845. Children with Clinical Plasmodium falciparum Infection Have Increased Sharing of Haplotypes with Household Members as well as Temporally Proximal, Symptomatic Peers

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Session: 82. Global Health: Outbreaks, Controls, and Genetics
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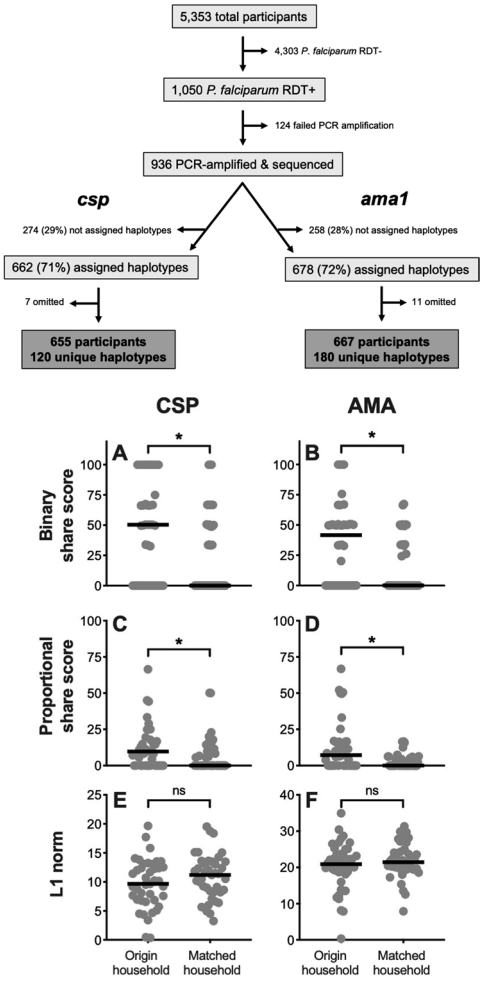
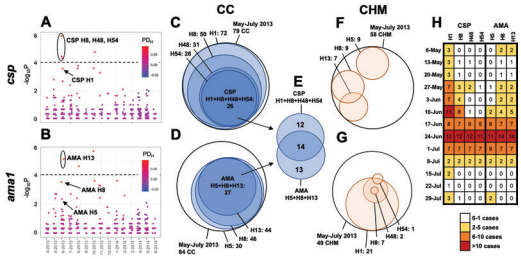
Background. Falciparum malaria transmission has failed to decline in proportion to control efforts in certain regions such as Bungoma county, western Kenya. One proposed strategy to eradicate malaria is ring testing and treatment; however, it remains unknown whether infections spread locally or if asymptomatically infected household members are a risk factor for clinical disease.

Methods. From April 2013 to June 2014, we enrolled 442 cases (RDT+ children hospitalized with malaria) and 442 matched controls; all household members of cases and controls were also enrolled and tested, of which 13.6% (n = 608/4449) were RDT+. From each RDT+ participant, parasite gDNA was PCR-amplified at both Pf circumsporozoite protein (*csp*) and apical membrane antigen 1 (*ama1*) loci, amplicons sequenced on an Illumina Miseq, and haplotypes inferred using dada2.

Results. We identified 120 *csp* and 180 *ama1* unique haplotypes (Figure 1). We evaluated the genetic distance between infected individuals using three novel indices: sharing of parasite haplotypes on binary and proportional scales and the L1 norm. Case children median [IQR] binary/proportional sharing of both *csp* and *ama1* haplotypes was significantly increased with members of their origin household (e.g., *csp* binary sharing: origin = 50.3 [0–87.5] vs. similar household = 0 [0–50.3]; P = 0.01; Wilcoxon sign-rank test), indicating that cases are more likely to share haplotype-identical parasites with members of their own household (Figure 2). We also computed population-level haplotype sharing indices for all pairs of case children and observed no association between genetic relatedness and geographic distance. In contrast, we identified a strong inverse relationship between haplotype sharing and temporal distance, which we exploited to identify the molecular signature of an outbreak (Figure 3).

Conclusion. Overall, these findings suggest that, although haplotype sharing is more common within households, temporal rather than geographic proximity predicts parasite genetic similarity. The observation that identical haplotype combinations are found nearly simultaneously across the study area implies that ring testing approaches may not effectively reduce transmission.





Disclosures. **All Authors:** No reported Disclosures.

846. Postnatally Acquired Zika Virus (ZIKV) Infection in Infants and Young Children in Guatemala: Serologic and Neurodevelopmental (ND) Evaluation

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Background. Diagnosing ZIKV infection in children in dengue (DENV) endemic regions is challenging. The kinetics and effects of maternal Ab on infant infection responses remain unknown, as do the ND effects of ZIKV acquired in early life.

Methods. This is a population-based prospective cohort study in infant–mother pairs and children <5 years in a rural DENV endemic area of Guatemala evaluating the incidence and ND outcomes of postnatally cquired ZIKV infection. Subjects were followed 1 year for symptoms of flavivirus-like illness (FLI), serologic and virologic evidence of ZIKV or DENV infection and ND outcomes. ZIKV and DENV neutralizing antibodies (NAb) were measured at enrollment and longitudinally. Subjects were classified as ZIKV- or DENV-infected based on NAb. Specimens from acute illnesses were tested for viral RNA by rRT-PCR. ND was assessed at enrollment and longitudinally using an adapted Mullen Scales of Early Learning (MSEL).

Results. In total, 1,371 subjects (374 children 1–5 years, 500 infants, 497 mothers) were enrolled from June 2017 to July 2018. Among 1,335 evaluable subjects, 7.6% (101) had serologic evidence of recent ZIKV infection (NAb >500 or >100 and DENV-neg); 13.2% (176) were DENV-pos only; 44.8% (598) were ZIKV-neg (NAb15 –<100) or low (<500) ZIKV and DENV NAb, suggesting prior flavivirus infection or cross-reactivity (Figures 1 and 2). ZIKV infection alone was more prevalent in children 1–5 years, while infants' serologic pattern was similar to that of their mothers. One child ZIKV seroconverted. In 391 FLI episodes (67 children 1–5 years and 215 infants with fever, rash, myalgia, and conjunctivitis; 109 mothers with fever, myalgia, and joint pain), acute DENV infections, but not ZIKV, were identified by rRT-PCR. MSEL scores were similar to US norms in infants <12 m (composite mean 94.8, SD 11.9), but lower in children 1–5 years in all domains (mean 75.1, SD 17.4, P < 0.0001) (Figure 3).

Conclusion. Serologic evidence of recent ZIKV infection, but no acute ZIKV, was documented in young children in Guatemala. Infant seroreactivity derives from prior maternal infection and DENV cross-reactivity. Observed substantial differences in ND scores between infants and children 1–5 years challenge the ability to isolate the potential effects of ZIKV infection in early life. NIAID Contract HHSN272201300015I Task Order HHSN27200013. FMM and EJA Co-PIs.

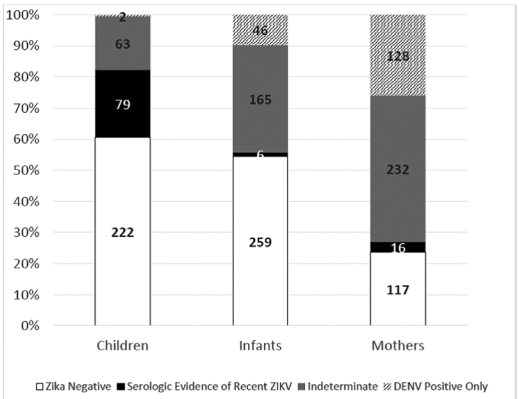

Figure 1. Categorization of study subjects' serologic status based on ZIKV and DENV NAb at enrollment, by cohort.

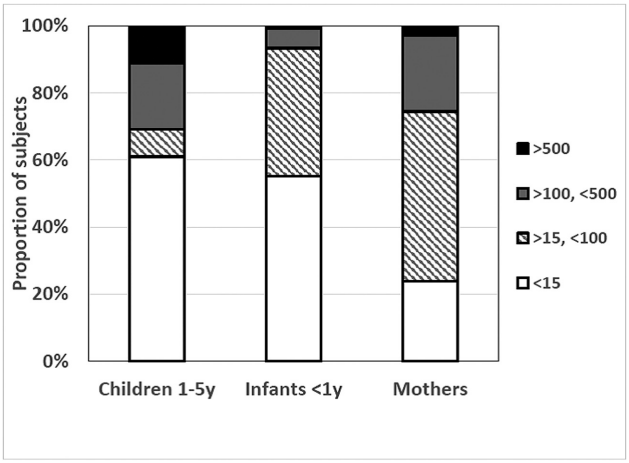

Figure 2. Proportion of subjects with detected ZIKV NAb by level and cohort at enrollment

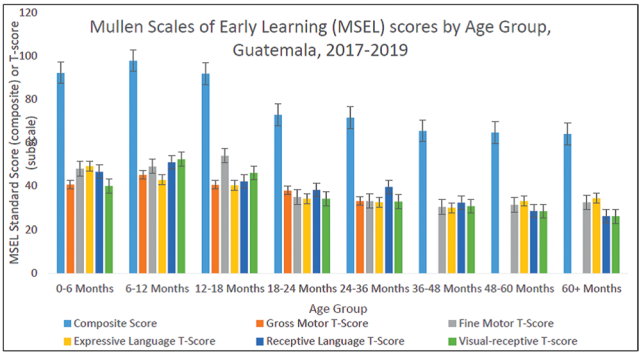

Figure 3. Mullen Scale of Early Learning (MSEL) composite (Standard score) and subdomain (T-score) results in infants and children by age.

Note: Composite score standard norm is 100, while subdomain standard norm is 50.

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847. The Effect of Antimicrobial Administration on Blood Culture Positivity in Patients with Severe Manifestations of Sepsis

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Session: 84. Novel Insights into Bacteremia and Endocarditis
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Background. Current guidelines recommend obtaining blood cultures prior to antimicrobial therapy in patients with sepsis. Administering antimicrobials immediately without waiting for blood cultures could potentially decrease time to treatment and improve outcomes, but it is unclear the degree to which this strategy impacts diagnostic yield.

Methods. We performed a patient-level, single-arm, diagnostic trial. Seven urban emergency departments affiliated with academic medical centers across Canada and the United States participated in the study. Adults ≥18 years of age presenting to the emergency department with evidence of severe manifestations of sepsis, including a systolic blood pressure <90 mmHg and/or a serum lactate ≥4 mmol/L were included. Study participants had 2 sets of blood cultures drawn prior to and immediately following antimicrobial administration. The primary outcome was the difference in blood culture pathogen recovery rates before and after administration of antimicrobial therapy.

Results. Of the 3,164 participants screened, 325 were included in the study (mean age, 65.6 years; 63.0% men) and had repeat blood cultures drawn after the initiation of antimicrobial therapy (median time of 70 minutes, IQR 50 to 110 minutes). Pre-antimicrobial blood cultures were positive for one or more microbial pathogens in 102/325 (31.4%) patients. Fifty-four participants (52.9%) had matching blood culture results after initiation of antimicrobial treatment. The absolute difference in pathogen recovery rates was 14.5% ([95% CI 8.0 to 21.0%]; $P < 0.0001$) between pre- and post-antimicrobial blood cultures. Results were consistent in an analysis of the per-protocol population (absolute difference, 13.3% [95% CI 6.1 to 20.4%]; $P < 0.0001$). Including the results of other microbiological cultures done as part of routine care, microbial pathogens were recovered in 69 of 102 (67.7%) participants (absolute difference, 10.2% [95% CI 3.4 to 16.8%]; $P < 0.0001$).

Conclusion. Among patients with severe manifestations of sepsis, the administration of empiric antimicrobial therapy significantly reduces the yield of pathogen recovery when blood cultures are drawn shortly after treatment initiation.

Figure 1 – Patient flow

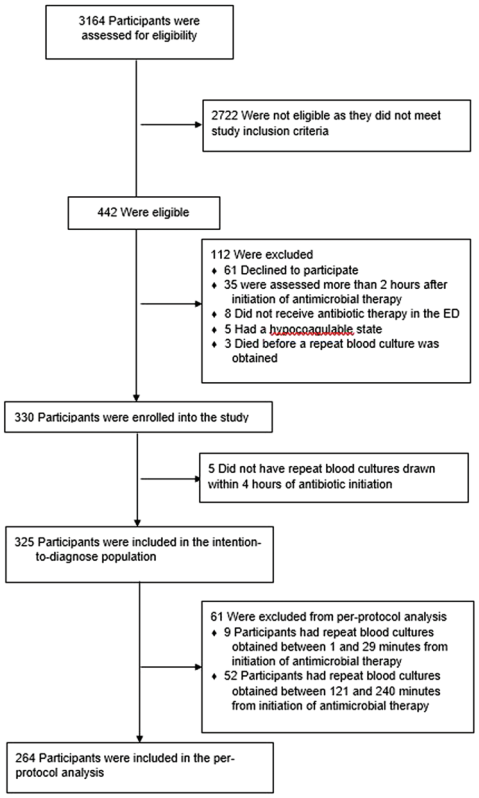

Figure 2– Difference in blood culture positivity rates between pre and post-antimicrobial blood cultures[1]

Time post-ABx administration	Total patients	Blood culture (+) pre-ABx	Blood culture (+) post-ABx	Absolute difference in positivity rates[2] [95% CI[3]]
30-60 minutes	124	45 (36.3%)	29 (23.4%)	12.9% [1.6-24.2]
61-120 minutes	140	35 (25.0%)	16 (11.4%)	13.6% [4.7-22.5]
121-240 minutes	52	21 (40.4%)	9 (17.3%)	23.1% [6.2-39.9]
Intention-to-diagnose population[4]	325	102 (31.4%)	54 (16.5%)	14.8% [8.3-21.2]
Per-protocol population[5]	264	80 (30.3%)	45 (17.0%)	13.3% [6.1-20.4]

[1]Compared to pathogens recovered in the pre-antimicrobial blood culture, excluding contaminants;
[2]Difference in blood culture positivity rates between pre and post-antimicrobial blood cultures;
[3]Exact binomial confidence intervals;
[4]Includes 9 patients who had their post-antimicrobial blood culture obtained within 30 minutes of initiation of antimicrobial therapy
[5]Defined as patients who had repeat blood cultures between 30 and 120 minutes from initiation of antimicrobial therapy