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14. ABSTRACT This contract represents the continuation of support from USAMRAA for medical science and research programs on behalf of the U.S. Army Medical Research and Materiel Command (USAMRMC) and its subordinate laboratory, the Walter Reed Army Institute of Research (WRAIR) and its Special Foreign Activity (SFA) the U.S. Army Medical Research Unit Kenya (USAMRU-K). Previous support was provided under contract DAMD17-02-2-0022 for the period 01 March 2002 to 31 December 2006. USAMRU-K's mission is focused on developing and testing improved means for predicting, detecting, preventing and treating worldwide infectious disease threats to deployed US military personnel. The unit is also involved in global surveillance, training, research, and response to emerging infectious disease threats. Several diseases that are currently endemic to Kenya have historically impacted military operations. Malaria is hyper-endemic in the coastal lowlands and lake regions of Kenya, leishmaniasis focally distributed in Baringo district and the arid northeastern portion of the country while HIV/AIDS and enterics are present throughout the country with a higher prevalence in urban slum areas.					
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1. INTRODUCTION:

This P6 Cooperative Agreement (ICA) provided continued support for testing and developing new agents (drugs and vaccines) that prevent and treat infectious disease threats to the war fighter. The recipient further increased an understanding of how these microbes cause death and disease by studying semi-immune and non-immune populations in areas where they are endemic. It further facilitated the development of improved tools and methods to predict, detect and prevent arthropod-borne disease threats to military and civilians to regions of the world where these diseases are endemic. Research was undertaken in malaria, HIV/AIDS, entomology, enterics, leishmaniasis and other military-relevant tropical diseases.

2. KEYWORDS:

ACRONYMS AND ABBREVIATIONS

ACTG	-	AIDS Clinical Trials Group
AFHSC	-	Armed Forces Health Surveillance Center
AFI	-	Acute Febrile Illness
AIDS	-	Acquired Immune Deficiency Syndrome
ART	-	Antiretroviral therapy
CAP	-	College of American Pathologists
CRC	-	Clinical Research Center
DEID	-	Department of Emerging Infectious Diseases
EQA	-	External Quality Assessment
GEIS	-	Global Emergent Infections Surveillance
HIV	-	Human Immunodeficiency Virus
IRIS	-	Incidence And Immunopathogenesis Of Immune Reconstitution Syndrome
KEMRI	-	Kenya Medical Research Institute
KWDSS	-	Kisumu West Health and Demographic Surveillance System
MDC	-	Malaria Diagnostics Center
MDR	-	Malaria Drug Resistance
MEDCAP	-	Medical Civic Action Program
MOH	-	Ministry of Health
WHO	-	World Health Organization
WRP	-	Walter Reed Program

3. OVERALL PROJECT SUMMARY:

a. Task 1 – Malaria: Malaria research is centered in Nyanza province around the city of Kisumu and its environs. Current efforts focus on drug sensitivity testing for antimalarials, vaccine trials and field research to determine vector capacity. The Malaria Drug Screening Laboratory conducts research aimed at malaria drug discovery and monitoring of drug resistance. The Clinical Research Center in Kombewa conducts vaccine and drug clinical trials in

collaboration with pharmaceutical companies and the Entomology laboratory conducts studies on vector surveillance and control.

Plasmodium continues to complicate prophylaxis and treatment of malaria. Chloroquine remains relatively ineffective in most of the malaria endemic areas of Africa. New drug and drug combinations will continue to be tested for treatment and prophylaxis. Antimalarial drug sensitivity of isolates from defined populations in the region will continue to be monitored and data used to map the distribution of drug resistant genes. The only centralized laboratory in Equatorial Africa for routine determination of antimalarial chemosensitivities has now been established in USAMRU-K facilities. Molecular biology, immunological, and biochemical techniques will continue to be used to characterize an expanding archive of *plasmodium* isolates from defined geographic region to provide data that may instruct about mechanisms of parasite resistance and potentially impact ongoing drug development efforts.

P. falciparum (Pf) drug resistance, conferred largely by mutations, is expected to continue evolving in Kenya. Information from in vitro Pf malaria drug resistance patterns and molecular mutations is critical in tracking new patterns of emergence or disappearance and can be used in selecting effective malaria drugs. The SYBR Green I-based IC50 drug sensitivity assay is used for ex vivo and in vitro drug sensitivity testing. In vitro drug sensitivity testing is done using the newly installed liquid handler, drug testing platform, Biomek FXp.

Molecular analysis is currently done using conventional PCR, real-time PCR, Capillary Electrophoresis, Allelic discrimination assays and Sanger sequencing. Genes analyzed include *Pfmdr-1*, *Pfcrt*, *Pfdhfr*, *Pfdhps*, *Pfmrp*, *Pfcytb*, *Pfnhe-1*, *pfmdr-6*, *Pfmdt* and *Pftetq*. These genes are linked to resistance of different drugs that are found in our in vitro test panels. Over 1,600 sample isolates have been collected during the contract period.

Microscopy remains the standard method for malaria diagnosis. Evolving methods such as rapid tests have been introduced to augment diagnosis where reliable laboratory services are not available or feasible. Limitations of these methods in clinical and research settings are well documented. This heightens the risk of misdiagnosis for US soldiers serving in endemic areas as well as failure of research studies conducted by US DOD facilities. It is therefore important that laboratory personnel involved in malaria diagnosis be trained in proper microscopic diagnosis and relevant quality systems in order to improve reliability of results. This should be followed by provision of external quality assurance and supportive supervision to ensure that skills attained and standards established are maintained. These can only be done if reference malaria blood films are made available. Evolving methods such as rapid tests and related molecular assays need evaluation using characterized specimen such as whole blood, dried blood spots and tubes. These are useful for both laboratory and field based evaluations. From these, approximately 5000 blood films and 300 whole blood aliquots were prepared for microscopy training and evaluation of alternative malaria diagnostic tests. During this contract period, over 1300 laboratory personnel were trained on malaria microscopy.

Field trials have been conducted to determine efficacy of candidate vaccines against malaria. In 2009, a Phase 1b malaria vaccine trial (MSP-1 FVO) was completed in 30 adults (37) and Mal 55 (Phase III RTS,S malaria vaccine trial from GlaxoSmith Kline – GSK) began. Mal 55 tested the RTS,S vaccine in 1,631 infants and children enrolled in Kombewa (one of 11 sites

in 7 African countries; total of 16,000 infants/children (27)). MAL58 (Phase III RTS,S safety and immunogenicity in 123 HIV-infected infants) began in 2010.

KEMRI/Walter Reed Project - Kisumu operates a Health and Demographic Surveillance System (HDSS) in Seme Sub County and Parts of Kisumu Sub-County (under the new devolved structure). The program is designed to track the evolving health status and demographics of the study population over time and to detect and signal if there is an outbreak or emergence of a new disease. This platform offers tremendous capability to conduct population-based surveillance at the individual, household/compound and community level. Already, three protocols for surveillance of specific infectious diseases in this community setting (rotavirus, influenza, and tuberculosis) have been designed. The Kisumu West DSS recently became a full member of the INDEPTH network (<http://www.indepth-network.org/>) and is continuing to grow and mature into a sustainable platform collecting high quality data. The program has added a strong health surveying component and is currently conducting routine bi-annual surveying of every household. Currently, the HDSS program shares aggregate demographic data with local MOH and PEPFAR leadership to inform programs and interventions, but this link is further set to be expanded and strengthened. The program is currently conducting the third round of Bi-annual household surveys. A population of 143,273 individuals drawn from 27,879 households is currently being monitored for demographic (Births, Deaths, Migrations) and Health (Causes of Morbidity) changes. Information on pregnancy as well as Verbal Autopsy interviews (to determine causes of death on reported deaths) is also being collected. A total of 855 Verbal Autopsy interviews have been conducted (out of the 1160 reported deaths during the first round of survey). The information will provide crucial cause of death data important for conducting research and public health interventions in the study area.

b. Task 2 – HIV-AIDS: The United States Army Medical Research Unit-Kenya (USAMRU-K) is the primary field station for the U.S. Military HIV Program. USAMRU-K provides regional coordination between our programs in Uganda, Tanzania, and Kenya. The primary mission of the HIV-AIDS program is to develop and test vaccines based on the genetics and subtypes or clades of the viruses prevalent in this region of the world. The following protocols are currently ongoing, in follow up or in analysis:

(1) AFRICOS/RV 329/WRAIR 1897 is a 15 year, open-ended prospective cohort study, enrolling 3000 HIV infected adults and 600 HIV uninfected adults at MHRP PEPFAR-associated clinical sites in Kenya, Tanzania, Uganda and Nigeria (ongoing).

(2) RV 364/WRAIR 1918, Effect of Disclosure status on medical outcomes in HIV Infected adolescents in Kericho Kenya, is a 2 year study that looks for correlations between disclosure status and ART adherence, as measured by clinician documentation in medical charts. The study also aims to describe the clinical outcomes of adolescent clients related to their disclosure status. This will include anthropomorphic measurements, presence of opportunistic infections, CD4 counts, viral load (when available), hospitalizations, and overall survival (ongoing).

(3) RV217, HIV-1 Prevalence, Incidence, Cohort Retention and Host Genetics and Viral Diversity in Cohorts in East Africa and Thailand, is a 10 year study to characterize recruitment, retention, human immunodeficiency virus (HIV) prevalence, HIV incidence and

biological characteristics of acute HIV infection in high-risk volunteers in Africa and Southeast Asia. Archived plasma and cells are will be used in immunological assays to support vaccine trials and define clinical correlates for protection (in follow up).

(4) RV262, A Phase I Study of the Safety and Immunogenicity of Pennvax™-G DNA (env and gag) Administered by Intramuscular Biojector®2000 or Cellectra® Intramuscular Electroporation Device Followed by MVA-CMDR (HIV-1 CM235 env/CM240 gag/pol) Boost in Healthy, HIV-Uninfected Adults. The primary objective of this study is to evaluate the safety and tolerability of PENNVAX™-G DNA (env & gag) administered by IM Biojector® 2000 or IM CELLECTRA® electroporation followed by IM MVA-CMDR (HIV-1 CM235 env/ CM240 gag/pol) boost in healthy HIV-uninfected adult participants. The secondary objective is to evaluate the ability of PENNVAX™-G DNA (env & gag) and MVA-CMDR (HIV-1 CM235 env/ CM240 gag/pol) in a DNA/MVA prime/boost strategy to induce HIV antigen specific cellular and humoral immune responses (in follow up).

(5) RV 246/IRIS, A Cohort Observational Study Evaluating The Incidence And Immunopathogenesis Of Immune Reconstitution Syndrome (IRIS) In HIV-1 Infected Patients With CD4 Count <100 Cells/μL Who Are Initiating Antiretroviral Therapy. The primary study objectives are to identify baseline predictors of IRIS within 6 months of HAART initiation prospectively in a group of HIV-1 infected patients with advanced disease who are starting antiretroviral therapy and to evaluate the immunopathogenesis of IRIS with the goal to identify more appropriate targets for future therapeutic interventions (in analysis).

(6) RV172, Phase I/II Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiclade HIV-1 DNA Plasmid Vaccine (VRC-HIVDNA016-00-VP) Boosted by a Multiclade HIV-1 Recombinant Adenovirus-5 Vector Vaccine (VRC-HIV ADV014-00-VP) in HIV-uninfected Adult Volunteers in East Africa. The primary objectives of this 2 year study are to evaluate the safety and tolerability of VRC HIV-1 recombinant adenovirus-5 vector (rAd5) vaccine at various concentrations in HIV-1 uninfected adults and the safety and tolerability of three VRC HIV-1 DNA-six-plasmid vaccines in HIV-1 uninfected adults versus those boosted with VRC HIV-1 rAd5 vaccine at various concentrations in HIV-1 uninfected adults. RV172 was the first vaccine clinical trial conducted by the HIV program in Kericho, the first HIV vaccine clinical trial conducted outside of Nairobi, and is the largest HIV vaccine trial to date in Kenya's history. With vaccinations concluding in 23rd February 2007, participants have now completed long term follow-up and data analysis is ongoing (in analysis).

c. Task 3 – Enterics: Acute gastroenteritis is a debilitating disease and is considered a major disease nonbattle injury for deployed U.S. military personnel. A clinical surveillance protocol (WRAIR #1549) to identify microbial pathogens from human stool specimens collected at sites within the GEIS network in Kenya is currently being conducted at the Microbiology Hub Kericho (MHK), USAMRU-Kenya/KEMRI. This protocol is a case (volunteers with acute diarrhea) control (volunteers with no diarrhea) study that allows for the collection of stool specimens recruited at an outpatient clinical setting. Briefly, stool specimens are collected in preservation media at the surveillance sites and transported to the MHK where they are processed and tested for bacterial, parasitic, and viral pathogens. Enteric bacteria identification and antibiotic susceptibility are conducted. The greatest benefit to the DoD is having a highly

competent microbial disease clinical laboratory that will provide much needed support to the AFRICOM mission. Scientifically, the enterics surveillance conducted is providing valuable data on the prevalence of enteric pathogens in Kenya as well as potential patterns of antibiotic resistance among bacterial isolates in Kenya. During the contract period, over 5,700 stool samples have been collected and tested by the MHK. Additionally, the Microbiology Hub Kericho achieved the prestigious College of American Pathologists (CAP) certification in 2012

Task 4 – Leishmania: The Entomology Program/Vector Biology Unit conducts research on the biology and ecology of vectors of military important diseases with a focus on the development of integrated disease surveillance and management strategies. The goals of the Entomology program are to develop products, tools, and methods to mitigate risk and/or prevent vector-borne diseases. The following protocols are currently ongoing, in follow up or in analysis:

(1) Assessment of Leishmania Risk in Kenya: Human Infections, Animals, Vector and Climate. This project seeks to conduct a coordinated collection of human cases, vector infection rates, animal reservoirs and ecological data sets. To do this, patients with febrile illnesses attending hospitals at geographically diverse areas of Kenya provide specimens for case detection. USAMRU-K vector surveillance team organizes vector surveillance and sandfly infection rates determination in areas found to have significant leishmania burden. The Kenya government veterinary team organizes animal surveillances to identify animal reservoirs. Remotely sensed metrics derived from the leishmania human cases/landscape/reservoir will be used for modeling to allow risk factors determination and ways of mitigating them (ongoing).

(2) Colonization and Bionomics of the Sand Fly *Phlebotomus orientalis* (Diptera: Psychodidae) in Kenya. The overall aim of this project is to gain a better understanding of the bionomics of the visceral leishmaniasis sand fly vector, *Phlebotomus orientalis*, in Kenya which could potentially lead to the development of oviposition traps which could be used to trap this species in the wild. This will be done through the initiation of a colony at USAMRU-K, conducting laboratory experiments and field surveillance of breeding areas (ongoing).

(3) Evaluation of Repellents, Inhibitors, Barrier Treatments, and ULV Insecticides, and other New Products in sub-Saharan Africa. The goal of this study is to evaluate the efficacy and longevity of ULV and barrier spray treatments of military desert radar-scattering camouflage netting and HESCO barriers in controlling important mosquito and sand fly vectors in dry and hot environments in sub-Saharan Africa (ongoing).

(4) Modeling sand fly vectors of visceral leishmaniasis to characterize the threat of visceral leishmaniasis in Kenya. The primary aim of this project is to develop distributional and climate change models of *Phlebotomus orientalis* and *P. martini*, the primary vectors of visceral leishmaniasis in Kenya, using remotely sensed imagery, elevation, climate data, vegetation indices, and vector data, to serve as a VL threat characterization tool (ongoing).

(5) Evaluation of Multiplexed Detection Tools for Quick and Accurate Identification of Leishmania and Sand Fly Fever Virus in Sand Flies. Rapid assays provide the best opportunity to identify threats and target pest management operations. Field testing and validation of these assays for sand fly, mosquito, and tick-borne pathogens in the vector is a priority. Approaches

that include combination assays (e.g., sand fly fever and leishmaniasis assays, multiple virus assays) are applicable. Approaches should include multiple platforms: PCR-based, immunodiagnosics-based, others as applicable. Products already in development should be the primary targets for this objective. Multi-lab collaborations will assist in providing the best products (in analysis).

(6) Sand Fly Surveillance and Estimation of Endemic *Leishmania* spp. Infection Rates for Sand Fly Populations in Kenya and Neighboring Countries. This project supported development of a field based leishmaniasis surveillance program to screen for and identify *Leishmania* spp. infected sand flies. This work focused on the development of a robust sand fly surveillance system with two main aims: 1) develop a detailed database on sand fly distribution and population structure over time; and 2) estimate and track sand fly infection rates. These data can then be used to look for predictive observations for use in alerting public health officials of possible risk from disease. Additionally, including this information in future epidemiological studies will provide more powerful insights into the environmental and sociological factors contributing to these outbreaks (in analysis).

4. KEY RESEARCH ACCOMPLISHMENTS:

a. Task 1 – Malaria

(1) 2007, the Malaria Drug Resistance laboratory (MDR) screened the activities of over 150 pure compounds in collaboration with the University of Nairobi, making the lab the largest drug assessment facility in the country.

(2) 2008, the MDR became the first lab in East Africa to establish the non radio-isotopic, field expedient and expandable SYBR green I-based *in vitro* malaria drug sensitivity assay.

(3) January 2011, the Malaria Diagnostics Center (MDC) submitted the Kenya National Malaria Indicator Survey 2010 report to the Kenya Division of Malaria Control. A total 25,406 slides were received for staining, reading and archiving. Of the 12,728 slides meeting the criteria for reading, 11,140 (87.4%) were Negative and 1,588(12.5%) were Positive.

(4) 2011, The baseline census survey for the Demographic Surveillance System (DSS) entire study area was completed on 16SEP11. The enumerators then embarked on capturing the missed households up to 11NOV11. A total of 29,394 households were censused in the district giving a population of 121,875.

b. Task 2 – HIV-AIDS

(1) 2007, Completed the RV172 Phase I/II HIV DNA-rAd5 vaccine study, the first HIV vaccine study in USAMRU-K, the first outside of Nairobi, and the largest HIV vaccine study in Kenya to date.

(2) 2008, USAMRU-K Kericho Field Station became a DAIDS AIDS Clinical Trials Group (ACTG) Clinical Trials Unit overseeing 2 clinical research sites (Kericho and Eldoret).

(3) 2012, Kericho Field Station CRC was re-accredited by the prestigious College of American Pathologists (CAP).

c. Task 3 – Enterics

(1) 2009, Opened a new 9,000 sq ft microbiology laboratory in Kericho with a focus on enteric pathogens. This laboratory includes automated bacterial identification and susceptibility testing, rotavirus EIA and limited parasite EIA testing (Giardia, Cryptococcus, Entamoeba) and has advanced microbiology and enterics research at USAMRU-K.

(2) 2012, Micro-hub Kericho received its first College of American Pathologists (CAP) accreditation.

d. Task 4 – Leishmaniasis

(1) 2007-2013, The Entomology laboratory increased sand fly surveillance from three to seven sites in East Africa.

(2) 2013, The Entomology sand fly team responded to a visceral leishmaniasis outbreak in Wajir where they conducted sand fly vector collections in collaboration with the Kenya Ministry of Public Health and Sanitation's Division of Vector Borne Diseases.

5. CONCLUSION:

KEMRI provides critical support to USAMRU-K's emerging infectious disease surveillance program in Kenya. Without KEMRI, USAMRU-K would not be able to execute its mission. KEMRI provides the legal and regulatory framework, personnel, and laboratory structure necessary to carry out scientific work. The organizations exist in partnership, with USAMRU-K working fully under the KEMRI umbrella in Kenya. Together, we have made great strides in establishing surveillance capabilities in the areas of malaria, HIV/AIDS, enterics and leishmania. KEMRI maintains both surveillance sites and central laboratories to accomplish this mission.

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7. INVENTIONS, PATENTS AND LICENSES:

- a. Docket No. WRAIR 11-27X: 61/584,977 Waitumbi, John Njenga, "Use of Magnetism to Inactivate, Kill and/or Remove Malaria Parasites from Transfused Blood and Apparatus and Kits for Accomplishing the Same," filed 10 Jan 2012.
- b. Docket No. WRAIR 11-26X: 61/584,932 Waitumbi, John Njenga, "Use of Magnets to Inhibit the Spread of Malaria and Apparatus for Accomplishing the Same," filed 10 Jan 2012.

8. REPORTABLE OUTCOMES: Nothing to report.

9. OTHER ACHIEVEMENTS:

Awards:

a. Dr. Doug Shaffer, Dr. Fred Sawe, Dr. Kibet Shikuku, Dr. Charles Sigei - Meritorious Honor Award (US Department of State) April 2009. For extraordinary interagency and interdisciplinary performance resulting in a high quality and comprehensive program of HIV prevention, care, support and treatment activities, that is helping Kenya turn the tide of the epidemic.

b. Dr. John Waitumbi, European and Developing Clinical Trial Program(EDCTP, 2011): In recognition for contribution to Developing Countries Coordinating Committee (DCCC), which is part of the governance structure of EDCTP.