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The impact of malaria chemoprophylaxis on the immune status of Africans

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The small number of studies undertaken so far indicates that malaria control with chemoprophylaxis depresses serum gamma-globulin levels and interferes with the development of the malaria antibodies detected by standard serological tests. Whether these serological changes are associated with defective development of clinical immunity has yet to be clearly established.

Chemoprophylaxis for high-risk groups, such as children under the age of 5 years and pregnant women, is a possible approach to the control of malaria in areas of Africa where the infection is endemic and where vector control is impossible. Mass chemoprophylaxis, if properly administered, can probably prevent deaths from malaria, but it favours the emergence of drug-resistant parasites and it may interfere with the development of natural immunity to the infection. Critics of the concept of mass chemoprophylaxis argue that there is little point in protecting a child from malaria during the first 5 years of life if the child is likely to die from malaria as soon as prophylaxis is stopped. Whether this is a real or only a theoretical risk has never been clearly established.

CLINICAL MALARIA AFTER A PERIOD OF CHEMOPROPHYLAXIS

Repeated antigenic stimulation is required to maintain established immunity to malaria and adult Africans who return to an endemic area after a period abroad may experience a clinical attack of the infection (*1*). However, such attacks are rarely severe, even in individuals who have been away for many years, indicating that a degree of immunity can be preserved in the absence of exposure for a considerable period. Thus, it is unlikely that pregnant women with established malaria immunity will lose this as a result of taking chemoprophylaxis for only a few months during pregnancy. In children, the situation may be different.

Very few formal studies of the consequences of stopping malaria chemoprophylaxis have been undertaken in Africa. Pringle & Avery-Jones (*2*) reported that severe attacks of malaria occurred in Tanzanian schoolchildren who had been protected from malaria for only a few months by treatment with chloroquine and primaquine. However, "rebound malaria" was not observed in a group of Nigerian schoolchildren when chemoprophylaxis with pyrimethamine was stopped after a 1–2 year period of drug administration (*3*). A group of 94 young Nigerian children were carefully followed for 6 months after chemoprophylaxis was stopped (*4*). These children had received chloroquine weekly from shortly after birth until the age of 1 or 2 years. Only 1 death, for which no cause could be established, occurred during the follow-up period, which, for most children, covered a rainy season. No increase in the incidence of severe febrile illnesses was noted although morbidity was not formally assessed in this study.

Some indications of the likely effects of mass chemoprophylaxis on the development of immunity to malaria can be obtained from study of projects in which malaria control was successfully achieved for a limited period by vector control or by vector control combined with chemoprophylaxis. Unfortunately, few studies were made of the impact on health of the vector control programmes undertaken in tropical Africa during the 1950s and 1960s. The control scheme carried out in the Pare region of the United Republic of Tanzania was an important exception. In this area, malaria was effectively controlled for a period of 3 years by spraying with dieldrin. Pringle (*5*) studied what happened when malaria control was stopped. The number of clinical cases of malaria in the area and the prevalence of parasitaemia in schoolchildren increased about 1 year after the final round of spraying (Fig. 1) and this increase persisted into the following year. However, no increase in the incidence of deaths from malaria was reported. At Garki, in northern Nigeria, very effective malaria control was achieved over a period of two rainy

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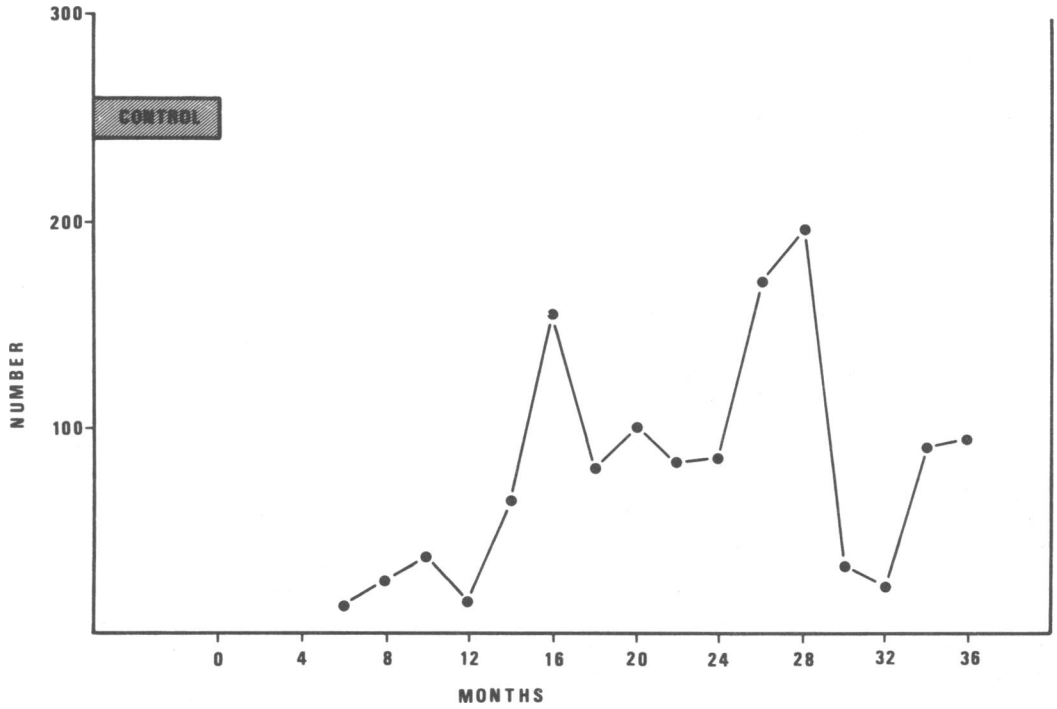

Fig. 1. Number of Tanzanian children aged 2–9 years with malaria parasitaemia at varying times between 6 and 36 months after interruption of a malaria control programme. (From Pringle (*5*)).

seasons by a combination of vector control and chemoprophylaxis (*6*). Following the interruption of control measures, the prevalence of malaria parasitaemia gradually rose to the pre-intervention level (Fig. 2) and the prevalence of *Plasmodium falciparum* parasitaemia in previously protected subjects over the age of 10 years temporarily exceeded the level found in controls (Fig. 3). However, this effect was not marked and it was not accompanied by any increase in the incidence of febrile illnesses. Chloroquine was widely available in the study area during the post-intervention period and this may have contributed to the absence of such an increase.

CHEMOPROPHYLAXIS AND THE ANTIBODY RESPONSE TO MALARIA

Few studies of the effects of chemoprophylaxis on the antibody response to malaria have been undertaken. Early studies by McGregor and his colleagues (*7–9*) showed that serum gamma-globulin levels were lower in Gambian children and pregnant women who received regular chemoprophylaxis than in controls (Table 1). In children, a difference was present between the two groups by the age of 2 years.

Voller & Wilson (*10*) measured malaria antibodies by the fluorescent antibody technique in a small number of Gambian infants and mothers who were protected from malaria by weekly administration of pyrimethamine. At a mean age of 7 months, fluor-

Table 1. Mean serum gamma-globulin levels (expressed as a percentage of total serum protein) in Gambian children maintained on chemoprophylaxis with chloroquine and in age-matched control children[a]

Age (years)	Protected children		Control children	
	Number	Mean	Number	Mean
1	27	19.7±4.7	29	19.7±4.1
2	22	20.6±3.9[b]	21	26.1±5.5
4	16	24.3±5.7[b]	13	32.2±4.4
5	21	23.9±3.1[b]	13	27.7±4.6
6	20	25.2±3.9[b]	11	31.4±3.5

[a] Compiled from data from Gilles & McGregor (*7*) and from McGregor & Gilles (*8*).

[b] Differences between groups statistically significant.

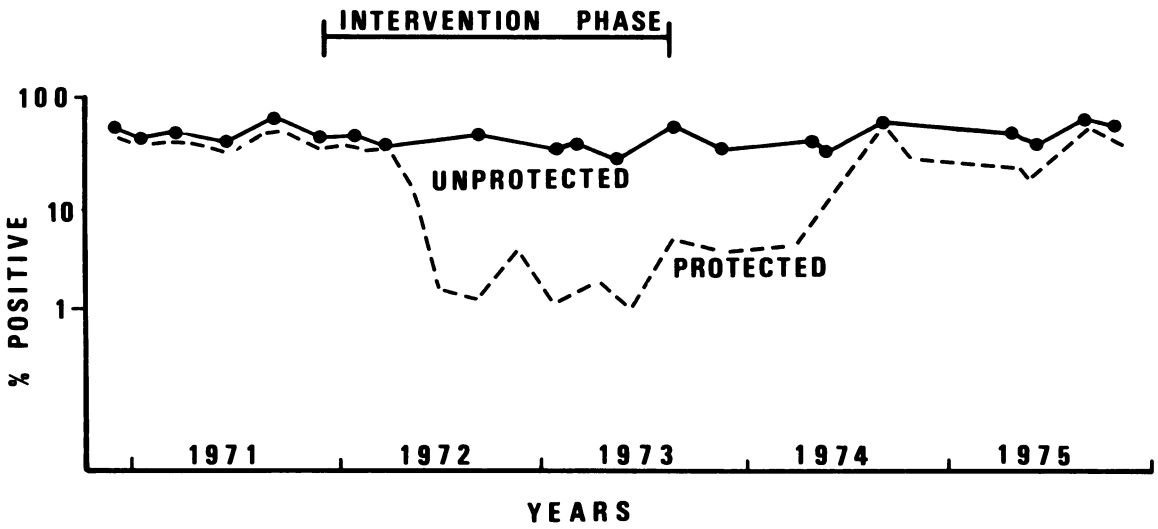

Fig. 2. The prevalence of *P. falciparum* parasitaemia during the 1970s at Garki (northern Nigeria) before, during, and after a malaria control programme ("intervention phase"). (From Molineaux & Gramiccia (*6*)).

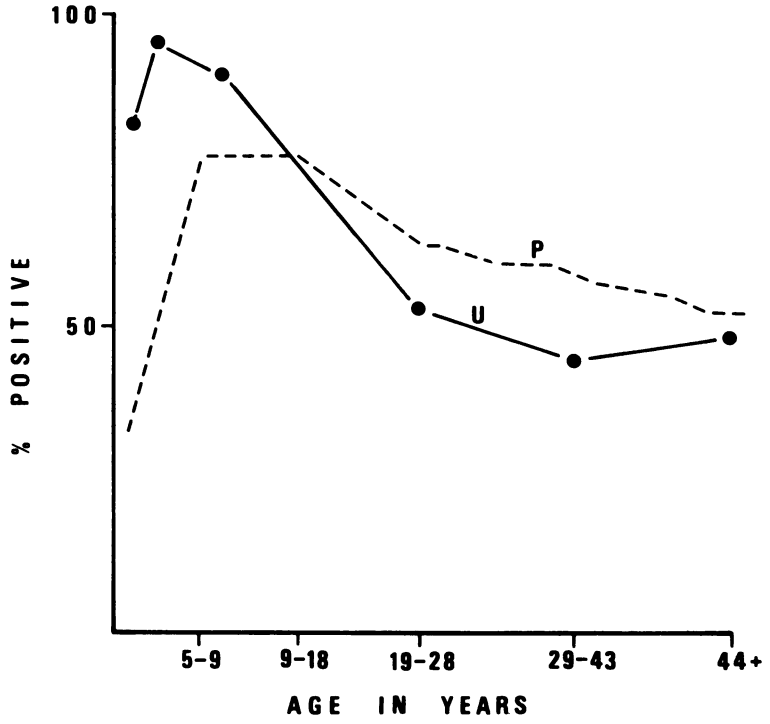

Fig. 3. The prevalence of parasitaemia with asexual forms of *P. falciparum*, by age group, in Nigerians previously protected from malaria for two wet seasons (P) and in unprotected controls (U). (From Molineaux & Gramiccia (*6*)).

Table 2. The influence of weekly chemoprophylaxis with chloroquine, given for 1 or 2 years from shortly after birth, on the development of malaria antibodies in Nigerian children[a]

Antibody measurement technique	Age (years)	Protected children			Control children		
		No. tested	No. positive	Percentage positive	No. tested	No. positive	Percentage positive
Precipitin technique	1	21	10	48	11	10	91
	2	23	18	78	22	20	91
ELISA[b]	1	42	13	31	39	26	67
	2	53	36	68	54	50	93
Fluorescent antibody technique[c]	1	10	9	90	8	8	100
	2	10	7	70	15	15	100

[a] From Bradley-Moore (*4*).

[b] Sera giving an absorbance of 0.2 or greater were considered positive.

[c] Sera giving fluorescence at a titre of 1:20 or greater were considered positive.

escent antibody was found in all of 7 control infants but in none of 7 protected children. The mean fluorescent antibody titre found in pregnant women who received chemoprophylaxis was about one third of the mean titre found in control women. In Uganda, fluorescent antibody was found in a higher proportion of supposedly protected children (12 of 26) but these children were older than the infants studied in the Gambia (*11*). Ibeziako & Williams (*12*) found low levels of fluorescent malaria antibody in a group of pregnant Nigerian women who had been given pyrimethamine throughout pregnancy but, as control sera were not tested at the same time, these data are difficult to interpret.

In the Malumfashi study (*4*), malaria antibody levels were measured at intervals in children given chloroquine weekly throughout the first 2 years of life. Antibodies were measured by the fluorescent antibody technique, enzyme-linked immunosorbent assay (ELISA), and precipitin techniques. The findings of this study are summarized in Table 2. Differences were found between the two groups but, by the age of 2 years, a high proportion of children who had received chemoprophylaxis had developed antibody.

The effects of chemoprophylaxis on the development of malaria antibodies have been studied at the community level by Onori et al. (*13*) who measured malaria antibodies by the fluorescent antibody technique in 300 subjects from Mto-wa-Mbu in the United Republic of Tanzania, where chloroquine has been used widely for chemoprophylaxis for nearly 20 years. Despite high levels of parasitaemia (average 47%), only 67% of the population had fluorescent antibody at a titre of 1:20 or greater and mean titres were low in subjects in each age group. Antibody was not detected in sera from nearly one half of children with parasitaemia. Unfortunately, no pre-intervention data on antibody levels had been collected in this

Table 3. Prevalence of a positive fluorescent malaria antibody test by age in Muheza-Ubembe, United Republic of Tanzania, in 1967 and in Mto-wa-Mbu in 1981[a]

Muheza-Ubembe, 1967			Mto-wa-Mbu, 1981[b]		
Age group (years)	No. of people examined	Percentage positive	Age group (years)	No. of people examined	Percentage positive
<1	25	71	<1	20	40
1	21	84	1	11	46
2–5	102	85	2–4	39	56
6–10	124	92	5–9	48	40
11–15	120	92	10–14	34	65
⩾16	403	98	⩾15	148	84

[a] Based on data from Onori et al. (*13*).

[b] Chemoprophylaxis with chloroquine has been practised in Mto-wa-Mbu for two decades. Prior to intervention the prevalence of parasitaemia in the two communities was similar.

population, but the antibody levels found in 1981 at Mto-wa-Mbu were much lower than those recorded previously in other parts of Tanzania where no chemoprophylaxis had been given (Table 3). The antigen used to measure antibodies in sera from Mto-wa-Mbu was a Gambian isolate of *P. falciparum* that had been kept in culture for many years. It is possible that use of this strain, rather than a fresh Tanzanian isolate, may have influenced the serological results obtained.

The most detailed information collected to date on the influence of malaria control on the development of malaria antibodies has come from the Garki study, in which malaria control was achieved by a combination of insecticide spraying and chemoprophylaxis (*6*). At Garki, malaria antibodies were measured by the fluorescent antibody technique, indirect haemagglutination, and precipitin techniques, and serum immunoglobulin levels were determined by the Mancini method. Serum IgM and malaria antibody levels fell significantly following intervention. For IgM the difference between protected and control subjects was most marked in adults, while differences in malaria antibody levels were most marked in children. Very low malaria antibody levels were found in a group of protected infants followed up from birth until the age of 1 year (Fig. 4). During the 2-year period of observation that followed interruption of malaria control, immunoglobulin and malaria antibody levels gradually increased and the level of haemagglutinating *P. falciparum* antibody in the previously protected group temporarily exceeded the level found in controls, an observation in keeping with the parasitological changes found at this time.

CHEMOPROPHYLAXIS AND THE IMMUNE RESPONSE TO IMMUNIZATION

The antibody response of children with acute malaria to immunization with tetanus, typhoid, and meningococcal vaccines is impaired (*14–16*) and this generalized depression of humoral immunity may contribute to the increased susceptibility of children with malaria to secondary bacterial infections, such as salmonellosis. Immunodepression induced by malaria could also be one of the factors responsible for the poor response to routine immunization some-

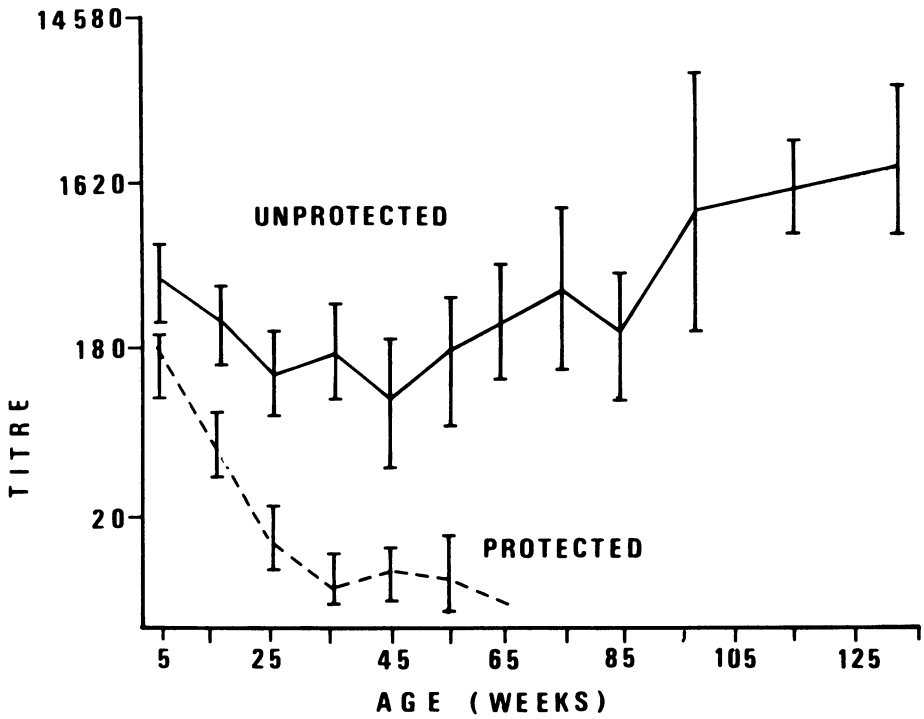

Fig. 4. Titres of fluorescent antibodies to *P. falciparum* (mean and 95% confidence limits) in Nigerian infants protected from malaria from birth and in control infants. (From Molineaux & Gramiccia (*6*)).

Table 4. Seroconversion rates to routine immunization in Nigerian children given weekly chemoprophylaxis with chloroquine from birth and in age-matched controls[a]

Vaccine	Protected children[b]		Control children[b]	
	Proportion who sero-converted	%	Proportion who sero-converted	%
Diphtheria	134/135	99	127/130	98
Tetanus	134/135	99	127/128	99
Poliomyelitis (type 1)	13/27	48	11/19	58
Measles	90/91	99	90/91	99
Meningococcal group A	13/18	72	15/18	83
Meningococcal group C	41/48[c]	85	30/49	61
Typhoid	3/3	100	3/3	100

[a] From Bradley-Moore (*4*).

[b] Data are presented for children who did not have antibody at the time of vaccination.

[c] $P = 0.01$.

times observed in communities where malaria is endemic. This possibility was investigated in the Malumfashi study in which the immune response to a standard programme of infant immunization was determined in a group of Nigerian infants who received chemoprophylaxis with chloroquine from shortly after birth and in a group of control children (*4–17*). Significant differences between the two groups were found only for meningococcal polysaccharide vaccine (Table 4), a finding in keeping with the observation that, in a malaria endemic area, the immune response to this vaccine can be improved by prior administration of chloroquine (*18*).

CONCLUSIONS

The limited number of studies that have been undertaken so far show that control of malaria produces a fall in malaria antibody levels in the protected population and that the magnitude of this fall is related to the efficacy of the control programme. Thus, at Garki, where very effective malaria control was achieved by a combination of insecticide spraying and chemoprophylaxis, very low malaria antibody levels were found in a group of infants protected from birth. On the other hand, at Malumfashi, where less effective malaria control was achieved, most protected children had malaria antibodies by the age of 2 years. The results of the Malumfashi study are likely to be a closer reflection of what would happen following the introduction of malaria chemoprophylaxis into a primary health care programme than the results obtained at Garki.

None of the antibodies measured in standard serological tests is related to clinical immunity and it would be of interest to know what influence chemoprophylaxis might have on the development of merozoite-growth-inhibiting, opsonizing, and adherence-inhibiting antibodies, each of which may have an important biological function.

No properly controlled studies of the effects of malaria chemoprophylaxis on the development of protective immunity have been undertaken. It seems unlikely that chemoprophylaxis could be given sufficiently effectively at the community level to prevent all episodes of parasitaemia and the consequent development of some protective immunity. Whether or not this is the case must be firmly established before chemoprophylaxis is introduced widely into primary health care programmes throughout Africa.

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RÉSUMÉ

L'IMPACT DE LA CHIMIOPROPHYLAXIE DU PALUDISME SUR L'ÉTAT IMMUNITAIRE DES AFRICAINS

Les études, peu nombreuses, entreprises jusqu'ici indiquent que du fait de la lutte antipaludique, il se produit une chute des taux d'anticorps antiplasmodies dans les populations protégées et que l'importance de cette chute est en rapport avec l'efficacité du programme de lutte. Ainsi, à Garki, où l'on est parvenu à lutter très efficacement contre le paludisme en combinant les pulvérisations d'insecticides et la chimioprophylaxie, on a trouvé des taux d'anticorps très faibles dans un groupe de nourrissons protégés depuis la naissance. D'autre part, à Malumfashi, où l'on n'a pas réussi à contenir aussi efficacement le paludisme, la majorité des enfants protégés possédaient encore des anticorps à l'âge de 2 ans. Les résultats de l'étude de Malumfashi sont susceptibles d'être plus représentatifs que ceux de Garki de l'impact que pourrait avoir la chimioprophylaxie antipaludique menée dans le cadre des soins de

santé primaires.

L'un des anticorps titré selon les méthodes sérologiques classiques est en rapport avec l'immunité clinique et il serait intéressant de savoir quelle influence la chimioprophylaxie pourrait avoir sur l'apparition d'anticorps inhibant la croissance des mérozoïtes, d'opsonines et d'anticorps inhibiteurs de l'adhérence, chacun d'eux ayant une importante fonction biologique.

Aucune étude, convenablement contrôlée, des effets de la chimioprophylaxie antipaludique sur le développement de l'immunoprotection n'a été réalisée. Il semble en tous cas improbable que la chimioprophylaxie puisse être administrée assez efficacement au niveau communautaire pour prévenir tous les épisodes de parasitémie et empêcher, par suite, l'apparition d'une immunoprotection. C'est là une hypothèse qu'il convient de confirmer avant d'introduire largement la chimioprophylaxie dans les programmes de soins de santé primaires dans toute l'Afrique.

REFERENCES

1. COLBOURNE, M. J. Malaria in Gold Coast students on their return from the United Kingdom. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **49**: 483–487 (1955).
2. PRINGLE, G. & AVERY-JONES, S. Observations on the early course of untreated falciparum malaria in semi-immune African children following a short period of protection. *Bulletin of the World Health Organization*, **34**: 269–272 (1966).
3. ARCHIBALD, H. M. & BRUCE-CHWATT, L. J. Suppression of malaria with pyrimethamine in Nigerian schoolchildren. *Bulletin of the World Health Organization*, **15**: 775–784 (1956).
4. BRADLEY-MOORE, A. M. *Immunosuppression and malaria*. Thesis, University of London, 1982.
5. PRINGLE, G. Malaria in the Pare area of Tanzania. III. The course of malaria transmission since the suspension of an experimental programme of residual insecticide spraying. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **61**: 69–79 (1967).
6. MOLINEAUX, L. & GRAMICCIA, G. *The Garki project*. Geneva, World Health Organization, 1980.
7. GILLES, H. M. & MCGREGOR, I. A. Studies on the significance of high serum gamma-globulin concentrations in Gambian Africans. I. Gamma-globulin concentrations of Gambian children in the first two years of life. *Annals of tropical medicine and parasitology*, **53**: 492–500 (1959).
8. MCGREGOR, I. A. & GILLES, H. M. Studies on the significance of high serum gamma-globulin concentrations in Gambian Africans. II. Gamma-globulin concentrations of Gambian children in the fourth, fifth and sixth years of life. *Annals of tropical medicine and parasitology*, **54**: 275–280 (1960).
9. GILLES, H. M. & MCGREGOR, I. A. Studies on the significance of high serum gamma-globulin concentrations in Gambian Africans. III. Gamma-globulin concentrations of Gambian women protected from malaria for two years. *Annals of tropical medicine and parasitology*, **55**: 463–467 (1961).
10. VOLLER, A. & WILSON, H. Immunological aspects of a population under prophylaxis against malaria. *British medical journal*, **2**: 551–552 (1964).
11. HARLAND, P. S. E. G. ET AL. Some effects of partial malaria suppression in Ugandan children during the first 3 years of life. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **69**: 261–262 (1975).
12. IBEZIAKO, P. A. & WILLIAMS, A. I. O. The effect of malaria chemoprophylaxis on immunoglobulin levels of pregnant Nigerian women and their newborn. *British journal of obstetrics and gynaecology*, **87**: 976–982 (1980).
13. ONORI, E. ET AL. Incipient resistance of *Plasmodium falciparum* to chloroquine among a semi-immune population of the United Republic of Tanzania. 2. The impact of chloroquine used as a chemosuppressant on the immune status of the population. *Bulletin of the World Health Organization*, **60**: 899–906 (1982).
14. MCGREGOR, I. A. & BARR, M. Antibody response to tetanus inoculations in malarious and non-malarious Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **56**: 364–367 (1962).
15. GREENWOOD, B. M. ET AL. Immunosuppression in children with malaria. *Lancet*, **1**: 169–172 (1972).
16. WILLIAMSON, W. A. & GREENWOOD, B. M. Impairment of the immune response to vaccination after acute malaria. *Lancet*, **1**: 1328–1329 (1978).
17. GILLES, H. M. ET AL. The Malumfashi Project — an epidemiological, clinical and laboratory study. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **77**: 24–31 (1983).
18. GREENWOOD, A. M. ET AL. Enhancement of the immune response to meningococcal polysaccharide vaccine in a malaria endemic area by administration of chloroquine. *Annals of tropical medicine and parasitology*, **75**: 261–263 (1981).