Subnational mapping of anemia and etiologic factors in the West and Central African Region

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Ethical Standards Disclosure: This is a secondary analysis of Demographic and Health Survey (DHS) data. The ethical responsibility for the DHS lies with the institutions that conducted the surveys in each country; we, therefore, did not require ethics approval for this study.

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Abstract

Objectives: Despite bold commitments to reduce anemia, little change in prevalence was observed over the past decade. We aimed to generate subnational maps of anemia among women of reproductive age (WRA), malaria transmission, and hemoglobinopathies to identify priority areas, but also explore their geographical overlap.

Design: Using the most recent Demographic and Health Surveys (DHS), we first mapped anemia clusters across Sub-Sahara Africa (SSA) and identified the WCA as a major cluster. Geographic clusters with high anemia and related etiologic factors were identified using spatial statistics. Multilevel regression models were run to identify factors associated with any, moderate and severe anemia.

Settings: West and Central African countries (n=17).

Participants: WRA (n= 112,024) residing in 17 WCA countries.

Results: There was a significant overlap in geographical clusters of anemia, malaria, and hemoglobinopathies, particularly in the coastal areas of the WCA region. Low birth interval (0.86 [0.77, 0.97]), number of childbirth (1.12 [1.02, 1.23]), being in the 15-19 age range (1.47 [1.09, 1.98])) were associated with increased odds of any anemia. Unimproved toilet facility and open defecation were associated with any anemia, whereas the use of unclean cooking fuel was associated with moderate/severe anemia ($P<0.05$). Access to health care facility, living in malaria prone areas, and hemoglobinopathies (HbC and HbS) were all associated with any, moderate or severe anemia.

Conclusion: Interlinkages between infection, hemoglobinopathies, and nutritional deficiencies complicate the etiology of anemia in the WCA region. Without renewed efforts to integrate activities and align various sectors in the prevention of anemia, progress is likely to remain elusive.

Keyword: anemia, etiology, women, hemoglobinopathy, infection, malaria

Introduction

Globally, 30% of non-pregnant women of reproductive age (WRA) were estimated to be anemic in 2019.[1] The consequences of anemia include poor physical performance, impaired cognitive function, and adverse perinatal outcomes. Women living in low- and middle-income countries (LMICs) are disproportionally affected by anemia, further hindering health and economic progress.[1] Recognizing this, in 2012 the World Health Assembly (WHA) approved a commitment to halve the anemia prevalence among WRA by 2025, which was later extended to 2030 to align with the Sustainable Development Goals (SDGs).[2] Despite these bold commitments, the anemia prevalence has shown little change over the past couple of decades,[1,3] questioning our understanding of the etiology of anemia and the appropriateness of the interventions put in place to achieve the targets.

The West and Central African (WCA) region has one of the highest prevalence of anemia in WRA in the world. According to recent estimates, about 55% of WRA in the WCA region are anemic, and the region has witnessed little progress over the years.[1,4] Understanding the geographic distribution of any, moderate, and severe anemia and their etiologic factors at subnational level is critical to effectively address and prioritize interventions aimed at preventing and treating anemia.[5] Many earlier studies often equated anemia to iron deficiency, which led to wide-held beliefs among program managers and implementers that anemia is best prevented and even treated with iron supplementation. Recent studies have reminded the complexity of the etiology of anemia, particularly in regions like WCA, where nutritional deficiencies, infections, malaria and hemoglobinopathies can overlap.[6,7]

The present study aimed to map any, moderate and severe anemia, risk of malaria transmission, and hemoglobinopathies to explore geographical overlaps to guide decision on where to intervene and which package to provide. We then evaluated the association between anemia (any and moderate/severe) and non-nutritional factors to inform complementary interventions, that if implemented along with existing nutritional interventions, can maximize anemia reduction.

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Methods

Overview and data source

First, we mapped high (any, moderate, and severe) anemia prevalence clusters for Sub-Sahara Africa to identify high prevalence clusters in the continent. We then pooled data on anemia and related factors from 17 countries in WCA region, by considering data from the most recent (post-2010) Demographic and Health Surveys (DHS), yielding a sample of 112,024 women of reproductive age. Given the very limited temporal change in anemia prevalence observed over the last decade in the region, we considered that the difference in survey years between countries is unlikely to affect comparability between countries.

Geo-referenced data related to hemoglobinopathies, and malaria risk were extracted from the Malaria Atlas Project database (MAPAtlas).[8] Data extracted from MAPAtlas were i) Sickle hemoglobin HbS allele frequency, ii) Hemoglobin C allele frequency (HbC), iii) Glucose-6-phosphate dehydrogenase (G6PD), and iv) temperature suitable for malaria transmission index. Data for HbC, HbS, G6PD, and temperature were downloaded in a spatial raster file from the MAPAtlas interface, and the raster files were imported to QGIS. Using the longitude and latitude coordinates of the DHS survey, we extracted the values of the geo-coordinates corresponding to each location and integrated them into our dataset for further analyses.

Outcomes

The prevalence and case-load distribution of anemia was mapped for the WCA region. Anemia was categorized into any, moderate, and severe anemia, after adjusting hemoglobin values for altitude and smoking. The following WHO recommended cut-offs were used to define the severity of anemia: mild anemia (11.0-11.9 g/dL), moderate anemia (8.0-10.9 g/dL), and severe anemia (< 8.0 g/dL). "Any anemia" in this study is defined as the occurrence of anemia at any severity level, including mild, moderate, or severe forms. The DHS program measures hemoglobin concentrations in a small volume of capillary blood with the HemoCue 201+ or the 301+ system.[9] Overlaps between any anemia, risk of malaria transmission, and hemoglobinopathy clusters were identified and mapped. Individual, household, and community-level factors associated with any and moderate/severe anemia were identified.

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Statistical analyses

Spatial statistics

First, we applied a Kulldoruff scan statistics on anemia data from SSA using the most recent (post-2010) DHS.[10] Geographic areas of (any, severe and moderate) anemia case distribution that is significantly different from what would have been obtained if the distribution was random were identified by a circular window. Confirmatory spatial analyses were run using SATScan by applying purely spatial Poisson scan statistics, and only clusters with statistically significant values ($P< 0.05$) were retained. Second, by selecting the WCA anemia cluster, we focused our analyses on data from 17 countries, for which hotspot maps were generated. The prevalence and caseload (density) of anemia were estimated for unmeasured areas using ordinary kringing via the software SAGA GIS.[11]

Univariate and Multilevel logistic regression

Univariate logistic regression with any anemia as an outcome was run. Variables with $P<0.02$ were included in the multilevel logistic regression. Multilevel logistic regression was run to identify factors associated with clustering of (any) anemia among WRA. Separate logistic regression models were run for 'any' and 'moderate and severe' anemia. Considering the hierarchical nature of the DHS data, we run a multilevel logistic regression at the individual and community levels.[12] First, a null model (M0) that is without independent variables was run to measure random variability using the Intra Cluster Correlation (ICC). The ICC was used to determine cluster level variation.[13] The second model (M1) was adapted to all lower level (individual level) factors; the third model (M2) was used for all higher-level household and individual factors; and the fourth model (M3) accounted for both lower and higher-level factors. The model goodness-of-fit was checked by the Akaike Information Criterion (AIC).

Given recent evidence of potentially issues of misclassification related to the use of capillary blood and hemocue for hemoglobin measurement, we have run additional multilevel regression model on the hemoglobin concentration as a dependent variable (**Supplementary file: Table S3**). Statistical analyses were conducted using Stata v14.

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Ethics

All data used in this study are publicly available and de-identified; ethics clearance and consent were obtained by the institutions that conducted the surveys.

Results

Our analyses were conducted on a total sample of 112, 024 women of reproductive age, of which 56,346 (50.3%) were anemic. Among the anemic women, 39.4 % (20, 854) had moderate anemia and 2.4 % (1,326) had severe forms of anemia. **Figure 1 (A)** shows maps with significant clusters of anemia for the most recent DHS survey rounds. A total of eight significant clusters of any anemia were identified for the SSA region. The biggest anemia concentration clusters were found in the WCA region and covered almost all the WCA countries. **Figure 1 (B)** shows temporal trend in the anemia prevalence between 2010 and 2019. A decrease of only three percentage points was observed for the WCA region. Further disaggregation of anemia trend figures shows that these declines are largely driven by anemia reductions observed in few countries like Ghana and Gambia (**Supplementary file: Table S1**). In contrast, countries like Mali, Niger, and Sierra Leone have seen increases in the anemia prevalence over the last decade.

Figure 2 presents the subnational distribution of the anemia prevalence (A) and caseload/density (B), by severity. Most countries in the region had areas with prevalence of any anemia exceeding 60%, but countries like Nigeria, Gabon, Mali, Benin, and Cote d'Ivoire had widespread areas with very high prevalence of any anemia (> 60%). However, when we considered moderate and severe forms of anemia, regions with prevalence above >30% were concentrated in Nigeria, Benin, part of Sierra Leone, Liberia and Burkina Faso. Severe forms of anemia were concentrated in Mali, Senegal, Guinea, Niger, Benin, and pockets in Nigeria. The highest density of (any) anemia cases were found in the coastal areas of the region, and most of Benin, Togo, Burkina Faso, and northern Nigeria. Examples of subnational maps of countries in the region with varying prevalence of anemia (**Supplementary file: Figure S1**) illustrate the between and within-country heterogeneity for various forms (severity) of anemia.

Figure 3 and 4 present maps showing concentration clusters of malaria and blood disorders such as HbS, HbC, and G6PD. HbS concentration clusters were found in Nigeria, Benin, Guinea,

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Sierra Leone, Gabon and part of DRC. HbC was concentrated in Southern Mali, Guinea, Northern Cote D'Ivoire, Burkina Faso, Northern Ghana, Togo and Benin. The main G6PD concentration clusters were found in Cote D'Ivoire, Central Nigeria, Western DRC, Southern Benin and Togo. Many of the coastal areas of West Africa had temperatures suitable for malaria transmission. Six clusters where anemia, malaria, and blood disorders (HbS, HbC, or G6PD) overlapped were identified and these included the following countries: Liberia, Sierra Leonne, Guinea, Ghana, Côte d'ivoire, Nigeria, and Benin. In Gabon and Mali, the anemia clusters overlapped only with blood disorders.

Figure 5 presents a forest plot showing factors significantly associated with any or moderate/severe forms of anemia in the adjusted multilevel model. Detailed results of the model are presented in Table **S2**. A number of individual factors like low birth interval (< 24 months), number of childbirths over the last 5 years, and being in the 15-19 age range (adolescent) was associated with increased odds of any anemia. In contrast, overweight was associated with reduced odds of anemia. Being adolescent, reported HIV positive were factors that were significantly associated with increased odds of moderate/severe anemia. In contrast, overweight was associated with reduced odds of moderate/severe anemia. Among household/community factors, unimproved toilet facilities and open defecation were associated with any anemia, whereas the use of polluting cooking fuel was associated with moderate/severe anemia only.

Among environmental factors, difficulty of accessing the nearest health care facility, living in areas with temperature suitable for malaria, and areas with high HbS allele frequency were associated with any anemia. Among these, living in malaria prone areas was not associated with moderate or severe forms of anemia. HbC allele frequency, rural residence and living in altitude lower than 1500 masl was significantly associated with higher odds of moderate/severe forms of anemia.

Discussion

The present study aimed to characterize the geographic distribution of anemia and identify social, environmental and health factors that contribute to the anemia burden of WRA in West and Central Africa. Our study showed that the WCA region is home to the biggest anemia cluster in Sub-Saharan Africa. Subnational mapping of anemia revealed that areas with high anemia

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prevalence (> 50%) were widespread. Higher risk for anemia, malaria transmission, and related blood disorders like sickle-cell trait overlapped in the coastal areas of the WCA region. A number of individual-, household-, and environmental- factors were associated with anemia, suggesting that the health and WASH sectors should more prominently engage with the nutrition sector in the fight against anemia.

Despite bold commitments to reduce the burden and prevalence of anemia (e.g. SDGs), little progress has been observed over the last decade. Regions like the WCA constitute anemia hotspot areas, with one of the world's highest reported prevalence of anemia. Our estimate from this study suggests that one out of every two women is anemic, a finding in line with recent global estimates.[1] Only three percentage point reduction in anemia prevalence was observed between 2010 and 2019, clearly indicating that efforts put towards anemia prevention are either suboptimal, not effective, or at times misguided by the believe that anemia is iron related. Indeed, the main, if not the only, existing public health interventions directed towards anemia prevention and treatment are IFA and malaria control, mirroring the two immediate factors that are nutritional deficiencies and diseases. Although these interventions are proven to be effective,[14] first they are not always effectively implemented at scale and in a convergent manner, particularly in the high anemia clusters identified. Both interventions are implemented in silo, by distinct sectors (health and nutrition) and with no or limited interaction. Second, even when implemented well, these interventions would only address anemia related to malaria or iron-folic acid deficiency; consequently, their impacts are attenuated in areas where the etiology of anemia is much more complex and involves a number of overlapping factors including underlying socioeconomic contexts.

Our regression model identified a number of individual, household, and environmental factors. Reproductive health related factors such as birth interval and parity, infections like HIV and malaria, and sanitation (i.e. open defecation and unimproved toilet facility) were all significant non-nutritional predictors of anemia. Hemoglobinopathies (HbS and HbC) were widespread and were significantly associated with any anemia for HbS, and moderate and severe forms for HbC. Although these are non-nutritional factors *per se*, they co-exist and interact with nutrition-related factors and can influence the effectiveness of existing nutritional interventions. For example, poor sanitation could increase the risk of helminth transmission, which can lead to hemolysis

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(e.g. hookworm) and poor absorption of nutrients.[6] Similarly, malaria and other infections/inflammation can reduce iron absorption through the up-regulation of hepcidin.[15,16] In such context, the prioritization of interventions may also change, with infection treatment being more favorable than iron supplementation that could override the "natural" defense mechanism that sequesters iron to make it less accessible to the infectious agent. [17,18] Also equally important would be to prevent infections and inflammation through better WASH, living conditions, and the prevention of indoor pollution related to the use of cooking fuel.[5]

In line with earlier studies, our study confirmed that blood disorders, malaria endemic areas, and anemia concentration clusters overlap.[19] Such overlap is expected as blood disorders like sickle cell are known to induce anemia that was reported to provide protection against severe malarial anemia, high density parasitemia, and reduce all-cause mortality.[20] However, sickle cell trait/disease has also been associated with nutrient deficiencies, including those of zinc, vitamin D, and folate. Depending on the severity of the sickle cell condition, nutritional interventions may have contrasting health impact. For example, prophylactic dosage of folic acid is helpful and currently used in the management of HbS,[21] whereas iron supplementation can have adverse outcomes by reversing the protection conferred by sickle cell and anemia against malaria and other infections.[22] Indeed, the British society of hematology guideline suggests that *"Iron supplementation should be given to women with proven iron deficiency (serum ferritin <30 μg/l); it should not be given empirically as for anaemic women without haemoglobinopathy".* Therefore, considering the risk of multiple micronutrient deficiencies, the risks associated with iron supply in face of the high malaria infections and sickle cell traits, perhaps a low iron-containing multiple micronutrient supplementation (MMS) may be a better and safer alternative to IFA in clusters where anemia overlap with sickle cell trait and malaria; However, this warrants a study of its own.

The present study has a number of limitations that needs to be considered when interpreting the findings. First, due to the cross-sectional nature of the surveys, the relationships reported in this study should be interpreted not as a causal relationship, but as associations. Second, although a comprehensive list of non-nutritional factors was included in our study, given the complex and multifaceted cause of anemia, these may not be complete. Third, hemoglobin data from the DHS are from capillary blood whose accuracy has been questioned in recent years. Fourth, because of

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the intricate relationship between non-nutritional and nutritional causes of anemia, teasing out their respective share was challenging, but rather our finding suggest that these two broad categories of etiologic factors should be addressed together. Notwithstanding the above limitations, the present study provides a unique and comprehensive assessment of the relationship between anemia, reproductive health, infection, hemoglobinopathy and other related factors.

The identification and mapping of clusters can help prioritize efforts and contribute to the design of more effective programs where multiple factors complicating the management of the prevention of anemia overlap. In view of the complexity of the etiology of anemia in the region, currently implemented prevention interventions are limited and simplistic. The etiology of anemia in this region is further complicated by the interlinkages between infection, hemoglobinopathies, and nutritional deficiencies. Without renewed effort to integrate efforts from various sectors, and recognizing the additional complication caused by hemoglobinopathies in the WCA region, progress is likely to remain elusive. In this study, we have identified geographical areas (overlap clusters) where such integration can be prioritized. Studies on the most optimal treatment and mix of interventions are urgently needed, but the whole region is likely to benefit from heightened malaria and infection prevention and treatment, reproductive health interventions that help increase birth interval, and improved nutrient intake through improved diets or nutritional supplementation. However, iron-containing supplements may need to be contextually evaluated and adapted. Although a transition from IFA to a low iron-containing MMS is likely to be beneficial in this context of widespread infection and sickle cell trait, this warrants to be studied urgently.

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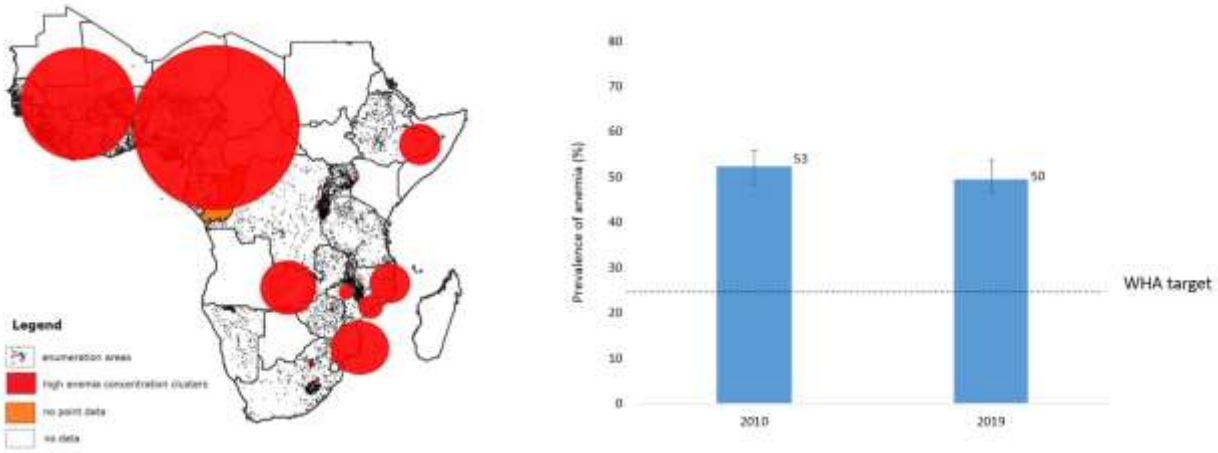

Figure 1 High anemia clusters in Sub-Saharan Africa (A) and the trend in anemia prevalence (%) in West Africa for women of reproductive age

Values represented by the bar charts are median (quartile 1, quartile 3); data is from 15 West African countries with post-2010 DHS data

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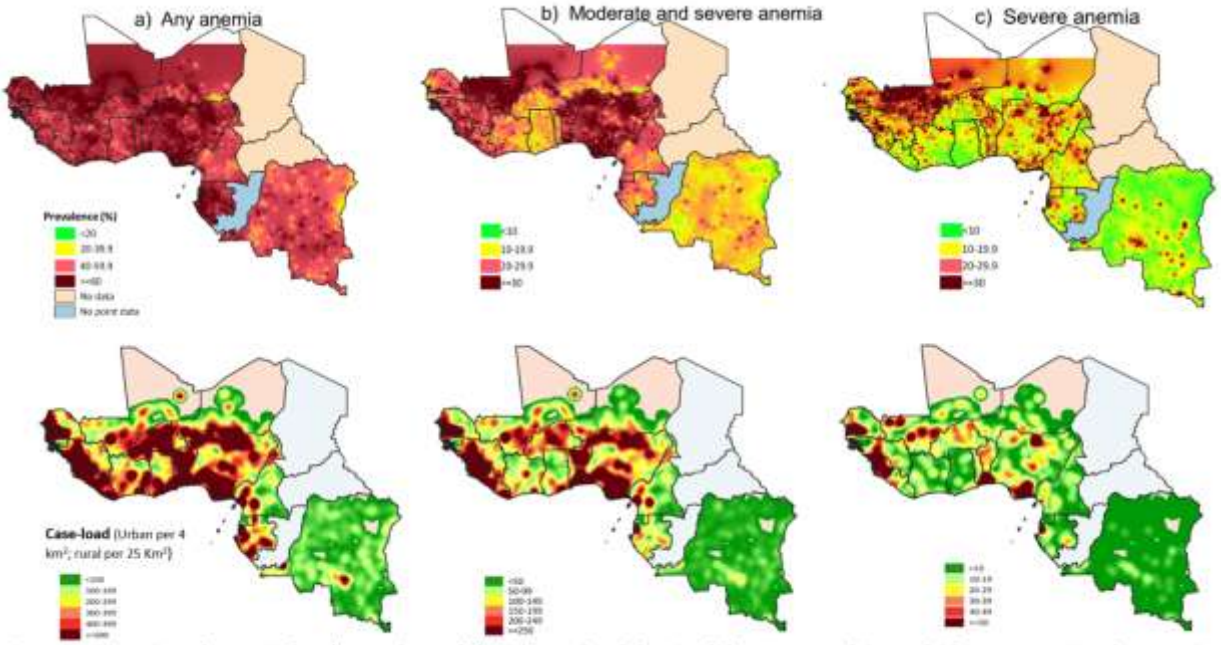

Figure 2 Mapping of anemia (any) prevalence (A) and case-load density (B) in West and Central African countries, by severity

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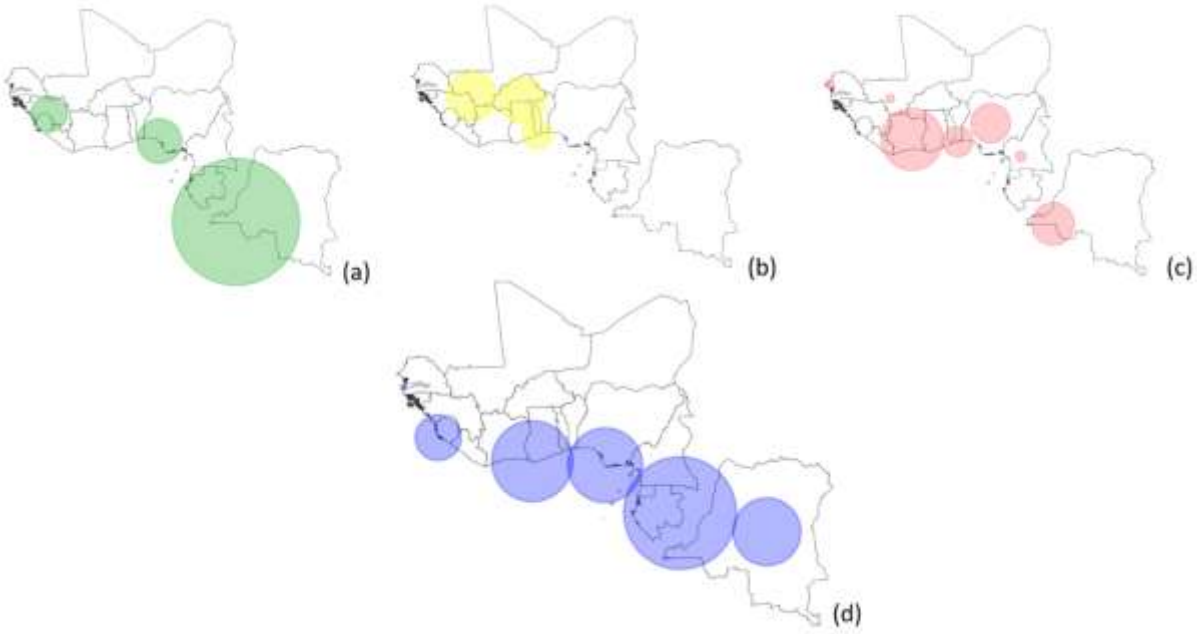

Figure 3 HbS (a), HbC (b), G6PD (c), and malaria (d) significant geographic clusters

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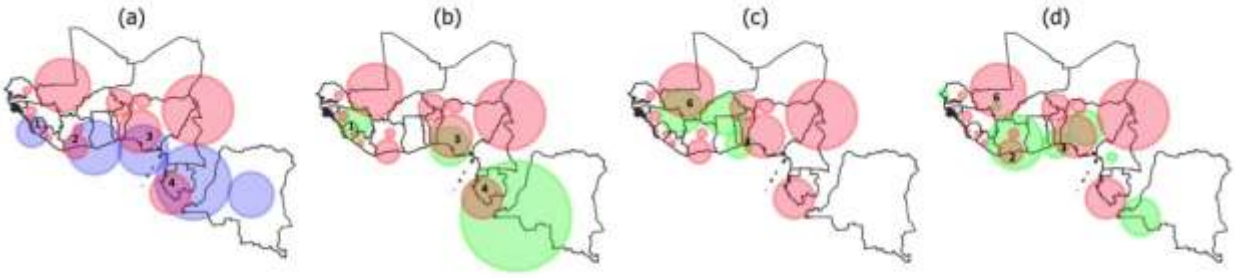

Clusters	Location	Overlaps
1	N. Liberia, Sierra Leone, S. Guinea	Anemia-malaria-HbS, HbC
2	S. Liberia, Cote d'Ivoire, Ghana	Anemia-malaria-G6PD
3	Nigeria, S. Benin	Anemia-malaria-HbS-HbC
4	Gabon	Anemia-HbS-HbC
5	Cote d'Ivoire	Anemia-Malaria-G6PD
6	S. Mali	Anemia-HbC-G6PD

Figure 4 Overlap between clusters of temperature suitable for malaria (a), HbS(b), HbS (c), G6PD (d) and anemia

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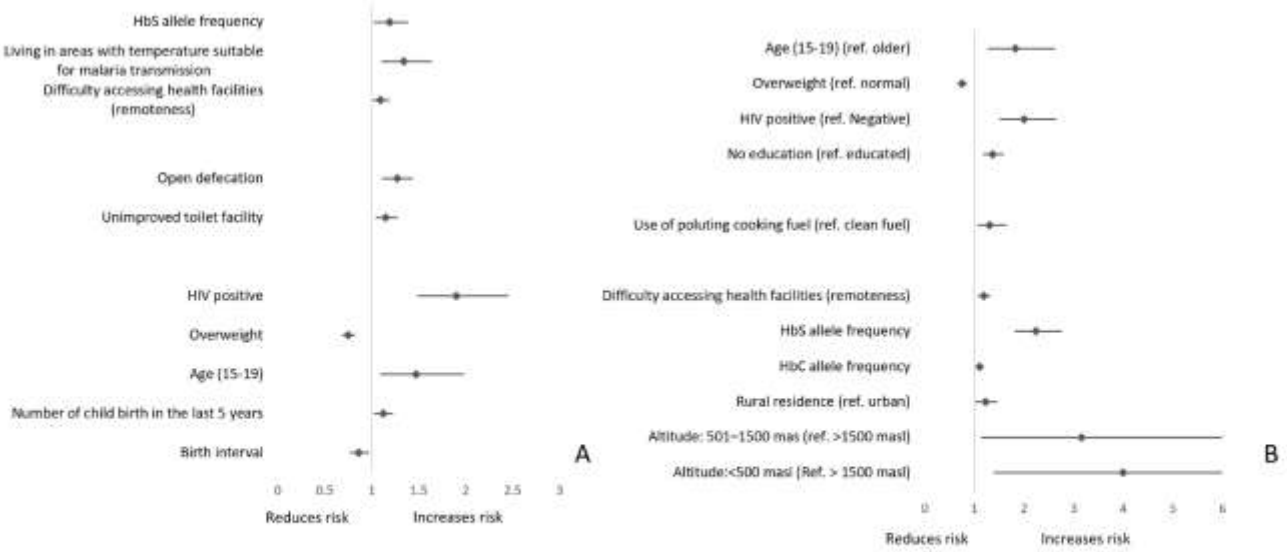

Figure 5 Factors significantly associated with any anemia (A) and moderate/severe anemia, adjusted multilevel regression model

All values are statistically significant (p< 0.05)

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