

THE PUBLIC HEALTH IMPACT OF CHLOROQUINE RESISTANCE IN AFRICA

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Abstract. Between 1978 and 1988 *Plasmodium falciparum* resistance to chloroquine has been reported in all countries of tropical Africa. Despite the intensification of resistance during the last 2 decades, chloroquine remains in 2000 the first-line treatment for malaria in most of these countries. Here we review published data on the public health impact of antimalarial drug resistance in Africa. These data show that since the late 1980s convincing evidence of a major public health impact of the spread of chloroquine resistance has been available. Hospital studies in various African countries have documented a 2- or 3-fold increase in malaria deaths and admissions for severe malaria, an increase temporally related to the emergence of chloroquine resistance. Data from sentinel demographic surveillance systems in Senegal indicated that mortality attributable to malaria in children increased by as much as 6-fold among populations where low levels of malaria mortality had been achieved because of efficient health services before the emergence of chloroquine resistance. Increasing incidence of severe malarial anemia also contributed to human immunodeficiency virus dissemination. The dramatic impact of chloroquine resistance on malaria mortality has long been underestimated because only a low proportion of malaria attacks are potentially lethal among persons continuously exposed since birth to high levels of transmission. There is an urgent need to change treatment policies in Africa.

INTRODUCTION

Malaria control in Africa is based almost exclusively on chemotherapy, mainly by using chloroquine, the cheapest antimalarial drug. Chloroquine is routinely prescribed by outpatient clinics to treat fevers. Along with aspirin, it is also the only drug that is frequently kept at home by families and used for self-treatment. In most African countries, chloroquine remains in 2000 the only drug recommended by health authorities for the first-line treatment of uncomplicated malaria. Quinine is recommended for the treatment of severe and complicated malaria, and other drugs are rarely available in public health structures, even when mentioned in national malaria control programs as the second-line treatment for uncomplicated malaria.

Chloroquine-resistant strains of *Plasmodium falciparum* were first observed during 1978 in East Africa. Between 1978 and 1988, resistant parasites have been reported in all countries of tropical Africa. In each newly affected country, chloroquine resistance has progressed in 3 different ways: 1) it has spread in a growing number of locations and regions in the country; 2) the prevalence of resistant strains in each area has increased; and 3) the degree of resistance has intensified, with a relative reduction in RI-type responses in favor of RII- and RIII-type responses.

In 1993 Malawi became the first African country to change its national policy for the treatment of uncomplicated malaria from chloroquine to sulfadoxine-pyrimethamine.¹ More recently, Kenya and South Africa have also modified their national policies and have introduced sulfadoxine-pyrimethamine as the first-line treatment of malaria attacks. However, even in these countries chloroquine remains widely used, at least for self-treatment of fever cases. The reluctance of many African countries to reconsider the place of chloroquine in the treatment of malaria is based largely on the frequent observation that most patients treated with this drug improve clinically even though they remain parasitemic after treatment.

In Senegal, sentinel demographic surveillance systems have documented in 3 areas of the country a dramatic increase in malaria-attributable mortality temporally related to

the emergence of chloroquine resistance.² In this article, we review available data on the public health impact of antimalarial drug resistance in Africa. These data show that since the late 1980s convincing evidence of a major public health impact of the spread of chloroquine resistance has been available. The dramatic impact of chloroquine resistance on malaria mortality has long been underestimated because only a low proportion of malaria attacks are potentially lethal among African children exposed to high transmission.

MATERIALS AND METHODS

We have searched published literature to identify population-based studies and hospital-based studies in which malaria-specific mortality was monitored continuously when chloroquine resistance was emerging in the area. For each study with yearly estimates of malaria-specific mortality over a minimum period of 2 yr, we examined whether the study period was likely to cover the emergence of chloroquine resistance in the area, first by comparing the dates of data collection with those of the first report of chloroquine resistance in the country³ and then by further research of specific reports for the study area and population. For hospital-based studies, we also considered studies in which the prevalence of severe malaria among admitted children was monitored when chloroquine resistance was emerging and studies investigating direct or indirect morbidity and mortality attributable to the ineffectiveness of chloroquine treatment.

RESULTS

Population-based studies. Three studies measured malaria-specific mortality in childhood before, during, and after the emergence of chloroquine resistance. All were conducted in Senegal from 1984–1985 to 1995, in the Mlomp area (rain forest), the Niakhar area (Sahel), and the Bandafassi area (Sudan savanna).² The first therapeutic failures with chloroquine were observed in 1990 in Mlomp, in 1992 in Niakhar, and in 1993 in Bandafassi.⁴ In the following years, stan-

standardized surveys documented the intensification of chloroquine resistance. High levels of chloroquine resistance appeared rapidly in Mlomp (RII/RIII: 36% in 1991, 46% in 1995). Chloroquine resistance progressed less rapidly in Niakhar (RII/RIII: 10% in 1993, 29% in 1996) and in Bandafassi (RII: 6% in 1994, 16% in 1995). The emergence of chloroquine resistance has been associated with a dramatic increase in malaria mortality in each of the studied populations. In Mlomp, where malaria was hypoendemic and child mortality was low because of the widespread use of chloroquine for prophylaxis and treatment and because of important health programs, malaria became mesoendemic, and the incidence of malaria deaths in children under 10 yr has risen 5.5-fold. The increase in malaria mortality was particularly dramatic among children under 5 yr, with 0.5, 3.4, and 5.5 deaths per thousand children per year for the periods 1985–1989, 1990–1992, and 1993–1995, respectively. In Bandafassi, a holoendemic area where access to health care was limited, mortality attributable to malaria in children under 5 yr has risen 2.5-fold, from 4.2 to 11.4 per thousand per year for the periods 1984–1992 and 1993–1995, respectively. In Niakhar, a mesoendemic area where malaria transmission was the lowest of the 3 study areas, mortality attributable to malaria in children under 10 yr has doubled, from 4.0 to 8.2 per thousand per year for the periods 1984–1991 and 1992–1995, respectively.

Except in Senegal, studies of malaria mortality at the community level conducted between 1977 and 1999 in Africa either have been short term or were initiated after the emergence of chloroquine resistance. However, 2 studies were conducted a few years apart in the same area. At Bagamayo, a rural area of coastal Tanzania, mortality rates and causes of death were investigated during the years 1984–1985, i.e., when chloroquine resistance was emerging, and in 1992–1994, i.e., 10 yr after the emergence of chloroquine resistance.^{5–7} Overall child mortality remained unchanged between the 2 surveys, despite the introduction of a successful immunization program and a village health system. However, the proportion of deaths attributed to malaria was 2-fold higher during the more recent study.

Hospital-based studies. In Malawi, national health statistics of hospital admissions and deaths indicated that the incidence of admissions for malaria among children under 5 yr of age more than doubled during the period 1978–1983, with the case fatality rate remaining relatively constant and averaging 5%.⁸ Case reports of chloroquine prophylaxis failure in nonimmune visitors to Malawi had substantiated local emergence of resistant *P. falciparum* during this period,^{9,10} and studies among Malawian children conducted in 1984 at 6 surveillance sites in the country indicated that on average, 57% of children were parasitemic on Day 7 after standard malaria therapy with chloroquine.⁸

In Tanzania, data from mission hospitals indicated dramatic changes in malaria morbidity and mortality over the period 1968–1985.⁶ Whereas the rate of admissions due to malaria in these hospitals fluctuated around 10% during the late 1960s and throughout the 1970s, it has consistently risen during the early 1980s and was at 23% in 1985. Similarly, the percentage of total deaths due to malaria hovered around 3% during the 1970s, has constantly grown since 1981, and was 14% in 1985. Chloroquine resistance was demonstrated

for the first time in semi-immune Tanzanians in 1982.¹¹ The following year, a chloroquine resistance rate of 34% was reported among a Zanzibar school population.¹² Studies conducted between 1982 and 1985 in various areas of the country indicated that the median *in vivo* resistance rate in school children was 20%.⁶

In Congo-Kinshasa, a study was conducted from 1982 to 1986 at Mama Yemo Hospital, which was the largest medical center in Kinshasa and which served as a referral center for patients with severe malaria who had not responded to antimalarial therapy either at home or at 1 of the many clinics in the city.¹³ From 1982 to 1986, the total number of pediatric admissions and deaths remained relatively constant, but the proportional malaria admission rate increased significantly, from 29.5% in 1983 to 41.7% in 1984, to 45.6% in 1985, and to 56.4% in 1986. The proportional malaria mortality rate increased from 4.8% in 1982 to 7.0% in 1983, to 7.9% in 1984, to 8.9% in 1985, and to 15.3% in 1986. During this period, there were no significant changes in diagnostic capabilities or in medical personnel at the hospital that could account for the results. However, chloroquine-resistant *P. falciparum* malaria emerged in Kinshasa during the 5-yr study interval. In 1982, no case of *in vivo* or *in vitro* chloroquine-resistant malaria was detected in Kinshasa.¹⁴ The first evidence of *in vivo* chloroquine resistance in the city was observed in 1984,¹⁵ and by 1985 a total of 56% of *P. falciparum* infections in Kinshasa children were not cured by a standard regimen of 25 mg/kg chloroquine.¹⁶ By 1986 a total of 82% of *P. falciparum* parasites isolated from children at Mama Yemo Hospital exhibited *in vitro* resistance to the drug.¹⁷

Chloroquine resistance was first detected in Brazzaville, Congo, in 1985, and by December of that year 39% of Brazzaville children were not cured by 25 mg/kg chloroquine.¹⁸ Trends in the incidence of malaria admissions and cerebral malaria deaths in the 4 hospitals of Brazzaville were studied during the period 1983–1989.¹⁹ From 1983 to 1986, malaria admissions increased from 22% to 54% of total pediatric admissions and stabilized in the following years. Cerebral malaria deaths more than doubled during the period 1986–1989 compared to the period 1983–1985.

During the period 1986–1988, an upsurge of malaria-related convulsions was observed in the pediatric emergency room of Calabar Hospital, Nigeria.²⁰ The number of cerebral malaria cases more than doubled during this period. The increase in the incidence of cerebral malaria corresponded to the emergence of chloroquine resistance in this area of Nigeria, and 81% of children who were admitted to Calabar Hospital in 1988 for malaria-related convulsions did not respond to chloroquine.

In the absence of malaria treatment, anemia is a frequent complication of *P. falciparum* attacks in young children. In the late 1940s severe malarial anemia was the leading cause of malaria deaths in areas of Congo with limited access to antimalarial drugs.²¹ Its incidence decreased considerably when chloroquine became widely used, and severe malarial anemia was observed in less than 10% of the patients hospitalized with severe malaria in Brazzaville during the early 1980s (Trape JF, unpublished data).²² Until the late 1980s, few hospital studies in the literature mentioned anemia as a severe complication of *P. falciparum*, and most of them fo-

cused only on cerebral malaria. By contrast, since the late 1980s, numerous studies have highlighted the high prevalence of severe malarial anemia among hospitalized children, and most of these studies were conducted in areas with high levels of chloroquine resistance. In Banjul, The Gambia, a prospective study of 9,584 consecutive pediatric admissions to the Royal Victoria Hospital was conducted over 3 yr, from 1988 to 1990, when chloroquine resistance was emerging. During the study, there was a 27% annual increase in severe anemia owing to malaria.²³

Blood transfusions are widely used in referral hospitals to treat severe anemia, and this is likely to constitute a cause of human immunodeficiency virus (HIV) contamination in young children. The association between chloroquine resistance, severe anemia, blood transfusions, and HIV seropositivity was investigated in Kinshasa.²⁴ Malaria was the most frequent indication for blood transfusions in both hospitalized and emergency-ward pediatric patients. The annual number of blood transfusions remained unchanged from 1982 to 1985 and doubled in 1986 after the emergence of chloroquine resistance. A strong positive association between transfusions and HIV seropositivity was detected. Compared with children who received no transfusion, children who received 1 transfusion were 2.8 times more likely to be HIV seropositive, those who received 2 transfusions were 7.9 times more likely to be HIV seropositive, and those who received 3 transfusions were 21.9 times more likely to be HIV seropositive.

After the emergence of chloroquine resistance, a study in a district hospital in Kenya indicated that among children hospitalized for malaria, the risk of dying during hospitalization or within 8 wk after initial admission to hospital was associated with the antimalarial treatment received at admission.²⁵ Children who received chloroquine were significantly more at risk of dying than those who received either sulfadoxine-pyrimethamine, quinine, or sulfamethoxazole-trimethoprim. The risk of dying was increased significantly both in hospital and out of hospital, and for both children with severe anemia and those without severe anemia. The overall proportion of deaths attributable to the ineffectiveness of chloroquine treatment was 60%. Because of the striking effect of treatment on survival from malaria, sulfadoxine-pyrimethamine was provided as the first-line therapy for children admitted to that hospital with malaria beginning in February 1992. The case fatality rates decreased from 9.9% in 1991 to 5.1%, 3.6%, and 3.3% in 1992, 1993, and 1994, respectively (Zucker JR and others, unpublished data).

It has been a general observation from malaria control programs using DDT spraying, insecticide-impregnated bed nets, and chemoprophylaxis that effective malaria control may prevent more deaths than the number of deaths previously attributed to malaria in the same population.²⁶ One reason is the contribution of the health services—created or improved for malaria control—to the management of other health problems as well as to the general health information and education of the population. However, another possible factor is that malaria affects the capacity of the organism to resist concomitant diseases. It has been shown that drug resistance is an important factor in producing anemia or preventing optimal hematologic recovery in children receiving noneffective malaria treatment.^{1,27} It is likely that the case

fatality of certain diseases increases in the presence of malaria-associated anemia, which is related to the intensity and duration of parasitemia.

Other possible consequences of chloroquine resistance.

In most areas of tropical Africa, chloroquine chemoprophylaxis is now poorly effective for preventing *P. falciparum* infections during pregnancy. Malaria in the pregnant woman increases the risk of low birth weight, which represents the greatest single risk factor for neonatal and early infant mortality.^{28,29} This suggests that chloroquine resistance may also have resulted in higher levels of infant mortality through decreased efficacy of chemoprophylaxis recommended to pregnant women.

Chloroquine was not only a very effective drug before resistance emerged, but also a safer antimalarial when used orally. Although the problem of the true incidence of severe side effects of most antimalarials is poorly documented, there is little doubt that the increasing use of alternative antimalarials has increased the risk of serious drug-related adverse effects and also the risk of septic and traumatic complications associated with increased use of intramuscular injections.³⁰ Persons living in highly malaria-endemic areas develop an average of about 100 episodes of fever during their lives, and about half of these episodes are malaria attacks.³¹ Even if the incidence of serious adverse effects is relatively low when dosage is correct (e.g., between 0.5 and 1 instances per 10,000 treatments for sulfadoxine-pyrimethamine and amodiaquine),^{32,33} the use of alternative drugs may mean that about 0.5% of Africans would become potentially at risk of severe side effects of antimalarials during their life.

For most African countries, there are no national data on causes of death. However, data on the levels and trends of overall child mortality are often available at the national level from surveys and censuses. In the case of Senegal, the risk that a newborn child would die before the age of 5 yr declined to 287, 236, 191, and 131 per 1,000 during the periods 1971–1975, 1976–1980, 1981–1986, and 1988–1992, respectively.³⁴ By contrast, the most recent survey indicated that child mortality was 139 per 1,000 during the period from March 1992 to March 1997. This change in the national trend was concomitant with the generalization of chloroquine resistance in the whole country and the increase in malaria mortality in the 3 sites with continuous health and demographic surveillance systems, an indication that the recent increase in child mortality in Senegal could be related to chloroquine-resistant malaria.² In The Gambia, data from population censuses and various other sources showed rapid improvements in mortality among those younger than 5 yr from the late 1960s to the late 1980s; however, as in Senegal, overall mortality stabilized or even increased in the early 1990s when chloroquine resistance emerged.³⁵

DISCUSSION

There is now strong evidence that the emergence and spread of chloroquine resistance has had a dramatic public health impact in Africa. Although here and elsewhere other factors—such as civil unrest, environmental changes, deterioration of public health systems, HIV dissemination, decreasing availability or increasing cost of drugs, and changes in treatment-seeking behaviors—could also be occurring

contemporaneously with rising chloroquine resistance and could be contributing to increased malaria mortality, in most studies reviewed here these factors could be reasonably excluded. Furthermore, the emergence of chloroquine-resistant *P. falciparum* was generally explosive and was immediately followed by a dramatic increase in malaria mortality, with these 2 phenomenon being clearly temporally related. There was also evidence that even moderate levels of chloroquine resistance—i.e., 15–25% RII parasitological responses in semi-immune children—could be associated with a significant increase in malaria mortality. Because high levels of chloroquine resistance are currently observed in most densely populated areas of tropical Africa, we suggest that malaria-specific mortality has probably doubled or more in Africa during the last 15 yr. Furthermore, it is likely that increased malaria-related anemia has had significant effects on mortality from other diseases and has contributed to HIV dissemination among children. Such a dramatic impact was considered as certain by most experts in the 1970s and early 1980s, i.e., before the emergence and spread of chloroquine resistance, and was rapidly confirmed by national health statistics in Malawi⁸ and Tanzania⁶ and by a hospital-based study in Kinshasa.¹³ However, by contrast, many subsequent studies in Africa concluded that there was no urgent need to change national policies for the treatment of malaria from chloroquine to alternative drugs.

We believe that 2 main factors have long masked the real impact of chloroquine resistance. First, only limited data from prospective mortality studies were available. Although several dozens of community studies of malaria mortality have been conducted in Africa,³⁶ most of them have been short term, and only those conducted in Senegal have collected data in the same community before, during, and after the emergence of chloroquine resistance. The number of hospital-based studies that documented the impact of chloroquine resistance was also limited. Second, by contrast, a number of *in vivo* studies of chloroquine efficacy were carried out. With the progression of chloroquine resistance, these studies indicated that an increasing number of patients treated with chloroquine did not clear their parasitemia, but also that severe complications were rarely seen. Because most patients improved clinically within a few days, even in the case of parasitological failure, the assumption was that chloroquine retained sufficient efficacy to justify its use even though a majority of patients remained parasitemic.^{1,37}

To explain this paradox, it is necessary to consider the potential lethality of each malaria attack occurring among patients living in highly malaria-endemic areas. The daily clinical monitoring of cohorts of children in Congo and Senegal has shown that most individuals suffer several dozens of malaria attacks during childhood.^{31,38} Over a period of 1 yr, a cohort of 1,000 children aged 0–4 yr presents about 2,000 malaria attacks in areas of moderate seasonal transmission and 4,000 malaria attacks in areas of intense perennial transmission. Even when malaria mortality is high, e.g., 15 malaria deaths per 1,000 children per year (as observed in African populations with poor access to antimalarials or high levels of chloroquine resistance), this implies that the risk of death for each malaria attack remains very low, because the 985 surviving children will total 1,970 (or 3,940) malaria attacks during this given year. For the whole cohort

of 1,000 children aged 0–4 yr, only 1 attack out of 132 (or 264) will lead to death, even though these children represent the most at-risk group in the community. In the case of the Mlomp study in Senegal, analysis of demographic, epidemiological, and clinical data indicated that only 1 malaria attack in 500 was lethal in children aged 0–4 yr after the emergence of chloroquine resistance despite an 11-fold increase in malaria mortality in this age group due to chloroquine resistance (Trape JF, unpublished data).² The low lethality of malaria attacks under conditions of high endemicity explains why severe complications occur rarely during *in vivo* tests, even when they are conducted among young children using poorly effective drugs. Furthermore, for evident ethical reasons, most *in vivo* studies of chloroquine efficacy in Africa were carried out under close clinical surveillance and among either asymptomatic subjects, patients belonging to age groups not exposed to high malaria mortality, or selected young children with mild or very mild malaria symptoms. In semi-immune children and adults, the peaks of high parasitemia that are responsible for fever are spontaneously controlled within a few hours or days, and symptoms would disappear rapidly even if no malaria treatment were available.^{39,40}

CONCLUSIONS

Since the early 1950s, chloroquine has saved the life of dozens of millions of Africans. There is now strong evidence that the spread of chloroquine resistance is having a dramatic impact on public health, with hundreds of thousands of children dying each year because this drug has lost its efficacy. The primary purpose of a malaria drug policy is to ensure prompt, effective, and safe treatment of malaria disease.⁴¹ Clearly, this is no longer the case today in many parts of Africa where high levels of chloroquine resistance have been documented for many years. Although many factors need to be considered in the development of a national antimalarial drug policy,⁴² effective alternative drugs exist and can be used in a way that minimizes the selection pressure for drug resistance.⁴³ Amodiaquine and sulfadoxine-pyrimethamine are still very effective in most parts of Africa, and their lifespan can be extended by combination with artemisin in derivatives or other antimalarials. These drugs must be rapidly available for the first-line treatment of malaria attacks in young children, and they must be part of large programs with close monitoring of malaria-specific and all-cause mortality in children, side effects of drugs, treatment-seeking behavior, and trends in parasite sensitivity to drugs. Clearly, there is an urgent need to change treatment policies in Africa.

Acknowledgments: We are grateful to Peter Bloland and Trenton Ruebush, who stimulated the idea for this review. A first draft was prepared as a position paper for the Centers for Disease Control meeting “Confronting the Challenges of Antimalarial Drug Resistance in Africa,” Harare, Zimbabwe, November 9–12, 1998, and was also presented at the Multilateral Initiative on Malaria’s African Malaria Conference, Durban, South Africa, March 14–19, 1999.

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