A decline and age shift in malaria incidence in rural Mali following implementation of seasonal malaria chemoprevention and indoor residual spraying

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Abstract

Background

Declines in malaria incidence attributed to the implementation of control strategies have been reported in many African countries. The declines are often accompanied by a shift in clinical burden to older children. In Mali, artemisinin-based combination therapy (ACT) was introduced in 2004, and Long-lasting insecticide-treated nets (LLINs) have been partially distributed free of charge since 2007. In Bandiagara, a study conducted from 2009 to 2013 showed a stable incidence of malaria compared to 1999 despite the use of ACTs and LLINs. Since 2016, seasonal malaria chemoprevention (SMC) has been scaled up across the country. In addition to these strategies, the population of Bandiagara benefited the universal bed net coverage and indoor residual spray (IRS) implementation in 2017 and 2018.

This study aimed to measure the incidence of malaria in the context of recent scaling-up of control strategies.

Methods

A cohort of 300 children aged 6 months to 15 years was followed from October 2017 to December 2018 in Mali. Monthly cross-sectional surveys were done to measure the prevalence of malaria infection by microscopy and anaemia. The study outcomes included the monthly prevalence of malaria infection and the incidence of symptomatic malaria.

Results

The incidence of symptomatic malaria was 0.5 episodes/person-year. The average prevalence of malaria parasitaemia was 6.7%. The incidence was higher in the oldest age group than the youngest one (0.6 episodes/person-year in children above 10 years vs 0.29 in 6 months to 5 years age group).

Conclusions

This study showed a reduction of malaria incidence compared to 1999 and 2009-2013. An age shift in the susceptibility to malaria was also observed; older children experienced more clinical malaria than younger ones. These findings suggest to extend malaria control efforts to older children.

Background

Malaria is one of the deadliest diseases on Earth. In 2018, the World Health Organization estimates that 219 million cases of malaria occurred worldwide. Africa accounted for 93% of the cases (1).

Over the last decade, remarkable achievements in malaria control have been accomplished through large-scale implementation of high-impact interventions, including rapid case management with the rapid diagnosis test (RDT) and treatment with artemisinin-based combination therapy (ACT), prevention and
control of malaria among pregnant women using intermittent preventive therapy (IPT), vector control strategies including insecticide-treated bed nets (ITNs), and indoor residual spray (IRS) (2–5).

In Mali, malaria is characterized by its endemicity in the central and southern regions and epidemic potential in the northern regions. Since 2007, children aged 0 to 5 years old have benefited from several malaria control interventions provided free of charge. These include long-lasting insecticide-treated nets (LLINs), rapid diagnostic tests (RDT), and ACTs. In 2016, seasonal malaria chemoprevention (SMC) was implemented nationwide for children aged 3 months to 5 years. These strategies have had an impact on morbidity and mortality related to malaria (6).

Despite the implementation of these measures, a study done in Bandiagara from 2009 to 2013 showed a stable malaria incidence compared to 1999 (7). Since that study, seasonal malaria chemoprevention has been implemented in Bandiagara, as well as universal bed net coverage and indoor residual spraying (IRS) in 2017 and 2018. We hypothesized that the implementation of these additional control interventions may reduce the incidence of clinical malaria and malaria infection in Bandiagara.

Methods

Study area

This study was conducted in Bandiagara, a town of approximately 20,000 inhabitants located in central region of Mali, on a rocky plain. Bandiagara is a sentinel site of the National Malaria Control Program and a research site for the Malaria Research and Training Center since 1998, and it has been developed as malaria vaccines testing site. A detailed description of the study site can be found elsewhere (7). In addition, Duffy blood group negative subjects were observed to be persistently infected by P. vivax (8).

Subject recruitment and enrollment

Before starting the study, community permission was obtained as described by Diallo et al. (9). Parents were invited to accompany children to the Bandiagara Malaria Project (BMP) Research Clinic to be screened for eligibility. Participants were enrolled on a first-come first-served basis until the study target number was reached.

Inclusion and exclusion criteria

Children aged from 6 months-15 years inclusive at the time of screening residing in Bandiagara town and meeting the following inclusion criteria were enrolled: general good health based on clinical evaluation, written informed consent obtained from the parent/guardian, assent from children aged 13 years and above, and availability to participate in follow-up for the duration of study.

Exclusion criteria were simultaneous participation in an interventional clinical trial and chronic use of a medication with known antimalarial activity such as trimethoprim-sulfamethoxazole.
Ethical clearance

The study protocol and informed consent/assent process were reviewed and approved by the institutional review boards of the Faculty of Medicine, Pharmacy and Dentistry of the University of Sciences, Techniques and Technologies of Bamako. Permission to work in the community was obtained from local official authorities. Individual written informed consent was obtained from parents, or guardians and assent was obtained from children aged 13 years and older.

Study procedures

Passive and active surveillance were done to capture malaria infection and disease. Active surveillance consisted of scheduled monthly visits (every four weeks) with the aim of detecting asymptomatic malaria infection and anaemia. At each visit, participants were questioned for symptoms of malaria and examined. Finger prick blood was collected for malaria thick smear and hemoglobin level. Smears were not read contemporaneously unless symptoms or signs of malaria were present.

Passive surveillance consisted of continuous availability of free, basic medical care at the BMP Research Clinic and Bandiagara District Hospital. Parents/guardians were encouraged to visit the clinic at any time when their child got sick. Children were examined by a physician. If symptoms or signs compatible with malaria were present, finger prick blood was collected for a blood film, which was read immediately. Uncomplicated malaria was treated with artemisinin combination therapy (artemether/lumefantrine) according to the guidelines of the Mali National Malaria Control Program. Parents/guardians were instructed to administer only drugs given or prescribed by the research team and to avoid as much as possible self-medication. Clinical malaria was defined by the presence of symptoms consistent with malaria and presence of asexual malaria parasites at any density. Anaemia was defined as a haemoglobin level < 10 g/dL.

Sample size estimation

To adequately estimate malaria incidence assuming an average of 0.75 clinical episodes per subject per year, we determined that with 300 total subjects, we could assess the malaria incidence in the cohort with 80% power and a confidence level of 95%.

Laboratory assays

Malaria thick smears were Giemsa-stained and parasites counted against 300 leukocytes to give parasite counts/mm³, assuming a leukocyte count of 7,500/mm³. Standard operating procedures were developed to ensure uniform and high-quality malaria smears, including training and certified malaria microscopists. Haemoglobin level was determined using Hemocue haemoglobin analyzers (Hemocue Inc, Cypress, CA).

Statistical methods
Data were entered into a Microsoft ACCESS 2013 data base. The analysis was performed using STATA software, version 12 (Stata Corp, College Station, TX). Descriptive statistics were used to summarize baseline values and demographic characteristics (age, gender, and ethnicity). Pearson chi-square tests or exact probabilities statistics were used to compare categorical variables. All $p$ values $<0.05$ were considered statistically significant.

The incidence rate of clinical malaria was calculated as the number of episodes per person per year.

**Results**

**Socio-demographic and baseline characteristics**

A total of 326 participants were screened. Of these, 300 volunteers who met inclusion criteria were enrolled (Fig. 1). The main reason for non-inclusion was willingness to travel out of the study area. The sex ratio was 1.05 in favor of girls (154 females vs 146 males), (Table 1). The mean age was 7.9 years old [Std. Err 0.22 CI 95% (7.46–8.36)]. Dogon was the main ethnic group (74%).

Approximately 98% (298/300) of children reported sleeping under insecticide-treated bed net during the enrollment visit.

**Clinical malaria**

Among the 300 participants, 107 experienced at least one clinical malaria episode. Two participants had 4 episodes. $\chi^2 = 14.6648 \; p = 0.06.6$.

Among children who experienced one episode, 45.4% were at least 10 years old (Table 2). Most children who had two clinical episodes of malaria were in the 6–10 years age group (53.1%; Table 2). Most participants with three or four episodes were in the >10 years old group (54.5% and 100%, respectively).

The overall incidence rate after 15 months of follow-up was 0.5 clinical malaria episodes (Table 3). The age-specific incidence was 0.29, 0.57, and 0.6 episodes / person-year, respectively, in the 6 months-5 years, 6–10 years, and above 10 years age categories.

**Prevalence of infection**

The highest prevalence of infection was 13.5% noticed in May 2018. The lowest prevalence of infection recorded in June 2018 was 2.0% (Fig. 2). The average prevalence of malaria infection for the study period was 6.8%.

Monthly infection prevalence has shown the highest prevalence of malaria (18.1%) in children over 10 years old in October 2017. In the low malaria transmission season spanning December to May, the highest malaria prevalence was 16.5% occurred in May 2018 in children above 10 years old. The lowest prevalence of infection in children from 0–5 years was 1.2% in October 2017 (Fig. 2). For children 6–10 years old, no parasite was detected in June 2018.
**Prevalence of anaemia**

The overall prevalence of anaemia was 2.3% (Fig. 3). The highest prevalence of anaemia was 7.1% recorded in November 2018.

The highest prevalence of anaemia was 18.2% occurred in children aged 0 to 5 years old in November 2018. For children aged above 10 years, monthly anaemia prevalence do not exceeded 5% during the study (Fig. 3)

**Discussion**

Tools and strategies for malaria control such as artemisinin-based combination therapy, long-lasting insecticide-treated bed nets, intermittent preventive treatment in pregnancy, and intermittent preventive treatment in infancy and seasonal malaria chemoprevention in children have shown efficacy in malaria control (1, 10). In Bandiagara, following implementation of long-lasting insecticide-treated bed nets, rapid diagnostic tests, and artemisinin-based combination therapy, a study showed a comparable incidence to what was observed in 1999, prior to implementation of these control strategies (7). Seasonal malaria chemoprevention was scaled up in 2016 in Mali, and in 2017–2018, the health district of Bandiagara benefitted from a large distribution of long-lasting insecticide-treated bed nets and indoor residual spraying. As new interventions need to be monitored for proper implementation and potential impact, we measured the incidence of malaria in the pediatric population, predicting a decline.

A cohort of three hundred children was followed using active and passive surveillance to capture all clinical episodes of malaria that occurred in the cohort during the study period. This study showed a reduction of malaria incidence among under 5-year-olds.

The low prevalence of infection (Fig. 2) attests the reduction of the transmission intensity and may be due to the combination of implementation of SMC, use of LLITN and IRS in Bandiagara. The highest prevalence of infection was observed in the dry season May 2018 (Fig. 2). All parasite carriers at that period were asymptomatic. The highest prevalence of malaria infection was noticed in children aged above 10 years old.

The prevalence of anaemia rose in October 2018, peaking at 18.2% the following month in the 0–5 years age group. The prevalence remained less than 5% in older age groups irrespective of month. This rise paralleled a rise in malaria prevalence, but other contributors to anaemia include malnutrition. At our study site, a food shortage is generally observed from August to December, which could contribute to the high prevalence of anaemia in that period in young children, who are also more susceptible to other infections than older children.

The overall malaria incidence rate was 0.5 episodes/person-year; the age-specific incidence was 0.29, 0.57, and 0.6 episodes per person-year observed, in the 6 months-5 years, 6–10 years, and above 10 years old groups, respectively (Table 2). Children aged 6 months to 5 years had a lower malaria incidence than
those older than 5 years of age. This is unusual, given that in high transmission settings, the highest malaria incidence has classically been seen in younger children (11).

Previous studies in Bandiagara determined an incidence of malaria of 1.7 episodes per person / 24 weeks in 1999, and 1.4 episodes per person-years from 2009–2013. The decrease in malaria incidence established by this current study may due to the combined effect of the use of long-lasting insecticide-treated bed nets, seasonal malaria chemoprevention, and IRS, suggesting that malaria may be eliminated with the proper implementation of all of the prevention tools available today. Older children (more than five years old) experienced more malaria clinical episodes than the youngest group. These findings confirm the age shift in the susceptibility to malaria recently reported by multiple authors in regions where control strategies were implemented (7, 12, 13).

One additional consideration for malaria elimination is that a previous study revealed the presence of \textit{P. vivax} in Duffy blood group negative children residing in our study site (8). We did not perform molecular testing for \textit{P. vivax} in this study. The decline in the incidence of \textit{Plasmodium falciparum} infection has generated enthusiasm for the elimination of malaria. However, there is growing evidence of \textit{P. vivax} infection in Duffy blood group negative populations (14–17), and the species shift (18) may jeopardize malaria control efforts. Particular attention needs to be given to this species through extensive prevalence studies and control program adaptations.

Some limitations of this study include the lack of entomological parameters of transmission to support clinical findings and the relative short study period.

**Conclusions**

A decline in malaria incidence at a Malian site with intense seasonal transmission was observed following the combined implementation of control strategies that included seasonal malaria chemoprevention and indoor residual spraying. An age shift to older children in terms of susceptibility to malaria was observed, supporting extending malaria control efforts to this age group.

**Abbreviations**

ACT
Artemisinin-based combination therapy
DBS
Dried Blood Spot
LLIN
Long-lasting insecticide-treated net
IPT
Intermittent Preventive Therapy
IRS
Indoor Residual Spray
ITN
Insecticide Treated Net
SMC
Seasonal Malaria Chemoprevention
RDT
Rapid Diagnostic Test

Declarations

Ethics approval and consent to participate

The study protocol and informed consent/assent process were reviewed and approved by the institutional review boards of the Faculty of Medicine, Pharmacy and Dentistry of the University of Sciences, Techniques and Technologies of Bamako. Permission to work in the community was obtained from local official authorities. Individual written informed consent was obtained from parents, or guardians and assent was obtained from children aged 13 years and older.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors’ contributions

DC, OKD, MAThera conceived and designed the study. KT, BG, FM, AD YT, AKK, AN and Antar conducted the study and collected data. DC, MAThera, analyzed the data. MAThera, DC, contributed to data analysis,
interpretation and manuscript review. DC wrote the manuscript. All authors read and approved the final manuscript.

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References


Figures
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Diagram of study design
Figure 2

Monthly time point prevalence of malaria infection from October 2017 to December 2018. Monthly prevalences across all age groups indicated in black, for 0-5 years old in blue, 6-10 years old in orange, and greater than 10 years old in green.
Figure 3

Monthly time point prevalence of anaemia from October 2017 to December 2018. Monthly prevalences across all age groups indicated in black, for 0-5 years old in blue, 6-10 years old in orange, and greater than 10 years old in green.

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