Impact of chloroquine resistance on malaria mortality

Impact de la résistance à la chloroquine sur la mortalité palustre

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Abstract – Over 12 years, from 1984 to 1995, we conducted a prospective study of overall and malaria specific mortality among three rural populations in the Sahel, savanna and forest areas of Senegal. The emergence of chloroquine resistance has been associated with a dramatic increase in malaria mortality in each of the studied populations. After the emergence of chloroquine resistance, the risk of malaria death among children 0–9 years old in the three populations was multiplied by 2.1, 2.5 and 5.5, respectively. This is the first study to document malaria mortality at the community level in Africa before and after the emergence of chloroquine resistance. Findings suggest that the spread of chloroquine resistance has had a dramatic impact on the level of malaria mortality in most epidemiological contexts in tropical Africa. (© Académie des sciences / Elsevier, Paris.)

malaria / *Plasmodium falciparum* / drug resistance / chloroquine / mortality / Africa

Résumé – L'évolution de la mortalité palustre et de la mortalité générale a été suivie prospectivement pendant 12 ans, de 1984 à 1995, dans trois populations rurales du Sénégal situées respectivement au Sahel, en savane soudanienne et en zone de forêt. Dans chacune de ces communautés, l'émergence de la résistance à la chloroquine a été associée à une forte augmentation de la mortalité palustre. Après l'émergence de la résistance à la chloroquine, le risque de décès palustre chez les enfants de 0 à 9 ans a été multiplié par 2,1, 2,5 et 5,5, respectivement, dans les trois populations. Cette étude est la première qui documente la mortalité palustre au niveau communautaire en Afrique avant et après l'émergence de la résistance à la chloroquine. Ses résultats suggèrent que la diffusion de la résistance à la chloroquine a eu un impact majeur sur le niveau de la mortalité palustre dans la plupart des contextes épidémiologiques rencontrés en Afrique tropicale. (© Académie des sciences / Elsevier, Paris.)

paludisme / *Plasmodium falciparum* / résistance médicamenteuse / chloroquine / mortalité / Afrique

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La lutte antipaludique en Afrique tropicale est presque exclusivement basée sur le traitement présomptif des cas de fièvre, principalement en utilisant la chloroquine qui est le moins cher des médicaments antipaludiques. Ces 15 dernières années, la résistance de *Plasmodium falciparum* à la chloroquine s'est étendue à l'ensemble de l'Afrique mais son impact sur la mortalité palustre n'est pas connu. Pendant 12 ans, de 1984 à 1995, nous avons conduit une étude prospective de la mortalité palustre et de la mortalité générale dans trois populations rurales du Sénégal situées respectivement en zone de savanne soudanienne (Bandafassi : 38 villages, 8 612 habitants en 1995), au Sahel (Niakhar : 30 villages, 28 399 habitants en 1995) et en zone de forêt (Mlomp : 11 villages, 7 287 habitants en 1995). Tous les décés qui survenaient dans les trois populations d'études ont été étudiés par la technique de l'autopsie verbale et l'examen des données de source médicale éventuellement disponibles. Les niveaux de résistance à la chloroquine ont été déterminés par des tests in vivo.

L'émergence de la résistance à la chloroquine, qui est survenue en 1990 à Mlomp, en 1992 à Niakhar et en 1993 à Bandafassi, a été associée à une augmentation considérable de la mortalité palustre dans chacune des populations d'étude. À Mlomp, où le paludisme était hypoendémique et la mortalité des enfants était faible en raison de la mise en oeuvre d'une chloroquinisation de masse et d'importants programmes de santé, le paludisme est devenu mésoendémique et la mortalité attribuable au paludisme chez les enfants de moins de 10 ans a augmenté de 5,5 fois. L'augmentation de la mortalité palustre a été particulièrement forte entre 0 et 4 ans, avec respectivement 0,5, 3,4 et 5,5 décès pour 1 000 enfants annuellement lors des périodes 1985–1989, 1990–1992 et 1993–1995. À Bandafassi, une zone de paludisme holoendémique où l'accès à des structures médicales était particulièrement difficile, la mortalité attribuable au paludisme chez les enfants de moins de 5 ans a augmenté de 2,5 fois, atteignant respectivement 4,2 et 10,3 pour 1 000 annuellement lors de périodes 1984–1992 et 1993–1995. À Niakhar, où la transmission du paludisme était la plus faible des trois zones d'études (environ dix piqures infectantes par personne par an, soit environ trois fois moins qu'à Mlomp et 40 fois moins qu'à Bandafassi) la mortalité attribuable au paludisme chez les enfants de moins de 10 ans a doublée, atteignant respectivement 4,0 et 8,2 pour 1 000 annuellement lors des périodes 1984–1991 et 1992–1995.

Ces données sont les premières qui décrivent l'évolution de la mortalité palustre dans des populations africaines avant, pendant et après l'émergence de la résistance à la chloroquine. Elles suggèrent que la diffusion de la résistance à la chloroquine a eu un impact très grave sur la mortalité palustre dans une grande diversité de contextes épidémiologiques en Afrique. Dans le cas du Sénégal, ces observations pourraient expliquer pourquoi la mortalité générale des enfants, qui était en diminution constante depuis les années 1950, à cesser de décroitre depuis le début des années 1990.

1. Introduction

Plasmodium falciparum malaria is one of the main causes of morbidity and mortality in tropical Africa. According to WHO, it is responsible for about 270–480 million clinical attacks and 1.4–2.6 million deaths every year [1]. Malaria control in Africa is almost exclusively based on chemotherapy, mainly using chloroquine which is the cheapest antimalarial drug [2]. Easy to use and until recently highly effective, chloroquine is routinely prescribed by out-patient clinics to treat fevers. Along with aspirin, it is also the only drug which is frequently kept at home by families and used for self-treatment.

Chloroquine-resistant strains of *P. falciparum* were first observed during 1978 in East Africa. Between 1978 and 1988, resistant parasites have been reported in all countries of tropical Africa [3]. In each newly affected country, chloroquine resistance has progressed in three different ways: a) it has spread in a growing number of locations and regions in the country; b) the prevalence of resistant strains in each area has increased; c) the degree of resistance has intensified, with a relative reduction in RI type responses (initial disappearance of parasitaemia when treated, but with further reappearance) in favour of RII type responses (initial reduction without disappearance of parasitaemia following standard treatment) and the occurrence of RIII type responses (absence of a reduction of parasitaemia when treated).

The consequences of chloroquine resistance on the evolution of malaria mortality in Africa are poorly known. Most studies of malaria mortality at the community level have been short term. None of 28 studies recently reviewed [4] included data collected from the same community prior to and following the emergence of chloroquine resistance. Furthermore, few hospital data are available. To our knowledge, the only studies published concern hospitals in Malawi, Kinshasa (Zaire) and Brazzaville (Congo), where an increase in malaria patients and malaria deaths temporally related to the emergence of chloroquine resistance has been observed [5–7].

In Senegal, long-term demographic surveillance programmes were initiated in three rural areas of the country between 1963 and 1984 [8–10]. Since 1984, a continuous study of the causes of death has been added to the registration of demographic events and specific data on malaria have been collected in each area. The data collected are presented and discussed in this article. They suggest that the emergence of chloroquine resistance has had dramatic effects on malaria mortality in each of the three study populations.

2. Methods

2.1. Study areas and populations

2.1.1. The Bandafassi study area

The Bandafassi study area is located in the Sudan savanna of southeastern Senegal (*figure 1*). Rains are concentrated over a 6-month period from May to October, and annual rainfall averaged 1 097 mm during the period 1984–1995 (*table I*). The population comprises 8 612 inhabitants (our 1995 census) belonging to three ethnic groups (Mandinka, Fula and Bedik) who live in 38 villages. This is one of the remotest areas in Senegal. There is one small dispensary within the study area but access to health care is always difficult for most villages and almost impossible during the rainy season where the rare tracks are impassable. Since 1970, demographic data have been collected annually [11]. Mortality in children under five was initially higher than 400 per thousand but decreased in the 1980s following the launch of the Expanded Programme on Immunisation [12].

Malaria in Bandafassi is holoendemic with parasite rates in children ranging between 90 and 100 % ([13]; Trape, unpublished). A survey of malaria transmission conducted from November 1995 to December 1996 indicated an annual entomological inoculation rate ranging from 206 to 647 infective bites per person per year according to village (Trape and Fontenille, unpublished). Transmission is seasonal, from June to December, and four anopheline species play a role as vector: *An. gambiae*, *An. funestus*, *An. arabiensis* and *An. nili*.

Table I. Annual rainfall in the three study areas, 1984–1995.

Year	Bandafasssi*	Niakhar	Mlomp°
1984	1 222	371	1 186
1985	1 272	395	1 076
1986	1 173	227	1 079
1987	1 103	547	1 277
1988	995	506	1 284
1989	1 031	514	1 598
1990	808	311	1 255
1991	1 126	382	1 428
1992	936	395	1 051
1993	1 167	444	1 231
1994	1 289	525	1 200
1995	1 041	614	1 097
Mean	1 097	436	1 230

* Kedougou station (14 km from Bandafassi), ° Oussouye station (12 km from Mlomp).

2.1.2. The Niakhar study area

The Niakhar study area is located in the Sahel, 120 km southeast of the capital city of Dakar (*figure 1*). Rains are concentrated over a 3-month period, from July to the beginning of October. Annual rainfall averaged 436 mm for the period 1984–1995 (*table I*). The population comprises 28 399 inhabitants (our 1995 census), belonging to the Sereer ethnic group, who are distributed among 30

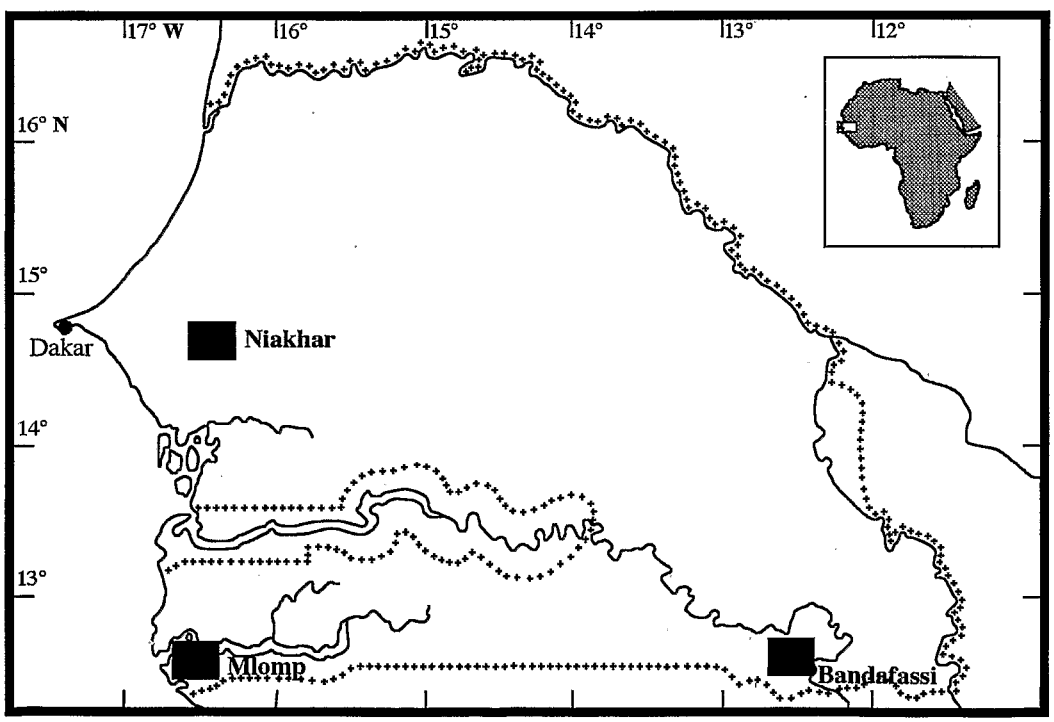

Figure 1. Map of Senegal showing the localisation of the three study areas.

villages made up of several different hamlets. There are three dispensaries within the study area. Demographic surveillance was started in 1963, and from 1983 onwards it was extended to the whole current study area [14]. Immunisation coverage of children has considerably improved since 1987 when the study area was selected for clinical trials of new vaccines against measles and whooping cough [15–18].

Old and recent malaria surveys conducted in Niakhar show that the parasite rate in children is usually less than 50 % but can reach 80 % at the end of the rainy season (Trape et al., unpublished). A survey carried out in 1995, a year of heavy rainfall, showed an average entomological inoculation rate of ten infective bites per person per year [19]. Transmission by *An. arabiensis* is almost exclusively concentrated in September and October.

2.1.3. The Mlomp study area

The Mlomp study area is located in southwestern Senegal (Casamance), an area of forest and mangrove (*figure 1*). Rains are concentrated over a 6-month period, from June to November. The average annual rainfall was 1 230 mm for the period 1984–1995 (*table I*). The population comprises 7 287 inhabitants (1995), belonging to the Joola ethnic group, who are distributed among 11 villages with houses scattered in the forest. Since 1961 the study area has had particularly active health services run by nun nurses from a Catholic heath centre which includes a maternity clinic, an out-patient clinic, 12 in-patient beds and a small laboratory. Important health care programmes were gradually set up between 1961 and 1975 and they were all very well supported by the community. The probability of dying before the age of five, which, from 1930 to 1965, was between 350 and 400 per thousand livebirths, subsequently decreased to less than 100 per thousand in the 1980s [10].

Malaria surveys carried out in the 1960s indicated that malaria was mesoendemic. From 1975 to 1994, a control programme promoting chloroquine chemoprophylaxis during the rainy season and home treatment of fever was conducted each year by the nuns and the local health committee. Until 1989, this programme reduced the parasite rate of children during the rainy season to less than 10 % [10]. Following the emergence of chloroquine resistance in 1990, the parasite rate of children rose sharply reaching 46 % in 1992 and 51 % in 1994 [20]. A survey of malaria transmission carried out in 1995 showed an entomological inoculation rate of 30 infective bites per person per year (Trape and Fontenille, unpublished). Malaria transmission, almost exclusively by *An. gambiae s.s.*, is strictly seasonal from July to December.

2.2. Assessment of the rates and causes of mortality

The mortality data presented in this article cover a 12-year period (1984–1995) for the Niakhar and Bandafassi study areas, and an 11-year period (1985–1995) for the Mlomp study area. The demographic monitoring systems for each study population have been presented elsewhere [10, 11, 14]. Briefly, annual censuses were conducted to collect information on births, deaths, migrations and marriages. In Niakhar, each compound was visited once a week from 1987 to 1995; the demographic information was collected during these weekly visits and its accuracy was checked during the annual census.

All deaths which occurred among the three study populations (except adult deaths in Bandafassi) were the subject of a post mortem investigation among bereaved relatives using the verbal autopsy technique. For each study area, there were no changes in the technique of verbal autopsy during the study period. The same questionnaire was used for the three studies [21]. The causes of deaths were determined from the responses to these questionnaires and from any available medical information. For Bandafassi, and to a lesser extent Niakhar, data collected by verbal autopsy were the main source of information allowing the circumstances and causes of death to be established. Each questionnaire was examined by two or three physicians and the cause of death was attributed by concensus between at least two reviewers. Every death for which the cause was classified as undetermined and a sample of deaths from each determined cause were re-examined at the end of the study.

In the case of Mlomp, medical information was available for 73 % of deaths. For each activity (consultation, hospitalisation, laboratory tests, monthly weighing of children under 3 years, prenatal visits, birth delivery, vaccination) detailed registers were kept by the missionary nurses. For each patient, the consultation register in particular noted which signs and symptoms had been observed, the laboratory test results, the diagnosis and which treatment had been administered. Morever, a special register was kept to record all the deaths that the staff of the health centre was aware of, whether or not the patient had died at home or during hospitalisation. The causes of death were established by a physician after reviewing medical registers and verbal autopsy. If there was any discrepancy between the information supplied by verbal autopsy and that supplied by the registers, a supplement enquiry was carried out among the nursing staff and the deceased's family.

2.3. Emergence and evolution of chloroquine resistance

In Senegal, chloroquine-resistant *P. falciparum* initially emerged in October 1988 in Dakar [22]. The first cases of in vivo resistance in other regions of the country were observed in 1990, including cases at the RIII level [23]. However, only isolated cases were found at that time and, in 1990 and 1991, most rural areas were considered free of chloroquine resistance despite the rapid progression of the prevalence of resistant strains in Dakar. In the case of the three study areas, the first therapeutic failures with chloroquine were observed by the out-patient clinic staff of Mlomp in 1990, Niakhar in 1992 and Bandafassi in

1993. These dates were considered as the first year with chloroquine resistance in these areas [20]. The following years, standardised surveys of the prevalence of chloroquine-resistant *P. falciparum* were carried out in Mlomp (four annual surveys from 1991 to 1994), in Niakhar (four annual surveys from 1993 to 1996) and in Bandafassi (two surveys in 1994 and 1995). The results of these surveys have been presented in detail elsewhere [20]. High levels of chloroquine resistance appeared rapidly in Mlomp (RII and RIII: 36 % in 1991, 30 % in 1992, 41 % in 1994, 46 % in 1995). Chloroquine resistance progressed less rapidly in Niakhar (RII and RIII: 10 % in 1993, 15 % in 1994, 17 % in 1995, 29 % in 1996) and in Bandafassi (RII: 6 % in 1994, 16 % in 1995).

2.4. Statistical analysis

To investigate the impact of chloroquine resistance on malaria mortality, we used a Poisson regression analysis available in the software package EGRET® (Statistical and Epidemiology Research Corp., Seattle, WA, USA). The outcome variable was the number of deaths attributable to malaria and the rate multipliate variable was the number of person-years under survey.

3. Results

3.1. Bandafassi study area

Table II shows the evolution of overall mortality in children from 1984 to 1995. The risk for a new born child to die before reaching age 5 years, which was approximately 350 per thousand until 1985, fluctuated between 200 and 300 per thousand the following years. It was on average 260 per thousand for the period 1993–1995.

Table II. Trends in overall mortality, Bandafassi, 1984–1995: probability for a new born child of dying before its first birthday ($_1q_0$), or before reaching age 5 ($_5q_0$), probablity of dying between the ages of 1 and 5 ($_4q_1$), probability of dying between the ages of 5 and 10 ($_5q_5$), per thousand.

Year	$_1q_0$	$_4q_1$	$_5q_0$	$_5q_5$
1984	200	155	324	79
1985	170	242	370	26
1986	146	100	232	21
1987	139	137	256	20
1988	131	105	222	20
1989	144	162	282	37
1990	102	110	201	14
1991	152	166	293	21
1992	159	148	284	45
1993	178	149	301	16
1994	138	148	266	46
1995	113	113	213	19

Malaria attributable mortality was exclusively concentrated in children under 5 (*figure 2*). From 1984 to 1992, it fluctuated depending on the year between 2.3 and 7.4 annual deaths per thousand and was on average 4.2 per thousand. From 1992 to 1995, it fluctuated between 8.4 and 11.4 per thousand and reached an average of 10.3 per thousand.

3.2. Niakhar study area

Table III shows the evolution of overall mortality in children from 1984 to 1995. The risk for a new born child to die before reaching age 5 years, which was above 300 per thousand the first 2 years of the study, decreased significantly until 1990, when it stabilised around 200 per thou-

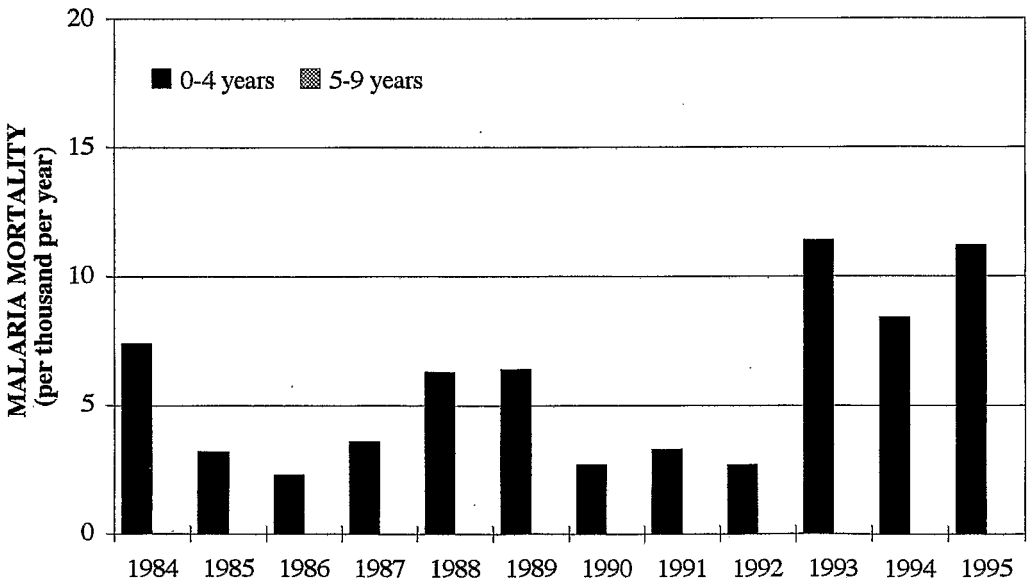

Figure 2. Trends in mortality rates attributable to malaria (deaths/1 000 person-year at risk) for children aged 0–4 years, Bandafassi, 1984–1995. No deaths were attributed to malaria among chidren aged 5–9 years.

Table III. Trends in overall mortality, Niakhar, 1984–1995.

Year	$_1q_0$	$_4q_1$	$_5q_0$	$_5q_5$
1984	129	197	301	29
1985	128	259	354	36
1986	106	154	244	24
1987	121	173	273	30
1988	125	131	239	15
1989	84	111	186	16
1990	96	92	179	15
1991	76	132	198	17
1992	85	130	204	27
1993	86	139	214	27
1994	69	102	164	32
1995	78	124	193	30

sand. The mortality of children of 5–9 years old dropped by a half between 1984–1985 and 1991, but rose again from 1992 onwards.

Figure 3 shows the evolution of malaria attributable mortality in children under 10. Until 1991, a marked tendency for a decrease in malaria mortality was observed. From 1984 to 1987, the average malaria mortality rate was 7.1 annual deaths per thousand in children under 5 and 1.1 per thousand in children 5–9 years old. From 1988 to 1991, the average malaria mortality rate was 5.4 per thousand per year in children under 5 and 1.2 per thousand per year in children 5–9 years old. From 1992 onwards, a large increase in the number of malaria deaths was observed. During the period 1992–1995, malaria mortality averaged 12.4 per thousand per year in children under 5 and 3.3 per thousand per year in childen 5–9 years old.

3.3. Mlomp study area

Table IV shows that of the three study areas, child mortality was lowest in Mlomp. It increased from 1990 onwards: the risk for a new born child to die before reaching age 5 years was on average 94, 120 and 122 per thousand during the periods 1985–1989, 1990–1992 and 1993–1995, respectively. As neonatal mortality had varied very little between 1985 and 1995, this evolution was exclusively due to the increase in deaths occurring after 1 month of age.

Table IV. Trends in overall mortality, Mlomp, 1985–1995.

year	$_1q_0$	$_4q_1$	$_5q_0$	$_5q_5$
1985	68	25	91	6
1986	69	42	108	22
1987	69	91	154	23
1988	32	25	56	11
1989	37	25	61	11
1990	33	145	173	24
1991	47	30	76	17
1992	66	48	111	40
1993	76	43	116	12
1994	70	49	116	12
1995	61	79	135	12

Accurate medical information was available for almost all deaths compatible with a diagnosis of malaria. Furthermore, thick smears were systematically taken from hospitalised and out-clinic patients with a variety of clinical presentations, thus allowing a detailed picture of malaria related deaths to be drawn up. Between 1985 and 1995, a total of 32 deaths were attributed to malaria for

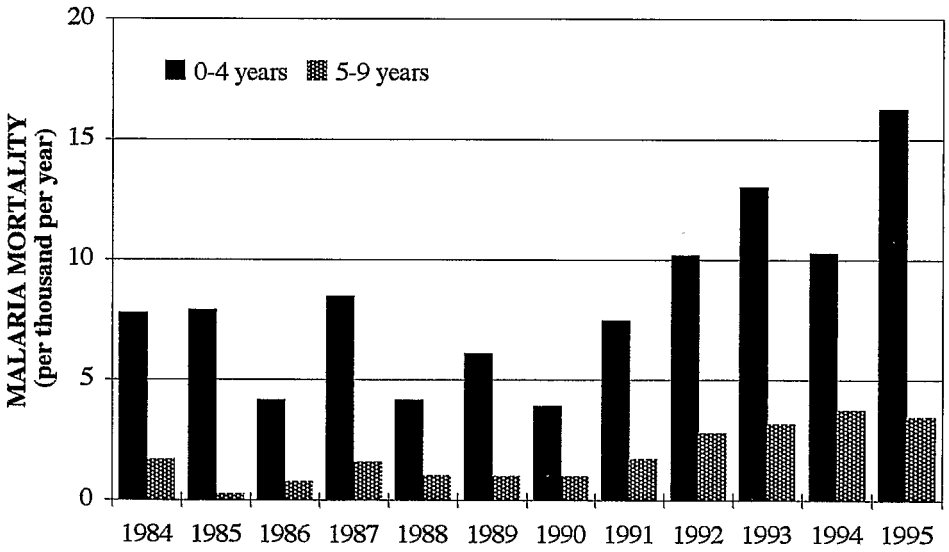

Figure 3. Trends in mortality rates attributable to malaria (deaths/1 000 person-year at risk) for children aged 0–4 years and 5–9 years, Niakhar, 1984–1995.

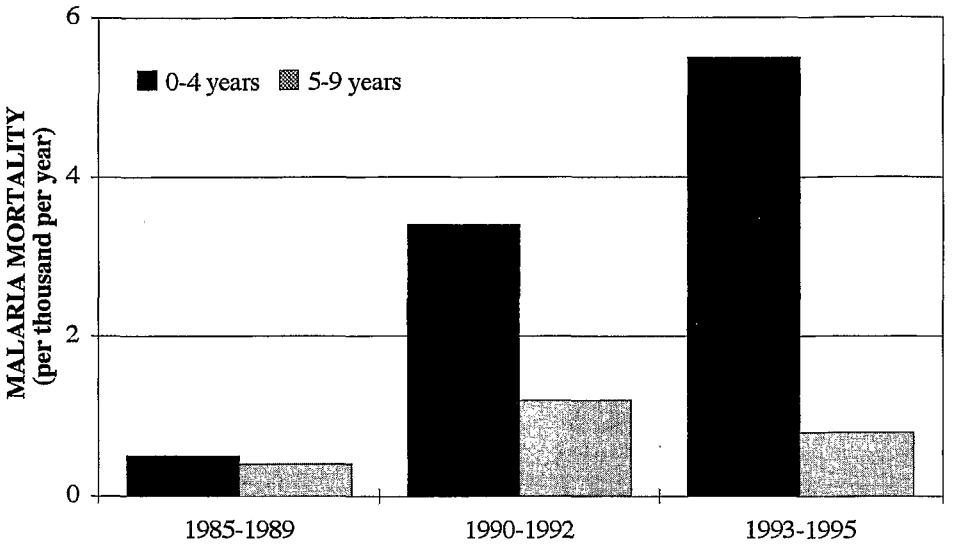

Figure 4. Average mortality rates attributable to malaria (deaths/1 000 person-year at risk) for children aged 0–4 years and 5–9 years, Mlomp, periods 1985–1989, 1990–1992 and 1993–1995.

the whole population of Mlomp. There were 28 cases of cerebral malaria and four cases of severe malarial anaemia. In 31 cases, patients had been hospitalised or had consulted at the out-patient clinic during their terminal illness. Between 1985 and 1989 only four deaths from malaria were observed, and all were cases of cerebral malaria. During this period, the average annual malaria mortality rate was 0.4 per thousand per year in children 0–4 years old and 0.5 per thousand per year in children 5–9 years old. Between 1990 and 1995, 28 deaths from malaria were observed, including a child aged 11 years and a 15-year-old adolescent who had spent most of his life in Dakar. *Figure 4* shows that since 1990 the increase in malaria mortality has been particularly large in young children. The average malaria mortality rate in children under 5 reached 3.3 per thousand per year for the period 1990–1992 and 5.5 per thousand per year for the period 1993–1995.

3.1. Global analysis

After the emergence of chloroquine resistance, the risk of malaria death among children 0–9 years old was multiplied by 5.5 (CI 95 %: 1.9–15.8) in Mlomp, by 2.5 (1.7–3.6) in Bandafassi and by 2.1 (1.8–2.5) in Niakhar. Among children 0–4 years old, the risk of malaria death was multiplied by 8.8 (2.1–37.7) in Mlomp, by 2.5 (1.7–3.7) in Bandafassi and by 2.0 (1.7–2.4) in Niakhar. In this age group, there was a significant interaction between the effects of the study area and the occurrence of chloroquine resistance ($P = 0.04$). Differences in malaria mortality between the three study areas were reduced by the emergence of chloroquine resistance. Before resistance, the risk of malaria death was 8.3 (2.0–34.1) times higher in Bandafassi than in Mlomp, and 12.3 (3.0–49.6) times higher in Niakhar than in Mlomp. After the emergence of chloroquine resistance, the risk of malaria death was only 2.3 (1.4–3.9) times higher in Bandafassi than in Mlomp, and 2.8 (1.8–4.4) times higher in Niakhar than in Mlomp.

4. Discussion

Our findings show that since the beginning of the 1990s, malaria mortality in three areas of Senegal has increased considerably. In Mlomp, it was 11 times higher in children of 0–4 years during 1993–1995 than during 1985–1989. In Bandafassi, mortality attributed to malaria has increased by a factor of 2.5 during the period 1993–1995 compared to its average value for the previous 9 years. Finally, in Niakhar, mortality attributed to malaria in children of 0–4 years and 5–9 years was 2.3 times and 2.7 times higher during 1992–1995 than during 1988–1991, respectively.

In most rural areas of tropical Africa, health services are few and badly equipped. Since most deaths occur at home, verbal autopsy is generally the only possible source of information available to determine the cause of death. Therefore, almost all data, old or recent, on malaria mortality in rural populations in Africa were based on studies which have used the verbal autopsy technique. However, verbal autopsy is difficult to standardise and to validate, and the estimation – necessarily indirect – of its sensitivity and specificity is problematic [24]. In our study, it is unlikely that another specific disease – confused with malaria – could have been the cause of the recent dramatic increase in deaths attributed to malaria among the three study populations. In Niakhar, most deaths attributed to malaria presented with high fever, generalised convul-

sions and/or coma, and these clinical patterns were closely associated with the very short annual peak in malaria transmission at the end of the rainy season. In Mlomp, where the increase in malaria mortality has been the largest, very accurate medical data were available for almost all deaths attributed to malaria and also for most of those which had been attributed a different cause of death.

Several hypotheses can be considered to explain the increase in malaria mortality: a) a change in the level of malaria endemicity due to climatic and/or other environmental factors; b) a change in the incidence of non-malaria diseases that would affect malaria mortality; c) a reduction in recourse to health care; d) a reduced effectiveness in curative and/or preventive treatment. None of the first three hypotheses seem to explain our observations. No obvious change in the natural environment of the three study areas occurred between 1984 and 1995. In particular, there were no abrupt changes in the environment because of development projects, for example, or for other reasons. Neither can the drought, which has affected Sub-Saharan West Africa since 1969, nor the fluctuations in rainfall during the study period, explain the increase in malaria mortality. In Mlomp and Bandafassi, where rainfall is high, the average rainfall was similar before and after the increase in malaria mortality. In Niakhar, malaria mortality was much higher from 1992 onwards than in previous records during years of high rainfall. Changes in health care and variations in the incidence of diseases other than malaria also does not seem to explain the increase in malaria mortality. In Niakhar and Bandafassi, practically none of the children or their mother had been vaccinated before 1987, which explains the high mortality due to measles, whooping cough and neonatal tetanus which had then been observed. During specific years, many children were killed by cholera epidemics. In 1990, young boys from Mlomp spent several weeks in the forest without their mothers to take part in a traditional circumcision ceremony and many deaths due to diarrhoea occurred. Variations in the incidence of various diseases clearly influenced the relative part of malaria mortality, but they do not explain the recent dramatic increase in the level of malaria deaths. The sustained improvement of health care in Niakhar and Bandafassi originally meant a decrease in child mortality and then its stabilisation when malaria mortality increased. In the case of Mlomp, chemoprophylaxis was only discouraged after 1994 when it had become obvious that it failed to prevent a strong increase in malaria mortality.

In each of the study areas, the increase in malaria mortality corresponded to the emergence of chloroquine resistance. This emergence was particularly abrupt in Mlomp because of high drug pressure. In the cases of Niakhar and Bandafassi, increase in chloroquine resistance was slower and levels reached in 1995 were still relatively low compared to other areas in Africa. The gravity of the impact of mild levels of resistance suggested by our findings opposes the general impression that chloroquine remains globally effective for malaria treatment in Africa. Our study is the first to measure malaria mortality at the community level before and after the emergence of chloroquine resistance. We believe that the real impact of chloroquine resistance in Africa could have been hindered by the low proportion of malaria attacks that are potentially lethal in young children frequently reinfected. In the case of Mlomp, in spite of an 11-fold increase in malaria mortality in children under 5, only one malaria attack in five hundred is currently fatal in this age group.

The comparison of the three study areas confirms that the level of malaria transmission is not an important determinant of the global level of malaria mortality in the majority of epidemiological contexts observed in tropical Africa [4, 25, 26]. It is in Niakhar that malaria mortality was highest despite an entomological inoculation rate 20 to 65 times lower than in Bandafassi. In Mlomp, the widespread use of chloroquine almost totally suppressed malaria mortality in the 1980s despite a high incidence of clinical attacks [10, 20]. Similar observations were made in Congo and Kenya [25, 27, 28] and this was also probably the case in numerous other regions of tropical Africa where fever and related symptoms are almost systematically self-treated by chloroquine.

In Senegal, as in almost all African countries, there is no national data on causes of death. However, information which allows us to estimate the levels and trends of total (all causes) child mortality is available at the national level from surveys and censuses [29]. These data indicated that Senegal has undergone a continuous decrease in child mortality since World War II. From approximately 400 per thousand, the risk that a new born child die before the age of 5 declined to 287, 236, 191 and 131 per thousand during the periods 1971–1975, 1976–1980, 1981–1986 and 1988–1992, respectively [29]. In contrast, the most recent survey (Demographic and Health Survey, DHS-III) indicated that child mortality was 139 per thousand during the period from March 1992 to March 1997 [30]. The change in the national trend is concomitant with the increase in malaria mortality observed in our studies, an indication that the recent stop in the decrease of child mortality in Senegal could be related to malaria.

5. Conclusion

Clearly, our observations in Senegal suggest that the impact of chloroquine resistance on malaria mortality in Africa is much higher than previously believed. The possible alternatives to chloroquine are few, difficult to implement and their efficacy is all the more uncertain for the medium and long term as very little research has been conducted to prevent the worsening of the situation. Redefining the therapeutic strategies, as in the example of Malawi [31], and improving health care seem nevertheless the only current possible way of reducing malaria

mortality [32]. A broad international initiative should urgently be set up to help African countries carry out research to help define and then accompany new drug policies.

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