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TIMING AND SPATIAL HETEROGENEITY OF LEPTOSPIROSIS TRANSMISSION IN NORTHEAST THAILAND

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Thailand experienced an explosive country-wide outbreak of leptospirosis in the late 1990s, followed by high endemic transmission. The key barrier to effective control has been a lack of knowledge about the factors driving the timing and spatial distribution of this persistent transmission. We obtained data on weekly leptospirosis incidence in the 320 districts of northeastern Thailand between 2000 and 2014 from the Thai passive notifiable disease surveillance system (R506). We modeled incidence using a spatiotemporally explicit Poisson model and first examined the effects of current and lagged rainfall and temperature (Thai Meteorology Department). We then collected data on environmental covariates—land use (Thai Land Development Department), livestock and irrigation (FAO), NDVI, NDWI, and elevation (Google Earth Engine)—and evaluated their effects on spatial variation in incidence. Between 2000 and 2014, 53,719 cases of leptospirosis were reported in northeastern Thailand. The timing of peak incidence varied between early August and mid-October and did not coincide with periods of rice planting or harvesting. Instead, weekly incidence was strongly associated with rainfall and temperature in the current and two prior weeks. Districts with high flooding propensity (NWDI, OR = 95.24 per 0.01 index point), a high percentage of rice paddies (OR = 1.057 per %), and low cattle density (OR = 0.98 per head) had significantly higher leptospirosis incidence. We also encountered significant spatiotemporal residuals in our model that appear to represent focal outbreaks. Our study found that rainfall and temperature, not specific events in the agricultural cycle, were the main determinants of peak transmission. We also identified specific environmental features associated with persistent high transmission which may serve as targets for prevention. However, in addition to this endemic pattern, outbreaks contribute to the burden of leptospirosis. Understanding the sources of these epidemics will be important for leptospirosis control in this region.

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DNA AND RNA SEQUENCING-BASED METAGENOMICS FOR UNBIASED PATHOGEN DETECTION AMONG TANZANIAN ADULTS WITH UNDIFFERENTIATED FEBRILE ILLNESS

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In cohort studies of febrile illness in the tropics, conventional infectious disease diagnostics achieve a laboratory-confirmed diagnosis for only 40-50% of participants. We assessed the ability of unbiased next-generation sequencing-based metagenomics to identify an etiologic pathogen in Tanzanian patients with undifferentiated febrile illness (UFI, defined as the subset of febrile patients enrolled into our fever study who had no cough, diarrhea, stiff neck, or symptoms localizing to skin, soft tissue, joint or bone). Utilizing plasma samples from 65 UFI patients (median age 37 [interquartile range 23-45] years, 41 [63%] females) who had negative aerobic blood culture and negative malaria blood smear results, we performed RNA and DNA sequencing on the Ilumina NextSeq and analyzed the sequencing output with Taxonomer, an ultra-rapid, web-based metagenomics data analysis tool. This unbiased metagenomics approach detected an etiologic pathogen in 17 (26%) patients. *Plasmodium falciparum* was detected in 2 patients. Bacterial pathogens were detected in 8 patients: Enterobacteriaciae (n=3), Legionella spp. (n=2), and Mycobacterium sp., Pantoea sp., and Stenotrophomonas maltophila (n=1 patient, respectively, for the latter 3 bacteria). Parvovirus B19 was detected in 7 patients. HIV was identified in 6 patients (subtype D, n=3; subtype C, n=2; subtype A1, n=1), and viruses of unclear pathogenicity were detected in 11 patients (anellovirus, n=7; and GB virus C, n=4). Independent molecular testing is underway to confirm the presence of each etiologic pathogen in the original plasma sample. Our findings indicate that among patients presenting with febrile illness in the tropics, unbiased metagenomics can increase the proportion of patients with a laboratory-confirmed diagnosis. Identification of unsuspected parvovirus B19 illness is consistent with findings from a metagenomics study of febrile illness in Kenya. Metagenomics pathogen detection has the potential to become an important diagnostic modality for epidemiologic surveillance of fever in the tropics.

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SYSTEMIC INFLAMMATION AND NEURODEVELOPMENTAL OUTCOMES IN BANGLADESHI INFANTS GROWING UP IN ADVERSITY

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Hundreds of millions of children who grow up in poverty do not meet their full developmental potentials, which in turn affects their academic performance and future earnings. The identification of biomarkers that predict future neurodevelopmental outcomes offers a promising approach toward allowing for early identification of at-risk children. We previously published a study linking systemic inflammation to the neurodevelopment of children from a slum community in Dhaka, Bangladesh. We have validated our initial findings of systemic inflammation and neurodevelopment in a second cohort in Dhaka. We have also implemented advanced neuroimaging testing in these children via EEG, NIRs, and fMRI. We sought to determine whether elevated levels of the inflammatory markers CRP and soluble CD14 (sCD14) are associated with neurodevelopmental outcomes in Bangladeshi children. 422 infant-mother pairs from an urban slum in Dhaka, Bangladesh were enrolled at birth and followed prospectively. Inflammation was measured with sCD14, IL-1β and IL-6 at 18 weeks, and CRP at 6, 18, 40, and 53 weeks. Psychologists assessed cognitive, language, motor, and social emotional development using the Bayley Scales of Infant and Toddler Development at 78 and 104 weeks of age. We tested for the ability of inflammatory markers to predict developmental outcomes, independent of known predictors. Every 10 pg/mL increase in sCD14 was associated with a 1.1 to 2.0 decrement in cognitive and motor scores at 78 weeks and in all domains at 104 weeks. The cumulative number of CRP elevations that a child experienced in the first year of life, as well as IL-1β and IL-6 at 18 weeks of age, were also negative predictors of Bayley Scales results (all $p < 0.05$). In conclusion, elevated CRP, sCD14, IL-1β and IL-6 were associated with lower neurodevelopmental outcomes. Our findings implicate a role of inflammation in the neurodevelopment of children growing up in adversity and identify a strategy to predict children at-risk for developmental impairment. Further studies are needed to identify cut-off levels of these biomarkers at which targeted interventions should be implemented.