

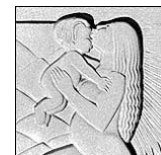
Lessons from the BCG-REVAC: a large randomised trial of the efficacy of BCG revaccination

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Outline of the presentation

Overview of tuberculosis, BCG vaccine

Overview of the design and main findings
of the BCG-REVAC Trial

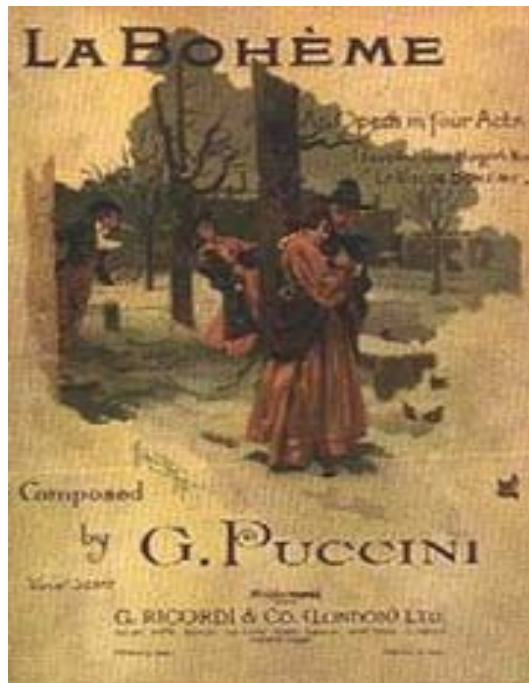
More detailed look at methods and process
used a lessons learned



Overview of tuberculosis, and BCG vaccine



Tuberculosis in the world today:



Every year:

New Cases: 8 million

Infectious: 3.5 million

Deaths: Just under 2 million



Multi drug resistance

HIV & AIDS





BCG: an old vaccine against tuberculosis

Recommended by the League of Nations in 1928

The most widely used vaccine
Protection is complex

No correlates of protection

Not safe in persons with AIDS

New vaccines in development



Léon Charles
Albert Calmette



Camille Guerin



Neonatal BCG is recommended when

rate of (smear-positive pulmonary) tuberculosis of 5 per 100 000 population

or

rate of tuberculous meningitis in children under five of 1 per 10 million population



Neonatal BCG is estimated to have prevented between 25 000 to 50 000 cases of tuberculous meningitis a year

in addition to cases of pulmonary tuberculosis, of other forms of tuberculosis, and cases of leprosy...

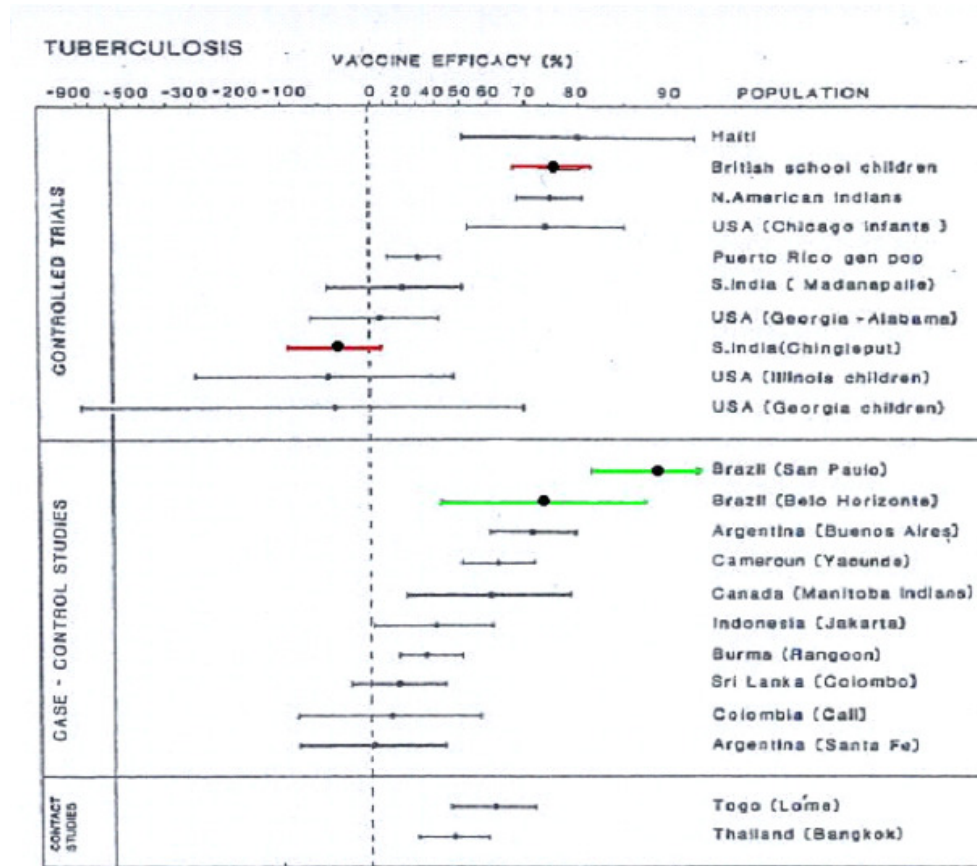
*Leprosy Archives
The Maltese Islands*



*Compiled by
C. Savona-Ventura*



BCG protection against pulmonary tuberculosis varies



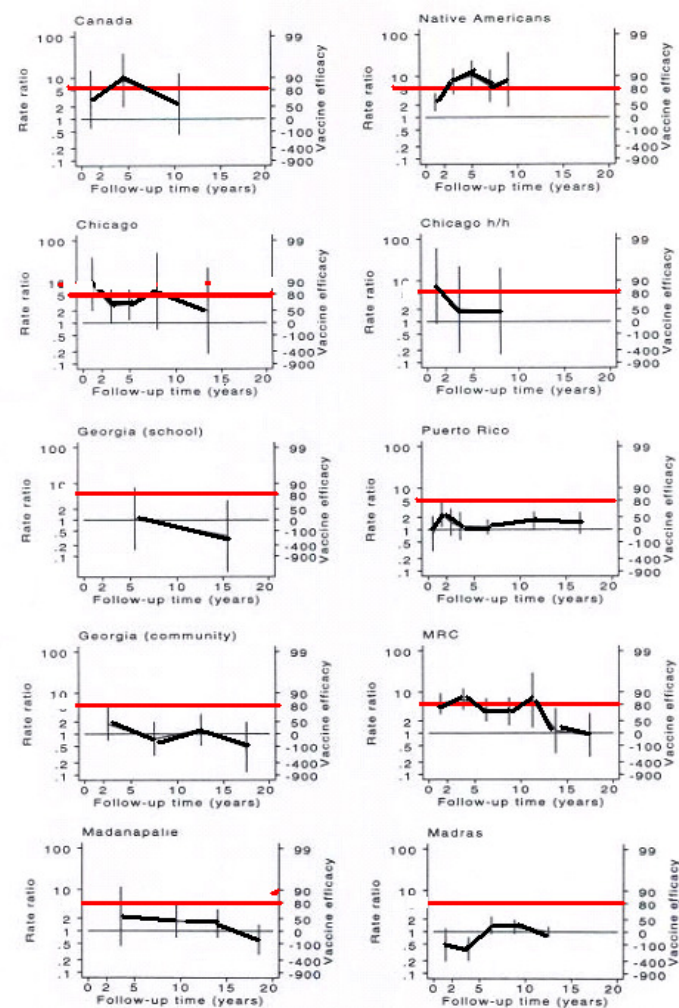
Pine & Rodrigues, Lancet 1990

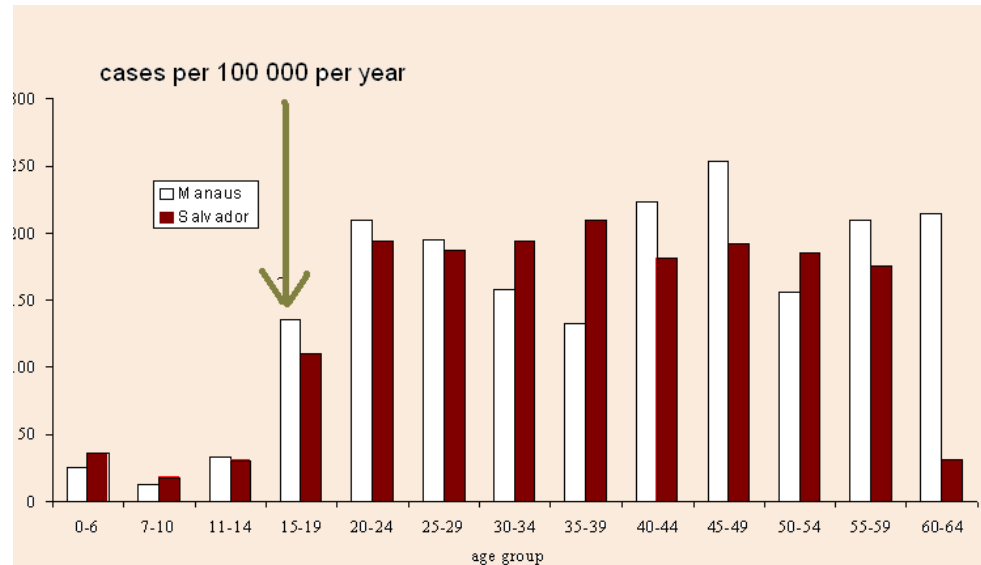


Does BCG protection last?

Meta-analysis of data from
10 published trials

No evidence of protection
lasting more than 10
years





The incidence of tuberculosis increases in young adults

If neonatal BCG protection doesn't last, should we revaccinate with BCG while we wait for new tuberculosis vaccines to be developed?



Revaccinate with BCG?

1995 – Many countries revaccinated but there was no substantive evidence either way

WHO recommended NOT to revaccinate!

Brazilian TB control program recommended revaccinate!

Brazilian states disagreed!



Overview of the design and main findings of the BCG-REVAC Trial



Manaus



Salvador



BCG-REVACC TRIAL

A trial of the protection of BCG revaccination against tuberculosis



Main Objective:

To evaluate the impact of a BCG dose at school age on tuberculosis incidence in a population with high coverage of neonatal BCG

Secondary objectives:

- a- to evaluate the impact on leprosy;
- b- in long term, to compare the BCG effect in places environmentally different (differences in the prevalence of environmental mycobacteria?)





Preparation



Meetings with Federal, State
and Local level
Governmental Health and
Education agencies



Meetings with the Paediatrics and
Pulmonary Medicine Brazilian
Societies



Meeting with participating
schools's staff and parents



costs

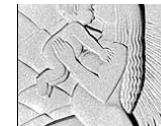
Initial funding:

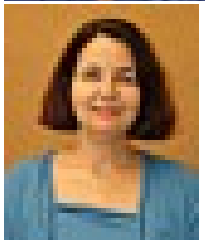
£180 000 UK Dept for International Development, UK
(equivalent to £240 000 today: under half a million dollars)

Matched by Brazilian funding
(Tuberculosis control programme)



Other additional, smaller grants for continued follow up





Study design

- Design: Cluster Randomised Controlled Trial
- Schools randomized (in pairs) to BCG revaccination/no revaccination
- Population: school children (7-14)
- Recruitment: school records, visit, confirm ID, examine arm for BCG scar
- Cases: from tuberculosis control program, validated & linked to database



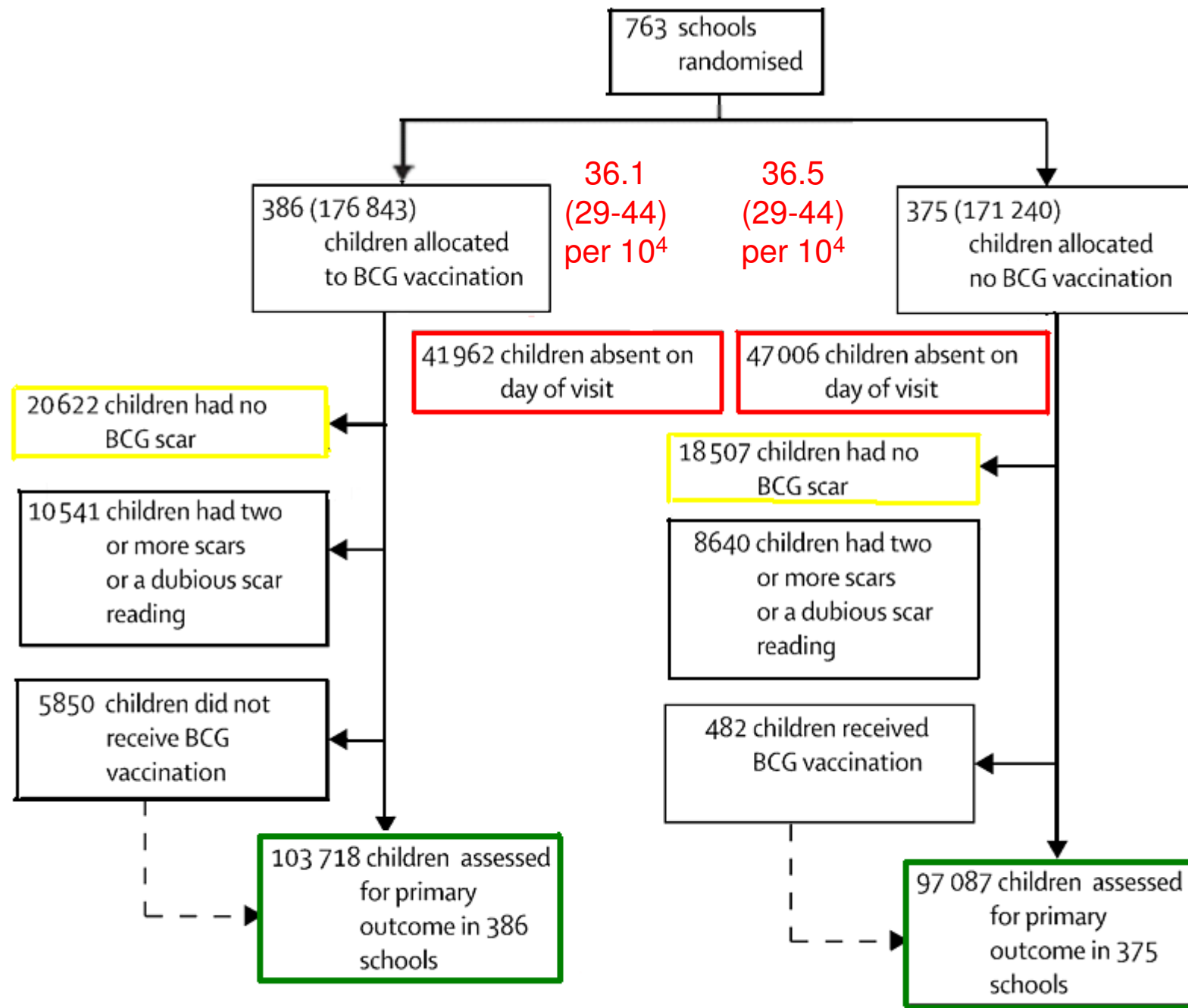
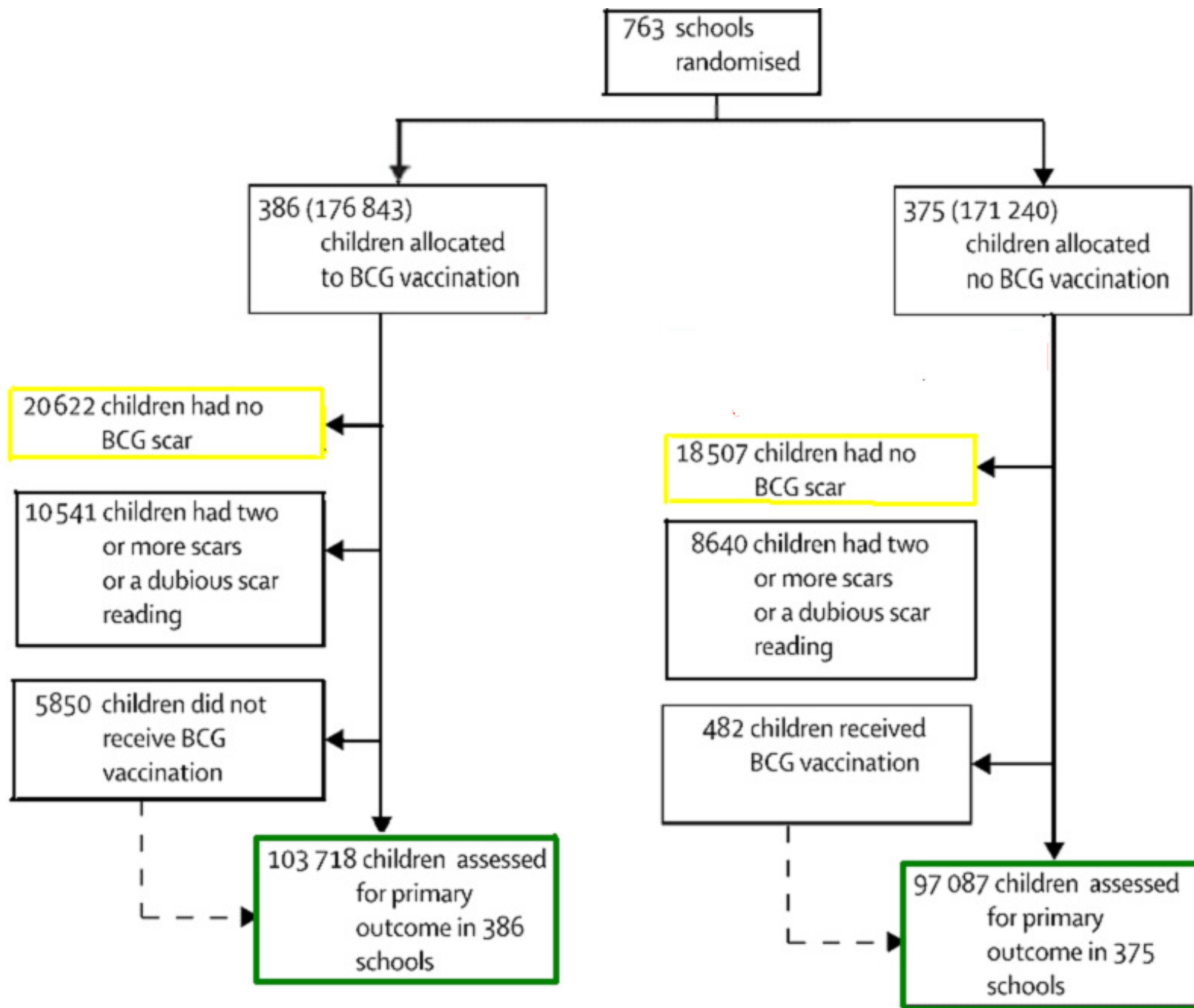
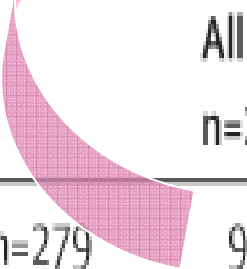


Figure: Trial profile



Protection by BCG revaccination

9% (-16 to 29)



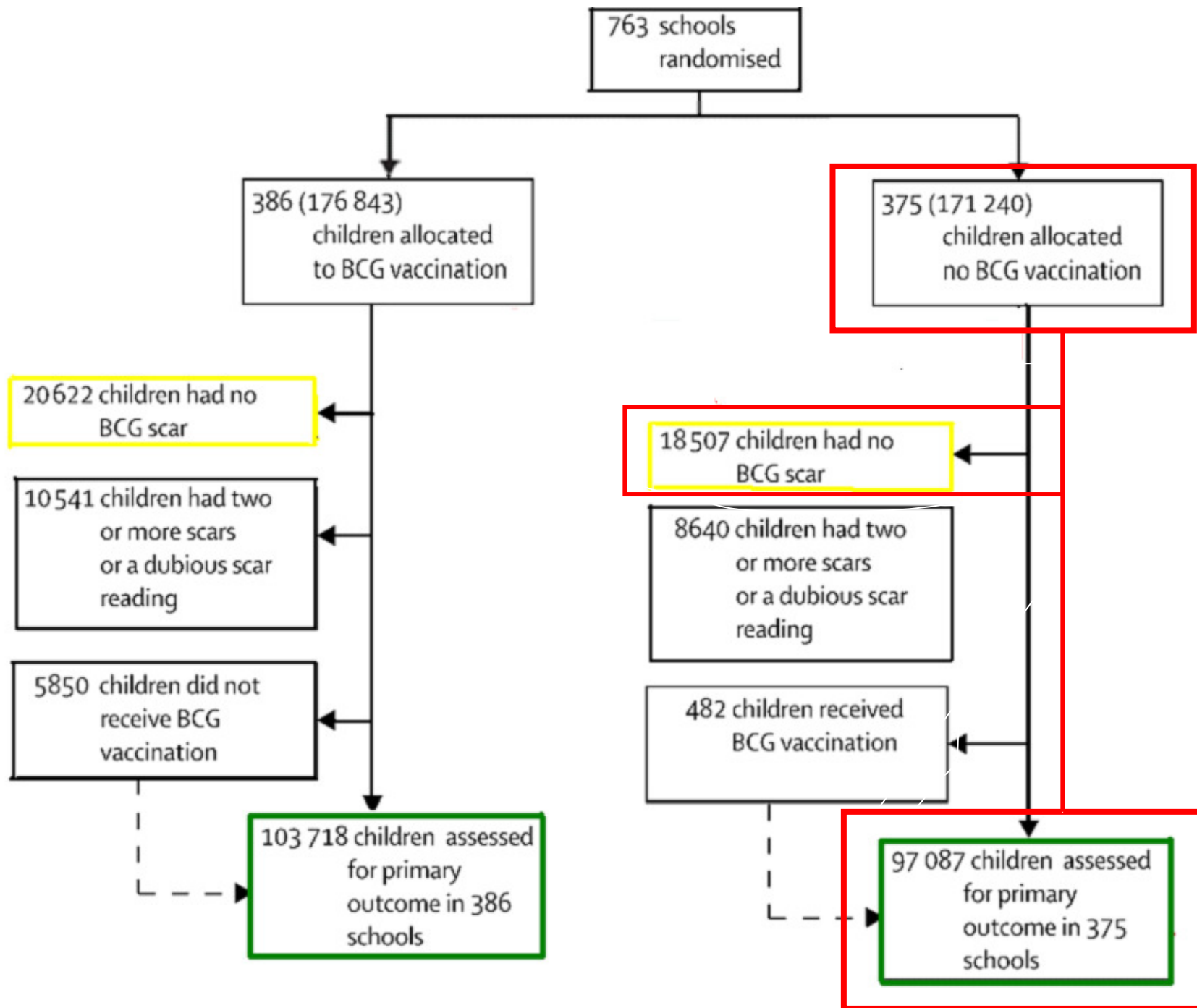
	All types of tuberculosis n=279 (95% CI)	Pulmonary tuberculosis n=215	Non-pulmonary tuberculosis n=64
Both cities n=279	9% (-16 to 29)	-1% (-24 to 18)	37% (-3 to 61)
Salvador n=183	11% (-20 to 34)	10% (-45 to 29)	14% (-72 to 57)
Manaus n=96	-2% (-54 to 32)	-30% (-108 to 19)	68% (-2 to 90)

Brazilian government suspended recommendation of revaccination



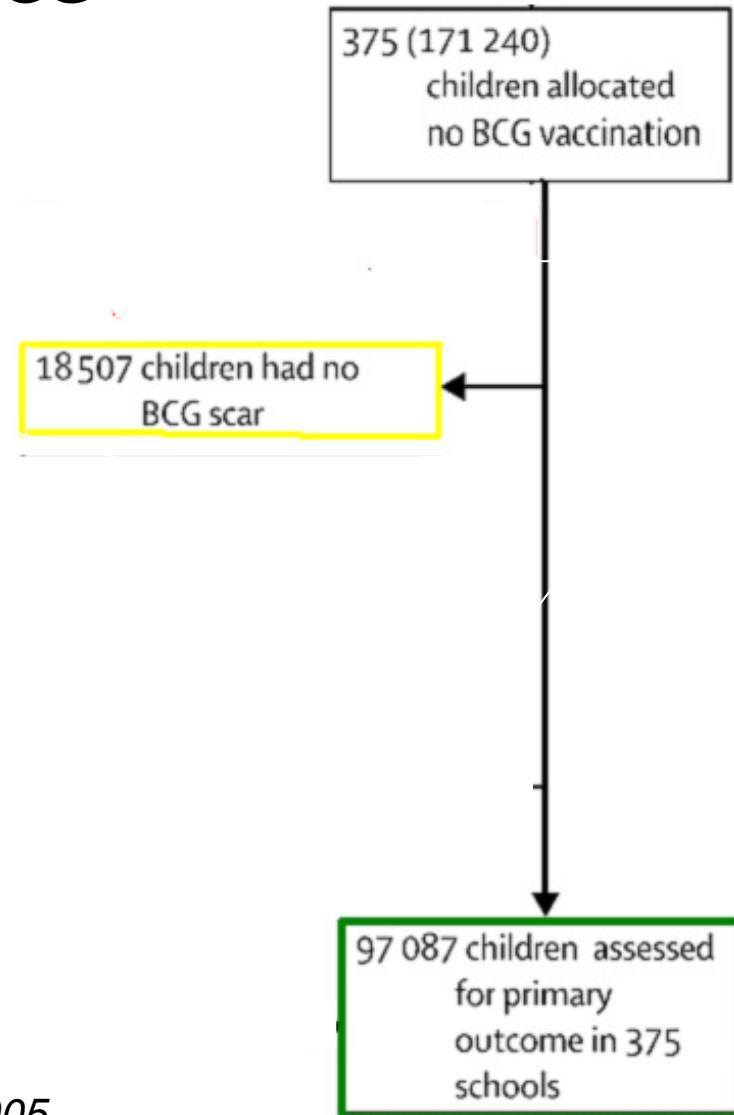
Rodrigues et al, Lancet 2005





Protection of neonatal BCG with time since vaccination

In Salvador
protection was
52% (24-69)
15 to 20 years
after vaccination



Findings

BCG revaccination does not confer additional protection

Neonatal BCG protection can last up to 20 years after vaccination (maybe 40!)

Methodologically sound & logistically possible to do very large trials of vaccines against tuberculosis



More detailed look at
methods and process
used and lessons
learned



Randomisation, population registration

Number of clusters (schools): 763

Large number of clusters possible as activities were very simple .



Schools as the unit

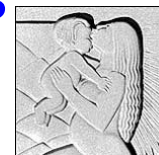
Possible in places with high rate of schooling

Makes delivering the intervention/registration/baseline data collection in extremely large trials easier

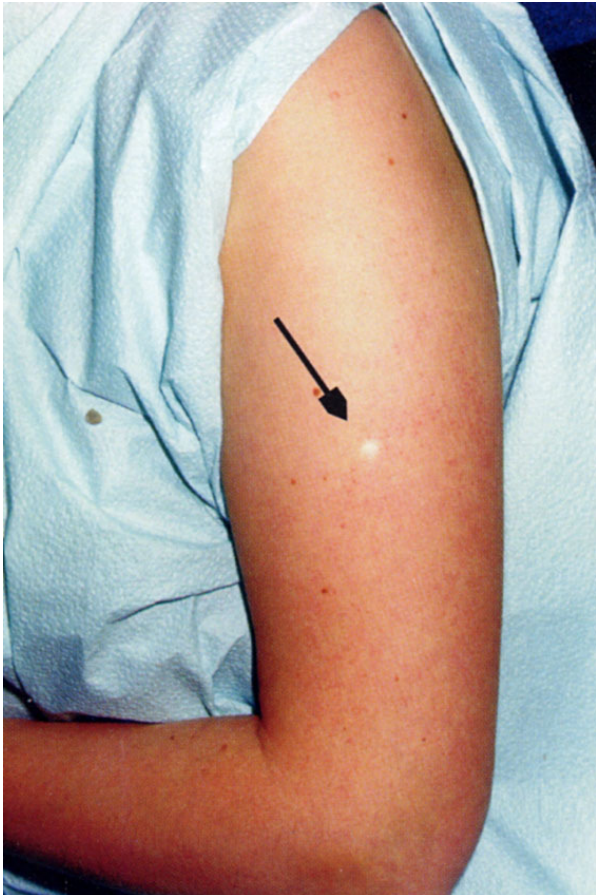
If done a few years later, schools would have had computerized registers of children



Need the support of the education authorities



Simple + validation: Presence of BCG scar



By trained auxiliary nurses:

- `control` schools: after registration
- `vaccination` schools: in the vaccination day

without scar (0), 1, 2, +2, doubtful



Validation of BCG scar reading

Repeatability between 2 blinded examiners

Manaus: 90,8%, kappa=0,81; $p < 0,001$

Salvador: 95,2%, kappa=0,84; $p < 0,001$



Validity (Gold standard: vaccine card + information)

	Manaus	Salvador
• sensitivity:	96,6% (96,0; 97,1)	98,0 (97,1; 98,6)
• specificity:	71,1% (55,7; 83,7)	84,6 (54,6; 98,1)



Simple + validation: Follow up using routinely ascertained cases

Ascertainment of cases - cases diagnosed by the Tuberculosis Control Program

Weekly contact with TCP officers and visits to key health services;

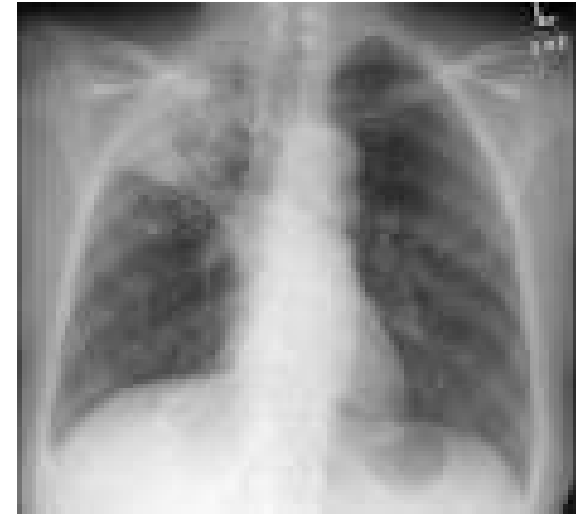
Including cases born a bit outside the range of dates of birth in the study study population.



Validation of diagnosis

Abstracted clinical, radiological and laboratory data from cases

Review done by 2 independent chest physicians and blinded to vaccine status and PPD result



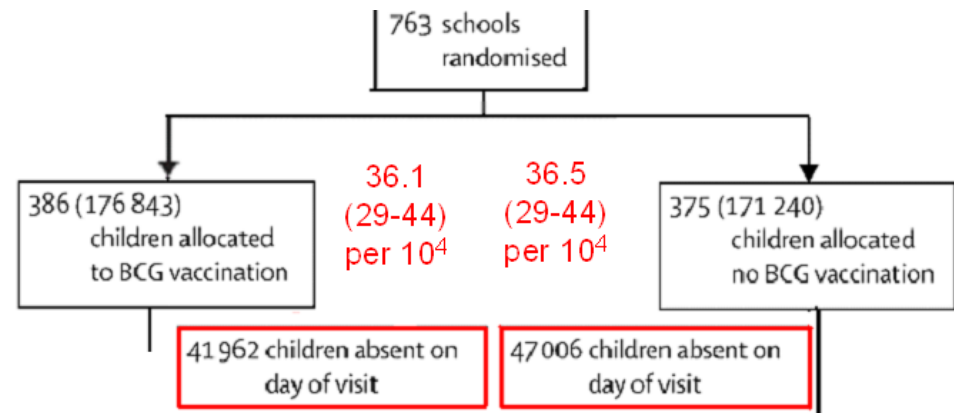
Classification of cases in confirmed, probable (“I would treat based on this information”), possible (“not enough information to decide”) and not tuberculosis

Third chest physician reviewed cases disagreements

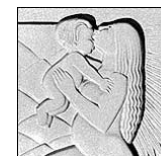


Simple + validation: Follow up using routinely ascertained cases

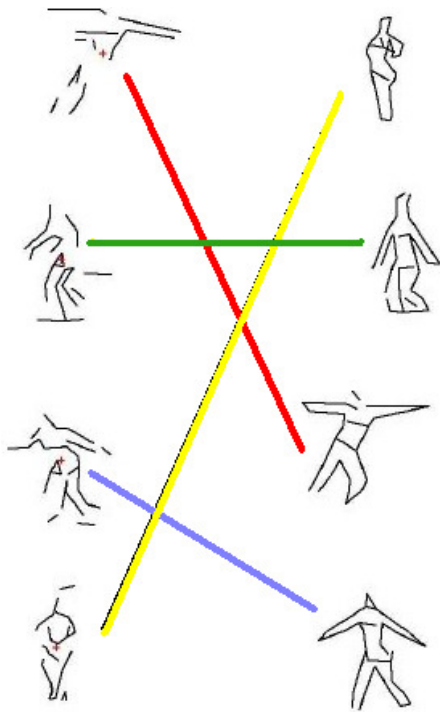
Assessment of comparability of those not receiving the treatment they were allocated to



Avoided need for intention to treat analyses when almost a quarter of the kids did not receive the allocated treatment



Simple + validation: Linkage of cases to database



Blind to allocation group and vaccine status

Based on child's name, date of birth and mother's name

Validation: Home visit to those not linked to confirm they were not in the trial population



Preparation

Good collaboration between academia and health and other relevant services essential

The support of the government and different groups and organizations at national, local (and also at international levels) is essential

We get : information, staff, and help in earning trust locally

They get: their priorities incorporated and evidence to inform choice of best policy



Finally

Many obstacles can be overcome by creative (and rigorous) use of existing resources (routine, simple methods and validation) in the context where the trial is conducted.

Large trials require patient work to gain involvement and support of social and scientific networks, not only to address ethical concerns, but to harvest their knowledge of local resources and to help implementation.



Existing structures and processes

Simple methods + validation

Engagement with local, state and
national institutions





It is possible to do
very large,
relatively inexpensive
and scientifically rigorous
RCTs in developing
countries



Thank you!

