

# Safety of BCG in HIV infected patients - Review of evidence.

Is there a need to change the  
WHO policy?

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**IIDMM**



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Short communication

## The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children

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Table 2

Calculated risk of distant or disseminated BCG disease in HIV-infected children based on the known maternal antenatal HIV prevalence, assumed rates of vertical HIV transmission and estimates of total mid-year population of children <1 year, Western Cape Province, South Africa

Risk scenarios of disseminated BCG disease	Cases/year 2002	Cases/year 2003	Cases/year 2004
Actual cases/year	2	2	3
Risk of disseminated BCG disease			
Case scenario 1, assuming 5% total vertical HIV infection	$2/571 = 350/100,000/\text{year}$	$2/608 = 329/100,000/\text{year}$	$3/719 = 417/100,000/\text{year}$
Case scenario 2, assuming 10% total vertical HIV infection	$2/1142 = 175/100,000/\text{year}$	$2/1217 = 164/100,000/\text{year}$	$3/1439 = 208/100,000/\text{year}$
Case scenario 3, assuming 15% total vertical HIV infection	$2/1713 = 117/100,000/\text{year}$	$2/1825 = 110/100,000/\text{year}$	$3/2158 = 139/100,000/\text{year}$

Data for Cape Town children less than 2 years of age

TB incidence: 860/100000 person-years

TBM & MTB incidence: 61/100000 person-years

TBM & MTB account for 7% of all cases of TB

*Mahomed et al. Ped Infect Dis J. Dec 2006*

Rate of TBM in infants in Western Cape: 32/100000

*Kibel et al. Tuberc Lung Dis. Dec 1992*

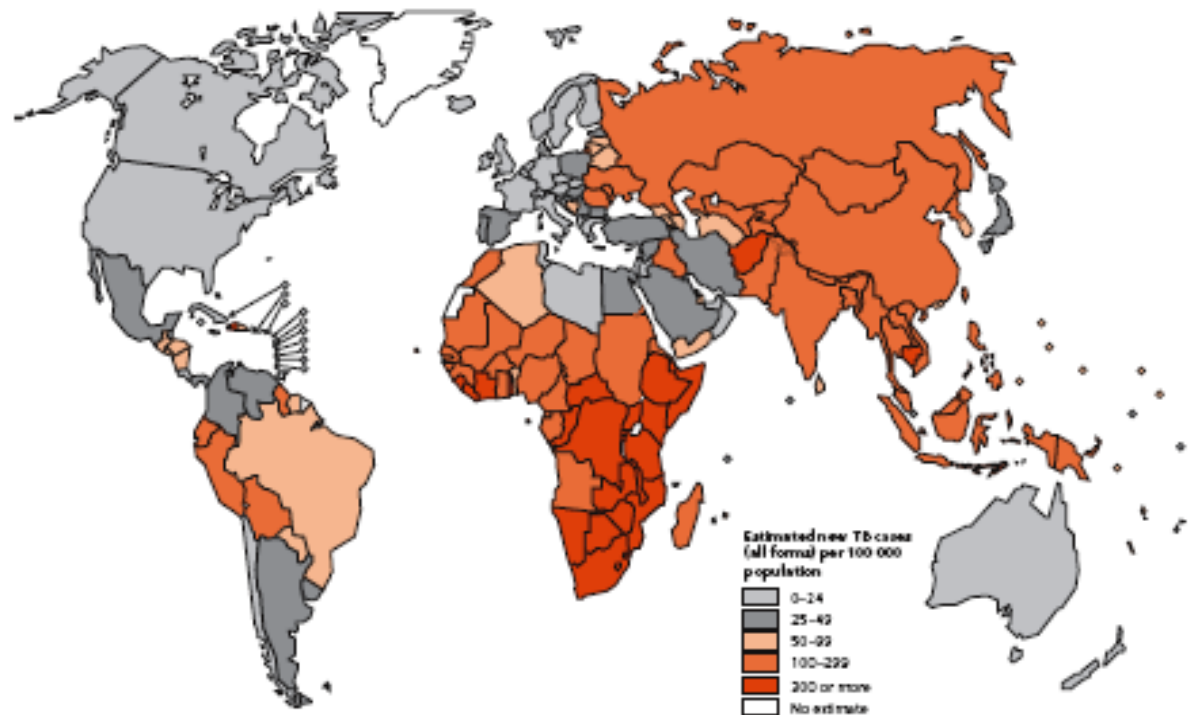
# Outline of presentation

- Context – TB and HIV epidemic
- History of BCG
- What do we know about BCG vaccine efficacy
- Current WHO policy
- Natural history of BCG vaccine
- BCG vaccination in HIV positive persons
  - significant local reactions
  - disseminated *M bovis* BCG disease
  - efficacy
- BCG and IRIS
- Recommendations

# TB problem worldwide

- 9 million new cases per year, including one million cases in children
- Proportion of paediatric cases varies from 3-25%
- 2 million TB deaths per year

**FIGURE 3**  
Estimated TB incidence rates, 2004



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2005. All rights reserved

## Global summary of the AIDS epidemic December 2006

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### Number of people living with HIV in 2006

Total	39.5 million (34.1–47.1 million)
Adults	37.2 million (32.1–44.5 million)
Women	17.7 million (15.1–20.9 million)
Children under 15 years	2.3 million (1.7–3.5 million)

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### People newly infected with HIV in 2006

Total	4.3 million (3.6–6.6 million)
Adults	3.8 million (3.2–5.7 million)
Children under 15 years	530 000 (410 000–660 000)

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### AIDS deaths in 2006

Total	2.9 million (2.5–3.5 million)
Adults	2.6 million (2.2–3.0 million)
Children under 15 years	380 000 (290 000–500 000)

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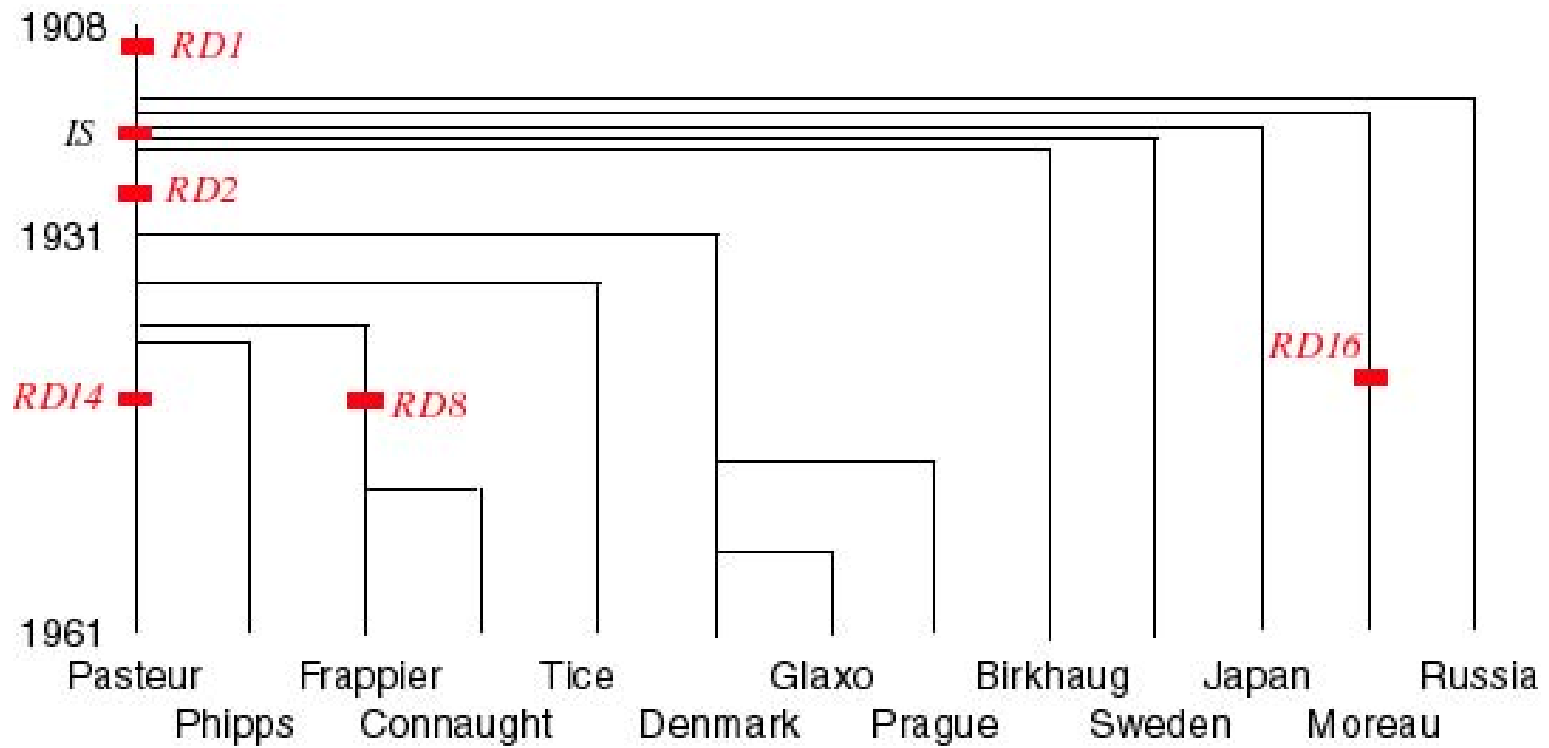
The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information.

- 60% of TB cases are HIV positive
- HIV increases risk of death from TB 5-10X

# History of BCG vaccine

- 1882 Koch discovered bacillus
- 1902 M bovis isolated
- 1908 BCG vaccine development
- 1921 BCG administered orally
- 1927 Intradermal BCG
- 1930 BCG Randomised trials
- 1968 Chingleput trial
- 1974 WHO EPI programme
- 1993 TB declared a worldwide emergency

# BCG strains



Profusion of phenotypically different daughter strains

# Current BCG policy

- Indications:
  - All infants living in areas where TB is highly endemic
  - Infants and children at particular risk of TB exposure in low- endemic countries (*Sm+ rate <5/100000 and TBM <1/1000000*).
- Route: Administered via intradermal injection
- Age at administration: As soon as possible after birth.
- Dosage: Single dose - repeat inoculation is of no documented value

# Administration of BCG



Source: G. Hussey, UCT



Source: G. Hussey, UCT

# Contraindications for BCG

- Persons with impaired immunity
- Known or suspected congenital immunodeficiency
- Leukaemia, lymphoma or generalised malignant disease
- Immunosuppressive therapy
- Pregnancy

# BCG and HIV infection

- Recommended for HIV positive infants who are asymptomatic and living in endemic TB countries.
- Efficacy of BCG vaccine in HIV positive infants is not known.

# Existing BCG policy documents

- Issues relating to the use of BCG in immunization programs. WHO/V&B/99.23
- WHO position paper on BCG. Weekly Epidemiological Report 23 Jan 2004
- Guidance for national TB programmes on the management of TB in children. WHO/HTM/TB/2006.371
- GACVS reviews 2004 & 2005

# Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness

B Bourdin Trunz, PEM Fine, C Dye

*Lancet 8 Apr 2006*

## Summary

**Background** BCG vaccine has shown consistently high efficacy against childhood tuberculous meningitis and miliary tuberculosis, but variable efficacy against adult pulmonary tuberculosis and other mycobacterial diseases. We assess and compare the costs and effects of BCG as an intervention against severe childhood tuberculosis in different regions of the world.

**Methods** We calculated the number of tuberculous meningitis and miliary tuberculosis cases that have been and will be prevented in all children born in 2002, by combining estimates of the annual risk of tuberculosis infection, the proportion of infections that lead to either of these diseases in unvaccinated children, the number of children vaccinated, and BCG efficacy.

**Findings** We estimated that the 100.5 million BCG vaccinations given to infants in 2002 will have prevented 29 729 cases of tuberculous meningitis (5th–95th centiles, 24 063–36 192) in children during their first 5 years of life, or one case for every 3435 vaccinations (2771–4177), and 11 486 cases of miliary tuberculosis (7304–16 280), or one case for every 9314 vaccinations (6172–13 729). The numbers of cases prevented would be highest in South East Asia (46%), sub-Saharan Africa (27%), the western Pacific region (15%), and where the risk of tuberculosis infection and vaccine coverage are also highest. At US\$2–3 per dose, BCG vaccination costs US\$206 (150–272) per year of healthy life gained.

**Interpretation** BCG vaccination is a highly cost-effective intervention against severe childhood tuberculosis; it should be retained in high-incidence countries as a strategy to supplement the chemotherapy of active tuberculosis.

**Lancet 2006; 367: 1173–80**

See [Comment](#) page 1122

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Correspondence to: Dr C Dye  
[dye@who.int](mailto:dye@who.int)

- 100m doses of BCG administered annually
- Prevents 30000 cases of TBM & 11000 cases of MTB
- One severe case of TB prevented for 2500 vaccinations
- As cost-effective as short course chemotherapy

## BCG global annual reported coverage, 1980-2005

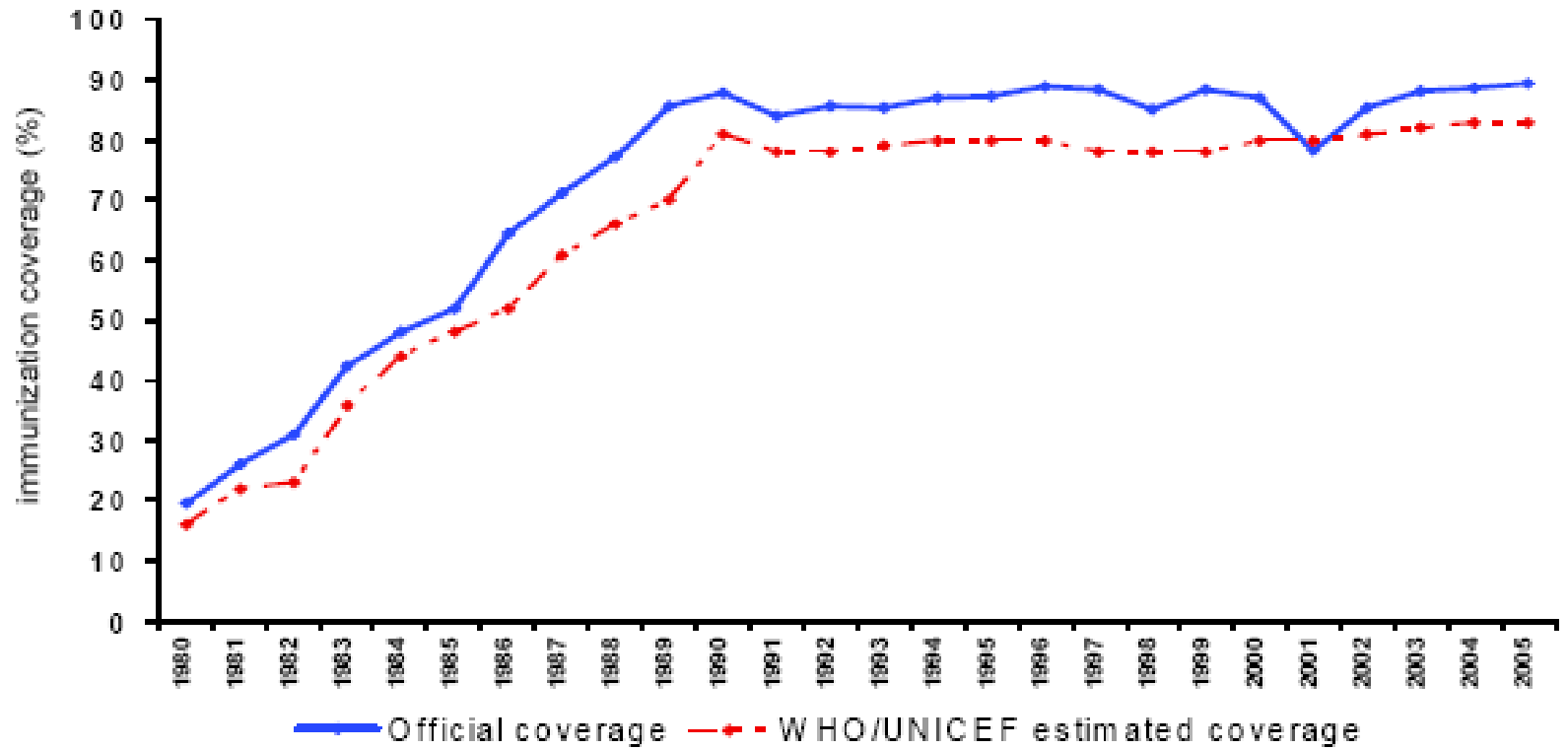
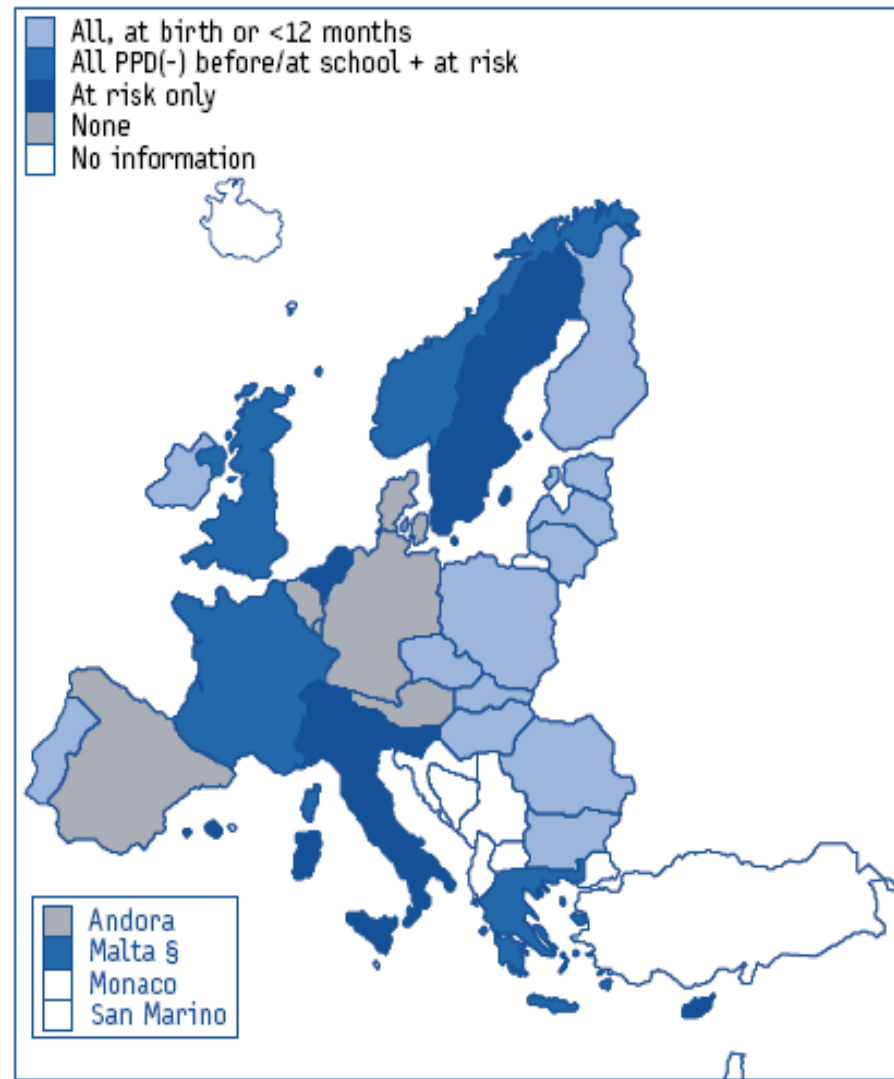


FIGURE 1

Groups of children targeted for BCG in national recommendations\*, Europe, 2005





Source: G. Hussey, UCT

# Natural history of BCG vaccination



**At 3 weeks**



**At 10 weeks**  
Shallow ulceration with crusting



**At 6 weeks**  
A raised papule with slight redness



**At 14 weeks**  
Healing - dry around edges

# Evolution of local BCG VAE over 8 wks



Source: G. Hussey, UCT



Source: G. Hussey, UCT



Source: G. Hussey, UCT



Source: G. Hussey, UCT



Source: G. Hussey, UCT

# Rate of adverse events following BCG vaccination

BCG Adverse Event	INCIDENCE *		INCIDENCE SA Study**
	GENERAL POPULATION (Age < 1 year)		
	Per mill doses	%	%
LOCALIZED	100-400	<0.04%	0.04%
DISSEMINATED	0.1-2	<0.0002 %	0.009%

\* Milstien, JB Gibson JJ Bull WHO 1990; 68:93-108.

\* Lotte A et al Bull Int Union Tuber Lung Dis 1988; 63:47-57

\*\* Hawkrigde et al, IUALTD conf 2006

# Factors influencing occurrence of local AEs following BCG vaccine

- Vaccine strain – Pasteur, Danish, Tokyo
- Dose
- Route of administration – errors
- Population variability - age
- Policy changes
- Reporting systems

# What do we know about the efficacy of BCG vaccine?

- Prevents severe TB in children
- Reduces TB specific mortality
- Prevents TB infection
- Not effective in preventing adult pulmonary disease
- Reduces all cause mortality in children
- Enhances immune responses to other EPI vaccines
- Effective in preventing leprosy
- Used as therapy in bladder cancer
- May prevent allergic diseases

# Safety of BCG vaccine in HIV positive children



Source: G. Hussey, UCT

# Local AEs following BCG vaccination

	HIV pos	HIV neg
Zambia 89	1/42 (2.3%)	3/40 (7.5%)
Congo 91 .	5/21 (23.8%)	28/154 (18.2%)
Rwanda 91	1/37 (2.7%)	4/200 (2%)
Zaire 92	0/21	1/42 (2.3%)
Zaire 93	2/40 (2.5%)	13/440 (0.7%)
<b>Total</b>	<b>9/161 (5.6%)</b>	<b>49/876 (5.6%)</b>
Haiti 94	4/13 (30.7%)	16/166 (9.6%)

Thailand 2000 (*SEAJTMPH*) – 223 HIV+ infants – no BCG AEs  
 Argentina 2001 HIV+ children *Fallo et al. (IDSA2001)* – 24/310 7.8%

# BCG Vaccinated patients

	<b>With Complications N= 28</b>	<b>Without Complications N= 246</b>	<b>p</b>
<b>Mean time follow-up</b>	5.9 ± 5 years	6.2 ± 6 years	NS
<b>Category C (CDC)</b>	61%	48%	NS
<b>Mean Viral Load (log)</b>	5.2 ± 0.3	4.9 ± 1	NS
<b>Mean CD4 %</b>	13.6 ± 11	20 ± 12	< 0.01

# Disseminated disease?

- In all studies - no reports of disseminated disease (clinical).
- However disseminated cases could have been missed.
- Follow-up period varied from 9-36 months.
- Some infants lost to follow-up.

# Immunogenicity of BCG vaccine in HIV positive children

No published data.

Study in progress (Hussey et al) comparing vaccine induced immunity if HIV infected, HIV exposed and HIV uninfected infants.

# Efficacy of BCG vaccine in HIV positive persons

*Bhat et al. J Trop Peds 1993*

*Marsh et al – AIDS 1997*

*Arbelaez et al. Int J Epidemiol 2000*

*Fallo et al. (IDSAS2001) Abstract # 788*

## BCG and HIV - Zambia

HIV	Scar		Odds ratio
	Yes	No	
Positive			1.0(0.2, 4.6)
TB Case	30	6	
Control	15	3	
Negative			0.41(0.18.0.92)
TB Case	45	15	
Control	102	14	

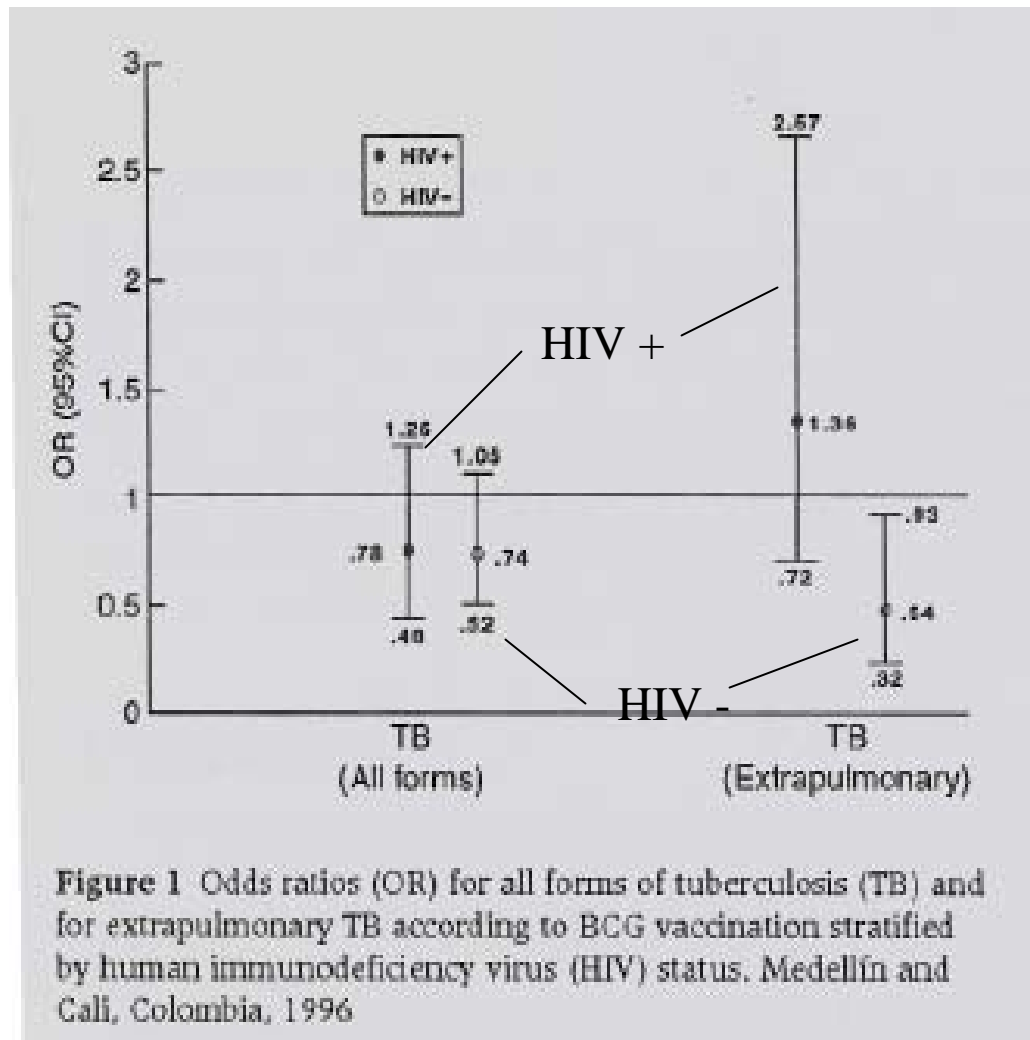
## Protective effect of BCG vaccine in preventing disseminated TB disease

**Table 2.** Rate of *Mycobacterium tuberculosis* bacteremia and selected patient characteristics by bacille Calmette–Guérin (BCG) status among 126 AIDS patients in Trinidad.

	BCG-positive* (n = 58)	BCG-negative (n = 68)
<i>M. tuberculosis</i> bacteremia	1 (2)	7 (10) <sup>†</sup>
Mean CD4 count ( $\times 10^6/l$ )	114	99
Men	44 (76)	49 (72)
Homeless	10 (17)	9 (13)
Recreational drug use	5 (8.6)	8 (12)
History of prostitution	13 (22)	14 (21)

Values are numbers (%), unless otherwise indicated. \*By either history or scar. <sup>†</sup> $P = 0.05$ , Fisher's exact test, one-tailed.

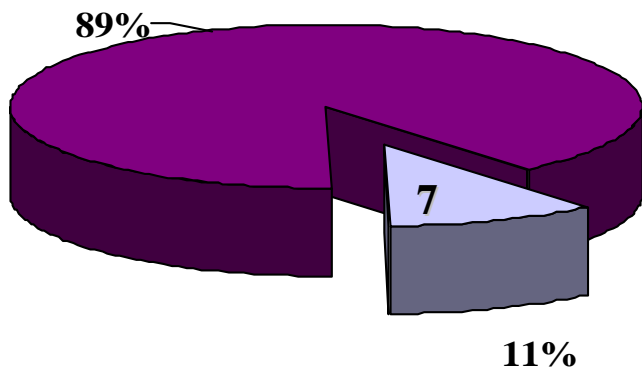
# BCG efficacy in preventing TB



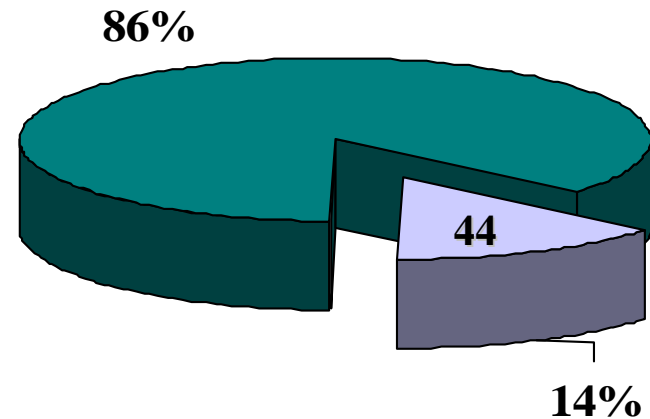
# Tuberculosis in HIV-infected children

**n = 51/374 (12.5%)**

**NON - VACCINATED 64**



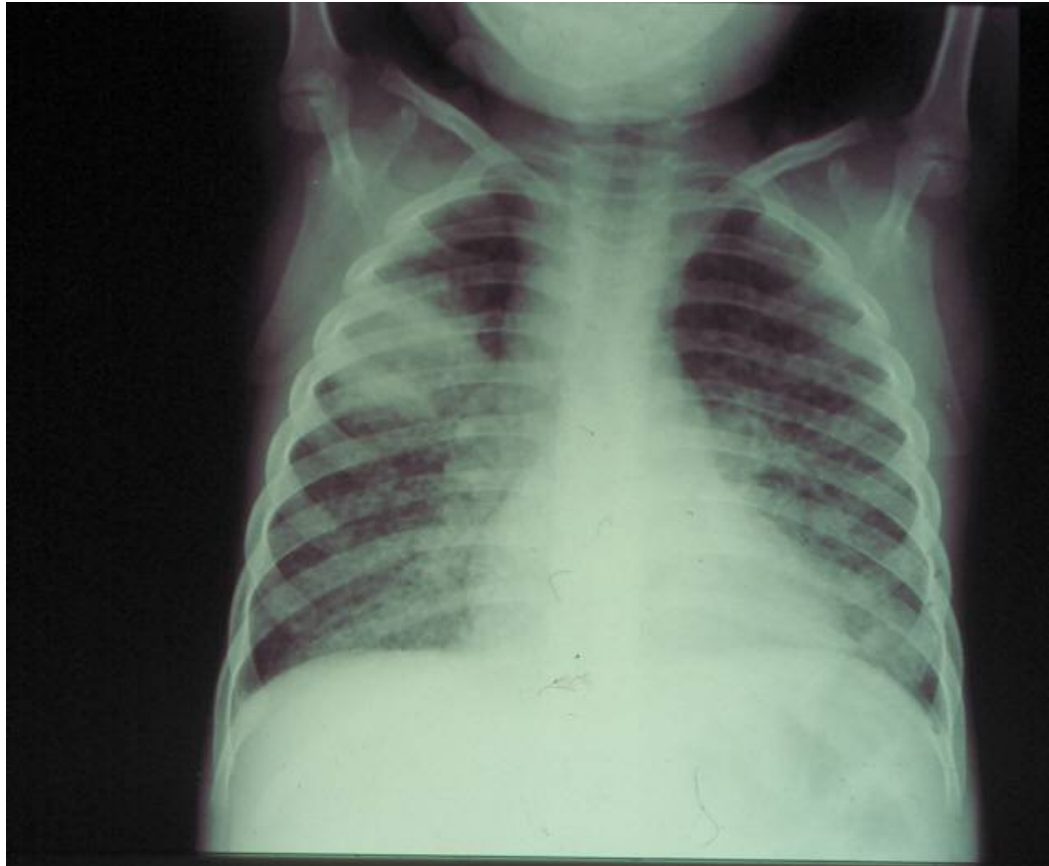
**BCG VACCINATED: 310**



■ TB disease

**11 % vs 14% p= NS**

# Disseminated *M bovis* BCG disease



Source: G. Hussey, UCT

# Sources

- Individual case reports
- Cohort studies
- Cross-sectional studies
- Retrospective reviews

# Definition

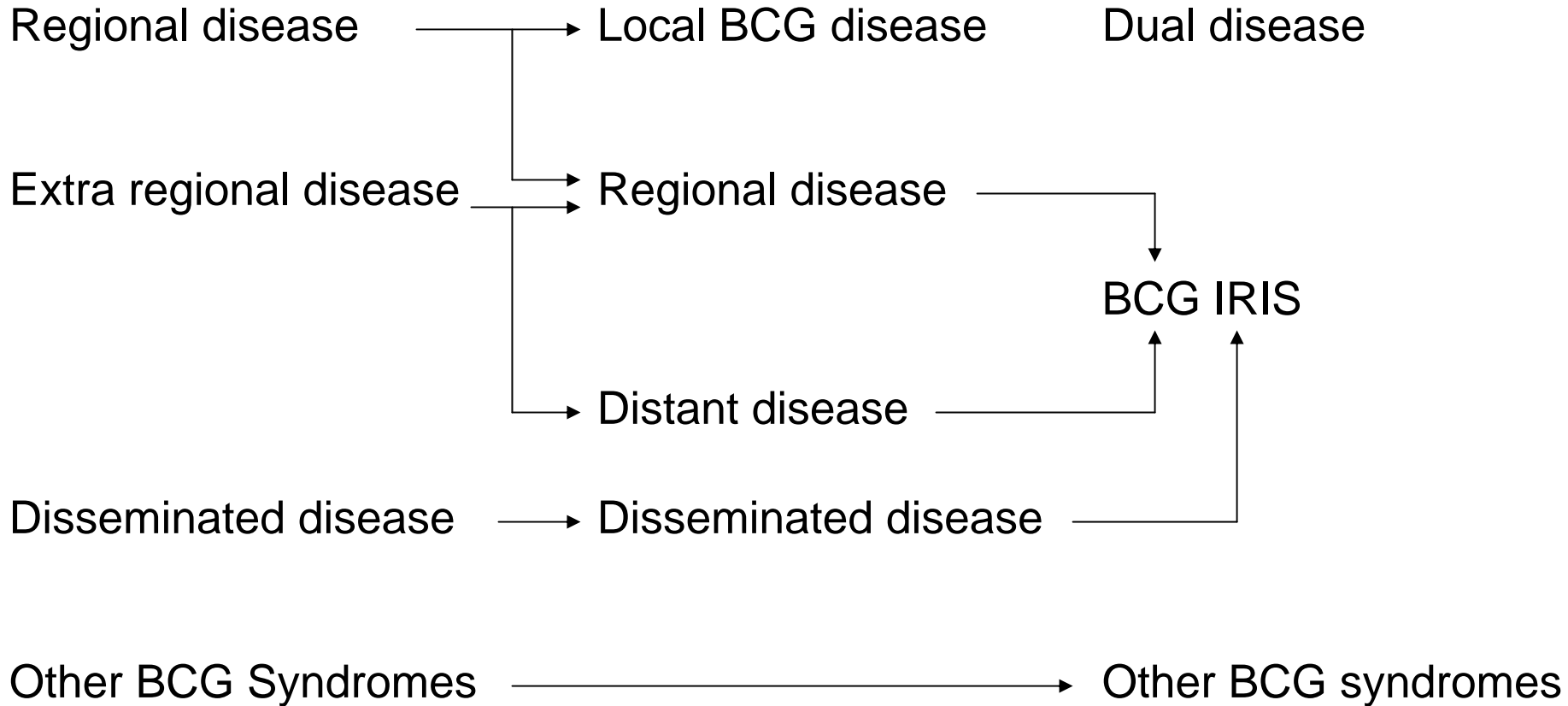
## Talbot - CID 2002

- Positive BCG culture
- Systemic manifestations
- Evidence of dissemination
  - Positive blood or bone marrow culture
  - or
  - Infection involving 2 or more sites beyond the region of vaccination

# Revised paediatric classification

Talbot classification

Revised Hesseling classification



# Case reports

- 11 cases:
  - 8 in children: 3 months – 5 years old
  - 3 in adults: 29,31,34 years old.
- Patients significantly immunocompromised
- High mortality.

# Case series – *M bovis* BCG disseminated disease

	No	%
France – Blanche <i>J Pediatr</i> 1986	3/18	17
France – Besnard <i>PIDJ</i> 1993	2/68	3
Argentina – Bologna <i>X111 AIDS Conf</i> , 2000	12/645	1.8
Argentina - Fallo <i>IDSA</i> , 2001	4/310	1.3

# Cross sectional studies – mycobacterial blood cultures



**BD BACTEC™ MGIT™ 960 System  
for Mycobacteria Testing**

Courtesy and © Becton, Dickinson and Company

## The risks and benefits of childhood bacille Calmette–Guérin immunization among adults with AIDS

Bryan J. Marsh, C. Fordham von Reyn, Jeffrey Edwards\*,  
Matti A. Ristola<sup>†</sup>, Courtenay Bartholomew\*, Richard J. Brindle<sup>‡</sup>,  
Charles F. Gilks<sup>‡</sup>, Richard Waddell, Anna N.A. Tosteson<sup>§</sup>, Robert Pelz,  
Carol H. Sox, Richard Frothingham<sup>¶</sup>, Robert D. Arbeit\*\*  
and the International MAC Study Group<sup>††</sup>

AIDS 1997;11:669

USA, FIN, TRN, KEN  
N=556 hiv + adults

## Bacteremia due to *Mycobacterium tuberculosis* or *M. bovis*, Bacille Calmette–Guérin (BCG) among HIV-positive children and adults in Zambia

Richard D. Waddell, Kennedy Lishimpi<sup>a</sup>, C. Fordham von Reyn,  
Chifumbe Chintu<sup>a</sup>, K.S. Baboo<sup>a</sup>, Barry Kreiswirth<sup>b</sup>, Elizabeth A. Talbot<sup>c</sup>,  
Margaret R. Karagas and the Dartmouth/UCLMS/UNZA Collaborative  
Study Group\*

AIDS 2001;15:55

ZAM  
N=387 ch+ 196 ch-  
N=344 HIV + adults

## Epidemiology of Bloodstream Infections in a Bacille Calmette–Guérin–Vaccinated Pediatric Population in Malawi

Lennox K. Archibald,<sup>1\*</sup> Peter N. Kazembe,<sup>2</sup> Okey Nwanyamwu,<sup>4\*</sup> Charles Mwansambo,<sup>3</sup> L. Barth Reller,<sup>2</sup>  
and William R. Jarvis<sup>1</sup>

JID 2003;188:202

Malawi  
63 HIV + ch  
166 HIV - ch

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, Georgia; <sup>2</sup>Clinical Microbiology Laboratory, Duke University Medical Center, Durham, North Carolina; <sup>3</sup>Lilongwe Central Hospital and <sup>4</sup>United States Agency for International Development, Lilongwe, Malawi

# Mycobacterial blood culture results

	TB complex cultures	
	Cases	Controls
<b>Marsh et al</b> <b>USA, FIN, TRN, KEN</b> <b>556 adult pos</b>	<b>21 <i>M tb</i> positive</b>	
<b>Waddell et al</b> <b>ZAM</b> <b>387 children pos</b> <b>196 children neg</b> <b>344 adult pos</b>	<b>5 <i>M tb</i> and 1 <i>M bovis BCG</i></b>  <b>36 <i>M tb</i></b>	<b>1 <i>M tb</i></b>
<b>Archibald et al</b> <b>Malawi</b> <b>166 children neg</b> <b>63 children pos</b>	<b>0</b>	<b>0</b>

# Blood culture results

	n	<i>M tb</i>	<i>M bovis BCG</i>
HIV pos adults	900	57 (6.3%)	0
HIV pos children	450	5 (1.1%)	1 (0.2%)
HIV neg children	362	1 (0.2%)	0

# Summary of blood culture data

- Disseminated tuberculosis
  - Common in adults with HIV infection.
  - Less common in children
    - Protective effect of BCG?
- Disseminated BCG infection
  - uncommon in adults and children previously immunized with BCG
  - only one reported case

# Danish Bacille Calmette-Guérin Vaccine–Induced Disease in Human Immunodeficiency Virus–Infected Children

A. C. Hesseling,<sup>1</sup> H. S. Schaaf,<sup>1</sup> W. A. Hanekom,<sup>3</sup> N. Beyers,<sup>1</sup> M. F. Cotton,<sup>1</sup> R. P. Gie,<sup>1</sup> B. J. Marais,<sup>1</sup> P. van Helden,<sup>2</sup> and R. M. Warren<sup>2</sup>

<sup>1</sup>Centre for Tuberculosis Research and Education (CENTRE), Department of Pediatrics and Child Health, Tygerberg Children's Hospital, and <sup>2</sup>Department of Medical Biochemistry, Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa; and <sup>3</sup>Division of Infectious Diseases and Immunology, Department of Pediatrics, School of Medicine, University of Miami, Miami, Florida

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An analysis of isolates of *Mycobacterium tuberculosis* complex was performed to determine the prevalence of bacille Calmette-Guérin (BCG) disease among human immunodeficiency virus (HIV)–infected children. Speciation was done with polymerase chain reaction; 183 isolates from mycobacterial cultures for 49 HIV-infected patients were analyzed. The Danish *Mycobacterium bovis* BCG strain was isolated from 5 patients. No cases of Tokyo *M. bovis* BCG strain disease were detected. All patients were asymptomatic at birth, <12 months of age, and severely immunodeficient at presentation. Four patients had regional axillary adenitis ipsilateral to the vaccination site, and 2 had pulmonary BCG disease. Two patients with regional BCG disease had simultaneous pulmonary *M. tuberculosis* infection. Although chest radiographic features were similar to those seen in patients with tuberculosis, BCG disease should be considered in HIV-infected infants with right axillary adenitis ipsilateral to the vaccination site. Young, symptomatic, HIV-infected infants are at risk for BCG-related complications. Controlled, population-based studies are needed to assess the risk of BCG in HIV-infected children.

# Hesseling paper

- 21 patients – Tokyo vaccine: no AEs
- 29 patients – Danish vaccine: 5 AEs
  - 2 had disseminated disease – pos GWs
  - 3 had severe local AE
- Vaccine strain and route important?

# Hesseling paper

- Pre 2000 – Tokyo PC – poor penetration  
*(Kibel & Hussey, SAMJ 1995)*
- Case series - 10 HIV positive infants (given Danish ID) with local adenitis had no evidence of dissemination  
*(Jeena et al. Bull WHO, 2001)*
- PC vs ID Tokyo BCG vaccine – no diff in SAE rate between 2 routes  
*(Hussey CID , 2004)*

# Bacille Calmette-Guérin Vaccine–Induced Disease in HIV-Infected and HIV-Uninfected Children

A. C. Hesselning,<sup>1</sup> H. Rabie,<sup>1</sup> B. J. Marais,<sup>1</sup> M. Manders,<sup>3</sup> M. Lips,<sup>3</sup> H. S. Schaaf,<sup>1</sup> R. P. Gie,<sup>1</sup> M. E. Cotton,<sup>1</sup>  
P. D. van Helden,<sup>2</sup> R. M. Warren,<sup>2</sup> and N. Beyers<sup>1</sup>

<sup>1</sup>Desmond Tutu TB Centre and Department of Pediatrics and Child Health and <sup>2</sup>DST/NRF Centre of Excellence in Biomedical Tuberculosis Research/MRC Centre for Molecular and Cellular Biology, Department of Medical Biochemistry, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa; and <sup>3</sup>Academic Medical Centre, Amsterdam, The Netherlands

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22 children with local disease

8 with distant or disseminated disease – 6 HIV positive

*Median CD4% - 7%*

Mortality rate – 75%



Short communication

## The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children

Anneke C. Hesselning<sup>a,b,\*</sup>, Ben J. Marais<sup>a</sup>, Robert P. Gie<sup>a</sup>, H. Simon Schaaf<sup>a</sup>, Paul E.M. Fine<sup>b</sup>, Peter Godfrey-Faussett<sup>b</sup>, Nulda Beyers<sup>a</sup>

<sup>a</sup> Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, P.O. Box 19063, Tygerberg, 7505, South Africa

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Received 16 May 2006; received in revised form 15 July 2006; accepted 16 July 2006

Table 2

Calculated risk of distant or disseminated BCG disease in HIV-infected children based on the known maternal antenatal HIV prevalence, assumed rates of vertical HIV transmission and estimates of total mid-year population of children <1 year, Western Cape Province, South Africa

Risk scenarios of disseminated BCG disease	Cases/year 2002	Cases/year 2003	Cases/year 2004
Actual cases/year	2	2	3
Risk of disseminated BCG disease			
Case scenario 1, assuming 5% total vertical HIV infection	2/571 = 350/100,000/year	2/608 = 329/100,000/year	3/719 = 417/100,000/year
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Case scenario 3, assuming 15% total vertical HIV infection	2/1713 = 117/100,000/year	2/1825 = 110/100,000/year	3/2158 = 139/100,000/year

# Immune reconstitution inflammatory syndrome

- Patients with AIDS
- On HAART
- Improvement in CD4 count and decrease in VL
- Symptoms consistent with an infectious / inflammatory condition
- Symptoms not explained by newly acquired infection

# IRIS associated with BCG vaccine

- Sharp, 1998 – 1 case
- Puthanakit, 2005 – 4/150 children on HAART
- Hesselning, 2006 – 4 cases
- Nuttall (unpublished) 21/352 children on HAART

# Conclusion: HIV negative children

- In HIV negative children
- BCG vaccine protects against severe disease
- Frequency of SAEs following BCG vaccine - uncommon
- Benefits outweigh risks

## Conclusion: HIV positive children

- Efficacy of BCG vaccine not known
- SAEs do occur – *disseminated M bovis BCG is a problem.*
- Current policy – BCG is recommended for HIV positive infants who are asymptomatic and living in endemic TB countries.
- Risk benefit ratio not known.

# Options

- Change policy
- Make HIV infection a contraindication to BCG vaccination  
*Problem: definition of HIV in early infancy*
- Delay BCG vaccination until infant's HIV status known eg 6 week EPI visit or later  
*Problem: risks and benefits of TB vs BCG disease*
- Major programmatic issues in implementation

# South Africa example

Annual birth cohort 1.1 million

25% of pregnant women HIV positive: 275000 HIV exposed infants

With no ARV prophylaxis in pregnancy: 90000 HIV positive infants

With HIV proph (50-75% effective): 22750- 45000 HIV positive infants

HIV negative infants: 1055000 - 1077250

# Conclusion

- No change in policy given logistical issues.
- Future policy should be informed by good data.
- In absence of data – modelling.
- Consider other alternatives for preventing rapid progression of HIV and prevention of TB in HIV positive children
  - Strengthen HIV services
  - HAART for all infants
  - INH prophylaxis:

*Zar et al, BMJ 2006*

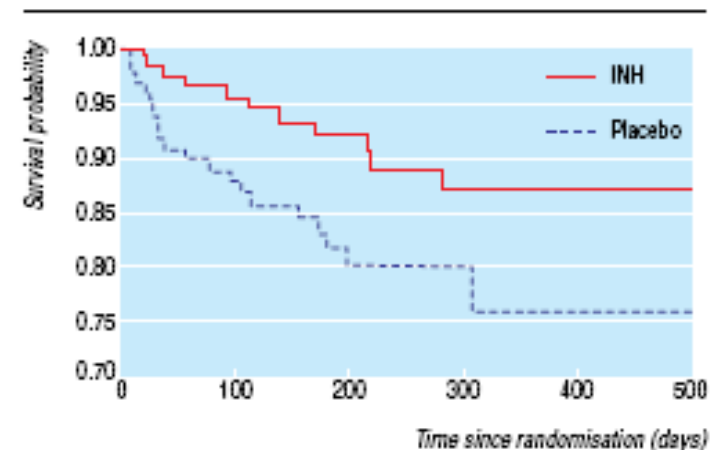


Fig 2 Survival in children on isoniazid (INH) or placebo