

## Prevalence of Malaria among Infants and Children with febrile illness: A Hospital Based Study

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### ABSTRACT



**Background:** About half of the world's population is at risk of malaria and the burden is particularly high in low-income countries like Nepal. Infants and children are more vulnerable to malaria. Acute febrile illness is the commonest presentation of malaria. Since it is one of the major causes of persistent febrile illnesses in Nepal, empirical antimalarial therapy is usually practiced, especially the endemic areas. A better understanding of the prevalence and clinical profile of malaria helps to tailor the treatment accordingly in cases of undifferentiated febrile illnesses and make the use of antimalarials more rational.

**Methods:** A cross-sectional observational study was conducted on 200 infants and children presenting with acute febrile illness in the Departments of Pediatrics, Nepalgunj Medical College, from June 2018 to May 2019. Patients were divided in two groups based on the Malarial parasite antigen status. Clinical and laboratory profile of both the groups were compared using Chi square Test.

**Results:** Maximum number of cases in the malaria positive group were of age group 12-15 years. Pallor, icterus, hepatomegaly and splenomegaly were significantly more in malaria positive cases (p-value <0.001 in all cases) eosinophilia and leucopenia were common in malaria positive cases. Diagnostic accuracy of malaria was found to be 82 % on combining serology with clinical findings.

**Conclusion:** Prevalence of malaria was found to be more among children than the infants. Although symptoms of malaria are non-specific, clinical findings like pallor, icterus, hepatomegaly and splenomegaly were found to have a significant association with malaria. Combining serology with clinical profile in the prediction of malaria helps promote rational use of antimalarial drugs.

**Keywords:** Anti-malarial, malaria, seropositivity, splenomegaly, plasmodium, prevalence of malaria

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## INTRODUCTION

Malaria is a life-threatening infectious disease caused by plasmodium, a protozoan parasite. It is a major public health problem with estimated 229 million cases and 4,09,000 deaths in 2019.<sup>1</sup> About half of the world's population is at risk of malaria, particularly those living in lower income countries. Owing to poverty and poor sanitation, the morbidity and mortality due to malaria is high in Nepal. Children under five years of age are most vulnerable to malaria and constitute 67% of global malaria deaths.<sup>1</sup> Malaria is listed among the the top 10 causes of neonatal and under 5 mortality rate in Nepal.<sup>2</sup> Although Malaria can have vague and non-specific symptoms, the most common presentation is usually that of an acute febrile illness.<sup>3</sup> In areas of the world where malaria is endemic and the diagnostic services are inadequate, empirical antibiotics and antimalarials are generally used for the treatment of acute febrile illness.<sup>4</sup> Malaria being of the common causes of persistent febrile illnesses in Nepal, empirical antimalarial therapy is usually practiced, specially the endemic areas.<sup>5</sup> A better understanding of the prevalence and clinical profile of malaria helps to tailor the treatment accordingly in cases of undifferentiated febrile illnesses and to avoid maltreatments as well.<sup>6</sup>

## MATERIALS AND METHODS

This is a hospital-based cross-sectional observational study carried out among the out-patient and in-patients in Departments of Pediatrics in Nepalgunj Medical College, Nepalgunj from June 2018 to May 2019 among infants and children. A total of 200 infants and children under 15 years of age with acute febrile illness were enrolled in the study. Children in critical condition with unstable

vitals, those who expired before investigations, those with obvious bacterial and viral infection or malignancies and those who refused to give consent were excluded from the study.

Ethical approval for the study was taken from the department of pediatrics and department of pathology, Nepalgunj medical college. Likewise, written consent from parents of the children was taken. Malarial parasite (MP) serology and the routine tests for febrile illnesses were done in all cases. Thick and thin film blood smears were also prepared. Bone marrow examination, Montoux test, Chest X-ray, USG of abdomen, Lumber Puncture and CSF examination were carried out according to the need of the patients. MP serology positive cases were placed in Group I treated with antimalarials. MP serology negative cases constituted with group II. Their treatment was tailored according to the clinical profile, antimalarials were given in those not responding to the treatment. Outcome of treatment was measured in terms of improvement, deterioration, death, referral to other centers and left against medical advice (LAMA). Statistical analysis of the data was done using Statistical Package for Social Sciences, Version 15.0. Inter- group comparison was done using Chi-square test. Diagnostic efficacy of clinical criteria was assessed in terms of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. Confidence level of the study was kept at 95% and p value  $\leq 0.05$  was considered statistically significant.

## RESULTS

A total of 200 children with febrile illness were enrolled in the study. On performing Mp serology, 49 out of 200 (24.5%) subjects were found to be malaria positive and comprised

the Group I of the study and remaining 151 (75.5%) were found to be malaria negative and

were placed in Group II of the study. Majority of participants were males in both the groups (Table1).

Table 1: Sex-wise Distribution of cases according to confirmed diagnosis (n=200)

|    | Gender | Group I (n=49) |             | Group II (n=151) |      | $\chi^2$ test and p-value |
|----|--------|----------------|-------------|------------------|------|---------------------------|
|    |        | No.            | Percent (%) | No.              | %    |                           |
| 1. | Male   | 32             | 65.3        | 106              | 70.2 | $\chi^2=0.414,$<br>0.520  |
| 2. | Female | 17             | 34.7        | 45               | 29.8 |                           |

Maximum number of cases in malaria positive group were in age group 12-15 years (36.7%) whereas maximum number of cases in malaria negative group were in age group 1-3 years. Statistically, there was a significant difference

in age between two groups ( $p=0.003$ ). Mean age of patients in Group I was  $8.81 \pm 4.98$  years (range 0.9-15 years) whereas the same in Group II was 5.52 years (range 0.10 to 15 years) (Table 2).

Table 2: Distribution of Patients in Two Groups according to age

| SN | Age Group in year | Group I (n=49) |             | Group II (n=151) |             |
|----|-------------------|----------------|-------------|------------------|-------------|
|    |                   | Frequency      | Percent (%) | Frequency        | Percent (%) |
| 1. | Up to 1           | 2              | 4.1         | 20               | 13.2        |
| 2. | 1-3               | 9              | 18.4        | 50               | 33.1        |
| 3. | 3-6               | 6              | 12.2        | 24               | 15.9        |
| 4. | 6-9               | 8              | 16.3        | 24               | 15.9        |
| 5. | 9-12              | 6              | 12.2        | 14               | 9.3         |
| 6. | 12-15             | 18             | 36.7        | 19               | 12.6        |

$\chi^2=17.875$  (DF=5);  $p=0.003$

Pallor was the most common finding. The proportion of patients with pallor was significantly higher in Group I (89.8%) as compared to 51.0% in Group II ( $p<0.001$ ). Similarly, proportion of patients with splenomegaly, hepatomegaly and icterus was significantly higher among patients with malaria as compared to malaria negative patients. However, proportion of patients with convulsions was significantly higher in malaria negative cases as compared to those with malaria ( $p<0.001$ ). Purpura, unconsciousness and respiratory distress were some of the less common findings and did not show a significant difference between two groups

( $p>0.05$ ). None of the patients had meningeal signs (Table 3).

In terms of hematological investigations, eosinophilia was more common in Malaria positive cases while leukocytosis was significantly less common as compared to non malaria cases. Anemia was found to be an important association with Malaria (Table 4). All the 49 (100%) cases of Group I was seropositive. A total of 3 (6.1%) cases in Group I were found to be positive for malaria parasite on bone marrow examination too. None of the cases were found to be positive on CSF examination. None of the cases in Group II were found to be positive using any of the three confirmatory investigations.

Table 3: Comparison of two groups for presence of different signs and symptoms

| SN  | Signs and symptoms   | Group I (n=49) |      | Group II (n=151) |      | Significance of association |        |
|-----|----------------------|----------------|------|------------------|------|-----------------------------|--------|
|     |                      | No.            | %    | No.              | %    | $\chi^2$                    | P      |
| 1.  | Fever                | 49             | 100  | 150              | 99.3 | 0.326                       | 0.568  |
| 2.  | Chills and rigors    | 16             | 32.7 | 24               | 15.9 | 6.494                       | 0.011  |
| 3.  | Convulsions          | 10             | 20.4 | 58               | 38.7 | 5.474                       | 0.019  |
| 4.  | Pallor               | 44             | 89.8 | 77               | 51.0 | 23.308                      | <0.001 |
| 5.  | Icterus              | 16             | 32.7 | 10               | 6.6  | 22.164                      | <0.001 |
| 6.  | Purpura              | 1              | 2.0  | 1                | 0.7  | 0.710                       | 0.399  |
| 7.  | Unconsciousness      | 1              | 2.0  | 5                | 3.3  | 0.205                       | 0.651  |
| 8.  | Respiratory distress | 0              | 0.0  | 1                | 0.7  | 0.326                       | 0.568  |
| 9.  | Splenomegaly         | 37             | 75.5 | 26               | 17.2 | 58.258                      | <0.001 |
| 10. | Hepatomegaly         | 16             | 32.7 | 10               | 6.6  | 22.164                      | <0.001 |
| 11. | Meningeal signs      | 0              | 0    | 0                | 0    | -                           | -      |

Table 4: Distribution of subjects in two groups according to hematological findings

| SN  | Hematological Findings      | Group I (n=49) |      | Group II (n=151) |      | Significance of association |        |
|-----|-----------------------------|----------------|------|------------------|------|-----------------------------|--------|
|     |                             | No.            | %    | No.              | %    | $\chi^2$                    | P      |
| 1.  | Hemoglobin                  |                |      |                  |      | 34.991                      | <0.001 |
|     | > 11.0 mg/dl                | 5              | 10.2 | 69               | 45.7 |                             |        |
|     | 8-11.0 mg/dl                | 24             | 49.0 | 68               | 45.0 |                             |        |
|     | 6-8.0 mg/dl                 | 8              | 16.3 | 4                | 2.6  |                             |        |
|     | <6 mg/dl                    | 12             | 24.5 | 10               | 6.6  |                             |        |
| 2.  | Iron deficiency (RDW >14.5) | 32             | 65.3 | 71               | 47.0 | 4.953                       | 0.026  |
| 3.  | Leucocytosis                | 18             | 36.7 | 66               | 43.7 | 0.739                       | 0.390  |
| 4.  | Leucopenia                  | 7              | 14.3 | 1                | 0.7  | 17.755                      | <0.001 |
| 5.  | Neutrophillia               | 6              | 12.2 | 19               | 12.6 | 0.004                       | 0.950  |
| 6.  | Neutropenia                 | 5              | 10.2 | 5                | 3.3  | 3.700                       | 0.054  |
| 7.  | Lymphocytosis               | 14             | 28.6 | 31               | 20.5 | 1.372                       | 0.241  |
| 8.  | Lymphopenia                 | 4              | 8.2  | 5                | 3.3  | 2.027                       | 0.155  |
| 9.  | Monocytosis                 | 2              | 4.1  | 1                | 0.7  | 2.928                       | 0.087  |
| 10. | Eosinophilia                | 16             | 32.7 | 18               | 11.9 | 11.270                      | 0.001  |

In majority of cases, the causative agent for malaria was Plasmodium vivax (87.8%). There were a total of 6 (12.2%) cases in which

causative agent was Plasmodium falciparum (Figure 1).

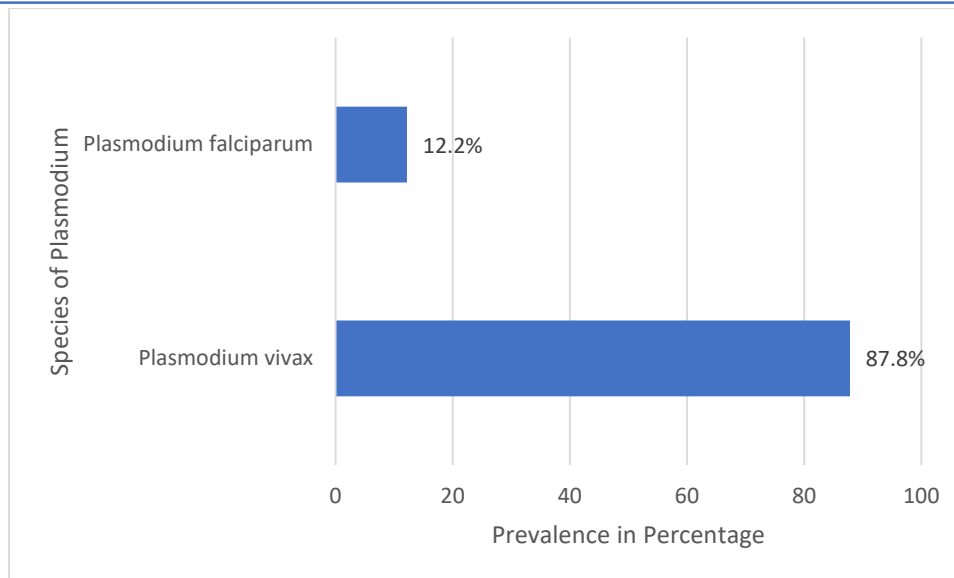


Figure 1: Distribution of subjects according to causative agent of malaria (n=49)

Using the combined approach enhanced the sensitivity considerably to a level of 87.8% while specificity was compromised only

slightly yet still remaining at 80.1%. The negative predictive value was excellent 95.3% and overall accuracy was 82% (Table 5).

Table 5: Combined Criteria of Hepatomegaly + Splenomegaly alone or in combination for differentiation of seropositive and seronegative groups

| Hepatomegaly/ Splenomegaly alone or in combination |             | Seropositivity |          | Total    |
|--|-------------|----------------|----------|----------|
|  |             | Positive       | Negative |          |
| Yes  |             | 43             | 30       | 73       |
| No   |             | 6              | 121      | 127      |
| Total  |             | 49             | 151      | 200      |
| Sensitivity  | Specificity | PPV            | NPV      | Accuracy |
| 87.8%  | 80.1%       | 58.9%          | 95.3%    | 82.0%    |

All patients in Group I were treated with antimalarials. The treatment in Group II was tailored according to the clinical profile, antimalarials were given in those not responding to the treatment (Table 6).

Table 6: Distribution of Subjects according to first line of treatment

| SN | Response                 | Group I (n=49) |      | Group II (n=151) |      |
|----|--------------------------|----------------|------|------------------|------|
|    |                          | No.            | %    | No.              | %    |
| 1. | Chloroquine              | 36             | 73.5 | 29               | 19.2 |
| 2. | Quinine                  | 11             | 22.4 | 2                | 1.4  |
| 3. | Other than anti-malarial | 0              | 0.0  | 120              | 79.5 |
| 4. | Artemether               | 2              | 4.1  | 0                | 0.0  |

The recovery rate was 100 % in Group I. 98.7 % cases in Group II recovered in Group II and he rest 1.3 % left against medical advice. (Table 7)

Table 7: Outcome of Treatment

| SN | Response  | Group I (n=49) |       | Group II (n=151) |      |
|----|-----------|----------------|-------|------------------|------|
|    |           | No.            | %     | No.              | %    |
| 1. | Recovered | 49             | 100.0 | 149              | 98.7 |
| 2. | LAMA      | 0              | 0     | 2                | 1.3  |

## DISCUSSION

In Nepal, malaria is a major public health concerns in terms of mortality, morbidity and the subsequent overall impact on the national economy. Malaria is endemic specially in the southern plain of Nepal, where it shares its border with India.<sup>7</sup> This hospital based study is done in one of the major tertiary hospitals in the southern belt of Nepal.

The prevalence of malaria in present study was observed to be 24.5% and was maximum in age group >12-15 years. These findings are in accordance with the observations of Parajuli and Ghimire who have reported the prevalence of malaria to be less than half in children aged <9 years as compared to those aged between 10-20 years.<sup>8</sup> Contrary to this, in a study by Haque et al<sup>9</sup> from neighboring country, Bangladesh, the prevalence was found to be higher in 0-4 year's age group (11.34%) as compared to those aged between 5-14 years (8.69%). The relationship between age and malaria has been reported in varied manner and has been stated to be dependent on intensity, severity of malaria and seasonal variability.<sup>10</sup>

In this study, majority of cases in both malaria and non-malaria groups were males. It is difficult to comment whether gender has a role to play in determining the prevalence of malaria, instead it seems to be driven by the gender bias in health services utilization

pattern of Nepalese society which is chiefly male dominated. These findings are in accordance with the observations of Parajuli et al.<sup>8</sup> who also reported a male dominance (75% males as compared to 25% females) in their cross-sectional study. It is pertinent to mention here that in a protected society like Nepal, especially among low and poor socioeconomic strata, girls are generally confined to household and generally sleep inside the house whereas the male adults and children usually sleep outside the house. The higher level of exposure to outdoor environment increases the chances of mosquito bite and hence malaria. Moreover, the proportion of males is not only higher among those inflicted with malaria but it is of similar order among cases that were not confirmed as malaria thus substantiating the assumption that higher outdoor exposure makes male children more susceptible to acquiring infection.

The symptoms of uncomplicated malaria are non-specific: fever, chills, rigors, headache and joint pains. Fever is one of the classical manifestations of malaria and has been reported to be present in almost all the cases of malaria in a number of studies<sup>11-14</sup> while devising a symptom based scoring system for malaria, enlisted fever to be the first and most important symptom while diagnosing malaria. Thus, malaria is an important differential in all

cases of febrile illnesses, more so in the endemic areas.

The proportion of patients with pallor was significantly higher in Group I (89.8%) as compared to Group II (51.0%) ( $p < 0.001$ ). During high transmission season, pallor has been reported to be one of the most sensitive signs after fever that has been associated with malaria in children.<sup>15-17</sup>. Pallor is considered as an indicator of anemia and its severity is judged as an indicator of degree of anemia and iron deficiency in an individual.<sup>18</sup> Anand et al.<sup>19</sup> also mentioned presence of mild to severe pallor among cases with malaria to be associated with severity of anemia in their patients. In present study too, almost 90% of the children confirmed as malaria had mild to severe anemia and almost two-third (65.3%) had iron deficiency anemia too. However, the fact that majority of children in non-malaria group too showed the presence of pallor could lead us to the inference that pallor without malaria is a general marker for weakness, loss of hemoglobin and iron deficiency as encountered in most of the cases in present study irrespective of their malarial status.

Icterus was found to be significantly associated with malaria in our study with almost one third patients of malaria having icterus as compared to only 10 of non-malaria patients. Icterus is common in falciparum malaria. Most often it is caused by hemolysis and accordingly there is elevation of unconjugated bilirubin levels.<sup>20</sup> Thus presence of icterus may indicate a higher risk of malaria (RR-5.16).

Splenomegaly and hepatomegaly were commonly found in malaria positive cases. Generally, repeated malarial infections cause

splenomegaly. This is caused by the immune response, and formation of large number of antibodies in the body subsequently leading to formation of immune complexes. As the number of these immune complexes increases, the spleen enlarges to bear the load. With increasing size of spleen it becomes difficult for the blood to pass through the congested spleen and this in turn causes hepatomegaly.<sup>21</sup> Anand et al.<sup>19</sup> have reported presence of splenomegaly to be highly specific (93%) for differentiation of malaria from seronegative cases.

In present study, majority of cases in both the groups were anemic. However, the proportion of patients with anemia was higher in malaria group as compared to that in non-malaria group. Anemia among children is a quite common phenomenon in Nepal. In an epidemiological study, Siegel et al.<sup>22</sup> had reported the prevalence of anemia to be 58% along with a reported prevalence of iron deficiency to be 43%. Thus, it could be reflective of population figures.

Anemia in malaria is caused by a variety of patho-physiological mechanisms. In areas where malaria infection is endemic, co-morbidities like other parasitic infestations, iron, folate and Vitamin B12 deficiency, deficiency of other nutrients and anemia aggravated by anti-malarial drugs both through immune and non-immune mechanisms.<sup>23</sup> According to Halder and Mohandas<sup>24</sup> malarial anemia appears to be multi-factorial. It involves increased removal of circulating erythrocytes as well as decreased production of erythrocytes in the bone marrow. Polymorphisms in cytokines have been associated with susceptibility to severe



malarial anemia: these cytokines and malaria “toxins” likely function by perturbing erythropoiesis. Finally a number of co-infections increase susceptibility to malarial anemia, likely because they exacerbate inflammation caused by malaria. Eosinophilia and leucopenia were reported considerably in malaria patients as compared to non-malaria patients. Leucopenia has been reported to be associated with both falciparum and vivax types of malaria in a bicentric study at Thailand and Peru.<sup>25</sup>

Seropositivity was taken as the gold standard and was found to be positive in all the 49 cases diagnosed as malaria positive. Bone marrow positivity was observed in only 3 (6.1%) cases. Plasmodium vivax (87.8%) was found to be commoner than Plasmodium falciparum (12.2%). No case of mixed infection was reported. These findings are in accordance with the epidemiological profile of malaria as reported to be dominated by P. vivax.<sup>8,26</sup> Out of four species of malaria parasites causing malaria in humans, two species namely Plasmodium vivax and Plasmodium falciparum are the only parasites detected in Nepal till date.

The diagnostic accuracy, sensitivity as well as specificity was found to be markedly raised on combining serology with clinical criterion of hepatomegaly and splenomegaly. Such combined approach could help ease to make the choice of using antimalarial drug in serology negative cases and also to avoid unnecessary empirical use of anti-malarial drugs.

## CONCLUSION

Prevalence of malaria was found to be more among children than the infants. Anemia and palor were significant findings in patients with malaria although it was found in malaria negative cases. Combined use of serology and clinical findings of hepatomegaly and splenomegaly can increase the diagnostic accuracy of malaria. Thus in resource poor settings where detailed work up might not be possible for all cases of persistent febrile illness, antimalarials can be used based on the combined predictive value. This also helps to avoid the unnecessary use of antimalarial in febrile illness cases that are less likely of being malaria as per the combined approach.

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