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The Risks and Severity of Malaria in Pregnant Women

Including a Summary of Current Field Research with Identification of Research Priorities Related to Appropriate Methods of Prevention of Malaria in Pregnancy

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SUMMARY

This analysis reviews the current state of knowledge on the effects of malaria in pregnancy in different conditions of malaria endemicity and the efficacy of malaria chemoprophylaxis in reducing morbidity and mortality associated with malaria in pregnancy. A summary of published studies on the epidemiology of malaria in pregnancy is outlined. The lack of information on delivery complications such as post-partum haemorrhage in relation to placental malaria is emphasized. The report assesses the potential effects of control measures on the outcome of pregnancy and on the incidence of associated complications, such as stillbirth, abortion, prematurity, intrauterine growth retardation and considers the effects of maternal prophylaxis on infant parasite rates.

The interactions of malaria and anaemia in pregnancy are assessed, and the efficacy of chemoprophylaxis in reducing anaemia in pregnancy. It reviews the accumulatory evidence that anaemia is not only a major cause of maternal mortality but has possibly direct effect on outcome of pregnancy in terms of birth weight, placenta to fetal weight ratios, cord haemoglobin values and infant parasite rates. It follows that studies estimating complication rates related to malaria in pregnancy need to control for the effects of anaemia.

The report summarizes current studies which may clarify some of the above issues drawing attention to the different methodologies and outcome variables. Priorities for future research are outlined which include: assessment of compliance with malaria chemoprophylaxis and attendance at maternal child health clinics; seasonal effects of variation in malaria prevalence; factors responsible for triggering severe haemolytic anaemia; maternal: new born interactions; maternal risk factors for infant parasitaemia; prevalence of abruptio placentae and post-partum haemorrhage in relation to placental malaria; classification of babies into wasted or stunted with anthropometry in the newborn and the use of ultrasound to measure utero-placental blood flow.

In low endemicity areas epidemiological studies are required, with a priority for clinical as well as immunological investigations. There is little information available from *P. vivax* endemic areas or locations where malaria is focal and unstable.

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INTRODUCTION

Malaria causes serious complications in pregnancy. In this report quantitative measures of the frequency of these complications are assessed in relation to the endemic conditions under which women are living. Quantitative measures of the relative benefits of malaria chemoprophylaxis are put forward. Several of the important publications on malaria in pregnancy were issued between 1950 and 1980. Since then there has been renewed interest in the epidemiology of malaria in pregnancy and in issues related to the alteration of host immunity to malaria which occurs in first pregnancies in semi-immune women.

With the emergence of chloroquine resistance to malaria an increased effort has been made to determine the therapeutic and prophylactic efficacy of alternative drug regimens in pregnancy. Some of these studies are currently under way, but where possible, descriptive details have been given in this report. There are compelling arguments for maintaining chemoprophylaxis as the mainstay of malaria control in pregnancy and controlled trials of antimalarials in pregnant women will be an important component of future research. This should be complemented by social research to find ways to maintain and improve compliance.

A second major problem which requires further research concerns the complications related to anaemia in pregnancy and how these are affected by iron deficiency which is prevalent in so many developing countries. The extent to which malaria control can reduce the risk of low-birth-weight* using drug treatment and chemoprophylaxis will vary in relation to the prevalence and causes of anaemia in women. Early pregnancy anaemia, which follows-on early pregnancy parasitaemia in primigravidae is highlighted as a special problem because of its potential consequences for fetal growth. Several indicators emphasize early pregnancy as the critical period for malaria control. The process of placentation itself may be abnormal with early gestational malaria.

There are several studies of malaria-specific immunity in pregnancy which mostly concern antibody-mediated responses. As the emphasis of this report is on "at-risk" approaches, with stress on research priorities in malaria control, it was felt a detailed discussion of immunological questions was inappropriate. However, this is an important area and there is sufficient information accumulating to present a separate review on this topic in the future.

The scope of the subject of malaria in pregnancy is wide. It forms a meeting place for research on epidemiology, parasite and nutritional interactions in relation to host immunity with potential benefits for mother and child with improved malaria control. With the increasing mobility of women and with early teenage marriage, specific problems arise. Re-location of whole populations in re-settlement schemes creates circumstances of acute public health importance.

* Low-birth-weight is defined as <2500 gms; preterm delivery as less than 37 weeks gestation. (*International Classification of Diseases, 9th Revision, 1978*)

SECTION I. EPIDEMIOLOGY OF MALARIA IN PREGNANCY

1. Parasitological observations

a) *Cross-sectional studies - Africa*

The epidemiology of malaria in pregnancy has been studied primarily in Western and sub-Saharan Africa in regions where malaria is either holoendemic or hyperendemic or in areas with marked seasonal transmission. The majority of investigations report cross-sectional studies of parasite prevalence at delivery. A summary of reports since 1950 is given in table 1 for rural and urban areas of Africa. Although comparison of studies is complicated by differences in prior antimalarial use and rural and urban locations of different study samples, nevertheless all studies demonstrate the increased susceptibility of primigravidae to malaria. In all of these reports the majority of infections are *P. falciparum.*

b) *Cross-sectional studies - Asia*

There appear to be no reports of cross-sectional surveys for this region. Four studies report case histories on hospital admissions living in areas mostly unstable for malaria. These reports concern pregnancy complications and are discussed in the next section *(12, 13, 14, 15).*

c) *Cross-sectional studies - Pacific and Oceania*

There are three reports from Papua New Guinea and a single report from the Solomon Islands. These New Guinea studies show comparable prevalence at delivery for all parities. Higher parasite rates are also reported for primigravidae *(16, 17) (Table 2).*

Thus epidemiological evidence from cross-sectional surveys indicates that parity influences susceptibility to malaria to an important degree. Parasite densities are also increased in the first pregnancy*(8).* This change in susceptibility may partly be age-dependent. However, McGregor *(8)* has pointed out that in many malarious countries the difference between mean ages at which first and second pregnancies occur is small, being probably less than 3 years in the Gambia. He concludes that it is difficult to understand how such minor age differences could materially influence the immune status of young women. Recovery from pregnancy-related *P. falciparum* parasitaemias in primigravidae may lead to improved host immunity, thus reducing susceptibility in later pregnancies *(19).*

d) *Longitudinal studies - Africa*

Two prospective studies from Ibadan, Nigeria have reported detailed parasitological data *(20, 21).* Gilles studied multiparous women followed during their first pregnancy. Of 38 women not given antimalarials until treatment made it necessary, 30 developed parasitaemia during pregnancy compared to 13 episodes in the same women before pregnancy. Parasitaemia occurred 4 to 12 times more frequently during pregnancy, than before, or than in the non-pregnant control group. Parasite density increased significantly during pregnancy (1775 parasites per mm^3 in 38 pregnant women; 140 parasites per mm^3 in these 38 women before conception).

Similarly Dada *(21)* observed a significant increase in parasite rates in primigravidae reaching 30%-40% above non-pregnant values. This increase was not observed in multiparae, whose parasite rates approached normal values in the general adult population. Parasite densities also showed a marked rise in primigravidae, particularly at the beginning of the third trimester when values similar to young children were found. This was not apparent in multigravidae. In primigravidae parasitaemia was present for prolonged periods of up to 9 weeks in 5 cases. Persistent parasitaemia and high parasite rates have also been reported by Fleming *et al. (22)* in primigravidae not receiving malaria prophylaxis in Zaria, Northern Nigeria.

In a study of 26 women unprotected with prophylaxis in rural Tanzania, Kortmann *(5)* showed that the parasite rate and density during pregnancy were about twice the values as after delivery. In particular, the number of heavy infections (> 1600 per mm^3 was much larger during pregnancy. The number of attacks of clinical malaria (i.e., patent parasitaemia and fever) during pregnancy was also much greater than after. In the studies by Kortmann, Fleming *et al.* and Gilles *et al.*, parasitaemia was virtually abolished in pregnant women receiving chemoprophylaxis.

Brabin *(19)* reported parasite rates at successive antenatal visits in women attending a rural antenatal clinic in Western Kenya. Monthly prophylactic chloroquine was administered (not weekly) as this was hospital policy. On this regime parasite rates were approximately halved *(23)*.

e) *Longitudinal studies - Central and South America.*

There is a single recent longitudinal study from Central America (El Salvador) reported by Campbell *et al. (24)*. In this region *P. vivax* occurs with almost equal frequency to *P. falciparum*. 55.8% of women had malaria at some stage of pregnancy. Differences by parity were not reported and comparison of pregnancy and non-pregnant study groups were not controlled for person-months of follow-up. Unusual findings in this study were that parasite prevalence was not influenced by gestational age despite a significant increase in parasite density in pregnant women. An increased risk of low-birth-weight was not observed but no data were given to evaluate this statement. This study is of importance for its serological findings.

f) *Longitudinal studies - Papua New Guinea*

620 women living under endemic conditions with year-round transmission in coastal rural Madang were followed while attending mobile antenatal clinics and receiving chloroquine prophylaxis. Susceptibility was increased in primigravidae to *P. falciparum* malaria but not other malaria species, with peak prevalence in primigravidae at 9-16 weeks gestation. Incidence of *P. falciparum* per person-month was 20% for primigravidae, 25% for secundigravidae, 17% for multigravidae (> 3 pregnancies), and 14% for non-pregnant multiparae. 8.7% primigravidae had persistent parasitaemia *(25)*.

In the Papua New Guinea study only small differences in prevalence were reported in women with a recent history of chloroquine use *(25)*. In a cross-sectional study in Zaire no difference in prevalence among women with a recent history of antimalarial drug use was

also observed *(11)*. This finding probably relates to the high level of chloroquine drug resistance in these areas *(26)*.

2. Gestational changes in parasite rates

In several studies parasitaemia rates at different stages of pregnancy in women attending ante-natal clinics have been reported *(19)*. Comparison is difficult between the studies because of the different gestational periods considered and none report prevalence in seasonal cohorts. These studies were undertaken in areas of perennial transmission and Pingoud *(27)*, Kortmann *(5)*, Bray and Anderson *(7)*, and Brabin *(19)* stated that women selected had not taken antimalarials.

The highest prevalence of infection in all these studies occurred in the second trimester with infection rates at delivery and in the postnatal period approximating to levels in non-pregnant women. In three of these studies peak prevalence is greater than 50% in mid-pregnancy for women of all parities. In Western Kenya Brabin *(19)* reported a peak prevalence at 13-16 weeks gestation in primigravidae (85.7%) and multigravidae (51.7%). The same investigators observed a peak prevalence at 9-16 weeks gestation in primigravidae (55.2%), but not multigravidae, attending rural antenatal clinics in Madang, Papua New Guinea. Placental infection rates also decrease with increasing gestational age *(28)*.

All of these studies indicated that *P. falciparum* prevalence increases in the first half of pregnancy in women living under holoendemic conditions, and that later in gestation prevalence decreases to about pre-pregnant levels. This pattern predominates in primigravidae. Data on incidence rates of *P. falciparum* during pregnancy further indicate that incidence remains uniform during gestation *(25)*, which suggests that there is a decrease in the recovery rate from infection from early in pregnancy which results in increased prevalence due to persistent parasitaemias.

Rapid spontaneous postpartum clearance of *P. falciparum* parasitaemia is described in women from Zaire, Malawi and Tanzania *(5, 29)*.

3. Gestational changes in spleen rates and size

There are a number of studies from Africa which report changes in spleen size and rates in pregnant women. All of these report an increase in spleen rate in pregnant women compared to non-pregnant controls *(Table 3)*. In the study from Papua New Guinea a significant increase in spleen rate occurred for all gravidae at 0-16 weeks gestation. Alteration in splenic function in early pregnancy may result in increased susceptibility to *P. falciparum* infection. Persistent parasitaemias may lead to chronic splenomegaly during pregnancy associated with haemolytic anaemia *(20, 30, 34)*. In Zaria, Nigeria, Fleming has estimated that 20% develop hypersplenism while 5% develop a haemolytic anaemia *(34)*. With recovery from pregnancy parasitaemia, spleen rates probably decrease. This is also associated with the development of the placenta as an alternative site for the accumulation of infected red cells, which could reduce the need for splenic clearance. Significant alterations in spleen rates and size during pregnancy have been reported by Kortmann *(5)* and Brabin *et al. (17)*, with lower spleen rates in late pregnancy.

4. Parasite species

The above studies refer principally to *P. falciparum* which is the commonest cause of malaria infection in pregnancy in Africa and Papua New Guinea. Other than the single study by Campbell *et al. (24)*, epidemiological observations have not been collected in areas where *P. vivax* is the main parasite species. In a study in Kampala, Uganda, where the predominant parasite found was *P. falciparum* 20.7% of placental smears showed the presence of *P. malariae* and 4.3% showed mixed infections of *P. falciparum* and *P. malariae (99)*. Evidence from case histories and reports from babies with congenital vivax malaria, suggest that relapses occur with *P. vivax* in mid-pregnancy. Examples are cases of infection with *P. vivax* and *P. malariae* occurring at four months gestation in immigrants in the United States several years after immigration. No exo-erythrocytic forms of *P. malariae* have been found; reappearance of parasitaemia with clinical symptoms after periods of latency is presumably due to the recrudescence of the primary attack from persistent erythrocytic forms of *P. malariae* in internal organs. The gestational age at relapse may be later than that for peak prevalence of *P. falciparum* under holoendemic conditions (13-16 weeks gestation). Numerous complications of vivax malaria in pregnancy are reported and these are discussed in a later section.

5. Effect of haemoglobinopathies

Brabin and Perrin *(35)* reported no significant difference in *P. falciparum* prevalence or density in subjects with HbAA or HbAS from Western Kenya. Molez *et al.* (personal communication) in Burkina Faso have also not observed a protective effect for those with HbAS. Fleming *et al. (36)* in Zaria, Nigeria reported a slight protective effect in primigravidae. There appears to be no further information on the influence of other haemoglobinopathies on malaria epidemiology during pregnancy.

Both Fleming *et al. (37)* and Kortmann *(5)* provide evidence that sickle cell trait affords some protection against the development of severe pregnancy anaemia in pregnancy associated with gross splenomegaly.

SECTION II. COMPLICATIONS OF MALARIA IN PREGNANCY

1. Anaemia

a) *Type and incidence*

Severe anaemia in pregnancy is a major obstetric problem in malaria endemic areas, where it is responsible for a large proportion of the maternal morbidity and mortality. Several studies have investigated the relationship between malaria, anaemia and pregnancy, and although different factors cause anaemia, the evidence implicates malaria as a major contributing factor.

Gilles *et al. (20)* reported a 63% incidence of anaemia in primigravidae not receiving antimalarials and compared with a small non-randomised control group demonstrated that administration of weekly antimalarial chemoprophylaxis prevented the haemolytic type of anaemia. The anaemia developed between the 16th and 24th weeks of gestation following the period of acute *P. falciparum* infection. The prevalence of anaemia in primigravidae is known to be higher in women from malaria endemic areas *(5, 38, 39)*, and this has been

significantly associated with the higher prevalence of malaria in primigravidae *(40)*. In general, parasite densities are too low to explain the degree of anaemia which occurs and persistent haemolysis could explain its occurrence in the absence of parasitaemia. Haemolysis would be expected to decrease after delivery when malaria prevalence falls, and this may partly explain the lower proportion of women screened post-natally with anaemia *(39)*. Haptoglobin levels are low in groups of pregnant women experiencing malaria in pregnancy indicating active haemolysis *(20, 41, 42)*. A definition of haemolytic anaemia in pregnancy should be used to enable comparison of its occurrence in different studies. There is a need to establish criteria by which haemolytic anaemia due to malaria can be distinguished. Coomb's test results rarely have been reported for anaemias associated with malaria in pregnancy *(43)*.

Figure 1 shows the pattern and prevalence of what is probably haemolytic anaemia for women experiencing early pregnancy parasitaemias. This association explains why there is no correlation in individuals between haemoglobin level and parasite density, as it is clearly possible for a person to have a high parasitaemia at the time of acute infection with a normal haemoglobin, or anaemia with a low parasite count. Equally it explains the apparently paradoxical observation that groups of individuals with malaria are likely to have anaemia.

Table 4 summarizes haemoglobin levels in studies reporting mean levels in pregnant women with and without malaria parasitaemia at delivery. Lower mean values are consistently observed in primigravidae and in groups with malaria. Conversely several studies have shown that prevention of anaemia is a major result of the protection against malaria *(5, 20, 22, 30)*. Low grade parasitaemias do not always produce anaemia *(5, 6, 44)*.

Folacin deficiency and megaloblastic anaemia is a well described complication of malaria in pregnancy *(34)* in Northern Nigeria. The consequences of folacin deficiency in pregnancy may lead to the development of megaloblastic haemopoiesis and anaemia. Marrow aspiration is required for certain diagnosis, particularly when iron deficiency, the invariable accompaniment of folacin deficiency in pregnancy, makes diagnosis of megaloblastosis difficult from peripheral blood *(45)*. Marrow aspiration shows that megaloblastosis is present in about one quarter of all pregnant women near term not taking folacin supplements. This has been demonstrated in the USA, Britain, Canada, South Africa, India and Iceland *(46)*. Malaria increases folacin requirements as reticulocytosis occurs secondary to malaria anaemia and this would explain the high prevalance in Nigeria.

In Western Kenya a high prevalence of low serum folacin levels have been reported in pregnant women experiencing malaria in pregnancy, although in that study serum folacin values had poor specificity for low red blood cell folacin concentrations. This is due to the high erythrocyte folacin concentrations which have been reported in malaria infected red cells in pregnant women. These high concentrations relate at least in part to reticulocytosis, as reticulocytes have high red cell folacin concentrations *(39)*. Allowance should be made for this in interpreting red cell folacin values in women from malaria endemic areas. In the Kenyan study megaloblastosis was not observed on peripheral smears, but the sensitivity of the peripheral smear is low in determining megaloblastosis in iron deficient women *(39)*.

b) *Episodes of anaemia and malaria chemoprophylaxis*

Kortmann *(5)*, Gilles *et al. (20)* and Fleming *et al. (22)* , have shown that pregnant women regularly protected with antimalarials do not become severely anaemic after commencement of malaria prophylaxis provided this is not started late in pregnancy. Both

Fleming *et al. (37)* and Kortmann *(5)* , provide good evidence that sickle cell trait affords a degree of protection against the development of severe anaemia, although pregnant women with the trait may still develop severe anaemia *(44)*. Interestingly Jilly *(44)* showed that the degree of anaemia was closely correlated to the extent of phagocytic activity observed in the placenta and in 4 of his patients the extent of phagocytosis and anaemia was extreme.

Protection against malaria also reduces the risk of megaloblastic anaemia resulting from increased folacin requirements due to erythropoiesis. In Fleming's study, in the group protected against malaria but not receiving folic acid supplements, the incidence of megaloblatosis was halved *(22)*.

c) *Episodes of severe anaemia and splenomegaly.*

There are two groups of women who are characterized by severe anaemia and splenomegaly associated with malaria in pregnancy. These are:

(i) A syndrome of acute severe haemolytic anaemia in pregnancy as described in Nigeria, Uganda and Tanzania *(5, 20, 34, 48, 49)*. This occurs in mid-pregnancy in many cases (as in figure 1) and is generally responsive to treatment which may include steriods.

(ii) Those with chronic splenomegaly, probably related to hyper-reactive malaria splenomegaly, as described in Uganda and Papua New Guinea *(16, 17, 50)*. Some of the cases from Nigeria which were unresponsive to treatment may be included this group.

Both types carry major complications in maternal mortality and morbidity. Severe acute haemolytic anaemias usually respond to steroids and antimalarials, although the syndrome is likely to recur in subsequent pregnancies. Those patients who are non-responsive, although presenting with an acute haemolytic process in pregnancy, are likely to be characterized by chronic splenomegaly *(49, 50)*.

Severe anaemia may develop in pregnancy in women with or without persistent splenomegaly and other causes such as iron or folacin deficiency should be considered. Good evidence of the importance of splenomegaly in producing pregnancy anaemia is shown in *Table 5* which summarizes data from a longitudinal pregnancy study in Papua New Guinea *(30)*. A significant reduction in mean haemoglobin concentration occurs with increasing spleen size. In this study population 44% of primigravidae and 29% of multigravidae had severe anaemia (Hb less than 8 gm. dl) at booking before receiving antimalarials or iron and folic acid supplements. Splenomegaly appears a more important cause of anaemia in primigravidae than multigravidae.

2. Low birthweight and pre-term delivery

a) *Population risk of low birthweight in primigravidae due to malaria*

More than one hundred years ago an effect of malaria during pregnancy on birthweight was proposed *(52)*. *Table 6* summarizes studies reporting the effect of placental infection on birthweight (from *WHO Bulletin, 61; 1005, 1983*). Birthweight differences between babies of mothers infected or non-infected at delivery are variable but in all studies lower mean birthweights are associated with placental malaria. Significant differences in mean birthweight

values have been reported only for primigravidae *(8)*. Jelliffe *(4)* and Kortmann *(5)* have also reported greater differences in mean birthweight for primigravidae (321 gms and 636 gms respectively).

Kramer *(56)* has estimated the magnitude of the effect of malaria on birthweight at a population level. Utilizing McGregor's data he estimates a 170 gm deficit among women with placental malaria, and an associated placental malaria infection rate of 20.2%. The overall effect on a population with this rate of placental infection would then be 170 x 0.202 or about 34 gms per pregnancy. Kramer points out that this estimate is much lower than the 147 gm increase in birthweight observed in a study from the Solomon Islands following introduction of malaria control measures which would have protected women throughout pregnancy *(57)*. If low birthweight is the result of an effect on fetal growth (and the evidence is that it is, under conditions of holo- or hyperendemic malaria, *vide infra*), then intervention studies that protect the mother throughout pregnancy might be expected to show greater differences in mean birthweight values between treated and untreated groups. An important problem with Kramer's population estimate is that it takes no account of an effect of malaria on fetal growth in early pregnancy in women who may have become aparasitaemic by the time of delivery, either due to treatment or immune clearance.

For this reason it is useful to examine the relative risk for low birthweight (< 2500 gms) in primigravidae as a group irrespective of malaria positivity at delivery. The relative risk is defined as the ratio of risk of low birthweight among primigravidae compared to the risk among multigravidae. A useful method for doing this is to calculate the relative risk from the same population living under the same malaria endemic conditions. The increased risk of low birthweight in primiparae can then be compared in areas with differing levels of malaria endemicity and to populations from non-endemic malaria areas. The important point is that malaria is the only known specific environmental factor which selectively depresses birthweight to a greater extent in primigravidae than multigravidae, and this relates to the much higher prevalence and density of malaria in primigravidae. Smoking, nutritional deprivation and pre-eclampsia are not thought to have such a parity-specific effect on fetal growth, although pre-eclampsia has a higher prevalence in primigravidae.

The relative risk for low birthweight associated with primiparity in regions where malaria is not a problem is about 1.23 *(56)*. This figure was calculated from 4 studies with a total sample size of 142,259. The equivalent value for the relative risk for coastal Papua New Guinea was more than double at 2.9 (95% confidence limits; 1.9-4.5). By way of comparison McGregor *et al. (8)* report the incidence of low birthweight by parity in urban and rural Gambia and calculation from their data of the relative risk for low birthweight which is associated with primiparity gives values of 1.4 for the urban sample ($P < 0.06$) and 2.9 for the rural sample ($P < 0.0001$). The latter value is comparable to that calculated for coastal Papua New Guinea. This may indicate that malaria in primigravidae has an equivalent effect in reducing fetal growth even in populations with considerable differences in average birth size *(58)*.

The population attributable risk for low birthweight in primigravidae due to malaria is about 30% for coastal Papua New Guinea and rural Gambia. Other estimates for this population attributable risk in rural endemic malaria regions of sub-Saharan Africa range from 9-40% *(58)*. This risk is related to the proportion of primigravidae in the population and the parasite prevalence in primigravidae. There is a significant association between population

attributable risk of low birthweight in primigravidae and parasite rates in primigravidae at delivery *(58)*. These findings indicate that malaria is an important associated factor related to the incidence of low birthweight in primigravidae living in malaria endemic areas. These estimates are larger than predicted by Kramer.

b) *Assessment of gestational age*

Few studies of the effects of malaria in pregnancy on outcome of pregnancy have controlled for gestational age utilizing the Dubowitz assessment of gestational maturity *(59)*. Reinhardt *et al. (6)* in a study from the Ivory Coast reported impairment of fetal growth for primiparae, and Watkinson *et al. (60)* in a study from the Gambia showed preterm deliveries were not increased in the group with malaria infected placenta. A recent study of 600 pregnant women in Madang, Papua New Guinea did not report an increased risk for preterm delivery in primigravidae compared to multigravidae. The overall percentage of pre-term deliveries (< 10%) was comparable to that for the United States *(61)* and England *(62)*. The high prevalence of severe anaemia and malaria in this New Guinea population does not therefore lead to a significant increase in premature labour. Conversely there was a high rate for intra-uterine growth retardation, which was 37% for primigravidae and 19% for multigravidae. The outcome in these areas of high endemicity is different from areas of low endemicity. In non-immune women for example, the risk for preterm delivery is significantly increased. This aspect is reviewed in the section on perinatal mortality.

3. Fetal and perinatal mortality

a) *Preterm delivery in non-immune women*

Premature and false labour occur in malarious mothers *(38, 44, 63)*, although the incidence of preterm delivery is likely to be significantly increased only in non-immune mothers or those with a low level of acquired immunity. A high risk for preterm delivery (54.5%) was reported by Wickramasuriya *(64)* during the Ceylon epidemic of 1935. A 49% risk for preterm delivery was reported by Le Van Hung *(13)* in 130 selected hospital patients in Saigon, although this sample probably included small for gestational age babies. Premature labour occurred following both *P. falciparum* and *P. vivax* infections, and many of the women were known to have low malaria immunity. In Zimbabwe, of 61 women with probable low levels of immunity, 50% went into premature labour (< 38 weeks gestation) *(65)*. In this study the induction of premature labour was significantly more likely after presenting with malaria in the third than in the second trimester (50% v 17%). Under conditions of year round transmission in Papua New Guinea, premature labour (< 37 weeks gestation) occurred in less than 10% of women. The rate was increased in primigra-vidae severely anaemic (< 8 gms. dl) at booking, compared to those not severely anaemic (17% v 9%) *(30)*.

b) *Stillbirth rates*

In the last century it was considered that stillbirths frequently complicated malaria in pregnancy *(66)*. Since that time numerous case studies have reported fetal malaria in stillborn babies *(67)*. In a proportion of these cases fetal malaria was demonstrable at autopsy. In these cases with intra-uterine transmission, the causes of intra-uterine death relate to massive infection of the placenta, persistently high fevers and possibly a failure of successful placentation. This situation is uncommon and occurs chiefly in severe and untreated *P. falciparum* infection. In the Ceylon epidemic there were 13.4% fresh stillbirths and 10.2% macerated stillbirths in 253 women experiencing acute malaria *(64)*. In Malaysia in women with low

immunity, the rate was 22.7% (5 out of 22 women) (14). For 61 patients with acute malaria living in mostly urban areas of Zimbabwe, 2 still births were reported (3.8%) *(65)*. In Chandigarh, India of 78 cases of pregnancy malaria (59%, *P. vivax*) there were 4 stillbirths (5%) *(15)*.

In *Table 7* comparative stillbirth rates are summarized for studies reporting data from areas with seasonal or holoendemic malaria. In all of these studies, except for urban Gambia, higher stillbirth rates are observed in primigravidae. In rural Gambia the stillbirth rates are significantly increased in primigravidae ($p = 0.0002$; *Table 8)*. These higher rates are observed for women with or without placental malaria at delivery, and are higher than reported elsewhere. Greenwood *et al. (47)* also have observed significantly more stillbirth or neonatal deaths among primigravidae (11.5%) than among multigravidae (5.6%). In a recent study from rural Gambia of a smaller study sample of women followed prospectively, 3.5% of 672 women experienced stillbirths *(68)*. In urban Gambia (Banjul) higher stillbirth rates were not observed in primigravidae *(Table 9)*. However primigravidae had significantly higher stillbirth rates if placental malaria was present at delivery *(Table 9)*. Similarly Greenwood *et al.* observed in rural Gambia that a bad outcome (stillbirths or neonatal deaths) was recorded in a lower proportion of primigravidae who had taken Maloprim (8.1%) than among primigravidae who had taken placebo *(47)*.

Kasaje *et al. (69)*, in a review of 92 pregnancy histories of women from Western Kenya, report that malaria was the most frequent problem preceding the last stillbirth. The stillbirth rate was 9.8%. Correa *et al. (138)* reported a stillbirth rate of 11% in urban Senegal. Blacklock and Gordon *(70)* also found a positive correlation between maternal infection of the placenta with malaria and death of the child *in utero* or shortly after birth. A recent study of displaced Khmers on the Thai-Kampuchean border reported a stillbirth rate of 5.2% in 193 pregnant women with falciparum malaria, although parity was not reported *(139)*.

This evidence suggests that placental malaria may have an important effect on increasing the risk of stillbirth particularly in primigravidae in rural areas. In women with lower immunity, stillbirth rates would also be increased in multigravidae as observed in urban Gambia. In non-endemic malaria areas stillbirth rates are not increased in primigravidae *(62)*. In immigrant Negroid and Asian populations in the Netherlands, stillbirth rates ranged from 1.5% to 2.6% for data collected over a 10 year period *(71)*.

Seasonal differences in stillbirth rates do not reach statistical significance in either urban or rural Gambia, although the lowest stillbirth rates (all parities) occur for the 3 month period of the late dry season when placental malaria has the lowest prevalence *(8)*. Greenwood *et al.* also did not observe a seasonal difference in stillbirth rates in rural Gambia (Farafenni). However placental malaria is still frequently observed in women delivering during the dry season from rural areas in the Gambia *(8)*.

c) *Miscarriage rates*

Garnham *(72)* concluded that the incidence of miscarriage varies inversely with the degree of immunity of the mother. In table 10 high miscarriage rates are reported for non-immunes or for those with low immunity. Under these circumstances 60% of pregnancies may miscarry. Correa *et al. (138)* in a large sample of febrile women from urban Senegal reported a miscarriage rate of 23.7%, although only 9.5% of these were parasitaemic.

Steketee *et al. (11)*, in a retrospective study, reported an 8% rate with no difference in rates by parity until the seventh or subsequent pregnancy. These women were semi-immune and some may have received antimalarials. A similar miscarriage rate in semi-immunes has been reported in several early studies summarized by Laffont and reported by Le Van Hung *(13)*.

Because, under holoendemic conditions, there is a high parasite rate, especially in primigravidae in the first half of pregnancy, an association between parasitaemia and miscarriage would be unlikely, as most primigravidae - whether experiencing abortion or not - would demonstrate parasitaemia before 20 weeks gestation. In general, there is possibly a 5-10% risk per pregnancy in women living under holoendemic conditions. Few women report their pregnancies until after the first trimester and in retrospective studies under-reporting is very likely. Low rates have been reported by Reinhardt *et al. (6)* for the Ivory Coast (2.8%) and by Greenwood *et al. (68)* for rural Gambia (1.5%).

4. Maternal anaemia and perinatal mortality

a) *Perinatal mortality*

There is compelling evidence that risk of perinatal death increases in severely anaemic women. *Table 11* summarizes four studies from malaria endemic areas. There is good agreement between the studies for perinatal mortality risk in severely anaemic women. Fleming also observed that fetal survival was greatly increased in mothers with severe anaemia who were successfully treated for anaemia at least six weeks before delivery compared to those untreated at the time of delivery *(34)*. In non-endemic areas perinatal mortality also increases with anaemia. The British perinatal mortality survey of 1958 showed that a haemoglobin concentration of 8.9 gm. dl was associated with a 2-fold greater risk of perinatal death *(62)*.

In Papua New Guinea 44% of primigravidae and 29% of multigravidae attending clinics for the first time in the last trimester were severely anaemic (Hb <8 g. dl) *(30)*. Primigravidae were more at risk of severe anaemia if parasitaemic.

b) *Stillbirth rates*

Table 12 summarizes data for the risk of stillbirth in relation to maternal anaemia. All of these studies are from malaria endemic areas and McGregor (M.W.) reported higher stillbirth rates in those with severe anaemia and concurrent malaria parasitaemia. Stillbirth rates in pregnant African women with megaloblastosis and iron deficiency anaemias have been reported as 12% and 5% respectively *(78)*. The former is a frequent secondary complication of malaria in pregnancy in women on marginal folacin intake, and the latter is a common associated condition.

c) *Maternal mortality*

(i) *Mortality with low maternal immunity*

In non-immunes maternal mortality is high. Torpin *(63)* reported a 4% risk for a small series with acute malaria in the United States and a similar rate has recently been reported in India *(15)*. In the Ceylon epidemic the figure reached 13.1% of 358 treated

cases. In Malaysia, in women with low immunity, a comparable figure has been reported (13.6%) *(14)*. In Thailand *P. falciparum* malaria is the commonest cause of maternal mortality and is often complicated by cerebral malaria. In a recent study of Thai-Kampuchean migrants a 10% case fatality rate was reported for pregnant women with malaria *(139)*.

(ii) *Mortality and severe anaemia in semi-immune women.*

The importance of anaemia in increasing risk is demonstrated in table 13. In anaemic women the danger of postpartum haemorrhage leading to maternal death is greatly increased. In women in coastal Papua New Guinea, rural Gambia, Tanzania and Nigeria, postpartum haemorrhage is an important cause of maternal death *(30, 68, 79)*. Maternal mortality is also associated with severe anaemia in non-endemic areas *(80)*.

5. Cerebral malaria

It is frequently stated that in subjects with low levels of immunity cerebral malaria is more frequent in pregnant than non-pregnant women, although the evidence for this is not substantiated. This information is not easily attainable. High pregnancy rates are shown in table 14 in groups of pregnant women with acute malaria, but with low pre-pregnancy immunity. The high associated mortality is shown in four of these studies. The zero mortality in the Herd and Jordan report *(65)* is in contrast to the other series. Improvement in treatment regimes may partly explain this. In Thailand, 50% of pregnant women who become unrousable during the course of falciparum malaria die, and the fetus is stillborn in most of these cases irrespective of maternal outcome (Warrell *et al.*, unpublished observations). Stillbirth associated with cerebral malaria in pregnancy is also reported from Senegal *(81)*. The likelihood of developing cerebral symptoms without warning was highlighted by Wickramasuriya who commented that in spite of treatment and even when appearing to be doing well, pregnant women can suddenly collapse *(64)*.

In semi-immune subjects in areas of high endemicity cerebral malaria is rare in pregnancy. It should be emphasised that in longitudinal studies of pregnant women in Kenya and Papua New Guinea no cases occurred (Brabin, unpublished observations).

6. Congenital malaria

Covell *(112)* commented that none of the theories advanced to account for the transmission of malaria from mother to child was supported by concrete evidence. This statement is still true today. Congenital malaria with peripheral blood parasitaemia may be symptomatic or asymptomatic at birth and in a proportion of cases only cord parasitaemia occurs. Kortmann *(5)* summarizes 16 reports including several large series from Africa covering the years 1915-1972 and in none of these was there a congenital infection rate in the babies' peripheral blood of greater than 0.7% observed. The highest rate in the umbilical cord was 6.0%. Several studies had a zero cord infection rate despite a high malaria prevalence in the mothers. Higher cord parasite rates in primigravidae are reported *(5, 6)* and this presumably relates to the higher placental parasite densities which occur in primi-

gravidae. In cases with intra-uterine fetal death, in which parasites have been found in brain and spleen, intense placental infection was present *(64)*. These findings suggest that transplacental infection chiefly occurs with dense placental infection or in untreated cases of severe *P. falciparum* infection. This is most likely to occur in non-immune women. Treatment late in pregnancy may clear cord parasitaemia and this may have occurred in Torpin's series *(63)* in which no case of congenital malaria was found in 17 non-immune women with acute malaria at 8 months gestation.

High cord infection rates in subjects with placental malaria have been reported by Reinhardt *et al. (6)*, 55%; Kortmann *(5)*, 18.1%; Le Van Hung *(13)*, 35.8%; Nnatu *et al. (10)*, 15%; Marshall *(33)*, 46%; Ezeoke *et al. (82)*, 16.8%, and in three Nigerian reports *(83)*. Such high rates in semi-immune women suggest that under particular circumstances parasites may cross the placenta. Infants born to these mothers are at higher risk of low-birth-weight *(5)*, although this may be because a higher proportion were primigravidae. In such cases it is likely that parasitaemia clears from peripheral infant blood rapidly or within a few weeks of birth *(84)*, unlike in those cases with severe placental infection in which infants are born with symptomatic congenital malaria, or, if asymptomatic at birth, develop clinical signs in the neonatal period.

The circumstances under which parasites can cross the placenta in semi-immune women deserves further investigation. Information on maternal and cord haemoglobin concentrations is not reported in cases cited, and this may be important as Oppenheimer *et al.(85)* have shown that parasite prevalence in infancy correlates with birth haemoglobin values. Placental hypertrophy secondary to maternal anaemia may alter the risk of transmission.

7. General complications

a) *Hypoglycaemia*

White *et al. (86)* observed that in falciparum malaria, quinine-induced insulin secretion may precipitate hypoglycaemia. Other factors including the large glucose requirements of the malaria parasite, may contribute. Hypoglycaemia is associated with pregnancy and severe disease and should be considered in any pregnant women with impaired consciousness, abnormal behaviour, fits or cerebral malaria. The overall incidence of hypoglycaemia in cerebral malaria in the study by White *et al.* was 8.0%. In immune women clinical hypoglycaemia is not apparent during pregnancy and the complication is possibly confined to those with a low level of immunity.

b) *Puerperal sepsis*

This was mentioned by Wickramasuriya *(64)* as complicating a number of maternal deaths associated with malaria. A mild infection may prove fatal to a woman debilitated by severe pregnancy malaria and anaemia. Perinatal infection rates may be increased in anaemic women at delivery and malaria may present as puerperal pyrexia following delivery in women with low immunity.

c) *Postpartum haemorrhage*

This was an important complication of both the Wickramasuriya *(64)* and Le Van Hung *(13)* series in women with low malaria immunity. In immune women it is a frequent cause of maternal death *(68)* and in coastal New Guinea it is one of the most common delivery complications. Significantly higher placental parasite rates were noted in women from rural Madang (Papua New Guinea) with a blood loss greater than 200 cc at delivery (Brabin, unpublished observations). Postpartum haemorrhage is usually defined as a blood loss over 500 cc, although in anaemic women a smaller loss may lead to significant morbidity. Postpartum haemorrhage was reported as a frequent complication by Harrison *(77)*. In this large series from Northern Nigeria of 7654 unbooked pregnancies, 391 had postpartum haemorrhage, but details of malaria infection were not given.

d) *Fever and acute symptoms*

In semi-immune women acute symptoms are infrequent unless an acute haemolytic syndrome occurs. Symptoms are more probable with high parasite densities *(87)* and therefore are more frequent with *P. falciparum* infections and in primigravidae. Many immune women remain asymptomatic despite a chronic low grade parasitaemia and persistent splenomegaly, unless they become severely anaemic *(88)*. Renal insufficiency is a rare complication *(81,89)*.

As fever may be absent in a high proportion of semi-immune women during pregnancy despite parasitaemia, it cannot be relied upon either as a measure of malaria frequency, or as a symptom on which drug related malaria control be based.

In non-immune women classical symptoms develop including blackwater fever with haemoglobinuria. The high fever may precipitate premature labour or fetal death *(63, 90, 91)*.

SECTION III. METHODOLOGICAL ASSESSMENT OF PUBLISHED STUDIES OF MALARIA IN PREGNANCY IN RELATION TO ASSOCIATED FACTORS

Several topics related to the impact of malaria and its control in pregnancy have not been investigated in the studies reviewed in Sections I and II. The discussion below highlights these areas in relation to future research needs. In particular, the percentage risk of low birthweight and maternal anaemia are essential indicators for evaluating any system of malaria control in pregnancy and they both serve as a basis for identifying problems and designing and implementing intervention strategies.

1. Maternal anaemia, birth weight and perinatal mortality

Although several published studies have investigated the effect of malaria on birth weight or the effect of malaria on maternal anaemia, only recently has attention been

given to the interaction of malaria and anaemia on pregnancy outcome. This is an important area for future research. This is because the prevalence of nutritional anaemias in pregnancy is high in many developing countries and the added complication of inadequate malaria control in already anaemic women is likely to compound the effects of malaria on pregnancy outcome.

To illustrate this, *Table 15* lists several studies which indicate the differences in risk for low-birth-weight in relation to maternal anaemia in subjects from both malaria-endemic and non-endemic areas. In all of the studies listed in *Table 15* an increased risk of low-birth-weight was reported with pregnancy anaemia. *Tables 11* and *12* indicate the increased risk of perinatal death or stillbirth with severe pregnancy anaemia. Herd and Jordan *(65)*, in 61 women with mostly low levels of acquired immunity, observed that in many cases of malaria in pregnancy there was a positive correlation between anaemia (taken as haemoglobin concentration less than 10 g. dl) and abortion, or an adverse effect on pregnancy. Lieberman *et al. (61)*, in a sample from Boston, USA, demonstrated that even when controlling for multiple confounding factors, haematocrit is a major predictor of preterm delivery. Brabin *et al. (30)* demonstrated an increased risk of low-birth-weight (primarily intra-uterine growth retardation) in primigravidae at haemoglobin concentrations below 8 gm. dl, when controlling for the presence or absence of malaria at delivery.

Low-birth-weight has been ascribed to anaemia at the time of conception and in early pregnancy whether the cause of the anaemia was beta-thalassaemia, stomatocytosis or iron deficiency *(97)*. Before 20 weeks gestation there is maximal velocity for growth in fetal length *(98)*, and growth retardation in this period would lead to stunted but well proportioned rather than wasted babies. Anthropometric measurements of babies born in Uganda have also shown a reduction in weight and length in those born to mothers with evidence of placental malaria *(99)*, although data on anaemia in pregnancy was not reported. Evidence from the Papua New Guinea study of Brabin *et al. (30)* indicated that early rather than late pregnancy anaemia was the more important factor related to risk of low-birth-weight in primigravidae.

The advantages accrued by multigravidae in pregnancy outcome, despite severe anaemia, iron deficiency and malaria during pregnancy, are striking, especially as there are no differences in physiological requirements between them and primigravidae once adolescent growth is completed. Immunological mechanisms may be important since multigravidae have better immunity to malaria.

What evidence is there that malaria parasitaemia has a direct effect on placental function causing growth retardation and low-birth-weight? None of the studies listed in *Table 6* controlled for anaemia. In the study from Papua New Guinea, malaria as a chronic cause of splenomegaly and anaemia appeared to be of greater importance *(30)*. Placental function and decreased oxygen delivery to the fetus could be affected by malaria pathologic changes which have been reported in several studies *(100)*. Beischer *et al.* reported a correlation between severe anaemia (haemoglobin < 8 gms. dl) and increased placental weight in several tropical countries, including Papua New Guinea *(101)*. Despite this evidence, increased placental weight has not been reported for malaria infected placentae, despite the probability of associated maternal anaemias causing placental hypertrophy.

In a study from Gabon, the mean weight of placentas with malaria changes was significantly less than that of placentas without such changes *(100)*. Similar findings have been reported from the Ivory Coast *(6)* and Uganda *(99)*, although evidence from the Gambia indicates that placental weights were not decreased in those with placental malaria *(8)*, however a different study reported lower placental weights in pigmented placentas *(102)*. In none of these reports was placental weight increased and it is possible that placental malaria limits the ability to compensate for maternal anaemia with placental hypertrophy. Anaemic women experiencing malaria in pregnancy would therefore be most at risk of delivering low-birth-weight infants. Low plasma oestradiols have also been reported with malaria placental pigmentation *(60)* and anaemia *(103)*.

2. Placental : fetal weight ratios

Previous studies have shown that mean placental indices (ratio of placental weight to birth-weight) decrease with advancing gestational age *(71)*. McGregor *(18)* used the index to infer that high indices in women with malaria at delivery indicate shorter gestational age. A difficulty with this assumption is that anaemia also increases the index, and as malarious patients are likely to be anaemic, then this factor, rather than prematurity, may explain their observations. In *Tables 16* and *17* a comparison of McGregor's observations is made with those of three other studies whose authors investigated changes in the index in relation to anaemia in women from both malaria-endemic and non-endemic countries. These data show that the differences observed between those with and without malaria could readily be explained by differences in anaemia prevalence. If the differences reported by McGregor *et al.* were due to a gestational effect alone, it would indicate that the mean gestational age of babies born to mothers with placental malaria was about 37 weeks. Other data from the Gambia do not suggest that such a high prematurity rate occurs in malarious patients *(60)*. These observations highlight the importance of controlling for anaemia in studies investigating the effects of malaria on pregnancy outcome.

3. Maternal and cord haemoglobin values in malaria-endemic and non-endemic areas and their relation to infant parasitaemia

The importance of maternal anaemia and its relation to malaria in pregnancy and low- birth-weight is further emphasized by the association between maternal and cord haemoglobin mean concentrations. In most studies a correlation between individual values for maternal-cord paired samples has not been reported. However, a re-analysis of grouped data shows a very significant correlation between mean data and mean cord values for several studies from malaria endemic areas *(Table 18) (105)*. The correlation coefficient for this comparison is high (0.81) and statistically significant ($P < 0.02$). One reason why a correlation between haemoglobin values has not been found in paired samples would be if the change in cord haemoglobin lagged behind any change in maternal haemoglobin concentration. The association would then only become apparent if group values were compared. The explanation of this correlation in samples collected from malaria endemic areas has still to be investigated. The role of iron, erythropoetin and malaria haemolysins should be investigated. Of particular interest is that the probability of

hospital admission by one year of age was influenced by birth haemoglobin concentration in a longitudinal study from Papua New Guinea *(85)*. The same authors demonstrated an association between birth haemoglobin and malaria parasite prevalence at six and twelve months of age in infants.

Newborn splenic volumes measured by ultrasound were significantly increased in babies born in a malaria endemic area of Papua New Guinea compared to values measured in a non-endemic highland area of New Guinea. In turn, newborn splenic volume was positively and significantly correlated with cord haemoglobin concentration *(106)*. These findings are considered to relate either to a haematological interaction between mother and fetus or prenatal fetal immune stimulation secondary to malaria in pregnancy.

It is apparent from these studies that longitudinal studies are required to investigate the epidemiology of malaria in infants in relation to the pattern of malaria and anaemia in pregnancy. Improved malaria control in pregnancy may have important effects on infant health in relation to these interactions, independent of any effect of malaria control on birthweight.

4. Antenatal attendances at maternal child health clinics

Antenatal care is an accepted means of detecting complications of pregnancy. Its role in maintaining compliance with chemoprophylaxis and preventing malaria in pregnancy is paramount. Three important factors which influence birthweight and relate to malaria in pregnancy can be improved by antenatal care:

(i) Anaemia in pregnancy
(ii) Maternal nutrition
(iii) Placental pathologic damage.

Despite the potential impact of antenatal care on pregnancy outcome in malaria endemic areas, there is little quantitative information that determines how antenatal care influences outcome in relation to frequency and regularity of attendance in malaria endemic areas. Trials of chemoprophylaxis should control for these variables. Mothers with preterm delivery may not receive prenatal care and chemoprophylaxis because the early birth of the infant intervenes. Treatment and control groups in intervention trials should therefore have comparable antenatal care records.

All the published intervention trials of chemoprophylaxis for malaria control show improved birthweight in the treated groups *(20, 50, 113)*, and in one study this benefit occurred for both primigravidae and multigravidae *(113)* or grand multiparae *(47)*. These trials did not control for confounding due to differences in compliance or attendance between study groups. In a trial of malaria chemoprophylaxis and nutritional supplementation in Nigeria, Fleming *et al.(22)* estimated that attendance histories were comparable in study groups. No benefit on pregnancy outcome in terms of birthweight was demonstrated, but for many subjects village deliveries occurred and their birthweights

were unknown. *Table 19* gives a summary of attendance rates from that study. These figures illustrate the difficulties in achieving controlled study design for assessment of malaria chemoprophylaxis intervention regimes in rural areas.

Tables 20 and *21* show that in studies from Africa and Papua New Guinea, under 10% women attend in the first trimester for antenatal care. In Papua New Guinea fewer primigravidae than multigravidae attended early *(Table 22)*. Failure to attend early is of great importance because of the advantages to be gained from malaria control in early pregnancy (see **Section III.1**). The differences between those who do and do not attend early in pregnancy need to be investigated. It cannot be assumed that it is only the least educated who attend late. Reasons for non-compliance with malaria chemoprophylaxis are not the same as those for non-attendance at antenatal clinics. The potential impact of improved early antenatal attendance on pregnancy outcome needs to be estimated, providing compliance with malaria prophylaxis is maintained.

5. Assessment of compliance with malaria chemoprophylaxis

Prophylaxis regimes vary from region to region. The World Health Organization recommends a treatment dose of antimalarials at first attendance followed by regular chemoprophylaxis. Compliance with weekly chloroquine prophylaxis has been found to be adequate in a longitudinal pregnancy study in Papua New Guinea. Compliance was assessed in two ways. Firstly by keeping a record of tablet usage by counting remaining chloroquine tablets in returned bottles distributed at each monthly visit, and secondly by screening delivery blood samples for whole blood chloroquine using an ELISA assay. ELISA assays have also been developed for determining mefloquine, dapsone, pyrimethamine and proguanil and its derivatives in blood *(115)* and these can be applied to study compliance in pregnant women. Dapsone and pyrimethamine ELISA have been used in a prophylaxis trial in The Gambia for this purpose *(47)*.

a) *Tablet usage*

In the Papua New Guinea study 68.4% of attenders returned drug bottles at subsequent antenatal visits. 11.7% of those returning bottles were non-compliant with prophylaxis and the average number of tablets remaining out of 8 supplied monthly (300 mg chloroquine weekly) was 3.5 per non-compliant visit *(Table 23)*. Irregular attenders may have returned an empty bottle at the time of their late follow-up visit but would still have been prophylactic failures for the period of non-attendance. The 11.7% estimate of non-compliance is a minimum figure for inadequate prophylaxis for this reason. Nevertheless it was in good agreement with a separate method of assessment utilizing the ELISA whole blood chloroquine assay.

b) *ELISA whole blood chloroquine assay (116).*

At delivery samples from 248 subjects who had attended antenatal clinics were screened for whole blood chloroquine estimation. Of these 217 (87.5%) had ELISA

values equal to or greater than those of 9 women who received supervised weekly chloroquine prophylaxis. Therefore an estimated 12.5% of women may not have taken a prophylactic dose in the previous 7 days or more to their delivery (95% confidence interval, 8.4-16.6%). A missed monthly attendance occurred in approximately 12% of women in the last trimester and these non-attendances would comprise a proportion of those with low blood chloroquine concentrations at delivery. Therefore, for regular attenders non-compliance at the time of delivery was estimated at under 10%. These results are summarized from Brabin *et al. (25)*.

Assessment of non-compliance by these two methods shows reasonable agreement, and the New Guinea study indicates that good compliance rates with weekly prophylactic chloroquine can be achieved with supervised distribution of tablets at monthly antenatal clinics. The use of small plastic bottles for distribution and adequate explanation at the commencement of prophylaxis were important components of that study.

Good compliance with daily proguanil in pregnant women has been achieved in Zaria, Nigeria (Fleming A.F. and Harrison, K, personal communications). It is within the Hausa tribe tradition and beliefs of health that "magani" should be taken to prepare for future rest. Magani is medicine of any kind including herbs (Fleming, A.F., personal communication). Low compliance with malaria chemoprophylaxis (29.1%) was found in a sub-sample of women for whom chloroquine prophylaxis was available free of charge through community health workers in Saradidi, Kenya *(69)*. The results from the Saradidi study showed that the community health worker programme did not provide effective malaria prophylaxis to pregnant women even though malaria is perceived as an important health problem and cause of abortions and stillbirths. Most pregnant women interviewed were not taking chloroquine for logistical or organizational reasons, and there were problems in training and communication. Antenatal care was not offered by the community health workers and the investigators concluded that providing chemoprophylaxis in antenatal clinics may be more effective *(69)*. Low compliance has also been reported by McDermott *et al. (88)* in Malawi.

The potential for, and ways of, achieving satisfactory compliance need to be assessed in relation to antenatal care. Mobile maternal-child health clinics offer several advantages to harness the clinic system to identification and treatment of women at risk of malaria in pregnancy. These advantages are:

(i) Chemoprophylaxis is linked to antenatal care.
(ii) Chemoprophylaxis is linked to the identification of anaemic women.
(iii) A simple antenatal record system can be utilized.
(iv) Rationale of chemoprophylaxis can be carefully explained initially and questions answered on subsequent visits.
(v) Subsequent infant follow-up can be facilitated.
(vi) An organizational framework through which the system can operate can be established and strengthened.

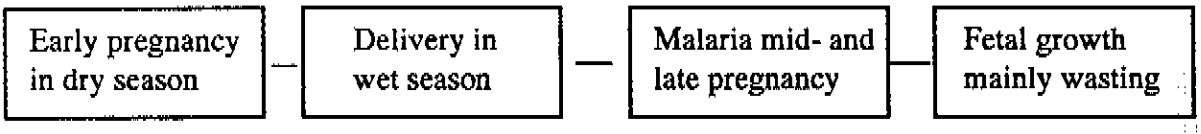
The alternative or parallel utilization of village health workers or traditional birth attendants is discussed in **Section IV** as part of an assessment of current studies.

6. Seasonal variation in malaria and associated factors

High parasite rates in pregnant women in the wet season result not only from an increased number of new infections but also from an increased prevalence of persistent infections due to a decrease in the recovery rate of infection in pregnancy. A proportion of wet season primary infections will persist through the dry season, especially in primigravidae. This proportion will also relate to the efficacy of treatment or prophylaxis schedules given to pregnant women during the wet season, and to the number of women in early or late pregnancy during wet and dry seasons. The epidemiology of malaria during pregnancy is therefore very different under conditions of seasonal transmission.

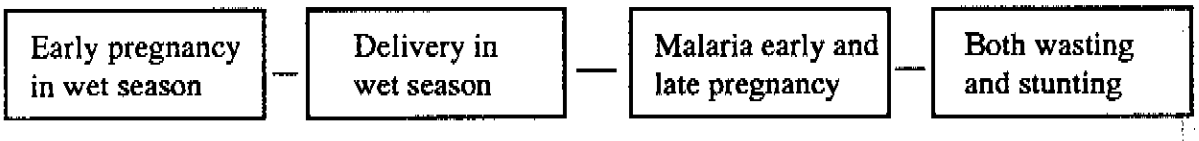
In general three patterns of infection could be considered, grouped as in the diagram, for regions where there are single main wet and dry seasons. The fetal growth classification is based on timing factors outlined by Villar and Belizan, (*98*).

GROUP 1



GROUP 2

GROUP 3



In the diagram early pregnancy refers to the first trimester and late pregnancy to the third trimester. The fourth possibility of early pregnancy in the dry season and delivery in the following dry season would result in most of the middle period of pregnancy occurring in the wet season, and in this situation some part of the first and third trimester would still occur in the wet season. This essentially is group three in the diagram.

It would be difficult to distinguish differences in pregnancy outcome in terms of birth weight between these three groups, unless anthropometric measurements were available to distinguish wasting and stunting in the newborn. The possibility that these distinguishing outcomes really occur has still to be investigated. A study design to investigate this would need to control for confounding due to seasonal variation in anaemia incidence due to nutritional factors, as well as seasonal shortages in food.

In general, primigravidae delivering in the late wet or early dry seasons would be at greatest risk for low-birth-weight because they have been at risk for malaria throughout most of their pregnancy. In order to have reliable data on monthly variations, data is required over a period of several years. Seasonal variations, or monthly variations in mean birth weight values have been reported by a number of investigators but it is difficult to interpret this information in relation to malaria prevalence *(6, 8, 117)*, especially as antenatal attendance may vary due to seasonal factors.

The persistence of parasitaemias in the dry season also complicates this analysis. *Table 24* lists parasite prevalence in wet and dry seasons for several African studies. The seasonal differences were more marked for urban areas of Senegal than for rural Gambia or Nigeria. Although comparison between these studies is difficult, it is apparent that a significant number of infections still occur during the dry season.

7. The placenta

"Intrinsic 'placental insufficiency' is extremely rare and it is becoming clear that this clinical syndrome is usually due to a restricted supply of maternal oxygen and nutrients as a result of inadequate transformation of spiral arteries into uteroplacental vessels. This failure of placentation represents an abnormality of the relationship between fetal and maternal tissues at a relatively early stage of pregnancy" *(121)*. It is only by gaining a better understanding of the relationship between placentation and early pregnancy infection with malaria in primigravidae will the problem of intra-uterine growth retardation associated with malaria be completely answered. Several studies have demonstrated placental damage associated with malaria infection *(100, 138, 122, 123)*, but the placenta has considerable functional reserve capacity, easily repairs ischaemic damage and is able to compensate for toxic injury *(121)*. Fox also considers that while infections of the placenta are important they do not influence placental function and also that there is currently no firm evidence that the placenta suffers immune-mediated damage.

Sequestration of *P. falciparum* occurs in the intervillous spaces, but the mechanism of sequestration remains unclear *(124)*. However, placental damage has been described for both *P. falciparum* and *P. malariae* infected placenta *(100)*. Lower birth weights have been reported for *P. falciparum* compared to *P. malariae* placental infections. *P. falciparum* infections are denser in intervillous spaces which could be the main reason for this difference in mean birthweight by malaria species observed by Jelliffe *(4)*.

There is a good correlation between placental parasitization and peripheral blood parasitaemia despite seasonal changes in prevalence *(19, 102)*. In areas with high antimalarial drug utilization a poorer correlation might be expected due to clearance of peripheral but not placental parasitaemia. This may explain the higher proportion of placental infections compared to peripheral infections in women receiving prophylaxis observed by McDermott *et al. (88)* in Malawi, and Molez *et al.* (personal communication) in Burkina Faso. In Papua New Guinea a good correlation was observed in women receiving prophylaxis (Brabin, unpublished data), but peripheral parasite clearance was poor.

SECTION IV. ASSESSMENT OF CURRENT STUDIES ON MALARIA IN PREGNANCY

The objectives of current studies have been to:

(i) Confirm the effects of chemoprophylaxis on improving mean birthweight;
(ii) Measurement of drug efficacy in clearing or suppressing parasitaemia with alternative drug treatment or prophylactic regimens;
(iii) Evaluate different modes of delivery, e.g. MCH clinics, traditional birth attendants;
(iv) Measure drug efficacy in relation to change in mean haemoglobin and haemocrit values;
(v) Evaluate malaria control in pregnancy on acquisition of malaria infection in infants;
(vi) Measure alterations in malaria-specific immunity, particularly malaria-specific antibody;
(vii) Measure perinatal mortality and the effect of malaria on its rate;
(viii) Compare *in vivo* sensitivity of pregnant and non-pregnant women to anti-malarials.

Investigators have mostly concentrated on a limited number of the above objectives. Several studies, although completed, are not yet reported and detailed analysis of their findings must await further review. *Tables 25* and *26* provide descriptive summaries of current investigations and *Table 27* lists the outcome variables used to measure drug efficacy. Some of these investigations have been undertaken in malaria drug resistant areas and efficacy quantified under different conditions. For this reason and because study design and mode of drug distribution have differed, recent investigations have produced variable results. Main issues concerning these studies are outlined below.

1. Duration of prophylaxis in pregnancy

All of the investigations have relied on the mothers' presentation at the antenatal clinic or to the community health worker and therefore most interventions have had limited effect on malaria infections in the first half of pregnancy. There is good evidence to suggest that interventions which can operate from early in pregnancy will have maximal effect on pregnancy outcome and maternal haemoglobin concentration (see **Section 2.1**). None of the studies listed in *Tables 25, 26* and *27* address this issue satisfactorily.

2. Seasonal factors and anaemia prevalence

Fleming *et al. (22)*, as well as others, have reported compelling evidence that the risk of maternal anaemia is reduced with malaria chemoprophylaxis. Even in areas with chloroquine resistant malaria an effect has been observed on increasing maternal haemoglobin with prophylaxis *(30)*. Because seasonal factors are important in relation to maternal anaemia prevalence and low-birth-weight risk studies investigating the impact of malaria control in pregnancy should span at least two years to obtain adequate epidemiological data. As shown in *Table 25* a number of recent studies were of two years duration or longer. Longer term studies have been proposed in order to investigate the effects of malaria control in a first pregnancy on the pattern of malaria in the subsequent pregnancy. One current study is addressing this question (Greenwood *et al.*, The Gambia).

3. Drug distribution

Some studies have utilized village health workers and there are conflicting views on their effectiveness. In Saradidi in Western Kenya, it was felt that asking village health workers to give malaria chemoprophylaxis to pregnant women in addition to other responsibilities was too difficult *(69)*. In The Gambia the use of traditional birth attendants achieved drug distribution to 87% of pregnancies in the study area (fortnightly Maloprim), and effective prophylaxis was achieved over a 3 year study period for women attending in the last trimester of pregnancy (Greenwood, personal communication). However, in that study many women also attended antenatal clinics at some time.

The relative benefits of community health workers for malaria control in pregnancy have not been evaluated in a comparative study with the benefits of antenatal clinic attendance for distribution of chemoprophylaxis. There is evidence from two recent studies that good compliance can be obtained with correct supervision through antenatal mobile clinics (**Section III.5**). Low compliance is a concern of a current study operating through antenatal clinics in Malawi (Steketee, personal communication). The reasons for this low compliance are being studied.

4. Fetal growth retardation

Few recent studies have investigated the incidence of intra-uterine growth retardation and prematurity in study cohorts by undertaking gestational age assessment of the newborn. What evidence is available indicates fetal growth retardation as the primary problem for women living under holoendemic conditions. There is little information on how nutritional factors affect the risk of growth retardation in these women.

5. Parasitaemia in infancy and maternal chemoprophylaxis

In infants there is some recent evidence for an interaction between chloroquine prophylaxis in pregnancy and risk of malaria infection in the first year of life *(125)*. A number of studies listed in *Table 26* may be able to clarify further the nature of this association. It is not clear from the review data available to what extent current investigations can clarify which maternal factors are associated with risk of parasitaemia in infants. Careful attention to haematological and nutritional interaction will be required.

6. Antimalarial use, drug resistance and efficacy

The apparent resistance of *P. falciparum* to chloroquine is increased in pregnant women. This has been demonstrated in two studies from Malawi *(11)* and Papua New Guinea *(26)*. Both studies employed 28-day follow-up *in vivo* schedules. A high sensitivity to mefloquine has been observed *in vivo* studies from Malawi (Steketee, personal communication) and in *in vitro* studies from Papua New Guinea *(26)*. Chloroquine and chlorproguanil are not effective as prophylactics in Malawi *(88)*, Mozambique *(126)*, and Papua New Guinea *(25)*, although chlorproguanil has not been tested in New Guinea. In Papua New Guinea propopylactic chloroquine is reduced in efficacy because of chloroquine resistance

(45% RI resistance). Despite this a missed clinic attendance at all parities resulted in a two-fold increase in incidence (change from parasite negative to parasite positive at monthly visit), indicating that chloroquine prophylaxis was having some effect *(25)*. Reduction in anaemia prevalence also occurred in that study. In Cameroun, an area of low chloroquine resistance, prophylactic chloroquine given monthly (600 mg) or weekly (300 mg) halved fever episodes, reduced parasite prevalence and increased birth weight, although subject numbers were small in this study *(127)*. In Nigeria improved parasite clearance in pregnancy was observed with chloroquine compard to pyrimethamine *(128)*. Parasitologic failure rates did not differ between the pyrimethanmine-treated (8/34) and the control (ll/37) group not receiving chloroquine during the 16 week follow-up. Thus pyrimethamine was not an effective suppressive or causal prophylactic in these pregnant women. Outcome of pregnancy was not measured *(128)*.

Proguanil is considered a safe prophylactic in pregnancy in East and West Africa *(22, 129)* and one author has suggested it may be the prophylactic of choice in tropical Africa *(34)*. Quinine is recently reported as causing hypoglycaemia *(86)*, but does not lead to increased oxytocic action *(130)*. The safety of quinine in not causing oxytocic action was recognized by Wickramasuriya *(64)*. The results of mefloquine trials in Malawi and Thailand are still to be reported (*Tables 25* and *27*). Mefloquine has been successfully used in drug resistant falciparum malaria in pregnancy *(131)*. A recent study from China reports the use of artemisin (Quinghaosu) and artemether in treating malaria in pregnant women *(132)*. Amodiaquine has also been used successfully for *P. falciparum* malaria in pregnant women in Burma *(141)*.

Section V. Conclusions and Areas for Future Research

This section is divided into 2 parts and conclusions have been listed for clarity. Areas of research which are most appropriate in relation to methods of prevention of malaria in pregnancy are emphasized.

1. Priorities for future research

(i) The methodology, research design and statistical analysis of epidemiological studies should be better described. Where relevant, seasonally distinct cohorts should be defined. Data should be collected prospectively and randomized clinical trials used when feasible. Observational studies should control for confounding variables. A review of methodological issues in pregnancy studies is required.

(ii) Antenatal care can be studied using an experimental design and emphasis should be placed to identify those nutritional factors influenced by antenatal care which have an effect on the impact of malaria control in pregnancy, especially anaemia. Special importance should be given to study locations where investigations of the impact of malaria control in early pregnancy can be quantified. At the present time the efficacy of malaria control during pregnancy has been quantified only with interventions during the last trimester of pregnancy.

(iii) The preventive efficacy (for parasitaemia) and the potential benefits on pregnancy out come with drug distribution through maternal-child health clinics should be better quantified. The advantages of linking malaria drug distribution to antenatal care need to be assessed especially in terms of improving drug compliance. Good compliance rates have been achieved through drug distribution in mobile MCH clinics in coastal Papua New Guinea. The level of compliance (i.e. none-, partial-, or complete) needs to be evaluated in relation to the operational efficiency of MCH clinics in given locations. It is important to distinguish between non-compliance and non-attendance. As there is compelling evidence for the benefits of malaria control in pregnancy on mother and infant, a real effort needs to be established to improve compliance in areas where it is low. Such effort will have wider consequences for primary health care in an area if linked to antenatal care. This effort will involve sociological and operational studies. Assessment of efficacy should not stratify only into compliant and non-compliant groups as a degree of efficacy may be achieved with partial compliance.

(iv) It might be appropriate to design a trial to measure compliance by comparing community health worker distribution of drugs with that through mobile MCH clinics in a suitable location. These methods are not viewed as either/or alternatives but rather as different ways or options to achieve maximal compliance which can be linked to antenatal care.

(v) Studies to assess daily proguanil as a chemoprophylactic are required in tropical Africa and Oceania including Papua New Guinea. Good compliance has been achieved with this drug in Nigeria and this observational data needs to be quantified. It is a very safe drug with few side-effects. It should not be assumed that daily dosage will be unsatisfactory.

(vi) Side-effects from chloroquine are variable. For example, there is a low rate of skin pruritis in coastal Papua New Guinea, but a high rate amongst the Luo of Western Kenya *(69)*. Further attention should be given to quantifying these side-effects in longitudinal studies.

(vii) There is good evidence that maternal anaemia affects pregnancy outcome. Antimalarial drug efficacy should therefore be quantified in relation to:

a) Initial prevalence of anaemia in the study population
b) Effects on maternal anaemia prevalence of drug prophylaxis or use

The factors responsible for triggering severe haemolytic anaemias in falciparum malaria require further study. The incidence of severe haemolytic anaemia in pregnancy cohorts on different drug regimes should be established.

(viii) A prospective trial of Imferon, intra-muscular iron injection, on malaria incidence should be designed, as preliminary evidence from a single retrospective trial indicates it may influence incidence *(133)*. As anaemic women who receive Imferon are more likely to be parasitaemic anyway, the evidence from retrospective data is inadequate.

(ix) Maternal-newborn interactions require further study. There is reasonable evidence for an association between mean maternal and cord haemoglobin values in malaria-endemic areas and cord haemoglobin values have been related to malaria parasite prevalence in infants. Infants of mothers receiving malaria prophylaxis have lower parasite rates in the first year of life *(125)*. Drug efficacy in pregnancy therefore needs to be quantified in terms of these interactions. There is a need for studies to keep in sight infant and child mortality and morbidity and functional performance, since birth weight is important only insofar as it effects these outcomes.

(x) Establishment of a direct link between a risk factor and true outcomes (mortality, morbidity, childhood anaemia, nutritional status) requires the use of large sample sizes and long-term follow-up.

(xi) Percentage low-birth-weight should always be reported by parity group and not just by mean birth weight values. Relative risk estimates of risk of low-birth-weight in primi-gravidae should be evaluated as a major outcome variable in intervention studies. Changes in population attributable risk of low-birth-weight in primigravidae could then be estimated following the intervention.

(xii) Epidemiological studies are required in low endemicity areas. There is almost no information available from India and South America and several parts of South-East Asia. There is little data from *P. vivax* endemic areas. There is a priority for research in these locations. In Ethiopia, where *P. vivax* is endemic, resettlement schemes have re-located hundreds of thousands of non-immune subjects to areas where malaria in endemic. A high priority should be given to epidemiological, clinical and immunological investigations in these areas.

(xiii) Studies of cost/benefit analysis for drug distribution are required in relation to different delivery systems. These studies need to be completed by experienced health economists. The cost/benefits of integrated drug regimes should be assessed as weekly malaria drug regimes can be linked to the treatment and prevention of anaemia in pregnancy with iron and folacin supplements.

2. Factors requiring further study

(i) Research is required to explain the evidence for raised stillbirth rates in primigravidae in malarious areas. Studies should quantify fetuses as macerated or fresh.

(ii) The prevalence of antepartum and postpartum haemorrhage should be studied in relation to placental malaria. Both are common in certain areas where malaria is endemic. Hospital delivery data which records these complications should be analysed to compare rates in malaria-endemic and non-endemic areas, in primigravidae and multi-gravidae and for seasonal differences.

(iii) Anthropometric measurements of newborns should clarify the risk of stunting and wasting in growth retarded infants in relation to malaria in pregnancy and parity.

(iv) Ultrasound measurements of newborn spleen volumes should be done in relation to maternal characteristics and cord haematology.

(v) Ultrasound measurements of utero-placental blood flow should be made in differ ent parity groups and compared in women shown subsequently to have or not have placental malaria. Ultrasound measurements should be performed as a method for assessment in controlled trials.

(vi) Information on the effects of maternal anaemia on placental weight is required in women with and without placental malaria. Ultrasound measurements of utero-placental blood flow might be considered in these groups.

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FIGURE

TABLES

REFERENCES

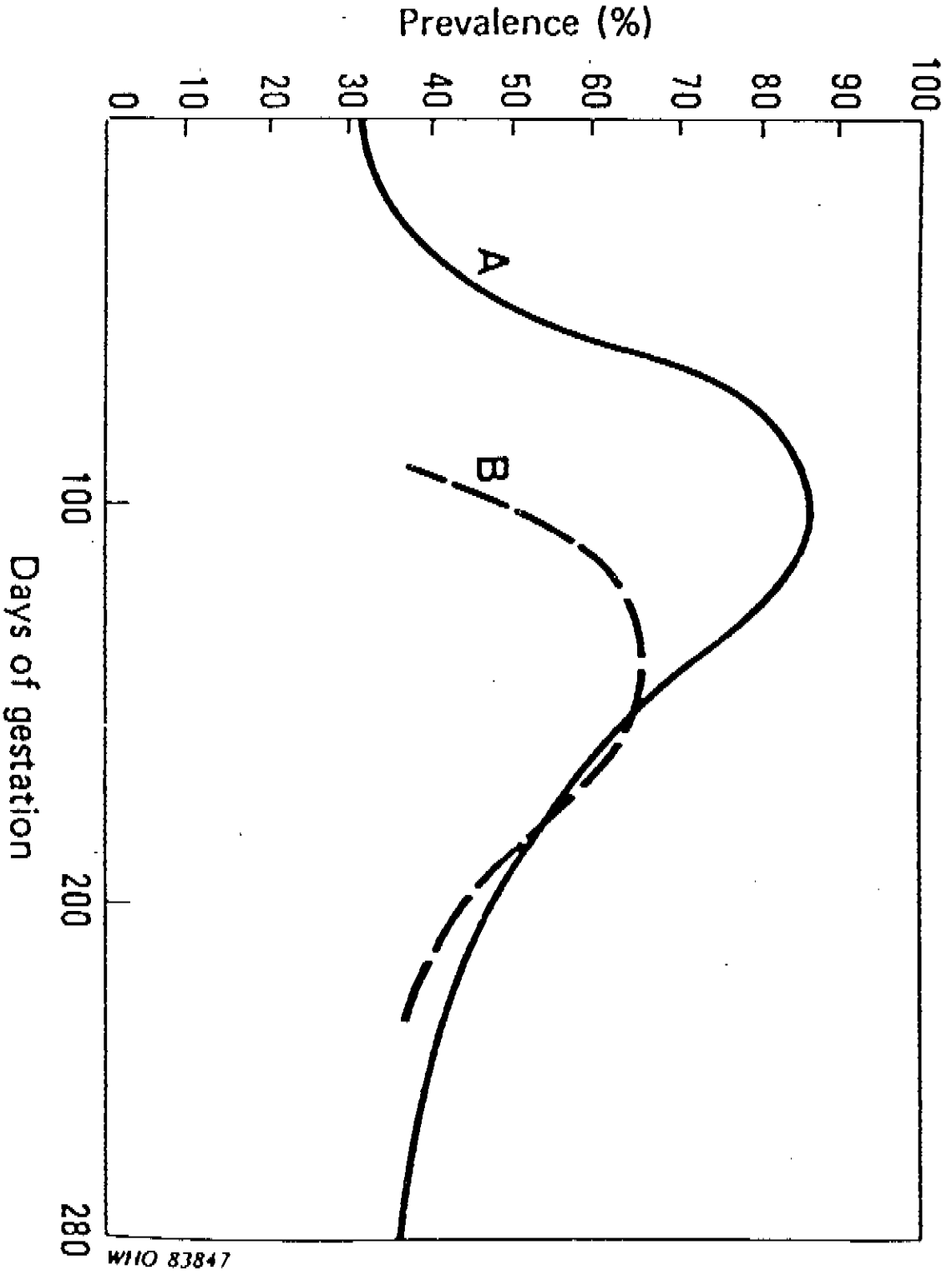

FIGURE. Prevalence of parasitaemia (A) and haemolytic anaemia associated with splenomegaly (B) in primigravidae.

Curve A is derived from data obtained in West Kenya. Curve B is interpolated from published studies on aneamia in Nigeria.

Table 1

Prevalence of malaria (placental infection or parasitaemia) among women in Africa by parity at delivery.

Source	Area	Prevalence % PG	Prevalence % MG*	Number
Archibald (1956) (1)	W. Nigeria	20.2	11.2	451
Cannon (1958) (2)	Nigeria (Ilesha)	62.5	25.3	392
Spitz (1959) (3)	E. Nigeria	36.4	16.3	575
Jelliffe (1968) (4)	Uganda (Kampala)	21.7	14.7	570
Kortmann (1972) (5)	Tanzania (Muheza)	37.0	33.0	413
Reinhardt *et al.* (1978) (6)	Ivory Coast (Abidjan)	55.0	36.2	192
Bray & Anderson (1979) (7)	Gambia (rural)	59.1	35.2	1000**
McGregor *et al.* (1983) (8)	Gambia - Banjul	15.7	8.8	2765
	- Provinces	46.7	20.4	3194
McGregor (1984) (9)	Gambia - Keneba	64.0	26.3	532
Nnatu (1987) (10)	Nigeria (Lagos)	40.0	8.0	230
Steketee (1988) (11)	Zaire (urban and rural)	38.0	15.0	291

All data were collected in hospitals or health centres. Details of antimalarial use before delivery were generally not reported.

* PG = primigravidae, MG = multigravidae.
**Antenatal parasite prevalence

Table 2

Prevalence of malaria (placental infection or parasitaemia) among women in Oceania at delivery.

Source	Area	Prevalence % PG	MG	All	Number
Brabin *et al.* (1988) (30)	Papua New Guinea Madang (rural)	40.4	25.9	29.4	582
Lehner and Andrews (1988) (31)	Papua New Guinea Madang (urban)	--	--	29.4	51
Sehgal (1988) (32)	Papua New Guinea Madang (rural)	--	--	25.7	101
Marshall (1983) (33)	Solomon Islands (Malaita)	--	--	7.8	180

Table 3

Splenomegaly in pregnant and non-pregnant women from malaria endemic areas.

Source	Area	Spleen rate % Pregnant	Non-pregnant	Spleen size (cms) Pregnant	Non-pregnant
Gilles *et al.* (1969) (20)	Nigeria (Ibadan)	42 (38)	16 (38)	0.5-3.0	0.5-6.0
Pingoud (1969) (27)	W. Nigeria	38 (150)	20 (135)	1.6	1.3
Kortmann (1972) (5)	Tanzania (Muheza)	40 (123)	8 (153)	--	--
Brabin (1988a) (17)	Papua New Guinea	73 (15)	40 (15)	--	--

Gilles *et al.* (20) and Brabin *et al.* (17) report spleen rates in non-pregnant women who were subsequently followed through pregnancy. Spleen rates are mid-pregnancy observations except for the study of Brabin *et al.*, where measurements were taken at less than 16 weeks gestation.

Group numbers in parenthesis.

Table 4

Mean haemoglobin values (gms. dl) in pregnant women with and without malaria parasitaemia at delivery.

Source	Area	Haemoglobin (gms. dl)			
		Parasite positive		Parasite negative	
		PG	MG	PG	MG
Kortmann (1972) (5)	Tanzania	10.0 (9)	10.1 (26)	11.3 (5)	11.5 (19)
Reinhardt *et al.* (1978) (6)	Ivory Coast	---11.1 ± 0.2--- (78)		----11.5 ± 0.2---- (120)	
McGregor (1984) (9)	Gambia*	10.5 (48)	10.7 (121)	11.7 (27)	10.9 (336)
Fleming *et al.* (1986) (36)	Nigeria (Zaria)	—10.3 ± 1.6--- (55)		---11.6 ± 1.5— (173)	
Nnatu *et al.* (1987) (10)	Nigeria (Lagos)	—8.5---- (20)		----10.8---- (210)	
Brabin *et al.* (1990) (30)	Papua New Guinea*	8.1±1.4 (20)	8.7±1.2 (71)	8.8±1.9 (38)	8.8±1.5 (153)
	**	9.5±1.8 (17)	9.1±1.8 (40)	9.6±1.8 (39)	9.4±1.7 (175)

PG = primigravidae ; MG = multigravidae. Group numbers in parenthesis. ± standard deviation if available

* At antenatal booking; ** At delivery after receiving iron and folate supplements

Table 5

Mean haemoglobin (gms. dl + S.D.) in relation to spleen size at booking (from Brabin *et al.*, 1990, (30).

Gravida	Spleen size (cms)		
	0	1-5	> 6
Primigravidae	9.1 + 1.6 (38)	8.4 + 1.5 (15)	6.9 + 1.9 (7)
Multigravidae	8.9 + 1.4 (100)	8.6 + 1.4 (62)	8.6 + 1.5 (35)

Parenthesis = number of women.

Table 6

Effect of placental infection on birthweight (early studies).

Source	Area	Mean birthweight (g) With Malaria	Mean birthweight (g) Without Malaria	Difference (g)
Bruce-Chwatt (1952) (51)	S. Nigeria	2903±540 (73)	3048±470 (237)	145
Archibald (1956) (53)	W. Nigeria	2722±312 (68)	2892±454 (395)	170
Archibald (1958) (54)	N. Nigeria	2778±408 (62)	3076±465 (378)	298
Cannon (1958) (2)	Nigeria	2610 (130)	2920 (262)	310
Spitz (1959) (3)	E. Nigeria	2851 (136)	2940 (440)	89
MacLaren and Ward (1962) (55)	Tanzania	3037±461 (86)	3092±409 (314)	55
Jelliffe (1968) (4)	Uganda	2805 (92)	3068 (478)	263
Jilly (1969) (44)	Ghana	2855 (30)	3033 (20)	178
Kortmann (1972) (5)	Tanzania	2945 (141)	3020 (413)	75
Reinhardt (1978) (6)	Ivory Coast	2960±460 (78)	3080±457 (120)	120

± standard deviation given if reported; number in parenthesis.

Table 7

Comparative stillbirth rates in malaria endemic areas by parity.

Source	Area	Stillbirth Rate (%)			Malaria Prevalence (%)		
		P0	P>1	All	P0	P>1	All
Reinhardt *et al.* (1978) (6)	Ivory Coast	1.5 (1831)	1.0 (5794)	0.9 (7625)	50.9 (51)	36.2 (141)	41.1 (192)
McGregor *et al.**(1983) (8)	Urban Gambia	3.1 (1275)	5.9 (1652)	4.7 (2927)	15.7 (1226)	8.7 (1539)	11.8 (2765)
	Rural Gambia	10.6 (894)	6.9 (2606)	7.9 (3500)	46.7 (782)	20.4 (2412)	26.8 (3194)
Steketee *et al.***(1988)(11)	Urban Zaire	3.2 (453)	0.9 (681)	1.8 (1116)	38.0 (116)	15.0 (175)	24.0 (291)
Brabin *et al.** (1990) (30)	Rural Papua New Guinea	2.3 (129)	1.0 (387)	1.4 (516)	40.0 (141)	25.8 (441)	29.0 (582)
Anangos *et al.* (1986) (67)	Rural Zaire	--	--	7.0 (100)	--	--	64.0 (100)

P0 indicates primigravidae; P > 1 indicates multigravidae

* Singleton deliveries only; ** P0, indicates first and second pregnancies.

Malaria prevalence figures are obtained in most cases from smaller samples. Group numbers in parenthesis.

Table 8

Stillbirth rates in women from Gambian Provinces by parity and placental parasitization.*

Placental Smear	Stillbirth rate (%) Parity 0	Parity > 1	Relative Risk	95% Confidence limits	P value
Malaria negative	10.1 (475)	7.0 (2077)	1.49	1.06-2.09	0.009
Malaria positive	11.2 (419)	6.6 (529)	1.78	1.13-2.81	0.0062
All	10.6 (894)	6.9 (2606)	1.59	1.23-2.06	0.0058

Group numbers in parenthesis.

* Data re-grouped from Table V, McGregor et al, (8).

Table 9

Stillbirth rates in women from Gambia (Banjul) by parity and placental parasitization.*

Placental Smear	Stillbirth rate (%) Parity 0	Parity > 1	Relative Risk	95% Confidence limits	P value
Malaria negative	2.7 (1070)	5.8 (1505)	0.45	0.29-0.69	0.0001
Malaria positive	5.4 (205)	7.5 (147)	0.71	0.30-1.66	0.209
Odds Ratio	2.03	1.32			
95% Confidence limits	1.01-4.09	0.69-2.52			
P value	0.023	0.203			

Group numbers in parenthesis.

* Data re-grouped from table V, McGregor et al. (8)

Table 10

Miscarriage rates in women with low immunity to malaria and presenting with acute malaria

Source	Area	Number of Pregnancies	Miscarriage Rate(%)	Adjusted Miscarriage Rate (%)*
Torpin (1941) (63)	United States of America	27	22.2 (6)	60.0 (6)
Wickramasuriya (1935) (12)	Ceylon	253	8.3 (21)	–
Le Van Hung (1951) (13)	Saigon (Indo China)	58	6.9 (4)	19.0 (4)
Menon (1972) (14)	Malaysia	22	13.6 (3)	60.0 (3)
Herd and Jordan (1981) (65)	Zimbabwe	61	39.3 (24)	–
Meek (139) (1988)	Thai-Kampuchean border	193	56.5 (109)	–

Parenthesis indicates number of aborting pregnancies.

* Adjusted rate excludes pregnancies presenting with malaria in the third trimester.

Table 11

Perinatal mortality and severe anaemia in mothers.

Source	Area (survey years)	No.	Perinatal mortality(per 1000) Severe anaemia	Not severe	Twins included
Llewellyn-Jones (1965) (73)	Malaysia (1953-1962)	73048	131 (Hb < 6.5 g.dl)	68	Yes (?)
Tasker (1958) (74)	Malaysia Kuala Lumpur	27678	132 (Hb < 6.5 g.dl)	63	Yes (?)
Harrison (1973) (75)	Nigeria Ibadan	429	132 (Ht < 16%)	32	No
Brabin *et al.* (1990) (30)	Papua New Guinea	328	55 (Hb < 8 g.dl)	22	No

Table 12

Stillbirth rates and severe anaemia in mothers.

Source	Area	No.	Stillbirth Rate (per 1000 births)		Twins included
			Severe anaemia	Not severe	
Llewellyn-Jones (1965) (73)	Malaysia	73048	91 (Hb < 6.5 g.dl)	16	Yes
Wickramasuriya (1937) (64)	Ceylon	2384 -macerated -fresh	38 138 (hookworm* positive)	4 32 (hookworm negative)	No (?)
McGregor, M.W. (1963) (76)	Kenya (Mombasa)	3950	150 (Hb < 8.8 g.dl)	51	Yes (?)
		59 (malaria smear positive)	222 (Hb < 7.4 g.dl)	80	–
Harrison *et al* (1985) (77)	Nigeria (Zaria)	20025	354 (Ht < 25%)	56	No

* Assumed heavy hookworm infections were associated with maternal anaemia.

Table 13

Maternal mortality and severe anaemia in women from malaria endemic areas.*

Source	Area	No.	Case fatality rate (%)	
			Severe anaemia	Not severe
Llewellyn-Jones (1965) (73)	Malaysia (Kuala Lumpur)	73048	1.5 (Hb < 6.5 g.dl)	0.3
Harrison[1] (1975) (92)	Nigeria (Ibadan)	566	3.1 (Ht < 18%)	0.4
Tasker (1958) (74)	Malaysia (Kuala Lumpur)	27494	1.7 (Hb < 6.5 g.dl)	0.4
Wickramasuriya (1937) (64)	Ceylon	2384	4.1 (hookworm positive)	2.0 (hookworm negative)
Fullerton[2] (1962) (93)	Nigeria	92	20.0 (Ht < 13%)	-

* Causes of severe anaemia include iron, folacin deficiency, malaria and haemoglobinopathies.

[1] *In treated women*

[2] *In untreated women (no exchange transfusion)*

Table 14

Cerebral malaria*, incidence and maternal mortality.

Source	Area	Immunity to Malaria	Cerebral malaria (%)	Mortality Rate (%)
Herd and Jordan (1981) (65)	Zimbabwe	Low	13.1 (61)	0.0
Torpin (1941) (63)	USA	Low	3.7 (27)	100.0
Menon (1972) (14)	Malaysia	Low	13.6 (22)	100.0
Wickramasuriya (1937) (64)	Ceylon	Low	4.7 (358)	89.5
Sholapurkar *et al.* (1988) (15)	India	Low	7.0 (78)	33.0

* The diagnostic criteria for cerebral malaria may not be comparable in these studies
Group numbers in parentheses.

Table 15

Maternal anaemia and low-birth-weight (%) in malaria endemic and non-endemic areas.

Source	Area	No.	% < 2500 gms.		
			Severe anaemia	Moderate anaemia	Mild or no anaemia
Malaria endemic areas					
McGregor (M.W.) (1963)(76)	Kenya (Mombasa)	3950	42.0 (Hb < 7.5 g.dl)	32.0 (Hb 7.5-8.8 g.dl)	12.7 (Hb > 8.8 g.dl)
Brabin et al. (1990)(30)	Papua New Guinea (Madang)	primigravidae 43	65.0 (Hb < 8.0 g.dl)	27.0 (Hb 8.0-14.0 g.dl)	–
		multigravidae 182	11.0 (Hb < 8.0 g.dl)	19.0 (Hb 8.0-14.0 g.dl)	–
Non-endemic areas					
Klein (1962) (94)	USA	3329	–	13.8 (Hb < 10.0 g.dl)	7.6 (Hb > 10.0g.dl)
Kaltreider (1976) (95)	USA	8648	33.3 (Hb < 8.0 g.dl)	18.1 (Hb 8.0-9.9g.dl)	16.8 (Hb >10.0g.dl)
Gosh et al. (1977)(96)	India (South Delhi)	1999	23.9 (Hb < 8.0 g.dl)	19.7 (Hb 8.0-10.0g.dl)	18.2 (Hb > 10.0g.dl)

Table 16

Placental : Fetal weight ratios in primigravidae with and without malaria at delivery.*

Source	Infant Sex	Placental : Fetal weight ratio		Difference
		Malaria positive	Malaria negative	
McGregor *et al.* (1983) (8)	female	0.1777 + 0.0370 (53)	0.1659 + 0.031 (237)	0.0118
Urban (Banjul)	male	0.1848 + 0.323 (47)	0.1699 + 0.0287 (211)	0.0149
McGregor *et al.* (1983) (8)	female	0.1844 + 0.041 (100)	0.1727 + 0.0351 (85)	0.0117
Rural Gambia	male	0.1897 + 0.033 (83)	0.1812 + 0.0338 (72)	0.0085

Parenthesis = group numbers.

* No significant differences were observed between malaria positive and negative groups at higher parities.

Table 17

Placental : Fetal weight ratios for pregnant women with and without anaemia at delivery.

Source	Area	Placental : Fetal weight ratio		Difference
		Anaemia	No anaemia	
		Hb <8 g. dl	Hb >10 g. dl	
Beischer *et al.* (1970) (101)	Melbourne	0.1863 (77)	0.1667(2485)	0.0196
	Singapore	0.1791(122)	0.1600(1016)	0.0190
	India	0.2110(199)	0.1852 (302)	0.0258
	Thailand	0.2082 (67)	0.1784 (202)	0.0298
	Papua New Guinea	0.2199(267)	0.1926 (237)	0.0273
		Hb <10 g.dl	Hb >10 g.dl	
Reinhardt *et al.* (1978) (6)	Ivory Coast	0.1630(39)	0.1543 (158)	0.0087
		Hb <6.0 g.dl	Hb >11.0 g.dl	
Singla *et al.* (1978) (105)	India	0.1559 (14)	0.1368 (16)	0.0191

Group numbers in parenthesis.

Table 18

Maternal and cord haemoglobin concentrations (g. dl) from studies in Papua New Guinea, and Africa

Location	No.	Cord Hb	Maternal Hb	Reference
PAPUA NEW GUINEA				
Rabaul	350	15.0	10.5 + 1.3 (1607)	Kariks, 1969 (107)
Madang-Urban (Study A)	20	12.9 + 1.6	10.4 + 2.2	Corkill *et al.*, 1989 (106)
Madang-Urban (Study B)	35	12.3 + 1.6	9.2 (362)	Oppenheimer *et al.*, 1984 (108)
Madang-Rural	51	12.4 + 1.9	9.3 + 1.9	Brabin, 1989c (105)
AFRICA				
Dar-es Salaam (Study A)	67	13.4 + 1.8	10.4 + 1.7	Rowland, 1968 (109)
Dar-es Salaam (Study B)	432	13.4 + 1.7	10.6 + 1.7	Nhonoli *et al.*, 1975 (110)
Ivory Coast (Abidjan)	198	15.1 + 1.8	10.9 + 1.9	Reinhardt *et al.*, 1978 (6)
Kenya (Nangina)	35	14.7	11.6 (56)	Brabin, 1985 (111) Brabin *et al.*, 1986 (39)

Brackets indicate sample size for maternal values if different from number of cord samples screened.

Table 19

Missed attendances during malaria chemoprophylaxis trial in Zaria, Nigeria.*

Attendance Record	Before 28 weeks gestation		Between 28-36 weeks gestation	
	Number	%	Number	%
Complete	128	64	104	54
Missed < 2 weeks	51	26	46	24
Missed 3-5 weeks	14	7	23	12
Defaulters	7	4	20	10
All	200	100	193	100

* Data taken from Fleming *et al.*, 1986, (22).

Table 20

Distribution of frequency of first antenatal attendances.

Source	Country	1st Trimester	2nd Trimester	3rd Trimester	Delivery
Osuhor, (1982) (114)	Nigeria	15.3	63.2	21.5	–
Brabin (Unpublished data)	Papua New Guinea	9.0	70.0	15.0	6.0

Table 21

Antenatal attendance histories in Papua New Guinea and Zaire.

Source	Country	Mean gestation at first visit (months)	Mean number of antenatal visits	Non-attendance at antenatal clinic (%)
Steketee *et al.*, (1988) (4 Health Centres) (11)	Zaire	6.1 to 7.2 (+ 1.7)	3.2 to 4.6 (+ 3.2)	11.0
Brabin unpublished data (17 mobile clinics)	Papua New Guinea	5.7 + 1.9	3.4 + 1.7	6.0
Kaseje *et al.*, (1987) (69)	Kenya	–	–	47.7*

Parenthesis: standard deviation.

* In this study a community health programme was in operation.

Table 22

Regularity of antenatal attendance at clinics.

Source	Country	Gestation			
		Before 24 weeks		Between 28-36 weeks	
		Defaulters (%)	Missed Attendances (%)	Defaulters (%)	Missed Attendances (%)
Fleming *et al.(1986)(22)*	Nigeria (Zaria)	3.5	32.5	10.4	35.7
Brabin (unpublished data)	Papua New Guinea (Madang)				
	PG	--	3.8	--	13.0
	MG	--	15.3	--	10.8
	All	--	10.6	--	11.6

PG = primigravidae; MG = multigravidae

See table 19 for details of missed attendances in study of Fleming *et al.*

In study of Brabin denominators were person-months. Some women may have missed more than one attendance in the same pregnancy, therefore, the proportion of women not attending per pregnancy is less than that stated.

Table 23

Estimate of compliance with chloroquine chemoprophylaxis from tablet usage in rural clinics in Madang, Papua New Guinea.*

Total person-months (all attendances)	Bottles returned (number)	Total tablets not taken	Person-months non-compliant
1421	972 (68.4%)	399 (3.5 tablets per non-compliant visit)	114 (11.7%)

* Unpublished data, B. Brabin.

Table 24

Parasite rates in pregnant women in wet and dry seasons.

Source	Area	Parasite Rate (%) Wet	Dry	Comment	Number
Walton (1949) (118)	Sierra Leone	38.7	22.2	First attendance	1345
Fleming *et al.* (1984) (36)	Nigeria (Zaria) (asexual forms)	29.8	20.1	First attendance < 24 wks gestation	228
		19.2	9.7	(gametocytes)	
Williams (1973) (119)	Nigeria (Ibadan)	10.2	8.6	Adeogo State Hospital and Osegore Health Centre (placenta)	1085
McGregor *et al.* (1984) (9)	Gambia (rural)	27.6	26.4	Placental blood	3500
Bah *et al.* (1981) (120)	Senegal	48.8	7.3	First attendance Urban Dakar	866
Diallo *et al.* (1983) (84)	Senegal	24.1	8.8	Urban Thies (blood)	444
		7.2	5.2	(placenta)	443

Table 25 - Summary of current and recent field studies of malaria chemosuppression in pregnant women - study designs.

Source*	Area	Endemicity	Drug Regimes	Study Started	Study Design	Sample Size	Placebo Group	Study Period	Study Completed	Drug distrib. system Hosp	MCH	CHW	TBA
Greenwood *et al* (47)	Gambia (rural)	Seasonal	(1) Maloprim fortnightly Dapsone 100 mg, Pyrimethamine 25 mg (2) Placebo	1984	Longitudinal	1000 (approx)	Yes	3 years	Yes	No	No	No	Yes
Brabin *et al* 1990 (25)	Papua New Guinea	Year-round	(1) Chloroquine 25 mg/k treatment and then 300 mg prophylaxis weekly	1985	Longitudinal and cross-sectional	600	No	2 years	Yes	No	Yes	No	No
Steketee *et al*	Malawi (rural)	Seasonal	(1) Chloroquine 300 mg prophylaxis weekly	1987	Longitudinal and cross-sectional	600 (min.)	No	3 years (min.)	Yes	Yes	Yes	No	
			(2) Choloroquine 25mg/k treatment monthly			600 (min.)	No		Yes	No	Yes	Yes	No
			(3) Chloroquine 25mg/k treatment and then 300 mg prophylaxis weekly			600 (min.)	No		Yes	No	Yes	Yes	No
			(4) Mefloquine 750 mg treatment and 250 mg prophylaxis weekly			600 (min.)	No		Yes	No	Yes	Yes	No
Fleming *et al* 1986 (22)	Nigeria (Zaria)	Seasonal	(1) Chloroquine 25 mg/k treatment and then 100 mg Proguanil daily (2) Placebo group	1984	Longitudinal (primigravidae)	200	Yes	--	Yes	Yes	No	Yes	No
Spencer *et al* (1987) (125)	Kenya (Western)	Year-round	(1) Chloroquine 300 mg prophylaxis weekly	1982	Total population (Random)	357 573 Control villages	No	3 years	Yes	No	No	Yes	No
Mutabingwa *et al*	Tanzania (Muheza)	Seasonal	(1) Proguanil 200 mg daily	1988	Random sample	200	No	4 1/2 years	No	No	Yes	Yes	No
			(2) Proguanil 200 mg daily & Chloroquine weekly			200							
			(3) Chloroquine weekly 5 mg/kg			200							

Table 26 - Summary of Current Field Studies of Malaria Chemosuppression in Pregnant Women - Outcome Variables

Investigators (Unpublished report if year not stated)	Greenwood *et al.* (47)	Brabin *et al.* 1989 (16,17,25,30,105)	Sicketee *et al.*	Fleming *et al.* 1986 (22)	Harinasuta *et al.* In vivo study drug efficacy	Keuter *et al. In vivo* study drug efficacy	Mutabingwa *et al.*	Spencer *et al.* 1987 (88)	McDermott *et al.* 1988	Mefloquine prophylaxis trial	Molez *et al.* Urban (135)	Cot *et al.* Rural	Garner *et al.* (134)
Outcome variables:	Gambia	Papua New Guinea	Malawi	Nigeria	Thailand	Kenya	Tanzania	Kenya	Malawi	Thailand	Burkino Faso		Papua New Guinea
Parasite Prevalence	+	+	+	+	+	+	+	+	+	+	+	+	+
Parasite Incidence	-	+	-	-	-	-	-	-	+	+	-	+	-
Spleen Rate	-	+	-	-	-	-	-	-	-	-	-	-	+
Placental Infection Rate	-	+	+	-	-	-	+	-	+	?-	+	+	-
Anaemia	+	+	+	+	+	+	+	+	+	+	+	+	+
Nutritional Status	iron status	iron status	-	iron folacin	-	-	-	-	-	+	-	-	+
Birthweight	Single-tons	Single-tons	+	±	+	-	-	-	-	+	+	+	+
Gestational Age	-	+	+	-	-	+	-	-	-	+	-	+	+
Parity	+	+	+	primig. only	-	+	+	+	+	+	+	+	+
Season	+	+	+	-	-	-	+	-	-	+	+	+	-
Perinatal Mortality	+	+	+	+	+	-	+	-	-	+	-	-	+
Maternal Mortality	+	+	+	+	+	-	+	-	-	+	-	+	-
Antenatal Attendance	-	+	+	+	-	-	+	+	-	+	-	+	+
Compliance Assessment													
History	+	+	+	+	-	-	-	+	-	-	-	-	-
Observation	+	-	+	-	+	+	+	-	+	+	-	+	-
Tablet Use	+	+	-	+	-	-	+	-	-	-	-	-	-
Biochemistry	+	+	+	-	-	-	+	+	+	-	-	-	+
Postpartum Haemorrhage	+	+	-	-	-	-	+	-	-	+	-	-	-
Delivery Complications	+	+	+	-	+	-	+	-	-	+	-	+	-
Infant Follow-up	+	±	+	-	-	-	+	+	-	+	-	-	+
	See table 25 for study design	See table 25 for study design	See table 25 for study design	See table 25 for study design	Harinasuta, Keitinun) TDR/CHEMAL) Boudreau, Canfield) see table 27	See table 27 for study design	See table 25 for study design	See table 25 for study design	See table 25 for study design	See table 25 for study design	See table 25 for study design		See table 25 for study design

Table 27 - Summary of recent in vivo studies of therapeutic drug efficacy in pregnant women.

Source	Area	Year	Drug Regime	Dosage	Study Design	Hospital or MCH clinic	Estimated drug efficacy (%) (parasite clearance)
Harinasuta *et al.*, (TDR/CHEMAL)	Thailand	1983 (Chantabury)	(1) Mefloquine	500 mg	Double blind (2) Quinine	Hospital --	91.0 Random 70.0
Looareesuwan *et al.*, 1985 (130)	Thailand (Pra Pokklao)	1985	(1) Quinine	i.v. 10-20 mg/kg 8 hourly	Patients with severe P. falciparum	Hospital	see reference
Klever *et al.*, 1988 (26)	Papua New Guinea (Madang)	1987	(1) Chloroquine	25 mg/kg	28 days in vivo test	Health Centre	68.0-pregnant 80.0-nonpregnant
Keuter *et al.*, 1990 (140)	Kenya (Western)	1988	(1) Chloroquine (2) Pyrimethamine Sulphadoxine (3) Chlorproguanil Dapsone	25 mg/kg 75 mg) 1500 mg) 1.2 mg/kg) 2.4 mg/kg)	Randomized 4 week in vivo follow-up	Hospital/ MCH	13.0 81.0 33.0
Steketee *et al.*, 1987 (136)	Kenya (Siaya)	1986	(1) Chloroquine (2) Chloroquine (3) Amodiaquine	25 mg/kg 5 mg/kg/week 25mg/kg	28 day in vivo test pregnant 7 day test	Hospital	19.0-pregnant 24.0-nulligravid 48.4-pregnant 24.0-nulligravid 78.0-all gravida
Rolfe, 1988 (137)	Zambia	1983	(1) Choloroquine (2) Fansidar (3) Amodiaquine (4) Quinine and Clindamycin	25mg/kg (2 doses)	In vivo follow-up In vitro drug tests	Hospital	Multiple drug resistance
Nahlan *et al.*, 1989 (128)	Nigeria	1988	(1) Pyrimethamine (2) Chloroquine (3) Chloroquine	25 mg dose 25mg/kg 5 mg/kg	28 day in vivo test 7 day in vivo test 14 day test	Hospital	40% - (day 14) 100% 100%

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