Trial Design Considerations in Pediatric Trials of Antituberculosis Drugs

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How Childhood TB Differs From Adult TB

- Develops more rapidly after infection [< 2 years]
- Smaller burden of organisms
- Only 30% of cases can be confirmed microbiologically
- Diagnostic tetrad: symptoms, radiology/physical examination, test of infection, epidemiology [recent contact] – **Standardized research definitions exist**
- Increased propensity for extrathoracic disease, especially meningeal and disseminated [miliary]
- Relapse and failure difficult to define, rarely marked by positive cultures
- Children tolerate most TB drugs better
- Fewer children have other significant medical problems – hepatic, renal, cardiac

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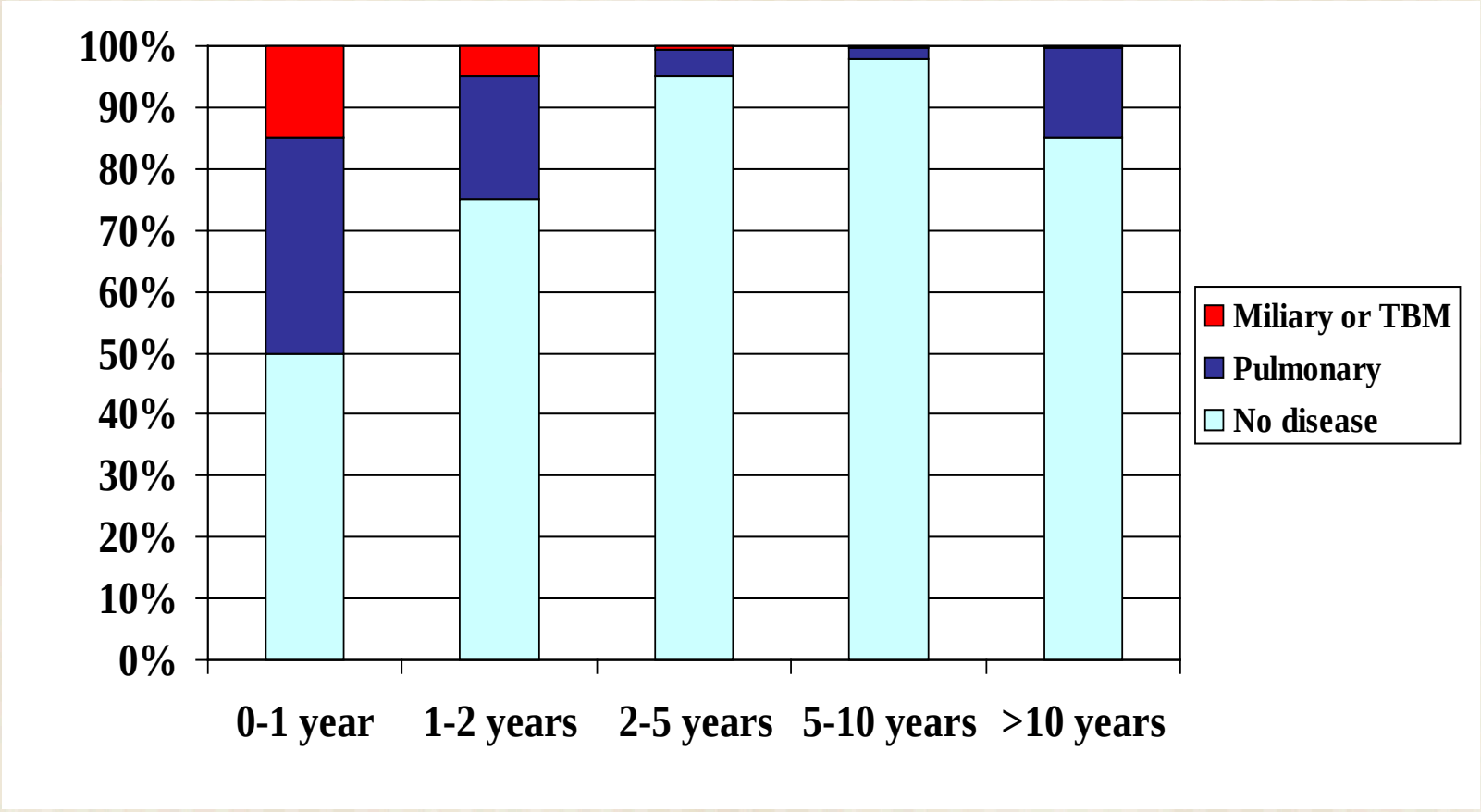
AVERAGE AGE RISK FOR TB DISEASE AFTER INFECTION (PRE-BCG)



Adapted from Marais B, et al. Int J Tuberc Lung Dis 2004

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Childhood TB Burden

- Global burden of childhood TB (2015)[1]
  - Estimated incident cases: 1 Million (5-10% HIV+)
  - Only 384,035 notified to WHO
  - Estimated mortality – 210,000 (40,000 HIV+)
- Global burden of MDR-TB in children
  - Estimated incident cases– 25,000-32,000/y[2,3]
  - Small minority identified and properly treated
  - HIV-associated with poor outcome

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[1] WHO Global TB Report, 2016; [2] Jenkins, H. E., et al. *Lancet* 2014.; [3] Dodd PJ, et al. *Lancet Inf Dis* 2016.

Childhood TB Burden

- Est. burden of LTBI in children
  - DS-TB – Total currently infected 67,000,000 [1]
  - MDR-TB – Total currently infected 2,000,000 [1]
  - Estimated child household contacts <5y eligible for LTBI treatment globally is 1.22 million (range 1.18-1.26)

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[1] Dodd PJ, et al. *Lancet Inf Dis* 2016.

Current TB Treatment in Children

Drug-susceptible TB disease	2RHZ(E)/4RH (Rif 8-12mg/kg increased to 10-20mg/kg)
Drug-susceptible TB infection	6-9H, 4R, 3HP (≥2 years)
Multidrug-resistant TB disease	9-12 months – 4-5 Km-Mfx-PTO-CFZ-hdINH-EMB-PZA/5-7 Mfx-PTO-CFZ-EMB-PZA; Other "local" regimens up to 18 months (6 months injectable)
Multidrug-resistant TB infection	Levofloxacin - ?duration, ? second drug

Some Current Knowledge Gaps in Treatment of Childhood Tuberculosis

- pK and adverse effect profiles of existing Group 2-5 TB drugs in children
- Optimal duration and follow up of TB regimens for DS- and DR-TB
- Adequate drug combinations and relevant doses for some forms of EPTB that are more common in children [osteoarthritis, meningitis]
- Optimal duration and combination of drugs for TB treatment in children living with HIV
- Optimal drug combinations and durations for MDR-TB in children, especially those with minimal disease

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Some Barriers to Inclusion of Children in TB Studies

- Difficulty of microbiologic confirmation of disease, failure and relapse
- Difficulty in performing pK sampling in children, especially infants and toddlers
- Complacency about the effectiveness of existing regimens
- Trial design issues: endpoints, sample sizes
- Capacity: lack of adequate trial sites
- Complicating research oversight and regulatory concerns
- Taking research funds away from adult studies

However, children have >10% of the disease burden but pediatric studies have < 2% of the research funding

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Regulatory Issues

European Union

- Regulation EC 1901/2006: requires an early Pediatric Investigation Plan no later than the completion of pK studies in adults

United States

- TB drugs qualify for orphan designation; inclusion of children in prelicensure trials is not required

South Africa

- No specific pediatric considerations – “Special attention to minors”

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Some TB Drug Trials in Children

Selected ongoing or planned pediatric TB trials – DS-TB, TB-HIV

Trial	Summary	HIV	Other
DATiC (NIH)	PK and safety of **first-line TB drugs** in children using 2010 WHO dosing	HIV+/-	Completed enrolment HIV-
Infant TB (TBA)	Evaluate the PK and safety of **first line TB drugs** using 2010 WHO dosing in infants < 12 months	HIV+/-	Completed 2015
Opti-Rif (TBA)	Evaluate optimal dosing and safety of **rifampicin** in HIV-uninfected children	HIV- only	Anticipated opening in 2017
Study 35 (CDC/TBTC)	PK and safety study of **RFPT**/INH co-formulation in children for prevention of TB	HIV+/-	Anticipated opening 2017
IMPAACT P1101 (NIH)	Phase I/II, dose-finding, safety, tolerance, and PK study of **RAL**- naïve children on RIF-based TB therapy	HIV+ only	Enroling
RTV super-booster for HIV-TB coinfection (DNDi)	Phase I/II, PK and safety, to develop a stand-alone ritonavir (RTV) booster formulation to be added to the optimized LPV/r-based paediatric ARV regimen	HIV+ only	Completed enrolment
IMPAACT P1106 and P1026s (NIH)	PK of ARVs and TB medications in low-birth wt and premature infants, and pregnant women	HIV+/-	Ongoing

Some TB Drug Trials in Children

Selected ongoing or planned pediatric TB trials – MDR-TB

Trial	Summary	HIV	Other
232/233 (Otsuka)	Phase I/II, PK and safety of **delamanid** PK and safety in children with MDR-TB	HIV- only	Paed formulation; completed enrolment Gr 1-3, enroling Gr 4
IMPAACT 2005 (NIH)	Phase I/II, PK and safety of **delamanid** in children with MDR-TB	HIV+/-	Paed formulation; anticipated opening Q2-3 2017
C211 Paediatric Bedaquiline (Jannsen)	Phase I/II study of **bedaquiline** PK and safety in children with MDR-TB	HIV- only	Paed formulation; enrolling Gr 1 from 2016
IMPAACT P1108 (NIH)	Phase I/II study of **bedaquilne** PK and safety in children with MDR-TB	HIV+/-	? Paed formulation; anticipated opening Q1 2017
MDRPK1 (NICHD)	PK and safety of **second-line TB medications** in HIV-infected and – uninfected children	HIV+/-	Completed enrolment
MDRPK2 (NICHD)	Optimized dosing of key second-line TB medications (**Mfx, Lfx, Lzd**) in children with MDR-TB (crushing, palatability)	HIV+/-	Enroling
TB-CHAMP (BMRC/SAMRC)	Phase III, to evaluate the efficacy of **Lfx** vs. placebo for the prevention of MDR-TB in child household contacts	HIV+/-	Anticipated opening 2016

Nachman et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis 2015; 15:711.

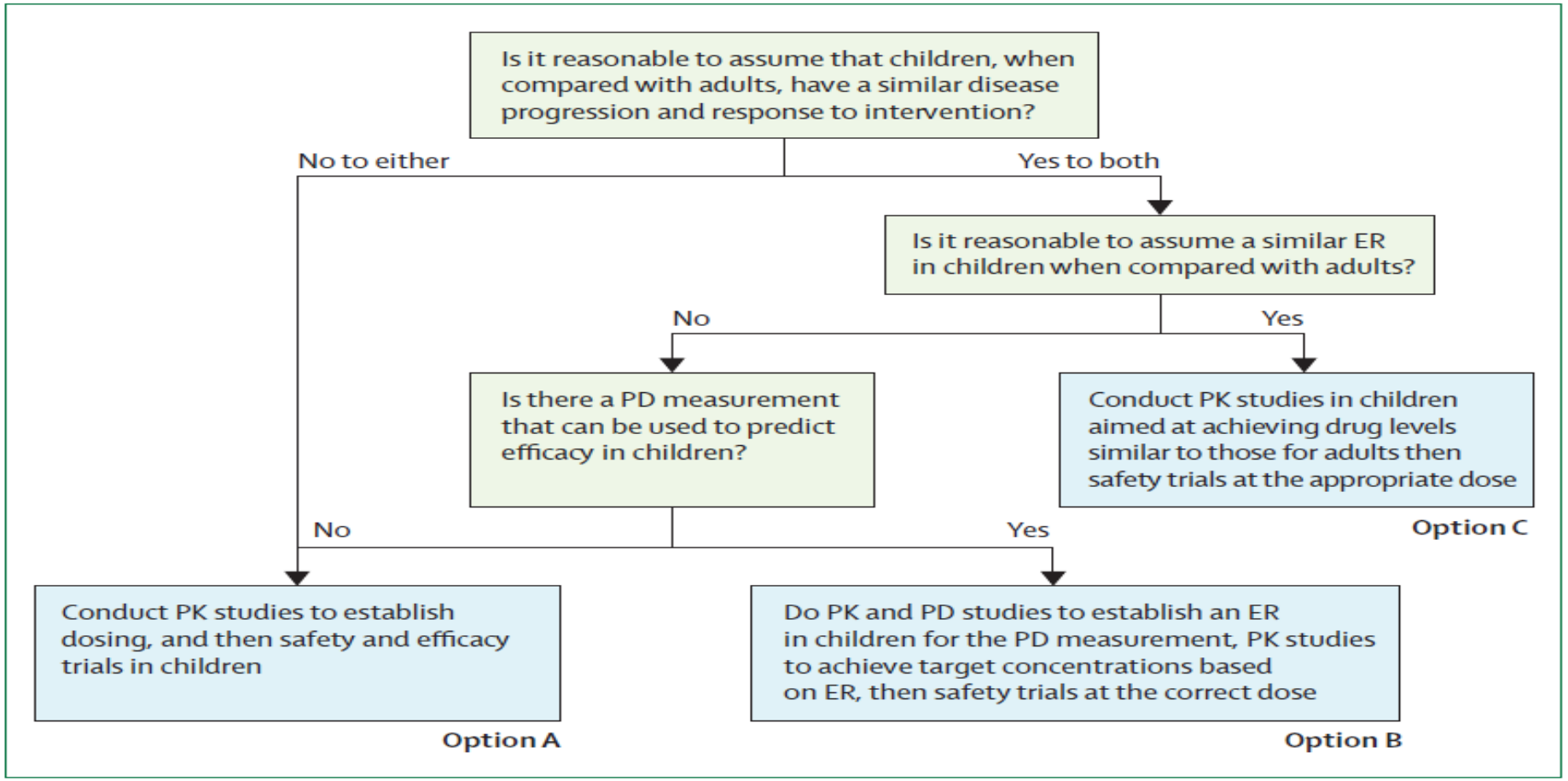

Figure 2: **Paediatric studies decision tree**
Reproduced from the US Food and Drug Administration.[66] ER=exposure-response. PD=pharmacodynamic. PK=pharmacokinetic.

TB Drug Trials in Children: Challenges and Lessons Learned

Efficacy

- Difficult to study regimens [as opposed to individual drugs] in children – sample size, cost, capacity, lack of microbiologic markers
- Efficacy studies of regimens for intrathoracic TB in children usually not necessary to allow pediatric treatment
- Aim is to match pK of individual drugs in children with pK in adults proven to be safe and effective
- Efficacy studies in children might be needed for some forms of EPTB and prevention
- Some children with milder forms of disease may require fewer drugs for a shorter period of time

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Nachman et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis 2015; 15:711.

Enrollment of children in drug research after:

- Full range of non-clinical studies in adult animals
- Safety, pharmacology and genotoxicity studies and appropriate juvenile animal studies do not suggest cause for concern
- Animal and human studies have substantiated anti-*Mycobacterium tuberculosis* activity
- pK and PD data from adults allow for selection of appropriate pK targets for children, or a safe dose has been established for adults [Phase IIb]
- Data on drug interactions with ARV drugs used in children

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TB Drug Trials in Children: Challenges and Lessons Learned

When to Begin Pediatric Studies

- Previous practice to wait until licensure **ensured** lack of data on pK, safety and tolerability and lack of pediatric dosage forms
- Pediatric studies should begin when safety and basic pK are established in adults – Phase IIb
- Adolescents [> 10 years old] should be included in late phase [IIb] adult studies
- Begin development of pediatric dosage forms at Phase IIa so available after Phase IIb

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Murray et al. Accelerating clinical drug development for children with tuberculosis. IJTLD 2015; 19:S69.

Table An overview of historical and current development strategies and the newly proposed paradigm for drug development in pediatric tuberculosis

	Historical	Current	Proposed/accelerated pediatric development
Development strategy	No specific pediatric development; children are given adult doses, or doses are adjusted according to weight	Pediatric development is generally initiated once a drug or regimen is approved for adults, starting with adolescents and gradually moving to younger children	Single-dose PK studies begin as soon as successful phase II adult studies are complete. Study multiple dose/comprehensive PK and safety in all children (no age de-escalation) in parallel with phase III (in adults)
Challenges	Drugs in regimens are administered using ad hoc methods (administering adult-sized pills, crushing, dispersion in liquids etc.). Pediatric safe/efficient dosing often unknown	Significant delays for access to new drug or regimens for children	Overcoming traditional clinical and ethical considerations of how children can be studied

PK = pharmacokinetic.

TB Drug Trials in Children: Challenges and Lessons Learned

Pharmacokinetics and Study Design

- Conservative approach was step-wise age de-escalation, often took years
- Age de-escalation now widely accepted as unnecessary for the vast majority of drugs unless there are specific safety concerns
- Developmental pK and PD especially important for infants and toddlers
- Suggested age ranges for study: 0-3 months; 3-24 months; 2-4 years; 5-10 years; and > 10 years.

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TB Drug Trials in Children: Challenges and Lessons Learned

Pharmacokinetics and Study Design Issues

- Appropriate sample size for pK within each age group
- Single-dose sampling in all age groups, then move to multiple dose sampling
- Rationalizing sample points – reducing the burden of number and size of blood draws
- Drug concentrations in CSF
- Use of dosing simulations
- Trial design for children with HIV infection

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TB Drug Trials in Children: Challenges and Lessons Learned

Dosage formulations

- Age-specific, palatability, taste, acceptability

Trial capacity

- Need a more robust trial network in various geographic locales with sustained funding
- Need to develop pediatric investigators

Incentives for child studies and formulations

- Extended market exclusivity and priority review vouchers have been ineffective for pediatrics
- Advance Market Commitment?
- Include pediatric experts on DSMBs
- Require pediatric studies for public funding

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Traditional Development vs. Accelerated Development

TRADITIONAL:

Adult Drug Development Process

7+ years

Pediatric Drug Development Process

7+ years

ACCELERATED:

- Juvenile toxicology
- Formulation Work
- BE Studies

- Single- and multiple-dose pK studies simultaneously in ages 0 to 16

- Consider inclusion of children (≥10 Y) and adolescents in adult Phase 3 studies

Integrated Adult & Pediatric Development Process

An accelerated pediatric drug development pathway could allow life-saving treatments to reach children sooner than they do today

Murray et al. Accelerating clinical drug development for children with tuberculosis. IJTLD 2015; 19:S69.

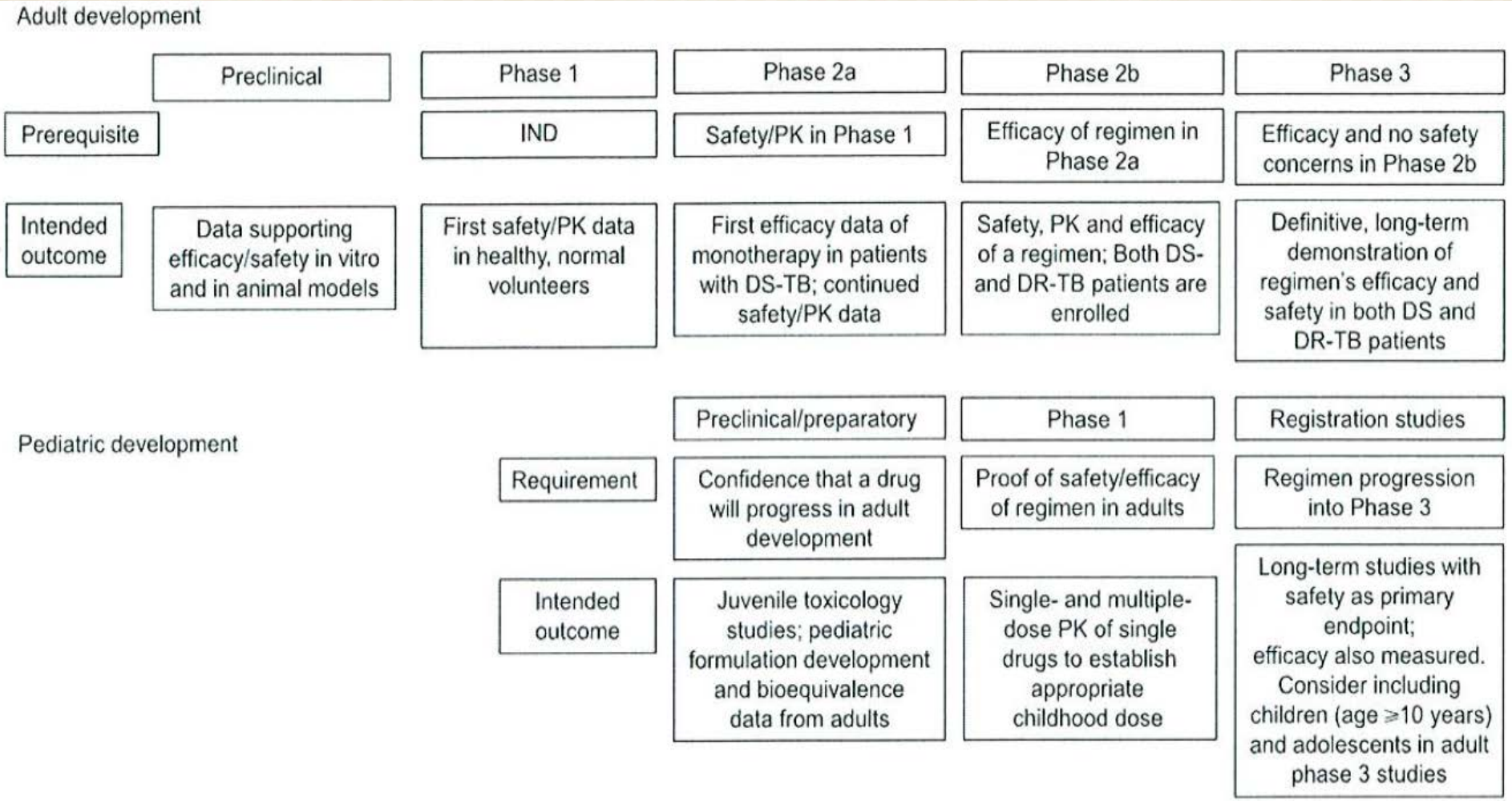

Figure Optimized anti-tuberculosis drug development: integrated adult and pediatric clinical trials. PK = pharmacokinetic; DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB; TB = tuberculosis.

Overview of Approach to Studying TB Drugs in Children

- Create regulatory and economic incentives for industry and academia to develop and study pediatric formulations of old and new drugs
- Create capacity building for pediatric trials
- Start development of “child-friendly” pediatric drug formulations earlier
- Start pediatric pK studies concomitantly with Phase IIb studies in adults
- Establish function within childhood TB community similar to the Pediatric Antiretroviral Drug Optimization efforts
  - Develop **consensus priorities** on key drugs, formulations, strengths
  - Identify key research gaps
  - Include specific representation of pediatric HIV expertise

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Burman et al. Ensuring the involvement of children in the evaluation of new tuberculosis treatment regimens. PLoS Med 2008; 5:e176.

- An overzealous attempt to protect some children from the possible harms of research perversely causes harm, by either denying access to treatment or through exposing children to the risks of inappropriate dosages of new medications.

- “Children have the same right to benefit from research as do adults.”

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