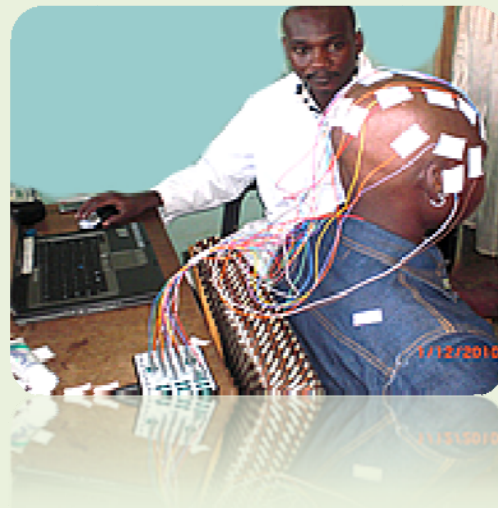


PROJECT SYNOPSIS 2011

KINTAMPO HEALTH RESEARCH CENTRE



SHIFTING FROM PRESUMPTIVE TO CONFIRMATION-BASED MANAGEMENT OF MALARIA IN GHANA

ACT PROJECT

The ACT study is an operational research project designed to provide evidence that will guide the Ghana National Malaria Control Program (NMCP) as it seeks to implement test-based management of malaria and in the process, optimise the use of the artemisinin-based combination therapy (ACTs).

The study is run in two phases.

Phase 1 of the study run from January 2009 to March 2010, and it involved the evaluation of CARESTART™, a brand of rapid diagnostic test (RDT) for malaria. This brand was supplied by the NMCP and was among brands that the program was considering deploying in the country. This component of the study was run in the Out-patient Department of the Municipal Hospital. The Kintampo Municipal Hospital was a collaborator in this component of the study. The second component of Phase 1 of the study was an observational study to assess IMCI implementation in five district hospitals (Jema, St. Therasas, Techiman, Nsawkaw, Busunya) and 10 health centers across five districts in the region. These are New Longoro, Nkoranza, Nkwabeng, Dromakese, Offuman, Aworowa, Tanoso, Debibi and Menji Health Centers. Using structured observation, the entire process of activities involved in the care of children with acute, uncomplicated febrile illnesses was observed. Nearly 2000 cases were observed.

Phase 2 of the study is currently on-going and is assessing the long-term effect of test-based management of malaria. It will be conducted in health centers within six districts of the region. It is a cluster randomised control trials in which half of the 32 facilities have been resourced to be able to strictly implement test-based management, while the other half implement routine IMCI-based care. The hypothesis underpinning this stage of the project derives from the concern that a level of herd immunity will be removed ACT use is restricted to only test-positive cases. The hypothesis is that the reduced “herd immunity” would lead to repeat febrile episodes and anemia in children. Such effect could offset whatever short-term gains may be derived from the reduction in the wasteful use of ACT. Whether this hypothesis will be proven will be known in

RESEARCH BRIEF OF THE KINTAMPO HEALTH RESEARCH CENTER

the next stage of the project. One hundred children living within 3km of the facilities have enumerated and constitute a cohort of children who will be observed for the frequency of malaria and anaemia between the two arms of the study.

To minimize the effect of financial barrier on attendance to health facility, children enrolled in the cohort have been put on the NHIS by the project. Fieldworkers have been stationed in each of the facilities to receive study children who report ill. Field supervisors also conduct monthly visits to the homes of all members of the cohort. This phase of the project is expected to end in August 2012.

The ACT project is funded by the ACT-Consortium and is being conducted in collaboration with the London School of Hygiene and Tropical Medicine. The study has received ethical clearance from the National Ethics Review Committee of the Ghana Health Service and the Ethical Review Committee of the Kintampo Health Research Center.

Attached

List of facilities in Phase 2

Health Facilities & Districts in Stage 2

HEALTH FACILITY	DISTRICTS
<i>Dawadawa H/C</i>	KINTAMPO NORTH
<i>New longoro H/</i>	
<i>Kunsu Rural Clinic</i>	
<i>Busuama Rural Clinic</i>	
<i>Amoma H/C</i>	KINTAMPO SOUTH
<i>Apesika Rural Clinic C</i>	
<i>Anyima H/C</i>	
<i>Mansie H/C</i>	
<i>Dromankese H/C</i>	NKORANZA NORTH
<i>Busunya H/C</i>	
<i>Kranka H/</i>	
<i>Yefri H/C</i>	
<i>Nkoranza H/C</i>	NKORANZA SOUTH
<i>Ayerede H/C</i>	
<i>Ahyiyem H/C</i>	
<i>Akuma H/C</i>	
<i>Nkwabeng H/C</i>	
<i>Donkro Nkwanta H/C</i>	
<i>Bonsu H/C</i>	
<i>Tanoso H/C</i>	TECHIMAN
<i>Buoyem H/C</i>	
<i>Aworowa H/</i>	
<i>Oforikrom H/</i>	
<i>Offuman H/C</i>	
<i>Tuobodom H/C</i>	
<i>Nsuta H/C</i>	
<i>Nsawkaw H/C</i>	TAIN
<i>Banda Ahenkoro H/C</i>	
<i>Sabie H/C</i>	
<i>Debibi H/C</i>	
<i>Menji H/C</i>	
<i>Seikwa</i>	

**DETERMINATION OF BASELINE MALARIA EPIDEMIOLOGY AMONG A
BIRTH COHORT OF CHILDREN IN THE MIDDLE BELT OF GHANA FOR
MALARIA INTERVENTIONS.**

DMID Protocol Number:

07-0086

Sponsored by:

National Institute of Allergy and Infectious Diseases (NIAID)

DMID Funding Mechanism:

Contract No. HHSN266200400016C

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1.0 Summary

Title **DETERMINATION OF BASELINE MALARIA EPIDEMIOLOGY AMONG A BIRTH COHORT OF CHILDREN IN THE MIDDLE BELT OF GHANA FOR MALARIA INTERVENTIONS.**

Study Rationale: Malaria vaccine development is currently ongoing in many parts of the world at various stages in the development pipeline. Baseline epidemiological data are required to adequately evaluate new malaria vaccines among endemic populations.

The Kintampo Health Research Centre is located in the middle belt of Ghana. Its aim is to conduct epidemiological and interventional studies of public health relevance locally and internationally.

In 2003 – 2004 the centre conducted malaria epidemiological studies among the local population with the aim of providing data that can be used as end points for malaria drug and vaccine evaluation. The prevalence of malaria parasitemia was > 50% at all times in the year with an incidence of clinical malaria of about 8 attacks per child (< 5yrs) per person-year). Entomological inoculation rate was found to be 269 infective bites per year. Since 2004, several public health interventions to reduce malaria such as education and treated bed-net distribution have been undertaken in the whole country including the study area. These may have affected the epidemiology of malaria in the study area and the available data needs to be updated prior to any evaluation of novel malaria interventions such as vaccines.

No studies have been conducted in the study area to determine baseline immunological correlates of clinical immunity to malaria in children aged 0-2 years which are important for vaccine development and testing. There is also the need to determine, host immunity which may vary among the various age-groups of children 0 – 2 years in this area where malaria transmission is high.

A prospective cohort study will be conducted in the study area to determine current malaria epidemiology and immunology necessary for evaluating new malaria vaccines.

Primary objective:

To determine the incidence of clinical malaria disease in a cohort of young children in the study area from birth to 2 years.

Secondary objectives:

1. To determine the incidence of severe malaria among the cohort of young children.
2. To determine hemoglobin levels and pattern of change in the hemoglobin levels among the cohort of young children.
3. To determine attributable fraction of fevers due to malaria in the birth cohort
4. To determine mortality trends among the cohort of children in the study area.
5. To identify immunological correlate (*i.e. antibodies to CSP, SSP2, MSP1, MSP3, MSP4, LSA1, AMA1, EBA175*) of clinical immunity to malaria in children aged 0-2 years.
6. To identify host genetic factors associated with resistance or susceptibility to severe malaria *such as G6PD deficiency, Hemoglobin S, C, E, Thalassaemias, HLA-A, -B, and -DR, and immune response genes for TNF- α , iNOS, IFN- γ receptor, and IL-12.*
7. To determine whether the multiplicity of infection is different in severe malaria cases, mild malaria and normal controls among the cohort of children.
8. To determine the effect of maternal malaria (stratified by gravidity *i.e.* multigravidae vrs primigravidae) on the risk of malaria during infancy.

Study Design: Prospective Cohort Design

Methodology:

Study Area and Recruitment: The study will be carried out in the Kintampo North and South Districts in the middle belt of Ghana where at least 3000 births occur per annum **from which a sample size of 1944 will be obtained.** Pregnant mothers in the study area will be identified using the Kintampo Demographic Surveillance System and their births identified within four weeks. Other sites such as the Nkoranza North and South Districts may be included if the numbers being recruited do not meet the targets. Mothers and their live infants who agree to stay within the study area and comply with study procedures will be recruited. A standard questionnaire will be used to capture demographic indices, household characteristics, treated bed-net use (by the mother during pregnancy and by the child) and history of prevention of malaria during the pregnancy by intermittent treatment. One (1ml) of venous blood will be obtained by a trained nurse at each of the monthly visits during pregnancy to determine malaria parasitemia as a prediction of placental malaria infection. The blood will also be used predict placental malaria using validated cellular peripheral immunological markers (TNF, TNF-RI TNF-RII, IL-1, IL-10, Ferritin) in the absence of peripheral parasitemia determine by microscopy At birth, maternal blood sample, cord blood and placental tissue will be collected to determine immunological parameters. At birth, an eligible child will be physically examined including weight and length measurements. Blood samples will be obtained at birth or at first contact to measure hemoglobin levels, maternal antibodies to malaria and other immunological parameters.

Scheduled follow up visits: Children will be visited at home monthly. At each of these visits the child will be examined and a standard questionnaire administered to capture antimalarial use and treated bed-net use. Blood samples will be collected **by a trained nurse** to determine malaria parasitaemia, haemoglobin levels and immunological parameters such as TNF- α , iNOS,.

Passive health facility visits: The incidence of uncomplicated malaria and severe malaria will be determined. Trained community based field workers will assist all children who are said to be ill to the nearest health facility. At each of these visits, the following assessments will be made; a physical assessment, laboratory assessment including blood smears and blood for immunological parameters. Diagnosis will be classified as uncomplicated malaria, severe malaria and other diseases based on case definitions. Treatment will be given along the Ghana Health Service treatment guidelines.

Health interventions especially malaria interventions implemented by the district health administrations will be recorded on quarterly basis. This will be necessary to interpret malaria indices collected over the study duration.

Sample size: A total of 1944 new births will be recruited into the study over a period of 1 year.

Data collection and procedures: All data (field and laboratory) collected will be guided by standard operating procedures agreed on before the start of the study. Laboratory specimens will be processed in the laboratories of Kintampo Health Research Centre (KHRC). Biochemical, hematological, PCR/ ELISA for entomology and malaria parasitaemia will be conducted in KHRC. The immunology unit of Noguchi Memorial Institute for Medical Research has expertise in malaria immunology and will be consulted for the analysis of immunological responses in the samples obtained from KHRC.

All data collected will be double entered into a database and verified prior to analysis.

Analyses: Data will be analyzed using STATA 8.0. A detailed analysis plan will be drawn up prior to study start. A definition for clinical malaria, that will include a threshold for parasitaemia and the presence of fever, will be employed and used to calculate the incidence of clinical malaria among the cohort of children. Attributable fraction of fevers due to malaria will be determined by logistic regression modeling of the relationship between parasitaemia and fever. Means of hematological measurements and percentages of malaria parasitaemia will be determined and their trends determined for age groups. Multiple logistic regressions will be used to analyze any associations between antibody responses and categorical variables such as presence or absence of clinical malaria episodes while linear regression models will be used in analyzing the relationship between antibody responses and continuous variables such as hemoglobin levels. The difference in the incidence of clinical outcomes will be used to examine specific allelic variants at candidate loci on malaria resistance or susceptibility. The effect of maternal antenatal history (such as ITN use and SP use), and placental malaria on risk of clinical malaria among children will be assessed.

Ethical issues: Parents of children will be allowed to sign or thumbprint a consent form which will specify the study's aims, objectives, procedures, duration and benefit/risk. Confidentiality of all data collected will be ensured. Ethical approval will be obtained from ethics committees of all collaborating institutions.

2.0 Collaborating Institutions and Key Roles.

Kintampo Health Research Centre

Kintampo Health Research Centre (KHRC), Ghana Health Service, P. O. Box 200, Kintampo is located in the Kintampo District of the Brong Ahafo Region. KHRC was established in 1994 under the Health Research Unit of the Ghana Health Service. It is located in the middle belt of Ghana where acute febrile diseases such as malaria are common among children. It is about 600Km or about seven (7) hours drive from the international airport in Accra, the capital city of Ghana, and about two hours drive from local airports in the same region where KHRC is located.

The centers' vision is to serve as a centre of excellence in carrying out relevant field/ clinical epidemiological studies that evaluate the impact of health interventions. KHRC has an outstanding track record in designing and implementing complex research projects. It has collaborated with local and international institutions such as London School of Hygiene, Malaria Vaccine Initiative, the Wellcome Trust, World Health Organization among others to achieve its objectives

KHRC has developed the protocol with input from our collaborators and will implement the day to day activities to achieve the study's objectives.

Noguchi Memorial Institute for Medical Research, LG 581, Legon-Accra, Ghana

Founded in 1979, the Noguchi Memorial Institute for Medical Research is the leading biomedical research institute in Ghana. A member of the College of Health and Sciences at the University of Ghana, it is composed of nine academic departments and operates several facilities, including a laboratory for animal experimentation and a biosafety level 3 laboratory. Its research focuses on communicable diseases and nutrition.

Role of the Health facilities:

Cord blood and placental tissues will be collected from the recruited mothers at the maternity wards. Subsequently, children who fall ill will be managed at the health facilities close to the where they live.

Study timelines: The study is expected to end by Dec. 2012.

Epilepsy Study Summary

What is Epilepsy? Epilepsy is a neurological disorder that affects the brain. It can affect people at different ages in their lifetime. Any trauma or damage to the brain can eventually cause epilepsy. These risk factors for the disorder include difficult labour, infections, brain tumour convulsions, genetic predisposition and accidents that involve impacts on the head.

What does the Epilepsy Study involve? The Epilepsy Study is being carried out in five sub-Saharan African countries including Kintampo the Kintampo Site in Ghana. The other countries are Kenya, South Africa, Tanzania and Uganda.

The Epilepsy Study at the Kintampo Site involves a series of activities summarized below:

1. A three-stage screening procedure that is aimed finally at getting people with epilepsy.
2. At Stages I, fieldworkers visit every household in the Kintampo Municipality and the Kintampo South district and ask two broad questions about fits, convulsions and other febrile seizures.
3. At Stage II the Epilepsy supervisors follow Stage I positives, and ask 10 questions narrowing down to the symptoms of epilepsy.
4. Those who meet the criteria of active convulsive epilepsy (ACE) are referred to the Epilepsy Clinic at the Kintampo Municipal Hospital for neurological examination and clinical history. When the clinical history confirms the diagnosis of ACE an electroencephalography (EEG) is conducted and the patients are put on the appropriate antiepileptic medication. Blood is drawn from the patients who consent to it, for eventual genetic analysis.
5. Age-matched controls are also invited to the clinic for clinical history, neurological examination and blood draw, if they consent to it.
6. Active convulsive epilepsy is defined operationally as “two or more seizures in the past five years with at least one of the seizures occurring in the last 12 months”.
7. The **EEG** involves planting electrodes at specific locations on the head, connecting them to the machine to read the surface activity of the cerebral cortex. Those found to have ACE are put on medication.
8. The Epilepsy Study is being carried out in Kintampo in collaboration with a neurologist and an EEG technologist from the Korle-Bu Teaching Hospital.

Indepth Phase IV Effectiveness and Safety Studies (INESS) of Antimalarials in Africa

The general objective of this project is to provide national, regional and international health decision makers with independent and objective evidence on the safety and effectiveness of new antimalarial drugs as a basis for malaria treatment policy in Africa.

The specific objectives are:

- i. To assess the effectiveness of new malaria treatments and its determinants in real life health systems
- ii. To evaluate the safety of new malaria treatments through comprehensive pharmacovigilance in an African health systems context

This project is being carried out in 8 Health and Demographic Surveillance Systems (HDSS) sites in 4 sub-Saharan African countries (Ghana, Tanzania, Burkina Faso and Mozambique) over a four year period under the auspices of the INDEPTH Network. In Ghana, all the three health research centres within the Ghana Health Service namely Dodowa, Kintampo and Navrongo Health Research Centres. The sites involved in Tanzania are Ifakara, Rufiji and Ulaga HDSS. The remaining sites are Manhica HDSS in Mozambique and Nouna HDSS in Bourkina Faso.

Study Design

The project is taking place in both Kintampo North Municipality and Kintampo South District and linked with the Kintampo Health and Demographic Surveillance System. The INESS project is a population-based longitudinal phase VI study which is divided into two broad modules: Systems Effectiveness and Safety modules. The involvement of both private and public health facilities is an essential component of the project. There is also a data-linkage system which attempts to link health facility data to population based (DSS) data to facilitate identification and follow-up of the population. Modular data collection for all year round will be employed in some cases and stratified into high and low malaria transmission seasons for others.

Effectiveness and Safety Modules

This project employs seven modules to assess the effectiveness of antimalarial drugs. These include:

1. Access
2. Patient Adherence
3. Targeting Accuracy and
4. Provider Compliance
5. Patient and Community Acceptability
6. Cost and Cost-effectiveness
7. Other Measures of Effect and Contextual Determinants of Malaria

The safety of the antimalarial drugs is being monitored through Spontaneous Adverse Events Reporting System (SAERS) and Cohort Event Monitoring (CEM).

Access -The objective of the access module is to determine the fever situation and the proportion of fever cases that need to seek care that actually gain physical access to a point of care; Three types of surveys are employed to address the access and this include household fever survey, household access and cost and cost effectiveness survey and then population parasite prevalence. Data for all three surveys is collected all year round, however whereas the household fever survey is targeted at all households, the other two are targeted at sampled and randomly selected households.

Targeting Accuracy and Provider Compliance – These two modules also referred to as health facility surveys (HFS) are aimed at assessing the quality of malaria case management through health facility surveys. A team visits all health facilities in the study area once or two in the low and high malaria transmission seasons to conduct exit interviews among patients who are visiting the facility for initial illness consultation, health facility interviews among health facility in-charges and also health workers interviews among health personnel who did consultations on the day of visit. At part of the exit interviews blood samples are obtained for blood slides.

Patient Adherence - The objective of this module is to determine the proportion of patients treated with an ACT who complete the recommended age-specific course of treatment. Patients who report to the health facility and have been given the recommended ACT are enrolled and follow up interviews conducted on

either day one, two or day three from the day of enrolment. Patients followed up on day three are also followed up on day 28. At enrolment and on day twenty-eight, blood samples are obtained for blood slides and Rapid Diagnostic Test (RDT).

Community and Provider Acceptability- The aim of this qualitative module is to examine the social, cultural, and behavioral factors that facilitate or impede the uptake and adherence to new antimalarial combination therapies as they are introduced into real-life settings. Data collection techniques such as Focus Group Discussions (FGDs), In-depth Interviews (IDIs) and Illness Narratives Interviews (INIs) are employed to collect data from the community seasonally.

Cost and cost-effectiveness - The aim of this module is to provide evidence on whether the new antimalarial is of high, moderate, or low cost-effectiveness compared to the existing first line drugs in use. This is valuable information to decision-makers health planners on the cash expenditures (the financial costs) needed to introduce a new policy for the new antimalarials. Data is obtained from the households and health facilities.

Other measures of effects and contextual determinants of malaria- The objective of this module is to document and interpret the trends of malaria morbidity and mortality taking all other contextual determinants into consideration. Data will be obtained from varied sources including the health facilities, District Health Administration and District Assemblies.

Safety Monitoring of the antimalarial drugs

Two modules will be employed to monitor the safety of the antimalarial drugs: spontaneous adverse event reporting system and cohort event monitoring.

Spontaneous Adverse Event Reporting System (SAERS) - The aim is to strengthen the already existing system where the reporting form, often called 'yellow forms' or 'blue forms', which are intended to be completed by clinicians, pharmacists, other health workers and sometimes patients when they suspect that a patient's condition may be a result of an adverse reaction to a drug.

Cohort Event Monitoring (CEM) – The CEM is being used whereby all patients prescribed antimalarials are enrolled and followed up between day three (3) and day seven (7) of enrolment and all adverse events recorded. Patients are given the opportunity to report all adverse events of concern to the study team up to 28 days post drug administration. This will provide real-life safety data in real time

and will complement the data obtained from the spontaneous adverse event monitoring system.

Data linkage

Data linkage which aims to link community data with health facility data is an essential component INESS. The community data or otherwise HDSS data is being upgraded to include passport size picture and biometric (scanned figure print) data for the entire HDSS population at the site. Provision of picture identification cards to the resident population is part of this exercise. After the first stage which is the enrolment, the upgraded HDSS data will be placed at the health facilities where patients reporting to the health facility can be linked to their respective data in the DSS database. Altimately health information will be linked to the population data to facilitate identification and follow up and open further research avenues within both the health system and research centre and to forge closer collaboration.

Kintampo Health Research Centre MAL 55 Study Synopsis

A phase III, double blind (observer-blind), randomized, controlled multi-center study to evaluate, in infants and children, the efficacy of the RTS,S/AS01E candidate vaccine against malaria disease caused by *P. falciparum* infection, across diverse malaria transmission settings in Africa.

About the Phase III trial

The RTS,S Phase III trial seeks to demonstrate the vaccine's efficacy in two groups of children - one aged 6-12 weeks and a second aged 5-17 months - in different transmission settings across a wide geographic region. In all, the study is being conducted in 11 sites including the Kintampo Health Research Centre in seven African countries. The trial has been designed in consultation with appropriate regulatory authorities in Africa, including the Ghana Health Service, Ghana Food and Drugs Board, and other northern institutions such as the European Union, the United States, and the World Health Organization.

Rationale

The trial has been designed to address the key safety and efficacy information required for the vaccine licensure. In addition, other disease endpoints that allow the evaluation of the public health impact and cost and cost effectiveness of vaccine implementation are included. Co-primary objectives will investigate the efficacy against clinical disease in children from 5-17 months of age at first dose and the efficacy in infants 6-12 weeks of age who receive the vaccine in co-administration with EPI antigens (i.e. DTPw Hep B/Hib).

Study procedures:

All children will be screened by a qualified medical personnel before enrollment. After enrolments, the study children are randomized to receive the experimental malaria vaccine or a control vaccine (Rabies or meningococcal vaccine). The children will then be followed up for the occurrence of clinical malaria, severe illness and immune boost. Each child will be followed up for a period of 32 months.

All subjects presenting to health facilities in the study area will be evaluated as potential cases of clinical malaria disease. A blood sample will be taken for evaluation of malaria parasites in all children who are reported to have had a fever within 24 hours of presentation or have a measured axillary temperature of 37.5°C.

All subjects presenting for admission through the outpatient and emergency departments of hospitals in the study areas will be evaluated as potential cases of severe malaria disease following a protocol-defined algorithm. During any hospitalization, the subject's course will be monitored to capture the signs and blood parameters indicative of severe malaria disease. If the subjects condition changes from admission and he/she meets one of the criteria for additional investigation, these will be performed.

Harmonization of case evaluation across centers will be assured by training of clinicians in the assessment of clinical signs and the standardization of equipment and processes used for laboratory investigations.

The screening for the enrolment of the study participants in Kintampo started in August 2009. A total of 1137 children of 5-17 months old have been recruited from the study area. This was followed by recruiting 358 infants aged 6-12 weeks. The study subjects have reached stages of the study.

APPROVALS

As per International Conference of Harmonization Regulations, the plans and conduct of the trial were reviewed and authorized by the following Institutional Review Boards prior to the beginning of the trial:

- Ghana Health Service Ethical Review Committee,
- Food and Drug Board of Ghana,
- Kintampo Health Research Centre Institutional Ethics Committee,
- Kintampo Health Research Centre Scientific Review Committee,
- Western Institutional Review Board in the USA
- Ethics Committee of the London School of Hygiene and Tropical Medicine.

Partners in this trial.

The Kintampo Health Research Centre, Ghana Health Service is implementing the trial in Kintampo. GSK Biologicals (Belgium) provides the vaccines used in this trial. They also provide monitoring support during the conduct of the study. The Malaria Vaccine Initiative (MVI) of Program for Appropriate Technology in Health (PATH), USA pays for the conduct of this study.

Role of the Kintampo Municipal Hospital and other health facilities.

Children will be screened and vaccinated at the vaccination centre of Kintampo Municipal Hospital and the clinical trial facilities at Amoma, Busuama and Jema.

Children who fall ill will also be reviewed at the health facilities. However, severely ill patients will be admitted and treated at the childrens' ward of the Kintampo Municipal Hospital.

Study Timelines: The study is expected to end by 2013.

For Further clarification, contact
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Tel: 0244 560213

NeoVitA

Project title:

Efficacy of newborn vitamin A supplementation in improving child survival in rural Ghana: generation of evidence necessary for informing global policy

Investigators:

Dr. Sam Newton, Ghana
Drs. Karen Edmond and Betty Kirkwood, London

Collaborators:

London School of Hygiene and Tropical Medicine; WHO Geneva; Bill and Melinda Gates Foundation

Background:

Data from 6 trials involving 42,508 infants suggested no evidence of a reduced risk of mortality due to any cause during first year of life in infants who were supplemented with vitamin A during the neonatal period in comparison to those who received placebo. However, this analysis was under-powered to detect a 15% reduction in mortality. Thus, there is thus an insufficient evidence base currently available to make a public health recommendation for neonatal vitamin A supplementation. A technical consultation convened by WHO and UNICEF in December 2008 recommended an additional set of randomized placebo-controlled trials in settings with high infant mortality, at least two in Africa and one in Asia, to determine the effect of neonatal vitamin A supplementation given within the first two days after birth on mortality in the first six months of life. Additionally, the consultation identified the need to study the biological mechanisms of action that may explain the possible beneficial effect of vitamin A supplementation of this intervention. In January 2009 WHO sent out a call for expressions of interest from study sites interested in conducting randomised controlled trials in newborn vitamin A supplementation. The London School for Hygiene and Tropical Medicine in collaboration with the KHRC was chosen to conduct one of the three trials. The other two trials are being conducted in India and Tanzania.

Objectives of the research:

Primary

- To determine if vitamin A supplementation (50,000 IU) given to neonates once orally either on the day of birth or in the next 2 days will reduce mortality in the first half of infancy by at least 15% as compared to placebo.

Secondary

- To determine if vitamin A supplementation (50,000 IU) given to neonates once orally either on the day of birth or in the next 2 days will reduce mortality in infancy (0-12 months) by at least 15% as compared to placebo.
- To determine the efficacy of vitamin A supplementation (50,000 IU) given to neonates once orally either on the day of birth or in the next 2 days in reducing mortality in the neonatal period (first month of life).
- To determine the efficacy of the above intervention in reducing the incidence of severe morbidity defined as hospitalizations due to any illness in the first 6 months of infancy.

- To document the potential adverse effects of vitamin A such as bulging fontanelle, vomiting, irritability, fever, diarrhea, inability to suck or feed, convulsions or any other condition that caused parents to be concerned, in the 3 day period following administration of the supplement.
- To determine the vitamin A and c reactive protein (CRP) status of a subsample of infants at 2 weeks and 3 months of age in the vitamin A supplementation and placebo groups.

How is the research undertaken?

The study is a placebo-controlled, double-blinded, individually randomized control trial of 32,000 infants. Infants will be enrolled from Kintampo North and South, Nkoranza North and South, Techiman, Wenchi and Tain districts. Infants will be followed at one month intervals for 12 months. Enrolment began on 16 August 2010. As of the end of March 2011, 11,007 infants have been enrolled and we have completed over 30,000 follow-up visits of enrolled infants. Our oldest infants are now 7 months. Verbal autopsy are conducted for all infants reported to have died and this aspect of the work began in February 2011. In April of 2011, we will begin the last aspect of the field work, which is a random sample of 2 week old infants and 3 month old infants and their mothers for a blood draw. The blood will be used to compare vitamin A levels between the placebo and control groups, and as well to determine underlying vitamin A deficiency among the study's population of mothers. Recruitment is expected to end in April 2012 and follow-up will continue until the end of 2012.

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Impact on postpartum hemorrhage of prophylactic administration of oxytocin 10 IU via Uniject™ by peripheral health care providers at homebirths: design of a community-based cluster-randomized trial

Methods/Design

This study is designed as a cluster-randomized community-based trial in which Ghana Health Service (GHS) Community Health Officers (CHOs) are randomized into one of two study arms determining the care that CHOs provide to enrolled women during their home-based deliveries. For the purposes of this trial, all deliveries assisted by an individual CHO constitute a cluster. The trial is designed to determine if intramuscular administration of 10 IU of oxytocin in Uniject™ during the third stage of labor by a CHO will reduce the risk of PPH by 50% relative to deliveries attended by a CHO who does not provide the prophylactic intervention. This is not, however, a drug efficacy trial. The trial is designed to assess the mode of service delivery.

Study site

The trial is being conducted in four predominantly rural districts of Brong-Ahafo region in central Ghana. The study districts, which are under demographic surveillance by the Kintampo Health Research Centre (KHRC), are Kintampo North and South and Nkoranza North and South with a combined population of approximately 260,000. KHRC is a field research center operating since 1994 under the GHS and responsible for many large-scale, prospective clinical and community-based trials. The selected districts are an excellent context in which to assess home-based PPH prevention because maternal mortality in this area is high (at approximately 350 to 400 maternal deaths per 100,000 pregnancies and approximately 30% of births occur at home).

Field staff

Field staff for this trial consist of 69 field workers, with at least senior-high school education, dedicated to this study and resident in the communities for which they are responsible, and nine field supervisors. The field workers were provided with bicycles and the supervisors were provided with motorcycles to facilitate movement within their areas of work. All field staff participated in a three-day training prior to the start of the study.

Extensive consultations were required during the design phase of the study between KHRC leadership, study investigators, and GHS staff at both the district and regional levels regarding the involvement of GHS CHOs as the agents to administer the study intervention. CHOs are the centerpiece of the GHS Community-based Health Planning and Services (CHPS) Initiative, which has the goal of expanding access to basic health care for the rural population. CHO services include childhood vaccination, antenatal and postnatal care, family planning outreach, emergency deliveries, and referral for complications during pregnancy and delivery. While CHOs are permitted to administer ergometrine tablets in an emergency for treatment of postpartum hemorrhage, they are not currently permitted to administer injectable uterotonics. Following training, CHOs are posted to a CHPS compound from which their clinical and outreach work is based.

The study facilitated the placement of CHOs into communities in study districts where there were no CHOs and provided resources to improve CHO compounds where these were inadequate. Prior to the start of the study, all CHOs completed a five-day training course and were required to pass a competency-based examination specific to their cluster allocation. Throughout the course of the study, CHOs are provided with some allowance to purchase credit for their mobile phones as well as basic comfort items such as solar lamps and beds. The compounds are also provided with basic hospital equipment such as examination couches and cupboards for storage of medical supplies as a contribution to the expansion of the CHPS initiative. Study-related work by the CHOs is jointly supervised by the GHS and KHRC.

Randomization

Among the four participating districts, 52 CHO areas were identified and categorized as either “near” (≤ 10 km) and “far” (> 10 km) from a facility with capacity for emergency obstetric care. The categorization resulted in eight strata (4 district x 2 distance), two of which contained an odd number ($n=7, 7$) and six of which contained an even number of CHOs ($n=6, 10, 4, 4, 8, 6$). A temporary placeholder CHO was added to each of the two strata containing an odd number of CHOs, and all units were randomly allocated to either the oxytocin in Uniject group or the Comparison group using the STATA utility “ralloc”, stratified on district and distance. This random allocation was repeated 10,000 times. Among the 4,995 allocation sequences that assigned the placeholder CHOs to opposite groups, a single allocation was selected at random, and the two placeholder CHOs were discarded. This resulted in 52 total CHOs evenly allocated overall (26 vs. 26), within each of the six strata with an even number of CHOs, and in a ratio of 4:3 and 3:4 in the two strata with an odd number of CHOs

Procurement of oxytocin in Uniject™

Oxytocin in Uniject™ injection devices with time-temperature indicators were produced by Instituto Biológico Argentino (BIOL), a pharmaceutical producer in Argentina, and imported into Ghana as clinical study supplies after obtaining a clinical sample import permit from the Ghana Food and Drug Board. They are transported to KHRC under cold chain conditions and are distributed from KHRC refrigerators on a weekly or as-needed basis to CHOs, who store them in their compounds in a cool place. Storing oxytocin out of the cold chain is being done to ensure that the intervention is being conducted under conditions as similar as possible to a scaled-up government service. To the best of our knowledge, this study constitutes the first randomized controlled trial in which the oxytocin in Uniject™ injection system has been used.

Recruitment

Prior to the start of field work, community meetings were held with GHS authorities in various communities, opinion leaders, chiefs, and community members regarding the objectives of the study. KHRC field workers then began identifying on a weekly basis all households with a pregnant woman within their allotted communities. There are no exclusion criteria for this study. As pregnant women at seven months or more gestation are identified, the study is explained to them and they are asked for initial consent to participate in the study. Initial consent indicates that a woman is interested in having a CHO present at her delivery should she be unable to travel to a health facility or should she choose to deliver at home. Field workers remain in contact with women who have initially consented, and where possible, they arrange to introduce the CHO to the pregnant woman’s family. They then wait to see if the woman calls the field worker at the onset of her labor. When field workers are contacted, they phone the CHO and both travel to the

woman's household, though the field worker will generally remain outside of the house. Final consent for full participation is obtained at this time.

Trial implementation

Once in the home and after administration of final consent, CHOs in both groups place a BRASSS-V calibrated drape designed to collect postpartum blood under the woman's body before birth of the baby. Women are asked to remain recumbent, if possible, for one hour if bleeding ceases within one hour, or for two hours if active bleeding continues at one hour. The blood loss measure excludes fluid, urine, and feces passed during the birthing process. All blood collected in the drape is scooped into the pouch. The drape is removed from the woman and held up vertically in order to obtain the blood loss reading. This method has been validated and used in a number of previous and ongoing trials. If a woman in either arm of the trial is actively bleeding when she has lost 400 mL blood, referral is initiated via mobile phone for emergency transport. To identify active bleeding, all CHOs are trained to monitor pulse, uterine tone, and vaginal bleeding every 15 minutes for the first two hours after delivery of the baby. Study-sponsored vehicles and drivers specifically available for this purpose immediately respond to emergency calls. In the event of PPH (defined as ≥ 500 mL blood loss) early treatment with one injection of 10 IU of oxytocin and fundal massage will be provided by the CHO. This same treatment response may also be provided in the event of gushing blood, a uterus that is neither hard nor round, and/or blood clots the size of a lime following delivery of the baby. Palpation for a second twin is done prior to all injections of oxytocin. Emergency referral and transport is available to women and newborns in both arms of the study for any type of complication.

The intervention

While all CHOs measure blood loss and provide treatment and referral (if necessary), CHOs randomized to the intervention arm provide one injection of 10 IU of oxytocin administered via Uniject in the thigh within one minute after delivery of the baby. CHOs in both arms collaborate with the birth attendant to conduct their study-related responsibilities and do not directly manage the delivery.

Follow-up

Two to three days following delivery, the field worker visits the house of all enrolled women for a follow-up interview with questions regarding the care they received, and in particular, the timing relative to delivery of the baby and of any injections they may have received. When necessary, a family member who was present during the birth may assist in responding to these questions. In cases where traditional birth attendants managed the delivery, a similar interview is also conducted with them.

Sample size estimation

The sample size estimation procedure followed a standard approach for cluster-randomized trials. First, having *a priori* determined that the desired recruitment period for the active comparative phase of the trial would be 9 months, we estimated the expected mean number of observed deliveries per CHO over this time period (mean cluster size = 24), derived from available estimates of (1) the crude birth rate (27 per 1,000), (2) the mean population size covered by a CHO (4,250), and (3) the total proportion of deliveries that would be conducted at home and reachable by CHOs (28%). Second, in the absence of prior information on the incidence of PPH in this setting, we estimated from a previous community-based trial in rural India that the

observed frequency of PPH among women delivering in the presence of comparison CHOs would be approximately 10.0%, and we assumed a conservatively high variation coefficient (“k” = 0.35) across CHOs. Setting the Type I error rate to 5% and assuming 10% loss per cluster, we estimated that 26 CHOs (or 564 pregnancies) would be required within each group (i.e., total = 1128) in order to detect reductions in PPH of 50% or more with at least 80% power.

Data management

CHOs, KHRC field workers, and supervisors collect data using paper-based forms during their contacts with pregnant women and family members. These included a Background Information form filled at the time of the preliminary consent (approximately seven months gestation); a CHO form filled at and soon after the observed delivery; and follow-up forms with the delivered woman, a family member, and, if present, the traditional birth attendant that assisted at the time of delivery. All forms filled by CHOs and field workers are checked by supervisors for completeness and consistency, and then transferred to the KHRC Computer Center for double data entry into a customized Visual FoxPro database. Consistency, validity, and referential integrity are enforced. Basic enrollment status reports are generated fortnightly.

Data analysis

Both the interim and final analyses will begin with descriptive information regarding the extent (i.e., total numbers) of enrollment, the dynamic of enrollment over the period of the trial, and variation between the clusters in terms of enrollment. Given the importance of assessing feasibility of this intervention in any scaled-up program, particular focus will be placed on describing the frequency with which women in labor contact the CHO to request her presence and the proportion of these women for whom the CHO arrives before delivery. Reasons for not contacting the CHO or for non-arrival by the CHO will be estimated and compared across the groups. Enrolled women will be defined as those for whom (1) the field worker/CHO arrived at the home prior to delivery, (2) consent to participate was reconfirmed (“final consent”), and (3) the CHO was present at the delivery. Among enrolled women, a range of covariates will be compared to determine if the cluster randomization achieved balance across socio-economic, household, and maternal characteristics.

Primary Outcome: The primary outcome of this trial is PPH. This outcome was selected based on (1) extended discussions with an international technical advisory group established for the study, which concluded that for policy impact, it would be insufficient to assume a health benefit from this intervention given the use of minimally trained health care providers and use of a new technology; (2) a general consensus that blood loss greater than 500mL constitutes PPH; and (3) the availability of a validated tool for the measurement of blood loss in a home setting.

PPH will be defined using three different definitions. The strictest definition will be cumulative blood loss of $\geq 500\text{mL}$ as measured by the BRASSS-V drape at the end of the first hour after birth, or in the case of active bleeding at one hour, at the end of the second hour after birth. Under this definition, all women who have blood loss measured will be included; those with $\geq 500\text{mL}$ will be included in the numerator and all others with a quantitative measure will be in the denominator. We note, however, that this strict definition is problematic in two ways. First, some women (in both groups) will be provided a treatment dose either before one hour is complete, or prior to reaching 500mL; this dose could obscure the total amount of blood loss that might have occurred in the absence of this rapid treatment response. Therefore, a second broader

definition will include in the numerator all women with $\geq 500\text{mL}$ measured blood loss OR women receiving a treatment dose of oxytocin (regardless of final measured blood loss) and will be assessed among all enrolled women. Furthermore, some women may be referred by the CHO for postpartum blood loss, yet not be included in the numerator (or the denominator) of either the prior two definitions. Thus, the final definition will include in the numerator all women with one or more of the criteria ($\geq 500\text{mL}$ blood loss, receipt of a treatment dose, referral for blood loss) and will be assessed among all enrolled women.

Analysis of each of these three definitions will follow an intent-to-treat approach; that is, women will be included in the analysis according to their cluster allocation, regardless of their specific receipt (or non-receipt) of the assigned intervention. Separately for each definition, the proportion of women in each group meeting the criteria will be estimated, and the risk of the outcome in the intervention group relative to the control group will be calculated (i.e., risk ratio) using a binomial regression model with log link function. Standard errors will be adjusted for the clustered allocation using the generalized estimating equation approach, and 95% confidence intervals will be estimated. If necessary, regression models will be adjusted for any imbalance(s) between the groups, previously identified during the descriptive analysis phase.

Secondary Outcomes: Given concerns regarding the safety of the intervention and its programmatic feasibility, several secondary outcomes were selected. The predominant safety concern is administration of oxytocin for induction, or more likely, for augmentation of labor. Use of any intramuscular uterotonic drug before the birth of the infant is regarded as dangerous because it is not possible to adjust the dosage if it causes hyper stimulation and cannot be adapted to the level of uterine activity, as is possible with the monitored administration of intravenous oxytocin in health facilities. Hyper stimulation of the uterus can lead to uterine rupture, fetal asphyxia or fetal demise. Thus, the key secondary outcome for this trial is mistimed use of oxytocin, and will be defined as any use of oxytocin prior to delivery of the (last) baby. The proportion of deliveries in which a CHO, traditional birth attendant, or pregnant woman/family member reports that oxytocin in UnijectTM was given prior to delivery of the (last) baby will be estimated, and a 95% confidence interval constructed. If appropriate, this outcome will be examined separately by allocation group and compared using standard methods (again, adjusting standard errors for cluster randomization).

Other safety outcomes include individual and composite estimates of the frequency of adverse maternal, fetal, and neonatal events, including maternal deaths, stillbirths, early neonatal deaths, birth asphyxia, need for newborn resuscitation, uterine rupture, and referral and/or transport to a higher-level facility. Among participating women, comparisons will be made for all deliveries across both arms of the trial and also restricted to deliveries for which oxytocin was given before delivery of the baby. For each comparison (and the composite measure), proportions will be estimated, and 95% confidence intervals constructed. Comparisons across groups will utilize binomial regression with a log link function, will account for clustered allocation using GEE, and will adjust for imbalance as necessary. Analyses of feasibility outcomes will be descriptive in nature (estimating proportions, means, etc.). These include, among others, the proportion of deliveries in which the CHO arrives late, the mean time between call and arrival of the CHO, proportion of participating pregnancies (initial consent given) that become participants (final consent given), and the proportion of oxytocin in Uniject injection systems disposed of properly.

Data Safety and Monitoring Board and interim analyses

An independent Data Safety and Monitoring Board (DSMB) consisting of national and regional experts was established. A single interim analysis will take place at approximately the 50% mark of planned overall recruitment (anticipated for November 2011). Stopping guidelines for efficacy were agreed upon by the DSMB members and the investigating team prior to the trial, using Lan-DeMets boundaries and nominal p-values for group sequential analyses estimated using O'Brien-Fleming spending function.

Approvals and registration

The study protocol was approved by the Institutional Ethics Committee of the KHRC, GHS Ethical Review Committee, Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health (#00002673), and the Research Ethics Committee of PATH (#547). The protocol is reviewed and reapproved on an annual basis. The trial is registered at ClinicalTrials.gov: HCT01108289.

Severe malaria in children in the Kintampo districts of Ghana.

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Severe malaria presents as several different syndromes. In Africa, cerebral malaria, metabolic malaria (acidosis, hyperlactaemia or respiratory distress) and severe anaemia are the common presentations of severe malaria. Impaired consciousness, hyperlactaemia, hypoglycaemia and respiratory distress have been found to increase the risk of mortality but the pattern of disease (frequency of these syndromes as well as the mortality associated with these syndromes) differs in different places. This underscores the need to have relevant local data on the clinical and laboratory course of severe malaria in the Kintampo study area.

Risk factors (factors which make an individual more susceptible or resistant to severe malaria) may include socio-demographic factors, parasite genetic factors, host genetic and acquired immune factors. Associations between host genotypes including HLA alleles and Non-HLA alleles and red cell abnormalities like Haemoglobins C, E and S have also been observed. Polymorphisms in some cytokine genes like Tumour necrosis factor alpha (TNF- α) and inducible Nitric oxide synthase (iNOS) and other genes like Intercellular adhesion molecule-1 (ICAM-1), complement receptor-1, mannose binding lectin also appear to affect susceptibility.

Micronutrients like vitamin A and Zinc have been shown to reduce morbidity from infections like respiratory infections and diarrhea. Research on effects of these micronutrients have shown mixed results on morbidity from falciparum malaria and more knowledge is needed especially on their effect on severity of malaria and on co-infections.

Knowledge and understanding of the factors which place a person at increased risk of severe malaria and increased risk of mortality from severe malaria are important because this can help in developing preventive and therapeutic tools against severe malaria. Knowledge of host genetic risk factors and immunological correlates of protection can help in understanding the mechanisms of the body's natural defense against malaria which is important in developing an effective vaccine against the disease.

Severe malaria presents with similar signs and symptoms as most other severe acute medical illnesses in children. In addition, concurrent co-morbidity with infections is not unusual. Sometimes, it is reasonably easy to distinguish some of these illnesses from severe malaria because of localizing signs and symptoms which can be picked up without sophisticated laboratory analyses. Some infections are however often clinically indistinguishable from severe malaria and can be misdiagnosed as severe malaria especially in the rural district hospital setting where facilities for laboratory investigations like blood culture, chest x-ray, lactate and base excess are unavailable or inadequate. In particular, infections which can be misdiagnosed as severe malaria include pneumonia, meningitis, sepsis and gastroenteritis with severe dehydration. In the rural district hospital setting incidence of these infections is underestimated and it is possible that these infections (as sole cause or co-infection with malaria) account for a considerable proportion of morbidity and fatality in acutely ill children admitted to hospital diagnosed with severe malaria. Most studies done on severe malaria in the past have not specifically sought out for co-infections and may have overestimated the contributions of malaria in acutely ill children.

Knowledge of the incidence of these bacterial co-infections and their impact on the presentation and course of disease will help in designing simple algorithms to aid clinicians in the clinical management of severely ill febrile children in the district and will also help in determining case definitions for severe malaria in vaccine trials with severe disease as an endpoint.

Objectives:

To describe severe malaria and common bacterial co-infections and identify possible host and parasite factors which predispose children to severe malaria disease and identify prognostic factors for fatality in children.

Primary outcome measure:

Odds ratios of identified host and parasite factors.

Secondary Outcome Measures:

1. Proportion of study children with severe malaria alone, severe malaria with bacterial co-infection or other severe acute medical illnesses.
2. Frequency of indicators of severity in study children with severe malaria (all definitions)
3. Clinical outcomes (survived, died, lost to follow-up)
4. Frequency of bacterial infections and co-infections in study children.
5. Frequency and type of bacteria isolated and correlation with mortality.
6. Mean titres of specified immunologic factors

Study population:

- Children aged 0 to 59 months admitted to the Kintampo District hospital with an acute medical illness.
- Children aged 0 months to 59 months reporting to the OPD of KDH and other health facilities in the study area with uncomplicated malaria.
- Healthy asymptomatic children aged 0 months to 59 months residing in the study area.

Study design:

A Case control study to determine risk factors for development of severe malaria and a descriptive study of severe malaria will be conducted. All children admitted with an acute medical illness who satisfy inclusion/exclusion criteria will be enrolled and evaluated as potential severe malaria disease patients. Their clinical and laboratory presentation and course of illness will be documented until day 14. Children who satisfy the protocol primary definition of severe malaria disease will be designated as cases in the case-control study. Two sets of controls (age, sex and location-matched controls) will be selected for each case: OPD controls: Two children with uncomplicated malaria recruited from Out-patient department.

Community controls: Two healthy asymptomatic children recruited from community.

Study duration: The study is expected to end by December 2011

Role of Health facility:

Children who are admitted at the children's hospital in the Kintampo Municipal Hospital will be enrolled by physicians