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**AFRICA CHILD SURVIVAL INITIATIVE
COMBATting CHILDHOOD COMMUNICABLE DISEASES
(ACSI-CCCD)**

MALARIA PREVENTION IN PREGNANCY: THE MANGOCHI MALARIA RESEARCH PROJECT



MALARIA



UNITED STATES AGENCY FOR INTERNATIONAL DEVELOPMENT
Africa Regional Project (698-0421)



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
and Prevention
International Health Program Office



**Malaria Prevention in Pregnancy:
The Effects of Treatment and Chemoprophylaxis on
Placental Malaria Infection,
Low Birth Weight, and Fetal, Infant, and Child Survival**

Mangochi Malaria Research Project (MMRP)

**Africa Child Survival Initiative -
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ABBREVIATIONS

ACSI-CCCD	AFRICA CHILD SURVIVAL INITIATIVE - COMBATTING CHILDHOOD COMMUNICABLE DISEASES
A.I.D.	AGENCY FOR INTERNATIONAL DEVELOPMENT
ANC	ANTENATAL CLINIC
CI	CONFIDENCE INTERVAL
CQ	CHLOROQUINE
GMPD	GEOMETRIC MEAN PARASITE DENSITY
HCT	HEMATOCRIT
HIV-1	HUMAN IMMUNODEFICIENCY VIRUS - TYPE 1
HIV-	HIV-1-SERONEGATIVE
HIV+	HIV-1-SEROPOSITIVE
IUGR	INTRAUTERINE GROWTH RETARDATION
LBW	LOW BIRTH WEIGHT
MH	MANTEL HAENSZEL
MHA-TP	MICROHEMAGGLUTINATION ASSAY FOR ANTIBODIES TO <i>TREPONEMA PALLIDUM</i> (SEROLOGIC TEST FOR SYPHILIS)
MOH	MINISTRY OF HEALTH
MQ	MEFLOQUINE
MMRP	MANGOCHI MALARIA RESEARCH PROJECT
NMR	NEONATAL MORTALITY RATE
OR	ODDS RATIO
PNMR	POSTNEONATAL MORTALITY RATE
RPR	RAPID PLASMA REAGIN (SEROLOGIC TEST FOR SYPHILIS)
RR	RELATIVE RISK
SD	STANDARD DEVIATION
SP	SULFA-PYRIMETHAMINE (E.G., SULFADOXINE-PYRIMETHAMINE, SULFALENE-PYRIMETHAMINE)
USAID	UNITED STATES AGENCY FOR INTERNATIONAL DEVELOPMENT
VDRL	VENEREAL DISEASE RESEARCH LABORATORY (SEROLOGIC TEST FOR SYPHILIS)
WHO	WORLD HEALTH ORGANIZATION

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I. EXECUTIVE SUMMARY AND KEY FINDINGS

Plasmodium falciparum infection in pregnant women leads to placental infection and low birth weight (LBW: <2500 grams) of the infant, particularly in the areas of high malaria transmission found in sub-Saharan Africa. Low birth weight is widely known to be an important risk factor for early infant mortality. To reduce the risk that maternal malaria infection poses to child survival, many antenatal clinic programs provide and recommend antimalarial chemoprophylaxis, often with chloroquine (CQ), as a recommended element for prenatal care. Prior to the 1980s, despite widespread advocacy for this intervention, little was known about the effect of this intervention strategy.

During the 1980s, CQ resistance spread rapidly across the African continent, and malaria control programs were increasingly faced with the concern that chemoprophylaxis with CQ was becoming less effective. In addition, other concerns regarding prenatal malaria prevention program effectiveness loomed. Could the malaria intervention be targeted to "high-risk" pregnancies on the basis of parity, season, or other criteria, and could such targeting allow for improved coverage? How much LBW and which types of LBW (due to prematurity or intrauterine growth retardation [IUGR]) were attributable to malaria and could be prevented, and what impact would this have on mortality reduction in infancy? What alternative regimens or drugs could be used to enhance the efficacy and effectiveness of malaria control programs? What were the best strategies to address other infectious diseases such as syphilis and human immunodeficiency virus–type 1 (HIV) in pregnant women and the interaction of the diseases with each other? Health planners recognized the importance of defining how malaria control in pregnancy could best be linked with other services in a rational and affordable program.

Under the United States Agency for International Development (A.I.D.) Africa Child Survival Initiative - Combatting Childhood Communicable Diseases (ACSI-CCCD) Project, the Malaria Branch and the International Health Program Office of the Centers for Disease Control and Prevention collaborated with the Malawi Ministry of Health to address these regionally important issues.

Four major questions were addressed by the Mangochi Malaria Research Project (MMRP) investigation of malaria treatment and prevention in pregnant women:

- 1) How much LBW and infant mortality could be reversed by a highly efficacious intervention in pregnancy against *Plasmodium falciparum* infection?
- 2) Could target groups for intervention be defined by identifying characteristics of pregnancies at highest risk of *P. falciparum* infection and LBW?
- 3) What are the characteristics of an efficacious drug regimen in terms of timing of delivery and impact on parasitemia and placental malaria infection?
- 4) What are the optimal methods to implement an efficacious intervention program?

The MMRP was developed as a longitudinal project to examine the first three questions with the expectation that the answers to the questions, coupled with project experience and work by other investigators, would help answer the fourth question.

Several issues were critical to the establishment of the MMRP. The site of the study, Mangochi District, with its four antenatal clinics and delivery units, provided a setting of high *P. falciparum* transmission with some seasonal variation; the area was rural with a local economy based on family farming and some fishing. Thus, the setting was representative of many parts of rural sub-Saharan Africa. The sample size of the study needed to be large enough to examine 1) malaria infection in the mother and her infant and 2) birth weight as the outcome of interest among women on different regimens of antimalarial treatment and chemoprophylaxis. The study needed to be conducted long enough to follow infants through their first year of life to determine the effect of birth weight on infant survival. A sufficient sample size was established — 4220 pregnant women and their children; the study lasted nearly 3 years, from September 1987



through June 1990. The study site chosen had to be one where high rates of follow-up of both pregnant women and their infants could be achieved, and local information suggested that migration in and out of Mangochi District was limited. Finally, a spirit of collaboration had to exist to ensure the high degree of community and national involvement desired. The Ministry of Health and the Malawian collaborators had previously developed excellent relations with local health staff, including traditional birth attendants in the district.

Principal Findings

Gravidity-specific risk for malaria infection in pregnancy: Pregnancy number was an important determinant of malaria infection in the woman, her placenta, and the umbilical cord blood of the newborn. At enrollment, 44.5% of all women were parasitemic; 67% of primigravidas were parasitemic. At delivery, placental malaria was identified in 19.9% of all women and in 29.9% of primigravidas.

Gravidity-specific and seasonally associated effects of *P. falciparum* on birth weight: The mean birth weight of the babies born to women enrolled in the study was 2905 grams; 16.6% had LBW. Birth order was an important predictor of LBW: firstborns were 3.1-fold (28%) more likely to be born with LBW than infants of subsequent birth order (11.1%), respectively, $p < 10^{-6}$. The incidence of LBW in each parity group was higher for babies born to women with placental malaria infection than for those without placental malaria. The association between placental malaria infection and LBW in firstborns was observed particularly among women whose third trimester of pregnancy was exposed to high malaria transmission during the rainy and early post-rainy season.

Congenital malaria infection: Umbilical cord blood malaria infection was identified in 7.1% of newborns and was highly correlated with the density of placental malaria infection. Umbilical cord blood malaria was associated with LBW, and particularly with preterm-LBW.

Attributable risk of malaria infection and low birth weight: The study demonstrates that umbilical cord blood malaria is associated with preterm-LBW and that placental malaria infection is associated with IUGR-LBW and possibly preterm-LBW in firstborns. Overall, malaria in pregnancy may account for as much as 12% of LBW babies born to women in this area of high malaria transmission.

Comparison of the effect of CQ and mefloquine (MQ) on placental infection and on birth weight: Mefloquine was much more likely than CQ to clear placental infection. Of the primigravidas on CQ, 46% had placental malaria infection compared with 9% of the primigravidas on MQ. Mefloquine was more effective among multigravidas as well: 15% on CQ and 3% on MQ had placental malaria infection. In each parity group, the incidence of LBW was lower for women who had no placental malaria, regardless of the drug used to keep the placenta parasite-free. Women in this study were followed for an average of just over 3 months. Clearance of placental infection in the last trimester of pregnancy appeared adequate for the effect of improved birth weight among protected women.

Birth weight as a determinant of neonatal and infant survival: The neonatal mortality rate in the study was 48.7 per 1000 live births. Compared with babies of normal birth weight, babies born in the lower weight groups of 2000-2499 grams, 1500-1999 grams, and below 1500 grams were 2.4, 11.5, and 27.1 times more likely to die in the neonatal period. Mortality in the postneonatal period was also associated with birth weight. Compared with infants of normal birth weight who survived the neonatal period, infants of LBW who survived the neonatal period had a 4.1-fold higher risk of dying in the postneonatal period.

Emerging impact of HIV on *P. falciparum* infection, birth weight, and survival: Compared with HIV-1–seronegative (HIV–) women, HIV-1–seropositive (HIV+) women were more likely to have a higher prevalence and density of malaria parasitemia at enrollment, at follow-up on CQ chemoprophylaxis, and at delivery. Increased rates and density of placental parasitemia were observed in HIV+ mothers compared with HIV– mothers. The difference was greatest in later parities; one explanation is that HIV adversely affects the malaria-immune response that is established following malaria infection in the early pregnancies. HIV infection of the mother was also associated with a 2.5-fold increased risk of LBW. HIV was associated with high mortality among women during the study and may have contributed to the deaths of 7 of the 12 women who died after the postpartum interval.

The effect of other infectious agents in pregnant women and their newborns: Syphilis during pregnancy had a significant effect on fetal, neonatal, and postneonatal mortality. Women with active syphilis were more likely to have a stillborn infant or to deliver a baby with LBW. Babies born to women with active syphilis were more likely to die in the neonatal and postneonatal periods. An estimated 9% of neonatal deaths were caused by tetanus, using the case definition of the World Health Organization (WHO). This relatively small but preventable fraction may reflect the limitations of the impact of the antenatal tetanus immunization program.

The delivery of antimalarial interventions within the antenatal care system in Malawi: Almost all pregnant women in Malawi attend antenatal clinic at least once, and 85% attend two or more times during the pregnancy. Local beliefs that lead women to avoid bitter substances such as CQ during pregnancy and the difficulty of remembering to take weekly prophylaxis at home led to low levels of overall compliance with weekly CQ prophylaxis. The prevailing practice at the time of the study of providing health education and a 4-week supply of CQ prophylaxis was linked to an overall compliance rate of approximately 35% of attending women taking regular chemoprophylaxis.

Conclusions

This study determined that use of an efficacious antimalarial drug will reduce malaria infection in the pregnant woman, her placenta, and the umbilical cord blood, and that this will lead to improved birth weight in the population. These data from the MMRP clearly establish that interventions are required and should be promoted to reduce the effect of *P. falciparum* infection in pregnancy on LBW and its attendant risk for neonatal and infant mortality.

The antimalarial drug must essentially eliminate placental parasitemia and be administered presumptively. Although clearance of malaria infection throughout pregnancy is ideal, it appears that administration of antimalarials only during the third trimester will still have a beneficial effect on reducing the incidence of LBW.

The intervention can and should be targeted to “high-risk pregnancies” on the basis of gravidity and season. In settings of high endemicity and perennial transmission, women in their first and second pregnancies should receive the intervention, particularly women whose second half of pregnancy occurs during the high transmission season.

Control of parasite density may have an important effect on other health conditions (e.g., anemia), which may also place a woman or her infant at risk of illness or death.

The increasing incidence and prevalence of HIV infection may increase the impact of *P. falciparum* in pregnancy. Beyond HIV’s potentiation of *P. falciparum* infection in pregnancy, *P. falciparum* in combination with HIV may markedly increase the risk of infant mortality. Although these

interactions require further exploration, they have implications for expanding the range of "high-risk pregnancies" requiring malaria prevention to include women with HIV infection.

An antimalarial intervention strategy for "high-risk pregnancies" should be incorporated in a malaria control program or antenatal care program.

Several drugs are available that share the characteristics demonstrated by MQ in this study. The ideal is a safe drug that provides complete clearance of parasites from the placental blood and has pharmacokinetic properties that allow intermittent treatment or chemoprophylaxis. In areas where the drug is known to be highly efficacious in clearing malaria parasites, CQ (in settings like Haiti), sulfa-pyrimethamine combinations (e.g., sulfadoxine-pyrimethamine, sulfalene-pyrimethamine) in sub-Saharan Africa, and MQ all have these properties. Recent studies conducted at the Mangochi study site have demonstrated that a regimen of sulfadoxine-pyrimethamine given as a treatment dose at the first antenatal clinic visit and again at the beginning of the third trimester was highly effective in reducing malaria infection in mothers and their placentas. This identification of an effective, affordable, and deliverable intervention has been pivotal in offering health workers a practical tool for the prevention of malaria and LBW in African settings. Major challenges to increased program effectiveness include the requirements for complete coverage of the "high-risk pregnancies" and full acceptance and compliance among these women. In some settings (e.g., rural Kenya), the primigravidas at highest risk of the effects of *P. falciparum* infection are the least likely to attend antenatal clinics for preventive services. Thus, strategies to increase access for these women must be a high priority in the program.

Finally, in our efforts to improve child survival in sub-Saharan Africa, we must take a broad perspective. The mother's health both during pregnancy and postpartum may determine as much or more than 30% of the risk for child mortality in sub-Saharan Africa. Although treatment and prevention of *P. falciparum* infection in pregnancy was the focus of the MMRP, the studies have identified a series of interrelated nutritional, infectious, socioeconomic, and educational factors that must be addressed. Antenatal care programs must pay special attention to women in their first pregnancies and, particularly, young women in their first pregnancies. The recognition and management of HIV and syphilis infection must be strengthened. Although sometimes based outside antenatal care programs, tetanus prevention efforts must continue to be programmed using vaccine and clean delivery methods as prevention. Improving micronutrient deficiency (e.g., iron and folate), improving general nutrition, and reducing caloric expenditure in pregnant women who often work in the fields must remain a priority. Finally, access to antenatal care and to delivery attended by trained health care workers will be a critical feature of identifying and managing high-risk pregnancies. These factors must be addressed as a package of services and not in a fragmented fashion if antenatal clinic services are to be effective in promoting maternal health care and improved newborn, infant, and child survival.

II. THE PROBLEM OF MALARIA AND MALARIA CONTROL IN PREGNANCY

A. THE EPIDEMIOLOGY OF MALARIA IN PREGNANCY

The clinical effects of malaria on a community are determined by the degree of the residents' exposure to malaria and the age-specific levels of immunity. Compared with nonpregnant women, pregnant women are at increased risk of malaria infection and its disease consequences in settings of both low and high transmission of malaria (1-4). However, the actual manifestations of malaria may differ between settings with low and high transmission and consequent low and high levels of antimalarial immunity.

In settings with low levels of malaria transmission, where women of reproductive age have relatively low levels of acquired immunity, all pregnant women are comparably susceptible to malaria. Reports of adverse outcomes of pregnancy associated with *P. falciparum* infection have included an increase in maternal illness (3-6) (e.g., fever or severe malaria with central nervous system complications), fetal loss (3-5,7,8) (abortions [gestational age <28 weeks] or still-birth [gestational age \geq 28 weeks]), and congenital infection possibly leading to symptomatic malaria in early infancy (8,10).

In much of sub-Saharan Africa, where stable transmission of *P. falciparum* malaria is the rule, women of child-bearing age have acquired a relatively high degree of immunity to the parasite through repeated exposure. During pregnancy, through mechanisms that are not fully understood, women demonstrate an increased susceptibility to *P. falciparum* and experience a higher frequency and density of parasitemia (9,11,12), particularly in the first "malaria-exposed" pregnancy (13). In subsequent pregnancies, multigravidas generally do not have a higher risk of malaria, as measured by prevalence or density of parasitemia, than do nonpregnant women of similar age in the same setting (1,2,9). Despite the acquired immunity in these women, the utero-placental vascular space apparently provides a protected site for parasite sequestration and development (11,14). It is this parasite replication in the placenta, the potential local effects on altered nutrient transport across the placenta, and the passage of parasitized red blood cells to the fetus which, although causing no symptoms in the mother, may seriously compromise fetal growth and the survival of the newborn infant.

The following discussion addresses the effects of malaria on pregnant women, their fetuses, newborns, and infants in a setting of high malaria transmission. The setting chosen for this study, rural Malawi, is a high transmission area and is representative of large areas of sub-Saharan Africa, where P. falciparum infects pregnant women.

Complications of malaria in pregnancy: maternal effects

Maternal malaria infection: Numerous studies have shown that the frequency and density of malaria infection in pregnant women is higher than in nonpregnant women in the same setting (2,9). Early investigations concluded that all pregnant women are more susceptible to malaria infection, and recent information has shown that this susceptibility is most striking in women in their first pregnancies, and to a lesser degree in second pregnancies. In later pregnancies, the prevalence and density of malaria infection is not notably increased (15). Assuming that pregnant women have experienced the same relative level of exposure to malaria over their lifetimes, this finding of different risk by pregnancy number suggests that exposure to malaria during one pregnancy may confer some protection in a subsequent pregnancy, and after several pregnancies have been exposed to malaria, pregnancy-specific immunity is well established.

The mechanism of increased susceptibility during pregnancy has not been elucidated. Hormonal changes during pregnancy may affect immunologic response (16). However, this explanation does not account for the differences observed in successive pregnancies as each pregnancy should experience the same type of hormonal changes. Thus, diminished immune responsiveness due to pregnancy will not fully explain the gravidity-specific differences in susceptibility to malaria.

Maternal illness: Few investigators have reported on clinical malaria in pregnant women in highly endemic malarious areas, probably because, despite increased rates of parasitemia and higher parasite density, pregnant women do not exhibit marked clinical signs of malaria (e.g., high fever, chills) with high frequency. These women may experience clinical malaria; however, it is not a prominent feature of the infection.

Maternal anemia: Pregnant women are more likely than nonpregnant women to be anemic for a variety of reasons. The dilutional effect of increased plasma volume is well known and leads to a normal decrease in hemoglobin and hematocrit, approximately 10% to 15% below the normal values for a nonpregnant woman (17). In women with poor iron stores, the increased demands of the fetus may lead to relative deficiencies of iron, which will lead to anemia. Similarly, the increased need for folic acid in pregnancy requires that dietary sources be increased or supplements given to prevent folate-deficiency-associated anemia (18). In the context of sub-Saharan Africa, hemoglobinopathies (e.g., sickle-cell trait), marginal nutrition with protein-energy expenditure greater than intake, and infections with malaria, hookworm, and other viral, bacterial, or parasitic pathogens may also contribute to anemia in pregnant women (19). Finally, acute bleeding episodes due to complications of pregnancy (e.g., placenta previa, abruptio placenta) may lead to acute, severe anemia with serious consequences to the mother and fetus.

Given these multiple causes of anemia in pregnancy, the contribution of malaria to maternal anemia has been difficult to ascertain. Studies in hospital settings have led the investigators to be alarmed at the severity of the problem of malaria-associated anemia in pregnancy (20,21). However, other studies have demonstrated relatively minor changes in mean hemoglobin levels due to malaria infection (19,22); the effect has been greatest in women of lower gravidity — the women who are more susceptible to malaria infection and higher density parasitemia.

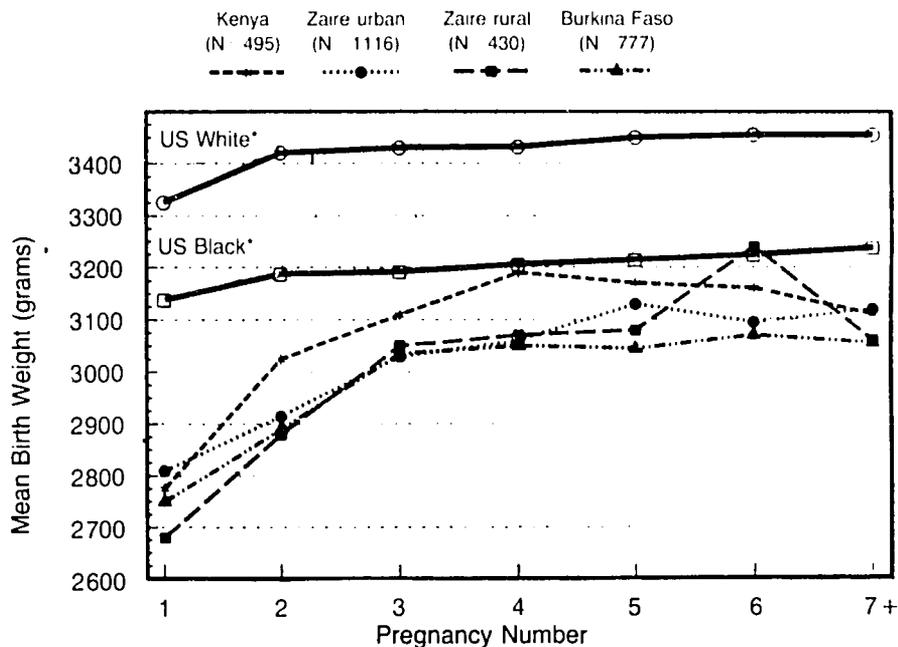
In malarious areas, the effect of maternal anemia on the outcome of pregnancy is also not fully understood. Certainly, the acute bleeding episodes described above have dire consequences for the survival of both the mother and fetus. However, most studies of the effect of mild-to-moderate pregnancy-associated anemia have been conducted in nonmalarious areas. The effects on the outcome of the pregnancy and the survival of the fetus may be difficult to interpret in Africa, where more than 50% of the population of pregnant women would be considered anemic by World Health Organization (WHO) standards (hemoglobin < 11.0 g/dl.).

Maternal mortality: In general, severe malaria illness has not been shown to be increased during pregnancy in settings of high malaria transmission, and maternal mortality due to malaria is uncommon. Few studies in sub-Saharan Africa have examined either the direct effect of malaria on maternal mortality or the secondary effect of malaria-associated anemia on maternal mortality, chiefly because, despite relatively high levels of maternal mortality, malaria-related mortality during pregnancy in areas with stable transmission appears infrequent, often occurs outside the health care setting, and is associated with other causes including hemorrhage and sepsis.

Complications of malaria in pregnancy for the fetus and newborn

Low birth weight: Low birth weight (LBW) represents the greatest single risk factor for neonatal and early infant mortality (23). Thus, the birth-weight distribution in a population will have a great effect on early infant mortality in that population. Figure 1 shows the mean birth weights by birth order (pregnancy number) of two U.S. populations (black and white) and four African populations. The greatest difference in mean birth weights of African infants and black infants born in the United States is found in first- and second-born children. The explanation for the observed differences in birth-weight distributions in the populations is multifactorial; however, the marked discrepancy in first and second births may be partially related to *P. falciparum* infection, which has its greatest effect on these pregnancies.

Figure 1. Mean birth weight of different populations in the United States and in sub-Saharan African countries.



*Data from NCHS, 1980.

The biologic mechanism by which placental malaria infection leads to LBW is not fully established. The presence of the parasite in the placenta causes thickening of the basement membrane of the placental trophoblast cells (cells at the utero-fetal interface) with the potential consequence of reduced nutrient transfer to the fetus (1-4,24). The placental infection is also frequently accompanied by a monocytic and macrophage infiltrate (1-4,24); however, mechanisms

by which the infiltrates might alter nutrient transport or stimulate premature delivery have not been described.

Although changes such as microinfarcts could occur, these changes have not been reported. Finally, passage of parasite-infected red blood cells from uterus to fetus does occur. This fetal infection may have consequences for nutrient use in the fetus, or the infection may stimulate early delivery — again, no mechanisms to explain this have been described.

Several investigations have demonstrated an association between placental infection and LBW of the infant, particularly in firstborns (2,9). The largest investigation of this problem occurred in The Gambia, where the effect of placental malaria on LBW was greatest and significant only in firstborn babies (11). Although pregnant women in settings of high malaria transmission generally remain asymptomatic despite their parasitemia and placental malaria infection, their newborns are at risk of LBW and its attendant link to early mortality.

Birth-weight-specific mortality rates are not uniform and depend directly on the cause of the LBW — either prematurity (delivery at less than 37 weeks gestation) or intrauterine growth retardation (IUGR [LBW for gestational age]) (25). Few data have been available from sub-Saharan Africa on birth-weight-specific and prematurity- or IUGR-specific mortality rates; data from developed countries suggest that early infant mortality rates associated with prematurity are much higher than mortality rates in IUGR infants (25).

Prematurity: Literature citations prior to 1976 stated that malaria in pregnancy caused prematurity, and no distinction was made between types of LBW — prematurity or IUGR (26-30). However, more recent studies have not been able to demonstrate an effect of placental malaria on preterm delivery. Studies in The Gambia found some evidence to suggest that malaria in pregnancy was associated with prematurity (differences in fetal-placental weight ratios) (11) but could not demonstrate this definitively because of imprecise gestational age determination due to difficulties in obtaining a history of the last menstrual period or recognition of the first fetal movement.

IUGR: Recent studies (2,11,31,32) have suggested that malaria leads to IUGR and not prematurity. However, the distinction between IUGR and prematurity may have been difficult for the same reason as in the study in The Gambia. One explanation of the mechanism of placental infection leading to LBW presumes an altered maternal-fetal nutrient transport induced by the parasite. This explanation supports malaria infection's link to IUGR rather than to prematurity.

Based on limited supporting data, the consensus is that placental infection with *P. falciparum* leads to IUGR, but whether placental malaria infection contributes to prematurity in areas of high malaria transmission is unclear.

Congenital infection: The incidence of congenital malaria infection (malaria infection in early infancy due to passage of parasites from mother to fetus) in highly-endemic malarious areas has been thought to be low. Numerous studies, some of which have been summarized by Kortmann (9), demonstrated that among women with demonstrated placental malaria infection, approximately 12% of their babies had umbilical cord blood parasitemia and fewer than 1% of newborns had peripheral parasitemia. Because of these findings and because of the paucity of neonates with clinical malaria in African pediatric wards, congenital malaria was assumed to be of little clinical importance in areas of high malaria endemicity.

The biologic explanation for this observed lack of congenital malaria has been that mothers pass high levels of antimalarial antibodies to their infants and that this passively acquired protection keeps the infant parasite-free (33-35).

The effect of malaria in pregnancy on fetal and infant survival

Abortions: There are limited data about the effect of malaria on fetal survival in highly endemic areas (1,2,13,32,36). While this lack may reflect limitations on the part of the health infrastructure to report fetal loss in association with malaria in pregnancy, in populations with relatively high levels of immunity to malaria, malaria is not believed to be an important contributor to fetal loss (1,9). However, there is not full agreement on this issue (2).

Perinatal deaths: The perinatal period overlapping birth (from >28 weeks gestation to 7 days after birth) is often examined as a unit because the causes of morbidity and mortality for stillbirths and early neonatal deaths are frequently the same or closely related. In addition, the identification of a stillbirth versus a live birth who dies soon after delivery is frequently culturally defined, and standard definitions are often difficult to apply. The effect of malaria on perinatal death in highly endemic areas has been examined in several studies, and no clear contribution has been observed. However, few studies have examined simultaneously additional factors that contribute to perinatal mortality such as syphilis or human immunodeficiency virus–type 1 (HIV) infection. Consequently, because malaria is not thought to contribute greatly to stillbirth, malaria's contribution to perinatal death may be only in the early neonatal period through LBW-associated mortality.

Neonatal and infant deaths: Although the contribution of malaria to neonatal and postneonatal death is thought to be largely due to malaria's contribution to LBW, the effect of malaria-associated LBW on infant death has not been quantified. Because of the important effect of LBW on infant mortality, one would expect that the effect of malaria in pregnancy on infant mortality would be mediated through its effect on LBW and would be substantial.

Other conditions contributing to fetal or early infant mortality: Several infectious diseases (e.g., HIV, syphilis) that are relatively common in Africa south of the Sahara may contribute to perinatal mortality. Thus, in examining the role of malaria and its contribution to perinatal mortality in the African context, the contribution of other diseases must be examined at the same time; few studies have examined different infectious diseases simultaneously.

The effect of malaria in pregnancy on malaria protection in infancy

Numerous reports suggest that mothers pass to their newborns a certain degree of protection that may be related to the amount of acquired immunity the mother has gained with repeated exposure to malaria (33,37-40). The degree of protection and the length of protection from malaria infection and illness have been less clear (33,40) and may vary with the transmission setting (40). In general, infants in areas with stable and intense transmission appear to have a 1- to 3-month interval, which roughly correlates with the half-life of maternally derived immunoglobulin G levels, before they experience their first malaria parasitemia. Increasing parasitemia levels and parasitemia associated with clinical symptoms develop, in general, after 4 to 6 months, when maternally derived immunoglobulin G is nearly absent. Information does not exist to describe which of these conditions is operating and whether placental malaria has an effect on the protection against malaria in the newborn.

Transplacental passage of parasite antigen and its priming of the fetal immune response have been suggested but not fully explained (41). Malaria infection during pregnancy may simply add to the mother's exposure and stimulation of antimalarial antibodies. The infection may confer additional protection to the newborn. Alternatively, maternal infection may constitute an antigen load that engages existing antibodies and potentially lowers the total amount of antibody available for passive transfer to the newborn. A third possibility is that in cases where the mother has experienced hundreds to thousands of malaria infections during her lifetime, the stimulus in antibody production has little effect on the amount of transplacental antibody passage because of the relatively few infections the mother experiences during pregnancy.

B. MALARIA CONTROL IN PREGNANCY

Antimalarial drugs for use in pregnancy: A limited number of alternative drugs for use by pregnant women are both safe and effective. For symptomatic malaria (notably uncommon in areas with high levels of exposure and acquired immunity), treatment is extremely important, and concerns about toxicity of the drug are outweighed by the potential danger that malaria causes to the mother and fetus. Consequently, in the setting of acute illness, quinine, mefloquine (MQ), sulfadoxine-pyrimethamine (or other sulfa-pyrimethamine [SP] combinations), amodiaquine, or other medications could be used, despite their potential adverse effects (42,43).

For malaria prophylaxis in pregnancy, chloroquine (CQ) has been the mainstay in sub-Saharan Africa. Alternatives to CQ are available for prophylaxis, but the risk-benefit evaluation is different. The risk of malaria infection leading to LBW, which in turn confers an increased risk of early infant mortality, is of obvious concern. However, in the absence of diagnosed infection, the risk of malaria is only a potential risk. Therefore, the benefit obtained by a prophylaxis regimen must greatly exceed any risk that might be conferred by taking the drug. Alternatives to CQ that have been used or considered as prophylaxis in pregnant women include MQ, SP combinations, and the biguanides (proguanil or chlorproguanil). Quinine, while effective and apparently safe, must be given as multiple daily doses, and can cause the uncomfortable side effects of dizziness and cinchonism. Because safer and more effective drugs are available, amodiaquine is contraindicated for prophylaxis because of bone marrow and liver toxicity, and tetracycline is contraindicated in pregnancy because of its adverse effects on the fetus' developing teeth and bones and on the mother's liver. Artemisinin compounds have short half-lives (like quinine), and data on use in pregnant women are limited. Current experience is too limited with other antimalarial drugs to evaluate their safety and efficacy.

In addition to being safe and effective, medications for prophylaxis must be acceptable to pregnant women. The required frequency of dosing may affect both the efficacy and acceptability of drugs for prevention in pregnancy. CQ has been given as a weekly regimen. After four weekly doses, blood levels remain effective for at least 7 to 10 days for CQ-sensitive parasites; the woman must be able to remember and choose to take the drug each week. For drugs that must be given daily, such as proguanil or chlorproguanil, the woman becomes susceptible as early as the day after missing one dose; therefore, she must be able to take the medication daily without missing a single dose. Consequently, the choice of a daily or weekly prophylaxis regimen depends on the difficulty of remembering a daily or weekly dose and the risk of immediate susceptibility after forgetting the dose. Consideration must also be given to other factors affecting compliance: local beliefs regarding the use of medication, the frequency of side effects, taste, or likelihood of saving the medication for other uses (e.g., to treat a family member).

In summary, the choice of an alternative antimalarial drug in areas of CQ-resistant parasites is determined by the efficacy and safety of the drug. The dosing regimen required and the compliance obtainable with that regimen must be considered. Although compliance is important, an effective and safe drug is critical. While poor compliance will reduce effectiveness of the regimen, good compliance cannot improve the benefit of an ineffective regimen.

Other protection measures: In addition to the use of antimalarial drugs, additional measures to prevent the adverse effects of malaria in pregnant women may include personal protection with insecticide-impregnated bed nets or vector control in the community. Although the effect of reduced transmission through vector control on malaria morbidity in pregnancy has been examined in one study (44), no studies to date have examined the role of insecticide-impregnated bed nets in malaria prevention in pregnancy.

The status of malaria control in pregnancy in 1987¹

Recommendations for malaria prevention in pregnancy: Because of concerns related to malaria in pregnant women, WHO had recommended that pregnant women with demonstrable malaria infections receive prompt treatment with an effective and safe antimalarial drug and was advising that women presenting to the antenatal care system receive an initial treatment dose followed by regular prophylaxis with an effective and safe antimalarial drug (45). Chloroquine was being used most widely in Africa as the chemoprophylaxis agent of choice. Results from one investigation (46) and from extensive general experience showing no observed adverse effects on the woman or newborn attributable to the drug provided the evidence that CQ was safe in pregnancy. Chloroquine had demonstrated efficacy in sub-Saharan Africa until the late 1970s. However, with the spread of CQ-resistant parasites across East, Central, and West Africa, there was increasing concern that prophylactic doses of CQ (5 mg base/kg/week or 300 mg base/week) were not completely effective in preventing *P. falciparum* infection.

Programs for malaria control in pregnancy: Despite the biologic rationale for focusing on malaria control efforts during pregnancy, by the mid- to late-1980s, few African countries had implemented programs that had achieved wide coverage of the population of pregnant women. A large, well-supported community health project in western Kenya emphasizing village health worker delivery of chemoprophylaxis to pregnant women was able to deliver weekly CQ chemoprophylaxis to only 29% of primigravidas (47). In Malawi, where a high proportion of pregnant women attend antenatal clinics, cultural barriers (local taboos against ingesting bitter substances, such as CQ, during pregnancy) limited pregnant women's acceptance of the antimalarial chemoprophylaxis program (48). Within the Africa Child Survival Initiative - Combating Childhood Communicable Diseases (ACSI-CCCD) Project, surveys in seven regions in four countries demonstrated that although 51% to 68% of women reported using antimalarial medication during their pregnancies, only 1%-18% reported using an antimalarial drug on a weekly basis at a dosage near the WHO recommendation (Table 1).

¹The historical perspective of 1987 is used because that was the time of onset of the Mangochi Malaria Research Project study.

**SECTION II:
MALARIA AND PREGNANCY**

Table 1. Community-based surveys of malaria control programs in 7 regions of 4 countries participating in the CCCD Project, 1984-1987.

COUNTRY	NUMBER OF WOMEN	PRENATAL CLINIC VISIT		ANTIMALARIAL ADVICE GIVEN		TOOK ANY ANTIMALARIAL		TOOK WEEKLY ANTIMALARIAL	
		N	(%)	N	(%) ^a	N	(%) ^b	N ⁰	(%) ^b
LIBERIA	1785	876	(49)	590	(67)	134	(15)	—	
TOGO	2998	796	(82)	2217	(74)	2035	(68)	507	(17)
CAR-BANGUI	—	—		—		75	(55)	24	(18)
CAR-BAMBARI	—	—		—		—	(34)	—	(9)
ZAIRE	1791	1576	(88)	—		609	(34)	—	
ZAIRE	4172	3546	(85)	—		1192	(43)	130	(5)
ZAIRE	5685	4775	(84)	—		908	(36)	18	(1)

^a Percentage of women attending prenatal clinic

^b Percentage of all women.

Thus, despite widespread acceptance of malaria as a problem in pregnancy, the administrative requirements of developing an affordable program with wide coverage and acceptance by pregnant women presented a public health challenge of substantial magnitude. This programmatic challenge, coupled with a lack of information demonstrating that the proposed intervention (antimalarial chemoprophylaxis) would substantially alter the effect of malaria in pregnancy, led to the current study.

C. KEY OUTSTANDING ISSUES

Major doubts existed that CQ was "working" as chemoprophylaxis in pregnant women. Few alternative drugs had been identified as alternatives to CQ, and the efficacy of antimalarial chemoprophylaxis in pregnant women had never been demonstrated, either with CQ or any other drug.

The low coverage of pregnant women by healthcare programs was discouraging, and the women most at risk (primigravidas) often had the least access to prophylaxis.

HIV infection and disease were emerging in populations of women of reproductive age, and adverse effects on women and infants through vertical transmission were becoming increasingly important in an environment with limited resources for most public health programs.

Consequently, for public health investment in malaria prevention programs for pregnant women to be justified, the at-risk population of pregnant women needed to be further defined, treatment options needed to be explored, and the efficacy of the treatment or chemoprophylaxis interventions needed to be demonstrated.

III. THE MANGOCHI MALARIA RESEARCH PROJECT (MMRP) INVESTIGATION AND STUDY OBJECTIVES

Despite the recognized association between malaria infection in pregnant women and adverse birth outcomes, no prior study had demonstrated the effectiveness of an antimalarial program in reducing both placental infection and the frequency of LBW.

The role of malaria treatment and prevention with antimalarial drugs in pregnancy needed to be defined in a setting with the following characteristics: 1) malaria was endemic, 2) resistance to CQ was present, 3) LBW was a common event and thought to be an important contributor to infant mortality, 4) pregnant women were accessible and were likely to participate in a study, 5) local practices were not likely to interfere with the scientific aspects of the study (e.g., antimalarial drugs were available and under the control of the health system), 6) local health officials and clinic staff were interested in the problem and in collaboration, and 7) the results of the study were likely to be examined in the context of national policy on malaria prevention in pregnancy. On the basis of these criteria and extensive discussions with officials from the Malawi Ministry of Health (MOH), the United States Agency for International Development (A.I.D.), and the ACSI-CCCD Project, the rural district of Mangochi in Malawi was chosen as a study site.

In Malawi in 1987, the national malaria control policy recommended weekly CQ prophylaxis for pregnant women attending antenatal clinics; high levels of *P. falciparum* resistance to CQ were known to exist (49), and sensitivity to MQ was documented (see below). In this setting, we examined the efficacy of CQ and MQ treatment and prevention in pregnant women.

We conducted a longitudinal investigation of pregnant women who were enrolled at their first antenatal clinic visit and followed them through pregnancy, at delivery, and for the first year postpartum. The study examined the effect of malaria (peripheral parasitemia and placental infection) on fetal survival, gestational age, birth weight, and neonatal and infant survival. The effect of CQ and MQ on clearing or preventing peripheral and placental malaria infection was examined, and by extension, the effects of these drugs on LBW and infant survival.

Because of the importance of other maternal characteristics potentially affecting birth outcomes and infant survival, we also examined additional characteristics and outcomes: HIV infection, syphilis infection, neonatal tetanus infection, multiple pregnancy, and maternal mortality.

A. PRELIMINARY STUDIES

Prior to the start of the study, a series of preliminary investigations was conducted in Mangochi District to examine important factors related to antimalarial drug efficacy and women's characteristics and practices that might affect the study design and outcomes. Preliminary findings included the following:

Chloroquine efficacy: In 1987, therapeutic doses of 25 mg/kg CQ in divided doses failed to clear peripheral parasitemia within 7 days in 27% of 33 pregnant women, with poorest clearance rates observed in primigravidas.

Mefloquine and sulfadoxine-pyrimethamine efficacy: Mefloquine given in a single dose of 750 mg was highly effective in clearing peripheral parasitemia in pregnant women (>95% clearance within 7 days). This suggested that the efficacy of MQ would be substantially better than that of CQ in this population and that MQ could be used as a highly effective agent to clear periph-

eral and placental malaria infection in the study. Sulfadoxine-pyrimethamine (3 tablets, single dose) was also highly effective in clearing peripheral parasitemia in pregnant women (>95% clearance within 7 days).

Compliance as a determinant of program effectiveness: Compliance with CQ prophylaxis, as determined by urine and blood CQ levels at follow-up antenatal clinic (ANC) visits was low; approximately 35% of women had measurable CQ in their blood or urine. A model of program effectiveness showed that poor compliance with CQ was a major determinant of poor program effectiveness.

Knowledge, attitudes, and practices: Approximately 90% of all pregnant women in Malawi attend antenatal clinics (ANCs) at least once during their pregnancy, and 85% of these women attend at least twice; on average, women attend ANCs four to five times during their pregnancy. This finding suggested that the population of pregnant women had access to antenatal care, and because most women attended clinic, the study could be considered representative of the population of pregnant women in this area of Malawi.

B. STUDY OBJECTIVES

The objectives of the Mangochi Malaria Research Project investigation were to determine the efficacy of CQ or MQ antimalarial chemoprophylaxis in an area of CQ-resistant *P. falciparum* on the following outcomes:

- ◆ frequency of placental malaria infection
- ◆ birth weight
- ◆ gestational age
- ◆ frequency of maternal illness

The investigation was not designed to evaluate the role of antimalarial chemoprophylaxis and treatment on mortality reduction, but because children born to study women were scheduled to be followed for up to 2 years of life, the study allowed for an examination of mortality and morbidity in this population. Although the investigators recognized that the sample size was insufficient to provide detailed analysis of mortality and morbidity, these outcomes could be analyzed in a descriptive fashion:

- ◆ fetal, perinatal, neonatal, postneonatal, infant, and second-year mortality
- ◆ infant acquisition of malaria infection and malaria immunity

In addition to the outcome measures listed above, the study design allowed for the evaluation of two additional aspects of maternal and infant health:

- ◆ other determinants of the above-listed outcomes in addition to malaria prevention (e.g., maternal characteristics)
- ◆ cause-specific mortality in the above mentioned fetal and childhood periods

Finally, because of the information gathered, the study evaluated the effects of other conditions on maternal and child health:

- ◆ maternal HIV infection
- ◆ maternal syphilis infection
- ◆ neonatal tetanus
- ◆ multiple pregnancy
- ◆ maternal mortality

IV. MMRP STUDY METHODS

A. COUNTRY BACKGROUND

The study was conducted in Malawi between September 1987 and June 1990 in the Mangochi District, located at the southern end of Lake Malawi. The study area encompassed the town of Mangochi (population approximately 10,000) and approximately 155 rural villages with an estimated total population of 120,000. Small scale agriculture (maize as the staple crop) and fishing are the primary sources of food and income for most residents. The area is approximately 150-180 meters above sea level and has an average annual temperature of 23.7°C (ranging from an average in June and July of 19.7°C to 27.1°C in November) and an average annual rainfall of 824 mm (10-year average). There are three distinct seasons: the rainy season (January-April), post-rainy season (May-August), and dry season (September-December). These seasons determine the levels of malaria transmission, which peaks March-May, drops rapidly in August, and stays at low levels until the next rainy season. The seasons likewise dictate the agricultural activities of land preparation (October and November), planting (December), cultivating (January-April) and harvest (May and June). Women, including pregnant women, are generally responsible for care of the household. In addition, they labor in the fields throughout the year's agricultural seasons, which coincide with the high malaria transmission season.

Malaria transmission (primarily *P. falciparum* [90%] and some *P. malariae* [10%]) occurs year round but with seasonal variation; village and outpatient clinic surveys of children less than 5 years of age show parasite prevalence in excess of 75% in March-June, with prevalence dropping to 30%-40% in December, the late dry season. The prevalence of CQ-resistant *P. falciparum* in young children has been monitored in urban and rural settings in Malawi since 1984 and had progressed from 50% to approximately 80% levels of combined RI, RH, and RII (WHO-defined levels of resistance to antimalarials) by 1990.

Figure 2. Map of Malawi.

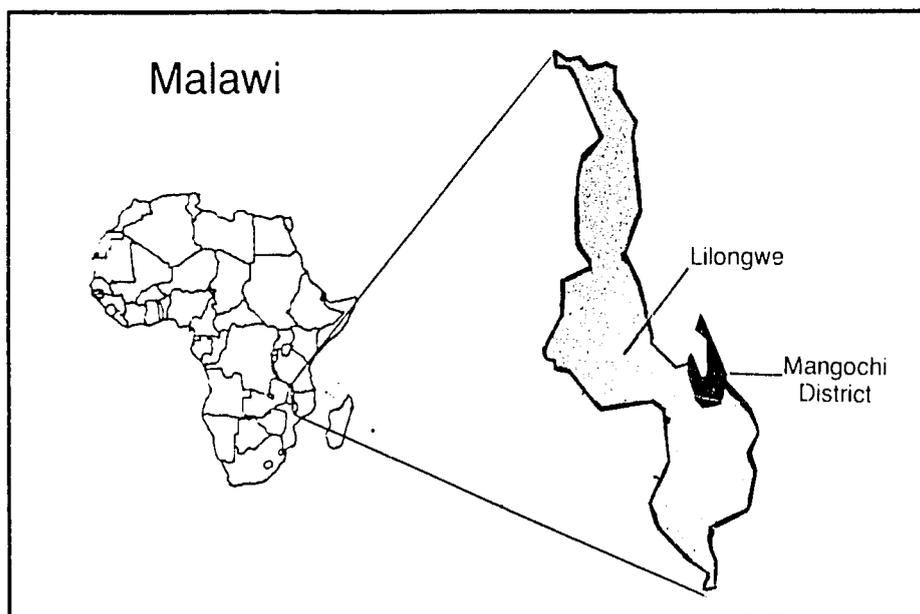
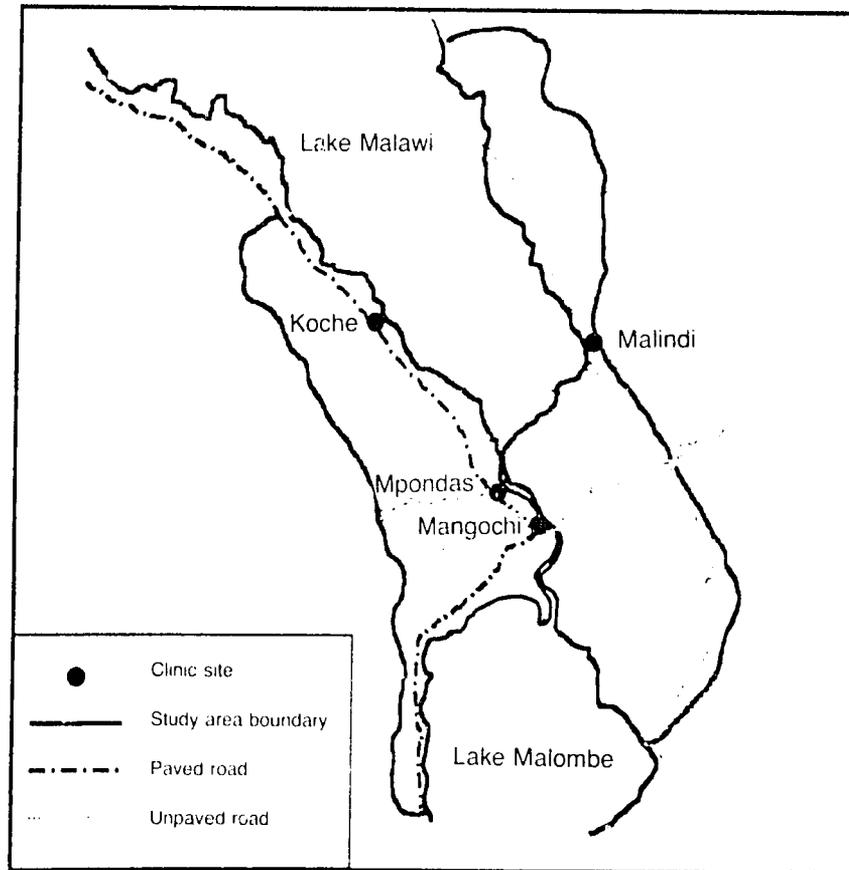


Figure 3. Map of Mangochi Malaria Research Project study area.



B. ENROLLMENT METHODS

Women were enrolled at four antenatal clinics that are located in the central portion of Mangochi District and serve approximately 120 villages. Consecutive attendees at their first antenatal clinic visit were enrolled at three sites (two mission clinics with attached delivery units [Mpondas Clinic and Koche Clinic] and one small mission hospital with an antenatal and delivery unit [St. Martins Hospital-Malindi]). At the fourth site, the government district hospital in the town of Mangochi, consecutive first attendees in their first or second pregnancies were enrolled; women with two or more previous pregnancies were not enrolled because of the large numbers of patients attending the clinic each day and the limited study team staff. At this site, primigravidas and secundigravidas were chosen because previous reports suggested that these women were at higher risk for malaria and malaria-associated complications than multigravidas.

Using a standard procedure for informed consent approved by the MOH in Malawi and by the Centers for Disease Control (now the Centers for Disease Control and Prevention), a study team member explained the study objectives and procedures to potential enrollees. At enrollment, a questionnaire was administered by a study team member, who obtained information on age, village of residence, previous obstetrical history, illness and treatment during the current pregnancy, knowledge of malaria and malaria prevention, education, and socioeconomic status (determined by type of house construction and level of education as coded indicators). Women were weighed on a standard adult scale, and their height was measured in centimeters; capillary

blood was drawn for thick blood smears for malaria parasites, hematocrit, and serum. Urine was collected and examined for protein, glucose, and 4-aminoquinolines (CQ being the only locally available 4-aminoquinoline). Women underwent the usual clinic registration and examination. Women received iron and folate therapy and a tetanus toxoid immunization from the clinic and were treated as necessary for any medical conditions not associated with malaria.

C. TREATMENT AND CHEMOPROPHYLAXIS GROUPS

During this first visit, women returned to the study team after their antenatal exam and were systematically assigned to receive one of four regimens of antimalarial treatment and/or chemoprophylaxis:

- Regimen A.* CQ treatment dose of 25 mg of base/kg given as a divided dose over 2 days, followed by 300 mg weekly
- Regimen B.* CQ treatment dose of 25 mg of base/kg given as a divided dose over 2 days and repeated every 4 weeks
- Regimen C.* CQ 300 mg base weekly (Malawi national policy)
- Regimen D.* MQ treatment dose of 750 mg as a single dose followed by 250 mg weekly

Regimen A represented the WHO recommendation for CQ. Regimen B was chosen to examine a monthly treatment dose of CQ, where the first dose could be administered at each monthly clinic visit and thus eliminate weekly doses at home, a regimen previously identified as a hindrance to compliance. Regimen C was the Malawi national policy at the start of the study. Regimen D represented an optimal treatment and prophylactic dose of the most effective available drug (MQ), with a dosing schedule based on previous pharmacokinetic studies in pregnant women in Thailand (NJ White, personal communication, 1987).

The assignment of regimens was based on the day of enrollment. All women making their first antenatal clinic visit on a given day were assigned to the same regimen; the following day, enrolled women were assigned a different regimen. Women at each of the four clinic sites had the opportunity to be assigned to either a CQ or an MQ treatment group. Enrollment continued the longest at the government hospital, where only women in their first or second pregnancies were enrolled (see above). Because women in their first two pregnancies were thought to be at highest risk, an effort was made to alternate between assignment to MQ or CQ so that an adequate proportion of all primigravidas or secundigravidas in the study received MQ. During the 27 months of enrollment, the systematic, alternating enrollment was not expected to introduce any selection bias into the study. The characteristics of women in each group were examined to confirm that no significant differences existed among women on each of the regimens. Where differences in characteristics occurred among the groups, results were adjusted by stratified or multivariate analysis techniques.

D. FOLLOW-UP EVALUATION

Each dose of medication was given under observation by a study team member either at the clinic or at home. At that time, the woman was questioned to determine a history of fever, use of other medications, and side effects attributed to the medication in the interval since the previous dose. At 4-week intervals after enrollment, capillary blood was collected for a thick blood smear to detect malaria parasites and for a serum sample. A urine specimen was collected at the first 4-week visit and tested for levels of 4-aminoquinolines to verify the ingestion and absorption of CQ.

E. DELIVERY CARE

Approximately 40% of the women in this population deliver in a delivery unit, and the remainder deliver at home with other women (sometimes trained traditional birth attendants) assisting in delivery. For the purposes of optimal assessment of study outcomes, women in the study were encouraged to deliver their baby at the delivery unit. At that time, they received the usual clinical care from the attending nurse midwife or physician. A member of the study team administered a questionnaire and obtained additional information regarding the current pregnancy. Capillary blood was again collected for a thick blood smear and for a serum sample. Following delivery of the baby and placenta, blood was collected from the maternal side of the placenta and the placental umbilical cord for a thick blood smear. The placenta was placed in a metal dish, and a serum sample was collected from the retroplacental blood that drained from the placenta. After the attending nurse midwife determined APGAR scores at 1 and 5 minutes, the newborn was given a standardized modified Dubowitz examination for gestational age and was checked for any physical abnormalities. The baby's length and head circumference were measured. The baby was weighed on a Mettler² (Rite-Weight, Inc., Duluth, Georgia [US]) digital scale accurate to the nearest gram.

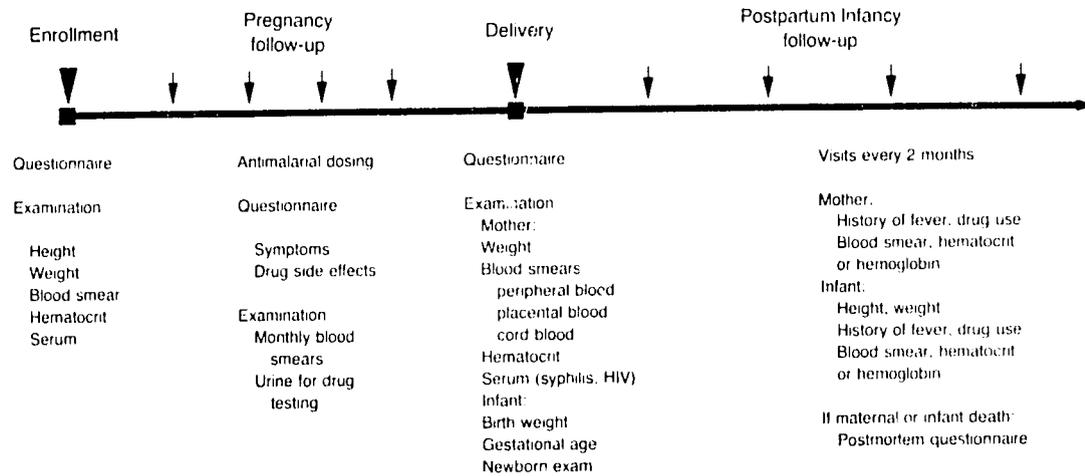
As a separate aspect of the study, all women not enrolled in the study who delivered in the same delivery units as women in the study were examined in the same fashion at the time of delivery. This examination included a questionnaire, capillary blood samples, and newborn physical examination including birth weight and gestational age. The group of women and infants not participating in the study were not followed after discharge from the delivery unit.

F. POSTPARTUM FOLLOW-UP

Mothers and infants were followed postpartum; efforts were made to see the mother and infant every 2 months. At that time, mothers were questioned about febrile illness, other illness, and medication use by both mother and infant since their last visit. The mother was weighed and the infant was weighed and measured; both had capillary blood collected for a thick blood smear and hematocrit. Postpartum follow-up continued for at least 12 months for all deliveries, and for up to 36 months for deliveries that occurred early in the study. If either the mother or baby died, family members were queried to ascertain symptoms associated with the fatal illness (see Section V.).

²Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Figure 4. MMRP enrollment and follow-up — timing of activities.



G. LABORATORY STUDIES

Malaria parasitemia: Peripheral capillary blood, placental blood, and umbilical cord blood were obtained and applied to glass slides. These thick blood smears were stained with Giemsa and examined for parasites. Parasites and leukocytes were counted in the same fields until 300 leukocytes or 500 parasites were counted; parasite densities were estimated using an assumed leukocyte count of 6000 leukocytes per mm^3 of blood. The limits of detection were < 10 parasites/ mm^3 of blood. Scoring of infection rates for placental infection is described below.

Urine testing: Urine was tested for protein and glucose using a dipstick method and for 4-aminoquinolines using the Saker-Solomons method (50).

Hematology: Tubes containing heparinized capillary blood were centrifuged at 10,000 cps for 3 minutes to determine packed cell volume (hematocrit). Capillary blood collected for serum specimens was separated on the same day and frozen. During infant follow-up visits, capillary blood samples were collected for hemoglobin determination (HemoCue, Mission Viejo, California [US]) in the field and recorded to the nearest 0.1 g/dL.

Serum: Under approved modifications of the protocol, serum specimens were later tested for evidence of antimalarial antibodies and other infectious agents:

1) Sera were tested for reactivity of antibodies to Pf155-RESA epitopes using the Falcon Assay Screening Test-Enzyme Linked Immunosorbent Assay (FAST-ELISA) with three synthetic peptides (EENV)₁, (EENVEHDA)₁, and (DDEHVEEPTVA)₃ reproducing repeated B cell epitopes, and the peptide (PNAN)₅ reproducing the repeated epitope of the circumsporozoite protein (51).

2) Antibodies to HIV were detected by enzyme immunoassay (EIA) (Organon Technika), and positives were confirmed by Western Blot (Organon Technika) using standard procedures.

3) Sera that had been collected during the antenatal period and stored frozen were tested in 1991-1992 for syphilis, using Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR) tests and microhemagglutination assay for antibodies to *Treponema pallidum* (MHA-TP). All VDRL/RPR reactive serologies were diluted to an endpoint titer.

H. PROTOCOL REVIEW AND INFORMED CONSENT

The study protocol was developed in a collaborative fashion by investigators at the CDC and the Ministry of Health in Malawi. The protocol was also reviewed by staff at the USAID Malawi Mission and in USAID-Washington offices. The protocol was also reviewed and approved by the Institutional Review Board at CDC and by the Health Research Committee and National Research Council in Malawi.

Pregnant women meeting eligibility criteria for the study were considered for enrollment. The usual procedure for informed consent in Malawi was used; the Malawi MOH uses informed verbal consent for all investigations involving human subjects. Potential enrollees were read a statement that described the purpose of the study and the study procedures (use of antimalarial drugs and required visits, laboratory investigations and needed blood drawing, examination at delivery, and postdelivery follow-up). Women were then asked if they understood the study and were encouraged to ask questions. They were informed that their decision to participate or not participate in the study would not affect their health care in any way and that they were free to withdraw at any time during the study. After questions were answered to their satisfaction, they were asked if they agreed to participate in the study. If they gave their verbal consent, they were enrolled.

Except for the provision of antimalarial treatment or chemoprophylaxis, the usual antenatal clinic procedures were followed for all study subjects. Women received a standard history and examination, tetanus immunization at appropriate intervals, and iron and folic acid in tablet form to be taken at home. Women with a history of a stillbirth or abortion were tested for syphilis (VDRL) and treated with penicillin if positive. Screening of all women for syphilis was not available locally. During a review of the project in 1988, MOH officials requested that serum collected during the study be tested for syphilis as syphilis may be an important contributor to fetal and infant survival. The testing was performed at CDC's Sexually Transmitted Diseases Laboratory with Malawian laboratory technicians participating in the testing. Results were provided so that the women with positive serologic results could be located and treated.

During the study, two modifications in the protocol occurred, both of which were approved by the CDC and Malawi MOH research review committees. The first revision added at each of the four clinic sites a comparison group who received a treatment and chemoprophylaxis regimen of MQ at 750 mg single dose treatment at first antenatal clinic visit followed by 250 mg weekly. The second revision arose as a result of a WHO-Global Programme on AIDS-funded portion of the study that required blind testing for HIV on serum collected at the time of delivery. The protocol for HIV testing was also reviewed and approved by WHO. Identifiers from data bases and serum specimens were removed, but linked records allowing an examination of characteristics of mothers and infants and their serologic status were retained. Malawian laboratory technicians participated in the testing in Malawi and in the AIDS laboratory at CDC.

V. MMRP STUDY ANALYSIS

A. DEFINITIONS

Malaria infection: A woman or baby was considered to have a malaria infection if any asexual blood stage parasites were seen on a thick smear of capillary blood or umbilical cord blood for newborns. Comparisons of density of parasitemia among different groups were done using geometric means of parasite density (GMPD). To examine the effect of antimalarial regimens on parasite clearance and the new development of parasitemia while a woman was taking an anti-malarial regimen, study team members took blood smears at monthly follow-ups after enrollment and initial treatment or chemoprophylaxis, and any parasitemia found was categorized as "resistant" or "breakthrough."⁴ If a woman was parasitemic at enrollment and remained parasitemic while receiving her treatment and/or chemoprophylaxis, she was considered to have a resistant infection; if a woman was initially a parasitemic or became a parasitemic after an initial treatment and 4 weeks of chemoprophylaxis but then developed parasitemia, she was considered to have a breakthrough infection.

Placental infection: Placental and umbilical cord blood smears were stained and examined in the same way as peripheral blood smears, with the microscopist unaware of the enrollee's study group status. Parasite density and presence or absence of malarial pigment were recorded. Blood smears were coded a parasitemic or parasitemic and densities calculated in the same way as for peripheral smears. The presence or absence of late stage parasites (late trophozoites and schizonts) was recorded on a 1-4+ scale that reflected the percentage of late stage parasites and used quartiles: (+ = $\leq 25\%$; ++ = 26%-50%; +++ = 51%-75%; and ++++ = 76%-100%). Malaria pigment may be formed in the placental macrophages following the killing of parasites in placental blood; this finding of malarial pigment in placental macrophages indicates prior infection⁴ with parasites. Pigment was also scored on a 1-4+ scale that reflected the proportion of macrophages with pigment (+ = $\leq 10\%$; ++ = 10%-25%; +++ = 26%-50%; and ++++ = $\geq 50\%$). Women were categorized as infected (code 3, 4, or 5), not infected (code 1), or unknown (code 2) using the following codes for placental infection status:

- 1 = negative placental smear
- 2 = no placental smear available, negative peripheral smear
- 3 = no placental smear available, positive peripheral smear
- 4 = malarial pigment in placental macrophages, no asexual parasites
- 5 = asexual parasites in the placenta

Length of enrollment in the study: For the purposes of analysis of malaria prevention and infant outcome (LBW and survival), we analyzed the group of women on a CQ regimen or the MQ regimen only if they were enrolled in the study for 6 or more weeks (≥ 42 days) prior to delivery and had received the appropriate amount of medication during their participation. This group was subsequently compared with women who were enrolled but participated in the study for less than 6 weeks prior to delivery and to the group of comparison women who delivered in the same facilities but were not enrolled in the study.

⁴The investigators established these categories for descriptive purposes of this study only; they recognize that these categories are not standard procedure for evaluating malaria parasite resistance to drugs

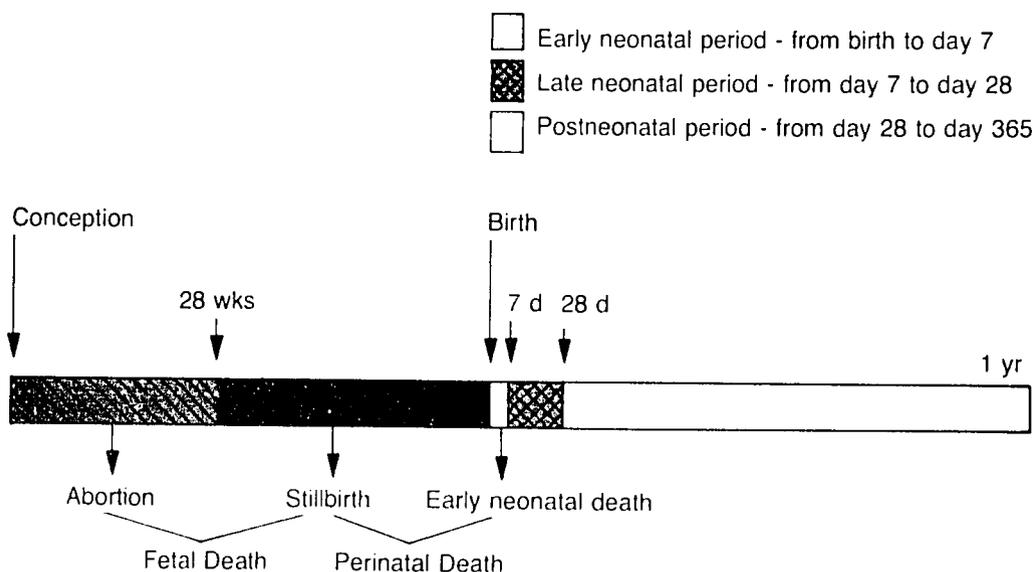
⁵The duration of prior infection cannot be determined by the presence of placental malaria pigment; however, study results suggest that pigment may persist for as much as 3 months after clearance of parasites by an effective antimalarial drug (data not presented)

Low birth weight: Low birth weight was defined as less than 2500 grams. Birth-weight data were not used if weight was recorded more than 24 hours after delivery. Birth-weight distribution, mean birth weights, and proportion of LBW infants were examined for differences between populations of pregnant women.

Gestational age: In this population, gestational age was difficult to determine by history of last menstrual period because many women did not remember or report that event. Consequently, gestational age was determined by a modification of the Dubowitz examination of the newborn for neurologic and physical signs (52-55) and expressed as a score and as weeks gestation. A newborn was considered premature if its Dubowitz score was ≤ 51 (a Dubowitz score of 50-52 is consistent with a gestational age of 36 weeks). Since a baby is generally considered premature if born before the completion of 37 weeks of gestation, a conservative estimate of prematurity was used. Newborns were then categorized as premature (< 37 weeks gestation and < 2500 grams), IUGR (< 37 weeks gestation and < 2500 grams), and normal birth weight (≥ 2500 grams). Although premature babies could also have IUGR, in this analysis, infants who were both premature and growth-retarded were included in the premature category because their expected risk of mortality was believed to be similar to that for premature infants.

Fetal and perinatal death: The following standard intervals of fetal and newborn life were used for evaluation of survival in the perinatal period. *Abortion:* death of fetus before 28 weeks gestation. Few women were enrolled in their first trimester, and as a consequence recorded abortions represent second trimester abortions. *Stillbirth:* death of a fetus ≥ 28 weeks gestation. If information was available, stillbirths were further classified into *fresh* (no signs of decomposition at the time of delivery), or *macerated* (decomposition had begun before delivery). Generally, fresh stillbirths are associated with a cause of death related to labor and delivery, and a macerated stillbirth is associated with a cause of death that occurred before labor began. *Fetal death:* death of a fetus at any time before birth — may refer to an abortion or a stillbirth. *Live birth:* an infant that is recognized as exhibiting signs of life at birth. *Neonatal death:* death of a live-born infant within the first 27 days of life. The neonatal period is divided into *early* (up to day 7) and *late* (day 7 to day 27). Perinatal deaths include stillbirths and early neonatal deaths (Figure 5).

Figure 5. Intervals of fetal and newborn life.



Survival/Cause of death: Survival or death in mothers and infants was determined by questioning at each follow-up home visit. For infants reported to have died since their last visit, a standard questionnaire was administered to the mother or family member by a study team member. Efforts were made to determine date of death and events leading to the death. When exact dates were not available, the study team member made the best estimate according to the interview with the mother or family member. Causes of death were determined by several methods. The mother's reported cause of death was recorded and coded in a standard fashion; the interviewer also recorded his/her assessment of cause of death on the basis of information gained during the interview; and answers to a series of standard questions regarding type and duration of symptoms were recorded and analyzed by a study physician. For the few children who were seen at health facilities before death, clinic records were reviewed. Finally, a group of three physicians reviewed the information on each child's death and made a final determination of primary cause of death using general categories (e.g., respiratory death, diarrheal death). Deaths for which no cause could be determined using these methods were recorded as unknown. Deaths in the early neonatal period were particularly difficult to categorize and were more frequently recorded as due to an unknown cause. Evaluation of deaths in the neonatal period are further described in Section VIII.E.

HIV: Women whose sera tested positive for HIV antibodies on both ELISA and Western Blot were considered HIV seropositive (HIV+). Women whose sera was negative on ELISA testing were considered HIV seronegative (HIV-). Women with positive ELISA results and negative Western Blot results or inadequate quantities of sera for full testing with Western Blot were not included in the analysis.

Syphilis: Definitions of syphilis used in this study were based on expected serologic results for the various stages of syphilis (56). Women with a VDRL RPR titer $\geq 1:8$ and reactive MHA-TP were considered to be syphilis-active with a recently acquired infection. Women with both non-reactive VDRL RPR and MHA-TP tests were considered to be syphilis-negative. Women with reactive VDRL RPR and nonreactive MHA-TP were considered to be syphilis-false positive (although this group might also include some very early cases of syphilis). Women with a reactive MHA-TP and a nonreactive VDRL RPR were considered to be syphilis-resolved (old cases, treated or untreated). Women with a VDRL RPR titer less than 1:8 and reactive MHA-TP had a mixture of old treated or untreated infections and newly acquired (less than 6 weeks) infections, and were considered to be syphilis-old new. Because the interpretation of a few specimens with inconsistent serologic results was difficult (either VDRL RPR or MHA-TP was discordant), we compared women with serologic results consistent with active syphilis (VDRL RPR reactive with titer $\geq 1:8$ and reactive MHA-TP) with women with no evidence of syphilis (nonreactive VDRL RPR and MHA-TP) to identify and quantify risk factors for active syphilis and to estimate the contribution of syphilis to poor pregnancy outcomes. To avoid potential confounding between HIV infection and twins on the effect of syphilis, we included in the analysis only women who tested HIV- by ELISA within 2 months of delivery and delivered singleton births.

B. STUDY VARIABLES

Characteristics of women in the study: The study examined the following characteristics: pregnancy number (gravidity); season of enrollment and delivery (rainy, postrainy, and dry season); treatment regimen; length of participation in the study; maternal age; education level; socioeconomic status; maternal height and weight at enrollment; weight at delivery and weight change during the study; hematocrit at enrollment and delivery; change in hematocrit during the study; febrile illness; use of tobacco products; use of alcohol; ethnicity; and sex of the newborn. Maternal malaria infections at enrollment, at follow-up visits, and at delivery (peripheral blood, placental blood, and newborn cord blood) were considered both outcome and indicator variables. Birth weight and gestational age were examined as outcome variables and were included as indicator variables in the analysis of perinatal, neonatal, and postneonatal infant survival.

Comparison among treatment groups: Characteristics of women in the three CQ treatment and prophylaxis groups and the MQ treatment-prophylaxis group were examined for differences (see Section VI.). Because the characteristics of women on CQ were similar at enrollment (e.g., same prevalence of parasitemia) and because the CQ regimens had similar effects on their parasite clearance (Figure 9), women in the three groups receiving CQ were considered as one group for many of the analyses.

C. STATISTICAL PROCEDURES

The statistical significance of categorical variables was assessed using the chi-square or Fisher's exact test; the statistical significance of continuous variables was assessed using Student's *t*-test or Wilcoxon rank sums test; and analysis of continuous variables by categorical explanatory variables was assessed using analysis of variance. Cox's proportional hazard method was used to compare survival among children in different groupings of characteristics (e.g., children with hematocrit values below 25% compared with children with values of 25% and higher). EPIINFO software was used to calculate relative risk (RR) or odds ratios (OR) (using the method of Greenland and Robins) and the 95% confidence intervals (95% CI) (using the method of Cornfield). Risk estimates for multiple strata were examined using weighted Mantel Haenszel (MH) estimates of the OR. *P* values less than 0.05 were considered significant. Odds ratios, means, and rates were standardized by gravidity or parity where indicated, with the normal population distribution of women seeking care at antenatal clinics as the standard.

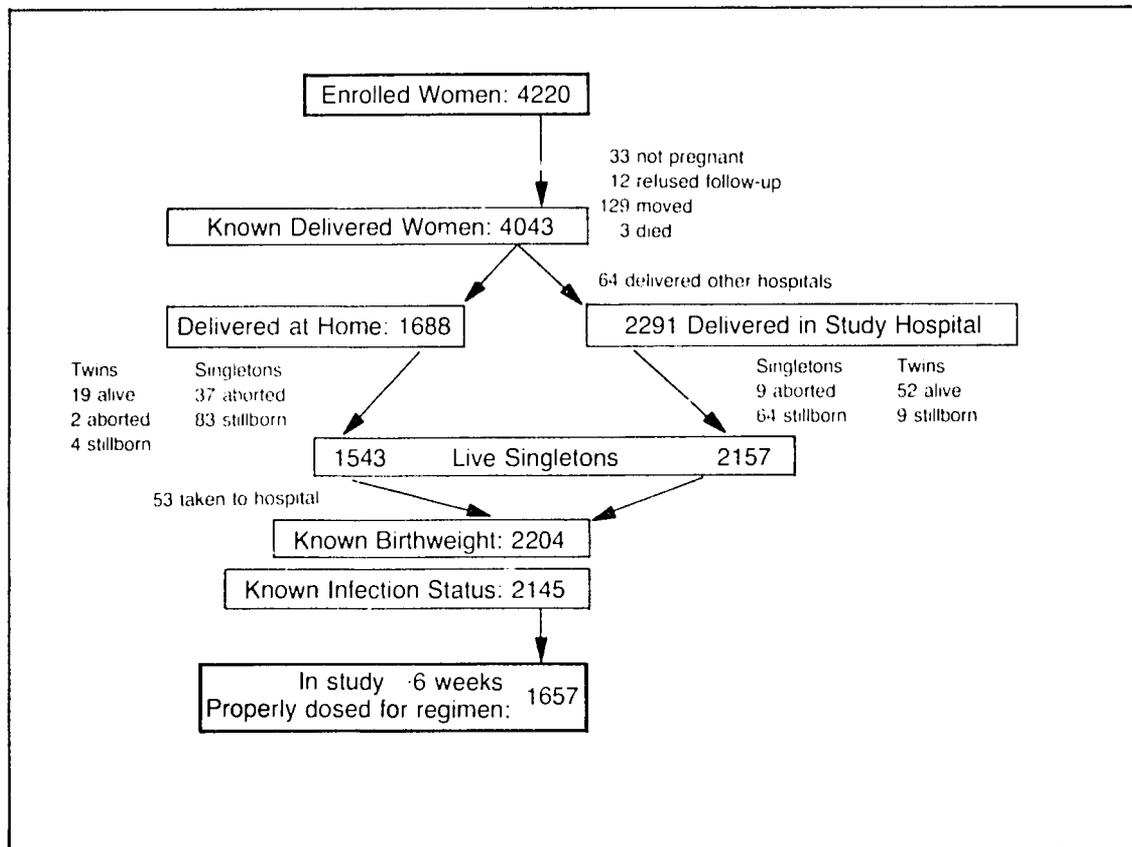
Birth-order-adjusted univariate analysis of factors associated with LBW was conducted using conditional logistic regression (PROC LOGISTIC, SAS). Multivariate models were examined in SAS, and variables included in the model were those that were significant in the univariate or adjusted univariate testing or those that were shown from previous studies to be potentially biologically important, even if they were not significant in univariate testing. Models were developed using a combination of backward and forward elimination or inclusion of variables. First-order interaction terms were examined in the models for all sets of variables that were considered to have plausible biologic interaction. Variables in the final multivariate models were those that remained significant when included in the model. Attributable risk estimates were made using risk estimates from the multivariate models and prevalence of the risk factor in the population using the method of Levin.

VI. MMRP STUDY RESULTS: MALARIA INFECTION, MALARIA PREVENTION, BIRTH WEIGHT, AND GESTATIONAL AGE

A. ENROLLMENT

A total of 4220 women were enrolled in the study; 33 (0.8%) were not pregnant, 12 (0.3%) refused follow-up, 129 (3.1%) moved from the study area, and 3 died prior to delivery, leaving 4043 (95.8%) women who were known to have delivered. Of these, 1688 (41.8%) delivered at home, 64 (1.6%) delivered in nonstudy delivery units, and 2291 (56.7%) delivered in study area delivery units. Among the study area facility deliveries, 61 (2.7%) women delivered twins, and an additional 73 (3.1%) of the singleton births were born dead, leaving 2204 live singleton in-facility deliveries; 2145 (97%) had known birth weight and known malaria infection status at delivery, and 1657 (77%) of these were in the study for more than 6 weeks and received all of the required doses of their antimalarial regimen⁵ (Figure 6).

Figure 6. Study participants at enrollment, follow-up and delivery, MMRP, 1987-1990.



⁵The actual number of women or infants examined in any given analysis is dependent on the variables examined and may be larger than 1657 (e.g., examining enrollment parasitemia in all enrolled women) or smaller than 1657 because of missing values for certain variables.

Women's characteristics

The characteristics of women receiving CQ or MQ were similar except for those affected by increased enrollment of women in their first and second pregnancies (younger women) in the MQ group. Table 2 presents characteristics of women receiving either CQ or MQ standardized by pregnancy number to a standard population of pregnant women in this district.

Table 2. Characteristics of women receiving chloroquine (CQ) or mefloquine (MQ) for malaria prevention in pregnancy, MMRP, 1987-1990.^a

CHARACTERISTIC	CHLOROQUINE GROUP (N=1196)		MEFLOQUINE GROUP (N=461)		P VALUE
	MEAN OR %	(SD)	MEAN OR %	(SD)	
MEAN AGE (YEARS) *	25.0	(6.3)	24.3	(5.0)	0.03
MEAN GRAVIDITY *	3.4	(2.6)	2.3	(2.0)	< 10 ⁻⁶
MEAN WEIGHT (KGS) *	54.1	(6.8)	54.9	(6.9)	0.03
MEAN HEIGHT (CMS)	155.2	(6.3)	155.4	(6.6)	0.57
MEAN DAYS IN STUDY	102	(36)	102	(35)	0.85
REPORTED FEVER 14 DAYS PRIOR TO DELIVERY (%)	6.2		4.2		0.11
USED TOBACCO (%)	3.3		4.7		0.16
USED ALCOHOL (%)	1.0		0.2		0.11
NOT LITERATE (%) *	70.6		65.1		0.03
SOCIOECONOMIC STATUS (CODE ^b) *	4.8	(1.8)	5.1	(2.2)	0.005
MEAN HEMATOCRIT (%) *	33.7	(5.5)	32.9	(5.9)	0.01
MALARIA INFECTION AT ENROLLMENT (%)	41.4		36.2		0.06
MALARIA INFECTION AT DELIVERY (%) *	25.0		4.8		< 10 ⁻⁶
NEWBORN GENDER (% MALE)	49.7		49.1		0.81
MEAN BIRTH WEIGHT (GM) *	2929	(454)	3012	(479)	0.001
LBW (%)	15.0		12.9		0.26

^aWomen in the study > 16 weeks, taking all doses, and delivering a live singleton baby with known birth weight and known placental infection status. All means and percentages (except for mean gravidity) are adjusted for pregnancy number (1, 2, or 3) using as a standard the population of all women attending antenatal clinics (22.1% primigravidas, 17.7% secondgravidas and 60.2% multigravidas).

^bSocioeconomic status code based on house construction characteristics (minimum = 3, maximum = 9).

* Characteristics significantly different between women on CQ or MQ.

The population of women in the study demonstrates several important characteristics that are consistent with populations of women of reproductive age in the rest of the country and elsewhere in the region. First, the pregnant women enrolled were young (mean age 18.0 years) at their first pregnancy, and age and parity were highly correlated ($R = 0.82$, 95% CI 0.82,0.84). Many of the women were short (13.9% with height < 150 cms) and relatively light (23.8% with weight < 50 kgs at their first antenatal clinic visit, which was usually in their mid-second trimester). Overall, few women reported fever during the pregnancy prior to their first antenatal clinic visit, and very few reported using alcohol or tobacco during pregnancy. A high proportion (69%) of women could not read or write, and most women were poor by socioeconomic assessment criteria. Malaria, anemia, and LBW were common features in the population.

Because of the study design and the effort to enroll adequate numbers of women at highest risk for malaria in the MQ group, women in the MQ group were more likely to be in an early pregnancy and consequently younger. Because of the differences established by study design, univariate analyses were adjusted by pregnancy number (gravidity). After adjusting for pregnancy number, certain characteristics of the CQ and MQ treatment groups were significantly different: maternal weight, literacy, socioeconomic status, and enrollment hematocrit. In general, the differences were small. These characteristics were included in the multivariate models when outcomes of interest in the study (e.g., LBW, prematurity) were examined.

Malaria parasitemia

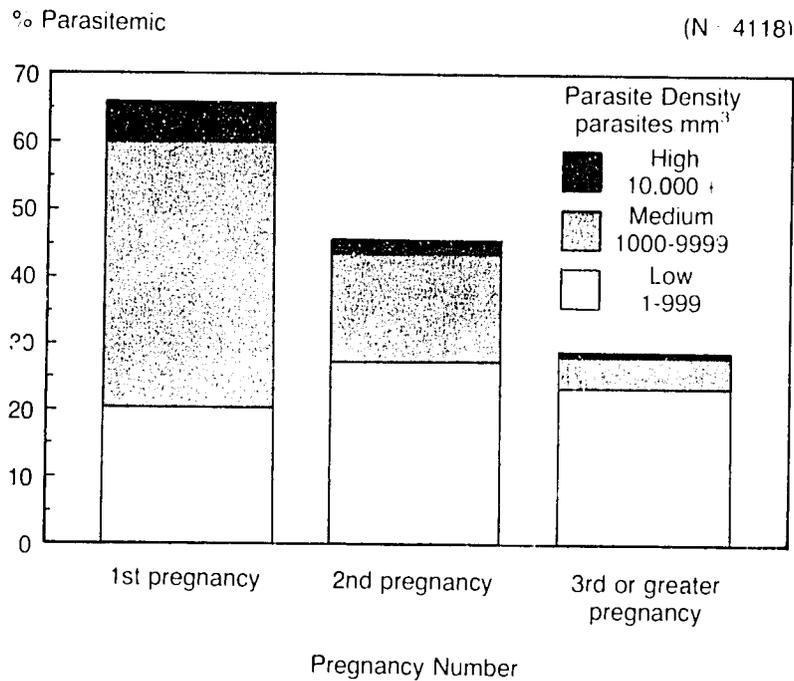
Among the 4127 women with enrollment blood smear results, 1836 (44.5%) were parasitemic (Table 3); very few women had parasite densities greater than 10,000 parasites per microliter of blood.

Table 3. Parasitemia at enrollment in women enrolled in study.

	POSITIVE	
	NUMBER	(%)
WOMEN TESTED: 4127	1836	(44.5)
PARASITE DENSITY (PARASITES/MM ³ OF BLOOD)		
1-999	967	(23.4)
1000-9999	768	(18.6)
≥10,000	101	(2.5)

Sixty-five percent of primigravidas had detectable parasitemia at enrollment; this rate decreased with successive pregnancies (Figure 7). The proportion of low density parasitemia was similar in all pregnancies (approximately 25% with parasite density < 1000 parasites mm^3 of blood); the excess parasitemia seen in first and second pregnancies consisted primarily of higher density parasitemia.

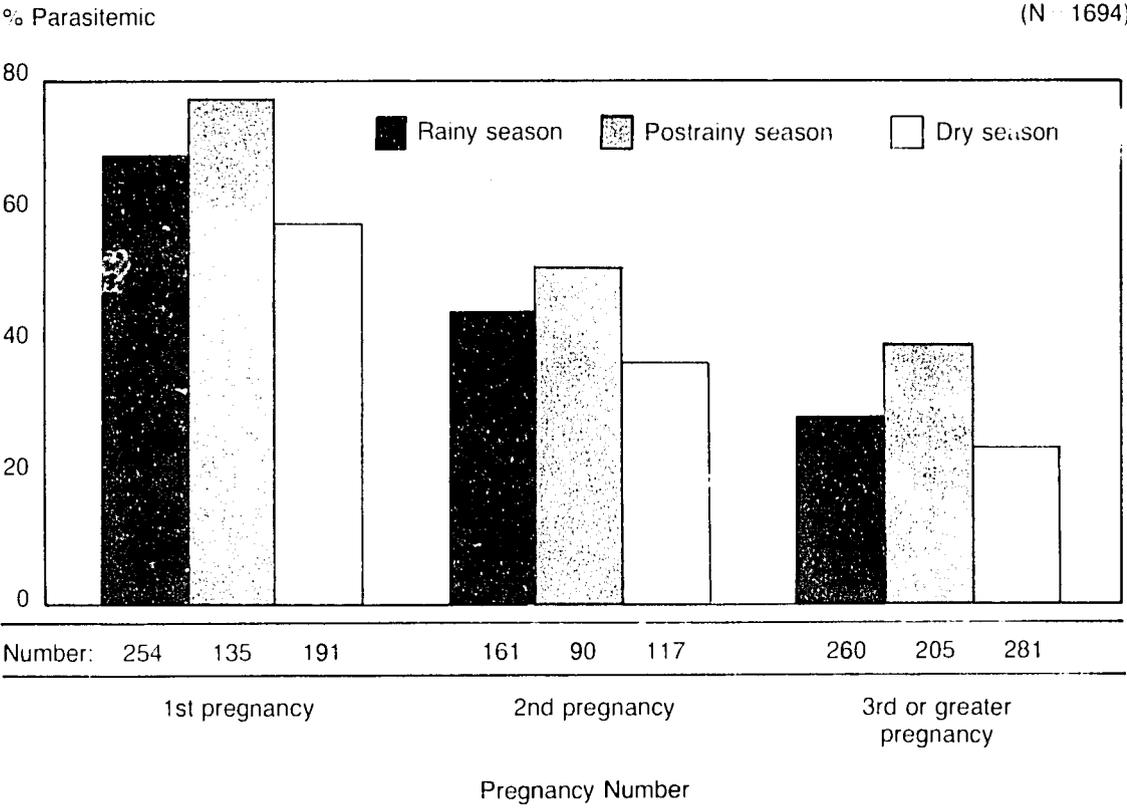
Figure 7. Prevalence and density of parasitemia in pregnant women at enrollment, by gravidity, MMRP, 1987-1990.



The finding of higher prevalence and density of parasitemia in primigravidas is consistent with findings from many other studies and highlights the increased risk from malaria in primigravidas, and, to a lesser extent, in secundigravidas.

The prevalence of parasitemia at enrollment varied by season within gravidity groups (Figure 8). Enrollment parasitemia rates were highest in the postrainy season and lowest in the dry season.

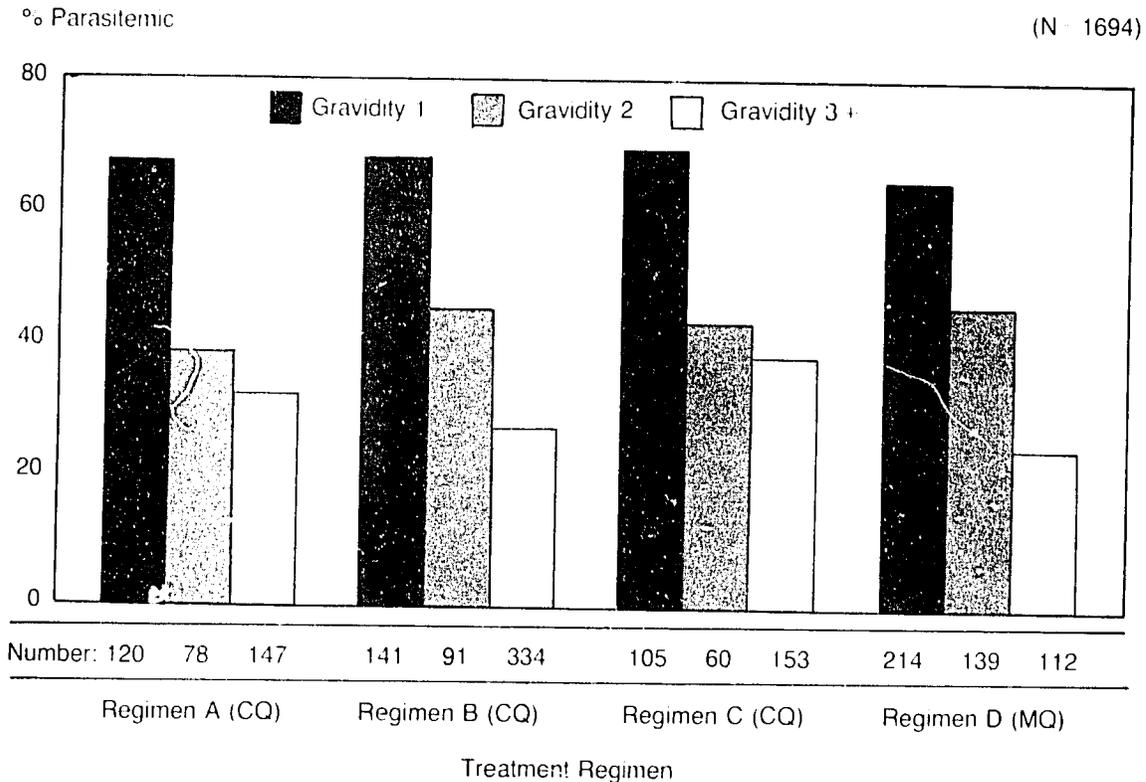
Figure 8. Prevalence of parasitemia in pregnant women at enrollment, by gravidity and season, MMRP, 1987-1990.



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RESULTS**

Treatment groups had similar levels of parasitemia at enrollment in the study (Figure 9). No significant differences were seen in enrollment parasitemia by treatment group within each gravidity category.

Figure 9. Prevalence of parasitemia in pregnant women at enrollment, by gravidity and treatment group, MMRP, 1987-1990.



Summary findings:

The women in the study, selected from the population of pregnant women in rural Malawi, were generally young, in an early pregnancy (by study design), poor, and frequently not literate. Short stature, low weight, anemia, and malaria were common in the population. Reported febrile illness and use of alcohol or tobacco were uncommon in these women. Women in the different treatment groups, for the most part, shared similar characteristics.

Parasite prevalence at enrollment was high; overall, 45% were parasitemic, and 67% of primigravidas and 44% of secundigravidas were parasitemic. The finding of highest parasite prevalence in primigravidas and secundigravidas is consistent with all earlier studies and reconfirms that these women represent the most important target group.

Parasite prevalence at enrollment was similar in each of the treatment groups; women appeared to be similar at the time of enrollment with regard to exposure to malaria parasites.

B. FOLLOW-UP

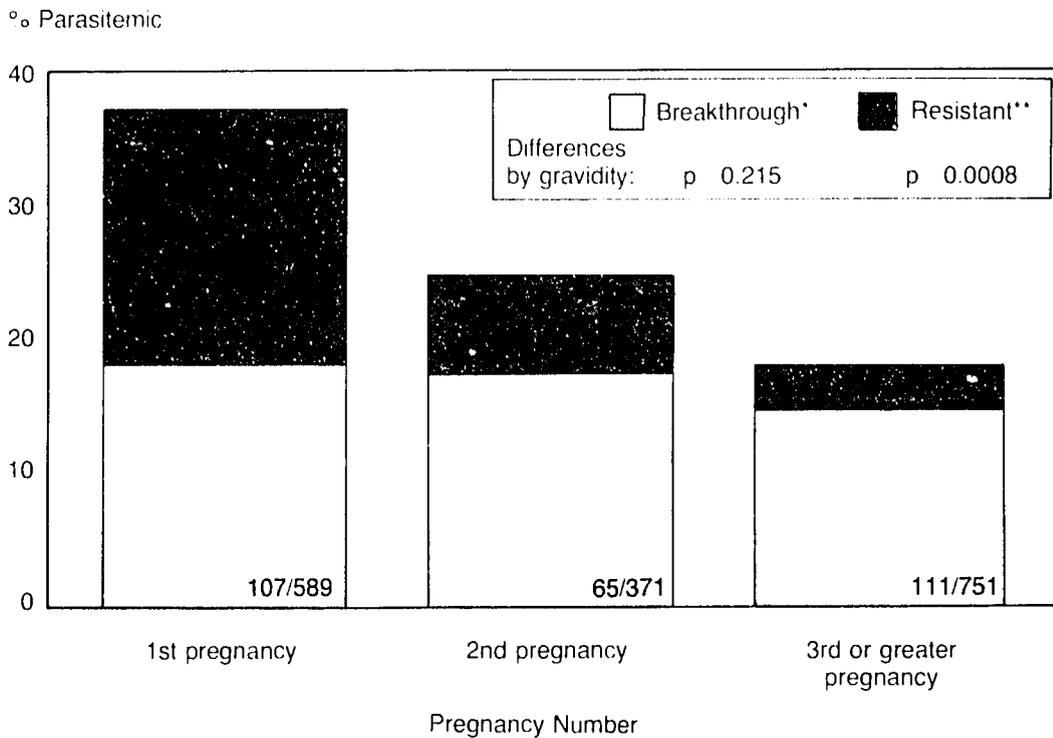
A total of 3150 women received monthly follow-up examinations, had known regular ingestion of their antimalarial drug, and had blood smear results.

Parasitemia (resistant and breakthrough)

Resistant infections (no evidence of parasite clearance) were identified in 277 (8.8%) women with parasitemia at enrollment. Breakthrough infections were observed overall in 517 (16.8%) of 3080 women who were followed up and in 511 (18.8%) of 1670 women who were aparasitemic at enrollment.

Breakthrough parasitemia rates were similar in women in each of the gravidity categories. Primigravidas were more likely to have resistant infections, and the excess parasitemia at follow-up in primigravidas and secundigravidas appears to be due to resistant infections (Figure 10).

Figure 10. Prevalence of parasitemia in pregnant women at follow-up, by gravidity, MMRP, 1987-1990.

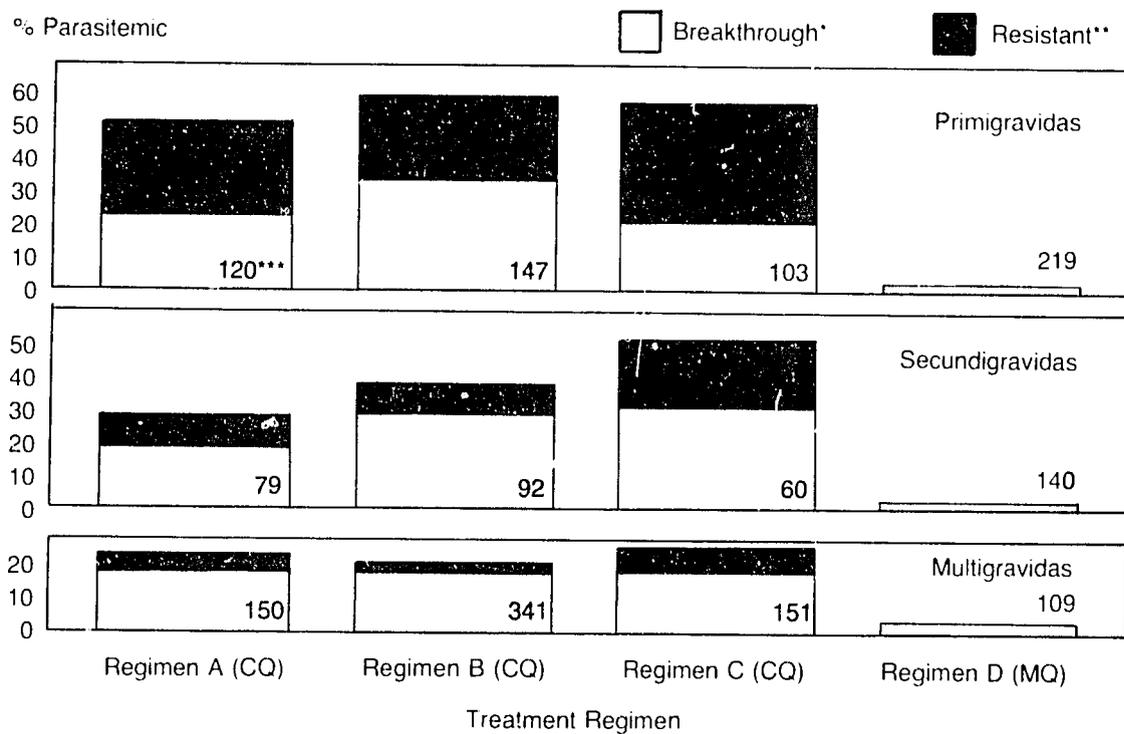


* Breakthrough: initially aparasitemic, parasitemic on follow up
 ** Resistant: initially parasitemic, parasitemic on 1st follow up

**SECTION VI:
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Resistant and breakthrough infections were common in each of the three CQ regimens, but seen in fewer than 5% of women on MQ. The Malawi national policy for prophylaxis in pregnancy at the start of the study (weekly CQ alone, Group C) showed the highest frequency of follow-up infections, and the excess compared with the other CQ regimens was caused by resistant infections (Figure 11). This finding suggests that an initial treatment dose of CQ, even in a setting with high levels of CQ-resistant *P. falciparum* malaria, is more effective in clearing parasitemia than regimens using only weekly prophylaxis doses.

Figure 11. Resistant and breakthrough parasitemia by treatment regimen and gravidity, MMRP, 1987-1990.



* Breakthrough: initially aparasitemic, parasitemic on follow up

** Resistant: initially parasitemic, parasitemic on 1st follow up

*** Total number in each group

Summary findings:

After women began to receive their designated antimalarial regimens, parasitemia was most common in primigravidas on CQ and least common in multigravidas on MQ. Thus, pregnancy number and the efficacy of the antimalarial drug were the two most important determinants of persistent malaria infection in the population of pregnant women.

C. DELIVERY

Malaria infection was examined at the time of delivery in maternal peripheral blood (capillary blood from a finger-prick), placental blood, and umbilical cord blood. A total of 1790 women delivered in the hospital, had received proper dosing on their antimalarial regimen, and had their blood examined.

Maternal peripheral parasitemia

At the time of delivery, 283 (15.8%) of 1790 women had peripheral parasitemia detected on blood smear; the GMPD was 459 parasites/mm³. Primigravidas had the highest rates and densities of parasitemia; the season of delivery and antimalarial treatment regimen were important determinants of the presence and density of parasitemia.

Maternal peripheral parasitemia and gravidity: Primigravid women were more likely than women in subsequent pregnancies to have parasitemia and to have higher density parasitemia (Table 4).

Table 4. Maternal parasitemia at delivery by gravidity, MMRP, 1987-1990.

PREGNANCY NUMBER	NUMBER	PARASITEMIC NUMBER (%)	PARASITEMIC: LOW DENSITY (1-999 PARASITES/MM ³)	PARASITEMIC: MEDIUM DENSITY (1000-9999 PARASITES/MM ³)	PARASITEMIC: HIGH DENSITY (≥10,000 PARASITES/MM ³)
			NUMBER (%)	NUMBER (%)	NUMBER (%)
1	612	143 (23.4)	85 (13.9)	37 (6.0)	21 (3.4)
2	382	60 (15.7)	33 (8.6)	24 (6.3)	3 (0.8)
3	796	80 (10.1)	62 (7.8)	17 (2.1)	1 (0.1)
TOTAL	1790	283 (15.8)	180 (10.1)	78 (4.4)	25 (1.4)

Differences by gravidity were significant in each grouping of parasite density (chi-square, p < 0.05)

Maternal peripheral parasitemia and transmission season: Women delivering in the rainy and postrainy season were more likely than women delivering in the dry season to have parasitemia and to have higher density parasitemia (Table 5).

Table 5. Maternal parasitemia at delivery by season, MMRP, 1987-1990.

SEASON	NUMBER	PARASITEMIC PLACENTA NUMBER (%)	PARASITEMIC: LOW DENSITY (1-999 PARASITES/MM ³)	PARASITEMIC: MEDIUM DENSITY (1000-9999 PARASITES/MM ³)	PARASITEMIC: HIGH DENSITY (≥10,000 PARASITES/MM ³)
			NUMBER (%)	NUMBER (%)	NUMBER (%)
RAINY	577	120 (20.8)	63 (10.9)	41 (7.1)	16 (2.8)
POSTRAINY	768	136 (17.7)	97 (12.6)	32 (4.2)	7 (0.9)
DRY	445	27 (6.1)	20 (4.5)	5 (1.1)	2 (0.4)
TOTAL	1790	283 (15.8)	180 (10.1)	78 (4.4)	25 (1.4)

Differences by season are significant in each grouping of parasite density (chi-square, p < 0.05)

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Maternal peripheral parasitemia and treatment regimen: Women on a CQ regimen were more likely than women on the MQ regimen to have parasitemia and to have higher density parasitemia (Table 6).

Table 6. Maternal parasitemia at delivery by treatment regimen, MMRP, 1987-1990.

TREATMENT REGIMEN	NUMBER	PARASITEMIC		PARASITEMIC: LOW DENSITY (1-999 PARASITES/MM ³)		PARASITEMIC: MEDIUM DENSITY (1000-9999 PARASITES/MM ³)		PARASITEMIC: HIGH DENSITY (≥10,000 PARASITES/MM ³)	
		NUMBER	(%)	NUMBER	(%)	NUMBER	(%)	NUMBER	(%)
CQ	1297	263	(20.3)	167	(12.9)	74	(5.7)	22	(1.7)
MQ	493	20	(4.1)	13	(2.6)	4	(0.8)	3	(0.6)
TOTAL	1790	283	(15.8)	180	(10.1)	78	(4.4)	25	(1.4)

Differences by treatment group are significant in each grouping of parasite density (chi square, p < 0.05)

Summary findings: maternal peripheral parasitemia at delivery

Parasitemia at delivery was 23.4% in primigravidas, 15.7% in secundigravidas, and 10.1% in multigravidas. The peripheral parasitemia rate in women on CQ was more than 5 times the rate in women on MQ. This confirms the markedly different efficacy of the two drugs and the relatively poor efficacy of CQ in this area of rural Malawi.

Placental parasitemia

Malaria infection of the placenta was identified in 346 (19.9%) of 1743 women who received regular dosing on their regimen and had a placental examination at the time of delivery.

Placental parasitemia and parity: Primigravid women were more likely than women in subsequent pregnancies to have placental parasitemia and to have higher density parasitemia (Table 7).

Table 7. Placental parasitemia at delivery by gravidity, MMRP, 1987-1990.

PREGNANCY NUMBER	NUMBER	PARASITEMIC		PARASITEMIC: LOW DENSITY (1-999 PARASITES/MM ³)		PARASITEMIC: MEDIUM DENSITY (1000-9999 PARASITES/MM ³)		PARASITEMIC: HIGH DENSITY (≥10,000 PARASITES/MM ³)	
		NUMBER	(%)	NUMBER	(%)	NUMBER	(%)	NUMBER	(%)
1	599	177	(29.5)	97	(16.2)	48	(8.0)	32	(5.3)
2	377	75	(19.9)	39	(10.3)	29	(7.7)	7	(1.9)
3	767	94	(12.2)	50	(6.5)	37	(4.8)	7	(0.9)
TOTAL	1743	346	(19.9)	186	(10.7)	114	(6.5)	46	(2.6)

Differences by gravidity are significant in each grouping of parasite density (chi square, p < 0.05)

Placental parasitemia and transmission season: Women delivering in the rainy and postrainy seasons were more likely than women delivering in the dry season to have placental malaria infection and to have higher density parasitemia (Table 8).

Table 8. Placental parasitemia at delivery by season, MMRP, 1987-1990.

SEASON	NUMBER	PARASITEMIC PLACENTA NUMBER (%)	PARASITEMIC:	PARASITEMIC:	PARASITEMIC:
			LOW DENSITY (1-999 PARASITES/MM ³)	MEDIUM DENSITY (1000-9999 PARASITES/MM ³)	HIGH DENSITY (≥ 10,000 PARASITES/MM ³)
RAINY	559	154 (27.5)	76 (13.6)	49 (8.8)	29 (5.2)
POSTRAINY	760	160 (21.1)	91 (12.0)	56 (7.4)	13 (1.7)
DRY	424	32 (7.5)	19 (4.5)	9 (2.1)	4 (0.9)
TOTAL	1743	346 (19.9)	186 (10.7)	114 (6.5)	46 (2.6)

Differences by season are significant in each grouping of parasite density (chi-square, $p < 0.05$)

Placental parasitemia and treatment regimen: Women assigned a CQ regimen were more likely than women assigned a MQ regimen to have placental malaria infection and to have higher density parasitemia (Table 9).

Table 9. Placental parasitemia at delivery by treatment regimen, MMRP, 1987-1990.

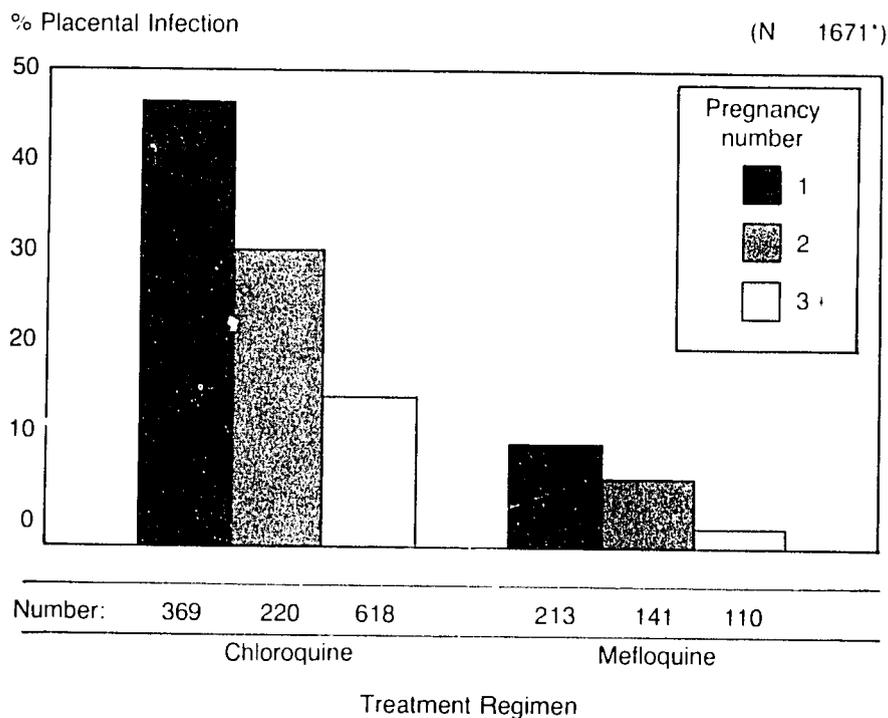
TREATMENT REGIMEN	NUMBER	PARASITEMIC NUMBER (%)	PARASITEMIC:	PARASITEMIC:	PARASITEMIC:
			LOW DENSITY (1-999 PARASITES/MM ³)	MEDIUM DENSITY (1000-9999 PARASITES/MM ³)	HIGH DENSITY (≥ 10,000 PARASITES/MM ³)
CQ	1262	316 (25.0)	169 (13.4)	105 (8.3)	42 (3.3)
MQ	481	30 (6.2)	17 (3.5)	9 (1.9)	4 (0.8)
TOTAL	1743	346 (19.9)	186 (10.7)	114 (6.5)	46 (2.6)

Differences by treatment regimen are significant in each grouping of parasite density (chi-square, $p < 0.05$)

**SECTION VI:
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Placental *P. falciparum* infection rates, like peripheral parasitemia rates, were associated with gravidity, season, and the antimalarial drug regimen. Primigravidas and women on CQ had higher rates of placental infection. On average, 46.6% of primigravidas on one of the CQ regimens showed placental infection at delivery compared with 15.4% of multigravidas (< 3rd pregnancy) on CQ. Fewer than 11% of primigravidas on MQ had evidence of placental infection and fewer than 3% of multigravidas on MQ had placental infection (Figure 12). Placental infection was most common in primiparous women on CQ delivering in the rainy season (55% infected) and least common in multiparous women on MQ delivering in the dry season (none infected).

Figure 12. Placental malaria infection by gravidity and antimalarial drug regimen, MMRP, 1987-1990.

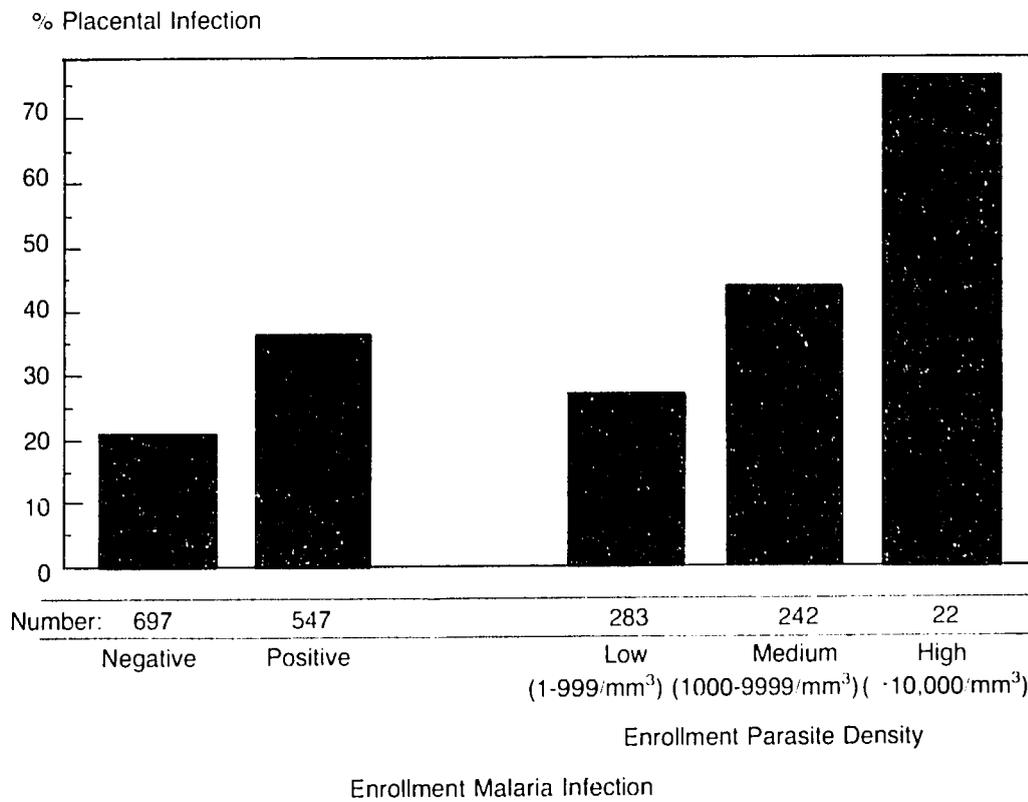


* Women dosed properly, in study more than 6 weeks

Findings consistently suggest that MQ was highly effective in keeping the placenta clear of malaria parasites and that MQ was superior, regardless of gravidity or season.

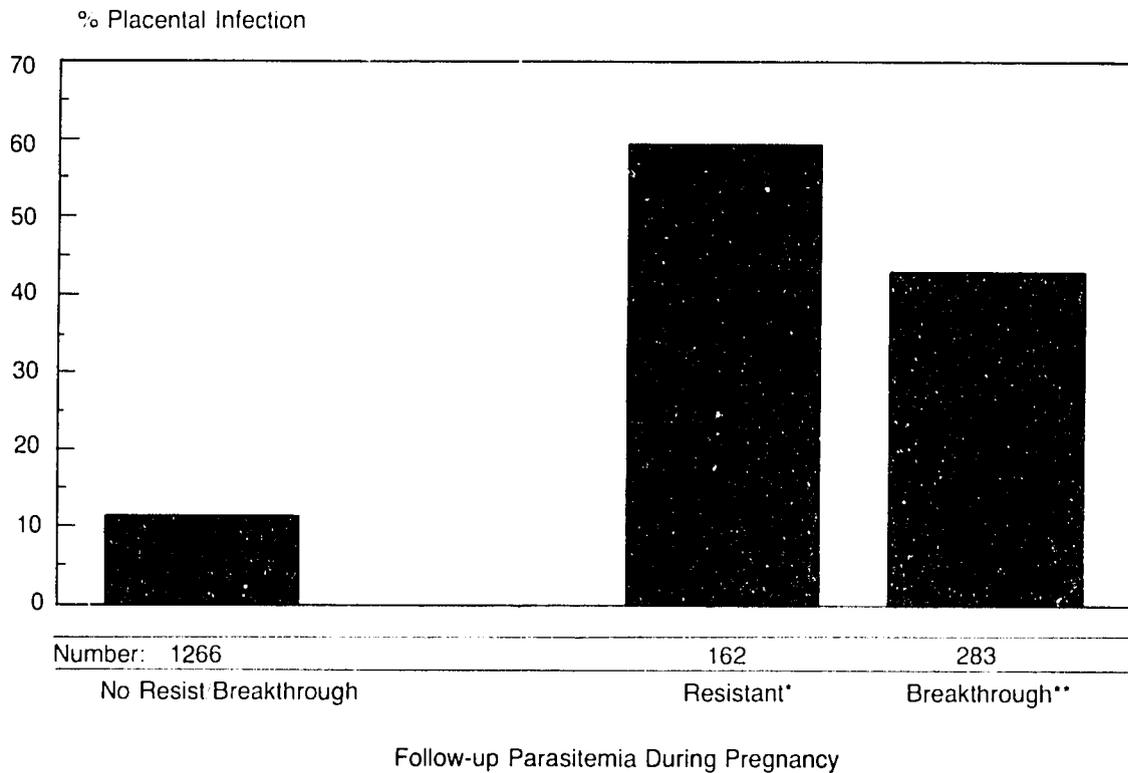
The determinants of placental malaria infection were further examined. The presence of parasitemia at enrollment was a predictor of the likelihood of placental malaria at delivery. Women on a CQ regimen who were parasitemic at enrollment were more likely to have placental infection at delivery than women on a CQ regimen who were a parasitemic at enrollment. Similarly, a higher density of enrollment parasitemia was associated with an increased likelihood of placental infection at delivery in these CQ-treated women (Figure 13).

Figure 13. Placental malaria infection by enrollment parasitemia among chloroquine-treated women, MMRP, 1987-1990.



Follow-up parasitemia while on one of the regimens was also a predictor of placental infection at the time of delivery. Women who had either resistant or breakthrough parasitemia on follow-up visits were more likely to have placental infection, regardless of the regimen used, although, as noted above, many fewer women showed resistant or breakthrough infection on the MQ regimen (Figure 14).

Figure 14. Placental malaria infection by follow-up parasitemia, MMRP, 1987-1990.



* Resistant: initially parasitemic, parasitemic on 1st follow-up

** Breakthrough: initially aparasitemic, parasitemic on follow-up

Summary findings: placental malaria infection

Placental parasite infection was most common in primigravidas on one of the CQ regimens: 46% of primigravidas on CQ had placental malaria infection compared with 9% of primigravidas on MQ, and 15% of multigravidas on CQ and fewer than 3% of multigravidas on MQ had placental malaria infection.

In addition to gravidity and drug regimen, the presence of enrollment and follow-up parasitemia were important predictors of placental malaria infection.

Umbilical cord parasitemia

Malaria infection of the umbilical cord blood was identified in 123 (7.1%) of 1732 women who received regular dosing on their regimen and had cord blood examined at the time of delivery. Factors associated with umbilical cord parasitemia were examined.

Umbilical cord parasitemia and birth order: Firstborn babies were more likely than babies of subsequent birth order to have umbilical cord parasitemia and to have higher density parasitemia (Table 10).

Table 10. Umbilical cord parasitemia by birth order, MMRP, 1987-1990.

BIRTH ORDER	NUMBER	PARASITEMIC NUMBER (%)	PARASITEMIC:	PARASITEMIC:	PARASITEMIC:
			LOW DENSITY (1-999 PARASITES/MM ³)	MEDIUM DENSITY (1000-9999 PARASITES/MM ³)	HIGH DENSITY (≥10,000 PARASITES/MM ³)
			NUMBER (%)	NUMBER (%)	NUMBER (%)
1	585	72 (12.3)	58 (9.9)	8 (1.4)	6 (1.0)
2	375	18 (4.8)	16 (4.3)	0 —	2 (0.5)
3	772	33 (4.3)	29 (3.8)	4 (0.5)	0 —
TOTAL	1732	123 (7.1)	103 (5.9)	12 (0.7)	8 (0.5)

Differences by birth order are significant overall and for low density parasitemia (chi-square, $p < 0.05$)

Umbilical cord parasitemia and transmission season: Women delivering in the rainy and postrainy seasons were more likely than women delivering in the dry season to have babies with umbilical cord malaria infection and to have higher density cord parasitemia (Table 11).

Table 11. Umbilical cord parasitemia by season, MMRP, 1987-1990.

SEASON	NUMBER	PARASITEMIC NUMBER (%)	PARASITEMIC:	PARASITEMIC:	PARASITEMIC:
			LOW DENSITY (1-999 PARASITES/MM ³)	MEDIUM DENSITY (1000-9999 PARASITES/MM ³)	HIGH DENSITY (≥10,000 PARASITES/MM ³)
			NUMBER (%)	NUMBER (%)	NUMBER (%)
RAINY	563	51 (9.1)	42 (7.5)	4 (0.7)	5 (0.9)
POSTRAINY	748	62 (8.3)	53 (7.1)	7 (0.9)	2 (0.3)
DRY	421	10 (2.4)	8 (1.9)	1 (0.2)	1 (0.2)
TOTAL	1732	123 (7.1)	103 (5.9)	12 (0.7)	8 (0.5)

Differences by season are significant for rainy and postrainy seasons compared with dry season overall (chi-square, $p < 0.05$)

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Umbilical cord parasitemia and treatment regimen: Women on a CQ regimen were more likely than women on an MQ regimen to have umbilical cord malaria infection and to have higher density parasitemia (Table 12).

Table 12. Umbilical cord parasitemia by treatment regimen, MMRP, 1987-1990.

TREATMENT REGIMEN	NUMBER	PARASITEMIC NUMBER (%)	PARASITEMIC: LOW DENSITY (1-999 PARASITES/MM ³)	PARASITEMIC: MEDIUM DENSITY (1,000-9999 PARASITES/MM ³)	PARASITEMIC: HIGH DENSITY (≥10,000 PARASITES/MM ³)
			NUMBER (%)	NUMBER (%)	NUMBER (%)
CQ	1252	108 (8.6)	92 (7.3)	10 (0.8)	6 (0.5)
MQ	480	15 (3.1)	11 (2.3)	2 (0.4)	2 (0.4)
TOTAL	1732	123 (7.1)	103 (5.9)	12 (0.7)	8 (0.5)

Differences by treatment group are significant in each grouping of parasite density (chi square, p < 0.05)

Relationship of maternal peripheral, placental, and umbilical cord parasitemia

Malaria infection rates were 15.8% for maternal infection, 19.9% for placental infection, and 7.1% for umbilical cord blood infection; they were highly correlated. Table 13 shows that for women with parasite densities >1000/mm³, more than 95% had placental infection. However, 7.5% of aparasitemic women had placental malaria infection; thus, maternal peripheral parasitemia did not fully identify all women with placental malaria infection.

Table 13. Likelihood of placental infection in women with peripheral parasitemia at delivery, MMRP, 1987-1990.

MATERNAL MALARIA PARASITE DENSITY (PARASITES/MM ³)	NUMBER	PERCENTAGE WITH PLACENTAL MALARIA INFECTION
0	1491	7.5%
1-999	175	75.4%
1000-9999	78	97.4%
≥ 10,000	23	95.7%

Despite reports in the literature suggesting that congenital malaria is uncommon (2,9), babies born to women with placental malaria infection had a high frequency of umbilical cord blood parasitemia. In fact, density of parasitemia (both maternal peripheral parasitemia and placental parasitemia) was an important predictor of which children had umbilical cord blood parasitemia (Table 14). See Section IX.A. for further discussion of congenital malaria infection.

Table 14. Likelihood of umbilical cord parasitemia according to maternal peripheral blood or placental malaria infection, MMRP, 1987-1990.

MATERNAL PARASITE DENSITY (/MM ³)		PERCENTAGE WITH UMBILICAL CORD PARASITEMIA	PLACENTAL PARASITE DENSITY (/MM ³)		PERCENTAGE WITH UMBILICAL CORD PARASITEMIA
	NUMBER			NUMBER	
0	1487	1.8%	0	1419	0.3%
1-999	173	24.2%	1-999	185	20.5%
1000-9999	77	46.8%	1000-9999	116	38.8%
>10,000	23	87.0%	>10,000	44	61.4%

Chi-square test for trend for increasing cord blood parasitemia with increasing parasite density of maternal or placental infection: $p < .01$.

Summary findings: relationship of maternal peripheral, placental, and umbilical cord parasitemia

Umbilical cord blood P. falciparum infection rates were highly correlated with placental infection and were also associated with gravidity, season, and antimalarial drug regimen. Primigravidas and women taking CQ had higher rates of umbilical cord blood parasitemia. On average, 16% of babies born to primigravidas on one of the CQ regimens showed umbilical cord parasitemia, compared with 5% of babies born to multigravidas (>3rd pregnancy) on CQ. Fewer than 6% of babies born to primigravidas on MQ had evidence of umbilical cord blood infection, and none of the 117 babies born to multigravid women on MQ had umbilical cord blood infection.

These findings suggest that a high proportion of fetuses are exposed to malaria parasites if the mother has peripheral or placental malaria infection. While we cannot be sure that exposure occurs in utero throughout pregnancy, the finding that more than 50% of babies have cord blood parasitemia when the mother has a high density of peripheral or placental parasitemia strongly suggests that if the pregnant woman has a malaria infection, a high likelihood exists that the fetus will be exposed to malaria parasites.

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D. MATERNAL HIV INFECTION

Overall, 7.1% of the 4131 serum specimens collected were ELISA- and Western Blot-positive for antibodies to HIV. High rates of HIV seropositivity were seen in the Mangochi and Koche facilities, which are located in towns; lower rates of seropositivity were seen in Mpondas and Malindi, which serve women in more rural areas (Table 15).

Table 15. HIV seropositivity by antenatal clinic site, MMRP, 1987-1990.

CLINIC SITE*	NUMBER	HIV SEROPOSITIVE	
		NUMBER	(%)
MANGOCHI HOSPITAL	1086	124	(11.4)
KOCHE CLINIC	734	80	(10.9)
MPONDAS CLINIC	631	32	(5.1)
MALINDI HOSPITAL	1680	57	(3.4)
TOTAL	4131	293	(7.1)

In 3 years, the overall HIV-seropositivity rate changed from 4.2% to 8.0% (Chi-square test for trend, $p = 0.012$) (Table 16). This increase in seropositivity over time was seen in all but one of the sites.

Table 16. HIV seropositivity by year of delivery, MMRP, 1987-1989.*

YEAR OF TESTING:	1987		1988		1989	
	NUMBER	(% POSITIVE)	NUMBER	(% POSITIVE)	NUMBER	(% POSITIVE)
TOTAL TESTED	477		2130		1522	
HIV POSITIVE	20	(4.2%)	152	(7.1%)	121	(8.0%)

* Only two women delivered in 1990; this information was not included in the table.

Factors associated with HIV seropositivity

We examined maternal characteristics that were associated with HIV seropositivity including gravidity, education, socioeconomic status, height, weight at first clinic visit, weight at delivery, weight gain during pregnancy, distance between home and delivery facility, history of fever in pregnancy, hematocrit at enrollment and delivery, serologic evidence of active syphilis, and adverse reproductive outcomes prior to the current pregnancy.

Pregnancy number and maternal age: Women in their first or second pregnancies were more likely to be HIV + compared with women in later pregnancies (Table 17). Because pregnancy number and age were very closely linked, the same results are seen if age categories are used. This finding may be in part due to higher rates of enrollment of young women in early pregnancies at the Mangochi site where HIV seroprevalence was relatively high.

Table 17. HIV seropositivity by pregnancy number, MMRP, 1987-1990.

PREGNANCY NUMBER	NUMBER	HIV SEROPOSITIVE	
		NUMBER	(%)
1	1266	107	(8.5)
2	984	85	(8.6)
3	1799	95	(5.3)
TOTAL	4049	287	(7.1)

Seropositivity by gravidity number is significantly different. (chi square, $p = 0.0005$)

Maternal education: Women with higher levels of education were more likely to be HIV + (Table 18); differences were highly significant, $p = 10^{-6}$.

Table 18. HIV seropositivity by maternal education, MMRP, 1987-1990.

EDUCATION LEVEL ACHIEVED	NUMBER	HIV SEROPOSITIVE	
		NUMBER	(%)
NO FORMAL EDUCATION	2859	136	(4.8)
ELEMENTARY (< 6 YEARS)	357	32	(9.0)
SECONDARY (> 7 YEARS)	912	124	(13.6)
TOTAL	4128	292	(7.1)

Chi square for trend of increasing HIV seropositivity rates with increasing education = 81.3, $p = 10^{-7}$

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Maternal socioeconomic status: Women of higher socioeconomic status were more likely to be HIV + (Table 19); differences were highly significant, $p < 10^{-6}$.

Table 19. HIV seropositivity by maternal socioeconomic status, MMRP, 1987-1990.

SOCIOECONOMIC STATUS (CODED BY TYPE OF HOUSE CONSTRUCTION)	NUMBER	HIV SEROPOSITIVE	
		NUMBER	(%)
LOW	2782	156	(5.6)
MIDDLE	819	69	(8.4)
HIGH	525	67	(12.8)
TOTAL	4126	292	(7.1)

Chi-square for trend of increasing HIV seropositivity rates with increasing socioeconomic status = 36.6, $p < 10^{-5}$.

Maternal stature: Taller women (≥ 150 cm in height) were significantly more likely to be HIV + than shorter women, $p = 0.006$ (Table 20). In this setting, height may be associated with nutritional status and socioeconomic factors; thus, although height was associated with HIV serostatus, height may be a marker for other risk factors.

Table 20. HIV seropositivity by maternal height, MMRP, 1987-1990.

MATERNAL HEIGHT	NUMBER	HIV SEROPOSITIVE	
		NUMBER	(%)
SHORT (< 149 CM TALL)	571	25	(4.4)
NORMAL (≥ 150 CM TALL)	3529	267	(7.6)
TOTAL	4100	292	(7.1)

HIV seropositivity rates differed by maternal height (chi-square, $p = 0.006$)

Maternal weight and weight gain during pregnancy: Maternal weight at the time of first ANC visit was not associated with HIV serostatus. The 952 women weighing ≤ 49 kgs (7.3% HIV +) were not significantly more likely to be HIV + than the 3157 women weighing ≥ 50 kgs (7.0% HIV +) ($p = 0.71$). Weight was measured at each follow-up visit and at delivery. The 224 women who lost weight between their first ANC visit and delivery (11.6% HIV +) were more likely to be HIV + than the 1149 women who gained weight in that interval (8.2% HIV +); however, the difference was not statistically significant ($p = 0.097$).

Distance between home and antenatal clinic: Women who were HIV + were more likely to live closer to the clinic. The average distance between home and clinic for HIV + women was 5.5 km (standard deviation [SD] ± 5.0 km), compared with 7.3 km (SD ± 6.1 km) for HIV- women, ($p < 10^{-6}$). Because the clinics are located in towns or large village clusters, the distance measure may be a surrogate for a woman's proximity to a large population base.

History of fever during pregnancy: At first ANC visit, women were asked about their experience with febrile illness during the pregnancy. The 292 HIV+ women were significantly more likely to report febrile illness (36.3%) than were the 3828 HIV- women (24.1%) ($p < 10^{-5}$). Information was not available to determine whether the fevers were associated only with HIV virus or the presence of another infecting organism, e.g., malaria parasites.

Maternal hematocrit: The mean hematocrit of 264 HIV+ women (33.0% [SD \pm 5.4]) was only slightly lower than the mean hematocrit in 3397 HIV- women (33.5% [SD \pm 5.8]); however, the difference was not statistically significant, $p = 0.22$. A further examination of the proportion of women with anemia showed that 23.9% of HIV+ women and 18.9% of HIV- women had hematocrits $< 30\%$, $p = 0.047$. However, 5.3% of HIV+ and 6.3% of HIV- women had hematocrits $< 25\%$, $p = 0.53$. Thus, while there may be some effect of HIV on anemia, the effect appears to be mild and is not associated with an increase in severe anemia. When women were examined at delivery, no effect of HIV serostatus on maternal hematocrit was observed.

Maternal syphilis infection: Among 3599 women with both syphilis and HIV serologic results, 4.2% had evidence of an active syphilis infection. HIV+ women had higher rates of active syphilis (5.5%) than HIV- women (4.1%), but these differences were not statistically significant, $p = 0.3$. A total of 9.6% of women had evidence of active or recent syphilis infection; evidence of active or recent syphilis infection was seen in 14.7% of HIV+ women and 9.3% of HIV- women, $p = 0.006$.

Summary findings: maternal HIV infection

These results provide information on HIV infection rates in the population of pregnant women at their first ANC visit between September 1987 and June 1989 in Mangochi District. The information was collected in a similar fashion to studies conducted in the large cities of Blantyre and Lilongwe in early 1989, which demonstrated 17.6% HIV seropositivity among pregnant women (57). Although HIV-seropositivity rates were lower in Mangochi District, rates varied significantly between the town areas and the rural villages (from approximately 12.6% in towns to less than 5.0% in rural villages). This information can be used as an estimate of seropositivity elsewhere in the country. The time span of 3 years, while short, was adequate to identify significant increases in seropositivity over time, suggesting that many of these HIV+ women may have been recently infected.

Factors associated with HIV infection in these sexually active women of reproductive age included age and parity, high maternal education, high socioeconomic status, tall stature (possibly a marker of nutritional and socioeconomic status), close proximity to the antenatal clinic, reported febrile illness during pregnancy, mild but not severe anemia, and maternal syphilis infection.

Association between HIV seropositivity and malaria in pregnancy

The impact of HIV infection on malaria in pregnant women was investigated. This investigation was limited to women receiving CQ because almost all women receiving MQ became parasite-free, leaving too few for comparison.

A total of 2946 women who were placed on CQ prophylaxis and monitored throughout pregnancy and delivery were evaluated for possible interaction between HIV and malaria during pregnancy. HIV test results were available for 2781 (94%) of the women. One hundred and fifty-two women (5.5%) tested positive by ELISA and Western blot for antibodies to HIV. Malaria

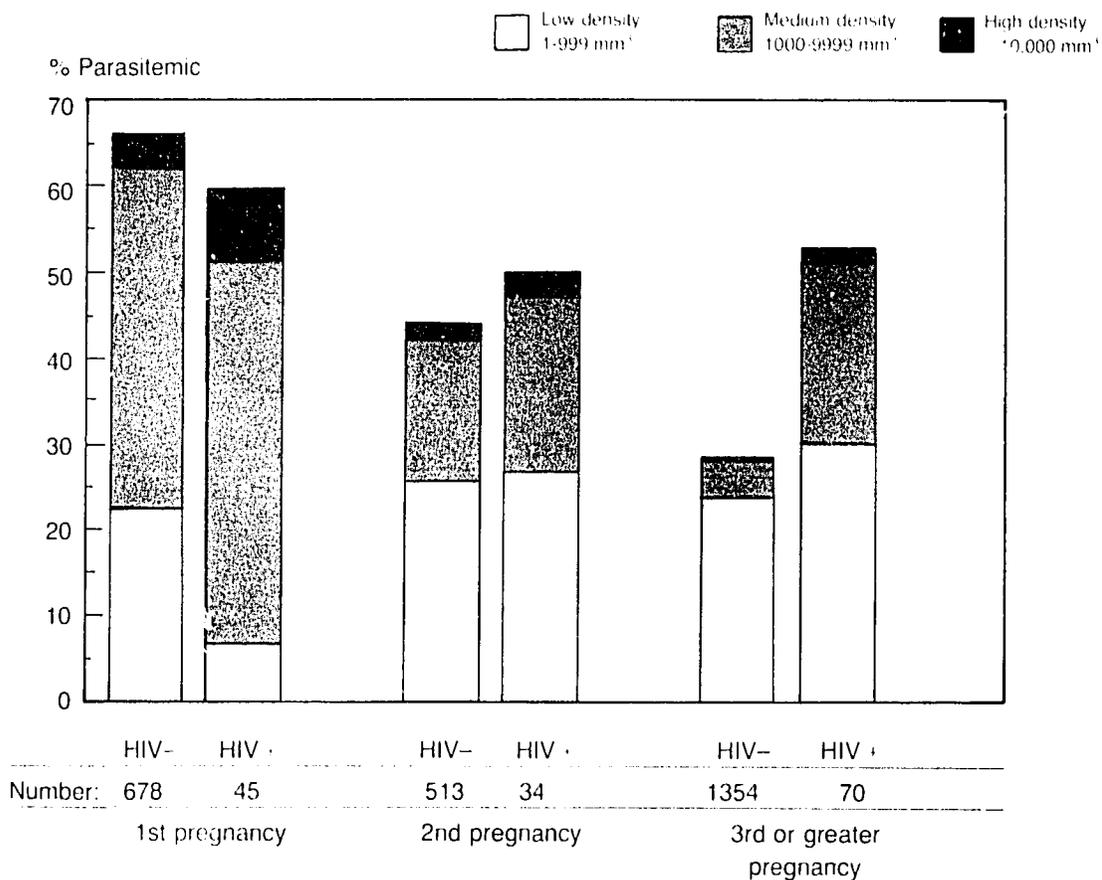
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parasitemia was found in 12% of women at enrollment, 30.6% of women during follow-up, and 19.1% of women at delivery.

Interaction between HIV and malaria

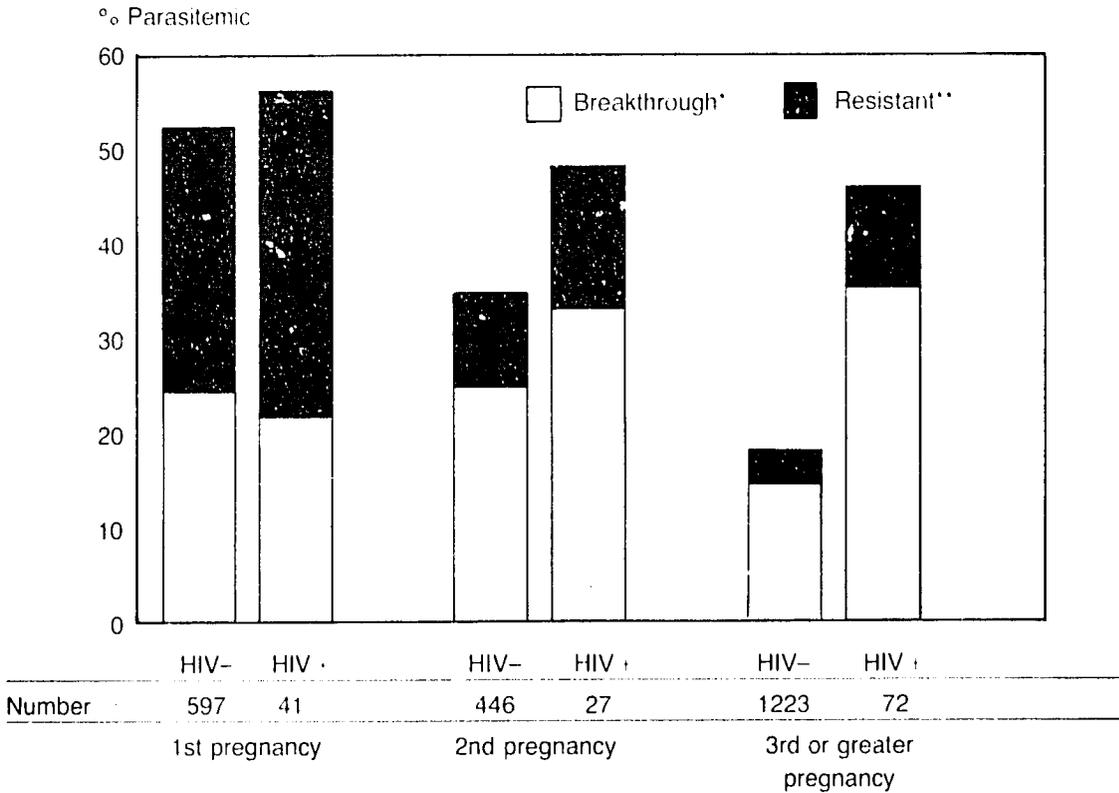
Enrollment: At enrollment, parasite prevalence was higher in HIV+ women (54.1%) than in HIV- women (41.7%) (RR = 1.31, CI = 1.12-1.52). After enrollment parasitemia was stratified by gravidity in women with or without HIV infection, two patterns emerged. First, the difference in prevalence of parasitemia between HIV+ and HIV- women increased with increasing gravidity (Figure 15). The prevalence of parasitemia was similar in primigravid HIV+ (60.0%) and HIV- women (66.1%) (RR = 0.91, CI = 0.71-1.16), but higher in multigravid HIV+ (52.9%) than in HIV- women (28.5%) (RR = 1.85, CI = 1.46-2.35). Secondly, in primigravidas, GMPDs were higher in HIV+ women (1390 parasites per mm³ of blood) than in HIV- women (1375 parasites per mm³ of blood) (p = 0.0005). While GMPDs decreased with gravidity, they were consistently higher in HIV+ women than in HIV- women.

Figure 15. *Plasmodium falciparum* prevalence and density at antenatal clinic enrollment among HIV+ and HIV- pregnant women receiving chloroquine chemoprophylaxis, by gravidity. (N = 2694). MMRP, 1987-1990.



Parasitemia during monthly follow-up visits: Persistent and breakthrough parasitemia at follow-up visits was more common in HIV+ than in HIV- women. Persistent infections in HIV+ women were 19% and 11% in HIV- women (RR = 1.92, CI = 1.19-3.09); breakthrough infections in HIV+ women were 31% and 20% in HIV- women (RR = 1.57, CI = 1.20-2.05). Again, this pattern was most pronounced in multigravidas, in whom the relative risks of resistant and breakthrough infections associated with HIV infection were 3.66 in HIV+ women (CI = 1.69-7.90) and 2.33 in HIV- women (CI = 1.63-3.32) (Figure 16).

Figure 16. Resistant and breakthrough *Plasmodium falciparum* infection at follow-up visits among HIV+ and HIV- pregnant women receiving chloroquine prophylaxis (N = 2399), MMRP, 1987-1990.

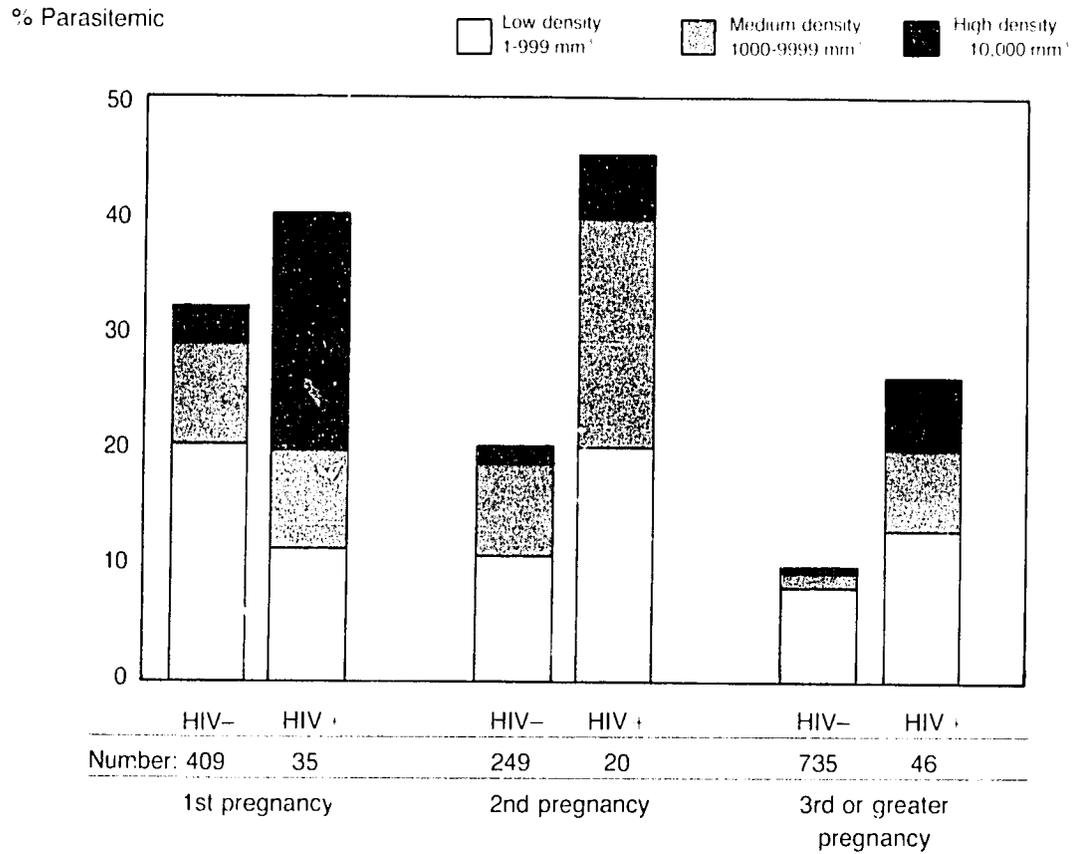


* Breakthrough: a parasitemic - parasitemic on follow up
 ** Resistant: initially parasitemic - parasitemic on 1st follow up

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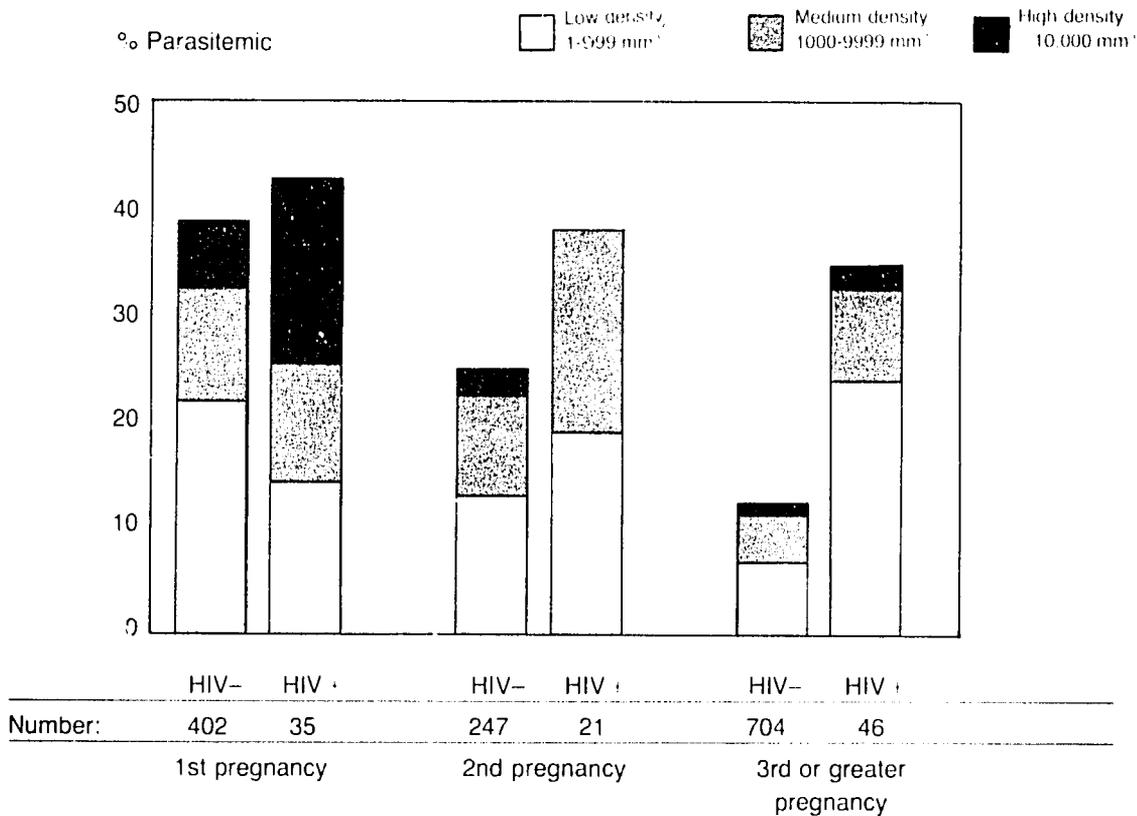
Maternal parasitemia at delivery: At the time of delivery, HIV+ women had a higher parasite prevalence (34.7%) than HIV- women (18.2%), (RR = 1.91, CI = 1.43-2.55). The differences in parasite prevalence associated with HIV infection were greatest in multigravidas (RR = 2.66, CI = 1.56-4.54) (Figure 17).

Figure 17. *Plasmodium falciparum* prevalence and density in maternal peripheral blood smears at delivery in HIV+ and HIV- pregnant women, (N = 1494), MMRP, 1987-1990.



Placental infection at delivery: Among women who delivered in hospital, the prevalence of placental infection in HIV+ women was 38.2% and in HIV- women 22.5% (RR = 1.70, CI = 1.30-2.21) (Figure 18). Among HIV- women, the prevalence of placental malaria infection decreased dramatically with increasing gravidity. However, HIV+ women did not demonstrate a marked decrease in infection rates with increasing gravidity. Among multigravidas, HIV+ women had a significantly higher prevalence of placental malaria (34.8%) than HIV- women (12.4%), (RR = 2.81, CI = 1.81-4.38).

Figure 18. *Plasmodium falciparum* prevalence and density in placental blood smears at delivery in HIV+ and HIV- women (N = 1455), MMRP



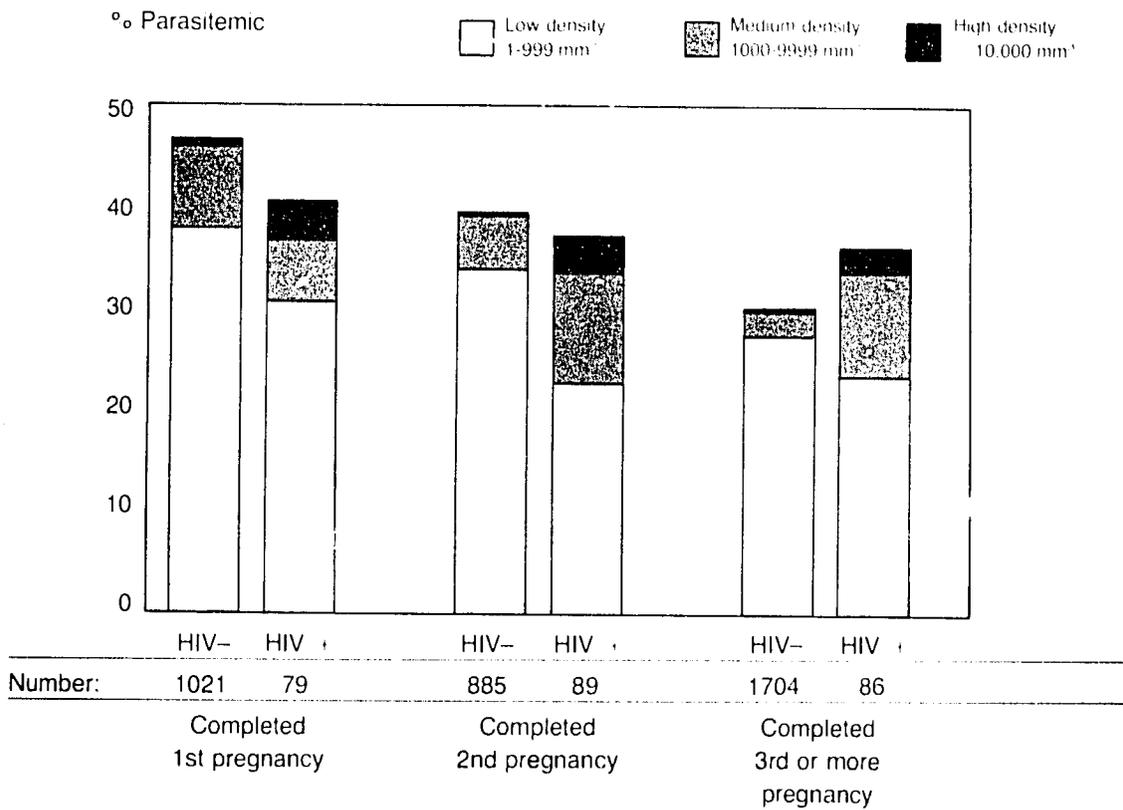
Umbilical cord blood infection at delivery: Among newborns delivered in hospital, the prevalence of umbilical cord blood infection in those whose mothers were HIV+ and HIV- was 25.5% and 6.8%, respectively, (RR = 3.76, CI = 2.54-5.57). The prevalence of umbilical cord blood malaria infection decreased with increasing gravidity; however, the difference in infection rates by gravidity was less prominent among infants born to HIV+ women than those born to HIV- women. Among multigravidas, infants born to HIV+ women had a significantly higher prevalence of umbilical cord blood malaria (28.6%) than infants born to HIV- women (3.6%) (RR = 6.67, CI = 3.43-12.95).

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Because umbilical cord blood parasitemia was seen only in neonates born to women with placental malaria infection, we examined the effect of HIV infection on the frequency of umbilical cord blood parasitemia only in neonates born to women with placental infection. Again, umbilical cord blood infection was more common in neonates born to HIV+ mothers (RR = 2.06, CI = 1.52-2.79).

Postpartum parasitemia. The prevalence and density of malaria parasitemia in women in the postpartum period (< 60 days after delivery) was not significantly different between HIV+ and HIV- women overall or within parity groupings (Figure 19).

Figure 19. *Plasmodium falciparum* prevalence and density during the postpartum period among HIV+ and HIV- women, (N = 3864 postpartum visits), MMRP, 1987-1990.



All blood smears taken < 60 days after delivery; study data represent combination of cross sectional examinations during the postpartum period.

Summary findings: association between HIV infection and malaria

*This investigation demonstrated that compared with HIV - pregnant women, HIV + pregnant women were more likely to have a higher prevalence and density of malaria parasitemia at enrollment into ANC, at follow-up visits while on CQ chemoprophylaxis, and at delivery (reflected also in placental blood smears). In addition, the neonates born to HIV + women were more likely to have umbilical cord blood parasitemia. The HIV-associated differences seen in parasite prevalence and density at each point were greatest in women with three or more pregnancies (multigravidas) compared with primigravidas or secundigravidas. The magnitude and consistency of these findings provide evidence for a biologic interaction whereby *P. falciparum* infection is less well controlled in HIV-infected pregnant women, particularly in those who should have established and maintained a malaria-specific immune response from exposure to malaria parasites in a previous pregnancy.*

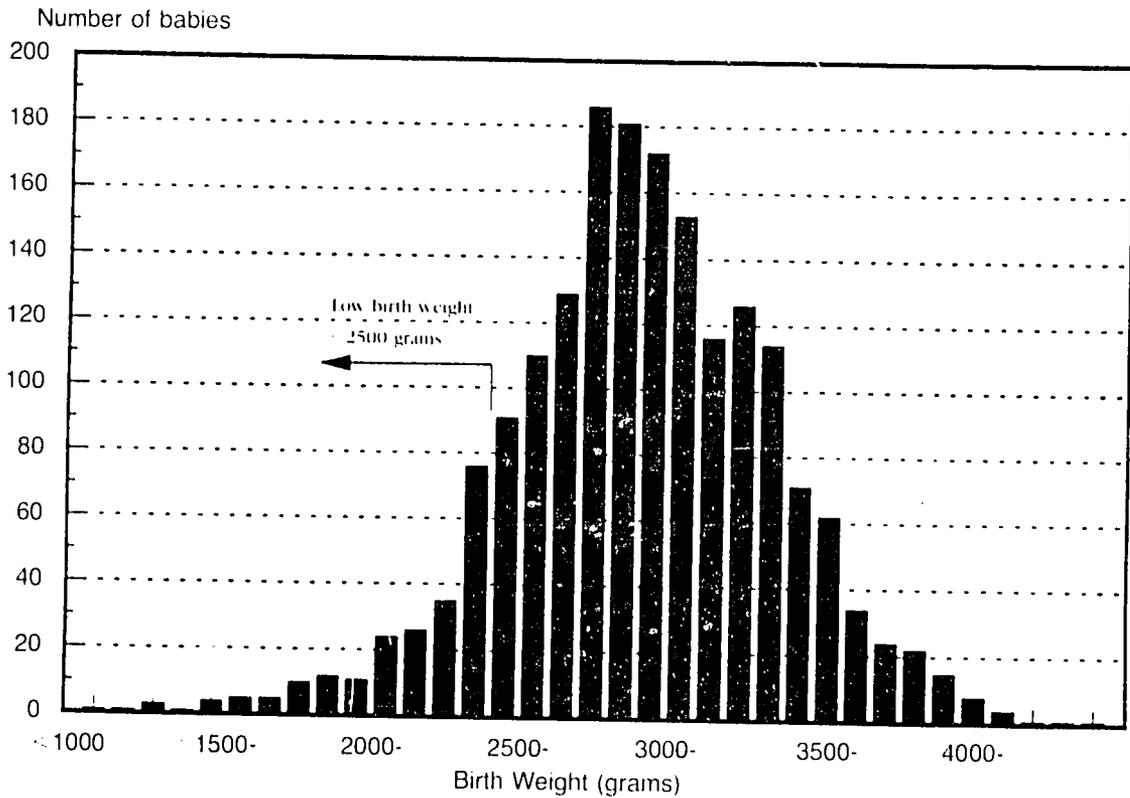
The most likely explanation for the gravidity-specific effect observed in our study is that HIV infection interferes with the maintenance of immune recognition of malaria, which starts to occur with the first malaria-exposed pregnancy. If this is the case, one would expect little or no difference between primigravidas with and without HIV infection because both groups would not have acquired the necessary pregnancy-specific immunity and would exhibit the same high risk of malaria infection; our findings bear this out. The greatest effect should be, and is, on multigravidas, who have experienced previous malaria-exposed pregnancies and should have established a moderate degree of immune protection, which is normally maintained across pregnancies. Women in their second pregnancy who have experienced only one previous malaria-exposed pregnancy would likely have some degree of immune protection and fall between "unprotected" primigravidas and "protected" multigravidas.

E. BIRTH WEIGHT

Birth weight was the principal outcome measurement in the investigation. The overall mean birth weight in the population of singleton liveborn infants was 2905 grams (SD ± 459 gm); 16.6% were born with LBW.

Birth-weight distribution and incidence of low birth weight

Figure 20. Birth-weight distribution in babies born to women in the study. (N = 1642). MMRP, 1987-1990.



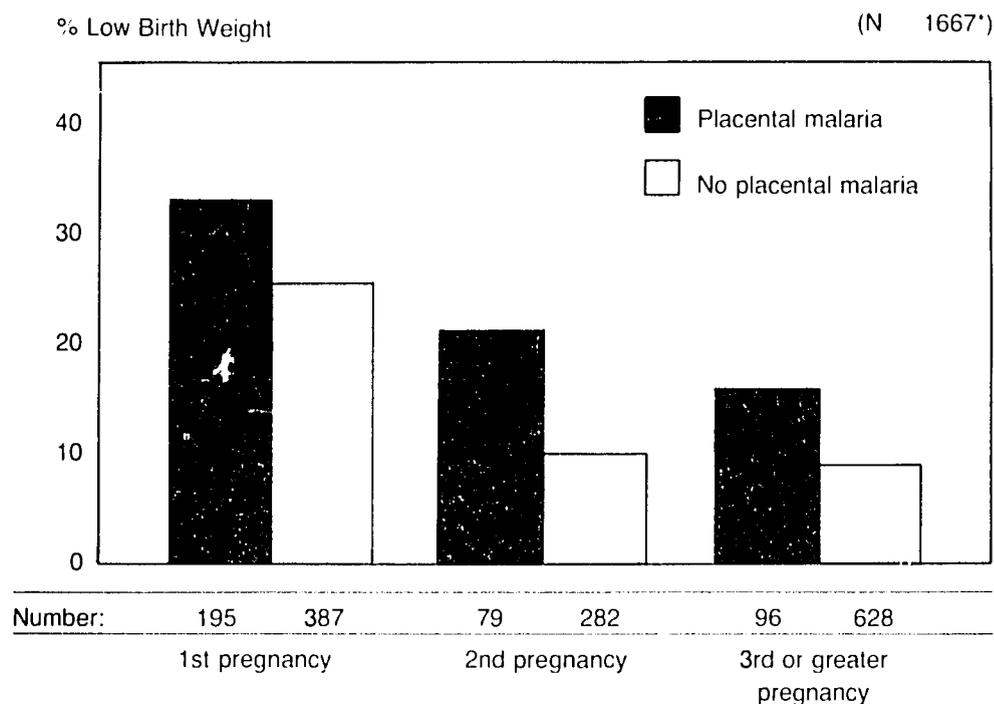
Firstborns had a lower mean birth weight and were more likely to be born with LBW than infants of subsequent birth order. Table 21 shows the mean birth weight and the proportion of infants with LBW for each birth-order stratum. The mean birth weight increased significantly, and the proportion of LBW decreased significantly with increasing birth order.

Table 21. Mean birth weight and percent low birth weight by parity, MMRP, 1987-1990.

PREGNANCY NUMBER	NUMBER	BIRTH WEIGHT		PERCENT LOW BIRTH WEIGHT
		MEAN	(\pm SD)	
1	603	2721	445	28.0%
2	384	2942	436	12.5%
≥ 3	781	3027	438	10.4%
TOTAL	1768	2905	459	16.6%

The incidence of LBW* was significantly higher in each gravidity group for those babies born to women with placental malaria than for babies born to women without placental infection (Figure 21).

Figure 21. Incidence of low birth weight by birth order and placental malaria infection status, (N = 1677), MMRP, 1987-1990.

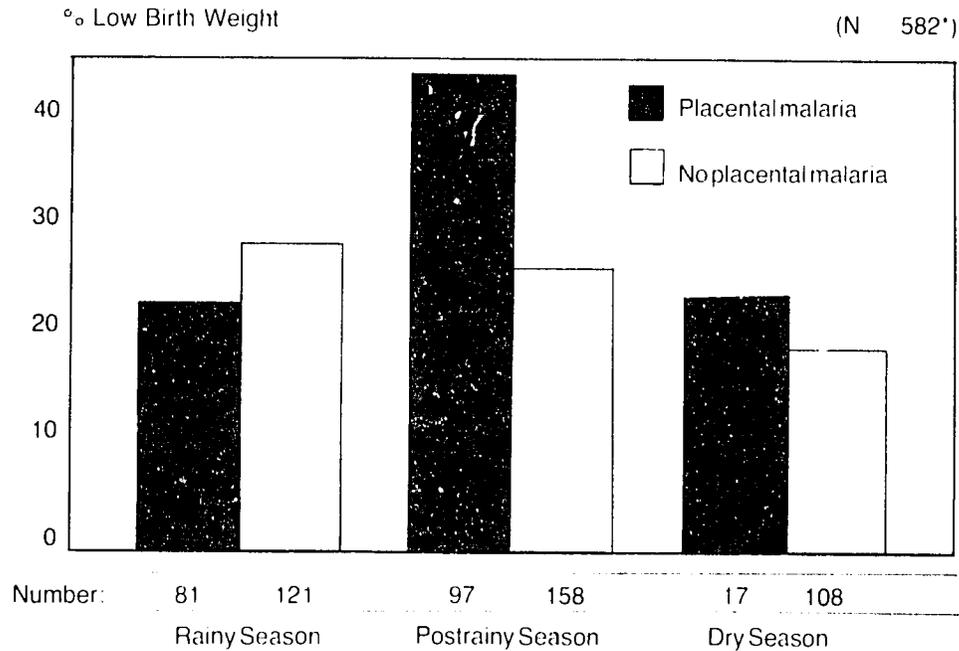


* Singleton liveborn babies born to women in study > 6 weeks and dosed properly. Differences in % low birth weight are significant in each birth order.

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In firstborns, the association between placental malaria infection and percentage LBW was observed only among women whose third trimester of pregnancy was exposed to high malaria transmission during the rainy and early postrainy seasons (OR = 2.11, 95% CI = 1.19-3.73) (Figure 22). In babies of higher birth order (second and above), although the association between placental malaria infection and LBW varied by season, this variation was not significant.

Figure 22. Incidence of low birth weight in firstborns by season and placental malaria infection status. (N = 582). MMRP, 1987-1990.

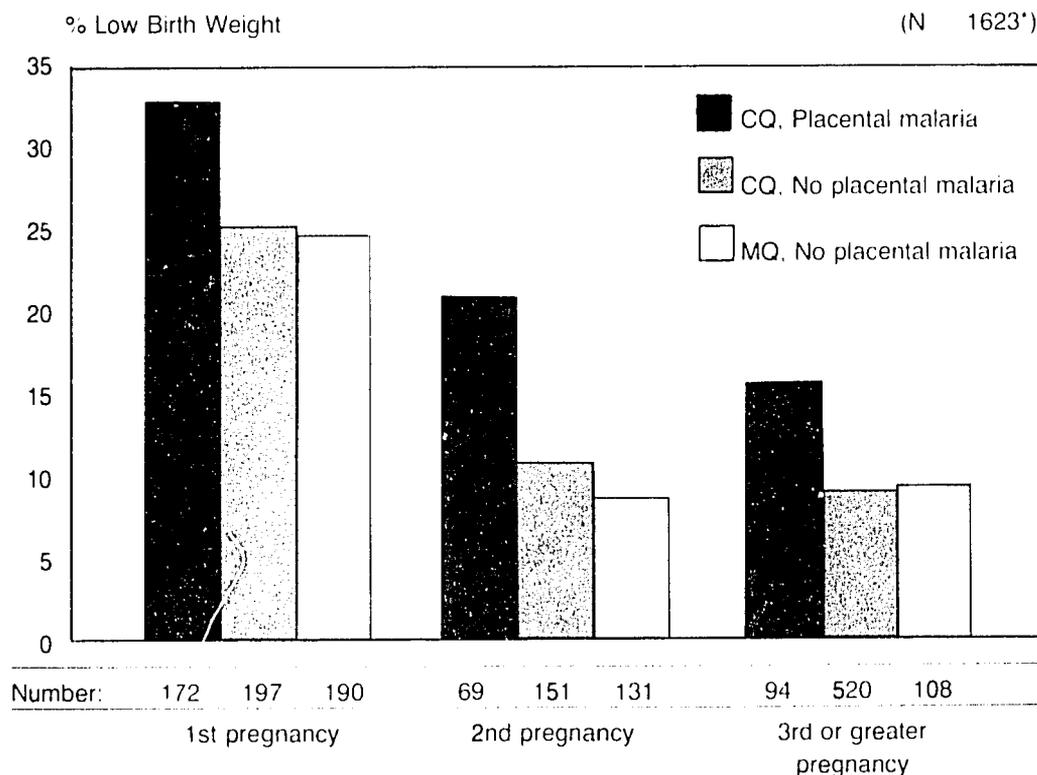


* Singleton liveborn babies born to women in study > 6 weeks and dosed properly.
Differences in % low birth weight are significant only in the postrainy season.

In each gravidity group, the incidence of LBW was significantly lower for women who had no placental malaria, regardless of the drug used to keep the placenta parasite-free (Figure 23).⁶ As noted earlier, MQ was much more likely than CQ to clear placental malaria infection.

⁶Mantel-Haenszel-weighted OR for the three strata in Figure 23 was 1.71 (95% CI 1.26-2.36)

Figure 25. Incidence of low birth weight by treatment regimen, placental infection status, and birth order. (N = 1623), MMRP, 1987-1990.



* Singleton liveborn babies born to women in study - 6 weeks and dosed properly

Adjusted univariate analysis

Using logistic regression, we examined the association between LBW and several maternal and newborn characteristics: malaria prevention regimen (CQ vs MQ), placental malaria infection, enrollment malaria infection, maternal height and weight, maternal education and socioeconomic status, maternal HIV and syphilis infection status, maternal anemia, season of delivery, and sex of the newborn. Because of the strong association between birth order and LBW previously described, the models for each of these factors were adjusted for birth order using a dichotomous variable (birth order = 1 or ≥ 2) (Table 22).

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Table 22. Association between low birth weight and maternal and infant characteristics; single variable analysis adjusted for birth order, MMRP, 1987-1990.

CHARACTERISTIC ^a	PREVALENCE (%)	ODDS RATIO	95% CONFIDENCE INTERVAL
MATERNAL WEIGHT < 50 KG AT ENROLLMENT *	23.6	1.83	1.40, 2.41
MATERNAL HEIGHT < 150 CM *	13.3	1.59	1.14, 2.22
NOT LITERATE	66.8	0.94	0.72, 1.23
LOW SOCIOECONOMIC STATUS ^b	64.3	0.92	0.71, 1.19
HEMATOCRIT < 25%	5.7	1.32	0.77, 2.25
HEMATOCRIT < 30%	18.7	1.11	0.79, 1.55
ENROLLMENT MALARIA PARASITEMIA	45.2	0.98	0.75, 1.29
PLACENTAL MALARIA INFECTION *	22.1	1.76	1.32, 2.34
UMBILICAL CORD MALARIA INFECTION *	7.3	2.66	1.78, 3.97
USED CQ ^c **	72.9	1.33	0.99, 1.79
FEMALE INFANT *	50.2	1.96	1.51, 2.54
RAINY SEASON ^d	32.3	1.24	0.96, 1.62
RAINY + POSTRAINY SEASON *	65.2	1.52	1.15, 2.01
MATERNAL SYPHILIS INFECTION ** (VDRL & MHA-TP SEROPOSITIVE)	2.6	2.17	0.99, 4.73
MATERNAL HIV INFECTION *	7.8	1.63	1.08, 2.47

* Factors associated with increased risk of LBW in univariate analysis (when adjusted for gravidity groupings of 1, or >2). Because of adjustment for gravidity, gravidity and age (highly correlated with gravidity) were not examined in this analysis.

** "Used chloroquine prophylaxis" and maternal syphilis infection were borderline significant.

^d Characteristics of women enrolled for < 6 weeks, receiving all doses of antimalarial drug and delivering a liveborn singleton infant with known birth weight. Except where noted, the reference group for comparison is those women without the characteristic.

^b Socioeconomic status defined by surrogate measures of four household construction characteristics; low socioeconomic status was defined as all four characteristics at the lowest grade.

^c Reference group for women using chloroquine was women using mefloquine.

^d Seasons were grouped as rainy (January-April), post-rainy (May-August), and dry (September-December).

Multivariate analysis

To determine the strongest predictors of LBW, we performed a multivariate analysis and further examined the maternal and infant characteristics described in the adjusted univariate analysis. In addition to the known effects of birth order and female sex, placental and umbilical cord blood malaria infection, low maternal weight (less than 50 kgs) at first ANC visit, and maternal HIV infection were associated with LBW (Table 23).

Table 23. Maternal and infant characteristics associated with low birth weight in a multivariate model, MMRP, 1987-1990.

MATERNAL OR INFANT CHARACTERISTIC	PREVALENCE	ODDS RATIO	95% CONFIDENCE INTERVALS
FIRST BIRTH*	33.9%	4.46	2.77, 7.16
UMBILICAL CORD MALARIA INFECTION	7.3%	1.76	1.06, 2.92
PLACENTAL MALARIA	22.1%	1.39	0.97, 2.00
ENROLLMENT MATERNAL WEIGHT < 50 KG	23.6%	1.90	1.41, 2.55
FEMALE BABY	50.2%	3.02	1.96, 4.64
HIV SEROPOSITIVE	7.8%	2.56	1.43, 4.58

*The reference group for first births is birth order = 2

Because umbilical cord parasitemia and placental parasitemia are highly correlated and their prevalence differs, we reexamined the model without umbilical cord blood parasitemia as a variable. Whereas risk estimates for the other variables were essentially unchanged, the odds ratio for placental malaria increased to 1.71 (95% CI = 1.27, 2.32; $p = 0.005$) and rainy and postrainy season entered the model (OR = 1.40, 95% CI = 1.03, 1.90) ($p = 0.0323$). As described in earlier sections, umbilical cord blood parasitemia is correlated with density of placental infection, and the frequency and density of infection are highest during the high malaria transmission season (rainy and postrainy season).

We further examined the role of antimalarial drug use in pregnancy and its role in LBW prevention. Because antimalarial drug use was an important predictor of umbilical cord blood and placental malaria, we generated a model in which placental and umbilical cord malaria infections were replaced with CQ use (vs MQ use) as the exposure of interest (Table 24). In this model, CQ use compared with MQ use was identified as a significant risk factor for LBW, suggesting that, indeed, effective malaria prevention is important for the reduction of LBW.

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Table 24. Maternal and infant characteristics (examining antimalarial drug use) associated with low birth weight in a multivariate model, MMRP, 1987-1990.

MATERNAL OR INFANT CHARACTERISTIC	PREVALENCE	ODDS RATIO	95% CONFIDENCE INTERVALS
FIRST BIRTH ^a	33.9%	5.08	3.23, 7.99
CHLOROQUINE USE ^b	72.9%	1.38	1.02, 1.87
ENROLLMENT MATERNAL WEIGHT < 50 KG	23.6%	1.83	1.38, 2.42
RAINY AND POSTRAINY SEASON	65.2%	1.46	1.09, 1.95
FEMALE BABY	50.2%	2.84	1.88, 4.30
HIV SEROPOSITIVE	7.8%	2.61	1.46, 4.64

^a The reference group for first births is birth order greater than or equal to two.

^b The reference group for women who received chloroquine was women who received mefloquine.

When both placental infection status and antimalarial drug use were examined in the same model, placental infection was a stronger predictor of LBW (OR = 1.59, CI = 1.14-2.19) than CQ (OR = 1.12, CI = 0.81-1.55), suggesting that the effect of antimalarial drug use on LBW occurred through its effect on placental infection.

Summary findings:

The mean birth weight of babies born in the hospitals and clinics in the study was 2905 grams (SD = 459 grams), and 16.6% had LBW. In the multivariate analysis, birth order was the strongest predictor of LBW (OR = 4.66, CI = 2.91-7.44).

In univariate analyses adjusted for birth order, factors associated with LBW were short maternal stature, low maternal weight at enrollment, maternal HIV infection, maternal syphilis infection, enrollment during high transmission season, female sex of the infant, malaria infection of the umbilical cord blood, malaria infection of placental blood, and use of CQ compared with MQ for malaria prevention. In the multivariate analyses, birth order, low maternal weight at enrollment, season, female sex of the baby, HIV seropositivity, and umbilical cord blood malaria were associated with LBW; placental malaria was borderline significant. The association between LBW and umbilical cord blood infection has not been previously examined in other studies and is further evaluated in the following section on prematurity and IUGR.

Use of a less-than-optimally-effective antimalarial drug (CQ) was associated with LBW; this association is believed to be due to CQ's poor efficacy in clearing placental malaria.

F. PREMATUREITY AND INTRAUTERINE GROWTH RETARDATION

The two causes of LBW are prematurity and IUGR. Infants born prematurely (< 37 complete weeks of gestation) frequently weigh less than 2500 grams because they are born before they achieve their term birth weight. Infants with IUGR are born at term but weigh less than 2500 grams because of inadequate nutrient transfer across the placenta. LBW may be due to a combination of both prematurity and IUGR; however, for the subsequent analyses, we categorized preterm infants with birth weight < 2500 grams as preterm-LBW and term infants with birth weight < 2500 grams as IUGR-LBW.

We examined the role of malaria infection and malaria prevention on gestational age and birth weight and examined other risk factors for preterm-LBW and IUGR-LBW in the population.

Overall, 6.9% of singleton liveborn babies were preterm; the mean birth weight in the 121 preterm infants was 2205 grams (\pm 406 grams), ranging from 1340 to 3350 grams; 82.6% of these, or 5.7% overall, were preterm-LBW. Among the 1623 term infants, the mean birth weight was 2968 grams (\pm 402 grams). Their weights ranged from 1701 to 4450 grams, and 11.1% were IUGR-LBW. Among LBW singleton liveborn babies, 36% were premature, and 64% were IUGR.

Characteristics associated with preterm-LBW and IUGR-LBW

In univariate analyses, factors associated with preterm-LBW were first birth, placental malaria, umbilical cord malaria, short maternal stature, low maternal weight, enrollment in the rainy or postrainy season, low maternal age, maternal syphilis, and female sex of the infant. Factors associated with IUGR-LBW were first birth, placental malaria infection, malaria parasitemia at enrollment, short maternal stature, low maternal weight, rainy season, low maternal age, and female sex of the infant (Table 25). Low socioeconomic status and low education level were not associated with increased risk of either preterm-LBW or IUGR-LBW. Although HIV seropositivity was identified as a risk factor for LBW overall, it was not significantly associated with an elevated risk in the univariate model for either IUGR-LBW or preterm-LBW.

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Table 25. Association between maternal and infant characteristics and low birth weight due to intrauterine growth retardation (IUGR) or prematurity in a univariate analysis, MMRP, 1987-1990.

CHARACTERISTIC ^a	PREVALENCE (%)	INTRAUTERINE GROWTH RETARDATION		PREMATURITY	
		OR	95% C.I.	OR	95% C.I.
MATERNAL AGE < 19 ^{*,**}	26.4	2.33	1.70, 3.19	1.80	1.24, 2.60
FIRST BIRTH ^{*,**}	33.9	2.55	1.87, 3.47	2.42	1.69, 3.45
MATERNAL WEIGHT < 50 KG ^{*,**}	23.6	1.85	1.33, 2.57	1.91	1.31, 2.78
HEIGHT < 150 CM ^{*,**}	13.3	1.52	1.02, 2.28	1.60	1.01, 2.53
NOT LITERATE	66.8	0.95	0.69, 1.31	0.76	0.53, 1.09
LOW SOCIOECONOMIC STATUS ^b	64.4	0.95	0.69, 1.31	0.82	0.57, 1.18
HEMATOCRIT < 25%	5.7	1.33	0.71, 2.50	1.46	0.71, 2.98
HEMATOCRIT < 30%	18.7	1.10	0.73, 1.64	1.34	0.84, 2.11
DELIVERY HEMATOCRIT < 30%	13.3	1.09	0.63, 1.87	1.16	0.65, 2.06
ENROLLMENT MALARIA [*]	45.2	1.40	1.03, 1.91	1.25	0.88, 1.78
PLACENTAL MALARIA ^{*,**}	22.1	1.97	1.40, 2.77	1.87	1.26, 2.78
UMBILICAL CORD MALARIA ^{*,**}	7.3	2.01	1.22, 3.31	2.71	1.59, 4.60
USED CHLOROQUINE ^c	72.9	1.34	0.92, 1.95	0.81	0.55, 1.19
FEMALE INFANT ^{*,**}	50.2	2.09	1.52, 2.89	1.61	1.12, 2.31
RAINY SEASON ^{*,d}	32.3	1.40	1.02, 1.92	1.23	0.85, 1.78
RAINY & POSTRAINY SEASON ^{*,**d}	75.6	1.04	0.72, 1.49	2.02	1.23, 3.33
SYPHILIS ^{**}	3.1	0.37	0.09, 1.55	3.49	1.69, 7.22
HIV INFECTION	7.8	1.44	0.87, 2.41	1.57	0.87, 2.82

^{*} Characteristics that are significantly associated with an increased risk of IUGR/LBW

^{**} Characteristics that are significantly associated with an increased risk of preterm-LBW

^a Characteristics of women enrolled for > 6 weeks, receiving all doses of antimalarial drug and delivering a liveborn singleton infant with known birth weight. Except where noted, the reference group for comparison is those women without the characteristic.

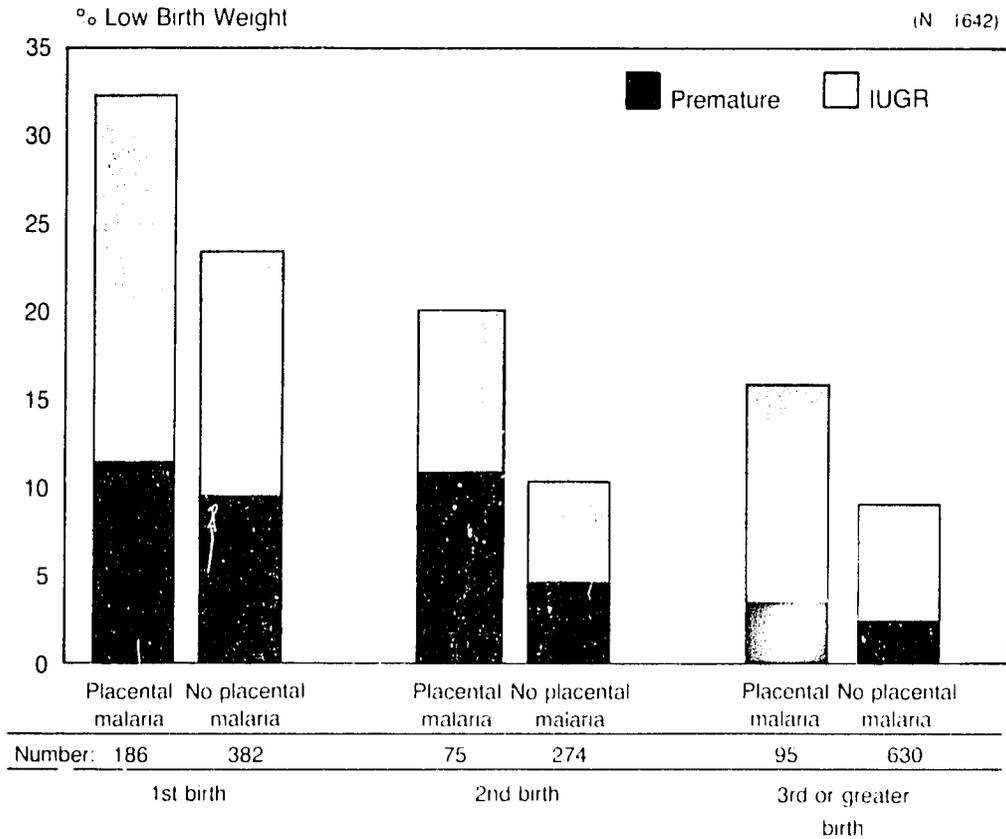
^b Socioeconomic status defined by surrogate measures of four household construction characteristics, low socioeconomic status was defined as all four characteristics at the lowest grade.

^c Reference group for women using chloroquine was women using metloquine.

^d Seasons were grouped as rainy (January-April), post-rainy (May-August), and dry (September-December).

The contribution of placental malaria to IUGR-LBW and preterm-LBW within birth order groups is shown in Figure 24. These data suggest that the incidence of preterm-LBW and IUGR-LBW is higher in women with placental malaria infection than in women without placental malaria infection.

Figure 24. Incidence of preterm-LBW and intrauterine growth retardation (IUGR)-LBW by placental malaria infection and birth order, MMRP, 1987-1990.

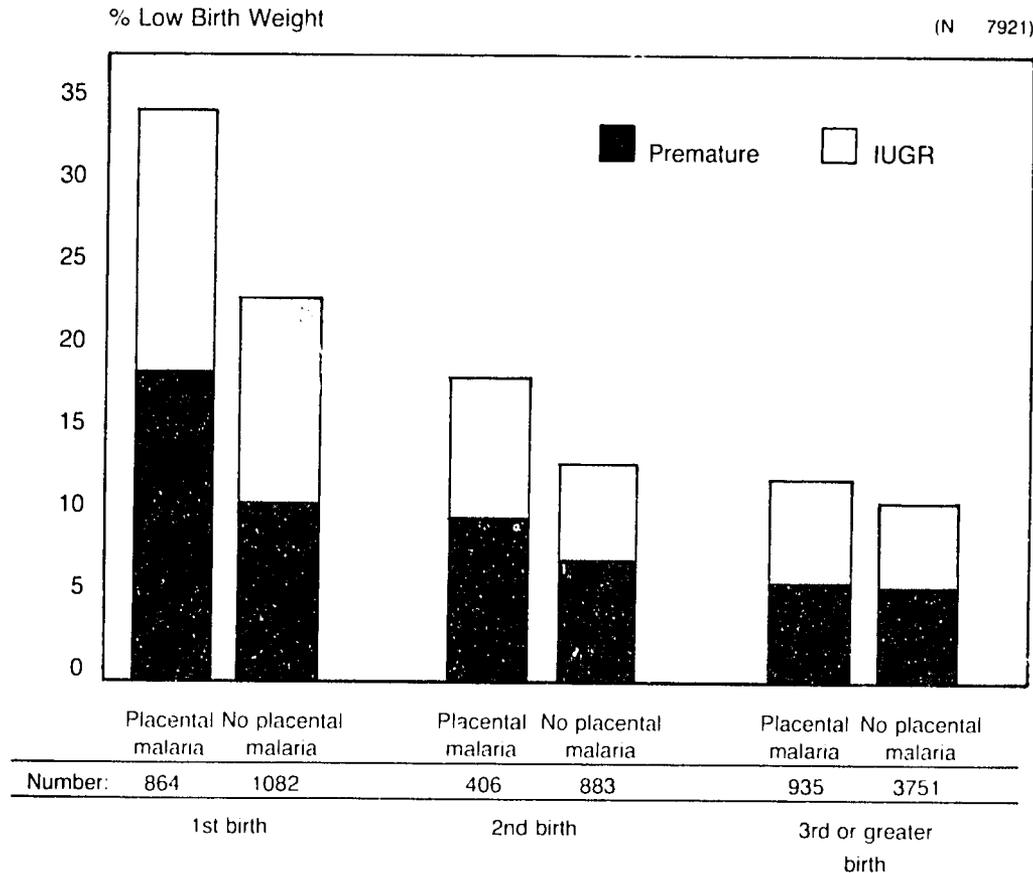


In the above stratified analysis of preterm-LBW and IUGR-LBW, which shows an association with placental malaria infection within birth order groups, the power of the analysis was limited by low numbers in certain groups. Because of these limitations, further evaluation of the relationship between placental malaria infection and IUGR-LBW and preterm-LBW was carried out in the larger group of all mothers and babies born in study site hospitals during the time of the study. As noted in the description of methods (Section IV.E.), all women and their babies were examined in the same fashion at the time of delivery.

Similar findings of an association between placental malaria infection and both IUGR and prematurity were seen in the larger group of all women delivering at the study facilities, regardless of enrollment in the study (Figure 25).

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Figure 25. Incidence of preterm-LBW and intrauterine growth retardation (IUGR)-LBW by placental malaria infection and birth order, in both women enrolled and not enrolled in the study and their babies, MMRP, 1987-1990.



Multivariate analysis

To determine the strongest predictors of preterm-LBW and IUGR-LBW, we performed a multivariate analysis and further examined the maternal and infant characteristics associated with preterm-LBW or IUGR-LBW in the univariate analysis (Table 26). Characteristics associated with preterm-LBW were first birth, low maternal weight, female sex of the newborn, maternal reactive syphilis serology, and malaria infection of the umbilical cord blood. Placental malaria infection did not remain in the final model for prematurity; however, if the umbilical cord blood infection variable was withdrawn from the model, placental malaria was borderline significant with a 1.16-fold increased risk for prematurity (OR = 1.16, CI = 0.94-2.28, $p = 0.096$), and the variable rainy and postrainy season stayed in the model (OR = 1.92, CI = 1.04-3.53, $p = .036$).

Characteristics associated with IUGR-LBW included first birth, placental malaria infection, low maternal weight, and female sex of the baby.

Table 26. Risk factors associated with preterm-LBW and IUGR-LBW in multivariate models for women enrolled in the study, MMRP, 1987-1990.

CHARACTERISTIC	PRETERM-LBW		IUGR-LBW	
	ODDS RATIO	95% CONFIDENCE INTERVALS	ODDS RATIO	95% CONFIDENCE INTERVALS
FIRST BIRTH	2.01	1.32, 3.06	5.22	2.83, 9.64
UMBILICAL CORD MALARIA	2.20	1.21, 4.01	*	*
PLACENTAL MALARIA	*	*	1.70	1.19, 2.43
MATERNAL WEIGHT < 50 KG	1.80	1.17, 2.78	1.73	1.22, 2.44
FEMALE BABY	1.69	1.11, 2.57	4.57	2.56, 8.15
SYPHILIS	3.62	1.64, 7.96	*	*

* Variable not significant in the multivariate model

To evaluate the role of antimalarial drug use in malaria prevention and the risk of preterm-LBW and IUGR-LBW, we included the variable CQ compared with MQ in the model in place of malaria infection of the placenta and umbilical cord blood. Poorly effective malaria prevention with CQ was not associated with preterm-LBW (OR = 0.90, CI = 0.58-1.38). However, when the placental malaria variable was replaced by the CQ-use variable, CQ use (compared with MQ use) was significantly associated with IUGR-LBW (OR = 1.63, CI = 1.16-2.29). If both placental malaria and CQ use were included in the model, placental malaria remained significantly associated with IUGR-LBW and CQ use did not, suggesting that the effect of the antimalarial regimen occurs through its effect on placental infection.

Because previous studies have not implicated maternal or fetal malaria infection as a contributor to prematurity, we examined this relationship further. In the above model (Table 26), umbilical cord blood parasitemia was associated with preterm-LBW, but placental malaria was not. When umbilical cord malaria was replaced by placental malaria as the exposure variable of interest, placental malaria was associated with an elevated risk for preterm-LBW; however, this was not significant (see above).

The larger population of all pregnant women delivering at study hospitals, regardless of their enrollment in the study, was then examined. In univariate analyses, among these 1972 women with full information available, both cord blood parasitemia (OR = 1.44, CI = 1.11-1.87) and placental malaria infection (OR = 1.26, CI = 1.04-1.54) were associated with LBW. In the multivariate models for preterm-LBW, cord blood parasitemia in all pregnancies and placental infection in primigravidas were associated with prematurity (Table 27).

⁷HIV and syphilis serologic test results were available only for women enrolled in the study.

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Table 27. Risk factors associated with preterm-LBW in multivariate models for all women delivering in study site hospitals, (N = 4972), MMRP, 1987-1990.

CHARACTERISTIC ^a	PREVALENCE (%)	ODDS RATIO	95% CONFIDENCE INTERVAL
FIRST BIRTH ^b	25.1	1.89	1.39, 2.58
UMBILICAL CORD MALARIA	9.3	1.72	1.24, 2.36
MATERNAL WEIGHT < 50 KGS	10.0	3.05	2.12, 4.39
HEMATOCRIT < 30%	8.7	1.66	1.21, 2.26
FEMALE INFANT	48.3	1.55	1.26, 1.91

^a Short maternal stature was borderline significant in the final models (OR = 1.29, CI = 0.99-1.67); its inclusion in the final model did not significantly alter the risk estimates for the other variables.

^b The reference group for this variable was < 2 birth. A first order interaction term which was significant in the final model was identified for firstborns with placental malaria. The term "firstborn*placental malaria" acted as a multiplier (1.58, 95% CI = 1.01-2.47) of the odds ratio for the combination of these two conditions. The variable "placental malaria in < 2nd pregnancies" was not identified as a significant interaction term associated with an elevated risk for preterm LBW (multiplier in the model for "Placental malaria" < 2 pregnancies = 1.00, CI = 0.72-1.39).

Attributable risk of malaria to LBW

Because LBW may be caused by or associated with multiple factors, it is important to establish the amount of LBW that can be accounted for by a given risk factor. The proportion of LBW (either preterm-LBW or IUGR-LBW) that can be attributed to the effect of malaria on the pregnant woman can be estimated using the prevalence of placental or umbilical cord blood malaria infection in the population and its associated risk estimate. Population attributable risk estimates for LBW overall range from 5.3% for umbilical cord blood parasitemia to 13.6% for placental malaria infection. With a placental infection prevalence in the population of 22% and a risk estimate of approximately 1.7, approximately 13% of IUGR-LBW in this population can be attributed to placental malaria. The estimated population attributable risk for umbilical cord blood parasitemia and preterm-LBW was 8.1% in women enrolled in the study and 6.5% in the larger population of all women.

Summary findings:

In this study population of babies delivered in hospitals, the frequency of premature-LBW was 5.7% and the frequency of IUGR was 11.1%.

Data from analyses of babies born to women in the study and of babies born to all women (including women in the study) in study site hospitals showed that factors associated with preterm-LBW were first birth, low maternal weight, maternal anemia, female infant, maternal syphilis infection, malaria infection of the umbilical cord blood, and malaria infection of the placenta in primigravidas only.

Factors associated with IUGR-LBW in the study population were first birth, low maternal weight, female sex of the baby, and placental malaria infection.

Overall, we estimate that between 5% and 14% of LBW in this population can be attributed to malaria infection of the placenta or umbilical cord blood.

G. DISCUSSION

The MMRP investigation was designed to examine the efficacy of antimalarial treatment and chemoprophylaxis in reducing the frequency of LBW in babies born in an area of high malaria transmission. Pregnant women were enrolled at their first antenatal clinic visit, placed on either CQ (having limited efficacy in parasite clearance, but national policy in Malawi) or MQ (highly efficacious against the parasite) and followed until delivery.

An examination at enrollment of women participating in the study demonstrated that a high proportion of the women were parasitemic (44.5% overall and 67% of primigravidas) and that the characteristics of women in the different treatment groups were similar. In general, the women were young, had short stature, were poor, and had low rates of literacy — similar to women in much of the region in sub-Saharan Africa. Anemia, active maternal syphilis, and HIV infection were identified in the population, and although they were not highly prevalent conditions, they were potentially important contributors to adverse pregnancy outcomes.

Evaluation of the women at follow-up visits and at delivery demonstrated that CQ had poor efficacy in clearing parasites or keeping a woman free of parasites. In contrast, MQ was confirmed to be highly effective against the parasite. At delivery, maternal peripheral blood parasitemia was frequent enough (15.8%), as were placental blood (19.9%) and umbilical cord blood parasitemia (7.1%), to allow for the evaluation of the role of malaria and birth outcomes — LBW and its causes, prematurity, and IU GR. Low birth weight due to prematurity was identified in 5.7% of the women and IU GR in 11.1%.

In a multivariate analysis, umbilical cord and placental blood infection with *P. falciparum* were shown to be important factors associated with LBW, prematurity, and IU GR. The finding of an association between placental malaria infection and LBW has been previously described by many investigators (2). Results of this study showed the same association and, on the basis of our multivariate models, we can state that malaria infection in pregnancy may account for between 5% and 11% of LBW in this population.

Placental malaria infection has been thought to contribute to LBW through its contribution to IU GR, and our findings support this. From our multivariate models and the prevalence of placental malaria infection in the population, we estimate that approximately 13% of IU GR-LBW in this population can be attributed to placental malaria. The mechanism by which placental malaria infection contributes to IU GR is not fully understood. It is presumed, however, to be due to a reduction in nutrient (oxygen or sugar) transport to the fetus, caused by a mechanical blockage arising from thickening of trophoblast basement membrane or by increased nutrient use or poor nutrient transfer from the parasitized red blood cells sequestered in the placenta. In any case, the mechanism leading to IU GR-LBW appears to occur in the placenta.

In addition to the association between placental malaria and IU GR-LBW, we have identified an association between a malaria parasite infection of umbilical cord blood and premature delivery of the infant. On the basis of the models examining women in the study and models examining all women delivering in study hospitals, we estimate that 5%–6% of preterm-LBW deliveries in this setting can be explained by malaria infection in umbilical cord (fetal) blood. In addition, the larger of the two models (approximately 5000 mother-infant pairs), shows that placental malaria infection in primigravidas may contribute to preterm-LBW. Together, umbilical cord blood malaria and placental infection in primigravidas may account for as much as 12% of preterm-LBW in this population.

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The biologic mechanism by which transplacental passage of malaria parasites might contribute to prematurity is unknown. Other pathogens (e.g., *Treponema pallidum*) are known to infect fetal blood and are also associated with prematurity; consequently, the stress of fetal infection with malaria may lead to premature delivery as it does with other microbial agents.

Finally, we demonstrated that, compared with women who used MQ, women who used CQ were at increased risk for delivering LBW infants. Both placental infection and umbilical cord blood infection were reduced markedly in women treated and given prophylaxis with MQ; the multivariate models suggest that the higher risk of LBW among women using CQ or the improvement of birth weight among women using MQ was directly due to the drug's effect on clearance of placental and umbilical cord blood infections.

VII. MMRP RESULTS: MATERNAL ILLNESS DURING PREGNANCY

A. FEVER AND PARASITEMIA

Maternal illness during the early months of pregnancy was assessed at the time of enrollment. In addition, pregnant women were asked at each follow-up visit about symptoms since the last visit (Section IV.D.).

Maternal illness prior to enrollment: Fever prior to enrollment was reported by 1048 (24.9%) women; 633 (60.4%) of these women reported two or more previous episodes. Among women reporting fever, 739 (70.5%) reported taking a drug to treat the episode; 402 (38.4%) reported taking CQ, and fewer than 1% reported taking any other antimalarials (amodiaquine, SP, MQ, or quinine). Among women at enrollment, 32 (< 1%) reported taking CQ prophylaxis prior to enrollment, and only 9 women reported taking two tablets of CQ weekly prior to enrollment; others used different numbers of tablets or different frequencies.

Women who were parasitemic at enrollment were no more likely to report having had a fever (24.4%) than aparasitemic women (25.4%). However, women with higher density parasitemia were more likely to have reported fever than women with no parasites or those with low density parasitemia (Table 28).

Table 28. Reported fever at enrollment by parasitemia levels in pregnant women, MMRP, 1987-1990.

PARASITEMIA (PER MM ³ OF BLOOD)	NONE	LOW (1-999)	MEDIUM (1000-9999)	HIGH (≥10,000)	TOTAL
TOTAL NUMBER OF WOMEN:	2289	962	196	98	4116
REPORTED FEVER(%)	25.4%	21.4%	25.6%	44.9%	25.0%

Chi square for trend from low to high parasitemia = 199, p = 10⁻⁵

Although the density of parasitemia was associated with the likelihood of a woman reporting fever prior to enrollment, only 44% of women with high density parasitemia reported fever.

Illness in women during pregnancy follow-up: During the follow-up period, despite the high proportion of women who remained or became parasitemic, few women reported fever or other symptoms of malaria.

Women who delivered in the hospital were asked at the time of delivery if they had experienced a febrile illness during the pregnancy. A total of 570 (25.7%) of the 2221 delivering in a hospital reported fever during their pregnancy; they reported a total of 727 febrile episodes or 1.3 episodes per woman with reported fever. Women were more likely to report fever during the fifth to ninth month of gestation (18.3% on average) than during earlier months (9.0% on average); however, this may have been due to recall bias, with women less likely to remember fevers that occurred in the more distant past.

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Febrile illness near the time of delivery: Fever in the 2 weeks prior to delivery was reported by 136 (6.1%) of the 2221 women delivering in the hospital. Reported fever in the prior 2 weeks did not vary significantly with season. Compared with aparasitemic women (6.0%), women with peripheral parasitemia at the time of delivery (9.1%) were more likely to report fever in the previous 2 weeks ($p = 0.05$); however, the frequency of reported fever was low in both groups and, compared with women with lower density parasitemia, women with higher density parasitemia were no more likely to report recent fever.

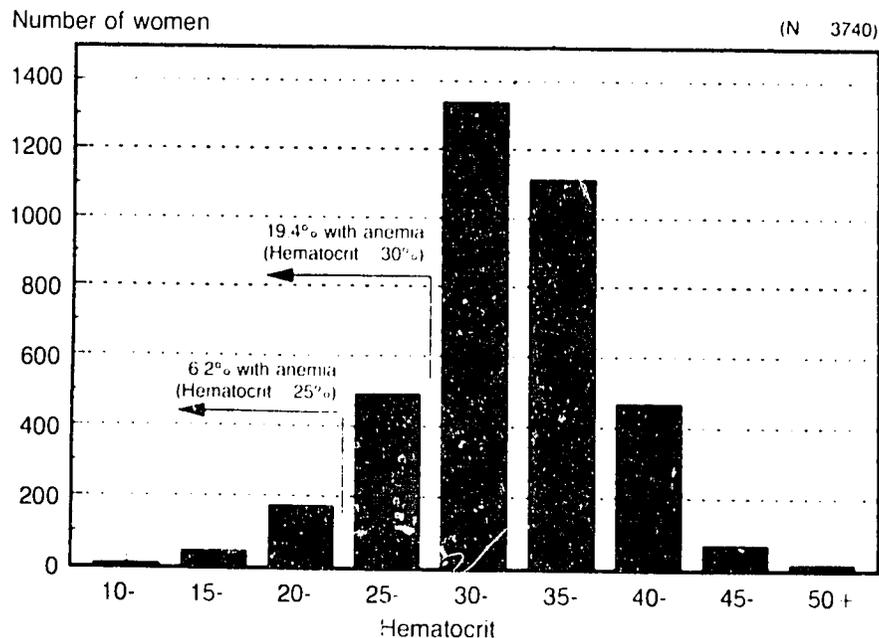
Summary findings:

Febrile illness during pregnancy (during the previous 4-5 months on average) was reported by approximately 25% of women at the time of their first ANC visit; fever was reported by approximately 6% of women in the 2 weeks prior to delivery. However, only in the approximately 2.5% of women who had high density parasitemia was reported fever associated with malaria. Thus, febrile illness was not a good predictor of which women were parasitemic. Severe malaria illness was rare in this population.

B. MATERNAL ANEMIA

Women's hematologic status was evaluated at enrollment and at delivery. Anemia, defined as a hematocrit $< 30\%$ was observed in 709 (19.4%) of 3657 women tested at enrollment (Figure 26); 225 (6.2%) women had a hematocrit $< 25\%$ at enrollment.

Figure 26. Hematocrit distribution at enrollment for women in the study, n'MRP, 1987-1990.



Overall, malaria parasitemia at the time of enrollment was associated with significant differences in the proportion of women with hematocrit $< 30\%$ or in mean hematocrit; the proportion of women who were anemic increased and their mean hematocrit decreased with increasing parasite density (Table 29).

Table 29. Anemia at enrollment by parasitemia levels in pregnant women, MMRP, 1987-1990.

PARASITEMIA: (PER MM ³ OF BLOOD)	NONE	LOW (1-999)	MEDIUM (1000-9999)	HIGH (≥10,000)	TOTAL
TOTAL NUMBER:	2033	851	693	86	3663
ANEMIA (HEMATOCRIT < 30%) ^a	18.3%	18.2%	22.1%	33.7%	19.4%
MEAN HEMATOCRIT (SD) ^b	33.8 (5.5)	33.5 (5.6)	32.7 (5.3)	31.6 (6.2)	33.5 (5.7)

^a Chi square for trend from none to high level of parasitemia = 10.4; p = 0.002

^b Differences between means among the categories of parasitemic women were significant; p = 0.001

Other maternal characteristics were examined for a possible association with anemia at enrollment: parity, age, socioeconomic status, education level, height and weight, season, history of fever, infection with syphilis (active or not), and infection with HIV. Characteristics that were independently and significantly associated with anemia were low parity, low age, HIV infection, and enrollment in the dry or rainy season (Table 30).

Table 30. Maternal characteristics associated with anemia at enrollment, MMRP, 1987-1990.

CHARACTERISTIC	NUMBER	HEMATOCRIT < 30% NUMBER	(%)	P VALUE*
GRAVIDITY				
1	1185	270	(22.8)	0.0005
2	898	177	(19.7)	
3	1656	280	(16.9)	
TOTAL	3739	727	(19.4)	
AGE (YEARS)				
< 14	29	7	(24.1)	0.003
15-19	1228	268	(21.8)	
20-24	1017	210	(20.6)	
25-29	684	105	(15.4)	
30-34	459	72	(15.7)	
≥ 35	236	50	(21.2)	
TOTAL	3653	712	(19.5)	
SEASON				
RAINY	1476	316	(21.4)	< 10 ⁻⁶
POSTRAINY	971	132	(13.6)	
DRY	1293	279	(21.6)	
TOTAL	3740	727	(19.4)	
HIV INFECTION				
POSITIVE	264	63	(23.9)	0.047
NEGATIVE	3397	641	(18.9)	
TOTAL	3661	704	(19.2)	

* P value determined from chi square test

Hematologic status at the time of delivery was examined in 1336 women who were followed throughout pregnancy, were dosed properly with antimalarials, delivered liveborn singletons in the hospital, and had their hematocrit measured prior to delivery. Of these women, 3.9% had a hematocrit $\leq 25\%$ and an additional 9.3% had a hematocrit between 25% and 29%. Maternal parasitemia or placental malaria infection was not associated with anemia; however, the prevalence of anemia and parasitemia may have been reduced by their use of malaria prevention measures. We also examined women not enrolled in the study but delivering in the same facilities as women in the study in the same way for anemia and parasitemia; no significant association was found between peripheral or placental parasitemia and anemia. In these 1602 parasitemic and 3514 aparasitemic women, 9.2% and 8.2% were anemic, respectively ($p = 0.26$). Thus, while parasitemia may contribute to anemia in some pregnant women, it is only one of a number of contributors to anemia in pregnant women (e.g., plasma volume expansion, iron and folate deficiency). However, the association between anemia and preterm-LBW in the multivariate models (OR 1.66, Table 27) suggests that prevention or management of anemia may be important to reduce preterm-LBW.

Summary findings:

At the time of enrollment, anemia (het $\leq 30\%$) was seen in 19.4% of women and severe anemia (het $\leq 25\%$) in 6.2%. At the time of delivery, anemia was seen in 13.2%, and severe anemia in 3.9%. Anemia was associated with malaria parasitemia at enrollment, but only in those with medium or higher density parasitemias (≥ 1000 parasites/ mm^3 of blood). Anemia was also more common in primigravidas (and younger women) during the dry and rainy season and in HIV+ women.

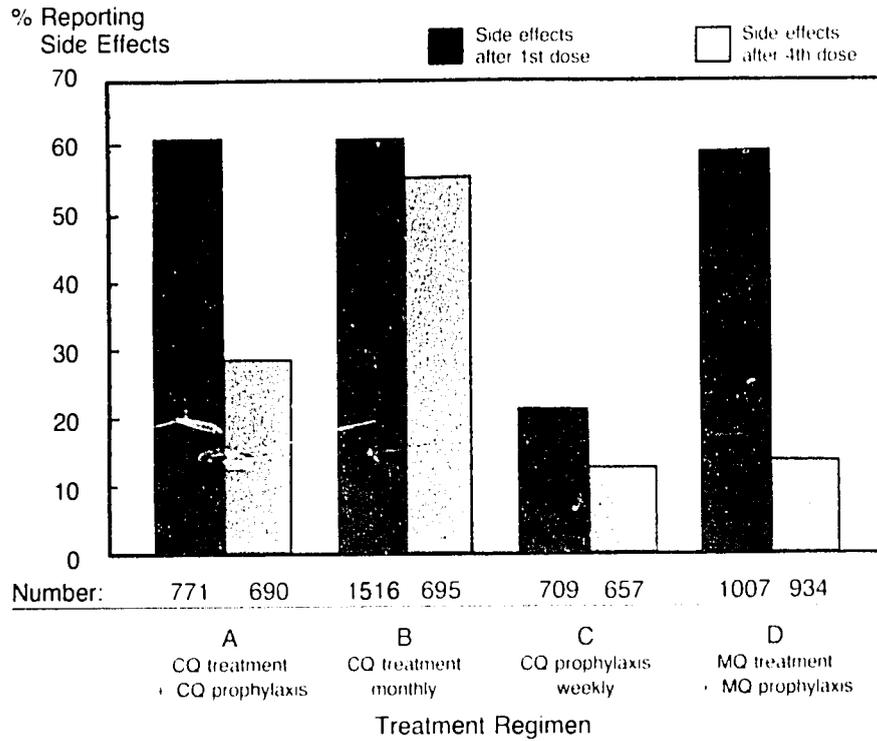
Maternal and placental malaria infections were not associated with anemia at delivery. Thus, in this population where all women received an antimalarial drug (even though CQ had low efficacy in clearing parasitemia), malaria could not be linked to anemia at delivery; severe anemia at delivery was relatively uncommon.

The mild increased risk of preterm-LBW associated with anemia (described in Section VI.F.) suggests that management or prevention of anemia in pregnant women may be important. Currently, other causes of anemia appear to be more important than malaria.

C. MATERNAL EXPERIENCE WITH ANTIMALARIAL DRUG USE

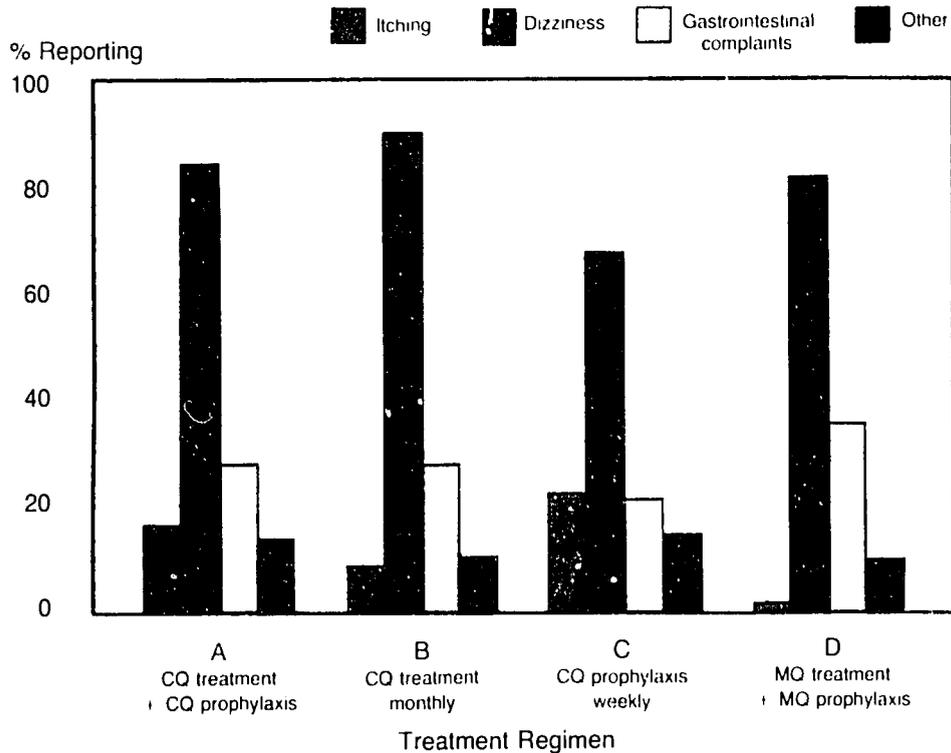
Women were questioned about symptoms occurring between each follow-up visit. Mothers' complaints were examined to determine adverse effects that might be associated with the use of the antimalarial drug. For the purpose of this analysis, reported side effects were tabulated for two periods: 1) after the first treatment dose of the medication (note that regimen C did not include an initial treatment dose) and 2) after the fourth dose of chemoprophylaxis (note that this corresponded to the second treatment dose for regimen B). Figure 27 shows that among 4101 women with initial follow-up and 2976 women with follow-up after 4 weeks, approximately 60% of women receiving a treatment dose of antimalarial drug (either CQ or MQ) reported side effects. After prophylactic doses of either CQ or MQ, fewer than 30% of women reported side effects. Rates of reported side effects were similar for the two drugs.

Figure 27. Reported side effects following antimalarial drug regimens, MMRP, 1987-1990.



The majority of complaints associated with antimalarial drug use involved itching, dizziness, and gastrointestinal disturbances (Figure 28). All other complaints (e.g., weakness, heart palpitations) were included in the category "other."

Figure 28. Type of side effects reported following antimalarial drug regimens, MMRP, 1987-1990.



**SECTION VII:
RESULTS**

First trimester antimalarial drug use: Most of the women in this investigation were enrolled in the second and third trimesters of pregnancy only. Fourteen women treated with MQ and 53 women treated with CQ were enrolled during the first trimester; consequently, this study provides little information regarding the effects of antimalarial use in the first trimester of pregnancy. Where first trimester drug ingestion occurred, no adverse outcomes were identified in the MQ group: one baby was delivered breech, all babies with known birth weight were normal birth weight, and the mean birth weight was 3009 grams. One stillbirth occurred in the CQ-treated group (macerated fetus following delivery by caesarian section). One set of twins was born in this group (birth weights of 2140 and 2120 grams); no other abnormalities were noted.

Although very few fetuses were exposed to MQ or CQ in the first trimester in this study, there was no evidence of abnormality that might be attributable to antimalarial drug use.

Summary findings:

Women were equally likely to report side effects of CQ and MQ and were more likely to report these events after an initial treatment dose compared with low dose chemoprophylaxis.

No adverse effects on the fetus were seen when women used CQ or MQ in the first trimester; however, few women were enrolled that early in their pregnancies.

D. MATERNAL MORTALITY

Of the 4220 women initially enrolled in the MMRP, 53 (1%) were not pregnant, and 134 (3.2%) were lost to follow-up during pregnancy, resulting in 4053 (96%) women for which delivery information is known. At some time during the period of the study, 27 women were known to have died. Three women (11%) died during the antenatal period, and 12 (44%) died within 6 weeks of delivery. The deaths occurring during this time frame are classified as maternal deaths. The remaining 12 (44%) women died between 3 and 10 months after delivery.

Among these 4053 women, 15 maternal deaths occurred, resulting in a maternal mortality rate of 370 per 100,000 women. Women were generally enrolled in their second or third trimesters, so mortality earlier in pregnancy was not determined and the maternal mortality rate must, therefore, be considered a low estimate. Because the number of women at risk for maternal death (i.e., the number of all pregnant women in a population) is often not known, the maternal mortality ratio (maternal deaths per 100,000 live births) is often reported. The maternal mortality ratio among women in the MMRP was 15/3922 or 382 per 100,000 live births.

Causes of maternal deaths (Table 31): Three of the 15 maternal deaths occurred in the antepartum period; the cause of death is known for only one and was reported as severe anemia. The four women who died within 24 hours of delivery all had home deliveries. Two of these women were reported to have had either antepartum or postpartum hemorrhage; the cause of death was unreported for the other two women, but was assumed to be delivery-related. Of the 6 women who died within 7-15 days of delivery, only one delivered at home. The condition of the other five women at the time of admission to the health facility is not known. The cause of death was reported for two of these six women; one had sepsis following a retained placenta, and the other had a ruptured uterus with twin pregnancy. These two women were able to survive the acute hemorrhage at the time of delivery but then succumbed to sequelae. Two women who died in this period were HIV+, but it is not known if the cause of their deaths was HIV-related. Two women died 1 month after delivery. Symptoms near the time of death are reported for one: severe headache, seizures, and paralysis for 15 days prior to death, compatible with an eclampsia-related stroke.

Table 31. Maternal deaths among women enrolled at first antenatal clinic visit, MMRP, 1987-1990.

WOMAN	AGE	HEIGHT	PREGNANCY NUMBER/LIVING ^a	ENROLLMENT HCT/ GESTATIONAL AGE ^b	HIV TATUS	PLACE OF DELIVERY	HCT AT DELIVERY	TIME/PLACE OF DEATH ^c	CAUSE OF DEATH	OUTCOME OF COMMENTS	OUTCOME OF INFANT
1	29	165 CM	6/3	35/17 DAYS BEFORE DEATH	NEG	NA	NA	ANTEPARTUM; HOSPITAL	SEVERE ANEMIA	T. TRANSFUSED; COMATOSE	STILLBIRTH
2	18	155 CM	2/1	30/1 MONTH BEFORE DEATH	NEG	NA	NA	ANTEPARTUM; CLINIC	UNKNOWN		STILLBIRTH
3	21	165 CM	2/0	7/8 WEEKS BEFORE DELIVERY	NEG	NA	NA	ANTEPARTUM; HOME	UNKNOWN		STILLBIRTH
4	31	160 CM	4/0	22/16-20 WEEKS	NEG	HOME	UNKNOWN	DAY OF DELIVERY; HOSPITAL	POSTPARTUM HEMORRHAGE	RETAINED PLACENTA	SURVIVED
5	20	154 CM	2/1	36/28 WEEKS	NEG	HOME	UNKNOWN	DAY OF DELIVERY; HOSPITAL	UNKNOWN		DEATH DAY 381
6	27	145 CM	4/1	34/32 WEEKS	NEG	HOME	UNKNOWN	DAY OF DELIVERY; ON WAY TO HOSPITAL	ANTEPARTUM HEMORRHAGE		DEATH DAY 362
7	38	155 CM	8/4	38/28 WEEKS	NEG	HOME	UNKNOWN	DAY OF DELIVERY; ?	UNKNOWN		SURVIVED
8	16	156 CM	1/0	30/34 WEEKS	POS	HOSPITAL	38%	ONE WEEK; HOME	UNKNOWN	VACUUM EXTRACTION	DEATH DAY 556
9	24	144 CM	1/0	32/32 WEEKS	NEG	HOSPITAL	31%	ONE WEEK; HOSPITAL	UNKNOWN	TWINS - VAGINAL DELIVERY	DEATHS DAY 14 AND 4 MONTHS
10	23	160 CM	2/1	32/28 WEEKS	NEG	HOSPITAL	41%	ONE WEEK; HOME	UNKNOWN		DEATH DAY 1
11	30	157 CM	5/3	39/32 WEEKS	POS	HOME	UNKNOWN	10 DAYS; HOSPITAL	UNKNOWN (AIDS?)		STILLBIRTH
12	16	156 CM	1/0	7/37 WEEKS	NEG	HOSPITAL	28%	13 DAYS; HOSPITAL	HEMORRHAGE	RETAINED PLACENTA; SCHOOL GIRL	DEATH DAY 1; WEIGHT = 1188
13	35	147 CM	9/8	30/34 WEEKS	NEG	HOSPITAL	UNKNOWN	15 DAYS; HOSPITAL	HEMORRHAGE	RUPTURED UTERUS; TWINS	STILLBIRTH?
14	28	152 CM	4/2	10/26 WEEKS	NEG	HOSPITAL	39%	30 DAYS; HOME	STROKE? POST ECLAMPSIA?	SICK FOR 15 DAYS; HEADACHE, SEIZURES, RIGHT-SIDED PARALYSIS	DEATH DAY 315
15	16	146 CM	1/0	34/36 WEEKS	?	HOME	UNKNOWN	30 DAYS; HOME	UNKNOWN		DEATH DAY 368

^a Number of current pregnancy and number of children still alive.^b Gestational age at the time of enrollment, which was also the time of hematocrit determination.^c First 3 women died antepartum; remaining women died at the time of or after delivery.

Of the 88 women with multiple births (twins or triplets), 2 died within the maternal mortality period resulting in a maternal mortality rate of 22.3 per 100,000 women with multiple births. This rate is 7 times the mortality rate of women with singleton births (1.3 per 3962 or 328 per 100,000 women).

Nonmaternal deaths (Table 32): Twelve women died 3-10 months after delivery. It is difficult to determine the number of women who were at risk for death during this time period. However, if the number of infants with known outcome at the end of a year is used as a proxy for the denominator, the mortality rate for these women is 12.3949 or 30.1 per 100,000 women. This rate is surprisingly similar to the maternal mortality rate. Although cause of death is not reported for 11 of the 12 women, 7 women were HIV+, and this most likely contributed to their death.

Table 32. Deaths in women in the study more than 6 weeks post delivery (nonmaternal deaths), MMRP, 1987-1990.

WOMAN	AGE	PREGNANCY NUMBER/LIVING*	HIV STATUS	TIME/PLACE OF DEATH AFTER DELIVERY	CAUSE OF DEATH	OUTCOME OF INFANT
1	18	1 0	NEG	3 MONTHS ?	UNKNOWN	DEATH DAY 231
2	20	1 0	POS	4 MONTHS ?	UNKNOWN	DEATH DAY 109
3	29	4 2	NEG	5 MONTHS ?	UNKNOWN	SURVIVED
4	23	1 0	POS	5 MONTHS ?	UNKNOWN	DEATH DAY 220
5	30	2 0	NEG	5 MONTHS ?	UNKNOWN	DEATH DAY 9
6	24	4 2	NEG	6 MONTHS ?	UNKNOWN	DEATH DAY 178
7	16	1 0	NEG	8 MONTHS ?	UNKNOWN	SURVIVED
8	18	1 0	POS	9 MONTHS ?	UNKNOWN	DEATH DAY 342
9	31	6 3	POS	9 MONTHS ?	UNKNOWN	SURVIVED
10	23	1 0	POS	9 MONTHS ?	UNKNOWN	SURVIVED
11	18	1 0	POS	10 MONTHS ?	UNKNOWN	DEATH DAY 349
12	19	2 1	POS	UNKNOWN-AFTER 3 MONTHS	AIDS	DEATH DAY 88

* Current pregnancy number and number of children from earlier pregnancies who were still alive

Impact of death of mother on infants: Mortality among infants of mothers who died was high. Only 6 children born to mothers who died survived the follow-up period. Of the 24 liveborn children, 4 (17%) died before the mother died, 5 (21%) died about the same time as the mother during the 3-10-month period after delivery, and 9 (38%) died well after the mother. Only 1 of the 9 children who died long after the mother's death was born to an HIV+ woman, so the deaths of these 8 HIV- mothers may have strongly contributed to the subsequent deaths in these infants.

Risk factors for maternal death: One of the constraints to identifying risk factors for maternal death is the large sample size needed. In this study, more than 4000 women were followed from the last trimester of pregnancy to more than a year after delivery. When maternal age, pregnancy number, and place of birth were examined for association with death of the women, no associations were found. It is possible that there was no true association, but it is more likely that the study did not have enough power to identify an association; sufficient power would only be achieved with a sample size of more than 10,000 women.

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RESULTS**

Impact of HIV infection on mortality: HIV serologic results were available for 26 of the 27 women who died. HIV infection was strongly associated with death among the women in the nonmaternal period of more than 6 weeks to 1 year post delivery (OR = 17.60, CI = 4.99, 64.13) (Table 33). If women who were HIV-infected are excluded from the analysis, 12 deaths among 3721 women would have occurred either during pregnancy or within 6 weeks post delivery, resulting in a maternal mortality rate of 322 per 100,000 women. Among 3711 women who were HIV-, 5 died in the nonmaternal interval, resulting in a mortality rate for this period of 135 per 100,000 women. Of these 17 deaths in HIV- women, 12 (70%) occurred during the maternal period. These data are consistent with those of previous studies, and complications of pregnancy remain a major cause of death in HIV- women of childbearing age. However, HIV infection appears to have more than doubled the mortality for women in the nonmaternal period and has become a significant cause of death for women of childbearing age.

Table 33. Odds ratios and 95% confidence intervals for mortality among women with singleton births and HIV infection compared with HIV- women with singleton births, MMRP, 1987-1990.

HIV STATUS	MATERNAL DEATH	MATERNAL SURVIVAL	ODDS RATIO (95% CI)	MORTALITY RATE ^a
MATERNAL PERIOD^b				
SEROPOSITIVE	2	295	2.10 (0.0, 17.82)	673
SERONEGATIVE	12	3709	REFERENCE	322
NONMATERNAL PERIOD^c				
SEROPOSITIVE	7	295	17.60 (4.99, 64.13)	2318
SERONEGATIVE	5	3709	REFERENCE	135

^a Mortality rate per 100,000 women

^b Pregnancy and up to 6 weeks post delivery

^c More than 6 weeks to 1 year post delivery

Summary findings:

The maternal mortality rate in the study population was 370 per 100,000 pregnancies; however, this is undoubtedly a low estimate due to the lack of information on women prior to their first ANC visit. This estimate is consistent with earlier studies that used retrospective data and estimated maternal mortality rates of between 400 and 700 deaths per 100,000 pregnancies.

HIV infection was an important risk factor for death in women of reproductive age, in both nonmaternal and maternal intervals.

Fetal and infant survival was seriously affected by maternal death: only 5 of 11 liveborn babies survived past 1 year, 3 of whom were known to have died in the second year of life.

VIII. MMRP RESULTS: PERINATAL AND POSTNATAL MORTALITY

The MMRP was not designed to evaluate the effect of antimalarial chemoprophylaxis on the reduction of child mortality. However, morbidity and mortality were monitored for up to 2 years after delivery. Thus, although we cannot provide a comprehensive review with the data available, mortality among the approximately 5900 singleton deliveries⁸ can be assessed in these periods: fetal, perinatal, neonatal, postneonatal, infant and second year of life. Rates of mortality (Table 34) and factors associated with mortality were examined in each of the intervals and are reported in the following sections.

Table 34. Mortality rates by fetal or infant age grouping among singleton deliveries, MMRP, 1987-1990.

INTERVAL OF DEATH	SOURCE OF THE NUMERATOR	SOURCE OF THE DENOMINATOR	RATE
ABORTIONS (FETAL LOSS < 28 WEEKS GESTATION)	REPORTED ABORTION (N = 47)	ALL SINGLETON PREGNANCIES ENROLLED BEFORE THE 3RD TRIMESTER WITH KNOWN DELIVERY OUTCOME (N = 1978)	23.8 PER 1000 PREGNANCIES
STILLBIRTHS (FETAL LOSS < 28 WEEKS GESTATION)	REPORTED STILLBIRTH (N = 148)	ALL SINGLETON PREGNANCIES < 28 WKS WITH KNOWN DELIVERY OUTCOME (N = 3962-47 = 3915)	37.8 PER 1000 PREGNANCIES < 28 WKS
EARLY NEONATAL (BIRTH TO DAY 7)	LIVE BIRTH WITH DEATH < DAY 7 (N = 116)	ALL SINGLETON LIVE BIRTHS WITH KNOWN OUTCOME AT DAY 7 LOST TO FOLLOW-UP < 49 (N = 3915-148-49 = 3718)	31.1 PER 1000 LIVE BIRTHS
PERINATAL (< 28 WKS GESTATION TO DAY 7)	STILLBIRTH + EARLY NEONATAL DEATH (N = 264)	ALL SINGLETON BIRTHS WITH KNOWN OUTCOME AT DAY 7 (N = 3915-49 = 3866)	68.3 PER 1000 BIRTHS
NEONATAL (BIRTH TO DAY 28)	LIVE BIRTH WITH DEATH < DAY 28 (N = 181)	ALL SINGLETON LIVE BIRTHS WITH KNOWN OUTCOME AT DAY 28 LOST TO FOLLOW-UP < DAY 28 = 51 (N = 3915-148-51 = 3716)	48.7 PER 1000 LIVE BIRTHS
POSTNEONATAL (DAY 28- DAY 365)	LIVE BIRTH WITH DEATH < 28 AND < DAY 365 (N = 392)	ALL SINGLETON LIVE BIRTHS WITH KNOWN OUTCOME AT DAY 365 LOST TO FOLLOW-UP < DAY 365 = 246 (N = 3915-148-246 = 3521)	111.3 PER 1000 LIVE BIRTHS
INFANT (BIRTH TO DAY 365)	NEONATAL DEATHS + POSTNEONATAL DEATHS (N = 573)	ALL SINGLETON LIVE BIRTHS WITH KNOWN OUTCOME AT DAY 365 LOST TO FOLLOW-UP < DAY 365 = 246 (N = 3915-148-246 = 3521)	162.7 PER 1000 LIVE BIRTHS
2ND YEAR (DAY 365-730)	LIVE BIRTH WITH AGE OF DEATH < 365 AND < 730 DAY (N = 142)	ALL SINGLETON LIVE BIRTHS WITH KNOWN OUTCOME AT DAY 730 LOST TO FOLLOW-UP < DAY 730 = 193 (N = 3915-148-193 = 1847)	76.9 PER 1000 LIVE BIRTHS

⁸Denominators change with the interval, all liveborn singletons were included in the analyses

**SECTION VIII:
RESULTS**

A. ABORTIONS

Fetal deaths before 28 weeks of gestation were reported by 47 women;⁹ however, the certainty about the week of gestation must be questioned. Most women in the study area were unable to recall the date of conception or of their last menstrual period; consequently, the gestational age estimated for these fetal deaths is only approximate. For the purposes of this study, these events probably represented midtrimester abortions or possibly early third trimester stillbirths; however, because of the uncertainty they were considered abortions and excluded from the subsequent analysis of perinatal mortality. The 47 abortions reported occurred in 1978 women who enrolled prior to the start of the third trimester, for an estimated second trimester crude fetal loss rate of 25.8 per 1000 pregnancies.

The frequency of second trimester fetal loss was similar among the 867 women who were parasitemic at enrollment (2.4% fetal loss rate) and the 921 women who were aparasitemic at enrollment (2.6% fetal loss rate). Thus, there is no evidence of an association between midtrimester malaria infection and abortion in this population.

Other maternal characteristics were examined as potential risk factors for abortion in this population: parity, age, socioeconomic status, education level, history of fever, HIV infection, syphilis infection, anemia, site of delivery, and history of previous adverse reproductive outcomes (either fetal or infant death). These factors were significantly associated with abortion: anemia, active syphilis, history of a previous adverse reproductive outcome, and delivery at home (Table 35).

Table 35. Maternal characteristics associated with second trimester abortion, MMRP, 1987-1990.

CHARACTERISTIC	NUMBER	ABORTION		P VALUE
		NUMBER	(%)	
HEMATOLOGIC STATUS				
ANEMIA (HCT < 30%)	642	14	(2.2%)	0.014
NO ANEMIA	2705	27	(1.0%)	
SYPHILIS INFECTION				
ACTIVE (MHA-TP + VDRL 1:8)	110	5	(4.5%)	0.002
REACTIVE BUT INACTIVE	514	7	(1.4%)	
NONREACTIVE	3066	30	(1.0%)	
PREVIOUS ADVERSE FETAL OR INFANT OUTCOME				
YES	1452	28	(1.9%)	0.0049
NO	2367	21	(0.9%)	
SITE OF DELIVERY				
HOME	1585	39	(2.5%)	< 10 ⁻⁶
HOSPITAL	2255	10	(0.4%)	

⁹Fetal deaths were reported by the woman or an immediate family member to a member of the study team. Efforts were then made to determine gestational age at the time of death by estimating the duration of the pregnancy.

Summary findings:

Most women in the study were enrolled in the middle trimester; consequently, information on abortion in this trimester is limited. The crude estimate of 23.8 second trimester fetal deaths per 1000 pregnancies is a high rate.

Four characteristics were found to be associated with second trimester fetal death: anemia, syphilis infection, previous adverse fetal or infant outcome, and site of delivery. Home deliveries may not actually be a risk factor for abortion but may mark deliveries that occur at home because of lack of time for transport to the hospital. Maternal malaria at enrollment was not associated with second trimester fetal loss.

B. PERINATAL MORTALITY (STILLBIRTHS AND EARLY NEONATAL DEATHS)

The perinatal period is defined as the time period from the 28th week of pregnancy to the seventh day after birth. A time period overlapping birth (rather than a time period divided into before and after birth) is useful for two reasons:

- 1) The causes of morbidity and mortality for stillborn infants and for infants during the early neonatal period are frequently the same or closely related.
- 2) The identification of a stillborn infant or a liveborn infant who dies within minutes, hours, or even days of birth is frequently culturally defined, and strict definitions are difficult to use.

The birth outcome during this period reflects both the medical and social condition of the mother and the care she and the fetus or infant receive during the last trimester of pregnancy, labor and delivery, and the immediate postdelivery period (58). The birth weight of the infant strongly influences the risk of mortality during this period. In the United States in 1980, the perinatal mortality rate was almost 200-fold higher for very LBW (< 1500 grams) infants than for infants of normal birth weight (59). The number of perinatal deaths is determined by the birth-weight distribution and the mortality rate within the birth-weight categories.

Distribution of perinatal deaths

Of the 3962 women with known singleton pregnancy outcome, 3602 (90.9%) had a liveborn infant who survived past the perinatal period; 264 (6.7%) had an infant who did not survive the perinatal period. Of these, 148 (55%) were recorded as stillbirths and 116 (44%) as early neonatal deaths. Forty-nine (1.2%) were lost to follow-up after delivery and before day 7, and 47 (1.2%) had abortions, for a perinatal mortality rate of 264/3866 or 68.3 per 1000 births.

Birth weight

Information on birth weight and known survival at day 7 was available for 2232 (58%) of the 3862 singleton births (Table 36). The perinatal mortality rate was highest in infants with birth weights < 1500 grams (577 per 1000 births) and decreased as birth weight increased (258 per 1000 births for infants in the 1500-1999-gram birth-weight category, 63 per 1000 births for infants in the 2000-2499-gram birth-weight category, and 38 per 1000 births for infants with birth weights > 2500 grams).

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Table 36. Birth weight-specific perinatal mortality rates, singleton births, MMRP, 1987-1990.

BIRTH-WEIGHT CATEGORY	PERINATAL DEATHS/BIRTHS	PERINATAL MORTALITY RATE PER 1000 BIRTHS
< 1500 GM	15/26	577
1500-1999 GM	17/66	258
2000-2499 GM	20/317	63
≥ 2500 GM	69/1822	38
TOTAL (KNOWN BIRTH WEIGHT)	121/2231	54
UNKNOWN WEIGHT	146/1634	89

Maternal characteristics associated with perinatal mortality

Characteristics of the women for whom the perinatal outcome is known are shown in Table 37.

Table 37. Characteristics of women with singleton births and known perinatal outcomes (survival or death), MMRP, 1987-1990.

CHARACTERISTIC	PERINATAL DEATH (N = 264)	PERINATAL SURVIVOR (N = 3602)	P VALUE
	PROPORTION WITH CHARACTERISTIC	PROPORTION WITH CHARACTERISTIC	
MATERNAL AGE ≥ 18 YEARS	21.2%	14.8%	0.007
FIRST PREGNANCY	44.7%	32.1%	0.00003
HOME DELIVERY	50.3%	41.0%	0.003
REACTIVE VDRL/RPR	28.4%	11.8%	10 ⁻⁶
REACTIVE HIV SEROLOGIC RESULTS	9.1%	7.3%	0.25
NOT LITERATE	74.2%	69.0%	0.07
LOW SOCIOECONOMIC STATUS	75.4%	67.1%	0.006
SHORT STATURE (< 150 CM)	22.7%	13.8%	0.0007
SMOKING	2.7%	3.1%	0.68
ALCOHOL USE	1.1%	0.8%	0.57
ANEMIA AT ENROLLMENT			
HCT < 29 GM %	19.2%	16.9%	0.38
PARASITEMIA AT ENROLLMENT	47.7%	43.8%	0.22

In the univariate analysis, maternal age ≥ 18 years, nulliparity, delivery at home, reactive VDRL, short stature (< 150 cm), and enrollment hematocrit < 25% were associated with perinatal death among women with singleton births. In the multivariate analysis, nulliparity, home delivery, reactive VDRL, and short stature were associated with perinatal death. Maternal age over 34, parity over 6, reactive HIV serologic results, illiteracy, low socioeconomic status, parasitemia at enrollment, and ANC site were not associated with perinatal death in either the univariate or the multivariate analysis.

Risk factors for stillbirth

The distribution of the type of stillbirth (macerated versus fresh) helps to identify causes of death. Among the 118 singleton stillbirths, 17 (32%) were reported as fresh and 28 (19%) as macerated, and for 73 (19%) the type was not reported. Risk factors for the two types of stillbirth were identified in univariate and multivariate analyses, using women with an infant who survived the perinatal period as the reference group. Reactive VDRL and enrollment hemato-crit $\geq 25\%$ were identified as risk factors for macerated stillbirth, reactive VDRL was identified as a risk factor for fresh stillbirth (Table 38). The largest number of stillbirths were those for which the type was not reported, risk factors identified in both univariate and multivariate analyses were home delivery, reactive VDRL, and short stature.

Risk factors for early neonatal death

In the univariate analysis, maternal age ≥ 18 years, first pregnancy, reactive VDRL, and short stature were associated with early neonatal death among women with singleton births. Nulliparity, reactive VDRL, and short stature remained significantly associated with early neonatal death in the multivariate analysis (Table 38); some factors were not examined (e.g. placental malaria infection) because information was available only for a small number of stillbirths.

Table 38. Odds ratio and 95% confidence intervals for significant risk factors for poor perinatal outcomes, MMRP, 1987-1990

RISK FACTOR	PREVALENCE ^b	PERINATAL DEATH	FRESH STILLBIRTH	MACERATED STILLBIRTH	UNKNOWN STILLBIRTH	EARLY NEONATAL DEATH
		(N=198)	(N=38)	(N=24)	(N=50)	(N=86)
		ODDS RATIO (95% CI) ^a				
PRIMIGRAVIDA	33%	1.74 (1.29, 2.34)	---	---	---	1.76 (1.10, 2.81)
HOME DELIVERY	40%	1.40 (1.05, 1.88)	---	---	1.96 (1.11, 3.15)	---
REACTIVE VDRL	12%	3.80 (2.76, 5.25)	4.25 (2.18, 8.30)	6.84 (3.04, 15.40)	3.83 (2.11, 7.00)	2.85 (1.72, 4.72)
SHORT STATURE ^c	14%	1.79 (1.26, 2.55)	---	---	2.37 (1.26, 4.45)	1.89 (1.11, 3.21)
ENROLLMENT HCT ^d	6%	---	---	3.31 (1.10, 9.97)	---	---

^aReference group is 2951 live births with known survival at day 7.

^bPrevalence is approximate and varies slightly due to loss to follow up in the interval.

^cHeight ≤ 159 cm.

^dHematocrit ≥ 25 .

Factors examined but not found to be significant at $p < 0.05$ in the multivariate model: maternal age ≥ 18 years, maternal age ≥ 35 years, parity ≥ 6 , reactive HIV serology, illiteracy, low socioeconomic status, parasitemia at enrollment.

Summary findings:

The perinatal mortality rate in the study population was 68.3 deaths per 1000 births. Birth weight was the most important predictor of perinatal mortality. Very LBW babies (< 1500 grams) had a 15-fold increased risk of perinatal mortality compared with normal birth-weight babies (> 2500 grams). In the multivariate model, first pregnancy, home delivery, maternal syphilis, and short maternal stature were associated with perinatal mortality in this population. Malaria infection in the mother was not associated with stillbirth.

C. SYPHILIS INFECTION AND ITS EFFECTS ON PERINATAL MORTALITY

The reported prevalence of syphilis among women attending ANCs in Africa ranges from 6% to 16%, with estimates of 20% to 40% of women with untreated syphilis experiencing a perinatal death (60). Although a screening test exists that is available for field use (61) and an effective drug (penicillin) has been identified for treatment (62), syphilis remains an ignored maternal and perinatal health problem in many developing countries. In Malawi, despite national policy, routine antenatal screening programs were discontinued in many rural district hospitals when they could not sustain the programmatic requirements.

The objectives of this analysis were to investigate the prevalence of syphilis among the study population, to quantify the association between active syphilis and pregnancy outcomes, and to identify risk factors for syphilis.

Of the 3591 HIV–women enrolled and tested, 130 (3.6%) had serologic results consistent with active syphilis (VDRL RPR reactive with titer \geq 1:8 and reactive MHA-TP), and 2968 (82.7%) were nonreactive by VDRL RPR and MHA-TP (Table 39).

Table 39. Syphilis serologic results among HIV–pregnant women with singleton births. (N = 3591), MMRP, 1987–90.

SEROLOGIC RESULT	INTERPRETATION	NUMBER	(PERCENT)
VDRL RPR AND MHA-TP NONREACTIVE	NO EVIDENCE OF SYPHILIS	2968	(82.7)
VDRL RPR REACTIVE AND MHA-TP NONREACTIVE	FALSE POSITIVE OR VERY EARLY INFECTIONS	187	(5.2)
VDRL RPR NONREACTIVE AND MHA-TP REACTIVE	OLD RESOLVED INFECTIONS	137	(3.8)
VDRL RPR REACTIVE (1:1:8) AND MHA-TP REACTIVE	OLD OR EARLY INFECTIONS	169	(4.7)
VDRL RPR REACTIVE (1:1:8) AND MHA-TP REACTIVE	ACTIVE SYPHILIS	130	(3.6)

In an antenatal syphilis screening program appropriate for a setting with limited resources, a qualitative VDRL or RPR without a confirmatory test such as MHA-TP would be used to identify women for syphilis treatment. On the basis of the findings in this study, 13%-14% of the women would have a qualitative reactive VDRL/RPR result, and 25-30% of these women would most likely have active syphilis. The remaining 70%-75% of the women with qualitative reactive results would have either a false positive result or early or late resolved syphilis infections. Serial VDRL titers were not available to define the distribution of these three categories of "nonactive" reactive serologic results, so the potential number of uninfected women included in the identified reactive group is unknown.

Compared with women without syphilis, women with active syphilis (reactive VDRL with titer $\geq 1:8$ and reactive MHA-TP) were more likely to have stillborn infants, infants who died during the neonatal period, and infants who died during the postneonatal period (Table 40). Women with active syphilis were 11 times more likely to have a stillbirth. This elevated risk associated with active syphilis extends not only into the neonatal period, but also into the postneonatal period.

Significant associations with poor pregnancy outcome, although at lower levels, were also found when women with reactive VDRL/RPR (qualitative serologic test) were compared with women with nonreactive VDRL/RPR (Table 40). The association did not extend into the postneonatal period.

Table 40. Odds ratios and 95% confidence intervals for active syphilis and reactive VDRL/RPR as risk factors for adverse outcomes among HIV- pregnant women with singleton births, multivariate analysis, MMRP, 1987-1990.

OUTCOME	ACTIVE SYPHILIS			REACTIVE VDRL/RPR		
	OUTCOME/ REFERENT	ACTIVE SYPHILIS	ODDS RATIO (95% CI)	OUTCOME/ REFERENT	REACTIVE VDRL	ODDS RATIO (95% CI)
STILLBIRTH ^a	99/2885	.04	10.89 (6.61, 17.93)	119/3340	.13	4.11 (2.78, 6.08)
NEONATAL DEATH ^c	135/2723	.03	4.86 (2.73, 8.66)	153/3148	.13	2.51 (1.63, 3.71)
PERINATAL DEATH ^b	190/2768	.04	9.03 (5.88, 13.84)	215/3207	.13	3.40 (2.48, 4.66)
POSTNEONATAL DEATH ^d	272/2333	.03	2.24 (1.26, 3.99)	318/2666	.12	NOT ASSOCIATED

^aReference group: Known live births

^bReference group: Live births with known survival to Day 7

^cReference group: Live births with known survival to Day 28

^dReference group: Live births with known survival to Day 365

Other variables examined in the model: late antenatal care, home delivery, first pregnancy, age ≥ 18 vs low socioeconomic status, illiteracy, clinic site, smoking, alcohol consumption, hemoglobin < 21 at enrollment, peripheral *P. falciparum* parasite density > 2000 at enrollment

Risk factors for active syphilis

Because women who are pregnant for the first time have not had the opportunity to experience a good or poor pregnancy outcome and because aspects of pregnancy outcome were potential risk factors for active syphilis (e.g., history of stillbirth), maternal characteristics were analyzed separately for primigravidas and multigravidas (Table 11). Among primigravidas, women with active syphilis were more than twice as likely not to be literate as women without syphilis. Among multigravidas, women with active syphilis were twice as likely to have had a home delivery or to have a history of child death in the previous pregnancy than women without syphilis. Multigravidas from the two clinics serving town areas were 2 to 3 times more likely to have active syphilis than those women who enrolled in the most rural clinic. A history of a stillbirth with the previous pregnancy was a very strong risk factor. The following characteristics were not associated with active syphilis in primigravidas or multigravidas: maternal age, alcohol use, parity, late antenatal care (begun less than 60 days before delivery), hematocrit less than 21 at enrollment, low socioeconomic status, and a history of a spontaneous abortion.

Table 41. Odds ratios and 95% confidence intervals for active syphilis among HIV- women with singleton births, univariate and multivariate analysis, MMRP, 1987-1990.

RISK FACTOR	PRIMIGRAVIDAS (ACTIVE SYPHILIS = 34; NO SYPHILIS = 1005)			MULTIGRAVIDAS (ACTIVE SYPHILIS = 96; NO SYPHILIS = 1962)		
	PRE- VALENCE	UNIVARIATE ODDS RATIO (95% CI)	MULTIVARIATE ODDS RATIO (95% CI)	PRE- VALENCE	UNIVARIATE ODDS RATIO (95% CI)	MULTIVARIATE ODDS RATIO (95% CI)
	MATERNAL AGE < 18	.45	0.64 (0.29, 1.42)	NS ^a	.03	0.36 (0.01, 2.17) ^c
LATE ANTENATAL CARE (< 60 D BEFORE DELIVERY)	28	1.59 (0.74, 3.39)	NS	29	1.17 (0.73, 1.86)	NS
HOME DELIVERY	.36	0.83 (0.37, 1.83)	NS	.43	1.57 (1.02, 2.43)	1.9 (1.24, 2.91)
NOT LITERATE	62	2.48 (1.04, 6.80) ^c	2.39 (1.03, 5.56)	75	1.75 (0.98, 3.16)	NS
LOW SOCIOECONOMIC STATUS	66	1.10 (0.50, 2.45)	NS	70	1.44 (0.86, 2.42)	NS
ANEMIA ^d	04	0.88 (0.02, 5.62) ^c	NS	03	1.23 (0.24, 3.93)	NS
MANGOCHI DISTRICT HOSPITAL CLINIC ^e	62	1.10 (0.45, 2.75)	NS	24	1.06 (0.50, 2.23)	NS
KOCHE CLINIC ^e	28	1.43 (0.40, 4.85)	NS	28	2.56 (1.49, 4.38)	2.94 (1.80, 4.81)
MPONDAS CLINIC ^e	29	1.07 (0.24, 3.93)	NS	24	2.05 (1.12, 3.73)	2.23 (1.29, 3.85)
HISTORY OF STILLBIRTH ^f				.07	3.39 (1.83, 6.04)	NOT IN MODEL ^g
PREVIOUS BIRTH- STILLBIRTH ^f				.03	5.92 (2.91, 11.32)	7.84 (4.05, 15.18)
HISTORY OF ABORTION ^f				.09	1.49 (0.75, 2.88)	NS
HISTORY OF CHILD DEATH ^f				.47	1.48 (0.96, 2.30)	NOT IN MODEL ^g
PREVIOUS BIRTH- CHILD DEATH ^f				21	2.24 (1.34, 3.73)	2.05 (1.28, 3.29)

^aNS = For the multivariate model, these variables were not significant at $p = .05$ after controlling for illiteracy and smoking, and were not entered into the model.

^bNS = For the multivariate model, these variables were not significant at $p = .05$ after controlling for home delivery, enrollment at Koche Clinic or Mpondas Clinic, and history of a stillbirth or child death with the previous pregnancy, and were not entered into the model.

^cExact confidence intervals.

^dHematocrit = 21% at enrollment.

^eReference clinic = St. Martins Hospital, Malindi Clinic (lowest rate of active syphilis).

^fThese variables were not included in the multivariate model for primigravidas.

^gThese variables were not included in the multivariate model because they were subsets of previous birth outcomes.

Summary findings and discussion:

Syphilis during pregnancy had a significant effect on fetal, neonatal, and postneonatal mortality. Nearly 1 of 4 stillbirths, 1 of 9 neonatal deaths, and 1 of 25 postneonatal deaths were attributed to maternal syphilis infection. This strong association between reactive syphilis serologic results and poor birth outcome indicates that the reactive serologic results were most likely due to venereal syphilis and not normal treponema infections (e.g., Yaws).

Syphilis during pregnancy has been recognized as a public health problem in Africa for many years, but there have been few sustainable intervention programs. Clinicians have attempted to identify women at risk for syphilis by limiting screening to women in urban areas or to women with a history of stillbirth as these criteria were assumed to be risk factors. From these data, the prevalence of active syphilis (3.6%) in the Mangochi community demonstrates that syphilis infection has extended into rural areas and emphasizes that syphilis screening programs should not be limited to urban areas. Although a history of the immediate previous birth as a stillbirth is an important risk factor in this population, it would identify none of the primigravidas and only 14 (15%) of the 96 multigravidas with active syphilis. Other risk factors identified for active syphilis (illiteracy, clinic site, home delivery, and history of the immediate previous birth as a child death) were not very useful in targeting women at high risk. A universal screening program using a qualitative reactive screening test appears to be the most appropriate option, even with the potential of overdiagnosing active syphilis in up to 10% of the women. Because available technology is not able to differentiate between true active infections and either false positive or old resolved infections and because of the strong causal relationship between syphilis and perinatal and infant mortality, the benefit gained by a universal screening program outweighs the cost of unnecessary treatment.

Identification and immediate proper treatment of women with reactive serologic results at the first ANC visit is the key element to a successful antenatal syphilis intervention program. The availability of the macroscopic rapid tests (RPR Card or TRUST) makes this possible. The results of the screening tests would be immediately available, and women with reactive tests could be treated at the first visit. Many of the logistic problems associated with identifying women with reactive results would be eliminated, and treatment would not be delayed until the next visit or missed altogether.

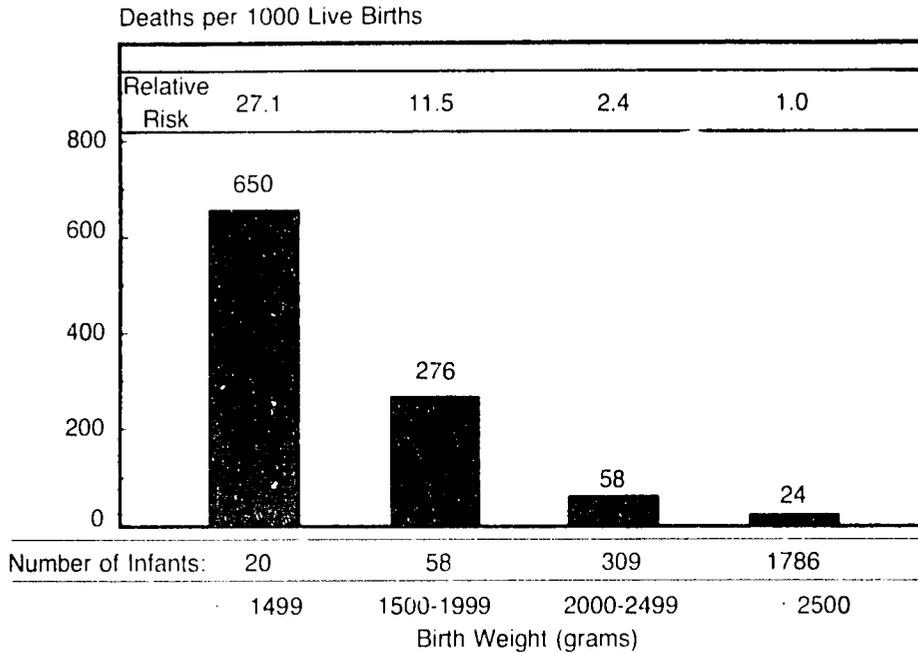
D. NEONATAL MORTALITY

During the neonatal period, 181 infants died, for a neonatal mortality rate (NMR = deaths in the neonatal period per 1000 live births) of 18.7/1000 live births.

Birth weight and gestational age

Birth weight was an important predictor of neonatal survival. The risk of mortality during the neonatal period increased with decreasing birth weight. Compared with babies born of normal birth weight, babies born in the successively lower birth-weight groups of 2000-2499 grams, 1500-1999 grams, and below 1500 grams had risks for neonatal mortality 2.1, 11.5, and 27.1 times higher, respectively (Figure 29).

Figure 29. Neonatal mortality rates by birth-weight categories for infants born to women in study, MMRP, 1987-1990.



Low birth weight was identified in 17.9% of babies born to women enrolled in the study.¹⁰ In this population, preterm-LBW and IUGR-LBW carried very different risks for neonatal mortality. The NMR was 192 for preterm-LBW babies and 51 for IUGR-LBW babies, compared with 23 for normal birth weight babies. Thus, the risk of neonatal mortality was approximately 2.2-fold higher for IUGR-LBW babies and 8.3-fold higher for preterm-LBW babies than for normal birth-weight babies (Table 42). Among the 87 neonatal deaths, 53% occurred in LBW babies and among the 46 deaths in LBW babies, 76% were in preterm-LBW babies.

Table 42. Neonatal mortality rates in premature, IUGR, and normal birth-weight babies, MMRP, 1987-1990.

	NUMBER OF LIVEBORN SINGLETONS*	DEATHS IN THE NEONATAL PERIOD	NMR	RISK RATIO
PREMATURE	182	35	192	8.3
IUGR	215	11	51	2.2
NORMAL BIRTH WEIGHT	1780	41	23	1.0
TOTAL	2177	87	40	1.7

* Infants with known birth weight, gestational age, and follow up through the neonatal period

¹⁰This figure is higher than the 16.6% LBW rate cited (Section VII) for babies born to women in the study who received all of the required antimalarial drugs and had participated in the study for more than 6 weeks at the time of delivery.

Malaria infection in pregnancy as a risk for neonatal mortality

Neonatal mortality rates were higher in infants born to women with placental or umbilical cord malaria infection than in those without this exposure. NMRs were 51/1000 for infants born to women with placental malaria infection and 38/1000 for those born to women without infected placentas; NMRs were 59/1000 for infants with umbilical cord parasitemia and 40/1000 for infants without umbilical cord blood parasitemia. However, these differences were not significant.¹¹

Summary findings:

The neonatal mortality rate in babies born to women in the study was 48.7 per 1000 live births. Low birth weight and prematurity were the most important predictors of neonatal mortality. Premature-LBW babies had an 8.3-fold increased risk of neonatal mortality compared with normal birth-weight babies.

Malaria infection of the mother, her placenta, or the umbilical cord of the infant was not significantly associated with increased risk of neonatal death; however, the study did not have sufficient power to assess these characteristics as risk factors.

E. NEONATAL TETANUS

Neonatal tetanus, caused by a spore-forming anaerobic bacillus, *Clostridium tetani*, is an important cause of mortality during the neonatal period. Neonates are generally infected either when the umbilical cord is cut with a contaminated instrument or when a dressing placed on the umbilicus is contaminated with the bacillus or spores (63). The incubation period ranges from 3 to 21 days, and the symptoms are caused by a neurotoxin produced by the bacteria or its spore in a low oxygen tension environment. Typically, symptoms begin in the first or second week of life and last 3 to 7 days. Sixty to ninety percent of the deaths occur within 10 days of the onset of symptoms. The case-fatality rate is very high and may exceed 80% in cases with short incubation periods.

The WHO clinical case definition for neonatal tetanus death uses the following criteria: death occurring between the third and the thirtieth day of life; normal breastfeeding and crying at birth and for 2 days following birth, followed by failure to suck at the onset of the disease; and generalized spasms, stiffness and trismus (lockjaw) before death (64).

Deaths in the first 30 days of life

There were 184 deaths from birth to 30 days after delivery among the 3716 singleton live births for which status at day 30 is known (51 live births were lost to follow-up before day 30). This results in a 30-day mortality rate of 50 per 1000 live births. Of these 184 deaths, 60 (33%) occurred within the first 2 days of life, a time period not compatible with neonatal tetanus (Table 43), leaving 124 deaths (67%) within the time frame for neonatal tetanus (death from day 3 to 30). Of these 124 deaths, information about the symptoms near the time of death is available for 112 (90%).

¹¹The sample size of the study was established to be able to examine birth weight as an outcome; the investigators recognized that this sample size would not allow for adequate power to detect significant differences in mortality rates among women with and without peripheral placental or umbilical cord parasitemia.

Table 15. Deaths from birth to day 30 among singleton births, MMRP, 1987-1990.

	ALL LIVE SINGLETON BIRTHS	IDENTIFIED AS NEONATAL TETANUS DEATH BY FAMILY
DEATHS BETWEEN BIRTH AND DAY 30	184	44
DEATHS IN FIRST 2 DAYS OF LIFE	60	8
DEATHS FROM DAY 3-30	124	36
INFORMATION ABOUT SYMPTOMS	112	36
MET THE WHO CASE DEFINITION FOR NEONATAL TETANUS	15	7

Neonatal tetanus identified by WHO case definition

Data collected for the WHO case definition were death from day 3 to day 30, and ability to suck well at birth, with subsequent inability to suck or cry at onset of disease (used to describe trismus). Fifteen (13%) of the 112 deaths for which symptom data were available met these criteria; the estimated neonatal tetanus mortality rate was 4.1/1000 live births. The duration of illness for these 15 infants ranged from 1 to 10 days with a mean duration of 3.0 days (SD = 2.42 days).

Reported symptoms and neonatal tetanus

Mothers or other family members identified 44 infant deaths as deaths due to neonatal tetanus. Deaths that occurred between days 3 and 30, the time period for neonatal tetanus, numbered 36 (82%). Of the 15 infants who met the WHO case definition, 7 (47%) were identified as neonatal tetanus deaths by their mothers or family members.

When mothers were initially asked an open-ended question about cause of death, 3 (8%) of the 36 infants who died between day 3 and 30 were reported to have had problems from birth (born cold, born unhealthy, or jaundiced from birth), histories that are not compatible with neonatal tetanus. Of the remaining 33 births, 15 (45%) also were reported to have had oozing or infected umbilicus; 11 (42%) were reported to have had twitching, spasms, or convulsions; and 6 (18%) were reported to have sucked well at birth and then not to have been able to cry or suck at the time of illness. In their open-ended answer to the cause of death of their child, 14 (42%) of the mothers or other family members spontaneously included neonatal tetanus. Duration of illness ranged from 0 to 21 days with the mean duration of 4.53 days (SD = 4.24) for these 33 infants.

**SECTION VIII:
RESULTS**

Immunization status

Information about neonatal tetanus immunization is available primarily for the infants who delivered in a health-care facility. Because the women followed in MMRP were identified through the ANC system, all should have received at least one immunization. Among the 2252 women with reported immunization histories, 2088 (93%) reported at least one neonatal tetanus immunization during their pregnancy, and 1693 (75%) reported two or more immunizations. All seven infants whose deaths met the WHO case definition for neonatal tetanus and whose mothers' immunization histories were known were born to women who had had at least one neonatal tetanus immunization, five mothers had had at least two. Compared with mothers whose infants died well after the neonatal period (> 15 days after delivery), mothers whose infants died between days 3 and 30 had lower rates of neonatal tetanus immunization (Table 14). No association between the lack of neonatal tetanus immunization and deaths from day 3 to 30 when compared with either deaths in the first 2 days of life or to all singleton live births is apparent.

Table 14. Tetanus toxoid immunization history as a risk factor for death, MMRP, 1987-1990.

TIME OF DEATH	NUMBER	NO IMMUNIZATION		ODDS RATIO AND P VALUE*
		RECORDED	NUMBER (%)	
SINGLETON LIVE BIRTH, SURVIVED	2121	149	(7.0)	REFERENCE
DEATH 1-2 DAYS AFTER DELIVERY	32	4	(12.5)	1.89 P = 0.28
DEATH 3-30 DAYS AFTER DELIVERY	52	7	(13.5)	2.06 P = 0.09
DEATH >45 DAYS AFTER DELIVERY	289	14	(4.8)	0.67 P = 0.17

* P value determined using Fisher's exact test or chi-square test.

Home delivery as a risk factor for neonatal tetanus

Of the 3752 women in the MMRP who delivered a singleton live birth, 41% (1539) delivered at home. Of the 112 infants who died sometime between days 3 and day 30, 58 (52%) were delivered at home, compared with 36% of the 59 infants who died during days 1 or 2 and with 45% of the 516 deaths after day 45. Of the 15 infants who met the WHO case definition for neonatal tetanus, 7 (47%) were delivered at home (Table 15). Compared to the risk of death for infants delivered in health facilities, the risk of death in home-delivered infants was significantly elevated for deaths from day 3 to 30, but not for the other time periods.¹²

¹²Further scrutiny of the data suggests that the lower rates of death in the first 3 days of life in home delivered infants may be due to an increased reported incidence of stillbirths in home delivered infants. Thus, perinatal mortality is higher in home delivered infants because some home delivered infants dying in the first 3 days of life may have been reported as stillbirths.

Table 45. Delivery at home as a risk factor for infant death, MMRP, 1987-1990.

	PLACE OF DELIVERY		ODDS RATIO (95% CONFIDENCE INTERVAL)
	HOME	HEALTH FACILITY	
SINGLETON LIVE BIRTH	1539	2213	REFERENCE
DEATH 0-2 DAYS	21	38	0.79 (0.45, 1.40)
DEATH 3-30 DAYS	58	54	1.54 (1.04, 2.29)
DEATH >45 DAYS	246	300	1.18 (0.98, 1.42)
MET WHO NEONATAL TETANUS CASE DEFINITION	7	8	1.26 (0.41, 3.82)

Summary findings and discussion:

The estimate of 9% of neonatal deaths due to neonatal tetanus (WHO case definition) is much lower than the estimate of 41% obtained from a random cluster survey conducted by a joint Malawi Government/Save the Children/WHO DANIDA team in Malawi in 1983 (65) and may reflect the impact of the tetanus immunization program initiated as a result of the 1983 survey. The high tetanus immunization coverage reported and the significant association of lack of tetanus immunization with deaths at age 3-30 days compared with deaths >45 days support this conclusion. Of the deaths meeting the WHO case definition of neonatal tetanus, 71% of the infants were born to mothers reported to have had two immunizations. This finding indicates a need to assess the adequacy of the cold chain, efficacy of the vaccines, and the timing of the immunizations. Also, the histories used to estimate coverage for the women of MMRP are based on those of women who delivered in health-care facilities and thus may overestimate the percentage of all pregnant women protected.

The almost equal distribution of deaths that met the WHO case definition for neonatal tetanus among home and facility deliveries is disturbing. Most infants are sent home 24-48 hours after a health facility delivery, so infection may occur among health facility deliveries because of the application of contaminated materials after discharge. However, unhygienic practices at the time of delivery in any site can be the source of neonatal tetanus infection. Adequate equipment and supplies and proper disinfection and sterilization are important whether the delivery is at home or in a health facility.

It is difficult to assign a cause of death in the neonatal period. Neonates do not always exhibit classical signs of diseases, and the complex of respiratory distress, hypothermia, hypoglycemia, and sepsis shares similar symptoms. Neonatal tetanus and sepsis both result from poor hygienic conditions at birth. Many authors (63,64,66,67) have recommended both improved hygienic conditions at time of delivery and tetanus immunization as control measures. The World Health Organization is currently recommending expansion of tetanus immunization programs from ANC's to programs that will immunize all women of childbearing age (63).

F. POSTNEONATAL INFANT MORTALITY

A total of 392 infants died during the postneonatal period for a postneonatal mortality rate (PNMR = deaths in the postneonatal period per 1000 live births) of 111.3 deaths per 1000 live births.

Birth weight and gestational age

Birth weight remained an important predictor of postneonatal mortality (Table 46).

Table 46. Birth-weight-specific postneonatal mortality rates among singleton births, MMRP, 1987-1990.

BIRTH-WEIGHT CATEGORY	NEONATAL DEATHS (LOST TO FOLLOW-UP IN NEONATAL PERIOD)		POSTNEONATAL DEATHS (LOST TO FOLLOW-UP IN POSTNEONATAL PERIOD)		LIVE BIRTHS WITH KNOWN POSTNEONATAL OUTCOME AT DAY 365	POSTNEONATAL MORTALITY RATE*	RISK OF POSTNEONATAL MORTALITY AMONG NEONATAL SURVIVORS WITH KNOWN OUTCOME AT DAY 365
	LIVE BIRTHS	NEONATAL SURVIVORS	UP IN POSTNEONATAL PERIOD	NEONATAL SURVIVORS			
1500	20	13 (0)	7	2 (1)	19	105	333 (2.6)
1500-1999	58	16 (0)	42	9 (3)	55	164	231 (9.39)
2000-2499	316	18 (7)	291	37 (13)	296	125	133 (37.278)
≥ 2500	1810	42 (24)	1744	173 (107)	1679	103	106 (173.1637)
TOTAL WITH KNOWN BIRTH WEIGHT	2204	89 (31)	2084	221 (124)	2049	108	113 (221.1960)
UNKNOWN BIRTH WEIGHT	1563	92 (20)	1451	171 (71)	1472	116	124 (171.1380)

* Postneonatal mortality rate = number of deaths from day 28 to day 365 per 1000 live births with known outcome at day 365; note that the rate is low for the very LBW category (< 1500 grams) due to the fact that 68% of babies born in this weight category died in the neonatal period.

Overall, there was a 1.45-fold increased risk of death ($p=0.03$) in the postneonatal period in LBW babies compared with the risk of death in normal birth weight babies. There were no significant differences in PNMRs between premature (PNMR = 127) and IUGR infants (PNMR = 137).¹³ Among the 220 postneonatal deaths occurring in babies with known birth weight and gestational age, 50 (22.7%) occurred in LBW babies; 22 (10%) in premature infants and 28 (12.7%) in IUGR infants (Table 47).

¹³ Rates were calculated after the exclusion of lost to follow-ups in the postneonatal period.

Table 17. Postneonatal mortality rates in premature, IUGR, and normal birth weight babies, MMRP 1987-1990.

	NUMBER OF LIVEBORN SINGLETONS WITH FOLLOW-UP ^a	DEATHS IN THE POSTNEONATAL PERIOD	POSTNEONATAL MORTALITY IN THE INTERVAL ^b	RISK RATIO
PREMATURE	138	22	159	1.53
IUGR	194	28	144	1.38
NORMAL BIRTH WEIGHT	1633	170	104	1.00
TOTAL	1965	220	112	

^a Infants with known birth weight, gestational age, survival of neonatal period, and follow up through the postneonatal period.

^b Denominator is the survivors through the neonatal period; therefore, it is not a true postneonatal mortality rate (per 1000 live births). Rates given in text for premature and IUGR = 127 and 157, respectively.

Summary findings:

The postneonatal infant mortality rate was 111.3 deaths per 1000 live births. Birth weight remained the most important predictor of postneonatal infant mortality. Postneonatal infant mortality rates were not significantly different in premature-LBW infants compared with IUGR-LBW infants. Despite the importance of the LBW risk, 77% of deaths in the postneonatal period occurred in normal birth-weight babies.

G. INFANT MORTALITY

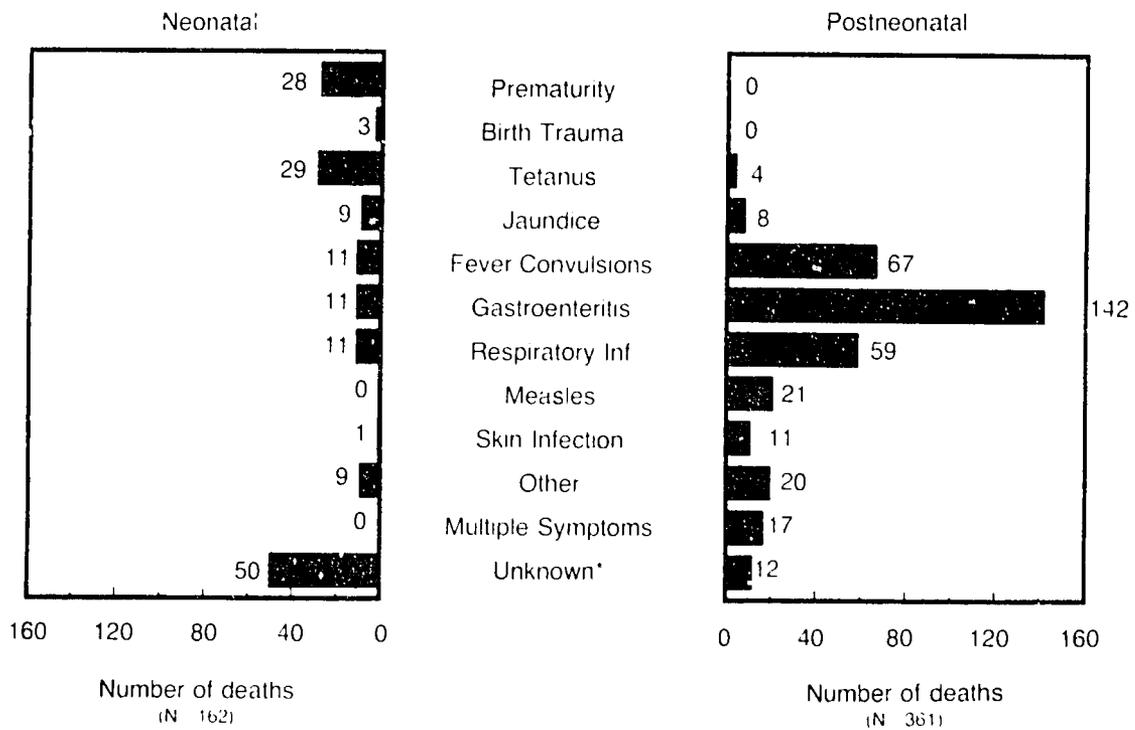
Among infants born to women in the study, 575 died during the first year of life for a crude infant mortality rate of 162.7 per 1000 live births. Factors associated with neonatal and postneonatal mortality have been described earlier; this section examines cause-specific mortality and certain features of mortality in infancy.

Cause-specific mortality in the neonatal and postneonatal periods

Information on cause of death was available on 162 (90%) neonatal deaths and 362 (92%) postneonatal deaths. The most commonly reported cause of death for the neonatal period was sepsis/neonatal tetanus; however, many deaths were recorded simply as due to unknown cause because of the infant's early demise, often within 5 days of birth, and the lack of specific symptoms that could indicate a specific cause. In the postneonatal period, diarrhea, fever, and respiratory illness were the three most common causes recorded, and together, they accounted for more than 75% of deaths in this interval. Figure 50 demonstrates the variation in cause of death by age. Respiratory disease peaked as a cause of death in the 2-6-month age group. Death associated with diarrhea was the most commonly reported cause after the neonatal period; mortality due to diarrhea was highest in the 7-12-month age group. The proportion of death from fever and measles increased with increasing age into the second year of life. Consequently, the proportional causes of mortality changed substantially during the first 2 years of childhood.

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Figure 30. Cause-specific mortality in the neonatal and postneonatal periods in the cohort of infants born to women in study, MMRP, 1987-1990.



*Unknown neonatal deaths were home deliveries

Although the technique of postmortem questioning to determine symptoms of illness prior to death has been used by a variety of investigators to ascertain cause of death, the technique has limitations. Deaths in the neonatal period, especially the early neonatal period, were frequently difficult to categorize because of the lack of a single or specific symptoms prior to death. In addition, anemia was observed to be relatively common in the population and is known to be associated with a substantial proportion of mortality in hospitalized children in this area. However, because of the lack of clear clinical signs and symptoms associated with anemia, anemia was seldom given as a diagnosis or cause of death by parents or guardians. Consequently, post-mortem questioning can be helpful for easily recognized and well-understood conditions, but is less helpful for neonatal deaths (except sepsis or neonatal tetanus) and for certain conditions in the postneonatal or childhood period (e.g., anemia).

Duration of illness prior to death

Information on the duration of illness prior to death was obtained for 705 deaths (556 infant deaths and 149 childhood deaths). According to the parent or caregiver, 493 (69.9%) of the deaths occurred within 7 days of the onset of illness. Of these, 38.3% died in the first 3 days of the illness, 31.6% died between days 4 and 7 of the illness, and only 15 (6.1%) of the deaths occurred after an illness of more than 1 month (Figure 31 and Table 18).

Figure 31. Duration of illness prior to death in infants, MMRP, 1987-1990.

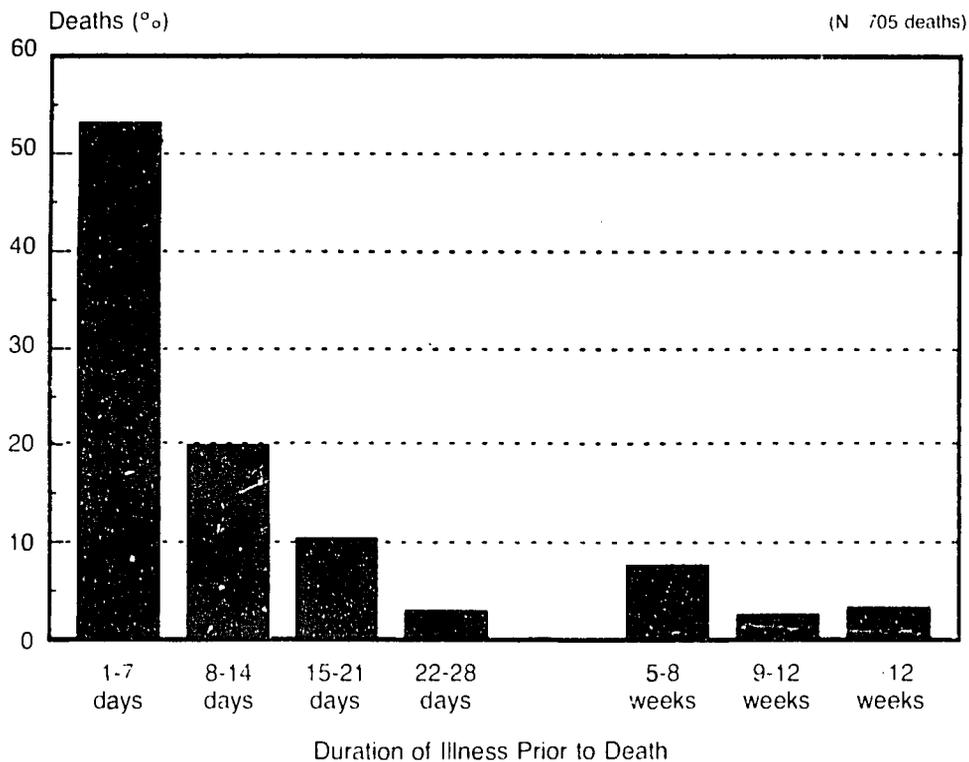


Table 48. Duration of illness leading to death by reported cause of death, MMRP, 1987-1990.

REPORTED CAUSE OF DEATH	NUMBER OF DEATHS	ILLNESS DURATION IN DAYS
		MEAN (SD)
RESPIRATORY	76	10.9 (14.1)
ANEMIA	22	20.3 (17.4)
FEVER	125	8.4 (16.0)
GASTROINTESTINAL	215	12.4 (18.9)
JAUNDICE	16	10.6 (15.6)
MALNUTRITION	31	44.7 (36.9)
MEASLES	73	15.8 (15.3)
SEPSIS/NEONATAL TETANUS	31	4.1 (3.0)
NEONATAL-OTHER	68	1.7 (2.1)
OTHER	28	11.8 (20.4)
UNKNOWN	40	3.3 (9.5)

The information on duration of disease prior to death was consistent with general knowledge about these diseases and conditions in the population. Deaths attributed to malnutrition, anemia, and measles were reported to have a long duration, and deaths attributed to sepsis or neonatal tetanus had a short duration. Deaths due to unknown causes were associated with very

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short illnesses; many of these were early neonatal deaths. Deaths associated with gastrointestinal, respiratory, or fever symptoms had preceding illnesses averaging 8-12 days.

Site of death

Overall, 54.2% of deaths occurred in a health facility, and the remainder occurred at home. Among deaths in the neonatal period, 47.5% occurred in the health facility; only 30.1% of deaths occurring in older infants were in health facilities. More than 65% of deaths due to respiratory disease, fever, gastroenteritis, malnutrition, measles, and sepsis occurred outside a health facility. Thus, in this environment and for these conditions, a reported pediatric death in a facility is indicative that two more deaths due to this condition occurred in the community. A higher proportion of deaths occurred in a health facility for only two conditions: neonatal deaths and anemia-associated deaths. This undoubtedly occurred because many neonatal deaths were in the first few days of life (prior to discharge for hospital-delivered babies) and because anemia was a diagnosis not commonly reported by parents unless the child had been admitted to a facility and diagnosed as having anemia by a health worker.

Effect of birth weight on cause of death

As noted above, birth weight was an important determinant of death in both the neonatal and postneonatal periods. Because of the large number of unknown causes of death in the neonatal period, we examined the role of birth weight on cause-specific mortality in the postneonatal period (Table 19). Mortality rates for diarrhea, fever, or malnutrition-associated deaths were nearly 1.5 to 2 times greater in LBW children than in children of normal birth weight; these causes accounted for 54 (77%) of the 71 postneonatal deaths in LBW infants. Postneonatal deaths attributed to respiratory disease were more common in normal birth-weight infants. Cause-specific mortality rates in infants of unknown birth weights (representing children born at home) generally fell between those rates observed for normal and LBW infants, except for deaths due to measles, which occurred twice as frequently in home-delivered infants and reportedly accounted for 13.6% of their deaths.

Table 19. Disease- and birth-weight-specific mortality rates in the postneonatal period, expressed as rate per 1000 live births (total # deaths in category), MMRP, 1987-1990.

	UNKNOWN BIRTH WEIGHT	VERY LOW (<1500 GM)	LOW (1500 - 2499 GM)	NORMAL (≥2500 GM)
TOTAL NUMBER LIVE BIRTHS IN CATEGORY:	1439	19	346	1650
RESP TRACT INFECTION	13.4 (19)	53 (1)	5.8 (2)	20.0 (33)
ANEMIA	3.5 (5)	0	2.9 (1)	7.3 (12)
FEVER ASSOCIATED	21.5 (31)	0	31.8 (11)	16.4 (27)
GI-DIARRHEAL	47.3 (68)	53 (1)	57.8 (20)	37.6 (62)
JAUNDICE	1.4 (2)	0	0	2.4 (4)
MALNUTRITION	4.2 (6)	0	8.7 (3)	3 (5)
MEASLES	14.6 (21)	0	8.7 (3)	7.9 (13)
SEPSIS/NEONATAL TETANUS	1.4 (2)	0	2.9 (1)	0

Summary findings:

The infant mortality rate was 162.7 per 1000 live births.

Diarrheal disease, fever-associated disease, respiratory disease, and measles were the most commonly reported causes of infant deaths. Deaths associated with respiratory disease were most common in the 2-6-month age group; deaths associated with diarrhea peaked in the 7-12-month age group. Deaths associated with febrile illness and measles increased with increasing age into the second year of life. Local data on death in hospitalized children suggest that death due to anemia is underreported by postmortem questioning of the family.

Approximately 70% of illnesses leading to death lasted less than 1 week. Deaths associated with malnutrition and anemia tended to have symptoms lasting for 3 or more weeks.

In this setting, approximately 35% of deaths occur in a health facility, and the remainder occur at home.

Low birth weight was a risk factor for mortality throughout the infant period.

H. SECOND-YEAR MORTALITY

A total of 142 children died during their second year of life; a crude estimate of second-year mortality was 76.9/1000 live births. However, this estimate is problematic; a large number of children were not followed through their entire second year of life, and the high proportion of lost-to-follow-ups may lead to inaccuracies in the crude estimate.

Cause-specific mortality in the second year of life: Postmortem questioning of the family showed diarrheal disease (30%), febrile illness (24%), measles (21%), respiratory illness (8%), and malnutrition (8%) to be the five leading reported causes of death during the second year of life. HIV-associated mortality is described in the following section.

Duration of illness prior to death: The mean duration of illness prior to death was 18 days; 58% of illnesses lasted ≤ 7 days before the child died. Febrile illnesses were associated with the shortest duration prior to death; 55% of children dying with an illness characterized primarily by fever died within 3 days of symptom onset. The mean duration of illness prior to death was longest for deaths attributed to malnutrition (60 days) and to anemia (15 days).

Effect of birth weight on cause of death: Among the 91 children with known birth weight who died after infancy, 20 (22%) had LBW. Children with LBW accounted for 40% of respiratory deaths, 33% of malnutrition deaths, and 29% of fever-associated deaths in the second year of life. Among the 40 deaths attributed to respiratory causes, malnutrition, or fever, 13 (33%) were in children with LBW. Of the 51 children dying of other causes, 7 (14%) were in children with LBW ($p = 0.03$).

I. EFFECT OF MATERNAL HIV ON BIRTH OUTCOME AND CHILD SURVIVAL

Outcomes of prior pregnancies and outcomes of the current pregnancy were compared for HIV+ and HIV- women.

Previous adverse reproductive outcomes: Women were asked about all previous pregnancies and adverse outcomes of those deliveries. When compared with HIV- women, HIV+ women were more likely to have experienced a second trimester abortion or stillbirth (4.8% versus 8.5%, OR = 1.66 [CI = 1.0-2.63]). Infant or childhood deaths were reported with similar frequency by HIV+ and HIV- women.

Birth weight: Birth weights of babies born to HIV+ women were significantly lower than those born to HIV- women. Because numerous factors may contribute to LBW in the population (e.g., parity, maternal nutritional status, malaria), the effect of HIV on birth weight was examined in a multivariate model. In the multivariate model, LBW was more common in babies born to HIV+ women than to HIV- women (OR = 2.62; CI = 1.47-4.08).¹⁴ The effect of HIV on birth weight appears to be primarily due to an increase in prematurity in babies born to HIV+ women.

Fetal loss: A total of 3987 women were enrolled at their first ANC visit and followed throughout their pregnancy to delivery. Among these women, 202 (5.1%) had a second or third trimester fetal death. The effect of HIV infection on fetal loss (i.e., second trimester abortion, fresh stillbirth, and macerated stillbirth) was then examined. Overall, HIV+ women (6.1%) were more likely to have a fetal death than HIV- women (4.8%) (OR = 1.5, CI = 0.76-2.19). However, on further examination, HIV+ women were more likely to have a fresh stillbirth (5.2% in HIV+ women and 3.0% in HIV- women, $p = 0.04$), but were not at any higher risk of having a second trimester abortion or a macerated stillbirth.

Neonatal mortality: Among 3706 women who delivered liveborn infants with known survival status after 28 days, 162 had infants who died in this neonatal interval for a NMR of 44/1000 live births. Compared with babies born to HIV- women, babies born to HIV+ women were more likely to die in the neonatal period (NMR = 43/1000 vs 53/1000, respectively); however, this difference was not statistically significant ($p = 0.48$). Thus, there is no evidence to suggest that NMRs were significantly higher in babies born to HIV+ mothers.

Postneonatal mortality: Among 3538 infants alive at 28 days with known survival status after 365 days, 397 died within 365 days, for a PNMR of 112/1000 infants. Postneonatal mortality rates were significantly higher in infants born to HIV+ women (PNMR = 242/1000) than in babies born to HIV- women (106/1000) ($p < 10^{-6}$).

Second-year mortality: Among 2893 infants born to mothers with known HIV serostatus and alive at 365 days, 1225 had known survival status after 730 days; 137 died during that interval for a crude second-year mortality rate of 112/1000 infants.¹⁵ Low birth weight was a significant risk factor for second-year mortality. Second-year mortality rates in children born to women with HIV infection were 209/1000 and for women without HIV infection, 106/1000, $p = 0.009$ (Table 50). HIV infection may have been associated with as much as 10% of all deaths in the second year of life.

¹⁴ Multiplicative interaction was observed with birth order where the effect of HIV on LBW was less in firstborns than in babies of higher birth order.

¹⁵ Because of the high number of children lost to follow-up, the crude second-year mortality rate may overestimate the actual second-year mortality rate. However, for the purposes of this analysis, crude rates in children born to women with and without HIV infection allow for a comparison of the effect of HIV on survival.

Table 50. Second-year child mortality rates by maternal HIV-1 serostatus, MMRP, 1987-1990.

SEROSTATUS	WOMEN TESTED	SECOND-YEAR DEATHS	
		NUMBER	(%)
HIV-1 SEROPOSITIVE	67	14	(20.9)
HIV-1 SERONEGATIVE	1158	123	(10.6)
TOTAL	1225	137	(11.2)

Cause of death: Causes of death among children born to seropositive mothers did not differ from those among children born to seronegative mothers during the neonatal period. During the postneonatal period, however, children born to HIV+ women had a higher risk of death associated with diarrhea or gastrointestinal disease than did children born to HIV- women (RR = 2.5, CI = 1.4-4.4, p = 0.002).

The effect of maternal HIV infection on postneonatal death was stratified by both birthweight and placental malaria infection status to control for potential confounding. After controlling for these factors, we found that children born to HIV+ mothers were at 2-fold higher risk of postneonatal death than children born to HIV- mothers (MH summary OR = 2.3, CI = 1.2-4.18, p = 0.009). Children born to HIV+ mothers had significantly increased odds of dying during the postneonatal period if also born with LBW (RR = 3.89, CI = 1.17-12.9, p = 0.025 compared with LBW children born to HIV- mothers) or if the mother had placental malaria infection (RR = 2.81, CI = 1.13-7.0, p = 0.028 compared with children born to seronegative, placentally-infected mothers). Furthermore, children born to HIV+ mothers with placental malaria infection were 11 times more likely to die during the postneonatal period than children born to HIV- mothers without placental malaria infection.

Summary findings:

In this investigation, HIV infection was shown to contribute to fresh stillbirths, to LBW babies, and to postneonatal infant mortality and second-year mortality, but not to neonatal mortality.

Compared with infants born to HIV- mothers, the infants born to HIV+ mothers had an approximate 2-fold increased risk of death after the neonatal period. This increased risk was seen particularly for those whose deaths were associated with a diarrheal illness. Malaria infection in a pregnant woman may confer an additional risk for death in babies born to HIV+ women.

J. MULTIPLE PREGNANCY

A multiple birth is a relatively infrequent event, but one that causes increased risk of morbidity and mortality both to the mother and to the fetuses. Women with multiple pregnancies are at increased risk for hypertensive disorders of pregnancy, placental abruption and previa, anemia, hyperemesis, and trauma or surgical intervention due to complications of labor and delivery (68). Infants of multiple pregnancies have 4-10 times the mortality rate of singleton births because of premature delivery, IUGR, placental and cord defects, and fetal distress and trauma from abnormal presentations in labor and delivery (69). The prevalence of twins varies widely, with the highest rates reported among the Yoruba people in Nigeria (45 per 1000 births [1 twin birth to 21 singleton births]) and the lowest rates among the Japanese (approximately 6 per 1000 births [1 twin birth to 172 singleton births]). Higher-order gestations (e.g., triplets, quadruplets) are more rare with prevalence rates of 0.4-2.1 per 1000 births (70-72). However, many of these estimates are based on small hospital-based studies, and population-based national estimates are usually available only from countries with reliable birth registration systems.

Few studies of perinatal mortality include multiple births, and cause-specific mortality analysis is usually limited to data from singleton births. The increased mortality and morbidity associated with multiple pregnancies could be an important cause of perinatal mortality in populations with relatively high prevalence rates and may be a cause that deserves more attention.

Prevalence of multiple pregnancies

Of the 4049 women enrolled in the MMRP for whom birth outcome is known, 87 (2.2%) had twins, and one had triplets. This is a ratio of 1 multiple birth to every 45 singleton births. Of the twins, 32 (36%) were the same sex, 39 (44%) were one of each sex, and 17 (19%) had one sex unknown in the pair. Type of twin (monozygotic versus dizygotic) is unknown.

Outcomes among infants of multiple pregnancies

Mortality was high. Of the 88 multiple births, both, or all three, of the infants either were still-born or died within the first year in 23% of the pregnancies; one of the infant pair died in 25% (Table 51). Only 33 (38%) of the mothers had both their infants survive up to 1 year. Of the 177 infants born as multiple births, 70 (40%) were either fetal or infant deaths compared with 768 (19%) of the 3962 singleton births ($p < .001$).

Table 51. Outcomes of 177 infants* born of multiple pregnancies, MMRP, 1987-1990.

OUTCOME	PREGNANCY N = 88	DEATHS*
BOTH SURVIVED	33 (38%)	0
BOTH OR ALL THREE DIED	20 (23%)	41
ONE SURVIVED & ONE DIED	22 (25%)	22
LOST TO FOLLOW-UP		
BOTH LOST TO FOLLOW-UP	5	—
ONE FETAL/INFANT DEATH & ONE LOST TO FOLLOW-UP	7	7
ONE SURVIVOR AND ONE LOST TO FOLLOW-UP	1	—

* 87 sets of twins and 1 set of triplets

Mortality rates among infants of multiple births compared with those among singletons: The risk of fetal or infant death for an infant of a multiple pregnancy was more than twice the risk for an infant of a single pregnancy. A significant difference was found in all time periods (Table 52). Perinatal mortality was increased 3.6 times and neonatal mortality 3.9 times for infants of multiple births compared with singletons. These findings are consistent with level of risk for multiple pregnancies reported in the United States (69,73). Of the 25 neonatal deaths, 18 (72%) occurred within the first 2 days of life compared with 60 (33%) among the 181 singleton neonatal deaths ($p < .001$).

Table 52. Mortality rates per 1000 live births and risk ratios for infants of single and multiple pregnancies, MMRP, 1987-1990.

	SINGLE PREGNANCY		MULTIPLE PREGNANCY		RISK RATIO ^b (95% CI)
	DEATHS/ BIRTHS ^a	RATE	DEATHS/ BIRTHS ^a	RATE	
INFANT DEATH	573/3521	163	48/137	350	2.15 (1.69, 2.74)
NEONATAL DEATH	181/3716	49	28/149	188	3.86 (2.68, 5.55)
POSTNEONATAL DEATH	392/3521	111	20/137	146	1.56 (1.04, 2.35)
PERINATAL DEATH ³	264/3866	68	41/165	248	3.64 (2.72, 4.86)

^a Number of births for which survival status was known at the end of the time period

^b Risk ratio and 95% confidence interval for death rate comparisons between multiple birth infants compared to singletons

Birth-weight distribution: Mortality rates among infants of LBW were higher than those of infants born at normal birth weights in all time periods during the first year of life. Because infants of multiple pregnancies are more likely to be smaller than infants of single pregnancies (73), the birth-weight distribution of the infants of multiple gestations may explain their higher mortality rates. Of the 120 (68%) infants with known birth weights, 90 (75%) were born with LBW compared with 18% (417/2263) among single births ($p < .001$). Also, 81% (38/47) of the deaths

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of the infants of multiple pregnancies were LBW as compared with 32% (118/369) of the deaths among singleton births ($p < .001$) (Table 5.3).

Table 5.3. Birth-weight distribution of infants of single and multiple pregnancies among all births and among infants who died during the study follow-up, MMRP, 1987-1990.

BIRTH-WEIGHT CATEGORY	SINGLE PREGNANCY		MULTIPLE PREGNANCY	
	ALL BIRTHS N = 3962	DEATHS N = 768	ALL BIRTHS N = 177	DEATHS N = 70
UNKNOWN	1699 (43%)	399 (52%)	57 (32%)	23 (33%)
KNOWN	2263	369	120	47
<1500 GM	27 (1%)	22 (6%)	17 (14%)	14 (30%)
1500-1999 GM	66 (3%)	33 (9%)	37 (31%)	13 (28%)
2000-2499 GM	324 (14%)	63 (17%)	36 (30%)	11 (23%)
≥2500 GM	1846 (82%)	251 (68%)	30 (25%)	9 (19%)

Birth-weight-specific infant mortality rates: To control for the difference in the birth-weight distribution, we compared birth-weight-specific mortality rates of the infants of multiple births with those of singletons. Most of the infants with reported birth weights were facility-based deliveries, whereas those with unknown birth weights were delivered at home. Birth-weight-specific infant mortality rates in babies of multiple pregnancies were significantly higher only for infants with birth weights ≥ 2500 grams (Table 5.4).

Table 5.4. Birth-weight-specific infant mortality rates and risk ratios for multiple and single pregnancies, MMRP, 1987-1990.

BIRTH-WEIGHT CATEGORY	SINGLE PREGNANCY		MULTIPLE PREGNANCY		RISK RATIO* (95% CI)
	DEATHS/ BIRTHS	RATE	DEATHS/ BIRTHS	RATE	
UNKNOWN WEIGHT	263/1472	179	10/38	263	1.47 (0.86, 2.54)
<1500 GM	15/19	789	11/14	786	1.00 (0.70, 1.42)
1500-1999 GM	25/55	455	11/31	355	0.78 (0.45, 1.36)
2000-2499 GM	55/296	186	9/29	310	1.67 (0.92, 3.02)
≥2500 GM	215/1679	128	7/25	280	2.09 (1.15, 4.05)

* Risk ratio and 95% confidence interval of mortality rates among multiple births compared with those of singletons.

The neonatal and postneonatal infant periods have different levels of risk and causes of mortality associated with them. When birth-weight-specific rates are compared for these periods (Tables 55 and 56), the mortality rate for multiple pregnancies is significantly different from the mortality rate in singleton infants only for infants with birth weights ≥ 2500 grams in the neonatal period, who have a risk almost five times that of singletons (Table 55). Although infants of multiple pregnancies had higher PNMRs in each birth-weight grouping than singletons, these differences were not significant (Table 56).

Table 55. Birth-weight-specific neonatal mortality rates per 1000 live births and risk ratios for multiple and single pregnancies, MMRP, 1987-1990.

BIRTH-WEIGHT CATEGORY	SINGLE PREGNANCY		MULTIPLE PREGNANCY		RISK RATIO (95% CI)
	DEATHS/BIRTHS	RATE	DEATHS/BIRTHS	RATE	
UNKNOWN WEIGHT	92/1543	60	10/41	244	4.07 (2.30, 7.26)
<1500 GM	13/20	650	9/14	643	0.99 (0.60, 1.64)
1500-1999 GM	16/58	276	3/34	88	0.32 (0.10, 1.02)
2000-2499 GM	18/309	58	3/34	88	1.51 (0.47, 4.88)
≥ 2500 GM	42/1786	24	3/26	115	4.79 (1.62, 14.82)

Table 56. Birth-weight-specific postneonatal mortality rates per 1000 live births and risk ratios for multiple and single pregnancies, MMRP, 1987-1990.

BIRTH-WEIGHT CATEGORY	SINGLE PREGNANCY		MULTIPLE PREGNANCY		RISK RATIO (95% CI)
	DEATHS/BIRTHS	RATE	DEATHS/BIRTHS	RATE	
UNKNOWN WEIGHT	171/1472	116	0/38	0	—
<1500 GM	2/19	105	2/14	143	1.36 (0.12, 15.96)
1500-1999 GM	9/55	164	8/31	258	1.58 (0.49, 5.06)
2000-2499 GM	37/296	125	6/29	207	1.66 (0.57, 4.54)
≥ 2500 GM	173/1679	103	4/25	160	1.55 (0.45, 4.77)

Birth-weight-specific perinatal mortality rates: The perinatal mortality rate is a common indicator of the level of health services and is also examined when there is concern that some early neonatal deaths are being misclassified as stillbirths (see Section VIII.B.). Once again, the perinatal mortality rate differed significantly between multiple and single birth infants only in the ≥ 2500 -gram birth-weight category (Table 57).

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Table 57. Birth-weight-specific perinatal mortality rates per 1000 fetal deaths and live births and risk ratios for multiple and single pregnancies, MMRP, 1987-1990.

BIRTH-WEIGHT CATEGORY	SINGLETON PREGNANCY		MULTIPLE PREGNANCY		RISK RATIO (95% CI)
	DEATHS/BIRTHS	RATE	DEATHS/BIRTHS	RATE	
UNKNOWN WEIGHT	146/1634	89	18/50	360	4.03 (2.70, 6.01)
<1500 GM	15/26	577	10/15	667	1.16 (0.71, 1.88)
1500-1999 GM	17/66	258	5/36	139	0.54 (0.22, 1.34)
2000-2499 GM	20/317	63	4/36	111	1.76 (0.64, 4.87)
≥2500 GM	66/1823	36	4/28	143	3.95 (1.54, 10.08)

Mortality rates among infants with unknown birth weight: Significant differences were also identified in all time periods for infants with unknown birth weights, primarily for infants who were delivered at home. Home delivery, in a setting where the risk status of the mother before and during labor and the skills of the birth attendant are not considered in the decision about delivery site, is associated with increased mortality. Because the birth weight of home-delivered infants is unknown, it is impossible to determine if the increased mortality of these infants, when compared with that of singletons, is due to the increased mortality associated with their smaller birth weight (birth-weight distribution), to the increased mortality associated with an inappropriate home delivery, or to a combination of both.

Summary findings and discussion:

In Malawi, multiple births were relatively common. This study documented the associated increased mortality in multiple pregnancies, even in infants who should have the lowest risk of mortality, those born with weights ≥2500 grams. Twins or triplets with birth weights ≥2500 grams were at more than twice the risk for perinatal death than singleton infants born with birth weights 2000-2499 grams. The lack of significant difference in the mortality among infants of multiple pregnancies with birth weights ≥2500 grams and singleton infants may be due to a true lack of a difference (LBW is more important than whether or not the infant was a single or multiple birth) or to insufficient sample size to detect a difference.

Because the birth-weight distribution of multiple births is skewed to the left (more babies born at LBW), interventions to increase their birth weight might be the strategy of choice. However, such interventions may be difficult to accomplish in a setting where women continue their farming, household, and child-care responsibilities throughout pregnancy.

Identification of a multiple pregnancy and advice to deliver in a health facility must continue to be emphasized. The causes of mortality among multiple pregnancies should be investigated further to provide information necessary to design specific interventions. Midwives, clinical officers, and physicians need the necessary knowledge and skills to manage pregnant women during the labor, delivery, and neonatal periods to reduce the risk for these infants.

K. DISCUSSION

Perinatal and infant mortality were high in the study population with rates of 68 per 1000 births and 163 per 1000 live births, respectively. Approximately 46% of the deaths occurred before birth or within 28 days of birth, and the remaining 54% occurred in the postneonatal infant period.

The perinatal and infant mortality rates were determined by two factors: the birth weight distribution of the infants and the birth-weight-specific mortality rates. Strategies to reduce mortality rates must address efforts to reduce the likelihood of infants being born into the lower birth-weight categories and efforts to reduce the mortality within the birth-weight categories. It is important to identify those strategies that will have the greatest effect on the reduction of mortality, given the available resources.

The risk of mortality among infants with birth weights ≥ 2500 grams increased in the perinatal, neonatal, and the postneonatal periods. Risk factors and the contribution of malaria during pregnancy to LBW and its components, prematurity and IU GR, were discussed earlier (Section VI.E., F., and G.).

Strategies to reduce birth-weight-specific mortality rates differ depending on the birth-weight category and the time of death. The highest mortality rates are among infants with birth weights ≤ 2000 grams. These infants are also primarily premature (91%). Once they are born, interventions to reduce the mortality among these infants will usually require a higher level of technology than is currently available in Malawi.

Of the LBW infants, 78% were in the 2000-2499-gram category, with perinatal, neonatal, and postneonatal mortality rates 1.2-2.5 times that of normal birth weight infants. Interventions to reduce the mortality among these infants are more likely to be less technologically sophisticated and available in Malawi. Improved quality and availability of care for these infants may also reduce the perinatal and neonatal mortality among the normal birth weight infants. The two higher birth-weight groups account for 96% of the births and 73% of the perinatal deaths.

Cause of death during the perinatal and neonatal periods is difficult to identify through verbal autopsy. However, syphilis in pregnancy, recognized by laboratory testing to identify reactive syphilis serologic results, has been identified as one of the most important contributors to perinatal mortality in this population and is addressed in Section VIII.C. First pregnancy, short stature, and home delivery were independently associated with perinatal mortality in this population. Further investigation into the preventable deaths in health facilities associated with first pregnancy and short stature, as well as the factors that increase the mortality among infants who deliver at home, is needed before interventions to reduce perinatal mortality associated with these risk factors can be identified.

Postneonatal mortality was high in Malawi. Compared with normal birth weight infants, infants with LBW were at increased risk for postneonatal death. Only 35% of the infants born with birth weight ≥ 1500 grams survived the neonatal period. This compares to 72%, 92%, and 96% of the infants in the 1500-1999-gram, 2000-2499-gram and ≥ 2500 -gram birth-weight categories, respectively. When cause of death in the postneonatal period was explored through verbal autopsy, diarrhea, febrile illness, or respiratory illness were reported to be the causes of death in more than 74% of the infants in the postneonatal period. Although the usefulness of post-mortem questioning to identify specific causes of death is limited, diseases characterized by these symptoms were important causes of mortality during this period. Further investigations should be conducted to identify direct and underlying causes of both neonatal and postneonatal mortality so that appropriate interventions can be better defined.

IX. MMRP RESULTS: MORBIDITY IN EARLY CHILDHOOD

A. MALARIA PARASITEMIA

Congenital malaria infection

We examined the incidence and consequences of congenital malaria infection in the cohort of infants born to women delivering in study maternity units. For the purposes of this evaluation, we defined congenital malaria infection as the presence of *P. falciparum* parasites in the umbilical cord blood of a newborn infant. (See Section VI.C. for information about the frequency of umbilical cord blood malaria infection). Congenital malaria illness was defined as umbilical cord blood parasitemia or parasitemia of the newborn with clinical signs of malaria (e.g., fever, altered feeding behavior, or irritability).

Umbilical cord parasitemia was detected in 7.1% overall; the likelihood of umbilical cord parasitemia was directly related to the density of parasites in the placenta (Table 14). When the density of placental infections was greater than 10,000 parasites mm^3 , 61% of newborns had evidence of umbilical cord blood parasitemia.

A group of 16 newborns with umbilical cord parasitemia was followed further to examine the natural history of this parasitemia and the frequency of developing associated clinical illnesses. Babies with umbilical cord parasitemia with a density of >500 parasites mm^3 were followed at 12, 24, 48, and 72 hours for thick blood smear and clinical evaluation. All peripheral and placental blood smears from their mothers demonstrated parasitemia (GMPDs: maternal = 2231, placental = 9605, and umbilical cord = 2490 parasites mm^3). Mothers' urines were examined for evidence of antimalarial drugs. No evidence of urine CQ was found in 56%, and 88% had <2 parts per million of urine CQ, suggesting that most women had not received CQ treatment within the previous 2 weeks. All (100%) of the 16 newborns were aparasitemic after 48 hours, and no clinical illness was observed within 72 hours of birth.

The findings suggest that in a setting where a high proportion of pregnant women are infected with *P. falciparum* malaria, their fetuses or newborns have a high probability of direct exposure to these parasites, but once the intrauterine exposure is ended, the newborn's peripheral blood is apparently cleared of parasites.

Malaria parasitemia in infancy

In malaria-endemic areas, infants are thought to be relatively well-protected against malaria during the first few months of life because of passively acquired immunity. Maternal malaria exposure during pregnancy might alter maternal production of antibodies and passive transfer of antibodies to the fetus, but it might also expose the fetus to passively transferred infected erythrocytes (see previous section on congenital malaria infection). We assessed prospectively the acquisition of malaria infection in an infant cohort and its relation to infant age, season of acquisition, season of birth, birth order, and maternal placental malaria infection.

Overall, 2470 children, representing 65.6% of the original birth cohort, had information on malaria smear positivity during the first year of life. All had at least one smear; 1378 (55.8%) were seen at least twice; 601 (24.3%) at least three times; 140 (5.7%) at least four times; and 18 (0.8%) infants were seen five times. The total number of follow-up visits for the 2470 children was 4607 (mean 1.9 visits per child).

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Visits occurred in approximately equal proportions throughout the first year of life (Table 58).

Table 58. Frequency of follow-up visits during infancy by age group, MMRP, 1988-1990.

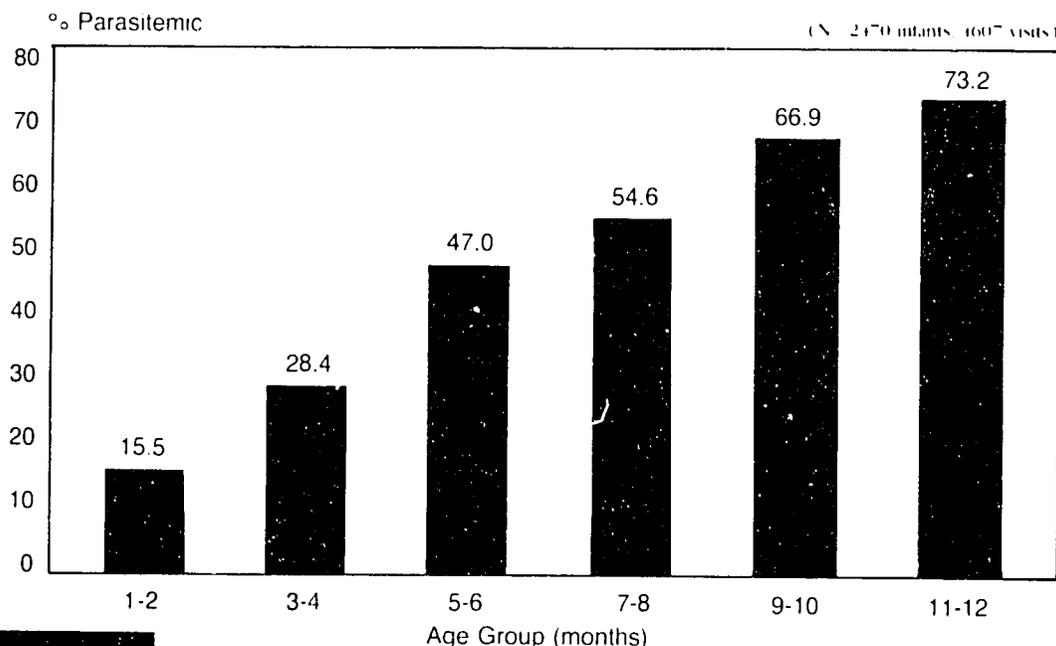
AGE GROUP (MONTHS)	NUMBER OF VISITS (%)
1 - 2	727 (15.8)
3 - 4	1142 (24.8)
5 - 6	702 (15.2)
7 - 8	737 (16.0)
9 - 10	623 (13.5)
11 - 12	676 (14.7)
TOTAL	4607 (100.0)

Among the 2470 infants, 732 (29.6%) were born to primigravidas, 581 (23.5%) to secundigravidas, and 1157 (46.8%) to women in their third or higher pregnancy. Among the infants whose mothers' malaria placental infection status was known at delivery, 1155 (80.6%) were born to mothers with uninfected placentas, and 275 (19.4%) were born to mothers who had malarial placental infection at delivery. Slightly more female infants (51.3%) than male infants (48.7%) were seen in follow-up.

Factors associated with parasitemia in infancy

Age: In the first year of life, increasing prevalence of parasitemia was highly correlated with increasing age. In the first 2 months of life, prevalence was 15.5%; this increased to 73.2% by age 11-12 months ($p < 0.001$) (Figure 32).

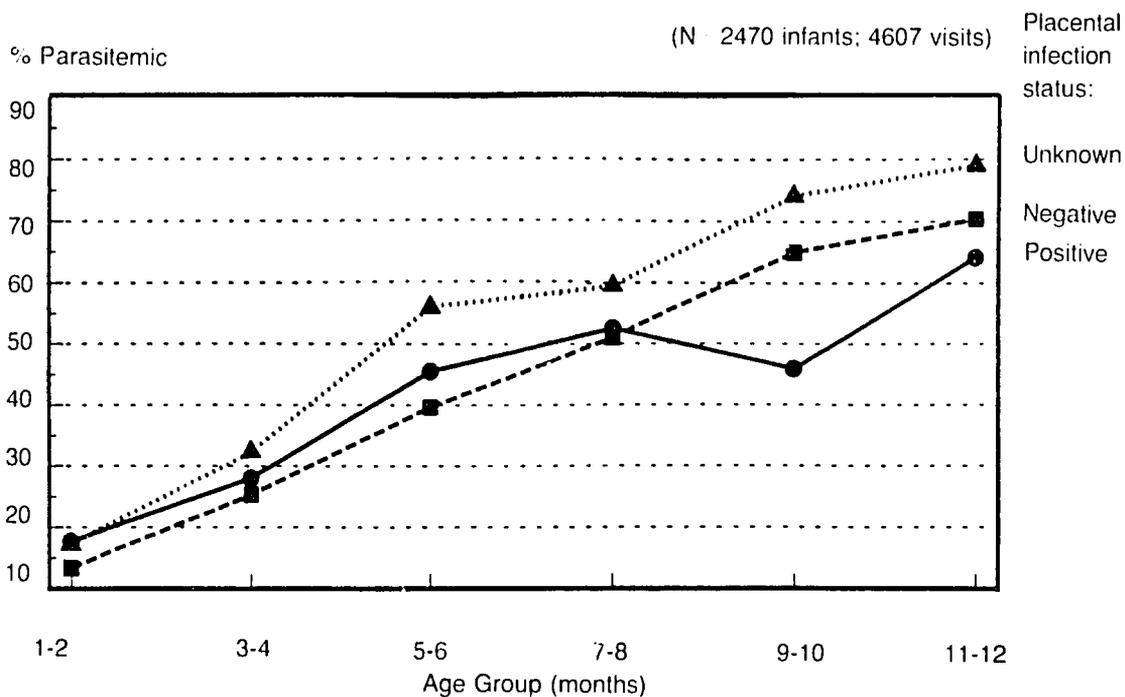
Figure 32. Infant parasite prevalence by age group, MMRP, 1987-1990.



Maternal placental malaria: The proportion of children with positive smears did not vary by the presence of maternal placental malaria. Of infants delivered to mothers with placental malaria infection, 928/2251 (41.6%) of smears were positive, compared with 215/532 (40.4%) of smears in infants born to mothers without placental malaria (MH chi-square, $P = 0.62$). The parasite prevalence in the first 6 months of life was slightly higher among those born to mothers with placental malaria infection than among those born to mothers with aparasitemic placentas, but these differences were not statistically significant (Figure 33). In the second 6 months of life, children born to women without malaria-infected placentas were more often smear positive than those born to women with placental malaria infection (MH summary chi-square, $P = 0.07$). Within particular age groups, the largest difference was noted in those ages 9-10 months; 195/300 (65.0%) of the blood smears of infants born to mothers without placental malaria were positive compared with 29/63 (46.0%) of smears of infants born to mothers with placental malaria (MH chi square, $P = 0.001$).

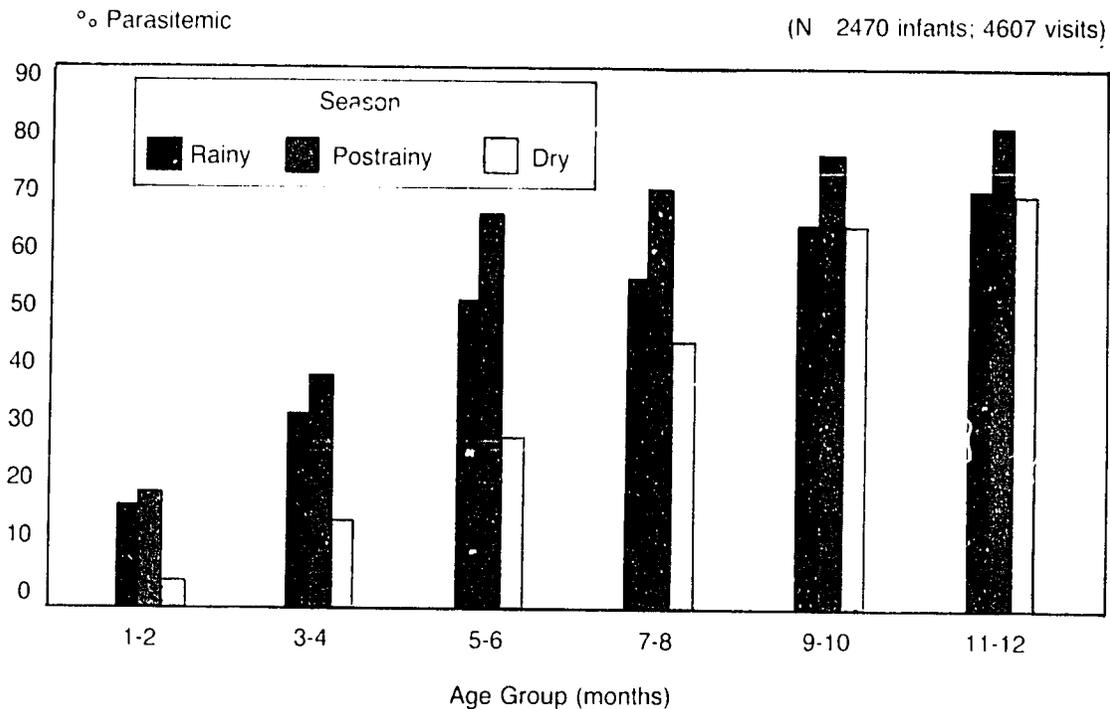
Interestingly, for all age groups, children born to mothers with unknown maternal placental malaria status had a significantly higher parasite prevalence than did children born to mothers with placental malaria infection (MH summary chi square, $P = 0.005$) or with placentas uninfected at delivery (MH summary chi square, $p = 0.0001$) (Figure 33).

Figure 33. Infant parasite prevalence by age group and placental malaria infection status, MMRP, 1987-1990.



Season of smear: The smear-positivity rates were 45.1% (871/1931) during the rainy season, 56.0% (729/1303) during the postrainy season, and 35.0% (181/517) during the dry season. Smear positivity varied by season within age groups (Figure 34). Highest positivity rates were seen in the postrainy season (May-August), with lowest rates generally in the dry season (September-December). Seasonal differences were more marked during the first 8 months of life; from 9-12 months, the smear-positivity rate ranged from 64% to 80%, regardless of season.

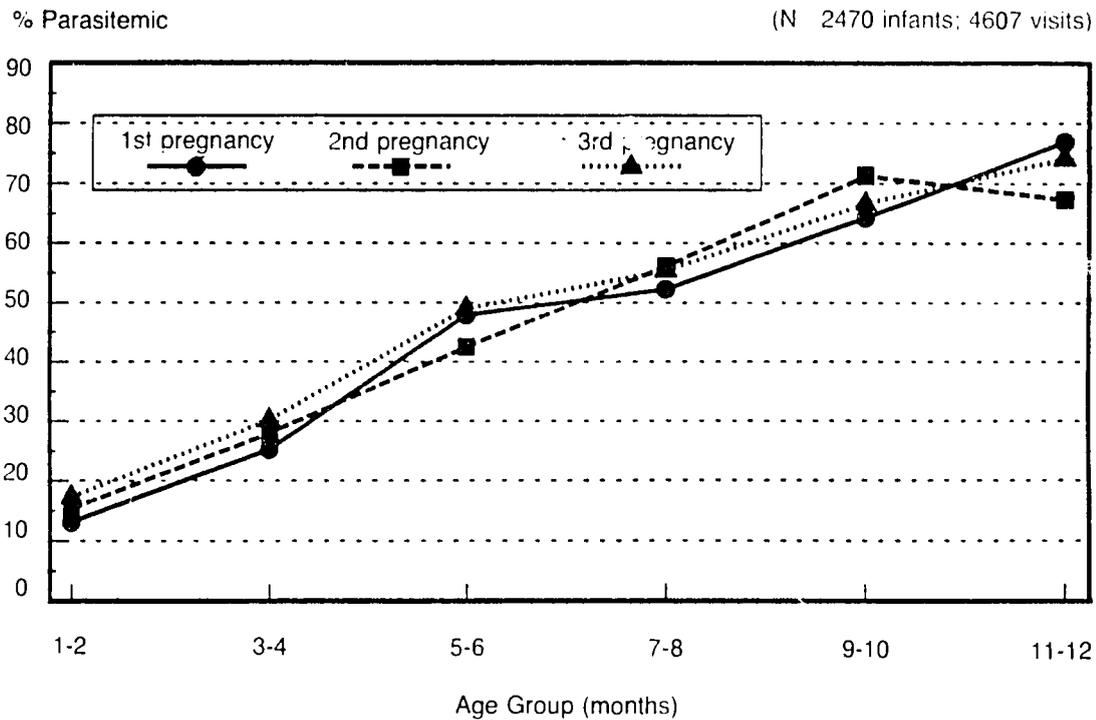
Figure 34. Infant parasite prevalence by age group and season, MMRP, 1987-1990.



The risk of a having a positive smear was significantly higher across all age groups in the post-rainy season compared with the dry season (MH-weighted OR 3.0, CI = 2.5-3.7, $p < 10^{-6}$). Similarly, the risk of smear positivity was elevated in the rainy season compared with the dry, although the difference was not as marked (MH-weighted OR 1.8, CI = 1.5-2.1, $p < 10^{-6}$). Of note, during the postrainy season, 19.4% of smears obtained in the first 2 months of life were positive, compared with 4.6% in this age group in the dry season (OR 5.0, CI = 2.0-14.3, $p < 10^{-6}$). Adjustment for season did not substantially alter the previously described relationship among smear positivity, age, and maternal placental malaria.

Maternal gravidity: Overall, smear-positivity rates were similar among infants delivered to primigravidas, 44.9% (618/1377), secundigravidas, 44.8% (506/1130), and women in their third or higher pregnancy, 45.8% (957/2100). When stratified by age, rates of infant smear positivity continued to be similar among women of different gravidities (Figure 35).

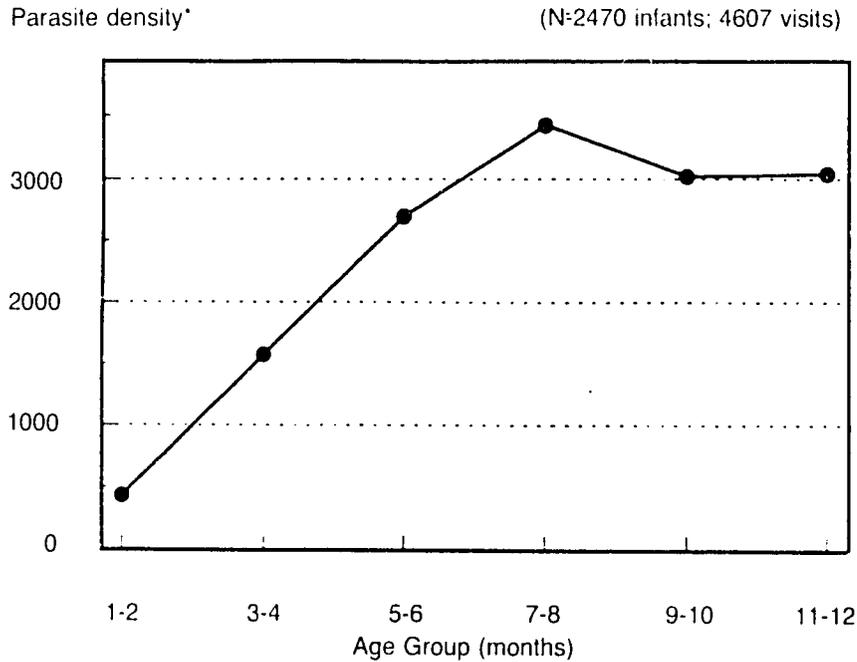
Figure 35. Infant parasite prevalence by age group and birth order, MM, 1987-1990.



Season of birth: The number and proportion of smears obtained from children born in the rainy (1473, 32.0%), postrainy (1779, 38.6%), and dry (1355, 29.4%) seasons were similar.

Density of parasitemia: Parasite density increased rapidly after 2 months of age (Figure 36). The increase was constant during the first 6 months of life, but then began to plateau after 7-8 months of age, remaining fairly constant through the remainder of infancy.

Figure 36. Geometric mean parasite density among infants by age group, MMRP, 1987-1990.



* Geometric mean (asexual parasites/mm³)

Summary findings:

These findings indicate that in this endemic area, malaria infection occurs early in infancy, with as many as 40% of infants parasitemic during the high transmission season by age 4 months; as many as 80% of infants aged 11-12 months are parasitemic during this period. Acquisition of parasitemia was strongly influenced by age and season. In early infancy (1-6 months), no consistent relationship was observed between maternal placental malaria infection status and infant parasitemia; however, in later infancy (7-12 months), there was a trend toward lower infection prevalence in infants born to mothers with malaria-infected placentas. When examined within age groups, birth order and season of birth did not substantially alter the prevalence of parasitemia during infancy.

B. ANEMIA IN INFANCY

Childhood anemia is increasingly recognized as a major public health problem in Africa (74-79). Recent studies on hospital management of severe anemia have identified blood transfusion as a major risk factor for HIV transmission and have documented the burden anemia places on health care facilities. Among hospitalized children, those with severe anemia are nearly 3 times as likely to die during hospitalization as those without severe anemia (76). Anemia appears to be much more common in children younger than 36 months of age and shows a sharp increase in prevalence between 2 and 6 months of age, the same age at which prevalence of malaria parasitemia increases (Malawi Ministry of Health, unpublished data, 1992). Rates of hospitalization for anemia also increase during the rainy season. These observations suggest that malaria plays a dominant role in the development of anemia in early childhood.

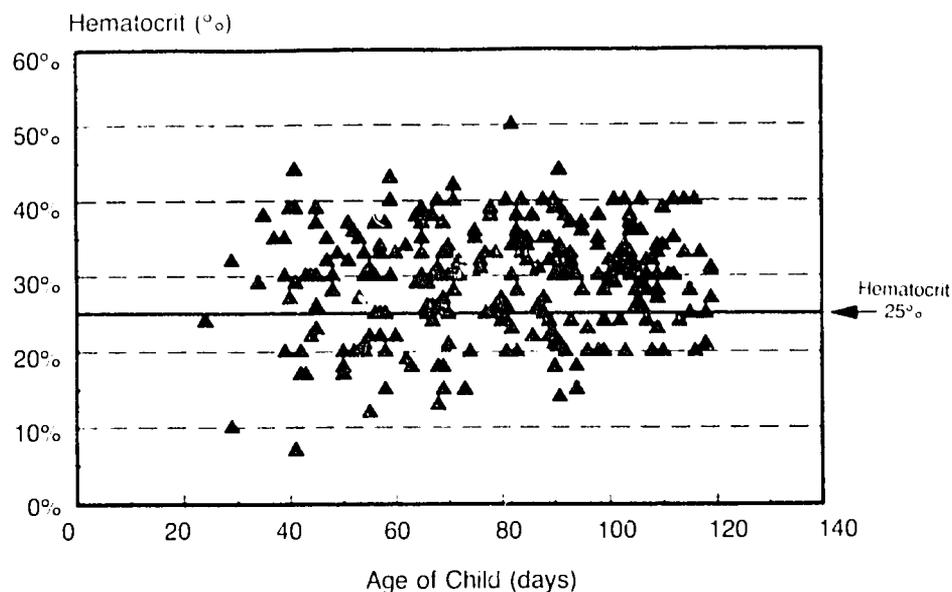
The pathophysiology of malaria-associated anemia is incompletely understood (80,81). Previous studies have suggested a complex pattern of increased destruction of erythrocytes, resulting from schizont rupture of erythrocytes, immune mechanisms (82), and dyserythropoiesis (83).

Children were included in the risk factor assessment of anemia if they were singleton births, were born in hospital, and had a hematocrit determination before reaching the age of 120 days. Characteristics of children with hematocrits below 25% were compared with those of children with hematocrits of 25% and higher.

A total of 253 children were seen before 120 days of age and had a hematocrit determination. The mean age (\pm SD) at the time of first follow-up visit for these 253 children was 78 (\pm 23) days. Of this group, 47% were male and their mean (\pm SD) birth weight was 2923 (\pm 435) grams. There were no differences between children enrolled and children seen in follow-up but not enrolled in mean age at first follow-up, proportion male, mean birth weight, or seasonal distribution of births.

The mean hematocrit (\pm SD) of the 253 children was 29.5% (\pm 7.2%) at first follow-up visit, and 65 children (25%) had hematocrit values below 25%. No relationship between age at the follow-up visit and hematocrit value was seen (Figure 37).

Figure 37. Age at first follow-up and hematocrit value, MMRP, 1987-1990.



Placental *P. falciparum* infection was the strongest risk factor for being anemic at first follow-up (Table 59). No other characteristic of the mother or the infant was statistically associated with the infant's anemia. The median hematocrit value for infants with malaria parasitemia was 28%, compared with 31% for those without parasitemia ($p=0.02$, Wilcoxon rank sums test). Infants who were born with placental malaria were no more likely to have *P. falciparum* infection at first follow-up than were infants without placental malaria.

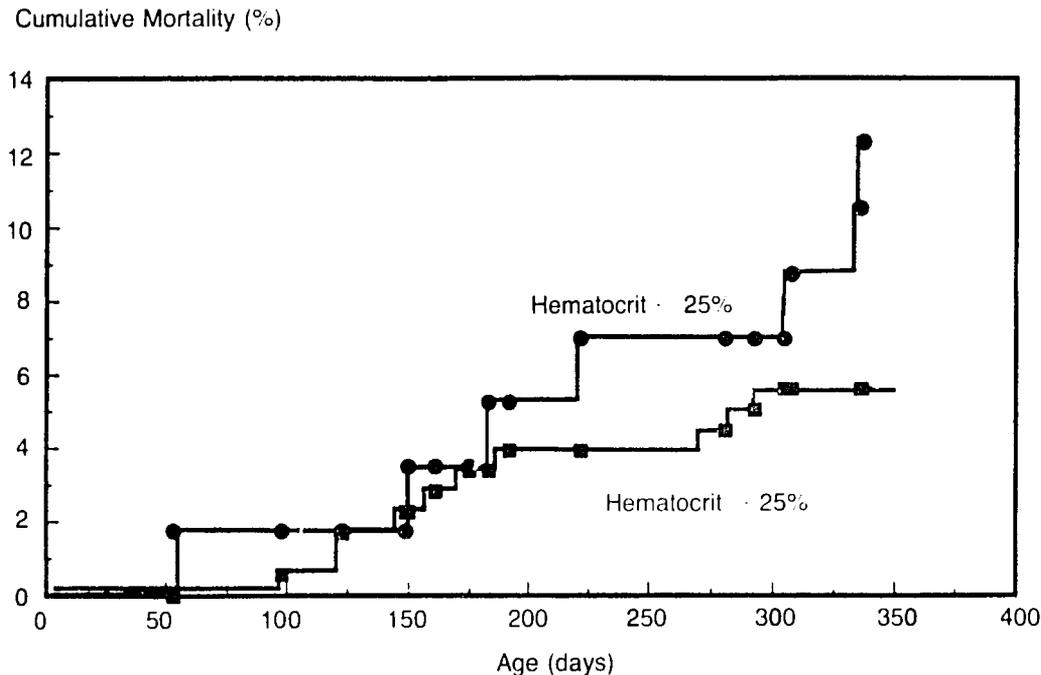
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Table 59. Risk factors for anemia at first infant follow-up visit, MMRP, 1988-1990.

RISK FACTOR	CHILDREN WITH HEMATOCRIT <25% AT FIRST FOLLOW-UP	CHILDREN WITH HEMATOCRIT ≥25% AT FIRST FOLLOW-UP	RELATIVE RISK FOR HAVING HEMATOCRIT <25% (95% CI)	P VALUE
PROPORTION WITH PLACENTAL MALARIA INFECTION	30%	15%	2.0 (1.3--3.0)	0.004
PROPORTION WITH ESTIMATED GESTATIONAL AGE 36 WEEKS OR LESS	10%	5%	1.7 (0.9--3.3)	0.21
PROPORTION WITH BIRTH WEIGHT BELOW 2500 G	11%	8%	1.3 (0.6--2.6)	0.58
PROPORTION WITH FEVER EPISODE SINCE BIRTH	16%	24%	0.7 (0.3--1.6)	0.51
PROPORTION WHOSE MOTHERS WERE PARA- SITEMIC AT ANTENATAL ENROLLMENT	41%	43%	0.9 (0.6--1.4)	0.68
PROPORTION WHOSE MOTHERS WERE PARA- SITEMIC AT DELIVERY	20%	15%	1.3 (0.8-2.2)	0.34
MEAN (±SD) HEMATOCRIT OF MOTHERS AT ANTENATAL ENROLLMENT	32% (7%)	33% (6.2%)	—	0.35
MEAN (±SD) HEMATO- CRIT OF MOTHERS AT DELIVERY	37% (9%)	37% (9%)	—	0.72

Among the 64 children with hematocrits below 25%, 7 (11%) died during the 1-year period of follow-up compared with 10 (5%) deaths among 189 children who had hematocrit values 25% and greater (RR 1.7, $p = 0.15$). Survival analysis showed a higher rate of death in children who were anemic at the first follow-up visit (Figure 38), but the difference in the two hazard curves was not statistically significant ($p = .13$). Among children who died, the mean age of death for 7 anemic children (227 days) was not significantly different from the mean age at death among the 10 children not anemic at first follow-up (190 days, $p = 0.28$, Wilcoxon rank sums test).

Figure 38. Proportion of children dying after first follow-up by hematocrit value at first follow-up, MMRP, 1987-1990.



Discussion

In this study, young infants experienced a lower nadir in hematocrit values than populations studied in the developed world. Although we did not measure hematocrit at birth in children in the study, the mean hematocrit value for 2,299 newborn infants born at this hospital was 66.9% (SD \pm 9.7%). Children born in Mangochi District appear to begin life with a hematologic status similar to that seen in the developed world, but they face a severe assault on the hematologic system early in life. In the current study, a high prevalence of anemia was found in children who were apparently healthy, and the levels of anemia described in hospitalized children were not limited to the select few who are typically brought to a health-care facility or who survive long enough to be hospitalized.

Placental infection was the strongest risk factor for being anemic at first follow-up. In a hospital-based study of anemia in children younger than 60 months of age, malnutrition, splenomegaly, history of fever, and parasitemia were associated with lower hematocrit (77). Although we did not perform detailed clinical evaluations on children at follow-up visits, children who experienced a febrile illness were no more likely to have hematocrit below 25% than those who had not had a febrile illness. Although malaria parasitemia was not associated with hematocrit below 25%, parasitemic children had lower hematocrit values than a parasitemic children. These data suggest that the onset of anemia in young children, even when related to acquired malaria infection, is frequently asymptomatic.

Placental malaria has been thought to affect child survival by reducing birth weight (1). In the current study, placental malaria had a stronger effect on hematologic status than LBW did and is thus independent of the effect LBW might have had on the child's hematologic status. This finding suggests another reason malaria programs should seek to reduce the rate of placental malaria infection by promoting malaria prevention during pregnancy.

Our study suggests that children with hematocrit values below 25% were more likely to die during the first year of life than children with higher hematocrit values, but because of the small sample size, this difference was not statistically significant. There was not a period of especially high risk after the first clinic visit, and the risk of death appeared to extend through the first year of life.

Innovative strategies to prevent malaria-associated anemia are needed. Our data suggest that treatment of febrile illness is unlikely to do so and that prophylaxis against malaria during pregnancy will be an important part of any approach to prevent anemia in young children. The association of parasitemia with lower hemoglobin in the absence of a similar association with febrile illness suggests that prevention, either through targeted prophylaxis or through personal protection measures, will also be needed.

Summary findings:

*Anemia is a common problem in severely ill, hospitalized infants in Africa, but little is known about anemia in nonhospitalized children. A total of 253 babies born to enrolled women were studied. At 2 months of age, the mean hematocrit of the 253 infants was 29.5%; 65 infants (25%) were anemic with hematocrit values below 25%. Placental malaria infection was associated with an infant having anemia at 2 months of age (RR = 2.0, $p = 0.003$). Infants who had *P. falciparum* parasitemia at age 2 months had lower hematocrit values than infants without parasitemia (median 28% versus 31%, $p = .02$). The mother's hematocrit at enrollment, her hematocrit at delivery, sex of the infant, and febrile illness in the infant were not associated with severe anemia. Although infants anemic at 2 months of age were more likely than nonanemic infants to die during the first year of life, this difference was not statistically significant (RR = 1.7, $p = 0.15$). In rural Malawi, anemia is a common problem in children, is acquired early in life, and is associated with an increased risk of death. Strategies to reduce severe anemia must address clinically silent *P. falciparum* infections, including placental malaria.*

X. PUBLIC HEALTH IMPLICATIONS OF STUDY FINDINGS

The results of the MMRP provide important definition to the problem of malaria in pregnancy, the population at risk, the requirements of an effective program, and the interactions between malaria and other diseases and conditions in pregnant women. The results of the MMRP also highlight factors that must be considered in the development of sound policy and strategies for malaria control in pregnant women in areas of high malaria transmission.

The MMRP clearly demonstrates that malaria in pregnant women is a risk for LBW due to both UGR and prematurity and that this is primarily seen in primigravidas and secundigravidas. In this highly endemic malarious area, the effect of malaria on the health of the woman (e.g., causing fever or anemia) may exist but is relatively less important and dramatic than the effect on LBW and its risk of infant mortality. Therefore, malaria management and prevention in pregnant women should be primarily considered a child survival intervention strategy in which prevention of malaria-associated LBW will reduce LBW-associated infant mortality.

The three most important factors determining which pregnant women will be infected with malaria are the woman's pregnancy number, the effectiveness of the antimalarial drug, and the transmission season. To be effective, control programs must identify an effective antimalarial drug and provide it to the at-risk women, those in their first or second pregnancies, especially during the high transmission seasons.

The MMRP also identified an interaction between HIV and malaria infection in pregnant women. HIV-infected women have higher rates and density of parasitemia and placental infection than women not infected with HIV, and the babies of HIV + women are more likely to have malaria infection in umbilical cord blood than babies born to women without the virus. Infant mortality is higher in babies born to HIV + women with placental malaria than in babies born to HIV + women without placental malaria. Although further evaluation of the cause of increased mortality is needed, the interaction requires increased efforts to recognize and manage HIV and malaria in pregnant women infected with both pathogens.

MALARIA PREVENTION IN PREGNANCY: POLICY AND PROGRAM CONSIDERATIONS

To formulate a sound policy for malaria management and prevention in pregnant women requires decisions:

- Who should receive an intervention;
- What is an effective intervention;
- What drug can be delivered to pregnant women and be safe, available, acceptable, affordable;
- What are the intervention's expected outcomes; and
- In what health delivery context should the intervention be provided.

Results of the MMRP provide important insights into several of these issues and may assist decision makers in the process of developing local or national policies in areas of similar malaria transmission in sub-Saharan Africa.

Who should receive an intervention? Results from the MMRP show that despite a high prevalence of parasitemia in pregnant women presenting at antenatal clinics, few women had a recent history of febrile illness that would lead to antimalarial treatment. In addition, while higher density parasitemias were associated with increased frequency of reported fever, fever was not a good predictor of parasitemia in this population. Thus, while antimalarial treatment for fever may

be important for the few women presenting with symptoms, a strategy to provide malaria treatment only to recently febrile pregnant women will not treat the majority of parasitemic women in the population. Consequently, malaria management and prevention efforts must be directed to both symptomatic and asymptomatic pregnant women.

This and other studies in Africa show that women in their first pregnancy are at highest risk of malaria infection and therefore represent an important target group for prevention. The prevalence of malaria parasitemia and placental malaria infection in pregnant women decreases with increasing pregnancy number, and women in their second pregnancies continue to have higher rates of malaria parasitemia and placental infection than women in later pregnancies. In addition, the incidence of LBW in the population is highest in firstborns, and decreases with increasing birth order. Finally, the link between malaria infection and LBW is most clearly seen in primigravidas, but may also exist for secundigravidas. As a consequence, the intervention should be targeted hierarchically: women in their first pregnancies constitute the primary group, women in their second pregnancies, the next most important, and finally, women in all subsequent pregnancies.

In the population of all pregnant women in this area of rural Malawi, 22.1% of pregnant women were primigravidas, 17.7% were secundigravidas, and the remaining 60.2% were multigravidas. Thus, the majority of the benefit of the intervention could be obtained by providing the intervention to less than 40% of the population of pregnant women.

What is an effective intervention? Results of the MMRP show that an effective intervention for malaria in pregnant women must clear parasites from the placenta. Clearance of parasites from the placenta apparently coincides with clearance of parasites in the umbilical cord blood and, for the most part, in the peripheral blood. It is the clearance of parasites from the placenta and umbilical cord that is associated with a reduction in the incidence of LBW and its subsequent risk to infant survival.

In the current studies, groups of women were treated with a therapeutic dose of either CQ (25 mg/kg in divided doses) or MQ (750 mg single dose). Mefloquine was shown to be significantly more effective than CQ in clearing parasites from peripheral, placental, and umbilical cord blood. In preliminary studies in 1987, the persistence of parasitemia 7 days after pregnant women were treated with CQ (27%) was approximately one-half the rate seen in children under the age of 5 years in the same site (57%) in 1986 and approximately equal to the rates in children age 5-9 years (27%) in 1986. The findings suggest that areas with CQ resistance in children may be expected to have CQ-resistant parasites in pregnant women and that the pattern of response may be similar to that of children aged 5-9 years. Thus, rates of CQ resistance in children may be useful in predicting the efficacy of CQ in pregnant women.

The clearance of parasites from the placenta and umbilical cord blood was associated with a reduced frequency of LBW in the population, including both preterm-LBW and IUGR-LBW. We conclude that an effective intervention to reduce LBW due to malaria in pregnancy must clear parasites from the placenta and umbilical cord blood and that, in this setting where CQ-resistant but MQ-sensitive *P. falciparum* has been documented, MQ is substantially more efficacious.

We also demonstrated that clearance of placental parasites is directly correlated with the frequency of LBW. In future attempts to examine antimalarial drug efficacy in pregnant women, clearance of parasites from the placenta or umbilical cord blood may be used as an outcome measure. In addition, peripheral parasitemia clearance may be used as a surrogate for placental parasite clearance. Public health officials may be able to use in vivo data from antimalarial drug efficacy studies in children as a proxy for parasite clearance in pregnant women.

In conclusion, the MMRP demonstrated that clearance of parasites is the critical issue in preventing LBW due to malaria in this setting. The actual name of the drug providing that clearance may change with changing patterns of parasite resistance, but the fundamental principle remains the same: the intervention must succeed in clearing placental and umbilical cord blood parasites.

What drug can be delivered to pregnant women and be safe, available, acceptable, and affordable? In addition to being efficacious and properly targeted to the at-risk population of pregnant women, the antimalarial drug must be safe, available, acceptable to the pregnant women, affordable to the women or the health-care system, and deliverable in a regimen convenient to the target population.

The ideal is a safe drug that provides complete clearance of parasites from the placental blood and has pharmacokinetic properties that allow intermittent treatment or chemoprophylaxis. Several drugs are available that share the characteristics demonstrated by mefloquine in this study. In areas where the drug is known to be highly efficacious in clearing malaria parasites, CQ (in settings like Haiti), SP combinations (e.g., sulfadoxine-pyrimethamine, sulfalene-pyrimethamine) in sub-Saharan Africa, and MQ have these properties. More recent studies conducted at the Mangochi study site (1991-1992) have demonstrated that a regimen of SP given as a treatment dose at the beginning of the second trimester and again at the beginning of the third trimester was highly effective in reducing malaria infection in mothers and their placentas. This regimen was also available in the country (approved in the national formulary and present in district medical pharmacies), affordable (its somewhat higher price was offset by the small number of doses required) and acceptable (women were accustomed to going to antenatal clinic and were willing to ingest this tasteless tablet).

Major challenges to increased program effectiveness include the availability of drugs and the need to obtain high coverage of the at-risk pregnant women. In some areas (e.g., rural Kenya), the primigravidas who are at highest risk of the effects of *P. falciparum* infection are the least likely to attend antenatal clinic for preventive services. Thus, strategies to increase their awareness of need for antenatal care and their access to and utilization of health services must be a high priority.

What are the intervention's expected outcomes? In the evaluation of survival of infants born with and without LBW, it is clear that birth weight is an important predictor of survival in both the neonatal and postneonatal periods of infancy. The MMRP was not designed to examine the effect of malaria prevention on the reduction in mortality during infancy, but extrapolations may be made. The attribution of approximately 12% of LBW to malaria in pregnant women and the risk of neonatal and postneonatal mortality associated with LBW suggest that the prevention of malaria in pregnancy is, indeed, a child survival intervention with a documentable outcome.

In what health delivery context should the intervention be provided? A number of conditions, risk factors and specific diseases lead to death in young children; LBW prevention is only one of a number of interventions which may improve child survival. Therefore, malaria and LBW prevention with an effective antimalarial drug should be provided as part of a package of services delivered through antenatal care programs.

Efforts to improve child survival in sub-Saharan Africa must take a broad perspective. The mother's health during pregnancy, at the time of delivery, and postpartum may determine as much as or more than 30% of the risk for child mortality in sub-Saharan Africa. Although treatment and prevention of *P. falciparum* infection in pregnancy was the focus of the MMRP, the studies identified a number of interrelated factors—infectious, nutritional, socioeconomic, and

educational—that must be addressed. All women should be screened for syphilis and treated if they have evidence of the infection. HIV is a growing problem; at this time no treatment strategy exists. Although sometimes based outside antenatal care programs, efforts to prevent neonatal tetanus (tetanus toxoid vaccine and clean delivery methods) must continue to be conducted in a schedule recommended by WHO. Improving micronutrient deficiency (e.g., iron and folate), improving general nutrition, and reducing caloric expenditure in pregnant women who often work in the fields must remain a priority. Access to antenatal care and to delivery attended by trained health care workers will significantly improve birth outcomes. Identification and referral of high-risk pregnancies and facility-based services (e.g., for blood transfusion or cesarian sections) will remain an important component of perinatal care. All of these factors must be addressed as a package if antenatal clinic services are to be effective in promoting maternal health care and improving newborn, infant, and child survival.

The development of malaria management and prevention programs in African settings requires several steps. First, the extent of malaria in pregnant women and LBW in their infants must be assessed, with attention to differences by gravidity and season. Secondly, existing programs for antenatal care services must be examined for current or potential inclusion of malaria prevention services and for current coverage of the at-risk population of pregnant women. Opportunities to reach and serve primigravidas and secundigravidas must be explored, possibly including the use of traditional birth attendants or other local health-extension workers to extend services to communities. Finally, an examination of potential impact and cost will be important as decisions for programming malaria prevention are formulated. The MMRP provides data on potential impact, and more recent work at the Magochi Research Station (not described in this report) suggests that incorporating an effective antimalarial drug and drug regimen in existing antenatal clinic services may be cost effective.

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