Incidence of tick-borne relapsing fever in west Africa: longitudinal study

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Summary

Background The ongoing drought in sub-Saharan countries has led to the colonisation of west African Savanna by *Ornithodoros sonrai*; this tick acts as a vector for *Borrelia crocidurae*, which causes tick-borne relapsing fever (TBRF). Our aim was to ascertain the incidence of TBRF in west Africa.

Methods From 1990 to 2003, we monitored the incidence of TBRF in Dielmo, Senegal, by daily clinical surveillance and by blood testing of individuals with a fever. From 2002 to 2005, we investigated the presence of *O sonrai* in 30 villages in Senegal, Mauritania, and Mali, and measured by PCR the prevalence of *B crocidurae*.

Findings The average incidence of TBRF over 14 years was 11 per 100 person-years (range from 4 in 1990 to 25 in 1997). All age-groups presented a high incidence of the disease. In addition to relapses, repeated infections in the same individuals were common, with some affected by up to six distinct infections during the study period. Epidemiological studies indicated that 26 of the 30 studied villages (87%) were colonised by the vector tick *O sonrai* and that the average *B crocidurae* infection rate of the vector was 31%.

Interpretation The incidence of TBRF at the community level is the highest described in Africa for any bacterial disease. The presence of the vector tick in most villages investigated and its high infection rate suggest that TBRF is a common cause of fever in most rural areas of Senegal, Mauritania, and Mali.

Introduction

In west Africa, tick-borne relapsing fever (TBRF) is caused by the spirochaete *Borrelia crocidurae*.[1–5] The pathogen is transmitted by the tick *Ornithodoros sonrai* (formerly *Alectorobius sonrai*),[6–8] which is an ectoparasite that lives on rodents and other insectivores.[9–11] People are generally infected during their sleep, when the hosts' burrows open into their bedrooms.[6,11] *B crocidurae* causes an acute febrile illness in people. If left untreated, patients have relapsing-remitting fever over several months, and severe meningo-encephalitic complications can ensue.[2,4,12,13] The precise incidence and distribution of TBRF in west Africa are unknown.[3,4,11] Reports of the disease are few and the distribution of the vector seems typically limited to the Sahel and Saharan regions;[11,14] however, findings of investigations done in Senegal indicate that TBRF is, after malaria, the most common cause of outpatient visits to a rural dispensary near Dakar. Furthermore, as a result of the ongoing drought in sub-Saharan countries (since 1970), the tick has now colonised the Sudan savanna.[4,11]

In 1990, as part of a malaria research programme, we enrolled a rural community of western-central Senegal in a continuous demographic and health surveillance survey.[15] The high incidence of TBRF that we noted has prompted us to investigate the long-term trends in the incidence of the disease at the community level and to undertake further epidemiological investigations across west Africa.

Methods

Participants

Between 1990 and 2003, we did a longitudinal study among the population of Dielmo, a village in the Sine-Saloum region of Senegal, which is an area of Sudan savannah, to assess the incidence of malaria, TBRF, and fever not associated with these diseases, and to describe the clinical manifestations of the diseases. Dielmo villagers are settled agricultural workers: millet and peanut crops are cultivated during the wet season; market gardening is the main agricultural activity during the dry season. Most of the houses are built in the traditional style with mud walls and thatched roofs. At the beginning of the study, we did a census for which we obtained, for each villager, details of genealogy and family ties, places of residence since birth, occupation, and other activities. We drew a detailed map of the village and of each compound, individually numbering all rooms in houses and other buildings, including granaries and shelters for animals. We recorded the use and characteristics—eg, material used for floor, walls, roof, and furnishings—of all buildings at the beginning of the project and updated the details in 2002.

We explained the study protocol and its objectives to assembled villagers and obtained individual informed oral consent from all participants or their parents at the beginning of the study and yearly thereafter. Every year, the project was assessed by the Conseil de Perfectionnement de l'Institut Pasteur de Dakar and by the population of the village. The Senegalese Ministry of Health approved the project.

Procedures

We did a medical examination of, and a series of biological tests for, every inhabitant, including basic haematology and thick blood film. Detection of individuals with fever was both passive and active. The dispensary created for

the project was open 24 h, 7 days a week. Every villager was visited daily at home for clinical monitoring. If a villager was absent, their place of stay was recorded. Thus, we knew the number of days in the village for each individual. We used this information to calculate the number of person-months or person-years included in the survey—ie, the denominators for the analysis of incidence rates. We prepared thick blood films and did detailed medical examinations of all individuals with recorded hyperthermia (defined by an axillary temperature >37·5°C) and of individuals who mentioned a history of fever or possibly fever-related symptoms (hot body feeling, vomiting, asthenia, headache) to staff at the dispensary or during home visits. At least once a year, we looked for the presence of borrelia in monthly series of thick blood films prepared from asymptomatic individuals for routine monitoring of malaria.

We provided all unwell individuals with symptomatic or specific treatment dependent on their diagnosis. We treated adults and children aged 8 years or older diagnosed with borreliosis with doxycycline (200 mg or 4 mg/kg daily over 10 days); we treated pregnant women and children aged younger than 8 years with erythromycin (2 g or 50 mg/kg daily over 10 days). We completed standardised cards for each episode of illness, recording physical findings, investigations done, treatment given, and response to treatment. We judged asthenia mild when it did not limit activity, moderate when it limited usual activity (play, school attendance, or agricultural work), and severe when it prevented a person from sitting for any length of time and confined them to bed.

We standardised all readings from thick blood films from patients and asymptomatic individuals. We examined 200 oil-immersion microscope fields on each slide, which corresponds to the examination of about 0·5 µL of blood (average number of leucocytes at the community level in blood films was 16 per oil-immersion field—ie, number of spirochaetes counted for about 3200 leucocytes). Since no instance of louse-borne relapsing fever has been reported in west Africa since the 1950s, we assumed that all episodes of fever accompanied by borrelia-positive thick blood films were cases of TBRF. We identified two or more instances of infection in a single person as distinct infections (rather than relapses of the same infection) if they were separated by a period of at least 6 months. For each new infection, we considered all positive blood films made during the first week as related to the initial fever episode; subsequent positive blood films indicated relapses (minimum time interval between two relapses was 1 week).

To document the presence of the vector tick *O sonrai* and to calculate its infection rate by *B crocidurae*, we investigated rodent burrows in Dielmo (two surveys, done in 1991 and 2002) and in 30 other villages of Senegal, Mauritania, and Mali (one survey, done between 2002 and 2005). Of these 30 villages, we selected 15 on the basis of their proximity to Dielmo—all were within 10 km of the village—and 15 along three transects north-to-south or west-to-east (figure 1). In Dielmo, we examined all burrows in compounds, noting on a map where they were situated in relation to places where people were sleeping and the characteristics of the implicated buildings. Elsewhere, we studied a sample of 30–60 burrows per village. We collected ticks by introducing a flexible tube into the burrows and sucking out their contents with a portable petrol-powered aspirator. We considered all specimens with morphological features of *O sonrai*, as described by Sautet and Witkowsky,[16] as belonging to this species. We tested ticks for borrelia by PCR amplification of the flagellin
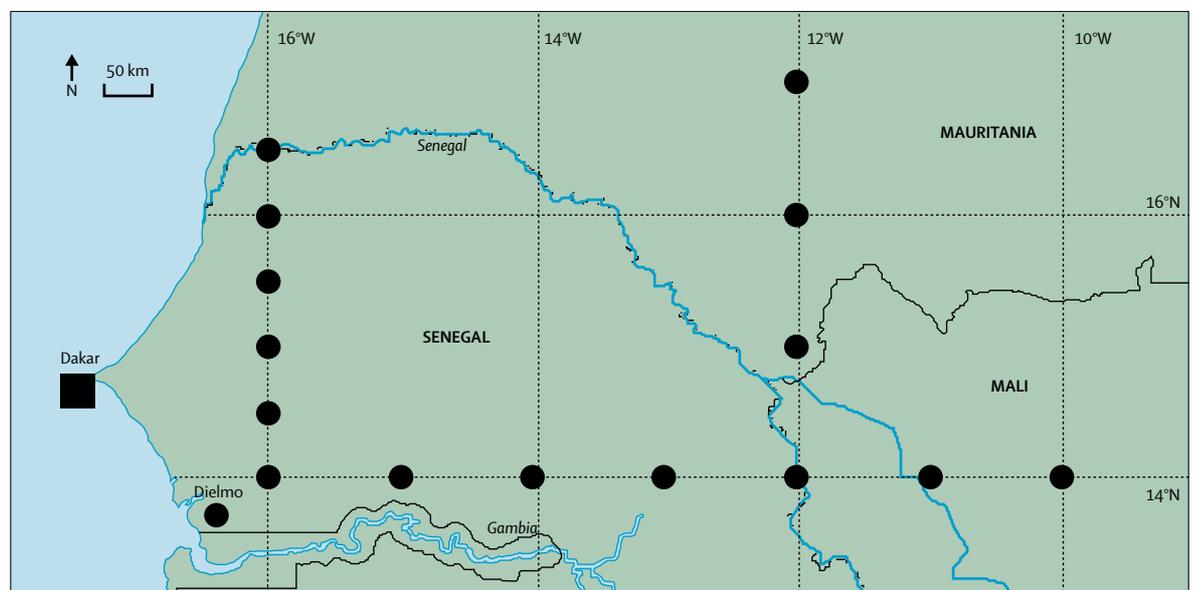

Figure 1: **Map of Senegal, Mali, and Mauritania, showing study areas (black circles)**

flaB gene, using primers and protocols previously designed for *Borrelia duttoni,* a species closely related to *B crocidurae.*[17,18] We sequenced the amplified products with an ABI PRISM 3730xl DNA analyser (Genome Express, Grenoble, France) to identify the *Borrelia* species through comparison with the previously published sequence of *B crocidurae* (GenBank accession number X75204)[19] and other *Borrelia* species.

To investigate the reservoir of *B crocidurae*, we captured rodents and insectivores living in Dielmo in 1991 and 2002. In every house of every compound, we set two latticework traps baited with peanut butter or onions on three successive afternoons and checked them the morning after. We anaesthetised the animals caught with chloroform and drew 1 mL of blood from each by cardiac puncture. We immediately prepared a thick blood film for detection of *B crocidurae*; we intraperitoneally inoculated two Swiss white mice with the remaining blood. We aseptically removed the brains of the caught animals and individually ground them in mortars and diluted them with 5 mL of physiological saline. We inoculated intraperitoneally two Swiss white mice with 0·3 mL of the suspension, as previously described.[20] 3, 6, and 10 days after inoculation with blood or cerebral tissue suspension, we prepared thick blood films from the mice to provide evidence for the presence of *B crocidurae*.

Statistical analysis

We tested the incidence of clinical episodes of TBRF, the frequency of clinical signs and symptoms, the densities of borrelia and the body temperatures with Poisson, logistic, and linear regression models, respectively. The interdependence of the observations made in the same individual was taken into account with a generalised estimating equation (GEE) approach,[21] using the statistical software package Stata (version 7.0). We used an interchangeable correlation structure, assuming the correlation between observations made on the same person at different times to be the same. The link functions for the Poisson, logistic, and linear regression models were the logarithm, logit, and identity functions, respectively. For the Poisson regression analysis, we chose the person-year under survey as the statistical unit, except for the analysis of the seasonality, for which the statistical unit was the person-month under survey. For the analysis of the effect of age on infection, we used a person's age at the beginning of the relevant period (year or month). Because the association between age and incidence of TBRF was not linear and could not be easily modelled, we investigated the effect of age as a dummy variable—ie, modelling age groups. We tested the effect of the location of the compounds in the village between four areas defined according to geographical and ecological characteristics—ie, distance from the river, isolation from rest of village, and position with respect to the main routes crossing the village. We
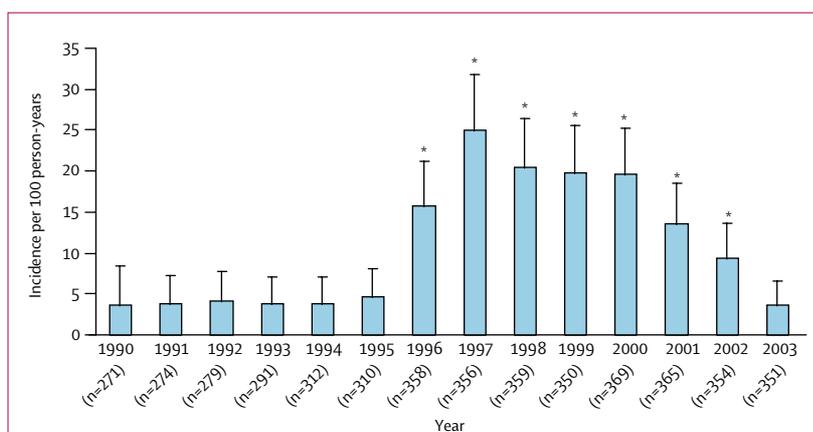

Figure 2: **Incidence (95% CI) of TBRF, 1990–2003**
*Significantly more cases of TBRF than in 1990 (p<0·05 with GEE model). Number of persons under survey ranged from minimum 271 in 1990 to maximum 369 in 2000.

tested the effects of sex, age, year, month, and condition of the compounds and their location individually as explanatory variables in GEE models with the Wald test. All the first-order interactions between significant variables were tested but none was significant. We investigated the individual effect with Poisson regression models with a person-specific random effect on the dataset aggregated by individual and year. We investigated the compound effect with Poisson regression models with a compound-specific random effect on the dataset aggregated by year, age group, and sex. The effect of the conditions in the compounds was assessed in 2002, considering the structure of floors and walls (mud *vs* cement), tidiness (tidy *vs* untidy, with respect to the number of items on the floor), and the presence of *O sonrai* in burrows for all bedrooms. For this analysis, we aggregated the dataset by bedroom, age group, and sex. Finally, we tested the compound effect, using a Poisson regression model, with a compound-specific random effect, whereas the significance of the fixed effects was tested with a GEE approach to ensure robust statistical inferences.

Results

In Dielmo, during 1 286 045 person-days of surveillance, we detected borrelia in 817 thick blood films, representing: 395 distinct TBRF infections, 206 relapses, and 216 treatment follow-up films. The TBRF cases occurred in 235 different individuals. The average number of people being studied at any one time was 328 (range 271–369), with 594 individuals monitored for between 1 week and 14 years.

The average incidence of TBRF infections over 14 years was 11 per 100 person-years, ranging from four per 100 person-years in 1990 to 25 per 100 person-years in 1997 (figure 2). We noted three distinct periods: from 1990 to 1995, the incidence of TBRF was stable and relatively low; from 1996 to 2002, there was an outbreak

	Person-years under survey	TBRF incidence			TBRF presentation					
		Number of cases	Incidence rate per 100 person-years (95% CI)	p*	Mean axillary temperature (0C)	Number of *Borrelia* per 200 fields	Hot body feeling n (%)	Vomiting n (%)	Headache n (%)	Asthenia n (%)
Age										
0–11 months	69·9	2	2·9 (0·3–10·3)	0·043	39·7	17·5	2 (2%)	2 (100%)	0	2 (100%)
12–23 months	137·4	7	5·1 (1·9–10·5)	0·037	39·2	21·7	6 (86%)	0	2 (29%)	6 (86%)
24–35 months	130·6	16	12·3 (7·5–20·6)	Reference	39·3	26·1	16 (100%)	2 (13%)	16 (100%)	11 (69%)
36–47 months	130·3	18	13·8 (8·2–21·8)	0·866	39·3	57·7	18 (100%)	4 (22%)	15 (83%)	16 (89%)
4–6 years	379·1	48	12·7 (9·3–16·8)	0·914	39·4	24·6	47 (97%)	7 (15%)	46 (96%)	35 (72%)
7–9 years	350·6	43	12·3 (8·9–16·5)	0·835	39·2	15·2	41 (95%)	8 (19%)	41 (95%)	30 (70%)
10–14 years	480·7	55	11·4 (8·6–14·9)	0·646	39·4	13·6	52 (95%)	7 (13%)	53 (97%)	48 (88%)
15–19 years	317·4	42	13·2 (9·5–17·9)	0·955	39·2	16·6	41 (98%)	7 (17%)	41 (97%)	34 (82%)
20–29 years	458·1	66	14·4 (11·2–18·5)	0·652	39·1	16·8	61 (92%)	10 (15%)	66 (100%)	58 (88%)
30–39 years	363·8	32	8·8 (6·1–12·6)	0·243	39·4	14·7	32 (100%)	5 (16%)	32 (100%)	30 (94%)
40–49 years	258·0	33	12·8 (8·8–18·0)	0·958	39·2	15·0	31 (94%)	7 (22%)	32 (97%)	30 (91%)
50–59 years	211·1	20	9·5 (5·8–14·6)	0·377	39·3	12·7	18 (90%)	2 (10%)	19 (95%)	16 (81%)
≥60 years	236·6	13	5·5 (2·9–9·4)	0·021	39·4	10·9	13 (100%)	0	9 (70%)	12 (92%)
Sex										
Female	1729·2	167	9·6 (8·2–11·2)	Reference	39·4	19·8	157 (94%)	25 (15%)	158 (95%)	135 (81%)
Male	1794·2	228	12·7 (11·1–14·6)	0·010	39·2	19·2	219 (96%)	38 (17%)	214 (94%)	193 (85%)

*Double-sided Wald test in Poisson regression analysis.

Table 1: Days of monitoring, incidence, and clinical presentation of TBRF, according to age and sex

of TBRF, with a rapid increase in incidence in 1996–97 and a slow decrease from 1998 to 2002; and, in 2003, incidence returned to a relatively low level. Infections with TBRF arose throughout the year, but were most common in March (dry season; incidence 1·4 per 100 person-months, p=0·037 compared with January) and least common in October (end of rainy season; 0·3 per 100 person-months, p=0·006 compared with January).

All age groups were affected by TBRF, with the lowest incidence noted among children aged 1 year or younger (table 1). Between age 2 and 59 years, incidence remained fairly constant, before dropping significantly at age 60 years and older. Men were affected significantly more often than women (table 1). The subject-specific effect was never significant in random-effect Poisson regression

models, indicating a negligible interdependence of the observations made in the same individual from one year to the next.

The number of distinct TBRF infections developed by a single individual over the study period ranged from one to six (n=131, 62, 32, 7, 2, and 1 individuals, respectively). The time interval between two distinct infections for a single patient ranged from 6 months to 10 years (6–11 months: n=43; 12–23 months: n=51; ≥24 months: n=66). Of the 121 TBRF cases followed by relapses before diagnosis and treatment, most presented one or two relapses (1 relapse: n=68; 2 relapses: n=33; 3 relapses: n=12; 4–6 relapses: n=8). No-one died during the study, but one of 16 infections that arose in pregnant women provoked early delivery.

The density of *Borrelia* in thick blood films was usually low, both for new infections and relapses; 75% of films contained less than 20 borrelia per 200 microscopic fields (figure 3). Furthermore, we identified 12 TBRF initial infections or relapses only after examination of 400–800 additional microscopic fields of negative thick-blood films made during episodes of fever, occurring within a 6-month period before and after a proven borrelia infection. The presence of borrelia in thick blood films was almost systematically associated with documented hyperthermia, which was above 38·7°C in more than 75% (n=615) of the cases (figure 4). Of 19 100 routine thick blood films made of samples taken from asymptomatic individuals over 14 years, all were negative for borrelia. Other than characteristic high fever, most patients presented with a headache (95% [n=375] of
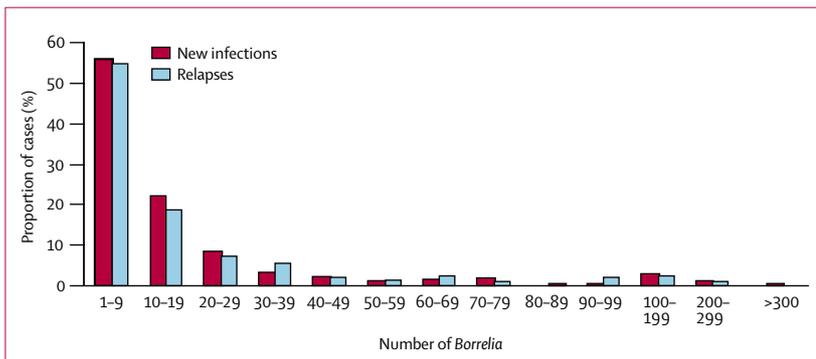

Figure 3: Number of *Borrelia* in thick blood films during TBRF episodes (200 oil-immersion fields, equivalent to 0·5 μL of blood)

new infections and 94% [n=194] of relapses) and middle-to-high asthenia (86% [n=340] and 78% [n=161]), and some with vomiting (18% [n=71] and 12% [n=25]). The clinical presentation and the density of borrelia in blood were not related to age or sex (table 1). Malaria parasites were present in 37% (n=301) of blood films with borrelia. Parasite density was low-to-moderate in most cases, and in only ten patients with fever (nine children and one adult) was the level of *Plasmodium falciparum* malaria parasitaemia sufficiently high[22] as to be a possible cause of the symptoms.

There were cases of TBRF in all the compounds of Dielmo that we monitored. Cases were not, however, randomly distributed in the village, and the average incidence of the disease for the study period ranged from 3 to 27 per 100 person-years, according to compound. Furthermore, the disease evolved differently over time in different compounds. The incidence in some compounds changed little over time, with generally few cases per year. In other compounds, we noted a major outbreak between 1996 and 2001, with a maximum incidence of 103 cases per 100 person-years. The compound-specific effect was significant (p<0·01) in random-effect Poisson regression models. Risk of TBRF was not associated with the location of the compounds in the village or their other investigated characteristics or with individual characteristics of inhabitants. The epidemiological survey in 2002 indicated that for all bedrooms with one or more burrows inhabited by *O sonrai* at least one villager developed TBRF during the corresponding year (incidence rate ratio 2·8 when compared with no burrows; 95% CI 1·1–7·2; p=0·03).

In 1991 and 2002, we examined 292 and 242 burrows, respectively, in Dielmo for the presence of the vector. We found *O sonrai* in 7% (n=20) and 8% (n=20) of the burrows. PCR amplification of the *flaB* gene isolated from 156 ticks collected in 2002 indicated than 75% (n=15) of the burrows with *O sonrai* contained at least
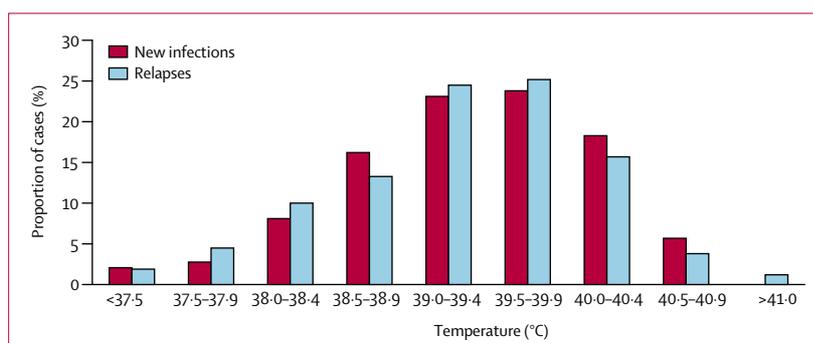

Figure 4: Maximum body temperatures recorded during episodes of TBRF

one infected tick. The average proportion of ticks infected by *B crocidurae* was 66%. Sequencing of amplified fragments of *flaB* (GenBank accession number DQ234749) did not reveal any genetic divergence; all were similar to each other and to the previously published *B crocidurae* sequence (only two nucleotides differed). Of 313 small mammals captured in 1991 and 2002 in Dielmo's houses, six species of rodents and one species of insectivore were represented. Five species were infected, and the average prevalence of *B crocidurae* was 12% (table 2).

O sonrai was also present in rodent burrows in 13 of 15 (87%) villages around Dielmo. Of 742 burrows investigated, 123 (17%) were inhabited by the vector. When present, the prevalence of *O sonrai* in burrows ranged from 2% to 58%, according to village (2–4%: 5 villages; 5–9%: 1 village; 10–29%: 3 villages; ≥30%: 4 villages). Of 146 ticks from 13 villages tested for *Borrelia*, 30 (21%) were infected.

Transect studies in the 15 villages of Senegal and adjacent areas of Mauritania and Mali along the 14th parallel and the 12th and 16th meridians indicated the presence of *O sonrai* in all villages except two. Of 540 burrows investigated, 169 (31%) were inhabited by the

	Species	Captured	Examined	Infection			
				Direct blood film	Blood inoculation	Brain inoculation	Any infection
1991	*Mastomys erythroleucus*	224	206	1/206	6/188	10/171	13 (6%)
	Arvicanthis niloticus	17	17	1/17	1/17	2/8	3 (18%)
	Rattus rattus	1	1	0/1	0/1	0/1	0
	Crocidura olivieri	1	1	0/1	0/1	..	0
	Crycetomys gambianus	5	5	0/5	0/4	0/3	0
2002	*Mastomys erythroleucus*	32	26	0/21	1/23	6/26	6 (23%)
	Arvicanthis niloticus	5	5	0/5	0/5	0/5	0
	Rattus rattus	3	2	0/1	0/1	2/2	2 (100%)
	Crocidura olivieri	13	11	0/9	1/9	8/11	8 (73%)
	Myomys daltoni	2	2	0/1	0/1	0/2	0
	Crycetomys gambianus	2	1	0/1	0/1	0/1	0
	Mus musculus	8	2	0/1	0/1	1/2	1 (50%)
Total	..	313	279	2/269	9/252	29/232	33 (12%)

Table 2: Prevalence of *Borrelia* infections in small mammals, by year

vector. When present, the prevalence of *O sonrai* in burrows ranged from 11% to 90%, according to village (11–29%: 5 villages; ≥30%: 8 villages). Of 406 ticks tested for *Borrelia*, 87 (21%) were infected.

Discussion

TBRF was a major cause of disease in our study population. Such high levels of incidence at the community level are exceptional for any infectious disease and are only comparable to those previously reported for *P falciparum* malaria or influenza.[23–25] We drew blood for most thick blood films from patients during peaks of fever, thus limiting the risk of underdiagnosis. The true incidence of TBRF might nevertheless have been even higher than reported because of the frequent low density of *B crocidurae* infections. A high proportion of individuals developed two or more distinct TBRF infections over 14 years and the incidence and severity of disease were not age-dependent, indicating that there was little or no acquired immunity. Antigenic variation and erythrocyte rosetting are the two main mechanisms that prevent efficient immune responses to *B crocidurae* infections.[26–28] TBRF in west Africa is probably less severe than the same disease in east Africa because of the organism involved; TBRF caused by *B duttoni* and louse-borne relapsing fever due to *B recurrentis* have high fatality rates.[2,3,29,30]

The incidence of TBRF increased greatly between 1996 and 2002. There was no change in surveillance or attendance of the study population, nor in methods used to stain or read blood films, and the incidence of malaria remained stable both in children and adults. During this period, the incidence of TBRF reached similar levels to those reported for *P falciparum* clinical malaria in adults.[24,31] There was no evidence of louse-borne relapsing fever caused by *B recurrentis* occurring in the study population or in the area. TBRF incidence peaked a few months after the high rains of 1995,[32] which might have affected the population dynamics of small mammals.[33]

The soft tick *O sonrai* is the only known vector of TBRF in west Africa.[3,11] The limited data that are available about its distribution suggest that the vector is present in the Sahara, Sahel, and Sudan savannah areas of Africa, where average yearly rainfall is less than 750 mm.[3,11,14] The frequent presence of *O sonrai* in burrows opening inside bedrooms or compounds and the high proportion of ticks infected by *B crocidurae* explain the frequent transmission of TBRF in homes, as suggested by the rapid increase in incidence of the disease during infancy and early childhood.

Many of the 30 villages that we studied in Senegal, Mali, and Mauritania were colonised by *O sonrai*, most to a greater extent than noted in Dielmo, where we monitored the incidence of TBRF. A high proportion of the ticks were infected by *B crocidurae,* suggesting that there is a high incidence of TBRF in rural populations in this part of west Africa. Laboratory tests are rarely used for the diagnosis of fever episodes in tropical Africa. *B crocidurae* is detectable in thick blood films only during fever, its density is usually very low, and its diagnosis necessitates trained microscopists. Furthermore, coinfections with malaria—which has similar presenting symptoms—are common, since up to 90% of children and 40% of adults are estimated to have latent disease.[15,34] TBRF is underdiagnosed in Africa. Treatment is cheap and available in most dispensaries, but medical personnel are generally not aware of the disease, which is often confused with drug resistant malaria. There is a need for much more training. Prevention of TBRF by filling burrows or using insecticides might be difficult to sustain on a large scale and needs more research.

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