



# **IMPAACT TB SCIENTIFIC COMMITTEE**

Anneke C Hesselink: Chair

Sharon Nachman: Interim Vice-Chair

IMPAACT Vice Chair



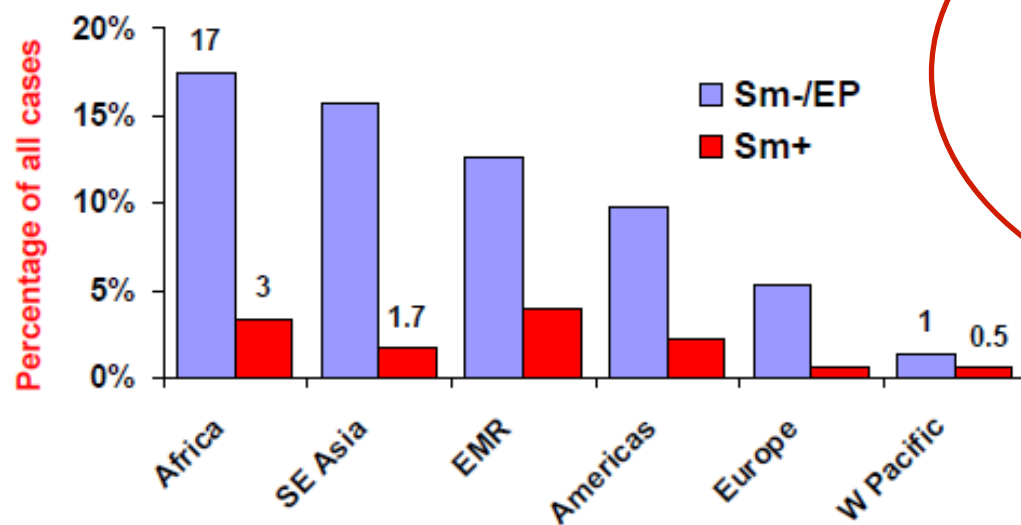
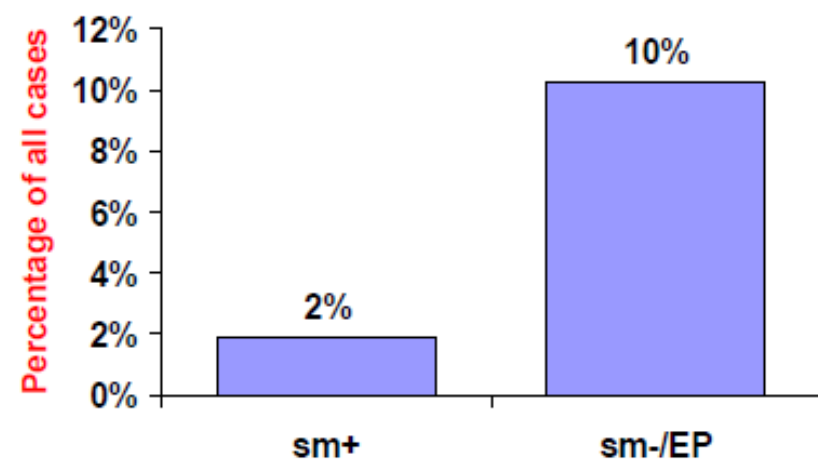
# Goal

- Address critical therapeutic research gaps in the prevention and treatment of tuberculosis in HIV-infected and uninfected children, adolescents and pregnant/breastfeeding women

# BURDEN OF TB IN CHILDREN

- Global: 2 billion latently infected, 8.8 million new cases
- >75% in 22 high-burden countries
- **Estimated 10% among (inaccurate estimates)**
- International and domestic problem
- Limited surveillance: challenges in diagnosis
- Limited programmatic emphasis (prevention and diagnosis)
- Diagnostic challenges
- Infection and disease both relevant entities

# Notifications among children, countries reporting age-disaggregated data, 2010



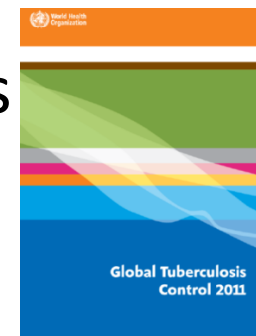
Estimated at least 6% of  
global notifications are  
among children



**BUT:** high levels of  
under-reporting of cases  
thought to exist e.g. due  
to lack of linkages  
between NTPs and  
paediatricians

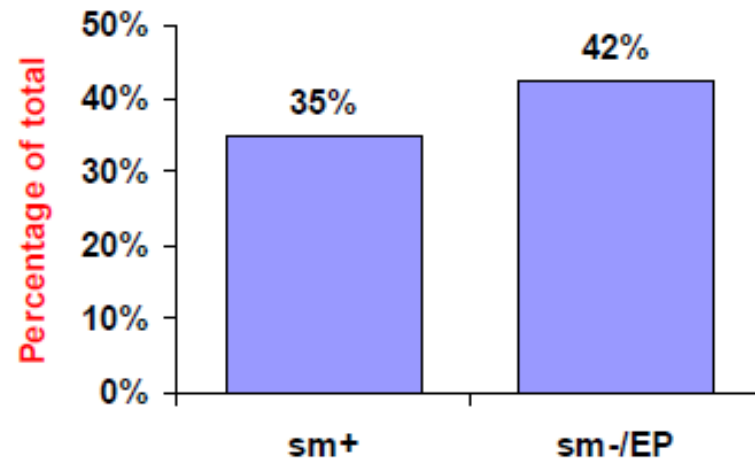
# TB IN WOMEN

- Estimated **3.2 million** (range: 3.0-3.5 million) new TB cases among women in 2010
- Estimated **820,000 deaths** in 2010
  - 320 000 deaths among HIV-negative women
  - 500,000 deaths among HIV-infected women
- Burden in pregnancy unknown (1-2.5% of HIV+ pregnant women) *Kali JAIDS 2006, Gupta CID 2011, Gounder JAIDS 2011*
- Peak incidence: reproductive age 15-45 years

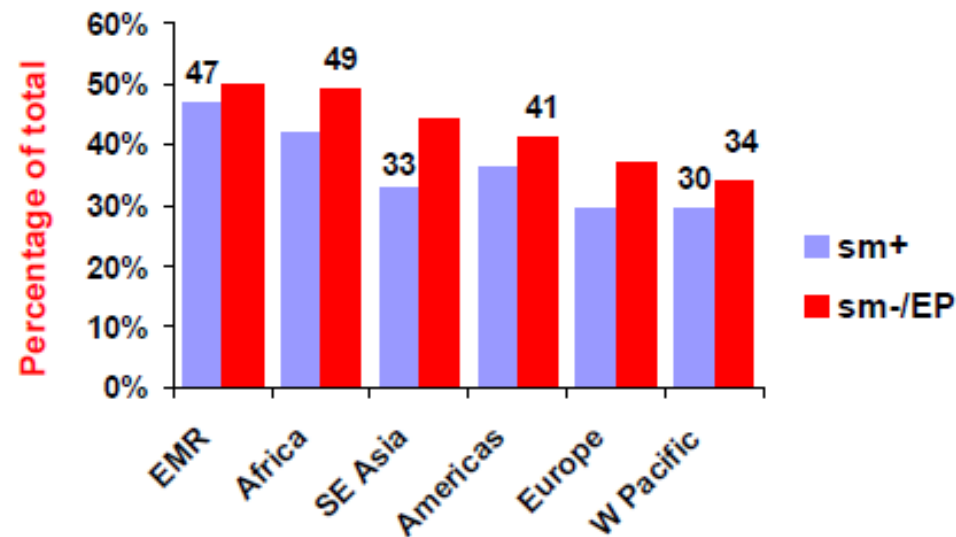


[www.who.int/tb/data](http://www.who.int/tb/data)

# Notifications among women, countries reporting cases disaggregated by sex, 2010



**~38% cases notified globally are among women**



**Variation by region – higher percentage of cases among women in Africa and EMR**

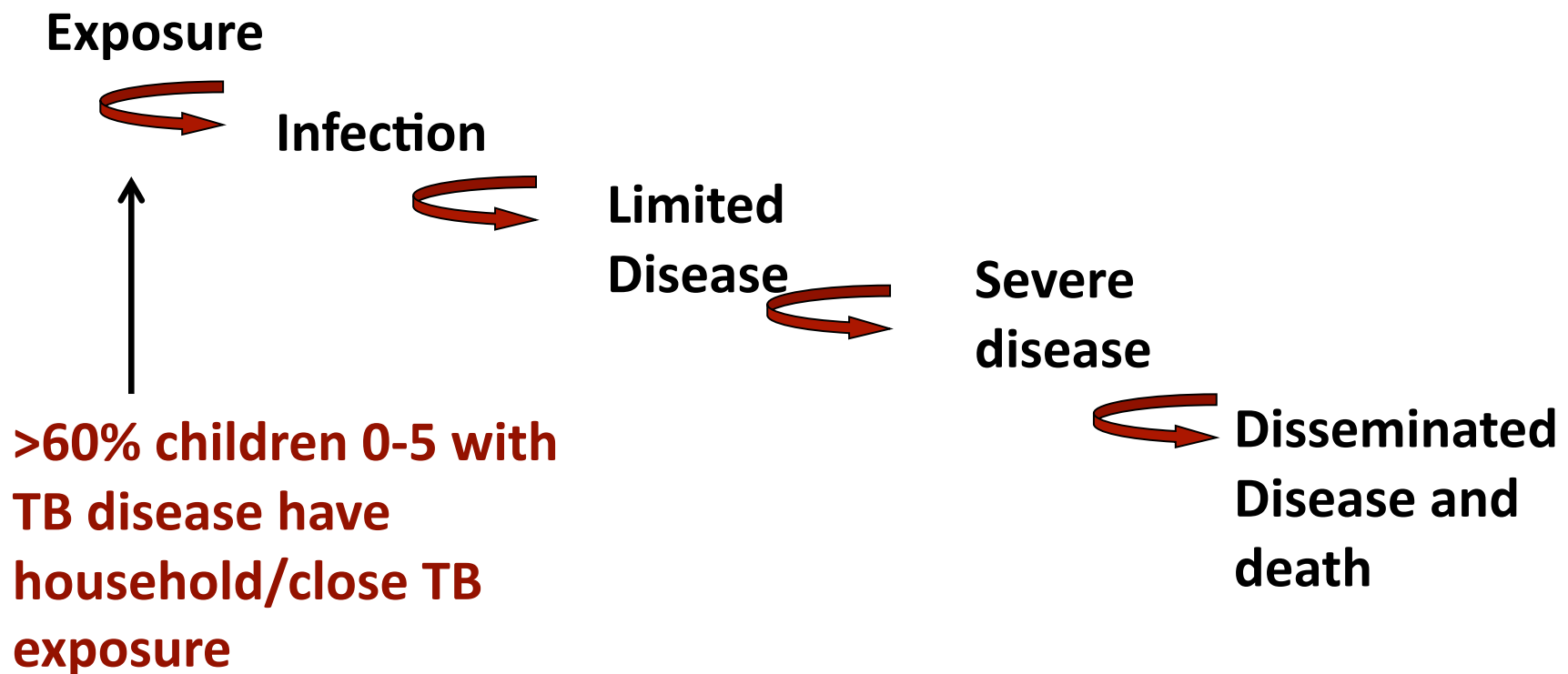
*WHO Global TB report 2011*  
[www.who.int](http://www.who.int)

# RELEVANCE OF PEDIATRIC TB

- Indication of epidemic control (sentinel surveillance): failure of health systems
- Recent transmission: DR, genotypes
- Unique spectrum and severity of disease
- Opportunity: study of distinct phenotypes (TBM)
- Preventable: epidemic control, IPT, vaccines

# TB IN CHILDREN: CONTINUUM OF TB INFECTION AND DISEASE : **WHAT DO WE WANT TO PREVENT, DIAGNOSE AND TREAT?**

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Exposure



Infection



Limited  
Disease



Severe  
disease



Disseminated  
disease and  
death



Age



HIV



Environmental factors, strain, nutrition, genetics



n Schum

# Relevance of TB in Pregnant/ breastfeeding women

- Key entry point into health care
- Data on TB drug PK, safety, maternal/fetal outcomes limited
- Usually excluded from drug trials
  - 13 trials of INH preventive therapy in HIV+
  - all excluded pregnant women at entry
- Women will be developing active TB in IMPAACT trials: PROMISE, P1078



# SCIENTIFIC PRIORITIES

1. Drugs
2. Vaccines
3. Diagnostics
4. Other activities

# PREVIOUS/CURRENT TB ACTIVITIES: IMPAACT

- **Treatment**
  - IMPAACT P1041: Primary IPT in HIV-infected and exposed infants (completed)
  - IMPAACT P1078: Safety of IPT strategies in HIV-infected pregnant women (2012)
- **Vaccines:** Areas 402, 422 (2012)
- **Diagnostics:** IGRA in HIV-infected and exposed infants (sub studies: 1041)
- **In development:**
  - pediatric MDR TB PK/safety study with TMC207
  - IMPAACT co-endorsement of A5279 (INH/rifapentine short course  $\geq 13$  years)

# **FUTURE PLANS**

# NEW TB DRUGS

DRUG/CLASS	ACTG	PAEDIATRIC EVALUATION	WHO?
Quinolones	Yes	Yes (PK, safety – non-TB)	Bayer
Rifapentine	Yes	Yes (PK, safety - IPT )	TBTC
Bedaquiline (TMC 207)	Yes	Yes (planned PK, safety in MDR-TB)	<b>IMPAACT</b> (in development)
Nitroimidazoprams: PA-824, Delamanid (OPC-67683)	Under discussion	No (under discussion)	?
Diamines (SQ-109)	Under discussion	No (under discussion)	<b>IMPAACT</b> <b>-CDA signed</b>
Oxazolidinones (PNU, AZ compounds)	Under discussion	No	?

- 10 other new compounds in development
- No studies including pregnant women

# Diagnostics/therapeutic monitoring approaches

Selected Diagnostic/monitoring Approaches
Selection and Optimization of specimen yield
GeneXpert
Hain strips
Urine antigen
PCR
Host gene expression profiling
PET imaging

Which should be considered for clinical trials in children with TB?



# PATHWAY FOR PEDIATRIC EVALUATION:NOVEL AGENTS

## Priorities:

- PK including dose-finding
- Safety/Toxicity
- Appropriate formulations
- -----
- *Efficacy*: lower priority, feasibility but may be relevant to preventive trials, pediatric disease spectrum (treatment shortening) when considering new drug combinations

# 1. THERAPEUTIC AGENDA:

## *A. DRUG SUSCEPTIBLE TB*

- **Treatment shortening:** TB disease (mild disease)
- **Shorter course INH preventive therapy:**
  - IPT plus X
- **Unknowns**
  - Where do HIV+ children fit in? IPT, Rx
  - New agents also for DS-TB?
- **Pregnant women, neonatal, infant studies**
  - HIV+ and HIV-
  - PK (opportunistic) and safety
  - Breast milk concentrations? Drug interactions?

## ***B. DRUG-RESISTANT TB***

- New therapeutics
  - Overall safety and PK (Sequella, Pfizer, Tibotec, Otsuka, others)
  - Treatment MDR-TB (TMC 207)
- Where do HIV+ populations fit in?
  - *inclusion, special considerations, ART interactions*
- Preventive therapy
  - INH plus XXX or new XXX alone
- Pregnant women, neonates/infants
  - Opportunistic PK and safety
  - HIV+, HIV-

## 2. VACCINES

- Aeras 402 (viral vectored), 422 (recombinant)
- Other candidates
  - Leverage studies to include: BCG prime, BCG boost, recombinant BCG
  - Safety
  - Immunogenicity
    - Difficult issue (correlates of protection?)
- Populations:
  - HIV unexposed
  - HIV exposed
  - HIV+
  - Adolescents (with HVTN)
  - Maternal?

### 3. DIAGNOSTICS

- Diagnostic challenges: disease
  - standard+ novel approaches
- Nested in other studies
  - Opportunity for investigator initiated studies
- Bio-repository linked to spectrum of infection, disease states and relevant clinical outcomes
- Standard approaches
- R01 and other mechanisms
  - Host and organism based approaches
- Diagnostic markers of protection/success
  - or failure
- Collaboration across networks and groups (FIND, TBTC, ACTG, AERAS, TB ALLIANCE, other groups)
- Lab work: protocol-driven, collaborative

## 4. OTHER ACTIVITIES

- Longterm registry of all subjects on TB studies
- Consensus statement on pediatric research pathway for trials of novel TB therapeutics
- SOPs
  - Labs
  - Diagnostics - novel
  - Clinical
- Network interactions: ACTG, HVTN, other
  - Current cross-cutting interactions: ACTG, TBTC, WHO, IUATLD, TDR, industry, foundations
  - Co-endorsement of protocols
- Strong focus on investigator-initiated grant applications

# ACTIVITIES: 2012-2014

1. 3-5 clinical trials
  - 2-3 treatment (CS4101: TMC207, MDR: PK and safety; opportunistic PK study in pregnant/BF women)
  - 1 vaccine (Aeras 402)
  - 2-3 nested diagnostic/biomarker studies
2. Consensus statement on trial implementation strategy of novel TB agents in children
3. SOP: for repository
  1. Diagnostics
  2. Clinical data including epi, end points
  3. Standardization of all implementation aspects
4. Strong industry and other partner engagement

# LAB REQUIREMENTS

- Protocol-driven
- Early consultation
- Lab team: Involvement on protocol teams
- Biorepository focus
- Scope for lab and clinical investigators to propose, implement lab-related capsules
- Close collaboration with IMPAACT Lab committee, HANC, SMILE etc



# Network TB Laboratory EQA (N=25)

	ACTG (21)	IMPAACT (13)	HPTN (8)	MTN (4)	HVTN (3)	Other (7)
ACTG	9	9	8	4	3	5
IMPAACT		2	6	4	2	5
HPTN			0	0	1	3
MTN				0	0	1
HVTN					0	1
OTHER						0

Establishing expanded International TB Laboratory Support

Planned ACTG/IMPAACT RFA to establish an international reference lab and 2-4 regional labs

## **Core labs**

- Extensive use of PK lab resources
- Also non-core regional accredited labs for PK (e.g. ACTG- PK and other); consulting PK and other experts

## **Specialty Labs**

- Xpert/other assays, genotyping, IGRA, novel biomarkers of TB disease, latency and TB treatment response, host genetics, micronutrients etc
- Diagnostics: routine e.g. culture, Xpert etc: on-site (real-time), HANC accreditation process
- Greater flexibility, inviting labs/groups to apply with scientific questions, expertise relevant to specific IMPAACT TB protocols.
- Regional and/or linked to existing IMPAACT sites and domestic
- Additional specialty lab platforms sought as relevant (protocol-driven); representation on protocol teams

# OTHER IMPAACT SUPPORT

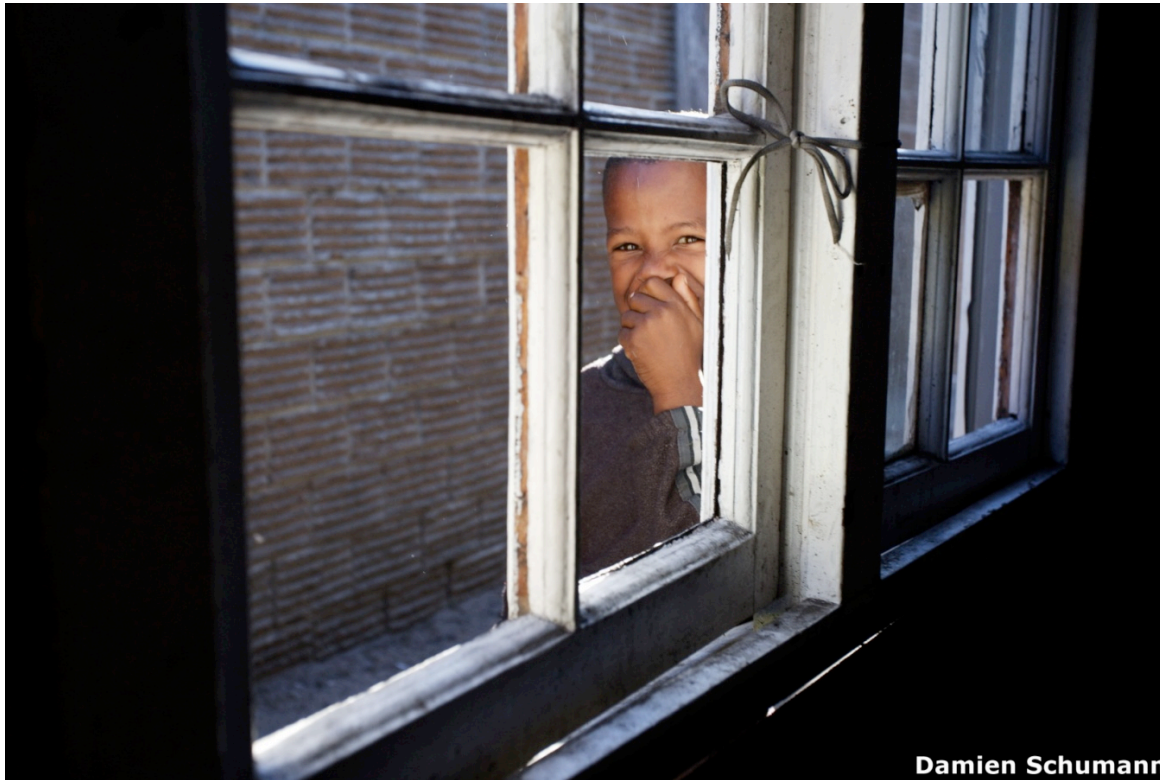
## **Statistical**

- SDAC support - primary and secondary objective analyses
- Additional/ exploratory analysis

## **IMPAACT Operations Center**

- Scientific Committee Coordinator
- Clinical Manager

# THANK YOU



***" A generation of children free of tuberculosis"***