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Burden of child mortality from malaria in high endemic areas: Results from the CHAMPS network using minimally invasive tissue sampling

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SUMMARY

Background: Malaria is a leading cause of childhood mortality worldwide. However, accurate estimates of malaria prevalence and causality among patients who die at the country level are lacking due to the limited specificity of diagnostic tools used to attribute etiologies. Accurate estimates are crucial for prioritizing interventions and resources aimed at reducing malaria-related mortality.

Methods: Seven Child Health and Mortality Prevention Surveillance (CHAMPS) Network sites collected comprehensive data on stillbirths and children < 5 years, using minimally invasive tissue sampling (MITS). A DeCoDe (Determination of Cause of Death) panel employed standardized protocols for assigning underlying, intermediate, and immediate causes of death, integrating sociodemographic, clinical, laboratory (including extensive microbiology, histopathology, and malaria testing), and verbal autopsy data. Analyses were conducted to ascertain the strength of evidence for cause of death (CoD), describe factors associated with malaria-related deaths, estimate malaria-specific mortality, and assess the proportion of preventable deaths.

Findings: Between December 3, 2016, and December 31, 2022, 2673 deaths underwent MITS and had a CoD attributed from four CHAMPS sites with at least 1 malaria-attributed death. No malaria-attributable deaths were documented among 891 stillbirths or 924 neonatal deaths, therefore this analysis concentrates on the remaining 858 deaths among children aged 1-59 months. Malaria was in the causal chain for 42.9% (126/294) of deaths from Sierra Leone, 31.4% (96/306) in Kenya, 18.2% (36/198) in Mozambique, 6.7% (4/60) in Mali, and 0.3% (1/292) in South Africa. Compared to non-malaria related deaths, malaria-related deaths skewed towards older infants and children ($p < 0.001$), with 71.0% among ages 12-59 months. Malaria was the sole infecting pathogen in 184 (70.2%) of malaria-attributed deaths, whereas bacterial and viral co-infections were identified in the causal pathway in 24·0% and 12.2% of cases, respectively. Malnutrition was found at a similar level in the causal pathway of both malaria (26.7%) and non-malaria (30.7%, p = 0.256) deaths. Less than two-thirds (164/262; 62.6%) of malaria deaths had received antimalarials prior to death. Nearly all (98·9%) malaria-related deaths were deemed preventable.

Interpretation: Malaria remains a significant cause of childhood mortality in the CHAMPS malaria-endemic sites. The high bacterial co-infection prevalence among malaria deaths underscores the potential benefits of antibiotics for severe malaria patients. Compared to non-malaria deaths, many of malaria-attributed deaths are preventable through accessible malaria control measures.

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Introduction

Malaria is the most important parasitic disease worldwide, with nearly 250 million clinical episodes occurring every year. In the latest World Malaria Report (2023), the World health Organization (WHO) estimated 608,000 malaria-associated deaths, a figure which entails significant uncertainty.[1] Despite significant improvements in malaria burden indicators between 2000-2015, malaria remains a major cause of global morbidity and mortality.[2] Additionally, following the COVID-19 pandemic, malaria deaths increased by 10% between 2019 and 2020.[3] Three quarters of malaria deaths occur in children aged < 5 years, constituting 7.8% of childhood mortality.[4] Over 90% of these malaria-associated childhood deaths occur in sub-Saharan Africa.

Despite the significant mortality burden, there is still much uncertainty regarding the true burden of malaria-associated mortality in malaria-endemic areas. In high transmission areas, children < 6 months of age have lower malaria infection rates due to maternal antibodies.[5] Thereafter, the young infant is susceptible to malaria disease and at risk of adverse outcomes if not treated rapidly.[6] As infancy progresses, repeated exposure to malaria parasites from the infective bites of female anopheline mosquitoes leads to the gradual development of partial naturally acquired immunity (NAI) against malarial disease. This NAI is the basis for the clinical tolerance to malarial infections exhibited by older children, adolescents, and adults. Young children, who are still developing NAI, remain vulnerable to clinical disease, resulting in concentrated morbidity and mortality among this age group. However, in malaria-endemic areas, many malaria infections in older children do not lead to classically defined clinical morbidity and are considered asymptomatic, or chronically infected.[7,8] Thus, the detection of malaria infection by microscopy or RDT in a sick child does not necessarily indicate that malaria is the cause of the illness, and many deaths may erroneously be attributed to malaria.[9] In addition, cause of death (CoD) in sub-Saharan Africa is largely determined by 1) available antemortem clinical records in deaths that occur at the health system level; and 2) verbal autopsy (VA), that often associates the reported history of fever with malaria, overestimating the contribution of malaria to mortality[10–12] particularly in older children and adults.[13] Antemortem clinical records in settings where diagnostic resources are scarce have been associated with important diagnostic errors and clinic-pathological discrepancies.[14,15] The poor reliability of VA in inferring cause of death at the individual level,[16,17] and the many shortcomings of pre-mortem clinical data are responsible for the large variability in malaria-attributable mortality estimates at the global level,[18] and for the large proportion of malaria attributable mortality in several epidemiological studies.[10,11,19] As an example, malaria-attributable mortality estimates for the year 2013 varied by as much as 131,000 deaths (25%) among different modeling groups consulted,[18] underscoring the inherent unreliability of both the models and data sources used. Importantly, VA and antemortem clinical data remain, as of today, the principal sources for global malaria mortality estimates.

Established in 2015, the Child Health and Mortality Prevention Surveillance (CHAMPS) conducts ongoing multi-site surveillance across sub-Saharan Africa and Asia to track causes of death in children aged < 5 years.[20] CHAMPS uses minimally invasive tissue sampling (MITS)[21] for CoD determination, a method validated for all age groups as an acceptable proxy to the “gold standard” complete diagnostic autopsy (CDA),[22] but which also has been shown to be more reliable than VA[16,23] and clinical records,[15,24] and more socially acceptable than the CDA.[25] Initial CHAMPS data showed that malaria was present in ≥10% of all deaths (in any position in the causal chain) in the post-neonatal period (1 month to < 60 months), but this figure pooled together malaria and non-malaria areas.[26] When malaria was identified, it was more frequently considered to be an underlying cause (80% of the

cases). Additionally, and compared to other infections, malaria deaths were less frequently associated to other co-infections.[26] Using this unique mortality surveillance platform, we aim to characterize the contribution of malaria infection to child mortality and to estimate the malaria-specific mortality fraction (MSMF) for the different CHAMPS sites in the network.

Materials and methods

Study sites

The CHAMPS Network collects cause of death data for stillbirths and children < 5 years of age across seven countries in sub-Saharan Africa and South Asia: Baliakandi and Faridpur, Bangladesh; Harar, Kersa and Haramaya, Ethiopia; Siaya and Kisumu, Kenya; Bamako, Mali; Manhiça and Quelimane, Mozambique; Makeni and Bo, Sierra Leone; and Soweto, South Africa. The CHAMPS site in Mozambique began enrollment in 2016; sites in South Africa, Kenya, Mali, and Bangladesh began in 2017; and Sierra Leone and Ethiopia began in 2019. Background under-five mortality rates (U5MR) were greater than 50 per 1000 live births at all sites in 2015. Malaria transmission is common in four of the countries (Sierra Leone, Kenya, Mozambique and Mali); endemicity, seasonality (if applicable) and first-line treatment for each site is shown in Supplementary Table 1.

Demographic surveillance system

Except for Sierra Leone, Quelimane in Mozambique, and Faridpur in Bangladesh, most sites implemented mortality surveillance as part of a health and demographic surveillance system (DSS). Each DSS platform collected sociodemographic data and recorded significant events such as births, deaths, pregnancies, and migration episodes within a defined geographical area, allowing for population size and structure estimation. The maturity levels of the DSS platforms varied across the CHAMPS network, with some systems newly established during the study period.

Mortality and demographic surveillance

According to the CHAMPS protocol,[27] stillborn babies or children < 5 years of age at the time of death and residing within the catchment area of a CHAMPS site, irrespective of their place of death (health facility or community) were eligible for enrollment. Such deaths are suitable for MITS if identified within 24 hours of their occurrence (36 hours if body refrigeration available). The MITS protocol[21] included post-mortem collection of blood, cerebrospinal fluid (CSF), stool, and nasopharyngeal (NP) swabs, and sampling of key organs (brain, lungs, and liver) using fine-needle biopsies. Clinical data (information on signs, symptoms, clinical evolution and supporting laboratory and imaging for any child having been seen at the health system prior to the death) from both the child and mother, if any available, pictures (for morphological identification), and post-mortem anthropometric measurements were also collected. Additional information on signs and symptoms, circumstances and narrative of the events leading to death were routinely collected using the VA tool (WHO 2016[28]).

Laboratory procedures

Samples obtained through MITS underwent comprehensive microbiological evaluation, involving on-site blood and CSF culture, and proactive screening using molecular methods (TaqMan Array cards; a customizable diagnostic platform that allows the performance of dozens of real-time PCR reactions simultaneously (TAC); ThermoFisher Scientific, Waltham, MA, USA). The TAC cards were tailored to specific syndromes, and customized to detect pathogens of significance in young children, encompassing bacteria (57 targets covering 30 genera), viruses (48 targets covering 40 viruses), parasites (8 targets covering 8 organisms, including the two main malaria species, *P. falciparum* and *P. vivax*), and fungi (3 targets covering 3 organisms).[29] Each enrolled death was screened for malaria using rapid diagnostic tests (typically HRP2-based) and microscopy, HIV infection using molecular methods, and tuberculosis using GeneXpert. Initial histopathological assessment, including hemozoin pigment evaluation for malaria, was conducted locally at each site. Additional staining, immunohistochemistry, and molecular methods were employed at the centralized pathology laboratories at the US Centers for Disease Control and Prevention (CDC) Infectious Diseases Pathology Branch if deemed necessary.[30]

Cause of death determination

All available data, including sociodemographic, clinical, laboratory (microbiological and histopathological), and VA narratives,[31] were compiled into standardized Determination of Cause of Death (DeCoDe) packages. These packages were reviewed by a panel of local experts consisting of pediatricians, obstetricians, public health specialists, pathologists, and microbiologists. The panel thoroughly discussed each case, considering all available information, including raw VA data and open summaries (excluding diagnoses). Through this collaborative process, the panel reached a cause of death (CoD) diagnosis, which included the underlying cause of death (UCoD; i.e. "the disease or injury that initiated the train of morbid events leading directly to death"[32]), intermediate (or morbid) conditions, and immediate cause of death (iCoD, i.e. "final event"), establishing the sequential chain of events leading to death. Maternal diagnoses were also incorporated, particularly for stillbirths and neonatal deaths. For this manuscript, analyses were limited to cases with a completed DeCoDe determination, regardless of whether a known cause of death was assigned.

Definitions

Cases were classified as malaria deaths if the DeCoDe panel assigned one of the following International Classification of Diseases, Revision 10 (ICD-10) codes in any causal chain position (immediate, underlying, and/or intermediate causes): B50 (*Plasmodium falciparum*), B51 (*Plasmodium vivax*), B52 (*Plasmodium malariae*), B53 (other specified malaria), B54 (unspecified malaria), with appropriate 4th character digit to specify complications related to malaria (for instance cerebral malaria, B50.0), and a malaria infection was documented by any of the available diagnostic methods. Conversely, malaria infections (as distinct from malaria deaths) were cases where a malaria infection (acute, recent, or past) was documented, but the DeCoDe panel determined that it played no role in the chain of events leading to death. Diagnoses followed the predefined CHAMPS-specific diagnosis standards[33] and were coded based on the level of certainty (strength of evidence), ranked by integers from 1 to 3, with 1 indicating the strongest evidence, and 3 the lowest. Certainty depended on the diagnostic method (e.g., blood smear, rapid diagnostic test, molecular diagnosis through the TaqMan array cards, histopathological evidence) and the presence or absence of clinical evidence. Other causes of death in the causal chain were classified using the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) categories. Supplementary Table 2 provides detailed malaria diagnosis standards, as defined in CHAMPS.

Analysis and statistical methods

Case characteristics (site, age, sex, death location, year, clinical characteristics, microbiological diagnoses, VA cause of death, etc.) were described for all DeCoDe panel-reviewed deaths.

The target population included all eligible deaths within respective catchment areas (if applicable) for each site.

Given the few cases documented of malaria deaths in stillbirths and neonatal periods, we concentrated most of our malaria analyses to post-neonatal (1 month to < 60 months) deaths.

At the population level, we evaluated test characteristics of verbal autopsy diagnoses (both inSilico and interVA methods) compared to DeCoDe panel CoD diagnoses including sensitivity, specificity, positive predictive value, and negative predictive value. Analyses were performed in R 4.2.1 (R Core Team, Vienna, Austria).

Cause-specific mortality fractions and rates

Crude and adjusted cause-specific mortality fractions (CSMF) and rates (CSMR) were calculated for each catchment area and site (Supplemental Methods).[34]

Human subjects protections

Ethics committees or institutional review boards overseeing investigators at each site and at Emory University approved the generic and site-specific protocols, as appropriate.

Protocols are available at https://champshealth.org/protocols/.

Informed consent, signed by parents/legal guardians, was obtained before all MITS procedures.

Results

Screening and enrollment

Between December 3, 2016, and December 31, 2022, 3942 stillbirths and 8193 children aged < 5 years were eligible in the 7 sites; 5894 (48·6%) underwent MITS, and 4661 cases (79·1%) had a CoD determined through a DeCoDe panel (See global study profile in Supplementary Fig. 1, *and site-specific study profiles in* Supplementary Fig. 2 and Supplementary Table 3). Considering the complete sequence of events leading to death, the majority of malaria-related fatalities were concentrated in four sites: Sierra Leone, Kenya, Mozambique, and Mali. A single malaria death was recorded in South Africa and no malaria deaths were recorded in Ethiopia or Bangladesh (Fig. 1).

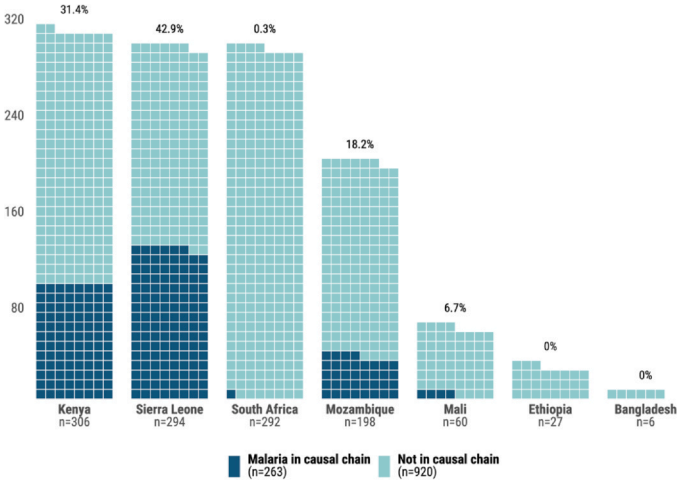


Fig. 1. Number of deaths by site and proportion of deaths that had malaria anywhere in the causal chain.

Malaria results and position in the chain of events

Routine screening and laboratory workup of all cases recruited in all sites detected a total of 383 malaria infections. DeCoDe panelists considered 263/383 (68.7%) of these infections relevant in the causal pathway to death: 126/189 (66.7%) in Sierra Leone; 96/135 (71.1%) in Kenya; 4/5 (80.0%) in Mali; 36/51 (70.6%) in Mozambique; and 1/3 (33.3%) in South Africa (Supplementary Table 3). All malaria-associated deaths were attributed to *P. falciparum* infections, whereas a single *P. vivax* infection documented in Ethiopia was not considered relevant in the cause of death.

Most malaria infections (325/383, 84.9%) were diagnosed in the post-neonatal period. None of the 1656 stillbirths were attributed to malaria, but 39 (2.4%) had evidence of maternal malaria during pregnancy (placental malaria or a history of maternal clinical malaria). Among neonatal deaths, 32 were found to be infected with malaria parasites, although none had malaria identified in the causal chain.

Across all sites, and after excluding stillbirths and neonates, 1183 deaths were DeCoDed in the 1-59 months age group. Given that no malaria diagnoses were made in Bangladesh or Ethiopia (with the exception of the aforementioned *P. vivax* infection) and only one in South Africa, we restricted our analysis to post-neonatal cases from the four sites (n = 858, with n = 262 malaria deaths; Table 1) characterized by moderate-to-high malaria endemicity (Sierra Leone, Kenya, Mali, and Mozambique).

Nearly all malaria-attributed deaths had strong evidence supporting the diagnosis; median strength of evidence was 1 (IQR 1-1; highest possible evidence) for all sites pooled together. The proportion of deaths with level 1 evidence ranged from 114/126 (90.5%) in Sierra Leone to 94/96 (97.9%) in Kenya.

Socio-demographic and clinical characteristics of malaria deaths

Malaria-attributed deaths (median: 22 months, IQR: 11-36) were found to occur at a significantly older age compared to non-malaria deaths (median: 10 months, IQR: 5-18) ($p < 0.001$). The male-to-female ratio for malaria-related deaths was 54% to 46% (Table 1). Among all malaria deaths, 193/262 (73.7%) occurred in hospitals, while 69/262 (26.3%) took place in the community. Of all malaria deaths, 21.8% (57/262) had no record of visiting the health system or receiving any medical care prior to death. Of the community deaths, 68.1% (47/69) had no documented previous contact with the health system for their illness. Sites in Kenya had the greatest proportion of out-of-hospital deaths (54.2%, 52/96). The distribution of location of death was not significantly different between malaria and non-malaria cases. A greater proportion of malaria deaths occurring in a healthcare facility died within the first 24 hours, in comparison to non-malaria deaths ($p < 0.001$). Among those who died in the hospital, malaria cases had a median time from hospital arrival until death of 16 h (IQR 6, 32). Other detailed clinical and laboratory variables are presented, per study site, in Supplementary Table 4.

Median time from death to MITS was 10 h (IQR 4-18). One-fifth (60/262) of malaria deaths occurred on the weekends.

A significant proportion of children who died from malaria exhibited pre-mortem symptoms such as fever (223/262; 85.1%), vomiting (156/262; 60.3%), respiratory distress (120/262; 45.8%), loss of consciousness (119/262; 45.4%), seizures (110/262; 42.0%), and neurological manifestations indicative of cerebral malaria (35/262; 13.4%), although the antemortem diagnosis of cerebral malaria (B50.0), as attributed by clinicians to the malaria deaths was much higher (167/262; 63.74%). Many cases presented with multiple concurrent clinical severity syndromes (Table 2). Among the malaria cases, 19 (7.3%) were co-infected with HIV, mostly in the Kenya sites (12/19, 63.2%). Compared to non-malaria deaths, malaria cases

Table 1
Characteristics of post-neonatal CHAMPS cases according to whether malaria was deemed to play a role in the death or no malaria was confirmed, per site.

Variables	Sierra Leone (N = 294)		Kenya (N = 306)		Mali (N = 60)		Mozambique (N = 198)		TOTAL (N = 858)		
	Malaria	No malaria	Malaria	No malaria	Malaria	No malaria	Malaria	No malaria	Malaria	No malaria	p value
	(N = 126; 42.9%)	(N = 168; 57.1%)	(N = 96; 31.4%)	(N = 210; 68.6%)	(N = 4; 6.7%)	(N = 56; 93.3%)	(N = 36; 18.2%)	(N = 162; 81.8%)	(N = 262; 30.5%)	(N = 596; 69.5%)	
Median (IQR) age in months	24 (13, 36)	11 (4, 16)	16 (8, 31)	9 (5, 18)	41 (27, 49)	10 (5, 18)	27 (15, 42)	13 (5, 24)	22 (11, 36)	10 (5, 18)	< 0.001
Age group (%)											< 0.001
Young infant (1 month to < 6 months)	67 (53.2)	96 (57.1)	13 (13.5)	67 (31.9)	0 (0.0)	20 (35.7)	1 (2.8)	42 (25.9)	22 (8.4)	187 (31.4)	
Older infant/child (≥6 months to < 60 months)	59 (46.8)	72 (42.9)	83 (86.5)	143 (68.1)	4 (100.0)	36 (64.3)	35 (97.2)	120 (74.1)	240 (91.6)	409 (68.6)	
Sex of the deceased (%)											1
Male	62 (52.5)	84 (57.5)	53 (55.2)	107 (51.0)	2 (50.0)	23 (41.1)	20 (55.6)	96 (59.3)	142 (54.2)	322 (54.0)	
Female	56 (47.5)	62 (42.5)	43 (44.8)	103 (49.0)	2 (50.0)	33 (58.9)	16 (44.4)	66 (40.7)	120 (45.8)	274 (46.0)	
Hours from death to MITS procedure (%) (N = 857)											0.161
≤24 hours	126 (100.0)	168 (100.0)	76 (79.2)	156 (74.3)	4 (100.0)	56 (100.0)	32 (88.9)	139 (86.3)	238 (90.8)	519 (87.2)	
> 24 hours	0 (0)	0 (0)	20 (20.8)	54 (25.7)	0 (0)	0 (0)	4 (11.1)	22 (13.7)	24 (9.2)	76 (12.8)	
Median (IQR) time in hours	6 (3, 12)	9 (3, 14)	18 (10, 23)	17 (9, 24)	16 (13, 17)	9 (4, 14)	10 (3, 19)	12 (4, 19)	10 (4, 18)	12 (5, 18)	0.077
Location of death (%)											0.718
Facility	105 (89.0)	126 (86.3)	44 (45.8)	129 (61.4)	3 (75.0)	29 (51.8)	34 (94.4)	123 (75.9)	193 (73.7)	429 (72.0)	
Community	13 (11.0)	20 (13.7)	52 (54.2)	81 (38.6)	1 (25.0)	26 (46.4)	2 (5.6)	39 (24.1)	69 (26.3)	166 (27.9)	
Median (IQR) of hours in hospital before death (N = 587)	14 (5, 27)	23 (8, 101)	17 (10, 47)	27 (11, 115)	6 (3, 10)	11 (3, 33)	23 (7, 50)	40 (9, 134)	16 (6, 32)	25 (8, 114)	< 0.001
Time of Hospital Death (%) (N = 587)											< 0.001
< 24 hours	78 (72.9)	71 (50.7)	25 (58.1)	53 (43.1)	2 (100.0)	16 (66.7)	16 (51.6)	52 (44.4)	121 (66.1)	192 (47.5)	
≥24 hours	29 (27.1)	69 (49.3)	18 (41.9)	70 (56.9)	0 (0.0)	8 (33.3)	15 (48.4)	65 (55.6)	62 (33.9)	212 (52.5)	
Medically attended (%)											0.867
Yes	110 (87.3)	145 (86.3)	62 (64.6)	177 (84.3)	2 (50.0)	28 (50.0)	31 (86.1)	121 (74.7)	205 (78.2)	471 (79.0)	
No	16 (12.7)	23 (13.7)	34 (35.4)	33 (15.7)	2 (50.0)	28 (50.0)	5 (13.9)	41 (25.3)	57 (21.8)	125 (21.0)	
Deaths occurring during the malaria season (%)	42 (33.3)	55 (32.7)	46 (47.9)	76 (36.2)	4 (100.0)	41 (73.2)	23 (63.9)	89 (54.9)	115 (43.9)	261 (43.8)	1
Deaths occurring during the weekends (%)	31 (24.6)	46 (27.4)	22 (22.9)	43 (20.5)	0 (0.0)	17 (30.4)	7 (19.4)	45 (27.8)	60 (22.9)	151 (25.3)	0.499
Count of causal conditions identified (%)											< 0.001
No condition identified by DeCoDe panel	0 (0.0)	26 (15.5)	0 (0.0)	6 (2.9)	0 (0.0)	1 (1.8)	0 (0.0)	5 (3.1)	0 (0.0)	38 (6.4)	
1	19 (15.1)	27 (16.1)	42 (43.8)	56 (26.7)	1 (25.0)	11 (19.6)	19 (52.8)	47 (29.0)	81 (30.9)	141 (23.7)	
2	45 (35.7)	35 (20.8)	31 (32.3)	92 (43.8)	2 (50.0)	11 (19.6)	10 (27.8)	60 (37.0)	88 (33.6)	198 (33.2)	
3	33 (26.2)	41 (24.4)	18 (18.8)	40 (19.0)	1 (25.0)	13 (23.2)	2 (5.6)	41 (25.3)	54 (20.6)	135 (22.7)	
≥4	29 (23.0)	39 (23.2)	5 (5.2)	16 (7.6)	0 (0.0)	20 (35.7)	5 (13.9)	9 (5.6)	39 (14.9)	84 (14.1)	
Median (IQR)	3 (2, 3)	2 (1, 3)	2 (1, 2)	2 (1, 3)	2 (2, 2)	3 (2, 4)	1 (1, 2)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.816
HIV status (%)											0.175
HIV unexposed or unknown	121 (96.0)	154 (91.7)	70 (72.9)	161 (76.7)	4 (100.0)	51 (91.1)	23 (63.9)	104 (64.2)	218 (83.2)	470 (78.9)	
HIV exposed but uninfected	1 (0.8)	0 (0.0)	15 (15.6)	28 (13.3)	0 (0)	0 (0)	11 (30.6)	36 (22.2)	27 (10.3)	64 (10.7)	
HIV infected	4 (3.2)	14 (8.3)	11 (11.5)	21 (10.0)	0 (0.0)	5 (8.9)	2 (5.6)	22 (13.6)	17 (6.5)	62 (10.4)	
Low birth weight (%) (N = 325)	2 (10.0)	7 (12.5)	6 (15.8)	20 (16.7)	0 (0)	9 (25.7)	0 (0.0)	11 (20.4)	8 (13.3)	47 (17.7)	0.528
Severe underweight (WAZ < −3 SD) (%) (N = 855)	27 (21.6)	78 (46.4)	43 (44.8)	100 (47.8)	0 (0.0)	24 (43.6)	10 (27.8)	74 (45.7)	80 (30.7)	276 (46.5)	< 0.001
Severe stunting (HAZ < −3 SD) (%) (N = 856)	12 (9.6)	34 (20.2)	24 (25.0)	41 (19.5)	0 (0.0)	13 (23.6)	12 (33.3)	66 (40.7)	48 (18.4)	154 (25.9)	0.022
Severe wasting (WHZ < −3 SD) (%) (N = 835)	29 (23.2)	80 (48.8)	38 (40.4)	90 (44.8)	0 (0.0)	33 (58.9)	8 (22.9)	55 (35.3)	75 (29.1)	258 (44.7)	< 0.001

Table 2
Comparison of clinical characteristics for post-neonatal CHAMPS deaths with and without malaria in the chain of events leading to death—Sierra Leone, Kenya, Mali and Mozambique.

Variables	Malaria (N = 262; 30.5%)	No malaria (N = 596; 69.5%)	p value
Clinical symptoms pre-mortem (%)			
Loss of consciousness	119 (45.4)	206 (34.6)	0.003
Seizure	110 (42.0)	179 (30.0)	0.001
Abdominal pain	52 (19.8)	120 (20.1)	0.997
Fever	223 (85.1)	425 (71.3)	< 0.001
Cough	103 (39.3)	295 (49.5)	0.007
Diarrhea	84 (32.1)	268 (45.0)	0.001
Headache	48 (18.3)	53 (8.9)	< 0.001
Vomiting	158 (60.3)	330 (55.4)	0.204
Altered mental state	35 (13.4)	121 (20.3)	0.02
Respiratory distress	120 (45.8)	254 (42.6)	0.429
Other skin or mucosal abnormalities	10 (3.8)	44 (7.4)	0.068
Hepatomegaly	80 (30.5)	117 (19.6)	0.001
Enlarged lymph nodes	28 (10.7)	35 (5.9)	0.019
Jaundice or icterus	84 (32.1)	68 (11.4)	< 0.001
Rash	14 (5.3)	44 (7.4)	0.343
Other causes of death in causal chain (%)			
Anemias	98 (37.4)	93 (15.6)	< 0.001
Congenital birth defects	1 (0.4)	50 (8.4)	< 0.001
Diarrheal diseases	12 (4.6)	122 (20.5)	< 0.001
Heart diseases	0 (0)	9 (1.5)	0.064
HIV	19 (7.3)	66 (11.1)	0.106
Injury	3 (1.1)	21 (3.5)	0.07
Lower respiratory infections	38 (14.5)	251 (42.1)	< 0.001
Malnutrition	70 (26.7)	183 (30.7)	0.256
Meningitis/Encephalitis	0 (0)	25 (4.2)	< 0.001
Neonatal preterm birth complications	3 (1.1)	12 (2.0)	0.572
Other endocrine, metabolic, blood, and immune disorders	2 (0.8)	6 (1.0)	1
Other infections	1 (0.4)	27 (4.5)	< 0.001
Other neonatal disorders	1 (0.4)	6 (1.0)	0.682
Other neurological disorders	0 (0)	13 (2.2)	0.013
Other respiratory disease	11 (4.2)	57 (9.6)	0.006
Other skin and subcutaneous diseases	1 (0.4)	6 (1.0)	0.682
Paralytic ileus and intestinal obstruction	0 (0)	7 (1.2)	0.108
Poisoning	0 (0)	6 (1.0)	0.186
Sepsis	44 (16.8)	235 (39.4)	< 0.001
Sickle cell disorders	4 (1.5)	11 (1.8)	1
Sudden infant death syndrome	0 (0)	5 (0.8)	0.331
Tuberculosis	3 (1.1)	3 (0.5)	0.378
Other[a]	6 (2.3)	47 (7.9)	0.001
Record of pre-mortem malaria test			
RDT	96 (36.6)	129 (21.6)	< 0.001
Blood smear	79 (30.2)	171 (28.7)	0.751
History of pre-mortem antimalarial treatment (%)	164 (62.6)	142 (23.8)	< 0.001
History of pre-mortem antibiotic treatment (%)	168 (64.1)	381 (63.9)	1
Treated for hypoglycemic (%)	102 (38.9)	184 (30.9)	0.026
Number (%) of deaths deemed preventable (%) (N = 849)	258 (98.9)	522 (88.8)	< 0.001

[a] Other includes: cancer (n = 5); congenital infection (n = 2); diabetes (n = 1); epilepsy (n = 2); kidney disease (n = 2); liver disease (n = 2); measles (n = 2); other (n = 26); other disorders of fluid, electrolyte and acid-base balance (n = 3); other immunodeficiencies (n = 4); rabies (n = 2); syphilis (n = 2); and upper respiratory infections (n = 1).

were less likely to have diarrheal diseases, lower respiratory infections, meningitis, and sepsis as comorbidities, but more likely to have anemia (p-values < 0.001). Approximately two-thirds of malaria deaths received treatment with antimalarial drugs (164/262, 62.6%) and antibiotics (168/262, 64.1%) prior to death, while 146/262 (55.7%) received both.

Differences between malaria-attributed deaths and malaria infections not related to the death event

Deaths with malaria in the causal chain (median: 22 months, IQR: 11-36) were significantly older than deaths with malaria infections detected that were not related to the fatal event (median: 16 months, IQR: 8-21) ($p = 0.003$). Severe wasting and severe underweight were more prevalent among deaths with incidental malaria infections compared to malaria deaths (45.8% vs 29.1% and 53.3% vs. 30.7%, respectively) (Table 3). Among the 262 malaria deaths, 91 (35.0%) and 66 (25.4%) had pre-mortem positive RDT and blood smear results, respectively. Post-mortem test positivity among malaria deaths were: TAC (85.5%), RDT (67.9%), blood smear (33.6%), immunohistochemistry (33.2%), and histopathology (28.6%). Deaths attributed to malaria had parasitological confirmation on a median of 3 (range 1-5) of the 5 assays used (TAC, blood smear, malaria RDT, immunohistochemistry and histopathology) compared to median of 1 diagnostic (range 1-4) for malaria infections that were not linked to death. TaqMan Array PCR was the most frequent positive assay in both groups, followed by malaria RDT. Histopathological evidence of past or chronic malaria infections was similar between the groups (5.7% for malaria deaths, 4.9% for non-fatal malaria infections) (Table 3).

Malaria and other co-morbidities and co-infections

P. falciparum was the sole infecting pathogen in 184/262 (70.2%) of malaria deaths, while co-infections with other pathogens in the causal chain were present in 78/262 (29.8%) (Table 4 and Supplementary Table 4). Bacterial invasive infections, identified through blood culture or Taqman Array PCR, were considered by the DeCoDe panel to contribute to the chain of events leading to death in 63/262 (24.0%) malaria deaths. The most frequently identified pathogens were *Klebsiella pneumoniae* (26 cases; 9.9%), *Streptococcus pneumoniae* (14 cases; 5.3%), and *Escherichia coli* (7 cases; 2·7%). *Salmonella spp*., often associated with severe malaria in the literature, were detected in only 2 malaria cases (0.8%). Viral infections were in the causal chain for 12.2% (n = 32) of all malaria deaths, primarily HIV (19/32; 59.4%), CMV (7/32; 21.9%), and adenovirus (6/32, 18.9%). A fungal co-infection (*Pneumocystis jirovecii*) was observed in only one malaria death, in a patient with malnutrition as the underlying cause of death and negative HIV serostatus. No other parasites were detected in the malaria deaths.

Of all malaria diagnoses in the causal chain, the majority (65.7%, 172/262) were the underlying CoD, while the rest (34.4%, 90/262) were intermediate or immediate causes. When malaria was the underlying cause, major intermediate or immediate causes included anemia (68 cases; 39.5%, significantly more frequently associated with malaria than with all other mortality causes), sepsis (18 cases; 10.5%), and lower respiratory infections (16 cases; 9.3%). In deaths where malaria was not the underlying CoD, major underlying causes included malnutrition (50 cases; 55.6%) and HIV (18 cases; 20.0%). The median number of steps in the chain of events leading to death for both malaria and non-malaria cases was 2 (IQR 1-3).

Preventable malaria deaths and opportunities for intervention

The DeCoDe panel deemed that 258/261 (98.9%) of the malaria deaths were preventable (254, 97.3%) or preventable under certain conditions (4, 1.5%); one death was missing a preventability determination. Compared to deaths without malaria in the causal chain, malaria deaths were determined to be more preventable (98.9% vs 88.8%, $p < 0.001$). Recommendations to prevent these

Table 3
Characteristics of post-neonatal CHAMPS cases with malaria infection detected, according to whether malaria was deemed to play a role in the death (malaria in the causal chain) or was considered an "innocent bystander" (malaria not in causal chain).

Variables	Sierra Leone (N = 155; 48.0%)		Kenya (N = 122; 37.8%)		Mali (N = 4; 1.2%)		Mozambique (N = 42; 13.0%)		TOTAL (N = 323)		
	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	p value
	(N = 126; 81.3%)	(N = 29; 18.7%)	(N = 96; 78.7%)	(N = 26; 21.3%)	(N = 4; 100%)	(N = 0; 0%)	(N = 36; 85.7%)	(N = 6; 14.3%)	(N = 262; 81.1%)	(N = 61; 18.9%)	
Median (IQR) age in months	24 (13, 36)	14 (7, 18)	16 (8, 31)	15 (7, 23)	41 (27, 49)		27 (15, 42)	19 (18, 23)	22 (11, 36)	16 (8, 21)	0.003
Age group (%)											0.045
Young infant (1 month to <6 months)	8 (6.3)	7 (24.1)	13 (13.5)	4 (15.4)	0 (0)	–	1 (2.8)	0 (0)	22 (8.4)	11 (18.0)	
Older infant/child (≥6 months to <60 months)	118 (93.7)	22 (75.9)	83 (86.5)	22 (84.6)	4 (100.0)	–	35 (97.2)	6 (100.0)	240 (91.6)	50 (82.0)	
Sex of the deceased (%)											0.738
Male	67 (53.2)	16 (55.2)	53 (55.2)	12 (46.2)	2 (50.0)	–	20 (55.6)	3 (50.0)	142 (54.2)	31 (50.8)	
Female	59 (46.8)	13 (44.8)	43 (44.8)	14 (53.8)	2 (50.0)	–	16 (44.4)	3 (50.0)	120 (45.8)	30 (49.2)	
Hours from death to MITS procedure (%)											0.488
≤24 hours	126 (100.0)	29 (100.0)	76 (79.2)	18 (69.2)	4 (100.0)	–	32 (88.9)	6 (100.0)	238 (90.8)	53 (86.9)	
> 24 hours	0 (0)	0 (0)	20 (20.8)	8 (30.8)	0 (0)	–	4 (11.1)	0 (0.0)	24 (9.2)	8 (13.1)	
Median (IQR) time in hours	6 [3,12]	13 [3,15]	18 [10,23]	19 [9,25]	16 (13, 17)	–	10 (3, 19)	4 (3, 6)	10 (4, 18)	13 (6, 19)	0.169
Location of death (%)											0.392
Facility	112 (88.9)	27 (93.1)	44 (45.8)	9 (34.6)	3 (75.0)	–	34 (94.4)	5 (83.3)	193 (73.7)	41 (67.2)	
Community	14 (11.1)	2 (6.9)	52 (54.2)	17 (65.4)	1 (25.0)	–	2 (5.6)	1 (16.7)	69 (26.3)	20 (32.8)	
Median (IQR) of hours in hospitalization (N = 224)	14 (5, 27)	40 (12, 88)	17 (9, 47)	11 (4, 48)	6 (3, 10)	–	23 (7, 50)	45 (24, 48)	16 (6, 32)	32 [11,77]	0.007
Time of Hospital Death (%) (N = 224)											0.013
< 24 hours	78 (72.9)	11 (40.7)	25 (58.1)	6 (66.7)	2 (100.0)	–	16 (51.6)	1 (20.0)	121 (66.1)	18 (43.9)	
≥24 hours	29 (27.1)	16 (59.3)	18 (41.9)	3 (33.3)	0 (0)	–	15 (48.4)	4 (80.0)	62 (33.9)	23 (56.1)	
Medically attended (%)											0.296
Yes	110 (87.3)	27 (93.1)	62 (64.6)	19 (73.1)	2 (50.0)	–	31 (86.1)	6 (100.0)	205 (78.2)	52 (85.2)	
No	16 (12.7)	2 (6.9)	34 (35.4)	7 (26.9)	2 (50.0)	–	5 (13.9)	0 (0.0)	57 (21.8)	9 (14.8)	
Pre-mortem malaria diagnosis (%)											
Maternal malaria	0 (0)	0 (0)	1 (1.0)	1 (3.8)	0 (0)	–	0 (0)	0 (0)	1 (0.4)	1 (1.6)	
RDT	61 (48.4)	7 (24.1)	6 (6.2)	1 (3.8)	1 (25.0)	–	23 (67.6)	2 (33.3)	91 (35.0)	10 (16.4)	0.008
Blood smear	23 (18.3)	2 (6.9)	22 (22.9)	1 (3.8)	0 (0)	–	21 (61.8)	1 (16.7)	66 (25.4)	4 (6.6)	0.002
Postmortem malaria testing (%)											
Taqman array	106 (84.1)	26 (89.7)	82 (85.4)	16 (61.5)	4 (100.0)	–	32 (88.9)	5 (83.3)	224 (85.5)	47 (77.0)	0.155
RDT	93 (73.8)	5 (17.2)	66 (68.8)	14 (53.8)	2 (50.0)	–	17 (47.2)	2 (33.3)	178 (67.9)	21 (34.4)	<0.001
Blood smear	46 (36.5)	1 (3.4)	25 (26.0)	1 (3.8)	3 (75.0)	–	14 (38.9)	0 (0.0)	88 (33.6)	2 (3.3)	<0.001
Histopathology acute infection	73 (57.9)	4 (13.8)	0 (0)	0 (0)	0 (0)	–	2 (5.6)	0 (0.0)	75 (28.6)	4 (6.6)	<0.001
Histopathology past/chronic infection	3 (2.4)	1 (3.4)	8 (8.3)	2 (7.7)	0 (0)	–	4 (11.1)	0 (0.0)	15 (5.7)	3 (4.9)	1
Immunohistochemistry	27 (21.4)	1 (3.4)	47 (49.0)	4 (15.4)	2 (50.0)	–	11 (30.6)	1 (16.7)	87 (33.2)	6 (9.8)	<0.001
Strength of evidence for Malaria diagnosis (%)											–
Median (IQR)	1 (1, 1)	–	1 (1, 1)	–	1 (1, 1.25)	–	1 (1, 1)	–	1 (1, 1)	–	
1	114 (90.5)	–	94 (97.9)	–	3 (75.0)	–	35 (97.2)	–	246 (93.9)	–	
2	9 (7.1)	–	1 (1.0)	–	1 (25.0)	–	1 (2.8)	–	11 (4.2)	–	
3	3 (2.4)	–	1 (1.0)	–	0 (0)	–	0 (0)	–	5 (1.9)	–	
HIV status (%)											0.399
HIV unexposed or unknown	121 (96.0)	29 (100.0)	70 (72.9)	20 (76.9)	4 (100.0)	–	23 (63.9)	4 (66.7)	218 (83.2)	53 (86.9)	
HIV exposed but uninfected	1 (0.8)	0 (0.0)	15 (15.6)	3 (11.5)	0 (0)	–	11 (30.6)	0 (0.0)	27 (10.3)	3 (4.9)	
HIV infected	4 (3.2)	0 (0.0)	11 (11.5)	3 (11.5)	0 (0)	–	2 (5.6)	2 (33.3)	17 (6.5)	5 (8.2)	

(*continued on next page*)

Table 3 (*continued*)

Variables	Sierra Leone (N = 155; 48.0%)		Kenya (N = 122; 37.8%)		Mali (N = 4; 1.2%)		Mozambique (N = 42; 13.0%)		TOTAL (N = 323)		
	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	Malaria in causal chain	Malaria not in causal chain	p value
	(N = 126; 81.3%)	(N = 29; 18.7%)	(N = 96; 78.7%)	(N = 26; 21.3%)	(N = 4; 100%)	(N = 0; 0%)	(N = 36; 85.7%)	(N = 6; 14.3%)	(N = 262; 81.1%)	(N = 61; 18.9%)	
Low birth weight (%) (N = 78)	2 (10.0)	0 (0.0)	6 (15.8)	0 (0.0)	0 (0)	–	0 (0)	0 (0)	8 (13.3)	0 (0.0)	0.233
Severe underweight (WAZ < −3 SD) (%) (N = 321)	27 (21.6)	15 (51.7)	43 (44.8)	12 (48.0)	0 (0)	–	10 (27.8)	5 (83.3)	80 (30.7)	32 (53.3)	0.002
Severe stunting (HAZ < −3 SD) (%) (N = 322)	12 (9.6)	5 (17.2)	24 (25.0)	5 (19.2)	0 (0)	–	12 (33.3)	4 (66.7)	48 (18.4)	14 (23.0)	0.527
Severe wasting (WHZ < −3 SD) (%) (N = 317)	29 (23.2)	14 (50.0)	38 (40.4)	10 (40.0)	0 (0)	–	8 (22.9)	3 (50.0)	75 (29.1)	27 (45.8)	0.02

Table 4
Comparison of co-infections for post-neonatal CHAMPS deaths with and without malaria in the chain of events leading to death—Sierra leone, Kenya, Mali and Mozambique.

Variables	Malaria (N = 262; 30.5%)	No malaria (N = 596; 69.5%)	p value
Malaria parasite (%)			
Plasmodium falciparum	262 (100.0)	0 (0)	
Co-infections in causal chain (%)			
No other infection	183 (69.8)	213 (35.7)	< 0.001
Any Bacteria	63 (24.0)	324 (54.4)	< 0.001
Gram positive bacteria	28 (10.7)	168 (28.2)	< 0.001
Enterococcus faecalis	2 (0.8)	9 (1.5)	
Enterococcus faecium	1 (0.4)	15 (2.5)	
Mycobacterium tuberculosis	3 (1.1)	2 (0.3)	
Staphylococcus aureus	1 (0.4)	17 (2.9)	
Streptococcus pneumoniae	14 (5.3)	107 (18.0)	
Streptococcus pyogenes	1 (0.4)	5 (0.8)	
Streptococcus spp.	8 (3.1)	22 (3.7)	
Other gram positive bacteria[a]	0 (0)	6 (1.0)	
Gram negative bacteria	46 (17.6)	252 (42.3)	< 0.001
Acinetobacter baumannii	3 (1.1)	12 (2.0)	
Campylobacter jejuni	0 (0)	6 (1.0)	
Escherichia coli	7 (2.7)	57 (9.6)	
Escherichia coli/Shigella spp.	1 (0.4)	8 (1.3)	
Haemophilus influenzae non-typable	6 (2.3)	35 (5.9)	
Haemophilus influenzae Type A	1 (0.4)	17 (2.9)	
Klebsiella pneumoniae	26 (9.9)	145 (24.3)	
Klebsiella spp.	1 (0.4)	4 (0.7)	
Moraxella catarrhalis	3 (1.1)	9 (1.5)	
Pseudomonas aeruginosa	2 (0.8)	19 (3.2)	
Salmonella spp.	2 (0.8)	28 (4.7)	
Other gram negative bacteria[b]	1 (0.4)	23 (4.3)	
Viruses	32 (12.2)	167 (28.0)	< 0.001
Adenovirus	6 (2.3)	28 (4.7)	
Cytomegalovirus (CMV)	7 (2.7)	45 (7.6)	
Human Immunodeficiency Virus	19 (7.3)	65 (10.9)	
Human metapneumovirus (HMPV)	0 (0)	5 (0.8)	
Influenza A	0 (0)	8 (1.3)	
Influenza B	0 (0)	5 (0.8)	
Respiratory syncytial virus (RSV)	0 (0)	14 (2.3)	
Rotavirus A	0 (0)	11 (1.8)	
Rotavirus non-typable	0 (0)	7 (1.2)	
Other viruses[c]	5 (1.9)	24 (4.0)	
Fungi	1 (0.4)	27 (4.5)	< 0.001
Pneumocystis jirovecii	1 (0.4)	14 (2.3)	
Candida albicans	0 (0)	10 (1.7)	
Other fungi[d]	0 (0)	4 (0.7)	
Other parasites[e]	0 (0)	4 (0.7)	0.319

[a] Other gram positive bacteria included: *Enterococcus spp* . (n = 1), *Staphylococcus epidermidis* (n = 1), *Staphylococcus haemolyticus* (n = 1), and *Streptococcus agalactiae* (n = 3).

[b] Other gram negative bacteria included: *Aeromonas spp*. (n = 2), *Bordetella pertussis* (n = 4), *Bordetella spp*. (n = 2), *Brucella spp*. (n = 1), *Citrobacter freundii* (n = 1), *Enterobacter cloacae* (n = 3), *Haemophilus influenzae* Type B (n = 3), *Haemophilus parainfluenzae* (n = 2), *Haemophilus spp*. (n = 2), *Klebsiella ornithinolytica* (n = 1), *Klebsiella oxytoca* (n = 1), *Proteus mirabilis* (n = 1), *Serratia marcescens* (n = 1), *Serratia odorifera* (n = 1), *Serratia spp*. (n = 1), *Shigella spp*. (n = 3), *Treponema pallidum* (n = 2), and *Vibrio cholerae* (n = 2).

[c] Other viruses included: astrovirus (n = 2), enterovirus (n = 3), Lassa Fever virus (n = 1), measles (n = 2), norovirus non-typable (n = 1), norovirus GI (n = 2), norovirus GII (n = 1), Parainfluenza virus type 1 (n = 4), Parainfluenza virus type 2 (n = 1), Parainfluenza virus type 3 (n = 2), Parainfluenza virus type 4 (n = 3), Parvovirus B19 (n = 1), rhinovirus (n = 2), sapovirus V (n = 1), and SARS-CoV-2 (n = 1).

[d] Other fungi included: Aspergillus (n = 1) and Candida spp. (n = 3).

[e] Other parasites included: *Ascaris lumbricoides* (n = 1), *Cryptosporidium parvum* (n = 2), and *Toxoplasma gondii* (n = 1).

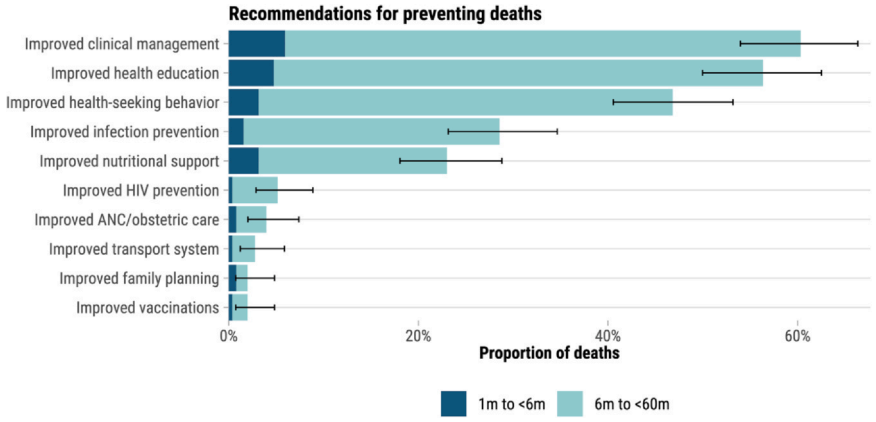


Fig. 2. Opportunities for intervention identified by Expert DeCoDe panelists which could have prevented some of the malaria deaths, according to age group.

deaths were available for 97.7% (252/258) of preventable deaths. Most common recommendations included improved clinical management and quality of care (60.3%, 152/252), improved health education (56.3%, 142/252), and improved health-seeking behavior (46.8%, 118/252) (Fig. 2).

Malaria-specific mortality rates

Adjusted mortality rates for malaria for children < 5 years in the malaria-endemic CHAMPS sites ranged from 0.8/1000 (Bamako, Mali) to 67/1000 (Siaya, Kenya) live births (Fig. 3). This corresponds to mortality fractions (CSMF) peaking at 33% when considering malaria as a cause anywhere in the causal chain. Siaya and Manyatta (Kenya) had the highest malaria mortality rates, followed by Makeni (Sierra Leone) and Quelimane (Mozambique).

Correlation between verbal autopsy and MITS results for malaria diagnosis

Supplementary Fig. 3 presents the comparison between VA derived (both using the interVA and inSilico analytical approaches) and MITS for malaria in terms of cause-specific mortality fractions, according to sites. Variability existed between VA methods and MITS, with minor discrepancies in some countries (Mozambique) and significant differences in others (Sierra Leone, Kenya).

The inSilico method for VA analysis had a sensitivity of 29·0% (95% CI: 23.6%-34.9%) (76/262) and a specificity of 86.6% (95% CI: 83.6%-89.2%) (516/596) in detecting malaria as a cause of death, as defined by MITS, whereas the InterVA approach yielded values of 18.4% (95% CI: 13.9%-23.6%) (48/262) and 95.1% (95% CI: 93.1%-96.7%) (567/596), respectively. The positive and negative predictive values for inSilico were 48.7% (95% CI: 40.6%-56.8%) and 73.5% (95% CI: 70.1%-76.7%), and for interVA were 62.3% (95% CI: 50.6%-73.1%) and 72.8% (95% CI: 69.4%-76.1%).

Discussion

This analysis of malaria-associated mortality among children under the age of five years in CHAMPS sites, using robust diagnostic methods, reinforces malaria's significant impact on child mortality in endemic countries, despite ongoing efforts in malaria prevention and control. Malaria emerged as a leading cause of death among children across CHAMPS sites, ranging from 6.7% in Mali to 42.9% in Sierra Leone. These estimates are derived after excluding malaria infections that were not considered to have played a significant role in the fatal event, constituting 50% of cases. Consistent with previous studies utilizing verbal autopsies, most malaria-attributable deaths occurred in older infants and children aged 1-4 years. Notably, there were no malaria deaths documented in neonates, and minimal deaths among infants < 6 months of age.[35] Malarial-attributed anemia contributed to 37% of all malaria deaths.

Minimally invasive tissue sampling (MITS) is a robust methodology offering valuable insights into individual CoD and presents a unique opportunity for obtaining specific CoD information. In our study, we used MITS to differentiate fatal malaria from non-lethal parasitemia without a pathophysiological link to mortality, as well as from chronic or past infections. Tissue histopathology examination emerged as a particularly effective method for this purpose, allowing differentiation between deaths attributable to malaria and non-fatal malaria infections. Molecular methods, histopathology (including immunohistochemistry), and malaria RDTs proved highly sensitive in detecting malaria infections. Conversely, conventional diagnostic methods like malaria microscopy were less effective in identifying these infections.

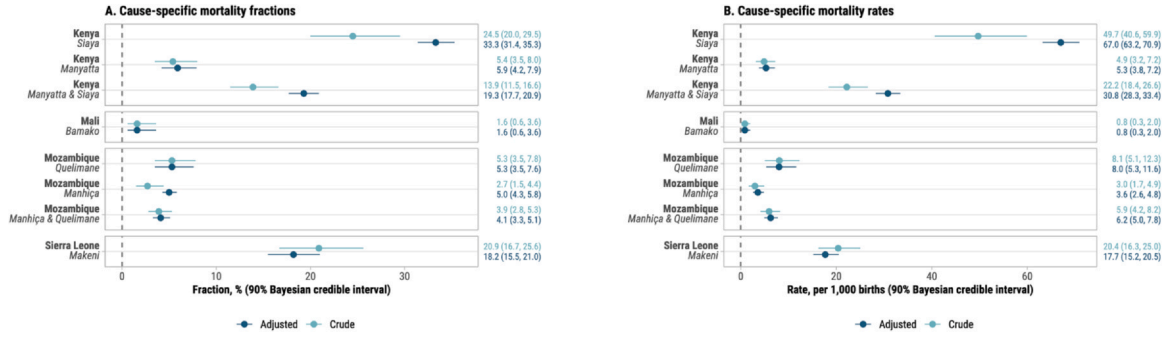


Fig. 3. Crude and adjusted total under-five mortality fractions, rates and 90% Bayesian credible intervals due to malaria at all sites and catchments within the CHAMPS Network.

MITS-based determined CoD in children are more credible and granular than CoD data derived from other methods, such as the VA and pre-mortem clinical data, currently still the main source of data feeding models used to produce global child mortality estimates. However, MITS-based mortality surveillance is an expensive and logistically complex methodology, something that necessarily hinders its widespread use and implementation. Robust data, as presented here, however, are of significant interest to modelers, and can be used to calibrate existing methods such as the VA,[36] and to correct VA misclassification bias in cause-specific mortality estimates.[37] This correction makes local estimates more extrapolatable to the regional and national level, thus contributing to overall burden of disease estimates.

Microbiology and pathology examination of MITS specimens, combined with a review of clinical findings, provides valuable insights into coexisting diseases, especially concomitant infections. Our analysis reaffirmed the significant role of severe bacterial infections in the chain of events leading to death in children with severe malaria. Approximately one-quarter of malaria-attributed deaths demonstrated the presence of bacteria in the blood via culture or molecular methods. These findings bolster the need for empirical antimicrobial inclusion in severe malaria management, as recommended in the 2014 WHO severe malaria treatment guidelines, despite inadequate implementation.[38] Our study revealed that only 168/262 (64.1%) of cases had received antimicrobials before death, indicating that one-third of malaria deaths were managed inadequately. The most identified bacterial pathogens were *Klebsiella pneumoniae*, *Streptococcus pneumoniae,* and *Escherichia coli*. Additionally, viral infections were detected in 12.2% of malaria deaths. CHAMPS investigations unveiled clear evidence of multiple infections at the time of death; however, our findings do not definitively establish whether malaria infections predisposed children to severe bacterial or viral infections, whether these infections increased the risk of progressing to severe malaria, or whether simply the highly sensitive molecular methods detected contaminant DNA. It is noteworthy that underweight and wasting were less prevalent among malaria-attributed deaths compared to deaths from other causes in this age group, suggesting that the immune dysfunction associated with malnutrition may have a lesser impact on malaria compared to other types of infections.

The majority of malaria deaths, except three cases, were considered preventable via interventions such as the optimized antimalarial use, antimicrobial incorporation, or preventive measures like insecticide-treated nets. Over one-third of malaria deaths had not received any antimalarial prior to death. Malaria deaths recruited from the community were less likely to have received medical attention than non-malaria deaths. Even among children who died within a healthcare facility, the time between admission and death was relatively short (median of 14 hours), indicating that children who died from malaria had already reached an advanced stage of the disease upon hospitalization. Further examination of the appropriateness of premortem malaria testing, antimalarial prescription practices, and the source and quality of these tests and treatments (clinic vs. pharmacy or market) is warranted. This analysis did not assess the potential relevance of antimalarial drug resistance or genetic deletions like HRP2 to malaria mortality. Ongoing investigations are evaluating malaria parasite sensitivity to artemisinins and other antimalarials, particularly considering the emerging tolerance to artemisinins in certain regions of Eastern Africa.[39,40] Furthermore, exploring the prevalence of genetic deletions among parasites from different cases could shed light on observed adverse outcomes, necessitating further investigation.

Enhancing clinical management, health education, and promoting improved health-seeking behaviors could significantly reduce malaria-related mortality, aligning with DeCoDe panel conclusions and other studies.[41] DeCoDe recommendations might clarify inter-country heterogeneity regarding health-seeking behavior patterns, management obstacles, or concurrent co-morbidities influencing fatal outcomes. Moreover, the recent introduction of the RTS,S/AS01$_E$ malaria vaccine (Mosquirix™), which is currently being implemented, and the most recent approval of the second malaria vaccine R21/Matrix-M,[42] are expected to further decrease malaria deaths.[43]

Representativeness of the site-specific data obtained from the CHAMPS sentinel sites remains a major limitation. Caution is advised when generalizing these results, not only to other malaria-endemic countries but also within the countries hosting CHAMPS sites. Nevertheless, the snapshots provided through this analysis offer valuable insights into understanding the contribution of malaria to mortality, particularly at the local level.

Conclusions

This analysis reinforces the significant impact of malaria on childhood mortality and highlights the exacerbating role of bacterial secondary infections in the progression to death. Fortunately, malaria remains a highly preventable disease, and implementing changes in health-seeking behavior, health education, and proactive management strategies at the community level, combined with the future wide implementation of the newly recommended RTS,S/AS01$_E$ and R21/Matrix-M vaccines, have the potential to significantly reduce malaria-related mortality.

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Role of the funding source

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Authors' contributions

CGW and DMB conceived the project and acquired the grant funds. DMB, QB, IUO, SOS, KLK, SEA, EG, IMM, SM, AS, NAs, designed the protocol and conducted the analysis. DMB, QB and ZJM directed the data management and analysis plan. QB and AMS drafted and revised the manuscript and had final responsibility for the decision to submit for publication. All authors reviewed the draft and approved the decision to submit for publication.

Data availability

CHAMPS follows an open approach to data and human sample sharing. Information on CHAMPS data availability can be found at https://champshealth.org.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclaimer

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CHAMPS dataverse

Child Health and Mortality Prevention Surveillance, 2022, "CHAMPS Custom Limited Dataset, v1.0", https://doi.org/10.15139/S3/PBEJDU, UNC Dataverse.

Appendix

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.01.006.

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