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

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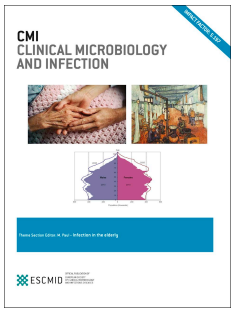

Large outbreak of urogenital schistosomiasis acquired in Southern Corsica: monitoring the early signs of the endemicization?

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Original article

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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, between 2011 and 2013. We set up a national surveillance of autochthonous urogenital schistosomiasis documenting the largest possible number of cases to identify potential sites of transmission and to determine the extent of the outbreakin France and Corsica.

Methods

The early response consisted mostly in prohibiting swimming in the river, a nationwide serological screening of all persons exposed to the river between 2011 and 2013, and treating confirmed cases. Physicians were asked to report all patients with ≥1 positive anti-schistosome serological test. Cases were defined as a resident of France with serological evidence of schistosomiasis or schistosome eggs in urine and no history of contact with freshwater in known endemic areas. We documented symptoms, place and time of exposure to fresh water of cases. 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 a log-linear autoregression.

Results

In 2014, 106 autochthonous cases were reported, including 35 with a symptomatic infection. 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.

Conclusion

Besides the 2013 outbreak, there is evidence of small-scale transmission in 2015 in Corsica. Early detection and control of recurrences requires community and medical awareness-raising.

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Introduction

Human urogenital schistosomiasis is a parasitic disease caused by *Schistosoma haematobium*, a trematode of the genus *Schistosoma*, endemic in Africa and the Middle East.[1]*S. haematobium*has a two-host lifecycle with a clonal multiplication in freshwater mollusksbelonging to the genus *Bulinus*, and a sexual stage within the human final host that can be infected through contact with contaminated freshwater.In Europe *S. haematobium* can theoretically be introduced in sites hosting*Bulinustruncatus*like were found in Corsica,[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.[5][1][7, 8]

In France, over 2,000 cases of imported *Schistosoma* spp. infection are diagnosed each year (SpFrance unpublished data).

In April 2014, clustered cases of urogenital schistosomiasis were diagnosed in French and German families returning from Corsica, with no history of contact with freshwater in known schistosoma-endemic areas.[9-11] The cases reported exposures in 2011-2013 to the Cavu River, a popular tourist site near Sainte-Lucie de Porto-Vecchio, Southern Corsica. Presence of *Bulinustruncatus* 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: (i) nationwide serological screening for urogenital schistosomiasis for all people with history of contact with water in the Cavu River between 2011 and 2013 and treatment of all infected persons; (ii) serological and parasitological screening of workers occupationally exposed to the Cavu (iii) closure of all swimming sites in the Cavu and putting up 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 with 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 anytime during the period 2011-2013 to seek medical attention and serological screening for urogenital schistosomiasis. Free call numbers were made available to the public to respond to questions on the disease, its transmission and treatment.

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

In France, the routine serodiagnosis of schistosomiasis is based on one first-line serological test (usually ELISA, haemagglutination or indirect immunofluorescence) with a control of positive serology by Western Blot (WB). To increase the sensitivity of the screening, the French High Council for Public Health recommended the combination of two non-operator-dependent first-line serological tests: ELISA and haemagglutination followed by WB if ≥1 was positive. The recommended diagnostic work-up of patients with positive anti-schistosome serology included parasitological 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, professionals who monitor swimming water quality throughout Corsica.

Surveillance of autochthonous schistosomiasis haematobium

In France, urogenital schistosomiasis is not a notifiable infectious disease. For the investigation, we defined an autochthonous case as 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 and possible according to laboratory criteria detailed in **Error! Reference source not found.**.

Physicians were asked to report all patients with ≥1 positive anti-schistosome serological test to the health authorities of the region of residence of the patient. In addition we contacted the parasitology laboratories of the French university hospitals for active case-finding. We interviewed physicians and their patients using a questionnaire exploring laboratory diagnosis, symptoms and clinical signs, diagnostic work-up 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 cases 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 cases that had acute schistosomiasis (at least fever and eosinophilia>0·5x10^9L), and ≥6 weeks for cases with other clinical presentations. The precise locations of swimming sites, in particular in the Cavu, were determined directly with the patients, using sites denominations, direction and distance to nearby landmarks, patients' photographs or, whenever possible, using GPS coordinates of sites marked on Google maps® by patients.

Statistical analysis

We compared demographical, clinical and biological 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 in Stata 12 (StataCorp LP, College Station, TX, USA). For comparison of medians, a nonparametric equality-of-medians test was used. Chi-square and Fischer's exact tests were used to determine statistical significance as appropriate ($p<0{\cdot}05$) for categorical variables.

Estimation of the 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 France. Both laboratories validate all positive ELISA or Indirect Haemagglutination Assay (IHA) test, by Western Blotting (Schistosoma WB IgG; LD BIO Diagnostics, Lyon, France). We obtained data on all anti-schistosome serology tests conducted during 2011-2015 including date of sampling, results (IHA, 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 was available on the origin of infection (imported vs. autochthonous).

We hypothesized that all cases diagnosed before the nationwide screening (the intervention) were imported. Based on 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 June 15, 2014. The time series of WB-positive cases was analysed in R (R Core Team, 2013) with the software package 'tscount'.[12] 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.[13] 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.[14] 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.[15] Additional details are available in the supplementary material.

Funding Source and Ethical Approval

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

Results

In June 2014, 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 anti-schistosome antibodies or parasite eggs in urine.

From April 2014 to July 2015, 133 cases screened positive for *S. haematobium* infection were reported. Of these, 27 did not meet the criteria of the case definitions: 1 had a history of imported schistosomiasis, 7 reported exposures in endemic areas, and 19 had a single positive serological test or discordant serological tests and a negative WB.

In total, among the 106 cases that met the criteria for autochthonous urogenital schistosomiasis, 32 (30%) were confirmed–with direct parasitological or histological evidence of infection–, 62 (58%) were probable and 12(11%) were possible.

Most cases were males (sex ratio M/F: 1·4), with a median age at presentation of 15 years (range: 3-71) (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> $0{\cdot}5x10^9$/L evidenced 1 month after swimming in the Cavu. One probable case reported bloody stools. Median time from the probable time of contamination to screening was 48 weeks (Interquartile range 40-56, N=83). The median time to first symptoms was 30 weeks (IQR 22-52, N=21).

Altogether confirmed cases were more likely to present with urogenital complaints (21/31, 68%) than probable and possible cases (14/72, 19%, p=0·04). At diagnosis, 4 patients had schistosomal obstructive uropathy and 6 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 cases had exposure to the Cavu at some point during the summer 2013, including 85 (80%) in August alone. However, about 34% (36/106) of cases had also been exposed to the Cavu during the years prior to 2013 or in 2014 (Table 2).

We obtained information on sites of exposure along the Cavu for 90 cases. Swimming sites were delineated in two main locations: “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-9°18'0·39"E) (Figure 2). Besides the Cavu, cases reported exposure to 24 other bodies of freshwater; the most frequent were two rivers of Southern Corsica: Osu (12%, 13/106) and Solenzara (11%, n=12/106).

There was a sharp increase in anti-schistosome serology testing in the French private laboratories immediately following the start of the nationwide screening, (Figure 1). As a result 38,310 individuals were serologically tested in 2014 versus 6,284, 5,974, and 7,599 in respectively 2011, 2012, and 2013. In 2015, this number pulled back to 12,465. In parallel, the number of WB-positive cases was 2,297 in 2011, 2,216 in 2012, 2,885 in 2013, 3,290 in 2014, and 2,570 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 the nationwide screening (p= 0·0357). The resulting overall increase in cases, that approximates the overall outbreak size, was estimated at 338 [95% Confidence Interval: 166-510], including 36 cases [95% CI: 18-53] diagnosed in 2015.

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 were exposed to the Cavuin 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 were also exposed in 2014 or before 2013. Disputed serological evidence of infection was reported in few international patients exposed in 2014 to the Cavu[16]. Therefore we cannot rule out that before 2015 transmission took also place in 2014 or prior to 2013. But if so, it remained most likely limited.

Case reporting substantially underestimated the overall outbreak size estimated at 338 cases by modelling. The 36 cases serodiagnosed in 2015 may be attributed to individuals infected in 2013 that engaged late in the screening, imported schistosomiasis or to 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.[17]

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

Serological testing proved important for the diagnosis of emerging schistosomiasis. Microscopic detectionof parasite eggs in urine or in the urinary tract, the gold standard for urogenital schistosomiasis diagnosis, was positivefor only 30% of the reported outbreak cases. [18, 19] However before prescribing any serological test, physicians should allow enough time after exposure for the development of detectable levels of anti-schistosome antibodies.[20]Reported cases were tested >6 weeks and often >6 months after their last contact with freshwater.

With 66% of asymptomatic cases, the clinical picture observed in this outbreak was very similar to that classically depicted in patients infected in knownurogenital schistosomiasis endemic areas. [21]

Introgressive hybrids of *S. haematobium* by *S. bovis* found in cases of the 2013 outbreak prompted the question of the existence of an animal reservoir near the Cavu.[22, 23] Indeed, *B. truncatus*, which presence in Corsica was first documented in 1962,served as intermediate host for *S. bovis*, which classically infects rodents and livestock.[2, 3] However phylogenetic analysis indicated that the introgressivehybridation took place most likely in Senegal where *S. haematobium/S. bovis* hybrids are prevalent.[23, 24] The negative results of early serological and parasitological investigations in rodents and livestock neighbouring the Cavuargue against the hypothesis that hybrids maintain their existence in a zoonotic cycle.[25] 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. [26] Even though molecular evidence is lacking to formally link cases diagnosed in 2015 to the 2013 outbreak, it appears very likely that the parasite re-infested 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]

Rapidly 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. Following 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 in Corsica but also in other European countries where snail vectors are present.

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Declaration of personal interests: The authors declare that there are no conflicts of interest.

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Table 1 : Laboratory criteria for case definition of autochthonous schistosomiasis

Case definition	Laboratory criteria
possible case	Isolated positive serological screening test (ELISA, IFT or IHA and, no WB OR 2 discordant screening serological tests (ELISA, IFT or IHA), no WB
probable case	2 positive serological screening tests using different techniques(ELISA, IFT or IHA), no WB OR a positive serological test (ELISA, IFT or IHA) and a positive Western blot serological test
confirmed case	*S. haematobium* eggs by urine examination or histological examination of a biopsy

IHA: Indirect Haemagglutination Assay test; IFT: Immunofluorescence test; WB: Western Blot test

Table 1 : Summary description of demographics, clinical presentation and exposure of possible, probable and confirmed cases of autochthonous urogenital schistosomiasis; April 2014-July 2015, Corsica, France.

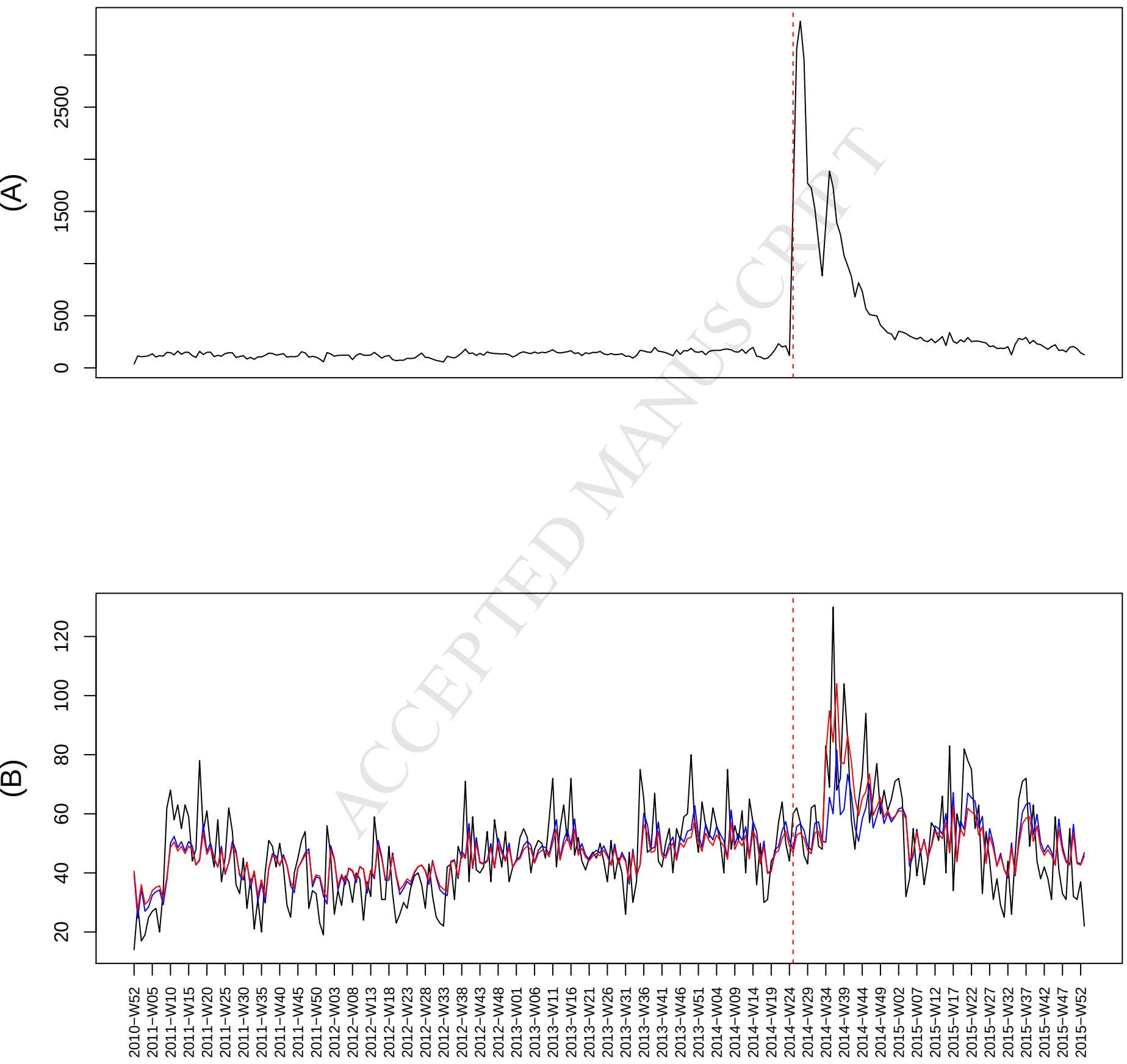
	Total (N = 106)	Possible cases	Probable cases	Confirmed cases
Demographics				
Males	61/106 (58%)	5/12 (42%)	36/62 (58%)	20/32 (63%)
Median age [IQR] ; n	17 [12-39] ;104	19[12-38] ;11	18 [13-40] ;61	15 [11-35] ;32
Residents of Corsica	31/106 (29%)	10/12 (83%)	13/62 (21%)	6/32 (19%)
Clinical manifestations (%)				
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 §	2/43 (5%)	1/7 (14%)	0 (0/24)	1/12 (8%)
Rectal bleeding $	1/60 (2%)	0/5	1/36 (3%)	0/19
Testicle pain $	3/60(5%)	0/5	1/36 (3%)	2/19 (11%)
Haemospermia $	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 >0.5x10^9/L	9/33 (27%)	0/1	4/14 (29%)	5/18 (28%)
Year of exposure to the 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–Cavu River (%)				
“3 piscines”	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%)

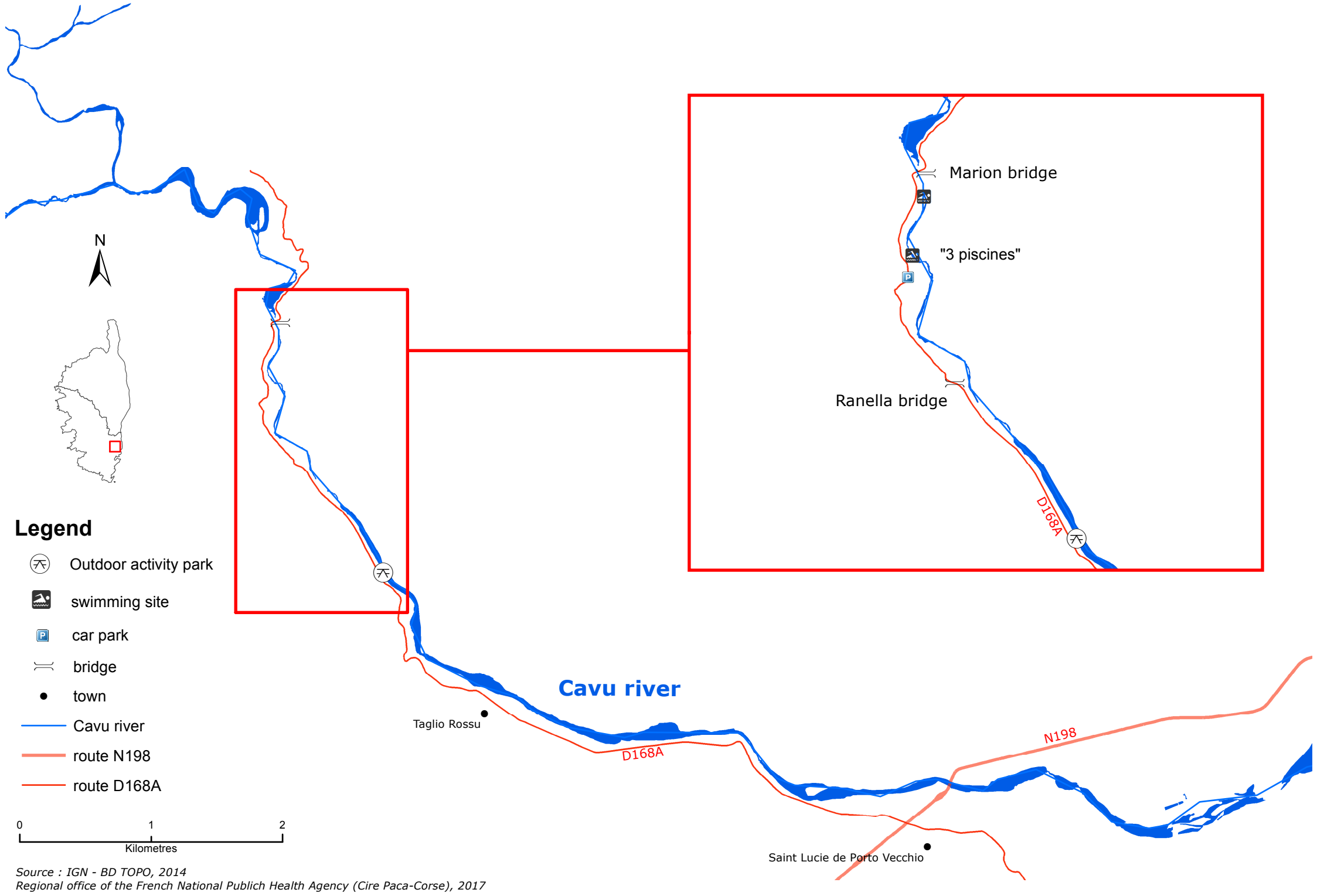
*significantly more frequent among patients with confirmed infection than those with possible or probable

infection (Chi-square test, $p<0.04$)

§ among females

$ among males





Source : IGN - BD TOPO, 2014
Regional office of the French National Publich Health Agency (Cire Paca-Corse), 2017