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Research Article

Factors Associated with a Poor Treatment Outcome among Children Treated for Malaria in Ibadan, Southwest Nigeria

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We present data on factors associated with poor treatment outcome (death or recovery with a neurological complication) among children treated for malaria in Ibadan, Nigeria. A total of 2468 children (1532 with uncomplicated and 936 with severe malaria) were recruited from three government facilities. History was obtained from caregivers and malarial parasite test was carried out on each child. About 76.0% of caregivers had instituted home treatment. Following treatment, 2207 (89.5%) children recovered without complications, 9.1% recovered with neurological complications, and 1.4% died. The possibility of poor treatment outcome increased with decreasing child's age ($P < 0.0001$). A statistically significant proportion of children with pallor, jaundice, hepatomegaly, splenomegaly, respiratory distress, and severe anaemia had poor treatment outcome. Following logistic regression, child's age < 12 months compared to older age groups (O.R = 5.99, 95% C.I = 1.15–31.15, and $P = 0.033$) and loss of consciousness (O.R = 4.55, 95% CI = 1.72–12.08, and $P = 0.002$) was significantly associated with poor treatment outcome. We recommend interventions to improve caregivers' awareness on the importance of seeking medical care early. This will enhance early diagnosis and treatment and reduce the likelihood of complications that lead to poor treatment outcomes.

1. Introduction

Malaria remains an important cause of morbidity and mortality in Africa in spite of all efforts at prevention and control. In 2010, there were about 660,000 malaria deaths around the world and, of these, approximately 86% were in children under five years of age [1]. The majority of cases (up to 80%) and deaths (up to 90%) due to malaria occur in Africa [1]. Malaria is still endemic in Nigeria with 97% of the population at risk of infection [2]. Findings from the 2010 Malaria Indicator Survey showed that about four out of ten children aged between six months and five years in Nigeria tested positive to malaria by blood smear test [3]. The Federal Ministry of Health estimates that every year malaria accounts for up to 110 million clinically diagnosed cases, 60% of outpatient visits, 30% of all hospitalizations, and more than 300,000 child deaths [2]. In addition to the high mortality, many children with the disease go on to develop short and long term complications such as anaemia, metabolic acidosis, hypoglycemia, hyperlacticacidemia, seizures, febrile convulsion and other complications affecting the central nervous system [4–6]. A number of factors have been suggested as predisposing to development of poor treatment outcomes among children with malaria. These include impaired consciousness, respiratory distress, hypoglycemia, and jaundice [7]. Knowledge of the factors that influence the outcome of malaria treatment is important in management of children with malaria in order to minimize morbidity and mortality from the disease. The paper discusses the factors associated with a poor outcome in children treated for malaria in Ibadan, Southwest Nigeria. Data for this paper was part of a larger study on genetic diversity and severe malaria.

2. Materials and Methods

The study was carried out in Ibadan, a city in southwest of Nigeria, a holoendemic area for malaria between 2007 and 2010. At the time of the study, the standard first-line treatment

for uncomplicated malaria was artemether-lumefantrine or another artemisinin-based combination therapy. Drugs recommended for severe malaria included the following: quinine, artemether, or artesunate. These are to be commenced parenterally and changed to oral administration once the patient can take the drugs orally [8]. However, chloroquine injection and tablets were still available and could be purchased over-the-counter in drug stores within the country.

Children were recruited from the children's emergency ward of the University College Hospital, Ibadan, the Adeoyo Maternity Hospital, Ibadan, and the Oni Memorial Hospital, Ibadan. A total of 2468 children who were diagnosed with malaria (children presenting with fever and who had a positive malaria parasite test result or a clinical diagnosis of malaria) were recruited. Clinical categorization of all eligible children into "uncomplicated malaria (UM)," and "severe malaria" groups was done using World Health Organization criteria (WHO 2000). According to the WHO classification, cases of severe malaria included those with impaired consciousness, cerebral malaria, severe malaria anaemia, and jaundice [9]. Children were excluded from the study if informed consent was not obtained from a relative (primary caregiver) or if an alternative diagnosis was made clinically or by investigation (such as cerebrospinal fluid examination, chest radiography, or blood culture). All the children were managed in line with the National Malaria Treatment Policy [8]. All the 936 children with severe malaria were hospitalised and treated with quinine according to the National Malaria Treatment Policy, that is, parenteral quinine which was changed to oral as soon as the child was able to tolerate it orally [8]. Those with uncomplicated malaria were treated on an outpatient basis with an ACT. Their caregivers were asked to bring them back on days 2, 7, and 14 for follow-up which included a clinical assessment and repeat malaria parasite test. In line with routine care, caregivers were asked to return to hospital immediately if there was no improvement in symptoms or if their child's health got worse. Children with an initial diagnosis of uncomplicated malaria who subsequently presented with symptoms of severe malaria were admitted and treated appropriately as cases of severe malaria.

Ethical approval was obtained from the Joint University of Ibadan/University College Hospital, Ibadan Ethical Committee, and from the Oyo State Health board. Informed consent was obtained from the parents or guardian of the patients prior to recruitment.

Demographic information, clinical history information obtained from caregivers of children, and clinical examination done were recorded in a well-structured case record form. Patients body temperature was categorized as normal (36.6–37.2°C), febrile (>37.2°C), subnormal (36.6–35°C), and hypothermia (< 35°C) [10]. Thick blood smears stained with giemsa were prepared for each child and examined for trophozoites of *P. falciparum*. Parasite densities were calculated based on assumed total WBC of 8000/μL. Blood films were defined as negative if there were no asexual forms of *P. falciparum* in 100 high power fields examined. The parasite densities were log transformed and the geometric means of the parasite densities were calculated. Blood was also sampled for haematocrit or packed cell volume (PCV). Patients were classified as having severe (PCV ≤ 15%), moderate (PCV = 16–23%), mild (PCV = 24–33%), and no (PCV > 33%) anaemia. The Pediatric Glasgow Coma Scale was used to assess level of consciousness [11].

Statistical analysis was done with the SPSS 16.0 for Windows (SPSS Inc., Chicago, USA). The prevalence of malaria parasitaemia, spleen rate, liver rates, and anaemia (PCV < 33%) was calculated as a proportion of children with those indices. Poor treatment outcome was defined as recovery (resolution of fever, recovery of consciousness in children who were unconscious, and negative blood film) with a neurological complication at discharge or death. Chi-square was used for association between categorical variables. Logistic regression was used to determine the predictors of poor treatment outcome. Statistical significance was set at $P < 0.05$.

3. Results

Results of 2468 children aged 1–156 months, of mean age 42.9 ± 29.7 months, are presented. There were slightly more male (53.35) than female (46.7%) patients. The highest level of education of 49.0% of respondents' mothers and 51.1% of their fathers was secondary education and majority of the parents (71.8% of mothers and 63.7% of fathers) were semiskilled workers.

The medical histories of the children are shown in Table 1. The commonest symptoms that patients presented with were fever (97.9%), rigors (17.8%), loss of appetite (39.1%), cough (33.1%), and vomiting (30.1%). About 17.0% of caregivers reported that their children were pale and three percent were jaundiced (described by caregivers as yellowness of their child's eyes) prior to presentation in hospital. More than 200 (8.5%) presented with a history of loss of consciousness and 535 (21.7%) had at least an episode of convulsion prior to presentation in the health facility. More than three-quarters of caregivers (76.3%) had instituted some home treatments, of which the majority 1,457 (65.1%) gave paracetamol (PCM). Drugs also administered by mothers were chloroquine—CQ (16%), amodiaquine—AQ (4%), and others, including sulphadoxine-Pyrimethamine—SP (15%). Only 340 of the caregivers (15.4%) had not had a prior visit to a health provider such as a private hospital (19.2%), health centre (24.7%), patent medicine vendors (39.5%), and others (1.2%). The median number of days of onset of illness prior to a hospital visit was three. Two hundred and sixty-two children were reportedly semiconscious when they arrived to the hospital.

Clinical examination of the children at presentation revealed that 21.3% were pale and 3.7% were jaundiced. In all, 1532 (62.1%) of children were diagnosed with uncomplicated malaria and 936 (37.9%) were diagnosed with severe malaria. The mean parasite density was 1584.89 ± 15.49 [3235.94 ± 18.62 among those with severe malaria and 891.25 ± 11.48 among those with uncomplicated malaria $P < 0.0001$]. All the 2468 children were treated in line with malaria treatment guidelines. The 936 children diagnosed with severe malaria

Table 1: Child's medical history and history of illness.

Illness history	*N*	%
Symptoms prior to presentation (multiple responses) (*N* = 2468)		
Fever	2415	97.9
Loss of appetite	966	39.1
Cough	819	33.1
Vomiting	890	30.1
Convulsion	535	21.7
Catarrh	485	19.7
Rigors	438	17.8
Pallor	409	16.6
Lethargy	339	13.7
Loss of consciousness	211	8.5
Fast breathing	161	6.5
Diarrhoea	157	6.4
Body aches	154	6.2
Irritability	99	4.0
Jaundice	76	3.0
Any home treatment (*N* = 2452)		
Yes	1872	76.3
No	579	23.7
Level of consciousness (Paediatric Glasgow Coma Scale) (*N* = 610)		
15 (normal)	76	12.5
8–14 (altered sensorium)	462	75.7
7 and below (coma)	72	11.8

Table 2: Sociodemographic factors associated with treatment outcome.

	Full recovery	Recovery + NC or death	Chi-square	*P* value
Sex (*N* = 2466)				
Male	1168 (88.8)	147 (11.2)	1.369	0.263
Female	1039 (90.3)	112 (9.7)		
Age group (months)				
<12	193 (74.8)	65 (25.2)	81.014	<0.0001*
12–23	425 (88.2)	57 (11.8)		
24–35	402 (89.5)	47 (10.5)		
36–47	333 (92.0)	29 (8.0)		
48–59	278 (95.2)	14 (4.8)		
≥60	576 (92.9)	44 (7.1)		
Mother's level of education (*N* = 2450)				
No formal	83 (50.9)	80 (49.1)	301.3	<0.0001*
Primary	528 (83.3)	106 (16.7)		
Secondary	1137 (95.1)	58 (4.9)		
Tertiary	455 (99.3)	3 (0.7)		
Father's level of education (*N* = 2435)				
No formal	51 (49.5)	52 (50.5)	303.251	<0.0001*
Primary	349 (76.4)	108 (23.6)		
Secondary	1168 (93.9)	76 (6.1)		
Tertiary	627 (99.4)	4 (0.6)		

NC: neurological complications.
*Statistically significant.

were admitted to hospital and treated with quinine (initially parenteral then changed to oral). The majority, 2207 (89.5%), of all 2468 children recovered fully without any neurological or other complications, 9.1% recovered but with neurological complications such as seizures and hearing deficit, and 1.4% died.

3.1. Sociodemographic Factors Associated with Treatment Outcome. Sociodemographic factors associated with a negative treatment outcome, recovery with a neurological complication (NC), or death are presented in Table 2. Child's age as well as the mother and fathers' level of education was significantly associated with an adverse treatment outcome. The possibility of adverse health income increased with decrease in child's age ($P < 0.0001$). The higher the level of education of a child's mother or father is, the less likely the occurrence of an adverse outcome will be ($P < 0.0001$).

3.2. Association between Illness History and Treatment Outcome. Illness history and prior treatment associated with a negative treatment outcome, recovery with a NC, or death are presented in Table 3. Use of PCM prior to presentation was significantly associated with a better treatment outcome ($P < 0.001$). More children with a history of jaundice, loss of consciousness, and convulsion had a negative treatment outcome ($P < 0.0001$). However, more of those who did not have a history of rigors (11.2%, $P < 0.01$), loss of appetite (13.6%, $P < 0.0001$), vomiting (11.5%, $P < 0.040$), or pallor (11.1%, $P < 0.022$) had negative treatment outcomes.

3.3. Association between Clinical Examination and Laboratory Findings and Treatment Outcome. Negative treatment outcome was observed more in patients with pallor (19%, $P < 0.0001$), jaundice (33.3%, $P < 0.0001$), subnormal temperature (20.0%, $P < 0.0001$), hepatomegaly (26.7%, $P < 0.0001$), splenomegaly (26.9%, $P < 0.0001$), and severe anaemia defined as PCV ≤ 15% (20.1%, $P < 0.0001$) at presentation than among their counterparts who did not have these findings on examination at the hospital (see Table 4).

Following bivariate analysis, factors significantly associated with poor treatment outcome ($P < 0.05$) were entered into the regression model and logistic regression analysis carried out. Child's age less than 12 months (O.R = 5.99, 95% C.I = 1.15–31.15, and $P = 0.033$), history of loss of consciousness (O.R = 4.55, 95% CI = 1.72–12.08, and $P = 0.002$), and subnormal temperature (O.R = 11.52, 95% CI =

Table 3: Illness history associated with outcome.

	Full recovery	Recovery + NC or death	Chi-square	*P* value
Any home treatment				
Yes	1683 (89.9)	189 (10.1)		
No	524 (90.5)	55 (9.5)	0.936	0.776
Any drug used prior to presentation (N = 2240)				
Yes	1553 (98.9)	17 (1.1)		
No	649 (96.9)	21 (3.1)	11.852	0.001
Drug used prior to presentation				
PCM				
Yes	1442 (99.0)	15 (1.0)		
No	757 (97.1)	23 (2.9)	11.206	0.001
CQ				
Yes	346 (98.3)	6 (1.7)		
No	1853 (98.3)	32 (1.7)	0.000	1.000
AQ (2237)				
Yes	93 (97.9)	2 (2.1)		
No	2106 (98.3)	36 (1.7)	0.098	1.000
SP				
Yes	21 (95.5)	1 (4.5)		
No	2178 (98.3)	37 (1.7)	1.078	0.315
Symptoms prior to presentation				
Fever (n = 2468)				
Yes	2165 (89.6)	250 (10.4)	2.426	0.116
No	44 (83.0)	9 (17.0)		
Rigors (n = 2468)				
Yes	407 (92.9)	31 (7.1)	6.618	0.010*
No	1802	228 (11.2)		
Loss of appetite (n = 2468)				
Yes	912 (94.4)	54 (5.6)	40.644	<0.0001*
No	1297 (86.4)	205 (13.6)		
Vomiting (n = 2468)				
Yes	812 (91.2)	78 (8.8)	4.437	0.040*
No	1397 (88.5)	181 (11.5)		
Diarrhoea (n = 2468)				
Yes	142 (90.4)	15 (9.6)	0.158	0.788
No	2067 (89.4)	244 (10.6)		
Jaundice (n = 2468)				
Yes	56 (73.7)	20 (26.3)		
No	2153 (90.0)	239 (10.0)	20.897	0.0001*
Pallor (n = 2467)				
Yes	379 (92.7)	30 (7.3)	5.222	0.022*
No	1829 (88.9)	229 (11.1)		
Fast breathing (N = 2468)				
Yes	140 (87.0)	21 (13.0)	1.192	0.286
No	2069 (89.7)	238 (10.3)		
Lethargy (n = 2468)				
Yes	298 (87.9)	41 (12.1)	1.071	0.295
No	1911 (89.8)	218 (10.2)		
Loss of consciousness (n = 2240)				
Yes	197 (93.4)	14 (6.6)	34.069	<0.0001*
No	2005 (98.8)	24 (1.2)		
Convulsion (n = 2466)				
Yes	449 (83.9)	86 (16.1)	22.566	<0.0001*
No	1758 (91.0)	173 (9.0)		

*Statistically significant.

1.07–123.64, and P = 0.044) were significant predictors of a poorer treatment outcome (Table 5).

4. Discussion

Despite intensified programs in disease control, malaria still remains a public health burden in Sub-Saharan Africa [1]. Although several factors were associated with a poor outcome, after conducting multiple logistic regression analysis, history of loss of consciousness and a child's age less than 12 months were significant predictors of a poorer treatment outcome. These conditions are recognized as pointers to severe malaria [9] and thus emphasize the need for prompt diagnosis and institution of appropriate treatment in the management of malaria. Children who were less than a year old were the most susceptible to neurological complications or even death after treatment and this susceptibility decreased with increasing age, with the lowest susceptibility recorded among children who aged 48–59 months. Riley et al. noted that, while research suggests that neonates and infants are relatively protected against malaria infection and death from severe malaria, this protection was not infallible and could be undermined in the presence of high transmission [12]. Thus infants could still be infected and could suffer from adverse outcomes and this was in keeping with our study findings. Our study also found that children with subnormal temperature at presentation had poorer outcomes than those with normal temperatures and febrile patients. However, the small number of patients in this subcategory could have accounted for this finding.

Table 4: Examination findings at presentation associated with outcome.

	Full recovery	Recovery with NC or death	Chi-square	*P* value
Pallor (n = 2445)				
Yes	423 (81.0)	99 (19.0)	51.096	<0.0001*
No	1766 (91.8)	157 (8.2)		
Jaundice (n = 2441)				
Yes	60 (66.7)	30 (33.3)	53.820	<0.0001*
No	2130 (90.6)	221 (9.4)		
Temperature (°C)				
Febrile (>37.2)	1133 (88.1)	153 (11.9)		
Normal (36.6–37.2)	1032 (94.7)	58 (5.3)		
Subnormal (36.6–35)	8 (80.0)	2 (20.0)		
Hypothermia (<35)	5 (100.0)	0	34.581	<0.0001*
Paediatric GCS				
≤7	68 (94.4)	4 (5.6)		
8–14	439 (95.0)	23 (5.0)		
15	73 (96.1)	3 (3.9)	0.219	0.896
Hepatomegaly (n = 2312)				
Yes	381 (73.3)	139 (26.7)	255.3	<0.0001*
No	1722 (96.3)	70 (3.9)		
Splenomegaly (n = 2253)				
Yes	209 (73.1)	77 (26.9)	216.4	<0.0001*
No	1894 (96.3)	73 (3.7)		
Anaemia packed cell volume (n = 2468)				
Severe (≤15%)	290 (79.9)	73 (20.1)		
Moderate (16–23%)	291 (82.2)	63 (17.8)		
Mild (24–33%)	863 (91.7)	78 (8.3)		
Normal (>33%)	765 (94.4)	45 (5.6)	81.736	<0.0001*

*Statistically significant.

The level of education of both the father and mother of the children surveyed was significantly related to the adverse outcome recorded. Gakidou et al. (2010) in their paper on the effect of increased educational attainment on child mortality in 175 countries between 1970 and 2009 noted that the education of women of reproductive age may account for as much as half of the reduction in under-5 mortality observed in their review [13]. Other studies have also found a relationship between higher levels of maternal education and better child heath outcome [14, 15].

Our study suggests a beneficial effect of prior administration of paracetamol as a lower proportion of children who

Table 5: Multivariate analysis of factors associated with poor treatment outcome.

	Odds ratio	95% C.I	*P* value
Sociodemographic characteristics			
Age group			
<12	5.99	1.15–31.15	0.033*
12–23	3.05	0.62–14.88	0.169
24–35	2.54	0.51–12.65	0.254
36–47	3.02	0.62–14.80	0.174
48–59	1		
≥60	1.08	0.16–6.85	0.939
Mother's highest level of education			
No formal	0.000	0.000	0.997
Primary	1.11	0.19–6.57	0.905
Secondary	1.19	0.23–6.11	0.835
Tertiary	1		
Father's highest level of education			
No formal	0.000	0.000	0.998
Primary	1.62	0.31–8.39	0.565
Secondary	2.0	0.48–8.35	0.342
Tertiary	1		
Illness history given by caregiver			
Any drug used prior to presentation			
Yes	1		
No	1.43	0.29–6.93	0.657
Use of PCM prior to presentation			
Yes	1		
No	1.31	0.27–6.44	0.738
Symptoms prior to presentation			
Rigors			
Yes	1		
No	1.51	0.57–4.03	0.409
Loss of appetite			
Yes	1		
No	1.70	0.78–3.70	0.180
Vomiting			
Yes	1		
No	0.64	0.31–1.32	0.226
Jaundice			
Yes	1.26	0.27–5.87	0.767
No	1		
Pallor			
Yes	1		
No	1.58	0.60–4.13	0.353
Loss of consciousness			
Yes	4.55	1.72–12.08	0.002*
No	1		

Table 5: Continued.

	Odds ratio	95% C.I	*P* value
Convulsion			
Yes	1.61	0.66–3.94	0.296
No	1		
Clinical examination findings			
Pallor			
Yes	2.54	0.90–7.16	0.078
No	1		
Jaundice			
Yes	2.05	0.55–7.64	0.284
No	1		
Patients' temperature			
Febrile	1.89	0.77–4.63	0.163
Normal	1		
Sub-normal	11.52	1.07–123.64	0.044*
Hypothermia	—		
Hepatomegaly			
Yes	1.17	0.51–2.68	0.709
No	1		
Splenomegaly			
Yes	1.95	0.82–4.62	0.129
No	1		
Respiratory distress			
Yes			
No			
Anaemia			
Severe	2.62	0.67–10.18	0.165
Mild	0.87	0.21–3.72	0.854
Moderate	1.50	0.45–5.01	0.507
No anaemia	1		

*Statistically significant.

had been given paracetamol developed negative outcomes after treatment compared to their counterparts who were not given paracetamol. Russel et al. (2003) in their review of the use of paracetamol in febrile children submitted that there was no clear evidence in support of its use in treating febrile children [16]. However, early diagnosis of malaria and institution of prompt treatment remain the gold standard for reducing morbidity and mortality from the disease.

Caregivers listed rigors, loss of appetite, vomiting, jaundice, pallor, loss of consciousness, and convulsion as symptoms they observed in their wards. These indicate that many caregivers recognized these symptoms. However more children were noted to be jaundiced, pale, and anaemic on clinical examination and following laboratory investigations conducted at the hospital compared with the caregivers self-report of these symptoms. This implies that many of these symptoms were missed by the caregivers and would therefore explain why a higher percentage of children who were not pale or jaundiced based on their caregivers report had a negative health outcome. This might also explain why a higher percentage of those who had jaundice, pallor, and severe anaemia on clinical examination and/or following laboratory investigations died or developed neurological disorders compared with those who did not have these symptoms or signs.

The study findings also revealed that more children who had not experienced rigors, lost appetite, or vomited had adverse health outcomes. It is thus possible that the caregivers had associated the lack of these symptoms with mild illness leading to delayed presentation at hospital and ultimately delay in commencement of appropriate treatment.

5. Conclusion

A history of loss of consciousness and child's age less than 12 months were significant predictors of poorer treatment outcome in our study sample. Although the caregivers mentioned a number of symptoms that their children had prior to presentation which were associated with poor outcome, the numbers of children who actually had these symptoms was higher on clinical examination and following laboratory investigation. Many of these symptoms such as pallor, jaundice, and severe anemia were positively associated with adverse treatment outcomes. This has implications for programmes that advocate for home management of malaria because commencement of home management relies on the caregivers ability to recognize mild symptoms of malaria. This approach might be counterproductive as complications may then set in especially when caregivers do not recognize symptoms of severe disease. In view of the study findings, we recommend that caregivers be properly educated so that they can seek medical care promptly in order to prevent progression to severe disease which is associated with poor treatment outcomes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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