

Multidrug Resistant Tuberculosis:

Emerging Global Challenge

International Science and Technology Center

Moscow, Russia

**The Global Burden of Drug-Resistant TB in Children:
the hidden epidemic**

14 November 2011

Carlos M. Perez-Velez, MD

Grupo Tuberculosis Valle-Colorado (GTVC)

Infectious Diseases Service

Clínica Leon XIII

Universidad de Antioquia

Medellin, Antioquia, Colombia

Why have we been so complacent with DR-TB in children?

Misconceptions / Dogmas

- *DR-TB is rare in children.*
- *DR-TB is not very virulent.*
- *Children are more likely to have previously-treated/secondary/acquired DR-TB than new, previously-untreated/primary/transmitted DR-TB.*
- *Children are not contagious.*

Why is DR-TB so concerning?

DR-TB is more difficult to treat, with consequences for...

- Patient: higher morbidity and mortality
 - Pan-susceptible TB: 7% mortality.
 - MDR/XDR-TB: >50% mortality.
- Community: higher risk of continued transmission which threatens the global control of TB
- *Only infectious disease to be declared a global emergency by the WHO*

Second-line drugs are less effective and tend to have more adverse effects.

Treatment much more costly—not only due to price of medications, but also to longer duration of treatment.

Why is DR-TB so concerning?

Global MDR-TB Epidemiology

- Prevalence of MDR-TB (2010): ~650,000 cases.
- Annual deaths due to MDR-TB (2008): ~150,000.
- Percent of patients currently being treated for MDR-TB, of all those who would be identified, if all newly-notified TB patients were tested for drug resistance (2010): ~16%.
- Previously-treated TB patients tested for MDR-TB (2010): ~6%.
- New bacteriologically-positive patients tested for MDR-TB (2010): 1.8%.

Why is DR-TB so concerning?

Trends in Global MDR-TB Epidemiology

The best estimates suggest that levels of MDR-TB among new TB patients are:

- Stable:** at global level; the Americas.
- Decreasing:** Eastern Mediterranean; South-East Asia; Western Pacific.
- Increasing:** Africa; Europe.

WHO Global Report on Surveillance and Response, 2011

Why is DR-TB so concerning?

MDR-TB in WHO Euro Region

Of the estimated 440,000 MDR-TB patients in the world, 81,000 are considered to be in the WHO European Region (18.4% of the global burden).

WHO. Global tuberculosis control: WHO report 2010. 2010

In 2009, the proportion of MDR-TB among new and previously-treated TB patients was 11.7% and 36.6% respectively.

ECDC/WHO. Tuberculosis surveillance in Europe 2009. 2011

Why is DR-TB so concerning?

MDR-TB in WHO Euro Region

Most countries in the Euro Region have reported XDR-TB (despite the very low coverage with DST for SLDs).

The top nine countries in the world with MDR-TB exceeding 12% among new TB cases are in the Euro Region.

The top six countries in the world exceeding 50% among previously treated TB cases are also in the Euro Region.

High correlation between MDR-TB and HIV has been documented in several Euro Region Member States.

- **Misconception:** DR-TB in children is rare.
- **Fact:** Molecular epidemiologic studies have confirmed what drug-susceptibility testing results often suggest: adults are generally the source of transmission to children.

Schaaf et al, 2003. *Arch Dis Child*. 88:1106

—The rates of infection in household contacts (including children) of MDR-TB cases may actually be higher compared to drug-susceptible cases, given the prolonged duration of infectivity of those who are not treated adequately and in a timely manner.

—**Corollary:** As the incidence and prevalence of DR-TB in adults *increase* in many parts of the world, one would expect these rates to *also increase* in children.

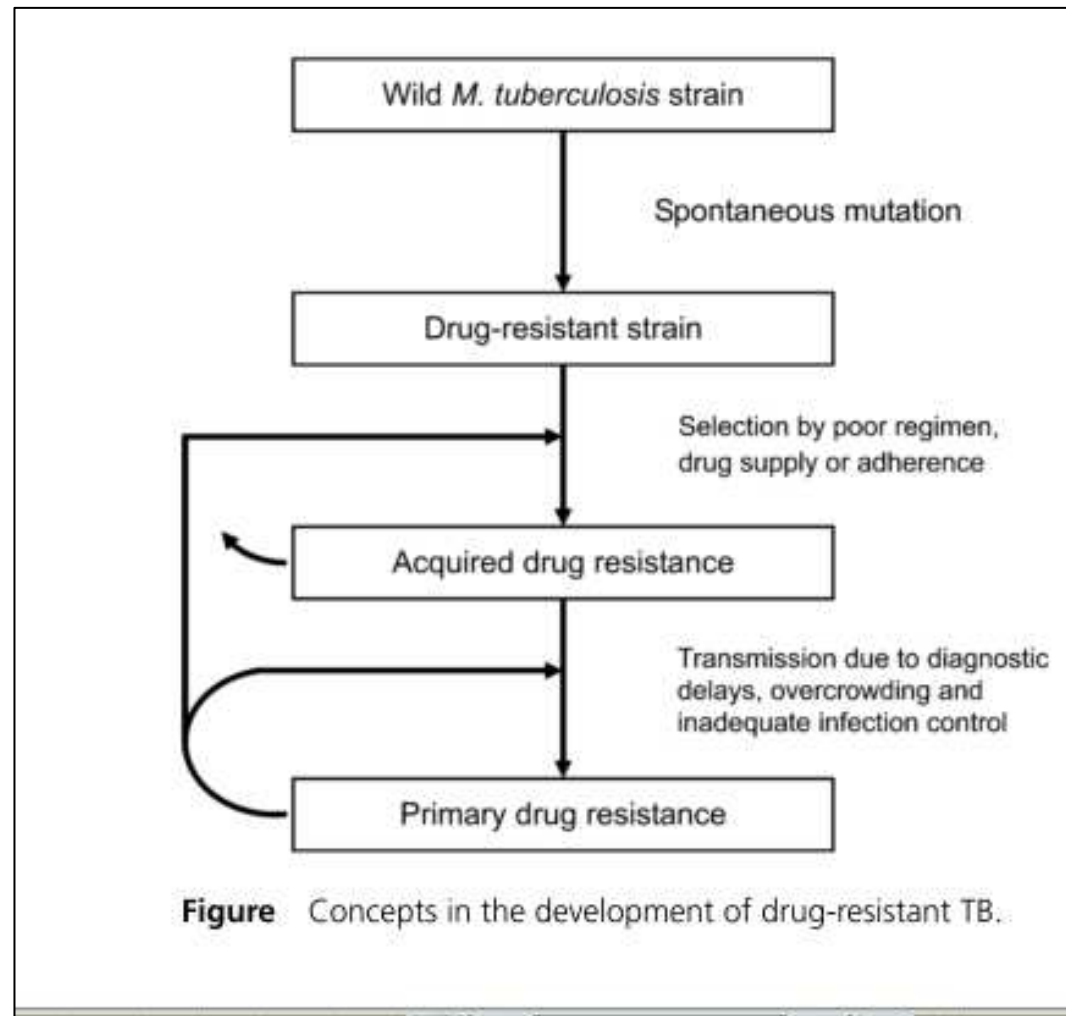
•**Misconception:** Children are more likely to have previously-treated/secondary/acquired MDR-TB than new, previously-untreated/primary/transmitted MDR-TB.

•**Fact:** Secondary/acquired MDR-TB is less likely in *young* children due to the paucibacillary nature of the primary disease (although possible with adult-type cavitary pulmonary disease).

Definitions

- **New, previously-untreated / primary / transmitted drug-resistance:**
 - Drug resistance seen in the first isolate taken from the patient *before* the patient received any TB medications.
- **Previously-treated / secondary / acquired drug-resistance:**
 - Drug resistance seen in isolates that are taken after initiation of TB therapy (> 1 month).

Drug-resistance in *M. tb*: Mechanisms & Risk Factors



Why is DR-TB in children so concerning?

TABLE 2—Drug Susceptibility Test Results for the 3 Surveys in the Western Cape Province of South Africa: August 1994–April 1998, March 2003–February 2005, and March 2005–February 2007

Drug Susceptibility Test Results	1994–1998 (n = 338), No. (%)	2003–2005 (n = 323), No. (%)	2005–2007 (n = 291), No. (%)	<i>p</i> ^a
Drug susceptibility test available	306 (90.5)	319 (98.8)	285 (97.9)	<.001
Drug susceptible ^b	285 (93.1)	278 (87.1)	242 (84.9)	.005
Any resistance ^b	21 (6.9)	41 (12.9)	43 (15.1)	.005
Isoniazid monoresistance	14 (4.6)	23 (7.2)	22 (7.7)	.24
Rifampin monoresistance	0	0	2 (0.7)	
Multidrug resistance ^b	7 (2.3)	18 (5.6)	19 (6.7)	.03

^a*P* values compare differences among all 3 groups.

^bDifference between last 2 surveys was not significant.

Why is DR-TB in children so concerning?

Epidemiology of Drug-Resistant TB in Children

Surveys ('94-'09) of children with culture-confirmed TB from the Western Cape Province of South Africa

- Despite previous treatment, more than 90% of all DR-TB in children was *most likely due to transmitted resistance* from adults.
 - **Corollary:** Treat children according to DST of adult source case until result of own culture and DST available.
 - **Problem:** Low rates (1.8 to 6%) of DST in adult source cases hampers effective management of child TB contacts.
- Children share a *disproportionate burden* of TB, compared to adults, because once they are infected they are more likely to progress to disease (usually within 12 months).
 - Incidence of MDR-TB amongst new cases: 1.8% adults ('02) vs. 5.6% children ('03-'05)
 - Incidence of adult MDR-TB amongst previously-treated cases: 6.7 (2002)
 - **Corollary:** *Children provide an accurate measure of transmitted DR because even children who have received previous treatment for TB tend to have transmitted rather than acquired drug resistance.*

TB in Children in Colombia (2001-2009): Drug Resistance

	#	%
Total	128	100
New (i.e., never treated before)	125	97.7
Pansusceptible	99	77.3
Primary Drug Resistance	26	20.8
Monoresistance (H / R / E / S)	14	10.9
Polyresistance (not including H+R)	8	6.3
MDR (H+R)	4	3.1
Previously Treated	3	2.3
Recurrences that were pansusceptible	2	1.6
<i>Tx Failure with Acquired Resistance (to H+R+Z+S)</i>	1	0.8

Why is it useful to monitor DR-TB in children?

Epidemiology of Drug-Resistant TB in Children

- Children tend to have paucibacillary disease, and consequently the risk of developing random drug resistance on treatment is low.
- **Corollary:** [2nd reason why...] Surveillance of drug-resistance patterns among children provides an accurate measure of transmitted DR-TB within a community.

Misconception: DR-strains are less transmissible than drug-susceptible strains.

Fact: A case-control study demonstrated that contacts of patients with DR-TB and with DS-TB had an equal prevalence of positive tuberculin skin tests.

Snider et al, 1985. Am Rev Respir Dis 132:125.

Misconception: DR-strains are less virulent than DS strains (*this was based on animal studies that showed that isoniazid-resistant strains caused significantly less disease in guinea pigs than drug-susceptible strains*).

Middlebrook, 1954. *Am Rev Tuberc* 69:471.

Riley, 1962. *Am Rev Respir Dis* 85:511.

Fact: DR-strains were just as robust *in vitro*, and in some cases slightly more so, than their DS parent strains.

Schoolnik et al, 2006. *Science*. 312(5782):1944

- **Misconception:** Children are not contagious
- **Fact:**
 - Young children (<7 y.o.) who are paucibacillary, and have a very weak cough, are rarely contagious.
 - Older children: (>7 y.o.) who are multibacillary (and can develop adult-type TB), and have an “effective” cough, can be contagious.

2011/2012 TUBERCULOSIS GLOBAL FACTS

Key messages

Tuberculosis (TB) is a leading cause of death and disability worldwide, killing more than 1.5 million people each year. TB is a preventable and treatable disease, but it remains a major public health problem in many countries.

The burden of TB is highest in low- and middle-income countries, where it is often associated with poverty, malnutrition, and HIV/AIDS. TB is also a leading cause of death in children.

The World Health Organization (WHO) estimates that there are 9.4 million people living with TB worldwide. In 2010, there were 1.4 million new TB cases and 1.5 million deaths.

TB is caused by a bacterium called *Mycobacterium tuberculosis*. It is spread through the air when a person with TB coughs or sneezes.

TB can be treated with a combination of drugs, but it takes a long time to cure. It is important to take all the medicine and to see a doctor regularly.

WHO is working to reduce the burden of TB by promoting early diagnosis and treatment, and by preventing TB in high-risk groups.

WHO is also working to improve the quality of TB care and to ensure that all people have access to the best available treatment.

WHO is also working to prevent TB in children and to reduce the impact of TB on people with HIV/AIDS.

WHO is also working to improve the quality of TB care and to ensure that all people have access to the best available treatment.

WHO is also working to improve the quality of TB care and to ensure that all people have access to the best available treatment.

WHO is also working to improve the quality of TB care and to ensure that all people have access to the best available treatment.

Key facts

Tuberculosis (TB) is a leading cause of death and disability worldwide, killing more than 1.5 million people each year. TB is a preventable and treatable disease, but it remains a major public health problem in many countries.

The burden of TB is highest in low- and middle-income countries, where it is often associated with poverty, malnutrition, and HIV/AIDS. TB is also a leading cause of death in children.

The World Health Organization (WHO) estimates that there are 9.4 million people living with TB worldwide. In 2010, there were 1.4 million new TB cases and 1.5 million deaths.

Global TB situation

TB is caused by a bacterium called *Mycobacterium tuberculosis*. It is spread through the air when a person with TB coughs or sneezes.

TB can be treated with a combination of drugs, but it takes a long time to cure. It is important to take all the medicine and to see a doctor regularly.

WHO's role

WHO is working to reduce the burden of TB by promoting early diagnosis and treatment, and by preventing TB in high-risk groups.

WHO's strategy

WHO is also working to improve the quality of TB care and to ensure that all people have access to the best available treatment.

WHO is also working to prevent TB in children and to reduce the impact of TB on people with HIV/AIDS.

WHO's vision

WHO is also working to improve the quality of TB care and to ensure that all people have access to the best available treatment.

The only fact mentioned regarding children was:

"In 2009, there were 9.7 million orphan children as a result of TB deaths"



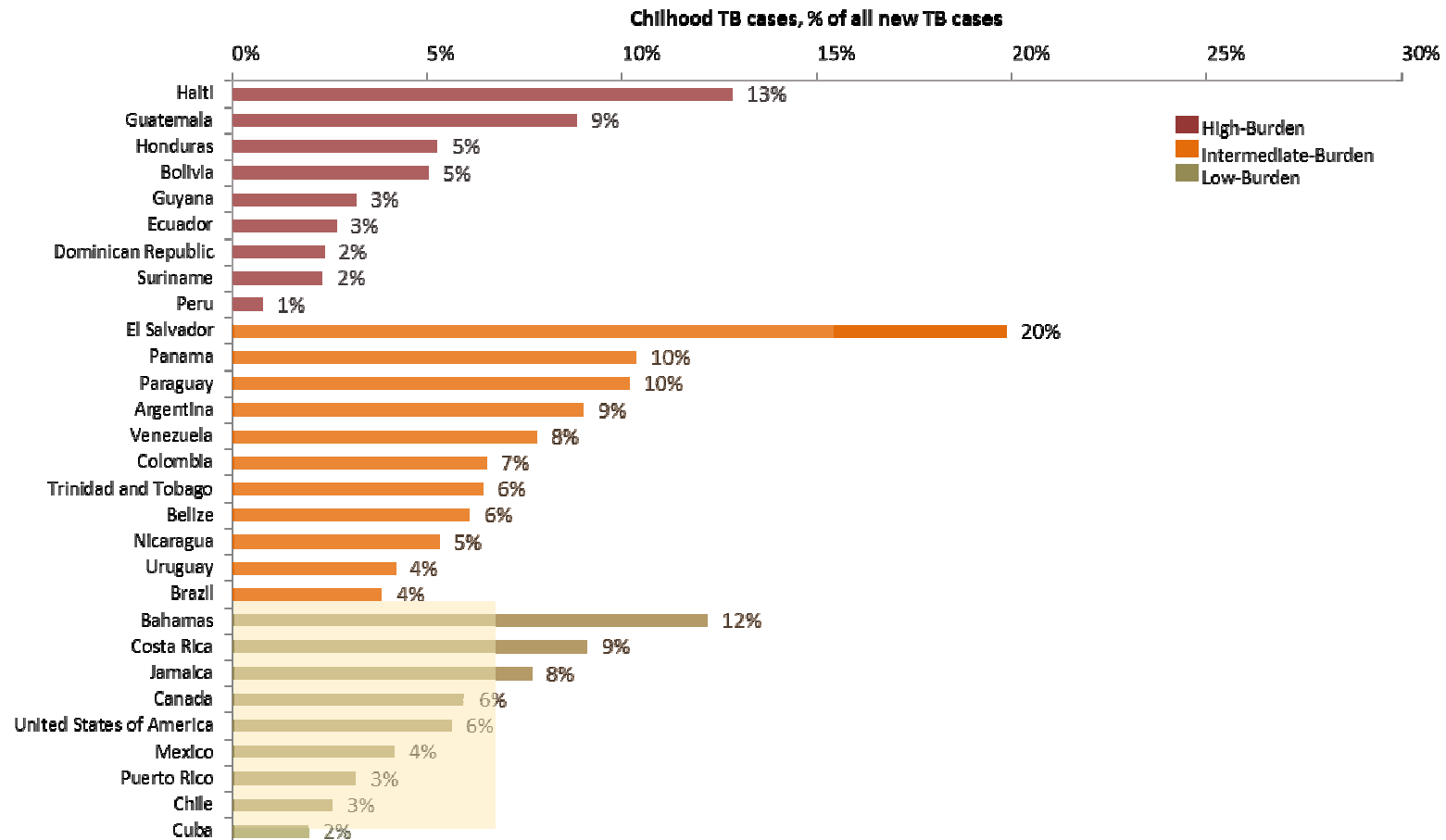
“The global plan to stop TB: Progress towards targets”:

Not a single target/indicator regarding children

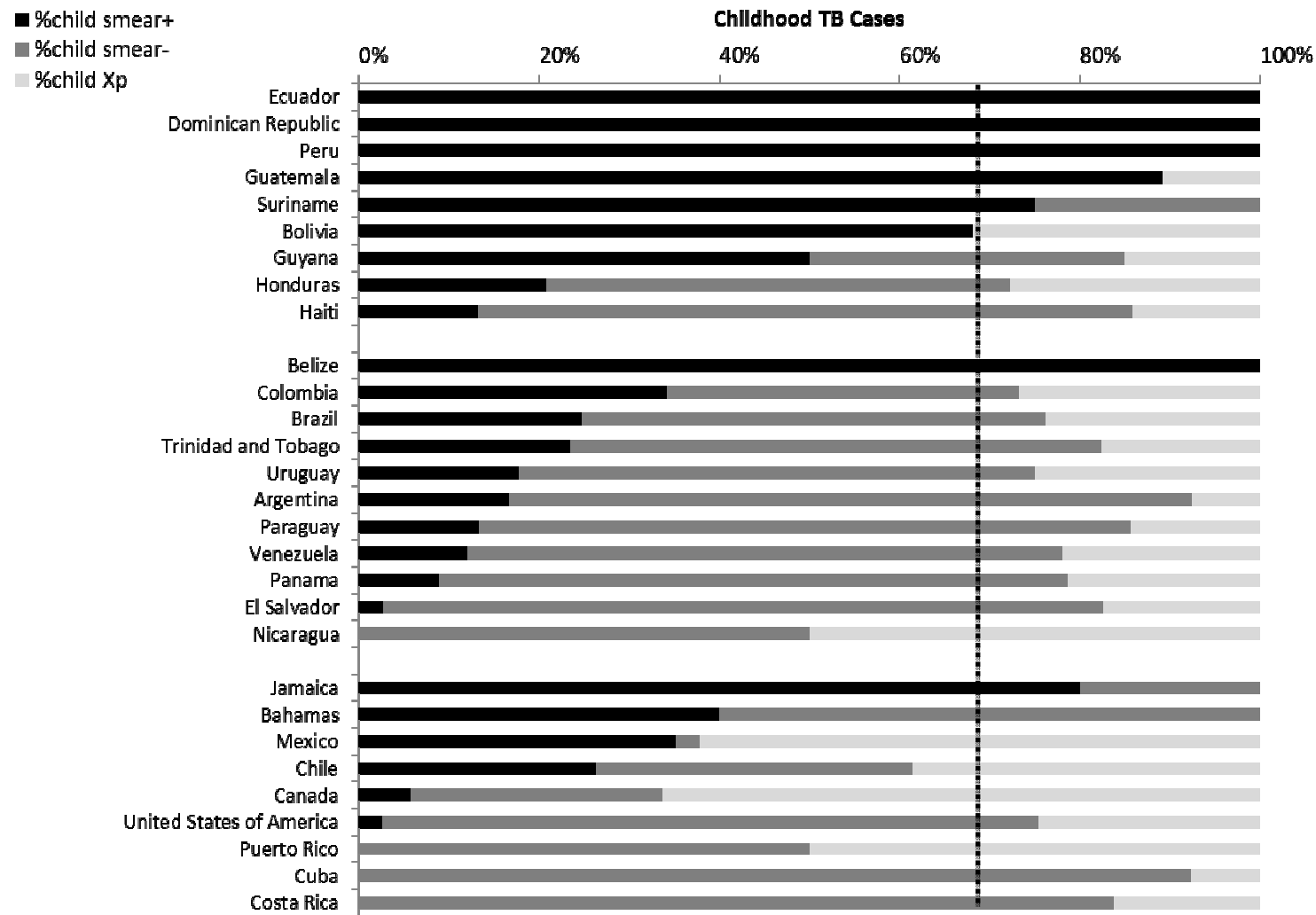
Why is surveillance data on DR-TB in children so limited?

- DR-TB is a bacteriological diagnosis
 - It is difficult to collect respiratory specimens in young children.
 - Young children are paucibacillary (smear-negative >90% of cases; culture-negative 60-90% of cases)
- WHO does not request—*although they welcome*—reporting of DR-TB cases in children <15 years of age.
 - Most of the data that has been reported has been from retrospective analyses.

Distribution of childhood TB cases as a proportion of all cases according to three levels of TB burden (2009).



Distribution of different forms of childhood TB cases and smear positivity by country.



Caseload Childhood TB mean in countries strata according to TB incidence and their gaps with the estimated benchmark

Incidence burden	N	Mean	Estimated benchmark	Gap	IC (95%)	t test	p-value
Low	22	5,83	10	-4,17	(-6,7 ; -1,6)	-3,74	0,000
Intermediate	13	8,15	20	-11,85	(-14,9 ; -8,8)	-8,77	0,000
High	9	4,82	30	-25,18	(-28,1 ; -22,3)	-19,9	0,006

Does HIV infection impact on the acquisition of DR-TB?

In a prospective case series of 596 children (<13 y.o.) with cultured-confirmed TB at two hospitals in Cape Town, South Africa (the largest study to date), DR-TB was not significantly different in HIV-infected children compared to HIV-uninfected.

Schaaf et al, 2007. *BMC Infect Dis* 7:140

Global Burden of Childhood DR-TB:

Key Points

The burden of TB in children is not well known, and much less so in DR-TB, but it is clear that it is grossly underdetected and under-reported.

- In countries with the highest rates of DR-TB (which tend to have the highest burdens of TB), children probably account for 20-30% of the caseload of TB in general (i.e., both pansusceptible and DR).
- The incidence of DR-TB in children is probably at least as much as in adults.
- Continuous surveillance with better data on the mortality and causes of death could elucidate the extent of the DR-TB epidemic among children.
- It may be feasible to estimate targets that could potentially serve to improve detection.