Entebbe Mother and Baby Study

PROTOCOL AMENDMENT

Amendment title: Appendix 14: The genetics of response to vaccination, infectious and inflammatory disease in the children from the Entebbe Mother and Baby Study (EMaBS)

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SUMMARY

This protocol amendment will provide a detailed genetic analysis of the children enrolled in the Entebbe Mother and Baby Study (EMaBS). The primary aim of this proposal is to understand the genetic basis of variability in the human immune response to childhood vaccination. In particular, we will measure the immune response to seven common childhood vaccines in samples already available from over 1200 one-year old children recruited as part of the EMaBS. We shall then undertake a genome-wide association study (GWAS) to identify genetic factors associated with variable immunogenicity of the seven vaccines in these one year olds. Following the extraction of the DNA from these children, it will subsequently be possible to perform more detailed genetic analyses including exome sequencing and whole-genome sequencing. This genetic data may be combined with both data already available and data which is still to be collected as part of the ongoing EMaBS to provide further insight into disease processes such as tuberculosis and asthma.

The additional activities proposed include, firstly, a measurement of the serological response to the seven vaccines using stored serum samples taken after the children had been vaccinated at one year of age. Secondly, we propose an extraction and genotyping of the DNA in each of these individuals also using stored blood specimens. We shall then combine both sets of data and perform a statistical analysis to undertake a GWAS. The DNA will be stored to enable future genetic studies which will include exome sequencing and whole-genome sequencing and the data will be stored securely and confidentially to permit future studies to investigate the children's response to infectious and inflammatory diseases.

BACKGROUND

The EMaBS was designed to investigate the hypothesis that helminth infections modulate the host immune response both to themselves and to unrelated immunogens, pathogens and allergens.[1] The study, which was a randomised, double-blind, placebo-controlled trial of antihelminthic treatment during pregnancy and early childhood, has been completed.

The trial found no major effect of maternal helminths, or of antihelminthic treatment during pregnancy, on the primary outcomes of infant responses to vaccines, or on susceptibility to infectious diseases.[2] Among secondary outcomes, there was a possible benefit of albendazole for maternal anaemia among mothers with heavy hookworm infections, but there were none of the expected benefits for birth weight or perinatal mortality.[3]

Despite the overall negative findings of the original study, its design makes it an ideal platform to investigate a range of other scientific questions. The mothers and children were managed in a carefully controlled environment ensuring that the children received all of their vaccinations in a timely manner to control for immunological response. The study revealed a significant variation in the children's serological response to the vaccinations the children had received.[2] For example, using a (log10+1) scale, the mean measured response to tetanus vaccination using total IgG at one year of age was 2.30 with standard deviation of 1.79, whereas for measles total IgG the mean at one year of age was 2.54 and standard deviation was 0.50. This observation of variation in response to vaccination has been reported extensively in the scientific literature and we plan to undertake a genetic analysis of the children in the EMaBS to identify the genetic factors responsible for this variation in more detail.

A genetic investigation of these EMaBS children may provide a further understanding of the children's immunological response to their environment and exposure to infectious disease as a part of other studies being undertaken as in Entebbe. A disease of major interest, for example, is tuberculosis. The original EMaBS study measured the response to vaccination with BCG using a series of cytokine measurements from the whole blood culture in the children in response to crude culture filtrate proteins from *Mycobacterium tuberculosis*. These measurements, for example, may be correlated with the children's genetics to understand which genetic factors are associated with the response to BCG vaccination. Another ongoing extension of the EMaBS is the investigation of how helminth infection may influence the development of inflammatory conditions such as asthma and eczema. Extending the genetic analyses proposed in this study to this extra work will provide a powerful adjunct to the understanding of the children's immune response to disease.

The work proposed here will involve genotyping each of the children at a number of genetic variant sites throughout the genome and performing quantitative GWAS using the response to vaccination as the measured phenotype to identify the genetic variants associated with the variable response to vaccination. A similar analysis may be performed using the same genetic data to undertake the further work suggested above.

RATIONALE FOR THE PROPOSED ADDITIONAL WORK

Vaccines have been pivotal in reducing the incidence of infections which once inflicted a global burden of disease with high rates of mortality. Despite their effectiveness, the protection afforded

by current vaccines is not guaranteed, and nearly all vaccines require multiple dosing to achieve their purpose. Human vaccination induces a variable serological response when administered. In addition to the measles and tetanus vaccines discussed above as part of the EMaBS, the hepatitis B vaccine, which is the most cited example, only achieves full protection in 90 % of vaccinees after the standard triple dosing regimen.[4] There is evidence that both host genetic and environmental factors are responsible for this variability in response to all vaccines but a significant proportion of the variability is thought to be due to heritable factors. Strong evidence supporting this view is provided by twin studies.[5] There have been a limited number of studies which have aimed to identify the particular genetic factors responsible for variation in response to HBV vaccination.[6-9] The general conclusion from all of these studies is that the HLA locus is responsible for part of this variability but other, as yet unrecognised, factors are also involved. We hope that our study will shed greater clarity on the genetic mechanisms underlying this variability in the Ugandan cohort.

By identifying the genetic factors involved in the response to vaccination we will aim to further understand the development of immunity following vaccination, and subsequently design more effective vaccines that provide a more consistent response. The eventual desired outcome will be a vaccine that can provide full protection in all individuals to a single infection following one dose. African populations would stand to benefit the most from such an intervention, given they suffer the highest burden of infectious disease, and such a strategy would minimise the need to repeatedly access hard-to-reach communities to administer multiple doses. Furthermore, if we could identify molecular pathways commonly involved in the response to vaccination we may be able to exploit this information to help design vaccines against diseases such as HIV and malaria.

Undertaking a genetic analysis of a cohort such as the EMaBS will provide a range of scientific benefits. The data acquired can be securely and confidentially stored with the potential to be used to answer a range of questions about the child's health. We envisage using the data to specifically investigate the individual's response, not only to vaccines but also other infectious diseases, and subsequently use this information to understand the development of inflammatory conditions such as asthma and eczema. Such analyses will provide a powerful ability to further our understanding of the relationship between human genetics and infectious disease in an African population.

HYPOTHESIS

Our hypothesis is that immunological factors such as cytokines and cytokine signalling receptors, intracellular messengers and transcription factors are predominantly responsible for the majority of the genetic contribution to variation in vaccine response.

OBJECTIVES

We plan to use blood samples already collected from the children enrolled in the EMaBS to achieve the specific objectives:

1. To measure immune responses to the seven common childhood vaccines: diphtheria, tetanus, pertussis*, Haemophilus influenzae*, hepatitis B, oral polio and measles at one year of age.

2. To undertake a genome-wide association study (GWAS) to identify genetic markers associated with variable immunogenicity of seven vaccines in these one year olds.

3. To anonymously store the genetic data (including GWAS, exome and whole-genome sequencing data) to assist in future research into infectious and inflammatory diseases in the Ugandan population.

METHODOLOGY

Study design

The Entebbe Mother and Baby Study (EMaBS), to which participants were recruited between 2003 and 2005, was a trial of anthelminthic treatment during pregnancy and early childhood.[10] The trial interventions, both of which have been completed, were as follows:

> During the second or third trimester of pregnancy, expectant mothers were randomised to receive single-dose albendazole (400 mg) or matching placebo and single-dose praziquantel (40 mg/kg) or matching placebo in a 2x2 factorial design.
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> From age 15 months to five years the offspring were randomised to receive quarterly albendazole or matching placebo. The dose was 200 mg while aged 15 to 21 months and 400 mg while aged two to five years.

The additional work proposed here will comprise a genetic analysis of the children already recruited as part of the study.

Study population

Women were recruited into the EMaBS at the Entebbe Hospital Antenatal Clinic if they were resident in the study area (Entebbe Municipality and the two neighbouring parishes of Katabi sub-county), planning to deliver in the hospital, willing to know their HIV status, and were in the second or third trimester of pregnancy. They were excluded if they had possible helminth-induced disease (haemoglobin <8.0 g/dL, clinically apparent severe liver disease, or diarrhoea with blood in stool) or a history of an adverse reaction to antihelminthic agents, if they had already been enrolled in the trial during an earlier pregnancy, or if the pregnancy was deemed abnormal by a midwife.

Follow-up of all children to five years was completed in 2011. Children were encouraged to attend the Entebbe Hospital for their routine immunisations. If children were immunised elsewhere this was verified from their health record card. Thus the database records the date of each immunisation, and whether it was given at Entebbe Hospital (under direct observation) or elsewhere, verified by the health card. Children were asked to attend for assessment at the study clinic every year on the day of their birthday, or as soon after this date as possible. Upon attendance their mother was questioned on various aspects of the child's health. A blood sample was taken from each child at the clinic when they were one year old, and at each subsequent annual visit. Plasma and serum were separated, divided into aliquots and stored to allow assessment of serological response or measurement of immune system activity. Whole cell pellets from EDTA anticoagulated blood were also stored, and this is ideal for the process of DNA extraction.

General data collection methods

All of the data required from the participants has already been collected from the children and mothers with informed consent from the mothers as part of the original EMaBS. The consent forms, to which the mothers gave agreement, stated that, "In general, blood samples will be used for tests for anaemia, malaria and other infections including HIV. Some will be used for tests of immunity and some may be stored for other tests in future." Data such as ethnicity, vaccination history, HIV status and general health of the child which is essential for the genetics project has already been obtained.

For this new work we shall make every effort to re-contact each mother and child to acquire informed assent and consent for extraction and analysis of the child's DNA from the stored blood samples over a three month period. If the child is aged eight or above and capable of providing it, informed assent will also be gained. The child's understanding will be assessed and documented using two simple questions: the first asking them what they understand a gene to be and the second asking them what they understand will be done with their blood samples. If a child is aged eight or above and is unable to provide assent because they have not yet reached an adequate level of education and understanding, this will be documented on the assent form and the individual's samples will not be used in this study. If, following initiation of the study, it is discovered that a large proportion of the children are unable to understand the principles of genetics and provide appropriate assent, we shall make a subsequent request for the committee to waive the requirement for assent and depend entirely on maternal consent instead. It may not be possible trace all of the children or their parents for whom we have samples available owing to the natural movement of study individuals, or the unfortunate death of either the mother or child. If there has been more than or equal to an 80 % consent and assent rate in those individuals contacted, we would request that the committee permit a waiver of consent and assent for those not contacted assuming that by initial enrolment and consent in the EMaBS the participants would agree to add this genetic analysis to the overall study design and objectives.

Laboratory Methods and Analysis Plan

Aim 1. To measure immune responses to the seven common childhood vaccines: diphtheria, tetanus, pertussis*, Haemophilus influenzae*, hepatitis B, oral polio and measles.

The serological response to measles and tetanus vaccine in each of the children at one year of age has already been measured as part of the original EMaBS protocol. There are sufficient blood samples available for over 1200 children who have received all of their vaccinations to perform a measurement of serological response to vaccination against all of the pathogens listed. We anticipate using Luminex technology to perform this analysis. A replication of the serology measurements of tetanus and measles using the Luminex technology could provide effective internal quality control and would subsequently provide consistency for the proposed future analysis of replication cohorts. A Luminex machine is expected in Entebbe, Uganda in 2012 and we shall develop a multiplex or suitable alternative assay to measure the serological response to diphtheria, tetanus, pertussis, *Haemophilus*, hepatitis B, oral polio and measles using this technology in all of the selected children.

We anticipate that all assays will be conducted in Uganda. If this is not possible then relevant material transfer agreements will be submitted for approval by the committee.

Aim 2. To undertake a genome-wide association study (GWAS) to identify genetic markers associated with variable immunogenicity of seven vaccines in these one year olds.

Each of the children recruited as part of the EMaBS have had blood samples taken providing sufficient remaining specimen to extract DNA for genetic analysis. We will use the QiaGen DNA extraction kit to acquire high quality DNA from the frozen EDTA stored whole blood pellets. These stored pellets are available from samples obtained at annual visits from age one to five years. It is anticipated that this step will be performed entirely in Uganda. We shall then transfer a suitable quantity of DNA for each individual to the University of Oxford, UK for subsequent genomic analysis in the laboratories of Professor Adrian Hill. An aliquot of DNA from each individual shall remain in Uganda for future analysis. In Oxford, the DNA shall undergo genotype analysis using a commercially available or custom designed microchip which will provide a unique genetic fingerprint for each individual. Typical current arrays use between 200 000 and 1 000 000 variants distributed across the genome. This data shall then undergo in-house quality control using PLINK or other suitable software. We shall subsequently combine the individual genotype analysis of each individual with the quantitative output of serological response to each vaccine to undertake a quantitative trait locus genome wide association study analysis.[11]

Aim 3. To anonymously store the genetic data (including GWAS, exome and whole-genome sequencing data) to assist in future research into infectious and inflammatory diseases in the Ugandan population.

Following the performance of the GWAS analysis the DNA will be stored with the potential for genome-wide genetic analyses such as exome and whole-genome sequencing which are now standard approaches in large scale human genetics studies. Routine procedures are in place to permit deposition of such genetic data in international repositories such as the European Bioinformatics Institute (EBI) in Hoxton, UK. The data is stored securely and anonymously and stringent protocols are empowered to ensure the data is released only to researchers with a specific scientific question. We anticipate that the data will be used almost exclusively in Oxford and Entebbe to investigate the EMaBS children's response to their environment, with infectious disease in particular, and how this influences the development of inflammatory conditions such as asthma and eczema. The cytokine response to BCG vaccination in the EMaBS children is already available, for example, and measurement of antibody responses to BCG is in progress. A combination of this data with the genetic information could provide insight into the mechanisms underlying variability of response to BCG vaccination. Furthermore, ongoing studies investigating the relationship of helminth infection with the development of inflammatory conditions in the EMaBS could be enhanced with the application of genetic analysis. It is further envisaged that the genetic data will be used in studies such as the African Genomes Project which is a proposed international consorted effort which will provide insight into the genetic heterogeneity of African populations. These studies have been developed to permit a global analysis of African genetic studies which are inherently complicated as a result of the diverse nature of African people.

Sample Size Considerations

With regards to the vaccine response GWAS (Aim 1 and 2), the serological response to measles vaccination has already been measured in the EMaBS cohort (mean of 621 and standard deviation of 1033 mIU/ml). Assuming a sample size of 1200 which should be the minimum achievable from the original EMaBS cohort this will have 80 % statistical power to detect a variant allele with a

minor allele frequency of 10 % causing a change in response to measles vaccination of between 372 to 456 mIU/ml. This calculation was performed using the QUANTO software (from hydra.usc.edu/gxe) seeking a GWAS level of statistical significance ($p < 5 \times 10^{-7}$) and assuming a dominant mode of inheritance. A larger effect size of an associated variant allele would be predicted using some recent preliminary work with candidate gene analyses and response to measles vaccination.[12] This study revealed effects of between 1000 to 2000 mIU/ml with some HLA haplotypes confirming that our study is sufficiently powered to identify associated variants.

By identifying variants in the genome associated with an increased or decreased response to vaccination we would aim to either identify novel genes and molecular pathways involved or replicate previous findings which should provide a deeper understanding of the immune response to vaccination. In order to confirm these findings we would aim to replicate our associations using an independently recruited cohort in Africa, and subsequently develop vaccines using knowledge gained from these studies to develop more immunogenic but safe vaccines for use in the African populations. Ethical approval for the replication cohort will be sought separately.

Ethical Considerations

Since the biological samples required for this proposal have already been collected from the children there will be no additional physical inconvenience to the children or their guardians. The majority of the mothers and children are still participating in long term follow up in Entebbe. We will seek consent from the mother, if available, or from the father or current guardian if the mother is not available. We will seek assent from the child if he or she has already attained eight years of age. The consent and assent will be sought to perform genetic analyses including genome-wide genotyping, and exome and whole genome sequencing on DNA from the EMaBS children. The research team and proposed collaborators have extensive experience of handling samples and data for genetic research. Our approach to obtaining informed assent and consent from the individuals in the study will be based on experience and findings from previous research investigating the ethical considerations of performing genetic studies in Africa.[13] The clinic staff and field workers who are already working with the individuals in the EMaBS will be trained to outline the nature of the work. They will seek to gain informed assent / consent with a written form requiring a signature or fingerprint, and complemented by verbal communication to explain the study if the literacy standard is poor. Particular factors regarding the study that will be stressed are:

- This study is trying to determine the heritable 'blood' factors associated with why most children are protected from infection by vaccination but some are not (heritable meaning being derived from parents and grandparents and shared by siblings).
- No further action needs to be taken by the mother or child for us to get the information we are looking for.
- This is all part of the study they are already enrolled in and there is no more clinical or non-clinical benefit to the child or the mother by participating in the study.
- We will use this information to design better vaccines in the future for people from Africa in particular.
- The genetic information will be stored to be used to answer future questions about how the children respond to infectious disease and why inflammatory conditions such as asthma and eczema develop.

- The individuals would be welcome to have access to their genetic data if they wish and results from the study will be available to them at any time if they are interested.
- The individuals can withdraw from the study at any time.

In order to maintain confidentiality, serum and DNA samples and data will be encoded with a unique identifier with no personal data associated with it. A list of the individuals including personal and clinical details will be kept separate from the genetic data. A separate list permitting the linking of the clinical and genetic data using the unique identifiers will be maintained, but access to this information will be limited to select individuals involved in the study on an as-required basis only. Such an approach is necessary to ensure confidentiality but also so that patient data is not replicated and to allow missing data to be acquired retrospectively if required. If a potentially deleterious variant is identified in any individual which is regarded to have major implications for their or their family's future health, the close follow up of the EMaBS will enable focussed re-contacting and counselling as appropriate to the condition in question.

DATA ENTRY, MANAGEMENT AND QUALITY ASSURANCE

Personal and clinical data for each of the individuals has already been collected and organised as part of the original EMaBS. Genetic and serological data will be recorded and organised electronically using the equipment and computers available in both the Entebbe and Oxford laboratories. The laboratory data will be merged with relevant clinical data to allow statistical analysis but all data processed in these steps will be anonymised with unique identifying codes to ensure confidentiality. To assure high quality data sets, a statistician / data manager will review entered data and generate queries at regular intervals which will be addressed by clinic or laboratory staff with corrections made as necessary. The data shall be anonymously and securely stored at a repository such as at the EBI as detailed in the methodology for Aim 3.

POTENTIAL LIMITATIONS; ANTICIPATED PROBLEMS

The EMaBS is one of the few birth cohorts that have been established in tropical Africa, and its size and design provides a unique ability to perform a carefully controlled genetic analysis which may be used to help identify the genetic variants associated with a variable response to vaccination.

There is the possibility that, despite the adequate power expected of the study to identify the genetic variants, none will be identified in this analysis. However, if so a larger scale study with greater statistical power would likely be required and the data obtained from this investigation would form a valuable part of that subsequent larger study. Such a negative result might alternatively be a result of the variable quality of DNA and serum collected which shall be several years old by the time of use. This is highly unlikely however, given that the specimens have been frozen at -80^{o}C which is well recognised to be sufficient to stabilise the samples and ensure the quality of the DNA and antibodies. Since the study shall investigate seven vaccines simultaneously, this substantially increases the likelihood that some important genetics factors will be identified.

SIGNIFICANCE OF THE PROPOSED WORK

Very little work has been performed investigating which genetic factors are responsible for an individual's variable response to vaccination. Fortunately, some of the preliminary studies which have been done demonstrating a strong heritability in the response to vaccination, particularly using twins, have been performed in African children. Initial gene identification studies which have been performed have, in general, been small or have produced inconsistent results. We plan to use the EMaBS as a basis to support the findings from these initial studies. The EMaBS is a unique birth cohort of African children who are carefully phenotyped which is ideally suited to a genetic interrogation. By performing a genetic analysis on these children we shall not only be able to provide insight into the response to vaccination but we will also analyse the genetic factors involved in other disease processes which are a current focus of the research group. These genetic studies may therefore have wide-ranging implications for the diagnosis, prevention or treatment of a variety of conditions affecting African children or indeed the worldwide population.

PLANS FOR DISSEMINATION

The Uganda Virus Research Institute is directly affiliated with the Ministry of Health in Uganda. This close contact enables us to disseminate our results to policy makers in Uganda. Furthermore, there is a long-standing tradition within the EMaBS of community and participant meetings, and will use these to inform the community of our findings. The academic community will be informed through local and international scientific meetings and the publication of papers in relevant journals.

All of the work shall also be disseminated through the University of Oxford Wellcome Trust Centre for Human Genetics. The Wellcome Trust Centre for Human Genetics assigns high priority to public engagement and increasing public awareness of our research activities and successes. The Centre has a post whose major responsibility is for public engagement activities which include workshops, articles for local publications, events for National Science and Engineering Week in the UK, and public resources within the Centre website. The Centre has strong links to The Oxford Trust, a regional science centre, and is currently expanding its activities to involve a wider audience in a larger geographical area.

Time frame

This part of the EMaBS is due to commence in August 2012. We plan to have gained consent from all of the children and mothers necessary by the beginning of November (three months). DNA extraction and aliquotting and serological measurement of 1200 children's samples would be expected to be completed within six months. The DNA would subsequently be shipped to Oxford for the GWAS and statistical analysis which would be expected to take 12 months. The aim is to have results of the GWAS available for dissemination by February 2014.

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