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ECONOMIC COSTS AND BENEFITS OF SCALING UP DISABILITY PREVENTION FOR LYMPHATIC FILARIASIS ACROSS INDIA

Eileen Stillwaggon[1], Larry Sawers[2]

[1]Gettysburg College, Gettysburg, PA, United States, [2]American University, Washington, DC, United States

Lymphatic filariasis (LF) is endemic in 73 countries, with 68 million people infected, of whom 36 million suffer serious disability (17 million with lymphedema, 19 million with hydrocele). Repeated acute attacks of fever and disabling pain (acute dermatolymphangioadenitis or ADLA) aggravate lymphedema and prevent work for 4-7 days per attack. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) has two goals: interrupting LF transmission by 2020, and caring for people already infected through morbidity management and disability prevention (MMDP). By 2014, 60 countries had ongoing mass drug administration to end LF transmission, but only 24 had begun MMDP, in part due to its perceived high cost and low return. Simple, low-cost interventions at the community level, including instruction in limb washing and provision of soap, topical antibiotics, and antifungals can reduce ADLA and slow progression of lymphedema. MMDP programs attenuate disability and productivity loss. For Khurda District, Odisha State, India, we estimated lifetime medical costs and earnings losses due to chronic lymphedema and acute dermatolymphangioadenitis (ADLA) with and without a community-based limb-care program. The program would reduce economic costs of lymphedema and ADLA over 60 years by 55%. Savings of US$ 1 648 for each affected person in the workforce are equivalent to 1 258 days of labor. Per-person savings are more than 130 times the per-person cost of the program. We then estimate the costs of scale-up for all Indian states for community-based programs of limb care for lymphedema. India has great diversity in levels of wages (and thus foregone earnings from disability that prevents working), prevalence of lymphatic filariasis, health systems, NGO involvement, and other factors that influence community health programs. In spite of the diversity of conditions, our cost estimates demonstrate the long-term economic benefits of simple limb care and provide an economic rationale in addition to the ethical mandate for MMDP, the second pillar of GPELF.

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APPLICATION OF ULTRASONOGRAPHY TO DETECT PERITONEAL FILARIAL DANCE SIGN IN PRECLINICAL RODENT *BRUGIA MALAYI* MACROFILARICIDAL DRUG SCREENING MODELS

Amy E. Marriott, Hanna Sjoberg, Darren Cook, Andrew Steven, Mark J. Taylor, Joseph D. Turner

Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Ultrasonography (USG) has been successfully used in placebo-controlled clinical trials to evaluate macrofilaricidal (curative) drug efficacy in onchocerciasis and lymphatic filariasis. Here we describe the application of a portable ultrasound machine (SonoSite MTurbo) to detect 'filarial dance sign' (FDS) in preclinical *Brugia malayi* rodent drug screening models. In these models, defined numbers of *B. malayi* adults were implanted into the peritoneum or, alternatively, variable *B. malayi* adult burdens were established from a unit intraperitoneal inoculum of infectious stage larvae either within inbred Severe-Combined ImmunoDeficient mice or outbred *Meriones unguiculatus* (Mongolian) gerbils. USG successfully detected FDS of mixed sex or single sex adult worm burdens to a degree of sensitivity of a single female worm or 2 male worms. USG could also be applied to semi-quantify worm loads based on strength and multiplicity of FDS signal within different peritoneal anatomical locations. In both non-blinded and blinded preclinical drug studies, USG detection of peritoneal FDS has subsequently been utilised to accurately predict macrofilaricidal outcome. This technique could therefore be highly beneficial in refining and reducing the number of animals used during drug screens and accelerating preclinical macrofilaricidal drug by being able to more rapidly detect drug efficacy by longitudinal exam of the same study group without the necessity of invasive surrogate filarial viability sampling.

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INVESTIGATING EARLY INFECTION STATUS OF THE FILARIAL PARASITE *BRUGIA MALAYI* IN THE CAT, THE LABORATORY MODEL FOR LYMPHATIC FILARIASIS

Erica J. Burkman, Katherine E. Hogan, Molly D. Savadelis, Michael T. Dzimianski, Andrew R. Moorhead

University of Georgia, College of Veterinary Medicine, Athens, GA, United States

Human lymphatic filariasis (LF) is a mosquito-borne disease primarily caused by the parasitic nematodes *Wuchereria bancrofti* and *Brugia malayi*. These parasites are a major cause of morbidity globally, with an estimated 120 million people infected. *Brugia malayi* is the preferred laboratory model for LF due to *W. bancrofti* requiring the use of primate hosts. Currently, the domestic cat is utilized as the primary non-rodent animal model for *B. malayi*. However, on average only 25%-50% of felines become patent, so a method of early detection would be invaluable. Currently, the only test to determine infection status is the detection of circulating microfilariae, which are usually detectable 4-6 months post-infection. In other filarial parasites such as *Dirofilaria immitis*, the Enzyme Linked Immunosorbent Assay (ELISA) is used to detect circulating female uterine antigen. Recently, it was suggested that heat treatment of serum or plasma may dissociate the antibody-antigen complex, potentially releasing the antigen so that it may be detected. Due to the close relationship of these filarial worms, there could be detectable cross-reactivity after heat treatment for *B. malayi* antigen in these capture-antibody tests. We hypothesized that we would be able to detect circulating antigen after heat treatment in the serum of these infected cats. Ten male domestic cats were infected by subcutaneous injection of 400 *B. malayi* third-stage larvae. Serum was collected at key time points post-infection. Both heat-treated and room temperature serum was tested for circulating antigen using the DiroCHEK® ELISA kit. Of the six cats that became microfilaremic, five tested antigen-positive, whereas only one cat with a low microfilaremia tested antigen-negative. These data may indicate a methodology other than microfilarial counts may be used to detect *B. malayi* infections in cats. Furthermore, heat treatment of serum could expose epitopes that cross-react with the antibody used in commercial *D. immitis* tests.

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CELLSCOPE-*LOA*: DISTRICT-WIDE DEPLOYMENT OF A POINT OF CARE TOOL FOR THE PREVENTION OF POST IVERMECTIN SERIOUS ADVERSE EVENTS IN *LOA LOA* ENDEMIC AREAS

Sebastien Pion[1], Joseph Kamgno[2], Matthew Bakalar[3], Jean Bopda[2], Cédric Chesnais[1], Mike D'Ambrosio[3], Raceline Gonoue Kamkumo[2], Charles D. Mackenzie[4], Steve Mbickmen Tchana[2], Hugues Clotaire Nana Djeunga[2], Narcisse Ngandjui[5], Guy Roger Njitchouang[2], Philippe Nwane[2], Jules Brice Tchatchueng Mbouga[2], Samuel Wanji[5], Amy Klion[6], Michel Boussinesq[1], Daniel Fletcher[3], Thomas B. Nutman[6]

[1]Institut de recherche pour le Développement, Montpellier, France, [2]Centre for Research on Filariasis and other Tropical Diseases, Yaounde, Cameroon, [3]University of California, Berkeley, CA, United States, [4]Liverpool School of Tropical Medicine, Liverpool, United Kingdom, [5]Research Foundation for Tropical Diseases and the Environment, Buea, Cameroon, [6]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States

Because of the marked adverse effects (functional impairment) and serious adverse events (SAEs, occasionally fatal but more often with potentially irreversible neurologic manifestations) that can occur when

Loa loa microfilariae (mf) levels exceed 8,000 mf/mL and 30,000 mf/mL, respectively, implementation of ivermectin (IVM)-based elimination programs for lymphatic filariasis (LF) and onchocerciasis in areas where loiasis is co-endemic has been extremely problematic. Identifying those individuals "at risk" for such SAEs would allow them to be excluded from IVM community treatment and prevent SAEs. This strategy, termed "Test and not Treat" (TNT), relies on the development of a rapid field-friendly test to quantify *L. loa* mf in peripheral blood. To this end, we developed a mobile phone-based video microscope (CellScope-Loa) that automatically quantifies *L. loa* mf in whole blood in less than 2 minutes without the need for conventional sample preparation or staining. Between August and October 2015, a field evaluation was conducted in a health district of Central Cameroon to assess the performance of the Cellscope-Loa in comparison to examination of a calibrated blood smear (the current standard method to assess *L. loa* mf densities). Among the 15,298 participants, 226 (1.5%) had mf densities above 30,000 mf/mL, when assessed by calibrated thick smear. There was a strong correlation (rho=0.84, p<0.0001) between mf densities estimated by the CellScope-Loa and those measured by the calibrated thick smear. Receiver operating characteristic (ROC) analysis demonstrated that the CellScope-Loa could identify individuals harboring > 30,000 mf/mL with 94.0 and 99.6% sensitivity for CellScope-Loa thresholds set at 20,000 and 10,000 mf/mL, respectively. Most importantly, it had a negative predictive value (probability that the mf density is actually below 30,000 mf/mL) of 99.9 and 100% for the same threshold values. The TNT strategy based on the Cellscope-Loa is an extremely promising and practical approach to the safe implementation of large-scale treatment for LF and onchocerciasis in *L. loa* co-endemic areas.

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SYNERGY OF ALBENDAZOLE AND RIFAMPICIN COMBINATION THERAPY IN A MURINE INFECTION MODEL OF HUMAN LYMPHATIC FILARIASIS

Raman Sharma, Joseph D. Turner, Ghaith Al Jayoussi, Hayley E. Tyrer, Joanne Gamble, Laura Hayward, Richard Priestly, Jill Davies, David Waterhouse, Darren A. Cook, Andrew Steven, Kelly L. Johnston, Louise Ford, Stephen A. Ward, Mark J. Taylor

Liverpool School of Tropical Medicine, Liverpool, United Kingdom

An estimated 120 million people are infected by lymphatic filariasis throughout the tropics leading to a profound public health and socio-economic burden in severely affected communities. Wolbachia is an essential endosymbiont of the filarial nematodes *Wuchereria bancrofti*, *Brugia malayi* the causative agents of lymphatic filariasis. Doxycycline is currently the gold standard for the targeting of Wolbachia in lymphatic filariasis chemotherapy. However, the current drug regimen is a 100-200 mg/day doxycycline dose given for 4 to 6 weeks to patients. The A·WOL consortium plan to reduce the current treatment time to 7 days or less to improve drug regimen adherence and to reduce drug resistance and costs of treatment. To achieve a rapid 7-day or less kill rate of Wolbachia, a number of drug combinations will be employed. These include different tetracyclines (Doxycycline and minocycline) rifamycins (Rifampicin or Rifapentine), Moxifloxacin as well as anti-helminthic drugs. The complexity of multiple drug combinations necessitates a rational approach in the identification and choice of the best treatments in in-vivo models and translating the animal treatments in the lab into clinical trials on the field. In this current study we apply a rational drug development approach using our on in our murine infection model of *B. malayi* and pharmacokinetic (PK) analysis to investigate the synergy of Albendazole and Rifampicin combination therapy on the macrofilaridal and anti-Wolbachia efficacy. Pharmacokinetic modelling and simulation allowed the administration of rifampicin dosages equivalent to a standard 10 mg/Kg or 600 mg dose or a 35 mg/Kg super-dose and albendazole equivalent to a 400-800mg clinical dose in our murine infection model of *B. malayi*, making drug exposure and efficacy results clinically relevant in comparison to traditional efficacy studies. We have found synergistic interaction between rifampicin and albendazole for both macrofilaricidal and anti-Wolbachia activities and have used PK analysis and parasitological methods to dissect the origins of these interactions.

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FACTORS PREDICTING TRANSMISSION ASSESSMENT SURVEY OUTCOMES FOR LYMPHATIC FILARIASIS

Katie Zoerhoff[1], Maureen Kelly[1], Rachel Stelmach[1], Angela Weaver[2], Margaret Baker[1], Molly Brady[1]

[1]RTI International, Washington, DC, United States, [2]U.S. Agency for International Development, Washington, DC, United States

National programs are progressing towards elimination of lymphatic filariasis (LF) as a public health problem. Nearly 300 transmission assessment surveys (TAS), population-based cluster surveys to determine whether prevalence has been lowered to a level at which mass drug administration (MDA) can be stopped, supported by USAID have been implemented in 14 countries. Since both failing TAS and continuing to implement MDA have financial and opportunity costs, TAS should be conducted at an appropriate time. A key question, which has not yet been analyzed using survey data, is therefore which factors increase the likelihood of passing TAS. We performed logistic regression analysis to examine whether the odds of passing TAS was related to baseline prevalence, number of MDA rounds implemented, or median epidemiological coverage. The analysis included data from 14 countries implementing 296 stop-MDA TAS between 2012-2015. Of these TAS, 90% of districts passed. We found that passing TAS was significantly associated with both baseline prevalence (OR 0.945, CI 0.915-0.976) and median epidemiological coverage (OR 1.044, CI 1.008-1.082) at alpha =0.05. While the number of MDA rounds was not significantly associated with passing TAS, it was important to control for as otherwise it confounded the relationship between baseline prevalence, median coverage, and passing TAS. The R-square value was low (0.0714), however; this indicates that this model does not include all of the factors that affect the likelihood of passing TAS. Ongoing analysis will incorporate additional factors that may affect the likelihood of passing TAS, such as vector species, diagnostic tests used to determine eligibility for TAS, and consecutive versus missed rounds of MDA, among others. These results confirm that it is important to achieve high coverage when implementing MDA, especially in districts with high baseline prevalence, and additional rounds of MDA may be necessary. National programs can increase the likelihood of passing TAS—and therefore achieving elimination—by implementing high-quality MDA throughout the program, rather than only in response to a failed TAS.

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THREE-DIMENSIONAL VISUALIZATION OF THE INTERNAL ARRANGEMENT OF ONCHOCERCAL (*ONCHOCERCA VOLVULUS*) NODULES USING HIGH-RESOLUTION MAGNETIC RESONANCE IMAGING

Maïda Cardoso[1], **Cédric B. Chesnais**[2], Sébastien D. Pion[2], Michel Boussinesq[2], Frédéric Ben Naïm[3], Christophe Goze-Bac[1], Michel Zanca[4]

[1]Laboratoire Charles Coulomb (L[2]C-UMR5221), BioNanoNMRI Group, University of Montpellier, Montpellier, France, [2]Institut de Recherche pour le Développement, Montpellier, France, [3]Intrasense society, Montpellier, France, [4]Laboratoire Charles Coulomb (L[2]C-UMR5221), BioNanoNMRI group, Nuclear Medicine, CMC Gui de Chauliac, University Hospital Montpellier, Montpellier, France

Adult stages of *Onchocerca volvulus* live in subcutaneous or deep nodules. For descriptive biology or drug effect assessment purpose, the nodules are generally processed using either histology (fixation and section, followed by staining) or enzymatic digestion (incubation in collagenase to eliminate host tissue and isolate adult worms). Non-invasive detection of adult *O. volvulus* using ultrasound has also been used, but has little indications