



UGANDA VIRUS RESEARCH INSTITUTE

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MRC/UVRI Uganda
Research Unit on AIDS

MRC/UVRI MONTHLY PUBLICATIONS DIGEST – MAY 2015

Wammes L, Mpairwe H, Elliott AM, Yazdanbakhsh M. Helminth therapy or elimination: epidemiological, immunological, and clinical considerations. *Lancet Infectious Diseases* 2014; 14(11):1150-1162

Deworming is rightly advocated to prevent helminth-induced morbidity. Nevertheless, in affluent countries, the deliberate infection of patients with worms is being explored as a possible treatment for inflammatory diseases. Several clinical trials are currently registered, for example, to assess the safety or efficacy of *Trichuris suis* ova in allergies, inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, psoriasis, and autism, and the *Necator americanus* larvae for allergic rhinitis, asthma, coeliac disease, and multiple sclerosis. Studies in animals provide strong evidence that helminths can not only down regulate parasite-specific immune responses, but also modulate autoimmune and allergic inflammatory responses and improve metabolic homeostasis. This finding suggests that deworming could lead to the emergence of inflammatory and metabolic conditions in countries that are not prepared for these new epidemics. Further studies in endemic countries are needed to assess this risk and to enhance understanding of how helminths modulate inflammatory and metabolic pathways. Studies are similarly needed in non-endemic countries to move helminth-related interventions that show promise in animals, and in phase 1 and 2 studies in human beings, into the therapeutic development pipeline.

Nakimuli A, Chazara O, Byamugisha J, Elliott AM, Kaleebu P, Mirembe F, Moffett A. Pregnancy, parturition and preeclampsia in women of African ancestry. *American Journal of Obstetrics and Gynecology*, 2014; 210(6):510-520.

Maternal and associated neonatal mortality rates in sub-Saharan Africa remain unacceptably high. In Mulago Hospital (Kampala, Uganda), 2 major causes of maternal death are preeclampsia and obstructed labor and their complications, conditions occurring at the extremes of the birth weight spectrum, a situation encapsulated as the obstetric dilemma. We have questioned whether the prevalence of these disorders occurs more frequently in indigenous African women and those with African ancestry elsewhere in the world by reviewing available literature. We conclude that these women are at greater risk of preeclampsia than other racial groups. At least part of this susceptibility seems independent of socioeconomic status and likely is due to biological or genetic factors. Evidence for a genetic contribution to preeclampsia is discussed. We go on to propose that the obstetric dilemma in humans is responsible for this situation and discuss how parturition and birth weight are subject to stabilizing selection. Other data we present also suggest that there are particularly strong evolutionary selective pressures operating during pregnancy and delivery in Africans. There is much greater genetic diversity and less linkage disequilibrium in Africa, and the genes responsible for regulating birth weight and placentation may therefore be easier to define than in non-African cohorts. Inclusion of African women into research on preeclampsia is an essential component in tackling this major disparity of maternal health.

Nampijja M, Webb E, Kaweesa J, Kizindo R, Namutebi M, Nakazibwe E, Oduru G, Kabuubi P, Kabagenyi J, Kizito D, Muhangi L, Akello M, Verweij JJ, Nerima B, Tukahebwa E, Elliott AM for the LaVIISWA trial team. The Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA; ISRCTN47196031): study protocol for a randomized controlled trial. *Trials*.2015, 16:187.

BACKGROUND:

The Hygiene Hypothesis proposes that infection exposure protects against inflammatory conditions. Helminths possess allergen-like molecules and may specifically modulate allergy-related immunological pathways to inhibit responses which protect against them. Mass drug administration is recommended for helminth-endemic communities to control helminth-induced pathology, but may also result in increased rates of inflammation-mediated diseases in resource-poor settings. Immunological studies integrated with implementation of helminth control measures may elucidate how helminth elimination contributes to on-going epidemics of inflammatory diseases. We present the design of the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA), a cluster-randomised trial evaluating the risks and benefits of intensive versus standard anthelmintic treatment for allergy-related diseases and other health outcomes.

METHODS/DESIGN:

The setting is comprised of island fishing communities in Mukono district, Uganda. Twenty-six communities have been randomised in a 1:1 ratio to receive standard or intensive anthelmintic intervention for a three-year period. Baseline characteristics were collected immediately prior to intervention rollout, commenced in February 2013. Primary outcomes are reported wheeze in the past 12 months and atopy (skin prick test response and allergen-specific immunoglobulin (asIg) E concentration). Secondary outcomes are visible flexural dermatitis, helminth infections, haemoglobin, growth parameters, hepatosplenomegaly, and responses to vaccine antigens. The trial provides a platform for in-depth analysis of clinical and immunological consequences of the contrasting interventions.

DISCUSSION:

The baseline survey has been completed successfully in a challenging environment. Baseline characteristics were balanced between trial arms. Prevalence of *Schistosoma mansoni*, hookworm, *Strongyloides stercoralis* and *Trichuris trichiura* was 52%, 23%, 13%, and 12%, respectively; 31% of *Schistosoma mansoni* infections were heavy (>400 eggs/gram). The prevalence of reported wheeze and positive skin prick test to any allergen was 5% and 20%, respectively. Respectively, 77% and 87% of participants had Dermatophagoides- and German cockroach-specific IgE above 0.35 kUA/L. These characteristics suggest that the LaVIISWA study will provide an excellent framework for investigating beneficial and detrimental effects of worms and their treatment, and the mechanisms of such effects.

Tuhebwe D, Bagonza J, Ekirapa-Kiracho, Adoke Y, Elliott AM, Nuwaha F. Uptake of Mass Drug Administration Programme for Schistosomiasis Control in Koome Islands, Central Uganda. *PLoS One*, 2015 Apr 1;10(4):e0123673.

INTRODUCTION:

Schistosomiasis is one of the neglected tropical diseases targeted for elimination in Uganda through the Mass Drug Administration(MDA) programme. Praziquantel has been distributed using community resource persons in fixed sites and house-to-house visits; however the uptake is still below target coverage. In 2011/2012 MDA exercise, uptake stood at 50% yet WHO target coverage is 75% at community level. We assessed the uptake of MDA and the associated factors in Koome Islands, Central Uganda.

METHODS:

In March 2013, we conducted a mixed methods cross sectional study in 15 randomly selected villages. We interviewed a total of 615 respondents aged 18 years and above using semi structured questionnaires and five key informants were also purposively selected. Univariate and multivariate analysis was done. MDA uptake was defined as self-reported swallowing of praziquantel during the last (2012) MDA campaign. We conducted key informant interviews with Ministry of Health, district health personnel and community health workers.

RESULTS:

Self-reported uptake of praziquantel was 44.7% (275/615), 95% confidence interval (CI) 40.8-48.7%. Of the 275 community members who said they had swallowed praziquantel, 142 (51.6%) reported that they had developed side effects. Uptake of MDA was more likely if the respondent was knowledgeable about schistosomiasis transmission and prevention (adjusted odds ratio [AOR] 1.85, 95% CI 1.22-2.81) and reported to have received health education from the health personnel (AOR 5.95, 95% CI 3.67-9.65). Service delivery challenges such as drug shortages and community health worker attrition also influenced MDA in Koome Islands.

CONCLUSIONS:

Uptake of MDA for schistosomiasis control in Koome was sub optimal. Lack of knowledge about schistosomiasis transmission and prevention, inadequate health education and drug shortages are some of the major factors associated with low uptake. These could be addressed through routine health education and systematic drug supply for the successful elimination of schistosomiasis on the islands.

Kirenga BJ, Levin J, Ayakaka I, Worodria W, Reilly N, Mumbowa F, Nabanjja H, Nyakoojo G, Fennelly K, Nakubluwa S, Joloba M, Okwera A, Eisenach KD, McNerney R, Elliott AM, Mugerwa R, Smith PG, Ellner JJ, Jones-Lopez EC. Treatment Outcomes of New Tuberculosis Patients Hospitalized in Kampala, Uganda: A Prospective Cohort Study. PLoS One. March 2014 DOI: 10.1371/journal.pone.0090614

BACKGROUND:

In most resource limited settings, new tuberculosis (TB) patients are usually treated as outpatients. We sought to investigate the reasons for hospitalisation and the predictors of poor treatment outcomes and mortality in cohort of hospitalized new TB patients in Kampala, Uganda.

METHODS AND FINDINGS:

Ninety-six new TB patients hospitalised between 2003 and 2006 were enrolled and followed for two years. Thirty two were HIV-uninfected and 64 were HIV-infected. Among the HIV-uninfected, the commonest reasons for hospitalization were low Karnofsky score (47%) and need for diagnostic evaluation (25%). HIV-infected patients were commonly hospitalized due to low Karnofsky score (72%), concurrent illness (16%) and diagnostic evaluation (14%). Eleven HIV uninfected patients died (mortality rate 19.7 per 100 person-years) while 41 deaths occurred among the HIV-infected patients (mortality rate 46.9 per 100 person years). In all patients an unsuccessful treatment outcome (treatment failure, death during the treatment period or an unknown outcome) was associated with duration of TB symptoms, with the odds of an unsuccessful outcome decreasing with increasing duration. Among HIV-infected patients, an unsuccessful treatment outcome was also associated with male sex ($P = 0.004$) and age ($P = 0.034$). Low Karnofsky score (aHR = 8.93, 95% CI 1.88 - 42.40, $P = 0.001$) was the only factor significantly associated with mortality among the HIV-uninfected. Mortality among the HIV-infected was associated with the composite variable of CD4 and ART use, with patients with baseline CD4 below 200 cells/ μ L

who were not on ART at a greater risk of death than those who were on ART, and low Karnofsky score (aHR = 2.02, 95% CI 1.02 - 4.01, P = 0.045).

CONCLUSION:

Poor health status is a common cause of hospitalisation for new TB patients. Mortality in this study was very high and associated with advanced HIV Disease and no use of ART.

Mpairwe H, Tweyongyere R, Elliott A. Pregnancy and helminth infections. *Parasite Immunology*, 2014, 36(8):328-37.

Helminth infections are highly prevalent. In 2006, it was estimated that over a billion people were infected with one or more species of soil-transmitted helminth, while 200 million were infected with schistosome. The prevalence of hookworm tends to increase with age and, although the intensity of schistosomiasis declines with age, the prevalence remains high among young adults in endemic communities. Thus, in endemic settings, there is a high burden of helminth infection among pregnant women, a group already at increased risk from malaria, and susceptible to anaemia and to nutritional stress. Implications for the mother and foetus include possible physiological effects on haemoglobin levels and on foetal growth and development, and possible immunological effects on both mother and foetus. This review will examine current evidence for such effects, focusing mainly on the latter, and discussing possible mechanisms for some of the immunological effects that have been observed.

Observational studies on the effects of helminth infections in humans are fraught with strong potential for both measured and unmeasured confounding, as helminths occur in the most disadvantaged communities alongside poverty, lack of education and malnutrition. Helminth-infected pregnant women are likely to be younger, less educated and of lower socio-economic status than uninfected women – all factors that may impact upon nutrition and upon health-seeking behaviour (importantly, uptake of iron and folate supplements, preventive treatment for malaria and use of bed nets) for themselves and their infants. They may come from different ethnic backgrounds and live in different environments, compared with uninfected women, and these factors may influence customs or behaviour, and exposure of themselves and their infants to helminths and other infections. Co-exposure of the foetus or infant to malaria may be more common for environmental reasons, or because of immunomodulating effects of helminths. Randomized clinical trials of anthelmintic treatment should help to address this and to identify reversible effects directly caused by helminths.

De Vries, J., A. Abayomi, K. Littler, E. Madden, S. McCurdy, O. O. M. Oukem-Boyer, J. Seeley, C. Staunton, G. Tangwa, P. Tindana and J. Troyer (2015). "Addressing ethical issues in H3Africa research -- the view of ethics committee members. Report of the H3Africa Ethics Consultation Meeting, 2nd June 2014." *The HUGO Journal* in press

Genomic research in Africa raises a number of unique ethical challenges, arising most prominently from the interplay between vanguard science and traditional communities and research contexts. H3Africa research, which seeks to foster genomic research on diseases pertinent to African people, needs to carefully consider these ethical challenges. In June 2014, the H3Africa Working Group on Ethics convened a consultative meeting with members of research ethics committees (RECs) from across Africa to discuss ethical challenges in H3Africa research, with particular focus on issues relating to broad consent, sample and data sharing. H3Africa is an international collaboration of scientists working to build genomic research capacity in Africa (H3Africa Consortium 2014). The goal is to support cutting edge research to advance understanding of the genetic and environmental determinants of common diseases in Africa and to use this knowledge to improve the health of African populations. A key component of H3Africa research is the global sharing of data and selected bio specimens to promote their utility and to speed up discovery of new knowledge that could impact disease prevention and management. This raises a number of key ethical considerations that need to be addressed in order for H3Africa research to be successful. To better understand these issues and the perspectives of research ethics committees on H3Africa research, the H3Africa Working Group on

Ethics hosted a consultation meeting to which we invited the Chairs of research ethics committees involved in the review of H3Africa projects. The meeting was attended by just over 80 people including 60 members of 40 research ethics committees from 18 African countries.¹ Also in attendance were a number of H3Africa researchers, members of the H3Africa Working Group on Ethics, and representatives of the two funding agencies that are supporting H3Africa research; the US National Institutes of Health and the Wellcome Trust. In this report, we share the main lessons learnt from this consultation meeting

Schatz, E. and J. Seeley (2015). "Gender, ageing and care work in East and Southern Africa: A review." *Global Public Health*(ahead-of-print): 1-16

An estimated 58 million persons aged 60-plus live in sub-Saharan Africa; by 2050 that number will rise sharply to 215 million. Older Africans traditionally get care in their old age from the middle generation. But in East and Southern Africa, HIV has hollowed out that generation, leaving many older persons to provide care for their children's children without someone to care for him or herself in old age. Simultaneously, the burden of disease among older persons is changing in this region. The result is a growing care deficit. This article examines the existing literature on care for and by older persons in this region, highlighting understudied aspects of older persons' experiences of ageing and care - including the positive impacts of care work, variation in the region and the role of resilience and pensions. We advance a conceptual framework of gendered identities - for both men and women - and intergenerational social exchange to help focus and understand the complex interdependent relationships around care work, which are paramount in addressing the needs of older persons in the current care deficit in this region, and the Global South more generally.

Settumba SN, Sweeney S, Seeley J, Biraro S, Mutungi G, Munderi P, et al. The health system burden of chronic disease care: an estimation of provider costs of selected chronic diseases in Uganda. *Tropical Medicine & International Health*. 2015;20(6):781-90

OBJECTIVE:

To explore the chronic disease services in Uganda: their level of utilisation, the total service costs and unit costs per visit.

METHODS:

Full financial and economic cost data were collected from 12 facilities in two districts, from the provider's perspective. A combination of ingredients-based and step-down allocation costing approaches was used. The diseases under study were diabetes, hypertension, chronic obstructive pulmonary disease (COPD), epilepsy and HIV infection. Data were collected through a review of facility records, direct observation and structured interviews with health workers.

RESULTS:

Provision of chronic care services was concentrated at higher-level facilities. Excluding drugs, the total costs for NCD care fell below 2% of total facility costs. Unit costs per visit varied widely, both across different levels of the health system, and between facilities of the same level. This variability was driven by differences in clinical and drug prescribing practices.

CONCLUSION:

Most patients reported directly to higher-level facilities, bypassing nearby peripheral facilities. NCD services in Uganda are underfunded particularly at peripheral facilities. There is a need to estimate the budget impact of improving NCD care and to standardise treatment guidelines.

Tindana P, J. De Vries, M. Campbell, K. Littler, J. Seeley, P. Marshall, J. Troyer, M. Ogundipe, V. P. Alibu, A. Yakubu and M. Parker (2015). "Community engagement strategies for genomic studies in Africa: a review of the literature." BMC Medical Ethics

BACKGROUND:

Community engagement has been recognised as an important aspect of the ethical conduct of biomedical research, especially when research is focused on ethnically or culturally distinct populations. While this is a generally accepted tenet of biomedical research, it is unclear what components are necessary for effective community engagement, particularly in the context of genomic research in Africa.

METHODS:

We conducted a review of the published literature to identify the community engagement strategies that can support the successful implementation of genomic studies in Africa. Our search strategy involved using online databases, Pubmed (National Library of Medicine), Medline and Google scholar. Search terms included a combination of the following: community engagement, community advisory boards, community consultation, community participation, effectiveness, genetic and genomic research, Africa, developing countries.

RESULTS:

A total of 44 articles and 1 thesis were retrieved of which 38 met the selection criteria. Of these, 21 were primary studies on community engagement, while the rest were secondary reports on community engagement efforts in biomedical research studies. 34 related to biomedical research generally, while 4 were specific to genetic and genomic research in Africa.

CONCLUSION:

We concluded that there were several community engagement strategies that could support genomic studies in Africa. While many of the strategies could support the early stages of a research project such as the recruitment of research participants, further research is needed to identify effective strategies to engage research participants and their communities beyond the participant recruitment stage. Research is also needed to address how the views of local communities should be incorporated into future uses of human biological samples. Finally, studies evaluating the impact of CE on genetic research are lacking. Systematic evaluation of CE strategies is essential to determine the most effective models of CE for genetic and genomic research conducted in African settings.

Omosa-Manyonyi G, Mpendo J, Ruzagira E, Kilembe W, Chomba E, Roman F et al. A Phase I Double Blind, Placebo-Controlled, Randomized Study of the Safety and Immunogenicity of an Adjuvanted HIV-1 Gag-Pol-Nef Fusion Protein and Adenovirus 35 Gag-RT-Int-Nef Vaccine in Healthy HIV-Uninfected African Adults. PLoS ONE 10 (5): e0125954

BACKGROUND:

Sequential prime-boost or co-administration of HIV vaccine candidates based on an adjuvanted clade B p24, RT, Nef, p17 fusionprotein (F4/AS01) plus a non-replicating adenovirus 35 expressing clade A Gag, RT, Int and Nef (Ad35-GRIN) may lead to a unique immune profile, inducing both strong T-cell and antibody responses.

METHODS:

In a phase 1, double-blind, placebo-controlled trial, 146 healthy adult volunteers were randomized to one of four regimens: heterologous prime-boost with two doses of F4/AS01E or F4/AS01B followed

by Ad35-GRIN; Ad35-GRIN followed by two doses of F4/AS01B; or three co-administrations of Ad35-GRIN and F4/AS01B. T cell and antibody responses were measured.

RESULTS:

The vaccines were generally well-tolerated, and did not cause serious adverse events. The response rate, by IFN- γ ELISPOT, was greater when Ad35-GRIN was the priming vaccine and in the co-administration groups. F4/AS01 induced CD4+ T-cells expressing primarily CD40L and IL2 +/- TNF- α , while Ad35-GRIN induced predominantly CD8+ T-cells expressing IFN- γ +/- IL2 or TNF- α . Viral inhibition was induced after Ad35-GRIN vaccination, regardless of the regimen. Strong F4-specific antibody responses were induced. Immune responses persisted at least a year after the last vaccination. The complementary response profiles, characteristic of each vaccine, were both expressed after co-administration.

CONCLUSION:

Co-administration of an adjuvanted protein and an adenovirus vector showed an acceptable safety and reactogenicity profile and resulted in strong, multifunctional and complementary HIV-specific immune responses.

Asiki G, Murphy G, Baisley K, Nsubuga RN, Karabarinde A, Newton R, Seeley J, Young EJ, Kamali A, Sandhu MS. Prevalence of dyslipidaemia and associated risk factors in a rural population in south-western Uganda: a community based survey. PLoS One. 2015 May 14;10(5):e0126166. doi: 10.1371/journal.pone.0126166. eCollection 2015. PMID:25974077

BACKGROUND:

The burden of dyslipidaemia is rising in many low income countries. However, there are few data on the prevalence of, or risk factors for, dyslipidaemia in Africa.

METHODS:

In 2011, we used the WHO Stepwise approach to collect cardiovascular risk data within a general population cohort in rural south-western Uganda. Dyslipidaemia was defined by high total cholesterol (TC) \geq 5.2mmol/L or low high density lipoprotein cholesterol (HDL-C) $<$ 1 mmol/L in men, and $<$ 1.3 mmol/L in women. Logistic regression was used to explore correlates of dyslipidaemia.

RESULTS:

Low HDL-C prevalence was 71.3% and high TC was 6.0%. In multivariate analysis, factors independently associated with low HDL-C among both men and women were: decreasing age, tribe (prevalence highest among Rwandese tribe), lower education, alcohol consumption (comparing current drinkers to never drinkers: men adjusted (a)OR=0.44, 95%CI=0.35-0.55; women aOR=0.51, 95%CI=0.41-0.64), consuming $<$ 5 servings of fruit/vegetable per day, daily vigorous physical activity (comparing those with none vs those with 5 days a week: men aOR=0.83 95%CI=0.67-1.02; women aOR=0.76, 95%CI=0.55-0.99), blood pressure (comparing those with hypertension to those with normal blood pressure: men aOR=0.57, 95%CI=0.43-0.75; women aOR=0.69, 95%CI=0.52-0.93) and HIV infection (HIV infected without ART vs. HIV negative: men aOR=2.45, 95%CI=1.53-3.94; women aOR=1.88, 95%CI=1.19-2.97). The odds of low HDL-C was also higher among men with high BMI or HbA1c \leq 6%, and women who were single or with abdominal obesity. Among both men and women, high TC was independently associated with increasing age, non-Rwandese tribe, high waist circumference (men aOR=5.70, 95%CI=1.97-16.49; women aOR=1.58, 95%CI=1.10-2.28), hypertension (men aOR=3.49, 95%CI=1.74-7.00; women aOR=1.47, 95%CI=0.96-2.23) and HbA1c $>$ 6% (men aOR=3.00, 95%CI=1.37-6.59; women aOR=2.74, 95%CI=1.77-4.27). The odds of high TC was also higher among married men, and women with higher education or high BMI.

CONCLUSION:

Low HDL-C prevalence in this relatively young rural population is high whereas high TC prevalence is low. The consequences of dyslipidaemia in African populations remain unclear and prospective follow-up is required.

Mugisha J, Muyinda H, Malamba S, Kinyanda E. Major depressive disorder seven years after the conflict in northern Uganda: burden, risk factors and impact on outcomes (The Wayo-Nero Study). BMC Psychiatry. 2015 Mar 14;15:48. doi:10.1186/s12888-015-0423-z.

BACKGROUND:

Major depressive disorder (MDD) is a major public health burden in conflict areas. However, it is not known for how long and by how much the observed high rates of MDD seen in conflict settings persist into the post-conflict period.

METHODS:

A cross sectional survey was employed seven years after the conflict in northern Uganda had ended in the three districts of Amuru, Gulu and Nwoya.

RESULTS:

The prevalence of major depressive disorder (MDD) was 24.7% (95% CI: 22.9%-26.4%). The distribution by gender was females 29.2% (95% CI: 14.6%-19.5%) and males 17.0% (95% CI: 26.9%-31.5%). The risk factors for MDD fell under the broad domains of socio-demographic factors (female gender, increasing age, being widowed and being separated/divorced); distal psychosocial vulnerability factors (being HIV positive, low social support, increasing war trauma events previously experienced, war trauma stress scores previously experienced, past psychiatric history, family history of mental illness, negative coping style, increasing childhood trauma scores, life-time attempted suicide, PTSD, generalized anxiety disorder and alcohol dependency disorder) and the psychosocial stressors (food insufficiency, increasing negative life event scores, increasing stress scores). 'Not receiving anti-retroviral therapy' for those who were HIV positive was the only negative clinical and behavioural outcome associated with MDD.

CONCLUSIONS:

These findings indicate that post-conflict northern Uganda still has high rates for MDD. The risk factors are quite many (including psychiatric, psychological and social factors) hence the need for effective multi-sectoral programs to address the high rates of MDD in the region. These programs should be long term in order to address the long term effects of war. Longitudinal studies are recommended to continuously assess the trends of MDD in the region and remedial action taken.