*Bulletin of the World Health Organization*, 61 (6): 1005-1016 (1983)


# An analysis of malaria in pregnancy in Africa*

B. J. BRABIN[1]

*This article summarizes information and specific evidence regarding the epidemiology of malaria in pregnancy in Africa. Malaria infection is more frequent and severe in primigravidae both during pregnancy and at the time of delivery. A study of pregnant women living under holoendemic conditions in western Kenya showed that the peak prevalence of infection in primigravidae (85.7%) and multigravidae (51.7%) occurred at 13-16 weeks' gestation. There were a similar number of recoveries in both groups during the second and third trimester. The loss of immunity in early pregnancy was equivalent to an 11-fold decrease in the rate of recovery from infection.*

*The recovery seen in late pregnancy suggests that the women mount a satisfactory immune response to malaria infection, reacquiring their pre-pregnancy immune status at about the time of delivery. The pattern of infection in pregnancy is comparable to that observed in infants and children. What the child achieves over several years the mother reachieves in nine months; the pattern is repeated in successive pregnancies. The practical implications of this pattern of malaria in pregnancy are discussed.*

It is generally agreed that women demonstrate an increased prevalence and severity of malarial infection during pregnancy. The mechanism of this differential response is unknown and the epidemiology has not been studied in women living under endemic and hyperendemic conditions. Until a clearer picture of what happens is available it will not be possible to determine why this alteration in host susceptibility occurs or to plan a rational programme of control. The factors involved in the immunity of individuals in hyperendemic communities were outlined by Schuffner over 60 years ago (*1*), and his ideas are still supported by many observed data. However, their relevance to what happens in pregnancy is not clear. There is a certain amount of information available from several countries in Africa on this subject, mainly concerned with circumstances at the time of delivery, or with the main indirect complications of the infection in pregnancy, such as anaemia and low birth weight. In this paper, the published data are examined and applied to the development of a theory of the epidemiology of malaria in pregnancy; the theory is supported by an analysis of data obtained recently in western Kenya. Congenital malaria is not discussed.

## DEFINITION OF INFECTION

Infected groups may be defined on the basis of parasitaemia during pregnancy or placental infection at the time of delivery. Subdivision according to the density of infection is straightforward for patients with parasitaemia, but parasite densities in placental infections are difficult to assess with accuracy and cannot readily be standardized. There appears to be no correlation between parasite density in peripheral blood and in the placenta in pregnant women with well-developed immunity (*2*), and in both primigravidae and multigravidae, placental infections are often substantially heavier than peripheral blood densities would suggest (*3*). The placenta may contain large numbers of infected red blood cells (as many as 65%) while the peripheral blood is free from parasites (*4*). Conversely, susceptible immigrants to endemic areas often show high parasitaemias without heavy placental infection (*5*). The species incidence of infection probably depends on the relative frequency of the different species of plasmodia. This report presents data referring principally to *Plasmodium falciparum*, which is the commonest cause of infection in pregnancy in Africa.

Table 1 shows the prevalence of malaria infection in peripheral blood and placenta in women giving birth in a hospital or health centre. The prevalence of parasitaemia was similar to that for placental infection for all areas except those reported by Blacklock & Gordon (*4*) (in which study some mothers received quinine before labour), van den Branden (*6*) (where the techniques of placental examination were almost certainly at fault), and Thonnard-Neumann (*7*) (where peripheral blood appears to have been examined only in those with placental infection). The total prevalence for both sites of infection was higher than the individual figures, since some women had demon-

* A portion of this paper was read at a joint meeting of the Dutch and Belgian Tropical Medicine Societies, Rotterdam, April 1982.

[1] Staff Member, Royal Tropical Institute, Mauritskade 63, Amsterdam 1092 AD, Netherlands.

Table 1. Prevalence of peripheral and placental malaria infection among women

| Source | Area | No. of women | Parasitaemia (%) | Placental infection (%) | Total infections (%) | Antimalarial drugs given before delivery |
|---|---|---|---|---|---|---|
| Clark, 1915 (*43*) | Panama (Canal Zone) | 400 | 2.0 | 4.7 | 4.7 | ? |
| Blacklock & Gordon, 1925 (*4*) | Sierra Leone (Freetown) | 173 | 6.9[a] | 38.1 | 38.1 | yes |
| van den Branden, 1927 (*6*) | Zaire (formerly Belgian Congo) | 55 | 56.0 | 2.0 | 56.0 | ? |
| Butler, 1930 (*20*) | Ghana (formerly Gold Coast) | 328 | 18.0 | 23.2 | 25.0 | ? |
| Lombart, 1931 (*44*) | Zaire (formerly Belgian Congo) | 50 | 58.0 | 56.0 | 62.0 | ? |
| Thonnard-Neumann, 1932 (*7*) | Panama | – | 5.0 | 20.0 | – | ? |
| Schwetz & Peel, 1934 (*19*) | Zaire (formerly Belgian Congo) | 50 | 76.0 | 74.0 | 86.0 | no |
| Garnham, 1938 (*21*) | Kenya (Kisumu) | 404 | 30.2 | 27.2[b] | 36.1 | ? no |
| Peel & van Hoof, 1948 (*22*) | Zaire (formerly Belgian Congo) | 403 | 60.2 | 53.9 | 66.2 | ? |
| Walton, 1949 (*10*) | Sierra Leone (Freetown) | 3582 | 5.5 | 4.8 | – | yes[c] |
| Bruce-Chwatt, 1952 (*23*) | Nigeria (Lagos) | 551 | 27.4[d] | 22.3 | 39.9 | no |
| Archibald, 1958 (*45*) | N. Nigeria | 484 | 13.6 | 13.4 | 15.1 | ? |
| Kortmann, 1972 (*2*) | United Republic of Tanzania (Muheza) | 499 | 33.9 | 29.7 | 37.7 | no |
| Reinhardt et al., 1978 (*33*) | Ivory Coast (Abidjan) | 198 | 32.8 | 33.3 | 39.4 | ? |

[a] Three of these women showed pigmented macrophages only.
[b] Includes placentas with pigment or parasites.
[c] Control measures to reduce transmission had been introduced.
[d] Calculated from a subsample of 323 women.

strable parasites in one site only, and was below 45% in all studies except those in Zaire (the former Belgian Congo). The prevalence of parasitaemia was usually closer to the overall prevalence and so is the better index of infection. Ideally, comparison should be made only between results from places where transmission is more or less perennial, for, where it is markedly seasonal, the inoculation rate and the period for which it is operative will affect the data.

## RELATIONSHIP BETWEEN INFECTION AND PARITY

Archibald (*8*) was the first to report a higher incidence of prematurity in malarious primigravidae and since then, several studies have confirmed that these women are more susceptible than multigravidae to malarial infection (Table 2). Although the figures show a wide range, partly because some of the studies were rural and others urban, the primigravidae consistently had approximately double the infection rate of multigravidae. The overall mean for both parity groups was below 42%. Multigravidae as a group demonstrated enhanced clearance of infection compared with primigravidae, at least at the time of delivery. The parasite rates greater than 40%, reported by some authors (Table 1), may be biased by a high number of primigravidae in the sample. A similar bias may exist for the selected group of hospital patients reported by Madecki & Kretschmar (*9*), who had a prevalence at delivery of 66.4%. Although some of these results have to be treated with reservation because of possible bias, they strongly suggest a differential host susceptibility between primigravidae and multigravidae.

Table 2. Prevalence of malaria infection among women in Africa by parity at delivery[a]

| Source | Area | Prevalence (%)[b] | | | | | | Antimalarial drugs given before delivery |
|---|---|---|---|---|---|---|---|---|
| | | Primigravidae | | Multigravidae | | All parities | | |
| Placental infection: | | | | | | | | |
| Archibald, 1956 (*8*) | W. Nigeria | 20.2 | (35) | 11.2 | (31) | 14.7 | (66) | ? |
| Cannon, 1958 (*29*) | Nigeria (Ilesha) | 62.5 | (75) | 25.3 | (55) | 33.0 | (130) | no |
| Spitz, 1959 (*28*) | E. Nigeria | 36.4 | (47) | 16.3 | (88) | 23.1 | (135) | yes |
| Jelliffe, 1968 (*27*) | Uganda (Kampala) | 21.7 | (25) | 14.7 | (67) | 16.1 | (92) | ? |
| Kortmann, 1972 (*2*) | United Republic of Tanzania (Muheza) | 33.3 | (37) | 28.6 | (111) | 29.7 | (148) | no |
| McGregor, 1978 (*3*) | Gambia (Banjul City) | 16.1 | (1275) | 8.9 | (1652) | 12.0 | (2927) | ? yes |
| | (Provinces) | 46.9 | (894) | 20.3 | (2606) | 27.0 | (3500) | ? no |
| Parasitaemia: | | | | | | | | |
| Hamilton et al., 1972 (*30*) | Uganda (Kampala) | 10.2 | (57) | 2.5 | (30) | 4.8 | (87) | ? |
| Kortmann, 1972 (*2*) | United Republic of Tanzania (Muheza) | 39.6 | (44) | 32.2 | (125) | 33.9 | (169) | no |
| Bray & Anderson, 1979 (*12*) | Gambia | 59.1 | (151) | 35.2 | (262) | 41.3 | (413) | ? |
| Parasitaemia and/or placental infection: | | | | | | | | |
| Reinhardt et al., 1978 (*33*) | Ivory Coast (Abidjan) | 54.9 | (28) | 36.2 | (51) | 41.1 | (79) | ? |

[a] All data were collected in urban or rural hospitals or health centres.

[b] Figures in parentheses give number of patients with a positive blood smear.

## PARASITE PREVALENCE DURING PREGNANCY

The implications and causes of the difference in parasite rate between primigravidae and multigravidae at the time of delivery, and its relationship with the inoculation rate, are not clear. Analysis of changes in parasite rates during pregnancy outlines the difference more clearly. A number of workers have reported infection rates at different stages of pregnancy for women attending antenatal clinics.In Table 3 these figures are presented so as to allow comparison between the various studies. The comparison is difficult because of the different gestational periods considered in the studies. Walton (*10*) and Pingoud (*11*) examined women on their first antenatal visit; Bray & Anderson (*12*) did not state if women were studied on their first attendance only; Kortmann (*2*) followed a small group of the same women throughout pregnancy (longitudinal). These studies were undertaken in areas of perennial transmission and Pingoud (*11*), Kortmann (*2*), and Bray & Anderson (*12*) stated that the women selected for study had not taken antimalarial drugs.

A pattern of events is apparent in these groups of women. The highest prevalence of infection occurs in the second trimester with infection rates at delivery and in the postnatal period approximating to levels in non-pregnant women. None of these authors divided their results during pregnancy according to parity. Some indication of parity differences during pregnancy is evident from a detailed study by Gilles et al. (*13*) of a small group of primigravidae followed longitudinally before and during their pregnancy at University College Hospital, Ibadan, Nigeria. These authors reported an increase in the number of women with parasitaemia from 13 (34%) before pregnancy to 30 (79%) during pregnancy. Similarly, in this group, the infection rate in non-pregnant women (40%) was close to the rate at delivery on the basis of placental pigment (44.4% for 9 patients who had not received antimalarials). The high infection rate in these primi-

Table 3. Parasitaemia rates in pregnant women in Africa

| Source | Area | Parasitaemia (%)[a] | | | | | | Situation | Antimalarial drugs given |
|---|---|---|---|---|---|---|---|---|---|
| | | Non-pregnant | 0–3 months | 4–6 months | 7–9 months | Delivery | Postnatal | | |
| Walton, 1949 (*10*) | Sierra Leone (Freetown) | 12.0 (50) | ← | 30.0 (400) | → | 12.0 (85) | – | Urban hospital; ? hyper-endemic | ? Yes (at delivery only) |
| Pingoud, 1969 (*11*) | W. Nigeria | 22.7 (150) | 40.0 (2) | 58.8 (30) | 43.0 (40) | – | – | Rural hospital; ? hyper-endemic | No |
| | | | 21–25 | 26–30 | 31–40 | | 4–29 | | |
| Kortmann, 1972 (*2*)[b] | United Republic of Tanzania (Muheza) | 10.0 (15) | 50.0 (10) | 38.0 (9) | 38.1 (24) | 33.9 (169) | 19.0 (20) | Rural hospital; highly endemic | No |
| | | | 0–24 | 25–36 | 37–40 | | 0–4 | | |
| Bray & Anderson, 1979 (*12*) | Gambia (provinces) | 35.3 (353) | 50.4 (139) | 38.9 (246) | 30.4 (92) | – | 31.0 (18) | Health centres; seasonal variation but perennial transmission | No |

[a] Figures in parentheses give number of patients with a positive blood smear. Numbers above arrows refer to gestation period in weeks.

[b] Results before and after delivery taken from repeated examinations of 26 unprotected women. Results at delivery calculated for a larger group of women with no history of chloroquine ingestion.

gravidae during pregnancy suggests that the parity-related differences seen at the end of pregnancy also occur during pregnancy. Fleming (*14*) observed no correlation between parasitaemia and period of gestation in a selected group of 11 patients, admitted to hospital with anaemia, who had not taken antimalarials. Of these 11 women, 10 were in their first or second pregnancy.

The development of immunity is reflected by the number of parasites in the blood. All of the authors mentioned in this section reported some information on parasite density. In all cases, except for the small selected group of Fleming (*14*), the number of parasites per unit volume of blood was greater in pregnant women than in non-pregnant groups. Bray & Anderson (*12*) clearly showed that densities were highest in primigravidae and primiparae, with a progressive fall with increasing parity. These authors, as well as Pingoud (*11*) and Kortmann (*2*), reported a peak in parasite densities before the 24th or 25th week of gestation (approximate range 1500–3200 parasites per $mm^3$), which corresponds to the period of high infection rates (Table 3). It would appear that women have an increased prevalence and severity of malaria early in pregnancy, with a likelihood of recovery to non-pregnant levels at, or close to, the time of delivery. The greater susceptibility of primigravidae has been established almost entirely from studies undertaken at the time of delivery.

## A MODEL FOR MALARIA IN PREGNANCY

The changes in prevalence during pregnancy can be considered in terms of the model of Ross (*15*):

$$X(t+1) = X(t) - rX(t) + h(1 - X(t))$$

where $X(t)$ is the prevalence of infection at time $t$ (expressed as a proportion);
$r$ is the recovery rate at time $t$;
and $h$ is the incidence of infection.

If the inoculation rate is assumed to be constant, the increase in prevalence during pregnancy can be explained by a decrease in the value of $r$, perhaps resulting from a loss of immunity. An increase in the proportion of women without infection in the third trimester would occur if the number of recoveries

exceeded the number of new infections at this time. The changes in prevalence during pregnancy can thus be explained by a decrease and subsequent increase in the value of $r$.

The difference in prevalence between primigravidae and multigravidae can be interpreted as representing the degree of immunity developed as a result of infection in the previous pregnancy. This assumes that inoculation rates are not affected by parity. The pattern of acquisition of immunity is similar to that in infancy with primigravidae demonstrating the highest prevalence (as seen, for example, in children under 2 years of age) and multigravidae showing a prevalence more comparable with that in schoolchildren. The application of such a theory to malaria in pregnancy needs further examination. Unfortunately, the prevalence data shown in Table 3 do not allow a more precise definition of prevalence for given gestational periods, particularly for the first and early part of the second trimester. This is necessary in order to identify the gestational age corresponding to peak parasitaemia. In the following section, the model is used to describe the dynamics of malarial infection in pregnancy, employing observed data obtained from a recent study in western Kenya.

*Application of model to the situation in Kenya*

Data were collected in western Kenya during a study of women from the Samia tribe attending a rural hospital in Nangina, close to the Lake Victoria shoreline, in an area which is considered holoendemic (*16*). Women were admitted to the study if they attended the antenatal clinic for the first time during the last 7 weeks of the dry season, or the first 6 weeks of the wet season, and had no history of chloroquine ingestion. At this first visit informed consent was obtained for the collection of a sample of blood by venepuncture. A slide was prepared with three thick drops and stained with Giemsa. All slides were read immediately after staining, using a Leitz Wetzlaar microscope (100 fields; 5 minutes screening); subsequently, a large subsample was checked in Amsterdam with a 10–15 minute screening time. Gestational period was calculated from the time of the last menstrual period (which was known in nearly all cases) and checked against fundal height. All women received routine antenatal medical care which included prophylactic chloroquine. The parasite rates among these women are shown in Table 4. The variation in prevalence for both parity groups was in good agreement with the results of other workers (Table 3).

The maximum parasite rate for all the women occurred at 13–16 weeks' gestation; at this time, the number of recoveries starts to exceed the number of new infections. The percentage of women positive at their first antenatal visit relative to the peak parasitaemia rate is shown in Fig. 1 for successive intervals of gestation. It is evident that, after 98 days' gestation, women of all parities recover effectively and that primigravidae and multigravidae show a similar improvement in recovery rates with time. The rate of fall of this line does not necessarily represent the

Table 4. Parasite rates among women presenting for their first antenatal examination in Nangina, Western Kenya

| Gestation (weeks) | Prevalence (%)[a] | | |
|---|---|---|---|
| | Primigravidae (140 subjects) | Multigravidae (315 subjects) | All parities (455 subjects) |
| 8–12 | 71.4 (10) | 31.0 ( 9) | 44.2 (19) |
| 13–16 | 85.7 (12) | 51.7 (15) | 62.8 (27) |
| 17–20 | 78.4 (29) | 43.9 (25) | 57.4 (54) |
| 21–24 | 66.7 (24) | 42.9 (36) | 50.0 (60) |
| 25–28 | 47.8 (11) | 35.2 (19) | 39.0 (30) |
| 29–32 | 66.6 (6) | 24.4 (10) | 32.0 (16) |
| 33–36 | 42.9 (3) | 23.5 (4) | 29.2 (7) |
| 37–40[b] | – | 0.0 (0) | 0.0 (0) |

[a] Figures in parentheses show number of individuals with positive smears.

[b] No primigravidae were seen in this period; 4 multigravidae seen had negative smears.

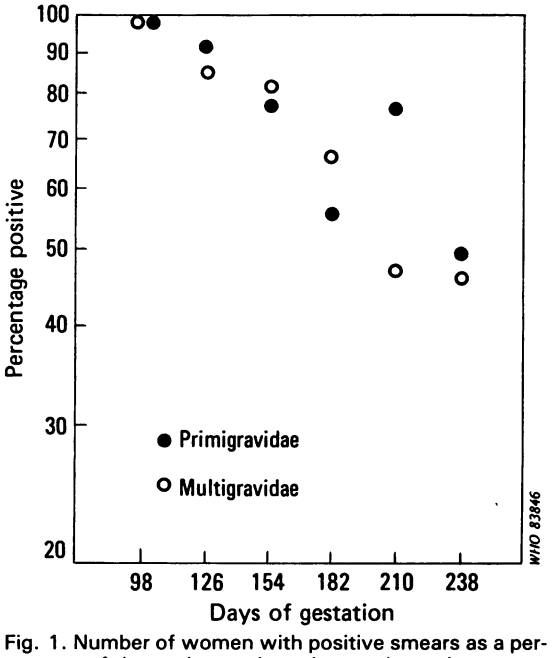



Fig. 1. Number of women with positive smears as a percentage of the peak parasitaemia rate, by parity.

recovery rate from a single infection since, in late pregnancy, superinfection may have occurred in some women. In general, however, the observed improvement in recovery during the second and third trimesters is comparable to estimated recovery rates in young non-pregnant immune adults (*17*).

The limiting prevalence of infection ($L$) in a population living under endemic conditions, according to the model of Ross (*15*), is given by:

$$L = h/(h+r) \qquad 1.$$

In the present situation, $h$ can be taken as 0.00958 per person per day.[a] For primigravidae the pre-pregnancy prevalence is taken as 35%, which is slightly lower than that observed at delivery (Table 4). This is the limiting prevalence ($L$) before pregnancy. Substituting in equation 1, the recovery rate before pregnancy is given by:

$$r = (0.00958/0.35) - 0.00958$$

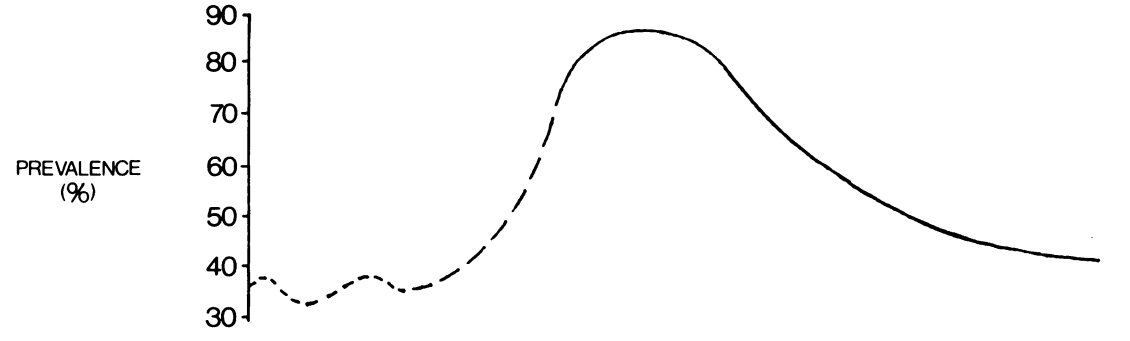
i.e., $r = 0.0178$. This is equivalent to an expected duration for each positive episode of 56 days. The observed increase in prevalence of infection in primigravidae at 13–16 weeks' gestation (85.7%) is equivalent to a decrease in the value of $r$ of approximately 11-fold to 0.0016 (giving an expected duration for each positive episode of 625 days). This assumes that the group is homogeneous and that the effect of mortality on the formula is negligible (this is justified, since none of the women is known to have died). The dynamics of this process in primigravidae are shown in Fig. 2. The acquired resistance in women with higher parity and the development of age-dependent immunity might be expected to restrain the upward trend of the curve eventually to bring it down, and this is the observed pattern shown by the mean figures for multigravidae in Table 4.

Interestingly, the recovery rate calculated for the first trimester in primigravidae is comparable to the estimated rate for infants 1–4 years of age in Nigeria (*17*). Here, it was estimated that the acquisition of immunity in childhood increases the rate of recovery from patent parasitaemia by a factor of up to 10-fold, which is similar to the observed decrease in the rate of recovery due to loss of immunity in the first trimester.

[a] This rate was found by Fontaine et al. (*16*) during a field trial 20 km west of Kisumu town, which is approximately 70 km south of the hospital location.

*Discussion*

More than 30 years ago, Walton (*10*) reported that pregnant women show the same pattern of malaria infection as schoolchildren. He stated that "during pregnancy the ability to limit the number of parasites appears to be lost and women revert to a 'child-type' reaction to infection". The observations in primigravidae in western Kenya demonstrated that the pattern of susceptibility is similar to that seen in infants, while multigravidae exhibit a pattern comparable to that in schoolchildren. The mother appears




| PARAMETERS | | | | |
|---|---|---|---|---|
| | h | 0·00958 | 0·00958 | 0·00958 |
| | L | 0·350 | 0·857 | 0·400 |
| | r | 0·0178 | 0·0016 | 0·0144 |

Fig. 2. Dynamics of malaria infection before and during pregnancy. The values given for $L$ at 100 and 280 days' gestation may not be limiting prevalences since it is unknown if equilibrium (i.e., a recovery rate equal to incidence) is achieved at precisely these times.

to lose her age-dependent immunity only to reacquire it within the space of 9 months, and remarkably exhibits recovery at about the time of delivery. An increase in "pregnancy immunity" is seen with increasing parity.

However, while the pattern of susceptibility to infection may be similar, the immunological basis of that susceptibility is likely to be different in young children (with their first malaria infection) and in pregnant women (with a long experience of malaria but showing a temporary state of reduced immunity). This distinction is apparent from differences in parasite densities which, although not low in pregnancy, do not attain the levels seen in early childhood (*18*). Also, the main change in immunity is towards asexual stages of the parasite, since gametocytes are rarely found, particularly at the time of delivery (*2*, *19–24*). Local factors operating at the level of the placenta may be involved.

In addition, the pregnant woman remains in most cases asymptomatic (*10*, *19*) while the child suffers clinical attacks. Lawson (*5*) stated that the pregnant mother "suffers febrile attacks as she did in childhood", but did not mention the level of endemicity or whether this referred to hospital patients or primigravidae.

## COMPLICATIONS OF MALARIA IN PREGNANCY

### *Birth weight*

Table 5 summarizes published observations on the effect of placental infection on mean birth weight. All the values are lower than those observed in northern Europe. For example, in England and Wales the mean birth weight is 3310 g, with 6.9% having a birth weight of less than 2500 g (*25*). In all cases, a reduction in birth weight was seen with infection, although the mean overall difference was small (168 g) and, in several cases, was not statistically significant. If the majority of mothers from holoendemic areas have recovered from their infection at term, it might be expected that birth weight differences would be small even though parasites may still be present in placentae. Differences are likely to be greater for

Table 5. Effect of placental infection on birth weight

| Source | Area | No. of births | Placental infection (%) | Mean birth weight (g) | | Difference (g) |
|---|---|---|---|---|---|---|
| | | | | with infection | without infection | |
| Bruce-Chwatt, 1952 (*23*)[a,b] | S. Nigeria | 310 | 23.6 | 2903 | 3048 | 145 |
| Archibald, 1956 (*8*) | W. Nigeria | 512 | 15.0 | 2722 | 2892 | 170 |
| Archibald, 1958 (*45*)[c] | N. Nigeria | 440 | 14.1 | 2778 | 3076 | 298 |
| Cannon, 1958 (*29*)[d] | Nigeria | 392 | 33.2 | 2610 | 2920 | 310 |
| Spitz, 1959 (*28*) | E. Nigeria | 576 | 23.7 | 2851 | 2940 | 89 |
| MacLaren & Ward, 1962 (*46*)[c] | United Republic of Tanzania | 400 | 21.5 | 3037 | 3092 | 55 |
| Jelliffe, 1968 (*27*)[b,c] | Uganda | 570 | 16.1 | 2805 | 3068 | 263 |
| Jilly, 1969 (*35*)[b] | Ghana | 50 | 43.7[e] | 2855 | 3033 | 178 |
| Kortmann, 1972 (*2*)[c,d] | United Republic of Tanzania | 413 | 34.1 | 2945 | 3020 | 75 |
| Reinhardt et al., 1978 (*33*) | Ivory Coast | 198 | 33.7 | 2960 | 3080 | 120[f] |

[a] In all studies, except that by Bruce-Chwatt, twins were excluded from the analysis.

[b] Included placental pigment as evidence of infection.

[c] Still births were excluded from the analysis.

[d] No antimalarials taken during late pregnancy.

[e] Calculated on the basis of peripheral infections in 80 women.

[f] Calculated on the basis of peripheral infections. When placental infections were considered, birth weight difference was 103 g, but mean values not given.

primigravidae, and this has, in fact, been observed. McGregor (*26*) has reported that, of 3194 infants, statistically significant differences in birth weight were found only in the case of first-born infants. Jelliffe (*27*) in Uganda, and Kortmann (*2*) in the United Republic of Tanzania, have also reported greater differences in mean birth weight for these infants (321 g and 636 g, respectively).

Since Peel & Van Hoff (*22*) first commented on the increased incidence of low birth weight in mothers with malaria, several studies have confirmed this observation, with the highest incidence occurring in infected primigravidae (*2*, *27–29*). McGregor (*3*) found no consistent trend towards lower birth weights with increasing parasite density, but low birth weights were unusually frequent in the small group of children born to mothers with the most densely parasitized placentae. This effect may be due either to an increased number of premature births or to retardation of growth. If low birth weight is the result of an effect on fetal growth, then intervention studies that protect the mother throughout pregnancy might be expected to show greater differences in birth weight values between treated and untreated groups. Four such studies are listed in Table 6. Although moderate differences were seen for primigravidae, the mean differences were not greater than those shown in Table 5. This may be because prophylaxis was started after the first trimester when the process of immune recovery had already begun (*13, 30, 31*). However, McGregor & Avery (*32*) used chemical control measures (which would have had some effect on mothers throughout pregnancy), and showed a small improvement in mean birth weight but a dramatic improvement in the percentage of low birth weight babies ($\leqslant$ 2500 g), from 41% to 19% within the space of about 2 years. This may indicate the importance of control in early pregnancy, but still does not clarify if the effect is

Table 6. Results of intervention studies aimed at protecting women against malaria infection during pregnancy

| Source | Area | Birth weight (g)[a] | | | | | | Intervention |
|---|---|---|---|---|---|---|---|---|
| | | Protected | | Unprotected | | Difference | | |
| | | Primigravidae | Multigravidae | Primigravidae | Multigravidae | Primigravidae | Multigravidae | |
| Morley, 1964 (*31*) | Nigeria (Imesi) | 2771 (27) | 2982 (169) | 2580 (28) | 2833 (168) | 191 | 149 | Pyrimethamine 50 mg monthly; chloroquine sulphate, 600 mg, given to members of both groups with fever. |
| Gilles et al., 1969 (*13*) | Nigeria (Ibadan) | 3005 (43) | – | 2920 (14) | – | 85 | – | Chloroquine base, 600 mg, at presentation, then pyrimethamine, 25 mg, weekly. |
| Hamilton et al., 1972 (*30*) | Uganda (Kampala) | 2935 (114) | 3071 (228) | 2862 (86) | 3043 (201) | 73 | 28 | Chloroquine phosphate 300 mg base, weekly. |
| McGregor & Avery, 1974 (*32*) | Solomon Islands | 2829 (337) | 3043 (1132) | 2577 (191) | 2941 (779) | 252 | 102 | Residual spraying with DDT. |

[a] No. of subjects is given in parentheses.

mainly on fetal growth or prematurity or both. Rhinehart et al. (*33*) showed that malaria infection had no effect on gestational age at delivery but did not analyse the data according to parity. However, for the whole group, primiparae showed a greater incidence of impairment of fetal growth and prematurity (*34*).

*Fetal mortality*

There is no doubt that premature and false labour commonly occur in malarious mothers (*5*, *35*), but some authors (*19*, *22*, *23*) have been unable to show a convincing relationship between infection and the incidence of still births or abortions in immune mothers. Garnham (*36*), however, concluded that the incidence of abortions varied inversely with the degree of immunity of the mother. If the interpretation of prevalence given in Fig. 2 is correct, then in the first trimester, immune women are likely to demonstrate parasitaemia, particularly if they are primigravidae. A relationship between infection and abortion would not therefore be expected in women living in holoendemic areas. For those living under conditions of lower endemicity, where host immunity is more unstable and the ability to recover in the second half of pregnancy less adequate, a relationship between abortion and infection is more probable. This situation is seen in non-immune women going to live in endemic areas (*5*). In this situation, much larger differences in birth weight may be expected between infected and non-infected individuals, but these have not so far been reported.

A clinical correlate of this process would be seen in immune women if they were treated for infection early in pregnancy but subsequently not maintained on prophylaxis. Such women would lose the opportunity for natural recovery during pregnancy and would be very susceptible to severe infections with high parasitaemia in late pregnancy when metabolic stresses are highest. A number of cases reported by Kortmann (*2*) and Gilles et al. (*13*) would fit well with this clinical category. In these studies, immune women were treated early in pregnancy; their blood smears remained negative until late in pregnancy, when they developed unusually high parasitaemia, which in some cases induced premature labour. Unprotected women, bitten by mosquitos for the first time in late pregnancy would fall into the same category, and those not infected in their first pregnancy are likely to be as susceptible as primigravidae in their subsequent pregnancy.

*Anaemia*

Anaemia related to malaria in pregnancy is common and is usually haemolytic (*13*, *14*). It is of interest that, although groups of women with malaria, like children, often have anaemia, there is no correlation in individuals between haemoglobin level and parasite index during pregnancy (*2*, *13*). For 80 parturient women, Jilly (*35*) showed that individual erythrocyte volume fraction (haematocrit) levels showed no correlation with either parasitaemia or with placental infection or pigment at term. Christophers (*18*) made the same observation on immune adults, and found that the haemoglobin level was actually lower in those with a lower degree of parasitaemia.

There is a distinct parallel between the pattern of haematological events in pregnancy and that seen in children following acute malarial infections in infancy. In children, the peak incidence of anaemia and splenomegaly occurs after one year of age, following the period of acute infestation (*3*). In pregnancy, patients with haemolysis and splenomegaly characteristically present between the 16th and 24th weeks of gestation (*13*, *14*) following the period of acute infection in the first trimester. This observation supports the hypothesis that the immune mechanisms related to anaemia in these groups are alike. Recent studies suggest that immunological factors play an important role in the etiology of anaemia associated with malaria (*37*), and that the reduction in red blood cell life span persists for several weeks after the acute infection (*13*, *38*).

Fig. 3 shows the pattern of prevalence of anaemia and parasitaemia during pregnancy. The time of occurrence of anaemia shows good correlation with the latent period known to occur in individuals between the onset of acute infection and haemolysis. This association also explains why there is no correlation in individuals between haemoglobin level

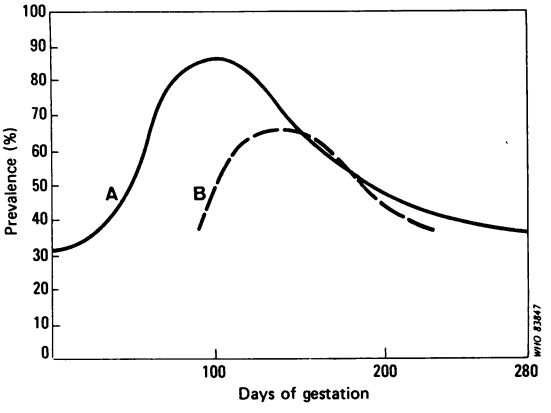



Fig. 3. Prevalence of parasitaemia (A) and haemolytic anaemia associated with splenomegaly (B) in primigravidae. Curve A is derived from the data obtained in west Kenya. Curve B is interpolated from the data of Gilles et al. (*13*) and Fleming et al. (*14*) obtained in Nigeria.

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 accounts for the apparently paradoxical observation that a group of individuals with malaria are likely to have anaemia. Secondary megaloblastic anaemia may occur, but this usually appears later in pregnancy and may have important consequences in itself for the child (*39*). The mechanism of haemolytic anaemia is probably distinct from that which induces immune tolerance to the parasite.

The slope of the anaemia prevalence curve after 24 weeks' gestation would not necessarily be altered by the administration of antimalarials alone at this time, because most mothers are already recovering. In clinical practice, it has been found that antimalarials given after 20–28 weeks' gestation will not correct established anaemia unless folic acid is given as well (*5*). Conversely, Gilles et al. (*13*), in their longitudinal study of primigravidae, demonstrated that prophylaxis from early in pregnancy resulted in none of the women developing a haemolytic anaemia.

It is thought that, in areas of high transmission, women have attained levels of immunity at which sickle cell trait confers no advantage (*40*). The situation may be different in areas of low transmission where the pattern of pregnancy immunity found in Fig. 2 would not be established. In holoendemic areas, similar haemoglobin levels are found in pregnant women with and without the trait (*2*), and similar morphological characteristics of placental infection are found in sicklers and in non-sicklers (*35*). However, a study of patients with anaemia in pregnancy (erythrocyte volume fraction $<0.23$) in Ibadan, Nigeria, showed that gross splenomegaly was significantly less common in the patients with sickle cell trait (*41*). Recent data from the Garki project suggest that the advantage of HbS is one of survival in childhood rather than increased maternal fertility. It is of interest, however, that Edington (*42*) showed that the mean birth weight of infants born to sickle-positive mothers was increased by 130 g, a difference that in itself may influence the chance of survival and curiously, is similar to the mean difference between infants born to mothers with and without placental infection at delivery (Table 5).

## CONCLUSIONS

The theory outlined to explain the epidemiology of malaria in pregnancy explains many of the observed features of the disease. The immunity which the child achieves over several years, the pregnant woman re-achieves in 9 months and, again, in successive pregnancies. Confirmation of these findings is required for women living under holoendemic conditions. Almost all the published literature on this topic refers to Africa, so there is a need for studies in other areas. The relationship between the pattern of malaria in individual mothers and that in their children is uncertain. Clarification of this would allow identification of the factors that promote maximal protective immunity under holoendemic conditions. Nutritional factors may be important in influencing host susceptibility in the first trimester and recovery during the second and third. Different guidelines may be required for the treatment and prophylaxis of women of different parities, especially in the light of drug resistance.

Although immunological correlates of malaria in pregnancy cannot at present be clearly defined, there is a need for the development of immunodiagnostic techniques to identify women who are susceptible late in pregnancy. It is probable that these women will deliver infants who are themselves susceptible. In view of this the relevance and usefulness of a future malaria vaccine in preventing infection in pregnancy should be assessed in terms of what this would mean for the child. The timing of loss of schizont immunity can be well defined during pregnancy and this may be important for testing any future vaccine derived from schizont antigens.

There are a number of biological implications of this "child-like" reaction in pregnancy, which may represent a mechanism to promote booster immunity in the developing fetus. Whatever its function, improvements in our understanding will be to the benefit of the child.

## ACKNOWLEDGEMENTS

The author is grateful to the provincial medical officer, Kakamega, and the district medical officer, Busia, for permission to work in the area; to Dr D. Wijers and staff at the Medical Research Centre, Nairobi, for logistic support for the field work undertaken; to Mr Peter Oboyo for excellent technical assistance, and the staff at Nangina Hospital for full cooperation. Miss A. C. Rijpstra (Department of Parasitology, University of Amsterdam) gave valuable help in checking microscopy results. Dr Luc Perrin and Professor P.H. Lambert kindly reviewed the manuscript. A special acknowledgement is due to Dr Louis Molineaux, World Health Organization, for assistance with the analysis of the prevalence data from west Kenya.

This paper is published with the permission of the Director of Medical Services, Kenya. Financial support for the field work was received from the Medical Research Centre, Kenya Medical Research Institute, Nairobi.

## RÉSUMÉ

### ANALYSE DU PALUDISME AU COURS DE LA GROSSESSE EN AFRIQUE

On estime généralement que, chez les femmes enceintes, la prévalence et la gravité de l'infection paludéenne sont accrues. Les groupes infectés peuvent être définis en fonction de la parasitémie ou bien d'une infection placentaire au moment de la délivrance. La prévalence de la parasitémie se rapproche plus étroitement de la prévalence globale combinée et représente donc le meilleur indice d'infection. Les rapports sur les taux d'infection en fonction de la parité montrent régulièrement que ce taux est à peu près deux fois plus élevé chez les primigestes que chez les multigestes, lors de l'accouchement. Dans diverses études, la prévalence moyenne globale pour les deux groupes de parité au moment de l'accouchement reste inférieur à 42%. Les taux de prévalence sont maximaux au cours du deuxième trimestre, alors que le niveau de l'infection au moment de l'accouchement ou à la période post-natale est voisin de ce qu'on observe chez les femmes qui ne sont pas enceintes. Les densités parasitaires les plus élevées s'observent aussi au début de la grossesse.

L'évolution des taux de prévalence pendant la grossesse peut s'expliquer par un abaissement du taux de guérison ($r$) pendant le premier trimestre et une augmentation de $r$ à la fin de la grossesse. Un modèle a été appliqué pour décrire cette série d'événements dans les régions holoendémiques et pour analyser des données récentes provenant de l'ouest du Kenya, ce qui permet une définition plus précise des taux de prévalence pour des périodes données de la gestation. C'était nécessaire pour pouvoir déterminer l'âge de la grossesse correspondant à la parasitémie maximale.

Des études ont été effectuées sur 455 femmes fréquentant un dispensaire prénatal rural dans l'ouest du Kenya. Pour les primigestes comme pour les multigestes, le taux maximal de parasitémie s'observait à 13–16 semaines de grossesse (85,7% pour les premières et 51,7% pour les secondes) et les deux groupes présentaient un abaissement similaire de la prévalence pendant la fin de la grossesse. En appliquant le modèle à ces données, on a constaté que si $r$ diminuait de 11 fois au cours du premier trimestre, cela fournirait une explication satisfaisante de la modification observée dans les taux de prévalence. La guérison de la femme enceinte pendant la deuxième moitié de la grossesse est comparable à l'acquisition de l'immunité dans l'enfance. (*17*).

Ce tableau indique que les femmes développent une réponse immunitaire satisfaisante à l'infection paludéenne à la fin de la grossesse. Cela concorde avec plusieurs observations sur les complications du paludisme au cours de la grossesse (poids à la naissance, mortalité fœtale, anémie). En particulier, cela explique pourquoi la prévalence maximale de l'anémie hémolytique survient pendant le deuxième trimestre. Cela rend compte également d'observations paradoxales, à savoir qu'il y n'a aucune relation entre les taux d'hémoglobine individuels et les densités parasitaires et que, cependant, les femmes atteintes de paludisme tendent à être anémiées.

Les conséquences pratiques de cette théorie présentent un intérêt en ce qui concerne le traitement clinique des malades et la mise au point de techniques de diagnostic immunologique en vue de dépister les femmes courant le plus grand risque. La connaissance de l'épidémiologie du paludisme au cours de la grossesse et de ses conséquences pour l'enfant est nécessaire avant qu'on puisse penser à appliquer un futur vaccin antipaludique au cours de la grossesse.


## REFERENCES


1. SCHUFFNER, W. A. P. Two subjects relating to the epidemiology of malaria. Reprinted in: *Journal of the Malaria Institute of India*, **1**: 221-256 (1938). (Originally published in *Mededeelingen van den burgerilijken geneeskundigen dienst in Nederlandsch-Indie* (1919)).
2. KORTMANN, H. F. C. M. *Malaria and pregnancy*. M.D. thesis. University of Amsterdam, Utrecht, Drukkerij Elinkwijk, 1972.
3. MCGREGOR, I. A. Topical aspects of the epidemiology of malaria. *Israel journal of medical sciences*, **14**: 523-533 (1978).
4. BLACKLOCK, D. B. & GORDON, R. M. Malaria infection as it occurs in late pregnancy; its relation to labour and early infancy. *Annals of tropical medicine and parasitology*, **19**: 327-363 (1925).
5. LAWSON, J. B. Malaria in pregnancy. In: Lawson, J. B. & Stewart. D. B., ed., *Obstetrics and gynaecology in the tropics and developing countries*. London, E. Arnold, 1967, pp. 59-72.
6. VAN DEN BRANDEN, F. Recherche sur la malaria congénitale, faite au Congo Belge (Léopoldville). *Bulletin de la Société de Pathologie Exotique*, **20**: 338-342 (1927).
7. THONNARD-NEUMANN, E. Plazentare Malariainfektion, kongenitale Malaria und Impfmalaria. *Münchener medizinische Wochenschrift*, **79** (10): 382-383 (1932) (Quoted in *Tropical diseases bulletin*, **29**: 697 (1932)).
8. ARCHIBALD, H. M. The influence of malarial infection of the placenta on the incidence of prematurity. *Bulletin of the World Health Organization*. **15**: 842-845 (1956).
9. MADECKI, O. & KRETSCHMAR, W. Haüfigkeit und Ursachen der angeborenen Malaria in West Africa. *Zeitschrift für Tropenmedizin und Parasitologie*, **17**: 195-210 (1966).
10. WALTON, G. A. On the control of malaria in Freetown, Sierra Leone. II. Control methods and the effects upon the transmission of *Plasmodium falciparum* resulting from the reduced abundance of *Anopheles gambiae*. *Annals of tropical medicine and parasitology*, **43**: 117-139 (1949).

11. PINGOUD, E. Malaria Plasmodien im Blute von Schwangeren und Nichtschwangeren in Abeokuta (West Nigeria). *Zeitschrift für Tropenmedizin und Parasitologie*, **20**: 279–287 (1969).
12. BRAY, R. S. & ANDERSON, M. J. Falciparum malaria and pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **73**: 427–431 (1979).
13. GILLES, H. M. ET AL. Malaria, anaemia and pregnancy. *Annals of tropical medicine and parasitology*, **63**: 245–263 (1969).
14. FLEMING, A. F. ET AL. Haemolytic anaemia in pregnancy in Nigeria: recognition by simple laboratory procedures. *West African medical journal*, **18** (3): 82–88 (1969).
15. ROSS, R. An application of the theory of probabilities to the study of *a priori* pathometry: Part I. *Proceedings of the Royal Society, Series A*, **92**: 204–230 (1916).
16. FONTAINE, R. E. ET AL. Evaluation of fenitrothion for the control of malaria. *Bulletin of the World Health Organization*, **56**: 445–452 (1978).
17. BEKESSY, A. ET AL. Estimation of incidence and recovery rates of *Plasmodium falciparum* parasitaemia from longitudinal data. *Bulletin of the World Health Organization*, **54**: 685–693 (1976).
18. CHRISTOPHERS, S. R. The mechanism of immunity against malaria in communities living under hyperendemic conditions. *Indian journal of medical research*, **12**: 273–294 (1924).
19. SCHWETZ, J. & PEEL, M. Congenital malaria and placental infections amongst the negroes of Central Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **28**: 167–174 (1934).
20. BUTLER, G. G. Malaria in parturient women. *Gold Coast report of laboratory services, year 1929–30*, appendix C pp. 31–33 (Quoted in *Tropical diseases bulletin*, **29**: 349–350 (1932)).
21. GARNHAM, P. C. C. The placenta in malaria with special reference to reticulo-endothelial immunity. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **32**: 13–34 (1938).
22. PEEL, E. & VAN HOOF, L. Le paludisme à la maternité indigène de Léopoldville. *Annales de la Société Belge de Médecine Tropicale*, **28**: 413–420 (1948).
23. BRUCE-CHWATT, L. J. Malaria in African infants and children in Southern Nigeria. *Annals of tropical medicine and parasitology*, **46**: 173–200 (1952).
24. GALBRAITH, R. M. ET AL. The human materno-foetal relationship in malaria: I. Identification of pigment and parasites in the placenta. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **74**: 52–60 (1980).
25. The incidence of low birth weight, a critical review of available information. *World health statistics quarterly*, **33**: 197–224 (1980).
26. MCGREGOR, I. A. Placental malaria. In: Sterky, G. & Mellander, L., ed., *Birth weight distribution an indicator of social development*. Uppsala, Swedish agency for research cooperation with developing countries, 1978, pp. 17–18 (Sarec report, No. R 2).
27. JELLIFFE, E. F. P. Low birth-weight and malarial infection of the placenta. *Bulletin of the World Health Organization*, **38**: 69–78 (1968).
28. SPITZ, A. J. W. Malaria infection of the placenta and its influence on the incidence of prematurity in Eastern Nigeria. *Bulletin of the World Health Organization*, **21**: 242–244 (1959).
29. CANNON, D. S. H. Malaria and prematurity in the Western region of Nigeria. *British medical journal*, **2**: 877–878 (1958).
30. HAMILTON, P. J. S. ET AL. The role of malaria, folic acid deficiency and haemoglobin AS in pregnancy at Mulago hospital. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **66**: 594–602 (1972).
31. MORLEY, D. ET AL. Controlled trial of pyrimethamine in pregnant women in an African village. *British medical journal*, **1**: 667–668 (1964).
32. MCGREGOR, J. D. & AVERY, J. G. Malaria transmission and fetal growth. *British medical journal*, **3**: 433–436 (1974).
33. REINHARDT, M. C. ET AL. Malaria at delivery in Abidjan. *Helvetica paediatrica acta*, **33** (Suppl. 41): 65–84 (1978).
34. REINHARDT, M. C. ET AL. A study of 204 consecutive deliveries in Abidjan — anthropometric data of newborns, mothers and placentas. *Helvetica paediatrica acta*, **33** (Suppl. 41): 21–42 (1978).
35. JILLY, P. Anaemia in parturient women, with special reference to malaria infection of the placenta. *Annals of tropical medicine and parasitology*, **63**: 109–116 (1969).
36. GARNHAM, P. C. C. Malarial immunity in Africans: effects in infancy and early childhood. *Annals of tropical medicine and parasitology*, **43**: 47–61 (1949).
37. PERRIN, L. H. ET AL. The haematology of malaria in man. *Seminars in haematology*, **19**: 70–81 (1982).
38. WOODRUFF, A. W. ET AL. Cause of anaemia in malaria. *Lancet*, **1**: 1055–1057 (1979).
39. BRABIN, B. J. Hypothesis: the importance of folacin in influencing susceptibility to malarial infection in infants. *American journal of clinical nutrition*, **35**: 146–151 (1982).
40. MOLINEAUX, L. & GRAMICCIA, G. *The Garki project. Research on the epidemiology and control of malaria in the Sudan Savanna of West Africa*. Geneva, World Health Organization, 1980.
41. FLEMING, A. F. ET AL. Splenomegaly and sickle cell trait. *Lancet*, **3**: 574–575 (1968).
42. EDINGTON, G. M. The pathology of sickle cell disease in West Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **49**: 253–267 (1955).
43. CLARK, H. C. The diagnostic value of the placental blood film in aestivo-autumnal malaria. *Journal of experimental medicine*, **22**: 427–444 (1915).
44. LOMBART, H. Congenital malaria among natives of Elisabethville. *Annales de la Société Belge de Médecine Tropicale*, **11**: 315–319 (1931).
45. ARCHIBALD, H. M. Influence of maternal malaria on newborn infants. *British medical journal*, **2**: 1512–1514 (1958).
46. MCLAREN, D. S. & WARD, P. G. Malarial infection of the placenta and foetal nutrition. *East African medical journal*, **39**: 182–189 (1962).