



Original article

Large outbreak of urogenital schistosomiasis acquired in Southern Corsica, France: monitoring early signs of endemicization?

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ABSTRACT

Objectives: Clustered cases of urogenital schistosomiasis were reported in April 2014 among French and German tourists linked to exposure in the Cavu River, Southern Corsica, France, between 2011 and 2013. We set up national surveillance for autochthonous urogenital schistosomiasis to document the largest possible number of cases in order to identify potential sites of transmission and to determine the extent of the outbreak in France and Corsica.

Methods: The early response consisted mostly of prohibiting swimming in the river, performing a nationwide serologic screening of all persons exposed to the river between 2011 and 2013 and treating confirmed cases. Physicians were asked to report all patients with one or more positive antischistosome serologic test. Cases were defined as occurring in a resident of France with serologic evidence of schistosomiasis or schistosome eggs in urine and no history of contact with freshwater in known endemic areas. We documented symptoms as well as place and time of exposure to freshwater for all subjects. To estimate the outbreak size, we modelled the effect of the 2014 nationwide screening on the 2011–2015 time series of serodiagnosed schistosomiasis cases using log-linear autoregression.

Results: In 2014, a total of 106 autochthonous cases were reported, including 35 symptomatic infections. All patients had swum in the Cavu during summer 2013. Over 30 000 persons were likely screened for autochthonous schistosomiasis. The model-estimated outbreak size was 338 cases, including 36 serodiagnosed in 2015.

Conclusions: Besides the 2013 outbreak, there is evidence of small-scale transmission in 2015 in Corsica. Early detection and control of recurrences requires raising community and medical awareness. **H. Noël, Clin Microbiol Infect 2018;24:295**

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Introduction

Human urogenital schistosomiasis is a parasitic disease caused by *Schistosoma haematobium*, a trematode of the genus *Schistosoma* which is endemic in Africa and the Middle East [1]. *S. haematobium* has a two-host life cycle: a clonal multiplication in freshwater

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mollusks belonging to the genus *Bulinus*, and a sexual stage within the human final host, who can be infected by contact with contaminated freshwater. In Europe, *S. haematobium* can theoretically be introduced in sites hosting *Bulinus truncatus*, as has been found in Corsica (France) [2,3], Spain [4], Portugal [5] and Sardinia [6]. However, no sustained transmission of the parasite has been reported since its elimination in Portugal in the 1950s [1,5,7,8].

In France, over 2000 cases of imported *Schistosoma* spp. infection are diagnosed each year (Santé publique France, unpublished data).

In April 2014, clustered cases of urogenital schistosomiasis were diagnosed in French and German families returning from Corsica; they had no history of contact with freshwater in known *Schistosoma*-endemic areas [9–11]. The patients reported exposures in 2011–2013 to the Cavu River, a popular tourist site near Sainte-Lucie de Porto-Vecchio, Southern Corsica. Presence of *B. truncatus* was confirmed at the swimming site indicated by the families.

On 16 June 2014, the French Public Health Authorities issued a European alert and took the following measures to control the emergence of *S. haematobium* in Corsica and prevent occurrence of complicated urogenital schistosomiasis: (a) nationwide serologic screening for urogenital schistosomiasis for all people with a history of contact with water in the Cavu River between 2011 and 2013 and treatment of all infected persons; (b) serologic and parasitologic screening of workers occupationally exposed to the Cavu; and (c) closure of all swimming sites in the Cavu and erection of signs not to urinate in rivers and lakes in Corsica.

We set up a surveillance system to determine the extent of the outbreak and to identify the foci of autochthonous transmission of *S. haematobium* in France and Corsica. In addition, we assessed the compliance to screening of persons exposed to the Cavu.

Methods

Nationwide screening of persons exposed to the Cavu River

In May 2014, the French public health authorities issued a press release to advise persons with a history of contact with water in the Cavu at any time during the period 2011–2013 to seek medical attention and serologic screening for urogenital schistosomiasis. Free call numbers were made available to the public to respond to questions on the disease, its transmission and its treatment.

The French Directorate for Public Health informed all general practitioners, hospital physicians, medical parasitologists and heads of diagnostic laboratories about the outbreak and asked physicians to screen all persons exposed to the Cavu at any time from 2011 to 2013, irrespective of the presence of symptoms.

In France, the routine serodiagnosis of schistosomiasis is based on one first-line serologic test (usually enzyme-linked immunosorbent assay (ELISA), haemagglutination or indirect immunofluorescence) with a control of positive serology by Western blot (WB) analysis. To increase the sensitivity of the screening, the French High Council for Public Health recommended the combination of two non-operator-dependent first-line serologic tests: ELISA and haemagglutination, followed by WB if one or both were positive. The recommended diagnostic workup of patients with positive antischistosomal serology included parasitologic examination of urine, serum creatinine, haemogram and ultrasound examination of the urinary tract.

The regional health authority of Corsica approached individually the following professionals occupationally exposed to the Cavu to offer them screening: local water sports and activities instructors, leaders of children in the holiday centres near the river and professionals who monitor swimming water quality throughout Corsica.

Surveillance of autochthonous S. haematobium

In France, urogenital schistosomiasis is not a notifiable infectious disease. For this investigation, we defined an autochthonous case as occurring in a person with laboratory evidence of *S. haematobium* infection and no history of contact with freshwater in known endemic areas. Cases were classified as confirmed, probable or possible according to laboratory criteria detailed in Table 1.

Physicians were asked to report all patients with one or more positive antischistosome serologic test to the health authorities of the region of residence of the patient. In addition, we contacted the parasitology laboratories of French university hospitals for active case finding. We interviewed physicians and their patients using a questionnaire exploring laboratory diagnosis, symptoms and clinical signs, diagnostic workup and lifetime exposure to freshwater in endemic areas throughout the world and in mainland France or Corsica in at least the 5 previous years.

For patients with a precise date of exposure, we defined the time of probable infection as the date of last contact with surface freshwater, respecting a minimum delay of symptom onset of 2 weeks for patients who had acute schistosomiasis (at least fever and eosinophilia of $>0.5 \times 10^9$ L) and ≥ 6 weeks for patients with other clinical presentations. The precise locations of swimming sites, in particular in the Cavu, were determined directly by the patients using site denominations, direction and distance to nearby landmarks, patients' photographs or, whenever possible, GPS coordinates of sites marked on Google Maps by patients.

Statistical analysis

We compared demographic, clinical and biologic characteristics between possible, probable and confirmed cases. The numbers and percentages were calculated for each field, excluding records with missing values. Data analyses were conducted by Stata 12 software (StataCorp, College Station, TX, USA). For comparison of medians, a nonparametric equality-of-medians test was used. Chi-square and Fisher's exact tests were used to determine statistical significance as appropriate ($p < 0.05$) for categorical variables.

Estimation of outbreak size

We used serology data from the national screening to estimate the outbreak size. In France, serodiagnosis of schistosomiasis is a specialized procedure not routinely performed in first-line private diagnostic laboratories. Two laboratories centralize anti-schistosome serology testing for private laboratories throughout

Table 1
Laboratory criteria for case definition of autochthonous schistosomiasis

Case definition	Laboratory criteria
Possible	Isolated positive serologic screening test (ELISA, IFT or IHA), no WB OR Two discordant screening serologic tests (ELISA, IFT or IHA), no WB
Probable	Two positive serologic screening tests using different techniques (ELISA, IFT or IHA), no WB OR Positive serologic test (ELISA, IFT or IHA) and positive WB serologic test
Confirmed	<i>Schistosoma haematobium</i> eggs by urine examination or histologic examination of biopsy sample

ELISA, enzyme-linked immunosorbent assay; IFT, immunofluorescence test; IHA, indirect haemagglutination assay; WB, Western blot.

France. Both laboratories validate all positive ELISA or indirect haemagglutination assay tests by WB (Schistosoma WB IgG; LD BIO Diagnostics, Lyon, France). We obtained data on all antischistosome serology tests conducted during 2011–2015 including date of sampling, results (indirect haemagglutination assay, ELISA and WB), patient's place of residence and a unique anonymized identifier. When several tests were conducted for the same patient, data of the first instance were kept and subsequent duplicates were removed from the time series. No data were available regarding the origin of infection (imported vs. autochthonous).

We hypothesized that all cases diagnosed before the nationwide screening (the intervention) were imported. On the basis of a conservative hypothesis, we assumed that the effect of the intervention would result in a transient frequency increase of WB-positive cases that would overlay the time series of imported cases after 15 June 2014. The time series of WB-positive cases was analysed in R (R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org/>) with the software package 'tscout' (<http://tscout.r-forge.r-project.org>). We modelled the weekly mean of the count time series, conditional on past observations, using a log-linear 'integer-valued generalized autoregressive conditional heteroscedastic' (INGARCH) process (https://www.statistik.tu-dortmund.de/fileadmin/user_upload/DP_0615_SFB823_Liboschik_Fokianos_Fried.pdf). To assess the impact of the nationwide screening on the observed weekly number of cases, we introduced in the model a transient intervention effect of the form of a steep rise followed by an exponential decay [12]. After fitting the model, the expected level of the time series in the absence of intervention was obtained by setting to zero the intervention parameter. Then the difference between the observed and expected weekly numbers of cases, cumulated over the whole time series, was used as an estimate of the outbreak size. We approximated the standard error of this quantity using the delta method [13]. Additional details are available in the Supplementary Material.

Funding source and ethical approval

This work was performed as part of the routine activities of Santé publique France. No specific funding was received for this work. It was carried out with the approval of the French Commission for Data Protection (Commission Nationale de l'Informatique et des Libertés).

Results

In June 2014, a total of 28 professionals occupationally exposed to freshwater throughout Corsica were screened, including 15 who did not report any previous contact with the Cavu River. None tested positive for serum antischistosome antibodies or parasite eggs in urine.

From April 2014 to July 2015, a total of 133 patients screened positive for *S. haematobium* infection. Of these, 27 did not meet the criteria of the case definitions: one had a history of imported schistosomiasis, seven reported exposures in endemic areas and 19 had a single positive serologic test, or discordant serologic tests and a negative WB.

In total, among the 106 patients who met the criteria for autochthonous urogenital schistosomiasis, 32 (30%) were confirmed by direct parasitologic or histologic evidence of infection, 62 (58%) were probable and 12 (11%) were possible.

Most cases occurred in male subjects (M/F sex ratio, 1:4), with a median age at presentation of 15 years (range, 3–71 years) (Table 2). Most cases occurred in asymptomatic persons (68/103, 66%) who presented for the nationwide screening. The most common symptoms were gross haematuria (19, 18%), dysuria (15, 15%) and pollakiuria ($n = 9$, 9%). We identified one probable case of acute schistosomiasis with fever and eosinophilia ($>0.5 \times 10^9/L$) evidenced 1 month after swimming in the Cavu. One probable case occurred in a patient who reported bloody stools. Median time from the probable time of contamination to screening was

Table 2
Summary description of cases of autochthonous urogenital schistosomiasis, April 2014 to July 2015, Corsica, France

Characteristic	Total (N = 106)	Possible cases	Probable cases	Confirmed cases
Demographic data				
Male sex	61/106 (58%)	5/12 (42%)	36/62 (58%)	20/32 (63%)
Age, years, median (IQR); n	17 (12–39); 104	19 (12–38); 11	18 (13–40); 61	15 (11–35); 32
Corsica resident	31/106 (29%)	10/12 (83%)	13/62 (21%)	6/32 (19%)
Clinical manifestations				
Presence of symptoms compatible with urogenital schistosomiasis	35/103 (34%)	4/12 (33%)	10/60 (17%)	21/31 (68%)*
Gross haematuria	19/103 (18%)	1/12 (8%)	2/60 (3%)	16/31 (52%)*
Dysuria	18/103 (17%)	2/12 (17%)	8/60 (13%)	8/31 (26%)
Pollakiuria	9/103 (9%)	1/12 (8%)	4/60 (7%)	4/31 (13%)
Abdominal pain or renal colic	5/103 (5%)	1/12 (8%)	1/60 (2%)	3/31 (10%)
Dyspareunia ^a	2/43 (5%)	1/7 (14%)	0 (0/24)	1/12 (8%)
Rectal bleeding ^b	1/60 (2%)	0/5	1/36 (3%)	0/19
Testicle pain ^b	3/60 (5%)	0/5	1/36 (3%)	2/19 (11%)
Haemospermia ^b	1/60 (2%)	0/5	0/36	1/19 (5%)
Laboratory data				
Microscopic haematuria	23/81 (28%)	0/11	2/41 (5%)	21/29 (72%)
Presence of eggs in urine	32/106 (30%)	0/12	0/62	32/32 (100%)
Eosinophilia ($>0.5 \times 10^9/L$)	9/33 (27%)	0/1	4/14 (29%)	5/18 (28%)
Year of exposure to Cavu River				
2014	8/106 (8%)	1/12 (8%)	6/62 (10%)	1/32 (3%)
2013	106/106 (100%)	12/12 (100%)	62/62 (100%)	32/32 (100%)
2012 and earlier	26/106 (25%)	5/12 (42%)	14/62 (23%)	7/32 (22%)
Reported swimming sites at Cavu River				
'3 piscines' location	49/90 (54%)	8/10 (80%)	28/54 (52%)	13/26 (50%)
'Outdoor activity park'	34/90 (38%)	2/10 (20%)	20/54 (37%)	12/26 (46%)
Downstream	14/90 (16%)	2/10 (20%)	9/54 (17%)	3/26 (12%)

*Statistically significantly more frequent among patients with confirmed infection than those with possible or probable infection (chi-square test, $p < 0.04$).

^a Among female subjects.

^b Among male subjects.

48 weeks (interquartile range, 40–56 weeks; $n = 83$). The median time to first symptoms was 30 weeks (interquartile range, 22–52 weeks; $n = 21$).

Taken together, patients with confirmed disease were more likely to present with urogenital complaints (21/31, 68%) than those with probable or possible infection (14/72, 19%, $p = 0.04$). At diagnosis, four patients had schistosomal obstructive uropathy, and six had bladder polyposis or bladder wall thickening.

No patient reported occupational contact with freshwater. Thirty-one (29%) were residents of Corsica. The remaining 75 (71%) were tourists originating from 27 French districts. All 106 patients had exposure to the Cavu at some point during summer 2013, including 85 (80%) in August alone. However, about 34% (36/106) of patients had also been exposed to the Cavu during the years before 2013 or in 2014 (Table 2).

There was a sharp increase in anti-schistosome serology testing in French private laboratories immediately after the start of the nationwide screening (Fig. 1). As a result, 38 310 individuals were serologically tested in 2014 vs. 6284, 5974 and 7599 in, respectively, 2011, 2012 and 2013. In 2015, this number was reduced to 12 465. In parallel, the number of WB-positive cases was 2297 in 2011, 2216 in 2012, 2885 in 2013, 3290 in 2014 and 2570 in 2015. The log-linear INGARCH modelling of the count time series of WB-positive cases identified a single 11-week lagged intervention effect after the initiation of nationwide screening ($p = 0.0357$). The resulting overall increase in cases, which approximates the overall outbreak size, was estimated at 338 (95% confidence interval, 166–510), including 36 cases (95% confidence interval, 18–53) diagnosed in 2015.

We obtained information on sites of exposure along the Cavu for 90 cases. Swimming sites were delineated in two main locations: an area known as ‘3 piscines’ (54%, 49/90, approximately latitude 41°43′56 66″N and longitude 9°17′38 11″E) and near an ‘outdoor activity park’ (38%, 34/90, 41°43′22 10″N and 9°18′0 39″E) (Fig. 2). Besides the Cavu, patients reported exposure to 24 other bodies of freshwater. The most frequent were two rivers in Southern Corsica, the Osu (12%, 13/106) and the Solenzara (11%, 12/106).

Discussion

The investigation of 106 urogenital schistosomiasis outbreak cases strongly suggests that the bulk of transmission was limited to the Cavu River. Indeed, all 106 cases reported in the first year of surveillance occurred in patients who had been exposed to the Cavu in 2013. Exposure to the other two most frequently reported swimming sites in Corsica could have explained at most 12% of the outbreak cases.

Some cases also occurred in patients exposed in 2014 or before 2013. Disputed serologic evidence of infection was reported in few international patients exposed in 2014 to the Cavu [14]. Therefore, we cannot rule out the possibility that before 2015, transmission took also place in 2014 or before 2013. But if so, it most likely remained limited.

Case reporting substantially underestimated the overall outbreak size, which was estimated at 338 cases by modelling. The 36 cases serodiagnosed in 2015 may be attributed to individuals infected in 2013 who were screened late, who had imported

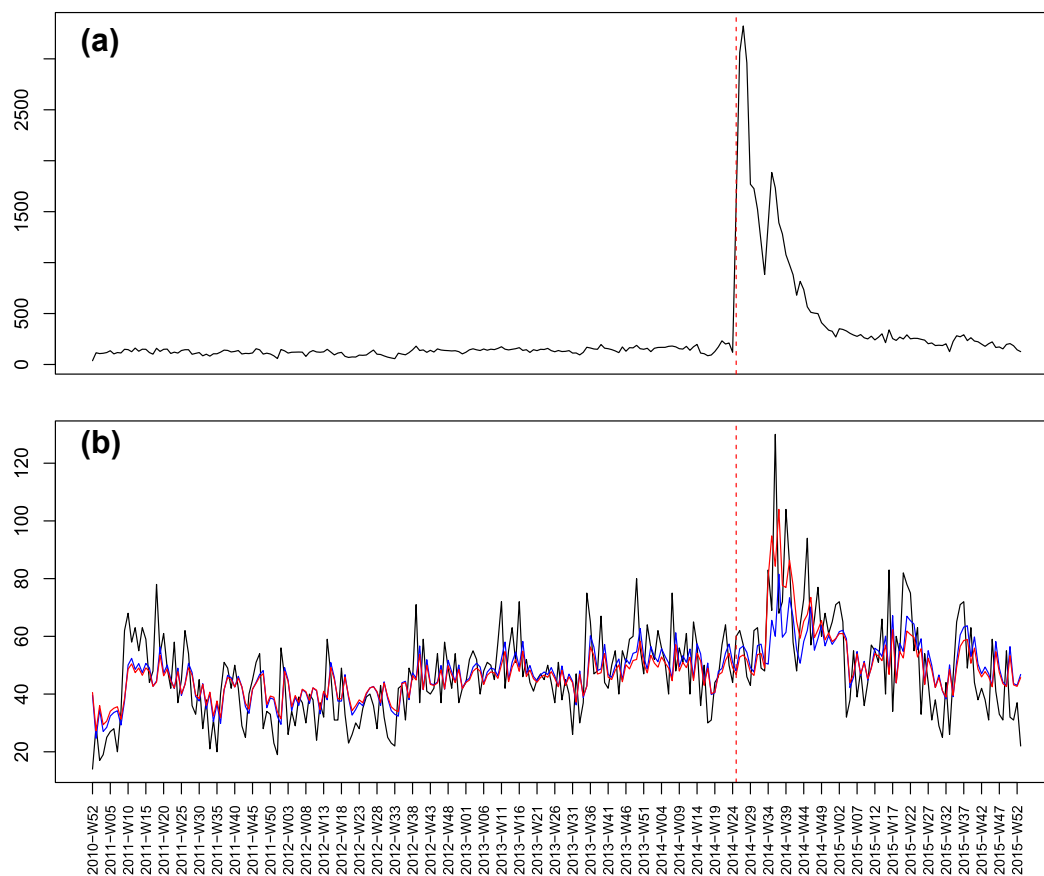


Fig. 1. Number of anti-schistosome serology test and *Schistosoma* Western Blot positive cases by week of sampling, France, 2011–2015. The curve in plot (a) delineates the observed weekly number of anti-schistosome serology tests. In plot (b) the black curve represents the observed number of patients with a positive Western-Blot (WB) test for *Schistosoma*. The solid red and blue lines represent the expected weekly number of WB-positive patients derived respectively from the fit of the INGARCH model with and without an intervention covariate accounting for the effect of the nationwide screening (starting after the vertical dashed red line – week 2014–25).

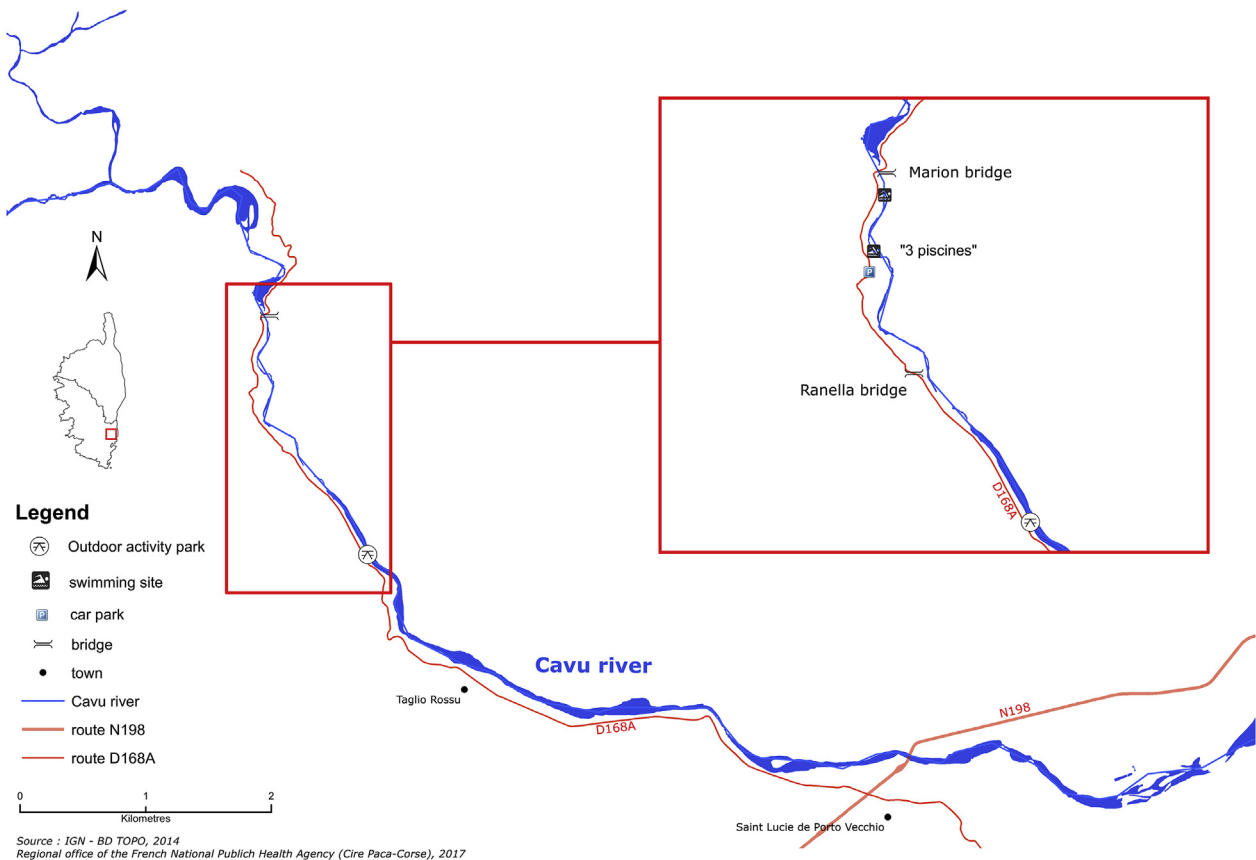


Fig. 2. Swimming sites in the Cavu River, Southern Corsica, France, 2014.

schistosomiasis or who had limited resumption of transmission in 2015. The report of an acute case of schistosomiasis acquired after bathing in the Cavu during the summer of 2015 substantiates the hypothesis of resumed transmission in 2015 [15].

Compared to the previous years, over 30 000 additional persons were tested for schistosomiasis in 2014. With an estimated 22 759 tourists visiting the area near the Cavu during the 2010–2013 period (according to the tourist office of Sainte-Lucie de Porto Vecchio), we believe that the overall compliance to the nationwide screening was good.

Serologic testing proved important for the diagnosis of emerging schistosomiasis. Microscopic detection of parasite eggs in urine or in the urinary tract, the reference standard for urogenital schistosomiasis diagnosis, was positive for only 30% of the reported outbreak cases [16,17]. However, before prescribing any serologic test, physicians should allow enough time after exposure for the development of detectable levels of antischistosome antibodies [18]. Reported patients were tested >6 weeks and often >6 months after their last contact with freshwater.

With 66% of the cases occurring in asymptomatic patients, the clinical picture observed in this outbreak was similar to that classically depicted in patients infected in known urogenital schistosomiasis–endemic areas [19].

Introggressive hybrids of *S. haematobium* by *Streptococcus bovis* found in cases of the 2013 outbreak prompted the question of the existence of an animal reservoir near the Cavu [20,21]. Indeed, *B. truncatus*, the presence of which in Corsica was first documented in 1962, served as an intermediate host for *S. bovis*, which classically infects rodents and livestock [2,3]. However, phylogenetic analysis

indicated that the introgressive hybridization most likely took place in Senegal, where *S. haematobium*/*S. bovis* hybrids are prevalent [21,22]. The negative results of early serologic and parasitologic investigations in rodents and livestock neighbouring the Cavu argue against the hypothesis that hybrids maintain their existence in a zoonotic cycle (<https://www.anses.fr/en/system/files/EAUX2015sa0036.pdf>). The documented longevity of adult vector snails and winter conditions make the year-on-year survival of infected snails and the parasites that they host unlikely in Corsica [23]. Even though molecular evidence is lacking to formally link cases diagnosed in 2015 to the 2013 outbreak, it appears likely that the parasite reinfested the Cavu River at the beginning of the summer 2015 via human carriers that were not screened in 2014.

Recurrence of schistosomiasis might become a concern across Southern Europe, as receptive sites can be assumed wherever bovine or human schistosomiasis used to be reported [4–6].

Soon after the recognition of the emergence of autochthonous urogenital schistosomiasis, the French public health authorities engaged in sustained efforts to detect early as many cases as possible for prompt treatment and to control further transmission in Corsica in the following seasons. After this outbreak, autochthonous urogenital schistosomiasis became a notifiable disease in mainland France and Corsica. Local actions were also implemented to raise public awareness, and sanitation facilities were installed for swimmers near the Cavu to prevent the development of a local human reservoir.

Screening and treatment of infected travellers and migrants from endemic areas remain at the forefront of control of the introduction of the parasite in Europe. However, physicians should consider diagnosing schistosomiasis in patients with compatible symptoms

and history of contact with freshwater not only in Corsica but also in other European countries where snail vectors are present.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cmi.2017.06.026>.

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