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Clinical manifestations and immune response to MSP 1_{19} in severe paediatric malaria in Adeoyo state maternity hospital, Ibadan

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Summary

A 10-week cross-sectional study was carried out at the Adeoyo State Maternity Hospital (Beere, Ibadan), Southwestern Nigeria in order to determine (a) the prevalence of severe malaria, (b) identify the predominant clinical presentations that characterise the disease in children below 5 years and the pattern of antibody responses to MSP 1_{19} elicited in severe malaria complications. Three thousand, one hundred and thirty-one cases reported to the Out Patients' Department; of these, 372 (11.8%) subjects were recruited on the basis of doctors' diagnosis of severe malaria, malaria and other complications. Six per cent (188/3131) of the patients were admitted. Serum samples for 320 of the 372 subjects were analysed for antibodies specific to MSP 1_{19} by ELISA. The highest antibody responses occurred in the age group 2-5 years. Parasite prevalence was 77.9% (290 of 372 subjects) and parasite density ranged from 80 to >100000 parasites/µL blood. Fever (an average temperature of 38.6 ±0.4 °C and peak at 41 °C) and severe malaria were the major clinical manifestations of malaria amongst the study population. Severe malaria was found to be associated with other features such as cough, vomiting and diarrhoea.

Keywords: *Clinical, severe, manifestation, anaemia, children*

Résumé

Une étude croisée était faite a l'hopital de la maternité d'Adéoyo au sud ouest du Nigéria pendant dix semaines pour évaluer la prevalence du paludisme sévere et identifier les symptomes cliniques prédominat qui charactérisent cette maladie chez les enfants de moins de 5 ans Aussi pour déterminer la frequence de stimulation des anticorps au MSP1 dans les complications du malaria sévere. Sur trios-mille cent-trente-un cas bénigne presenté en clinique génerale, 372(11.8%) étaient recruités sur le diagnostie du docteur ayant le paludisme sévere et d 'autres complications associées. Six pour cent (188/3131) était admis. Les échantillons du sérum de 320 des 372 sujects étaient analysés pour des anticorps spécifiques au MSP1-19 par la méthode d'ELISA. Le taux le plus elevé d'anticorps apparut entre l'age de 2-5 ans avec un taux de parasite de 77.9% (290/372) et une densité de parasites variant de 80 a >100000 parasites /ul de sang. La fiévre avec une température moyenne de 38.6±0.4 oC et un peak de 41 oC était observée et les symptomes du paludisme sévere étaient les manifestations majeur cliniques associées a la toux , vomissement et diarrhée parmi cette population étudiée.

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Introduction

Malaria is the leading cause of recurrent morbidity and mortality world-wide and remains a major public health problem in more than 90 countries of the world, especially in the world's poorest countries located in the Sub-Saharan zone of the African continent. Malaria mortality is high, between 1.5 – 2.7 million deaths annually, with about 1 million of these being in African children [1]. It accounts for an under-five death every 12 seconds. It causes 300 – 500 million episodes of acute illness globally, affecting up to one in ten of the world's population each year [2]. *Plasmodium falciparum* is the commonest species associated with malaria and its manifestations.

The World Health Organization (WHO) has defined severe *falciparum* malaria as the condition in any patient with malaria who is unable to swallow tablets, has any evidence of vital organ dysfunction or a high parasite count, and is thus at increased risk of dying [1]. Symptoms already identified for severe malaria include, fever, metabolic acidosis, hypoglycaemia, renal impairment, seizures, coma, cerebral oedema pulmonary oedema, respiratory distress, prostration, jaundice and severe anaemia [1,3,4]. The pathophysiological heterogeneity in severe malaria conditions and symptoms expressed by individuals and groups in a population has been previously highlighted [3,5]. The magnitude and significance of these differences have been attributed to host factors [6], exposure to different antigenic strains [7,8], antigenic variation of parasites [4], differences in species strains and some other factors, including environmental factors. These studies of the pathogenesis of severe malaria in African children have shown that though many of the underlying processes leading to the disease are probably common to all patient groups, there are important differences between the non-immune adult and African children. The degree of endemicity varies between countries and even within the same country.

The clinical outcome of severe malaria in children in the Northern parts of Nigeria has been described [9]. Febrile convulsion was found to be the most frequently occurring clinical manifestation, while cerebral malaria and severe malaria anaemia (though similar in frequency of occurrence) had lower rate of occurrence among the children. However, the immunological response elicited in these children as a result of malaria infection was not documented.

The C terminal 19KD protein of the *Plasmodium falciparum* merozoite surface protein 1 MSP 1_{19}, is a major candidate for malaria vaccine development. We have studied the peculiar clinical manifestations of severe falciparum infections in Nigerian children and the antibody response to MSP 1_{19} during these infections. Attempts to understand the pathogenesis of severe malaria are important for the study of malaria immunology and epidemiology in Nigeria, and would enhance the design of more effective interventions against malaria.

Materials and methods

This prospective study was carried out at the Adeoyo State Maternity Hospital among children with malaria attending the out patients' department (OPD). The period of study was April-June 2001. The hospital is state- owned, and operates some degree of free medical services (sponsored by the state government). It is located in Yemetu, Beere area, the heart of Ibadan city, Oyo State, South-western Nigeria. The majority of the population in this vicinity is Yoruba. This area is of cultural significance as the ancient settlement area of the forefathers of the Ibadan indigenes. The dominant occupation is petty trading, mainly by women. The houses are closely clustered, nutrition is generally poor, but personal physical hygiene is not good in this area. The land lies 400-600 feet above sea level and the climate consists of a warm and dry season (November-March), and a cooler rainy season from April to October (Data from International Institute of Tropical Agriculture, Ibadan). The main malaria vectors are *Anopheles gambiae sensu stricto, An. arabiense, An. melas* and *An. funestus* (10), with hyperendemic *falciparum* malaria of perennial transmission.

A sample of 372 children between the ages of 4 months and 6 years presenting with varying degrees of malaria symptoms were recruited into the study from the 3131 children that attended the out patient department (OPD). Some 188 of these children that attended the OPD were admitted to the ward because of the severity of their case. From this number, 49 children were included in our studies because they presented with acute severe or complicated malaria.

As a matter of policy, the children that attended the hospital were treated mostly with Chloroquine (CQ). However, Quinine Fansidar® and Halofantrine were administered where there was no clinical and parasitological response to CQ within 72 hours. Other treatment modalities administered where indicated included intravenous fluids, anti-convulsants, nasogastric tube feeding, blood transfusion and treatment of hypoglycaemia. Children with suspected bacteraemia received antibiotics in addition to anti-malarials.

Subjects were recruited into the study if the doctor had diagnosed them as suffering severe malaria and if there was pallor and PCV less than 20%. After obtaining the consent of parents or guardian, 200ul of blood was collected from each severe malaria patient. Questionnaires were administered to the patients and the medical personnel that diagnosed the patients to obtain demographic information and case history, signs and symptoms and possible diagnosis. Other information concerning treatment regimen such as haematinics use and dosage, blood transfusion needs, coma scale etc, was obtained from the hospital records. The children were grouped by age 0 - 6 months, 0.5 - 1 years >1 - 2 years, >2 – 5 years and >5 years.

Thick blood films were made and giemsa-stained and examined microscopically. Malaria parasites were counted against leukocytes, assuming a constant leukocytes count of 8000/µl blood. Temperature and weight of patients were obtained prior to blood sample collection and daily readings were taken for admitted patients. Blood (200µl) was collected once from the subjects soon after diagnosis; plasma was separated from red blood cell pellets after centrifugation and stored at <-20°C until analysed for antibodies to MSP 1_{19}.

Enzyme linked immunosorbent assay (ELISA) for MSP 1_{19} antigen

Using standard ELISA procedures (Blackman, 1991), microtitre Immunlon 2 (Dynatech, Chantilly) plate wells were coated with 50µl of MSP 1_{19} antigen diluted at 0.5µg/ml in 0.1M of Carbonate buffer (pH 9.6) and incubated overnight at 4 °C. Afterwards the plates were washed three times with 0.05% Tween in Phosphate buffered saline (Tween/PBS, pH 7.4). The wells were blocked with 50µl of 0.5% boiled Casein in Phosphate buffer (pH 7.4) and incubated for one hour at 37 °C. The plates were washed three times with 0.05% Tween/PBS (pH 7.4). Serum samples from the subjects were serially diluted 1:50 to 1:6400 in blocking buffer and incubated for one hour at 37 °C. Again the plates were washed three times with 0.05% Tween/PBS. Bound antibody was detected with Antibody-Horseradish Peroxidase (IgG/HRP) conjugate (Dako A/S, Germany) at 1:2000 dilution of blocking buffer. After incubation for one hour at 37 °C, the plates were washed three times with 0.05% Tween/PBS. Horseradish peroxidase substrate 2,2'-Azino-Bis (3-ethyl-benthiazoline) Sulphate VI (ABTS) and peroxidase substrate solution B (H_2O_2) (Kirkegaard and Perry Laboratories, Gaithersburg, MD) was used to develop the colour. The substrate solution turned green if anti-MSP 1 antibodies were present in the sample. The two solutions were mixed in a 1:1 ratio and 50?l of the solution placed in all the wells. The plates were incubated for 45 minutes in the dark at 37 °C and then read immediately at OD_{650} nm using the ELISA plate reader (Molecular Devices, Menlo Park, CA). The reciprocal end point titre (the highest dilution that gave an absorbance value above that of the negative control) was log transformed, and data were expressed as log reciprocal titres. Negative controls were selected from among the sample population.

Statistics and data analysis

Antibody titres were log transformed; malaria parasite density was defined as $\log_{10}$ of the number of asexual malaria parasite/ul blood in the thick blood films of malaria positive subjects to approximate normality. To obtain a description of clinical manifestations and antibody response, the children were grouped by age: 0 - 6 months, 0.5 - 1 year, >1 - 2 years, >2 – 5 years and >5 years. The data were analysed for differences between groups, for correlations using Pearson's coefficient of correlation and t-tests. The confidence level was set at P=0.05. Analyses were done with statistical software packages Microsoft Excel (Microsoft Corporation, 2000) and SPSS 7.5 (SPSS Inc., 1997).

Results

During the 10-week period of study, there were 3131 hospital attendants to the outpatient department (OPD) and 188 admissions to the children ward of paediatric cases. Majority, 2592 (82.7%), of these reports were children below the age of 6 years and the rest were above six years of age. The total

number of children recruited for this cross-sectional study (372 patients) formed 11.9% of the total number of cases during the period of study. Nearly a third (32.3%) of the subjects were aged 1-2 years of age and 205 (55%) were male. The male: female ratio was 2:1. Out of the 372 children, 106 (28.5%) male and 82 (22.0%) female subjects were admitted. The number of days spent on admission ranged between 2 – 11 days with an average of four and a half days.

Table 1: Age and Sex distribution of the recruited patients

Age (years)	M	F	Total	Total (%)
0 – 0.5 yrs.	4	6	10	2.7
>0.5 - 1yr.	65	50	116	31.2
>1 – 2 yrs.	70	50	120	32.3
>2 – 5 yrs.	55	50	105	28.2
>5 years	10	11	21	5.6
Total	205	167	372	100

Thirteen deaths were recorded, with 9 (69.2%) being among male children aged one to three years, while 6 (30.8%) were female of the same age range. The mortality attributable to severe malaria anaemia following *Plasmodium* infection was the highest: 38.8%. It ranked first to the other causes of paediatrics death such as sepsis, gastroenteritis, pneumonia and other bacterial infections (Table 2).

Table 2: Causes of death among children at Adeoyo Hospital

Causes of Death	No. of patients	Male	Female	% of Total
Anaemia	5	4	1	38.4
Gastroenteritis	3	3	-	23.1
Pneumonia	2	1	1	15.4
Sepsis	1	-	1	7.7
Others	2	1	1	15.4
Total no.	13	9	4	100.0

Microscopic examination of the thick blood film slides confirmed that 290 (78%) of the 372 patients were positive for *Plasmodium* parasites, the species being *P. falciparum* and *P. malariae*. Parasite density ranged from 80-100 000 parasites/µl of blood and was highest in the age group 2-5 years (Fig. 1)

According to the WHO (2000) only those with PCV ≤15% can be defined as severe malaria anaemia cases. Thus only 24 (8.3%) of the 290 parasitaemic children in our study had acute severe malaria anaemia. Nonetheless, the PCV, which was determined for 99 subjects, showed clearly that 82 subjects were anaemic.

Clinical manifestations of children with severe malaria

The clinical manifestations in the 372 subjects (all below the age of six years) are shown in Table 3. These included fever in 229 (61.9%) of the cases, anaemia in 105 (28.2%). Other features of severe malaria presented in these children were as follows: hyperpyrexia with temperatures above 40 °C in 9 children (1.6%), hyperparasitaemia in 79 (21.9%), cerebral malaria, 10 (5.3%) and febrile convulsions. Of those exhibiting hyperparasitaemia, 6 (7.6%) patients presented with altered consciousness but were rouseable (on the Blantyre scale they rated ≥ 7 of the 15 scoreable points).

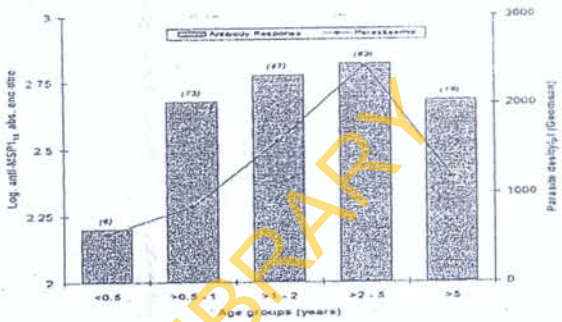

Fig. 1: Geometric mean parasite density (line) and mean log anti-MSP 119 antibody titre (shaded block) of the different age groups of children between <1-6 years of age that attended the Adeoyo hospital. The figures in parenthesis represent the number of individuals that are represented in each group

Table 3: Symptoms observed in children that visited the hospital with or without severe malaria.

Drugs	No. of Cases	% of Total
Fever	229	61.6
Anaemia	105	28.2
Vomiting	88	23.7
Watery Stool	86	23.1
Cough	64	17.2
Convulsion	41	11.0
Loss of Appetite	31	8.3
Febrility	25	6.7
Pallor	25	6.7
Weakness	12	3.2
Diarrhoea	10	2.7
Mucoid Stool	9	2.4
Dehydration	7	1.9
Altered Consciousness	6	1.6
Abdominal Pains	6	1.6
Gastroenteritis	6	1.6
Cold	4	1.1

The packed cell volume in the study population ranged from 5% - 45% with a mean of 23.55% (±1.74%) with 105 (28.2%) of the subjects (Table 3) presenting with varying degrees of anaemia. 35/105 (33.3%) however presented with severe anaemia (PCV≥15%) and were admitted (Table 4). These 35 subjects formed 18.6% of the 188 children that were admitted on the ward (Table 4). Twenty of the patients could afford the cost of blood transfusion, and were transfused. All but one of the transfused patients survived; however, one (AD179) of the transfused subjects developed post-transfusion parasitaemia.

Of the remaining 15 that could not afford the cost of transfusion, 5 subjects were placed on iron supplements and 10 subjects were discharged against medical advice at the

request of the parents or guardian. There seemed to be no significant association of parasitaemia with blood groups O, A and B, but the frequency of occurrence of these blood groups among the population decreased in that order.

Table 4: Clinical manifestation in 188 children admitted to the ward

Diagnosis	No. of Cases	Total (%)
Anaemia	35	18.6
Gastroenteritis	30	16.0
Pneumonia	21	11.2
Malaria	19	10.1
Cerebral Malaria	10	5.3
Febrile Convulsion	10	5.3
Other Infections	63	33.5
Total	188	100.0

Cerebral malaria was observed in 10 (5.3%) of the children admitted (Table 4). One of them was comatose for about 48 hrs. However, 6 of the 10 subjects initially showed some varying degrees of altered consciousness on consultation, but they were rousable and the other three were not particularly scored by the Blantyre scale. All these patients were anorexic and prostrate with distressed respiration.

Table 5: Transfusion in the Children Admitted to the Ward

Patients	Response		Post-transfusion complications(n)
Transfused*	Given Iron Supplts.	Survived	Died
20	0	19 (immediate)	1 Parasitaemia (1)
0	5	(over 2-4 days)	None

**Another 10 discharged themselves against medical advice, could not afford transfusion*

Febrile convulsion occurred commonly in the hospitalised patients, accounting for 41 (6.2%) of 372 patients and 21% of the 188 cases on admission. Thirty-nine (95.1%) of these patients were less than 3 years of age. Convulsions were more common at the temperature 38.4 (±0.3) °C than at higher temperatures.

Table 6: Prevalence of Anaemia among the children that attended Adeoyo State Maternity Hospital

Group	Total no of patients	No anaemic	Prevalence (%)
0-<1yr	86	23	26.7
1-<2yr	127	52	41
>2-5yr	105	19	18
>5yr	21	3	14.3
Total	339	97	

Clinical manifestation in patients admitted in the hospital

Anaemia was the major basis of paediatric admissions (Table 4). All the thirty-five (18.6%) of the 188 cases on admission that presented with anaemia were positive for malaria parasitaemia. The second commonest reason for admission was gastroenteritis (diarrhoea) (16%). However, more than 50% of these children had low parasitaemia (100-500 parasites/µl).

Cerebral malaria and febrile convulsion each accounted for 5.3% (10) morbidity of the total number of children admitted. Another 19 (10.1%) that were severely morbid but did not fulfil the WHO criteria for severe malaria were also admitted since they showed malaria related symptoms. The remaining 44% of those admitted were cases of bacterial (pneumonia) and other infections and were nonetheless treated for malaria to exclude the possibility of malaria infection.

Regarding treatment before the visit to the hospital, only 2 (0.5%) of the 372 patients admitted to the use of local herbs for treating their children (Table 7); others suspected to have used local herbs denied its use. Sixty-five (17.5%) alleged the use of Chloroquine (CQ), paracetamol, 36 (9.6%) and antibiotics (mostly Septrin®) 20 (5.3%). Fourteen (3.8%) could not remember the names of the drugs used. At the hospital most of the children that attended the OPD (77.7%) 289/372 , were treated with a combination of CQ , paracetamol and Piriton®. Of these, 52 (18.8%) were admitted and received their medications in the hospital. Twelve (3.2%) and thirteen (3.5%) of the 372 cases were treated with Paluther® and Quinine respectively in the ward. The severity of illness, packed cell volume and parasitaemia of the patients were used to determine the choice of the drugs to be administered at the time of admissions.

Table 7: Treatment and drugs used at home before attending the clinic

Drugs	Freq (%)
No drug /herb used	235 (63.2%)
CQ/others	65 (17.5%)
PCM	36 (9.6%)
Antibiotics	20 (5.4%)
Unknown Drugs	14 (3.8%)
Local Herbs	2 (0.5%)

Twenty-three (6.2%) cases that were treated with Fansidar® were patients that had an associated history of malaria resistance or had used CQ before but without parasite clearance. Most of the patients treated in the hospital (275) responded satisfactorily to the treatment they received at the hospital. The data on the rest were lacking because they did not return to the hospital after the initial treatment.

Antibody response to MSP 1_{19}

The ELISA method was used to detect the levels of the anti-MSP 1 antibodies. The results showed a high prevalence of anti-MSP 1_{19} antibodies in 320 subjects of the study population (Figure 1), 53 of whom were negative for *Plasmodium* parasitaemia. The highest antibody responses were recorded

in children within the age group 2-5 years. Children below the age of one year had very low anti-MSP 1_{19} responses. There was increasing antibody titre with increasing age, which dropped slightly at >5 years of age. There was a significant positive correlation (r=0.172, P=0.01) between parasitaemia and age (Figure 2) and between antibody titre and age; also a significant positive association was found between parasitaemia and antibody titre in the study population (*P*=0.01). Negative correlations were observed in the analysis for association between percentage PCV and both antibody response (r=-357, *P*=0.01) and parasitaemia (r=-301, *P*=0.01).

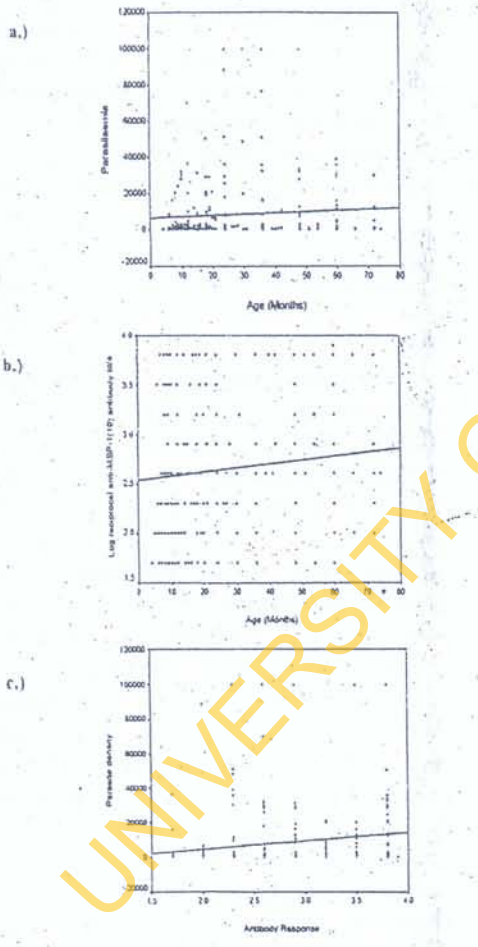

Fig. 2: Correlation between (a) parasite burden and age, (b) M/sP-1 antibodies and age (c) antibody titre and parasitaemia, in children with severe malaria.

Discussion

This study documents the prevalent symptoms and clinical manifestations in severe malaria amongst children in Ibadan, south-western Nigeria. These were compared with those of another study in Nigeria [9] and from other malaria endemic areas [5, 12, 13, 14, 15]. Many workers have described the severe malaria condition in many countries where malaria has remained endemic, accounting for considerable morbidity and mortality in children in our environment. This study corroborates results from other studies showing that most deaths from malaria are due to severe and complicated malaria [1,16,17]. Hence about 95% of the children in this study were under 5 years. Acute severe malaria accounted for 39.4% of paediatric admissions and 38.5% of all the deaths during the study period. It is known that in holoendemic areas such as ours, this age group (under 5 years) is the most vulnerable to severe and complicated malaria since their immunity to malaria is still very poor [17,18,19], and this was the group most commonly affected by this study (Table 1). Some of the features of severe malaria defined by the WHO [1] such as jaundice, renal failure, pulmonary oedema, disseminated intravascular coagulopathy and macroscopic haemoglobinuria were not observed in the 24 patients in our study diagnosed with severe malaria. These features have been reported to be rare in African children [5].

Persistent fever was a dominant feature in the patients and in fact a sign which led the patients to the hospital for treatment. At the time of the hospital visit, 61.6% of cases were still experiencing fever (Table 3). Hospital case history records for the patients showed that this number was considerably higher because the children that did not present with fever at consultation had done so at home and had presumably been given antipyretics. However, hyperpyrexia (>40°C) was common in many of the children regardless of their ages, but it was not exclusively associated with the development of febrile convulsion. This finding contradicts the reports from Jos (9) on the association of febrile convulsions with temperatures greater than 40°C in the northern parts of Nigeria, for in this studies febrile convulsions developed more frequently at lower temperatures among the children in Ibadan. The importance of teaching home management care of malaria in the tropics thus cannot be over emphasized. Since children are often unable to articulate their discomfort in the early stages of the infection when early intervention could prove to be life-saving, parents and guardians ought to be educated on the significance of the conditions their children or wards may exhibit. This is because fever has proven to be the interactive clinical indicator of malaria and perhaps of most other infections [20]

The most common clinical manifestation of acute severe malaria in this study was anaemia. It accounted for 18.6% of the admissions, comparable to the 16.6% reported in Jos [9]. The results showed that severe malaria anaemia was associated with either a short period of hyperparasitaemia or prolonged period of lower parasitaemia. Hence when other factors such as duraton of illness and degree of parasitaemia occur with the same frequency, younger children had a higher risk of developing severe malaria anaemia since their parasite to red cell ratio is smaller. The majority of patients who were anaemic (PCV≤15%) were aged 6 months – 2 years. This was not too surprising, since iron deficiency is common in Nigeria ,Tanzania and African children in the first and second years of life – a phenomenon that has been related to prolonged breast-feeding [14,21,22]. It is estimated that in this population weaning occurs at approximately 18 (±3) months of age (Popoola, personal communication). Therefore, the low iron content of the breast milk, the lack of iron rich food, and the age-related increase in iron requirements would predispose children from

this area to depletion of iron stores that occur at approximately one year of age. In addition, the major components of the diets of the young children in Nigeria are cereals and roots, which are not good sources of dietary iron in comparison with meat or fish.

The risk of anaemia in very young children 1-2 years decreased from 45% to 14.3% in over 5 year olds. This is consistent with other studies in the Sub-Saharan zone such as have been reported in Ghana [12], Gambia [13] and Tanzania [5]. In Southern Cameroon, the risk of anaemia was 42% (<3 years) and 21% (3-5 years) [14] and in Senegal 73.1% (0-3 years) and 52.1% (4-7 years)[5].

Malaria anaemia has been postulated to be secondary to direct destruction of both infected and uninfected red blood cells and to the suppression of bone marrow function (23,24,25). Increased parasite density may elicit high levels of humoral response in the patients, but is more likely to result in red cell destruction, and therefore in low PCV values as the parasites multiply. Thus, there was a negative correlation of the antibody response to MSP 1_{19}, a major vaccine candidate for malaria blood stages with PCV values in the population. Children above 5years of age are believed to mount a weak immune response to malaria, when compared with adults, however, there is need to understand the true role, impact and the functionality of the postulated mechanism(s) of immune response in children in mediating infection control.

Transfusion in severe malaria anaemia was over 95% successful in reversing severity of infection and risk factors for death. However, one child developed a post-transfusion parasitaemia as a result of infected blood transfusion. This underscores the potential of spreading other infections such as hepatitis and HIV in this manner, and as such should be a source of concern to health authorities and policy makers. As recommended in Venezuela [26], an evaluation of the risk factors in transfusion will enhance the understanding of the epidemiology of severe malaria, transmission blocking interventions of malaria, and reduce greatly, mortality amongst children and the immuno-compromised, who are the worst hit of transfusion-transmitted malaria.

Management of mild severe anaemia cases was achieved with the use of haematinics, dosage being given per weight (kg). Interestingly, nearly all the patients that were placed on haematinics and iron supplementation recovered and with good clinical indications within 36hrs - 72hrs. This finding supports reports from Ghana, Kenya and particularly Tanzania, where severe malaria anaemia was reduced by 50% and clinical malaria attacks by 59% [27,5,13] with the use of iron supplements. Iron supplements therefore, if administered from the early years of life would be a strategic, sustainable and effective preventive control to easy evolution of severe anaemia [27], cutting down on infant mortality and morbidity in malaria endemic and holoendemic zones and restricting the use of the transfusion only to the very extreme cases of anaemia.

There were higher deaths in males than females in this study (Table 2). The malaria attributable deaths of children in malaria endemic zones, especially in the high transmission seasons are the tip of the iceberg, as more than 80% deaths occur at home [6]. Factors such as access to medical care and patterns of health seeking behaviours vary between areas and will alter the pattern of presentation of cases; for instance, the gross denial of the use of local herbs by majority of those suspected to have used them, in order to avoid any form of provocation from the nurses or chiding from doctors. In this study, more boys were admitted with malaria. This imbalance may also represent household level gender-bias in treatment seeking behaviour or exposure. Thus, hospital-based studies may be a poor reflection of disease pattern in the community.

It is quite difficult to tell to what extent medication of children at home has gone to affect the development of severity in malaria, but findings from this study suggest that nearly 40% of the population (Table 7) would take to self-medication first, than attend the hospital on initial observation of illness. This has a great impact on the progression of illness and development of resistance if [i] an incomplete dosage of antimalarial drugs is used, or (ii) inappropriate, fake or adulterated drugs are used [20]. Therefore, there is a need for public enlightenment in the rural, semi-urban and even urban areas on the potential outcomes of this illness and the most efficient and safe methods for its treatment. Greater care is needed to monitor the quality of drugs sold by pharmacies and drug vendors and enforce the existing sanctions against defaulters.

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