

EXPLORATORY STUDY OF MALARIA SITUATION IN HANANG AND BABATI
DISTRICTS AFTER REPORTED MALARIA EPIDEMIC:
IV. ASSESSMENT OF MALARIA PARASITAEMIA, ANAEMIA AND
SULFADOXINE/PYRIMETHAMINE (SP) AND CHLOROQUINE EFFICACY

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Abstract: Babati and Hanang districts, in Arusha Region Northern Tanzania have been experiencing malaria epidemics since early 1940s. Following a reported malaria epidemic in April 1999, a study was conducted from 6 May- 15 June 1999 to determine possible risk factors for the epidemic. The objectives of the study were to determine the prevalence of malaria parasites, anaemia and antimalarial drug resistance among underfive children attending OPD at Babati Hospital and Bassotu (Hanang District) RHC. The study population was children aged 6-59 months suffering from uncomplicated *falciparum* malaria. Results obtained during the screening process indicated slide positivity rates of 23.4% and 38.7% at Babati and Hanang respectively. Severe anaemia (PCV<25%) was found in 9.8% and 5.9 % of the children at Babati and Hanang respectively. The test involved in the assessment of drug resistance was a modified 7-day therapeutic efficacy trial of chloroquine and sulfadoxine/pyrimethamine (SP). Evaluation of the data revealed the presence of a high degree (55.6%) of early treatment failure (ETF) with chloroquine.

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However, ETF in the SP group was around 16.3%. The followup period of 7 days allows for partial evaluation of late treatment failures (LTF) as well as adequate clinical response (ACR); these normally require 14- day follow-up to document fully. The cases of LTF were 2; 1 with CQ and the other 1 with SP. ACR was seen in 18 and 35 cases with CQ and SP. SP was superior to CQ in terms of parasite clearance at both day 3 and day 7 ($P < 0.001$). Efficacy results from Hanang have not been presented in details because the final cohort was too small for meaningful conclusions to be made. However, 7 out of 13 cases on CQ at Hanang were classified as ETF whilst those with ETF response in the SP group were 4 out of 11 cases.

Introduction

Babati and Hanang districts have been experiencing malaria epidemics since malaria became established in the area in the early 1940s (1). Malaria evaluation studies conducted in Hanang District in 1984 during which Babati was still part of Hanang District (2) showed that malaria ranged from mesoendemic in the highland to hyperendemic in the lowland. This suggests that a certain proportion of the people in the area particularly in the highland do not have sufficient immunity to malaria. Drug resistance assessment in the area showed that there was 27.5% and 12.0% *in vivo* resistance to chloroquine and amodiaquine respectively (2). Given that so many years have passed since the malaria evaluation was done, it might as well be that drug resistance situation has worsened like in many other parts of Tanzania. Of major concern is chloroquine resistance that has been shown to be widespread in Tanzania. Recent reports using WHO standard protocol (5) reported a national average of 42% treatment failure with this drug among children aged 6-59 months (3). Chloroquine resistance among indigenous Tanzanians first reported in 1982 (4) is now widespread and has reached alarming proportions in some areas. Considering that drug resistance could contribute to an increase in the number of malaria cases (6), it was thought necessary to include an efficacy trial in the epidemic evaluation exercise at Babati and Hanang. Chloroquine was selected since it was the recommended first-line antimalarial in the country. Sulfadoxine/pyrimethamine (SP) was also studied given the potential role of this drug as an alternative antimalarial to chloroquine in Tanzania. The main aim of this study was to assess the therapeutic efficacy of chloroquine and SP in uncomplicated *falciparum* malaria. We were also interested in determining the prevalence of anaemia and malaria parasitaemia among the screened children.

Material and Methods

The study was conducted in Babati and Hanang districts. At Babati hospital, oral chloroquine (CQ) or sulfadoxine/pyrimethamine (SP) was administered to suitable children aged 6-59 months, under supervision, according to weight. Chloroquine (25 mg/kg, over 3 days) was given to 54 children whilst a single dose SP (1.25 mg/kg pyrimethamine) was given to 47 children at the same hospital. However, complete follow-up data was available for 45 children on CQ and 43 on SP respectively. Clinical and parasitological follow-ups were made on several occasions over a 7-day period. These activities were carried out over a period of 40 days.

Screening for Malaria Parasites and Anaemia in Children

Axillary temperature of all children aged 6-59 months attending the OPD at Babati hospital and Bassotu (Hanang district) dispensary were measured with an electronic thermometer. Both febrile and afebrile children were screened. After explaining study aims, follow-up visits and obtaining verbal consent, children were examined for malaria parasites in Giemsa stained blood smears and anaemia by packed cell volume (PCV) estimation. Parasite enumeration against 200 leucocytes was done on thick films using the high power objective of a microscope. A blood film was declared negative after counting of 200 high power fields. Malarial parasite species confirmation was made on the thin film.

Clinical Examination and Selection of Cases

Fever cases were examined further by a clinician to exclude other febrile illnesses. Selection of cases for inclusion into the therapeutic trial was as given in a standard protocol (5) with some minor modifications. Previous history of chloroquine use was not among the exclusion criteria. Oral chloroquine (25 mg/kg, given over 3 days) or single dose SP equivalent to 1.25 mg/kg pyrimethamine, was administered under supervision. The children were allocated into either oral Chl. or Sp. antimalarial drug using a table of random numbers. Paracetamol was given to most children on the first day of medication. Children were observed for 30 minutes to ensure treatment was repeated in case of vomiting. Mothers were advised to use tepid sponging at home in case of fever.

Parasitological and Clinical Followup

Further clinical examination was done on days 1, 2, 3, and 7 or any other day depending on the clinical condition of the child. Parasitological assessment was made on days 3 and 7 or any other day in case of fever or deteriorating clinical condition.

Evaluation of Efficacy Results and Case Management

The evaluation of results was as recommended elsewhere⁵ with minor modifications. Briefly the evaluation scheme can be summarised thus: (1) early treatment failure (ETF) - the presence of parasitaemia and any of the following: development of danger signs or severe malaria on day 1, 2 or 3; axillary temperature $\geq 37.5^{\circ}\text{C}$ on day 2 or 3; day 3 count $\geq 25\%$ of day 0 count. (2) Late treatment failure (LTF) - presence of parasitaemia between day 4 and day 14 and any of the following: development of danger signs or severe malaria; axillary temperature $\geq 37.5^{\circ}\text{C}$. (3) adequate clinical

response (ACR) - those not meeting the criteria for ETF or LTF with any of the following: absence of parasitaemia on day 14 irrespective of axillary temperature; presence of parasitaemia but axillary temperature $<37.5^{\circ}\text{C}$.

Cases of treatment failure were given either amodiaquine or quinine according to weight. However, cases of severe malaria and those with danger signs were referred to paediatric ward at the hospital for quinine therapy and further case management.

Results

Screening for Malaria and Anaemia in Children

Out of 772 and 235 children (6-59 months) screened for malarial parasites 181 (23.4%) and 91 (38.7%) were

found positive at Babati and Hanang respectively. *P. falciparum* pure infection was seen in 79.6% (144/181) and 87.9% (80/91) of the malaria positive blood smears at the above localities. Mixed infections of *P. falciparum* with *P. malariae* were 19.3% (35/181) and with *P. ovale* (1.1%; 2/181) at Babati. The prevalence of falciparum parasitaemia stratified by age and study site is shown on Figure 1. The general trend was that of higher prevalence of *P. falciparum* in all age groups at Hanang compared to Babati, the exception being in infants. *P. falciparum* density given as log transformed data by age group is presented in Figure 2. It can be seen that parasite densities encountered at Babati were higher than those seen at Hanang. Indeed, they were high in all age groups.

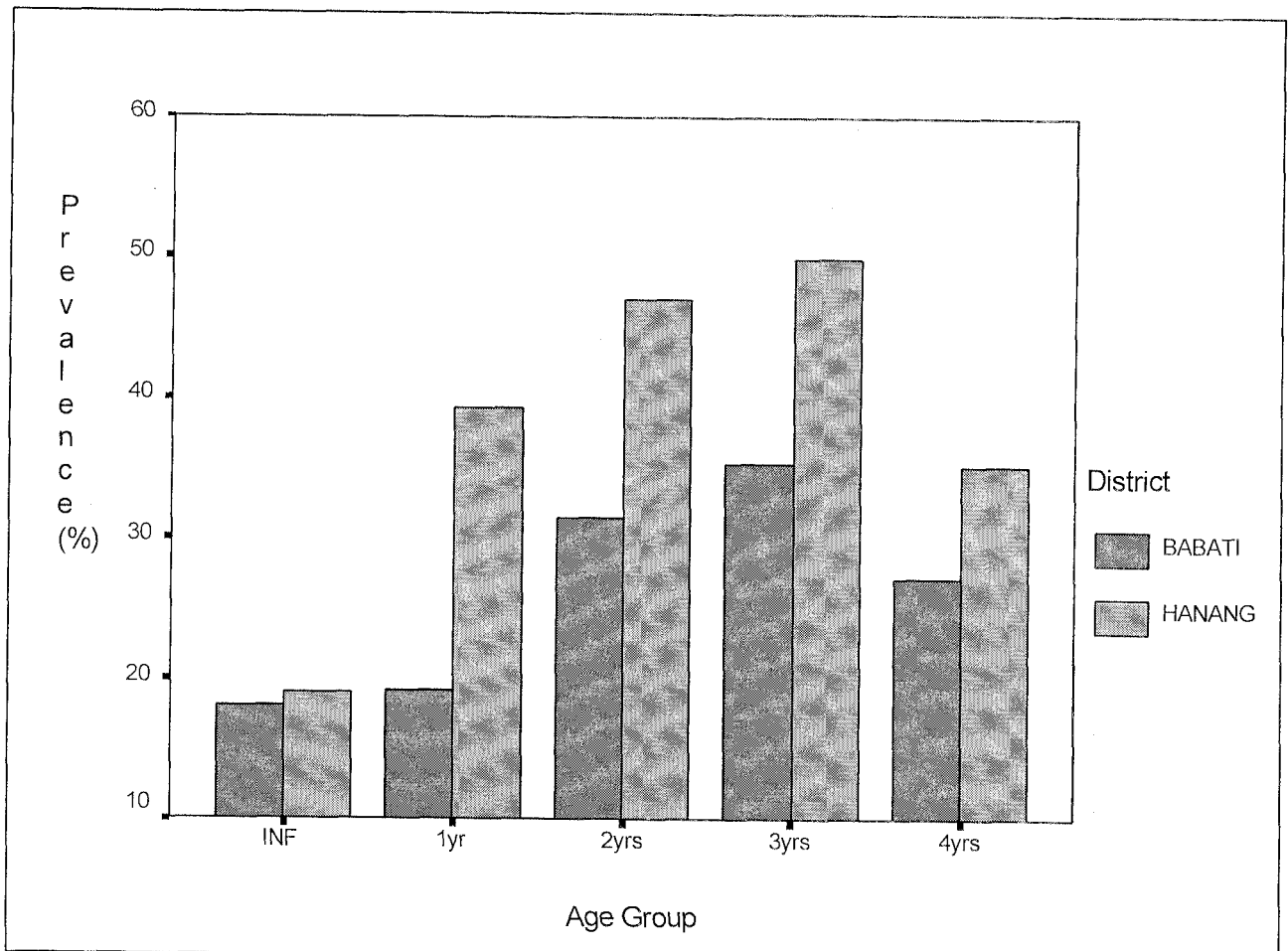


Fig. 1: Age Distribution of *P. falciparum* Prevalence

Packed cell volume estimation in 338 and 221 of the children showed a mean of 32.6% (95% CI=32.0%, 33.3%) at Babati and 33.5% (95% CI=32.9%, 34.2%)

at Hanang. The lowest haematocrit was observed in infants at Babati (Mean PCV =24.5%, 95% CI =19.7% to 29.4%).

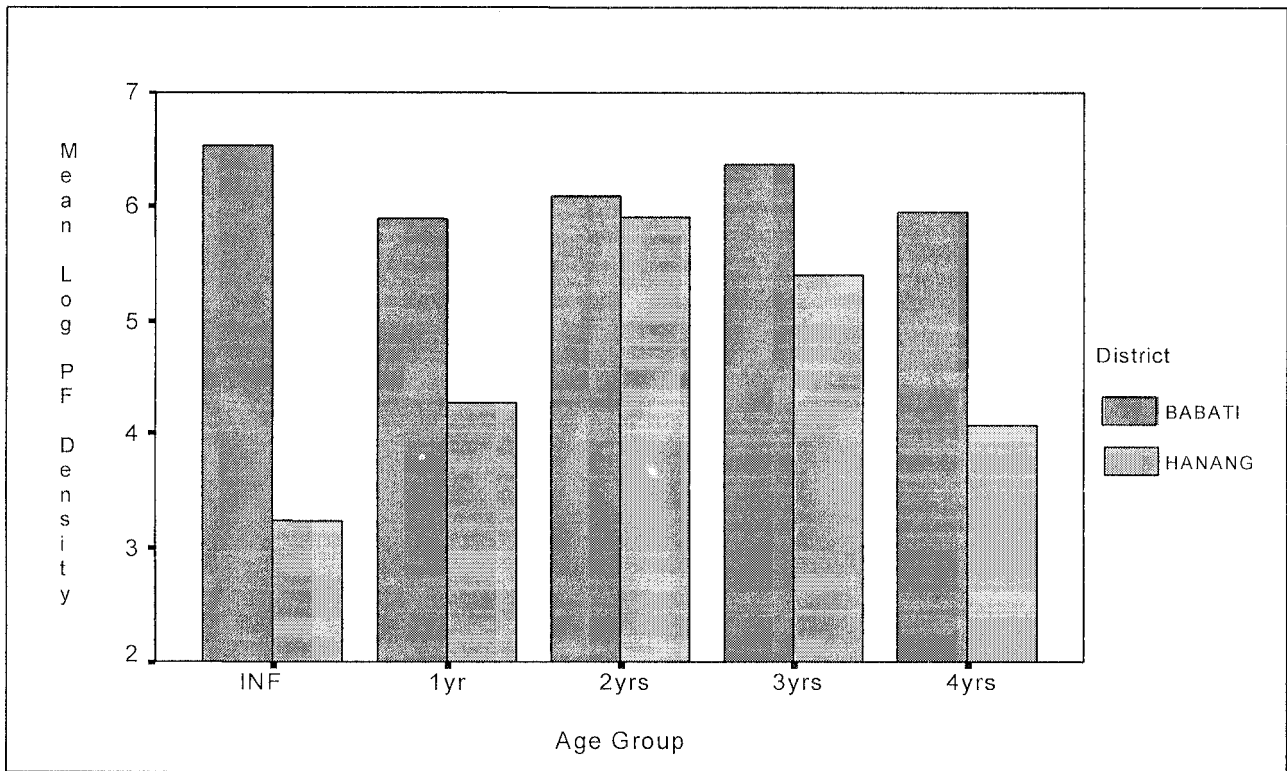


Fig. 2: Age Distribution of *P.falciparum* Parasite Density

A steady increase in PCV levels was observed with increasing age reaching peak in older children at Babati (Figure 3). On the other hand, most children at Hanang had high PCV levels even though the highest was seen

in those aged 4 years (Figure 3). Overall prevalence of severe anaemia (PCV <25%) was 9.8% (33/338) and 5.9% (13/221) at Babati and Hanang respectively. Figure 4 shows data on severe anaemia (PCV <25%) stratified

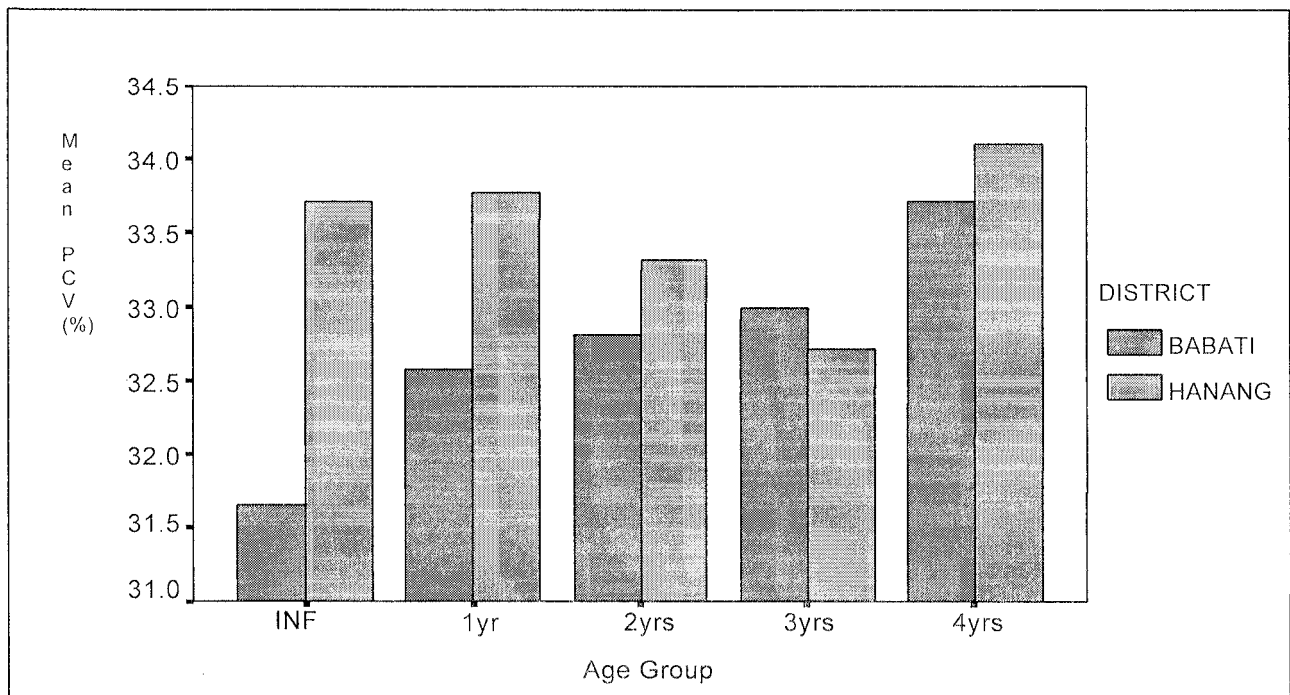


Fig. 3: Age Distribution of Mean Packed Cell Volume

by age group and study site. Higher prevalence of severe anaemia was observed among infants at Babati whereas for Hanang, most severe anaemia cases were in children

aged 2 years. Data comparing PCV and *P. falciparum* parasitaemia (Figure 5) indicate that lower PCV is found among those with parasitaemia.

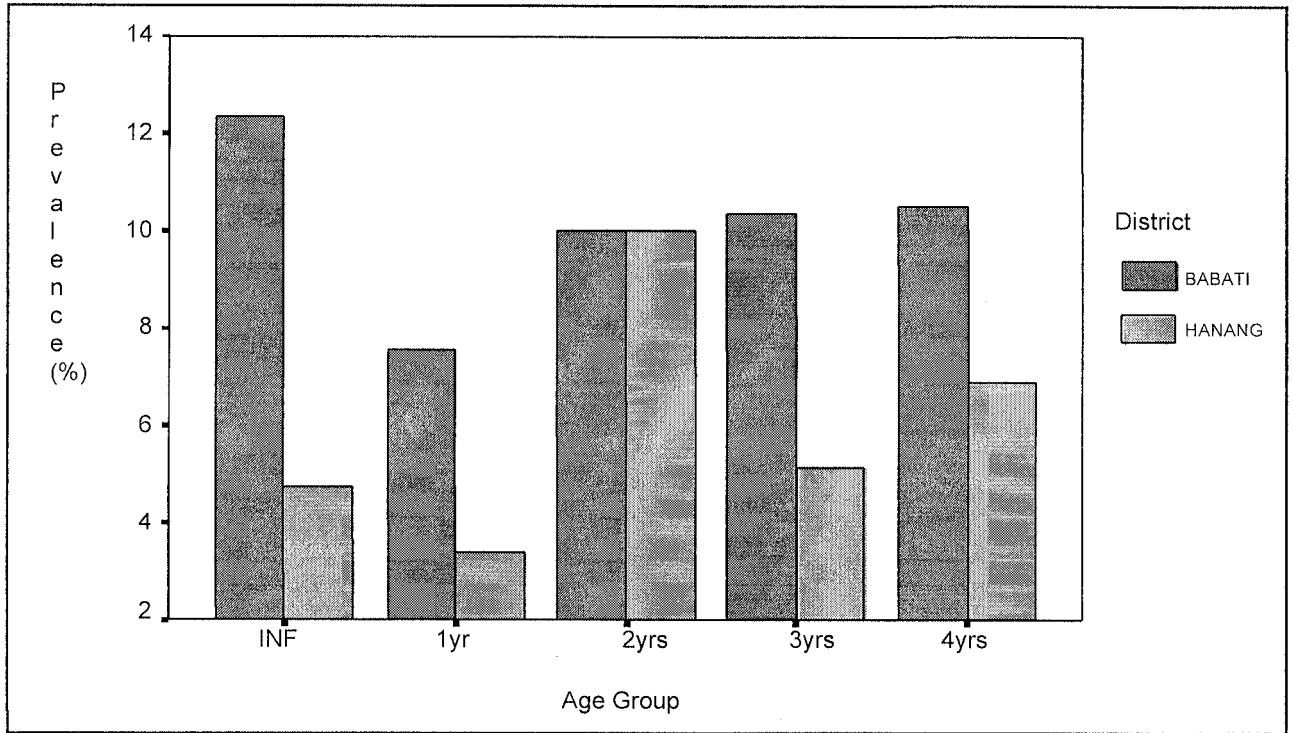


Fig. 4: Age Distribution of Severe Anaemia Prevalence

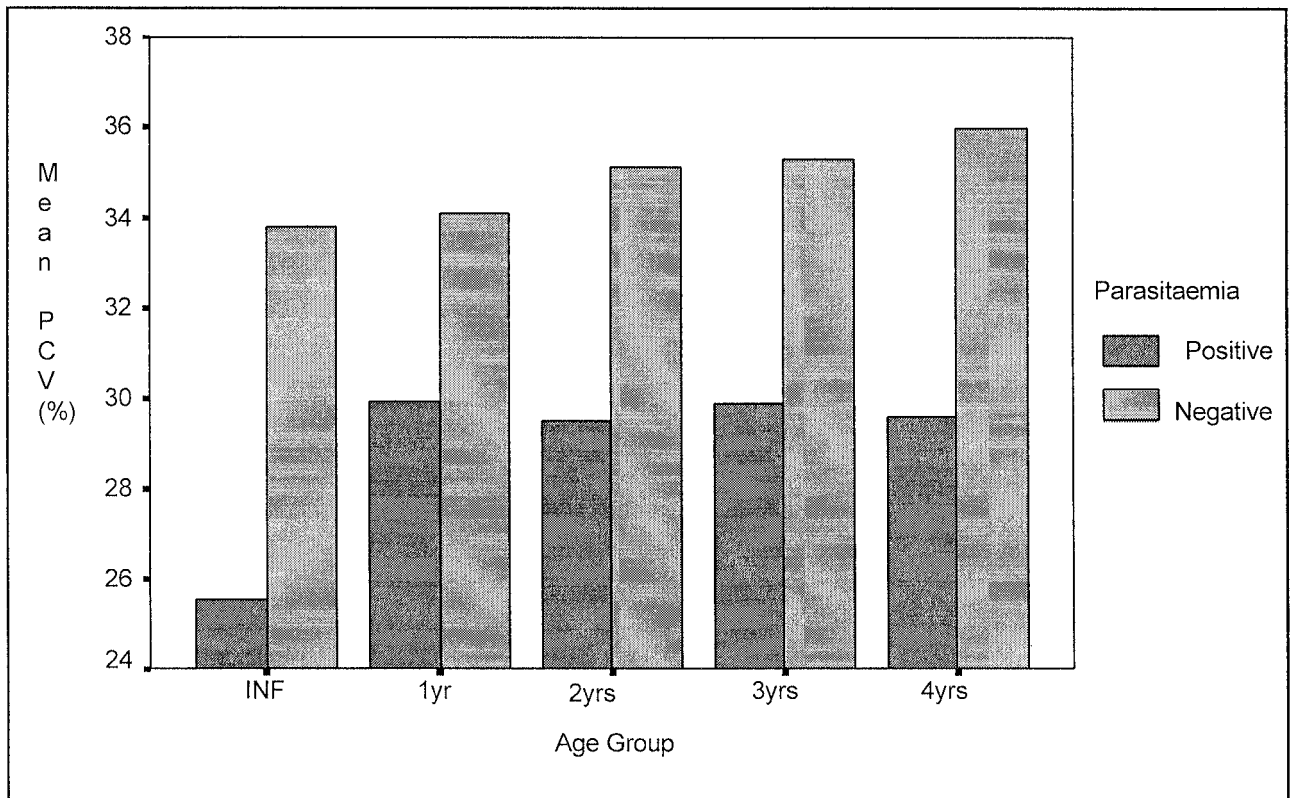


Fig. 5: Age Distribution of Mean PCV and Parasitaemia

Chloroquine and Sulfadoxine-pyrimethamine Therapeutic Efficacy Study

The results obtained revealed a high treatment failure with chloroquine in children at Babati. The results are given in the accompanying tables. Table 1 shows demographic features of the 54 and 47 children initially enrolled for the chloroquine (CQ) and sulfadoxine/

pyrimethamine (SP) efficacy study. The initial axillary temperature ranged from 36.0°C to 40.6°C whilst *P. falciparum* density ranged from 1000 to 400000 rings/ μ l. Fever ($\geq 37.5^\circ\text{C}$) was present in over 75% of the study cohort. Successfully followed up children were 45 and 43 on CQ and SP respectively (Table 2). They were similar to the initial cohort in all important parameters.

Table 1: Baseline Characteristics of Children Treated with Either Chloroquine (CQ) or Sulfadoxine/pyrimethamine (SP) for Uncomplicated *Falciparum* Malaria at Babati Hospital, Arusha Region (May/June, 1999)

	CQ (n=54)	SP (n=47)
Mean age (months, SD)	26.5 (14.5)	31.2 (15.0)
Age range (months)	6-59	6-58
Mean temperature ($^\circ\text{C}$, SD)	38.5 (1.1)	38.6 (1.2)
Temperature range ($^\circ\text{C}$)	36.0-40.2	36.8-40.6
Mean weight (kg, SD)	10.2 (2.4)	11.5 (2.4)
GM ^a parasite density (rings/ μ l, 95% CI ^b)	28708 (18072-45604)	38905 (24946-60674)
Parasite range (rings/ μ l)	1239-467735	1000-426580
PCV ^c (% , 95% CI)	27.7 (25.0, 30.3)	29.2 (26.7, 31.7)
Severe anaemia (PCV <25%)	6/19 (31.6%)	4/22 (18.2%)
Fever ($\geq 37.5^\circ\text{C}$)	39/46 (84.6%)	28/37 (75.7%)

^aGM = Geometric mean. ^b95% CI = 95% confidence intervals.

^cPCV = Packed cell volume.

Table 2: Evaluation of Treatment Outcome Among the Children with Complete Data in a Modified 7-day Therapeutic Efficacy Trial of CQ vs SP at Babati Hospital, Arusha Region (May/June, 1999)

	CQ (n=45) ^a	SP (n=43) ^a	P
Parasite negative on day 3	4/31 (12.9%)	22/39 (56.4%)	<0.001
Parasite negative on day 7	5/20 (25.0%)	32/37 (86.5%)	<0.001
Adequate clinical response (ACR)	18 [*]	35 [*]	-
Early treatment failure (ETF)	25 (55.6%)	7 (16.3%)	<0.001
Late treatment failure (LTF)	2 ^{**}	1 ^{**}	-

^a Cases excluded and lost to followup were 9 on CQ and 4 on SP.

* Outcome based on day 7 results. ** Outcome based on day 4-day 7 results.

Thirteen cases were excluded from the final data analysis (CQ=9, SP=4) for various reasons. Such reasons include: movement from site (2), loss to follow-up (3), incomplete treatment (1), unauthorised medication (4), and mixed infection observed during follow-up (3).

Seven SP ETF cases and 25 CQ ETF cases were referred to paediatric ward at the hospital in Babati for alternative antimalarial drug and further case management.

The limited efficacy data from Hanang revealed the

presence of ETF in 7 out of 13 cases on CQ. ETF response was observed in 4 out of 11 cases in the SP group. It was not easy to recruit sufficient number of patients due to constant movement of people. In fact most of those seen up to day 3, and hence completed their treatment, were not present on day 7 of follow-up.

Discussion

The results of the slide positivity rates among underfives revealed that at Hanang malaria prevalence was almost twice (38.7%) that seen at Babati (23.4%). This is in

agreement with hospital records on final diagnosis that seem to indicate that malaria admissions at Hanang were twice those at Babati (36.9% vs 14.5%). The higher proportion of malaria cases at Hanang might be due to the epidemic nature of malaria in this district. Malaria being seasonal would cause greater morbidity during the peak of the rainy season. On the other hand, the difference in the observed levels of slide positivity could be due to the fact that at Hanang the cases seen were of primary malaria infection whilst those at Babati might have been given treatment already at another lower level health facility.

The high rate of severe anaemia and low mean PCV values observed in infants at Babati could be directly attributed to malaria as evidenced by the high *P. falciparum* densities seen in these infants. However, at Hanang the high rate of severe anaemia and parasite density which were found in children aged 2 years was not associated with low mean PCV values. It seems at Hanang, the prevalence of severe anaemia is not as high as that seen at Babati. Anaemia therefore does not seem to be a major public health problem in Hanang unlike in Babati.

The main finding of the therapeutic efficacy trial is the presence of a high degree of chloroquine-resistant *falciparum* malaria among clinically ill underfive children at Babati. It was observed that while chloroquine was able to reduce parasitaemia considerably, its impact on temperature was negligible. It was also noted that presence of parasites on day 7 in the CQ and SP groups was 75.0% and 13.5% respectively. Moreover, the results of the efficacy trial indicate that the usefulness of chloroquine is limited given the high ETF level (55.6%) observed among underfives. On the other hand, SP efficacy in the study area seems to be good despite the observed ETF of 16.3%. The relatively high treatment failure with CQ could be explained by the fact that the study was conducted at the highest level of referral. Patients attending such a facility would normally be acute and sometimes might have taken antimalarials particularly chloroquine prior to this. The 7-day followup period has provided a reliable estimate of ETF rate at Babati as observed between day 1 and 3. This estimate is of clinical importance for case management. On the other hand, estimates of LTF and ACR are only partial because, for logistical reasons, the study could not cover

the recommended 14-day followup period. It was not possible to assess haematological response because of the short followup period.

Efficacy data from Hanang have not been presented in detail because the sample size was too small to make meaningful conclusions. This was partly due to the high dropout rates whereby at the end of the study half of the study cohort had been lost due to the nomadic nature of the population at Bassotu, Hanang.

Chloroquine appears to have been failing in the treatment of malaria in underfives. The drug as stipulated in the new national malaria treatment guidelines should no longer be used. Thus it is important to keep a good supply of the new first line drug (SP), amodiaquine, as well as quinine, ready for use during the peak malaria transmission and, in cases of an outbreak of an epidemic. There is also a need of sufficiently supplying the Babati hospital and Katesh health Centre and Dareda hospital with the requirements for management of malaria patients before the rains begin.

It is important to keep record of the sensitivity pattern of malaria parasites in epidemic prone areas. For this purpose regular attempts should be made to conduct drug sensitivity tests. Also, with widespread use of insecticide treated bednets it would be necessary to establish the baseline of malaria vector susceptibility to pyrethroid insecticides. This could be followed up once annually to pick any deviations from normal response to the insecticide used on nets.

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