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URBAN MALARIA INCIDENCE AND GEOGRAPHIC CLUSTERING ACROSS AN URBAN-TO-RURAL CONTINUUM: RESULTS FROM A CASE-CONTROL STUDY OF CHILDREN IN BLANTYRE, MALAWI

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Urban areas pose challenges to malaria prevention because the location of transmission is often unknown, household-level environmental conditions are highly diverse, and the definition of "urban" is debatable. As part of a case-control study of malaria among under-fives in and around Blantyre City, Malawi, we analyzed disease patterns and risk factors associated with environmental, demographic and infrastructural characteristics. Blantyre (~1.1M pop.) has highly diverse land use/land cover (LU/LC), house density, facilities and services inside its ~225 sq km city limits. Active surveillance at 6 health facilities (HFs) inside and peripheral to the city was undertaken from April 2012 - October 2014. Children with malaria symptoms who were PCR-positive for ***Plasmodium*** infection (cases) were age- and location-matched with one or two PCR-negative children (controls) from the same HF. A total of 202 cases and 353 controls met the eligibility, consent, and matching criteria. Follow-up household visits determined each house location, construction traits, and peri-domestic LU/LC. A standardized questionnaire addressed demographics, malaria prevention, and travel-associated risk. GIS analyses of household location, geographical features, and satellite-image derived LU/LC compared cases and controls, controlling for demographic and behavioral factors. The urban-rural status of each household was classified by measures e.g. census population, house density, peri-domestic agriculture, proximity to infrastructure, and a PCA-derived "urbanicity score." Multivariate statistics demonstrated no simple associations between case-control status and standard definitions of "urban." However, household-level LU/LC and geographic features were highly predictive of malaria risk. Spatial statistical analyses suggested clustering unrelated to governmental urban designations, whereas derived classifications involving LU/LC and other measures were more predictive. Our findings have important implications for household- and community-level malaria risk, and for where malaria control efforts might be most effective.

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USE OF LONG-READ DEEP-SEQUENCING TO CHARACTERIZE GENETIC DIVERSITY AND PATHOGENIC VARIANTS OF VAR2CSA IN WOMEN WITH PLACENTAL MALARIA

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Placental malaria causes maternal anemia, severe malaria, infant death, preterm birth and low birth weight (LBW), largely owing to ***Plasmodium falciparum*** sequestration in the placenta. The sequestration results from the binding of infected erythrocytes (IEs) to placental chondroitin sulfate A (CSA); this interaction is mediated by ***P. falciparum*** protein VAR2CSA expressed on the surface of IEs. Within VAR2CSA, the ID1-DBL2x-ID2 region both binds CSA with similar avidity as the entire protein as well as elicits cross-reactive immune responses ***in vitro***. Therefore, the ID1-DBL2x-ID2 region is a promising candidate for vaccines against placental malaria. Such a vaccine may be enhanced by the identification of pathogenic variants of VAR2CSA, owing to the great sequence diversity of var2csa genes. However, the extent of genetic diversity of the ID1-DBL2x-ID2 region is incompletely understood, and no pathogenic var2csa genotypes have been described. Using placental and peripheral blood samples from 150 ***P. falciparum*** infected pregnant women in Benin and Malawi, we are conducting a molecular epidemiologic study to use next-generation sequencing technology in order to characterize the genetic diversity of the 1.5kb ID1-DBL2x-ID2 region and identify pathogenic variants that are associated with adverse birth outcomes. Alpha (within group) and beta (between groups) diversity will be compared between pregnant women of differing gravidities and birth weight. Additionally, genetic diversity will be compared between paired peripheral and placental samples from women with malaria at delivery to better understand the role of var2csa in cytoadherence of IE to the CSA and the subsequent sequestration in the placenta. Initial testing of 7 clinical samples from Malawi yielded 15 unique haplotypes occurring at a wide range of frequencies (80-1%), indicating that there exists a large reservoir of quantifiable var2csa variants. By exploiting this diversity using new sequencing technologies and analytic approaches, the results from the study will help elucidate the pathogenesis of malaria in pregnancy and directly inform on-going vaccine development efforts.