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SCHOOL-BASED ANTIMALARIA INTERVENTIONS EFFICIENTLY REDUCE COMMUNITY-LEVEL *PLASMODIUM FALCIPARUM* PREVALENCE IN A HIGH-TRANSMISSION SETTING: A MATHEMATICAL MODELING STUDY

Andrea Geri Buchwald[1], Jenna E. Coalson[2], Lauren M. Cohee[1], Mark L. Wilson[3], Laura L. Hungerford[4], Terrie E. Taylor[5], Miriam K. Laufer[1]

[1]University of Maryland Baltimore, Baltimore, MD, United States, [2]The University of Arizona, Tucson, AZ, United States, [3]University of Michigan, School of Public Health, Ann Arbor, MI, United States, [4]Virginia-Maryland College of Veterinary Medicine, Blacksburg, VA, United States, [5]Michigan State University College of Osteopathic Medicine, East Lansing, MI, United States

Global antimalaria scale-up has significantly decreased malaria morbidity and mortality in many regions of the world. However, countries with the highest *Plasmodium falciparum* transmission have seen the slowest declines in malaria disease incidence and infection prevalence. In Malawi, uptake of antimalaria interventions is high among groups with the highest burden of disease (pregnant women and under-five children). Most *P. falciparum* infections, however, occur in school-aged children (5-15 years old) and prevention efforts have not been effective at reducing infection prevalence among this group. School-aged children are also less likely to receive anti-*P. falciparum* treatment, as many school-aged children's infections are asymptomatic. By targeting this highly-infected group, school-based interventions may be a cost-effective approach to reduce population-level transmission. We used a differential equation-based, deterministic, compartmental simulation model to evaluate how school-based interventions might affect community-level *P. falciparum* prevalence compared to current strategies (targeting pregnant women and under-five children) or community-based application of mass drug administrations (MDA) and mass screen-and-treat (MST) programs. The model, which accounted for asymptomatic infections, was fit to data from cross-sectional surveillance and longitudinal cohort studies in southern Malawi. We aimed to achieve a 50% decrease in community malaria prevalence while minimizing the number, frequency, and coverage of treatment campaigns as well as minimizing the number of individuals treated. The decrease in community infection prevalence was greatest when interventions were distributed randomly throughout the community. However, school-based interventions led to greater decreases in prevalence than MDA or MST targeting under-five children and pregnant women. While school-based interventions may not produce the greatest decrease in community infection prevalence, their comparative efficiency and potential cost-effectiveness may make them a better strategy for future malaria control programs.

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PROBABILISTIC MODEL OF *PLASMODIUM VIVAX* RELAPSE FOR IMPROVED ESTIMATION OF TREATMENT EFFICACY USING TIME-TO-RECURRENCE DYNAMICS

James Watson[1], Aimee R. Taylor[2], Caroline O. Buckee[2], Mallika Imwong[3], Cindy S. Chu[1], Nicholas J. White[1]

[1]Oxford University, Oxford, United Kingdom, [2]Harvard University, Boston, MA, United States, [3]Mahidol University, Bangkok, Thailand

Plasmodium vivax causes most of the malaria outside Sub-Saharan Africa. Vivax malaria in South East Asia exhibits the frequent relapse phenotype, with infections recurring at short intervals (3-4 weeks). As relapses from liver stage hypnozoites cannot be distinguished genetically from reinfections the radical curative efficacy of primaquine can only be characterized properly with placebo controlled trials (i.e. randomization to no radical cure) which is not possible in many countries where the standard of care includes radical cure. Data from a three way randomized controlled trial (n=600) comparing chloroquine (a slowly eliminated blood stage drug), chloroquine and primaquine together, and artesunate monotherapy (which is rapidly eliminated) were used to fit a Bayesian hierarchical model to the times to recurrent episodes (>1300 episodes recorded) conditioned on the treatments given. The relapse hazard rate is non-constant after acute vivax malaria. Tropical frequent relapse *P. vivax* on the Thai-Myanmar border area was well described by a triple mixture model with a relapse component (exponential waiting time), a `rapid' relapse component (normally distributed), and a `slow' relapse component (exponential waiting time). Time to recurrent episode provides discriminatory information between relapse and reinfection, thus providing a probabilistic framework for adjusting radical cure efficacy.

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NEUTROPHILS INFLUENCE ANTIGEN PRESENTATION DURING IMMUNE RESPONSE TO LIVE ATTENUATED LEISHMANIAL VACCINE

Parna Bhattacharya[1], Pradeep Dagur[2], Nevien Ismail[1], Kazuyo Takeda[1], Ranadhir Dey[1], Hira Nakhasi[1]

[1]Food and Drug Administration, Silver Spring, MD, United States, [2]National Institutes of Health, Rockville, MD, United States

No vaccine exists against Visceral Leishmaniasis. We have earlier reported the protective role of live attenuated centrin gene deleted *L. donovani* (*LdCen*$^{-/-}$) parasite vaccine in animal models. *LdCen*$^{-/-}$ induces strong innate immunity leading towards protective Th1 response. Neutrophils are indispensable for first line of defense against pathogens. Additionally, role of neutrophils as antigen presenting cells (APCs) has been demonstrated in enhancing virus based vaccine induced responses and tuberculosis vaccination. Emerging evidence suggests that neutrophils should be considered as important modulators of leishmaniasis. Although studies have shown the importance of neutrophils during *Leishmania* infection, none have shown its role in development of specific response to a Leishmania vaccine. Hence, we studied the role of neutrophils as APCs in the induction of specific response to *LdCen*$^{-/-}$ intradermal vaccination. Increased neutrophil migration with heightened microbicidal attributes was observed after infection with *LdCen*$^{-/-}$ compared to *LdWT in vitro*. *LdCen*$^{-/-}$ infection induced TLR activation and *NF-KB* pathway induction in macrophages was found to be essential for higher neutrophil recruitment in response to infection . Likewise, *in vivo* study showed that intradermal injection with *LdCen*$^{-/-}$ induces higher neutrophil recruitment at the site of injection (ear) and lymph nodes compared to *LdWT* parasites. Phenotypic characterization of recruited dermal neutrophils revealed the presence of heterogeneous neutrophil population. Low density neutrophils sort selected from *LdCen*$^{-/-}$ infected mice exhibited attenuated expression of pro-parasitic molecules compared to *LdWT*. Adoptive transfer of *LdCen*$^{-/-}$ parasite bearing neutrophils were able to induce heightened Th1 differentiation in visceral organs compared to *LdWT* thereby highlighting the robust APC feature of neutrophils in *LdCen*$^{-/-}$ induced immunity. Also, the engulfment of *LdCen*$^{-/-}$ parasitized neutrophil by dendritic cells (DCs) enhanced Ag presentation capability of DCs compared to *LdWT*. Thus neutrophils play novel role in shaping early vaccine immunity.

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PHARMACOKINETIC-PHARMACODYNAMIC ASSESSMENT OF THE SAFETY OF FEXINIDAZOLE FOR THE TREATMENT OF HUMAN AFRICAN TRYPANOSOMIASIS

James Watson[1], Nathalie Strub-Wourgraft[2], Antoine Tarral[2], Joel Tarning[1], Nicholas J. White[1]

[1]Oxford University, Oxford, United Kingdom, [2]Drugs for Neglected Diseases initiative, Geneva, Switzerland

Fexinidazole is a new oral treatment for *Trypanosoma brucei* (*T.b. gambiense*) human African trypanosomiasis (g-HAT). Fexinidazole *in vitro* is also active against other human kinetoplastid parasites, *T. cruzi* and *Leishmania donovani,* the causative agents of Chagas disease and visceral leishmaniasis, respectively. During a dose-ranging study conducted

in asymptomatic Bolivian Chagas patients, delayed neutropenia and significant increases in hepatic transaminases were observed and the clinical study was suspended. We analysed retrospectively all available pharmacokinetic (PK) and pharmacodynamic (PD) data on fexinidazole in healthy volunteers, Chagas patients and HAT patients to characterise the PK-PD relationships for oral fexinidazole in different regimens. A population PK model was fitted to data from three Phase I studies, two g-HAT field trials and one Chagas field trial. Bayesian exposure-response models were fitted to haematological indices and liver related PD outcomes in asymptomatic Chagas patients. These models were compared with observed data from the g-HAT trials and used to predict likely adverse events from the recommended g-HAT regimen. Asymptomatic delayed neutropenia and thrombocytopenia, and elevations in liver transaminases were found to be exposure related and thus dose-dependent in asymptomatic Chagas patients. Mild, asymptomatic haematological outcomes consistent with the exposure-response curves were observed in the g-HAT trials, confirming a haematological effect of fexinidazole. However, liver toxicity and biochemistry abnormalities were not observed in healthy volunteer studies nor in any g-HAT trials. Fexinidazole treatment results in a dose dependent delayed and reversible bone marrow suppression. The currently recommended g-HAT regimen (adult dose 1800mg for 4 days, then 1200mg for 6 days) provides exposures within a satisfactory safety margin for both neutropenia and hepatotoxicity. Liver toxicity appears to be specific to the Chagas population.

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INTERROGATING CHAGAS ANTIBODY RESPONSES WITH HIGH-THROUGHPUT PRECISION TOOLS: TOWARDS A COMPREHENSIVE CATALOG OF *TRYPANOSOMA CRUZI* ANTIGENS AND EPITOPES ACROSS AMERICA.

Alejandro D. Ricci[1], Janine Ramsey[2], Jaime Altcheh[3], Norival Kesper Jr[4], Melissa Nolan[5], Patricio Diosque[6], Juan C. Villar[7], Carlos A. Buscaglia[1], Fernán Agüero[1]

[1]Instituto de Investigaciones Biotecnológicas, UNSAM, San Martin, Provincia de Buenos Aires, Argentina, [2]Instituto Nacional de Salud Pública, Tapachula, Chiapas, Mexico, [3]Hospital de Niños Ricardo Gutiérrez, Ciudad Autónoma de Buenos Aires, Argentina, [4]Instituto de Medicina Tropical, Universidade de São Paulo, São Paulo, Brazil, [5]Baylor College of Medicine, Houston, TX, United States, [6]Instituto de Patología Experimental, Facultad de Ciencias de la Salud, Salta, Argentina, [7]Universidad Autónoma de Bucamaranga, Santander, Colombia

Using state of the art high-density peptide microarrays, we developed a highly multiplexed screening array design containing ~2.8 million unique peptides derived from the complete proteomes of Trypanosoma cruzi strains CL-Brener (hybrid DTU TcVI; 19,668 proteins) and Sylvio X10 (DTU TcI, 10,832 proteins). The full length of all 30,500 proteins encoded in these genomes were scanned using 16mer peptides with an overlap of 12 residues between each peptide. Using this platform, we screened sera pools from Chagas-positive and healthy volunteers from several regions across America: Argentina, Brazil, Colombia, Mexico and the United States. Screening of negative sera pools from healthy subjects allowed us to define a background baseline of antibody-binding signal against peptides, as well as to identify cross-reactive epitopes. Screening of Chagas-positive sera pools allowed us to identify specific antibody-binding against *Trypanosoma cruzi* peptides. Using a conservative signal threshold to define antigenic peaks in proteins, our analysis led to the discovery of more than 4,500 antigens (mostly novel), and to the identification of 22,747 antibody-binding peaks (epitopes) across all samples. Also, the comparative analysis of antibody-binding in different samples allowed us to define a core set of pan-Chagas antigens and epitopes with reactivity in all human samples, as well as sets of unique/differential antigens (only reactive in one population) or antigens with shared reactivity in a few samples (populations). In the presentation we will highlight interesting cases of shared/differential antibody responses in different samples, and will discuss next steps to use this high-throughput platform to decompose the sera pools and gain insights into the seroprevalence of these epitopes in each population. To the best of our knowledge this is the first proteome-wide catalog of antigenic determinants for a human infectious disease.

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EVALUATION OF A LOOP-MEDIATED ISOTHERMAL AMPLIFICATION (LAMP) KIT AS A MOLECULAR DIAGNOSTIC TEST FOR CONGENITAL CHAGAS DISEASE

Albert Picado[1], Susana A. Besuschio[2], Ismael Ibañez[3], Israel Cruz[1], Alejandro Benatar[2], Montserrat Gállego[4], Carme Muñoz[5], Joseph M. Ndung'u[1], Alejandro G. Schijman[2], Maria D. Flores-Chávez[3]

[1]FIND, Geneva, Switzerland, [2]Laboratorio de Biología Molecular de la Enfermedad de Chagas, INGEBI-CONICET, Buenos Aires, Argentina, [3]Instituto de Salud Carlos III, Madrid, Spain, [4]Facultat de Farmacia, Universitat de Barcelona, Barcelona, Spain, [5]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Molecular tests are used to diagnose congenital Chagas disease in some countries, mainly in Europe. Their use in endemic countries is still anecdotal. Technical and economic factors have been put forward to explain the poor penetration of molecular tests to diagnose Chagas disease in low and middle-income countries (LMIC). The use of loop-mediated isothermal amplification (LAMP) methods may overcome some of these limitations. A newly developed LAMP kit designed for detection of *Trypanosoma cruzi* DNA in human blood showed a good analytical performance and was easy to use. We evaluated the performance of a *T. cruzi* LAMP kit in stored clinical samples of congenital Chagas disease cases in Argentina and Spain. Clinical samples from 49 congenital Chagas disease cases (10 from Argentina and 39 from Spain) and 74 controls (26 from Argentina and 48 from Spain) were tested by the *T. cruzi* LAMP kit and qPCR. The *T. cruzi* LAMP results were read by naked eye and fluorimeter. The sensitivity and specificity of the *T. cruzi* LAMP was estimated using the standard case definition as reference e.g. baby with a positive microscopy, or culture between 0 and 1 months, or a positive serology for congenital Chagas disease at 9-10 months. We evaluated the agreement between *T. cruzi* LAMP read by naked eye and fluorimeter and between *T. cruzi* LAMP and qPCR using Cohen's kappa statistics (K). The sensitivity of *T. cruzi* LAMP was 98.0% (95% CI: 89.3 – 99.6%) both by naked eye and fluorimeter. Specificity was 93.2% (95% CI: 85.1 – 97.1%) by naked eye and 94.6% (95% CI: 86.9 – 97.9%) by fluorimeter. The sensitivity and specificity of *T. cruzi* LAMP improved when only the samples taken 0 to 1 months after birth were considered. There was very good agreement between *T. cruzi* LAMP read by naked eye and fluorimeter (K=0.98) and between *T. cruzi* LAMP and qPCR (K=0.87). The *T. cruzi* LAMP kit could be used as a diagnostic tool for congenital Chagas disease cases in endemic and non-endemic countries.

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DEVELOPMENT OF A NOVEL BENZTHIAZOLE SCAFFOLD FOR CHAGAS DISEASE

Frederick S. Buckner[1], J. Robert Gillespie[1], Richard R. Tidwell[2], Donald A. Patrick[2], Pendem Nagendar[1], Andriy Buchynskyy[1], Zackary M. Herbst[1], Ranae M. Ranade[1], Michael H. Gelb[1]

[1]University of Washington, Seattle, WA, United States, [2]University of North Carolina, Chapel Hill, NC, United States

An estimated 7 million people, mostly in Latin America, are infected with *Trypanosoma cruzi,* the etiologic agent of Chagas disease. This chronic infection leads to cardiomyopathy or mega-syndromes of the intestines in ~30% of infected individuals. The existing anti-parasitic drugs (two nitroaromatic compounds) are associated with high rates of side-effects that greatly limit their use. A better tolerated and safe drug with potent anti-*Trypanosoma cruzi* activity is desperately needed to treat scores of infected people before they develop irreversible end-organ disease. Towards this end we are developing a novel compound series built around a benzthiazole core. The initial hit compound was