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ORIGINAL RESEARCH ARTICLE

EARLY MANAGEMENT OF MALARIA IN THE CONTEXT OF ELIMINATION: OBSERVATIONS FROM CHITWAN MEDICAL COLLEGE, NEPAL

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ABSTRACT

Background: Nepal is entering a malaria elimination phase with the target for no indigenous cases set for 2025. The elimination phase is known to be a challenge due to knowledge and skills reduction as cases become rarer.

Methods: We audited all malaria parasitology tests in Chitwan Medical College from January 2017 to December 2018. Slide positive rate, case treatment and timings were identified from case note review.

Results: Over the 2 years, 1455 malaria tests were performed, 12 were positive, making the positive test rate at 0.83%. Eleven of these 12 case files were found. They were reviewed to find the case details. All cases were >16 years old. Four cases had *P. falciparum,* six cases had *P. vivax,and in* one case, the species was not identified. Four of the 12 cases fulfilled criteria for severe malaria. All *P. falciparum* cases had travelled outside Nepal in the past year. Median time from symptom onset to treatment was 170 hours. Median time from attendance to anti-malarial treatment was 9 hours. Three cases did not receive guideline antibiotics according to Nepal National Protocol.

Conclusions: In conclusion, immediate testing with malaria RDT in all febrile patients presenting to CMC for early diagnosis and prompt treatment is recommended. In addition, we urge to inform colleagues on the features of severe malaria and the national treatment protocol including use of Primaquine for progressing to elimination target.

INTRODUCTION

Chitwan Medical College (CMC) is located at 415m above sea level in the Terai, Nepal. It is surrounded by forest, national park, and farmland near the Narayani river, a suitable climate for the malaria vector. A malaria programme was started in this district in 1950.

Nepal has made significant progress in malaria control over the past few decades. The total confirmed malaria cases declined by 84% from 12,750 in the year 2002 to 2,092 in 2012.[1] The Nepal Malaria Strategic Plan 2014-2025 appeals to all stakeholders to support the goal of an indigenous malaria free nation by 2025.[2] However, pre-elimination is known to be challenging since case recognition, diagnostics and treatment availability can decline as cases become sparser, requiring a persistent conscious effort from all stakeholders.

The Nepal National Guidelines state that programs should ensure early diagnosis and effective treatment within 24-48hours of onset of symptoms. The Government of Nepal has set zero case mortality from 2012 onwards[3] as a key goal for achieving a malaria free Nepal. Severe malaria therefore should be recognized and treated particularly promptly as

it has a high associated mortality. Malaria diagnosis should be made by slide microscopy or antigen test, also known as Rapid Diagnostic Test (RDT) prior to treatment. With the use of Rapid Diagnostic Tests (RDTs) diagnosis is quick and easy even in primary health care and community settings. The study aimed to audit the slide positive malaria cases amongst patients presenting to CMC hospital in the two year period, 2017-18 and to report on their species, their degree of severity and their management.

METHODS

A retrospective analysis of malaria test outcome, malaria positive case review and audit against the Nepal National Protocol for Malaria 2015 at CMC. Data on all malaria tests and their outcome was collected from laboratory and central medical records of CMC hospital dated 01/01/2017 to 31/12/2018. Ethical clearance was obtained from CMC IRC.

Malaria suspected samples were sent for parasitological testing. RDT tests at CMC differentiate P. Vivax and P. falciparum. All RDT positive cases went on to have microscopy. Some cases with strong suspicion of malaria were sent directly for microscopy. Slide preparation at CMC hospital consists of whole blood sample collected in EDTA Vial. Thick and thin slides are prepared and Giemsa stained. Malaria slides were examined by a technician trained by Vector Borne Disease Control and Research Centre and attending regular competency refreshment sessions.

All parasitology results were collected and a positive test rate was calculated. Case files from positive cases were reviewed to identify: when malaria was tested for; when malaria treatment was initiated; which drug(s) were used; and any recorded travel history. Case treatment was compared with the Nepal Malaria Treatment Protocol.

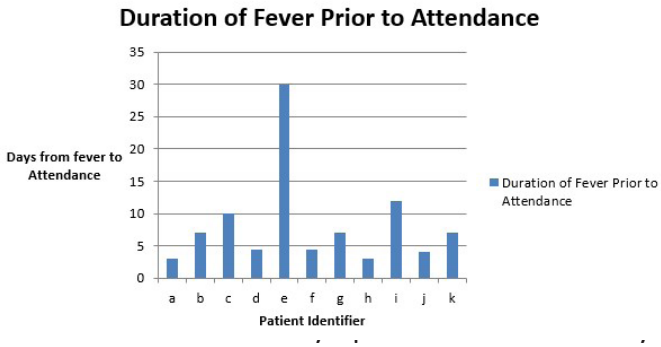
RESULTS

A total of 1455 slides were sent for parasitology testing during the two-year study period. Twelve patients were found to be slide positive. Two slides were reported as slide not received and non-reactive, they were excluded. Slide positive rate was 0.83% (Table 1). All patients were between 17-46 years, male to female ratio 9:3. No cases of malaria in pregnancy were identified.

Table 1: Parasitology positive rate

Total tests	Parasitology Negative	Microscopy Positive	Indeterminate Results	Parasitology positive rate
1455	1441	12	2	0.83%

Figure 1: Duration of fever prior to attendance



(range 3 - 30 days) prior to attendance at CMC Figure 1. Ten out of 11 patients had their malaria test on Day 0, admission day. One patient was tested on Day 1.

The majority of positive cases came from Chitwan and Navalparasi districts. Seven out of the eleven patients had a recorded travel history. Two had returned from abroad in the last month, one had travelled in the last year, one had no travel in the past year and in two cases dates were unrecorded. Travel locations were either India or Africa. All cases of *P. falciparum* had a history of travel outside of Nepal. The one case of severe *P. vivax* had no travel history for past two years. Patients' districts and their recorded travel history can be found in Table 2 and 3.

Table 2: District based distribution of positive cases

District	No. of Patients
Nawalparasi	5
Chitwan	2
Dhanusha	1
Lamjung	1
Makawanpur	1
Bara	1
Total	11

Table 3: Travel history of positive cases

Travelled outside Nepal	Cases (of which Severe)
India	3 (1)
Africa	3 (2)
No travel outside Nepal for >1 year	1 (1)
Travel history not recorded	4
Total	11 (4)

The median time from attendance to treatment was 9 hours (1hr50 – 90hrs15). However, the median time from start of symptoms to first anti-malarial is 170 hours (range 73-729 hours), mostly consisting of time to care seeking. All non-severe cases were treated with oral Chloroquine, within 16 hours of attendance. The case of severe *P. vivax* malaria was also treated with oral Chloroquine.

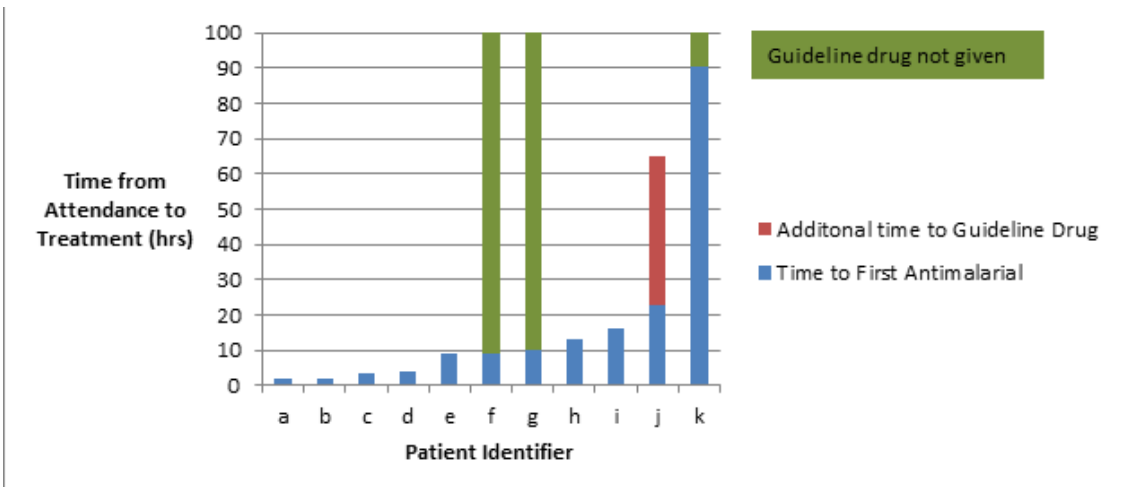
All *P. falciparum* cases were treated with an anti-malarial drug, within 23 hours of attendance. Three of four *P. falciparum* cases were severe. Two of these were given intravenous Artesunate, at two and nine hours after attendance. One was given Chloroquine on Day 0, Oral Quinine on Day 3, and Artemesin in Combination Therapy (ACT) on Day 5. The non-severe *P. falciparum* case was given oral Chloroquine on Day 1, Artesunate on Day 2 and ACT on Day 3. There was no inpatient mortality (Table 4 and Figure 2).

We note that one *P. Falciparum* patient was treated with Doxycycline on Day 0. Zero cases were treated with intravenous Quinine. Primaquine was given in four out of 11 cases.

Table 4: Positive cases and treatment by species

Malaria species	No. cases	Malaria Tested Day 0	Treated with an anti-malarial	Treated with guideline anti-malarial	Treated <24hrs with guideline anti -malarial
P. Vivax	6	5 (1 file not located)	5	5	5
Severe *P. Vivax*	1	1	1	0	0
P. Falciparum	1	1	1	1	0
Severe *P. Falciparum*	3	3	3	2	2
No species given	1	0	1		
Other species	0				
Mixed Species	0				
Total	12	10	11	8	7

Figure 2: Time to antimalarial treatment



DISCUSSION

Location of Malaria Acquisition

By government micro stratification on the 2018 Ward Level Risk Classification Chitwan, Makawanpur and most of Nawalparasi, Dhanusha and Lamjung are low risk or no risk zones. Low risk is defined as "evidence of transmission, but no indigenous case in the last three years".[4] From the information we have it remains uncertain which of our cases were indigenously acquired and from where and which were imported. However, one patient specifically stated no travel outside of Nepal for the past two years. A study in Korea found median short incubation of *P. vivax* malaria at 18 days and median long incubation at 332 days.[5] So our case would be extreme if considered to be imported. Each case was passed on from the hospital to public health authorities to investigate this further and treat the local surrounding area as appropriate.

The trend through Nepal is that imported cases remain high while indigenous cases are reducing.[6] Africa has high levels of *P. falciparum* so travel to Africa should raise concerns regarding this more deadly form of the disease. All of our cases of *P. falciparum* had travelled outside of Nepal.

Test Positive Rates

The overall number of malaria tests carried out at CMC is encouraging in a country entering the elimination phase. Passive Case Detection is a key part of optimizing case detection in an elimination strategy.[7] It suggests that malaria is still being thought of and actively tested for. High numbers of negative results are to be expected in an area looking for every last case and this is also the case at CMC. However, we note that we are not the only health facility in this area, therefore we cannot comment further on testing and slide positive rates more broadly.

Malaria Testing

Confirmed cases were all but one tested on the day of admission and for the other case this was tested on Day 1. We were unable to determine lab timings during this assessment but the head of the laboratory at CMC confirms that RDT results should be available at around 1 hour from receiving sample. Treatment should therefore be initiated shortly after this. Although staffing overnight prevents microscopy until morning, RDT at CMC does differentiate *P. Vivax* and *P. Falciparum* therefore timely treatment can be started immediately without waiting for microscopy results.

Features of Severe Malaria

Undifferentiated fever is the major symptom for suspicion of malaria, although there are several other infectious and non-infectious causes for this presentation which warrant further investigation. Non-severe *P. vivax* malaria was treated with guideline drug and in a timely manner. There were more inconsistencies with management of severe malaria. Problems occurred with recognition and treatment choice. Severe *P. falciparum* malaria is defined by positive parasitology with any of the features listed in Appendix 1. It must be noted that WHO also recognizes severe malaria in *P. vivax* and *P. knowlesi* using the same criteria as for *P. falciparum* but with differences in relevance in slide parasite density.[8]

Guideline Treatments

Two cases did not receive guideline treatment during admission and one remains unclear as the species was not identified. Treatment choice following testing should be determined by the Nepal national protocol, which is supported by the WHO. The guideline treatment for *P. vivax* malaria is Chloroquine or ACT, in addition to Primaquine for further prevention. The guideline treatment for *P. falciparum* malaria is with Artesunate or ACT, except for pregnant patients who should be treated with quinine. However, during the writing of this article the 2019 protocol was released which states that in *P falciparum* malaria in pregnancy ACT is the recommended treatment for all. For non-severe *P. falciparum* malaria the treatment is oral ACT (commonly Lumefantrine-artemether, sold under several brand names including Coartem). For any species severe malaria treat with intravenous Artesunate followed by oral ACT. In low risk zones *P. falciparum* patients should also receive primaquine[3] which was commonly forgotten in our cases but is considered a key intervention in WHO Framework for Malaria Elimination.[7]

We identified that one patient was given Doxycycline on day 0. This medication can be used for many causes of febrile illness and can be used as chemoprophylaxis for malaria. It is unclear if this was in-

tended to be used as an anti-malarial. However, they were not given another anti-malarial drug at the same time. It is important to note that Doxycycline is not on the National or WHO guideline for malaria treatment.

Treatment Timing

Treatment should be initiated within 24-48hrs of onset of symptoms, however none of our patients presented with symptoms in this timeframe. Bastaki et al found a median diagnosis of 4 days in the returned traveler.[9] Delay to intravenous Artesunate in severe malaria can lead to significant morbidity and mortality. Studies show that the malaria parasite count drops rapidly after drug administration. It should be given within the emergency or presenting department as soon as initial results are available. There are many causes for delay in presentation to hospital including: lack of recognition of illness type or severity, and barriers to access such as long distance, other priorities, money, low decision-making power. Studies in Ethiopia and Thailand found factors to delay included: low social support, self-treatment, infection with *P.vivax* malaria, >30mins to health facility, earning < 25USD per month and not being a member of community health insurance.[10,11] These delays allow patients to present later potentially in a worse condition.

At hospital severe malaria is now a relatively rare presentation so recognition may not have been made early or indeed at all. Likewise, the clinician may not be up to date with the treatment of severe malaria if they rarely see cases. Capacity building of the healthcare professional in microscopy, diagnosis and treatment has been a particular area of support for the WHO.[12] Rapid access to appropriate medication in hospital may also be limited since it is held at the public health facility, usually open during daytime hours.[13] To reduce in hospital delay in severe malaria, it would be appropriate to arrange an emergency supply at CMC. However, we appreciate that the reasons for attendance to first dose should be investigated further to determine key limiting factors.

CONCLUSIONS

In conclusion, immediate testing with malaria RDT in all febrile patients presenting to CMC for early diagnosis and prompt treatment is recommended. In addition, we urge to inform colleagues on the features of severe malaria and the national treatment protocol including use of Primaquine for progressing to elimination target. Further investigation of the causes of delay from attendance to receiving anti-malarial drug is highly recommended.

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