THE EPIDEMIOLOGY AND DIAGNOSIS OF CHILDHOOD TUBERCULOSIS

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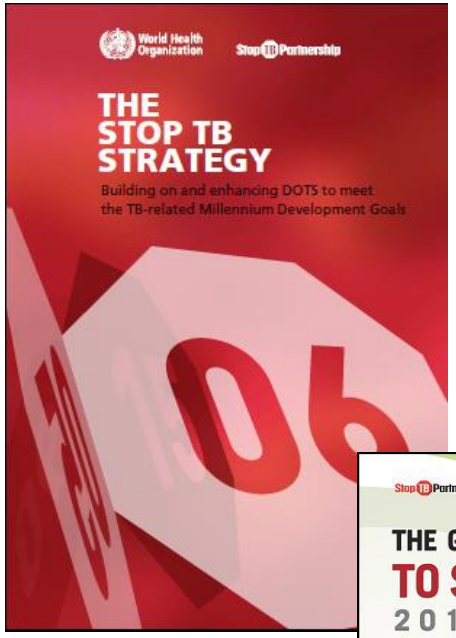
- Disclosure: No potential conflict of interest

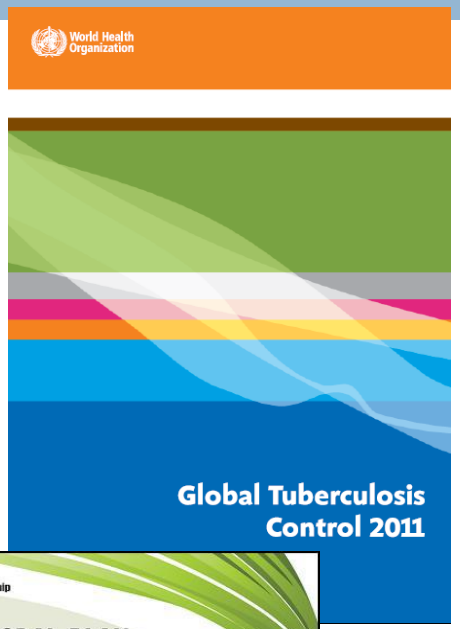
Outline

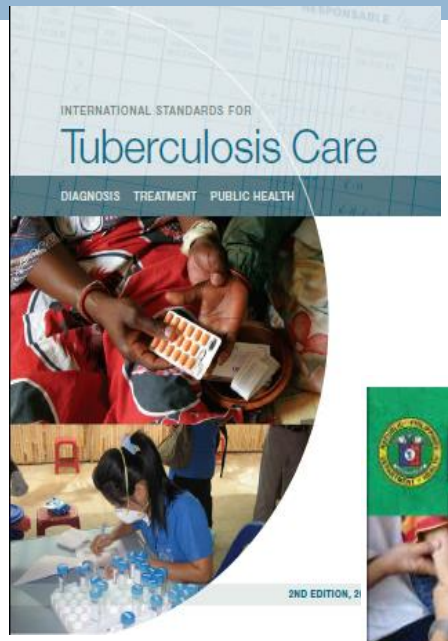
- **TB situation**
  - Targets and goals
  - Global and Philippine situation

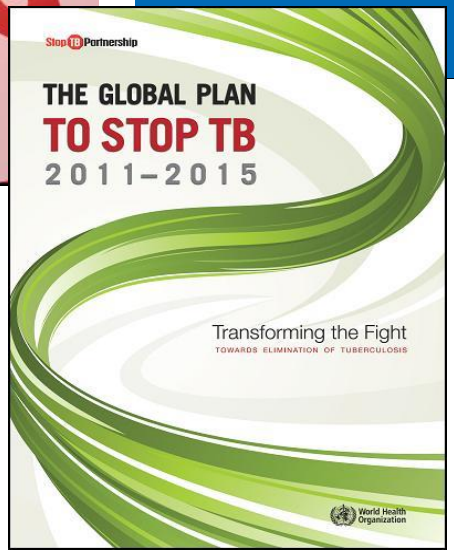
- **Diagnosis**
  - Current approach
  - New tools

References


World Health Organization
Stop TB Partnership
THE STOP TB STRATEGY
Building on and enhancing DOTS to meet the TB-related Millennium Development Goals


World Health Organization
Global Tuberculosis Control 2011


INTERNATIONAL STANDARDS FOR
Tuberculosis Care
DIAGNOSIS TREATMENT PUBLIC HEALTH


Stop TB Partnership
THE GLOBAL PLAN
TO STOP TB
2011–2015
Transforming the Fight
TOWARDS ELIMINATION OF TUBERCULOSIS
World Health Organization


HEALTH SECTOR
REFORM AGENDA
2010-2016
Philippine Plan of Action to Control Tuberculosis
(PhilPACT)
WORLD TB DAY

Global TB Control Targets

- **Millennium Development Goal 6 (Set for 2015):**
- Target 6c: to have halted and begun to reverse the incidence of TB (target 6C)

- **Stop TB Partnership:**
  - 2015: 50% reduction in TB prevalence and deaths from 1990 levels
  - 2050: elimination (<1 case per million population)

How can the 2015 targets be achieved?

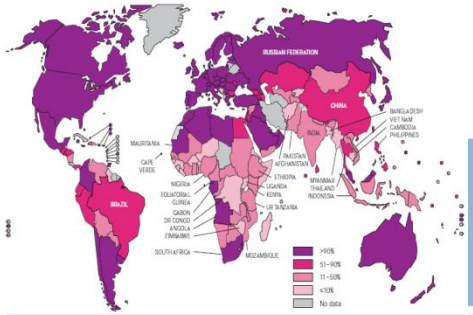
- **The Stop TB Strategy**
  - Pursue high-quality DOTS expansion and enhancement
  - Address TB/HIV, MDR-TB, and the needs of poor and vulnerable population
  - Contribute to HSS based on primary health care
  - Engage all care providers
  - Empower people with TB, and communities through partnership
  - Enable and promote research

Global, Philippine Situation

- Global, Philippine burden and trend

Global Burden of TB, 2010

Global TB Report/WHO/2011



	Estimated number of incident cases	Estimated number of deaths
All forms	8.8 M (8.5 – 9.2 M)	1.1 M* (0.9 – 1.2 M)
HIV-associated	1.1M (1 – 1.2 M)	0.35 M (0.32 – 0.39 M)
MDR-TB	0.650 M	*excluding HIV deaths
Children	0.968 M (11%)	

Estimated TB rates (/ 10^5 pop.), 2010

Global TB Report/WHO/2011

	Mortality	Prevalence	Incidence	HIV-positive incident TB cases
Global	15	178	128	13
HBC	20	231	166	12
WPR	7.5	139	93	2.1
PHL	33 (↑)	502 (↑)	275 (↑)	0.4 (↓)

Estimated rates of TB in children

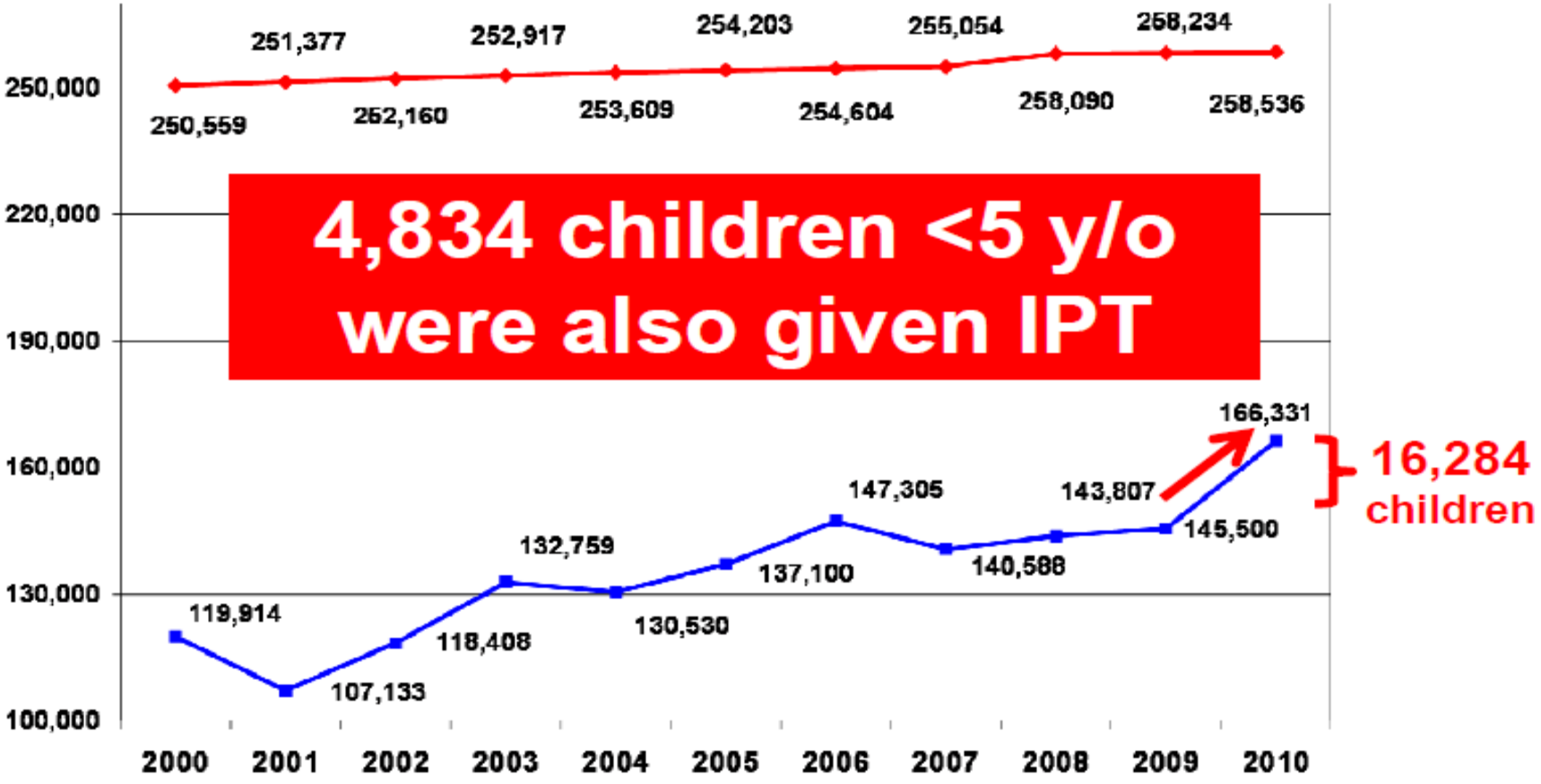
INT J TUBERC LUNG DIS 8(5):636–647. © 2004 IUATLD; Global epidemiology of childhood tuberc
Nelson, C. D. Wells

Table 1 Estimated numbers of new cases, case rates in children, overall case rates (all ages), and the percentage of all TB estimated to occur among children in the 22 high-burden countries

Country	Children aged 0–14 years	% of TB occurring in children	Estimated TB case rates <15 years of age*	Estimated case rate†
Afghanistan	17 540	25.3	189	324
Bangladesh	33 166	10.2	61	236
Brazil	23 520	20.7	47	66
Cambodia	3 966	5.3	70	571
China	86 978	5.3	27	129
Democratic Republic of Congo	24 052	16.1	106	306
Ethiopia	28 675	16.1	95	272
India	185 233	10.2	53	179
Indonesia	15 691	2.7	23	263
Kenya	22 124	16.1	167	450
Mozambique	7 703	16.1	98	268
Myanmar	8 007	10.2	51	165
Nigeria	32 310	12.4	63	228
Pakistan	61 905	25.3	103	172
Philippines	12 167	5.3	43	304
Russian Federation	7 778	4.2	30	126
South Africa	35 449	16.1	237	501
Thailand	2 317	2.7	15	141
Uganda	12 099	16.1	103	320
United Republic of Tanzania	18 890	16.1	118	337
Vietnam	7 559	5.3	29	183
Zimbabwe	12 267	16.1	221	603
Total for the 22 high-burden countries	659 397	9.6		

* Case rates per 100 000 children. United Nations population estimates used for denominator.
† Case rates per 100 000 population.
TB = tuberculosis.

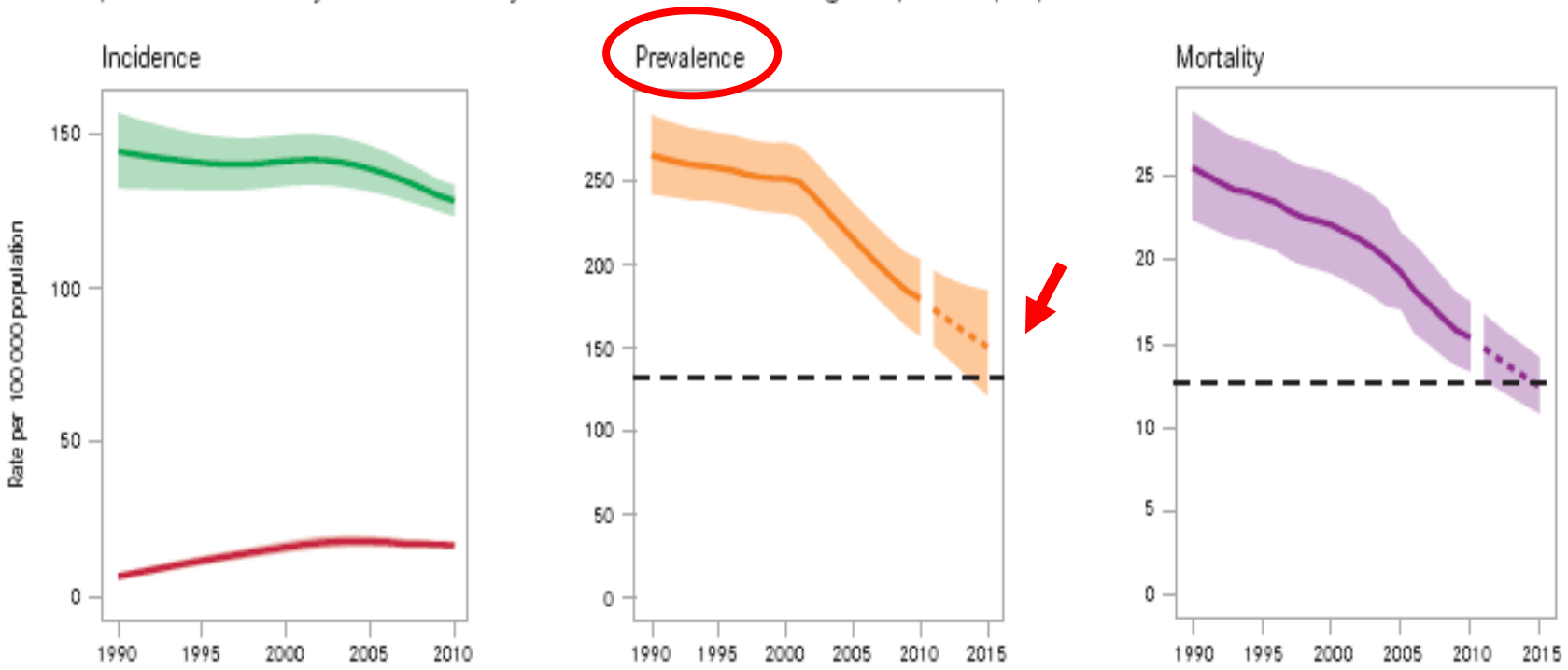
Case detection of all forms of TB (2000 -2010)



Source: NTP-DOH

Global trends

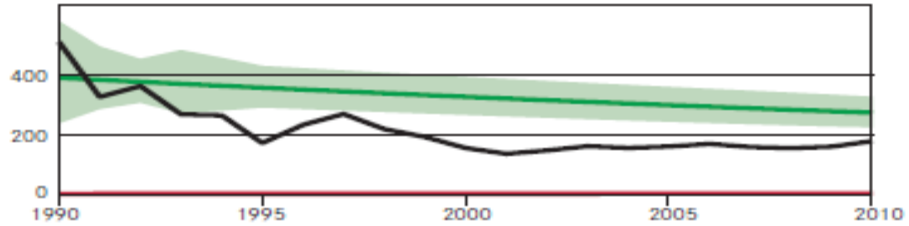
Global trends in estimated rates of TB incidence, prevalence and mortality. Left: Global trends in estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). Centre and right: Trends in estimated TB prevalence and mortality rates 1990–2010 and forecast TB prevalence and mortality rates 2011–2015. The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people.



Philippine trends

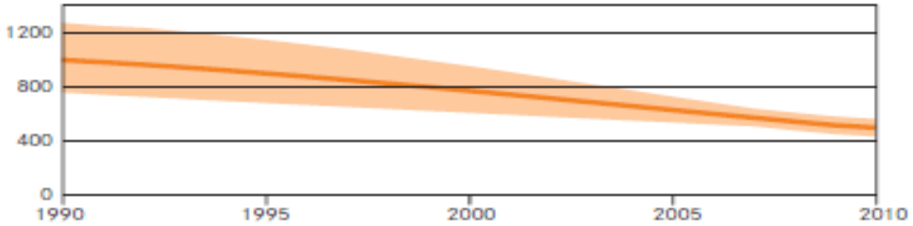
INCIDENCE (HIV+TB red), notifications (black)

(rates per 100 000 population)



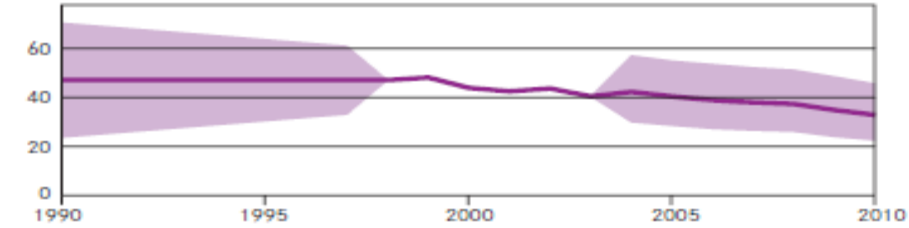
PREVALENCE

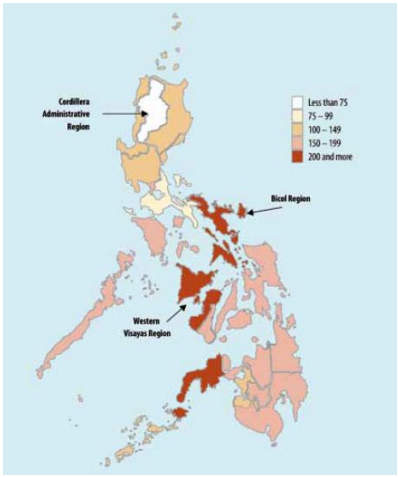
(rate per 100 000 population)



MORTALITY EXCLUDING HIV

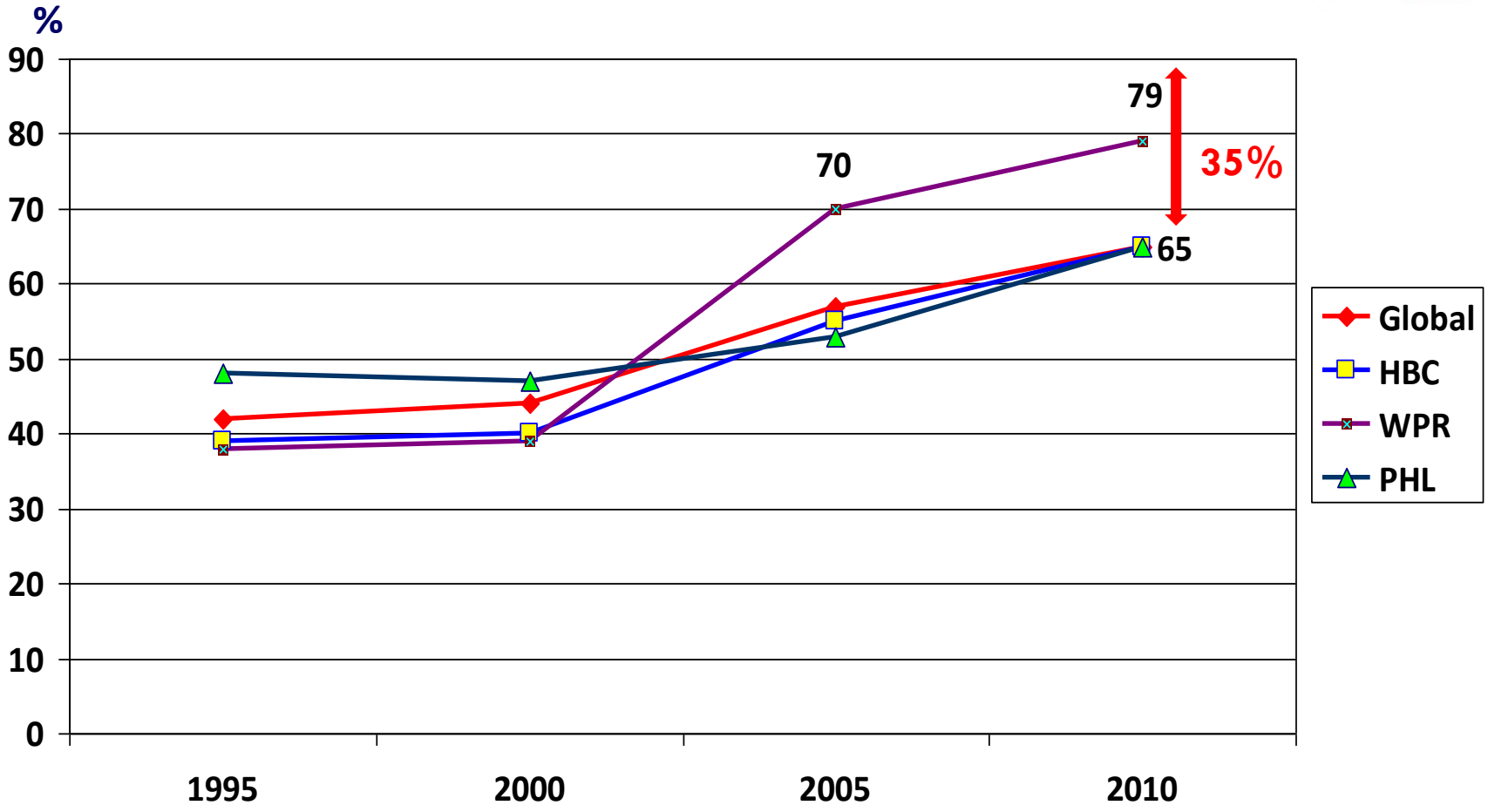
(rate per 100 000 population)





Estimates of the CDR for all forms of TB, 1995-2010

Global TB Report/WHO/2011



Global Situation

- Drug Resistant TB

Estimated proportion of TB cases that have MDR-TB Global TB Report/WHO/2011

	Estimated % of new TB cases with MDR-TB	Confidence interval	Estimated % of retreatment TB cases with MDR-TB	Confidence interval
Global	3.4	1.9-5.0	20	14-25
HBC	3.8	2.0-5.7	21	14-28
WPR	4.9	3.6-6.1	23	20-27
PHL (DRS, 2004)	**4.0**	2.9-5.5	**21**	14-29

No. of cases of MDR-TB estimated, notified & expected to be treated in 2010 (Global TB Report/WHO/2011)

	Estimated cases of MDR-TB **among notified cases of PTB** (A)	Notified cases of MDR-TB (B)	B/A (%)	Cases enrolled on treatment in 2010	Expected number of cases of MDR-TB to be treated	
					2011	2012
Global	290 000	53 108	18	45 553	54 022	64 324
27 HBC	250 000	46 748	19	38 652	44 177	51 992
WPR	77 000	4 222	5.5	2 210	11 285	11 352
PHL	**8 800**	**522**	**5.9**	548	3 500	2 372

Philippines - number of laboratory confirmed MDR/DR-TB cases detected

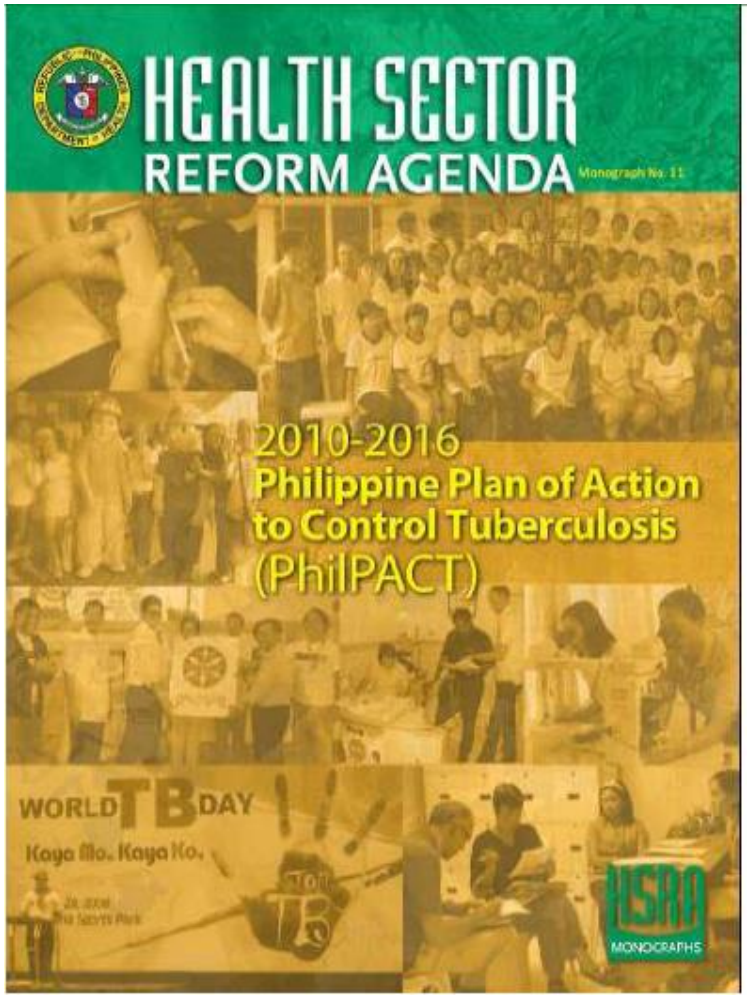
	2009		2010		2011 (Jan-Sept)	
Indicator	**Planned**	**Actual**	**Planned**	**Actual**	**Planned**	**Actual**
Number of laboratory confirmed MDR-TB cases detected	**1535**	**980 (64%)**	**2490**	**527 (21%)**	**3083**	**1529* (50 %)**
% of MDR-TB cases enrolled for treatment among those detected	83%					

•Of the 1529 actual cases detected, 427 patients were detected by GeneXpert beginning 4th quarter of 2011

Drug susceptibility test result of isolates from 91 pediatric cases <19 years old (2009 – 2011)

	Patients with DST results[1]	Total number (%)
I	Total susceptible to all first-line anti-TB drugs tested (H, R, E, S)[2]	29 (31.9%)
II	Any resistance to H	55 (60.4%)
	Any resistance to R	51 (56.0%)
	Any resistance to E	25 (27.5%)
	Any resistance to S	28 (30.8%)
III	Resistance to H only	4 (4.4%)
	Resistance to R only	1 (1.1%)
	Resistance to E only	0
	Resistance to S only	3 (3.3%)
Total mono-resistance		**8 (8.8%)**
IV	H + R	18 (19.8%)
	H + R + E	9 (9.9%)
	H + R + S	6 (6.6%)
	H + R + E + S	14 (15.4%)
Total multi-drug resistance (MDR)		**47 (51.7%)**
V	Total poly-resistance other than MDR	7 (7.7%)

NTP Roadmap


HEALTH SECTOR
REFORM AGENDA
Monograph No. 11
2010-2016
Philippine Plan of Action
to Control Tuberculosis
(PhilPACT)
WORLD TB DAY
Kaya Mo, Kaya Ko.
HSRA
MONOGRAPHS

PhilPACT (2010 – 2016) – NTP plan to for TB control

Objective	Strategies
1. Reduce local variation in TB control program performance	1. Localize implementation of TB control 2. Monitor health system performance
2. Scale up and sustain coverage of DOTS implementation	3. Engage both public and private health care providers 4. Promote and strengthen positive behavior of communities 5. Address MDR-TB, TB/HIV, and needs of vulnerable populations
3. Ensure provision of quality TB services	6. Regulate and make available quality TB diagnostic tests and drugs 7. Certify and accredit TB care providers
4. Reduce out of pocket expenses related to TB care	8. Secure adequate funding and improve allocation and efficiency of fund utilization

Beneficiaries of PhilPACT by 2015

Indicator	No. of beneficiaries
No. of symptomatics to be provided with DSSM	5 million
No. of adult TB patients to be provided treatment	1 million
No. of children to be provided with treatment and IPT	730,000
No. of MDR-TB patients to be treated	15, 500
No. of TB patients to be provided with PICT on HIV/AIDS	15,000

NTP Programs

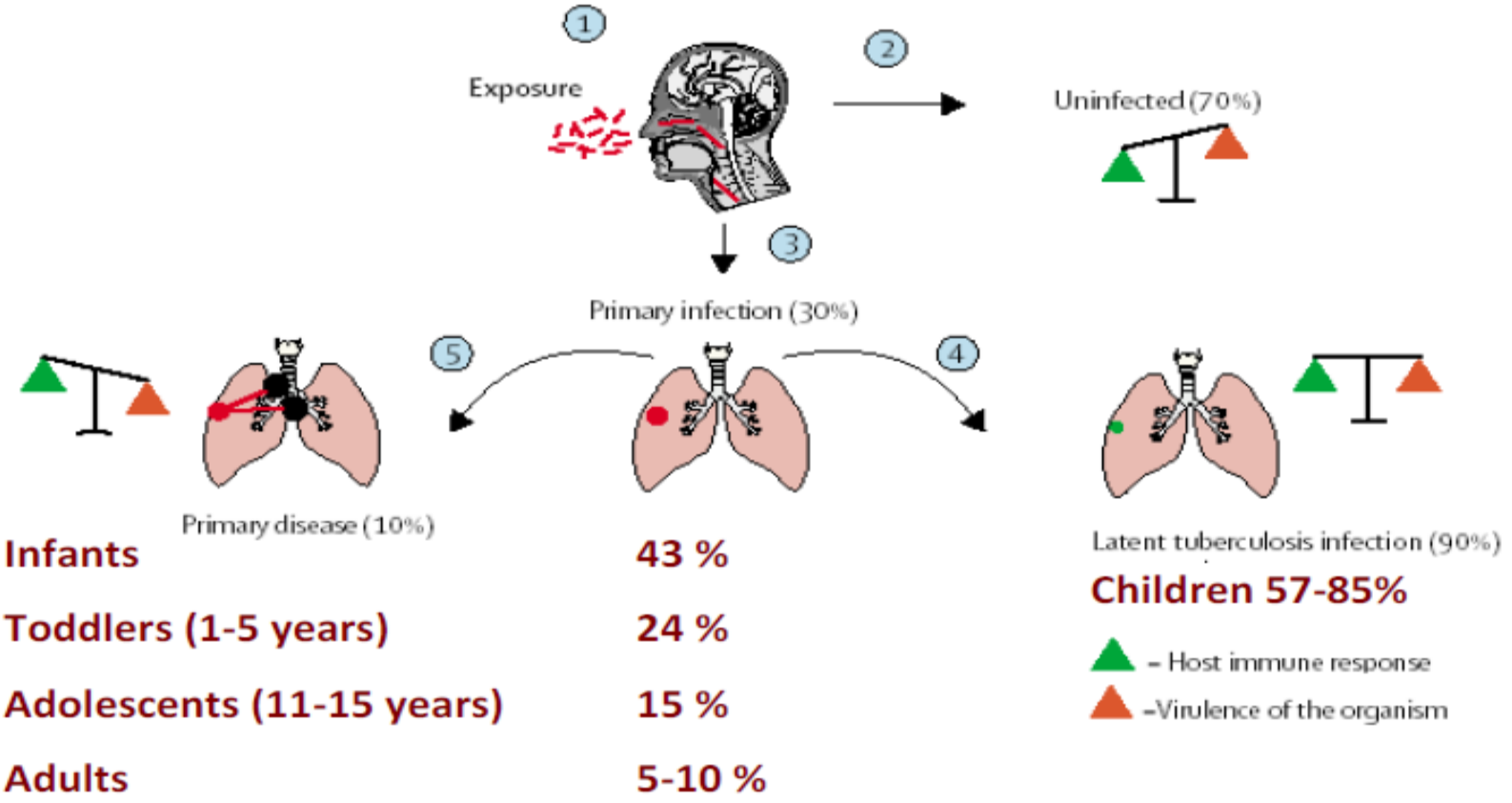
- Programmatic Management of Drug-Resistant TB (PMDT
- TB in children – started in 2008, nationwide implementation (Public and PPMD)
- TB in jails/prisons – started in 2009 (BJMP and BuCor); 130,000 inmates
- Hospital DOTS

Diagnosis of Childhood TB

References

- *Tuberculosis in Infancy and Childhood, 2010 (PPS)*
- *Evidence-based clinical practice guidelines for childhood tuberculosis, 2008 (PPS)*
- *Training modules for TB in children, 2008 (DOH/NTP)*
- *Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2006 (WHO)*

Risk for TB infection and disease



modified from Sharma SK, Lancet Infect Dis 2005

The spectrum of childhood TB

- *TB exposure*: child with close contact with a source case, no s/sx, (-) TST, no radiologic or lab findings for TB

- *TB infection*: child with (+) TST, no radiologic or lab findings for TB

- *TB disease*: child is TB symptomatic, with (+) TST and/or positive radiologic or lab findings suggestive of TB

Diagnosis of TB in children

- Children "< 15 years old"
- Culture = "gold standard"
- Difficult to confirm diagnosis:
  - Few bacilli
  - No specimen
- Current criteria rely on: history, chest X-ray, TST
  - Not totally accurate
  - 15-20% may not have TB *(Schaaf et al., 1995)*
- Need to standardize diagnostic criteria

Approach to diagnosis of TB in children (< 15 yrs)

- PPS, DOH, WHO

1. Careful history and P.E.
   - Signs and symptoms, history of contact
2. Tuberculin skin testing
3. Radiography
   - Chest x-ray
4. Bacteriological confirmation whenever possible

Symptomatic child

(3 out of 6 criteria:

TB symptomatic)

PPS/ DOH / WHO

- ✓ **Cough or wheezing of ≥ 2 weeks / 21 days**
- ✓ **Fever - >38 °C for 14 days**
- ✓ **Weight loss or failure to thrive**
- ✓ **Fatigue, reduced playfulness, or lethargy**
- ✓ **Failure to respond to 2 weeks of appropriate antibiotic**
- ✓ **Failure to regain previous state of health after 2 weeks of a viral infection or exanthem**
- ✓ ***Organ-specific symptoms (EPTB)***

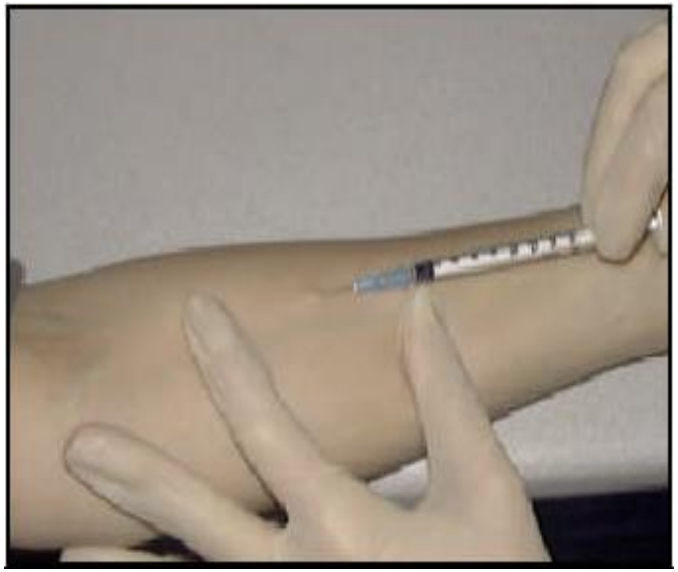
Exposure to a TB case

- **Exposure?**
- Does anyone in the home have TB?
- Has your child been in contact with anyone with TB?

- Close contact - living in the same household or in frequent contact with a source case with smear-positive PTB.
- Children are infectious if smear (+) or with cavitary TB
- Make an effort to find the source case and other undiagnosed cases!

Tuberculin Skin Test

- TST interpretation depends on two factors:
  - diameter of the induration;
  - person's risk of being infected with TB and risk of progression to disease if infected.



Tuberculin Skin Test

- A positive TST has an induration of:
  - ≥10 mm: in all other children (whether they have received BCG vaccination or not)
  - ≥5mm in immunocompromised individuals (HIV-infected children and those severely malnourished; in the presence of history of close contact, clinical findings suggestive of TB, CXR suggestive of TB)

- PPS/ DOH/ WHO

Chest Radiography and other investigations

PTB – CXR

- The commonest picture: persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands.
- A miliary pattern of opacification children is highly suggestive of TB.
- Adolescents:
  - large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation (similar to adults).
  - may also develop primary disease with hilar adenopathy and collapse lesions visible on CXR.

Bacteriological Confirmation

- Bacteriologic proof must be tried!
  - 3x sputum collection / gastric washing
  - Suspected site of infection
  - Microscopy – 2 positive out of 3 specimens

Gastric aspirate vs induced sputum

Gastric aspirate

- 30% to 50% yield
- Stain and culture yield from 3 GW higher than BAL[1]

Induced sputum

- Inhalation of 3-5% hypertonic saline
- Bronchospasm possible side effect
- Yield of 1 induced sputum equivalent to 3 GW[2]

1 Lighter Curr Probl Pediatr Adolesc Health Care 2009 2Zar Lancet 2005

Diagnosis of Pulmonary TB in children

- 3 of the following criteria:
  - Symptomatic
  - (+) exposure
  - (+) TST
  - (+) CXR findings
  - Bacteriologic confirmation (positive smear or culture)

Diagnosis in Adolescents

- Follows that in adults
  - Sputum smear microscopy (2 positive smears out of 3)
  - Spot, morning, spot
  - Chest radiograph
- New strategies
  - 1 positive smear out of 2 smears
  - Front-loading: same day collection

Drug - resistant TB

- Children are as susceptible to drug-resistant TB as to drug-sensitive TB.
- Drug-resistant TB is a laboratory diagnosis
- Drug susceptibility test on a positive culture is required
- In cases of a negative culture look for risk factors for MDR/DR-TB

Drug-resistant TB

- Drug-resistant TB should be suspected if any of the following are present.

  1. Features in the source case suggestive of drug-resistant TB:

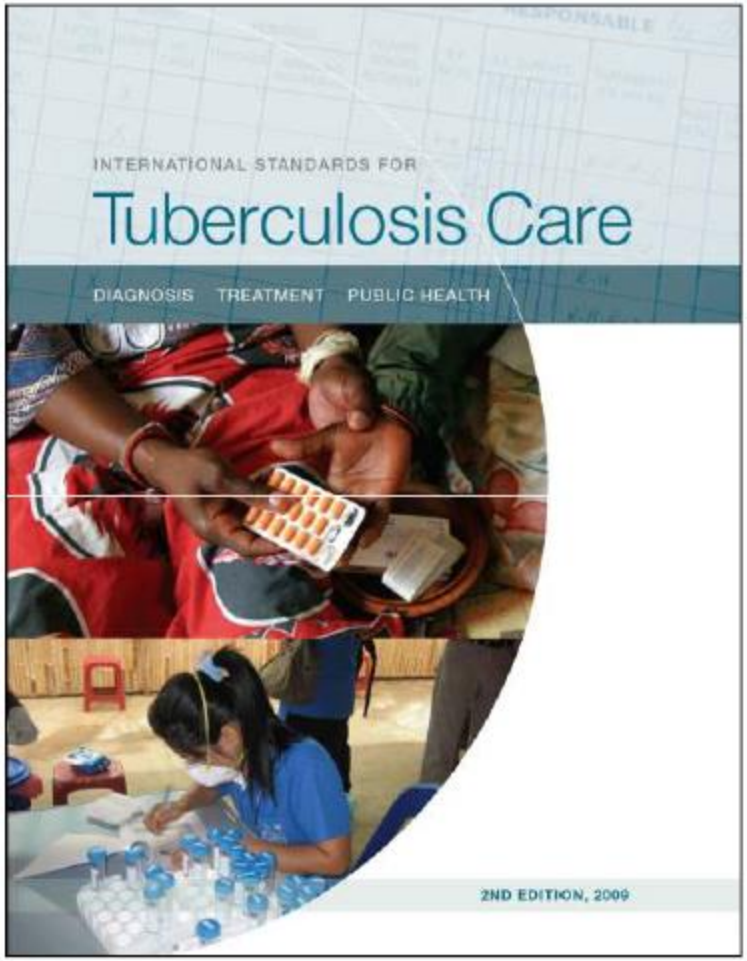
  - contact with a known case of drug-resistant TB
  - remains sputum smear-positive after 3 months of treatment
  - history of previously treated TB
  - history of treatment interruption.

  2. Features of a child suspected of having drug-resistant TB:

  - contact with a known case of drug-resistant TB
  - not responding to the anti-TB treatment regimen
  - recurrence of TB after adherence to treatment

- The diagnosis and treatment of drug-resistant TB in children is complex and should be carried out in referral centers

International Standards for Tuberculosis Care



http://www.tbcta.org/Uploaded_files/Zelf/ISTCReport2ndEdition1258118339.pdf

International Standards for Tuberculosis Care

Standards for Diagnosis	
1	All persons with unexplained cough >2 wks should be evaluated for TB
2	All px suspected of PTB should have at least 2 sputum specimens submitted for microscopy in a quality-assured lab.
3	EPTB: specimens from suspected site should be obtained for microscopy, culture and histopath exam
4	All persons with CXR findings suggestive of TB should have sputum specimens submitted for microbiologic exam
5	Dx of sputum smear (-) PTB: at least 2 (-) sputum smears (1 early morning sp); CXR findings; and lack of response to antibiotics
6	All children suspected of having intrathoracic TB: confirmation through sputum microscopy and culture (by expectoration, gastric washings, or induced sputum). For negative results: Dx should be based on CXR findings, Hx of exposure to infectious case, evidence of TB infection and suggestive clinical findings.

Contact investigation – important!

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OFFICIAL STATEMENT

Guidance for National Tuberculosis Programmes on the management of tuberculosis in children
CHAPTER 4 IN THE SERIES

Chapter 4: Childhood contact screening and management

Stop TB Partnership Childhood TB Subgroup
World Health Organization, Geneva, Switzerland

SUMMARY

Young children living in close contact with a case of smear- Breastfeeding can be safely continued in children during

Screening of the household contacts of an infectious source case is therefore recommended to identify children with TB and enable their prompt treatment, and to provide children who do not have TB with isoniazid preventive treatment. Isoniazid preventive treatment (IPT)

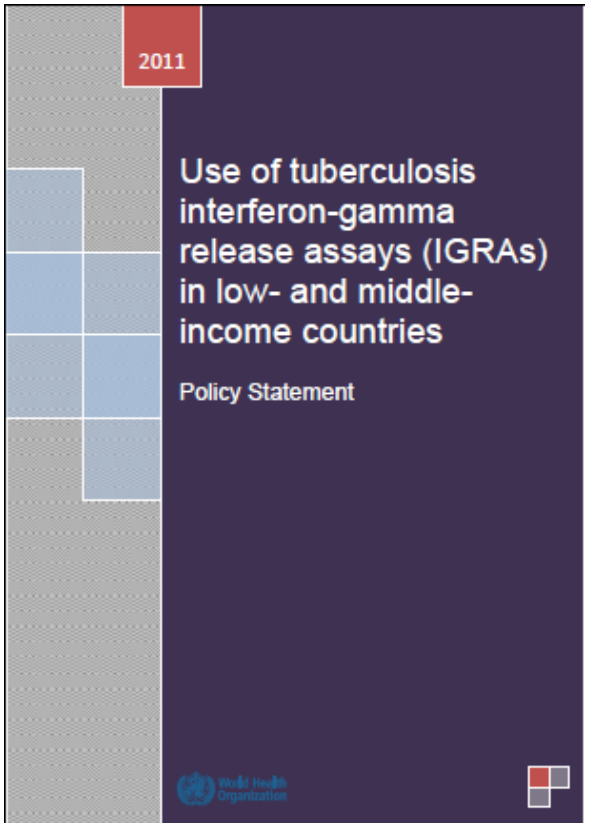
receive 6 months of H, followed by BCG vaccination.

Contact investigation

The inability to conduct targeted contact investigations results in missed opportunities to prevent additional cases of tuberculosis, especially among children. Thus, more energetic efforts are necessary to overcome these barriers to optimum tuberculosis control practices.

Policy recommendation: IGRAs

- Principle: T-cells of individuals with TB infection secrete IFN-γ in response to re-stimulation with *M. tb*-specific antigens



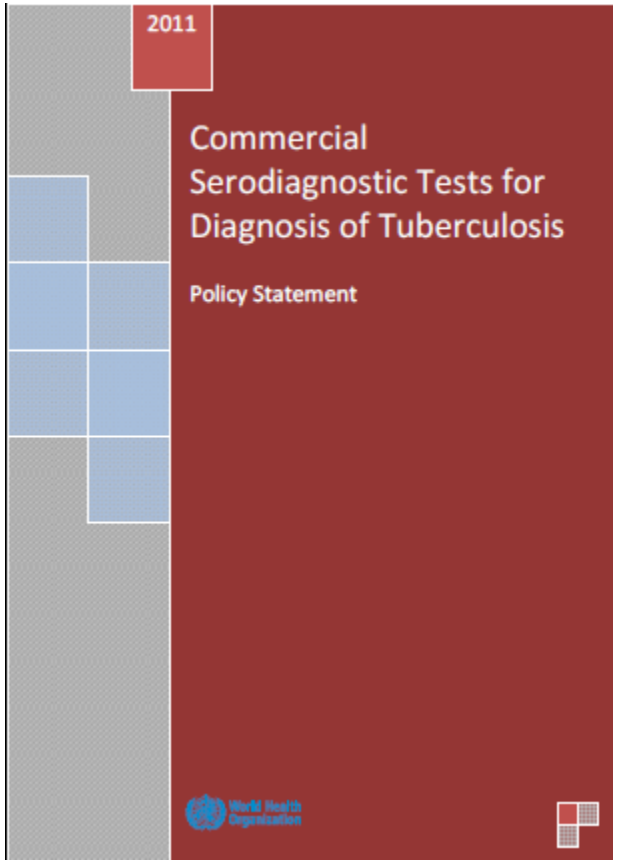
Policy recommendation: IGRAs

Overall conclusions

- Insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and/or HIV burden
- IGRAs and the TST cannot accurately predict the risk of infected individuals developing active TB disease
- Neither IGRAs nor the TST should be used for the diagnosis of active TB disease
- IGRAs are more costly and technically complex to do than the TST.
- Given comparable performance but increased cost, replacing the TST by IGRAs as a public health intervention in resource-constrained settings is not recommended.

TB Serodiagnostic Tests

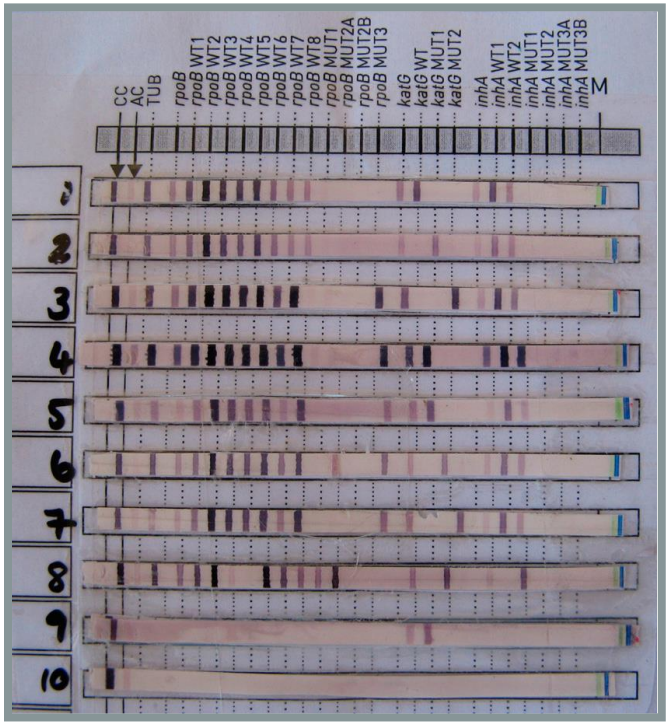
- Inconsistent and imprecise findings
- No evidence of improved patient outcomes
- High proportions of false-positive and false-negative results
- Very low data quality
- Recommendation: not to be used for the diagnosis of pulmonary and extra-pulmonary TB.



Rapid diagnostic tests

Molecular Line Probe Assay (LPA)

- Identifies *M.tb* and genetic mutations associated with INH and RIF resistance
- Can be used directly on sputum specimens, or on isolates
- results within 1-2 days
- Complex to perform



*GenoType MTDBRplus strips
(Hain Lifescience)

Line Probe Assay

Advantages:

- Rifampicin resistance: >97% sensitive and >98% specific
- INH resistance: >90% sensitivity, >98% specificity
- For rapid screening of MDR-TB
- Recommended for sputum smear (+) specimens

Considerations and requirements:

- Specificity is excellent for INH resistance but sensitivity estimates are modest and variable
- Geographical variation in prevalence of mutations associated with rifampicin and in particular INH resistance may result in varying performance

Automated Detection for MDR Screening : Xpert Mtb/Rif

- Rapid detection of *M.tb* and Rif resistance
- Sensitivity: 95-99.5%; specificity: 95%
- For sputum smear (+)/(-)
- Minimal training
- Minimal space requirements
- Fully automated
- Results in 2 hours

PMDT Treatment Center	GX Center	Culture Center	DST Center
Ilocos Training and Regional Medical Center	Ilocos Training and Regional Medical Center	Ilocos Training and Regional Medical Center	National TB Reference Lab.
Region I Medical Center			
De La Salle Health Sciences Institute	De La Salle Health Sciences Institute	De La Salle Health Sciences Institute	National TB Reference Lab.
Batangas Regional Hospital	National TB Reference Laboratory	National TB Reference Laboratory	
Sorsogon Medical Mission Group Hospital and Health Services Cooperative	Sorsogon Medical Mission Group Hospital and Health Services Cooperative	CHD V TB Reference Lab.	National TB Reference Lab.
Bicol Medical Center			
Western Visayas Medical Center	Western Visayas Medical Center	Cebu TB Reference Lab.	Cebu TB Reference Lab.
Dr. Pablo O. Torre Memorial Hospital			
Eversly Child's Sanitarium	Eversly Child's Sanitarium		
Zamboanga City Medical Center	Zamboanga City Medical Center		

PMDT Treatment Center	GX Center	Culture Center	DST Center
Xavier University- Community Health Care Center (Committee of German Doctors)	Xavier University- Community Health Care Center (Committee of German Doctors)	National TB Reference Laboratory	National TB Reference Laboratory
Iligan Society of Internist			
Southern Philippines Medical Center	CHD XI TB Reference Lab.		
Davao Regional Hospital			
Koronadal City Health Office	Koronadal City Health Office		
Baguio General Hospital and Medical Center	Baguio General Hospital and Medical Center	Ilocos Training and Regional Medical Center	
CARAGA Regional Hospital	*CARAGA TB Culture Center	National TB Reference Laboratory	
Lung Center of the Philippines	Lung Center of the Philippines	Lung Center of the Philippines	
Cainta Health Center			
Super Batasan Health Center			
Dr. Jose N. Rodriguez Memorial Hospital	Dr. Jose N. Rodriguez Memorial Hospital		
KASAKA	PTSI- Quezon Institute	PTSI- Quezon Institute	
PTSI TAYUMAN			
San Lazaro Hospital			
Lagrosa Health Center		UP-PGH Medical Research Lab.	
Gat. Andres Bonifacio Medical Center			
Tondo Foreshore Health Center			
Grace Park Health Center			
Lacson Health Center			
Moonwalk Health Center	National TB Reference Laboratory	National TB Reference Laboratory	

Summary

- TB incidence, prevalence and mortality rates show decreasing trends globally and in the Philippines
- MDG and STOP TB goals for TB incidence and mortality will likely be achieved but halving of prevalence rate is unlikely by 2015
- There is greater attention to other populations / forms of TB and not just smear (+) cases (TB in children, in prisons and all forms of TB)

Summary

- Diagnosis of TB pulmonary disease in children still relies on history, TST and radiologic findings
- Importance of contact investigation is highlighted
- LPA and GX are used to screen for MDR-TB in adults, adolescents and older children
- Usefulness of rapid tests in childhood TB remains to be seen

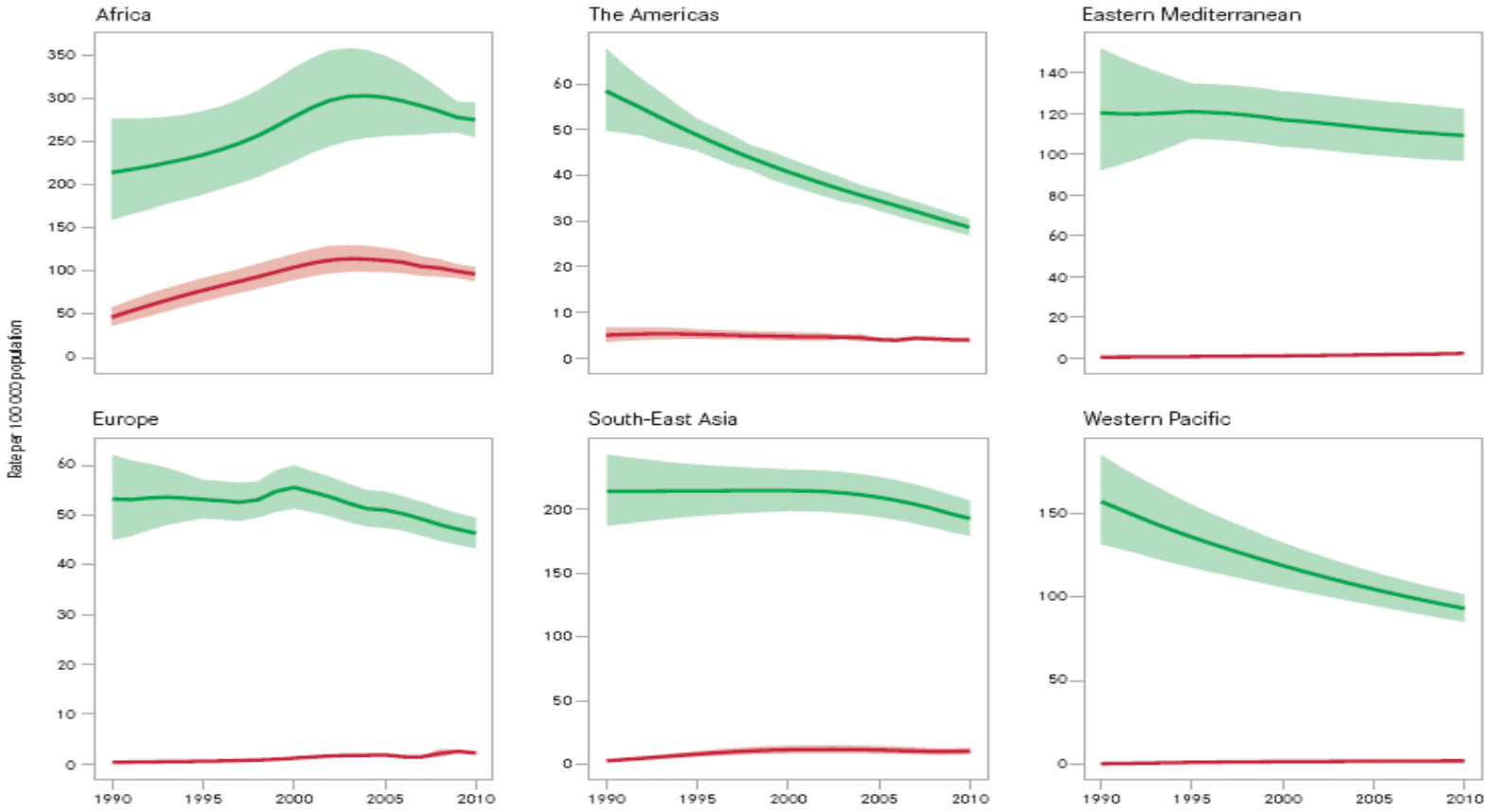
Acknowledgement

- Dr. Woojin Lew – WHO, Country Office
- Dr. Rosalind Vianzon – NTP Manager
- Dr. Lorelai Averilla – WHO, CATCH TB
- Dr. Vivian Lofranco – PMDT Manager
- Dr. Anne Detjen - Desmond Tutu TB Centre, Cape Town
- Dr. Klaus Magdorf - Charité University Hospital, Berlin

THANK YOU

Trends in incidence rates by WHO region – decreasing trend

Estimated TB incidence rates by WHO region, 1990–2010. Regional trends in estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands.



Trends in prevalence rates by WHO region – decreasing overall

Trends in estimated TB prevalence rates 1990–2010 and forecast TB prevalence rates 2011–2015, by WHO region
Shaded areas represent uncertainty bands. The horizontal dashed lines represent the Stop TB Partnership target of a 50% reduction in the prevalence rate by 2015 compared with 1990. The other dashed lines show projections up to 2015.

Trends in mortality

Trends in estimated TB mortality rates 1990–2010 and forecast TB mortality rates 2011–2015, by WHO region
Estimated TB mortality excludes TB deaths among HIV-positive people. Shaded areas represent uncertainty bands.[a] The horizontal dashed lines represent the Stop TB Partnership target of a 50% reduction in the mortality rate by 2015 compared with 1990. The other dashed lines show projections up to 2015.

[a] The width of uncertainty bands narrows as the proportion of regional mortality estimated using vital registration data increases.

Other Investigations

EPTB

Site	Practical approach to diagnosis
Peripheral lymph nodes (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest X-ray and lumbar puncture (to test for meningitis)
TB meningitis	Lumbar puncture (and computerized tomography where available)
Pleural effusion (older children and adolescents)	Chest X-ray, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound and ascitic tap
Osteoarticular	X-ray, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap

Contact investigation

STANDARD 18.

. All providers of care for patients with tuberculosis should ensure that persons who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed tuberculosis; 2) is at high risk of developing tuberculosis if infected; 3) is at risk of having severe tuberculosis if the disease develops; and 4) is at high risk of having been infected by the index case. The highest priority contacts for evaluation are:

- Persons with symptoms suggestive of tuberculosis
- Children aged <5 years
- Contacts with known or suspected immunocompromised states, particularly HIV infection
- Contacts of patients with MDR/XDR tuberculosis

Other close contacts are a lower priority group.