Trends in malaria prevalence and health related socioeconomic inequality in rural western Kenya: Results from repeated household malaria cross-sectional surveys from 2006–2013

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Manuscript title: Trends in malaria prevalence and health related socioeconomic inequality in rural western Kenya: Results from repeated household malaria cross-sectional surveys from 2006–2013

Running title: Socioeconomic health inequalities in malaria indicators

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Abstract

Objective: The objective of this analysis was to examine trends in malaria parasite prevalence and related socioeconomic inequalities in malaria indicators from 2006 to 2013 during a period of intensification of malaria control interventions in Siaya County, Western Kenya

Methods: Data were analyzed from eight independent annual cross-sectional surveys From a combined sample of 19,315 individuals selected from 7,253 households. Study setting was a health and demographic surveillance area of western Kenya. Data collected included demographic factors, household assets, fever, medication use, malaria parasitaemia by microscopy insecticide-treated bed net (ITN) use and care-seeking behaviour. Households were classified into five socioeconomic status (SES) and dichotomized into poorest households (poorest 60%) and less poor households (richest 40%).Adjusted prevalence ratios (aPR) were calculated using a multivariate generalized linear model accounted clustering and cox proportional hazard for pooled data assuming constant follow-up time.

Results: Overall, malaria infection prevalence was 36.5% and was significantly higher among poorest individuals compared to the less poor (39.9% versus 33.5%, aPR=1.17; 95%CI=1.11-1.23) but no change in prevalence over time (trend pvalue<0.256). Care-seeking (61.1% versus 62.5%, aPR=0.99; 95%CI=0.95-1.03) and use of any medication were similar among the poorest and less poor. Poorest individuals were less likely to use Artemether-Lumefantrine or quinine for malaria treatment (18.8% versus 22.1%, aPR=0.81, 95%CI=0.72-0.91) while use of ITNs was lower among the poorest individuals compared to less poor (54.8% versus 57.9%; aPR=0.95; 95%CI=0.91-0.99), but the difference was negligible

Conclusions: Despite attainment of equity in ITN use over time, socioeconomic inequalities still existed in the distribution of malaria. This might be due to a lower likelihood of treatment with an effective antimalarial and lower use of ITNs by poorest individuals. Additional strategies are necessary to reduce socioeconomic inequities in prevention and control of malaria in endemic areas in order to achive universal health coverage and SDGs

Key words: Socioeconomic, equity, inequalities, malaria, medication, Kenya

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Article Summary

Strengths and Limitations of the study

- Eight years of repeated annual cross-sectional pooled data provided more power to assess trends in socioeconomic inequalities and equity in malaria indicators over time. Such data have not been published in this setting

- Use of data from repeated cross sectional studies provides opportunity to monitor trends in malaria burden, socioeconomic inequalities and potential equity gaps or gains as malaria control interventions were intensified over time

- The main limitations include; Use of cross-sectional surveys prevented any evaluation of cause-and-effect of SES and policy interventions on malaria indicators over time. The surveys were analyzed as independent and not a cohorts of households

- Only households with children <5 years and a portion of persons ≥5 years were included in the surveys based on protocol-specific objectives due to logistics reasons

- Different sampling procedure was used in one year (2009) and may have resulted in selection bias of participants.

Background

Malaria is a global health problem and World Health Organization (WHO) reported that in 2017 there were 219 million cases and 435 million deaths compared with 239 million cases in 2010 (95% Confidence Intervals CI: 219–285 million) while in 2016, the cases were 217 million (95% CI: 200–259 million)[1]. A recent WHO report revealed there had been a stagnation in progress in reducing burden between 2015 and 2017[1]. Approximately 93% of all malaria deaths in 2017, and 90% of the estimated 445,000 malaria deaths worldwide occurred in the Africa region in 2016[2]. Despite massive distribution of malaria control interventions, a recent study showed that there still exists shortfalls and inequities in burden, coverage and utilizations of interventions [3]. Another study however showed that massive ITN distribution favoured the poorest households in most settings hence increasing equity [4]. In western Kenya, malaria is a major cause of morbidity and mortality with more than 70 percent of the population at risk[5]. In 2015, the prevalence of microscopically-confirmed malaria among children <15 years of age was eight percent nationally and 27% in the lake-endemic region of western Kenya[5]. In Western Kenya, routine and unpublished data had showed that the prevalence of malaria remained fairly stable since 2006 despite intensified control efforts during the study periods.

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Government of Kenya (GoK) and international partners spent approximated USD 810 million on malaria preventions and treatment programmes[6] which included distribution of long-lasting insecticide-treated bed nets (ITNs), indoor residual spraying (IRS) in selected areas, intermittent preventive treatment during pregnancy (IPTp) in malaria-endemic areas, and prompt and effective malaria case management [5 7 8]. Since 2004, Kenya national guidelines provided that first-line treatment for malaria was artemisinin-based combination therapies (ACT) [9-11]. By 2006, Artemether-Lumefantrine (AL), the first-line ACT, started becoming available in the public sector at no cost to patients, and the first free mass net distribution campaign targeting children <5 years and pregnant women was conducted in malaria endemic and epidemic-prone areas [11-13]. The second free mass net distribution campaign, with a goal of universal coverage (i.e., one net per two people per household), was conducted in a phased approach from 2011 to 2012, with households in western Kenya receiving LLINs in 2011[14]. Equitable distribution of health services or interventions is a principle advocated for in most national policies documents to achieve universal health coverage [15]. A recent paper outlined the five Sustainable Development Goals (SDGs) set of targets that relate to the reduction of health inequalities nationally and worldwide [16]. The study listed the SDG targets as poverty reduction, health and wellbeing for all, equitable education, gender equality, and reduction of inequalities within and between countries[16].

However, despite a national policy of free antimalarial medications for children <5 years in the public sector in Kenya and mass distribution of LLINs in Kenya, access and utilization of health services has been previously shown to vary substantially across socioeconomic groups, which undermines achieving health equity[17]. However there are no published data on the trends of socioeconomic inequalities in malaria indices over time in endemic areas on western Kenya.

A key pillar of the Kenya Health Policy 2014–2030 is to improve health indicators through equitable distribution of health services and interventions in line with the Sustainable Development Goal (SDG) to achieve universal access to safe, effective, quality and affordable health care services for all [15]. Health inequality and equity data on malaria indicators are often collected but not analysed from an economic or equity perspective. Yet, such data and analyses are important for monitoring health inequalities and assessing the impact of malaria control interventions at the microeconomic level[18]. Trends in malaria burden and socioeconomic inequalities between the poor and wealthier individuals has not

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been published in endemic western Kenya over time, yet socioeconomic inequalities are known barriers to health utilization and control efforts [18-20]. However lack of longitudinal data has undermined assessing trends in socioeconomic inequalities in malaria indices and potential equity effect of intensified control program on equity at the household over time. The objective of this analysis was to use data from repeated cross sectional surveys to examine the trends in malaria parasite prevalence and related socioeconomic inequalities in malaria indicators from 2006 to 2013 during a period of intensification of malaria control interventions in Siaya County, Western Kenya.

METHODS

Study design and site

Independent annual community-based, cross-sectional surveys were conducted between 2006 and 2013, between the months of April to July within the Kenya Medical Research Institute (KEMRI) and Centers for Disease Control and Prevention (CDC) Health and Demographic Surveillance System (HDSS) in Siaya County in western Kenya. The HDSS has been described in detail elsewhere.[21 22]Briefly, HDSS covers a population of approximately 223,000 people residing in 393 villages located in three of six sub-counties of Siaya County, an area of approximately 700 km^2 along the shores of Lake Victoria. The vast majority of the population are subsistence farmers and fishermen. Health indicators in Siaya County, part of the former Nyanza Province, are poor compared to national standards[23 24]. Nyanza Province had the highest rates of child mortality and an estimated 60% of the population lived below poverty level during the survey period.[25]

Population and sampling strategies

A total of 19,315 individuals in 7,253 households were surveyed between 2006 and 2013.Overall, 33.9% were children aged <5 years, 26.6% were children aged 5-14 years and the remaining 39.5% were 15 years old adults. Sample size in 2006 to 2013 were (2006 n=1,113; 2007 n =1,270; 2008 n=1,830; 2009 n=2,508; 2010 n=5,334; 2011 n=2,129; 2012 n=2,719; 2013 n=2,412 and the mean annual sample was 2414 (Table 2).

For each year from 2006-2013, different sampling strategies were selected for logistical purposes. Systematic sampling technique was used from a sample frame of eligible households and individuals enrolled into HDSS except in 2009 when a cluster sampling was used. Households were selected for participation in the surveys if they had at least a child <5years because many malaria control interventions targeted this age group. In the HDSS,

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each individual, household, compound and village is assigned a unique number. For the years when systematic sampling was used, a list of households and individuals was made ordered by the unique identifiers and by villages which are spread over the entire study area. Once a sample size for the individuals required in each year, the number of households was estimated assuming a household had an average of 5 members. The households were then systematically sampled from the list. The individuals sampled were then classified as <5, 5-14 and 15 years and above. In 2009, villages were randomly sampled as clusters and the number of households divided proportionately between the three study areas. Surveys were conducted in Rarieda, Gem and Alego-Usonga sub-counties in Siaya County except in 2006 when Alego-Usonga sub-county was not included.

Data collection

During the surveys, study participants were interviewed by trained staff using personal digital assistants (PDA) and tablets. Data collected included demographic factors, socioeconomic factors including asset ownership, characteristics and utilities, care-seeking behaviours, history of fever in the 2 weeks before the survey, ITN use and antimalarial medication use both recommended and non-recommended by polices.

During each survey, a blood specimen was obtained from all individuals providing consent in the sampled households using a finger prick and used for measurement of haemoglobin (HemoCue®; Ängelholm, Sweden) and to measure malaria parasitaemia by rapid diagnostic test(RDT) (Carestart™ Malaria HRP-2/pLDH (Pf/PAN) Combo, Somerset, NJ, USA). Individuals with a positive malaria RDT were treated in accordance with the Kenya national malaria treatment guidelines[10 12 26]. Thick and thin blood smears were obtained for malaria species' identification and parasite density.

Data management and analysis

Data coding, recoding, merging and analysis were conducted in Stata 14 (StataCorp, College Station, TX). The eight cross sectional surveys were first analyzed independently and then as pooled data. The key variables were identified for each year and then appended to each other to form a large dataset. Considering that more one person were selected in households, the analysis have considered clustering. Because these were data taken from different independent samples of the populations over time, there were bound to be missing data. In our analysis we conducted complete case analyses by excluding missing values [27]. Trends analysis was conducted using Cochrane trend test[28 29]. A generalized linear model (GLM),

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using a Poisson distribution with a log-link function, was used to estimate adjusted prevalence ratios (aPR) accounting for clustering at the household level for each individual year, to address potential section bias. Although these datasets were obtained from cross sectional studies, the pooled datasets combining all the years were analyzed using cox proportional hazard models assigning the same follow up time for each participant via a robust variance estimator to consider repeated measurements of over time. This is because it have been shown that by imposing a constant follow-up time for all individuals, Cox model can be adopted to estimate prevalence rate ratios in cross sectional studies and this addresses selection [30] [31]. Study outcomes included malaria parasitaemia infection, care seeking, medication and ITN use. The independent variables were SES, study areas (sub-counties), sex and age groups (<5, 5–14 and ≥15 years. SES indices were generated using MCA using the following variables; Occupation of household head, primary source of drinking water, type of cooking fuel, ownership of household assets and ownership of livestock.The households were categorised into five socio-economic quintiles and then classified into two groups for ease of comparisons. The first three lower quintiles were classified as the 'poorest' and the fourth and fifth quintiles classified as the 'less-poor'[32-34]. Backward selection criteria was used to include independent variables in the models and 95% confidence interval were estimated in each case.   All the analyses were weighted to account for sampling strategies. Sampling weights were created by dividing the population by the sample for each subgroup (age categories and study areas)

Patient and Public Involvement

The research questions of this study were informed by patient's priorities, experience and preferences and public were fully involved. Malaria disease is considered a priority to patients in this study areas because can cause disabilities and deaths amongst patients. Equally poverty is known problem hinder many patients from access and utilizing health interventions. Hence examining the trends in burden of malaria in population subgroup is key to informing policies that reduce the burden and improving access to interventions bu ensuring equity. Ethical considerations in this study required that a rigours community mobilization be done through their advisory committees, meetings with health management teams in the local areas, assuring participants during consenting that positive patients would be treated. For data collection we recruited field assistant from the same communities where we did our study and also with help of community health volunteers. Before conducting these surveys we do not know who is positive for malaria and hence no patients conducted the

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recruitment. Results of this study will be shared with the Siaya county health management team for policy considerations and with the Kenya national malaria control program who are charged with responsibilities of identifying priorities areas for interventions. Results will also be shared in workshops involving community members

RESULTS

Descriptive epidemiology

The prevalence of parasitaemia microscopy was 36.5% overall with substantial variation by age groups (38.2% in children <5 years; 56.8% in children 5–14 years; 20.9% for adults ≥15 years). The prevalence of malaria parasitaemia was relatively stable between 2006 (38.3%) and 2011 (39.8%), but reduced from 36.3% in 2012 to 34.5% in 2013. The proportion of individuals who received the first-line antimalarial medication, AL, in the two weeks prior to survey increased from 0% in 2006 to 44.0 %in 2013(Table 1).

Association of malaria infection, care seeking, medication use and ITN use with socioeconomic status

In the pooled data (n=11383), prevalence of malaria infection was significantly higher among poor individuals compared to less-poor overall (39.9% versus 33.5%; aPR=1.17; 95%CI=1.11-1.23). The prevalence of malaria infection was also significantly higher in poor individuals in each age group (children <5years: aPR=1.20[95%CI=1.11-1.31]; children 5-14 years: aPR=1.13[95%CI=1.06-1.21]); adults≥15years:aPR=1.18[95%CI=1.05-1.33]). There was no clear trend in malaria prevalence by SES either overall or stratified by age group over time for the pooled analysis (Table 3). For the pooled data , there was no significant difference in the proportion of individuals who sought care for illness between poor and less-poor households (61.1% versus 62.5%, aPR=0.99 [0.95-1.03]) overall or by age group and year (Table 4).Overall, medication use was similar among the poorest individuals and less poor (73.2% versus 76.2%, aPR=0.95 [0.92-1.00]). However, poorest individuals were less likely to use a recommended first-line antimalarial medication (i.e., AL or quinine for pregnant women) among those reporting fever in the 2 weeks prior to survey (18.8% versus 22.1%, aPR=0.81 [0.72-0.91]). Poorest households were slightly less likely to report ITN use the night prior to the survey (55.2% versus 57.8%, aPR=0.95 [0.91-0.99]).

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Trends in malaria parasite prevalence and malaria indicators from 2006 to 2013 by SES

Trends analysis for the period 2006 to 2013, showed non-significant change in parasitaemia (overall trend p=0.2560), amongst poorest (p=0.235) or amongst less poor (p=0.254) over time. However amongst children 5-15 years the burden significant reduced among wealthier individuals (trend test p=0.007) but not amongst poorest individuals (p=0.158). Care seeking for fever amongst poorest individuals did not change (p=0.059) but significantly increased amongst less poor individuals over time (p=0.012). Overall ITN use significantly increased between 2006 and 2013, and also increased amongst poorest individuals (p<0.001) and amongst those less poor (p<0.001). Utilization of medication for malaria increased in both the poorest and less poor individuals (p<0.001) overtime. ITN use also significantly increased over time in both groups and the gap were narrower over time (p<0.001) (Table 1, 4)

DISCUSSION

The study has established socioeconomic inequalities in the distribution of malaria parasitaemia between the poorest and the less poor with the poorest populations, across all age groups over time bearing the highest burden. Overall trends showed no significant change in prevalence in the eight years representing diminishing socioeconomic inequalities, and equity gains for the poor individuals. Although there were no significant differences in care-seeking behaviour between socioeconomic groups, poorest individuals were less likely to use the most effective antimalarial medications, AL and quinine, which have been the recommended first-line therapies in Kenya since 2006[12 26]. Statistically significant difference in ITN use between the poorest and less poor was negligible representing lack of socioeconomic which can be perhaps attributed to intensified distribution of LLINs over time which increased availability of ITNs in the households hence the increase in probability of usage. However, it's worthy to note that only half of the populations were using ITNs despite near equity in use.

The results are comparable to findings from the Kenya malaria indicator surveys, which showed that use of first-line antimalarial medications , ITN ownership and use were highest amongst wealthier quintiles while malaria prevalence were lower in wealthier households between 2007 and 2015[5 7 8]. In 2011, the national malaria control program launched the first nationwide mass distribution of free ITNs with the goal of universal coverage[14] and as a result, this study showed increased use of ITNs across the study period but use was unequally distributed between poorest and wealthier households . Results from Kenya

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national surveys already showed higher proportions of ITN ownership amongst wealth quintiles over time [5 7 8].

Similarly, a multi-country study had showed that household ownership of insecticide-treated mosquito nets (ITNs) varied from 5% to greater than 60%, and was equitable by urban/rural and wealth quintile status among 13 (52%) of 25 countries [35]. Although, there were no evidence of socioeconomic inequalities in care-seeking behaviour for fever, poor individuals were less likely to use the recommended first-line antimalarial medications, AL and quinine for pregnant women[10 12 26]. It has already been documented that the success of malaria control depends on high level of coverage of interventions and use of effective and recommended antimalarial but utilization has remained low[35]. A previous study had suggested that the use of AL was higher in children from the lowest wealth quintile compared to the highest wealth quintile because of policies that systematically affected access to malaria treatment for children such as cost of the medicines[36]. Prior to introduction of the Affordable Medicine Facility– malaria (AMFm) in Kenya in 2010, AL was significantly more expensive than other non-recommended antimalarial medicines in the private sector[37]. Evidence from a study from rural western Kenya showed that when adults are uncertain that fever is due to malaria, they tend to choose the lowest-priced antimalarial medicine from private-sector pharmacies and retail outlets[38]. Therefore, when antimalarial medications were not available in public health facilities during the study period, individuals from poor households might have preferentially purchased non-recommended antimalarial medications in the private sector due to lower prices[13]. But despite equity in care seeking, use of medications, universal coverage or use of ITN and recommended medication, there still exists socioeconomic inequalities in burden of malaria parasitemia. The study has established that only fewer poor individuals used ITN but reasons as to why the poor are less likely to use nets may require further qualitative research. Generally, poor individuals are known to be vulnerable and live in impoverished conditions including lack of proper dwellings, poor knowledge, are prone to other illness and may even lack enough sleeping places which increase their risk to poor health outcomes.

In conclusion, socioeconomic inequalities in malaria burden still existed despite intensification of control programs but there was equity in care seeking and medication use. These results could imply that even perfectly equitable access to interventions could have an inequitable impact since risk is so strongly linked to poverty. The result contribute to the goals of Kenya Health Policy 2014–2030 who aim was to achieve equity in the distribution of health services and interventions by 2030 [39]. Monitoring socioeconomic trends in the

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uptake and utilization of malaria interventions is important to identify gaps in equity at the microeconomic level. Provision of interventions for malaria control should aim to make them free to ensure equitable access among those least able to afford them especially amongst poor individuals [40] and eliminate any economic or financial barriers.

Strengths and limitations

The main strength of this paper is use of eight years of pooled data which provided more power to assess socioeconomic inequalities and equity. For lack of recent data, these historical data provided an opportunity to monitor socioeconomic inequalities and equity effect of interventions. There did not exist enough studies assessing socioeconomic inequalities over time and progress towards achieving SDG goals by 2030.The study had three main limitations. First, the findings were based on data from cross-sectional surveys preventing any evaluation of cause-and-effect of SES on malaria indicators over time. However, robust statistical analysis including accounting for households clustering. Secondly, only households with children <5 years were included in the surveys based on protocol-specific objectives. Although all children <5 years in a household were surveyed every year, only a small proportion of persons ≥5 years were included in the survey samples and lastly these results are generalizable to study area and not nationally. The difference in sampling techniques over time whereby in 2009, cluster sampling was used instead of systematic sampling may have in selection bias and may confound the interpretation of results.

Conclusion

Despite equity in ITN use over time and care seeking for fevers, malaria parasitaemia prevalence remains highest amongst poorest individuals in all age groups, which might be due in part to a lower likelihood of treatment with effective antimalarial medications when compared to less-poor individuals. The level of ITN usage still not optimal as only over half of the populations used ITNs which falls short of universal expectations, suggesting that additional strategies are necessary to achieve equity in prevention and treatment of malaria especially amongst poorest populations. Existence of socioeconomic inequalities in burden of malaria in a barrier to achieving universal health coverage and SGDs.

Declarations

Ethics Approval

KEMRI and CDC institutional review boards (IRB) approved the HDSS protocol (# 1801, Nairobi, Kenya) and (# 3308, Atlanta, GA), respectively; the malaria-specific surveys were also approval by KEMRI (#2031) and CDC (#6012). These protocols were approved by the respective IRBs annually. Following cultural customs, compound heads participating provided informed written consent for all compound members, including children, to participate in KEMRI/CDC HDSS activities. Any individual could refuse to participate at any time by verbal request. Additionally, written informed consent was obtained for adult participants providing biological samples.

Abbreviations

aPR: adjusted prevalence ratio; AL: Artemether-Lumefantrine; AMFm: Affordable Medicine Facility– malaria; CDC: Centers for Disease Control and Prevention; GOK: Government of Kenya; HDSS: health and demographic surveillance system; IRB: institutional review board; ITN: insecticide-treated bed net; KEMRI: Kenya Medical Research Institute; MCA: multiple correspondence analysis; RDT: rapid diagnostic test; MOH: Ministry of Health; SES: socioeconomic status; WHO: World Health Organization.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

MD, VW, SK conceived and designed the study. MD, VW, SK coordinated and performed the study. VW analysed the data. VW, MD, SK, AMB, AS, SPK, PPH, FtK, and LN drafted manuscript. All authors read and approved the final manuscript.

Disclaimer

The findings and conclusions presented in this manuscript are those of the authors and do not necessarily reflect the official position of KEMRI, Liverpool School of Tropical Medicine, U.S. President's Malaria Initiative, U.S. Agency for International Development or CDC.The corresponding author had full access to the study data and had final responsibility for the decision to submit for publication.

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Data Sharing Statement

Requests for the data used for this analyses may be made to the KEMRI data manager, Vincent Were, vwere@kemricdc.org and can be shared

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Table 1 Socio-demographic characteristics of study populations in Siaya County, Kenya, 2006-2013

	Years	2006	2007	2008	2009	2010	2011	2012	2013	Total
	Total[a]	1,113	1,270	1,830	2,508	5,334	2,129	2,719	2,412	19,315
Age in years Mean (SD)[b]		18.7 (20.1)	16.2 (18.2)	22.0 (31.4)	20.4 (20.8)	18.5 (19.2)	16.7 (18.9)	13.5 (17.3)	13.9 (17.6)	18.2 (21.3)
category	n/N	%	%	%	%	%	%	%	%	%
Malaria infection (Overall)	6,555/17937	38.3	29.6	27.5	39.0	39.7	39.2	34.1	34.5	36.5[f]
<5 years	2399/6274	40.6	35.0	32.9	43.6	42.6	42.4	35.5	34.9	38.2
5–14 years	2718/4784	62.7	50.8	47.4	60.7	60.2	55.2	60.3	50.8	56.8
≥15 years	1438/6879	21.9	15.7	14.9	23.3	21.6	26.2	21.2	22.2	20.9
Fever in last 2 weeks	8935/18132	33.8	50.6	39.3	46.3	50.9	50.8	53.9	51.9	49.3
Sought care	8021/13142	61.0	50.0	68.8	40.6	66.9	70.6	70.4	69.6	61.0
Medications for fever	7888/16852	88.7	76.8	75.3	33.6	42.3	46.9	46.3	43.5	46.8
AL[c]	1487/7888	0.0	4.7	6.0	9.0	14.7	21.4	25.3	44.0	18.8
Chloroquine	19/1099	2.1	1.3	2.1	2.9	0.6	0.2	0.4	0	1.7
Amodiaquine	59/1099	3.4	8.1	7.7	5.8	3.4	2.2	1.2	0.8	5.4
SP[d]	195/2410	5.6	9.8	3.2	11.8	-	0	0	0	8.1
Paracetemal	4060/6089	58.4	54.5	41.1	42.9	48.6	58.2	34.4	28.7	66.7
Quinine	234/7767	2.6	1.6	1.8	5.4	3.6	1.9	0.82	0.75	3.0
Septrin	664/7888	-	-	-	1.9	5.4	7.7	6.0	6.1	8.4
ITN use	10716/19315	41.4	25.5	37.1	37.6	56.5	62.2	65.0	77.4	55.5[g]
Wealth quintiles (SES)[e]										
Poorest 1	2332/11320	20.6	20.1	21.1	20.2	20.3	20.3	20.3	20.6	20.4
2	2264/11320	20.0	21.1	19.2	19.9	19.8	19.7	19.7	19.5	19.9
3	2287/11320	20.2	19.0	19.7	19.9	20.4	19.9	19.9	20.6	20.0
4	2207/11320	19.5	20.1	20.0	20.0	19.6	20.8	20.8	19.6	20.1
Least Poor 5	2219/11320	19.6	19.8	19.9	20.0	20.0	19.1	19.1	19.8	19.7

[a] <5 year: n=6,523 (33.9%); 5-14 years: n=5,116 (26.6%); ≥15 years: n=7,584 (39.5%); missing age: n=92 ; [b] SD=standard deviation [c] AL=artemether-lumefantrine [d] SP=sulphadoxine-pyrimethamine [e] SES=socioeconomic status [f] trend p-value=0.2560 ; [g] trend p<0.001

Table 2 Sampling size and techniques used to select individual participants in the surveys between 2006 and 2013

Month/Year	Sampling techniques	Total	<5 year	5-14 year	15+ years
April 2006	Systematic random sampling	1,113	255	306	552
April 2007	Systematic random sampling	1,270	260	364	629
April 2008	Systematic random sampling	1,830	296	509	950
April 2009	Cluster and stratified sampling	2,508	628	725	1,155
April 2010	Systematic random sampling	5,334	1,389	1,744	2,201
June 2011	Systematic random sampling	2,129	921	500	708
June 2012	Systematic random sampling	2,719	1,545	473	701
June 2013	Systematic random sampling	2,412	1,229	495	688
Pooled		19,315	6,523	5,116	7,584

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Table 3. Prevalence of malaria infection by household socioeconomic status and age group in Siaya County, western Kenya from 2006 to 2013

	Year	2006	2007	2008	2009	2010	2011	2012	2013	Total
Overall	n	690	707	677	1629	2681	991	2228	1778	11383
Poorest	%	183/435(42.1)	103/353(29.3)	106/361(29.4)	350/870(40.2)	619/1363(45.4)	240/536(44.8)	401/1070(37.5)	319/825(38.7)	2321/5813(39.9)
Less										
Poor	%	90/255(35.3)	99/354(28.0)	72/316(22.8)	286/761(37.6)	498/1318(37.8)	183/455(40.2)	338/1158(29.2)	300/953(31.5)	1866/5570(33.5)
	aPR‡	1.05	1.1	1.32	1.02	1.17	1.05	1.23	1.21	1.17
	(95%CI)	(0.83-1.32)	(0.83-1.46)	(1.01-1.72)	(0.90-1.17)	(1.06-1.29)	(0.90-1.23)	(1.08-1.41)	(1.06-1.39)	(1.11-1.23)
<5 years	n	169	162	127	393	695	407	1177	801	3931
Poorest	%	54/121(44.6)	34/93(36.6)	27/73(37.0)	100/225(44.4)	189/392(48.2)	107/224(47.8)	218/586(37.2)	150/393(38.2)	879/2107(41.7)
Less										
Poor	%	17/48(35.2)	21/69(30.4)	12/54(22.2)	69/168(41.1)	123/303(40.6)	73/183(39.9)	177/591(30.0)	137/408(33.6)	629/1824(34.5)
	aPR‡	1.1	1.17	1.79	1.06	1.17	1.18	1.22	1.13	1.2
	(95%CI)	(0.69-1.17)	(0.72-1.89)	1.03-3.09)	(0.82-1.36)	(0.98-1.39)	(0.94-1.48)	(1.03-1.45)	(0.93-1.37)	(1.11-1.31)
5-14 years	n	201	228	200	487	911	257	427	403	3114
Poorest	%	83/131(63.4)	53/99(53.5)	49/102(48.0)	152/268(56.7)	303/457(66.3)	91/145(62.8)	126/203(62.1)	105/189(55.6)	962/1594(60.4)
Less										
Poor	%	46/70(65.7)	55/129(42.6)	43/98(43.9)	138/219(63.0)	258/454(56.8)	67/112(59.8)	101/224(45.1)	102/214(47.7)	810/1520(53.3)*
	aPR‡	0.92	1.26	1.1	0.91	1.16	0.99	1.8	1.2	1.13
	(95%CI)	(0.73-1.17)	(0.91-1.73)	(0.80-1.52)	(0.78-1.07)	(1.04-1.30)	(0.79-1.24)	(1.31-2.74)	(0.98-1.47)	(1.06-1.21)
≥15 years	n	320	316	345	751	1075	327	624	574	4315
Less	%	46/183(25.1)	16/160(10.0)	15.8	98/377(26.0)	127/514(24.7)	42/167(25.2)	57/281(20.3)	64/243(26.3)	479/426(22.7)
Poor	%	27/137(19.7)	23/156(14.7)	9.9	79/374(21.1)	117/561(20.9)	43/160(26.9)	60/343(17.5)	61/331(18.4)	426/2223(19.2)
	aPR‡	1.27	0.7	1.57	1.22	1.16	0.87	1.1	1.43	1.18
	(95%CI)	(0.83-1.95)	(0.37-1.34)	(0.89-2.77)	(0.94-1.60)	(0.93-1.46)	(0.60-1.27)	(0.77-1.57)	(1.07-1.94)	(1.05-1.33)

ᴵ aPR adjusted prevalence ratio; CI confidence l interval; covariates in regression model included socioeconomic status, age group, sub-county, sex and insecticide-treated bed net use .Cochrane trend p-value=0.007,

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Table 4. **Care seeking, medication and ITN use by household socioeconomic status in Siaya County, western Kenya from 2006 to 2013**

	Year	2006	2007	2008	2009	2010	2011	2012	2013	Total
Care Seeking	n	1044	707	1145	1631	1343	498	1182	893	8443
Poorest	n/N(%)	401/647(62.0)	164/354(46.3)	416/772(53.9)	357/652(54.8)	470/886(53.1)	189/350(54.0)	411/825(49.8)	277/617(44.9)	2685/5103(52.6)
Less Poor	n/N(%)	249/397(63.0)	189/353(53.5)	174/373(46.7)	513/979(52.4)	250/457(54.7)	94/148(63.5)	187/357(52.4)	134/276(48.6)	1790/3340(53.6)*
	aPR[ɨ]	0.97	0.84	1.11	1.04	0.96	0.9	0.95	0.91	0.99
	(95%CI)	(0.86-1.11)	(0.70-1.00)	(1.00-1.23)	(0.90-1.20)	(0.88-1.05)	(0.80-1.01)	(0.87-1.04)	(0.85-1.04)	(0.95-1.03)
Took any medications for fever	n	138	111	176	736	1343	497	1180	834	5441
Poorest	n/N(%)	77/118(65.3)	31/73(42.5)	60/127(47.2)	288/536(53.7)	501/944(53.1)	205/374(54.8)	447/904(49.6)	307/665(46.2)	2588/5018(51.6)**
Less Poor	n/N(%)	10/20(50.0)	15/38(39.5)	32/49(65.3)	116/200(58.0)	218/399(54.6)	78/123(63.4)	151/276(54.7)	83/169(49.1)	2853/5651(50.5)**
	aPR[ɨ]	1.03	0.74	0.72	0.91	0.94	0.85	0.94	0.99	0.95
	(95%CI)	(0.80-1.33)	(0.43-1.27)	(0.51-1.02)	(0.78-1.06)	(0.84-1.05)	(0.75-0.97)	(0.87-1.00)	(0.74-1.11)	(0.92-1.00)
Took AL or Quinine	n	138	111	176	647	1343	374	904	665	4358
Poorest	n/N(%)	4/5(80.0)	1/4(25.0)	6/12(50.0)	49/88(55.7)	105/235(44.7)	44/85(51.8)	189/404(46.8)	133/297(44.8)	531/1130(46.9)**
Less Poor	n/N(%)	83/133(62.4)	45/107(42.1)	86/164(52.4)	292/559(52.2)	614/1108(55.4)	161/289(55.7)	258/500(51.6)	174/368(47.3)	1713/3228(53.1)**
	aPR	1.29	1.03	0.78	1.13	0.66	0.95	0.95	0.92	0.81
	(95%CI)	(0.30-5.5)	(0.37-2.89)	(0.29-2.09)	(0.74-1.72)	(0.51-0.85)	(0.66-1.38)	(0.76-1.20)	(0.77-1.09)	(0.72-0.91)
ITN Use	n	1044	707	1145	1631	2726	1003	2228	1811	12295
Poor	n/N(%)	256/425(60.2)	110/198(55.6)	232/455(50.9)	455/844(53.9)	795/1580(50.3)	306/611(50.1)	676/1449(46.7)	625/1355(46.1)	3455/6313(54.7)**
Less Poor	n/N(%)	394/619(63.7)	243/509(47.7)	358/690(51.9)	415/787(52.7)	598/1146(52.2)	236/392(60.2)	394/779(50.6)	220/456(48.3)	3462/5982(57.9)**
	aPR[ɨ]	0.91	1.25	0.97	1.02	0.96	0.85	0.96	0.98	0.95
	(95%CI)	(0.71-1.16)	(0.83-1.87)	(0.80-1.18)	(0.90-1.18)	(0.87-1.05)	(0.75-0.96)	(0.87-1.05)	(0.91-1.05)	(0.91-0.99)

*p=0.012 , **p<0.001, no stars = not significant results

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6 and 16
Outcome data	15*	Report numbers of outcome events or summary measures	6,16-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 16-19
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	13-17, 6-7
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends in malaria prevalence and health related socioeconomic inequality in rural western Kenya: Results from repeated household malaria cross-sectional surveys from 2006–2013

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Secondary Subject Heading:	Epidemiology, Infectious diseases, Public health
Keywords:	Socioeconomic, equity, inequalities, malaria, medication, Kenya

SCHOLARONE™
Manuscripts

Manuscript title: Trends in malaria prevalence and health related socioeconomic inequality in rural western Kenya: Results from repeated household malaria cross-sectional surveys from 2006–2013

Running title: Socioeconomic health inequalities in malaria indicators

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Abstract

Objective: The objective of this analysis was to examine trends in malaria parasite prevalence and related socioeconomic inequalities in malaria indicators from 2006 to 2013 during a period of intensification of malaria control interventions in Siaya County, Western Kenya

Methods: Data were analyzed from eight independent annual cross-sectional surveys from a combined sample of 19,315 individuals selected from 7,253 households. Study setting was a health and demographic surveillance area of western Kenya. Data collected included demographic factors, household assets, fever, and medication use, malaria parasitaemia by microscopy, insecticide-treated bed net (ITN) use and care-seeking behaviour. Households were classified into five socioeconomic status (SES) and dichotomized into poorest households (poorest 60%) and less poor households (richest 40%).Adjusted prevalence ratios (aPR) were calculated using a multivariate generalized linear model accounting for clustering and cox proportional hazard for pooled data assuming constant follow-up time.

Results: Overall, malaria infection prevalence was 36.5% and was significantly higher among poorest individuals compared to the less poor (39.9% versus 33.5%, aPR=1.17; 95%CI=1.11-1.23) but no change in prevalence over time (trend pvalue<0.256). Care-seeking (61.1% versus 62.5%, aPR=0.99; 95%CI=0.95-1.03) and use of any medication were similar among the poorest and less poor. Poorest individuals were less likely to use Artemether-Lumefantrine or quinine for malaria treatment (18.8% versus 22.1%, aPR=0.81, 95%CI=0.72-0.91) while use of ITNs was lower among the poorest individuals compared to less poor (54.8% versus 57.9%; aPR=0.95; 95%CI=0.91-0.99), but the difference was negligible

Conclusions: Despite attainment of equity in ITN use over time, socioeconomic inequalities still existed in the distribution of malaria. This might be due to a lower likelihood of treatment with an effective antimalarial and lower use of ITNs by poorest individuals. Additional strategies are necessary to reduce socioeconomic inequities in prevention and control of malaria in endemic areas in order to achive universal health coverage and SDGs

Key words: Socioeconomic, equity, inequalities, malaria, medication, Kenya

Article Summary

Strengths and Limitations of the study

- Eight years of repeated annual cross-sectional pooled data provided more power to assess trends in socioeconomic inequalities and equity in malaria indicators over time. Such data have not been published in this setting

- Use of data from repeated cross sectional studies provides opportunity to monitor trends in malaria burden, socioeconomic inequalities and potential equity gaps or gains as malaria control interventions are intensified over time

- The main limitations included; Use of cross-sectional surveys which prevented any evaluation of cause-and-effect of SES and policy interventions on malaria indicators over time.

- Only households with children <5 years and a portion of persons ≥5 years were included in the surveys based on protocol-specific objectives due to the need to ensure every households had at least under5, who had been the main target for interventions over time

- Different sampling procedure was used in one year (2009) and may have resulted in selection bias of participants.

Background

Malaria is a global health problem and World Health Organization (WHO) reported that in 2017 there were 219 million cases and 435 million deaths compared with 239 million cases in 2010 (95% Confidence Intervals CI: 219–285 million) while in 2016, the cases were 217 million (95% CI: 200–259 million)[1]. A recent WHO report revealed there had been a stagnation in progress in reducing burden between 2015 and 2017[1]. Approximately 93% of all malaria deaths in 2017, and 90% of the estimated 445,000 malaria deaths worldwide occurred in the Africa region in 2016[2]. Despite massive distribution of malaria control interventions, a recent study showed that there still exists shortfalls and inequities in burden, coverage and utilizations of interventions [3]. Another study however showed that massive ITN distribution favoured the poorest households in most settings hence increasing equity [4]. In western Kenya, malaria is a major cause of morbidity and mortality with more than 70 percent of the population at risk[5]. In 2015, the prevalence of microscopically-confirmed malaria among children <15 years of age was eight percent nationally and 27% in the lake-endemic region of western Kenya[5]. In Western Kenya, routine and unpublished data had

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showed that the prevalence of malaria remained fairly stable since 2006 despite intensified control efforts during the study periods.

Government of Kenya (GoK) and international partners spent approximated USD 810 million on malaria preventions and treatment programmes[6] which included distribution of long-lasting insecticide-treated bed nets (ITNs), indoor residual spraying (IRS) in selected areas, intermittent preventive treatment during pregnancy (IPTp) in malaria-endemic areas, and prompt and effective malaria case management [5 7 8] . Since 2004, Kenya national guidelines provided that first-line treatment for malaria was artemisinin-based combination therapies (ACT) [9-11]. By 2006, Artemether-Lumefantrine (AL), the first-line ACT, started becoming available in the public sector at no cost to patients, and the first free mass net distribution campaign targeting children <5 years and pregnant women was conducted in malaria endemic and epidemic-prone areas [11-13]. The second free mass net distribution campaign, with a goal of universal coverage (i.e., one net per two people per household), was conducted in a phased approach from 2011 to 2012, with households in western Kenya receiving LLINs in 2011[14]. Equitable distribution of health services or interventions is a principle advocated for in most national policies documents to achieve universal health coverage [15]. A recent paper outlined the five Sustainable Development Goals (SDGs) set of targets that relate to the reduction of health inequalities nationally and worldwide [16]. The study listed the SDG targets as poverty reduction, health and wellbeing for all, equitable education, gender equality, and reduction of inequalities within and between countries[16].

However, despite a national policy of free antimalarial medications for children <5 years in the public sector in Kenya and mass distribution of LLINs in Kenya, access and utilization of health services has been previously shown to vary substantially across socioeconomic groups, which undermines achieving health equity and universal health coverage[17]. However there are no published data on the trends of socioeconomic inequalities in malaria indices over time in endemic areas on western Kenya.

A key pillar of the Kenya Health Policy 2014–2030 is to improve health indicators through equitable distribution of health services and interventions in line with the Sustainable Development Goal (SDG) to achieve universal access to safe, effective, quality and affordable health care services for all [15]. Health inequality and equity data on malaria indicators are often collected but not analysed from an economic or equity perspective. Yet, such data and analyses are important for monitoring health inequalities and assessing the

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impact of malaria control interventions at the microeconomic level[18]. Trends in malaria burden and socioeconomic inequalities between the poor and wealthier individuals has not been published in endemic western Kenya over time, yet socioeconomic inequalities are known barriers to health utilization and control efforts [18-20]. However lack of longitudinal data has undermined assessing trends in socioeconomic inequalities in malaria indices and potential equity effect of intensified control program on equity at the household over time. The objective of this analysis was to use data from repeated cross sectional surveys to examine the trends in malaria parasite prevalence and related socioeconomic inequalities in malaria indicators from 2006 to 2013 during a period of intensification of malaria control interventions in Siaya County, Western Kenya.

METHODS

Study design and site

Independent annual community-based, cross-sectional surveys were conducted between 2006 and 2013, between the months of April to July within the Kenya Medical Research Institute (KEMRI) and Centers for Disease Control and Prevention (CDC) Health and Demographic Surveillance System (HDSS) in Siaya County in western Kenya. The HDSS has been described in detail elsewhere.[21 22]Briefly, HDSS covers a population of approximately 223,000 people residing in 393 villages located in three of six sub-counties of Siaya County, an area of approximately 700 km^2 along the shores of Lake Victoria. The vast majority of the population are subsistence farmers and fishermen. Health indicators in Siaya County, part of the former Nyanza Province, are poor compared to national standards[23 24]. Nyanza Province had the highest rates of child mortality and an estimated 60% of the population lived below poverty level during the survey period.[25]

Population and sampling strategies

A total of 19,315 individuals in 7,253 households were surveyed between 2006 and 2013.Overall, 33.9% were children aged <5 years, 26.6% were children aged 5-14 years and the remaining 39.5% were 15 years old adults. Sample size in 2006 to 2013 were (2006 n=1,113; 2007 n =1,270; 2008 n=1,830; 2009 n=2,508; 2010 n=5,334; 2011 n=2,129; 2012 n=2,719; 2013 n=2,412 and the mean annual sample was 2414 (Table 1).

For each year from 2006-2013, different sampling strategies were selected for logistical purposes. Systematic sampling technique was used from a sample frame of eligible households and individuals enrolled into HDSS except in 2009 when a cluster sampling was

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used (Table 2). Households were selected for participation in the surveys if they had at least a child <5years because many malaria control interventions targeted this age group. In the HDSS, each individual, household, compound and village is assigned a unique number. For the years when systematic sampling was used, a list of households and individuals was made ordered by the unique identifiers and by villages which are spread over the entire study area. Once a sample size for the individuals required in each year, the number of households was estimated assuming a household had an average of 5 members. The households were then systematically sampled from the list. The individuals sampled were then classified as <5, 5-14 and 15 years and above. In 2009, villages were randomly sampled as clusters and the number of households divided proportionately between the three study areas. Surveys were conducted in Rarieda, Gem and Alego-Usonga sub-counties in Siaya County except in 2006 when Alego-Usonga sub-county was not included.

Data collection

During the surveys, study participants were interviewed by trained staff using personal digital assistants (PDA) and tablets. Data collected included demographic factors, socioeconomic factors including asset ownership, characteristics and utilities, care-seeking behaviours, history of fever in the 2 weeks before the survey, ITN use and antimalarial medication use both recommended and non-recommended by polices.

During each survey, a blood specimen was obtained from all individuals providing consent in the sampled households using a finger prick and used for measurement of haemoglobin (HemoCue®; Ängelholm, Sweden) and to measure malaria parasitaemia by rapid diagnostic test(RDT) (Carestart™ Malaria HRP-2/pLDH (Pf/PAN) Combo, Somerset, NJ, USA). Individuals with a positive malaria RDT were treated in accordance with the Kenya national malaria treatment guidelines[10 12 26]. Thick and thin blood smears were obtained for malaria species' identification and parasite density.

Data management and analysis

Data coding, recoding, merging and analysis were conducted in Stata 14 (StataCorp, College Station, TX). The eight cross sectional surveys were first analyzed independently and then as pooled data. The key variables were identified for each year and then appended to each other to form a large dataset. Considering that more one person were selected in households, the analyses have considered clustering. Because these were data taken from different independent samples of the populations over time, there were bound to be missing data. In

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our analysis we conducted complete case analyses by excluding missing values [27]. Trend analysis was conducted using Cochrane trend test[28 29]. A generalized linear model (GLM), using a Poisson distribution with a log-link function, was used to estimate adjusted prevalence ratios (aPR) accounting for clustering at the household level for each individual year, to address potential section bias. Although these datasets were obtained from independent cross sectional studies, the pooled datasets combining all the years were analyzed using cox proportional hazard models assigning the same follow up time for each participant via a robust variance estimator to consider repeated measurements of over time. This was because it have been shown that by imposing a constant follow-up time for all individuals, Cox model can be adopted to estimate prevalence rate ratios in cross sectional studies and this addresses selection biases [30 31]. Study outcomes included malaria parasitaemia infection, care seeking, medication and ITN use. The independent variables were SES, study areas (sub-counties), sex and age groups (<5, 5–14 and ≥15 years. SES indices were generated using MCA using the following variables; Occupation of household head, primary source of drinking water, type of cooking fuel, ownership of household assets and ownership of livestock.The households were categorised into five socio-economic quintiles and then classified into two groups for ease of comparisons. The first three lower quintiles were classified as the 'poorest' and the fourth and fifth quintiles classified as the 'less-poor'[32-34]. Backward selection criteria was used to include independent variables in the models and 95% confidence interval of the prevalence rates were estimated in each case.   All the analyses were weighted to account for sampling strategies. Sampling weights were created by dividing the population by the sample for each subgroup (age categories and study areas)

Patient and Public Involvement

The research questions of this study were informed by patient's priorities, experience and preferences and public were fully involved. Malaria disease is considered a priority to patients in this study areas because it can cause disabilities and deaths amongst patients. Similarly, poverty is a known problem that hinder many patients from accessing and utilizing health interventions. Hence examining the trends in burden of malaria in population subgroup is key to informing policies that reduce the burden and improving access to interventions and at the same time ensuring equity. Ethical considerations in this study required that a rigours community mobilization be done through their advisory committees, meetings were held with health management teams in the local areas, participants were

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assured during consenting processes that patients who were found to have malaria parasites would be treated. For data collection we recruited field assistants from the same communities where we did our study and also with help of community health volunteers. Before conducting these surveys, we did not know who was positive for malaria and hence no patients conducted the recruitment. Results of this study will be shared with the Siaya county health management team for policy considerations and with the Kenya national malaria control program who are charged with responsibilities of identifying priorities areas for interventions. Results will also be shared in workshops involving community members

RESULTS

Descriptive epidemiology

Overall and in the pooled dataset, prevalence of malaria parasitaemia identified using microscopy was 36.5% with substantial variation between age groups (38.2% in children <5 years; 56.8% in children 5–14 years; 20.9% for adults ≥15 years). The prevalence of malaria parasitaemia was relatively stable between 2006 (38.3%) and 2011 (39.8%), but reduced from 36.3% in 2012 to 34.5% in 2013. The proportion of individuals who received the first-line antimalarial medication, AL, in the two weeks prior to survey increased from 0% in 2006 to 44.0 %in 2013(Table 1).

Association of malaria infection, care seeking, medication use and ITN use with socioeconomic status

In the pooled data (n=11383), prevalence of malaria infection was significantly higher among poor individuals compared to less-poor overall (39.9% versus 33.5%; aPR=1.17; 95%CI=1.11-1.23). The prevalence of malaria infection was also significantly higher in poor individuals in each age group (children <5years: aPR=1.20[95%CI=1.11-1.31]; children 5-14 years: aPR=1.13[95%CI=1.06-1.21]); adults≥15years:aPR=1.18[95%CI=1.05-1.33]). There was no clear trend in malaria prevalence by SES either overall or stratified by age group over time for the pooled analysis (Table 3). For the pooled data , there was no significant difference in the proportion of individuals who sought care for illness between poor and less-poor households (61.1% versus 62.5%, aPR=0.99 [0.95-1.03]) overall or by age group and year (Table 4).Overall, medication use was similar among the poorest individuals and less poor (73.2% versus 76.2%, aPR=0.95 [0.92-1.00]). However, poorest individuals were less likely to use a recommended first-line antimalarial medication (i.e., AL or quinine for pregnant women) among those reporting fever in the 2 weeks prior to survey (18.8% versus

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22.1%, aPR=0.81 [0.72-0.91]). Poorest households were slightly less likely to report ITN use the night prior to the survey (55.2% versus 57.8%, aPR=0.95 [0.91-0.99]).

Trends in malaria parasite prevalence and malaria indicators from 2006 to 2013 by SES

Trends analysis for the period 2006 to 2013, showed non-significant change in parasitaemia (overall trend p=0.2560), amongst poorest (p=0.235) or amongst less poor (p=0.254) over time. However amongst children 5-15 years the burden significant reduced among wealthier individuals (trend test p=0.007) but not amongst poorest individuals (p=0.158). Care seeking for fever amongst poorest individuals did not change (p=0.059) but significantly increased amongst less poor individuals over time (p=0.012). Overall ITN use significantly increased between 2006 and 2013, and also increased amongst poorest individuals (p<0.001) and amongst those less poor (p<0.001). Utilization of medication for malaria increased in both the poorest and less poor individuals (p<0.001) overtime. ITN use also significantly increased over time in both groups and the gap were narrower over time (p<0.001) (Table 4)

DISCUSSION

The study has established socioeconomic inequalities in the distribution of malaria parasitaemia between the poorest and the less poor with the poorest populations, across all age groups over time bearing the highest burden. Overall trends showed no significant change in prevalence in the eight years representing diminishing socioeconomic inequalities, and equity gains for the poor individuals. Although there were no significant differences in care-seeking behaviour between socioeconomic groups, poorest individuals were less likely to use the most effective antimalarial medications, AL and quinine, which have been the recommended first-line therapies in Kenya since 2006[12 26]. Statistically significant difference in ITN use between the poorest and less poor was negligible representing lack of socioeconomic inequalities which can be perhaps attributed to intensified distribution of LLINs over time , which increased availability of ITNs in the households hence the increase in probability of usage. However, it's worthy to note that only half of the populations were using ITNs despite near equity in use.

The results are comparable to findings from the Kenya malaria indicator surveys, which showed that use of first-line antimalarial medications , ITN ownership and use were highest amongst wealthier quintiles while malaria prevalence were lower in wealthier households between 2007 and 2015[5 7 8]. In 2011, the national malaria control program launched the first

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nationwide mass distribution of free ITNs with the goal of universal coverage[14] and as a result, this study showed increased use of ITNs across the study period but use was unequally distributed between poorest and wealthier households . Results from Kenya national surveys already showed higher proportions of ITN ownership amongst wealth quintiles over time [5][7][8].

Similarly, a multi-country study had showed that household ownership of insecticide-treated mosquito nets (ITNs) varied from 5% to greater than 60%, and was equitable by urban/rural and wealth quintile status among 13 (52%) of 25 countries [35]. Although, there were no evidence of socioeconomic inequalities in care-seeking behaviour for fever, poor individuals were less likely to use the recommended first-line antimalarial medications, AL and quinine for pregnant women[10][12][26]. It has already been documented that the success of malaria control depends on high level of coverage of interventions and use of effective and recommended antimalarial but utilization has remained low[35]. A previous study had suggested that the use of AL was higher in children from the lowest wealth quintile compared to the highest wealth quintile because of policies that systematically affected access to malaria treatment for children such as cost of the medicines[36]. Prior to introduction of the Affordable Medicine Facility– malaria (AMFm) in Kenya in 2010, AL was significantly more expensive than other non-recommended antimalarial medicines in the private sector[37]. Evidence from a study from rural western Kenya showed that when adults are uncertain that fever is due to malaria, they tend to choose the lowest-priced antimalarial medicine from private-sector pharmacies and retail outlets[38]. Therefore, when antimalarial medications were not available in public health facilities during the study period, individuals from poor households might have preferentially purchased non-recommended antimalarial medications in the private sector due to lower prices[13]. But despite equity in care seeking, use of medications, universal coverage or use of ITN and recommended medication, there still exists socioeconomic inequalities in burden of malaria parasitemia. The study has established that only fewer poor individuals used ITN but reasons as to why the poor are less likely to use nets may require further qualitative research. Generally, poor individuals are known to be vulnerable and live in impoverished conditions including lack of proper dwellings, poor knowledge, are prone to other illness and may even lack enough sleeping places which increase their risk to poor health outcomes.

In conclusion, socioeconomic inequalities in malaria burden still existed despite intensification of control programs but there was equity in care seeking and medication use. These results could imply that even perfectly equitable access to interventions could have an

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inequitable impact since risk is so strongly linked to poverty. The result contribute to the goals of Kenya Health Policy 2014–2030 who aim was to achieve equity in the distribution of health services and interventions by 2030 [39]. Monitoring socioeconomic trends in the uptake and utilization of malaria interventions is important to identify gaps in equity at the microeconomic level. Provision of interventions for malaria control should aim to make them free to ensure equitable access among those least able to afford them especially amongst poor individuals [40] and eliminate any economic or financial barriers.

Strengths and limitations

The main strength of this paper is use of eight years of pooled data which provided more power to assess socioeconomic inequalities and equity. For lack of recent data, these historical data provided an opportunity to monitor socioeconomic inequalities and equity effect of interventions. There did not exist enough studies assessing socioeconomic inequalities over time and progress towards achieving SDG goals by 2030. The study had three main limitations. First, the findings were based on data from cross-sectional surveys preventing any evaluation of cause-and-effect of SES on malaria indicators over time. However, robust statistical analysis including accounting for households clustering. Secondly, only households with children <5 years were included in the surveys based on protocol-specific objectives. Although all children <5 years in a household were surveyed every year, only a small proportion of persons ≥5 years were included in the survey samples and lastly these results are generalizable to study area and not nationally. The difference in sampling techniques over time whereby in 2009, cluster sampling was used instead of systematic sampling may have in selection bias and may confound the interpretation of results.

Conclusion

Despite equity in ITN use over time and care seeking for fevers, malaria parasitaemia prevalence remains highest amongst poorest individuals in all age groups, which might be due in part to a lower likelihood of treatment with effective antimalarial medications when compared to less-poor individuals. The level of ITN usage still not optimal as only over half of the populations used ITNs which falls short of universal expectations, suggesting that additional strategies are necessary to achieve equity in prevention and treatment of malaria especially amongst poorest populations. Existence of socioeconomic inequalities in burden of malaria in a barrier to achieving universal health coverage and SGDs.

Declarations

Ethics Approval

KEMRI and CDC institutional review boards (IRB) approved malaria-specific surveys; KEMRI (#2031) and CDC (#6012). These protocols were approved by the respective IRBs annually. Following cultural customs, compound heads participating provided informed written consent for all compound members, including children, to participate in KEMRI/CDC HDSS activities. Any individual could refuse to participate at any time by verbal request. Additionally, written informed consent was obtained for adult participants providing biological samples.

Abbreviations

aPR: adjusted prevalence ratio; AL: Artemether-Lumefantrine; AMFm: Affordable Medicine Facility– malaria; CDC: Centers for Disease Control and Prevention; GOK: Government of Kenya; HDSS: health and demographic surveillance system; IRB: institutional review board; ITN: insecticide-treated bed net; KEMRI: Kenya Medical Research Institute; MCA: multiple correspondence analysis; RDT: rapid diagnostic test; MOH: Ministry of Health; SES: socioeconomic status; WHO: World Health Organization.

Competing interest

None declared.

Authors' contributions

MD, VW, SK conceived and designed the study. MD, VW, SK coordinated and performed the study. VW analysed the data. VW, MD, SK, AMB, AS, SPK, PPH, FtK, and LN drafted manuscript. All authors read and approved the final manuscript.

Disclaimer

The findings and conclusions presented in this manuscript are those of the authors and do not necessarily reflect the official position of KEMRI, Liverpool School of Tropical Medicine, U.S. President's Malaria Initiative, U.S. Agency for International Development or CDC.The corresponding author had full access to the study data and had final responsibility for the decision to submit for publication.

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Table 1 Socio-demographic characteristics of study populations in Siaya County, Kenya, 2006-2013

	Years	2006	2007	2008	2009	2010	2011	2012	2013	Total
	Total[a]	1,113	1,270	1,830	2,508	5,334	2,129	2,719	2,412	19,315
Age in years		18.7	16.2	22.0	20.4	18.5	16.7	13.5	13.9	18.2
Mean (SD)[b]		(20.1)	(18.2)	(31.4)	(20.8)	(19.2)	(18.9)	(17.3)	(17.6)	(21.3)
category	n/N	%	%	%	%	%	%	%	%	%
Malaria infection (Overall)	6,555/17937	38.3	29.6	27.5	39.0	39.7	39.2	34.1	34.5	36.5[f]
<5 years	2399/6274	40.6	35.0	32.9	43.6	42.6	42.4	35.5	34.9	38.2
5–14 years	2718/4784	62.7	50.8	47.4	60.7	60.2	55.2	60.3	50.8	56.8
≥15 years	1438/6879	21.9	15.7	14.9	23.3	21.6	26.2	21.2	22.2	20.9
Fever in last 2 weeks	8935/18132	33.8	50.6	39.3	46.3	50.9	50.8	53.9	51.9	49.3
Sought care	8021/13142	61.0	50.0	68.8	40.6	66.9	70.6	70.4	69.6	61.0
Medications for fever	7888/16852	88.7	76.8	75.3	33.6	42.3	46.9	46.3	43.5	46.8
AL[c]	1487/7888	0.0	4.7	6.0	9.0	14.7	21.4	25.3	44.0	18.8
Chloroquine	19/1099	2.1	1.3	2.1	2.9	0.6	0.2	0.4	0	1.7
Amodiaquine	59/1099	3.4	8.1	7.7	5.8	3.4	2.2	1.2	0.8	5.4
SP[d]	195/2410	5.6	9.8	3.2	11.8	-	0	0	0	8.1
Paracetemal	4060/6089	58.4	54.5	41.1	42.9	48.6	58.2	34.4	28.7	66.7
Quinine	234/7767	2.6	1.6	1.8	5.4	3.6	1.9	0.82	0.75	3.0
Septrin	664/7888	-	-	-	1.9	5.4	7.7	6.0	6.1	8.4
ITN use	10716/19315	41.4	25.5	37.1	37.6	56.5	62.2	65.0	77.4	55.5[g]
Wealth quintiles (SES)[e]										
Poorest 1	2332/11320	20.6	20.1	21.1	20.2	20.3	20.3	20.3	20.6	20.4
2	2264/11320	20.0	21.1	19.2	19.9	19.8	19.7	19.7	19.5	19.9
3	2287/11320	20.2	19.0	19.7	19.9	20.4	19.9	19.9	20.6	20.0
4	2207/11320	19.5	20.1	20.0	20.0	19.6	20.8	20.8	19.6	20.1
Least Poor 5	2219/11320	19.6	19.8	19.9	20.0	20.0	19.1	19.1	19.8	19.7

[a] <5 year: n=6,523 (33.9%); 5-14 years: n=5,116 (26.6%); ≥15 years: n=7,584 (39.5%); missing age: n=92 ;[b] SD=standard deviation [c] AL=artemether-lumefantrine [d] SP=sulphadoxine-pyrimethamine [e] SES=socioeconomic status [f] trend p-value=0.2560 ; [g] trend p<0.001

Table 2 Sampling size and techniques used to select individual participants in the surveys between 2006 and 2013

Month/Year	Sampling techniques	Total	<5 year	5-14 year	15+ years
April 2006	Systematic random sampling	1,113	255	306	552
April 2007	Systematic random sampling	1,270	260	364	629
April 2008	Systematic random sampling	1,830	296	509	950
April 2009	Cluster and stratified sampling	2,508	628	725	1,155
April 2010	Systematic random sampling	5,334	1,389	1,744	2,201
June 2011	Systematic random sampling	2,129	921	500	708
June 2012	Systematic random sampling	2,719	1,545	473	701
June 2013	Systematic random sampling	2,412	1,229	495	688
Pooled		19,315	6,523	5,116	7,584

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Table 3. Prevalence of malaria infection by household socioeconomic status and age group in Siaya County, western Kenya from 2006 to 2013

	Year	2006	2007	2008	2009	2010	2011	2012	2013	Total
Overall	n	690	707	677	1629	2681	991	2228	1778	11383
Poorest Less	%	183/435(42.1)	103/353(29.3)	106/361(29.4)	350/870(40.2)	619/1363(45.4)	240/536(44.8)	401/1070(37.5)	319/825(38.7)	2321/5813(39.9)
Poor	%	90/255(35.3)	99/354(28.0)	72/316(22.8)	286/761(37.6)	498/1318(37.8)	183/455(40.2)	338/1158(29.2)	300/953(31.5)	1866/5570(33.5)
	aPR‡	1.05	1.1	1.32	1.02	1.17	1.05	1.23	1.21	1.17
	(95%CI)	(0.83-1.32)	(0.83-1.46)	(1.01-1.72)	(0.90-1.17)	(1.06-1.29)	(0.90-1.23)	(1.08-1.41)	(1.06-1.39)	(1.11-1.23)
<5 years	n	169	162	127	393	695	407	1177	801	3931
Poorest Less	%	54/121(44.6)	34/93(36.6)	27/73(37.0)	100/225(44.4)	189/392(48.2)	107/224(47.8)	218/586(37.2)	150/393(38.2)	879/2107(41.7)
Poor	%	17/48(35.2)	21/69(30.4)	12/54(22.2)	69/168(41.1)	123/303(40.6)	73/183(39.9)	177/591(30.0)	137/408(33.6)	629/1824(34.5)
	aPR‡	1.1	1.17	1.79	1.06	1.17	1.18	1.22	1.13	1.2
	(95%CI)	(0.69-1.17)	(0.72-1.89)	1.03-3.09	(0.82-1.36)	(0.98-1.39)	(0.94-1.48)	(1.03-1.45)	(0.93-1.37)	(1.11-1.31)
5-14 years	n	201	228	200	487	911	257	427	403	3114
Poorest Less	%	83/131(63.4)	53/99(53.5)	49/102(48.0)	152/268(56.7)	303/457(66.3)	91/145(62.8)	126/203(62.1)	105/189(55.6)	962/1594(60.4)
Poor	%	46/70(65.7)	55/129(42.6)	43/98(43.9)	138/219(63.0)	258/454(56.8)	67/112(59.8)	101/224(45.1)	102/214(47.7)	810/1520(53.3)*
	aPR‡	0.92	1.26	1.1	0.91	1.16	0.99	1.8	1.2	1.13
	(95%CI)	(0.73-1.17)	(0.91-1.73)	(0.80-1.52)	(0.78-1.07)	(1.04-1.30)	(0.79-1.24)	(1.31-2.74)	(0.98-1.47)	(1.06-1.21)
≥15 years	n	320	316	345	751	1075	327	624	574	4315
Poorest Less	%	46/183(25.1)	16/160(10.0)	15.8	98/377(26.0)	127/514(24.7)	42/167(25.2)	57/281(20.3)	64/243(26.3)	479/426(22.7)
Poor	%	27/137(19.7)	23/156(14.7)	9.9	79/374(21.1)	117/561(20.9)	43/160(26.9)	60/343(17.5)	61/331(18.4)	426/2223(19.2)
	aPR‡	1.27	0.7	1.57	1.22	1.16	0.87	1.1	1.43	1.18
	(95%CI)	(0.83-1.95)	(0.37-1.34)	(0.89-2.77)	(0.94-1.60)	(0.93-1.46)	(0.60-1.27)	(0.77-1.57)	(1.07-1.94)	(1.05-1.33)

ⁱ aPR adjusted prevalence ratio; CI confidence l interval; covariates in regression model included socioeconomic status, age group, sub-county, sex and insecticide-treated bed net use .Cochrane trend p-value=0.007,

Table 4. **Care seeking, medication and ITN use by household socioeconomic status in Siaya County, western Kenya from 2006 to 2013**

Year	2006	2007	2008	2009	2010	2011	2012	2013	Total
Care Seeking n	1044	707	1145	1631	1343	498	1182	893	8443
Poorest n/N(%)	401/647(62.0)	164/354(46.3)	416/772(53.9)	357/652(54.8)	470/886(53.1)	189/350(54.0)	411/825(49.8)	277/617(44.9)	2685/5103(52.6)
Less Poor n/N(%)	249/397(63.0)	189/353(53.5)	174/373(46.7)	513/979(52.4)	250/457(54.7)	94/148(63.5)	187/357(52.4)	134/276(48.6)	1790/3340(53.6)*
aPR‡	0.97	0.84	1.11	1.04	0.96	0.9	0.95	0.91	0.99
(95%CI)	(0.86-1.11)	(0.70-1.00)	(1.00-1.23)	(0.90-1.20)	(0.88-1.05)	(0.80-1.01)	(0.87-1.04)	(0.85-1.04)	(0.95-1.03)
Took any medications for fever n	138	111	176	736	1343	497	1180	834	5441
Poorest n/N(%)	77/118(65.3)	31/73(42.5)	60/127(47.2)	288/536(53.7)	501/944(53.1)	205/374(54.8)	447/904(49.6)	307/665(46.2)	2588/5018(51.6)**
Less Poor n/N(%)	10/20(50.0)	15/38(39.5)	32/49(65.3)	116/200(58.0)	218/399(54.6)	78/123(63.4)	151/276(54.7)	83/169(49.1)	2853/5651(50.5)**
aPR‡	1.03	0.74	0.72	0.91	0.94	0.85	0.94	0.99	0.95
(95%CI)	(0.80-1.33)	(0.43-1.27)	(0.51-1.02)	(0.78-1.06)	(0.84-1.05)	(0.75-0.97)	(0.87-1.00)	(0.74-1.11)	(0.92-1.00)
Took AL or Quinine n	138	111	176	647	1343	374	904	665	4358
Poorest n/N(%)	4/5(80.0)	1/4(25.0)	6/12(50.0)	49/88(55.7)	105/235(44.7)	44/85(51.8)	189/404(46.8)	133/297(44.8)	531/1130(46.9)**
Less Poor n/N(%)	83/133(62.4)	45/107(42.1)	86/164(52.4)	292/559(52.2)	614/1108(55.4)	161/289(55.7)	258/500(51.6)	174/368(47.3)	1713/3228(53.1)**
aPR	1.29	1.03	0.78	1.13	0.66	0.95	0.95	0.92	0.81
(95%CI)	(0.30-5.5)	(0.37-2.89)	(0.29-2.09)	(0.74-1.72)	(0.51-0.85)	(0.66-1.38)	(0.76-1.20)	(0.77-1.09)	(0.72-0.91)
ITN Use n	1044	707	1145	1631	2726	1003	2228	1811	12295
Poor n/N(%)	256/425(60.2)	110/198(55.6)	232/455(50.9)	455/844(53.9)	795/1580(50.3)	306/611(50.1)	676/1449(46.7)	625/1355(46.1)	3455/6313(54.7)**
Less Poor n/N(%)	394/619(63.7)	243/509(47.7)	358/690(51.9)	415/787(52.7)	598/1146(52.2)	236/392(60.2)	394/779(50.6)	220/456(48.3)	3462/5982(57.9)**
aPR‡	0.91	1.25	0.97	1.02	0.96	0.85	0.96	0.98	0.95
(95%CI)	(0.71-1.16)	(0.83-1.87)	(0.80-1.18)	(0.90-1.18)	(0.87-1.05)	(0.75-0.96)	(0.87-1.05)	(0.91-1.05)	(0.91-0.99)

*p=0.012 , **p<0.001, no stars = not significant results

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6 and 16
Outcome data	15*	Report numbers of outcome events or summary measures	6,16-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 16-19
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	13-17, 6-7
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.