Stratification at the Health District Level and Targeting of Malaria Control in Mali

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Abstract

Introduction
Malaria has been the leading cause of morbidity and mortality for several decades in Mali, with an increase from 2017 to 2020 (2,884,837 confirmed cases and 1,454 deaths). On the recommendation of the World Health Organization (WHO) and in the interests of efficient use of resources, Mali has begun a process of stratifying the health districts to target malaria control strategies.

Method
Malaria, entomological and environmental data were collected through the local health information system (LHIS), the Demographic and Health Survey (DHS 2018), research institutions and MALI-METEO services. The WHO has recommended stratification at the district level consisted of assigning each district to one of 4 classes according to criteria based on incidence adjusted for attendance rate. Variables associated with monthly malaria incidence at the district level were identified using a general additive non-linear regression model.
**Results**

From 2017 to 2019, the median incidence across 75 health districts of Mali was 129.34 cases per 1,000 person-year (IQR=86.48). The results showed different periods of high malaria transmission in health districts level and durations varying from 2 to 6 months, showing a double peak for some health districts, which were located in the flooded areas. Environmental variables such as rainfall, vegetation index (NDVI), maximum temperature and relative humidity were significantly associated at malaria incidence with a lag of around one month. A strata defines a geographical area with similar epidemiological, environmental and socio-economic factors. Stratification resulted in 12 health districts of very low transmission, 19 low transmission, 20 moderate transmission and 24 in high transmission areas. The number of rounds of season malaria chemoprevention will be based on the number of months in the high transmission period.

**Conclusion**

This first stratification in Mali will allow targeting malaria control strategies. This approach will be dynamic and revised yearly in order to integrate information from the national epidemiological surveillance.

**Keywords**: Stratification, Malaria, Interventions, geo-epidemiology, environment, Mali.

**Background**

Malaria remains the leading cause of morbidity and mortality in Mali. In 2020, the surveillance system reported 2,884,827 confirmed cases out of 4,252,213 people tested, of which 871,265 were severe cases. The number of deaths was 1,454 notified by the health facilities in 2019, still being the primary reason for health care visits with 36% of consultation due to malaria [1]. The main parasites responsible for malaria in Mali are: *Plasmodium falciparum* (more than 85%), *Plasmodium malariae* (10-15%) and *Plasmodium ovale* (1%) [2]. However, cases of *Plasmodium vivax* have been observed and documented in Mali [3,4]. Malaria is endemic in most localities in Mali with an increase due to the rainy season. The main vector species are: *Anopheles gambiae s.l.* (*Anopheles gambiae s.s.*), *Anopheles coluzzii* and *Anopheles gambiae and Anopheles arabiensis* and *Anopheles funestus* [5,6].

To control malaria, Mali has implemented a policy of prevention, monitoring and case management coordinated at different levels by the National Malaria Control Program (NMCP) following the World Health Organization (WHO) technical guidelines. The case management is concerned with the early diagnosis of malaria by rapid diagnosis test (RDT) and prompt treatment. Preventive interventions are vector control using insecticide-treated mosquito nets (ITNs) distributed every 3 years, and indoor residual spraying (IRS). Chemoprevention is concerned with Seasonal Malaria Chemoprevention
(SMC) for children under 5 years old during the periods of high transmission one per month from July to October using the Sulfadoxine-pyrimethamine (SP) associated Amodiaquine (AQ), and Intermittent Preventive Treatment (IPT) with Sulfadoxine-pyrimethamine (SP) for pregnant women from the 13th week of pregnancy.

Currently the period of SMC has been defined on a national basis, from July to October. However, the high transmission period may be different from place to place, notably the onset and the duration, according to different environmental and population characteristics. This may hinder the effectiveness of SMC in the situation of asynchronism between intervention and high transmission period.

WHO recommends that malaria-endemic countries adapt interventions as transmission evolves [7]. The intensity of malaria transmission is strongly dependent on environmental, socio-demographic characteristics and the malaria interventions implemented [8–12]. It is generally measured by the incidence of cases or the prevalence of infection in the population.

Malaria stratification is defined as the classification of geographical areas according to similar epidemiological, entomological, environmental and socio-economic factors, in order to guide malaria control interventions [7]. Health districts are classified according to the risk, based on factors that determine susceptibility and vulnerability to malaria transmission. The stratification reflects the varieties of the physical and human environments that condition the presence, behavior, and size of vector populations [13]. These criteria specify epidemiological profiles, or facies, that help in the choice of different malaria control strategies. These stratum or facies are places in which malaria presents the same characteristics of transmission, development of immunity and clinical manifestations. This stratification allows better targeting of malaria control strategies in Mali.

From the environmental perspective, Mali is divided into 5 zones corresponding to the initial epidemiological facies described in 1989: i) a Sudano-Guinean zone with a long seasonal transmission of 4 to 6 months; ii) a zone of short seasonal transmission of 3 to 4 months; iii) a zone of sporadic or epidemic transmission in the northern regions and some localities in the regions of Koulikoro, Segou, Mopti and Kayes; iv) zones of bi or multimodal transmission including the inner delta of the Niger River and the dam zones; v) zones that are less propitious to malaria transmission, particularly in urban areas as Bamako and Mopti where malaria is hypoendemic [14]. Since 1989, these profiles have evolved, due to sociological and climatic changes.

The objective of this study was to develop a new stratification of malaria in Mali in order to target interventions based on the intensity of transmission, the distribution of disease vectors and their resistance to current interventions, considering the different environmental zones. This will identify transmission periods by health districts to better target malaria control strategies including SMC.
Method

Study location

The Republic of Mali, a country located in West Africa and in the Sahelo-Saharan strip, has a population of 20,536,999 inhabitants in 2020 and a growth rate of 3.36% from General Population, Habitat Survey 2009 in Mali (GPHS 2009), updated by the National Population Direction). The relief is low and not very rugged: it is a country of plains and low plateaus. The average altitude is 500 meters. The hydrographic regime, dependent on the geographical configuration extending between 11° and 25° north latitude, is essentially constituted by the basins of Upper Senegal and Niger Rivers. There are several dams and flooded areas used for agriculture. The flooded areas extend along the Niger River: the inner delta of the Niger River extends from the Segou region in the center, through Mopti to the Timbuktu region in the north (Figure 1), and covers a maximum area of 41,000 km², including numerous lakes, ponds and swamps [15,16]. Annual rainfall data measured vary from less than 200 mm in the Saharan desertic zone to more than 1100 mm in the pre-Guinean zone (Figure 1): desertic zone (less than 200 mm), Sahelian zone (200 to 600 mm), Sudanian zone (600 to 800 mm), Sudano-Guinean zone (800 to 1100 mm) and the pre-Guinean zone (more than 1100 mm) [17].

Figure 1: Different ecoclimatic zones in Mali (Source: MRTC GIS/RS)

Mali is composed of 11 regions including the District of Bamako. The health system is divided into 75 health districts. At the institutional plan, the health system is structured on three levels:

- the operational: the health district is the operational unit responsible for planning, budgeting and managing health development;
- the regional: is the technical support level at the first level;
- the national: is the strategic level that defines strategic orientations and determines investments and operations.

Data collection

Clinical data

Malaria cases confirmed by a biological test (RDT or microscopy), notified monthly by the health districts were extracted from 2017 to 2019. The frequentation rate was also reported into the DHIS2 by the health district. The child mortality data were extracted from the DHS.

Local health information system (LHIS) data were implemented on the District Health Information Software 2 (DHIS2) platform. We obtained the authorization of the National Malaria Control Program (NMCP) for the use of anonymous data extracted from the LHIS.
Anonymous data coming from research institutions have been used in addition according to their availability. The quality of the routine data has been improved through supervision, auditing, and periodic data review sessions. For prevalence, the data collected are from DHS 2018 and studies from research institutions (Malaria Research and Training Center (MRTC), Laboratory of Applied Molecular Biology (LBMA) and National Institute of Public Health (INSP)).

**Population data**

Updated population data were obtained from the General Population and Housing Survey (GPHS 2009). These data were collected at the health district and regional levels.

**Environmental data**

Environmental data were collected from the MALI-METEO service (observational data from synoptic and agrometeorological stations for the Center and South regions) and from NASA satellites using the GIOVANNI platform (satellite data: giovanni.gsfc.nasa.gov/). The data collected are monthly rainfall in mm (IMERG 6, resolution 1°), monthly NDVI (MODIS-terra, resolution 0.05), monthly maximum and minimum temperature in Celsius degrees (AIRS, resolution 1°), monthly relative humidity (AIRS, resolution 1°), monthly soil moisture in m3 m-3 (MERRA-2, resolution 0.5 x 0.625°) and monthly mean wind speed in m/s (MERRA-2, resolution 0.5 x 0.625°) [18]. The land use data, i.e. percentage of cultivated area, percentage of urbanization, percentage of area occupied by trees and surface water, were obtained from the 2017 Copernicus Africa classification [19].

**Entomological data**

The entomological data presented here includes data from 2010 to 2019, from Malaria Research and Training Center (MRTC) and NMCP partner (VectoLink) carried to the sentinel sites of the NMCP [5,6,20,21]. Two parameters were studied: vector distribution, vector resistance to insecticides, and their mechanism. Monitoring of vector resistance to insecticides provided results for ten insecticides in five classes. These classes are: pyrethroids (PY), organochlorines (OC), organophosphates (OP), carbamates and neonicotinoids. The insecticides used were permethrin 0.75%, deltamethrin 0.05%, alphacypermethrin 0.05% and lambda-cyhalothrin 0.05% (pyrethroids), DDT 4% (organochlorinated), bendiocarb 0.1% and propoxur 0.1 (carbamates); pyrimiphos-methyl 0.25% and 1% and fenitrothion 1% (organophosphates) and clothianidin 2% (neonicotinoid). The tests performed were bioassays according to WHO recommendations [12] on the major malaria vector An. gambiae s.l.

**Data Analysis**

Incidence and prevalence data were presented in maps, tables, and figures.
Temporal analysis

To determine the periods of transmission at the national level, a breakdown of the malaria incidence curve in Mali was made using the change point analysis of the mean, which looks for points of change on the monthly incidence curve. The algorithm PELT was used [22], allowing the identification of periods of low and high transmission.

The determination of the periods of high transmission at the health district level was carried out to identify the periods of transmission and the endemic health districts. We presented time series data from 2017 to 2019 as a graph in a box plot by month. The duration of the high transmission period was defined for each health district to determine the number of SMC rounds (one per month).

As the impacts of environmental data on malaria incidence are well documented in Mali [9,23,24], we have presented malaria incidence and environmental data to observe a possible relationship between increasing incidence and lags. It was investigated with which lagged environmental factors best predicted the incidence time series.

To assess the relationship between environmental factors and the malaria case series, we provided synthetic meteorological indices (SMI) by using principal component analysis (PCA). This approach was necessary to take into account the curse of dimensionality and collinearities. The number SMI will be chosen according to the elbow criterion [25]. We analyzed the relationships between synthetic meteorological indices and malaria incidences by using Generalized Additive Model (GAM). This approach allowed to use Spline smoothing functions modeling non-linear relationships, Negative-binomial distribution for count data considering overdispersion, and log (Population) as offset to provide standardized incidence ratios (SIR). The time series of monthly cases was modeled as a function of meteorological factors grouped in synthetic meteorological indices by the PCA method with a lag of 1 to 4 months. The criterion for selecting the best model was the high explained deviance and the low model generalized cross-validation score (GCV).

The time series of the cases was analyzed according to the synthetic environmental lagged axes. To estimate the associated standardized incidence ratios (SIRs), the logarithm of the population was introduced in offset.

Spatial analysis

Monthly incidence was calculated with confirmed malaria cases reported by LHIS considering the population size and time (month).

\[
\text{incidence} = \frac{\text{cases}}{\text{population} \times \text{time}} \times 1,000 \quad (\text{Eq2})
\]
This does not reflect the real incidence of the disease in the population for the following reasons varying according to the health facilities:

- Health facility access and usage rate
- The availability and use of diagnostic tests
- The low completeness of the data by location.

Adjusted incidence was calculated per 1,000 person-years by adjusting for the health district usage rate. To account for this, the adjusted incidence was calculated.

\[
adjusted \text{ cases} = \left(\frac{\text{confirmed cases}}{\text{health facility usage rate}}\right) \times 100 \quad (\text{Eq3})
\]

\[
adjusted \text{ incidence} = \frac{\text{adjusted cases}}{\text{population} \times \text{time}} \times 1,000 \quad (\text{Eq4})
\]

Entomological data were presented in the form of maps to report the distribution of species and insecticide resistance.

Stratification and targeting of interventions

Adjusted incidence data from the health districts were used to determine the strata with meteorological and land use data. The classes were determined by the statistical method of Classification and Regression Tree (CART) [26,27]. For SMC eligibility, health districts with a malaria prevalence of less than 1% in DHS VI 2018 among children aged 3-59 months were excluded. Health districts without seasonality were excluded.

Software and packages

We used the software R version 3.4 for the different statistical analyses (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria), the packages \{mgcv\}, \{caschrono\}, \{FactoMineR\}, \{forecast\}, \{ggplot2\}, \{party\}, \{changepoint\} [28] [29]. ArcGIS Desktop version 10.1 software (Environmental Systems Research Institute (ESRI), 380 New York Street, Redlands, CA 92373-8100, USA) was used for mapping [30]. Paint.net software version 4.2.13 (Rick Brewster and al., Washington State University, USA) was used for image treatment.

Results

Temporal

Low and high malaria transmission period

Time series analysis of the monthly malaria incidence can be used to show the national and district transmission periods.
**Figure 2:** The grey band shows periods of high malaria transmission from 2017 to 2019. Rainfall in blue histogram on the left axis, and Malaria incidence in a red curve, the average monthly temperature in a black curve on the right axis.

Transmission period by health district

The monthly malaria incidence was presented as a boxplot graph by aggregating the monthly incidences from 2017 to 2019, to describe the period of high transmission (start, end, and annual duration) for some selected districts in figure 3 in different environmental areas.

**Figure 3:** Boxplot of crude malaria incidence for 4 selected health districts.

The period of high transmission varied from 2 to 6 months according to the health districts (Figure 3 and Table S1). Some health districts located in the Saharan zone do not have a well-defined transmission period (for example Tidermene). TinEssako has a very low incidence and Dire has a double peak.

Relationship between malaria and meteorological factors

Principal component analysis of meteorological factors

PCA analysis provided 2 synthetic meteorological indices (SEI).

**Figure 4:** synthetic indices from the Principal Component Analysis (PCA) of the different meteorological factors.

PCA permitted to obtain two Synthetic Environmental Indices (SEI) with 87.7% inertia (Figure 4 Panel a). SEI 1 was determined by rainfall, relative humidity, soil moisture and NDVI positively and wind speed negatively SEI 2 was determined by temperatures (Figure 4, Panel b).

Uni and multivariate regression analysis

The univariate regression analysis by using general additive modeling (GAM). Showed a month lag between SEI 1 (rainfall, relative humidity, vegetation index and soil moisture) and malaria and a zero-month lag between SEI 2 (temperature) and malaria incidence.

Considering these lags, the multivariate analysis showed a linear relationship between malaria incidence and the SEI 1 (rainfall, NDVI, relative humidity and soil moisture) (p-value < 0.001).
Malaria incidence first decreased at low temperatures with SEI 2, and then rapidly decreased with high temperature values (SEI 2) (p-value < 0.01).

**Figure 5:** Changes in malaria incidence as a function of meteorological factors; GAM multivariate analysis.

Malaria incidence increases linearly with rainfall, relative humidity, soil moisture and NDVI (**Figure 5, Panel a**). It decreases with increasing maximum temperature (**Figure 5, Panel b**) and wind speed.

**Spatial**

**Adjusted Malaria incidence**

Annual adjusted malaria incidence of malaria at the health district level for 2019 was categorized into five (5) classes per 1,000 person-years. The median incidence was 125.34 cases per 1,000 person-year with a standard deviation of 86.48.

**Figure 6:** Annual malaria incidence at the health district level, adjusted for health facility access, Mali, 2019.

According to the WHO classification, the adjusted malaria incidence in 2019, Mali, was distributed as follow (**Figure 6**):

- 12 out of 75 health districts in the zone of very low transmission with 100 cases per 1,000 person-years; 7 health districts an incidence between 5 to 50 cases per 1,000 person-years and 5 health districts an incidence between 50 and 100 cases per 1,000 person-years, all were northern;
- 19 out of 75 health districts in the low transmission zone;
- 20 out of 75 health districts in the moderate transmission zone;
- 24 out of 75 health districts in the high transmission zone.

**Situation of average rainfall between 2017 - 2019 by health district in Mali**

**Figure 7:** Map of average annual rainfall from 2017 to 2019 by health district in Mali.

The average annual rainfall from 2017 to 2019 varies from less than 200 mm in the desertic zone to more than 1100 mm in the Sudano-Guinean zone. Within the 75 health districts, 17 have a rainfall of less than 200 mm (desert zone), 20 have a rainfall between 200 and 600 mm (Sahelian zone), 10 have...
a rainfall between 600 and 800 mm, 21 have a rainfall between 800 and 1100 mm (Sudanese) and 7
have a rainfall above 1100 mm (Sudano-Guinean zone).

Percentage of the population outside a 5-km rayon of a health facility and Annual
incidence of malaria

Populations living outside at 5-km from a health facility were low in Mali, justifying the
implementation of specific strategies to improve care access.

Figure 8: Percentage of population outside at 5-km radius of a health facility in Mali 2019

Prevalence of malaria in children aged 3-59 months

The results below are from the 2018 Demographic and Health Survey (DHS-2018) of Mali among
children aged 3-59 months.

Figure 9: Malaria prevalence map for children aged 6-59 months according to DHS VI, Mali 2018.

Malaria prevalence according to DHS VI 2018 was 18.9% at the national level among children aged 6-
59 months in Mali. It was low in the northern regions of Kidal, Taoudenit, Tombouctou between 1 and
10% and the District of Bamako less than 1%. Some regions in the North such as Gao and Ménaka
showed a prevalence of over 10%. The regions of Sikasso, Ségou and Mopti showed the highest
prevalence with 29.7%, 25.9% and 24.9% respectively.

Child mortality in Mali

Mortality of children less than 5 years old data from DHS 2018 results were mapped by region
because the mortality information at the health district level is not available.

Figure 10: Map of mortality of children less than 5 years old from DHS 2018 survey in Mali.

The regions of Kidal and Gao and the District of Bamako showed the lowest mortality rates of 20%,
78% and 55% respectively.

Entomological results

The distribution of vector species and the insecticide susceptibility profile were mapped.
The malaria vectors found at the sentinel and research sites are distributed ubiquitously. These are *An. coluzzii*, *An. gambiae* and *An. arabiensis* (to a lesser degree compared to the first two). In the northern regions, Gao, Kidal and Timbuktu, the studies carried out were morphological identification. This means that at these regions, only *An. gambiae* s.l. was mentioned. The *An. funestus* group was also encountered particularly in the area of Niono (Segou Region), Banambani (Koulikoro Region) and Selingué (Sikasso Region).

**Figure 2:** Map distribution of resistance of *Anopheles gambiae* s.l., a major malaria vector to different insecticides from 2010 to 2019 in Mali.

Red dots show insecticide resistance in the health district, yellow dots show moderate sensitivity (below 90%) and green dots show a high sensitivity of major vectors to insecticide.

High resistance to pyrethroids and organochlorines was observed in several health districts. Resistance to carbamates (bendiocarb and propoxur) was also noted, although it appears to be less extensive than resistance to pyrethroids. The bioassays showed that the major malaria vector was sensitive to pyrimiphos-methyl (OP) and clothianidin (neonicotinoid). Sensitivity and resistance to fenitrothion (OP) were noted in sentinel sites where entomological surveillance was carried out.

**Stratification of malaria with the adjusted incidence in Mali, health district level**

**Figure 3:** Malaria transmission zones in Mali by adjusted incidence and prevalence

After stratifying the incidence adjusted with the attendance rate and the prevalence, we obtain the results for the 75 health districts:

- 12 health districts in the very low transmission zone
- 19 health districts in the low transmission zone
- 20 health districts in the moderate transmission zone
- 24 health districts in the high transmission zone.

**Stratification of malaria using adjusted incidence with meteorological and land use data in Mali, health district level**
Figure 14: Environmental class of malaria in Mali.

Class 1: Very low vegetation, no surface water and low average annual incidence, less than 50 cases per 1000 person-years for 6 health districts in the Sahara in northern Mali.

Class 2: Very low vegetation around oases or wadis and average annual incidence of less than 100 cases per 1000 person-years for 6 health districts in the Sahara in northern Mali.

Class 3: Low vegetation with an average annual incidence of 200 cases per 1000 person-years with 12 health districts in the North-East (South of the Sahara) and the presence of the Niger River.

Class 4: Presence of vegetation, low night temperature (<22°C) and daily temperature below 37.47°C and average annual incidence of malaria between 450-600 cases per 1000 person-years with 41 health districts in the Sahelian zone (central and south-eastern Mali) on the one hand and the rice-growing area along the river in the delta on the other hand.

Class 5: Presence of vegetation, high night-time temperature (>22°C), daily temperature above 37.47°C and average incidence between 200-400 cases per 1000 person-years with 3 health districts in the West.

Class 6: Presence of vegetation, urbanization, high night-time temperature (>22°C) and average incidence of malaria less than 200 cases per 1000 person-years with 7 health districts corresponding to the urban area of Bamako and the health districts of Kayes and Yélimané.

Targeting malaria strategies

The targeting of malaria interventions was based on the WHO global technical guidelines 2016-2030, national guidelines and the stratification.

Figure 15: Summary of interventions according to strata.

IRS: Indoor Residual Spraying
IPT: Intermittent Preventive Treatment for Pregnant Women
LLIN: Long-Lasting Insecticide Impregnated Mosquito Net
IG2-LLIN: 2nd Generation of Long-Lasting Insecticide Impregnated Mosquito Net
PBO-LLIN: Long-Lasting Insecticide Impregnated Mosquito Net with Piperonyl Butoxide
SMC: Seasonal malaria Chemoprevention.

We have eligible interventions according to strata and information on insecticide resistance in Mali.

Eligibility of health districts for SMC

Time series analysis of malaria incidence, intensity and prevalence allowed for mapping of eligibility of different health districts and the number of rounds. The malaria prevalence of DHS from 2018 of 1% malaria prevalence was used for the health districts of Bamako.

Figure 16: Length of SMC implementation per health district in Mali.
This classification provided 15 health districts no SMC, 3 health districts with two rounds, 10 health districts with three rounds, 32 health districts with four rounds and 15 health districts with five rounds.

Discussion

Malaria transmission remains seasonal in Mali with two transmission periods (Figure 2). The low transmission period is from January to June and the high transmission period is from July to December or even January [23]. Malaria transmission is characterized in some countries such as Burkina Faso by three periods of transmission with an intermediate period [31]. This situation was not observed in Mali.

Malaria transmission was very heterogeneous between health districts. In the health districts located in the south with early and abundant rainfall, the period of high transmission began from June to December (Table S1-2) with a monthly incidence of between 20 and 60 cases per 1,000 person-months. Health districts in the center, which were in the majority, had the standard high transmission period from July to December with an incidence of between 10 and 30 cases per 1,000 person-months. It represents the majority of health districts in Mali. For the northern health districts, the high transmission period was late, starting in August or even September and ending in January with an incidence drop for some in October. The incidence was often low, less than 5 cases per 1,000 person-months (Figure 3). These are generally health districts in the north and those located in flooded areas (Dire, Niafunké, Youwarou, Bourem, Gao, Timbuktu) [23].

In a randomized trial carried out in the Segou health district between 2014-2016, incidences were similar to these routine data [32].

The duration of the high transmission period varied from 2 to 6 months depending on the health district. The number of rounds for the SMC should be based on these results to be effective (Figure 15). In a context where financial resources are low, health districts needing more than four rounds may conduct a pilot cost/benefit study before scaling up [33,34].

This heterogeneity of transmission must be considered when implementing preventive interventions as seasonal malaria chemoprevention in children (SMC) and the number of rounds for an effective and efficient use of malaria control resources. Some health districts are not seasonal, which makes them ineligible for certain interventions targeting periods of high transmission as defined by WHO. This was the case in some health districts in Niger that have a low incidence of malaria [35]. These health districts must benefit from continuous weekly epidemiological surveillance to move towards case-by-case surveillance because of the low incidence level but also the risk of epidemics due to the lack of malaria premunition in the population.
To find a link between the incidence of malaria and environmental factors, the principal component analysis allowed us to select two axes that explained more than 80% of inertia (Figure 4). SEI 1 consisted of rainfall, soil moisture, relative humidity and NDVI. SEI 2 consisted of the maximum temperature [8, 23, 36, 37].

The adjusted incidence was calculated considering the frequentation rate to correct for the bias of under-attendance for several reasons.

Mapping of the adjusted incidence showed that more than a third of the health districts are the zone of high transmission in Mali with more than 450 cases per 1,000 person-years. These health districts are located in areas of high rainfall, along rivers and flooded areas. Health districts with moderate transmission were generally located in the Sahel with an incidence from 250 to 450 cases per 1,000 person-years. Health districts in areas of low and very low transmission account for 41%. They were located in areas of low rainfall with a very low population density of less than one habitat per km² (Figure 7). They are located in northern Mali (Figure 6 and 13). These low transmission areas could be potential candidates for the use of the mass treatment administration strategy to move towards malaria pre-elimination in Mali [38–40]. A Study carried out in Dire, in the Sahelian zone of Mali showed between incidence from 20 to 120 cases per 1,000 person-years [23].

A cohort study carried out in Bancoumana on the incidence of malaria confirmed these results with an incidence of 760 per 1,000 person-years in 2019 in the general population, 530 cases per 1,000 person-years in children under 5 years old and 890 cases per 1,000 for children aged 5 and 10 years old [41].

The prevalence results of the DHS only concerned children aged 3–59 months in the different regions. These results are in line with those of the incidence with low malaria prevalence in the northern regions of Mali and the urban area of Bamako. Several studies have confirmed the low prevalence of malaria in these areas due to the low density of malaria vectors linked to low rainfall on the one hand and urbanization on the other (Figure 8). This is the case in other major cities in West Africa [23, 42–44]. But the low prevalence of malaria does not take into consideration the peri-urban area with their specificity where the prevalence can be high or maintained [10]. Special arrangements must be made for these suburban areas to control malaria. The percentage of the population living outside a 5-km radius of a health center remains very high in the majority of Mali's health districts (Figure 7). It is 40 to 60% in the health districts of the center of the country and more than 80% in the northern health districts (Sahara zone).

Alternatives to improve accessibility outside of 5km, such as the introduction of community health agents, must be strengthened to compensate for this lack of access to healthcare for children and pregnant women. The involvement of these health workers in community diagnosis and treatment of uncomplicated malaria can help in the control of malaria [45–48].
DHS mortality data showed a low infant and child mortality rate, under 100 deaths per 1,000 in the northern regions and in Bamako, the capital, compared with 130 deaths per 1,000 in the southern regions (Kayes, Sikasso, Ségou and Mopti). The region of Tombouctou in the north had 131 deaths per 1,000. There was a sharp decline in mortality at the national level between 1987 and 2012, from 247 to 95 deaths per 1,000. It increased in 2018 to 101. This trend is found in the incidence data which have been on the rise in recent years according to the WHO annual report on malaria [49] and a study carried out on mapping child growth failure [50].

The available data on malaria vectors was based on research in the sentinel sites. These sites are representative of malaria transmission throughout the country. They carry out clinical, parasitological, and entomological surveillance. Resistance to insecticides [51–53] has been observed in the majority of A. gambiae vectors, with the exception of two which are pyrimiphos-methyl in Koulikoro [44] and Clothianidins (Neoticotinoid) [54]. This resistance appears to be widespread in Mali and could compromise the effectiveness of vector control. Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) is responsible for 70% of the reduction in malaria cases [55–57]. The increase in resistance is pushing countries like Mali to use 2nd generation combination insecticides and to increase surveillance on insecticides to continue to benefit from their efficacy (Figure 10-11).

Stratification has been done using data from Epidemiological surveillance or prevalence surveys [58]. The stratification of malaria in Mali was carried out based on incidence adjusted at the frequentation rate only [7] then with meteorological and land use data of the health districts [58]. The results of the two methods are almost similar. The north-south gradient is compromised by the presence of the River Niger in some northern health districts. The zones of very low and low transmission are made up of the health districts of the Sahara strip, part of the Sahel and the capital of Bamako with health districts of Kayes and Yélimané (Figure 14), which have better access to health care. Environmental classifications 1 and 2 are identical, but wadis and oasis are found in some class 2 health districts. These points, which are crossroads, can constitute malaria epidemic foyers in the rainy season [59]. These epidemics were described in the studies of Doumbo et al in the Sahara of Mali [60,61]. Class 3 is located south of the Sahara and has a high malaria risk than Class 1 and 2 because of the presence of the river. Class 5 is similar to class 3 in terms of incidence but there is the absence of the river which is replaced by the presence of low vegetation. This is a Saharan area with epidemic potential [62].

The health districts of the moderate transmission zone are located in the Sahelian zone of Mali, and the zone of high malaria transmission is located in the south, the Sudanian zone (Figure 1, 13-14). Class 4, where the majority of health districts are located, is the malaria endemic area of Mali. The risk is increased by the presence of the river and the cultivation areas in the delta. Consequently, the Niger River may have an important role in malaria transmission in Mali that must be considered in the implementation of control interventions [63–65]. Environmental class 6 is located in the Sahelian zone...
with an environmental risk as in class 4, but transmission is low due to urbanization and better access
to care. This is the capital city of Bamako and the health districts of Kayes, and Yélimané. The two
latter have many health care’s structures through the investment of expatriates (Figure 8).

After the stratification, interventions will be targeted according to strata. For health districts in the
very low transmission zone, priority interventions may be the strengthening of epidemiological
surveillance for the early detection of epidemics and molecular surveillance to maintain the level of
transmission [35,66], diagnosis and treatment. rapid malaria cases (DTCP) improving the capacity of
community health workers, routine use of PBO-LLIN and intermittent preventive treatment (IPT) with
Sulfadoxine Pyrimethamine (SP) during pregnancy. The use of Mass Drug Administration in the
general population by ACT, mass distribution of LLINs and IRS of a malaria epidemic event is
recommended. Countries such as Algeria and Mauritania that border health districts in this zone have
all eradicated malaria [67,68]. By keeping up the epidemic surveillance efforts that have been started,
Mali will be able to rapidly reach the pre-elimination phase in these areas. However, epidemiological
and molecular surveillance will be crucial with the resurgence of \textit{Plasmodium vivax} and \textit{Plasmodium
malaria} [69,70]. Diagnosis and treatment will be improved with the introduction of multi-species
rapid diagnostic tests (RDTs) to detect other species outside of \textit{Plasmodium falciparum} and staff
monitoring [71,72].

For the low transmission zone, the priority interventions are SMC, PBO-LLINs, IPT, DTCP including
community health agents. Mass drug administration may be applied targeting place and period in order
to limit malaria transmission, in a bottle-neck approach [73]. In the moderate transmission zone, the
interventions to be implemented are SMC, IG2-LLINs, IPT-PS, DTCP including community health
agents. Activities will be intensified in areas of high transmission to reduce the burden of malaria
(SMC, IRS, IG2 LLINs, IPT, and including by community health agents). These different
interventions will be supported by advocacy for funding and behavior change communication at all
levels. The choice to use IG2-LLIN and PBO-LLIN was due to the spread of insecticide resistance
[74–76].

The number of rounds per health district will depend on the duration of the period of high transmission
(Figure 15). Health districts with a long transmission period will be able to make 4-5 cycles and
health districts with a short transmission period will be able to make a maximum of 3 cycles. The
number of SMC rounds can also take into account the bimodal transmission of malaria, especially in
flooded areas [23].

The main limitation of this study was the choice of the health district scale. Malaria transmission is
heterogeneous within a health district (several health areas) and interventions can be inappropriate in
the whole district. However, this stratification is dynamic, a short revision mechanism must be put in
place to adjust for insufficiencies.
The limitations of this study are the period of data collection of confirmed cases and the time scale which was monthly. Another limitation is the unavailability of meteorological observation data in some health districts. However, we used remote sensing data for these health districts.

Conclusion

This stratification of malaria carried out at the health district level in Mali resulted in 12 health districts in the very low transmission zone, 19 in the low transmission zone, 20 in the moderate transmission zone and 24 in the high transmission zone. Meteorological and environmental factors associated with malaria transmission have been identified. It made it possible to move towards targeting priority interventions by strata.

Transmission periods were identified for each health district for the implementation of SMC and other appropriate interventions. It is a dynamic document that must be revised periodically to consider observations from epidemiological surveillance and research activities. It provides the starting point for a phase towards pre-elimination in targeting control strategies to a specific stratum which is, therefore, more optimized in terms of efficiency and resource-saving.

Availability of data and materials

The data and background maps are available at the level of the authors and the NMCP of Mali. Anyone wishing to consult or use these data are requested to contact us.

Abbreviations:

PCA: Principal Component Analysis
AIRS: Atmospheric Infrared Sounder
DDT: Dichloro-Diphenyl-Trichloroethane
DGSHP: Directorate-General for Health and Public Hygiene
DHIS 2: District Health Information Software 2
DNP: National Population Directorate
DRS: Direction Régionale de la Santé
DHS: Demographic and Health Survey

Eq: Equation

GPS: Global Positioning System

IMERG: The Integrated Multi-Satellite Retrievals for Global Precipitation Measurement

IRS: Indoor Residual Spraying

IPT: Intermittent Preventive Treatment for Pregnant Women

LLIN: Long Lasting Insecticide Impregnated Mosquito Net

IG2-LLIN: 2nd Generation of Long-Lasting Insecticide Impregnated Mosquito Net

PBO-LLIN: Long Lasting Insecticide Impregnated Mosquito Net with Piperonyl Butoxide

MODIS: Moderate Resolution Imaging Spectroradiometer

NDVI: Normalized Difference Vegetation Index (Enhanced Normalized Difference Vegetation Index)

OC: Organochlorines

OP: Organophosphates

PY: Pyrethroids

GPHS: General Population and Habitat Survey

s.l.: Sensu Lato (broad sense)

s.s. Sensu Stricto (strict sense)

GIS: Geographic Information System

SLIS: Local Health Information System

RDT: Rapid Diagnostic Test

DTCP: Diagnosis and treatment of malaria cases

Consent to publication:

Not applicable.
Authors' contribution

Authors' contribution: MC and IS designed the study; VS, MM and LS. collected the field study coordinated by MC; MC and IS. developed the statistical analysis plan with LS, MD, AK O, CSB, MDB, AMD, SD, JG, and MBC, MC carried out the statistical analysis and the supervised IS and JG. performed the cartographic analysis with the participation of MC, AMD, and IS. JG, DT, IC, BS, AMN, and MS participated in the statistical analysis and validated results. MC and IS wrote the manuscript. All authors participated and agreed to the published version of the manuscript.

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The authors declare no conflicts of interest.

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