Travel Medicine and Infectious Disease 64 (2025) 102822

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Landscape of guidance documents used at TropNet and GeoSentinel centres for the clinical management of schistosomiasis outside endemic areas: A systematic appraisal

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https://doi.org/10.1016/j.tmaid.2025.102822
Received 19 May 2024; Received in revised form 17 February 2025; Accepted 17 February 2025
Available online 19 February 2025

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ARTICLE INFO

Keywords:
Schistosomiasis
Travellers
Migrants
Diagnosis
Treatment
Guidelines

ABSTRACT

Background: The diagnostic and treatment approaches for schistosomiasis in individual patients, outside endemic areas, are not standardised. This study aimed to appraise the reference documents that the experts from the TropNet and GeoSentinel networks use in practice as guidance for the clinical management of their patients with (suspect) schistosomiasis.
Methods: We systematically appraised the following data from the referenced guidance documents: i) document type, ii) case definitions, iii) diagnostic techniques envisaged; iv) treatment recommendations; v) follow-up recommendations; vi) screening recommendations, and vii) symptom-based diagnostic suspicion.
Results: Twenty-two of the 30 responders (73.3 %) indicated 19 reference documents, three of which were WHO material not intended for individual clinical management. Only 4/19 (21.1 %) documents were national recommendations; no international guideline was indicated. Case definitions were explicitly presented in only one document (1/19; 5.3 %). Diagnostic tools were detailed in 11/16 (68.8 %) and follow-up guidance in 8/16 (50 %) documents. Treatment guidance was provided in 14/16 (87.5 %) documents.
Conclusions: Heterogeneity in clinical guidance was evident, although with noticeable overlap at least for chronic schistosomiasis. This confirms the need to formalise case definitions, which should be used to design trials to rigorously assess diagnostic tools and treatment schemes, and eventually come to harmonization of clinical management guidance.

1. Introduction

Schistosomiasis is a neglected tropical disease caused by infection with trematodes of the genus *Schistosoma*. Infection is acquired through contact with freshwater containing infective larvae (cercariae), where the parasite life cycle can take place in the presence of a suitable intermediate aquatic snail host, if freshwater is contaminated by urine and/or faeces of infected subjects. *Schistosoma haematobium*, residing in the pelvic plexus, causes urogenital schistosomiasis, while *S. mansoni, S. japonicum* and other species, residing in the mesenteric plexus, cause intestinal and hepatosplenic schistosomiasis [1]. In endemic areas, pathology is caused by chronic infections and constant re-infections; it is estimated that 250 million people in tropical and sub-tropical areas are affected, most of whom in sub-Saharan Africa [1].

Outside transmission areas, schistosomiasis is diagnosed in returning travellers and migrants from endemic areas, although the infection may be overlooked outside specialised centres [2–4]. Travellers who acquired the infection for the first time mostly present clinically with an acute schistosomiasis syndrome (also referred to as "Katayama fever" or "Katayama syndrome"), with or without prior transitory cercarial dermatitis, while chronic disease, developing from chronic, repeated infections, is less commonly observed in these patients. The pathophysiology of acute schistosomiasis is to be related to hypersensitivity against juvenile parasites migrating and developing in human tissues [5]. Migrants from endemic areas, on the contrary, usually present with chronic schistosomiasis, as mentioned before; in this case, pathology is caused by the chronic inflammatory and fibrotic reaction elicited around parasite eggs that fail to be released with excreta and are entrapped in tissues [1].

The diagnostic and treatment approaches for acute and chronic schistosomiasis in individual patients, outside transmission areas, are not standardised at international, and often also at national, level. International guidelines such as those published by the World Health Organization (WHO) [6,7] only pertain to control of schistosomiasis in endemic areas. In the latter context, diagnosis aims to estimate the prevalence of infection and treatment aims to reduce the parasite burden at population level. These goals are very different from those required at individual patient's level outside endemic areas, where diagnosis aims at identifying infection in individual subjects and treatment aims to their complete parasitological cure.

Diagnostic assays available in the clinical context encompass classical direct (stool and urine microscopy) and indirect (sero-assays detecting antibodies) tests, as well as newer ones such as PCR on blood and excreta, and antigen-detection tests [8]. Their diagnostic accuracy for diagnosis and follow-up (and especially for the identification of active infection, i.e. presence of live worms) vary between and within assay categories, and in the context of acute *vs* chronic infection. Praziquantel is the only currently available antiparasitic drug active against adult *Schistosoma* worms. In control programmes, single-dose treatment is used as a preventive chemotherapy approach, implemented through a mass drug administration strategy [6,7]. In the clinical context, for individual patients outside endemic areas, on the contrary, treatment schemes for acute and chronic schistosomiasis are not standardised. To complicate the picture further, the actual case definitions of "acute" and "chronic" schistosomiasis are not univocal [9], and there may be an overlap between the two phases [10,11].

A review by Cucchetto et al. [12], on praziquantel use in imported chronic schistosomiasis found that nearly 40 % of included publications, reporting cases managed in Europe, North America, Australia, and New Zealand, indicated the application of treatment schemes different from the standard 1-day WHO regimen. This heterogeneity in implemented practices is partly due to the absence of a gold standard approach to diagnose the presence of active infection and therefore assess treatment efficacy. Unfortunately, this systematic review did not address the management of acute schistosomiasis nor diagnostic approaches. In this study, taking advantage of the an international network of experts, as part of the planned activities of the TropNet (http://tropnet.eu/) Schisto Task Force group, we investigated if and what reference documents experts used to guide the diagnosis and clinical management of their patients with (suspect) schistosomiasis in non-endemic settings, and systematically appraised the content of these reference documents. The specific aims of this appraisal were i) to identify and systematically

examine what guidance is, in real practice, referred to by experts in laboratory diagnosis and treating physicians caring for patients with (suspect) imported schistosomiasis in specialised centres outside endemic areas; and ii) to evaluate to what extent the recommended diagnostic and treatment practices differed, with the final goal of evaluating whether a harmonization could be envisaged.

2. Materials and methods

2.1. Study design

This study was a systematic appraisal of the reference documents identified and used as a guidance by experts in the clinical management of imported schistosomiasis.

2.2. Experts

Experts in the clinical management of schistosomiasis who were invited to participate in this study were identified in the context of a previous Delphi study [9] aiming to achieve expert consensus, or quantify disagreement, on the definitions of clinical aspects of imported schistosomiasis. In that study, experts were identified as those working at TropNet and GeoSentinel-affiliated centres for the clinical management of imported schistosomiasis and who fulfilled the following criteria: i) attended patients with schistosomiasis and authored at least one publication on schistosomiasis in a peer-reviewed journal in the past ten years; or ii) authored at least five publications on schistosomiasis in a peer-reviewed journal in the past ten years. TropNet (http://tropnet.eu/) is a network of European specialised centres in tropical and travel medicine; GeoSentinel (https://geosentinel.org/) is an international network of clinics and healthcare providers dedicated to monitoring infectious diseases and other travel-related health issues among international travellers and migrants. Five external reviewers with different expertise (clinical, diagnostic, methodological) in schistosomiasis, who revised and pilot-test the Delphi questionnaires, were also invited to take part in this study and are referred to as "experts" in this study.

2.3. Data collection and analysis

The online REDCap tool used for the Delphi study [9] (available at https://zenodo.org/records/10351269) was also used to ask experts whether they 1) "*followed any guideline(s) or recommendation document when managing (diagnosis, treatment, follow-up) patients with (suspected) schistosomiasis*", and if yes, to "*please provide the reference (doi or URL or citation or actual document)*". The following data were extracted from the retrieved full text of the provided reference documents using an Excel datasheet: i) type of document (e.g. national guideline, published paper); ii) inclusion of case definitions of schistosomiasis (yes/no and details); iii) diagnostic techniques envisaged; iv) treatment guidance for acute and chronic schistosomiasis; v) follow-up recommendations; vi) recommendations provided regarding screening of asymptomatic individuals with risk factors (yes/no and details); and vii) guidance on what clinical signs/symptoms should prompt the implementation of diagnostic procedures (yes/no and details).

Results are presented descriptively and as absolute numbers and percentages, where appropriate.

3. Results

3.1. Characteristics of the involved experts

Thirty-three clinicians (i.e., physicians attending and clinically managing patients) and experts in laboratory diagnosis (i.e., physicians or biologists involved in carrying out and interpreting laboratory-based diagnosis) were invited to participate in the Delphi study [9], as either responders (n = 28) or external reviewers (n = 5): 27 were clinicians (24 from Europe and 3 from North America – 2 from Canada and 1 from the USA) and 6 were experts in laboratory diagnosis (5 from Europe and 1 from Canada). Thirty of these experts (91 %) replied about their use of guidance documents; the geographical origin and expertise of the responders is presented in Fig. 1. The three non-responders were clinicians, two from Europe and one from the USA.,

3.2. Type of guidance documents indicated by the experts

Eight of the 30 responders (27 %) stated that they did not use any guidance document. The remaining 22 experts indicated a total of 19 documents [6,7,13–29], 1 to 3 documents per expert (summarised in Table 1 and detailed in the Appendix in Table A1). Of these documents, two addressed schistosomiasis in the context of the assessment of eosinophilia, while 17 were documents, or sections of documents, specifically concerning schistosomiasis (Table A1). Of note, five out of the 22 responders (22.7 %), two experts in laboratory diagnosis and three clinicians, referred to WHO-published material not intended for individual clinical management.

3.3. Schistosomiasis case definitions in guidance documents

Case definitions of schistosomiasis were only explicitly presented in one document (1/19; 5.3 %) [21] (Table A1). Epidemiological, clinical and laboratory elements detailing these case definitions are depicted schematically in the Appendix in Fig. A1 and the definitions are presented in Table A2, together with two more recent documents [9,30] providing case definition of schistosomiasis, for comparison. Some information regarding time from infection defining acute schistosomiasis was indicated in two further documents: one [19] mentioned timing of cercarial dermatitis as <24 h and "second stage" (i.e., acute schistosomiasis) as 3–8 weeks after infection; in the other [18], early infection was identified within three months from infection. Three documents [14,23,29] specified that presence of parasite eggs defined proven infection, and one document [14] specified the conditions defining suspect acute schistosomiasis (eosinophilia, general symptoms, and permanence in endemic areas in the last three months) and suspect schistosomiasis (serology-positivity only).

3.4. Diagnostic setting and procedures in guidance documents

When considering the 16 documents referring to individual patients'

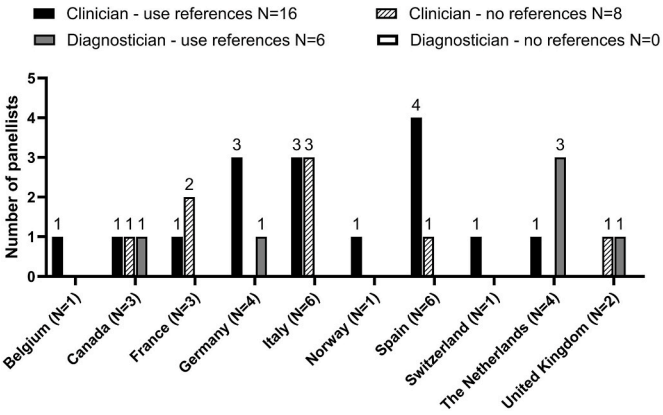

Fig. 1. Origin and expertise of the panellists, and answer about use (solid colour bars) or no use (dashed bars) of reference documents for the diagnosis and clinical management of schistosomiasis in migrants and travellers. Clinician: physician attending and managing patients. Diagnostician: expert in laboratory diagnosis, i.e., physician/biologist carrying out and interpreting laboratory-based diagnosis.

Table 1
Summary of documents cited as reference material for the clinical management of imported schistosomiasis by panellists of the TropNet and GeoSentinel networks.

Document type	Document reference	Number and countries of the experts citing the document type	Percentage of the 30 experts citing the document type
Scientific society recommendations	[14,15,19, 21,24]	Germany (N = 4), The Netherlands (N = 4), Spain (N = 1), Italy (N = 1)	33 %
Published papers	[13,23, 25–27]	Spain (N = 3), Canada (N = 1), UK (N = 1)	17 %
WHO material	[6,7,20]	Belgium (N = 1), Canada (N = 2), Italy (N = 1), UK (N = 1)	17 %
National recommendations	[17,22,29]	Canada (N = 1), France (N = 1), Germany (N = 1), Italy (N = 1), Norway (N = 1)	17 %
Scientific institute recommendations	[16]* [28]	Belgium (N = 1), Norway (N = 1), Spain (N = 1), Switzerland (N = 1)	13 %
Online clinical resource tool	[18]	Norway (N = 1), Spain (N = 1)	7 %
No document used	–	Canada (N = 1), France (N = 2), Italy (N = 3), Spain (N = 1), UK (N = 1)	27 %

*The document is a scientific institute recommendation, but schistosomiasis-specific pages are extracted and published as national recommendations.

management (i.e. excluding the WHO documents on infection control in endemic areas), diagnostic tools for diagnosis were mentioned in 11/16 (68.8 %) documents. The range of diagnostic tests envisaged for routine practice is shown in Fig. 2. Among these 16 papers, two [23,24] specifically concerned investigation of eosinophilia in subjects from endemic areas.

Symptoms/signs triggering diagnostic procedures were listed in 7/16 (43.8 %) documents, and guidance on screening of asymptomatic individuals with risk factors was provided in 8/16 (50 %) documents (Table A3).

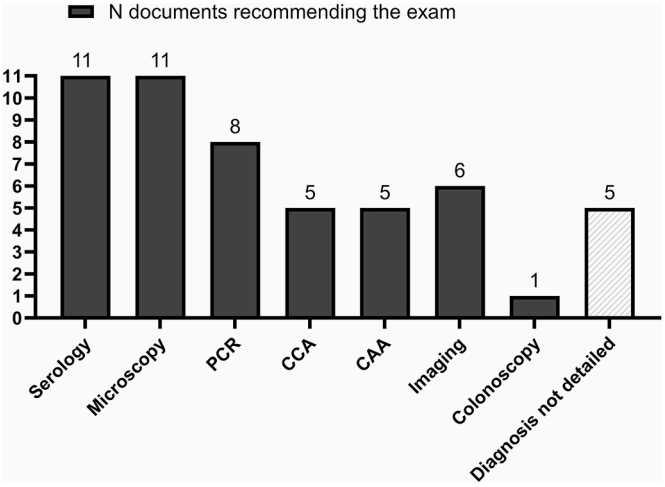

Fig. 2. Schistosoma-specific diagnostic tests envisaged for routine practice in the 11/16 reference documents indicated by the experts. CCA: Circulating Cathodic Antigen. CAA: Circulating Anodic Antigen.

3.5. Treatment guidance

Treatment guidance for acute and/or chronic schistosomiasis was provided in 14/16 (87.5 %) documents. Treatment schemes are summarised in Table A3 and schematised in Fig. 3. For chronic schistosomiasis (addressed in 13/16 documents; 81.3 %), the most frequent scheme was 1-day administration (11/13; 84.6 %); additional treatment after the first 1-day dose was recommended in five documents but schemes differed as for time between doses: 2–4 weeks, 3–4 weeks, 4 weeks, and every 1–3 months until normalization of eosinophilia and disappearance of eggs. Multiple consecutive days of praziquantel treatment were indicated in three documents: 3 days in two documents and the same cumulative dose divided in 2 days in one document. Treatment schedules for acute schistosomiasis were detailed in 7/16 (43.8 %) documents, while two further documents [14,22] just warned about the inefficacy and side effects of praziquantel during the acute phase. In all cases when treatment of acute schistosomiasis was detailed, schemes were heterogeneous and relied on corticosteroids variably associated with praziquantel (Table A3; Fig. 3).

3.6. Follow-up guidance

Follow-up guidance was detailed in 8/16 (50 %) documents (Table A3; Fig. 3); new evaluation of microscopy, if positive at diagnosis, was indicated in all documents, with time range spanning from as early as 3 weeks until 6–24 months after treatment. Serology was clearly mentioned as not useful for follow-up in 4/8 (50 %) of these documents [16–19], and mentioned as not recommended in 2/8 (25 %) [21,22], while one document instead recommended serology follow-up at 6, 12 and 24 months after treatment, and re-treatment in case antibody titres were stable or increasing [14]. The use of other tools such as imaging, PCR or antigen detection tests were variably mentioned in most documents (6/8; 75 %).

4. Discussion

This work aimed to assess the content of the documents indicated as reference by a group of expert clinicians and experts in laboratory diagnosis, for the clinical management of imported schistosomiasis. Only 4/19 (21.1 %) documents were national recommendations [16,17, 22,29] (Table 1 and Table A1); no international guideline was indicated (nor is available to the knowledge of the authors) for the diagnosis and clinical management of patients with schistosomiasis outside the context of control programmes in endemic areas.

Strikingly evident was the general lack of explicit clear definitions of acute and chronic schistosomiasis, and the heterogeneity thereof when these were mentioned. This picture confirms the need for formalising case definitions, which should be used then to rigorously assess diagnostic tools and treatment schemes and eventually come to harmonization of clinical management protocols. In this respect, several important aspects deserve to be highlighted. Since biological and clinical features of schistosomiasis are a continuum throughout the evolution of the infection [10,11], clear-cut case classifications can only be a "convention" deriving from agreement among the scientific community. Therefore, on the one hand, the formalization of case definitions should provide a clear and applicable frame to classify patients in scientific studies, to avoid results of trials being contradictory or difficult to compare as the sole consequence of participants being classified differently in different centres. Clinical practice, on the other hand, should always take into consideration and adapt any recommendation or guideline to the specific characteristics and presentation of each patient. For example, three months has been agreed upon in a recent Delphi study to be the maximum time required for adult worms development and therefore for praziquantel to be safely used [9]. However Neumayr et al. [31], reported one case of adverse events to praziquantel similar to those observed during acute schistosomiasis in one patient with early

ACUTE SCHISTOSOMIASIS

<---------Infection	Diagnosis	4 w	6 w	8 w	10 w	12 w	14 w	16 w
(13)	>3d CORT until symptoms end			PZQ + CORT			PZQ	
(15)	3d CORT + 3d PZQ							
(16)	3-6d CORT +/- PZQ on day 3					PZQ		
(18)	CORT until symptoms end				PZQ + 3d CORT			PZQ
(19)	1-5d CORT + PZQ		PZQ					
(21)	3d PZQ + CORT			PZQ				
(28)	3-7d CORT + 2d PZQ			PZQ				

CHRONIC SCHISTOSOMIASIS

	Treatment	Follow-up tests (repeated if positive at diagnosis) with mentioned timing for execution								
	Diagnosis	1 m		2 m	3 m	4 m	5 m	6 m //	12 m //	24 m
(14)	3d PZQ							Microscopy	Microscopy Serology Imaging	Microscopy Serology Imaging
(15)	1d PZQ	1d PZQ								
(16)	1d PZQ	1d PZQ			Microscopy CCA			Microscopy	Microscopy	
(17)	1d PZQ	+/- 1d PZQ		Microscopy						
(18)	1d PZQ				Microscopy					
(19)	1d PZQ				Microscopy CCA PCR			Microscopy CCA PCR	Microscopy CCA PCR	
(21)	3d PZQ	Imaging		Microscopy Imaging				Imaging		
(22)	2d PZQ	Microscopy								Serology
(23)	1d PZQ									
(24)	1d PZQ									
(27)	1d PZQ									
(28)	1d PZQ			1d PZQ if eosinophilia and/or eggs		1d PZQ if eosinophilia and/or eggs		1d PZQ if eosinophilia and/or eggs	---etc---	
(29)	1d PZQ				Microscopy			Microscopy	Microscopy	

Fig. 3. Schematic representation of treatment and follow-up guidance for acute and/or chronic schistosomiasis envisaged in the reference documents indicated by the panellists. Green column: referenced document [N]. CCA: Circulating Cathodic Antigen. CAA: Circulating Anodic Antigen. CORT: corticosteroids. PZQ: praziquantel. d: day(s). m: months. w: weeks. Note that depending on the document, treatment schedule for acute schistosomiasis refers to weeks from infection or weeks from onset of symptoms.

infection but exposed more than three months before, showing that clinical management must always be patient-tailored. Adverse events to praziquantel administered during acute schistosomiasis might occur in up to 40 % of cases and may be life-threatening [11,12,32]; therefore, a pivotal focus of future work aiming to harmonize the treatment of schistosomiasis will have to be on the use of praziquantel in acute schistosomiasis. This future work should also take into consideration the clinical differences between manifestations in adults and children [33].

When considering diagnosis and clinical management of imported schistosomiasis, heterogeneity in diagnostic, treatment and follow-up guidance in the cited documents was evident, as already found by Cucchetto et al. [12], who, however, made a literature review on schistosomiasis treatment and also did not include diagnostic procedures in their study. Also, in some cases, some strategies which lack an evidence base or rationale were present in the documents for diagnosis (such as the recommended use of first morning urine for the diagnosis of urinary schistosomiasis [29] or of colonoscopy in case of presence of *S. mansoni* eggs and infection likely older than one year [14]) or follow-up (e.g. recommended post-treatment monitoring with serology [22,29] and retreatment in case of antibody titers not showing any decline of titers after 24 months –without quantitative indication of this decline per assay used [14]). This heterogeneity likely derives from the variable diagnostic accuracy of assays used for diagnosis and follow-up (and especially for the identification of active infection, i.e. presence of live worms), which further varies between and within assay categories, and in the context of acute vs chronic infection. In general, sero-assays are more sensitive to detect an occurred contact/infection, but are unable to indicate active infection [34,35]. Visualisation of viable eggs in stool/urine and PCR indicate active infection in untreated patients; however, their value for the follow-up is limited by their generally low sensitivity, the need for evaluating viability of eggs on microscopy, and the long persistence of DNA in blood after treatment [8,13,36–38]. Finally, among antigen-detection assays, the commercially available POC-CCA (detecting the Circulating Cathodic Antigen – CCA – in urine) was reported to have variable performance, and often was found unsuitable for application in the clinical context mainly due to low specificity [39–43]. On the contrary, the assay detecting the Circulating Anodic Assay (CAA) in serum is currently showing the best performance for the identification of active infection [5,44–49], but is only available as a service from Leiden University Medical Centre (LUMC), the Netherlands.

On a positive note, although heterogeneous, a noticeable overlap exists between case definitions (Fig. A1 and Table A1), diagnostic methods, and recommended practices especially for chronic schistosomiasis (Fig. 3 and Table A3), which encourage the possibility of working towards harmonization. A first step forward has been recently carried out by the TropNet and GeoSentinel international networks, through the issue of a Delphi consensus on clinical case definitions of imported schistosomiasis [9]. However, further work is needed to agree on other aspects, such as meaningful metrics of successful treatment and definition of cure, in order to properly design the multicentric experimental research studies that would be needed to rigorously evaluate and

compare diagnostic, treatment and follow-up strategies. Nevertheless, a first harmonization attempt could still be performed through consensus agreement, leveraging on common practices supported by a rigorous appraisal of available scientific evidence and using the consensus case definitions to classify clinical groups in an unequivocal manner. While countries might have different policies in receiving and implementing guidelines, nonetheless such international expert consensus document could provide recommendations obtained through a rigorous methodology, and pose the case for development or alignment of national guidelines.

This study has the limitation that was performed only among clinicians and experts in laboratory diagnosis working in specialised centres, most of whom affiliated to two specific international networks; therefore, some reference documents accessed by physicians working outside these specialised centres or from other disciplines could not have been identified. Surely specialists of other disciplines would have to be involved in any future work towards harmonization of diagnostic and clinical practices, to recommend practically applicable procedures and guarantee a wide dissemination of guidance documents.

5. Conclusions

Heterogeneity in guidance documents for the diagnosis, treatment and follow-up of individual patients with acute and chronic imported schistosomiasis outside endemic areas, was evident. However, noticeable overlap in recommendations exist, at least for chronic schistosomiasis. This confirms the need and the possibility to come to harmonization of clinical management guidance.

Formalization of consensus case definitions and meaningful metrics of successful treatment and definition of cure will be needed to properly design the multicentric research studies that would be needed to rigorously evaluate and compare diagnostic, treatment and follow-up strategies, and produce evidence-based guidelines.

CRediT authorship contribution statement

Francesca Tamarozzi: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Cristina Mazzi:** Writing – review & editing, Methodology, Investigation, Data curation. **Spinello Antinori:** Writing – review & editing, Investigation. **Marta Arsuaga:** Writing – review & editing, Investigation. **Sören L. Becker:** Writing – review & editing, Investigation. **Cristina Bocanegra:** Writing – review & editing, Conceptualization. **Emmanuel Bottieau:** Writing – review & editing, Investigation. **Dora Buonfrate:** Writing – review & editing, Investigation. **Amaya L. Bustinduy:** Writing – review & editing, Investigation. **Daniel Camprubí-Ferrer:** Writing – review & editing, Investigation. **Eric Caumes:** Writing – review & editing, Investigation. **Alexandre Duvignaud:** Writing – review & editing, Investigation. **Martin P. Grobusch:** Writing – review & editing, Investigation. **Ralph Huits:** Writing – review & editing, Investigation. **Stephane Jaureguiberry:** Writing – review & editing, Investigation. **Sabine Jordan:** Writing – review & editing, Investigation. **Andreas Mueller:** Writing – review & editing, Investigation. **Momar Ndao:** Writing – review & editing, Investigation. **Andreas Neumayr:** Writing – review & editing, Investigation. **Jose A. Perez-Molina:** Writing – review & editing, Investigation. **Frank O. Pettersen:** Writing – review & editing, Investigation. **Camilla Rothe:** Writing – review & editing, Investigation, Conceptualization. **Joaquin Salas-Coronas:** Writing – review & editing, Investigation. **Fernando Salvador:** Writing – review & editing, Investigation. **J Russell Stothard:** Writing – review & editing, Investigation. **Lina R. Tomasoni:** Writing – review & editing, Investigation. **Jaap J. van Hellemond:** Writing – review & editing, Investigation. **Lisette van Lieshout:** Writing – review & editing, Investigation. **Stephen D. Vaughan:** Writing – review & editing, Investigation. **Linda J. Wammes:** Writing – review & editing, Investigation. **Cedric P. Yansouni:** Writing – review & editing, Investigation. **Lorenzo Zammarchi:** Writing – review & editing, Investigation. **Federico G. Gobbi:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

Data availability

All data are presented in the manuscript and Appendix.

Sources of funding

This work was supported by a Cooperative Agreement between International Society of Travel Medicine and US Centers for Disease Control and Prevention [Federal Award Number: 5-U01CK000632-03-00] and by Italian Ministry of Health [Fondi Ricerca Corrente – L2] to IRCCS Sacro Cuore Don Calabria Hospital. The funders had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are thankful to Kristina M Angelo for help in project preparation and startup and to Aisha Rizwan for supporting contacts with GeoSentinel centres and facilitating the administration of the first round of the original Delphi study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2025.102822.

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