

Malaria related deaths among children with manifestations of fever symptoms on admission in a secondary health care institution in Western Region of Ghana - a retrospective study

Short title: Retrospective study of malaria deaths among children in Ghana.

ABSTRACT

Background: Malaria is a major contributor to deaths in children especially in sub-Saharan Africa. Children less than five years of age are susceptible to malaria infection in endemic regions leading to serious complications. Malaria causes death in children either directly through Cerebral Malaria (CM) and Severe Malaria Anaemia (SMA) or indirectly through co-morbidity with pneumonia or a sequela like hypoglycaemia.

Methods: This retrospective study examined malaria-related deaths among children at Effia Nkwanta hospital within a study period of 3 years.

Results: A total of 1,416 medical records were reviewed, out of which 223 were medical records of children with fatal outcomes. Deaths over the study period due to all causes were 15.7% (223/1416) and to confirmed malaria was 13.7% (40/292). Deaths due to all causes and to confirmed malaria decreased from 21.6% and 24.3% in 2010 to 11.1% and 4.4% in 2012, respectively. Anti-malarial testing was done for 152 of the children with 40 positive and 112 negative results. Seventy-one children had no malaria testing done on them, with 23.4% in 2010 40.3% in 2011 and 35.5% in 2012. Anti-malarial treatment was administered to 83% of children who tested negative and 80% of children without anti-malarial testing.

Conclusion: Deaths in the children declined from 2010 to 2012 in this study. Despite this improvement there was poor anti-malarial testing and improper use of anti-malarial

25 treatment. National malaria program should ensure improvement in anti-malarial testing and
26 strict adherence to anti-malarial treatment protocol.

27 **Key words:** Malaria, Children, Mortality, Anemia, Death.

28 **Introduction**

29 Malaria remains a serious public health issue in malaria endemic areas with
30 residents at the risk of infection and higher risks are often seen in children and pregnant
31 women¹. This higher risk is translated to higher morbidity and mortality in the vulnerable
32 group especially children under five years of age. Children less than five years are susceptible
33 to malaria infection leading to serious complications and death if not promptly and
34 adequately treated with effective anti-malarial medications¹. *Plasmodium falciparum* is the
35 predominant species in sub-Saharan Africa, the major cause of severe disease leading to
36 death¹. The exposure of children to sub-lethal *P. falciparum* infection leads to gradual
37 acquisition of clinical immunity². However, some children unfortunately never live to
38 develop this immunity as their infection progress to severe disease leading to death before
39 adulthood³.

40 Malaria infection due to *P. falciparum* can causes mortality directly by being the
41 underlying cause of death. Cerebral malaria and severe malaria anemia are very common
42 direct causes of childhood mortality⁴. Cerebral malaria defined as confirmed *P. falciparum*
43 infection with unrousable coma⁵ causes death in children due to hypo-perfusion of brain cells
44 as a result of sequestration of infected red cells within cerebral capillaries⁶. Another common
45 direct cause of death in *P. falciparum* infected children is anemia, referred to as severe
46 malaria anemia (SMA)⁴. World Health Organization (WHO) defines SMA as a hemoglobin
47 level (Hb) below 5.0 g/dL in the presence of malaria parasites⁷. Indirect causes of death in

48 malaria are cases in which malaria is only a contributing factor, like a child with malaria
49 related anemia developing pneumonia or hypoglycemia and dying from it ⁸.

50 There is a reported 18% global decline in malaria cases from 262 million in the year
51 2000 to about 214 million in 2015.⁹ It was estimated that 88% of the new cases in 2015
52 occurred in sub-Saharan Africa⁹. However, the region has recorded a tremendous progress in
53 terms of reduction in the number of malaria deaths among children under 5 years of age, with
54 the bulk of global decrease occurring in the region.⁹ The estimated number of malaria deaths
55 among children under 5 years of age fell from 694,000 in 2000 to 292,000 in 2015.⁹ These
56 findings suggest that malaria is no longer the leading but the fourth leading cause of death
57 among children, accounting for about 10% in 2015.⁹ This declining mortality in children from
58 sub-Saharan Africa is due to the positive outcome from scale up of malaria intervention
59 programs deployed in the region.¹⁰ These control programs have facilitated the reduction of
60 childhood malaria morbidity and mortality in most parts of sub-Saharan Africa ^{11, 12} These
61 control program include house hold and community activities such as the use of insecticide
62 treated nets ITNs, indoor residual spraying IRS, larval control and health facilities activities
63 including adequate case management for malaria. ¹³

64 Adequate case management of malaria is a veritable arm of the malaria control
65 program. It is primarily carried out in health facilities. Invariably, the quality of care in health
66 facilities can impact greatly on mortality from malaria especially among children. The
67 general dilapidated state of health care in many Africa countries negatively impacted on the
68 quality of management and treatment of many diseases especially malaria in children.¹⁴
69 However, there have been some improvement in malaria case management over the years
70 with the improvement of diagnosis and treatment by the provision of tools for on the spot
71 diagnosis like rapid diagnostic test for malaria, effective drugs and skilled health care

72 personnel.^{14,15} Despite this, quality of care in hospitals and clinics still need improvement
73 since avoidable malaria deaths have been reported.¹⁶

74 In Ghana, childhood mortality is a serious public health issue as diseases like
75 pneumonia; diarrhea, malnutrition and malaria take their toll on children¹⁷. Malaria remains a
76 constant threat to the life of children in Ghana especially those who live in rural areas¹⁸. In
77 the first quarter of 2016 the country recorded a total of 2.2 million cases of malaria in all
78 health facilities nationwide. The number of malaria confirmed deaths recorded was 379
79 which was a 15.2% drop from the value in the first quarter of 2015. Of these, there were 152
80 malaria deaths in children under 5 years of age compared to 182 recorded in 2015¹⁹
81 However; this noted decline is not uniform within the country. It is very important to
82 constantly review mortality figures and pattern in different parts of the country to assess the
83 progress of malaria control programs and the dynamics in malaria infection. Hence, this
84 retrospective study evaluated the trend in malaria related deaths among children who died on
85 admission for febrile illness in a referral hospital in Sekondi-Takoradi metropolis Ghana over
86 a three-year period.

87 **Materials and Methods**

88 **Study Area**

89 Effia-Nkwanta Regional Hospital is a secondary health-care institution and is the only
90 referral hospital for the whole western region of Ghana. It is located at the Regional capital,
91 Sekondi-Takoradi. It serves all other hospitals within the entire 22 districts of the western
92 region and sub-divisions of 13 major districts. Details of the study area have been published
93 previously²⁰.

94 **Data Collection**

95 This is a retrospective study that was carried out at the Paediatric Unit of Effia-
96 Nkwanta Regional Hospital (ENRH). Before this study, Paediatric emergencies were seen

and where necessary, were admitted to the children's ward of the hospital. The patients admitted were recorded in the admissions register. The admissions register of the Accident and Emergency Unit of the hospital was used to collect folders numbers of children recruited into the study. Children admitted with fever as one of the presenting symptoms with subsequent fatal outcome over the study period of 2010, 2011 and 2012 were included in the study. Their medical records were searched and retrieved. Information on the demographics (i.e. age and sex), clinical and laboratory findings were collected. Clinical information retrieved included other symptoms accompanying fever, weight of the child and temperature as well as information on sickle cell trait and blood transfusion during admission. Reported laboratory findings included malaria parasite diagnosis, white blood cell counts, sickling status and haemoglobin concentration. Information on treatment histories were also collected as well as the number of days the patients spent in hospital. Ethical clearance was received from the Ghana Health Service Research Ethical Review Committee, Accra.

Patients with malaria admitted in the hospital were classified according to the WHO criteria for mild and severe malaria⁷. Diagnosis of malaria parasite was done using *P. falciparum* specific rapid diagnostic test kits (First Response, Premier Medical Corporation Ltd) and microscopy using Giemsa staining. The rapid response kit detects *P. falciparum* antigens and the presence of two lines in the test kit well indicate *P. falciparum* positive. Malaria parasites were confirmed with thick and thin peripheral blood smears stained with Giemsa and examined microscopically using 100 power fields under oil immersion. Two microscopists read the slides independently and a third microscopist was called upon to resolve discordant results. Haemoglobin estimation and white cell count were done as part of the complete blood count from an automated blood cells analyser machine (Sysmex Hematology Analyser, Xuzhou Hengda, China). Certification and establishment of cause of death were done mainly by using clinical judgement based on history, physical examination

and laboratory findings. These were done by experienced medical officers or specialist paediatricians after proper review of patient's records.

Malaria was defined as the presence of any asexual blood stages of *P. falciparum* species in the thick and thin smear blood film while malaria negative samples were confirmed when 100 high power fields have been examined using x100 oil immersion objective lens. Anaemia was defined based on WHO criteria of haemoglobin (Hb) levels <11 g/dL^{21, 22}, and categorized as mild anaemia (Hb <11 g/dL), moderate anaemia (Hb <10 g/dL) and severe anaemia (Hb <7 g/dL). Haemoglobin estimation was performed using cyanmethemoglobin method²³. A febrile malarial episode in children was defined as a reported history of fever within the last 24–72 h of admission or a measured temperature of 37.5°C or greater (or both), with a positive peripheral blood smear slide with asexual forms of *P. falciparum* at any level of parasite density at time of contact with ENRH clinic²⁴. A malaria death is defined as one death per parasitologically diagnosed clinical episode¹¹. We calculated malaria mortality (expressed as percentage) with the formula: malaria deaths per year / Number of children in the population at midyear. We calculated case fatality rate (express as percentage) with the formula: malaria deaths per year / Number of confirmed malaria cases among admitted children per year²⁵.

Statistical analysis

Univariable analyses were performed and results were presented as proportions. Statistical significance for cross-tabulations was performed using Pearson χ^2 test for categorical variables and ANOVA for the comparison of mean of the continuous variable. All tests were two-tailed and $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA).

Results

Characteristics of the study population

Table 1 describes the characteristics of the 223 children who died during the three years study period. Severe anaemia ($Hb < 7$ g/dL) was seen in 34.1% of the children while 18.8% of the children that died were not anaemic ($Hb > 11$ g/dL). Malaria diagnostic test was not performed in about 31.9% of the children that died. However, 17.9% of the children were laboratory confirmed malaria positives while 50.2% were malaria negatives. Ninety-seven children (43.5%) died within the first 24 hours of admission, 37.2% died within 72 hours and 19.3% after 72 hours of admission.

Figure 1 describes the percentage mortality of the children admitted into the children's ward. During the study period, a total of 1,416 children were admitted to the children unit of Effia-Nkwanta Regional Hospital. Out of this total number of admitted children, 1193 children were successfully treated and discharged home, while 223 children unfortunately died over the same period, with a percentage mortality of 15.7%. There was a progressive decline in the percentage mortality from 21.6% in 2010 to 11.1% in 2012 (Figure 1). Figure 2 describes malaria case fatality in the study population. During the three years study period, 40 children died out of the 292 admitted with supposedly malaria cases with a total case fatality rate of 13.7%. There was also a steady decline in the case fatality rate for laboratory confirmed malaria cases from 24.3% in 2010 to 4.4% in 2012 (Figure 2).

Table 2 shows the characteristics of the study population stratified against malaria laboratory investigations. A significant proportion of malaria diagnosis was done without malaria testing and some were negative on malaria test. Antimalaria treatments were accurately given to all of the children with confirmed malaria test, while 83% and 80% of the children that tested negative and those without malaria test respectively were incorrectly prescribed anti-malarial.

Children without malaria testing significantly decrease as they stayed longer in the hospital (>24hrs, 63.4%; <72hrs, 28.2%; >72hrs, 8.4%).

Figure 3 shows the malaria testing rate worsened over time with 23.4% of children not tested in 2010, 40.3% in 2011 and 35.1% not tested in 2012.

Figure 4 summarizes the combination of the prescribed medications during the study period stratified by year. Apparently, patients without laboratory confirmed malaria diagnosis or patients with malaria negative diagnosis were given parenteral anti-malarial treatment of either quinine or artemether.

Other Non-Malaria Causes of Death

Figure 5 shows the distribution of other non-malaria causes of death. Among these children that died from non-malaria causes, 12.1% were diagnosed with sepsis, 9.4% were diagnosed with bronchopneumonia, 8.5% were diagnosed with gastroenteritis, and 7.2% were diagnosed with severe anaemia. Children who died without a specific diagnosis were 19.7%.

Discussion

This study evaluated the contribution of malaria to the mortality of children in the children ward of Effia-Nkwanta Regional Hospital over a 3 year study period. There was a steep decline in malaria deaths from 2010 to 2012. This is a drastic drop and an interesting finding indeed. Firstly, there was high case fatality rate for malaria in 2010 compared to the subsequent years, which might be due to both in hospital and out of hospital factors. These factors have contributed to poor and fatal treatment outcomes in children with malaria²⁶. Late arrival to the hospital is one major out of hospital factor responsible for malaria mortality in children in many countries in sub-Saharan Africa especially Ghana²⁷. This is due to, poor health seeking behavior caused by poor understanding of the symptoms of malaria, over

194 reliance on home and herbal remedies and financial constraints^{27, 28}. In hospital factors,
 195 especially in Ghana are hinged majorly on the poor quality of care for the sick child,
 196 including poor and delayed diagnosis, lack of appropriate medications and treatment and lack
 197 of well-trained health care personnel^{29,30}. Poor quality of care has been reported in regional
 198 hospitals similar to the facility where the present study took place^{30,31}.

199 In 2011 there was a tremendous reduction in malaria confirmed deaths despite an increase in
 200 admitted confirmed malaria cases. An improvement in the arrival time of the sick children to
 201 the hospital and improvement in the quality of care in the hospital might have been
 202 responsible for this. Parents and care givers would have become better educated on, early
 203 recognition of symptoms and signs of malaria, the dangers of herbal medication and the
 204 importance of coming early to hospital with their sick children. This is the likely outcome of
 205 the various forms of health education carried out by the National Malaria Control Program¹⁹.
 206 More so the improved enrolment of patients to National Health Insurance scheme would have
 207 overcome the barrier of financial constraint allowing more patients to access health care in the
 208 hospital.^{29, 32}. Also, increase in the confirmed malaria cases on admission, might be due to an
 209 improvement in the malaria diagnosing capacity of the regional hospital based on massive
 210 deployment of rapid diagnostic test kits as well as training of health care personnel on the use
 211 of the test kits^{19, 33}. This improvement in case identification and diagnosis was invariably
 212 followed by prompt, adequate and successful treatment outcomes for majority of the children
 213 that was admitted in 2011. This success in treatment was perhaps due to better training of the
 214 health care personnel as well as the availability of appropriate therapeutic drugs and effective
 215 therapy with strict adherence to standard treatment guidelines¹⁹. Ghana adopted the WHO
 216 artemisinin based combination treatment (ACT) policy in 2004 with artesunate-amodiaquine
 217 as first line treatment and a subsequent review in 2009 involving the inclusion of artemether-
 218 lumefantrine and dihydroartemisinin-piperaquine as alternative first line drugs for children

who can tolerate artesunate-amodiaquine combination therapy. Parenteral treatment includes artemether and quinine injection for severe malaria. This study showed that these anti-malarial drugs were basically used in the management of malaria in the children in this hospital, but the details of how they were used and administered were not available. Studies however showed that there were challenges in the practicality of this policy as it took some time for health workers through frequent training to fully acquire the necessary skills to use these treatments effectively^{31, 34, 35}.

In 2012, there was further improvement in the case fatality rate coupled with a decline in admitted malaria confirmed cases despite an overall increase in admitted children. Decline in the admitted malaria confirmed cases might be a reflection of the overall decline in the global and regional malaria burden noted in the country^{9, 19}, or a dividend of activities of National Malaria Control Program involving continuous campaign on the use of ITNs and IRS¹⁹. Another possible reason for the decline might be that most parents or care givers have well improved knowledge in the home management of uncomplicated malaria with affordable ACT, thereby preventing complication that will warrant admission in hospital^{36, 37}. More so many primary health centers and clinics in the area are now well equipped with RDTs and ACTs to handle malaria in children^{37, 38}. The lowest case fatality for malaria recorded in 2012, was perhaps the result of progressive improvement in case management and strict observance of standard treatment guideline for malaria in the hospital³⁸.

It is important to highlight the ever-nagging problem of poor laboratory diagnosis of malaria observed in this study; as 31.9% of children who died never had malaria test done on them. This is a very common problem seen in many hospitals and clinics in developing countries and it has been blamed on incessant break down of diagnostic machine and frequent stock out of reagents^{39 40}. In all, the situation worsened from 2010 (23%) to 2012 (35%). Another study done among discharged children over the same period in the same hospital also reported a

significant proportion of children who were not tested for malaria^{20, 41}. However in this study, time spent on admission before death may have played a role in the number of children who died without malaria test done on them, as majority of children who died within the first 24 hours never had malaria test done on them. The chances of getting a malaria test done in the laboratory increased if the child survived beyond 72 hours before death. Presumptive diagnosis of malaria was woefully inaccurate in this study as significant proportions of the case diagnosed were not confirmed by laboratory investigation. This is really an important finding for clinicians to be reminded that in all cases, their clinical judgement should always be supported by laboratory investigations.

As seen in most studies, children under five years of age remain the most vulnerable group for fatal consequences of disease and infection^{42, 43}. The higher proportion of under five children among those who died with malaria in this study further buttresses the age specific severity of malaria morbidity and mortality as seen in malaria endemic areas^{19,42,43}. Taking a closer look at the specific diagnosis of children who tested positive for malaria in this study, CM and SMA were more common. CM and SMA are the most common complications of malaria linked with pediatric mortality^{4, 44}.

Aside malaria mortality, there was a progressive decline in overall mortality, despite the increased patient load over the study period. This decline is consistent with the declining trend in child mortality reported for sub-Saharan Africa over the years^{42, 43}. This can be attributed to the continuous improvement in the healthcare system and implementation of various preventative measures such as child survival programs and vaccinations as well as improvement in diagnostic methods and effective treatments that mitigate the impact of diseases responsible for child mortality in the region⁴⁵. Other diseases were responsible for child mortality in this study as more of these children that had malaria laboratory investigation done were negative. Bacterial and viral diseases, malnutrition, congenital

269 abnormalities, intrapartum events and injuries have all been implicated in child mortality^{42, 43}
270 ⁴⁵. This study noted a rather high number of children with missing/unknown diagnoses. The
271 probable clinical explanation for this would have been that children dying within few hours
272 of arrival to the ward or arriving at a period where the doctors and laboratory personnel are
273 not readily available on duty especially during the weekends. Weekend admissions would
274 have probably contributed to the mortality due to lack of quality care, which is a common
275 finding in hospitals in similar settings⁴⁶.

276 **Limitations**

277 Despite the fact that in this study the anti-malarial oral ACT and parenteral drugs used were
278 all documented, a detailed audit of how this treatment were used vis-à-vis dosages, timelines,
279 duration, ancillary treatment like infusions and correction of hypoglycemia, were not
280 documented. Availability of this document would definitely have revealed more information
281 on the outcome of the treatment. There is a possibility that some discharged children died at
282 home thereby making the mortality rate in this study a little conservative. Finally, it is
283 possible that the children who had no malaria test done on them would have skewed the result
284 in the comparison over time in this study.

285 **Conclusion**

286 This study noted a steep decline in all cause mortality and malaria confirmed deaths despite
287 an increase in admitted patients over a 3 years period in the pediatric department of Effia
288 Nkwanta hospital. There was however poor anti-malarial testing among the children, a
289 practice that worsen over the study period. There were incorrect diagnoses and treatments of
290 malaria noted in this study with a significant proportion of children wrongly diagnosed with
291 those negative for malaria and those not tested receiving anti-malarial treatment. Despite the
292 commendable decline of deaths in children noted in this study, there is room for improvement

vis-à-vis improvement in anti-malarial testing, and strict adherence to proper anti-malarial treatment protocol to ensure adequate case management which will go a long way in reducing malaria mortality in children.

References

1. Artavanis-Tsakonas K, Tongren JE, Riley EM. The war between the malaria parasite and the immune system: immunity, immunoregulation and immunopathology. *Clin Exp Immunol.* 2003;133(2):145-52.
2. Bull PC, Marsh K. The role of antibodies to *Plasmodium falciparum*-infected-erythrocyte surface antigens in naturally acquired immunity to malaria. *Trends Microbiol.* 2002;10(2):55-8.
3. Greenwood B, Marsh K, Snow R. Why do some African children develop severe malaria? *Parasitol Today.* 1991;7(10):277-81.
4. Menendez C, Fleming AF, Alonso PL. Malaria-related anaemia. *Parasitol Today.* 2000;16(11):469-76.
5. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med.* 1989;71(265):441-59.
6. Idro R, Jenkins NE, Newton CR. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. *Lancet neurology.* 2005;4(12):827-40.
7. WHO. Severe *falciparum* malaria. World Health Organization, Communicable Diseases Cluster. *Trans R Soc Trop Med Hyg.* 2000;94 Suppl 1:S1-90.
8. Rowe AK, Rowe SY, Snow RW, Korenromp EL, Schellenberg JR, Stein C, et al. The burden of malaria mortality among African children in the year 2000. *Int J Epidemiol.* 2006;35(3):691-704.

- 317 9. World Health Organization. (2016). World malaria report 2015. World Health
318 Organization.
- 319 10. World Health Organization. (2015). World malaria report 2014. Available:
320 http://www.who.int/malaria/publications/world_malaria_report_2014/en/.
- 321 11. Thwing J, Eisele TP, Steketee RW. Protective efficacy of malaria case management and
322 intermittent preventive treatment for preventing malaria mortality in children: a systematic
323 review for the Lives Saved Tool. BMC Public Health. 2011 Dec 1; 11:1-9.
- 324 12. O'Meara WP, Mangeni JN, Steketee R, Greenwood B. Changes in the burden of
325 malaria in sub-Saharan Africa. The Lancet infectious diseases. 2010 Aug 31; 10(8):545-55.
- 326 13. Nyarango, P. M., Gebremeskel, T., Mebrahtu, G., Mufunda, J., Abdumumini, U.,
327 Ogbamariam, A., ... & Okbaldet, Y. (2006). A steep decline of malaria morbidity and
328 mortality trends in Eritrea between 2000 and 2004: the effect of combination of control
329 methods. Malaria journal, 5(1), 33.
- 330 14. Bryan, L., Conway, M., Keesmaat, T., McKenna, S., & Richardson, B. (2010).
331 Strengthening sub-Saharan Africa's health systems: a practical approach. McKinsey
332 Quarterly.
- 333 15. Obonyo, C. O., Vulule, J., Akhwale, W. S., & Grobbee, D. E. (2007). In-hospital
334 morbidity and mortality due to severe malarial anemia in western Kenya. Obonyo CO, Vulule
335 J, Akhwale WS, Grobbee DE: In-hospital morbidity and mortality due to severe malarial
336 anemia in western Kenya. Am J Trop Med Hyg. 2007, 77: 23-28.
- 337 16. Biai, S., Rodrigues, A., Gomes, M., Ribeiro, I., Sodemann, M., Alves, F., & Aaby, P.
338 (2007). Reduced in-hospital mortality after improved management of children under 5 years
339 admitted to hospital with malaria: randomised trial. Bmj, 335(7625), 862.

- 17.Caulfield LE, de Onis M, Blossner M, Black RE. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. *Am J Clin Nutr*. 2004;80(1):193-8.
- 18.Binka FN, Indome F, Smith T. Impact of spatial distribution of permethrin-impregnated bed nets on child mortality in rural northern Ghana. *Am J Trop Med Hyg*. 1998;59(1):80-5.
- 19.Ghana Health Service. First Quarter Bulleting 2016. National Malaria Control Surveilance 2016
https://www.ghanahealthservice.org/downloads/1st%20Quarter%20Malaria%20Bulletin%20-%202016_14th%20July%202016.pdf. Site accessed 2018.
20. Orish, V. N., Ansong, J. Y., Anagi, I. B., Onyeabor, O. S., Sanyaolu, A. O., & Iriemenam, N. C. (2015). Malaria and associated co-morbidity in children admitted with fever manifestation in Western Ghana: A retrospective study. *The Journal of Infection in Developing Countries*, 9(11), 1257-1263.
21. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. <http://www.who.int/vmnis/indicators/haemoglobinpdf>. 2011.
22. DeMaeyer EM, Dallman P, Gurney JM, Hallberg L, Sood SK, Srikantia SG.Preventing and controlling iron deficiency anaemia through primary health care.
http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/9241542497.pdf. [Published 1989. Updated 1990].
23. Bhaskaram P, Balakrishna N, Radhakrishna KV, Krishnaswamy K. Validation of hemoglobin estimation using Hemocue. *Indian J Pediatr*. 2003;70(1):25-8.
24. Massaga JJ, Kitua AY, Lemnge MM, Akida JA, Malle LN, Rønn AM, Theander TG, Bygbjerg IC. Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. *The Lancet*. 2003 May 31;361(9372):1853-60.

- 365 25. Bonita R, Beaglehole R, Kjellström T. Basic epidemiology. World Health Organization;
366 2006.
- 367 26. Müller, O., Traoré, C., Becher, H., & Kouyaté, B. (2003). Malaria morbidity,
368 treatment-seeking behaviour, and mortality in a cohort of young children in rural Burkina
369 Faso. *Tropical Medicine & International Health*, 8(4), 290-296.
- 370 27. Hill, Z., Kendall, C., Arthur, P., Kirkwood, B., & Adjei, E. (2003). Recognizing
371 childhood illnesses and their traditional explanations: exploring options for care-seeking
372 interventions in the context of the IMCI strategy in rural Ghana. *Tropical Medicine &*
373 *International Health*, 8(7), 668-676.
- 374 28. Malik, E. M., Hanafi, K., Ali, S. H., Ahmed, E. S., & Mohamed, K. A. (2006).
375 Treatment-seeking behaviour for malaria in children under five years of age: implication for
376 home management in rural areas with high seasonal transmission in Sudan. *Malaria journal*,
377 5(1), 60.
- 378 29. Fenny, A. P., Hansen, K. S., Enemark, U., & Asante, F. A. (2014). Quality of
379 uncomplicated malaria case management in Ghana among insured and uninsured patients.
380 *International journal for equity in health*, 13(1), 63.
- 381 30. USAID/CDC/QHP, GHS/NMCP, WHO: Ghana – Nationwide Malaria Health Facility
382 Survey. Accra, Ghana: Quality Health Partners; 2008.
- 383 31. Zoyah, C. J., & Diedong, A. L. (2014). Health Professionals' Compliance with National
384 Treatment Guidelines for Treatment of Severe Malaria in Children in Bolgatanga Hospital,
385 Upper East, Ghana
- 386 32. Buabeng, K. O., Duwiejua, M., Dodoo, A. N., Matowe, L. K., & Enlund, H. (2007). Self-
387 reported use of anti-malarial drugs and health facility management of malaria in Ghana.
388 *Malaria journal*, 6(1), 85.

33. Chandler, C. I., Whitty, C. J., & Ansah, E. K. (2010). How can malaria rapid diagnostic tests achieve their potential? A qualitative study of a trial at health facilities in Ghana. *Malaria journal*, 9(1), 95.
34. Kwarteng, A., Asante, K. P., Abokyi, L., Gyaase, S., Febir, L. G., Mahama, E., ... & Amenga-Etego, S. (2015). Provider compliance to artemisinin-based combination therapy at primary health care facilities in the middle belt of Ghana. *Malaria journal*, 14(1), 361.
35. National Malaria Control Programme. (2011) Annual Report. Accra, Ghana.
36. Adjei, A. A., Winch, P., Laar, A., Sullivan, D. J., Sakyi, K. S., Stephens, J. K., ... & Tuakli, J. (2016). Insights into the Affordable Medicines Facility-malaria in Ghana: the role of caregivers and licensed chemical sellers in four regions. *Malaria journal*, 15(1), 263.
37. Ferrer, B. E., Webster, J., Bruce, J., Narh-Bana, S. A., Narh, C. T., Allotey, N. K., ... & Gyapong, M. (2016). Integrated community case management and community-based health planning and services: a cross sectional study on the effectiveness of the national implementation for the treatment of malaria, diarrhoea and pneumonia. *Malaria journal*, 15(1), 340.
38. Ameme, D. K., Afari, E. A., Nyarko, K. M., Malm, K. L., Sackey, S., & Wurapa, F. (2014). Direct observation of outpatient management of malaria in a rural Ghanaian district. *The Pan African medical journal*, 19.
39. Oladosu, O. O., & Oyibo, W. A. (2012). Overdiagnosis and overtreatment of malaria in children that presented with fever in Lagos, Nigeria. *ISRN Infectious Diseases*, 2013.
40. Okoro, C. I., Chukwuocha, U. M., Nwakwuo, G. C., & Ukaga, C. N. (2015). Presumptive Diagnosis and Treatment of Malaria in Febrile Children in Parts of South Eastern Nigeria. *Journal of Infectious Diseases & Therapy*. 3: 240

- 414 41. Orish VN, Ansong JY, Onyeabor OS, Sanyaolu AO, Oyibo WA, Iriemenam NC.
415 Overdiagnosis and overtreatment of malaria in children in a secondary healthcare centre in
416 Sekondi-Takoradi, Ghana. *Trop Doct*. 2016;46(4):191-8.
- 417 42. Masquelier B, Reniers G, Pison G. Divergences in trends in child and adult mortality in
418 sub-Saharan Africa: survey evidence on the survival of children and siblings. *Popul Stud*
419 (Camb). 2014;68(2):161-77.
- 420 43. Liu, L., Oza, S., Hogan, D., Perin, J., Rudan, I., Lawn, J. E., ... & Black, R. E. (2015).
421 Global, regional, and national causes of child mortality in 2000–13, with projections to
422 inform post-2015 priorities: an updated systematic analysis. *The Lancet*, 385(9966), 430-440.
- 423 44. Murphy SC, Breman JG. Gaps in the childhood malaria burden in Africa: cerebral
424 malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and
425 complications of pregnancy. *Am J Trop Med Hyg*. 2001;64(1-2 Suppl):57-67.
- 426 45. Tette, E. M., Neizer, M. L., Nyarko, M. Y., Sifah, E. K., Sagoe-Moses, I. A., & Nartey, E.
427 T. (2016). Observations from Mortality Trends at The Children's Hospital, Accra, 2003-
428 2013. *PloS one*, 11(12), e0167947.
- 429 46. Berkley JA, Brent A, Mwangi I, English M, Maitland K, Marsh K, et al. Mortality among
430 Kenyan children admitted to a rural district hospital on weekends as compared with
431 weekdays. *Pediatrics*. 2004;114(6):1737-8.

432

433

434

435

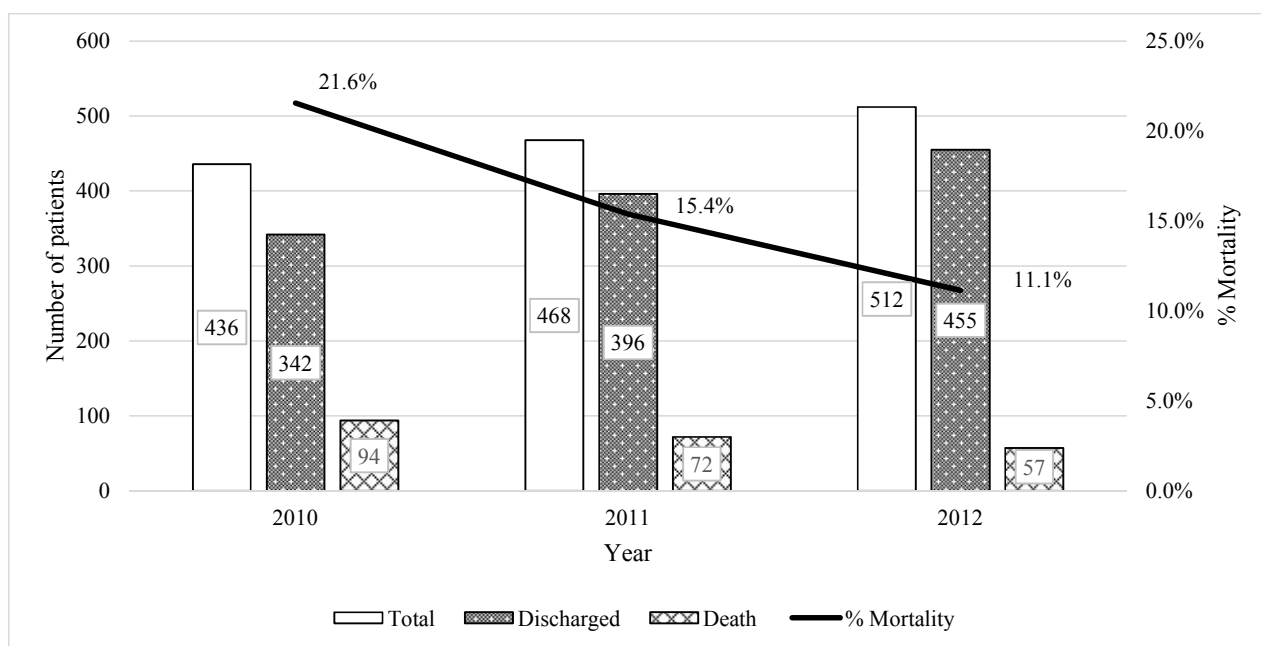
436

437

438

439

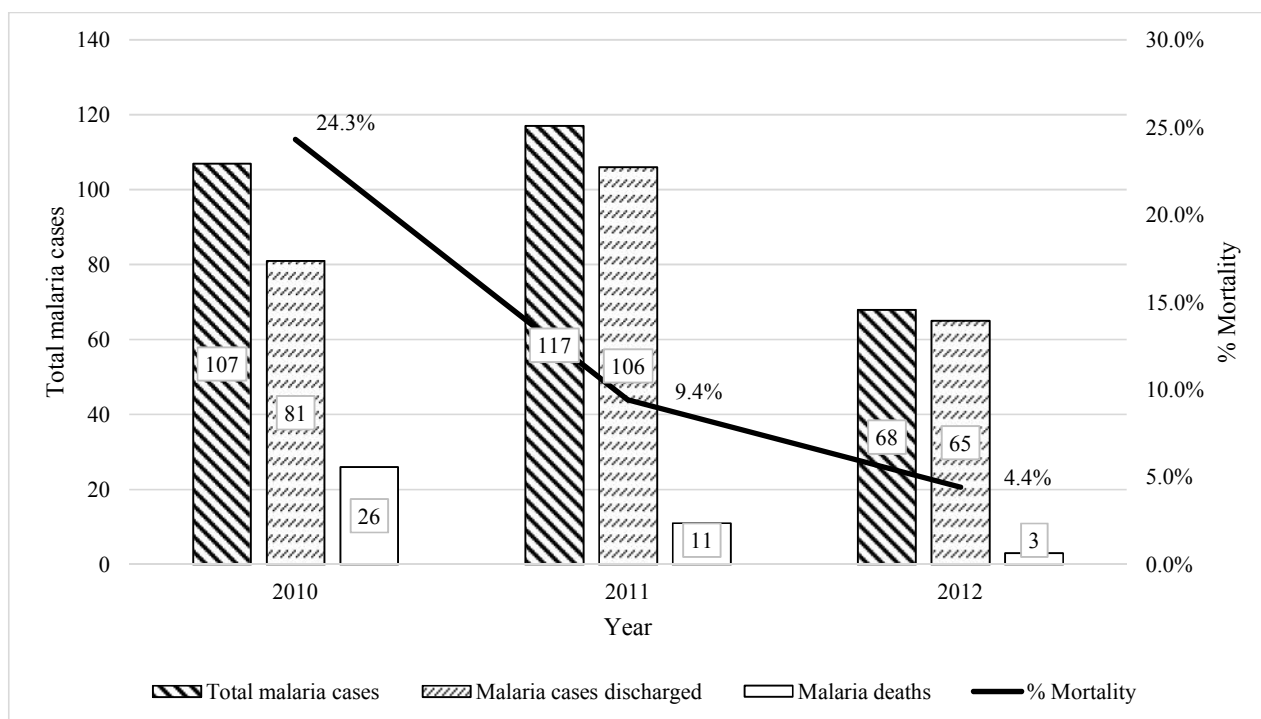
440 **Figure Legends**



441

442 **Figure 1: Percentage mortality from the year 2010 to 2012**

443



444

445 **Figure 2: Malaria case fatality rate**

446

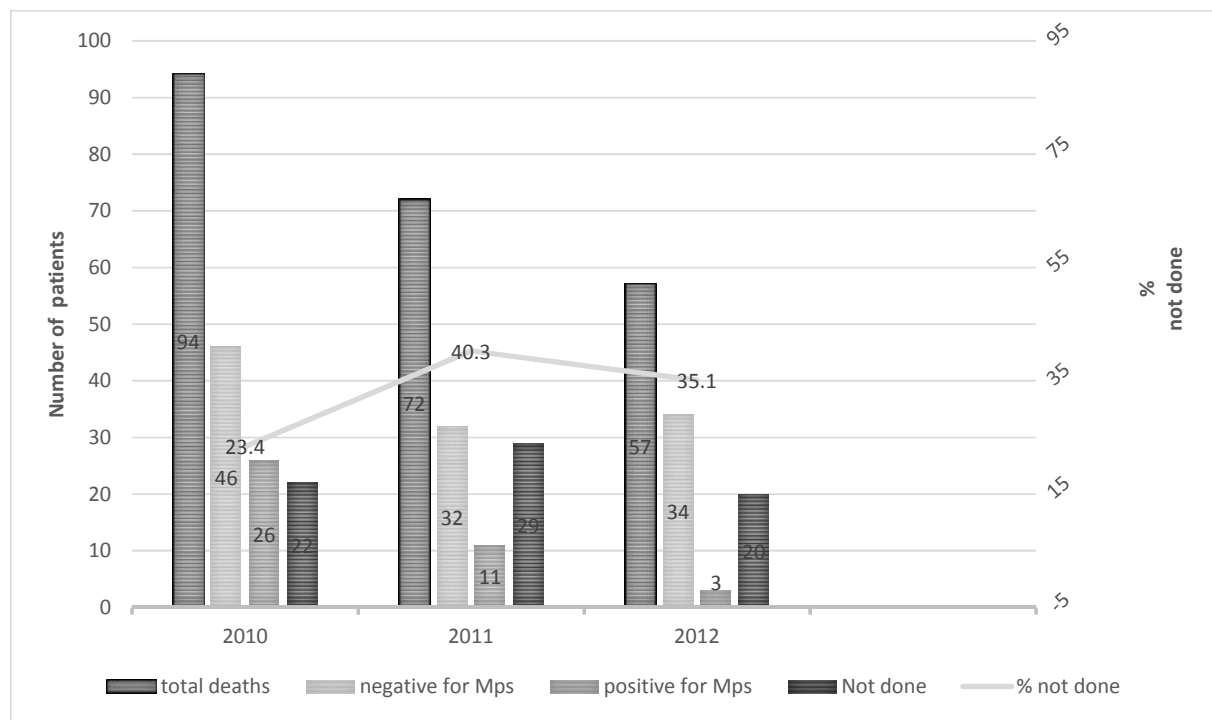


Figure 3 Malaria testing for year 2010 to 2012

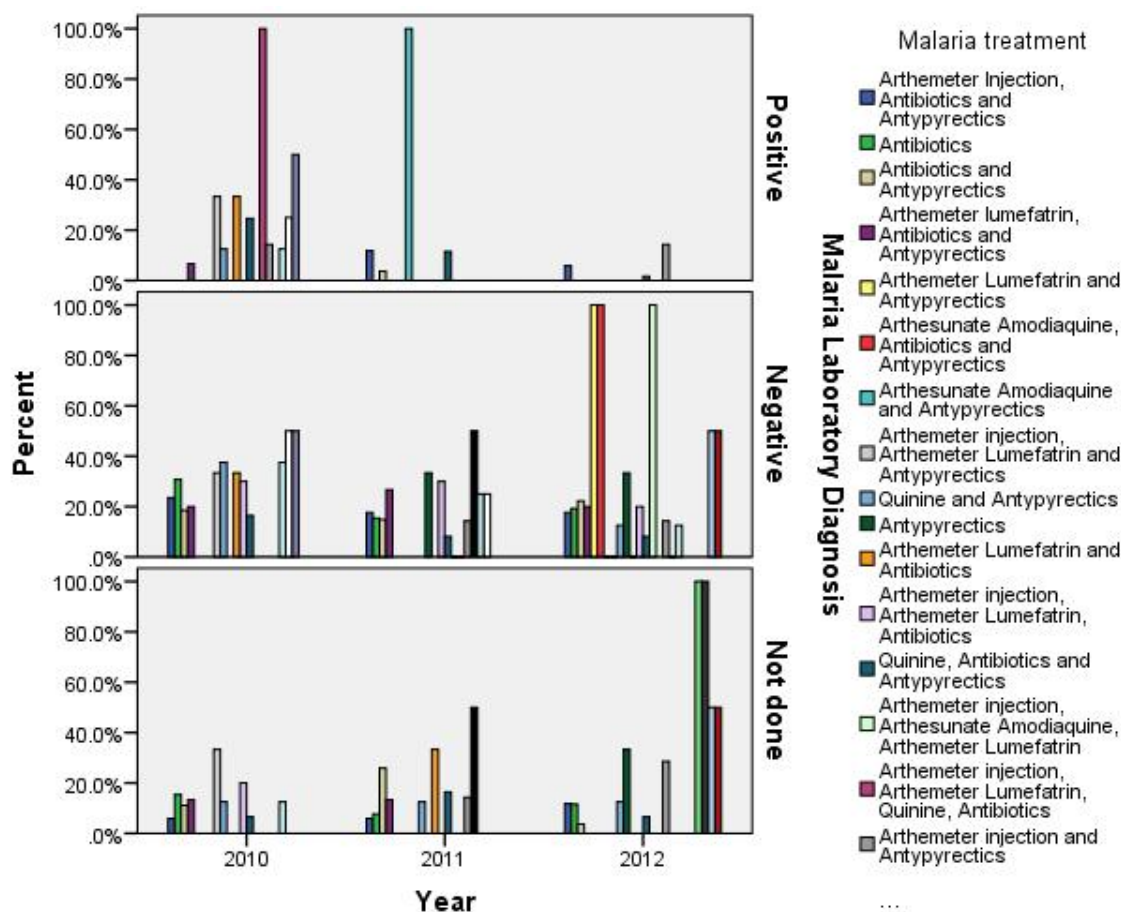


Figure 4: Treatment regimens against malaria laboratory investigation for the study period

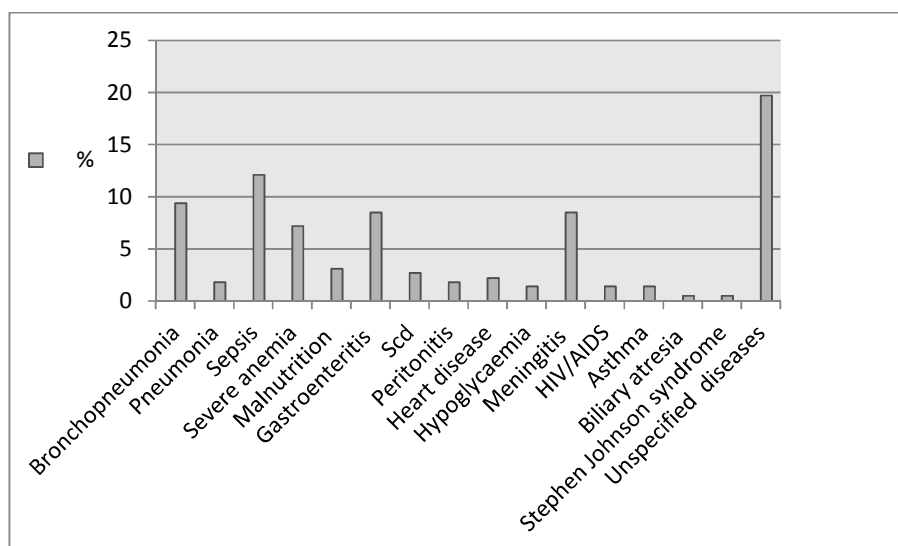


Figure 5: Other non-malaria causes of death.

Table 1: General characteristics of study population

Characteristics	Frequency (n=223)	Percentage (%)
Sex		
Male	122	54.7
Female	101	45.3
Age (Years)		
<1	110	49.3
2-5	63	28.3
>5	50	22.4
Hemoglobin		
<7 g/dL	76	34.1
<10 g/dL	75	33.6
<11 g/dL	30	13.5
≥11 g/dL	42	18.8
Sickle cell*		
HB (AS)	21	15.8
HB (SS)	6	4.5
HB (AA)	106	79.7
Malaria parasite		
MP Seen	112	50.2
No MP Seen	71	31.9
Not done		
Death on admission in hospital (Hours)		
<24	97	43.5
	83	37.2

<72	43	19.3
>72		

*Sickle cell (n=133). MP = Malaria parasites

Table 2: Patients characteristics stratified my malaria laboratory diagnosis

Clinical and demographic characteristics	Malaria positive n = 40 (%)	Malaria Negative N=112(%)	Not done N=71(%)	P VALUE
Age (Mean ± SD)	3.1 ± 3.1	2.9 ± 3.2	2.5± 3.5	0.6
Age (Years)				
<1	15(37.5)	57(50.9)	38(53.5)	0.01
2-5	20(50)	28 (25.0)	15(21.1)	
6-11	5(12.5)	27 (24.1)	18(25.4)	
Sex				
Male	24 (60)	66 (59)	32(45.1)	0.23
female	16 (40)	46 (41)	39(54.9)	
Hemoglobin				
<7g/dL	22 (55)	36 (32.1)	18(25.4)	0.18
<10g/dL	10 (25)	43 (38.4)	22(31.0)	
<11g/dL	4 (10)	12 (10.7)	14(19.7)	
≥11g/dL	4 (10)	21 (18.8)	17(23.9)	
Death on admission in hospital (Hours)				
<24	12 (30)			
<72	25 (62.5)	40 (35.7)	45(63.4)	0.001
>72	3 (7.5)	38 (33.9)	20(28.2)	
		34 (30.4)	6 (8.4)	
Blood transfusion				
Yes	22 (55)	36 (32.1)	17(23.9)	0.02
No	18 (45)	76 (67.9)	54(76.1)	
Presumptive diagnosis for malaria				
Severe malaria anaemia	12 (30)		10(14.08)	0.004
Cerebral malaria	16 (40)	30 (26.8)	14(19.7)	
Severe malaria	10 (25)	29 (25.9)	7(9.9)	
Bronchopneumonia +malaria	2 (5)	19 (16.9)	8(11.3)	
Epilepsy + malaria	0 (0)	17 (15.2)	3(4.2)	
Antimalaria treatment given				
Yes	40(100)	93(83.0)	57(80.3)	0.05
No	0(0)	19(17)	9(12.7)	

*Significant P-Value= (P<0.05); SD=Standard Deviation