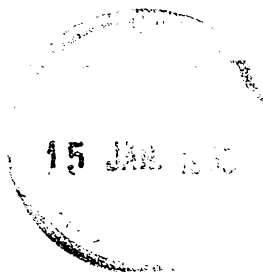


a 68250



WHO/Ma1/365 ✓  
21 November 1962

ORIGINAL: ENGLISH

IMMUNITY TO MALARIA IN ERADICATION  
OPERATIONS, WITH PARTICULAR REFERENCE  
TO HYPERENDEMIC AREAS OF EAST AFRICA<sup>1</sup>

by

G. Pringle  
East African Institute of Malaria and Vector-Borne Diseases  
Amani, Tanganyika

1. The Development of Immunity in a Hyperendemic Population

In this context McGregor (1960) has suggested that the following stages can be recognized:

Stage 1: an initial period of insusceptibility, lasting from birth to around the third month, due to passively acquired maternal antibodies. Most infections are aborted and those that do become patent are mild, both clinically and parasitologically.

Stage 2: that of primary attack, which occupies the middle period of infancy. Infections are followed by attacks of malaria which are nevertheless still moderated and foreshortened by the persistence of a shrinking residue of antibodies.

Stage 3: the trough of host resistance, entered before the first birthday. The child is no longer supported by any remnants of passive immunity and clinical sequelae to infection, and parasite densities are maximal. The duration of this period is related inversely to the frequency of infection: in areas of very intense malaria it is probably not prolonged beyond the second birthday.

---

<sup>1</sup> Working document submitted to the WHO Third African Malaria Conference (Yaoundé, Cameroun, 3-13 July 1962)

Stage 4: the period of evolving immunity. Immunological processes are aroused during Stage 2 but immunity does not begin to attain an effective level until the end of Stage 3. This stage, often extending into adolescence, is characterized by a progressive decline, and eventual disappearance, of clinical evidence of infection. However crops of parasites recur frequently in the peripheral blood and gametocytaemia often follows a period of active schizogony. This period is therefore one of increasing tolerance.

Stage 5: the stage of immunity. Only when transmission is intense is the ultimate level of immunological equilibrium attained before adolescence; indeed, complete insusceptibility to all local strains of parasite is rarely, if ever, achieved. In immune adults clinical evidence of malaria infection is characteristically lacking, and trophozoites and gametocytes are usually absent from the peripheral blood in other than insignificant densities.

Immunity is not retained indefinitely without the stimulus of repeated malaria infections. It has been demonstrated, for example, that the immunity acquired by the population during the course of a malaria epidemic is almost entirely dissipated within the subsequent decade. While the immunity developed by the African population of hyperendemic areas must be substantially greater than that acquired by the community during an isolated epidemic, there is evidence from many quarters that this also declines when the malaria risk is removed. Experience in East Africa suggests that a period of three or four years' residence in a non-malarious district is sufficient to lower immunity in the Bantu adult to the level at which malaria infection is followed by a clinical episode.

The degrees of immunity in various age-groups, and the response to a period of protection, have implications with regard to malaria eradication operations in equatorial Africa. These may now be reviewed briefly in the light of observations made recently in East Africa.

2. The Measurement of Transmission in an Incompletely Protected Population

During the Taveta-Pare Malaria Scheme the parasite rates of various age-groups were measured annually. The rates prevailing before and two and three years after the inception of residual spraying are compared in Table 1.

TABLE 1. PARASITE RATES IN TAVETA-PARE MALARIA CONTROL SCHEME DURING ONE PERIOD BEFORE, AND TWO PERIODS AFTER RESIDUAL SPRAYING STARTED IN 1955

Period Examined	Age-groups													
	0-11 months		12-23 months		2-4 years		5-9 years		10-14 years		15-19 years		Over 20	
	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.
1954/55	338	47	838	47	1 147	64	2 253	62	1 891	52	705	39	4 309	22
1957/58	394	2	714	4	889	12	2 162	16	1 570	17	501	7	2 655	5
1958/59	270	1	541	3	608	6	1 250	9	955	8	302	4	1 543	3

Exd. = numbers examined

P.R. = parasite rate per cent.

During the latter period it was noted that the parasite rate in children was consistently greater than that in infants or in adults. It was important to establish whether this was due to transmission that was manifesting itself mainly in children, or to abnormal delay in this age-group in the natural cure rate of old infections. An investigation, reported by Pringle et al. (1959), indicated that most, if not all, of these cases were evidence of transmission, to which both infants and adults were behaving as relatively insensitive indicators.

In the (unpublished) Progress Reports of the Zanzibar Malaria Eradication Programme, Stoker compared parasite rates in children of various ages before and after the introduction of residual spraying.

TABLE 2. PARASITE RATES IN CHILDREN IN ZANZIBAR BEFORE AND AFTER THE INCEPTION OF RESIDUAL SPRAYING (AFTER STOKER)

	Age-groups			
	0-11 months	12-23 months	2-5 years	6-9 years
Pre-spray	19%	44%	56%	47%
After two rounds of dieldrin spraying	0%	1%	7%	5%

It will be noted from the summary of these data in Table 2 that the pattern of infection rates in Zanzibar infants and children followed that seen in Taveta-Pare. Reasons for adult and infant insusceptibility, and its persistence for a number of years after the introduction of malaria control in a hyperendemic area, are reviewed above. It is less easy to understand why, under certain conditions, some degree of insensitivity may linger into early childhood. In this connexion it may be relevant to take note of a suggestion (Muirhead Thomson, 1951; Thomas, 1951; Clyde & Shute, 1958) that the attack rate of African anophelines on infants and young children may be reduced; either by the smaller exposed skin area available to the mosquito, or by an attraction less than that of adults.

A greater relative sensitivity of children to transmission presumably derives from the interaction of two opposing factors: a relative increase in the risk of anopheline attack from birth onward, and a decline in human susceptibility with age. The age of peak susceptibility, and sensitivity, is consequently influenced by the malaria experience of the community: occurring earlier in life, and being more transient, the greater the general malaria risk. In Taveta-Pare malarial endemicity ranged from the hyperendemic in a few districts, to the upper range of mesoendemicity in others. Under these circumstances the age-group most sensitive to malaria transmission appears to have been between five years and fourteen years. The parasite rate in these children was about eight times that in infants, and about three times that in the adult population, during a period of sharply reduced transmission.

In Zanzibar, before residual spraying, the general level of endemicity was probably higher than that in Taveta-Pare, and there is an indication in Table 2 that peak sensitivity in this group of Zanzibar children occurred at a correspondingly earlier age. The validity of these assumptions needs to be checked over a wider range of circumstances than those referred to in the above notes. If the principle is found to apply to other situations in equatorial Africa, a very considerable saving in effort should be possible during the attack and consolidation phases of eradication operations: the search for parasites can be concentrated in those age-groups which are likely to provide the most faithful reflection of current malaria risk.

### 3. Observations on the Efficiency of Case-detection in Taveta-Pare

The WHO Expert Committee on Malaria, in its Seventh Report, observed that, with some reservations, the examination of fever cases offers the most rewarding single method for the detection of malaria parasite carriers.

The last round of residual spraying in Taveta-Pare was completed in March 1959. In September of the same year a system of three-weekly house-to-house visits, for the treatment and detection of malaria cases, was launched throughout the area previously covered by the Malaria Control Scheme. In one of the most malarious sectors, the Gonja area of South Pare, 5 500 fever cases were examined during 1960 from a total population of 99 000 people. During February 1960 a mass examination of several communities in this sector was carried out with the object of measuring the over-all infection rate in this sector at that time. It was hoped that some idea of the efficiency of the case-detection system could be gleaned from a comparison of the number of infections brought to light from the examination of fever cases, with the total number of infected people estimated to be present at that time, calculated on the basis of the results of the random survey. The age-composition of the population of the Gonja area is known, and the latter figure could therefore be estimated with reasonable assurance. The relevant data are set out in Table 3.

TABLE 3. A COMPARISON OF THE NUMBER OF PARASITE CARRIERS IN A SECTOR OF TAVETA-PARE FOUND BY ACTIVE CASE-DETECTION WITH AN ESTIMATE OF THE TOTAL THEN PRESENT

	Age-groups										Total	
	Less than 2 years		2-4 years		5-9 years		10-19 years		Adults			
	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.	Exd.	P.R.
Parasite Rates, Random Survey, February 1960	47	2%	86	5%	647	7%	446	8%	376	4%	1 602	6%
Calculated Population in each age-group	711		792		1 026		1 404		5 067		9 000	
Calculated total parasite-carriers present in area in February 1960	15		40		72		112		203		442	
Number found by case-detection in February 1960	3		16		10		20		64		113	
Proportion of total cases revealed by case-detection	20%		40%		14%		18%		32%		26%	

It will be noted here that, from a calculated total of 472 parasite carriers living in the sector in February, only 113 were picked up by the case-detection team between the end of January and the middle of March.

This estimate of the over-all infection rate, based as it is on a relatively small sample, is subject to the error inherent in any such procedure. The statistical error would nevertheless be least in the 5-9-year and 10-19-year age-groups, which included children drawn from virtually every community in the sector, and almost half of the total children of these ages living there. In these two age-groups the malaria cases found by the case-detection team appear to have been less than 20 per cent. of the total number present in the sector at that time. The validity of the

recommendations of the Expert Committee on Malaria, in paragraph 3.5.3 of their Eighth Report, is therefore upheld, while that of the Seventh Report, referred to above, cannot be accepted unreservedly to apply to case-detection in previously hyperendemic communities.

#### 4. The Influence of Immunity on Tactics during Eradication Operations

The main natural impediment to malaria transmission in the hyperendemic community is the high level of human immunity; inducing both insusceptibility and a low gametocyte production. Despite a high potential reproduction rate (that for the Lira area of Uganda was estimated by Davidson (1955) to be around 1600), the net reproduction rate in stable hyperendemic communities nevertheless remains only slightly above unity. The fall in anopheline density and longevity brought about by a residual spraying programme may well cause the net reproduction rate to drop to a negligible level, and the transmission to cease.

This situation, albeit encouraging, often provides only a temporary respite. Interruption of the hitherto steady rate of fresh infections initiates a decline from the previously high levels of immunity in the human population. Arising from this change there will be an increasing tendency for any single infection to give rise to secondary cases. By this method of adjustment alone, with no alteration in the anopheline picture, the net reproduction rate may steadily revert to its previous level. Before epidemiological equilibrium is restored there is a general resurgence of malaria transmission.

Immunity thus assists at the outset any measure designed to break transmission. As an asset however its value diminishes from the time that the attack phase is launched. It is probably axiomatic that any operation in a hyperendemic area that fails to interrupt transmission completely from the outset until the moment when the parasite reservoir is entirely depleted, will be subject to a degree of failure that becomes more and more evident as the operation is prolonged.

Finally, a further attribute of the hyperendemic community is worth brief consideration. Premune individuals appear to require a relatively small dose of an antimalarial drug to clear malaria parasites from the blood. In the premune Bantu it is certain that radical cure of falciparum infections has often followed a single small dose of chloroquine. While there is little evidence with regard to the minimum dosage of this or other drug needed to eradicate infections with other parasites in a hyperendemic community, it is likely that parasite eradication will prove to be surprisingly easily achieved.

Unfortunately, in practice, mass chemotherapy is a difficult task, and a certain proportion of the population is very liable to escape treatment. It is probable nevertheless that failures of this method stem from a lack of confidence in its efficacy, inadequate preparation of public opinion and a lack of understanding of the most effective method for its application. One important requirement is to limit the operation to the minimum period only, i.e. that interval needed to exhaust the parasite reservoir in the anopheline population - probably less than eight weeks. Public co-operation on a sufficient scale can only be guaranteed for a limited period such as this. It is possible therefore that the full operational potentialities of antimalarial drugs have not yet been sufficiently explored or exploited. There is therefore a need for further investigation of the tactical use of antimalarial drugs in Africa.

## 5. Summary

- (1) In hyperendemic areas of Africa the influence of immunity on malaria eradication problems is particularly important.
- (2) Under these conditions immunity may conceal any malaria transmission that may be persisting in an eradication programme, and so may induce a false sense of security. During the later stages of the campaign it may complicate the problem of case-detection.
- (3) Immunity has nevertheless two helpful aspects: human insusceptibility helps the interruption of malaria transmission and immunity may enormously improve the prospects of radical cure of malaria infections following a single dose of an antimalarial drug.

REFERENCES

- Clyde, D. F. & Shute, G. (1958) Amer. J. trop. Med. Hyg. 7, 543
- Davidson, G. (1955) Trans. roy. Soc. trop. Med. Hyg. 49, 339
- McGregor, I. A. (1960) W. Afr. med. J. 9, 260
- Pringle, G., Draper, C. C. & Clyde, D. F. (1960) Trans. roy. Soc. trop. Med. Hyg.  
54, 434
- Thomas, T. C. E. (1951) Brit. med. J. 2, 1402
- Thomson, R. C. M. (1951) Brit. med. J. 1, 1114

The purpose of the WHO/Mal series of documents is threefold:

(a) to acquaint WHO staff, national institutes and individual research or public health workers with the changing trends of malaria research and the progress of malaria eradication by means of summaries of some relevant problems;

(b) to distribute to the groups mentioned above those field reports and other communications which are of particular interest but which would not normally be printed in any WHO publications;

(c) to make available to interested readers some papers which will eventually appear in print but which, on account of their immediate interest or importance, deserve to be known without undue delay.

The issue of a paper in this series does not therefore constitute formal publication and a paper so issued may, with the agreement of the author and WHO, be published in a WHO periodical or elsewhere.

Authors alone are responsible for views expressed in signed articles. The mention of manufacturing companies or of their proprietary products does not imply that they are recommended or endorsed by the World Health Organization.