



TB CHILDREN: A GLOBAL CRISIS AND A SOUTH AFRICAN PERSPECTIVE

23 March 2011

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OVERVIEW

1. Global burden
2. Diagnosis
3. Prevention through IPT
4. Integration essential
5. Treatment gaps
6. Vaccination
7. Call for action

WHO ESTIMATED TB CASES BY AGE, 2006

| Country | Total Cases | Cases in Children < 15 | % in Children |
|---------------------|------------------|------------------------|---------------|
| Myanmar | 78,489 | 8,007 | 10.2 |
| Nigeria | 261,404 | 32,310 | 12.4 |
| Pakistan | 244,736 | 61,905 | 25.3 |
| The Philippines | 230,217 | 12,167 | 5.3 |
| Russian Fed. | 183,373 | 7,778 | 4.2 |
| South Africa | 220,486 | 35,449 | 16.1 |
| Thailand | 85,928 | 2,317 | 2.7 |
| Uganda | 75,250 | 12,099 | 16.1 |
| Tanzania | 117,489 | 18,890 | 16.1 |
| Viet Nam | 143,023 | 7,559 | 5.3 |
| Zimbabwe | 76,296 | 12,267 | 16.1 |
| Total | 6,678,188 | 630,722 | 9.4 |

1 million paediatric TB cases?

Paediatric data, surveillance, reporting limited and neglected

1. TB IN CHILDREN IS A GLOBAL PROBLEM

- Indication of recent transmission in the household and larger community
- Indication of failure of TB control programs

- South Africa: 4th highest number all TB cases (454 000 new)
- Prevalence 998 per 100 000; 44% HIV-infected (2009)
- Childhood TB: 620/100 000 (2009)



CHILDHOOD TB IN THE EU

- A total of 39 695 childhood TB cases were notified between 2000 and 2009 by 27 EU-Member States and three EEA countries
- Transmission mostly **within** the EU

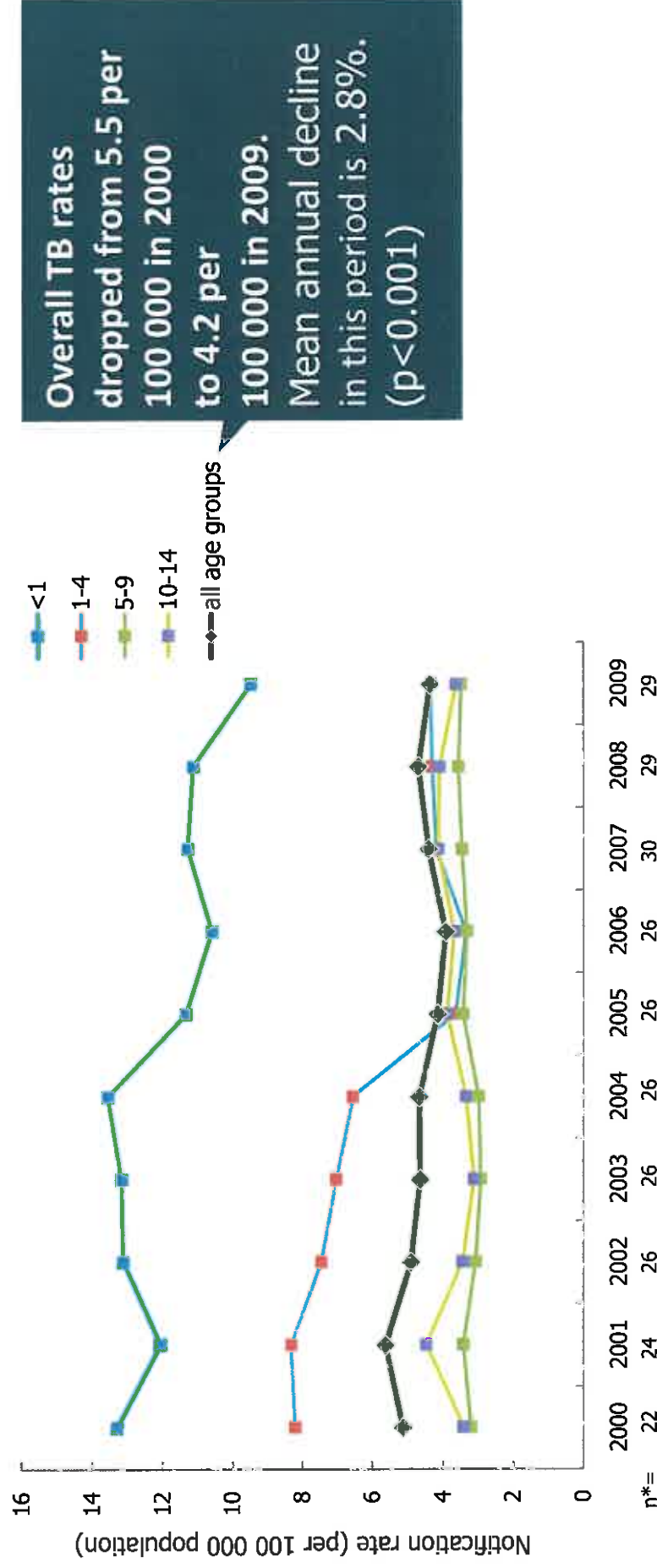


Figure: Age-specific notification rates of childhood TB in EU

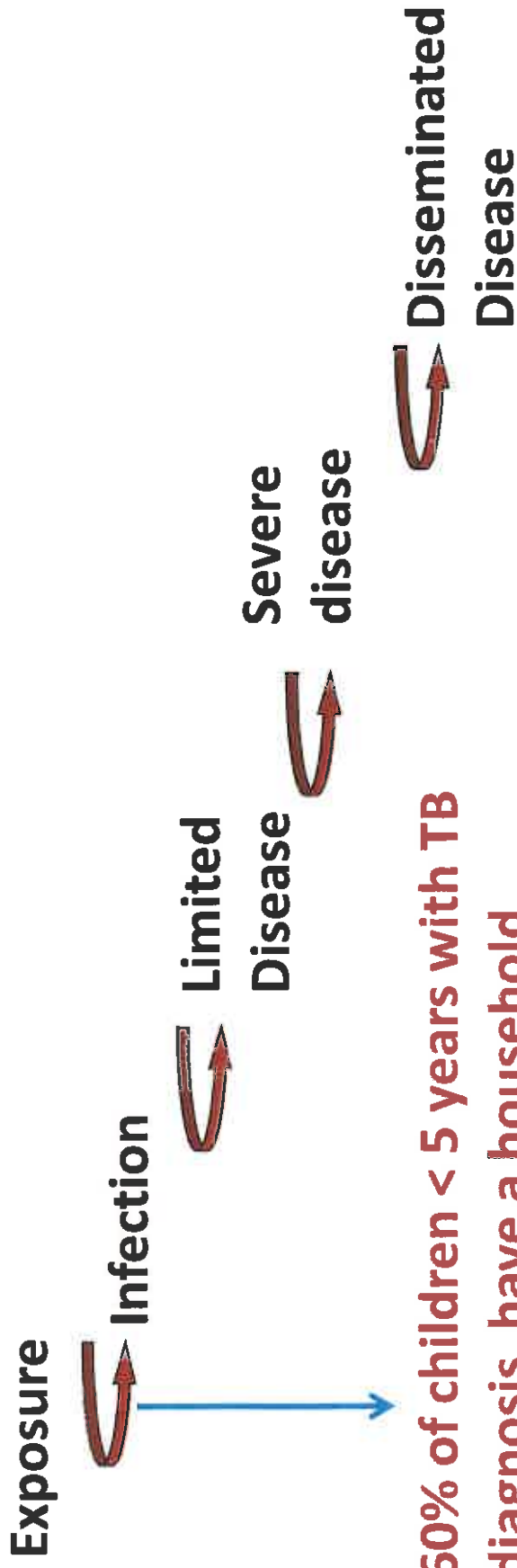
http://ecdc.europa.eu/en/healthtopics/spotlight/tuberculosis_2011/Pages/index.aspx

WHY ARE CHILDREN UNIQUELY VULNERABLE?

RISK OF DISEASE AFTER EXPOSURE

- **Young age**
 - 43% of **infants** (children < 1year)
 - 25% of children aged one to five years
 - 15% of **adolescents**
- **Recent infection (1-2 years): children with close contact**
- **HIV**
- **Malnutrition**
- **Environment**

CONTINUUM OF TB INFECTION AND DISEASE STATES IN CHILDREN



60% of children < 5 years with TB diagnosis have a household contact in high-burden settings
MISSED OPPURTUNITIES: IPT



Exposure



Infection

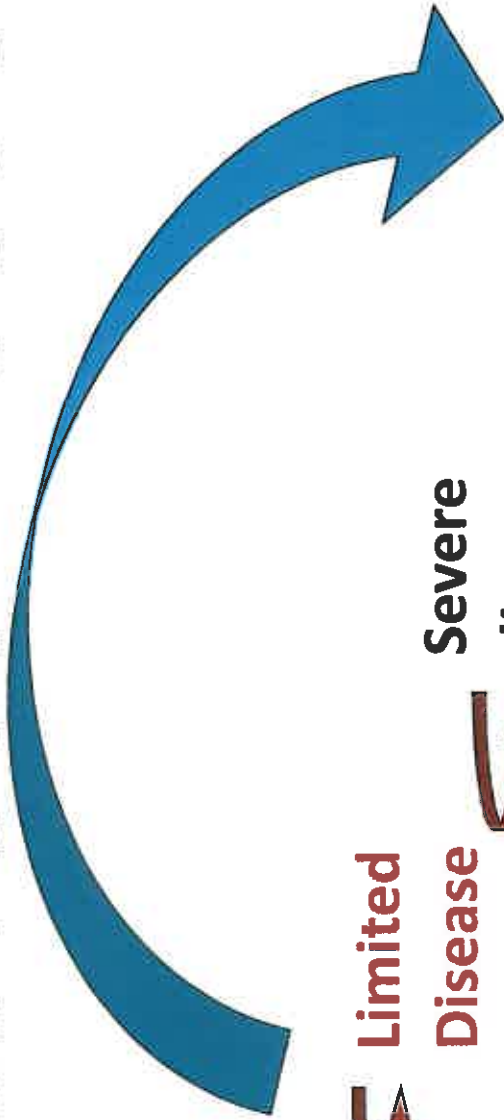


**Limited
Disease**

**Severe
disease**



**Disseminated
Disease**



2. DIAGNOSIS: CHALLENGING

TB DISEASE SPECTRUM AND CULTURE YIELD

| Disease manifestation | Total (%) N = 439 | Bacteriologic yield |
|--------------------------|----------------------|---------------------|
| Not TB | 60 (13.7) | |
| Intra-thoracic TB | 307 (69.9) | 120/195 (61.5) |
| Uncomplicated LN | 147 (47.9) | 22/64 (34.4) |
| Complicated LN | 106 (34.5) | 59/80 (73.5) |
| Other | 54 (17.5) | 39/51 (76.5) |
| Extra-thoracic TB | 72 (16.4) | 31/46 (67.4) |
| Cervical lymphadenitis | 35 (48.6) | 27/27 (100) |
| TBM | 14 (19.4) | 1/10 (10.0) |
| Other | 23 (31.9) | 5/9 (55.6) |
| Intra+Extra | 25 (5.7) | 12/13 (92.3) |

The NEW ENGLAND JOURNAL of MEDICINE

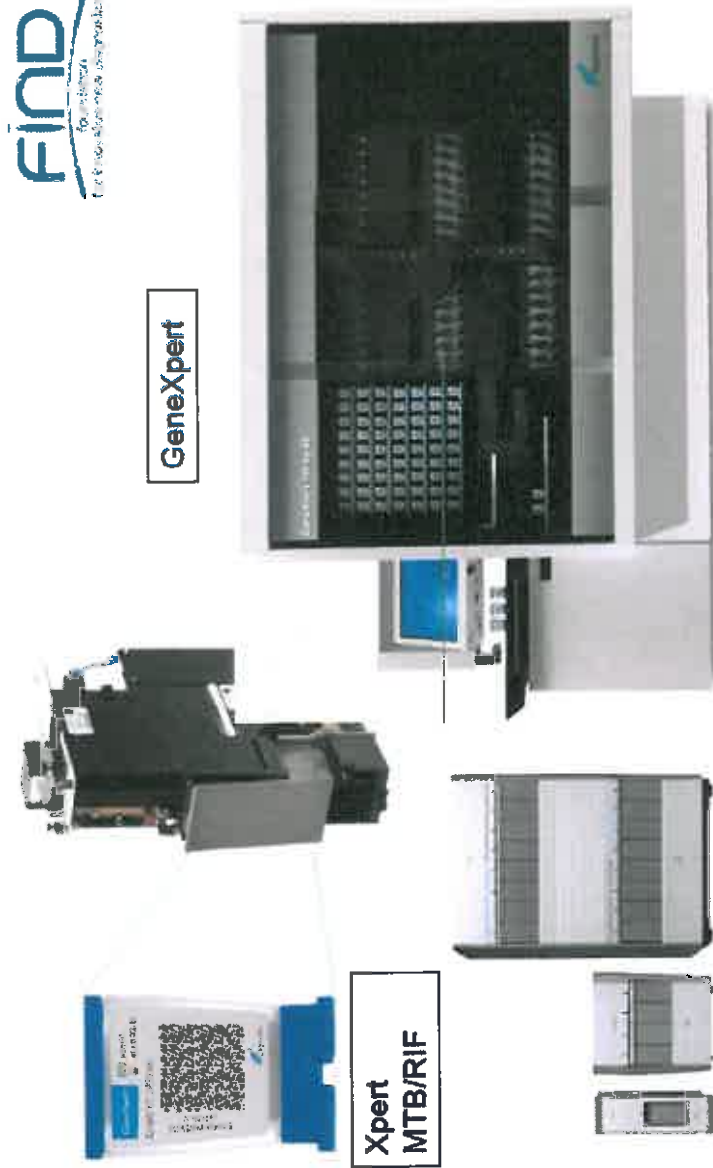
ESTABLISHED IN 1812

SEPTEMBER 9, 2010

VOL. 363 NO. 11

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillmann, Ph.D., Mark P. Nicol, Ph.D.,
Shubhada Shenai, Ph.D., Fiorella Knapp, M.D., Jenny Allen, B.Tech., Basim Tahirli, M.D., Robert Blackmore, B.S.,
Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D.,
David H. Persing, M.D., Ph.D., Sabine Ruesch-Geddes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D.,
David Alland, M.D., and Mark D. Perkins, M.D.



5

20

80

Samples per shift

500-1000

Table 1. Comparison of Xpert® MTB/RIF characteristics with the proposed minimum set of specifications for point-of-care diagnostic tests for TB.

| Test specification | Minimum required value | Xpert MTB/RIF specifications | Comparison with minimum requirement |
|---|---|---|-------------------------------------|
| Medical decision | Treatment initiation | Treatment initiation | Exceeded |
| Sensitivity for smear-positive culture-positive PTB in adults | ≥95% | 99.8% (95% CI: 99.0–100; three Xpert MTB/RIF assays compared with culture ¹) 98.2% (95% CI: 96.8–99.0; one Xpert MTB/RIF assay compared with culture ²) | Satisfied |
| Sensitivity for smear-negative culture-positive PTB in adults | 60–80% | 90.2% (95% CI: 84.9–93.8; three Xpert MTB/RIF assays compared with culture ¹) 72.5% (95% CI: 42.4–79.9; one Xpert MTB/RIF assay compared with culture ²) | Satisfied |
| Specificity in adults without TB | ≥95% | 98.1% (95% CI: 95.6–98.9; three Xpert MTB/RIF assays compared with culture ¹) 99.2% (95% CI: 98.1–99.6; one Xpert MTB/RIF assay compared with culture ²) | Satisfied |
| Sensitivity for all types of TB in children | 80% compared with culture 50% for probable TB | No data available | No data |
| Specificity in children | 95% compared with culture 90% for probable TB | No data available | No data |
| Time to results | ≤3 hours | 2 h | Exceeded |
| Throughput | 20 tests per day by one laboratory staff member | Total hands-on time of 2 min Total daily throughput depends on the size of the instrument | Satisfied |
| Specimen type | Adults: urine, oral, breath, venous blood and sputum Children: urine, oral and capillary blood | Sputum May work with other samples except for venous blood | Satisfied |

For reprint orders, please contact reprints@expert-reviews.com



Xpert® MTB/RIF for point-of-care diagnosis of TB in high-HIV burden, resource-limited countries: hype or hope?

Expert Rev. Infect. Dis. 2017; 9(1): 95-104 (2017)



Working Group on New Diagnostics:

Child TB Subgroup



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- Leadership

New Diagnostics Working Group Childhood TB Subgroup

WELCOME



The mission of the New Diagnostics: Child TB Subgroup

- To ensure that every child has access to effective diagnosis for TB
- To develop and implement new diagnostic tools and strategies to stop TB in children

Launch in Cancun 2009: During the annual Union meeting in Cancun during December 2009, the NDWG Childhood TB Subgroup will be officially launched during the NDWG session. Download the flyer below for more information.

Attachments:

 [NDWG Annual Meeting 2009](#) 582 Kb

3. PREVENTION THROUGH IPT IS CRITICAL BUT NEGLECTED

ALGORITHM FOR TB SCREENING IN CHILDREN LIVING WITH HIV WHO ARE MORE THAN 1 YEAR OLD

Child over 12 months of age and living with HIV*

Screen for TB with any one of the following:

- Poor weight gain**
- Fever
- Current cough
- Contact with a TB case

No

Yes

Assess for contraindications to IPT***

No

Yes

Give IPT

Defer IPT

Investigate for TB and other diseases****

Other diagnosis

Not TB

TB

Appropriate treatment and consider IPT

Follow up and consider IPT

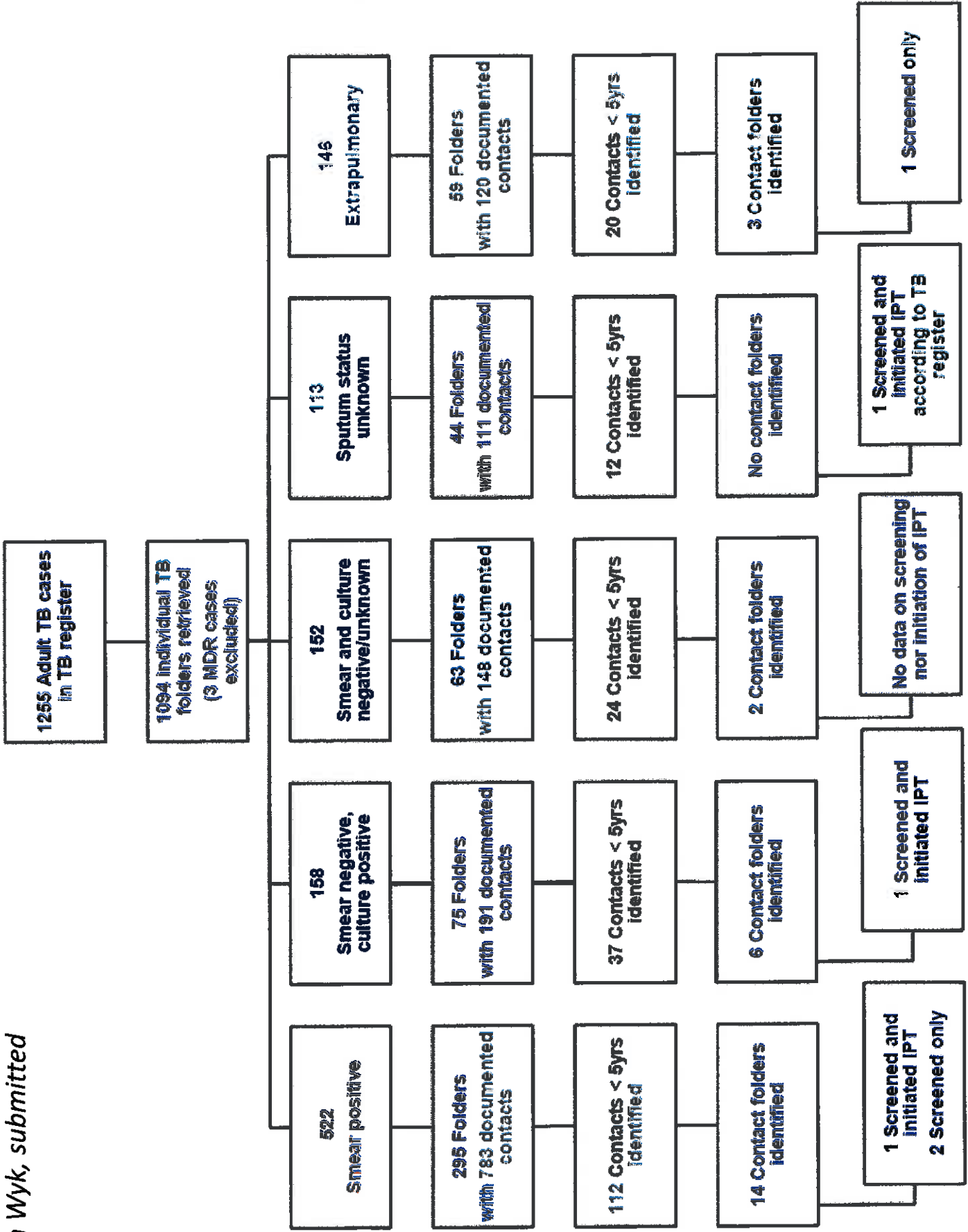
Treat for TB

Screen for TB regularly

WHO, 2010

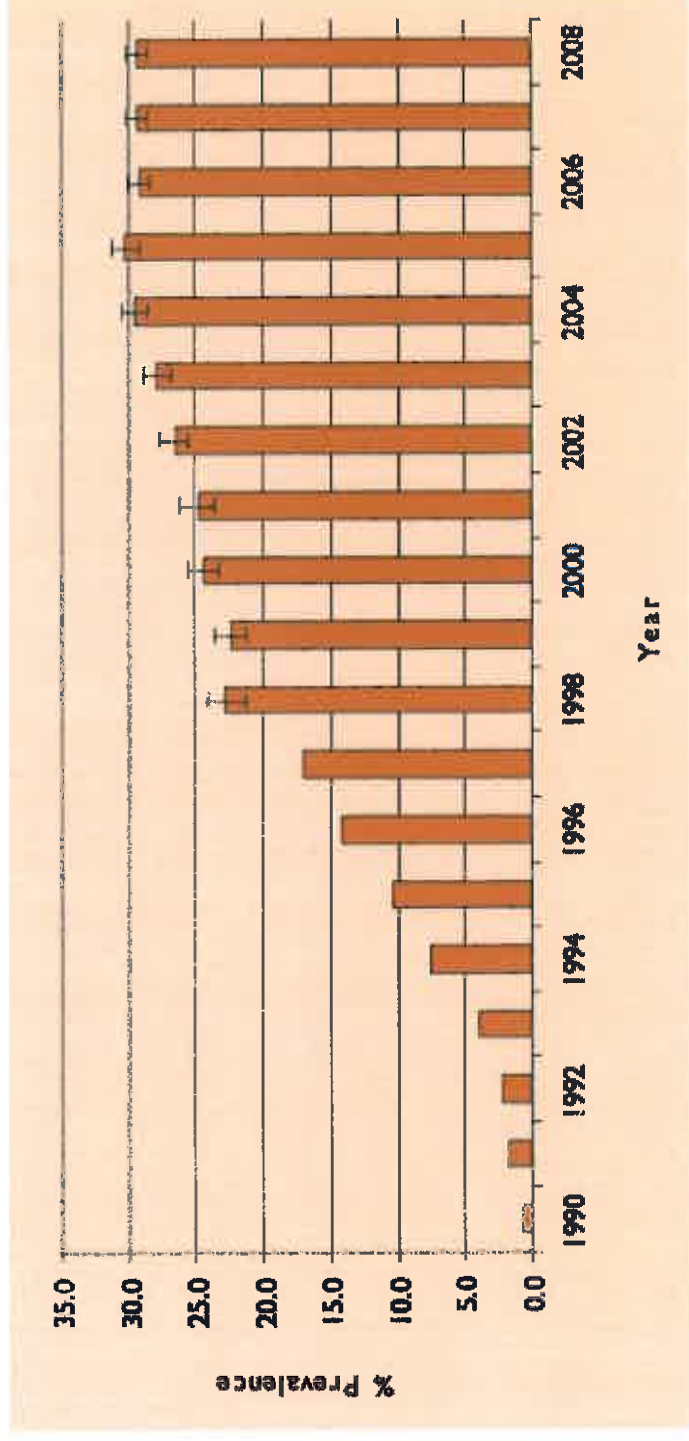
TB IS A FAMILY DISEASE

- **Contact tracing and IPT neglected in children**
- **Lack of reporting and recording systems**
- **IPT: Effective, safe and cost-effective**
- **Policy vs. implementation gap and infidelity**



4. NEED FOR INTEGRATED MATERNAL CHILD APPROACHES

HIV prevalence in women attending public clinics, South Africa



2008 National HIV and Syphilis seroprevalence survey, South Africa

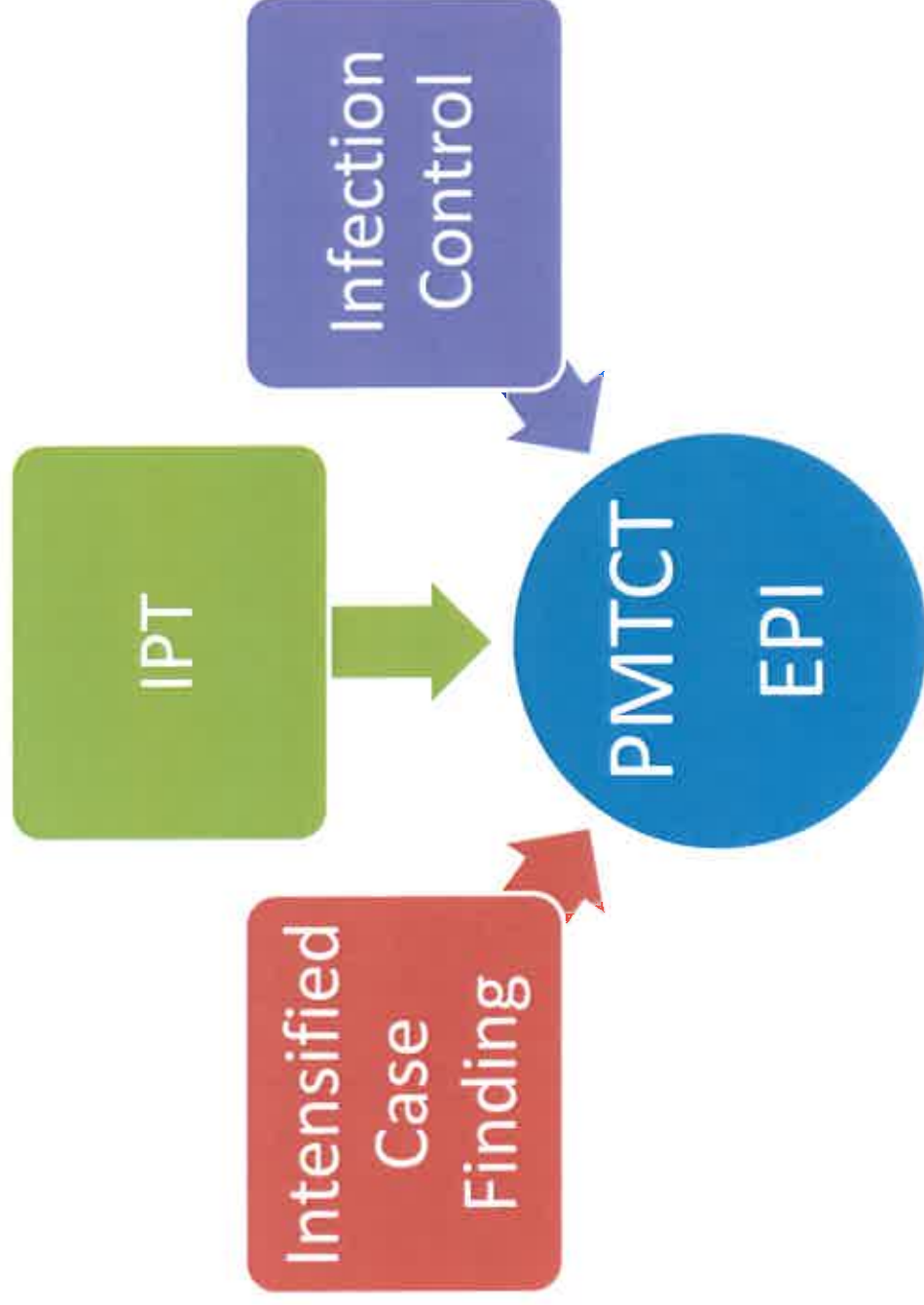
Vast majority of HIV-exposed infants escape infection

TB exposure screening for IMPAACT P1041 at 3 -4 months of age: Cape Town

| | Pre-Screened | Screened | Total |
|------------|--------------|-----------|-----------|
| | 111 | 658 | 769 |
| TB contact | 49 (44.1%) | 25 (3.8%) | 74 (9.6%) |

HIV in the household is proxy for TB exposure

The 4th I: Integrating Maternal and Infant TB/HIV Prevention and Control



5. DRUGS: WHAT IS DONE TO DEVELOP NEW TB DRUGS AND INVOLVE CHILDREN IN RESEARCH?

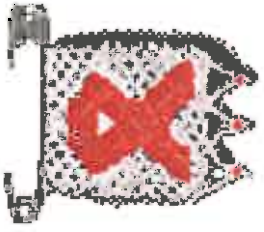


RAPID ADVICE

Treatment of tuberculosis in children



WHO/HTM/TB/2010.13



POLICY VS. PRACTICE?

- Training, technical assistance to NTP implement guidance for children
- Limited paediatric TB focus: Global fund and other sources
- **Limited child-friendly formulations and FDCs (first-line) for new dosing recommendations; none for 2nd line drugs**
- **Limited research**

PRIORITIES FOR DRUGRESEARCH: WHO RESEARCH ROADMAP (2011)

Key priority research areas for research and development of drugs:

- Development of **new TB drugs** (identification of optimal dosage, safety, and efficacy) and their interaction with other (TB and non-TB) drugs
- Identification of the optimal treatment regimens for all populations (i.e. patients with drug-sensitive TB, drug-resistant TB, TB/HIV co-infection **and children**).

CHALLENGES TO ACCESS TRIALS

1. **Diagnostic challenges** - case definitions: paucibacillary, spectrum
2. **Treatment outcome definitions:** markers of treatment response required (efficacy)
3. **Practical challenges:** adequate samples, PK, consent, experience, regulatory
4. **Limited advocacy:** mobilization of civil society, NTP, researchers, donors
5. **Perceived market share and funding?**



FRAMEWORK FOR PAEDIATRIC TB DRUG RESEARCH

- High-quality research, rigorous methodology
- Representative target study populations
- Age, HIV
- Adequate research infrastructure requirements needed
- Consideration of ethics of involving children
- Models of community involvement
- Ability to disseminate rapidly into policy and practice
- Partnerships: funders, WHO, industry, multicentre, networks (TB and HIV)

DO WE NEED EFFICACY TRIALS?

- Preventive therapy – short course: YES
- Shortened duration limited TB disease: YES
- Shorter duration: MDR disease: YES
- Novel agents, regimens: **Extrapolate adults; appropriate paediatric data needed**
- Priorities: PK: dosing, safety, tolerability, limited efficacy – reduce barriers

PK STUDIES AS PRIORITY

- First and secondline drugs
- Novel agents (N=6; PIPs?) – required: EMA, FDA
- Strategy: Age de-escalation, HIV
- Age groups (0-2) , HIV, target populations, geographically representative
- **TMC207**: submitted a PIP to the EMA Pediatric Development Committee : approved
- First TB drug to be developed for children “up front”: to conventional approach of extrapolating adult data to children
- Paediatric formulations



TBTC Paediatric Interest Group (PIG)



TB Trials Consortium



2010-2020

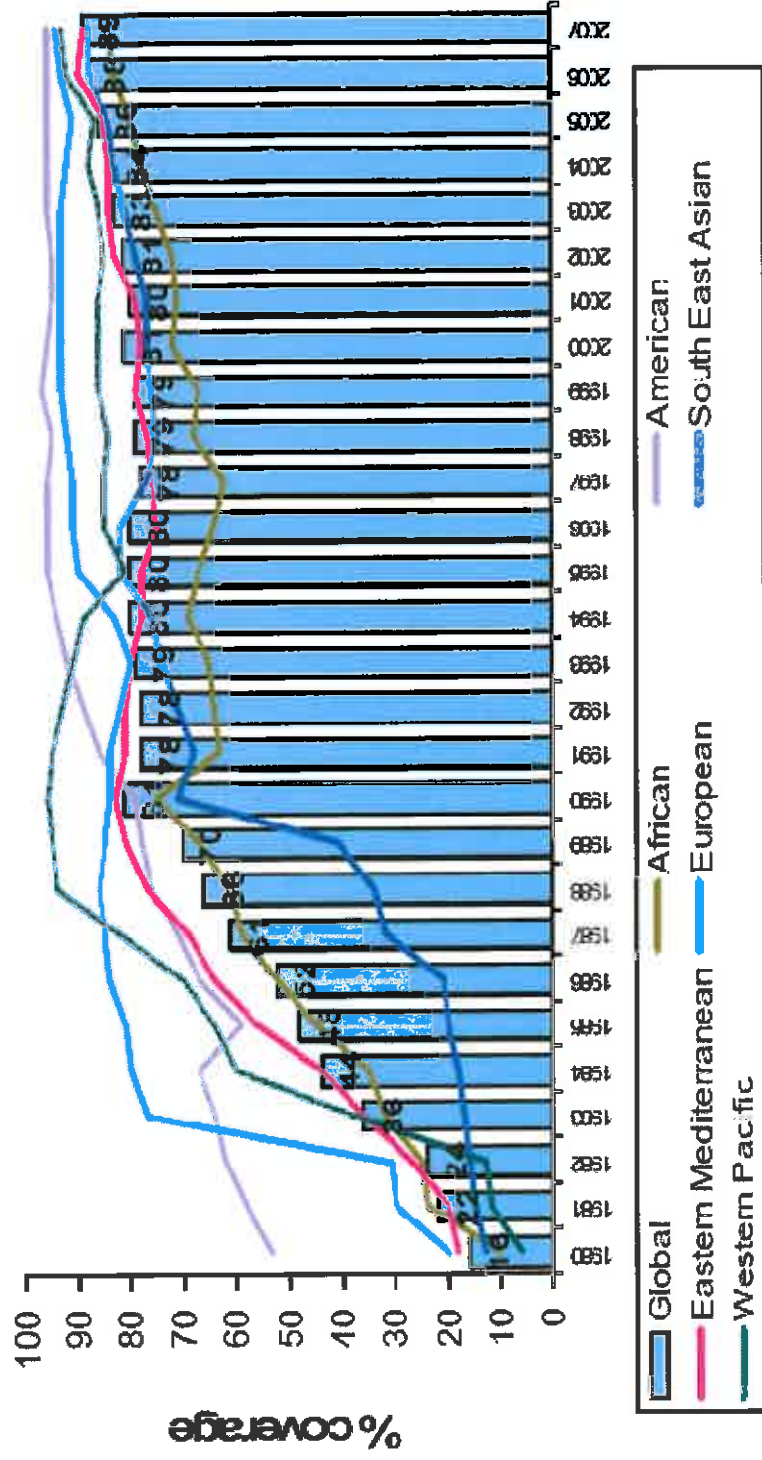
6. VACCINATION

BCG efficacy: disseminated TB

| | Publication date | Efficacy (%; 95% CI) | Publication date | Efficacy (%; 95% CI) | |
|-------------------------------|------------------|----------------------|-------------------------------|----------------------|-----------------------|
| Tuberculous meningitis | | | | | |
| Buenos Aires, Argentina | 1988 | 98% (70 to 100) | Buenos Aires, Argentina | 1988 | 78% (28 to 93) |
| Bahia, Brazil | 1991 | 91% (78 to 97) | Yangon, Burma | 1987 | 80% (45 to 92) |
| São Paulo, Brazil | 1990/93 | 87% (72 to 94) | Papua New Guinea* | 1980 | 70% (0 to 91) |
| São Paulo, Brazil | 1990/93 | 92% (65 to 98) | Djakarta, Indonesia | 1983 | 75% (5 to 94) |
| Belo Horizonte, Brazil | 1988 | 81% (47 to 93) | | | |
| Belo Horizonte, Brazil | 1988 | 65% (17 to 86) | | | |
| Yangon, Burma | 1987 | 52% (13 to 73) | | | |
| Nagpur, India | 1996 | 87% (70 to 94) | | | |
| Chennai, India | 1996 | 77% (63 to 86) | | | |
| Delhi, India | 1996 | 64% (30 to 81) | | | |
| Delhi, India | 1989 | 84% (69 to 97) | | | |
| Lucknow, India | 1999 | 47% (-6 to 74) | | | |
| Papua New Guinea* | 1980 | 58% (-36 to 87) | | | |
| Delhi, India | 1993 | 56% (-49 to 87) | | | |
| | | | Summary Efficacy | | |
| | | | Miliary Tuberculosis | | 77% (58 to 87) |
| | | | Summary Efficacy | | |
| | | | Tuberculous Meningitis | | 73% (67 to 79) |

Trunz, Fine, Dye. Lancet 2006

Global BCG coverage at birth: 89% in 2007



BCG SAFETY?



- Incidence of disseminated BCG incidence in HIV-infected infants: 992/100 000 (95% CI: 567-1495 per 100 000)
- Mortality >80%
- No HAART, low CD4 count, median age 6 months, mortality>75%

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

25 MAY 2007, 82nd YEAR / 25 MAI 2007, 82^e ANNÉE
No. 21, 2007, 82, 181–196
<http://www.who.int/wer>

Vaccination of infants with known HIV infection
fully contraindicated (2007)

BCG IRIS

- 5-10% incidence
- Not fatal



WHO EPI BCG review, 2006, Nuttall et al.
Int J Infect Dis. 2008, Smith, AIDS 2009

- HAART makes BCG safer
- BCG IRIS in infants with baseline CD4 $\geq 25\%$: Early vs. Deferred HAART (CHER study)

Table 4: BCG-IRIS in infants with baseline CD4 $\geq 25\%$ Early vs Deferred ART

| | Deferred Arm (n=83) | Early Treatment Arm (n=250) | P-value / Odds Ratio |
|-------------------|----------------------------------|---------------------------------|--------------------------------|
| Cases of IRIS(CI) | 13/83: 15.7% (8.6% - 25.3%) | 13/250: 5.20% (2.8% - 8.7%) | P=0.004 OR= 3.4 (1.5 - 7.7) |
| Incidence | 27.9 Events per 100 person years | 6.4 Events per 100 person years | |



- Prevention of maternal and child infections and early HAART will make BCG safer
- Newer effective and safer TB vaccines are needed in all children
- 14 candidates: 2 in trials in infants

Where are trials of new TB vaccines being conducted?

Novel candidates are being developed in

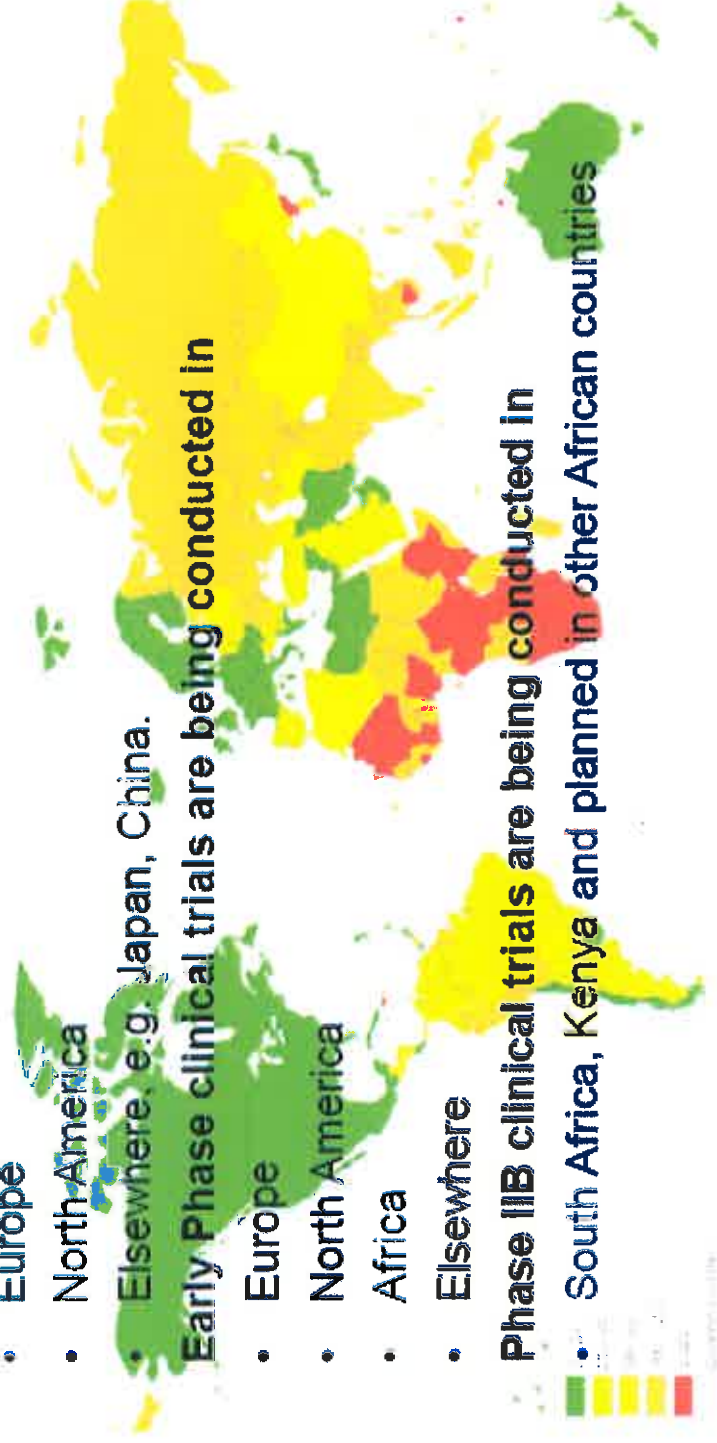
- Europe
- North America
- Elsewhere, e.g. Japan, China.

Early Phase clinical trials are being conducted in

- Europe
- North America
- Africa
- Elsewhere

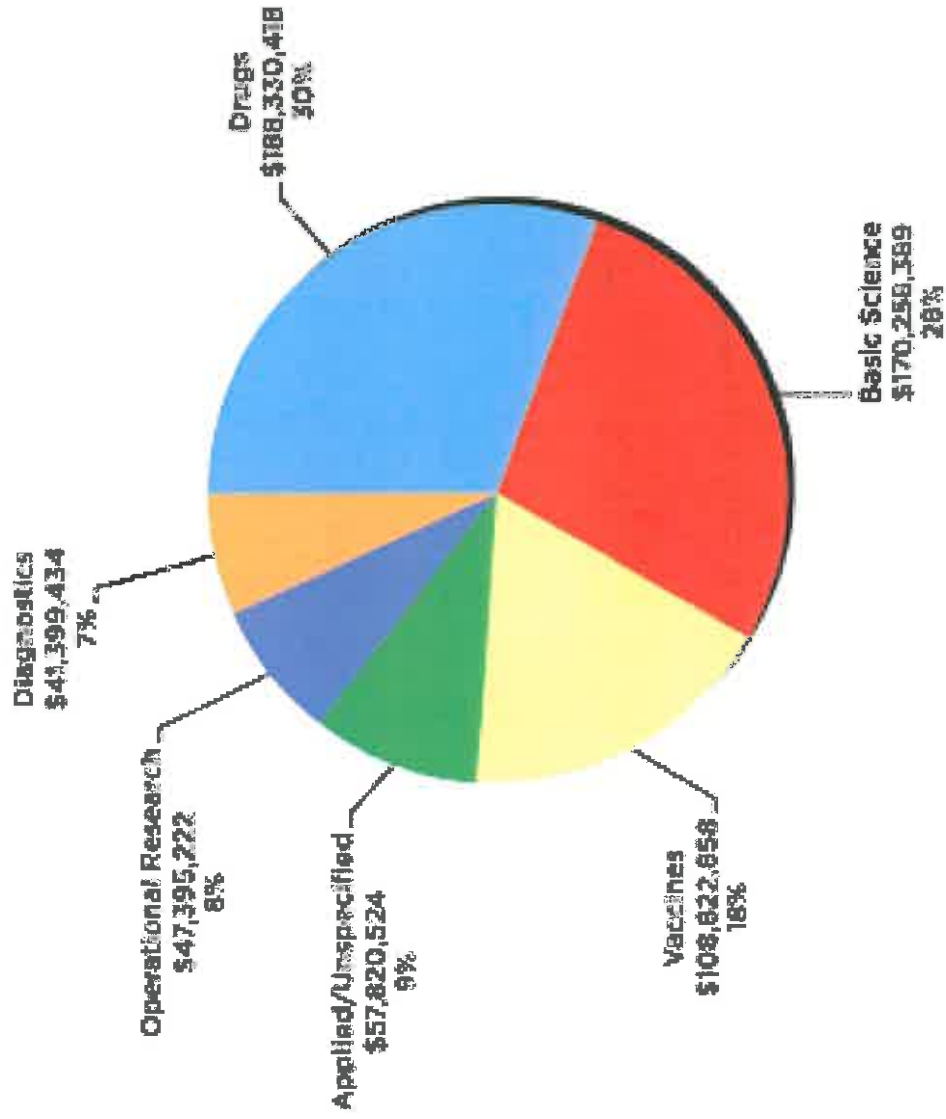
Phase IIB clinical trials are being conducted in

- South Africa, Kenya and planned in other African countries



TB R&D Investment by Research Category: 2009

\$614,026,843



STATEMENT BY THE PRESIDENT ON GLOBAL HEALTH INITIATIVE

*“ As a U.S. Senator, I joined a bipartisan majority in supporting the Bush Administration’s effective President’s Emergency Plan for AIDS Relief (PEPFAR). That plan has provided lifesaving medicines and prevention efforts to millions of people living in some of the world’s most extreme conditions.....But I also recognize that we will not be successful in our efforts to **end deaths from AIDS, malaria, and tuberculosis unless we do more to improve health systems around the world, focus our efforts on child and maternal health, and ensure that best practices drive the funding for these programs”***

World Tuberculosis Day 2011

Tuberculosis Elimination: Together We Can!

A Community Statement



In observance of March 24, 2011, as World Tuberculosis Day, and in recognition of the tremendous opportunities and challenges faced in eliminating Tuberculosis (TB) in the U.S. and around the world, we, the undersigned organizations, stand in support of the following statement.



We help the world breathe
PULMONARY • CRITICAL CARE • SLEEP

The Challenge

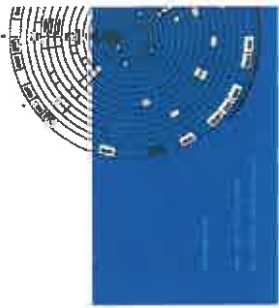
Tuberculosis is a contagious and airborne disease that disproportionately affects young adults in their most productive years. According to the World Health Organization (WHO) one-third of the world's population is thought to be infected with the microbe that causes TB. Worldwide, TB is the third leading cause of death among women of reproductive age, who are more susceptible than men of the same age. TB is the leading cause of death among people living with HIV/AIDS, has been known to cause infertility and contributes to poor reproductive health outcomes. Yet, According to the World Bank and public health experts, TB prevention, treatment and control is among the most cost-effective public health interventions available.



The U.S. is not immune. TB remains a public health problem in the U.S., particularly for border states. California, Texas, Florida and New York all face serious problems with TB and drug resistant TB poses a serious challenge in all states due to extremely high treatment costs.

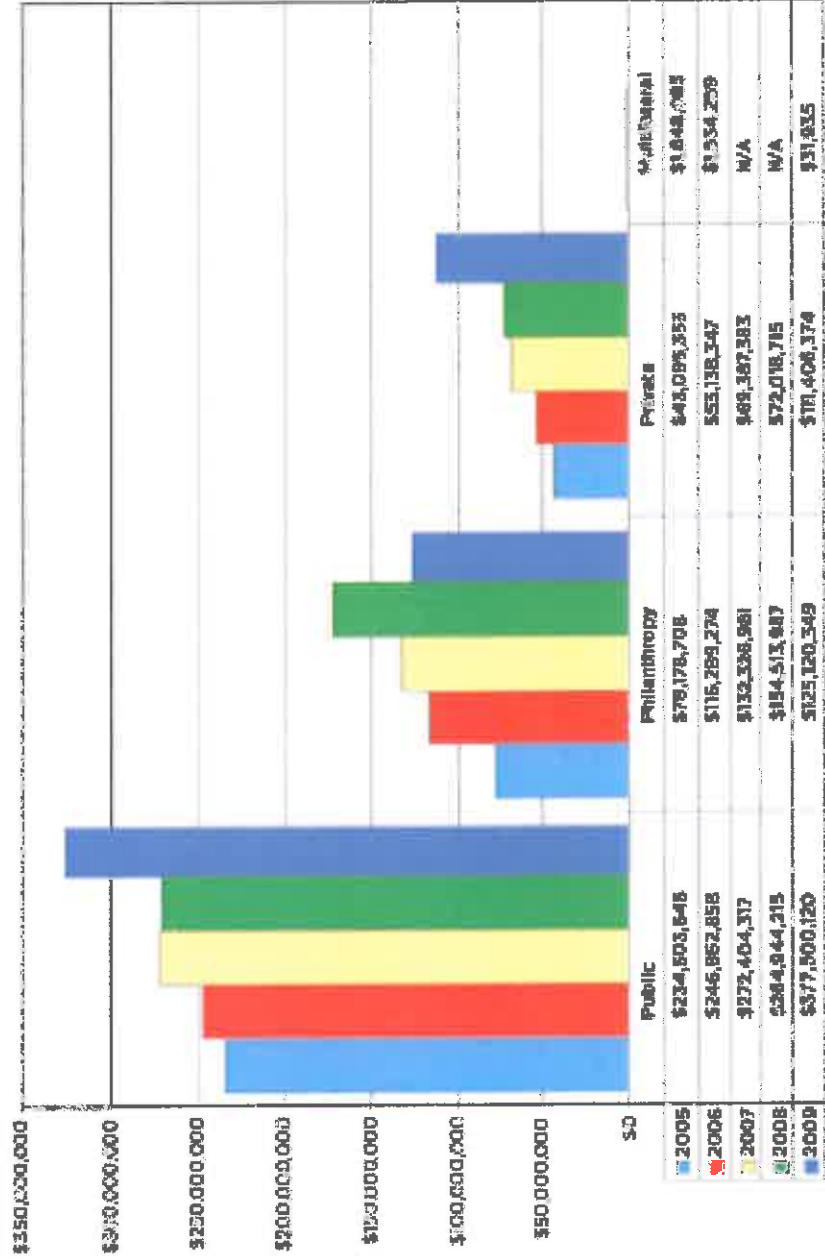


The problem continues to grow. In 2009, there were 9.4 million new TB cases globally -- including 3.3 million new cases among women and 1.1 million new cases among people living with HIV/AIDS. In that same year, 1.7 million people died from TB -- including 600,000 women and 380,000 people living with HIV/AIDS. The number of multidrug-resistant (MDR) and extensively drug-resistant (XDR) forms of TB continue to grow and threaten to undermine TB control efforts in both developed and developing nations.



TAG: trends in funding by donor sector, 2005-2009

Amounts and Proportions of Total TB R&D Funding by Donor Sector: 2005-2009



IS CHILDHOOD TB COMING OF AGE?



Damien Schumann

" A generation free of tuberculosis"

CALL TO ACTION FOR CHILDHOOD TB

All signatories should reply
to childhoodTB@treatmentactiongroup.org

Please submit your signatures by Thursday
March 24th.