

Estimating cases of severe malaria at the population-level: Analysis of household surveys from 19 malaria endemic countries in Africa

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Abstract

Background

The burden of severe malaria is uncertain at the population level because existing estimates rely exclusively on data from the formal healthcare system. Using data from population-based surveys this analysis examines severe malaria cases at the population level, which captures children whose caregivers 1) have taken the child to a healthcare facility but the child's illness did not resolve, or 2) have not sought care for the child's illness. Direct inclusion of these children in severe malaria estimates has been an underlying data gap.

Methods

This analysis examined data from 37 Demographic and Health Surveys and Malaria Indicator Surveys across 19 countries in sub-Saharan Africa collected between 2011 and 2018. The outcome of interest is severe malaria, defined as children age 6–59 months who were positive for malaria with at least one self-reported symptom for severe malaria, including loss of consciousness, rapid breathing, seizures, or severe anemia. The study includes a weighted descriptive, country-level analysis and a multilevel mixed-effects logistic regression model to assess the determinants of severe malaria.

Results

Among children positive for malaria across all surveys, 4.5% (95% CI 4.1–4.8) had at least one symptom of severe malaria, which was significantly associated with age, residence, wealth, and survey timing at a p-value less than 0.05. Children in the higher malaria transmission zone were more likely to have symptoms compared to those in the lowest transmission zone; however, these results were not statistically significant.

Conclusion

An accurate estimate of the burden of severe malaria is essential to assessing the impact of malaria interventions and to guiding future malaria investments. This analysis presents a novel approach of estimating the burden of severe malaria in children under age five in malaria endemic countries. Estimating severe malaria through household-based surveys allows countries to estimate severe malaria across time and to compare with other countries. Having a population level estimate of severe malaria helps further our understanding of the burden and epidemiology of severe malaria.

Background

In 2018, an estimated 405,000 deaths from malaria occurred globally, with an estimated 70% of all malaria deaths occurring in children under age 5 in sub-Saharan Africa (SSA) [1]. Malaria typically begins as an acute febrile illness. If not appropriately treated, *Plasmodium falciparum* (*P. falciparum*) malaria can progress to severe illness, and can often lead to death. Children with severe malaria frequently develop one or more of the following complications: severe anemia, respiratory distress, or cerebral malaria [2, 3]. The clinical manifestations of these severe malaria complications in children include impaired consciousness, respiratory distress (acidotic breathing), multiple convulsions, prostrations, shock, and jaundice [2, 4]. The clinical epidemiology of severe malaria can also present differently according to age and transmission intensity. Studies have shown that as the intensity of malaria transmission increases, the mean age of severe malaria decreases [5–8]. In high transmission areas, the risk for severe malaria is greatest among young children (the first few months of life to age 5). Severe malaria becomes less common in older children when acquired immunity provides a protective effect. Conversely, in low transmission areas, severe malaria is more common in older children and adults [7].

Although the clinical features and transmission patterns of severe malaria are well understood, accurately capturing the burden of severe malaria remains a challenge. First, severe malaria symptoms are non-specific, which makes it difficult to differentiate severe malaria cases from other diseases that are also common in malaria-endemic countries [2]. Second, severe malaria case estimates from routine data collected through formal healthcare services are often affected by variable data quality and non-standard case definitions, which make comparisons across countries challenging [9–11]. Finally, a proportion of severe malaria illnesses and deaths occur outside the formal healthcare system and are therefore undocumented [7, 9, 12–14].

An accurate estimate of the burden of severe malaria is essential to assess the impact of malaria prevention and control interventions and to guide future malaria investments. To date, the only robust estimates of severe malaria cases include children who present to the formal healthcare system or data from small epidemiological studies across SSA. It has been a challenge to use these data to model the number of severe malaria cases across SSA because of varying age ranges of reporting, different diagnosis techniques, surveillance methods, and health care utilization [5, 8]. The Demographic and Health Surveys (DHS) Program, the primary global source of population-based malaria data, tests children for malaria and also measures hemoglobin concentration to test for anemia. For children who test positive for malaria, The DHS Program collects data on severe malaria symptoms for referral purposes during data collection. However, this information has not been used to examine signs and symptoms of severe malaria. To better understand the burden of severe malaria in SSA, this paper presents an analysis of severe malaria symptoms in children age 6–59 months who are positive for *P. falciparum* malaria, and whose data are captured in population-based surveys.

Methods

Data on severe malaria

This study used data from DHS and Malaria Indicator Surveys (MIS), which are both nationally representative, population-based household surveys of The DHS Program [15]. All surveys are independent but use standardized data collection procedures and tools. When requested by the country, the DHS and MIS collect blood samples for anemia and malaria testing among children age 6–59 months. All children are tested regardless of whether they have signs or symptoms of malaria. Specially trained biomarker health technicians (who are usually nurses) take capillary blood obtained with a finger or heel prick. The blood is immediately tested for anemia and malaria in the field and the results are provided to respondents' parents or guardians within a few minutes.

In the field, biomarker health technicians use rapid diagnostic tests (RDT) to determine if children have malaria. The RDTs detect the histidine-rich protein II (HRP-II) antigen of *P. falciparum* in blood. *P. falciparum* is the primary cause of severe malaria and is the predominant species found in the countries included in this analysis[2, 7]. Often blood is also collected for the examination of blood smears by microscopy in the laboratory. DHS and MIS surveys also typically test children age 6–59 months for anemia with capillary blood collected through a finger or heel prick. The tests use the HemoCue 201 + and, on occasion, the HemoCue 301 point-of-care hemoglobin testing system.

When the DHS and MIS surveys first introduced malaria testing in 2006, biomarker health technicians offered antimalarial treatment to all children with positive RDT results. Beginning in 2011, The DHS Program instituted a referral system in which children who are positive for malaria but have no signs and symptoms of severe illness receive antimalarial treatment, and children with signs and symptoms of severe illness are referred to the nearest health facility for treatment.

At that time, additional questions were added to the survey's questionnaire to screen children for signs and symptoms of severe malaria. To assess severe malaria signs and symptoms, the caregiver is asked: "*Does (NAME) suffer from any of the following illnesses or symptoms: extreme weakness, heart problems, inability to drink or breastfeed, vomiting everything, loss of consciousness, rapid breathing, seizures, bleeding, jaundice, or dark urine?*" If the child is positive for malaria (by RDT) and the caregiver answers "Yes" to any of the signs and symptoms and/or if the child has a hemoglobin concentration of < 8 grams per deciliter (g/dL), the child is given a referral slip for severe malaria to take to the nearest healthcare facility for care[16]. A child who is negative for malaria (by RDT) is not asked about severe malaria symptoms. (See additional file 1 for more information about The DHS Program malaria referral process.)

Data analysis

Case definition of severe malaria

This analysis used a severe malaria case definition based on signs and symptoms captured in DHS and MIS surveys that most closely aligns with the clinical symptoms of malaria outlined in the World Health Organization (WHO) Management of Severe Malaria Handbook [2]. Of the 11 severe malaria signs and symptoms collected by DHS and MIS surveys, loss of consciousness, rapid breathing, seizures, or severe anemia (hemoglobin levels < 5 g/dL adjusted for altitude) were the four most common clinical manifestations of severe malaria in children that most closely align with the symptoms identified in the WHO Management of Severe Malaria Handbook. Hemoglobin levels are adjusted for the altitude in areas that are above 1,000 meters in elevation [17].

Study variables

Outcome variable: severe malaria. The outcome of interest is severe malaria, defined as children age 6–59 months who were positive for malaria with at least one symptomatic marker for severe malaria, including loss of consciousness, rapid breathing, seizures, or severe anemia. The authors calculated the percentage of children age 6–59 months with severe malaria of all children age 6–59 months who were positive for malaria, according to RDT.

Covariates: all potential confounders. For this analysis, variables found in the literature related to severe malaria were reviewed and included based on data availability. The model included the following covariates: sex, age, place of residence, wealth quintiles, malaria endemicity, survey timing, and country (Table 1). The child’s age was divided into four age categories: 6–23 months, 24–35 months, 36–47 months, and 48–59 months. Place of residence is defined as whether a household is located in a rural or urban area. Wealth quintiles were derived from the DHS wealth index, which measures the relative socioeconomic status of households based on household assets and amenities at a point in time [18]. Survey timing is divided into two equal categories based on the fieldwork dates of 2011–2014 and 2015–2018. To determine malaria endemicity, we assigned each child’s household enumeration area into geographical zones based on malaria transmission risk. To link the DHS and MIS geo-coordinates (latitude, longitude) of each survey enumeration area to transmission risk zones, we used geo-coordinated *P. falciparum* parasite prevalence rates among children age 2–10 ($PfPR_{2-10}$) from the Malaria Atlas Project 2015 [19]. We assigned every child’s household in an enumeration area from the DHS or MIS survey dataset to the same malaria transmission risk zone based on corresponding $PfPR_{2-10}$ data for that enumeration area. For the transmission zone categories, we used risk categories as outlined in the WHO Management of Severe Malaria Handbook [2] with low transmission defined as $PfPR_{2-10} \leq 10\%$ and high transmission defined as $PfPR_{2-10} > 50\%$. Due to a high number of children in the moderate risk category ($11\% < PfPR_{2-10} \leq 50\%$), we divided this risk group into two equal risk categories of moderate transmission A ($11\% < PfPR_{2-10} \leq 30\%$) and moderate transmission B ($31\% < PfPR_{2-10} \leq 50\%$).

Table 1
Descriptions of co-variables included in the analysis

Variable	Type	Option	Details of Measurement
Sex	Categorical	Two categories: male, female	Collected from the household questionnaire
Age Group	Categorical	Four categories (months): 6–23, 24–35, 36–47, 48–59	Based on date of birth and date of interview from the household questionnaire
Place of Residence	Categorical	Two categories: urban and rural	Household classified as being in an urban or rural area
Wealth Quintile	Categorical	Five categories: Lowest, Second, Middle, Fourth, Highest	Asset-based principal component analysis
Malaria Endemicity	Categorical	Four categories: low risk, intermediate risk A, intermediate risk B, and high risk	Categorized using Malaria Atlas Project (MAP) $PfPR_{2-10}$ values
Survey Timing	Categorical	Two categories: 2011–2014 and 2015–2018	Based on year of survey fieldwork
Country	Categorical	19 categories representing each of the country included in the study	Based on survey country

Study population

The inclusion criteria for the study were all malaria-endemic countries in SSA that have conducted a DHS or MIS survey in which children were tested for malaria and anemia, and the surveys included questions on signs or symptoms of severe malaria. In total, this analysis examined results from 37 surveys across 19 countries (Fig. 1). The study population for this analysis included children age 6–59 months who stayed in surveyed households the night before the survey and received *P. falciparum* malaria parasite (RDT) and anemia tests. Children with any missing household enumeration area $PfPR_{2-10}$ data were excluded from the analysis.

Regression analysis

The study includes a country-level descriptive analysis weighted for complex survey design and a multi-country weighted pooled analysis, both with 95% confidence intervals. The study used a multilevel (individual-level and country-level) unweighted mixed-effects logistic regression model to assess the determinants of severe malaria. The model includes sex, age of the child, residence, household wealth, malaria transmission zones, and survey timing. All analyses were conducted with StataSE16 (StataCorp LP, College Station, USA).

Results

Descriptive Analysis

Country-level analysis

A total of 183,265 children who met the inclusion criteria were included in the study of the 209,216 children age 6-59 months eligible for malaria and anemia testing. The overall prevalence of malaria infection in children age 6-59 months, as detected with RDTs, across all surveys was 26.0%, ranging from 0.6% (Senegal DHS 2015) to 61.4% (Burkina Faso MIS 2014). Among children positive for malaria across all surveys, 4.5% (95% CI 4.1–4.8) of children had at least one severe malaria symptom (loss of consciousness, seizures, rapid breathing, or severe anemia), ranging from <0.1% in the Senegal DHS 2015 to 17.4% in the Madagascar MIS 2011. The prevalence of individual symptoms varies by country. Mali DHS 2018 (2.3%) had the highest percentage of children with loss of consciousness, Guinea DHS 2012 (9.3%) the highest percentage of children with seizures, Madagascar MIS 2011 (14.2%) the highest percentage of children with rapid breathing, and Senegal DHS 2016 (3.2%) the highest percentage of children with severe anemia (Table 2).

Table 2

Percentage of children age 6–59 months with a malaria infection according to RDT, and among those with a malaria infection, the percentage with specified severe malaria symptoms, and the percentage with at least one severe malaria symptom, according to country and survey

Among children with a malaria infection										
Percentage with specified severe malaria symptoms										
	Percentage of children with a malaria infection		Number of children tested for malaria	Loss of consciousness	Seizures	Rapid breathing	Severe anemia (Hemoglobin < 5 grams per deciliter)	Percentage with at least one severe malaria symptom		Number of children with malaria infection
Country/Survey	%	95% CI		%	%	%	%	%	95% CI	
Angola DHS 2015-16	13.6	(11.8–15.6)	6,552	1	0.8	8.8	2.6	11.6	(7.5–17.3)	891
Benin DHS 2017-18	36.5	(34.1–38.9)	6,035	0.2	0.5	1.1	0.4	2.1	(1.5–3.0)	2,200
Burkina Faso MIS 2014	61.4	(58.5–64.2)	5,743	0.5	0.7	1.7	1.1	3.6	(2.9–4.5)	3,524
Burkina Faso MIS 2017	20.1	(17.8–22.5)	5,042	0.5	1.7	1.9	0.8	3.6	(2.4–5.3)	1,012
Burundi MIS 2012	22.2	(18.1–27.0)	3,774	2.0	2.8	9.0	1.6	10.2	(7.7–13.4)	838
Burundi DHS 2016–2017	38.7	(36.2–41.3)	5,639	0.6	1	3.3	1.1	4.3	(3.4–5.4)	2,184
DRC DHS 2013-14	31.0	(28.0–34.3)	7,329	0.9	2.2	5.0	0.8	7.3	(5.7–9.3)	2,276
Ghana DHS 2014	36.3	(32.7–40.0)	2,495	< 0.1	0.3	0.7	0.3	1.0	(0.6–1.9)	905
Ghana MIS 2016	28.1	(23.7–33.0)	2,624	< 0.1	0.4	0.5	1.0	1.7	(0.9–3.3)	739
Guinea DHS 2012	48.0	(44.1–51.9)	3,144	0.5	9.3	5.7	1.1	15.6	(11.7–20.6)	1,510
Kenya MIS 2015	9.9	(7.7–12.7)	2,790	< 0.1	< 0.1	0.3	< 0.1	0.3	(0.1–1.8)	277
Liberia MIS 2011	45.3	(41.6–49.1)	2,835	0.3	0.7	0.7	0.2	1.7	(1.0–3.0)	1,285
Liberia MIS 2016	45.3	(41.3–49.4)	2,822	0.1	1	1.9	0.5	2.9	(1.9–4.4)	1,278
Madagascar MIS 2011	8.8	(6.9–11.1)	6,188	1.0	3.7	14.2	< 0.1	17.4	(11.7–25.2)	542
Madagascar MIS 2013	10.1	(8.0–12.8)	5,490	1.8	4.8	5.3	0.4	9.2	(6.0–13.7)	557
Madagascar MIS 2016	5.2	(3.6–7.5)	6,480	< 0.1	0.1	2.1	0.4	2.5	(0.9–6.8)	337
Malawi MIS 2012	43.4	(37.7–49.2)	2,182	1.4	0.7	5.1	1.1	6.9	(4.6–10.3)	946
Malawi MIS 2014	37.1	(30.1–44.6)	1,991	0.1	< 0.1	1.2	0.2	1.4	(0.6–3.1)	738
Malawi MIS 2017	36.1	(31.3–41.2)	2,468	0.2	0.2	2.2	0.4	2.8	(1.6–4.7)	892
CI: confidence interval, DHS: Demographic and Health Survey, MIS: Malaria Indicator Survey, AIS: AIDS Indicator Survey										

Among children with a malaria infection										
Percentage with specified severe malaria symptoms										
Mali MIS 2015	32.4	(27.9–37.2)	7,080	0.3	1.3	3.8	2.5	6.6	(5.1–8.5)	2293
Mali DHS 2018	19.1	(16.6–21.9)	4,366	2.3	4.8	7.6	1.9	12.8	(9.4–17.1)	835
Mozambique AIS/MIS 2015	40.4	(36.5–44.4)	4,515	< 0.1	< 0.1	1.9	1.8	3.3	(2.1–5.2)	1,824
Mozambique MIS 2018	39.1	(34.5–44.0)	4,389	1.0	0.8	6.0	1.4	7.6	(5.4–10.7)	1,718
Nigeria MIS 2015	44.6	(40.9–48.4)	5,859	< 0.1	0.2	0.9	0.5	1.7	(1.2–2.4)	2,615
Nigeria DHS 2018-19	36.6	(34.7–38.4)	11,043	0.1	0.2	0.6	0.6	1.2	(0.8–1.6)	4,038
Senegal DHS 2012-13	3.4	(2.5–4.6)	5,155	< 0.1	< 0.1	0.5	< 0.1	2.6	(1.3–5.2)	174
Senegal DHS 2014	1.1	(0.7–1.9)	5,351	< 0.1	< 0.1	< 0.1	0.8	0.8	(0.1–4.8)	61
Senegal DHS 2015	0.6	(0.4–0.9)	5,348	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	(0.0–0.0)	31
Senegal DHS 2016	0.9	(0.7–1.2)	5,198	< 0.1	< 0.1	< 0.1	3.2	3.2	(1.0–9.9)	46
Sierra Leone MIS 2016	54.2	(51.0–57.4)	6,440	0.1	0.1	1.0	0.7	1.7	(1.3–2.3)	3491
Tanzania AIS/MIS 2011-12	9.1	(7.8–10.6)	7,129	0.9	1.2	1.7	1.6	4.5	(3.1–6.5)	649
Tanzania DHS 2015-16	14.6	(12.6–16.8)	8,546	0.5	0.7	2.1	0.9	3.4	(2.4–5.0)	1245
Tanzania MIS 2017	7.0	(5.8–8.6)	6,433	< 0.1	< 0.1	0.2	0.7	0.9	(0.4–2.1)	453
Togo DHS 2013-14	38.5	(35.1–42.0)	2,942	1.4	0.8	3.4	0.1	4.8	(3.4–6.8)	1,132
Togo MIS 2017	43.9	(39.8–48.1)	2,958	0.2	0.4	0.8	0.6	1.7	(1.1–2.5)	1,299
Uganda MIS 2014-15	32.2	(28.2–36.4)	4,347	0.2	0.5	1.6	0.3	2.3	(1.4–3.6)	1,398
Uganda DHS 2016	31.1	(28.6–33.8)	4,543	0.2	3.4	5.7	0.5	6.9	(5.2–9.1)	1,414
Total	26.0	(25.3–26.7)	183,265	0.5	1.2	2.8	0.9	4.5	(4.1–4.8)	47,647
CI: confidence interval, DHS: Demographic and Health Survey, MIS: Malaria Indicator Survey, AIS: AIDS Indicator Survey										

Multi-Country Pooled Analysis

An examination of the distribution of children with at least one severe malaria symptom by background characteristics revealed nearly identical proportions by sex (50.3% of males and 49.7% of females). The proportion of children with at least one severe malaria symptom decreased with age, ranging from 31.5% of children age 6-23 months (95% CI 29.0–34.1) to 19.9% of children age 48-59 months (95% CI 17.9–22.0). The majority of children symptomatic for severe malaria lived in rural areas (86.8%, 95% CI 84.1–89.2). In addition, a greater proportion of children from households in the lowest wealth quintile (34.3%, 95% CI 31.3–37.3) and in the moderate transmission zone A

(37.2%, 95% CI 33.4–41.2) had at least one symptom of severe malaria compared with those in higher wealth quintiles and other transmission zones. Slightly more than half (53.9%, 95% CI 49.8–57.9) of children with at least one severe malaria symptom were surveyed between 2015 and 2018 (Table 3).

Table 3
Percent distribution of children who had at least one severe malaria symptom among children who were positive for malaria, pooled weighted analysis

Background characteristics	Percent Distribution	95% Confidence Intervals	Number of children with a malaria infection
Child			
<i>Sex</i>			
Male	50.3	(47.7–52.9)	24,294
Female	49.7	(47.1–52.3)	23,353
<i>Age Group (months)</i>			
6–23	31.5	(29.0–34.1)	12,262
24–35	25.6	(23.5–27.8)	10,669
36–47	23.0	(21.1–25.1)	12,098
48–59	19.9	(17.9–22.0)	12,619
Household			
<i>Place of Residence</i>			
Rural	86.8	(84.1–89.2)	40,818
Urban	13.2	(10.8–15.9)	6,829
<i>Wealth Quintile</i>			
Lowest	34.3	(31.3–37.3)	15,302
Second	28.5	(26.1–31.0)	13,510
Middle	20.3	(18.2–22.7)	10,254
Fourth	14.3	(12.3–16.6)	6,518
Highest	2.6	(1.8–3.6)	2,063
<i>Malaria Endemicity</i>			
Low transmission < 10%	14.3	(11.9–17.1)	5,507
Moderate transmission A 11%-30%	37.2	(33.4–41.2)	18,531
Moderate transmission B 31%-50%	28.6	(25.0–32.4)	17,760
High transmission > 50%	19.9	(16.5–23.8)	5,849
Survey timing			
2011–2014	46.1	(42.1–50.2)	15,977
2015–2018	53.9	(49.8–57.9)	31,670
Total	100.0		47,647

Regression Analysis

The regression analysis shows the odds of reporting at least one symptomatic marker of severe malaria in relation to the different background characteristics of the children. Compared to children age 6-23 months, children age 36-47 months (AOR 0.73, 95% CI 0.65–0.82) and 48-59 months (AOR 0.58, 95% CI 0.51–0.66) were significantly less likely to report at least one symptomatic marker for severe

malaria. Urban children were significantly more likely to report at least one symptomatic marker for severe malaria as compared to rural children (AOR 1.28, 95% CI 1.12–1.48). Socioeconomic status of the household is associated with the likelihood of reporting a severe malaria symptom, with children in the highest wealth quintile having lower odds compared to those from households in the lowest quintile (AOR 0.56, 95% CI 0.42–0.76). Malaria endemicity defined by different transmission zones was not associated with the likelihood of reporting a symptom of severe malaria. Finally, the children surveyed between 2015-2018 were significantly less likely to report at least one symptomatic marker for severe malaria compared to children surveyed between 2011-2014 (AOR 0.72, 95% CI 0.62–0.83) (Table 4).

Table 4
Multilevel unweighted mixed effects logistic regression model of children who had at least one symptomatic marker for severe malaria among children who were positive for malaria, pooled analysis

Background Characteristic	Adjusted Odd Ratio	95% Confidence Intervals
Child		
<i>Sex</i>		
Male	1 (Reference)	
Female	0.95	0.87 – 1.04
<i>Age Group (months)</i>		
6–23	1 (Reference)	
24–35	0.91	0.81 – 1.02
36–47	0.73***	0.65 – 0.82
48–59	0.58***	0.51 – 0.66
Household		
<i>Place of Residence</i>		
Rural	1 (Reference)	
Urban	1.28***	1.12–1.48
<i>Wealth Quintile</i>		
Lowest	1 (Reference)	
Second	1.01	0.90 – 1.13
Middle	0.91	0.80 – 1.03
Fourth	0.99	0.85 – 1.14
Highest	0.56***	0.42 – 0.76
<i>Malaria Endemicity</i>		
Low Transmission < 10%	1 (Reference)	
Moderate Transmission A 11%-30%	1.01	0.86 – 1.19
Moderate Transmission B 31%-50%	0.99	0.81 – 1.22
High Transmission > 50%	1.06	0.83 – 1.34
Survey timing		
2011–2014	1 (Reference)	
2015–2018	0.72***	0.62 – 0.83
Level of statistical significance *** p < 0.001, ** p < 0.01, * p < 0.05		

Discussion

Despite improvements in the diagnosis and documentation of severe malaria cases, there remains uncertainty about the burden of severe malaria cases at the population level. Here we present a comprehensive estimate of severe malaria cases in children from 19 malaria-endemic countries in SSA. Our estimates are based on data from population-based household surveys that allow severe malaria cases outside of the formal healthcare system to be directly captured in estimates.

The prevalence estimate of severe malaria in this study (4.5% of malaria-infected children) is consistent with other estimates of severe malaria. This acknowledges that other estimates of severe malaria cases account only for children who access the formal healthcare system [1, 12]. Household surveys test all children age 6–59 months for malaria, and while some of the children who were showing signs of severe illness would have eventually accessed the formal healthcare system, some of these children would have died, recovered at home, or received care outside of the formal healthcare system [7, 9, 12–14]. Estimating severe malaria through household surveys provides countries with a standardized estimate of severe malaria that is comparable across time as well with other countries.

Findings from this study confirm previous observations that severe malaria is dependent on age and transmission intensity [5–8]. Younger children were significantly more likely to have severe malaria, and although not significant, the risk of severe malaria was greater in high malaria transmission zones. However, unlike previous research, we did not find an interaction between age and the intensity of malaria transmission in relation to having at least one symptom of severe malaria (data not shown) [5]. One explanation is the limited age range of children (6–59 months) in this analysis. Past studies that have examined the association of variations in age and endemicity on the clinical manifestation of severe malaria included children up to age 10 [5, 6, 8].

Children surveyed between 2015–2018 were significantly less likely to have severe malaria symptoms as compared to children surveyed between 2011–2015. This is controlling for malaria transmission level and is irrespective of variations in malaria prevalence since all children included in the analysis were positive for malaria, according to RDT. This finding aligns with the 2019 World Malaria Report, which reported a decrease in malaria deaths since 2010 [1]. While the role of malaria control interventions in this difference cannot be assumed, since 2015, there has been an increase in the number of malaria interventions in SSA, including the implementation of seasonal malaria chemoprevention and universal coverage of insecticide-treated nets [1]. The impact of these interventions on severe malaria cases needs further exploration.

This analysis also indirectly highlights potential variation in care-seeking patterns for severe malaria cases across SSA. Urban children were significantly more likely to have at least one severe malaria symptom as compared to rural children despite a higher prevalence of severe malaria among the rural population. In addition, the country was highly significant in the model even when controlling for malaria endemicity. By examining severe malaria cases at the household level, this analysis is more likely to include children whose caregivers have taken them to a healthcare facility but whose illness did not resolve or have not sought care for the child's illness. While the decision to seek care is ultimately decided by the caregiver, it is highly influenced by factors such as the availability of government-based facilities, country wealth, cost of care, and education [14, 20–23]. Further exploration is needed into country and urban-rural variations in care-seeking and its association with severe malaria burden estimates.

This study has a several limitations. Children with severe malaria frequently develop one or more complications, including severe anemia, respiratory distress, or cerebral malaria. This analysis examined children who had at least one symptomatic marker for severe malaria. We did not disaggregate this analysis by proxies for respiratory distress or cerebral malaria. Examining severe anemia is possible because this is a discrete diagnosis based on hemoglobin levels. However, to fully disaggregate by respiratory distress or cerebral malaria would require additional questions about symptoms such as prostration and the number and severity of convulsions [2].

The use of household-level data is a noteworthy advantage of this study, but it also introduces a principal limitation. There is a risk of including uncomplicated malaria cases or non-malaria cases in our proxy definition. Malaria positivity is based on RDT-detectable antigens that continue to circulate in the blood after the infection has cleared, and severe malaria symptoms are non-specific [24]. Our definition of severe malaria relies on caregiver self-report rather than a diagnosis by a clinician at a health facility. Although the interviewer for the biomarker questionnaire is a trained biomarker health technician (usually a nurse), which may improve the questionnaire responses, the non-specific nature of severe malaria remains an issue. We have addressed this limitation by narrowing the proxy definition of severe malaria to only examine loss of consciousness, rapid breathing, seizures, or severe anemia (hemoglobin < 5 g/dL adjusted for altitude). These symptoms are more distinct than some other symptoms (extreme weakness and heart problems) caregivers are asked and most closely align with the WHO clinical manifestations of severe malaria. We assumed these symptoms would not be confused by caregivers, even those with a limited education. However, we were unable to examine the reliability of reported signs and symptoms because caregivers were not asked questions on severe malaria symptoms for malaria negative children. In addition, by limiting our definition of severe malaria symptoms, there is the possibility that we may be missing cases.

This analysis only includes children with malaria according to RDT, which further minimizes the possibility that the child is sick with an illness other than severe malaria. However, as noted above, there is still a risk of including non-malaria cases in our proxy definition because malaria positivity is based on RDT-detectable antigen that circulates in the blood after the infection has cleared. More sensitive measures of malaria diagnosis than standard HRP-II RDTs should be explored, such as microscopy, highly sensitive RDTs, or polymerase chain reaction (PCR).

Conclusions

This analysis investigated severe malaria symptoms in children age 6–59 months who are positive for malaria as identified in population-based surveys. To date, there has been a gap in knowledge about the burden of severe malaria at the population level since previous estimates have relied exclusively on data from formal healthcare services. This analysis presents the most comprehensive estimate of the prevalence of severe malaria in children age 6–59 months from 19 countries across multiple malaria endemicity zones. The data in this analysis were initially collected for severe malaria case referral purposes, but also provide invaluable insights into severe malaria cases at the population level.

Abbreviations

DHS Demographic and Health Survey

g/dL grams per deciliter

HRP-II histidine-rich protein II

MIS Malaria Indicator Survey

PCR polymerase chain reaction

P. falciparum *Plasmodium falciparum*

RDT rapid diagnostic test

SSA sub-Saharan Africa

WHO World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets analyzed during the current study are available from The DHS Program web site, www.dhsprogram.com.

Competing interests

Not applicable

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Author's Contributions-

CT, SN, and JL conceived of and designed the study. CT and JU assisted in the collection of study variables. CT performed all data analysis with SN and YY contributing to the interpretation. CT wrote the manuscript with inputs from SN, JL, JU, and YY. All authors read and approved the final manuscript.

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Figures



Figure 1

Map of countries included in the study