Treatment uptake by individuals infected with *Plasmodium falciparum* in rural Gambia, West Africa

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**Objective** To find out what proportion of *Plasmodium falciparum* infections are treated in rural Gambia.

**Methods** Subjects from four villages in the Gambia were followed over nine months through visits to village health workers. Monthly cross-sectional malaria surveys measured the prevalence of *P. falciparum* infection. Linked databases were searched for treatment requests. Treated cases were individuals with parasitaemia who requested treatment during narrow or extended periods (14 or 28 days, respectively) before or after a positive blood film was obtained.

**Findings** Parasite prevalence peaked in November 1998, when 399/653 (61%) individuals had parasitaemia. Parasite prevalence was highest throughout the study in children aged 5–10 years. Although access to treatment was better than in most of sub-Saharan Africa, only 20% of infected individuals sought medical treatment up to 14 days before or after a positive blood film. Within two months of a positive blood film, 199/726 (27%) individuals with parasitaemia requested treatment. Despite easy access to health care, less than half (42%) of those with parasite densities consistent with malaria attacks (>5000/μl) requested treatment. High parasite density and infection during October–November were associated with more frequent treatment requests. Self-treatment was infrequent in study villages: in 3/120 (2.5%) households antimalarial drugs had been used in the preceding malaria season.

**Conclusion** Many *P. falciparum* infections may be untreated because of their subclinical nature. Intermittent presumptive treatment may reduce morbidity and mortality. It is likely that not all untreated infections were asymptomatic. Qualitative research should explore barriers to treatment uptake, to allow educational interventions to be planned.

**Keywords** Malaria, *Falciparum* /drug therapy /diagnosis; *Plasmodium falciparum* /pathogenicity; Parasitemia /epidemiology; Antimalarials /therapeutic use; Patient acceptance of health care; Self medication; Households; Rural population; Cross-sectional studies; Gambia (source: MeSH, NLM).

**Mots clés** Paludisme /plasmodium falciparum/chimiothérapie /diagnostic; *Plasmodium falciparum* /pathogénérité; Parasitémie /épidémiologie; Antipaludique /usage thérapeutique; Acceptation des soins; Auto-médication; Ménages; Population rurale; Etude section efficace; Gambie (source: MeSH, INSERM).

**Palabras clave** Paludismo falciparum/quimioterapia/diagnóstico; *Plasmodium falciparum* /patogenicidad; Parasitemia /epidemiología; Antimaláricos /uso terapéutico; Aceptación de la atención de salud; Automedicación; Hogares; Población rural; Estudios transversales; Gambie (fuente: DeCS, BIREME).


Introduction

*Plasmodium falciparum* infections are responsible for more than 200 million episodes of clinical malaria, which result in at least one million deaths per year (1). Since early effective treatment of malaria can reduce morbidity and mortality, case management at primary health centres is a main component of current malaria control strategies (2). The antimalarial drugs used most widely for case management in sub-Saharan Africa, chloroquine and pyrimethamine plus sulfadoxine (Fansidar), have little effect on gametocytes. Gametocytes, the sexual form of *P. falciparum*, do not cause symptoms, but they do infect mosquitoes during the blood meal and are thus essential for the completion of the life cycle of the parasite. It has been suggested that the introduction and widespread use of antimalarial drugs that have a suppressive effect on gametocytes, such as artemisinin derivatives, can decrease transmission of malaria.

In northern Thailand, artemisinin derivatives were introduced to improve case management of malaria strains resistant to multiple drugs. After widespread use of the...
artemisinin derivatives, malaria incidence decreased significantly (3). Artemisinin derivatives are cheap, safe and highly effective against sexual and asexual parasites and, therefore, are an attractive option for malaria control (4). The effect of case management on malaria transmission, however, also depends on the proportion of infections treated. In Thailand, a country with low malaria transmission, most infections are asymptomatic, treatment uptake is high and most infections are treated (5). In sub-Saharan Africa, malaria transmission is much higher, more individuals are exposed to P. falciparum infections, more infections are asymptomatic and the proportion of P. falciparum infections that are treated is usually unknown.

To have an effect on transmission, the prevalence of gametocytes has to be reduced below a critical threshold. Case management represents an attractive way to distribute drugs because of the pre-existing, widely accepted infrastructure, but it can only reduce malaria transmission if a high proportion of P. falciparum-infected individuals seek treatment. As part of a programme to investigate the potential of drug treatment to reduce malaria transmission, we carried out a study to quantify the proportion of P. falciparum infections likely to be treated under optimal circumstances in a rural Gambian community.

Methods
Setting
The Gambia has a population of about 1.4 million, and more than half live in rural settings. Four villages were chosen by the district health team as being representative of the socio-economic status and ethnic composition of rural Gambia. The study villages were within a 50 km radius of Farafenni — the administrative centre of the district. Yallal is 11 km to the west of Farafenni, where the nearest health centre and pharmacies are found. Villagers from the other three villages — Kumbija, Kani Kunda and Bambali — have to travel 15–25 km to the nearest health centre and dispensary in Ngeyen Sanjal. Before the start of the study, the census of each village was updated, and every villager was assigned a unique census number. The study villages were on the north bank of the river Gambia, 170 km east of the Atlantic coast. The climate in the chosen study area was characterised by seasonal rainfall between August and October. Agriculture is the only source of income for most villagers.

Treatment of malaria in study villages
All four villages have a primary health care worker whose responsibilities include the treatment of cases of malaria. During the study, drugs were offered free of charge to all individuals seeking treatment from the village health worker. For the study period, field workers helped the village health workers to diagnose and treat cases of malaria. Before they were posted to study villages, fieldworkers were trained to use a rapid parasite-detection test and to recognize and treat uncomplicated malaria. After fieldworkers were assigned a post, they stayed in that village for at least six days a week.

Every individual who presented with a history of fever was tested for P. falciparum infection using a rapid diagnostic test (ICT Malaria Pf; ICT Diagnostics, Sydney, Australia), and a blood film was obtained. Individuals who tested positive for P. falciparum infection using the rapid diagnostic test were treated immediately with a three-day course of chloroquine, in accordance with the Gambian government’s guidelines. The first dose was given under direct supervision. Individuals who presented without evidence of malaria and those who did not improve when taking chloroquine were referred to a health centre. Each requested treatment was entered into a computerized database, and the individual was identified by his or her census number.

Estimating parasite prevalence
In order to determine the proportion of parasite infections that led to a request for treatment, 150 residents in each of the four villages were selected using computer-generated random numbers. Between September 1998 and May 1999, these individuals were asked to provide a thick blood film once a month. Fieldworkers tried to obtain repeat samples from the same individuals. Participants who were absent or refused to give a blood sample were replaced with those of a similar age from the same compound. The results of the blood films were explained to the participants during the next visit. Free treatment was offered at that time, if it had not been given previously. The blood film results were entered in data files, in which each individual was identified by his or her census number.

Estimating home treatment
In each village, 30 randomly selected household heads were asked at the end of the malaria season whether they had purchased any medication during the preceding season and whether they kept any medication in the house. If the answer was yes, the drug names were recorded. In addition, all shopkeepers in the four villages were asked which antimalarial drugs they had in store at the time of the visit or had stocked during the preceding malaria season.

Laboratory methods
Thick blood films were left to dry for a minimum of 24 hours and were stained with Giemsa stain. The slides were stored and read during the next month. One experienced microscopist read 50 high power fields on a thick film. All categorization of individuals as infected or uninfected was based on blood film results. Parasite density was estimated on the assumption that one parasite per high power field equals 500 parasites per microlitre (6).

Analysis
For estimates of monthly parasite prevalence, we considered any individual with P. falciparum parasites at any density as infected. For each infected individual, the database was searched for a treatment request based on their unique census number. Once a treatment request by an infected individual was detected, the number of days between the date on which the positive blood film was obtained and that on which treatment was requested was calculated. Treated cases were defined as individuals with parasitaemia who requested treatment during a narrow period (14 days before or after a positive blood film was obtained) or an extended period (28 days before or after a positive blood film was obtained). Individuals who had parasitaemia at more than one monthly survey were considered treated if they requested treatment within 14 or 28 days of any positive blood film. Individuals who did not request treatment within the above time frame were considered untreated.
We classified each positive blood film as a treated or untreated episode to determine predisposing factors for treatment uptake. The relation of the outcome (treated or untreated) to the explanatory variables (parasite density, season and age) was assessed by applying generalized estimating equations (GEE) of the binomial family to the longitudinally collected data (7). This is a generalization of the usual logistic regression, which we used to include the effect of covariables in the model while allowing for correlation between repeated responses in the same individual (8). We used an unstructured form for the within-person correlation; this allowed correlations between each pair of months to be estimated separately. Other correlation structures produced very similar results. Sensitivity, specificity, positive predictive value and negative predictive values of rapid malaria detection tests were calculated as suggested by Giesecke (9). Analyses were performed with Stata version 6 (Statacorp, Texas).

The study was approved by the ethics review boards of the Gambian Government, Gambian Medical Research Council Laboratories and the London School of Hygiene and Tropical Medicine. The study methods were explained at village meetings, and consent was given at a village level. Individuals could refuse to participate at any time during the study.

Results

In 1998, 1906 people lived in the four villages. The largest ethnic group was the Mandinka (46%); this was followed by the Wolof (30%) and Fula (21%) groups. The remaining 3% were Serabuli, Jolla or of unknown ethnicity.

Treatment requests

Between September 1998 and May 1999, 1620 individuals living in a study village or a neighbouring hamlet asked for medical care from the village health worker or the field worker. Of these, 1150 (71%) had a temperature of 37.5°C or higher. Treatment was requested most frequently for children under 5 years of age (596/1620; 37%). More than half of all treatment requests occurred during October and November (1003/1620; 62%). Of the 1580 individuals who asked for treatment, 1209 (77%) were infected with *P. falciparum*; for 40 individuals, no test results were available. The rapid detection tests processed by the field workers in the villages had a sensitivity of 92%, specificity of 82%, positive predictive value of 90% and negative predictive value of 85%.

Cross-sectional surveys

During the study period, 1268 individuals agreed to give between one and nine blood samples during monthly surveys. Their ages ranged between 8 months and 89 years (median age 16 years). Of the 5400 thick blood films scheduled to be collected at monthly home visits over 9 months (150 blood films × 9 months × 4 villages), 5226 (97%) blood films were obtained (on average, 4.1 slides per individual). Microscopy showed *P. falciparum* infection in 1386/5226 (27%) slides. Overall, 726/1268 (57%) individuals had at least one *P. falciparum*-infected blood film. In 142/1268 (11%) individuals, the parasite density was 5000/μl or higher. *P. falciparum* infected blood films were seen on two or more sequentially obtained blood films in 232/1268 (18%) individuals.

The monthly parasite prevalence changed with season and age group. The parasite prevalence started to increase in October (122/544; 22%), peaked in November (399/653; 61%) and declined in December (299/707; 42%) (Fig. 1). Seasonal changes in parasite rates were observed in all age groups. Children aged 5–10 years, however, had the highest parasite prevalence throughout the follow-up period. Individuals aged over 40 years had the lowest parasite prevalence. In parallel with the parasite prevalence, parasite densities peaked in November, when 55/399 (14%) individuals had parasite densities >50 000/μl and 10/399 (2.5%) >50 000/μl.

Treatment requests

Of 726 individuals found to be infected with *P. falciparum* during cross-sectional surveys, only 146 (20%) individuals requested treatment at least once within a one-month window (14 days before or after the blood sample was obtained). An additional 53/726 (7.3%) requested treatment 14–28 days before or 14–28 days after the positive blood film was collected. Altogether, within two months of the collection of a positive blood film, only 199/726 (27%) individuals with parasitaemia requested treatment.

Treatment uptake varied significantly between villages. Uptake was highest in Yallal, where 72/192 infected individuals (38%, 95% confidence interval (CI) 31% to 45%) requested treatment. Treatment uptake was lowest in Kani Kunda, where only 6/136 infected individuals requested treatment (4.4%, CI 1.6% to 9.4%). In the remaining two villages (Kumbija and Bambali), 57/215 (27%, CI 21% to 33%) and 11/185 (6.0%, CI 3.0% to 10%), individuals requested treatment, respectively.

Factors influencing treatment requests

The proportion of individuals requesting treatment was greater in those with higher parasite density (Fig. 2). In total, 60/142 (42%) individuals requested treatment for 61/170 episodes (36%) of parasitaemia with a parasite density of 5000/μl or higher. Individuals with blood films with parasite densities ≥50 000/μl were five times more likely to request treatment than those with parasite densities <5000/μl (odds ratio 5.2, 3.6 to 7.4) (Table 1). The percentage of individuals who requested treatment varied with age: children aged <6 years with parasitaemia were brought for treatment most frequently (51/168; 30%), whereas treatment was requested for only 95/558 (17%) of children aged ≥6 years (odds ratio 1.8, 1.3 to 2.7). This odds ratio was not statistically significant, however, when we adjusted for parasite density, village and month (Table 1). Individuals who were infected during October and November were more likely to request treatment than those infected during the remaining months of the year (odds ratio 2.2, 1.6 to 3.2) (Table 1). We did not detect any interaction between requests for treatment and village, parasite density, season or age. The sex of infected individuals did not influence treatment uptake. The predisposing factors for episodes of parasitaemia that resulted in a treatment request were similar in the four villages.

Home treatment

After the malaria season, 120 household heads from the four villages were asked whether they had bought any medication for fever or kept any medication at home. In total, 15/120 (13%) reported home treatment with paracetamol and 3/120
(2.5%) with chloroquine during the preceding malaria season. Twenty shops in the four study villages were visited by a fieldworker; 13 (65%) of these kept paracetamol, but only one (5%) sold chloroquine. No other drugs with antimalarial activity were available for sale.

Discussion

At the peak of the malaria season, more than half (61%) of the study population were infected with *Plasmodium falciparum*. The highest prevalence was found in children aged 5–10 years. These findings are consistent with those in other regions with seasonal malaria, such as Dielmo in Senegal (10) and Garki in Nigeria (11).

Treatment requests

Overall, we found that only 20% of all infected individuals sought medical treatment within the 14 days before or after a positive blood film was obtained. Considerable variations in treatment uptake were seen between villages. Treatment uptake was highest (38%) in the village with the highest parasite prevalence and parasite density and lowest (4.4%) in the village with the lowest parasite prevalence and density. Even in the village with the highest uptake, only a third of infected individuals requested treatment; this level of treatment is unlikely to have an effect on transmission. The observed heterogeneity in treatment uptake between the villages is a source of concern. Villages with low uptake will remain a reservoir for *P. falciparum* infections.

Reasons for low treatment uptake

Symptomactiy

No single explanation can account for the high level of untreated infections. Several findings indicate that the majority of *P. falciparum* infections in the study area were asymptomatic and, therefore, were left untreated. For example, an infection was five times more likely to result in a treatment request if the parasite density was >5000/µl. Infections with parasite densities <5000/µl were more likely to have been asymptomatic and thus did not trigger a visit to a treatment centre. Infected children aged under five years were more frequently brought for treatment than older children or adults. Immunologically naive children are more likely to have high-density parasitaemias than older individuals, however, and thus are more likely to be symptomatic. After we adjusted for parasite density, village and month, however, the difference in treatment uptake with age was not statistically significant.

Infections detected during October and November were twice as likely to be treated as infections detected during the rest of the year. New *P. falciparum* infections are most frequently acquired during October and November — the peak of the malaria transmission season — and they are more likely to result in acute signs and symptoms than *P. falciparum* infections detected outside the transmission season, which may be chronic and asymptomatic in character.

Alternative treatments

Another potential reason for why so few infections were treated by the designated health care providers is that residents of the study villages seek treatment from alternative sources. It is unlikely that infected individuals would have spent time and money to obtain treatment outside their village, but antimalarials kept in the home for an emergency could have been a readily available source of treatment.

The reported use of home treatment in sub-Saharan Africa is very variable. A study conducted in Togo in 1989 found that 83% of febrile children received antimalarials at home (12). In the United Republic of Tanzania, 72% of respondents reported that they had treated themselves for a suspected attack of malaria with antimalarial drugs kept at home (13). Home treatment was found to be widespread in Ghana in a study in 1997 (14). A recent study in Yanfolila, Mali, found that 76% of interviewed mothers managed their child’s disease at home using traditional and biomedical treatment (15). Similarly, a study in Nigeria found that 71% of interviewed mothers had used antimalarials (16). High rates of self-treatment have been reported in rural Kenya. For example, in 1995, 60% of the respondents in a study were treated at home with herbal or biomedical remedies (17). More recently, 47% of febrile children were found to have received antimalarials at home (18). In contrast, self-treatment was not found to be common in rural Niger, probably because of the absence of antimalarials (19).

In an earlier survey in our study area, self-treatment was not found to be common practice (20). We also found that home treatment was uncommon in the study villages. Most (85%) households denied using home treatments, and only 3/120 reported the use of antimalarials. The apparent scarcity of home treatment with antimalaria drugs was corroborated by the absence of antimalarials in village shops. The questions
Individuals with signs and symptoms do not make use of the available treatment. Further research is required to determine how often and why untreated individuals with signs and symptoms but do not make use of the available treatment. The teaching of mothers seems to be a promising approach, as it is economical and acceptable for most communities. Previous experience with community-based interventions that increase treatment uptake in sub-Saharan Africa have had mixed success (20, 26, 27).

Other strategies to reach untreated individuals with asymptomatic infections need to be considered. While those with asymptomatic infection may not be acutely aware of their disease, they may still suffer from the long-term effects of the infection, most obviously anaemia. Furthermore, at some stage of their infection, individuals are likely to become gametocyte-\textit{a}m\textit{ic} and, therefore, will maintain infections in the population. Presumptive therapy is one approach to reducing the prevalence of asymptomatic \textit{P. falciparum} infections, as diagnosis of each infected individual is neither feasible nor cost-effective. In selected low-transmission scenarios, repeated mass administrations of antimarials can interrupt malaria transmission (28). A cluster, randomized, controlled trial using a single, mass administration of artesunate combined with pyrimethamine plus sulfadoxine given to all age groups failed to interrupt malaria transmission in the Gambia in 1999 (29). A temporary benefit observed in treated clusters compared with control clusters was most likely due to the prophylactic effect of pyrimethamine plus sulfadoxine.

Administering drugs to the whole population is an expensive undertaking, and it may be more cost-effective to focus such an intervention on high-risk populations, such as children and pregnant women. Recently, Schellenberg et al. showed that presumptive, intermittent therapy is highly effective in the reduction of malaria-related disease among infants in a hyperendemic region of Ifakara, southern Tanzania (30). It will be interesting to see whether this approach can be from seeking biomedical treatment. Such understanding is needed to plan interventions to improve the uptake of malaria treatment. An example of how treatment uptake can be improved has been demonstrated recently in Tigray, Ethiopia (25). The approach followed was the selection and training of mother coordinators to teach all mothers to recognize symptoms that might be caused by malaria and to give an appropriate course of chloroquine to children with malaria. A statistically significant reduction of 40% in malaria-related mortality in children under 5 years was observed in clusters that had received the intervention compared with control clusters. The teaching of mothers seems to be a promising approach, as it is economical and acceptable for most communities. Previous experience with community-based interventions that increase treatment uptake in sub-Saharan Africa have had mixed success (20, 26, 27).

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used in older age groups in the absence of an immunization programme as a delivery system.

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Conflicts of interest: none declared.

Résumé
Demande de traitement chez les sujets infectés par *Plasmodium falciparum* dans les zones rurales de Gambie (Afrique de l’Ouest)

Objetif Déterminer la proportion d’infections à *Plasmodium falciparum* traitées dans les zones rurales de Gambie.

Méthodes Des sujets provenant de quatre villages de Gambie ont été suivis pendant neuf mois lors de leurs visites aux agents de santé du village. Des enquêtes paludologiques transversales réalisées une fois par mois ont permis de mesurer la prévalence des infections à *P. falciparum*. Les demandes de traitement ont été recherchées par interrogation de bases de données raccordées. On a défini comme cas traités les sujets parasitémiques ayant fait une demande de traitement pendant une période de 14 jours ou de 28 jours avant ou après l’obtention d’un frottis sanguin positif.

Résultats La prévalence de la parasitémie a atteint sa valeur maximale en novembre 1998, avec 399 sujets parasitémiques sur 653 (61%). Elle est restée la plus élevée pendant toute la durée de l’étude chez les enfants de 5–10 ans. Bien que l’accès au traitement soit plus facile en Gambie que dans la majeure partie de l’Afrique subsaharienne, seuls 20% des sujets infectés ont fait une demande de traitement au cours des 14 jours précédant ou suivant l’obtention d’un frottis sanguin positif. Au cours de la période de deux mois entourant l’obtention d’un frottis positif, 199 sujets parasitémiques sur 726 (27%) ont fait une demande de traitement. Malgré la facilité d’accès aux soins, moins de la moitié (42%) des sujets présentant une densité parasitaire compatible avec une atteinte de paludisme (>5000/μl) ont fait une demande de traitement. La présence d’une forte densité parasitaire et la survenue de l’infection pendant les mois d’octobre et novembre étaient associées à une fréquence accrue des demandes de traitement. L’automédication était rare dans les villages d’étude : 3 chefs de famille sur 120 (2,5%) avaient donné eux-mêmes un traitement par des antipaludiques lors de la précédente saison palustre.

Conclusion Un grand nombre d’infections à *P. falciparum* peuvent rester sans traitement du fait de leur nature infraclinique. Un traitement préventif intermittent peut réduire la morbidité et la mortalité. Il est probable que toutes les infections non traitées n’étaient pas asymptomatiques. Des recherches qualitatives doivent être entreprises pour rechercher quels sont les obstacles à la demande de traitement, afin de planifier des interventions éducatives.

Resumen
Búsqueda de tratamiento entre las personas infectadas por *Plasmodium falciparum* en zonas rurales de Gambia (África occidental)

Objetivo Cuantificar la proporción de infecciones por *Plasmodium falciparum* tratadas en las zonas rurales de Gambia.

Métodos Se sometió a seguimiento a personas de cuatro pueblos de Gambia durante nueve meses a través de las visitas que efectuaban a los agentes de salud de aldea. La prevalencia de la infección por *P. falciparum* se midió mediante encuestas transversales mensuales sobre el paludismo. Se hicieron búsquedas en diversas bases de datos conectadas para determinar las solicitudes de tratamiento. Se consideraron casos tratados a los individuos con parasitemia que solicitaron tratamiento dentro de un periodo corto o largo (14 o 28 días, respectivamente) antes o después de dar positivo en un frotis de sangre.

Resultados La prevalencia del parásito mostro un pico en noviembre de 1998, momento en el que 399 de 653 (61%) individuos tenían parasitemia. La prevalencia del parásito fue máxima a lo largo de todo el estudio entre los niños de 5 a 10 años. Aunque el acceso al tratamiento fue mejor que en la mayoría del África subsahariana, sólo el 20% de los infectados solicitaron tratamiento médico como máximo 14 días antes o después de dar positivo en un frotis de sangre. Durante el mes anterior o posterior a la obtención de un resultado positivo, 199 de 726 individuos (27%) con parasitemia solicitaron tratamiento. Pese al fácil acceso a la atención de salud, menos de la mitad (42%) de quienes presentaban densidades de parásitos compatibles con ataques de paludismo (>5000/μl) solicitaron tratamiento. Los altos niveles de infección y de densidad de parásitos registrados durante los meses de octubre y noviembre se asociaron a una mayor frecuencia de solicitudes de tratamiento. La automedicación fue poco frecuente en las aldeas del estudio: 3 de 120 (2,5%) cabezas de familia se habían tratado con antipalúdicos en la temporada de paludismo precedente.

Conclusión Muchas infecciones por *P. falciparum* quedan sin tratar debido a su carácter subclínico. El tratamiento presuntivo intermitente puede reducir la morbilidad y la mortalidad. Probablemente no todas las infecciones no tratadas fueran asintomáticas. Deberían emprenderse investigaciones cualitativas para estudiar los factores que dificultan el comienzo del tratamiento, a fin de poder planificar las intervenciones educativas.
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