

Involving children in TB drug development: past, present, and future

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Changes in TB therapy, based on randomized trials, since 1962

1962

Regimen	3HSP, 21 HP
Duration (months)	24
# of doses	1460
Hospitalization	Yes
Treatment failure	10%
Relapse	2%
Acquired resistance	7%

Tubercle 1962;
43: 201-67

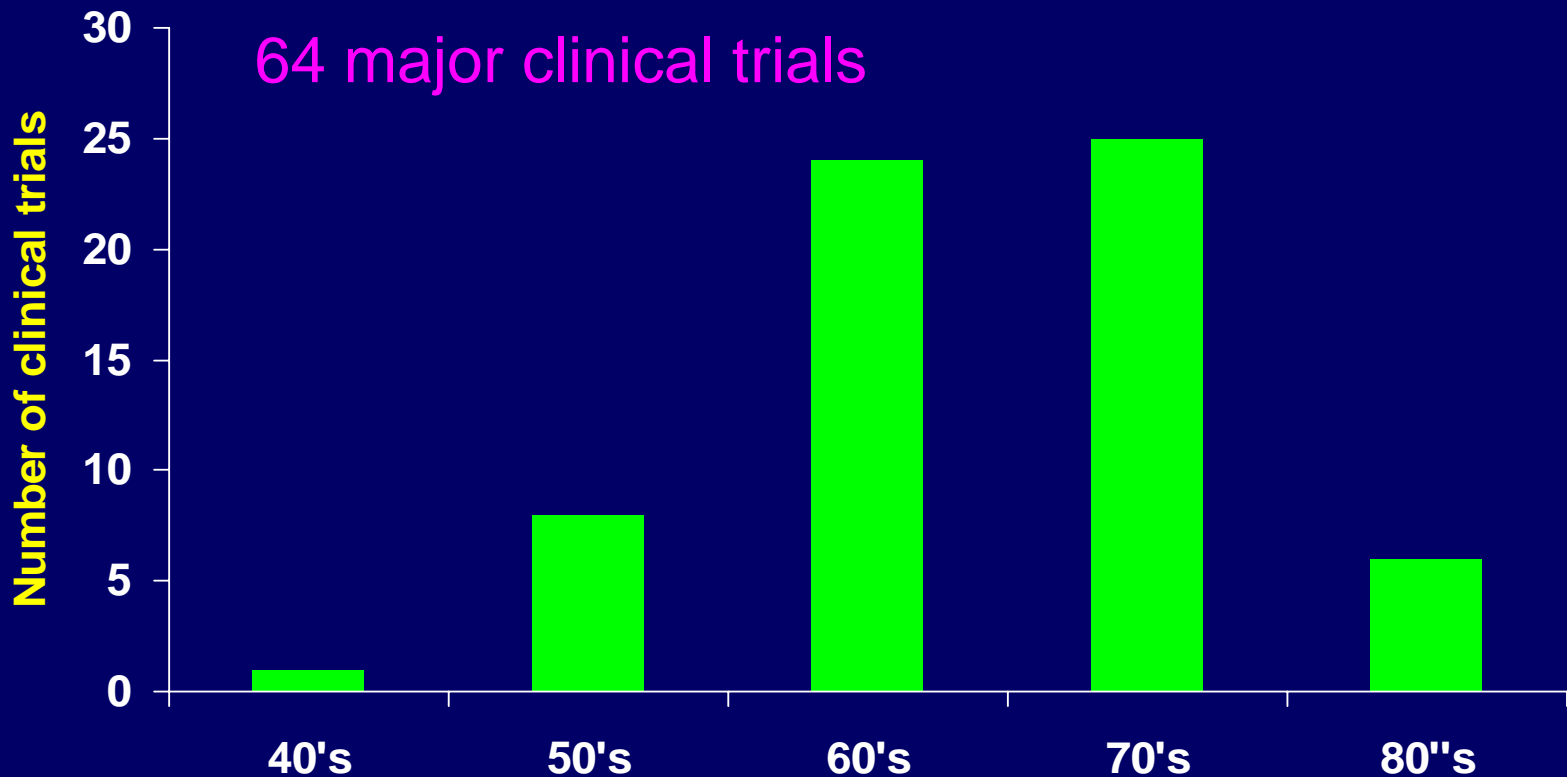
Changes in TB therapy, based on randomized trials, since 1962

	1962	1979
Regimen	3HSP, 21 HP	2HRZE, 4 HR
Duration (months)	24	6
# of doses	1460	96
Hospitalization	Yes	No
Treatment failure	10%	0
Relapse	2%	2%
Acquired resistance	7%	0

Tubercle 1962;
43: 201-67

Am Rev Respir
Dis 1979;579-85

Major randomized trials by the British Medical Research Council's TB Research Unit



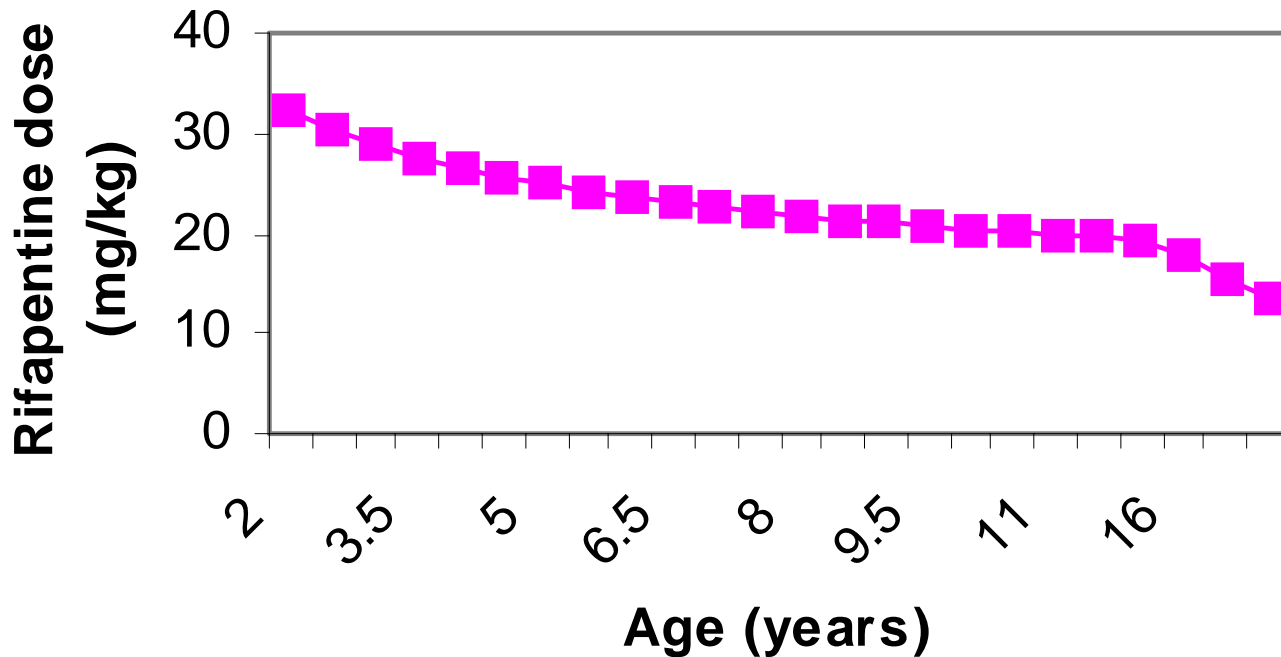
Involvement of children in the first 60 years of TB drug development

- Short-course chemotherapy for paediatric respiratory tuberculosis: 5-year report. *Int J Tuberc Lung Dis.* 2005; 9: 693-6.
- Twice weekly vs. daily chemotherapy for childhood tuberculosis. *Pediatr Infect Dis J.* 2000; 9: 405-10.
- Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatr Infect Dis J.* 1991;10:179-83.
- Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics.* 1997; 99: 226-31.
- A randomized trial of fully intermittent vs. daily followed by intermittent short course chemotherapy for childhood tuberculosis. *Pediatr Infect Dis J.* 1990; 9: 802-6.

Consequences of the lack of involvement of children in TB drug development

- Uncertainties about age-specific dosing recommendations for all TB drugs – likely under-dosing of key drugs

Changes in required dose of rifapentine (mg/kg), by age group



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- Lack of child-friendly formulations of TB drugs
- Uncertainty about how to use ethambutol safely
- Uncertainties about optimal duration of therapy
- Uncertainty about the adequacy of intermittent dosing, etc.

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1,000,000 pediatric TB cases, ~ 150,000 deaths per year

The example of antiretroviral therapeutics

- Children involved in drug development
- PK studies determined age-specific dosing
- Child-friendly formulations developed for most drugs
- Result – prompt and dramatic decreases in pediatric HIV-related mortality and morbidity soon after the availability of potent ART for adults

Involvement of children in TB drug development – present status

- Rifapentine – children (> age 2 years) being enrolled in large randomized trial of 9INH vs. 3 INH/rifapentine (TBTC Study 26); PK and tolerability being studied
- Moxifloxacin – no pediatrics plan announced
- High-dose rifampin – no pediatrics plan announced
- TMC207 – no pediatrics plan announced
- OPC67683 – no pediatrics plan announced
- PA824 – no pediatrics plan announced

Why were (and are) children left out?

- Infrequent transmission of TB from children to others
- Paucibacillary disease – infrequent culture-confirmation of active TB
- Frequency of extrapulmonary TB
- Existence of effective therapy for drug-susceptible TB
- Concerns about pediatric-specific side effects

Why were (and are) children left out?

- Uncertainties about the appropriate time to involve children in drug development and the optimal trial designs for doing so
- Regulatory requirements engendered by the inclusion of children
- Concerns about further subdividing the limited resources available for TB drug development

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All of these challenges are real; none of them should prevent children from being involved in TB drug development

What must be done?

- Articulate the necessity of involving children in TB drug development – to funders, regulatory agencies, investigators
- Develop a standard for the timing of involvement of children in TB drug development
 - Not appropriate to wait until evaluation among adults has been completed
 - Monitor and publicize the involvement of children (or lack thereof) in specific drug development programs

Trial design issues

- Difficulty in culture-confirming TB diagnosis
 - Obtain better specimens (e.g., induced sputum)
 - Use clinical definitions for diagnosis and response to therapy

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- Difficulty in culture-confirming TB diagnosis
 - Obtain better specimens (e.g., induced sputum)
 - Use clinical definitions for diagnosis and response to therapy
 - Limited ability to distinguish differences in efficacy of different potent regimens – children are not the population for definitive trials of new regimens
 - Primary endpoints of pediatric trials – PK and tolerability

Improving methodologies for PK studies in very young children

- Current methods
 - Limited sampling because of difficulty of repeated venipuncture
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- Current methods
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- Possible improvements
 - Dried blood spot PK
 - Bayesian analysis to decrease number of needed samples

Suggestions for timing of involvement of children in TB drug development

Phase in adults

Suggested pediatric studies

- Phase 2A (EBA)
 - Phase 2B
- Work on possible child-friendly formulations
 - Initial PK studies in children with TB – single-dose or multi-dose studies

Suggestions for timing of involvement of children in TB drug development

Phase in adults

Suggested pediatric studies

- Phase 3
 - Randomized comparison of new drug/regimen vs. standard
 - Tolerability and PK as primary endpoints
 - Efficacy (clinical, microbiological) as secondary endpoint

Suggestions for timing of involvement of children in TB drug development

Phase in adults

Suggested pediatric studies

- Phase 4
 - Additional studies of key sub-populations
 - Children < 3 years
 - HIV-infected children
 - Extrapulmonary involvement, especially meningitis
 - Validation of age-specific dosing recommendations

Regulatory issues with involving children in TB drug development

- IRB hassles – likely to be greater when children are involved
- NIH – requires involvement of children, unless there are specific reasons to exclude them
- EMEA – pediatric plan required for any drug that may be used in children
- FDA – increased ability to encourage pediatric studies

The future of TB drug development in children

- Recognition of the ethical imperative of involving children - clear standard of how and when to involve children
- Vigorous advocacy and monitoring
- Ear-marked funding for children – grow the pie
- Involvement of pediatric HIV trials groups / investigators
- Improved methodologies for PK studies
- Continued work on improving specimen quality and *M. tuberculosis* detection

Goals - 2018

- 3-month regimen for treatment of latent TB
- 3-month regimen for treatment of active TB
- Much more effective treatment for MDR-TB

Pediatric goals - 2018

- 3-month regimen for treatment of latent TB
 - Fully evaluated in HIV-positive and HIV-negative children of all age groups
- 3-month regimen for treatment of active TB
 - Fully evaluated in HIV-positive and HIV-negative children of all age groups
- Much more effective treatment for MDR-TB
 - PK and tolerability data for children

Workshop: Involving children in TB drug development

- June 2009
- Funders (NIH, CDC, BMRC, Gates), drug developers (industry, GATB), regulatory officials (FDA, EMEA, MCC), investigators (HIV, TB, PK experts), advocates
- Washington, DC
- Current co-sponsors: NIH, FDA
- Objective – develop guidelines for the field

Thanks to:

- Mark Cotton
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