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Study to compare two methods of treatment to prevent active tuberculosis (TB) in children

Submission date
24/06/2011

Recruitment status
No longer recruiting

Registration date
29/07/2011

Overall study status
Completed

Last Edited
08/06/2022

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Latent tuberculosis (TB) infection is an infection with TB that is asleep and is not causing the person to be sick or unwell. However, some people with latent TB infection can develop TB disease. We are doing a clinical trial to find out if a new treatment works to treat latent TB infection and prevent active TB. Isoniazid (INH) is an antibiotic that is about 90% effective if it is taken every day for 9 months. Rifampin (RIF) is another drug that we know is very effective to treat TB disease. However, rifampin has not been used much to treat latent TB infection. We wish to find out if RIF taken for only 4 months would be as effective as 9 months of INH to treat latent TB infection and prevent you from ever getting sick from TB.

Who can participate?
Children aged under 18 diagnosed with latent TB infection.

What does the study involve?
We expect that you will be in this study for 16 months (1 year and 4 months). If you agree to take part in this study you will be randomly allocated to take either 4 months of RIF OR 9 months of INH. Both INH and RIF are taken once a day and both may be taken as a pill or as a liquid. You will have regular follow-up visits with your doctor and/or the TB clinic nurses. This will mean coming back for visits at least every month for the first 2 months and then according to what your doctor feels would be needed until your treatment is finished. You will be asked about the treatment and whether you are having any difficulties taking it. Your doctor will examine you. Blood tests will be performed at the beginning of the treatment. Your doctor may want to see you and/or ask for blood tests more often. If so, you and your doctor will decide on this. After the treatment is finished we will contact you to check-up on you every 3 months up to 16 months from the day you started the study.

What are the possible benefits and risks of participating?
Some adults taking INH have had the following mild reactions: headaches, fatigue, weakness, stomach upset, heart burn, loss of appetite, diarrhea or a rash. Some people may have a more severe reaction, possibly affecting the liver, although this seems to be very rare (less than 1 in 1000 children). The following mild reactions have occurred in some adults taking RIF: headaches, fatigue, weakness, stomach upset, heart burn, loss of appetite, diarrhea or a rash. RIF can also

cause tears, sweat, saliva, faeces and urine to turn orange. Soft contact lenses may be permanently stained with this orange color. Some people may have a more severe reaction such as a reaction in the liver although this seems to be very rare (less than 1 in 100 people) in people taking RIF only. All of these types of reactions usually return to normal when the medication is stopped. You will have to do a blood test at the beginning of the study. This may cause some discomfort, including a brief pain from the needle stick, bruising, light-headedness and rarely infection where the needle enters the vein.

For female adolescents: INH and RIF have not been found to cause birth defects in babies. However, you should not take part in this study if you are pregnant or plan to become pregnant before completing the TB treatment. We strongly recommend you take all necessary measures to avoid becoming pregnant while on the TB treatment. RIF can make some forms of birth control, including the birth control pill, hormonal injections and implants less effective. If you are using any of these methods and take RIF, you should speak to your doctor about additional methods of birth control methods to use. These methods may include condoms, diaphragms, sponges, cervical caps or intra-uterine devices. If you become pregnant, you will be taken off the treatment for latent TB infection. Your doctor will decide with you about re-starting treatment for latent TB infection, after your baby is born.

When is the study starting and how long is it expected to run for?
Recruitment started in September 2011 and the study will finish in June 2015.

Where is the study run from?
In Montreal, Edmonton and Vancouver (Canada), Sydney (Australia), Cotonou (Benin), Rio de Janeiro (Brazil), Kumasi (Ghana), Conakry (Guinea), Bandung (Indonesia) and Riyadh (Saudi Arabia).

Who is funding the study?
Canadian Institutes of Health Research (Canada).

Who is the main contact?
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Scientific

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ClinicalTrials.gov (NCT)
NCT00170209

Protocol serial number
BMC-009-07b

Study information

Scientific Title
A randomized trial to compare completion and tolerability of 4 months rifampin (4 Rif) and 9 months isoniazid (9 INH) in treatment of latent TB in children

Acronym
P4v9

Study objectives
Among children at high risk for development of active TB, intolerance/adverse events will not be worse (non-inferiority), among those randomized to 4RIF compared to those randomized to 9INH. In addition completion of latent tuberculosis infection (LTBI) therapy will be significantly greater (superiority), and subsequent rates of active TB will not be significantly higher (non-inferiority) in children taking 4RIF.

On 22/01/2014 the target number of participants was changed from 900 to 822 and Brazil and Guinea were added to the countries of recruitment. As of this date the trial has just finished recruitment.

On 27/01/2015 the overall trial end date was changed from 01/08/2014 to 01/06/2015.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Research Ethics Board of the McGill University Hospital Centre, 13/06/2011, ref: BMC-09-007

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Tuberculosis

Interventions
1. The standard therapy will be daily self-administered INH,10-15 mg/kg/day for children (max=300mg/day) for 9 months (9INH)
2. As currently recommended vitamin B6 (pyridoxine) will be given with INH only to patients with risk factors for neuropathy - malnutrition, alcoholism, diabetes, or renal insufficiency or HIV positive
3. The experimental arm will be daily self-administered RIF, 10-20 mg/kg/day for children (max=600mg/day) for 4 months (4RIF)
4. For children, dosing for both INH and RIF will be age and weight dependent, with highest doses for infants, and lowest for adolescents

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Isoniazid, rifampin

Primary outcome(s)
To compare the rates of premature discontinuation of study therapy because of adverse events of all grades judged probably related to 4RIF or 9INH, by the majority of an independent panel of 3 reviewers, blinded to study drug

Key secondary outcome(s))
1. To compare the rates of study drug completion of all children randomized to 4RIF or 9INH. Completion will be defined as taking at least 80% of total planned doses within 23 weeks for 4RIF, or within 52 weeks for 9INH
2. To compare the rates of clinically diagnosed active TB as judged by an independent panel of paediatricians, up to 16 months post randomization in children who complete study therapy per protocol (efficacy)
3. To describe the occurrence of drug resistant microbiologically confirmed active TB among children randomized to the two arms, during 16 months post randomization

Completion date
01/06/2015

Eligibility

Key inclusion criteria
1. Children (age <18) with documented positive tuberculin skin testing (TST) as defined below and prescribed 9INH for LTBI, for the indications below:
Note: In the absence of a TST test, a positive QFT (or T-Spot) (according to manufacturers recommendations) (see screening, recruitment and randomisation procedures) is equivalent to a TST of 10 mm.
1.1. HIV positive (TST >5 mm or QFT +)
1.2. Age 5 or less (TST >5 mm or QFT +)
1.3. Other reason for immuno-compromised state - such as therapy for malignancy or post-transplant (TST >5 mm or QFT +)
1.4. Contact: with adult or adolescent with active contagious pulmonary TB TST >5 mm or QFT +)
1.5. Have both of the following factors if TST = 10-14mm or QFT + or one factor if TST >15mm :
1.5.1. Arrival in Canada, Australia, or Saudi Arabia in the past 2 years from countries with estimated annual incidence of active TB greater than 100 per 100,000
1.5.2. Body mass index (BMI) less than 10th percentile for their age
2. Interferon gamma release assays (IGRA's) are ex-vivo tests of immune response to TB antigens, that have been adopted in some centres as alternatives to the TST, although WHO has recently recommended IGRAs should not be used to replace the TST in low and middle-income countries
3. If an eligible child undergoes a commercially available IGRA (the Quantiferon-Gold or T-Spot. TB), instead of a TST, and the result is positive, then they will be considered eligible
4. If both TST and IGRA are done, then the TST result will be used to determine eligibility
5. The TST may be negative for up to 8 weeks after primary infection, before adequate cell mediated immunity develops
6. Because of this, current practice is to begin LTBI treatment therapy immediately for children < 5 years old, even if TST negative
7. After 8-10 weeks the TST is repeated; LTBI therapy is continued if now TST positive, and stopped if still negative
8. Providers may continue therapy in very young, HIV infected or malnourished children
9. We propose to enroll TST negative children aged < 5, if the treating physician prescribes LTBI therapy, because:
9.1. Primary endpoints are still relevant, and measurable in this group
9.2. Acceptability and completion in this sub-group are of particular interest
9.3. Children that have new primary TB are at particularly high risk to develop disease (this is the rationale for their treatment)
10. If the treating MD stops therapy because the TST is negative after 8-10 weeks, these children will be excluded from the analysis of treatment completion, but included in the incidence density analysis (person-time) of tolerability and safety

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Upper age limit

18 years

Sex
All

Key exclusion criteria
1. Children who were contacts of TB cases known to be resistant to INH, RIF, or both (i.e. MDR)
2. Known HIV-infected individuals on anti-retroviral agents whose efficacy would be substantially reduced by Rifampin, unless therapy can safely be changed to agents not affected by Rifampin
3. Pregnant women - Rifampin and INH are considered safe in pregnancy, but therapy is usually deferred until 2-3 months post-partum to avoid fetal risk and the potential for increased hepato-toxicity immediately post partum
4. Children on any medication with clinically important drug interactions with INH or RIF, which their physician believes would make either arm contra-indicated. This includes women taking hormonal contraceptives who will not take alternative contraception
5. History of allergy/hypersensitivity to Isoniazid or to Rifampin, Rifabutin or Rifapentine
6. Active TB. Children initially suspected to have active TB can be randomized once this has been excluded
7. Prior complete LTBI therapy or if children have taken >1 week and are still taking the treatment.. Children will be eligible if they took an incomplete LTBI therapy (less than 80% of recommended total dose) but > 6 months ago

Date of first enrolment
01/09/2011

Date of final enrolment
31/01/2014

Locations

Countries of recruitment
Australia

Benin

Brazil

Canada

Ghana

Guinea

Indonesia

Saudi Arabia

Study participating centre

Montreal Chest Institute
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Sponsor information

Organisation
Canadian Institutes of Health Research (Canada)

ROR
https://ror.org/01gavpb45

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research (Canada)

Alternative Name(s)
Instituts de Recherche en Santé du Canada, Canadian Institutes of Health Research (CIHR), CIHR_IRSC, Canadian Institutes of Health Research | Ottawa ON, CIHR - Welcome to the Canadian Institutes of Health Research, CIHR, IRSC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Canada

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	adverse events in adults	01/03/2020	10/08/2020	Yes	No
Results article	health system costs	04/08/2020	10/08/2020	Yes	No
Results article	safety and side effects in children	02/08/2018	10/08/2020	Yes	No
Other publications	health system costs	01/07/2010	10/08/2020	Yes	No
Other publications	risk factors for latent TB	18/11/2014	10/08/2020	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes