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

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Outline of the presentation

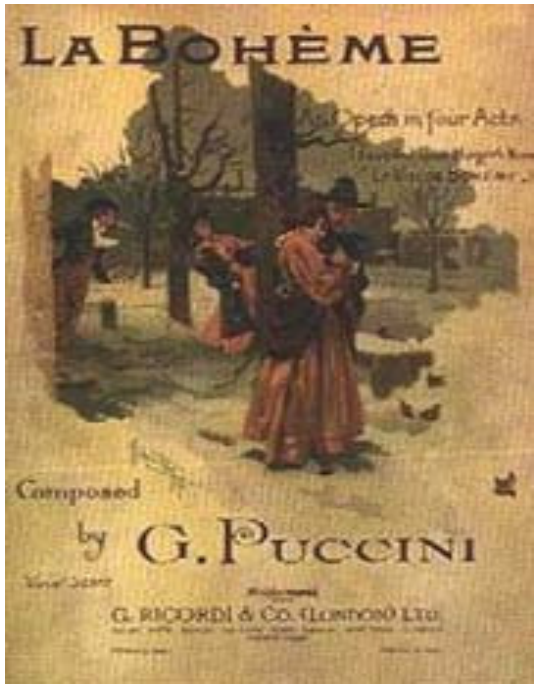
Overview of tuberculosis, BCG vaccine

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

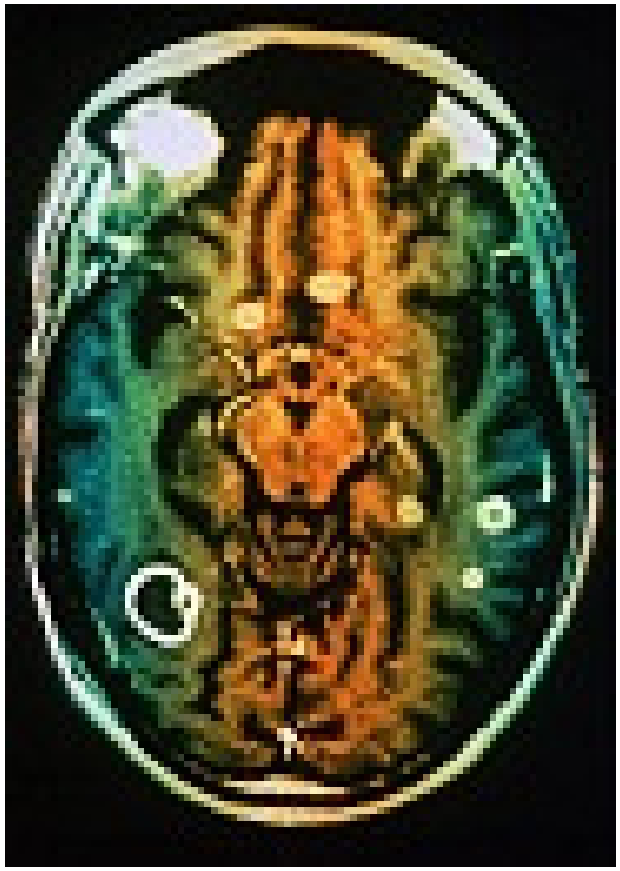
Camille Guerin

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



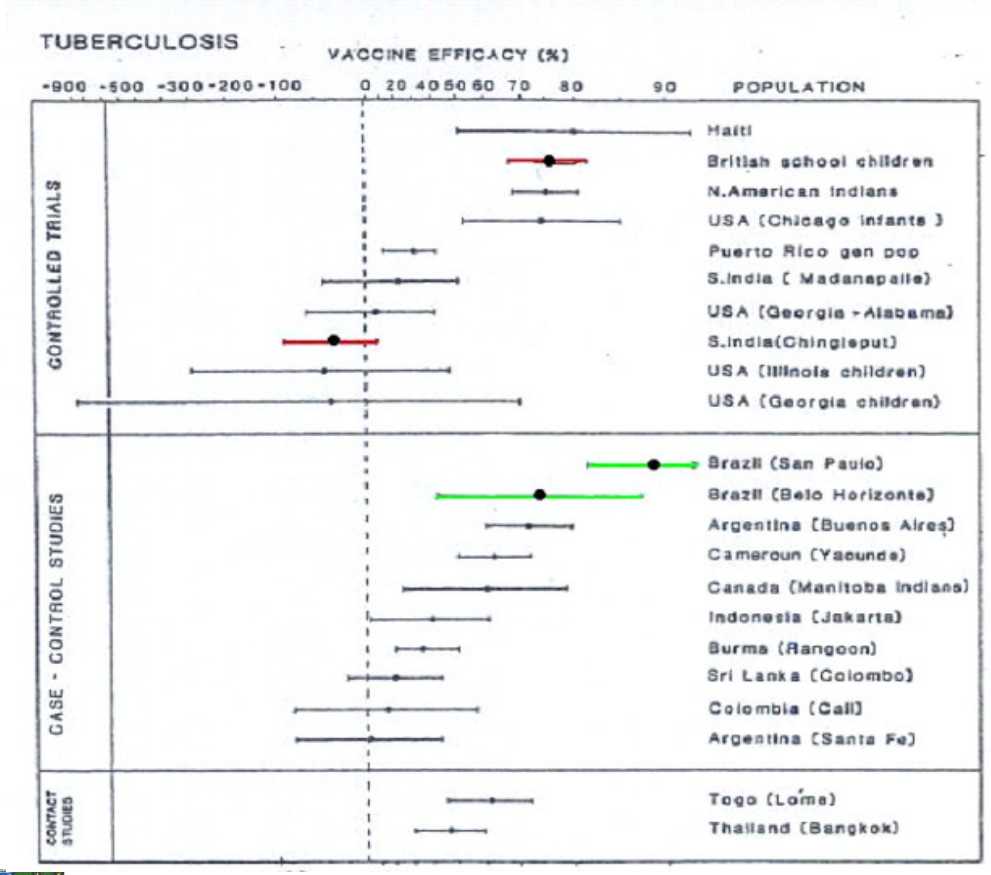
Neonatal BCG is estimated to have prevented between 25 000 to 50 000 cases of tuberculous meningitis a year

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

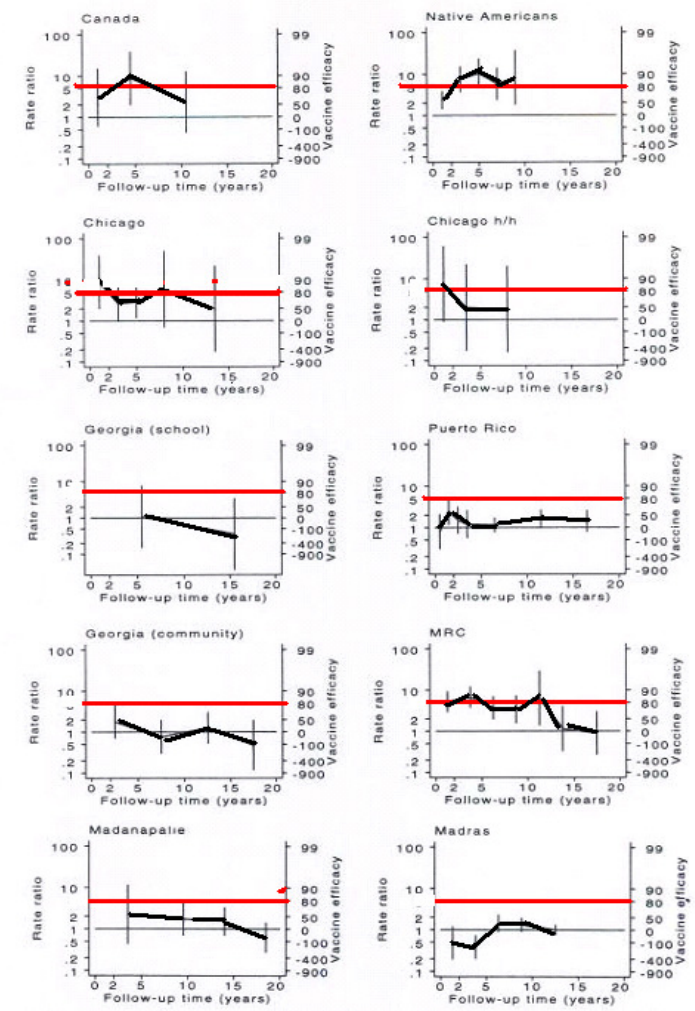


Fine & Rodrigues, Lancet 1990

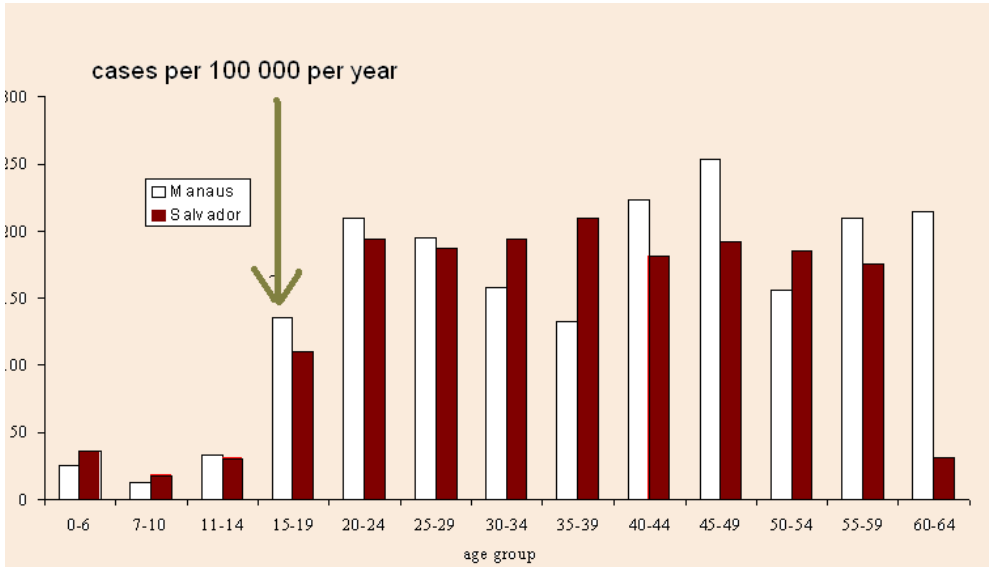
Does BCG protection last?

Meta-analysis of data from 10 published trials

No evidence of protection lasting more than 10 years



Sterne , Rodrigues & Guedes, Int J Tuberc Lung Dis 19 98



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

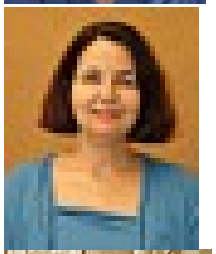
costs

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

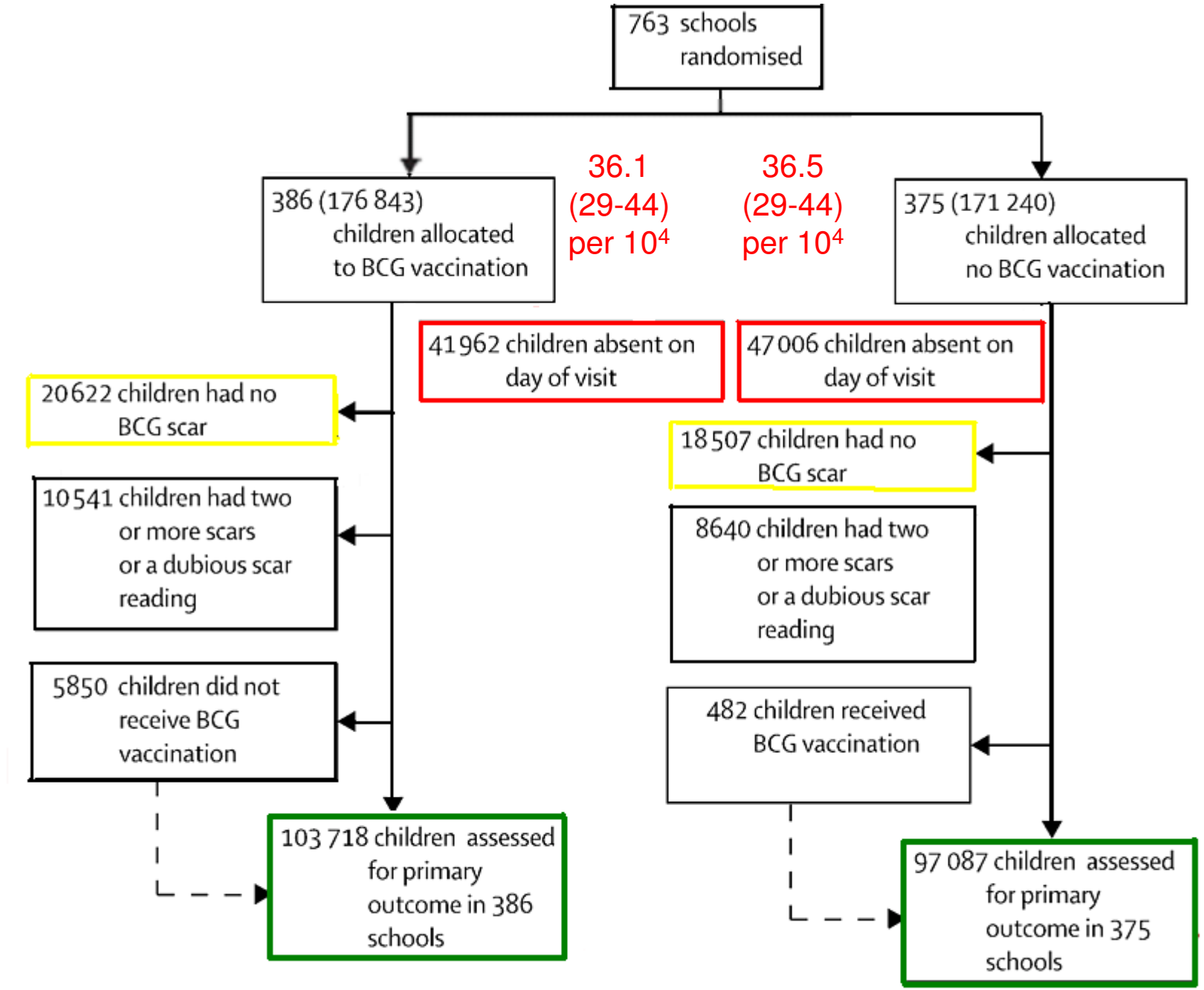
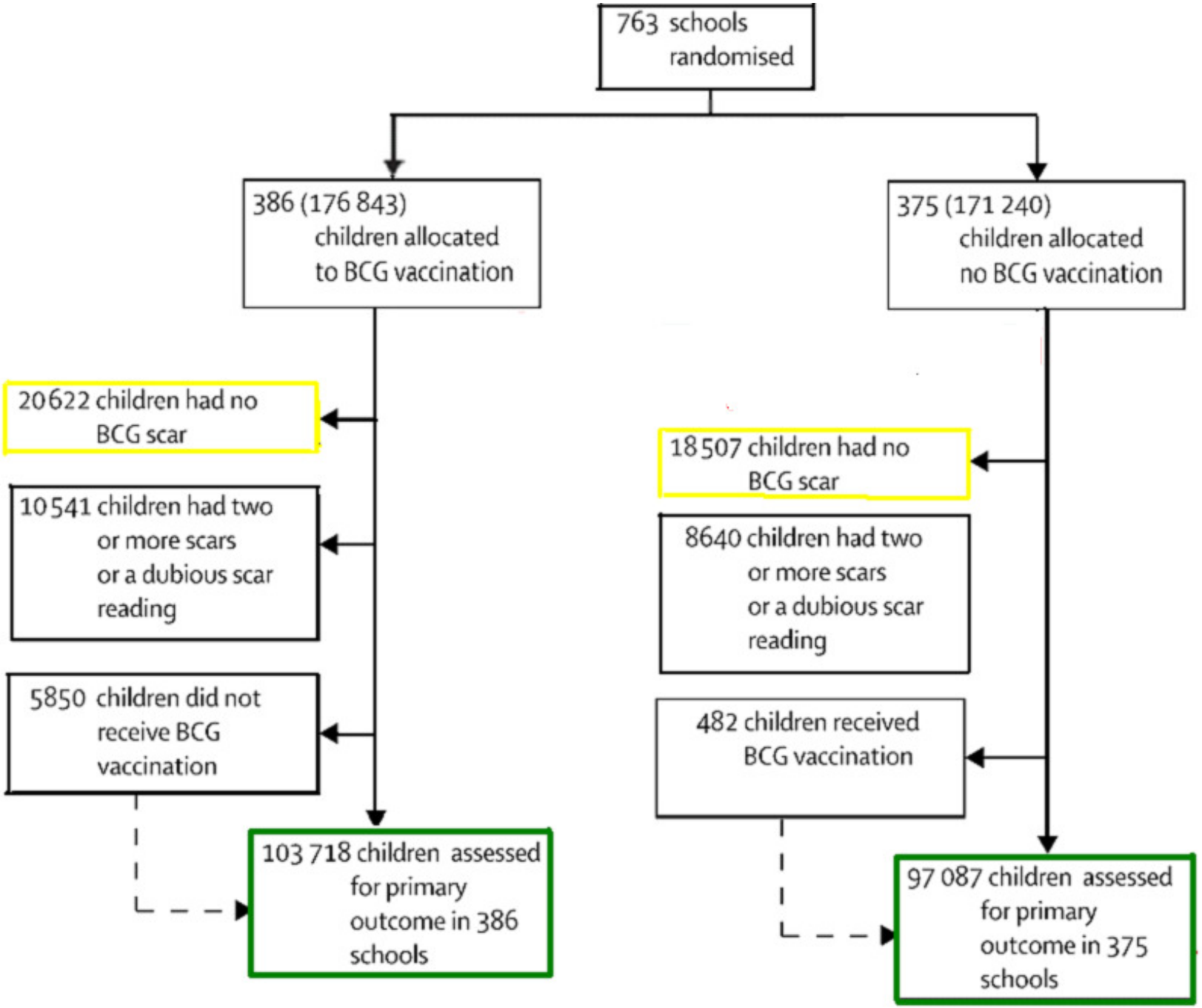


Figure: Trial profile

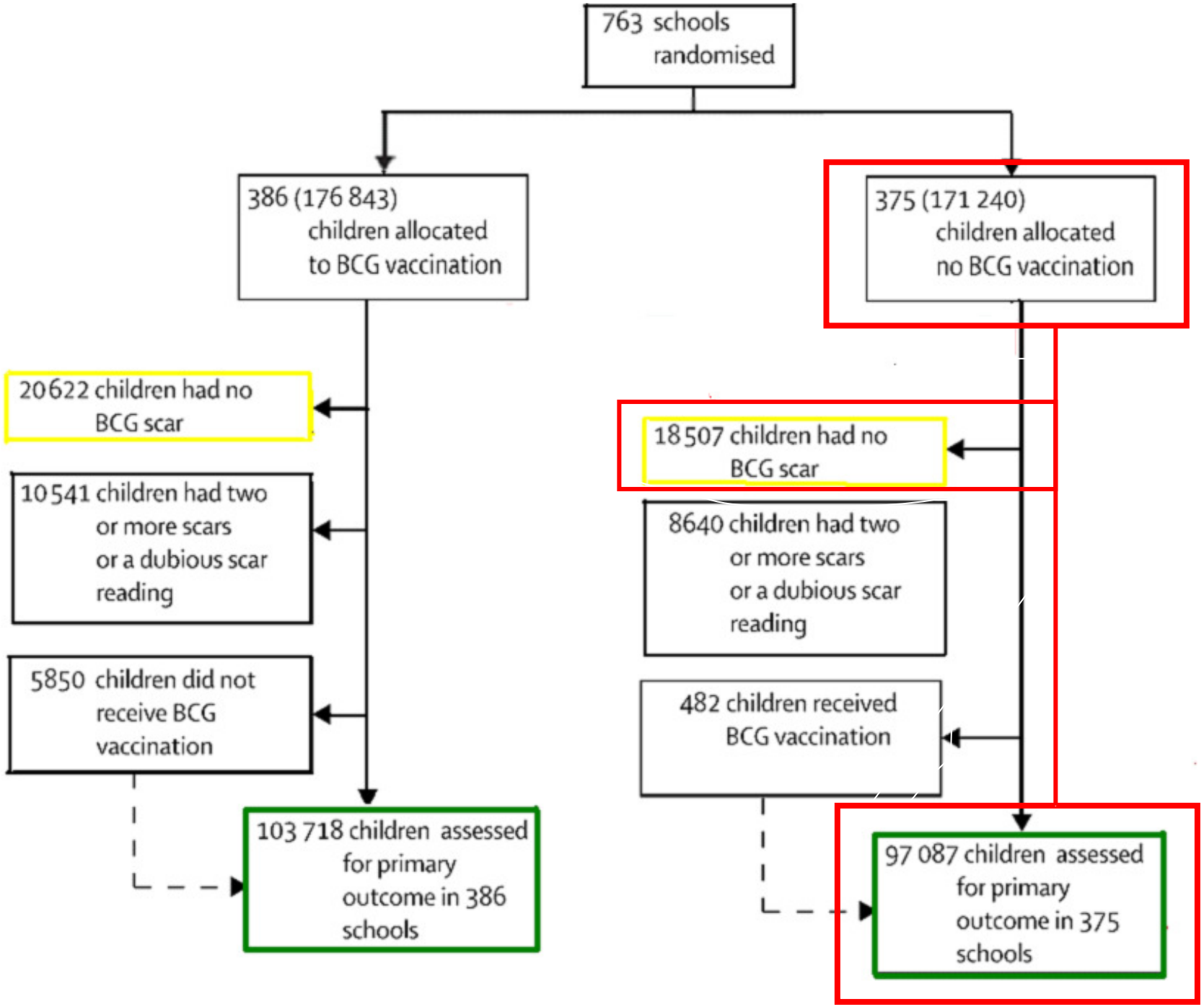

763 schools randomised
386 (176 843) children allocated to BCG vaccination
375 (171 240) children allocated no BCG vaccination
20622 children had no BCG scar
10541 children had two or more scars or a dubious scar reading
5850 children did not receive BCG vaccination
103 718 children assessed for primary outcome in 386 schools
18507 children had no BCG scar
8640 children had two or more scars or a dubious scar reading
482 children received BCG vaccination
97 087 children assessed for primary outcome in 375 schools

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% (-546 to 32)	-30% (-108 to 19)	68% (-2 to 90)

Brazilian government suspended recommendation of revaccination

Rodrigues et al, Lancet 2005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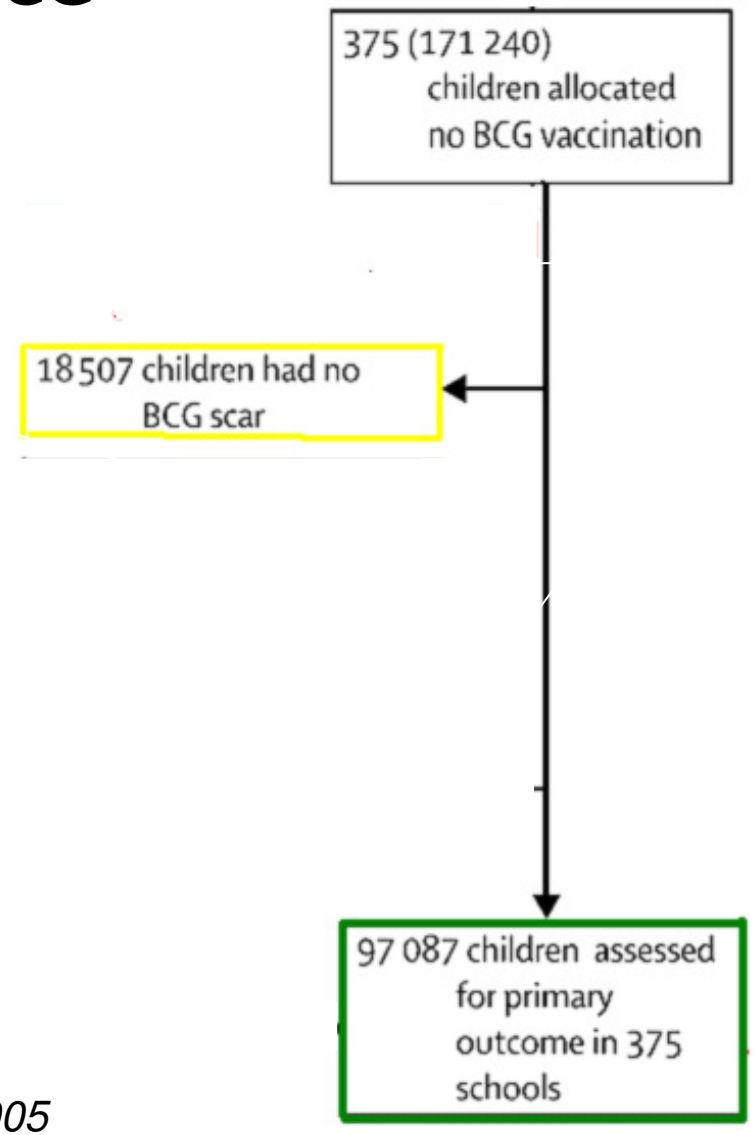
Protection of neonatal BCG with time since vaccination

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



Barreto et al, Int J Tuberc Lung Dis, 2005

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

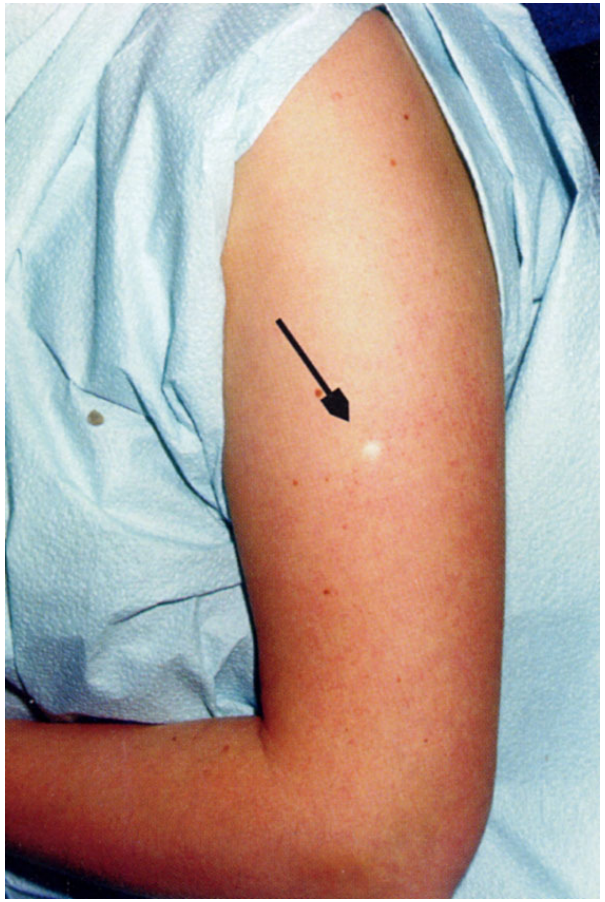
Possible in places with high rate of schooling

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)

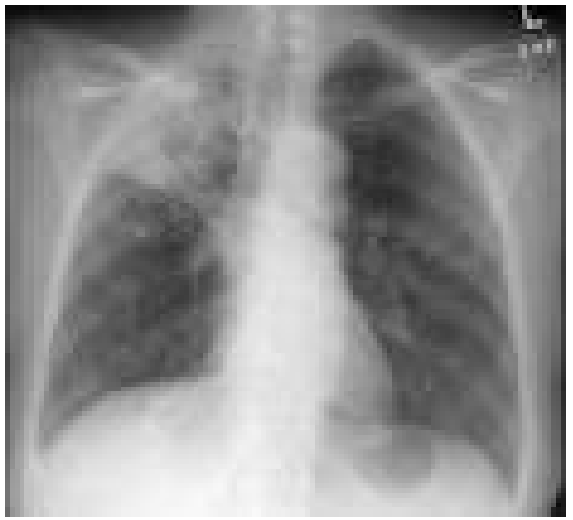
Simple + validation: Follow up using routinely ascertained cases

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

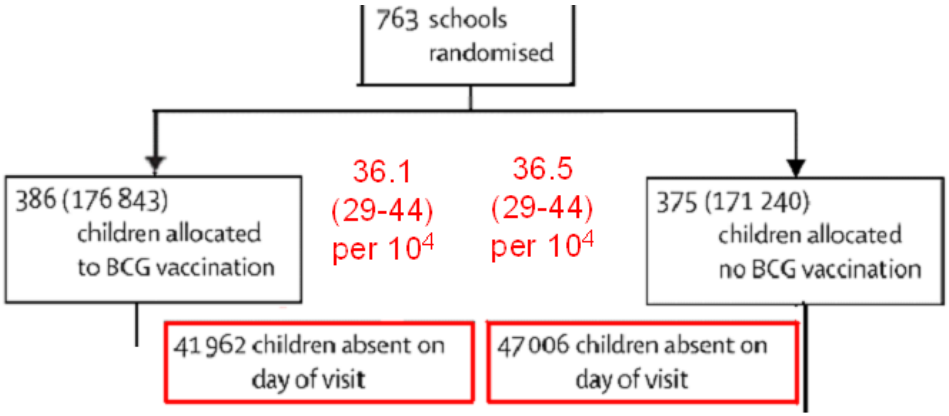
Review done by 2 independents chest physicians and blinded to vaccine status and PPD result

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

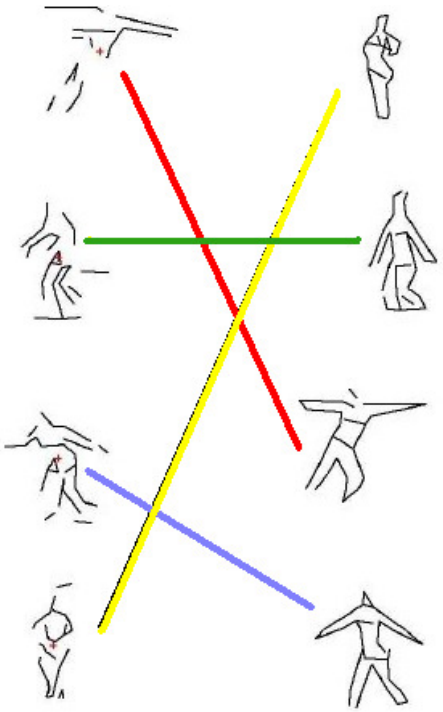
Simple + validation: Follow up using routinely ascertained cases

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 alocation 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!