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PREVALENCE AND MOLECULAR EPIDEMIOLOGY OF NOROVIRUS AMONG CHILDREN WITH MODERATE-TO-SEVERE DIARRHEA IN THREE SUB-SAHARAN AFRICAN COUNTRIES: PRELIMINARY FINDINGS FROM THE VACCINE IMPACT ON DIARRHEA IN AFRICA (VIDA) STUDY, 2015 -2018

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Norovirus is an important enteric viral agent causing acute gastroenteritis in children worldwide. Using data from Vaccine Impact on Diarrhea in Africa (VIDA), a prospective, health center and community-based case-control study from May 2015 - July 2018, we describe the epidemiology of norovirus among children <5 years old in The Gambia, Kenya, and Mali. An MSD case was defined as a child 0-59 months old, passing ≥3 loose stools in the previous 24 hours with ≥1 of the following: sunken eyes, poor skin turgor, dysentery, IV rehydration, or hospitalization within 7 days of diarrhea onset. Diarrhea-free controls matched for gender, age, time, and community were enrolled at home. Stools collected from cases and matching controls at enrolment were tested for a panel of enteropathogens, including norovirus genotype I (NVI) and II (NVII), using TaqMan Array Card (TAC). A TAC cut-off value of <35 Cq was considered positive. Adjusted attributable fractions (AF) for each pathogen significantly associated with MSD were derived for each site and age stratum using multiple conditional logistic regression (CLR). Using LR, adjusting for age, blood in stool, and study site, we evaluated factors associated with norovirus MSD. VIDA included 4, 779 MSD cases (221 NVI-positive and 550 NVII-positive), and 4750 controls (234 NVI-positive and 513 NVII-positive). Whereas NVI was not significantly associated with MSD, NVII was significantly associated with MSD in all sites in infants 0-11 months old (The Gambia AF 5.0, 95% CI [2.0-9.9]; Mali AF 7.9, 95% CI [3.7-12.4]; and Kenya AF 10.3, 95% CI [6.9-14.7]), and in Kenya among those 12-23 months (AF 5.6; 95% CI [3.0-9.6]). Compared to non-NVII MSD cases, NVII patients were more likely to be infants (284 [51.6%] vs. 1413 [33.4%], aOR 3.09, 95% CI 2.38-4.01) and to present with vomiting (308 [56%] vs. 1927 [45.6%], aOR=1.40, 95% CI 1.16-1.69), but were less likely to present with blood in stool (54 [9.8%] vs. 637 [15.1%], aOR =0.72, 95% CI 0.53-0.98). We found that infants bear the greatest burden of MSD associated with norovirus GII.

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USING KERNEL DENSITY ESTIMATES IN LIKELIHOOD RATIOS TO OPTIMIZE ETIOLOGICAL PREDICTIONS OF INFECTIOUS DIARRHEA IN RESOURCE-LIMITED SETTINGS

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Non-laboratory methods to more accurately assess etiology are needed for appropriate management of pediatric diarrhea in low and middle income countries (LMICs). In LMICs, etiological diagnosis is rarely made, and a large number (up to 70%) of diarrheal patients are prescribed antibiotics empirically. Our goal is to build an electronic clinical decision support system (eCDSS) with multiple data sources appropriate for use in LMICs. We use clinical and quantitative molecular etiologic data from the Global Enteric Multicenter Study (GEMS) to develop predictive models for viral-only diarrheal etiology in young children, given the lack of efficacy of antibiotics for viral-only infections. We use the post-test odds (PTO) formulation which allows for prior knowledge as well as flexible inclusion or omission of one or more "tests", or information sources, for evaluating the likelihood of an etiology. In addition to using current patient clinical predictors, other sources of data we consider are clinical data from previous patients and local climate data. For climate, we calculate a rolling weighted average of temperature and rain data from NOAA weather stations in order to capture weather pattern trends, and we calculate a weighted average of recent patient data to account for influxes of a particular etiologies. We build a parsimonious set of prediction variables from the full set of GEMS survey responses via random forest variable importance screening. Variables predictive of viral etiology include age, vomiting, BMI, bloody diarrhea, breastfeeding. We address uncertainty in predictions by constructing Gaussian kernel density estimates of likelihood ratios for each test based on training predictions. Cross-validation shows that use of PTO improves average AUC by up to 0.04 (from 0.81 to 0.85) by including recent weather patterns in addition to clinical predictors. Overall, our post-test odds model's performance suggests that incorporating additional data sources can improve the performance of a clinical prediction rule for etiological prediction of diarrhea in LMICs over what can be achieved with clinical information alone.

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MEMORY B AND FUNCTIONAL ANTIBODY RESPONSES TO PAMVAC VACCINE IN BENINESE NULLIGRAVID WOMEN DURING PHASE IB CLINICAL TRIAL

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Placental Malaria (PM) pathogenesis is caused by interactions between the parasite protein VAR2CSA and chondroitin sulfate A (CSA) in the human placenta. The PAMVAC vaccine is a VAR2CSA protein-based vaccine, aiming to protect fetus and mother against the adverse effects of PM. After a safe Phase Ib clinical trial conducted in Benin from November 2016 to September 2017, PAMVAC immunogenicity was explored in 21 healthy nulligravid adult females randomized in 3 groups (9 Alhydrogel, 9 GLA-SE, 3 Placebo). They received 3 doses of 50 μg of adjuvanted PAMVAC or Placebo 28 days apart (Day 0, 28 and 56). Plasma samples and PBMC harvested at Days (D) -1, 56, 84, 168, 252 were stored respectively at -20°C and in liquid nitrogen for immunoassays. Memory B cells were quantified by ELISpot and functional antibody properties assessed for Variant Surface Antigen (VSA) recognition and opsonic phagocytosis using FACS. PAMVAC vaccination induced a memory B response that increased noticeably after the 2nd dose of vaccine (D56) and persisted over time at levels substantially higher than those we have previously measured in multigravid Beninese. The frequency of PAMVAC-specific antibody-secreting B cells was notably higher with GLA-SE than with alum, and responses were stable between D56 and D84. PAMVAC-specific B cell responses were undetectable in the Placebo group. PAMVAC immunization also induced antibody-mediated homologous VSA recognition and opsonic phagocytosis activities. IgG1 and IgG3 responses to VSA were higher in both adjuvant groups compared with Placebo, and opsonic phagocytosis of infected red blood cells was observable from D56 in the vaccinated groups. PAMVAC with alum induced stronger opsonic phagocytosis than with GLA-SE. In conclusion, the combination of PAMVAC with GLA-SE rather than alum was associated with the strongest B cell responses, whilst the combination with alum was associated with stronger functional antibody responses in women of childbearing age before their first pregnancy.

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HUMAN MAB BLOCKS MALARIA TRANSMISSION IN *PLASMODIUM*-INFECTED MOSQUITOES

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Malaria transmission blocking vaccines (TBVs) target sexual stage proteins of *Plasmodium falciparum* parasite in the mosquito vector, thereby reducing transmission. To improve the design of transmission-blocking therapeutic approaches, functional antibodies generated against these proteins need to be better characterized. Here, we generated functional human mAbs against the protein Pfs230, a surface antigen of *P. falciparum* gametes. Pfs230-specific single B cells generated by the fourth dose of Pfs230D1-EPA/Alhydrogel® in Malian adults were sorted after labelling with antigen-tetramers, and both heavy and light antibody chains were sequenced. Paired BCR sequences were selected from two vaccinees, based on repeated frequency among sorted cells and high mutation rates, and two BCR sequences were chosen to generate fully human recombinant IgG1 by expression in HEK cells. These antibodies LMIV230-01 and LMIV230-02, bound to Pfs230D1 and to protein extract of female gametocytes. LMIV230-01 and LMIV230-02 demonstrated high and similar binding affinities to recombinant Pfs230D1 antigen. However, only LMIV230-01 strongly bound to the surface of live female gametes while LMIV230-02 reacted minimally. LMIV230-01 also bound to gametocytes and zygotes, but did not bind to ookinetes, as expected. LMIV230-01 reduced *P. falciparum* oocyst burden in mosquitoes by 99% at 1000 μg/mL while LMIV230-02 reduced by 60% at the same concentration, although activity of both antibodies was determined to be complement-dependent. Competition assays suggested that the two antibodies react to different epitopes, and their CDR3 in the heavy chain shares no similarity. These functional mAbs provide the basis for the rational design of an improved Pfs230 vaccine or of antibody-based interventions against mosquito-stage proteins that prevent malaria transmission through parasite neutralization.

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UNDERSTANDING THE PROCESSES GOVERNING THE POPULATION-LEVEL IMPACT OF A TRANSMISSION BLOCKING VACCINE AGAINST MALARIA IN FIELD TRIAL SETTINGS

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The transmission of malaria parasites from humans to the mosquito vector involves relativity small numbers of parasites and has long been viewed as a target for interrupting transmission. With this aim in mind, a number of vaccines are currently under development. We have developed a mathematical description of a vaccine for *Plasmodium falciparum*, targeting antigen *Pfs*230, based on trial data collected in Mali. Incorporating the vaccine into a widely-used model of malaria transmission allows us to estimate the population-level impact of the vaccine, as well as identify the key demographics to target in a vaccination campaign. As transmission-blocking interventions are commonly measured by a standard membrane feeding assay, we consider how best to translate transmission blocking and reducing activities into different measures of efficacy in clinical trial settings. Unlike conventional vaccines, a transmission blocking vaccine confers no direct individual-level protection against bites from infectious Anopheles mosquitoes so vaccine effectiveness will depend on clinical incidence in both vaccinated and unvaccinated individuals and their relative spatial distribution. A high degree of mixing between these sub-populations will lead to the vaccine-derived benefits being shared throughout the entire population. In contrast, in a scenario in which transmission is focal and vaccinated subjects cluster together, the impact will be focused upon the vaccinated population. Such effects, which we estimate with our model, must be appreciated to accurately assess the full impact of transmission blocking interventions.

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NEUTRALIZATION OF *PLASMODIUM VIVAX* BY NATURALLY-ACQUIRED HUMAN ANTIBODIES THAT TARGET THE DUFFY BINDING PROTEIN

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The *Plasmodium vivax* Duffy binding protein (DBP) is a prime target of the protective immune response and a promising vaccine candidate for *P. vivax* malaria. Naturally acquired immunity (NAI) protects against malaria in adults residing in infection-endemic regions, and the passive transfer of malarial immunity confers protection. A vaccine that replicates NAI will effectively prevent disease. Here, we report the structures of

Hountohotegbe T. S., Berry D. G., Hasang W., Aitken E., Gbedande K. B., Viwami F., Auussenac F., Issifou S., Avokpaho E., Nielsen M., Mordmuller B., Leroy O., Massougbodji A., Fievet Nadine, Rogerson S., Luty Adrian.

Memory B and functional antibody responses to PAMVAC vaccine in Beninese nulligravid women during phase ib clinical trial.

American Journal of Tropical Medicine and Hygiene, 2019, 101 (5_Suppl), p. 413-414.

ISSN 0002-9637