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Does giving a second BCG vaccination or adding a leprosy vaccine to BCG vaccination provide additional protection against leprosy and tuberculosis, compared with giving a single BCG vaccination?

Submission date
28/11/2019

Recruitment status
No longer recruiting

Registration date
13/12/2019

Overall study status
Completed

Last Edited
17/01/2023

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[X] Individual participant data

Plain English summary of protocol

Background and study aims:
Leprosy and tuberculosis (TB) are caused by infection with two types of Mycobacterium bacteria. Leprosy can damage nerves resulting in loss of sensation in the fingers and toes. This can result in damage and loss of the fingers and toes because people cannot feel when they have injured them or when there is infection. Leprosy can be treated with antibiotics and the number of cases worldwide has reduced significantly from the 1980s, when there were millions of people affected. TB mainly affects the lungs and still causes more than a million deaths per year worldwide. It can be prevented to some extent with the BCG vaccine (but protection varies greatly between countries) and treated with antibiotics, although there are strains that are resistant to drug treatment.
This trial started in 1985. It was designed to investigate two questions. The first was whether giving a second dose of the BCG vaccine would give people more protection against TB and leprosy than just one. The second question was whether adding killed leprosy bacteria to the BCG vaccine would increase protection against leprosy. The trial took place in Karonga District, a rural area in northern Malawi, as part of a large study of leprosy and TB which had begun in 1979, called the Lepra Evaluation Project.
Recruitment into the original trial took place between early 1986 and late 1989, and the first results were analysed and published in 1996, showing that repeating BCG vaccination gave approximately an additional 50% protection against leprosy but no significant protection against TB. There were suggestions in the results that the vaccines might give some protection against TB among those who were vaccinated at young age and that the vaccines might be providing protection against extrapulmonary TB (in which the disease is outside the lungs), but the numbers of cases in these groups were not large enough for the results to be convincing. In addition there was some evidence that the BCG vaccine might be associated with increased risk of TB among individuals who were HIV-positive.
The aim of the current study is to follow up on the people who participated in the original trial,

now that more than 30 years have passed and it will be possible to investigate the long-term effects of the vaccinations in different groups of participants, such as those who were vaccinated at a young age and those who subsequently became HIV-positive.

Who can participate?
All individuals aged between 3 months and 70 years of age in 1985 were eligible to participate in the original trial.

What does the study involve?
In the original study, more than 120,000 people were randomised in the following way. If they had no BCG vaccination scar, they were randomly allocated to receive plain BCG vaccine or BCG vaccine combined with killed leprosy bacteria. If they had a BCG vaccination scar, they were randomly allocated to receive either a second dose of BCG vaccine, a second dose of BCG vaccine combined with killed leprosy bacteria or a placebo (an injection with no vaccine). The entire population was then followed up and all cases of leprosy and TB were reported to the trial team.

What are the possible benefits and risks of participating?
All participants received at least one dose of BCG vaccine, which had already been shown to provide 50% protection against leprosy. Many of the participants received a second dose of BCG with or without killed leprosy bacteria, which might give them additional protection. Repeated BCG vaccination was policy in several countries at the time and known to be safe. The addition of killed leprosy bacteria to BCG had been shown to be safe in trials in Norway and Malawi.

Where is the study run from?
The trial headquarters were in Chilumba, a village in Karonga District, Malawi, which had been the headquarters of the Lepra Evaluation Project (LEP) since 1979. The LEP and the trial were closely linked to a research team at the London School of Hygiene and Tropical Medicine (UK). The Malawi activities of the trial are now carried out within the Malawi Epidemiology and Intervention Research Unit (MEIRU), which combines field research in Karonga District with parallel projects in an urban area in the capital city, Lilongwe.

When is the study starting and how long is it expected to run for?
January 1983 to December 2018

Who is funding the study?
The original trial was funded by the British Leprosy Relief Association (LEPRA), the International Federation of anti-Leprosy organisations (ILEP) and the Immunology of Leprosy (IMMLEP) Component of the WHO/World Bank/UNDP Tropical Disease Research Programme. The follow-up after 1996 was funded largely by the Wellcome Trust (UK). The current follow-up analyses are funded by the Bill & Melinda Gates Foundation (USA).

Who is the main contact?
Professor Paul Fine, paul.fine@lshtm.ac.uk

Contact information

Type(s)
Scientific

Contact name

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
N/A

Study information

Scientific Title
Randomised controlled trial of the efficacy of repeat BCG vaccine, or BCG plus killed M leprae vaccine, in the prevention of clinical leprosy and tuberculosis, in the general population of Karonga District, northern Malawi

Acronym
KPT (Karonga Prevention Trial)

Study objectives
1. Does repeated BCG vaccination give greater protection against leprosy and tuberculosis than a single vaccination?
2. Does a combined vaccine with BCG plus killed M leprae bacilli provide greater protection against leprosy than does BCG vaccine alone?
3. Is the protection induced by either of these vaccines greatest in those vaccinated at youngest ages?
4. Is the protection induced by either of these vaccines greatest among those without tuberculin reactivity at time of vaccination?
5. Does the protection induced by either of these vaccines decline with time since vaccination?
6. Does the protection induced by repeated BCG against tuberculosis differ as a function of the genetic lineage of M tuberculosis?
7. Is the protection induced by repeat BCG different by type of tuberculosis (pulmonary or glandular)?
8. Is the protection induced by these vaccines lower in individuals who are HIV-positive at time of diagnosis compared to those HIV-negative at diagnosis?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 16/09/1985, London School of Hygiene and Tropical Medicine Ethical Committee (Keppel St, London WC1E 7HT; Telephone number not provided as it is likely to be out of date; No email address), no reference number
2. Protocol amendment approved 22/12/1986, London School of Hygiene and Tropical Medicine Ethical Committee (Keppel St, London WC1E 7HT; Telephone number not provided as it is likely to be out of date; No email address), ref: 110
3. Update to cover epidemiology of mycobacterial and HIV infections in Northern Malawi approved 01/08/2001, London School of Hygiene and Tropical Medicine Ethics Committee (Keppel St, London WC1E 7HT; No telephone number; No email address), ref: 745A

The trial protocol was approved in 1985 by the Health Sciences Research Committee of the Malawi Ministry of Health, the Standing Committee on Research in Human Subjects of WHO, and the Ethics Committee of the London School of Hygiene and Tropical Medicine. Continued ascertainment of cases has been approved in the context of a series of subsequent studies.

Study design
Randomized double-blind placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Community

Study type(s)
Prevention

Participant information sheet
No participant information sheet available.

Health condition(s) or problem(s) studied
Leprosy and tuberculosis

Interventions
The trial was explained in public meetings with village headmen and to each household as they were visited.

Individuals with a BCG scar were randomised (by vaccine vial*) to receive either Glaxo's standard commercialised BCG vaccine, BCG + 6 x 10(8) killed Mycobacterium leprae vaccine (an investigational vaccine produced by Wellcome Laboratories) or placebo.
Individuals with no BCG scar were randomised (by vaccine vial) to receive either BCG vaccine, or BCG + 5 x 10(7) killed M leprae vaccine, or BCG + 6 x 10(8) killed M leprae vaccine
The placebo consisted of the dextran matrix of BCG vaccine, minus the bacilli. All vaccines were

given intradermally. Vaccine vials within each (scar-negative and scar-positive) group were identical, and coded independently by WHO-appointed trial monitor.

* Small group randomisation was used because vaccine vials were multidose (1 - 11 doses per vial).

Intervention Type
Biological/Vaccine

Phase
Phase III

Drug/device/biological/vaccine name(s)
1. BCG (Bacillus Calmette-Guerin) vaccine, produced by Glaxo 2. Killed Mycobacterium leprae vaccine, produced by Wellcome Laboratories 3. Placebo produced by Glaxo (dextran matrix of BCG vaccine)

Primary outcome measure
1. Presence of clinical leprosy, confirmed as certain or probable by an algorithm based upon clinical findings and biopsy, with onset at any time after vaccination until end of 2018. The algorithm for diagnostic certainty is described in detail in Pönnighaus et al, 1987.
2. Presence of clinical tuberculosis, confirmed as certain or probable based on sputum smear, sputum culture, biopsy and GeneXpert, and ascertained at least 6 months after vaccination until end of 2018:
2.1. Pulmonary tuberculosis was considered certain if culture-positive or GeneXpert-positive plus at least one other specimen positive on culture or GeneXpert or microscopy and probable if culture- or GeneXpert- or microscopy-positive but not fulfilling criteria for certain, excluding those with only a single scanty smear (i.e. fewer than 10 bacilli per 100 fields)
2.2. Extrapulmonary tuberculosis was considered certain if confirmed by histology or microscopy or culture/GeneXpert and probable if histology suggestive or clinical lymph node tuberculosis. Note that since only 2 of 96 extrapulmonary TB are 'probable' in new data, it was decided to restrict to histologically or microscopy or culture/GeneXpert confirmed.

Secondary outcome measures
1. Time since vaccination measured from the date of vaccination to the date when the individual was first seen by project staff with clinical signs (for leprosy) or to the earliest of the date of first diagnostic specimen, or of registration or of start of treatment (for tuberculosis)
2. Tuberculin status at vaccination assessed with RT23 tuberculin (produced by Danish Statens Serum Institut) 2 IU injected intradermally into the volar surface of the forearm. Induration was measured along and across arm after 48 – 72 hours. Average diameter was used in analyses.
3. M tuberculosis lineage assessed using assessed by whole genome sequence, if available, or, if unavailable, by restriction fragment length polymorphism, or spoligotype
4. HIV status assessed by algorithm based upon rapid tests. Individuals considered HIV negative if last negative report was <1 year before or any time after key date and as HIV positive if first positive report was any time before and up to 1 year after key date (unless known HIV negative at the key date). The participant's HIV status was classed as unknown otherwise. Self reports of HIV positivity or ART use were accepted as evidence of HIV positivity

Overall study start date
01/01/1983

Completion date
31/12/2018

Eligibility

Key inclusion criteria
1. Healthy
2. Aged over 3 months
3. Born after 1914
4. No history of leprosy or tuberculosis

Participant type(s)
All

Age group
All

Sex
Both

Target number of participants
120,000

Key exclusion criteria
1. Aged under 3 months
2. Born before 1914
3. Evidence of past or current leprosy or tuberculosis
4. Severe malnutrition or other severe illness

Date of first enrolment
09/01/1986

Date of final enrolment
30/11/1989

Locations

Countries of recruitment
Malawi

Study participating centre
Karonga Prevention Study
Chilumba
Malawi
-

Sponsor information

Organisation
London School of Hygiene and Tropical Medicine

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University/education

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ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Charity

Funder Name
British Leprosy Relief Association (LEPRA)

Funder Name
International Federation of Ant-Leprosy Associations (ILEP)

Funder Name
IMMLEP Component of WHO/TDR

Funder Name
Bill & Melinda Gates Foundation

Funder Name
The Wellcome Trust

Results and Publications

Publication and dissemination plan
The design and initial results of the trial have already been published. The current intention is to carry out a 30-year follow-up of the trial population and publish the results in 2020.

Intention to publish date
31/12/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Datacompass at LSHTM. Researchers should contact Paul Fine (paul.fine@lshtm.ac.uk). The datasets will be in CSV format sent by secure file transfer and will be available from one month after publication for one year minimum. Access will be dependent on an explicit collaborator agreement. Analyses relating to effectiveness of vaccines against leprosy and/or tuberculosis will be enabled. Participants consented verbally to trial participation. The data will be anonymised – no names, addresses, GPS coordinates, or precise birth dates will be included in shared data.
Any sharing agreement will include requirements (a) to obtain approval from original investigators and MEIRU of analyses in any publication based upon the shared data (b) for full acknowledgment and recognition of original investigators and MEIRU in any subsequent publication and (c) against onward sharing of the data provided without explicit permission from investigators and MEIRU.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other publications	methods	01/12/1993	29/11/2019	Yes	No
Protocol article	protocol	01/11/1988	29/11/2019	Yes	No
Results article	initial results	06/07/1996	29/11/2019	Yes	No
Results article	thirty-year follow-up results	05/07/2021	06/07/2021	Yes	No
Results article	30 year follow up results (Lancet)	01/10/2021	21/09/2021	Yes	No
Dataset		25/09/2020	17/01/2023	No	No