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Incidence, management, and reporting of severe and fatal *Plasmodium falciparum* malaria in secondary and tertiary health facilities of Alipurduar, India in 2009

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ABSTRACT

Background & objectives: The proportion of malaria cases that are complicated and fatal are not well described in India. Alipurduar sub-division of Jalpaiguri district in West Bengal is highly endemic for malaria. We constructed a retrospective cohort of severe malaria patients admitted in the secondary and tertiary care facilities in Alipurduar to determine the incidence, assess the management, and evaluate the reporting of severe and fatal malaria.

Methods: We reviewed routine surveillance data and the case records of all the malaria patients admitted in all secondary and tertiary care facilities, both public and private. We defined severe malaria cases as *Plasmodium falciparum* infection with clinical signs and symptoms of organ involvement in a resident of Alipurduar admitted during January to December 2009. We compared clinical and demographic characteristics of severe malaria cases that died with those who survived. We also reviewed human resources and laboratory facilities available for the treatment of severe malaria in these health facilities.

Results: During 2009, 6191 cases of *P. falciparum* in Alipurduar were reported to the malaria surveillance system. We identified 336 (5.4%) cases of severe malaria among which 33 (9.8%) patients died. Four malaria deaths were also recorded from primary health centres. Only 17 of the 37 (46%) total deaths recorded were reported to the routine surveillance system. Most severe cases were males (65%), aged ≥15 years (72%), and nearly half were admitted to secondary care hospitals (48%). In multivariate analysis, the risk factors associated with death included increased delay fever onset and hospitalization, treatment in a secondary level hospital, younger age, and multi-organ involvement. The secondary level public hospital had too few physicians and nurses for supporting severe malaria patients as well as inadequate laboratory facilities for monitoring such patients.

Conclusions: Severe and fatal malaria continue to burden Alipurduar and record keeping in health facilities was poor. Many malaria deaths were not routinely reported even in the public sector. Improved surveillance and increased human and laboratory resources are needed to reduce malaria mortality.

Key words Complicated; falciparum; fatality; India; malaria; risks

INTRODUCTION

Malaria deaths are difficult to measure. Similarly, determining the incidence of complicated malaria cases, which lead to death, requires identifying signs of severity using clinical skills and laboratory equipments that are often not available. Reducing malaria morbidity and mortality is the key goal for a control programme, and the number of severe malaria cases and malaria deaths are important indicators of programme performance. In India, the National Vector Borne Disease Control Programme (NVBDCP) reported 1.5 million cases and 767 deaths in 2010[1]. Estimates of total malaria deaths using models based on surveillance data ranged from 12,000 to 38,000 deaths while estimates from a verbal autopsy study suggested 205,000 deaths per year[2]. Empirical data on malaria mortality is needed to validate these models as well as to refine their estimates particularly at sub-national levels. Sentinel sites for monitoring severe cases and deaths were established by NVBDCP in some tertiary hospitals in 2010, but data from secondary health facilities and private hospitals are sparse.

Jalpaiguri district in the Indian state of West Bengal is highly endemic for malaria. The district experiences perennial malaria transmission with frequent outbreaks causing deaths[3,4]. During 2004–08, Alipurduar sub-division (2001 population: 1,336,858) accounted for 60% of the reported cases and 90% of reported deaths due to malaria in the district (Government of West Bengal, Department of Health, unpublished data). In Alipurduar, patients with severe malaria were referred for treatment to secondary and tertiary level health facilities at the sub-division. Data

on the number of severe cases were unavailable. We reviewed the records of hospitalized cases in health facilities in Alipurduar to measure the number of severe and fatal malaria cases, assess management including record keeping, and compare the recorded data with the reported data. We also analyzed the characteristics of patients who died with those who were discharged to identify factors associated with death.

METHODS

Study population and study design

We reviewed the malaria surveillance data in Alipurduar sub-division during January to December 2009 to understand its epidemiology. We reviewed the case records of all malaria cases admitted during the same period in all sub-division inpatient health facilities: the Alipurduar Sub-Division Hospital (SDH), a secondary level hospital, the North Bengal Medical College & Hospital, and three nursing homes in the private sector (tertiary level facilities) to retrospectively identify a cohort of severe malaria cases.

Case definitions

We used the definition from the malaria surveillance system, a patient positive for *Plasmodium* species by microscopy or rapid test, to define a case of malaria. A patient diagnosed with *P. falciparum* with clinical signs and symptoms of organ involvement was considered a case of severe malaria[5] and the subsequent death of such patient was considered as a malarial death. We considered the organ involvement in these patients based on their signs and symptoms [cerebral: patients with abnormal behaviour, impairment of consciousness, seizures, coma, or other neurological abnormalities; respiratory: chest pain, cough, pulmonary edema or acute respiratory distress syndrome (ARDS); renal: no or decreased urinary output; circulatory: circulatory collapse/shock (systolic blood pressure <80 mmHg, <70 mmHg in children); and gastro-intestinal: vomiting, diarrhea, jaundice][5]. All the cases must have been residents of Alipurduar in 2009 at the time of their reporting.

Data collection

We collected routine data on malaria incidence, reported deaths, and population from the Alipurduar subdivision office. Surveillance data consisted of microscopically or rapid test confirmed cases, presumptive treatment was not used. The cases are passively detected from all public sector health facilities as well as actively detected through fortnightly fever screening in the community by health workers. Private facilities such as tea plantations, dispensaries and hospitals also report to the surveillance system in Alipurduar. Species-wise data were unavailable by age category so the population proportion of *P. falciparum* was applied to each age group as its distribution is relatively uniform in the study area. We reviewed all the medical records of severe malaria patients admitted in the secondary and tertiary level health facilities and abstracted available demographic details, signs and symptoms, results of laboratory investigations, treatment details and outcome from each case. The data were entered into a Microsoft Excel database. We also reviewed the available human resources and laboratory facilities for the treatment of severe malaria in these health facilities through site visits and discussion with the facility director.

Data analysis

We analyzed the surveillance data to describe the malaria cases by time, place and person. We compared the severe malaria cases who died and who were cured after treatment with respect to age category, sex, time between fever onset and hospitalization, organ involvement, and facility type and calculated univariate risk ratios to identify the factors associated with malarial death. Variables with p-value <0.2 on univariate analysis were included in the multivariate regression model. We used log-risk models to calculate the univariate association and a Poisson model with robust standard error for the multivariate analysis as the log-risk model failed to converge. When the outcome is rare, the Poisson distribution approximates the binomial distribution and produces valid estimates of risk. We used Epi-info (version 3.5.1) and STATA (version 10) for all analyses.

Human subject's protection

The Institutional Ethics Committee of the North Bengal Medical College, West Bengal approved the study protocol. Permission to review the case-records of severe malaria cases was obtained from the respective hospital authorities.

RESULTS

Descriptive epidemiology

In Alipurduar sub-division, the routine surveillance system reported 8773 malaria cases from 496,775 screenings during January–December 2009 (Fig. 1). Cases were reported in all the months with peaks in June and November. Of the total malaria cases, 6191 (71%) were due to *P. falciparum.* Reported malaria was common among adolescents and adults (attack rate: 7.6 per 1000 and 6.5 per

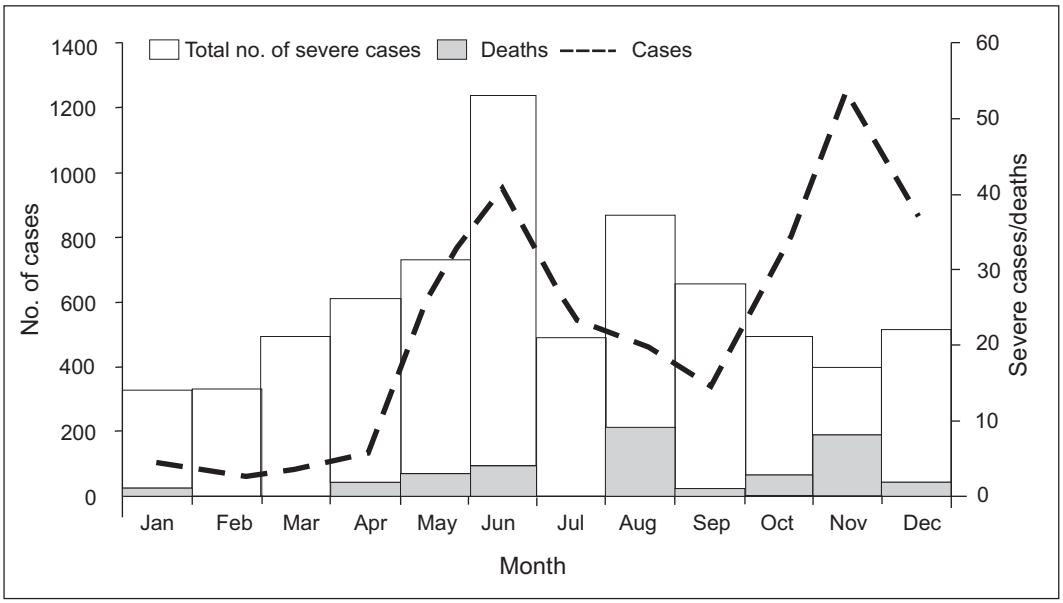

Fig. 1: Month-wise number of *P. falciparum* malaria cases, severe cases, and deaths reported in Alipurduar, India during 2009

1000) and males (attack rate: 7.7 per 1000) (Table 1). We identified 336 cases with severe malaria from the retrospective cohort (5.4% of *P. falciparum* cases) and 37 patients died (33 in secondary or tertiary health facilities and 4 in primary health care facilities), with an overall case fatality of 0.6%. Case fatality was higher among children aged 0–4 yr (2.1%) and females (1%) (Table 1). Only 17 of the 37 deaths identified were routinely reported (46% completeness) to the surveillance system. The public health facilities (17/33) reported a higher proportion of deaths than private health facilities (0/4). Hospitalization details of severe malaria cases treated at PHCs were not recorded and thus those deaths were excluded from the study cohort. However, primary health centre medical officers indicated that severe malaria cases were not routinely treated there. Such patients were transferred to a higher level facility as soon as possible, often with pre-referral treatment.

Severe malaria cohort

We identified 336 cases of severe malaria (Fig. 2). Majority of the severe malaria patients were males (65%), adults aged ≥15 yr (72%), and nearly half received treatment at the sub-division hospital (48%). Most of the patients were hospitalized for their symptoms within 72 h of onset of fever (69%). About 57% of the patients presented with symptoms of central nervous system involvement while the remaining had signs of respiratory, renal, and gastro-intestinal/hepatic system impairment. Pre-referral treatment data were not available for most of the

Table 1. Malaria indicators by age and sex, Alipurduar, India 2009

Characteristic	Population	Malaria cases	*P. falciparum* cases	Incidence/ 1000	Severe cases* (%)	Deaths	Case fatality rate	
							Severe	Total
Age group (yr)								
0–4	140,370	665	469	4.7	32 (6.8)	10	31.3	2.1
5–14	332,878	2526	1783	7.6	61 (3.4)	8	13.1	0.4
≥15	863,610	5582	3939	6.5	243 (6.2)	15	6.2	0.4
Sex								
Male	688,535	5276	3723	7.7	219 (5.9)	12	5.9	0.3
Female	648,323	3497	2468	5.4	117 (4.7)	21	20.5	1.0
Total	1,336,858	8773	6191	6.6	336 (5.4)	33	9.8	0.5**

*Among *Pf* cases only; **0.6% including four deaths recorded at PHCs.

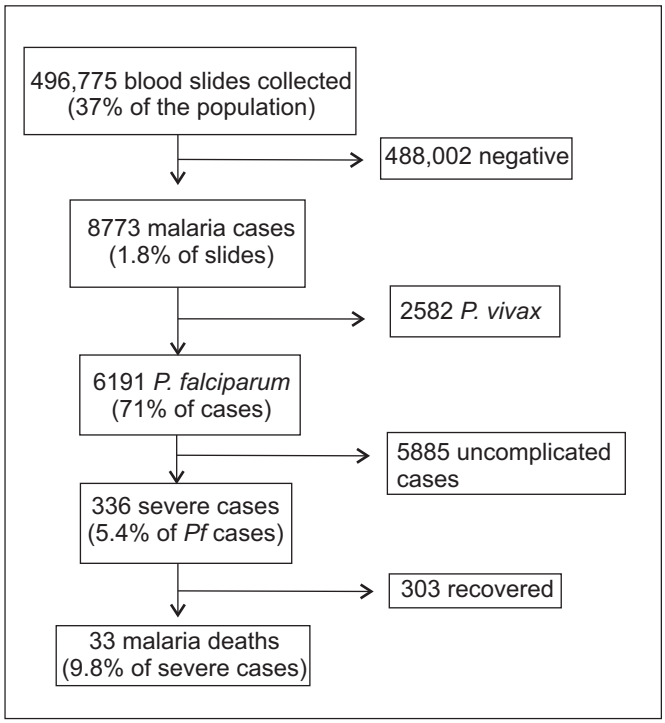

Fig. 2: Flow diagram of the retrospective study cohort, Alipurduar, India 2009

patients. Among the available records, most of the patients received artesunate+sulphadoxine-pyrimethamine but a few were treated with chloroquine. For inpatient management, α, β-arteether (E-mal) was the parenteral treatment used in available records though the use of other treatments (quinine, artesunate, etc) were noted in discussions with facility staff. In all, 33 of the 336 severe malaria cases died (9.8%). Among the 33 patients who died, the median duration of treatment following hospitalization was 14 h (range 1–68 h).

On unvariate analysis, the risk of death was higher among patients who were <5 yr (RR: 6.1, 95% CI: 3.1, 12), female (RR: 3.3, 95% CI: 1.7, 6.4), increased with greater delay in treatment after fever onset (3–4 days RR: 10.2, 95% CI: 2.79, 37.2; 5–6 days RR: 32.1, 95% CI: 9.63, 107 and ≥7 days RR: 59.7, 95% CI: 18.6, 191), and among patients who received treatment at the sub-division hospital (RR: 8.9, 95% CI: 2.2, 36) (Table 2). Adjusted for each of the other variables, risk factors associated with death among the severe malaria cases included increased delay in hospitalization, treatment from the sub-division hospital, child and adolescent age, and multiple organ involvement (Table 2).

Human resources for clinical management and laboratory facilities

In Alipurduar, severe malaria cases were treated either in the Sub-Division Hospital (bed strength: 400), one of three private nursing homes (bed strength: 75) or at the North Bengal Medical College & Hospital (bed

Table 2. Univariate and multivariate analysis of factors associated with death among severe malaria cases, Alipurduar, India 2009

Characteristics	Died (n=33)	Total (n=336)	Risk ratio (95% CI)	Adjusted RR (95% CI)
Type of health facility where hospitalized				
Medical college	2	105	1	1
Nursing homes	4	71	2.96 (0.56, 15.7)	1.97 (0.43–9.12)
Sub-Division Hospital	27	160	8.86 (2.15–36.5)	4.82 (1.23–18.9)
Age group (yr)				
0–4	12	32	6.08 (3.13–11.8)	6.23 (2.5–15.8)
5–14	6	61	1.59 (0.65–3.94)	2.94 (1.38–6.25)
≥15	15	243	1	1
Sex				
Male	12	219	1	1
Female	21	117	3.28 (1.67–6.42)	1.47 (0.86–2.51)
Fever onset and hospitalization				
≤2 days	3	233	1	1
3–4 days	8	61	10.2 (2.79–37.2)	13.5 (3.26–56.2)
5–6 days	12	29	32.1 (9.63–107)	14.9 (3.75–59.1)
≥7 days	10	13	59.7 (18.6–191)	33.5 (8.72–129)
Organ/system involvement				
Cerebral	15	192	1	1
Renal	3	22	1.75 (0.55–5.56)	0.55 (0.23–1.30)
Respiratory	9	80	1.44 (0.66–3.15)	1.80 (0.70–4.66)
Multiple	6	42	1.83 (0.75–4.43)	2.21 (1.06–4.59)

Table 3. Human resources and laboratory facilities to support clinical management at different health facilities in Alipurduar, West Bengal, 2009

Health facility	Sub-Division hospital	Nursing homes	Medical college
Number of facilities	1	3	1
Level of facility	Secondary	Tertiary	Tertiary
Type of facility	Public	Private	Public
Number of beds	400	75	1400
Annual bed occupancy rate (%)	91	51	70
Number of physicians	35	25	125
Doctor : Patient ratio	1:10	1:1.5	1:7
Number of nursing staff	55	60	270
Nurse : Patient ratio	1:6.5	1:0.6	1:3.6
Number of laboratory technicians	10	15	55
Frequency of case review by physician	12 h	3 h	6 h
Daily availability of laboratory tests	8 h	24 h	24 h
Laboratory tests available			
Blood smear or RDT	Y	Y	Y
SGOT/SGPT	Y	Y	Y
Urea/creatinine	N	Y	Y
Electrolytes	N	Y	Y

strength: 1400). Review of the hospital records of severe malaria patients admitted at the sub-division hospital revealed several deficiencies in their management. Though the patients were treated with appropriate antimalarials, their temperature as well as fluid inputs and outputs charts were not maintained properly. Laboratory facilities were available only for 8 h a day and tests of urea, creatinine, sodium, potassium, serum bilirubin, serum glutamate-oxaloacetate transaminase (SGOT) and serum glutamate-pyruvate transaminase (SGPT) were not available. Patients with severe malaria were also not monitored for hypoglycemia. The doctor: patient and nurse: patient ratios were 1:10 and 1: 6.5 respectively (Table 3). Only one onduty medical officer and two onduty nursing staff were responsible for all the indoor patients in the sub-division hospital. This further constrained the regular clinical monitoring of admitted severe malaria patients. In the nursing homes, the overall patient burden was low. The treating physician and nursing staff monitored severe malaria cases several times in a day. In the medical college, though there was only one duty medical officer in the ward, trainee doctors assisted them. Thus, severe malaria cases were supervised and monitored several times a day, by resident doctors in consultation with their seniors. Both the tertiary facilities also had the necessary laboratory support available around the clock.

DISCUSSION

Severe and fatal malaria continue to burden Alipurduar in 2009. The proportion of malaria cases with complications appears consistent with the epidemiological setting of low to medium transmission, where natural immunity to malaria is low[6]. The 9.8% fatality among severe cases in Alipurduar was lower than the 14% case fatality observed among a similar population at a tertiary centre in Odisha[7]. The overall case fatality of 0.6% among all malaria cases in Alipurduar was higher than that reported from community-based monitoring in Jabalpur, Madhya Pradesh (0.17%) but similar to that from health facilities in Sahibganj, Jharkhand (0.8%)[8]. Similarly, the predominance of adult males among the study population is consistent with malaria epidemiology from forest ecotypes where the risk of infections is occupationally linked[9]. Most malaria deaths which occur in the private sector are not routinely reported. In our study, none was reported. We, however, found that many deaths in public facilities, identified in our case record reviews were not recorded in the surveillance data. This finding suggests methods for estimating malaria burden that rely on surveillance data require correction for under reporting from public sector facilities. Further research to identify the reasons for under reporting (burden of paper work, unfamiliarity with notifiable diseases, etc.) could help improve the capture of critical data.

Patients who were younger, presented with multi-organ involvement, had delayed hospitalization after fever onset, and received treatment at the sub-division hospital were at increased risk of death. Younger patients and those with multi-organ failure are biologically more susceptible to a fatal outcome through well described mechanisms[10, 11]. However, the time to treatment and quality of care are

amenable risk factors that can be improved through public health intervention. Since 2008, the public health staff in Alipurduar has been generating awareness among rural residents about danger signs of malaria and among the peripheral health care providers about the need for early referral of malaria patients with complications. In spite of this, delays in hospitalization continue to be an important risk factor associated with malarial deaths. Several steps along the case management process, from choosing to seek treatment for symptoms, receiving a diagnosis and effective treatment, recognizing and referring complications, or transport time during referral could be responsible for the delay between fever onset and hospitalization.

Nearly half of the patients with severe malaria identified were hospitalized in the Alipurduar sub-divisional hospital. The patients who died were hospitalized for a median duration of 14 h and this duration was not different among patients admitted to different types of facilities. In spite of this, patients who were admitted in the sub-division hospital were at higher risk of adverse outcome. This could be on account of the limited number of medical officers and nursing staff as well as the lack of facilities for laboratory investigations available for supervision and monitoring of severe patients. In addition, most sub-division hospital physicians are generalists without a specialized training in internal medicine or pediatrics. Regardless, more training, tests, or drugs alone are unlikely to improve outcomes in the face of overburdened workers. Additional resources to reduce the patient to staff ratio are needed.

Our study had certain limitations. The accuracy of our case fatality estimates depends on how accurately we captured both the numerator (number of deaths) and denominator (number of cases)[12]. The surveillance system data may not have captured malaria cases or deaths that sought informal, no treatment, or care from other private practitioners. Similarly, the case record reviews may have missed in cases. However, care-seeking in Alipurduar is high. In a random survey of one year retrospective mortality among 1984 households in Alipurduar, 96% of the 118 total deaths sought care for their illness including 100% of the 14 deaths attributed to fever of unknown origin (Shah *et al*, unpublished data). Additionally, we included all healthcare facilities providing inpatient care. Next, information about the severe malaria patients was collected from hospital records instead of prospectively. Organ system involvement was based on clinical presentation and not any uniform protocol, including laboratory investigation, which may lead to the misclassification of disease severity. The interval between onset of fever and hospitalization was subject to recall by patients as well as correct history taking by medical officers. Finally, we did not measure severe or fatal *P. vivax* due to the unavailability of PCR diagnosis needed for accurate classification in such studies[13].

In conclusion, we propose a number of recommendations for reducing mortality and improving reporting. First, to focus interventions for reducing delays in initiating treatment it is necessary to identify the specific step responsible for most delays along the treatment process. Second, ensure adequate staff and improved laboratory facilities at Alipurduar Sub-Division Hospital, the designated first referral hospital for the PHCs in the sub-division. With documented differences in the case fatality rate among severe malaria cases between facilities, this indication is unambiguous. At the least, the creation of a 'severe malaria care unit' during the peak season, with round the clock medical and nursing staff as well as a uniform protocol for clinical and laboratory evaluation, could enable both the surveillance of severe cases and as well as quality management without delay. Finally, an annual review of case records at facilities, similar to our study, could help identify unreported deaths and increase reporting completeness.

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