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TB CARE II

DR|TB TRAINING NETWORK

RAISING VOICES: ADVOCACY ISSUES IN PEDIATRIC DR-TB

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Sentinel Project on pediatric drug-resistant tuberculosis

Friday
September 19, 2014

9:00 a.m. EDT
(GMT -5:00)

www.drtbnetwork.org

Objectives

- To discuss some of the major challenges in the diagnosis and treatment of children with DR-TB;
- To review current advocacy efforts by TAG, MSF, and the Sentinel Project in Pediatric DR-TB;
- To discuss future agenda and action steps for pediatric DR-TB advocacy

Pediatric DR-TB Needs

- Gaps discussed in prior Sentinel webinar sessions
- Better estimates of burden of disease (upcoming webinar)
- Sensitive diagnostics that can be run on easily obtained samples;
- Improved prevention strategies, including preventive therapy;
- Better treatment approaches with effective medications whose doses are well known in children, including new drugs;
- More palatable, easy to administer, and precise formulations;
- Improved psychosocial support for family centered care;
- Inclusion in global child health agenda

Burden of Disease

- Difficult to know as children not included in prevalence surveys
- Multiple models exist on burden of disease
- Will be discussed in detail on October 9 webinar
- Stories as an advocacy tool

BEING BRAVE: Stories of children with drug-resistant tuberculosis

Sentinel Project

From the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, March 2012

WE CAN HEAL

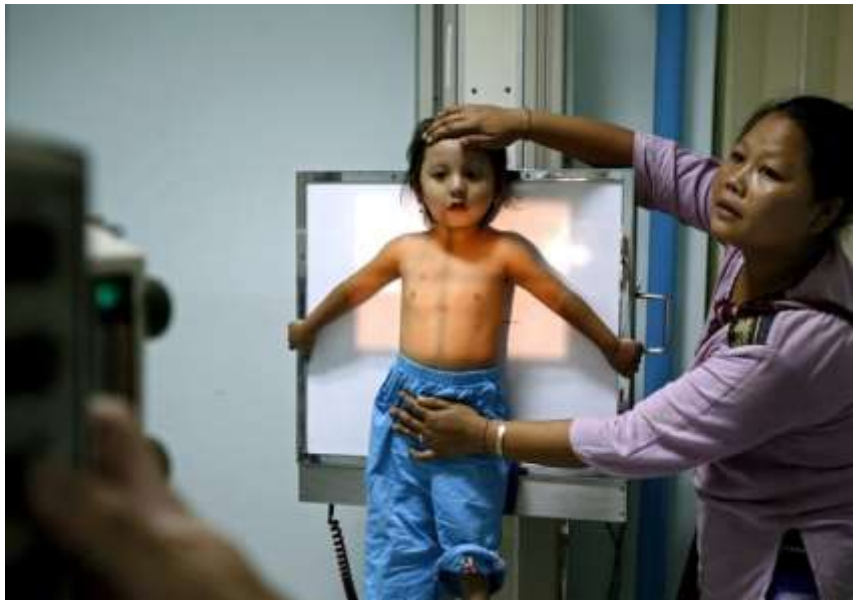
PREVENTION, DIAGNOSIS, TREATMENT, CARE, AND SUPPORT: ADDRESSING DRUG-RESISTANT TUBERCULOSIS IN CHILDREN

MARCH 2013

Treatment Action Group

Diagnostics

- Limited advocacy efforts
- Short-Term: strengthen implementation of sample collection procedures for paed TB diagnosis (IS, NPA, GA, LNA etc)
- Long-term: support R&D towards children-adapted, biomarker-based, non-sputum based test (NIH meeting May 2014) “Pediatric TB diagnosis: addressing research gaps in diagnostic TB biomarkers”



Prevention

- Several clinical trials being planned for MDR-TB household contacts through the British MRC, the South Africa MRC, and the U.S. NIH
- Sentinel completing a handbook for household interventions and plans to pilot it in sites in Peru, India, and South Africa

Treatment


PASER®
Aminosalicylic Acid
Delayed-release Granules
4 Grams
Damien Schumann

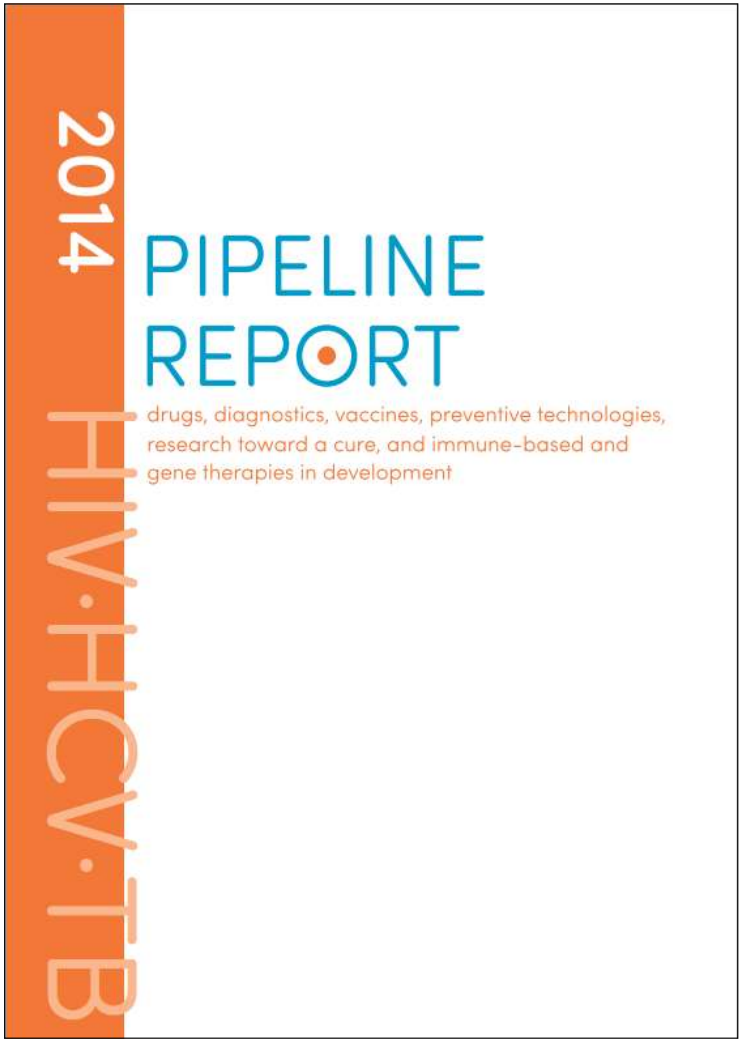
2014 Pipeline Report

- Annual update on drugs, diagnostics, and vaccines in-development for TB (HIV and HCV).

- Offers overviews of recently completed, planned, and ongoing trials for tools in the pipeline.

- Includes recommendations for researchers, funders, regulators, and advocates to take forward.

- This year's report includes a chapter focused on pediatric TB treatment.



Real Talk: Existing drugs

For TB drugs developed 50+ years ago we still lack evidence-based dosing for children, and where we do have evidence-based dosing, we lack appropriately dosed fixed-dose combinations.

TB Type	What we're working with	On the horizon
First-line drugs (DS-TB)	• Four years after the WHO revised dosing guidelines based on emerging PK data we are still waiting for FDCs to be reformulated in appropriate doses	• TB Alliance, under a UNITAID grant is working to catalyze market introduction of revised FDCs by late 2015
Second-line drugs (DR-TB)	• Treatment guided by findings extrapolated from adult data • Unpalatable pills designed for adults, must be split, crushed, and mixed with juice or foodstuffs to get them into children	• Ongoing studies in SA will provide PK data necessary to determine appropriate dosing to achieve drug exposures comparable to those in adults

Real Talk: Novel drugs

Delamanid | EMA approval April 2014

- Otsuka already enrolling the second cohort (6–11-year-olds) in its PK and safety study

Bedaquiline | FDA approval December 2012

- Janssen has yet to begin its planned PK and safety study in children and adolescents

PA824 | entering phase III trials

- TB Alliance not expecting to start studies in children and adolescents until 2016

WHY?

Differing regulatory requirements may explain these discordant timelines…

Regulatory Requirements

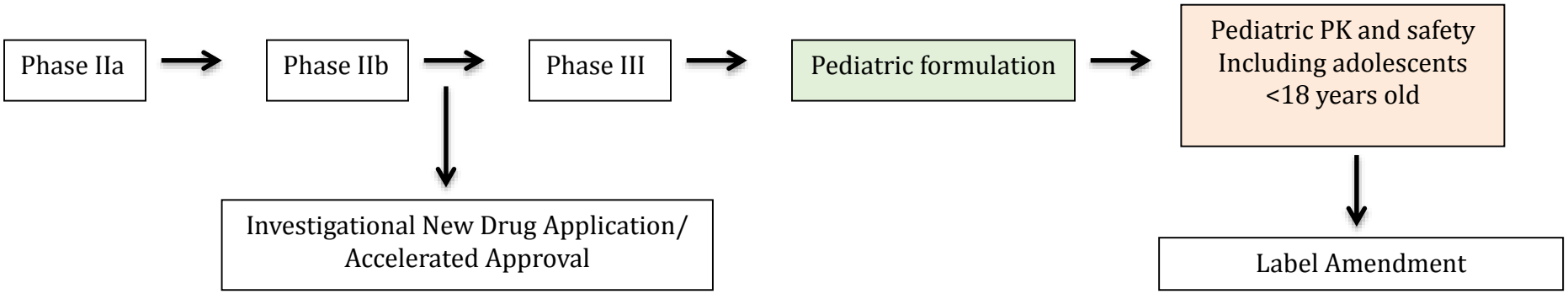
FDA	EMA
Pediatric study exemption for orphan drugs	Pediatric Investigational Program (PIP) requirement

Does your country drug regulatory authority require PK and safety studies in children?

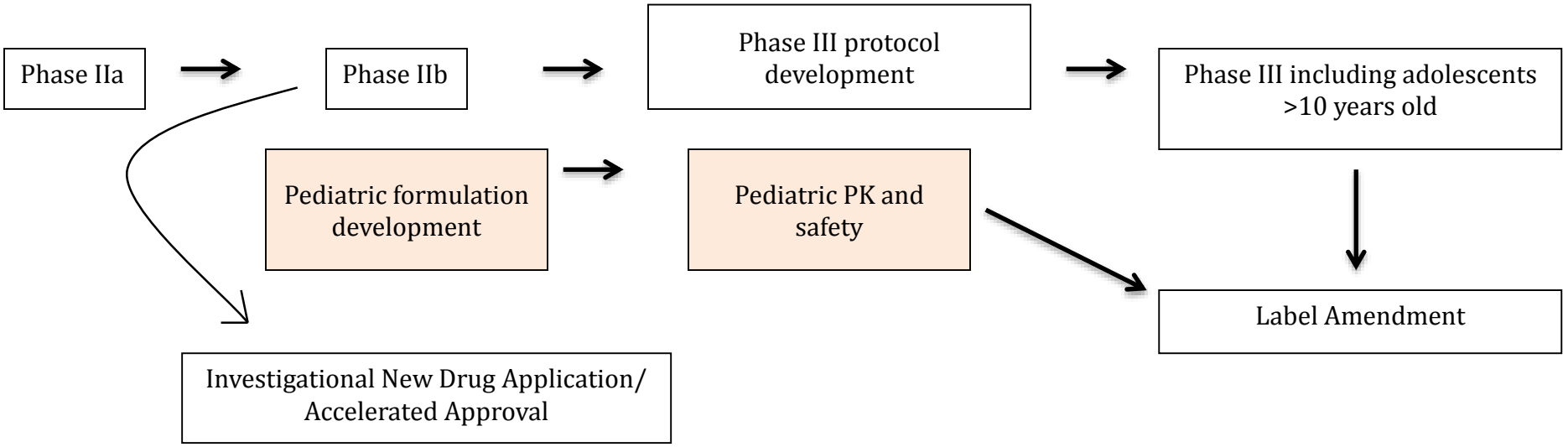
Regulatory requirement for drug development in children is urgently needed, especially for neglected diseases like TB, where private-sector developers are few and investments are shrinking.

The Novel Drug Development Pathway

What we have:



What we want:



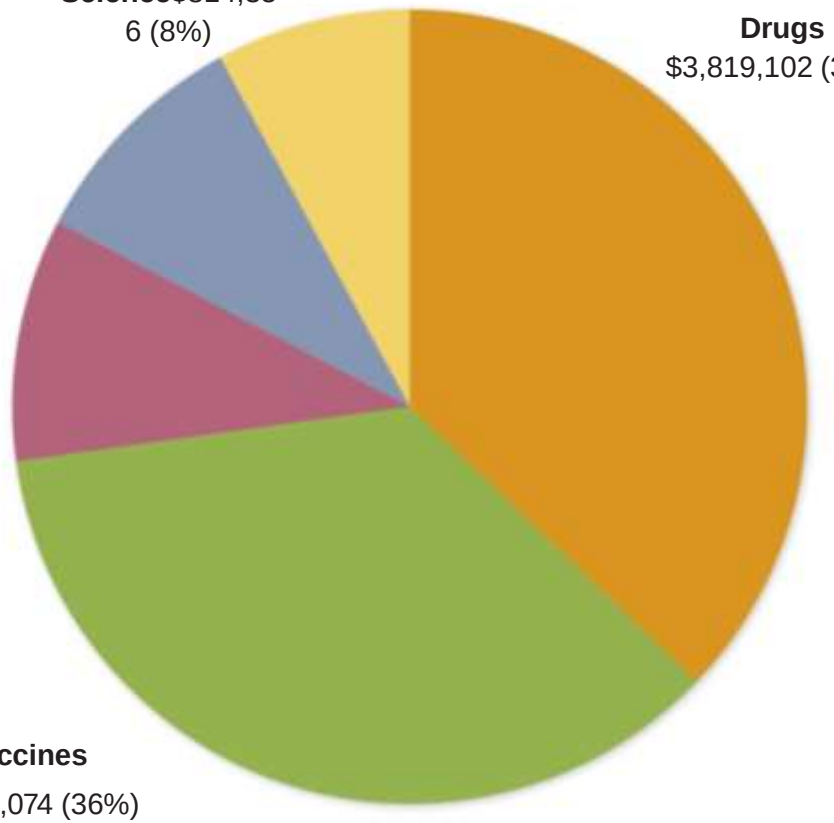
Real Talk: Regimens (novel + existing drugs)

Trial	Phase	TB Type	Adolescent Inclusion	Pediatric Component	Regimen
C213	III	MDR	✗	✓ (C232/233)	DLM + OBR (18–24 months)
STREAM	III	MDR	✗	✗	Stage 1: 9 month w/ injectable Stage 2: 9 month all oral w/ BDQ 6 month w/ injectable + BDQ
STAND	III	DS/MDR	✗	✗	6 month all oral (PaMZ)
Nix-TB	IIb	XDR	✓ (14+ yrs.)	✗	6–9 month all oral (Pa,LZD,BDQ,Z?)
MARVEL	IIb	MDR	?	✗	Shortened regimen (novel drugs–TBD)
NC005	IIb	DS/MDR	✗	✗	Shortened regimen (BDQ,Pa,Z)
TBTC S31	III	DS	✓ (12+ yrs.)	✗	4 month HPZE/HP 4 month HPZM/HPM
~~REMox~~	III	DS	✗	✗	4 month HRZM 4 month MRZE

Research and Access Gaps

- Revised dosing guidelines and child-friendly formulations for second line TB drugs;
- Data on the optimal role of each SLD in pediatric DR-TB treatment;
- Data on the role of fluoroquinolones in treatment shortening for pediatric DS-TB;
- Optimized treatment for drug-sensitive and drug-resistant TB meningitis; and
- Evidence-based guidance for preventive therapy in child contacts of DR-TB patients.

Pediatric TB R&D Funding by Category



What we need:
2011-2015: US$ 200 million

What we got:
2012: US$ 10.3 million

In 2012, out of US$237.8 million in total **TB drug R&D funding**, only US$3.8 million was invested in pediatric TB drug development

Playing Catch-Up: The Pediatric TB Treatment Pipeline

1. Integrate adult and pediatric TB drug research;
2. Mandate earlier inclusion of children in TB drug and regimen development;
3. Include adolescents in phase III TB drug trials;
4. Conduct progressive clinical trials to speed research on and access to TB drugs for children;
5. Develop a pediatric TB treatment research agenda;
6. Increase funding for pediatric TB drug development; and
7. Mandate the development of pediatric TB drugs.

Practical aspects of DR-TB in kids

- MSF projects treating DR-TB in kids includes Swaziland, SA, Kenya, Armenia, Colombia, Uzbekistan and Georgia.
- Most children doing well on treatment, less issues with side effects
- Importance of family centred care, and psychosocial support in treatment of DRTB in kids.
- Importance of decentralising care in children and support whole family

MSF experience of DR-TB in kids

- MSF programme in Tajikistan
- Specific paediatric DR-TB programme working closely with MoH with MSF support
- Challenges with paediatric preparations.
- Preparations: E, Z, Lfx, Mfx, Cs, Pto

Extemporaneous Preparation/Compounding

- Medicines **prescribed by a physician** and **compounded by a pharmacist** to **fit the unique need of a patient** in the absence of a commercially available, authorized, **age-appropriate dosage** or form of a medicine

- **Mixture of a** active pharmaceutical ingredient or **commercially available finished product -** usually a solid dose form such as a tablet- with an appropriate vehicle(s)

- Preparations are based on **elaborated formulas and are prepared through defined, standardized compounding procedures described in international pharmacopeias**

'Manipulation'

- Manipulation is not considered an extemporaneous preparation

- **Dispersing** tablets in liquids, **crushing** tablets or **opening capsule** and **mixing the powder/content with food or a liquid vehicles** like juice, milk etc.


100
90
80
DRA-BLEND

What is the current situation?

Commercially Available Paediatric Formulation

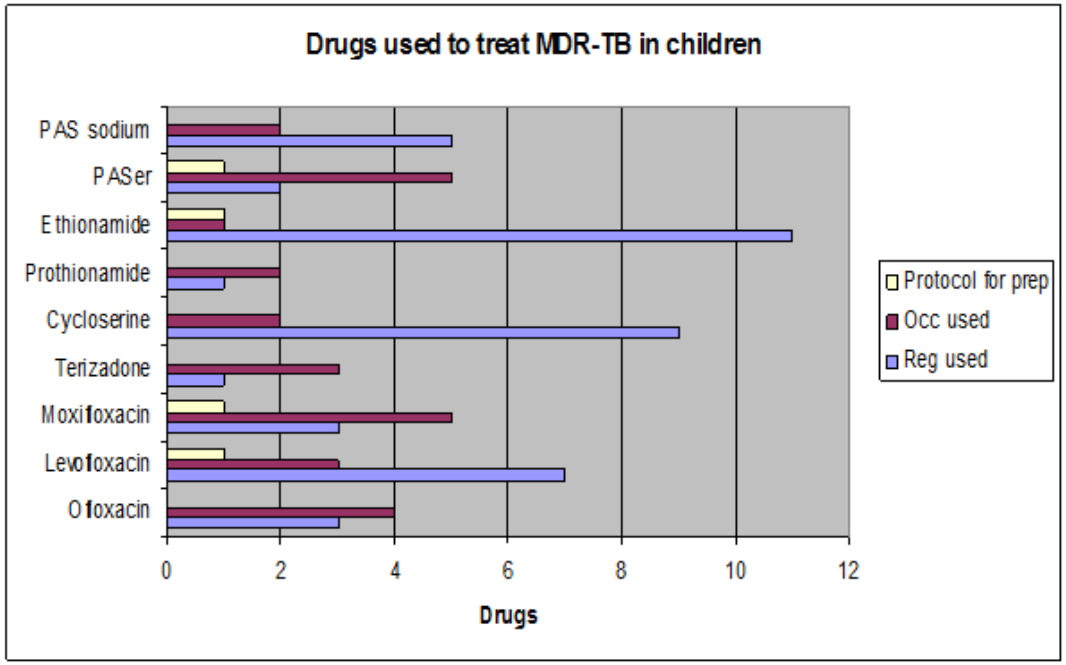
Fist Line Drugs (FLD)			Second (SLD) and Third Line (TLD) Drugs	
Single	**Old FDC**	**New FDC**	**SLD**	**TLD**
- R **- H** **- E**	**- RH 60/30** **- RHZ 60/30/150**	**- RH 75/50** **- RHZ 75/50/150**	**- Amikacin** **- Levofloxacin*** **- PAS (dosage spoon)**	**- H** **- Amx/Clv** **- Lzd**
1 single drug out of 3 FLD			3 out of 10 SLD	3 out of 5 TLD

*Levofloxacin Oral Solution: not recommended in children < 3y and composition not necessarily adapted for long-term use

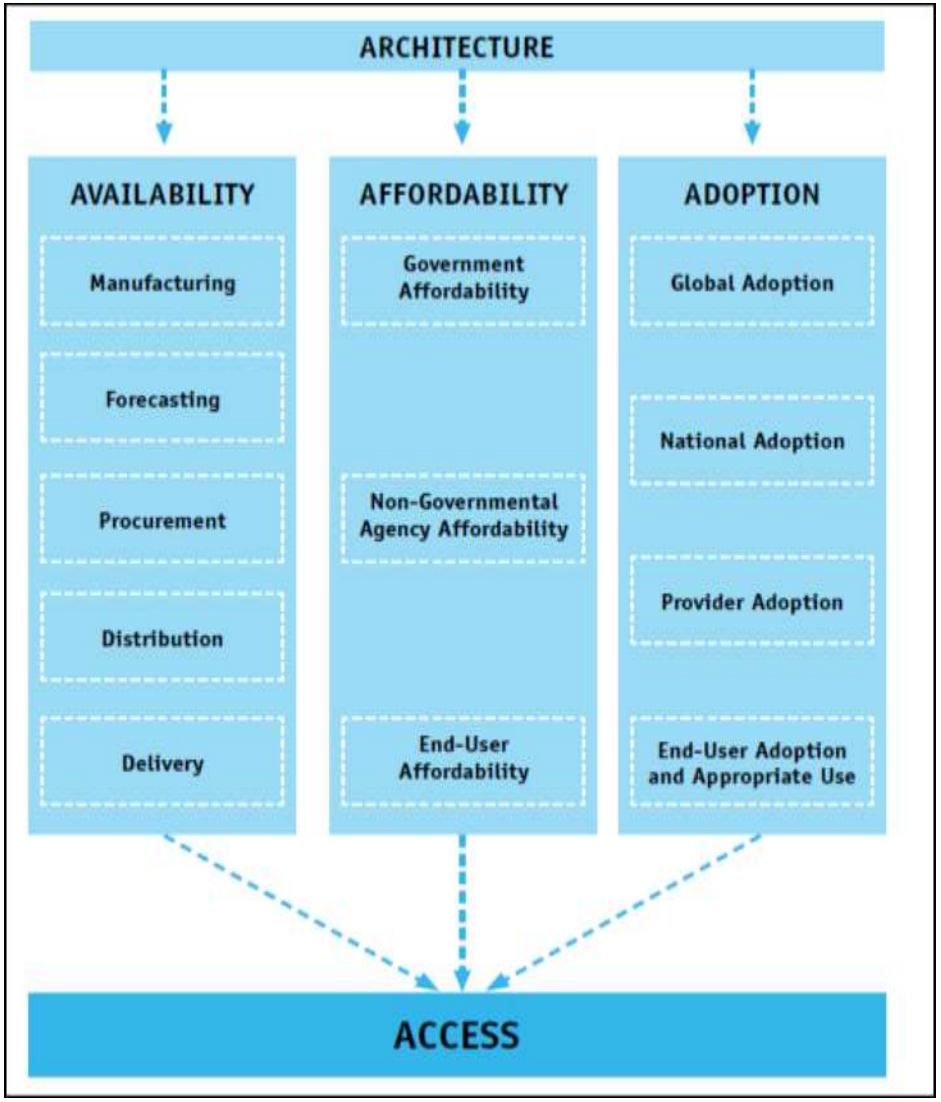
Granules and dosing spoon

Sentinel Survey on use of SLD

- Survey sent to Sentinel members about drugs used now for SLD
- How these drugs were prepared and the issues.
- Commonest drugs with issues with preparation are:
  - Cycloserine
  - PAS
  - Ethionamide
- Follow up work on TPP for SLD to meet the field and regulatory needs.



More than just new products required.



Sentinel Project: Improved Delivery Systems

- “Pudding Project”
- Work with MacLeods
- WHO dosing project (led by Anneke Hesseling)

Score Fo(u)r Pediatric MDR-TB

Inclusion in the Global Child Health Framework

Overlap with other MCH issues:

- Malnutrition
- HIV
- Pneumonia
- Other respiratory infections
- Meningitis
- Pre-term birth

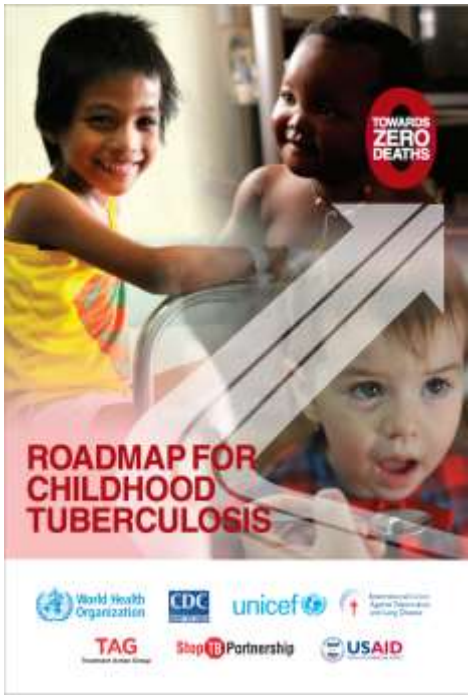
Childhood TB needs to be integrated into maternal and child health documents, plans, and activities. Childhood TB needs to be on the brain everywhere sick children and sick mothers access care.

Inclusion in the Global Child Health Framework

Roadmap for Childhood Tuberculosis: Towards Zero Deaths

Endorsed by:

- World Health Organization (WHO)
- U.S. Centers for Disease Control & Prevention (CDC)
- UNICEF
- International Union Against TB and Lung Disease
- Stop TB Partnership (STBP)
- U.S. Agency for International Development (USAID)



Push them to implement the roadmap they developed!

Available here: http://www.who.int/tb/challenges/children/en/

Summary and Future Plans

- Much work to be done but it has started
- Children need your voice
- Promote and ensure that consensus statements and TPP's are adopted
- Ensure trials and funders of programmes include children
- Push for more funds for paediatric TB in general.

We can treat children with DR-TB now with the tools we've got

Thank you!

Access Reports online

TAG reports:

Full Pipeline Report

http://www.pipelinereport.org/

Pediatric TB treatment chapter:

http://www.pipelinereport.org/2014/pediatric-tb-treatment

2013 Report on TB Research Funding Trends, 2005–2012

http://www.treatmentactiongroup.org/tbrd2013

Sentinel reports:

We can Heal

http://sentinelproject.files.wordpress.com/2013/03/sentinel_project_we_can_heal_20131.pdf

Being Brave

http://sentinelproject.files.wordpress.com/2012/03/stories-of-children-with-dr-tb2.pdf

MSF reports:

Out of the Dark

http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_Report_OOTD_Update_ENG_2012.pdf

http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_OutoftheDark_ENG_2011_Final.pdf

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