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Delayed BCG Study (DBS): determining whether BCG vaccination might protect infants against non-tuberculous invasive infectious disease by stimulating the innate immune system

Submission date
10/12/2013

Recruitment status
No longer recruiting

Registration date
14/01/2014

Overall study status
Completed

Last Edited
25/06/2020

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Current plain English summary as of 25/06/2020:
Background and study aims
This study aims to find out whether Bacillus-Calmette Guerin (BCG), the vaccine normally given to protect against tuberculosis, might also be able protect babies against other infections. One study in premature babies in Guinea-Bissau suggests that this might be the case, but we do not know if this wider protection also occurs in other countries and in babies born at the right time. It is also not yet known how BCG vaccination might protect against diseases other than tuberculosis. In this study we are aiming to see whether BCG vaccination can protect healthy Ugandan babies against diseases other than tuberculosis, and try to find an explanation as to how BCG produces this protection.

Who can participate?
Healthy babies born in Entebbe Grade B hospital in Uganda.

What does the study involve?
Mothers presenting in labour to one of the study hospitals will be approached to ask whether they would like to be involved in the study. If they agree and the baby is born healthy, the mother will be asked questions regarding her living circumstances and health, and details of the infant's birth will be recorded. A sample of blood will be taken from the umbilical cord after it has been detached from the baby. The mother will choose an envelope at random which will say whether the baby has been allocated to receive BCG vaccination at birth or at 6 weeks of age. The baby will be vaccinated immediately if in the 'at birth' group. All babies will receive their other immunisations at birth as normal. In the first 10 weeks of the baby's life the mothers will be asked to return to the clinic with the baby for two further blood samples (less than half a teaspoon of blood each), all routine immunisations, and BCG vaccination at 6 weeks of age if it was not given at birth. Each time the baby is seen at the clinic it will be reviewed by a doctor to

check that it remains well. Mothers will also be contacted by telephone weekly to double check the health of the baby. Participation in the study finishes after the baby has reached 10 weeks of age.

What are the possible benefits and risks to the participants?
All participants in the study will benefit from free, open access to medical care. We will also make sure that they receive all of their routine vaccinations at the correct time, which does not always happen in Uganda. Mothers will also be reimbursed their travel costs for each scheduled clinic visit (10,000 Ugandan Shillings - £2.50). The main risk to participants is of 6 weeks of possible exposure to tuberculosis before BCG vaccination. This risk will only apply to the half of infants allocated to receive BCG vaccination at 6 weeks of age. We believe that this risk is extremely small because it is very unusual for infants to contract tuberculosis this early in life. It is also no higher risk than is undergone by more than half of Ugandan babies currently, who do not receive BCG vaccination before 6 weeks of age. There is also some evidence that delaying BCG vaccination may improve the protection that the vaccine gives against tuberculosis, so these babies may have some benefits from receiving BCG vaccination at 6 weeks of age. We will monitor all the infants very closely to ensure there is no disadvantage to the infants in either group. The study will be stopped early if one group appears to be at higher risk than the other.

Where is the study run from?
The study will recruit infants from Entebbe Grade B Hospital in Uganda. The main research clinic where infants will be seen for follow-up will be at the Entebbe Mother and Baby Study Clinic, which is attached to Entebbe Grade B hospital. The study is co-ordinated through the Medical Research Council/Uganda Virus Research Institute on AIDS (Uganda), where the laboratory work will be conducted, and the London School of Hygiene and Tropical Medicine (UK).

When is the study starting and how long is it expected to run?
We aim to start recruiting babies in mid-March 2014. Recruitment and follow-up is likely to continue for 15 months, ending in June 2015. Laboratory analysis will continue for a further 6 months.

Who is funding the study?
The Wellcome Trust (UK).

Who is the main contact?
Dr Sarah Prentice
Sarah.prentice@nhs.net

Previous plain English summary:
Background and study aims
This study aims to find out whether Bacillus-Calmette Guerin (BCG), the vaccine normally given to protect against tuberculosis, might also be able protect babies against other infections. One study in premature babies in Guinea-Bissau suggests that this might be the case, but we do not know if this wider protection also occurs in other countries and in babies born at the right time. It is also not yet known how BCG vaccination might protect against diseases other than tuberculosis. In this study we are aiming to see whether BCG vaccination can protect healthy Ugandan babies against diseases other than tuberculosis, and try to find an explanation as to how BCG produces this protection.

Who can participate?
Healthy babies born in one of the two study hospitals (Entebbe Grade B and Kisubi Hospitals) in Uganda.

What does the study involve?
Mothers presenting in labour to one of the study hospitals will be approached to ask whether they would like to be involved in the study. If they agree and the baby is born healthy, the mother will be asked questions regarding her living circumstances and health, and details of the infant's birth will be recorded. A sample of blood will be taken from the umbilical cord after it has been detached from the baby. The mother will choose an envelope at random which will say whether the baby has been allocated to receive BCG vaccination at birth or at 6 weeks of age. The baby will be vaccinated immediately if in the 'at birth' group. All babies will receive their other immunisations at birth as normal. In the first 10 weeks of the baby's life the mothers will be asked to return to the clinic with the baby for two further blood samples (less than half a teaspoon of blood each), all routine immunisations, and BCG vaccination at 6 weeks of age if it was not given at birth. Each time the baby is seen at the clinic it will be reviewed by a doctor to check that it remains well. Mothers will also be contacted by telephone weekly to double check the health of the baby. Participation in the study finishes after the baby has reached 10 weeks of age.

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Who is funding the study?
The Wellcome Trust (UK).

Who is the main contact?
Dr Sarah Prentice
Sarah.prentice@lshtm.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Sarah Prentice

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
A randomised controlled trial of BCG vaccination at birth compared to at 6 weeks of age to investigate whether BCG provides protection against heterologous invasive infectious disease by stimulating the innate immune system

Acronym
DBS

Study objectives
We hypothesise that Bacillus-Calmette Guerin (BCG) vaccination stimulates the innate immune system in a non-specific manner, resulting in short and longer-term protection against heterologous invasive infectious disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Medical Research Council (MRC)/Uganda Virus Research Institute on AIDS, 26/11/2013, ref: GC /127/13/11/432
2. London School of Hygiene and Tropical Medicine (pending)
3. Uganda National Council for Science and Technology (pending)

Study design
Single-blind randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
All cause infectious disease

Interventions
Current interventions as of 25/06/2020:
560 Ugandan babies will be randomly assigned to receive BCG-Danish 0.05 ml intradermal to the right deltoid on either the day of birth or at six weeks of age.

Previous interventions:
560 Ugandan babies will be randomly assigned to receive BCG-Danish 0.05 ml intradermal to the left deltoid on either the day of birth or at six weeks of age.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
BCG vaccine

Primary outcome measure
Current primary outcome measure as of 25/06/2020:
This study will be divided into three separate immunological sub-studies with their own primary outcome measures:

Sub-study 1: Pro-inflammatory Cytokine Analysis
IL-1β, IL-6, TNF-α and IFN-γ cytokine levels following in vitro stimulation with S. aureus, S. pneumoniae, E. coli, Poly I:C and C. albicans (measured by ELISA):
1. Up to 1 week post-birth intervention
2. Immediately prior to first dose of primary immunisations (6 weeks post-birth intervention)
3. Up to 1 week post-6-week intervention
4. Immediately prior to second dose of primary immunisations (4 weeks post-6-week intervention)

Sub-study 2: Inflammatory Iron Status
Hepcidin levels (measured by ELISA) and transferrin saturation (measured using the Cobas-Integra automated analyser):
1. Up to 1 week post-birth intervention
2. Up to 1 week post first dose of primary interventions
3. Up to 1 week post-6-week intervention
4. Up to 1 week post second dose of primary interventions

Sub-study 3: Monocyte Epigenetic Modification
Tri-methylation of histone-3, lysine-4 at the promoter regions of pro-inflammatory cytokines in monocytes (measured by chromatin immunoprecipitation):
1. Up to 1 week post-birth intervention
2. Immediately prior to first dose of primary immunisations (6 weeks post-birth intervention)

Combined Studies - Clinical Illness Events
1. Physician-diagnosed Infectious Disease

Previous primary outcome measure:
This study will be divided into three separate immunological sub-studies with their own primary outcome measures:

Sub-study 1: Pro-inflammatory Cytokine Analysis
IL-1β, IL-6, TNF-α and IFN-γ cytokine levels following in vitro stimulation with S. aureus, S. pneumoniae, E. coli, FEC (influenza, Ebstein-Barr virus and cytomegalovirus combined viral stimulant) and C. albicans (measured by ELISA):
1. 24-72 hours post-birth intervention
2. Immediately prior to first dose of primary immunisations (6 weeks post-birth intervention)
3. 24-72 hours hours post-6-week intervention
4. Immediately prior to second dose of primary immunisations (4 weeks post-6-week intervention)

Sub-study 2: Inflammatory Iron Status
Hepcidin levels (measured by ELISA) and transferrin saturation (measured using the Cobas-Integra automated analyser):
1. 24-72 hours post-birth intervention
2. 24-72 hours post first dose of primary interventions
3. 24-72 hours post-6-week intervention
4. 24-72 hours post second dose of primary interventions

Sub-study 3: Monocyte Epigenetic Modification
Tri-methylation of histone-3, lysine-4 at the promoter regions of pro-inflammatory cytokines in monocytes (measured by chromatin immunoprecipitation):

1. 24-72 hours post-birth intervention
2. Immediately prior to first dose of primary immunisations (6 weeks post-birth intervention).

Secondary outcome measures
Current secondary outcome measures as of 25/06/2020:
1. Parent-reported invasive infectious disease
2. Blood culture positive invasive infectious disease
3. Death

Secondary outcomes will be collected up to 10 weeks of age. They will be measured via a combination of:
1. Questionnaires asking for parental recall of illness episodes, administered every time the participant is seen in the research clinic (this will be for the two blood samples and for all routine immunisations up to 10 weeks of age)
2. Physician case report forms, completed any time a child is seen in the clinic or the hospital during their participation in the study.

Previous secondary outcome measures:
All children in the study will be clinically followed up, providing combined secondary outcome measures:
1. Physician-diagnosed invasive infectious disease
2. Parent-reported invasive infectious disease
3. Blood culture positive invasive infectious disease
4. Death

Secondary outcomes will be collected up to 10 weeks of age. They will be measured via a combination of:
1. Questionnaires asking for parental recall of illness episodes, administered every time the participant is seen in the research clinic (this will be for the two blood samples and for all routine immunisations up to 10 weeks of age)
2. Physician case report forms, completed any time a child is seen in the clinic or the hospital during their participation in the study.

Overall study start date
15/03/2014

Completion date
15/07/2015

Eligibility

Key inclusion criteria
Neonates born to women delivering in Entebbe Grade B or Kisubi hospitals will be eligible for inclusion if:
1. Mother consents for participation
2. They reside in the study catchment areas
3. Mothers are HIV negative (based on records available from antenatal care received during this pregnancy)
4. The birth was sufficiently uncomplicated to allow the neonate to be discharged directly home

from hospital with no infant admission or treatment for complications
5. The neonate is of a gestational age and birth weight to allow discharge directly home from hospital (no requirement for supplemental oxygen or feeding)

Participant type(s)
Patient

Age group
Neonate

Sex
Both

Target number of participants
560

Key exclusion criteria
Neonates will be excluded from the study if:
1. Cord blood is not obtained
2. They have major congenital malformations
3. The infant is clinically unwell, as judged by a midwife
4. Known maternal tuberculosis (TB) or active TB within the family (based on direct questioning of mother during recruitment)
5. Maternal or family member positive for any TB screening symptoms:
5.1. Cough > 2 weeks
5.2. Recent haemoptysis
5.3. >3 kg weight loss in past month
5.4. Recurrent fevers/chills or night sweats for the past 3 days or more

Date of first enrolment
15/03/2014

Date of final enrolment
15/07/2015

Locations

Countries of recruitment
England

Uganda

United Kingdom

Study participating centre
London School of Hygiene and Tropical Medicine
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Sponsor information

Organisation
London School of Hygiene and Tropical Medicine (UK)

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Sponsor type
University/education

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ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust (UK), grant ref: ITCRZB84

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	11/04/2015		Yes	No
Results article	results	11/05/2018		Yes	No
Protocol file	version V2.5	24/04/2017	25/06/2020	No	No
Protocol file	version V2.4	01/12/2014	25/06/2020	No	No