



UNIVERSITY OF CAPE TOWN



**A Randomized, Controlled Trial Comparing the  
Efficacy of Percutaneous and Intradermal  
Vaccination of Tokyo 172 BCG in the Prevention of  
Tuberculosis in Infants Vaccinated at Birth**

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## Background

- The South African Department of Health changed its immunization policy in 2000 from percutaneous Tokyo 172 (vaccine locally produced and tools locally manufactured) to intradermal Danish 1331 BCG (imported)
- The decision to change was based on limited scientific data, as well as practical, political and economic considerations. The two routes had not hitherto been compared in a clinical trial.
- The consultative committee which made the recommendation emphasized the need for clarification around the question of which route was more efficacious – percutaneous or intradermal - and encouraged the South African TB vaccine community to conduct further studies in this regard.

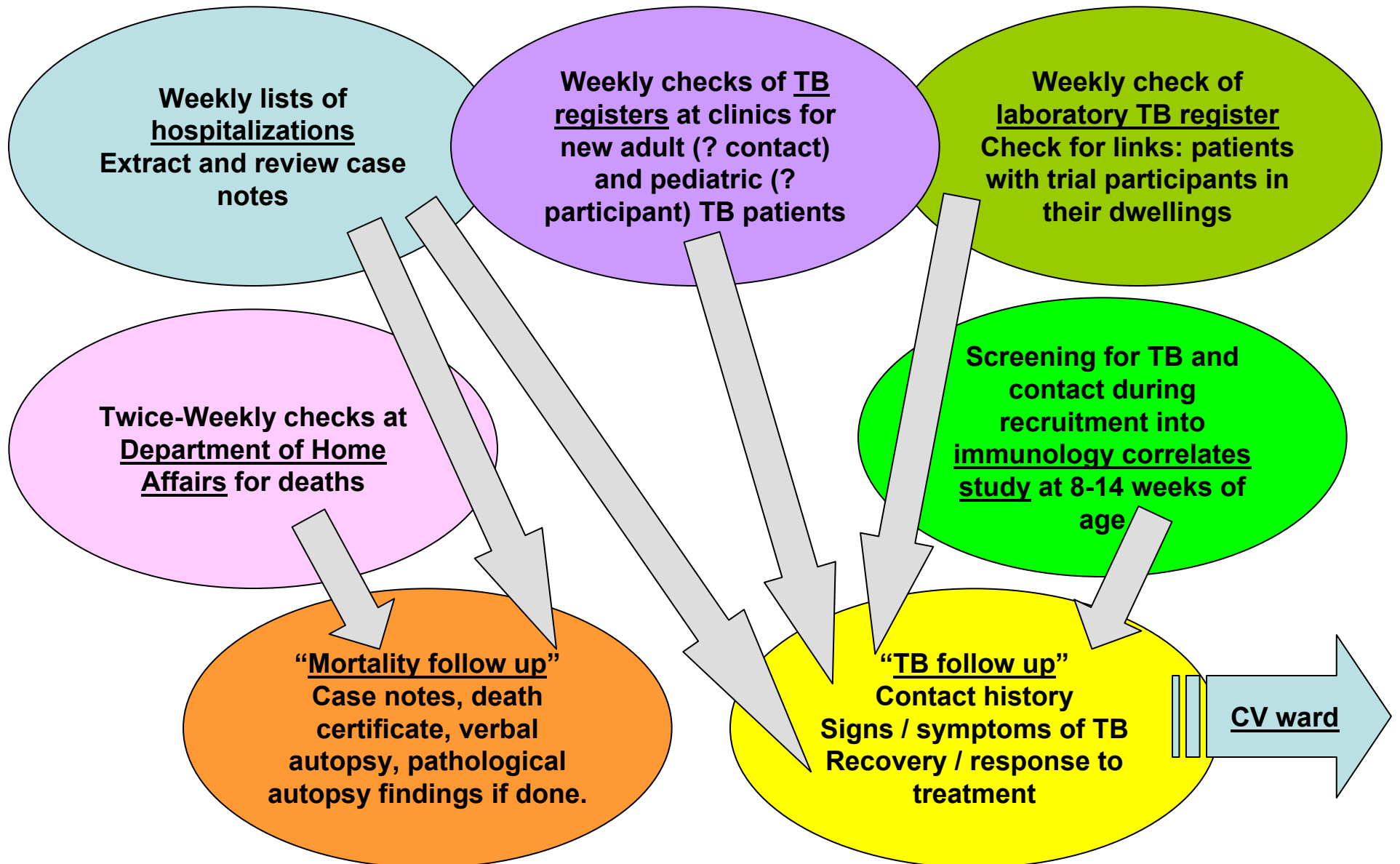
## Objectives

- The primary objective of the trial was to compare the efficacy of the percutaneous with the intradermal route of administration of Japanese (Tokyo) 172 BCG in the prevention of tuberculosis with bacteriological or histological confirmation or meeting strict clinical criteria, during the first two years of life.
- Two other important reasons to conduct the trial were:
  - To develop the trial site in preparation for future phase III trials of new TB vaccines and
  - To allow the performance of a nested case control study whose objective it is to determine whether the frequency of mycobacteria-specific CD4+ T cells in peripheral blood 14 weeks after newborn BCG vaccination correlates with protection against childhood tuberculosis in the first 4 years of life.

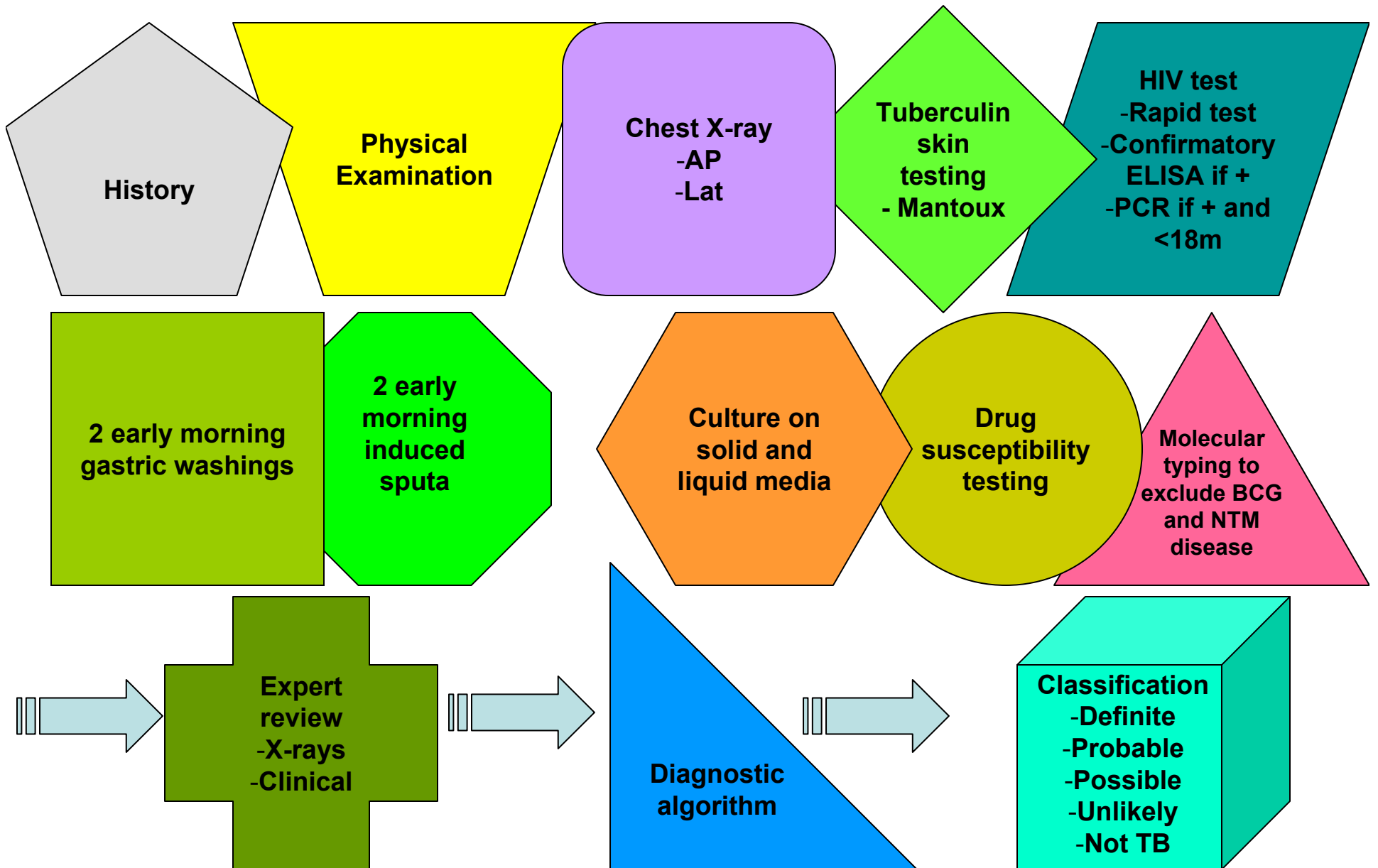
## Design

<b>Activity</b>	<b>Period</b>	<b>Personnel</b>	<b>Numbers</b>	<b>Comments</b>
<b>Recruitment and enrollment</b>	<b>3/01 – 7/04</b>	<b>Community counselors</b>	<b>13338</b>	
<b>Vaccination</b>	<b>3/01 – 7/04</b>	<b>Maternity ward nurses</b>	<b>11680</b> <b>- 5905 ID</b> <b>- 5775 PC</b>	<b>Randomized to PC/ID by week of birth</b>
<b>Follow up for vaccine reactions</b>	<b>4/01 – 10/04</b>	<b>Immunization clinic nurses</b>	<b>4851 infants seen at least once</b>	<b>At 3 sentinel clinics</b>
<b>Follow up for:</b> •Deaths •Hospitalizations and other SAE's •TB contacts and suspects	<b>3/01 – 7/06</b>	<b>Surveillance team (study staff)</b>	<b>11680</b>	<b>Largely passive</b>
<b>Investigation of all contacts and suspects</b>	<b>11/01 – 9/06</b>	<b>Case verification ward team (study staff)</b>	<b>1984 admissions</b> <b>1751 infants</b>	
<b>Review of all SAE's including deaths</b>	<b>11/01 – 9/06</b>	<b>SAE review team (study physicians)</b>	<b>3242 hospitalizations</b> <b>+ 187 deaths</b>	<b>Reviewed for BCG and TB relatedness and resolution</b>

# Surveillance



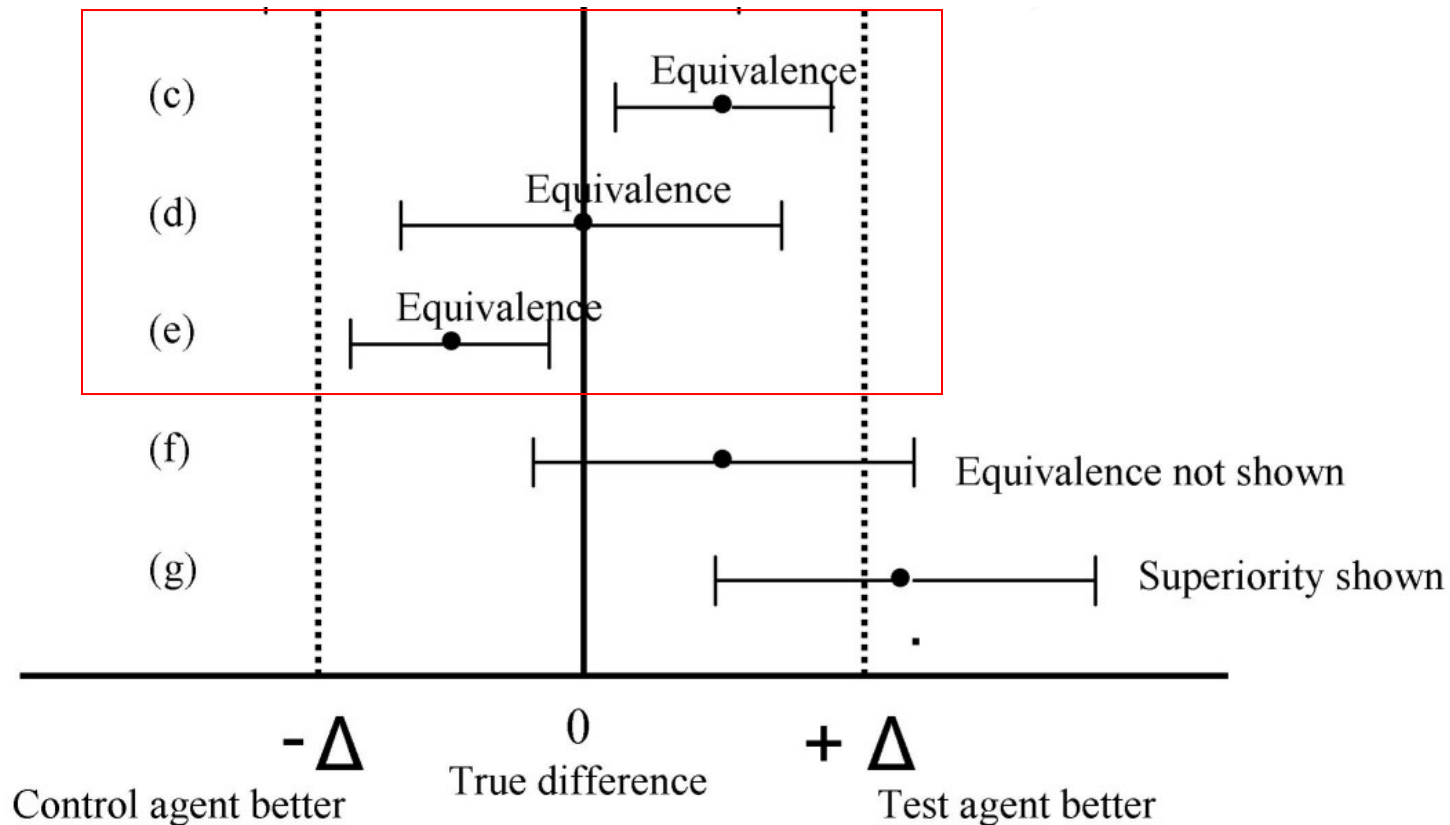
# Diagnosis



## Simplified Classification for pulmonary cases

<b>Classification</b>	<b>Culture for <i>Mycobacterium tuberculosis</i></b>	<b>Chest X-ray (2 of 3 experts had to agree)</b>	<b>Epidemiological / Clinical evidence</b>	<b>Other</b>
<b>Definite TB</b>	Positive	Either	Present or absent	
<b>Probable TB</b>	Negative / no result	Suggestive	Present	
<b>Possible TB</b>	Negative / no result	Suggestive	Absent or scanty	
<b>Unlikely TB</b>	Negative / no result	Not suggestive	Absent or scanty	Diagnosed as TB and started on TB treatment
<b>Not TB</b>	Negative / no result	Not suggestive	Absent or scanty	

## Equivalence margin



For an equivalence trial, the two-sided 95% confidence interval – defining the range of possible differences between the test and the control agent – should lie entirely within the interval ( $-\Delta$  to  $+\Delta$ ) (lines c, d, and e)

# Results

- All results are for
  - Intention to treat population
  - Events occurring up to 2 years after vaccination
- Confidence intervals are 95.5% to adjust for two interim analyses which were performed as part of the data safety monitoring plan

## Baseline comparisons

Factor	Intradermal (n=5905)	Percutaneous (n=5775)	Both routes (n=11680)	P value
Years of exposure	14576.9	14376.7	28953.6	
Male gender	3026 (51.2%)	2917 (50.5%)	5943 (50.9%)	0.43 (CMH)
Mean gestational age at birth (w)	38.57 (sd=2.23)	38.54 (sd=2.24)	38.56 (sd=2.23)	0.48 (ANOVA)
Preterm births (<37 weeks)	1038 (17.6%)	981 (17.0%)	2019 (17.3%)	
Caesarian sections	645 (10.9%)	635 (11.0%)	1280 (11.0%)	0.71 (CMH)
Multiple births	48 (0.8%)	70 (1.2%)	118 (1.0%)	0.04 (CMH)
Mean birth weight (kg)	2.93 (sd=0.53)	2.93 (sd=0.53)	2.93 (sd=0.53)	0.78 (ANOVA)
Low birth weight (<=2.5kg)	1234 (20.9%)	1185 (20.5%)	2419 (20.7%)	
Ethnicity (Black: "Colored")	977 (16.5%): 4622 (78.23%)	995 (17.2%): 4501 (77.9%)	1972 (16.9%): 9123 (78.1%)	
Mean maternal age at infant's birth (y)	25.70 (sd=6.45)	25.65 (sd=6.38)	25.67 (sd=6.42)	0.64 (ANOVA)

## Overall outcomes

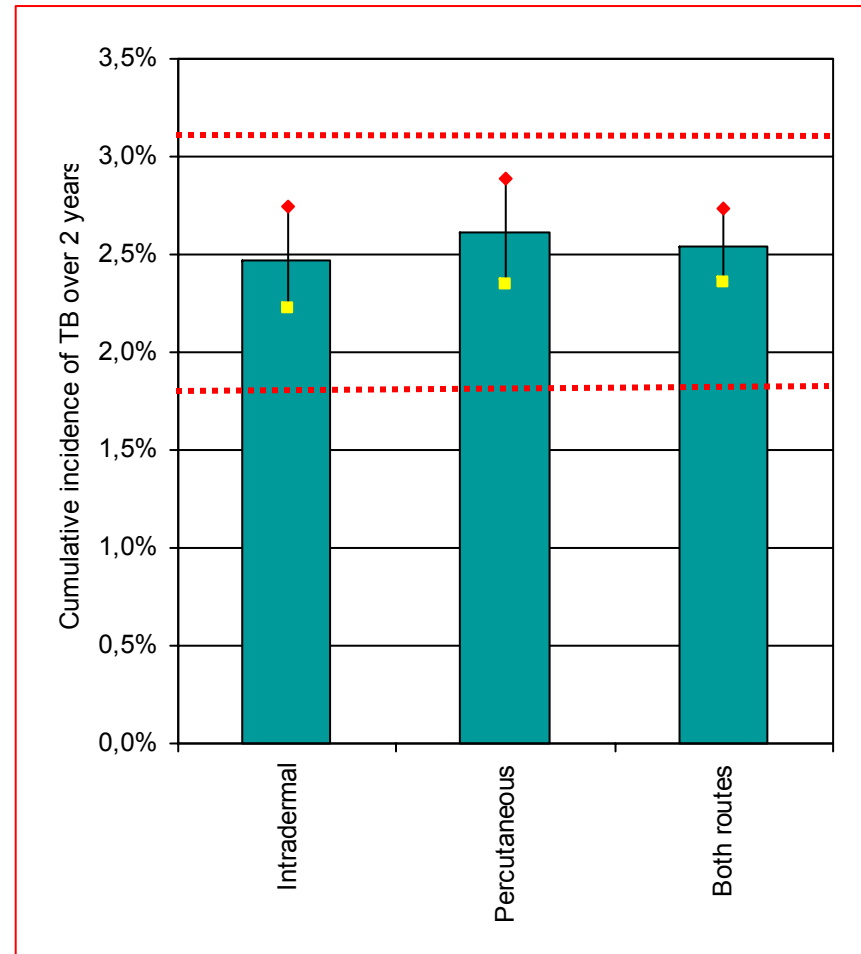
(Cumulative incidence over 2 years, diagnosed under 2 years of age, diagnosed in CV ward, ITT population)

Classification	Intradermal	Percutaneous	Total
Definite TB	89 (1.51%)	83 (1.44%)	172 (1.47%)
Probable TB	95 (1.61%)	118 (2.04%)	213 (1.82%)
Possible TB	177 (3.00%)	174 (3.01%)	351 (3.01%)
Unlikely TB	204 (3.45%)	232 (4.02%)	436 (3.73%)
Def + Prob + Poss	361 (6.12%)	375 (6.49%)	736 (6.3%)

## Efficacy by route: Definite, Probable and Possible TB Incidence rate

- Number of cases (incidence rate per 100 person-years of exposure):
  - Intradermal: 361 (2.47)
  - Percutaneous: 375 (2.60)
  - Both routes: 736 (2.54)
- Rate difference (95.5% CI):
  - -0.13 (-0.51 to 0.24)
- Rate ratio (95.5% CI):
  - 0.95 (0.82 to 1.10)

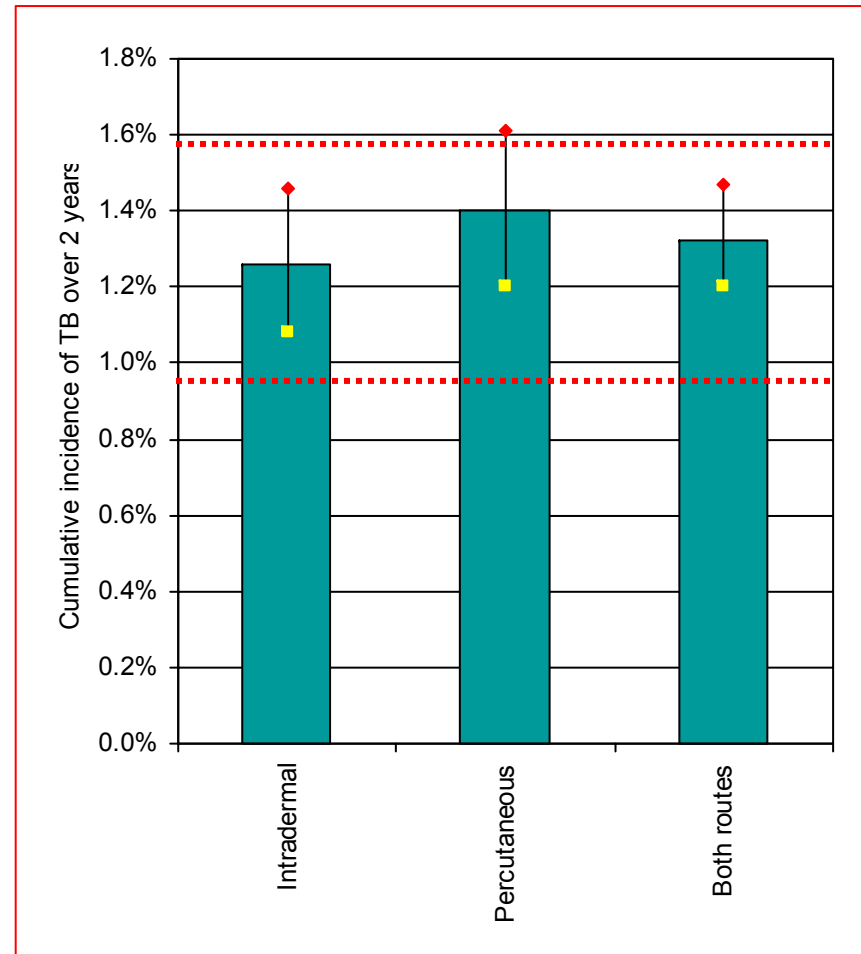
Dotted red lines = 75% and 125% of the ID incidence rate point estimate (1.85; 3.09)



## Efficacy by route: Definite and Probable TB Incidence rate

- Number of cases (incidence rate per 100 person-years of exposure):
  - Intradermal: 184 (1.26)
  - Percutaneous: 201 (1.40)
  - Both routes: 385 (1.33)
- Rate difference (95.5% CI):
  - -0.14 (-0.41 to 0.14)
- Rate ratio (95.5% CI):
  - 0.90 (0.73 to 1.11)

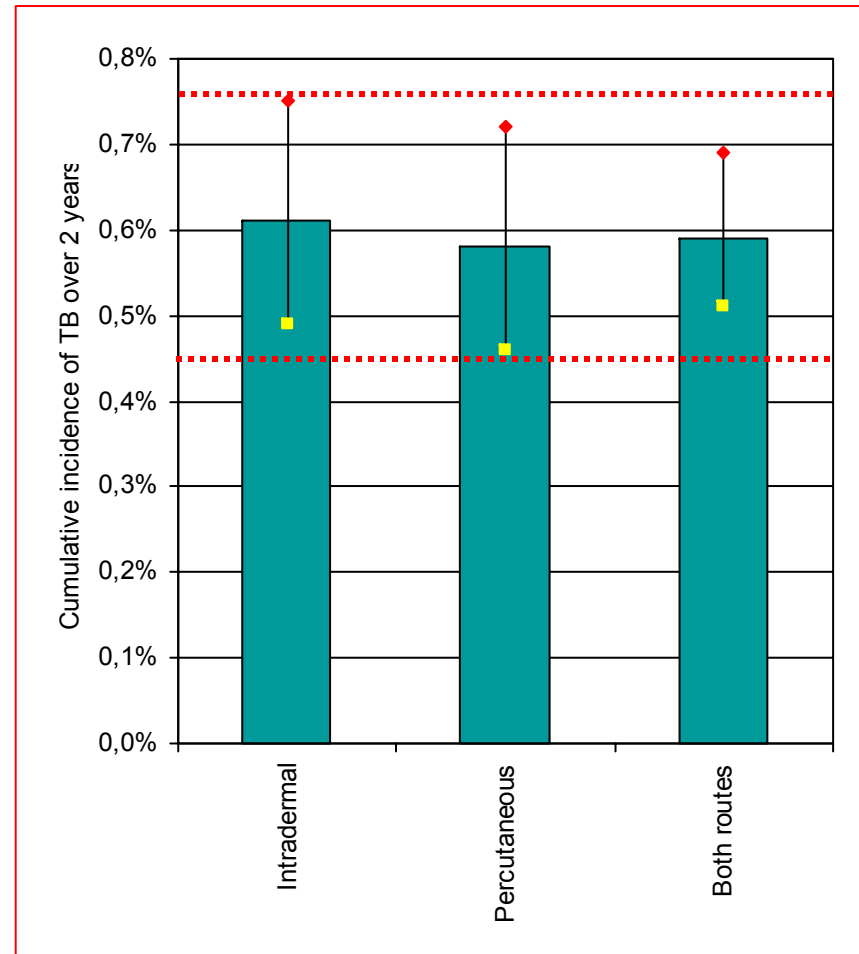
Dotted red lines = 75% and 125% of the ID incidence rate point estimate (0.95%; 1.58%)



## Efficacy by route: Definite TB only Incidence rate

- Number of cases (incidence rate per 100 person-years of exposure):
  - Intradermal: 89 (0.61)
  - Percutaneous: 83 (0.58)
  - Both routes: 172 (0.59)
- Rate difference (95.5% CI):
  - 0.03 (-0.14 to 0.21)
- Rate ratio (95.5% CI):
  - 1.06 (0.77 to 1.45)
- Note change in direction

Dotted red lines = 75% and 125% of the ID incidence rate point estimate (0.46; 0.76)

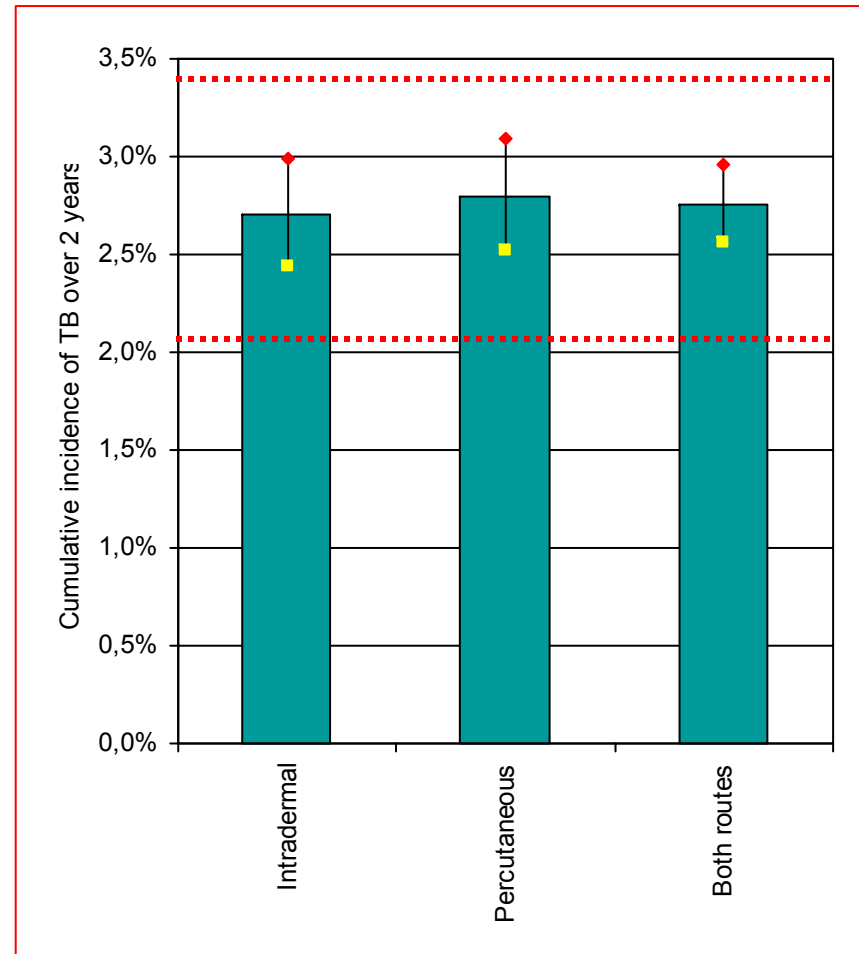


## Efficacy by route: Definite, Probable and Possible TB: cases diagnosed both in and outside the CV ward

### Incidence rate

- Number of cases (incidence rate per 100 person-years of exposure):
  - Intradermal: 395 (2.70)
  - Percutaneous: 402 (2.80)
  - Both routes: 797 (2.75)
- Rate difference (95.5% CI):
  - -0.08 (-0.05 to 0.30)
- Rate ratio (95.5% CI):
  - 0.97 (0.84 to 1.12)

Dotted red lines = 75% and 125% of the ID incidence rate point estimate (2.03; 3.38)



## Safety: Vaccine related adverse events

Type of event	Intradermal n (IR/100PYE)	Percutaneous n (IR/100PYE)	Both routes n (IR/100PYE)	Risk Difference (95.5% CI)	Risk ratio (95.5% CI)
Keloids	10 (0.07)	6 (0.04)	16 (0.06)	0.03 (-0.03 TO 0.08)	1.64 (0.53 to 5.66)
Suppurative lymphadenitis	2 (0.01)	3 (0.02)	5 (0.02)	-0.01 (-0.04 to 0.02)	0.66 (0.51 to 6.02)
Disseminated BCG disease	0 (0.000)	1 (0.007)	1 (0.003)	-0.007 (-0.021 to 0.007)	0 (0 to 43.396)

## Safety: Hospitalisations

Participants with at least one hospitalisation for ... ↓	Intradermal (n=5905)	Percutaneous (n=5775)	Both routes (n=11680)	Risk Difference (95.5% CI)	Risk ratio (95.5% CI)
All causes	1091 (18.49%)	1090 (18.88%)	2181 (18.68%)	-0.39% (-1.83 to 1.06%)	0.99 (0.94 to 1.04)
Infectious and parasitic causes	565 (9.57%)	563 (9.75%)	1128 (9.66%)	-0.18% (-1.28 to 0.92%)	0.98 (0.88 to 1.10)
Endocrine, nutritional and metabolic causes	116 (1.96%)	115 (1.99%)	231 (1.98%)	-0.03% (-0.54 to 0.49%)	0.99 (0.76 to 1.28)
Central nervous system causes	64 (1.08%)	69 (1.19%)	133 (1.14%)	-0.11% (-0.50 to 0.28%)	0.91 (0.64 to 1.28)
Eye and Ear causes	43 (0.73%)	58 (1.00%)	101 (0.86%)	-0.28% (-0.62 to 0.07%)	0.73 (0.49 to 1.08)
Respiratory system causes	495 (8.38%)	499 (8.64%)	994 (8.51%)	-0.26% (-1.29 to 0.77%)	0.97 (0.86 to 1.10)
Gastrointestinal causes	88 (1.49%)	69 (1.12%)	157 (1.34%)	0.30% (-0.13 to 0.72%)	1.25 (0.91 to 1.72)
Perinatal conditions	51 (0.86%)	67 (1.16%)	118 (1.01%)	-0.30% (-0.67 to 0.08%)	0.74 (0.51 to 1.08)

## Safety: Deaths

Item	Intradermal (n=5905)	Percutaneous (n=5775)	Both routes (n=11680)	Risk Difference (95.5% CI)	Risk ratio (95.5% CI)
All deaths	102 (1.73%)	85 (1.47%)	187 (1.60%)	0.03% (-0.21 to 0.72%)	1.17 (0.88 to 1.57)
Deaths due to TB	2 (0.03%)	2 (0.03%)	4 (0.03%)	0.00% (-0.07 to 0.07%)	0.98 (0.13 to 7.26)
Deaths due to infectious / parasitic disease	36 (0.61%)	32 (0.55%)	68 (0.58%)	0.06% (-0.22 to 0.34%)	1.10 (0.68 to 1.79)
Deaths due to respiratory disease	27 (0.46%)	18 (0.31%)	45 (0.39%)	0.15% (-0.08 to 0.37%)	1.47 (0.80 to 2.70)
Deaths due to perinatal conditions	7 (0.12%)	3 (0.05%)	10 (0.09%)	0.07% (-0.04 to 0.17%)	2.28 (0.57 to 9.10)
Deaths due to gastrointestinal conditions	17 (0.29%)	18 (0.31%)	35 (0.30%)	-0.02% (-0.23 to 0.18%)	0.92 (0.47 to 1.82)
Deaths due to unknown cause	21 (0.36%)	23 (0.41%)	44 (0.39%)	-0.04% (-0.27 to 0.18%)	0.86 (0.49 to 1.63)

## Other comparisons

- No difference when per protocol population substituted for intention to treat population
- Extrapulmonary TB (miliary, meningitic, other): very few cases after review and mostly after 2 years of age – rates not meaningful.
- Secondary analyses ongoing

## Conclusions and policy implications

- We found no significant differences between the intradermal and percutaneous routes of BCG vaccination in terms of safety or efficacy in the prevention of tuberculosis in infants and young children.
- We suggest that international bodies should recommend either route, not the ID route above the PC route, and that national vaccination programs should base their choice of route on issues other than the above, viz:
  - Cost of the vaccine and tools
  - Ease of procurement of vaccines and tools
  - Training and quality management issues
  - Ease of administration for local vaccination program staff

# Acknowledgments

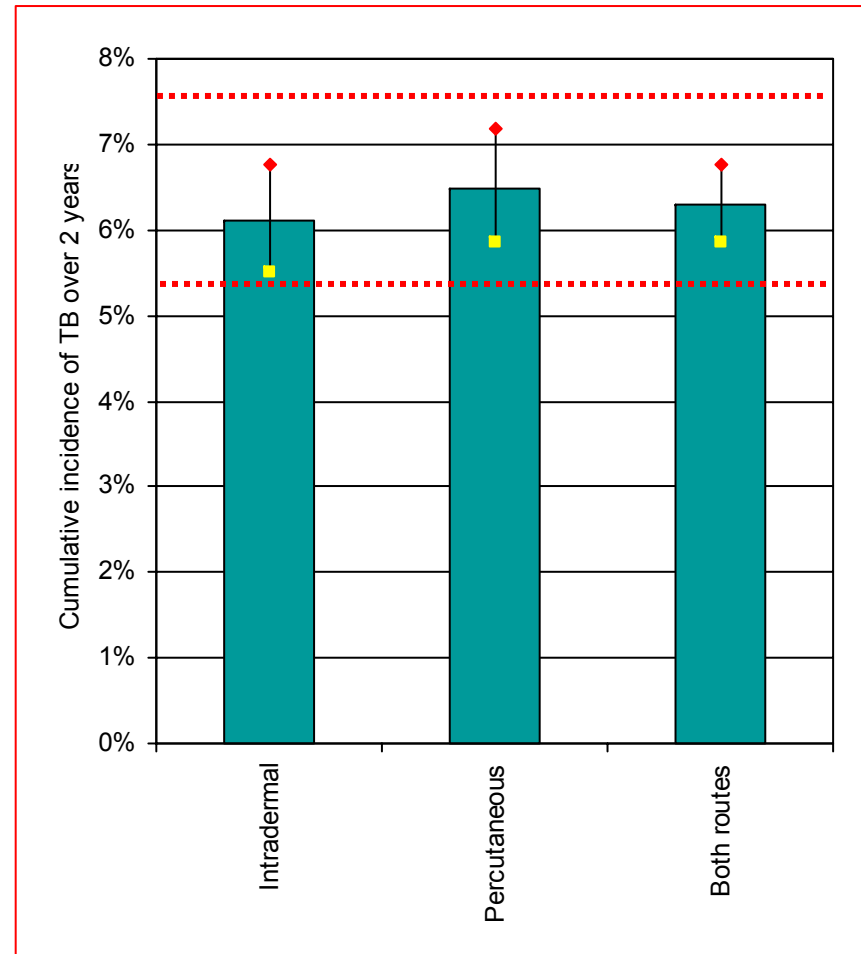
- **Cape Town, SA:**
  - Des Fransman
  - Francesca Little
  - Hassan Mahomed
  - Heather Zar
  - John Burgess
  - Karen Iloni
  - Lesley Workman
  - Maurice Kibel
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  - Aysel Gumusboga
  - Peggy Goetz
  - Angela West
- **PHRI, New Jersey**
  - Gilla Kaplan

Extra slides

## Efficacy by route: Definite, Probable and Possible TB Cumulative incidence / risk

- Number of cases (cumulative incidence over 2 years):
  - Intradermal: 361 (6.11%)
  - Percutaneous: 375 (6.49%)
  - Both routes: 736 (6.30%)
- Risk difference (95.5% CI):
  - -0.38% (-1.28 to 0.01%)
- Risk ratio (95.5% CI):
  - 0.94 (0.81 to 1.09)

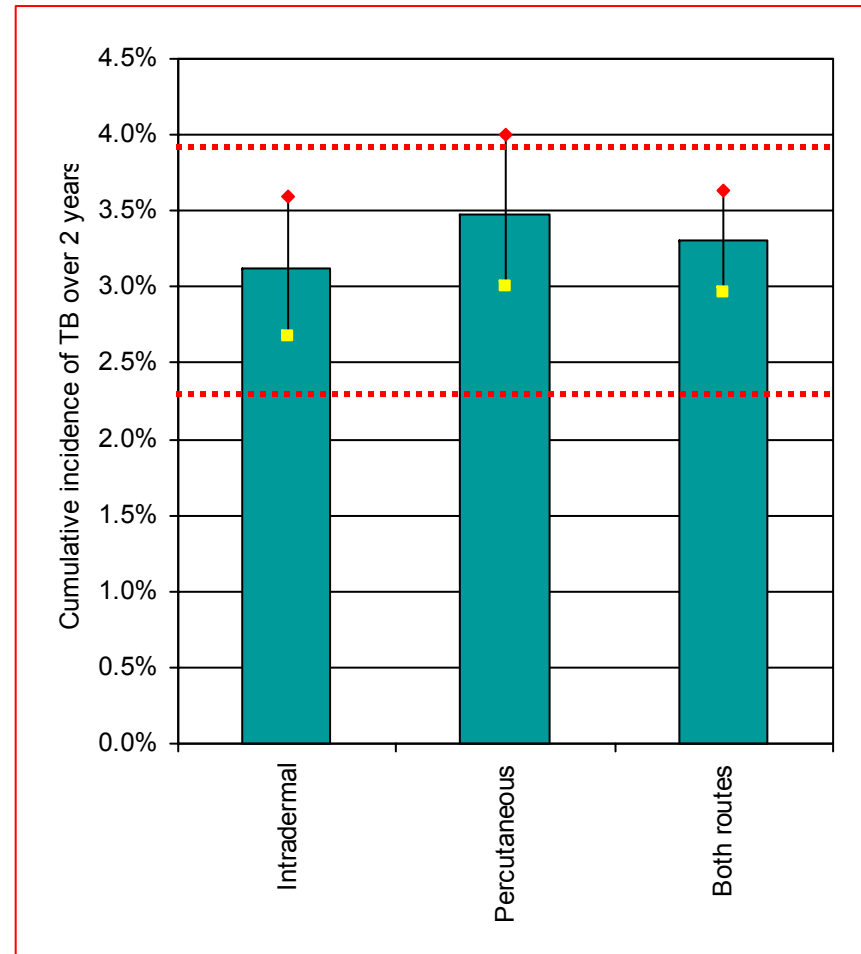
Dotted red lines = 75% and 125% of ID cumulative incidence point estimate (5.36%; 7.64%)



## Efficacy by route: Definite and Probable TB Cumulative incidence / risk

- Number of cases (cumulative incidence over 2 years):
  - Intradermal: 184 (3.12%)
  - Percutaneous: 201 (3.48%)
  - Both routes: 736 (3.30%)
- Risk difference (95.5% CI):
  - -0.36% (-1.03 to 0.30%)
- Risk ratio (95.5% CI):
  - 0.90 (0.73 to 1.09)

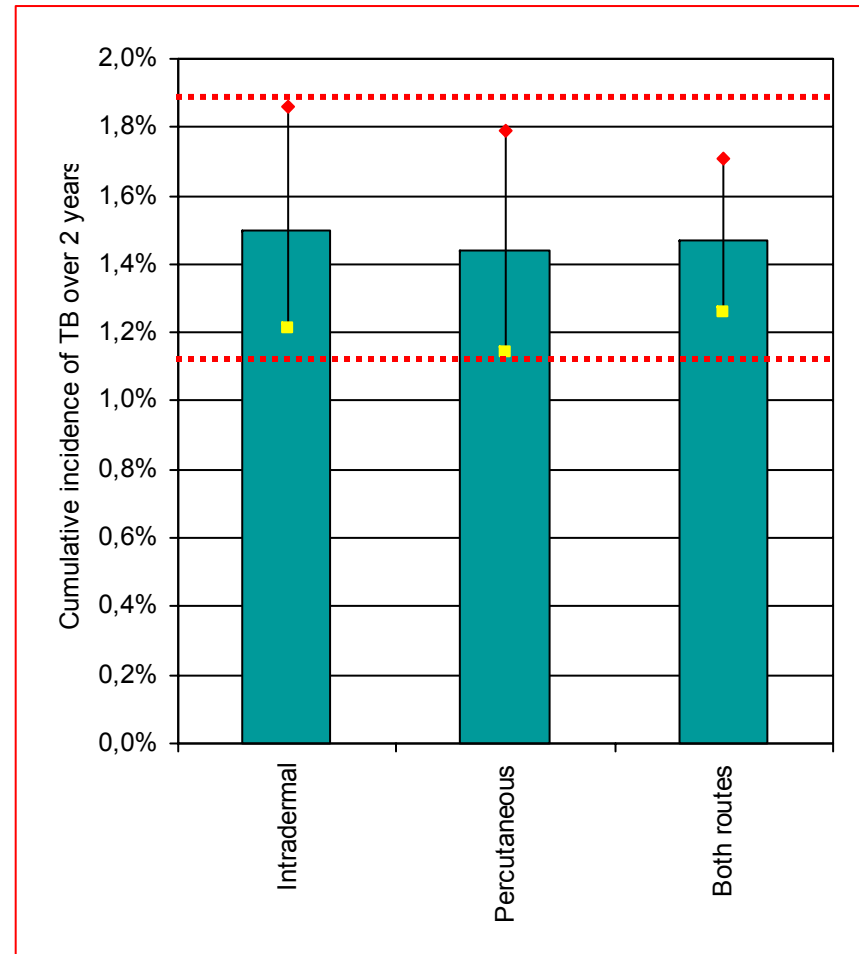
Dotted red lines = 75% and 125% of ID cumulative incidence point estimate (2.34%; 3.90%)



## Efficacy by route: Definite TB only Cumulative incidence / risk

- Number of cases (cumulative incidence over 2 years):
  - Intradermal: 89 (1.51%)
  - Percutaneous: 83 (1.44%)
  - Both routes: 172 (1.47%)
- Risk difference (95.5% CI):
  - 0.07% (-0.04 to 0.52%)
- Risk ratio (95.5% CI):
  - 1.05 (0.77 to 1.42)
- Note change in direction

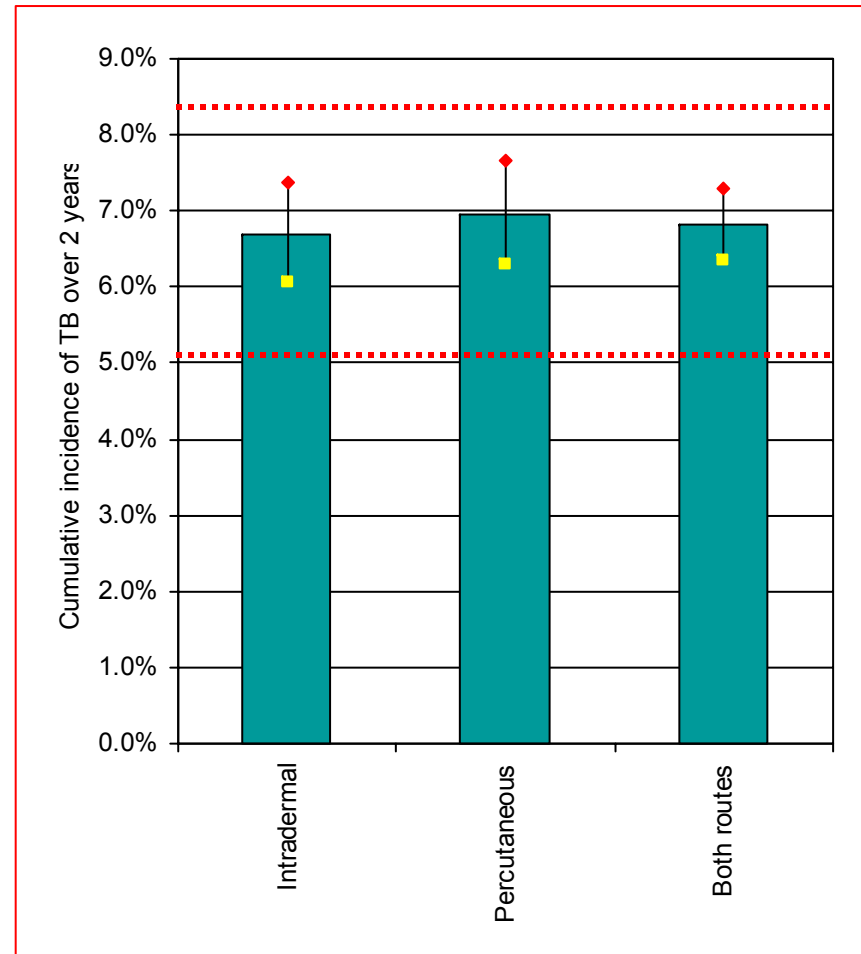
Dotted red lines = 75% and 125% of ID cumulative incidence point estimate (1.13%; 1.89%)



Efficacy by route: Definite, Probable and Possible TB: cases diagnosed both in and outside the CV ward  
Cumulative incidence / risk

- Number of cases (cumulative incidence over 2 years):
  - Intradermal: 395 (6.69%)
  - Percutaneous: 402 (6.96%)
  - Both routes: 797 (6.82%)
- Risk difference (95.5% CI):
  - -0.27% (-0.01 to 0.66%)
- Risk ratio (95.5% CI):
  - 0.96 (0.84 to 1.10)

Dotted red lines = 75% and 125% of ID cumulative incidence point estimate (5.02%; 8.36%)



## Safety: Minor Vaccine Reactions

Type of VR	Intradermal (n=2394 participants) # (%) with attribute at first visit)	Percutaneous (n=2456 participants) # (%) with attribute at first visit)	Both routes (n=4850 participants) # (%) with attribute at first visit)	Risk Difference (95.5% CI)	Risk ratio (95.5% CI)
Visible / palpable vaccination wound/scar	2265 (92.2%)	2372 (99.1%)	4637 (95.6%)	6.9%	1.07
Firm / swollen BCG site	404 (17.0%)	67 (2.7%)	471 (9.7%)	14.3%	6.3
Palpable axillary or other lymph nodes	53 (2.2%)	48 (2.0%)	101 (2.1%)	-0.2%	0.91

# Extrapulmonary TB cases Under 2 years

	ID	PC	Total
TBM	3	1	4
Miliary	0	1	1
Abdomen	0	1	1
Spine	0	1	1
Total	3	4	7