Malaria Risk Mapping for Control in the Republic of Sudan

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Abstract. Evidence shows that malaria risk maps are rarely tailored to address national control program ambitions. Here, we generate a malaria risk map adapted for malaria control in Sudan. Community Plasmodium falciparum parasite rate (P/PR) data from 2000 to 2010 were assembled and were standardized to 2–10 years of age (P/PR2–10). Space-time Bayesian geostatistical methods were used to generate a map of malaria risk for 2010. Surfaces of aridity, urbanization, irrigation schemes, and refugee camps were combined with the P/PR2–10 map to tailor the epidemiological stratification for appropriate intervention design. In 2010, a majority of the geographical area of the Sudan had risk of <1% P/PR2–10. Areas of meso- and hyperendemic risk were located in the south. About 80% of Sudan’s population in 2011 was in the areas in the desert, urban centers, or where risk was <1% P/PR2–10. Aggregated data suggest reducing risks in some high transmission areas since the 1960s.

BACKGROUND

During the era of the Global Malaria Eradication Program (GMEP) it was recognized that the paradigm of “one size fits all” for the selection of appropriate interventions would not work. Countries were encouraged to develop a reconnaissance of their malaria epidemiology that included mapping the intensity of transmission, distribution of dominant vectors, and epidemiological features important for local transmission, including population settlement, rivers, dams, and agricultural areas. Maps developed by national malaria control agencies during the GMEP varied in the information used but most were based on the association between rainfall duration and malaria seasons, altitude, proximity to breeding sites, and occasionally supported by empirical observations of incidence and prevalence of malaria. There was an obvious appetite for risk mapping over 60 years ago and a sense that these were important national atlases to guide disease control. The science and effort to mount malaria cartography across much of Africa diminished when the regional control agenda shifted from one of preventing infection to treating fevers in the late 1970s.

In 2011, the World Health Organization (WHO) Office for the Africa Region (AFRO) developed a manual to assist countries in developing their National Malaria Strategic (NMS) plans including, as a prelude, the undertaking of a National Malaria Program Performance Review (MPR). The MPR should include a detailed review of the malaria epidemiology and stratification including the geographical distribution of malaria burden, parasite prevalence, and parasite species. This renewed plea for national malaria risk mapping coincides with a time when the international donor community is constrained by the global financial crisis. Accessing overseas development assistance and national domestic funding for malaria control will require a much stronger evidence-based business case to define the needs of control and elimination sub-nationally to allocate limited financial resources more efficiently.

Over the last 15 years there has been a proliferation in the co-availability of 1) national, geo-coded parasite prevalence data; 2) spatially interpolated climate data derived from ground station observations; and 3) remotely sensed satellite surrogates of climate, urbanization, and topography. Advances in computing speeds and model-based geostatistical (MBG) techniques have increased our ability to define the spatial risks of malaria endemity using probabilistic approaches at high spatial resolutions. These advances have underpinned approaches to defining the global patterns of malaria transmission intensity and spurred a renaissance in malaria risk mapping at country-levels. Today, National Malaria Control Programs have access to a range of state of the art mapping products that might serve their planning needs. However, each country has specific epidemiological and intervention needs that must be accommodated with standard approaches to malaria risk mapping to provide adequate planning information.

Here, we examine the use of MBG applied to nationally assembled malariometric data in the Republic of Sudan to define the contemporary spatial intensity of Plasmodium falciparum transmission and use other remotely sensed data to define additional epidemiological strata important for sub-national malaria control. We discuss the applications of this map for the future of malaria control in the Sudan and compare the descriptions of malaria risk today with historical GMEP definitions 50 years earlier.

METHODS

Country context. Malaria transmission is maintained almost entirely by Anopheles arabiensis. Patron across all of the Republic of Sudan. There are possible foci of Anopheles gambiae s.s. transmission but these are considerably rarer; in only one of 50 sites surveyed in the Republic of Sudan, at Sennar, was An. gambiae s.s. identified. Both Anopheles nillii (Theobold) and Anopheles pharoensis (Theobold) have been reported but neither are thought to contribute to transmission. Over 90% of all infections are with P. falciparum; despite the presence of Duffy-receptive populations, Plasmodium vivax is rare.

The Sudan has a rich history of malaria control dating back over 100 years with the establishment of “mosquito sanitary workers” who maintained house-screening, larviciding, and
engineering works to mitigate against the seasonal flooding of the Nile.\cite{40-42} Indoor residual spraying (IRS) using dichlorodi-phenyltrichloroethane (DDT) was first introduced in 1946 and expanded to rural areas by 1951 following pilot success in larger towns. The areas of focal control included Fung District (Blue Nile Province), Kordofan, and Darfur Provinces. From the mid-1950s DDT was increasingly replaced by Gammaxene. The IRS and larval control were gradually extended to smaller towns and the cotton agriculture areas south of Khartoum. In the 1950s chemoprophylaxis was only reportedly used in school children, the armed forces, and the police force.\cite{43} By 1970 the WHO regarded Sudan to be in the attack phase of elimination and the government divided the country into three zones to shrink the malaria map under the aegis of the Malaria Eradication Training Center at Sennar.\cite{44} However, this did not translate into a definitive and implemented national elimination program. Over the next 30 years there were a number of focal malaria elimination projects including: targeted projects along the banks of the Blue Nile as part of the Gezira Irrigation scheme that began in the 1930s;\cite{45,46} expanded during the 1970s and 1980s;\cite{47,48} and resurrected as the Gezira Malaria Free Initiative in 1999\cite{49,50}; sustained urban malaria control from the 1970s until the late 1990s when the Khartoum Malaria Free Initiative (KMFI) was launched in response to rising epidemics in the 1990s;\cite{51,52} the long-term collaborative project between the Governments of Egypt and Sudan at Wadi Halfa started in 1948 to prevent the “invasion” of An. gambiae into Egypt\cite{53} from the Wadi Halfa region sustained since the 1950s;\cite{54} projects at the Sennar Sugar factories;\cite{55} Roseires Dam and expanded control in Blue Nile region to include the Rahad irrigation scheme completed in 1983.\cite{56}

In concert with tackling the pan-African epidemic, Sudan launched its first national malaria strategy in support of the Roll Back Malaria initiative soon after 2001. As with much of sub-Saharan Africa the focus of control during the early 2000s was on increasing coverage of insecticide-treated net (ITN) distributions, targeted IRS and larval control, intermittent presumptive treatment of pregnant women, and improved malaria case management, including replacing chloroquine with artesunate + sulphadoxine pyrimethamine in 2004.\cite{57,58} In 2007 a revised national strategy was launched that had as its vision a 50% reduction of malaria-related morbidity and mortality by 2012.\cite{59} This strategic plan recognized the diversity of malaria risks across the Republic and tailored priority interventions accordingly including specific elimination ambitions in targeted areas (Khartoum and Gezira).\cite{60} Of the important spatially defined risk groups the strategic plan identifies large urban settlements outside of Khartoum and refugee populations that have transformed epidemiological risks and have posed challenges to malaria control since the 1980s when people began to arrive, and settle from Eritrea, Ethiopia, Chad, the Democratic Republic of the Congo and Somalia and internally displaced populations resulting from the North-South Sudan and the Darfur conflicts.

The age-standardization algorithm computes the influence of age on the probability of detecting infection at a given cluster location, which by extension is a function of the underlying transmission of that cluster.\cite{61} Continuous surfaces of the age-standardized data (P/PR\textsubscript{2010}) were generated using a space-time Bayesian geostatistical framework described in detail elsewhere\cite{18,28,72} and implemented using the Markov Chain Monte Carlo algorithm. The value of P/PR\textsubscript{2010} was modeled as a transformation of a spatiotemporally structured field superimposed with unstructured (random) variation on a regular 5 x 5 km grid from 2005 and 2010. The number of P. falciparum positive responses from the total sample at each survey location was modeled as a conditionally independent binomial variate given the unobserved underlying P/PR\textsubscript{2010} and a linear function of climatic and environmental predictors.
The environmental covariates that were considered were synoptic annual average EVI and precipitation, urbanization, temperature suitability index for malaria transmission and distance from the Nile River and major irrigation schemes resampled to 5 × 5 km grids. The values of the underlying ecological and climatic covariates were extracted to each survey location using ArcGIS 10 Spatial Analyst tool. Distance to the Nile River and major irrigation schemes was log-transformed before analysis because of its high positive skew. The covariates were then included in total-sets analysis, which is an automatic model selection process based on a generalized linear regression model and implemented using the bestglm package in R. This approach selects the best combination of the covariates based on the value of the Bayesian information criteria (BIC) statistic, which selects the set of predictors with the lowest BIC as the best model fit.

For each 5 × 5 km grid location samples of the annual mean of the full posterior distribution of PfPR2−10 for each year were generated. The full posterior distribution of PfPR2−10 was then used to generate the following malaria endemicity classes: PfPR2−10 < 1%; 1–10%; ≥ 10–50%; and >50%. A spatially representative 10% holdout dataset was used for model validation and measures of model uncertainty included the mean prediction error (MPE) and the mean absolute prediction error (MAPE). The probability of membership of a survey location to its assigned endemicity class was computed from the posterior distributions resulting from the Bayesian geostatistical model.

The PfPR2−10 risk classification was combined with the maps of aridity, urbanization, refugee camps, and irrigation and dams to create an adapted map of malaria stratification for the Sudan. Within each risk strata the projected population at risk in 2011 was extracted from a high-resolution population grid map. Population data for refugee camps were obtained from recent estimates of the United Nations High Commission for Refugees (UNHCR) and are not necessarily specific to the year 2010. A combination of strategic approaches defined within the NMS 2011–2015, the WHO and UNHCR guidelines on malaria control among refugees and literature on the control of malaria in urban areas and documented practices in both the urban areas of Khartoum and Gezira Malaria Free Initiatives were then used together with the PfPR2−10 predictions to adapt epidemiologically appropriate interventions for each malaria risk stratum.

Comparing 2010 malaria transmission with 1960. Malaria risk stratification in Sudan began in the 1930s based largely on latitude and proximity to the seasonal rise and fall of the Nile. In the early 1960s the WHO recommended that a national pre-eradication survey be undertaken across the whole of Sudan to support plans for a country-wide malaria eradication program. The survey was undertaken from 1961 to 1963 and included spleen and parasite rates, detailed descriptions of seasonality, topography, and assembled health center morbidity and mortality reports and its rationale resonates with calls 50 years later by the WHO to improve current malaria intelligence. The surveys during the GMEP arguably provided a richer set of epidemiological data compared with most contemporary malaria indicator surveys. Despite repeated attempts to locate the sampled village-level data from this 1960s survey at archives across the Sudan these raw data appear to have been lost or located outside of the country. It was therefore not possible to compare directly the 1960s data using identical methods to those used to predict risks in 2010. Examination of summaries of the national sample survey estimates of infection prevalence
in 1961–63, 2005, and 2010 were instead undertaken across the previously defined state boundaries of Northern, Red Sea, River Nile, Khartoum, and Kassala. It was not possible for the malariologists of the time to use modern geostatistical methods to quantitatively define endemicity at high spatial resolutions. As such only semi-quantitative maps were produced to assist in prioritizing malaria control during the GMEP era. This 1960s malaria risk map was digitized and

Figure 2. Map of \( P/PR_{2-10} \) malaria endemicity showing the desert fringe, urban settlements, refugee camps, irrigation schemes, and dams.

Figure 3. A map of the probability that a 5 x 5 km location belongs to the endemicity class to which it has been assigned.
displayed at a scale similar to the contemporary risk map to allow for a more direct comparison.

RESULTS

Predicting malaria transmission intensity in 2010. A total of 2,604 community PR survey clusters from 913 unique locations for the period 2000–2010 were used to predict at unsampled 5 × 5 km grid locations to the year 2010 using the Bayesian space-time geostatistical model. The results of the total-set analysis showed that the model with urbanization, precipitation, and EVI as the best fit in predicting PR and these variables were subsequently included in the malaria prediction model. The binned categories of the predicted endemicity are shown in Figure 2 including the spatial delineation of special epidemiological populations living in major urban centers, irrigation zones and refugee settlements. The probability of class membership was > 0.25 indicating better than chance classifications of endemicity throughout (Figure 3). However, the probabilities were lowest in the higher risk areas in the south of the country where risk is very heterogeneous and with sparse data distribution. The overall MPE and MAPE were −1.4% and 0.01%, respectively, and area under the curve values of 0.70 indicating overall good model accuracy.

The refined matrix of malaria eco-epidemiology and control interventions is presented in Table 1. The aridity constrained malaria-free “Desert Fringe” areas constitute 1.1 million km² (or 59% of Sudan’s land mass) and were occupied by 4.5 million out of the 31 million in Sudan people in 2011. The areas on the margins of the Desert Fringe classified as low stable endemic control (PR2 < 1%) cover almost all of the states of Northern, Red Sea, River Nile, and Khartoum and large areas of states further south (Figure 2) covering ~8.2 million people or 26.5% of the total population in 2011 (Table 1). The hypoenemic class of ≥ 1 but < 10% PR2 was predicted across the states of Northern Darfur, Northern Kordofan, White Nile, Gezira, Kassala and parts of the southern states encompassing 3.4 million people, 11% of the 2011 population. The mesoendemic class with pockets of hyperendemicity is located mainly in areas between the latitude 12° and the

| Table 1 |
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| | Strata: transmission levels | Areas | Population in millions (%) | Main control interventions*† |
| Desert Fringe: Malaria free | Majority of areas in the North above latitude 15° | 4.5 (14.5) | - Case surveillance, detection, and investigation. |
| Low stable endemic control: outside the aridity mask but < 1% PR2 | Focal areas in the Northern, River Nile, and Red Seas states, rural areas in Khartoum, southern parts of North Darfur, northern parts of South, and West Darfur, southern parts of North Kordofan, northern parts of South Kordofan Blue Nile, White Nile, Sennar, Gezira, Gedaref, and Kassala. | 8.2 (26.5) | - Case surveillance - Entomological surveillance - Larval control - Spatially targeted IRS - Epidemic early warning, early detection, and rapid response. |
| Hypoenemic: outside the aridity mask but 1–10% PR2 | Other rural areas in Greater Darfur, Kordofan, Blue Nile, White Nile, Sennar Gezira Gedaref, Kassala, Khartoum states | 3.4 (11.0) | - Spatially targeted IRS coverage - Spatially targeted LLIN coverage - Epidemic early warning and rapid response. |
| Largely mesoendemic transmission with pockets of hyperendemicity: > 10% PR2 | Southern parts of South Darfur, West Darfur, South Kordofan, most of Blue Nile: eastern parts of Sennar and Gedaref | 3.4 (11.0) | - Universal LLIN coverage - Epidemic early warning, detection, and rapid response with targeted IRS as a supplementary intervention |
| Urban malaria: Cuts across all endemicities but generally low because of urbanization and/or ecology | Khartoum and all large cities and state capitals | 8.4 (27.0) | - Case surveillance - Entomological surveillance - Source reduction where appropriate (with community involvement) - Larval control - IRS during threat of epidemics - Entomological surveillance - Targeted IRS - Larviciding - LLIN coverage in areas where baseline transmission is ≥ 1% PR2 - Rapid screening of incoming populations - Surveillance, preferably integrated with other disease information systems - Source reduction - LLIN coverage in areas where receptive transmission is > 1% PR2 |

*All malaria strata include effective case-management as an intervention.
†To match appropriate interventions to a given epidemiological stratum various reference sources were used for: urban areas7,8,10,14,17; refugee camps and internally displaced persons settlements5,9,10; irrigation schemes10,12 and for all other strata5,6,11,101
‡Low stable endemic areas are defined as those where PR2 < 1% and are considered to be areas where it is technically feasible to undertake malaria elimination.102

PR2 = Plasmodium falciparum parasitic rate; IRS = indoor residual spraying; LLIN = long-lasting insecticidal nets.
border with South Sudan and inhabited by an estimated 3.4 million people. The urban areas in Sudan made up of the capital city Khartoum, all the state capitals and other major towns contained 8.4 (27%) million people exposed to largely very low malaria risks. The irrigation schemes covered a population of 3.1 (10%) million, whereas a total of 3.2 million people were estimated to live in refugee camps in the Sudan. Although some of the refugees were from neighboring countries, it is expected that most are internally displaced people as a result of the Darfur conflict or tribal skirmishes along the border with South Sudan. Estimates of the refugee population were computed separately from the overall analysis of the proportion of population in different malaria strata in the Sudan.

Comparing 2010 malaria transmission with 1960. The 1960s survey covered 24,373 children between 2 and 10 years of age in all the previous states that now form the Republic of Sudan (Table 2). The product of this survey data and informed expert opinion, based on proximity to the Nile, rainfall patterns, and deserts is a map shown in Figure 4. Striking is the broad consensus on the spatial distribution of endemicity risk classifications today (Figure 2) and 50 years previously (Figure 4), with the exception of the meso- and hyper-endemic classes that appear wider and more prolific 50 years ago. The examination of summaries of the national sample survey estimates of infection prevalence 1961–63, 2005, and 2010 suggests that across the previously defined state boundaries of Northern, Red Sea, River Nile, Khartoum, and Kassala, \( P/PR_{10} \) years has remained consistently low over the last 50 years (Table 2). In the southern states of Darfur and Kordofan there have been a long-term decline and some evidence of a more rapid decline since 2005; interestingly, the Blue Nile state, which has the majority of irrigated areas, has supported relatively low transmission across the state since the 1960s.

### DISCUSSION

The use of empirical data is important to develop the cartography of malaria risk and is now relatively easy to accomplish at high spatial resolutions with the availability of mathematical and statistical tools and advances in computing speeds. To date the Republic of Sudan has relied on expert opinion maps developed from an informed set of climatic and location parameters that can now be quantified and modeled.
more accurately. Here, we have adapted the risk classifications of malaria that are currently defined in the Sudan national malaria strategic plan to suit the ambitions of the National Malaria Control Program (NMCP). This was achieved by combining the interpolated P/PR$_2$.10 predictions with better definitions of aridity, urbanization, irrigation schemes, dams, camps for refugees and internally displaced persons settlements as shown in Figure 2. Table 1 shows a summary of the malaria strata matched with appropriate interventions defined through the use of WHO guidelines and other reference sources (see footnote to Table 1). The important differences between this matrix of malaria eco-epidemiology and control interventions and those currently used by the national program is the expanded extent and population at risk of the Desert Fringe, the more precise definition of the spatial extents of urban areas, irrigation schemes, refugee camps, and importantly, the disaggregation of the previous large area of “seasonal malaria” into hypo-, meso-, and hyper-endemic areas to support more targeted planning. The comparison of the historical malaria into hypo-, meso-, and hyper-endemic areas to spatial and contemporary $P/PR_2$.10 shows the possibility of a long-term epidemiological transition operating in areas of stable meso- to hyperendemic transmission which accelerates from 2005. This transition may partly be because of the significant scale-up of malaria interventions in Sudan in the last decade. Since 2004, almost 12 million long-lasting insecticidal nets (LLIN) were distributed in the country by the NMCP and partners (NMCP and partners, unpublished data) and by 2009 over 40% of households owned at least one LLIN.

Across Africa, linking the mapping of malaria risk to strategic plans is not as frequent as it should be, with only five countries using mapped malaria epidemiology to definitions of appropriate intervention within their national strategic plans or applications to the Global Fund. The reasons for this disconnect are not well understood but are likely to include the lack of any clear recommendations on the combinations of interventions that best suit a given eco-epidemiological risk strata. What is clear is that in areas with a historically low receptive endemicity that remain low today the universal distribution of ITN is unlikely to be a cost-efficient means of using limited malaria financial resources. Alternatives to control in these areas are likely to be active case detection and investigation and appropriate larval, source control methods at identifiable breeding sites. Conversely, high coverage of ITN in historically meso-/hyper-endemic areas is likely within a few years to result in low parasite prevalence and lead to substantial reductions in disease burden. The southern fringes of the southern states require rapidly scaled coverage of ITN, it would be reasonable to restrict ITN distribution to these areas only. Larval control, as currently promoted in the Khartoum and Gezira Free Malaria initiatives, is appropriate for the endemicity reductions in these areas, and could be expanded more aggressively to 16 of the 42 urban centers within the hypo-endemic belt (Figure 2). The feasibility of malaria elimination in the states of Northern, River Nile, and Red Sea with the dominant desert ecology and the large urban setting of Khartoum should be explored. Here, the wide-area modeling parasite prevalence survey data becomes less valuable. New techniques that combine improved clinical data, serological surveys, and mapping techniques that define hot-spots are necessary.

Malaria risk mapping was as important to control 50 years ago as it is today in the Republic of Sudan. Maps such as the one shown in Figure 2 developed using empirical national survey data are key to strategic planning of interventions for future malaria control and elimination in the Sudan. The study is a collaborative work with the Sudan NMCP and it anticipated this will facilitate the quick adoption of the malaria risk map for control planning. This, however, must be a dynamic exercise, which should be updated with new empirical and environmental data every few years. Special efforts must be invested in the data sparse areas along the southern border where predicted transmission is high but where, historically, insecurity has been a problem making the populations here even more vulnerable to the burden of malaria. Data in this area could be improved either by oversampling during the next MIS or by undertaking targeted surveys. Finally, the data required to develop empirical malaria risk maps are becoming increasingly available, but the geostatistical skills required to develop the spatial and temporal models are highly specialized and probably out of the reach of most national programs for the foreseeable future. The use of MCMC algorithms in which models take a long time to converge and require large computing resources is also an additional obstacle to routine development of geostatistical malaria maps. Recent developments of algorithms such as integrated nested Laplace approximations (INLA), however, offer opportunities for developing spatial-temporal models that converge rapidly without loss of predictive accuracy and can be run on an ordinary desktop.

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