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Newly transmitted *Plasmodium falciparum* malaria in the central highland plateaux of Madagascar: assessment of clinical impact in a rural community

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Plasmodium falciparum *has recently reappeared in the central highland plateaux of Madagascar. To define its role in the overall malaria pathology occurring during the rainy season, we conducted a clinical and parasitological study among the 2776 consultants of a malaria field health centre which we established in the middle of the transmission area. From January to June 1988 the overall parasite rate was 63.2% and did not vary with age; the overall splenic rate was 46.9%, decreasing in individuals over 15 years of age. After the beginning of the main transmission season, an increase in parasite rates and parasite densities was observed, while febrile illnesses associated with malaria parasitaemia decreased. During the second part of the rainy season the parasite densities started to decrease, while parasite rates and malaria-associated fevers remained at the same level. The frequency of fevers was not related to the malaria parasite density owing to individual and seasonal variations.*

Malaria due to *Plasmodium falciparum* has recently reappeared in the central highland plateaux of Madagascar (*1*) and, according to some reports, caused very high morbidity and mortality among the rural inhabitants of this area. Very little is known concerning the epidemiology and morbidity associated with this disease, but control measures are urgently needed. Epidemiological data on the disease and its effects in the population are essential prior to developing control strategy guidelines. We report here the results of a study on the role of *P. falciparum* malaria in the centre of the transmission area.

Subjects and methods

Study area

The study was conducted in Manarintsoa, a village at 1200 m altitude with about 1550 inhabitants, in the central highland plateaux, 20 km west of Antananarivo, the capital city. The characteristic tropical mountain climate has a dry cold season (June to November) and a hot rainy season. Intensive antivectorial control activities and mass drug administration conducted in the fifties led to the disappearance of *Anopheles funestus* in 1954. Since 1960, malaria eradication was obtained in nearly the whole plateaux area except for two small foci where seasonal transmission persisted at a reduced rate (*2*). In the mid-seventies, *A. funestus* reappeared. In early 1987, an unusual increase in the mortality of the population of Manarintsoa revealed the epidemic reappearance of falciparum malaria in the plateaux area (*1*). Since then, malaria seems to be highly endemic (*P. falciparum* being by far the most encountered species) and transmitted by both *A. funestus* and *A. gambiae* s.l. (*3*).

Subjects investigated

In March 1987, we established in Manarintsoa a field health centre (the only one within an 8 km range) where the population has free access to medical advice and drugs. From January to June 1988, all invididuals presenting at this health centre were examined clinically, the axillary temperature was measured with an electronic thermometer, spleen size was recorded, and blood was collected by fingerprick for thick and thin blood smear examinations. Blood smears were Giemsa-stained and malaria parasites were looked for by examination of 1000 leukocytes.

To assess the mortality related to malaria we

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reviewed all the deaths in Manarintsoa since the reappearance of malaria. A similar survey was conducted in Ambohimandry, a village located in the same area with 14 000 inhabitants, where the conditions of malaria transmission are supposed to be similar, but without any intervention measures.

Results

A total of 2776 patients were examined, 53.1% males and 46.9% females. The mean age of the population was 18.8 years with the following age distribution: <2 years (167), 2–9 years (725) 10–14 years (445), 15–19 years (362), 20–29 years (480), 30–39 years (344), and ⩾40 years (253). As no other health centre was available within an 8 km range, and as the consultations and treatment were free, most (66.2%) of the inhabitants of Manarintsoa presented at least once during the 6-month period of the study. Each month we examined an average of 22% of the total population of Manarintsoa. In addition, a few patients came from the neighbouring villages.

Prevalence and density of parasites

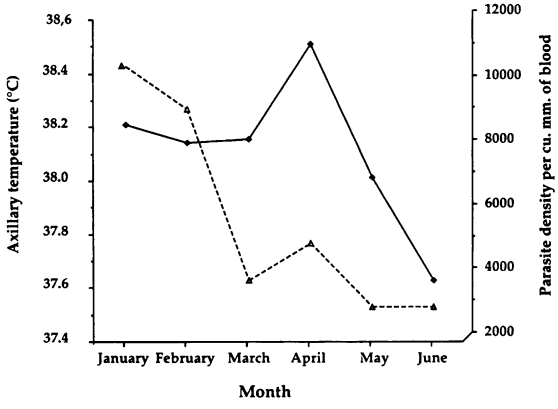
In all, 1754 (63.2%) individuals presented with *P. falciparum* parasitaemia and the parasite rate was similar among the various age groups (Table 1). The three other human *Plasmodium* species were observed at a much lower rate: *P. vivax* in 369 (13.3%) blood slides (associated with *P. falciparum* in 107 cases); *P. ovale* in 28 (1%) blood slides (associated with *P. falciparum* in 6 cases); and *P. malariae* in 3 (0.11%).

Prevalence of *P. falciparum* parasitaemia varied during the follow-up period (χ^2 test, $P < 10^{-6}$), increasing from 44.6% in January to a peak of 75.2% in April (χ^2 test for trend, $P < 10^{-6}$), then decreasing to 51.5% in June (χ^2 test for trend, $P < 10^{-6}$) (Table 2). The geometric mean parasite densities followed a similar pattern as the parasite rates with an initial value of 8682 parasites per μl, a peak value of 11 193 per μl in April, and decreasing by June to 3810 parasites per μl (Fig. 1).

Clinical findings and parasitological status

A total of 1299 (46.8%) patients exhibited spleen enlargment. Splenic rate varied with age (χ^2 test, $P < 10^{-6}$). It was above 65% in all groups under 15 years, and gradually decreased to 3.9% in subjects older than 40 years (χ^2 test for trend, $P < 10^{-6}$) (Table 1). Splenic rates were consistently higher in individuals infected with *P. falciparum* than in those who were not, but followed a similar evolution during the 6-month period of the study (χ^2 test, $P < 10^{-6}$) (Table 2). It gradually increased from 27.1% in January to 55.9%

Fig. 1. **Evolution, by month, of geometric mean parasite density (– – –) and mean axillary temperature (——) in *Plasmodium falciparum*-infected individuals seen in the Manarintsoa health centre.**



in May (χ^2 test for trend, $P < 10^{-6}$), then remained at this value (χ^2 test, NS).

A total of 1297 (46.8%) subjects seen at the health centre were febrile (axillary temperature ⩾37.5°C). The mean axillary temperature varied monthly from 37.4 °C to 38.0 °C, with an average value of 37.6 °C. When the population was split according to the parasitological status of the subjects, the mean axillary temperature of individuals presenting with *P. falciparum* decreased monthly from 38.4 °C in January to 37.6 °C in March, then remained constant (Fig. 1). The percentage of febrile subjects followed similar variations (χ^2 for trend, $P < 10^{-6}$) with an initial decrease from 70.8% in January to 42.5% in March (χ^2 test for trend, $P < 10^{-6}$) stabilizing thereafter (χ^2 test for trend, NS) (Table 2). In individuals not infected with *P. falciparum* the mean axillary temperature and percentage of febrile subjects did not follow a similar temporal evolution but remained constant with an average value of 37.3 °C and 37.7%, respectively, for the whole follow-up period (one way ANOVA and χ^2 test, NS) (Fig. 1).

Malaria-related mortality

Our investigations showed that 37 of the 1550 inhabitants of Manarintsoa died during the 2 months before our arrival in March 1987. This represents a 11.9‰ monthly mortality rate. From March to December 1987, one of us was present (on average, once or twice a week) and treated all fevers suspected to be due to malaria with antimalarial drugs. Monthly mortality rates were 4.5‰ in March–July 1987 (malaria transmission season) and 1.55‰ in

Table 1: **Clinical and parasitological findings in individuals seen in the Manarintsoa health centre, January–June 1988, by age**

Age (years)	No. of subjects	No. with splenomegaly	No. with *P. falciparum* parasitaemia	No. of fevers in *P. falciparum*-infected subjects
0–2	167	108 (64.7)[a]	87 (52.1)	65 (74.7)
2–9	725	560 (77.2)	474 (65.4)	263 (55.6)
10–14	445	313 (70.3)	284 (63.8)	156 (54.9)
15–19	362	143 (39.5)	249 (68.8)	125 (50.2)
20–29	480	86 (17.9)	305 (63.5)	160 (52.5)
30–39	344	80 (23.3)	226 (65.7)	105 (46.5)
⩾ 40	253	9 (3.6)	129 (51.0)	38 (29.5)
Total	2776	1299 (46.8)	1754 (63.2)	912 (52.0)

[a] Figures in parentheses are percentages.

Table 2: **Clinical and parasitological findings in individuals seen in the Manarintsoa health centre January–June 1988, by month**

Month	No. of subjects	No. with splenomegaly	No. with *P. falciparum* parasitaemia	No. of fevers in *P. falciparum*-infected subjects
January	269	73 (27.1)[a]	120 (44.6)	85 (70.8)
February	402	170 (42.3)	244 (60.7)	167 (68.4)
March	624	285 (45.7)	402 (64.4)	171 (42.5)
April	636	315 (49.5)	478 (75.2)	266 (55.6)
May	472	264 (55.9)	318 (67.4)	137 (43.1)
June	373	192 (51.5)	192 (51.5)	86 (44.8)
Total	2776	1299 (46.8)	1754 (63.2)	912 (52.0)

[a] Figures in parentheses are percentages.

August–December (when malaria is supposed to be not transmitted).

Since January 1988, the physician remained in the village on a permanent basis. The monthly mortality rate was 1.1‰ from January to June 1988, and no deaths were suspected to be due to malaria. By comparison, during the same semester of 1988, the average monthly mortality rate was 3.7‰ in Ambohimandry, the control village with no medical interventions.

Discussion

Malaria transmission

In this study, we investigated the importance of malaria in an area where *P. falciparum* malaria reappeared only recently after an absence of some years. This reappearance was detected one year before we initiated our study. Nevertheless, our results indicate that the level of endemicity was already high. Among individuals presenting to our health centre, *P. falciparum* parasite rates were consistently greater than 44% during the 6-month follow-up period. Splenic rates were consistently higher than 60% in the 2–9-year-old children. These results are in agreement with our previous findings where bi-monthly malaria surveys, conducted in the same area from October 1987 to March 1988 and in October 1988, demonstrated both parasite and splenic rates remaining consistently higher than 55% in 5–15-year-old healthy schoolchildren (*1*). (J.P. Lepers, unpublished results). These data allow us to consider this area of the highland plateaux of Madagascar, where schistosomiasis is absent, as hyperendemic for malaria.

The lack of age-related variations in *P. falciparum* prevalence (Table 1) is a peculiar feature of this area which is probably a consequence of the new malaria transmission. Adults, like young children, did not have the time to develop protective immunity. In this context, the inverse relationship between frequency of spleen enlargement and age may be related to the persistence of some degree of immune memory in adults who lived in a malaria transmission area when they were young. Alternatively, in older individuals, spleen tissues may be mechanically less susceptible to enlargement.

Clinical impact of malaria

This study was initiated after the first rains, a few weeks before the peak of malaria transmission (D. Fontenille, personal communication). During the first part of the follow-up, from January to April, monthly parasite rates and splenic rates gradually increased. Such augmentation was also observed for the geometric mean parasite densities (GMPDs) in *P. falciparum*-infected individuals, while their mean axillary temperatures and fever rates were decreasing. During the second part of the study, from April to June, both parasite and splenic rates remained stable in the population, as well as fever rates and mean temperatures in *P. falciparum*-infected individuals. Moreover, GMPDs decreased. During the whole follow-up period, monthly mean temperatures and percentages of fevers did not vary in individuals non-infected with *P. falciparum*, indicating that the observed variations were probably related to falciparum malaria. Thus, the clinical impact of *P. falciparum* malaria varied during the season of malaria transmission. Although endemicity remained high during the whole period of the study (as demonstrated by the persistence of elevated parasite rates) we observed a decrease in the clinical symptoms associated with malaria, followed two months later by a decrease in parasite densities. Such variations could be explained partly by an increase in uncontrolled antimalarial drug consumption by the population. However, we do not have any indication for such an increase in drug consumption. The other hypothesis suggests that, after a few months of malaria transmission, individuals developed mechanisms effective in partially controlling the disease-associated pathology. This fact is of particular interest as *P. falciparum* malaria was reintroduced very recently in Manarintsoa (*1*).

The importance of malaria as a cause of death in the plateaux area is difficult to evaluate. During the six months of our survey, no death appeared to be due to malaria among the inhabitants of Manarantsoa, but all individuals had free access to the medical centre, where clinical malaria attacks received prompt curative treatment. Under these circumstances, the mortality rate was similar to that during the dry and cold season, when malaria is not transmitted. In the control village, this mortality rate was more than three times greater than in Manarantsoa. If we consider that the difference is due only to malaria, then the malaria-related mortality rate can be estimated as 2.6‰ per month during the transmission season or 18.2‰ per year.

Assessing the importance of malaria as a cause of morbidity in a rural community where malaria is endemic is very difficult. A high proportion of healthy individuals present with a positive blood smear, and many febrile subjects will be infected with *P. falciparum* regardless of whether malaria is the cause of their illness or not. Various authors have suggested that this difference could be identified more easily by assessing the blood parasite density. We arbitrarily chose an axillary temperature of 37.5 °C to define important clinical episodes associated with malaria, as this value had been shown to be a useful threshold by various authors (*4*).[a] Among *P. falciparum*-infected patients, 52% were febrile; this proportion was lower (37.7%) in the other individuals (χ^2 test, $P < 10^{-6}$). The axillary temperature of individuals did not vary with their parasite count except for highly elevated axillary temperatures (> 39.5 °C) or high blood parasite densities (> 50 000 per μl) (Table 3). This relation was observed in the various age groups. Conversely, when malaria-infected subjects were classified according to their parasite density, a progressive increase in fever rates with the level of parasitaemia (χ^2 test for trend, $P < 10^{-6}$) was observed (Fig. 2). Such an association between temperature and malaria parasitaemia has already been reported (*4*, *5*); however, one third of non-infected individuals were febrile, and only half of the subjects with a *P. falciparum* parasite density as high as 10 000 to 20 000 per μl of blood were presenting with a febrile illness; even patients with higher parasite densities were not all febrile. A similar observation was reported in Nigeria (*5*), and suggests an individual susceptibility to the pyrogenic stimulus of the malaria infection. This relationship between fever and parasite density varied also during the course of the transmission season, since in January 70.8% of all *P. falciparum*-infected individuals were febrile whatever their blood parasite density, and even parasitaemias lower than 500 per μl were associated with fever in more than 60% of occasions. In various endemic areas, it has been proposed to determine a pyrogenic threshold of parasitaemia, above which fever and clinical symptoms are likely to be a consequence of the *P. falciparum* infection. Trape et al. (*6*) found that a parasite count of 5000 per μl in sick children from the Congo allowed one to separate those in whom malaria was probably the cause of their illness from other children. Similarly, Baudon et al. (*7*) defined the parasitological threshold for fever as 10 000 parasites per μl in a rural savannah area of Burkina Faso. In the central highland plateaux of Madagascar, such a threshold appears to be of poor predictive value because of individual and seasonal variability.

[a] **Delfini, L.F.** *The relationship between body temperature and malaria parasitaemia in rural forest of Western Nigeria.* Unpublished document WHO/MAL/64.654 (1964).

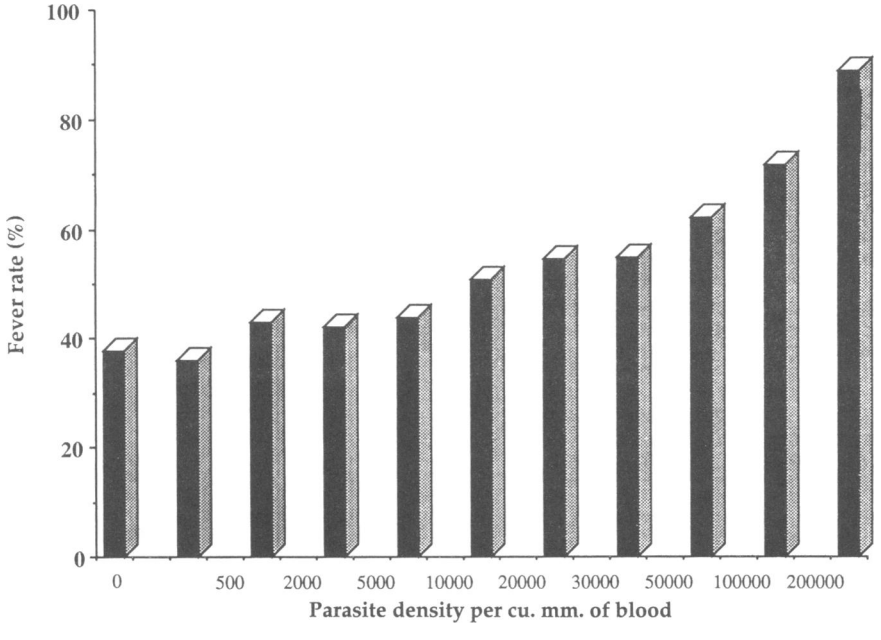
Table 3: **Parasite density of individuals seen in the Manarintsoa health-centre January–June 1988, by age group and by temperature group**

Age group	Parasite density[a]	Axillary temperature (°C)				
		≤37	37.1–37.5	37.6–38.5	38.6–39.5	>39.5
0–4 years	0	46.5[b]	50.0	46.8	37.0	28.0
	≤500	11.8	8.8	8.3	5.0	2.0
	501–5000	12.5	10.3	15.6	7.0	6.0
	5001–50 000	20.8	25.0	12.8	22.0	16.0
	>50 000	8.3	5.9	16.5	29.0	48.0
5–15 years	0	37.3	49.2	35.4	27.8	34.2
	≤500	11.7	6.2	7.6	6.7	2.6
	501–5000	17.3	15.4	16.2	13.9	10.5
	5001–50 000	29.0	23.8	27.3	33.9	30.3
	>50 000	4.7	5.4	13.6	17.8	22.4
>15 years	0	42.4	54.5	31.3	25.0	23.0
	≤500	10.5	11.0	10.9	6.3	3.4
	501–5000	14.5	10.5	16.6	18.1	12.6
	5001–50 000	26.5	17.8	34.3	38.9	32.2
	>50 000	6.2	6.3	6.8	11.8	28.7

[a] Number of asexual *P. falciparum* parasites per μl of blood.
[b] Percentage of individuals in a temperature group presenting with a given parasite density.

In the central highland plateaux of Madagascar, malaria is seasonally transmitted. After the beginning of the main transmission season, an increase in parasite rates and parasite densities was observed, while febrile illnesses associated with malaria were decreasing. During the second part of the rainy season parasite densities started to decrease, while parasite rates and fevers associated with malaria remained at the same level. This suggests that the clinical impact of malaria occurred mainly during the former part of the transmission season, although the parasite and splenic rates had not reached their maximum value. Thus, intervention measures aiming at a decrease in malaria-associated morbidity should

Fig. 2. **The relationship between *Plasmodium falciparum* blood parasite density and episodes of fever (axillary temperature ≥37.5 °C) in individuals seen in the Manarintsoa health centre.**



mainly be conducted in the beginning of the rainy season. Control campaigns (insecticidal house-spraying and mass drug administration) were started in the whole plateaux area in the early part of 1989 and we are following the evolution of malaria endemy.

Acknowledgements

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Résumé

Réapparition du paludisme à *Plasmodium falciparum* dans les hauts plateaux du centre de Madagascar: estimation de son impact clinique dans une communauté rurale.

Le paludisme à *Plasmodium falciparum*, qui avait disparu depuis plus de 20 ans de la région des hauts plateaux centraux de Madagascar, y a récemment été réintroduit. Afin de préciser les répercussions du paludisme dans la population, nous avons étudié le rôle de *P. falciparum* dans la pathologie des consultants d'un dispensaire que nous avions installé à Mianarintsoa, au centre de la région de transmission. Durant la deuxième saison de transmission, de janvier à juin 1988, tous les individus se présentant à ce dispensaire ont fait l'objet d'un examen clinique et d'un prélèvement sanguin pour confection d'une goutte épaisse. Au total, 2776 sujets ont été étudiés dont 1754 (63,2%) étaient parasités par *P. falciparum*; la proportion de sujets parasités ne variait pas avec l'âge mais avec la saison: la prévalence est passée de 44,6% en janvier à 75,2% en avril, puis est redescendue à 51,5% en juin. Les densités parasitaires moyennes ont suivi des variations identiques. Mille deux cent quatre vingt dix neuf sujets (46,8%) étaient porteurs d'une splénomégalie; l'indice splénique restait en plateau à 65% jusqu'à 15 ans, puis diminuait progressivement jusqu'à 3,9% chez les individus de plus de 40 ans. Cet indice est passé de 27,1% en janvier à 55,9% en mai, puis est resté constant. Il était plus élevé chez les individus présentant une infestation à *P. falciparum* que chez les autres, mais suivait les mêmes variations dans le temps. Au total, 1297 (46,8%) consultants du dispensaire étaient fébriles. Parmi les sujets infestés par *P. falciparum* la proportion de sujets fébriles est passée de 70,8% en janvier à 42,5% en mars et leur température axillaire moyenne de 38,4 °C à 37,6 °C pendant la même période; ces deux variables sont ensuite restées constantes. Chez les individus ayant une goutte épaisse négative, la proportion de sujets fébriles et la température moyenne sont restées constamment autour de 37,7% et de 37,3 °C respectivement. L'impact clinique du paludisme à *P. falciparum* varie donc au cours de la saison de transmission. Bien que le niveau d'endémicité reste élevé (pendant toute la durée de cette saison, la fréquence des fièvres associées au paludisme a diminué rapidement, suivie 2 mois plus tard d'une diminution des densités parasitaires. Le taux de mortalité par paludisme a également été évalué en examinant les registres de mortalité de Mianarintsoa et d'endroits situés en dehors de notre zone d'intervention. Ce taux a été estimé à 2,6‰ par mois au cours de la saison de transmission, et à 18,2‰ par an. L'expression clinique du paludisme, qui s'observe surtout au début de la saison de transmission de la maladie (alors que les indices parasitaires et spléniques n'ont pas encore atteint leurs valeurs maximales) est un élément important dont il faut tenir compte lors de l'élaboration de stratégies d'intervention visant à diminuer la morbidité liée au paludisme à *P. falciparum* sur les hauts plateaux de Madagascar.

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