 [72%] of 22 said <3 months for acute and 12 [75%] of 16 said >3 months for chronic schistosomiasis). Other elements deemed important or maybe important to be included in the definition of acute and chronic schistosomiasis by most experts were the occurrence of signs or symptoms (88% for acute and 92% for chronic) and results of *Schistosoma*-specific laboratory assays (100% for both acute and chronic). Experts were also asked whether results of a list of

	1—completely disagree	2	3	4	5—completely agree
In all cases of ectopic schistosomiasis (eg, involvement of CNS or heart)	1 (6%)	1 (6%)	2 (11%)	1 (6%)	13 (72%)
In acute schistosomiasis, severity of clinical picture defined as requiring hospitalisation	0 (0%)	5 (28%)	2 (11%)	3 (17%)	7 (39%)
In chronic schistosomiasis, severity of organ involvement defined as requiring hospitalisation	0 (0%)	3 (17%)	3 (17%)	1 (6%)	11 (61%)
In chronic schistosomiasis, necessity of other interventions in addition to treatment with praziquantel	0 (0%)	0 (0%)	0 (0%)	6 (33%)	12 (67%)
In chronic schistosomiasis, no regression after treatment with praziquantel	1 (6%)	2 (11%)	6 (33%)	4 (22%)	5 (28%)
In chronic schistosomiasis, presence of signs or symptoms	6 (33%)	7 (39%)	3 (17%)	0 (0%)	2 (11%)
Residual permanent organ damage after parasitological cure should be defined as complicated schistosomiasis	4 (22%)	4 (22%)	3 (17%)	1 (6%)	5 (28%)
Residual permanent organ damage after parasitological cure should be defined as sequelae	1 (6%)	0 (0%)	1 (6%)	0 (0%)	16 (89%)

Data are n (%). The total number of experts who responded to this questionnaire is 18. The Likert scale went from 1=completely disagree to 5=completely agree.

Table 2: **Panel's opinion on elements defining complicated schistosomiasis on a Likert scale**

laboratory tests, as well as signs (including eosinophilia) and symptoms, should be included in the definitions of possible, probable, or confirmed acute and chronic schistosomiasis, of active schistosomiasis, and of complicated schistosomiasis. The majority of experts (22 [88%] of 25) agreed that acute schistosomiasis could be diagnosed as a clinical entity even if no eventual infection with adult worms was established. 16 (64%) of 25 experts thought that permanent organ damage remaining after parasitological cure should have a definition of its own, different than those of acute or chronic schistosomiasis.

The Round 2 questionnaire was revised and pilot-tested by three external reviewers and answered by 18 (64%) of 28 experts. Questions included in Round 2 concerned the categorisation of signs and symptoms and laboratory results into pathognomonic, evocative, or compatible with acute or chronic schistosomiasis and from what combinations of these clinical and laboratory elements they would define possible, probable, or confirmed acute and chronic schistosomiasis. The definitions of pathognomonic (ie, no other pathology can cause the condition, therefore its presence alone gives the diagnosis of schistosomiasis), evocative (ie, strongly suggestive of schistosomiasis in the right epidemiological context but not pathognomonic of schistosomiasis), and compatible (ie, presence does occur in schistosomiasis but it is largely non-specific) were provided to the panel, as well as reference papers on clinical aspects of female genital schistosomiasis[17] and periportal fibrosis patterns of hepatosplenic schistosomiasis.[18] Expert replies are summarised in the appendix (pp 1–16). Katayama syndrome was defined as evocative of acute schistosomiasis by 16 (89%) of 18 experts. The classification of symptoms and signs of chronic schistosomiasis according to the panel's replies is summarised in the appendix (pp 17–18). The majority of experts did not identify pathognomonic signs of acute or chronic schistosomiasis (16 of 18 for acute schistosomiasis and 15 of 17 for chronic schistosomiasis).

The panel's opinion on the broad tentative case definitions of possible, probable, or confirmed acute and chronic schistosomiasis, deriving from the analysis of Round 1, is summarised in the appendix (pp 6–12). Briefly, experts were presented with short sentences which could, alone or in combination, constitute a case definition and asked whether the sentence would define a case as possible, probable, or confirmed acute or chronic schistosomiasis. Table 1 shows the panel's opinion on elements defining active schistosomiasis and table 2 for complicated schistosomiasis. The opinions receiving approval from the majority of experts were included in the case definitions presented in Round 3.

Finally, an exploratory question was asked as to whether, regardless of the presumed time from exposure, schistosomiasis should be designated as non-complicated (ie, absence of irreversible signs and symptoms or presence of reversible signs and symptoms—eg, Katayama syndrome, lung nodules, or bladder polyps) or complicated (ie, presence of irreversible signs and symptoms—eg, bladder cancer or periportal fibrosis), rather than acute or chronic schistosomiasis. Since 55% of experts rated this proposal 3 or lower on the Likert scale (median 3; IQR 3) and all experts who scored 3 indicated that they would still prefer to maintain the acute or chronic classification, this question was not resubmitted to Round 3 and the proposal was discarded.

The Round 3 questionnaire was revised and pilot-tested by three external reviewers and answered by 19 (68%) of 28 experts. The questionnaire had 15 questions and aimed to verify the agreement on the list of signs and symptoms deemed compatible, evocative, or pathognomonic of schistosomiasis and the final set of elements that would form the case definitions of possible, probable, or confirmed acute and chronic schistosomiasis, active schistosomiasis, and complicated schistosomiasis.

Experts' replies are summarised in the appendix (pp 19–27). Figure 3 shows the lists of signs and symptoms identified in Round 2 as associated with Katayama syndrome or as compatible or evocative of schistosomiasis and the scores given by the panel.

In the instance of pathognomonic signs, only patterns of periportal fibrosis were presented for opinion to the experts. Indeed, other signs and symptoms indicated by some panellists as pathognomonic in Round 2 (appendix

pp 17–18) could be easily attributed to other causes and there was little uncertainty about this (0–6% "Don't know" replies); therefore, it was decided to consider them de facto not pathognomonic. On the contrary, 11–28% of experts could not provide an opinion on periportal fibrosis imaging patterns, which were indicated as pathognomonic by 6–11% of experts. Experts were also asked to provide examples of differential diagnoses for these imaging patterns. For these questions, 32% (on patterns D–F) and 53% (on tortoise-back pattern) of experts replied that they did not know or were not qualified to answer. No consensus threshold was achieved, but since the panellists provided a list of differential diagnoses, these patterns were considered de facto not pathognomonic.

The panellists were also asked to clarify their opinion on the clinical meaning of a positive result of circulating cathodic antigen (CCA) and circulating anodic antigen (CAA) assays, since in Round 2 (table 1) the experts' replies on the value of the results of these assays were polarised in two discordant opinions. For CAA, four (21%) of 19 experts did not know or did not feel qualified to reply, whereas 13 (68%) of 19 agreed that "CAA can be considered specific for the individual diagnosis of *Schistosoma* infection, at a clinical level" (median score 5; IQR 1). As for CCA, six (32%) of 19 experts did not know or did not feel qualified to reply, whereas 11 (58%) of 19 agreed that "CCA is not specific enough for the individual diagnosis of *Schistosoma* infection, at a clinical level".

The appendix (pp 20–27) shows the final list of elements to be possibly included in the definitions of possible, probable, or confirmed acute and chronic schistosomiasis, active schistosomiasis, complicated schistosomiasis, and sequelae, deriving from the synthesis of replies in Round 2 and the scores provided by the panellists. Since per-protocol agreement was achieved on each definition, the study was concluded at Round 3.

The final case definitions, with experts' scores, are provided in table 3. When more than one mutually exclusive definition reached consensus thresholds

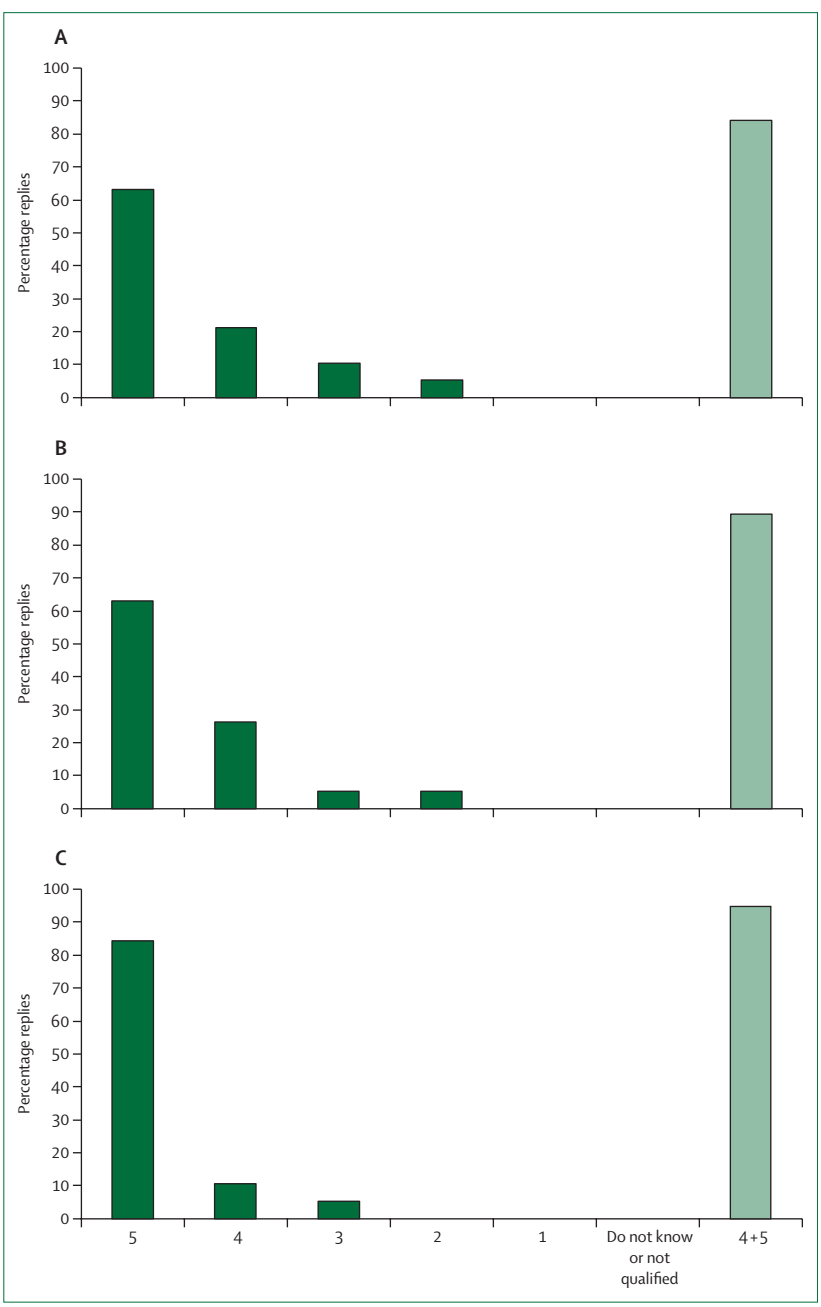

Figure 3: **The final panel's agreement scores with statements about acute and chronic schistosomiasis**

(A) Percentage replies to the statement "Katayama syndrome in an infection-naïve person with potential exposure <3 months before is evocative (not pathognomonic) of acute schistosomiasis", where Katayama syndrome included at least two of the following: fever, general symptoms (eg, malaise), rash, itching, cough, diarrhoea, abdominal pain, eosinophilia, lung ground-glass opacities, and hepatosplenomegaly. (B) Percentage replies to the statement "Signs and symptoms listed are evocative of chronic schistosomiasis", where the signs and symptoms were: bladder mucosa thickening or masses; bladder wall calcifications; haematuria; haemospermia; grainy sandy patches on colposcopy; homogeneous yellow sandy patches on colposcopy; rubbery papules in colposcopy; patterns D–F hepatic periportal fibrosis (on the Niamey–Belo Horizonte classification); tortoise-black hepatic fibrosis pattern; portal hypertension; splenomegaly; intestinal polyps; lung nodules; eosinophilia; development deficiency in children; and CNS focal lesions. (C) Percentage replies to the statement "Signs and symptoms listed are compatible with chronic schistosomiasis", where signs and symptoms listed were: fatigue; dysuria, urgency, or suprapubic pain; pelvic pain; coital pain or dyspareunia; vaginal discharge; spotting or bleeding after intercourse; genital itching or burning sensation; contact bleeding of cervicovaginal mucosa; abnormal vessels on colposcopy; swelling or calcifications of testicles or male genital gland; vaginal ulcers; infertility; obstetric problems (eg, ectopic pregnancy); pattern C hepatic periportal fibrosis (Niamey–Belo Horizonte classification); upper gastrointestinal bleeding; hepatomegaly; chronic diarrhoea; blood in stool; abdominal pain; pulmonary hypertension; and anaemia. Across all statements, evocative was defined as strongly suggestive of schistosomiasis in the right epidemiological context but not pathognomonic; pathognomonic was defined as no other pathology can cause the condition, therefore its presence alone gives the diagnosis of schistosomiasis; and compatible was defined as present in schistosomiasis but symptoms are largely non-specific. Scores went from 5=completely agree to 1=completely disagree.

	Definitions	Criteria required	Agreement , N=19	Likert score
Confirmed acute schistosomiasis	Can be defined in a person with relevant epidemiological history (generally a traveller in an endemic area with no previous history of infection) and possible infective contact from 3 weeks to 3 months before, with or without* history of swimmer's itch or presence of symptoms or signs of Katayama syndrome, and with presence of eggs in biological material, positive PCR on biological material, positive CAA antigen test, or documented seroconversion	Epidemiological plus laboratory (ie, microscopy, PCR, CAA, or seroconversion)	84% (16)	5 (0)
Probable acute schistosomiasis	Can be defined in a person with relevant epidemiological history (generally a traveller in an endemic area with no previous history of infection) and possible infective contact 3 weeks to 3 months before, with or without* history of swimmer's itch or presence of signs or symptoms of Katayama syndrome and with: positive serology; or positive CCA test	Epidemiological plus clinical plus laboratory (serology or CCA)	With positive serology: 84% (16); with positive CCA test: 83% (15/18)	With positive serology: 5 (0); with positive CCA test: 5 (0)
Confirmed or probable acute schistosomiasis	Results of laboratory tests alone, as specified in acute schistosomiasis definitions, can define a diagnosis of probable and confirmed acute schistosomiasis even in the absence of a history of swimmer's itch or presence of symptoms or signs of Katayama syndrome, if there is absolutely no evidence of previous exposure	Epidemiology plus laboratory	79% (15)	5 (1)
Possible acute schistosomiasis	Can be defined in a person with relevant epidemiological history (generally a traveller in an endemic area with no previous history of infection) and possible infective contact 3 weeks to 3 months before, with signs or symptoms of Katayama syndrome, alone (ie, no laboratory test carried out or not positive)	Epidemiological plus clinical	79% (15)	5 (0)
Confirmed chronic schistosomiasis	Can be defined in a person with relevant epidemiological history, possible infection >3 months beforehand, no history of curative treatment† after possible infection, and presence of eggs in any biological material, positive PCR on any biological material, positive CAA antigen test, or documented seroconversion—independent of the presence of signs or symptoms	Epidemiological plus laboratory (microscopy, or PCR or CAA or seroconversion)	100% (19)	5 (0)
Probable chronic schistosomiasis	Can be defined in a person with relevant epidemiological history, possible infection >3 months beforehand, no history of curative treatment† after possible infection, and: the presence of compatible signs or symptoms and positive serology; the presence of evocative signs or symptoms and positive serology; the presence of compatible signs or symptoms and positive CCA; the presence of evocative signs or symptoms and positive CCA; or regression of reversible signs or symptoms after praziquantel treatment	Epidemiological plus clinical plus laboratory (ie, serology or CCA)	Presence of compatible signs and positive serology 84% (16); presence of evocative signs and positive serology 100% (19); presence of compatible signs and positive CCA 79% (15); presence of evocative signs and positive CCA 84% (16); regression of reversible signs after praziquantel treatment 84% (16)	Presence of compatible signs and positive serology 5 (1); presence of evocative signs and positive serology 5 (0); presence of compatible signs and positive CCA 5 (0); presence of evocative signs and positive CCA 5 (0); regression of reversible signs after praziquantel treatment 4·5 (1)
Possible chronic schistosomiasis	Can be defined in an asymptomatic person with relevant epidemiological history, possible infection >3 months beforehand, no history of curative treatment† after possible infection, and positive serology	Epidemiological plus laboratory (ie, serology)	79% (15)	5 (1)
Active schistosomiasis	Can be defined in a person with confirmed acute or chronic schistosomiasis and no history of curative treatment† with praziquantel (or long enough after treatment—where long enough depends on the test applied and the possibility of re-infection) and: presence of viable eggs; positive CAA test; or positive PCR on any biological materials.	Laboratory (microscopy for egg viability, CAA, or PCR)	Viable eggs 100% (19); positive CAA antigen test 84% (16); positive PCR on any biological materials 79% (15)	Viable eggs 5 (0); positive CAA antigen test 5 (0); positive PCR on any biological materials 5 (1)
Complicated schistosomiasis	Can be defined in a person with active acute or chronic infection: in all cases of symptomatic involvement of a non-typical‡ organ; or in case of organ involvement requiring interventions other than praziquantel (or corticosteroids, or both, in the case of acute schistosomiasis)	Clinical	All cases of symptomatic involvement of a non-typical organ 89% (17); in case of organ involvement requiring interventions other than praziquantel or corticosteroids 84% (16)	All cases of symptomatic involvement of a non-typical organ 5 (0·75); in case of organ involvement requiring interventions other than praziquantel or corticosteroids 5 (0)
Sequelae	In the absence of active acute or chronic schistosomiasis (ie, after parasitological cure), residual permanent organ alterations can be defined as sequelae	Clinical and laboratory (absence of criteria for active infection)	89% (17)	5 (0)
Complicated sequelae	Sequelae can also be complicated if requiring further interventions	Clinical and laboratory (absence of criteria for active infection)	95% (18)	5 (0)

Data are % (n) or median (IQR). Within each definition, the way diagnostic or clinical items are listed does not reflect their prioritisation. Agreement percentage is shown as the number of replies showing agreement (scores 4 + 5 on the Likert scale)/total panel giving feedback on the statement. CAA=circulating anodic antigen. CCA=circulating cathodic antigen. *If there is absolutely no evidence of previous exposure. †No record of previous treatment with curative intent after last at-risk exposure. ‡Non-typical=involving organs different than gastrointestinal tract, liver, urogenital tract, or lung.

Table 3: **Case definition as agreed by the panel of experts**

(appendix pp 20–27), the option with the highest percentage agreement, highest median score, and lowest IQR was retained. A schematic representation of case definitions is provided in the appendix (p 28).

Discussion

In this study, a panel of experts affiliated with the GeoSentinel and TropNet international networks reached consensus case definitions of possible, probable, or confirmed acute and chronic schistosomiasis, active schistosomiasis, complicated schistosomiasis, and sequelae (table 3; appendix p 28), through a Delphi methodology.

Consensus definitions in clinical medicine are pivotal for scientific communications and research, and clinical descriptions and decision making. In the absence of consensus definitions for terms such as acute schistosomiasis versus chronic schistosomiasis patients can, for example, be classified differently in different centres and results of the same diagnostic assay or treatment protocol might provide discordant results as the sole consequence of different patients' classification. Since the treatment of patients with schistosomiasis outside endemic areas is not standardised and several aspects (eg, how to evaluate parasitological cure) are still open to research, it is pivotal to ground clinical and diagnostic trials on shared, unequivocal patient classification and case definitions. Our consensus definitions are therefore important to support trials focusing on the uncertain areas in schistosomiasis. Based on these case definitions, future studies will be able to better ascertain the performance of diagnostic assays and the effectiveness of antiparasitic treatment schedules on patients grouped into defined categories, with the aim of optimising clinical management. Furthermore, our definitions have important implications in clinical practice. For instance, the definition of active infection implies that not all patients generically diagnosed with schistosomiasis (eg, on the basis of positive serology only) harbour living parasites and therefore should be treated with praziquantel, avoiding overtreatment with attendant exposure to adverse events and costs.

In analysing the panellists' replies, we noticed that heterogeneous opinions occurred mainly for definitions concerning acute schistosomiasis and the interpretation of assays detecting circulating parasite antigens (ie, CCA and CAA). Discrepant opinions about acute schistosomiasis were expected. This condition manifests clinically with heterogeneous and non-specific symptoms and signs, and diagnostic assays can provide very different results in early infection (eg, positivity in serology and PCR on blood but negativity of microscopy). Even the biological events defining its occurrence have been debated.[3] Because the start of egg production by female worms does not seem necessary for the development of symptoms,[4] the prepatent period cannot be used unequivocally to determine the timespan for defining acute schistosomiasis.

Importantly, the consensus reached here for acute schistosomiasis (table 3) establishes that the development of patent infection (ie, development of adult parasites producing eggs) is not necessary to confirm acute schistosomiasis. Our panellists also agreed that results of laboratory tests alone could define a diagnosis of acute schistosomiasis, even in the absence of clinical manifestations, if previous exposure is excluded with certainty. This definition is important because it implies that acute schistosomiasis might be defined exclusively on the basis of laboratory results and exposure history in asymptomatic patients. Despite the acknowledged heterogeneity of assays available for the diagnosis of schistosomiasis, interpretation of PCR and serology results (routine assays in many centres) did not emerge as a source of disagreement among the experts, whereas the role of CCA and CAA tests initially led to discrepant opinions. CCA and CAA tests are the newest assays available for the diagnosis of schistosomiasis, despite development over a decade ago, therefore discrepant opinions were expected. The CCA assay is commercially available and proved suitable for use in control programmes in endemic areas,[19] but its sensitivity and specificity in the clinical setting have been less consistent.[20–23] On the contrary, CAA is proving a reliable marker of active infection in both endemic and non-endemic settings.[4,24–26] However, CAA testing is currently available only as a diagnostic service from Leiden University Medical Center (Leiden, Netherlands). Therefore, heterogeneity in opinions was expected, deriving from different first-hand experience with these assays and level of knowledge of the studies available on them.

The number of participants and external reviewers, as well as the agreement thresholds and termination criteria of this study, can be considered appropriate for the study aim.[14,15,27,28] However, this study has the limitation of having been done among clinicians and diagnosticians working in two specific international networks. This limitation implies that the opinions of several top experts in the field and from different medical specialties were not gauged. Nevertheless, when external reviewers were informally asked their opinion, general agreement was obtained with the consensus definitions. Furthermore, our case definitions are generally comparable with those recently suggested by Comelli and colleagues.[29] This publication in 2023 was supported by ten Italian scientific societies, whereas our Delphi study was conducted among clinicians and diagnosticians from Europe and North America with specific expertise in travel and infectious–tropical medicine. The main differences between the definitions included in the Italian consensus document[29] and those achieved by our international panel were that in Comelli and colleagues'

paper was the absence of case definitions for active schistosomiasis, complicated schistosomiasis, and sequelae; the absence of inclusion of CCA assay results and PCR on materials other than stool and urine; the absence of a definition of asymptomatic acute schistosomiasis; and some differences in the definitions of possible versus probable schistosomiasis. Another limitation is that it is possible that this broad definition could still not include some uncommon clinical pictures; however, this limitation is implicit in all classifications.

All things considered, we believe that our case definitions would be accepted by the broader clinical and scientific community, or at least be a starting point to reach a broader consensus among physicians of other disciplines. Furthermore, although this study specifically related to schistosomiasis in travellers and migrants diagnosed outside endemic areas, the definitions of chronic schistosomiasis could possibly also be applied in endemic settings, after taking into consideration the specific conditions and practical applications.

Conclusions

We obtained consensus on case definitions of several clinical characteristics of imported schistosomiasis from experts across two international networks dedicated to the diagnosis, surveillance, and clinical management of infectious diseases in travellers and migrants. Consensus definitions will foster harmonised scientific and clinical communication and support further studies to generate stronger evidence on management of schistosomiasis.

Contributors

FG conceived the study. FT designed the study. FT and CM coordinated and implemented the study. SA, MA, SLB, EB, DC-F, EC, AD, MPG, SJa, SJo, AM, JAP-M, AN, JS-C, FS, LRT, SDV, JJvH, LJW, LZ, DB, RH, LvL, and FG provided study data. FT analysed and interpreted the data. FT, DB, and FG drafted the manuscript. All authors edited the draft, and reviewed and approved the submitted version of the manuscript.

Declaration of interests

We declare no competing interests.

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