Programmatic options and challenges for LTBI diagnosis and treatment in low and high TB burden settings

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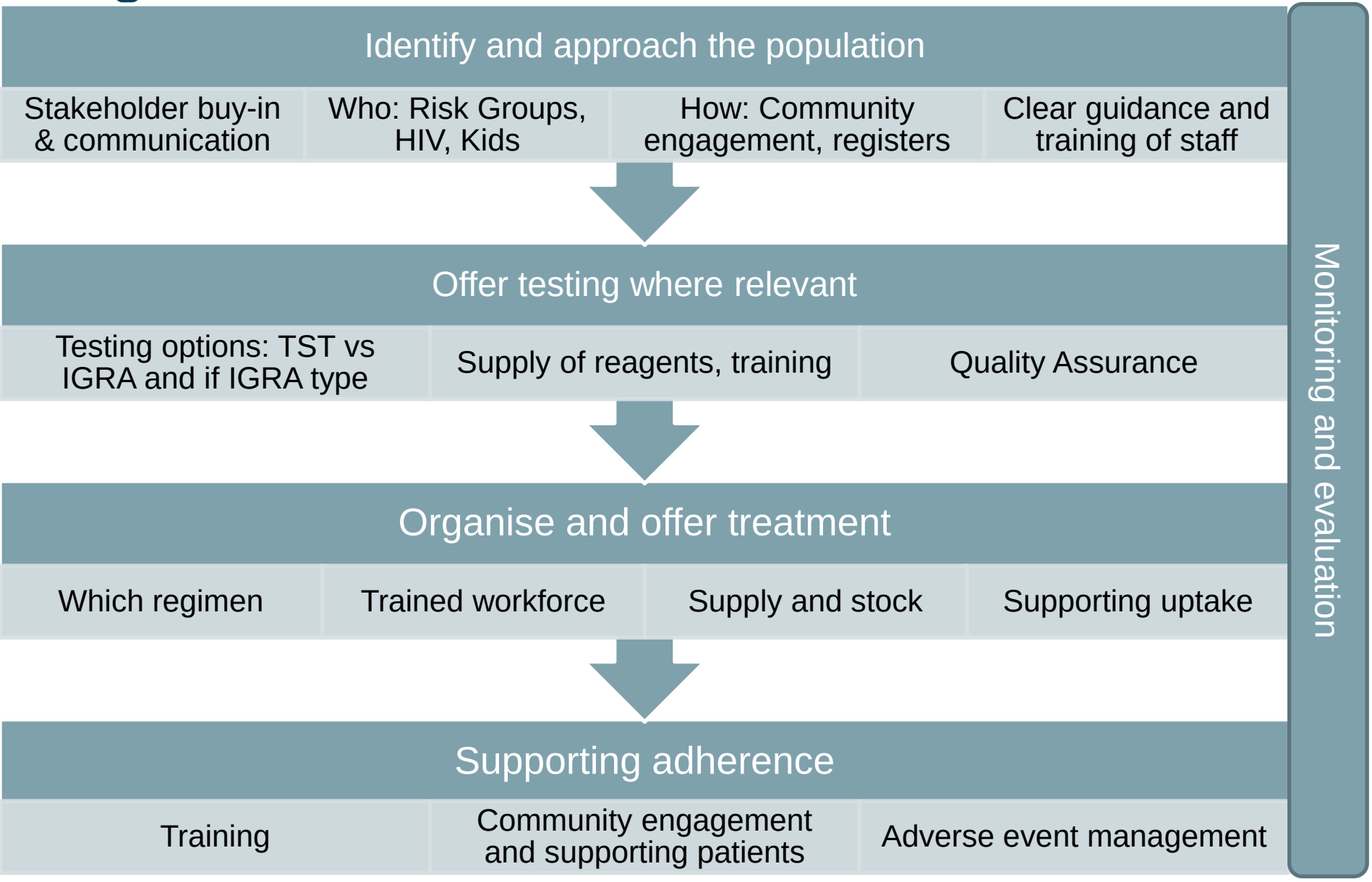
London

Outline

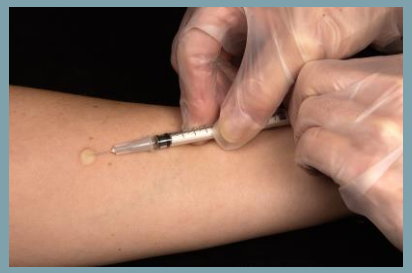
- Programmatic cascade
- Diagnostic options
- Diagnostic issues
- Diagnostic challenges
- Treatment evidence
- Treatment regimen
- Treatment challenges issues
- Programmatic challenges

Programmatic cascade

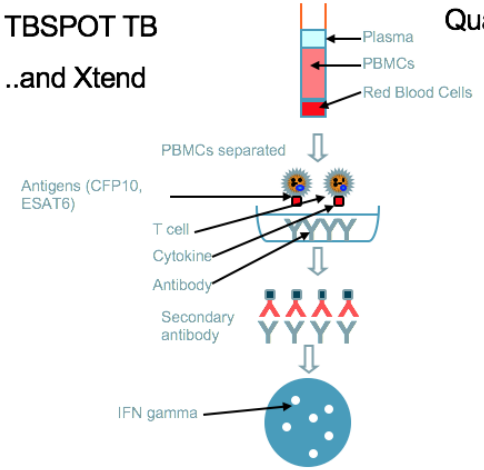


Diagnostic test options

Tuberculin Skin Test

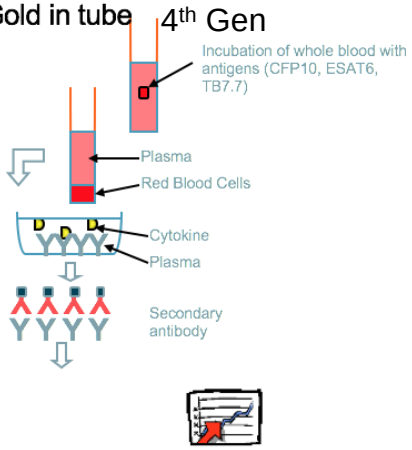


TBSPOT TB ..and Xtend



Positive > = 6 spots

Quantiferon Gold in tube 4th Gen



> = 0.35 iu/ml

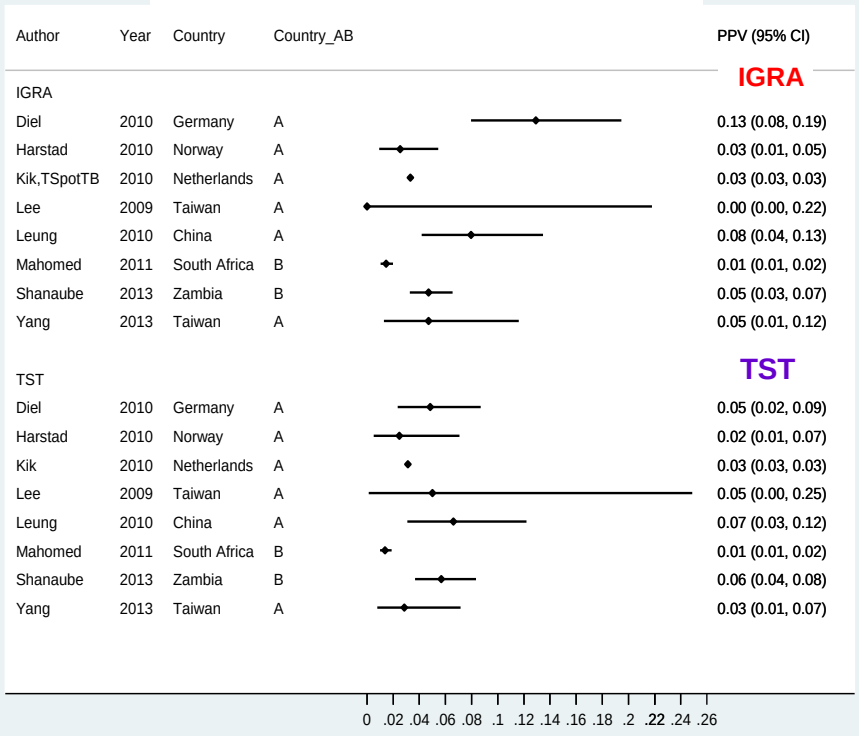
What next?

1. Ctb test: soon

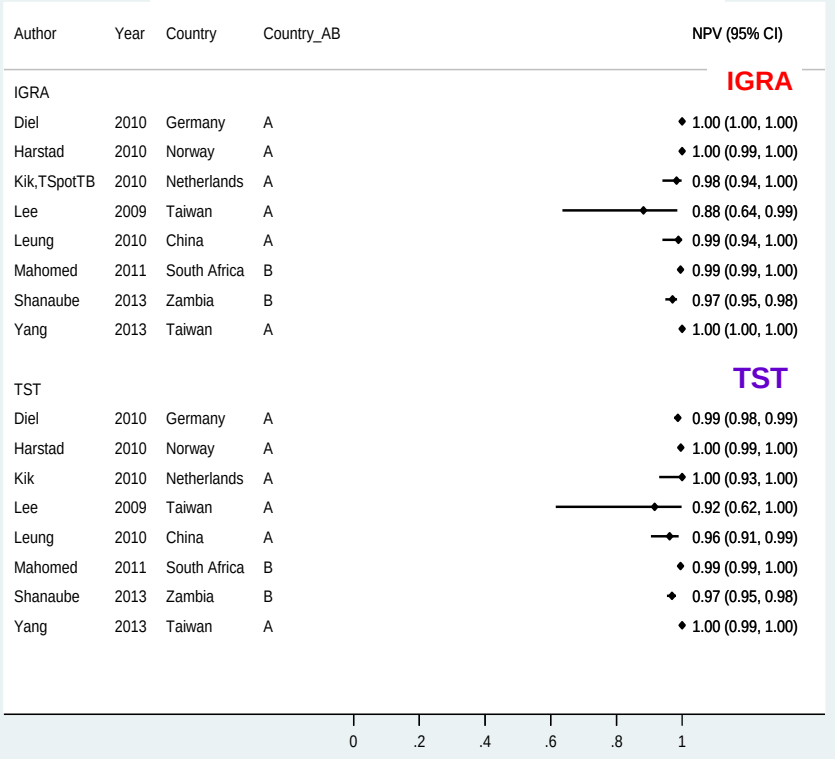
2. Other technologies: Trancriptomics, Proteomics, Metabolomics
Still primarily research tools with no programmatic relevance

Diagnostic issues: Positive and Negative Predictive Values

PPV of IGRA and TST in studies that assessed both tests



NPV of IGRA and TST in studies that assessed both tests



Low PPV

High and comparable NPV

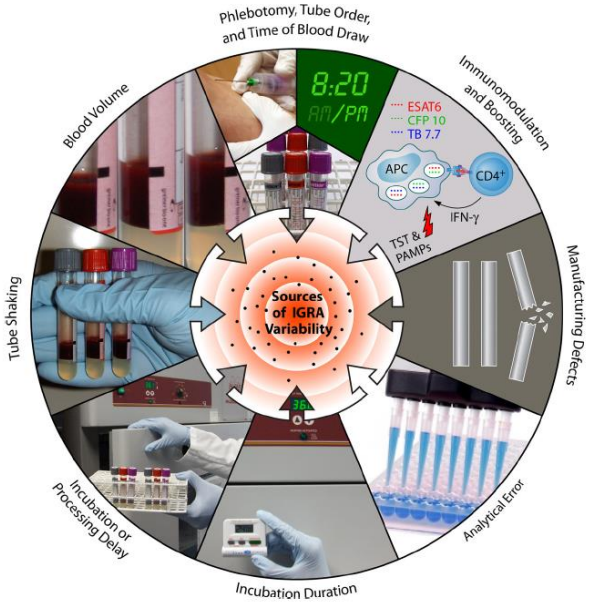
IGRA has greater specificity

Cant distinguish remote and recent infection

Diagnostic issues: variability and reversions/conversions

Variability of results

- TST – reader etc
- IGRA – range of issues



Reversion & conversions

- Recognised phenomonon for both IGRA and TST

Pai IJTLD 2009 Aichelburg et al JID 2014

Diagnostic issues: Immunocompromised and serial testing

Immunocompromised

- HIV
- Transplant
- Anti TNF alpha
- Silicosis

- Lower sensitivity than in immunocompetent

Serial testing in HCW

- In low to moderate incidence countries, IGRA positivity less prevalent than TST
- Higher false conversions with IGRA than TST

- Zwerling et al Thorax 2012
- Ringhausen et al JOMT 2012

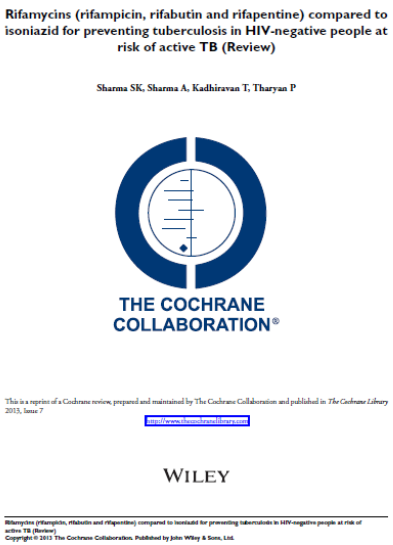
Diagnosis: Challenges

- Accuracy and predictive value
- Return to read TST test….and cascade
- Need for a laboratory for IGRAs
- Cost of tests to programmes
- Quality assurance
- Monitoring challenges

Treatment: evidence

- INH: 6 and 12 month INH regimens are effective
- Rifamycins as good as INH; ? Better adherence
- HIV: INH effective; no difference by TST
- KIDS: INH works; some interaction by age

INH


Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB (Review)

Sharma SK, Sharma A, Kadhiravan T, Tharyan P

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Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB (Review)
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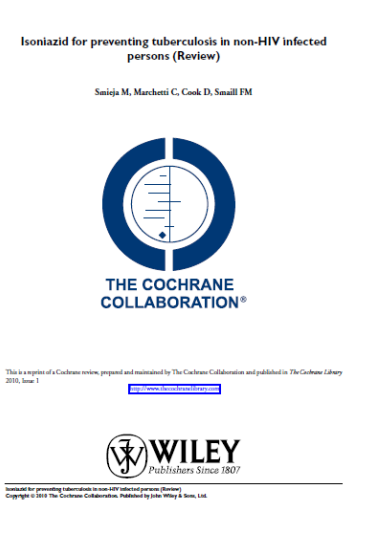
Rifamycins


Isoniazid for preventing tuberculosis in non-HIV infected persons (Review)

Smieja M, Marchetti C, Cook D, Smaill FM

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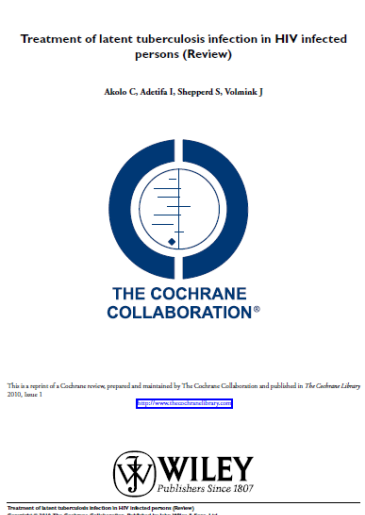
HIV


Treatment of latent tuberculosis infection in HIV infected persons (Review)

Akolo C, Adetifa I, Shepperd S, Volmink J

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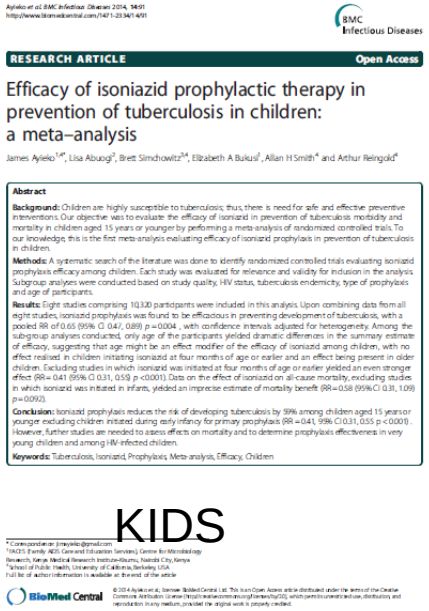
KIDS


Ayieko et al. BMC Infectious Diseases 2014, 14:91
http://www.biomedcentral.com/1471-2334/14/91

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis

James Ayieko[1,4*], Lisa Abuogi[2], Brett Simchowitz[3,4], Elizabeth A Bukusi[1], Allan H Smith[4] and Arthur Reingold[4]

Abstract

Background: Children are highly susceptible to tuberculosis; thus, there is need for safe and effective preventive interventions. Our objective was to evaluate the efficacy of isoniazid in prevention of tuberculosis morbidity and mortality in children aged 15 years or younger by performing a meta-analysis of randomized controlled trials. To our knowledge, this is the first meta-analysis evaluating efficacy of isoniazid prophylaxis in prevention of tuberculosis in children.

Methods: A systematic search of the literature was done to identify randomized controlled trials evaluating isoniazid prophylaxis efficacy among children. Each study was evaluated for relevance and validity for inclusion in the analysis. Subgroup analyses were conducted based on study quality, HIV status, tuberculosis endemicity, type of prophylaxis and age of participants.

Results: Eight studies comprising 10,300 participants were included in this analysis. Upon combining data from all eight studies, isoniazid prophylaxis was found to be efficacious in preventing development of tuberculosis, with a pooled RR of 0.65 (95% CI: 0.47, 0.89) $p = 0.004$, with confidence intervals adjusted for heterogeneity. Among the subgroup analyses conducted, only age of the participants yielded dramatic differences in the summary estimate of efficacy, suggesting that age might be an effect modifier of the efficacy of isoniazid among children, with no effect realised in children initiating isoniazid at four months of age or earlier and an effect being present in older children. Excluding studies in which isoniazid was initiated at four months of age or earlier yielded an even stronger effect (RR = 0.41 (95% CI: 0.31, 0.55) $p < 0.0001$). Data on the effect of isoniazid on all-cause mortality, excluding studies in which isoniazid was initiated in infants, yielded an imprecise estimate of mortality benefit (RR = 0.58 (95% CI: 0.31, 1.09) $p = 0.092$).

Conclusion: Isoniazid prophylaxis reduces the risk of developing tuberculosis by 59% among children aged 15 years or younger excluding children initiated during early infancy for primary prophylaxis (RR = 0.41, 95% CI: 0.31, 0.55 $p < 0.001$). However, further studies are needed to assess effects on mortality and to determine prophylaxis effectiveness in very young children and among HIV-infected children.

Keywords: Tuberculosis, Isoniazid, Prophylaxis, Meta-analysis, Efficacy, Children

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Annals of Internal Medicine | Review

Treatment of Latent Tuberculosis Infection

A Network Meta-analysis

Helen R. Stagg, PhD*; Dominik Zenner, MD*; Ross J. Harris, MSc; Laura Muñoz, MD; Marc C. Lipman, MD; and Ibrahim Abubakar, MBBS, PhD

Background: Effective treatment of latent tuberculosis infection (LTBI) is an important component of TB elimination programs. Promising new regimens that may be more effective are being introduced. Because few regimens can be directly compared, network meta-analyses, which allow indirect comparisons to be made, strengthen conclusions.

Purpose: To determine the most efficacious regimen for preventing active TB with the lowest likelihood of adverse events to inform LTBI treatment policies.

Data Sources: PubMed, EMBASE, and Web of Science up to 29 January 2014; clinical trial registries; and conference abstracts.

Study Selection: Randomized, controlled trials that evaluated LTBI treatment in humans and recorded at least 1 of 2 prespecified end points (preventing active TB or hepatotoxicity), without language or date restrictions.

Data Extraction: Data from eligible studies were independently extracted by 2 investigators according to a standard protocol.

Data Synthesis: Of the 1516 articles identified, 53 studies met the inclusion criteria. Data on 15 regimens were available; of 105 possible comparisons, 42 (40%) were compared directly. Compared with placebo, isoniazid for 6 months (odds ratio [OR], 0.64 [95% credible interval {CrI}, 0.48 to 0.83]) or 12 months or longer (OR, 0.52 [CrI, 0.41 to 0.66]), rifampicin for 3 to 4 months (OR, 0.41 [CrI, 0.18 to 0.86]), and rifampicin–isoniazid regimens for 3 to 4 months (OR, 0.52 [CrI, 0.34 to 0.79]) were efficacious within the network.

Limitations: The risk of bias was unclear for many studies across various domains. Evidence was sparse for some comparisons, particularly hepatotoxicity.

Conclusion: Comparison of different LTBI treatment regimens showed that various therapies containing rifamycins for 3 months or more were efficacious at preventing active TB, potentially more so than isoniazid alone. Regimens containing rifamycins may be effective alternatives to isoniazid monotherapy.

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For author affiliations, see end of text.

* Drs. Stagg and Zenner contributed equally to this work.

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In many countries with a low incidence of tuberculosis (TB), many new cases emerge as a result of reactivation of latent TB infection (LTBI), which is often acquired in high-incidence areas or from recent exposure in occasional outbreaks. Therefore, such countries have had a renewed interest in LTBI screening and treatment, generally for groups at particularly high risk for reactivation, such as contacts of patients with pulmonary TB, persons who are immunocompromised, and migrants from high-incidence areas.

Although efficient and safe, LTBI treatment regimens are lengthy. It is thus essential to offer the least toxic and shortest possible effective regimen to ensure high completion rates. Globally, it is most common to use 6 to 9 months of isoniazid (INH) monotherapy; in the United States, 9 months is recommended (1). Three months of INH plus rifampicin (RMP) and 3 to 4 months of RMP alone may be equally as efficacious as INH regimens (2, 3). Twelve weeks of INH plus rifapentine (RPT) has been shown to be noninferior to 9 months of INH alone (4) and is now included in Centers for Disease Control and Prevention guidelines (1).

To date, all reviews of LTBI treatment have used conventional meta-analyses. By allowing only direct comparisons between regimens, such analyses were severely limited in the inferences they could make about relative efficacy and toxicity. Bayesian hierarchical models use a network approach that also enables the indirect comparison of regimens and thus produces inferences of relative efficacy that would not otherwise be possible (5, 6). We therefore undertook a systematic review using such an analytic approach to provide an up-to-date summary of the randomized, controlled trials (RCTs) that have evaluated LTBI treatment and an informative comparison of the relative efficacies and adverse event (AE) profiles of different regimens.

Methods

Data Sources and Searches

PubMed, EMBASE, and the Web of Science were mined by using the preestablished search terms "chemoprevention," "preventive therapy," "chemoprophylaxis," or "treatment" AND "latent tuberculosis," "tuberculous infection," or "latent TB infection," and filters to select RCTs and human studies applied wherever possible. Reference lists of included papers and review articles were also

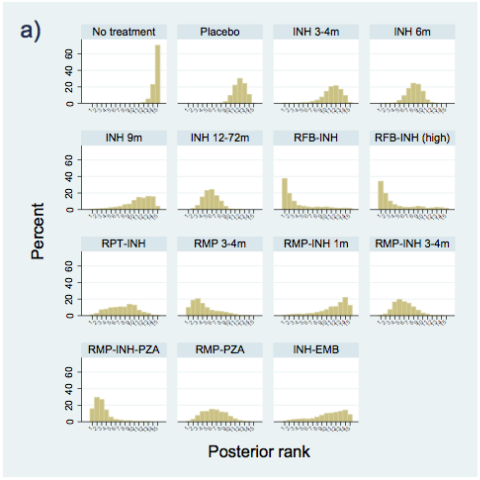
See also:

Editorial comment 449

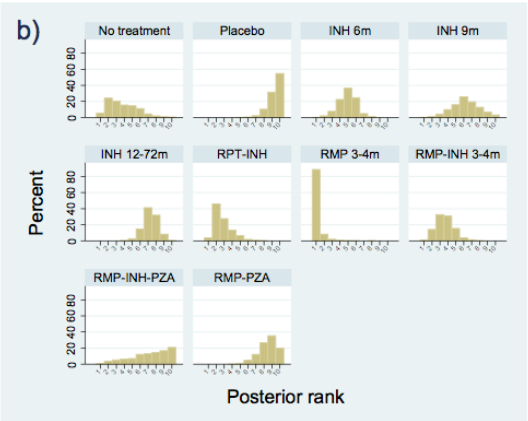
Web-Only
Supplements
CME quiz

- Network meta-analysis approach
- 53 trials

Recommended regimen



Regimen	OR (95% CrI)
No treatment	1.82 (1.05–3.05)
INH 3-4 m	0.94 (0.53–1.56)
INH 6 m	0.64 (0.48–0.83)
INH 9 m	0.94 (0.40–2.10)
INH 12-72 m	0.52 (0.41–0.66)
RFB-INH	0.28 (0.05–1.49)
RFB-INH (high)	0.31 (0.06–1.59)
RPT-INH	0.61 (0.29–1.22)
RMP	0.41 (0.18–0.86)
RMP-INH 1 m	1.07 (0.36–2.79)
RMP-INH 3-4 m	0.52 (0.34–0.79)



Regimen	OR (95% CrI)
No treatment	0.14 (0.02 - 0.71)
INH 6 m	0.21 (0.07 - 0.54)
INH 9 m	0.33 (0.05 - 1.34)
INH 12-72 m	0.46 (0.15 - 1.10)
RPT-INH	0.10 (0.02 - 0.38)
RMP	0.03 (<0.02 - 0.14)
RMP-INH 3-4 m	0.14 (0.03 - 0.43)
RMP-INH-PZA	0.49 (0.05 - 3.22)
RMP-PZA	0.70 (0.18 - 2.19)

Daily Isoniazid alone for 6 or 9 months

Daily Rifampicin alone for 3-4 months

Daily isoniazid plus rifampicin for 3–4 months

Weekly rifapentine plus isoniazid for 3 months (12 doses)

High burden countries

- HIV (36 months IPT conditional)

Challenges

- Adverse events: Monitoring – limited evidence
- Drug resistance: No difference in resistance
- Adherence: certain factors increase risk
- Ethics
- Cost effectiveness
- Monitoring and evaluation
- Wider programmatic consideration of the full cascade


Nienhaus *et al. BMC Health Services Research* 2011, **11**:247
http://www.biomedcentral.com/1472-6963/11/247

BMC Health Services Research

RESEARCH ARTICLE Open Access

Systematic review of cost and cost-effectiveness of different TB-screening strategies

Albert Nienhaus[1*], Anja Schablon[1], José Torres Costa[2] and Roland Diel[3]

Challenges

High burden resource constraint settings

- Programme management and collaboration
- Programmatic work load
- HCW workload
- Tuberculin and drug sourcing, stock management and distribution
- Algorithms/variation
- Link from national programmes to regions/provinces and districts
- Competing for limited resources
- Enrolling participants/uptake
- Accessing vulnerable groups
- Confidentiality in contact tracing
- Supporting adherence
- Rifapentine approval
- Monitoring adverse events
- Monitoring TB/HIV and kids LTBI
- Role of TST in screening
- Perception of drug resistance risk
- Provider opinion
- No MDR TB regimen

Low burden resource rich settings

- Predictive value of IGRAs
- Cost effectiveness
- Selection of risk groups: Know your epidemiology - migrants, indigenous populations, prisons

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KNCV

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