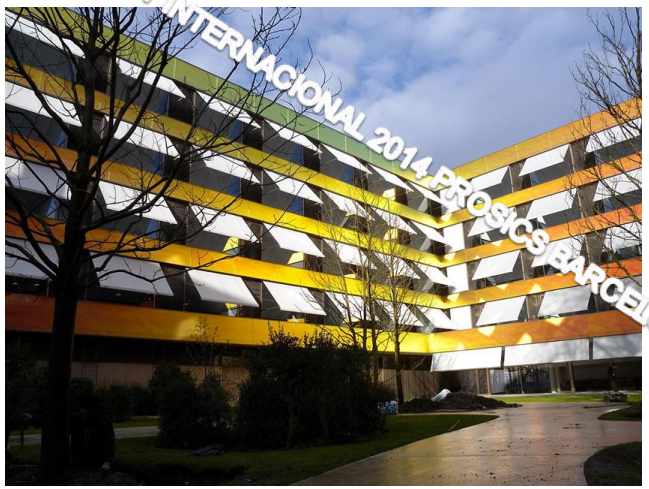
VII Jornadas Catalanas de Salud Internacional

BCG vaccine

- Why BCG
- Facts and history of BCG
- Protective efficacy
- Duration of protection
- Immunisation coverage
- Recommendations
- Revaccination
- Adverse effects

Bacille-Calmette-Guérin (BCG) vaccine: current knowledge of a 90-year-old vaccine



Dr. med Nicole Ritz, PhD
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Facts about BCG

Currently the only licensed vaccine against TB

Oldest vaccine still in use (1921)

Developed by Albert Calmette and Camille Guérin

Attenuated *Mycobacterium bovis*

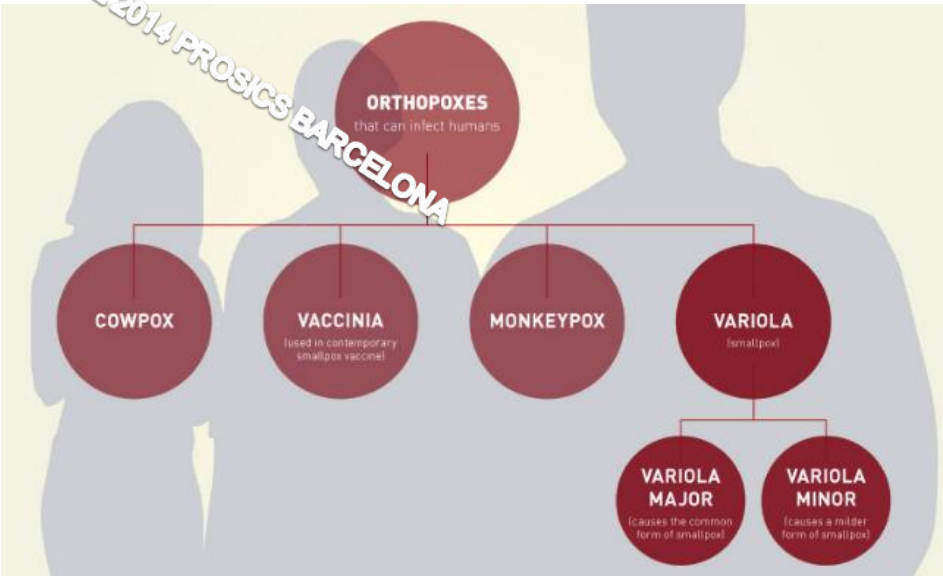
Live vaccine

Why BCG?

Common principles and ideas of vaccination (from vacca: cow): Smallpox (variola) and BCG

An English Doctor (Edward Jenner) learned from a milkmaid that she believed herself protected from smallpox because she had caught cowpox from a cow.

He tested this idea in (1796) and could show that infection with cowpox could protect a person from smallpox.

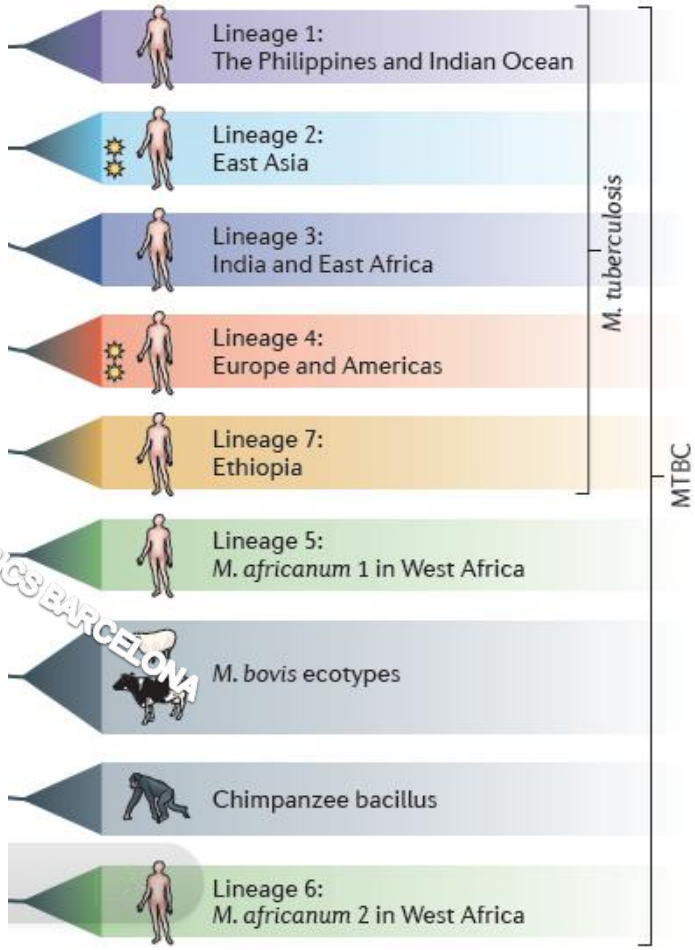


Same principle for BCG

1882 Robert Koch discovered the "Koch bacillus"

Children with cervical lymphadenitis after drinking milk contaminated with *Mycobacterium bovis* appeared protected against TB

Calmette and Guérin (at the Institut Pasteur in Lille, France) isolated *M. bovis* from a cow with mastitis and cultured it on ox bile



Galagam JB, Nat Genet 2014

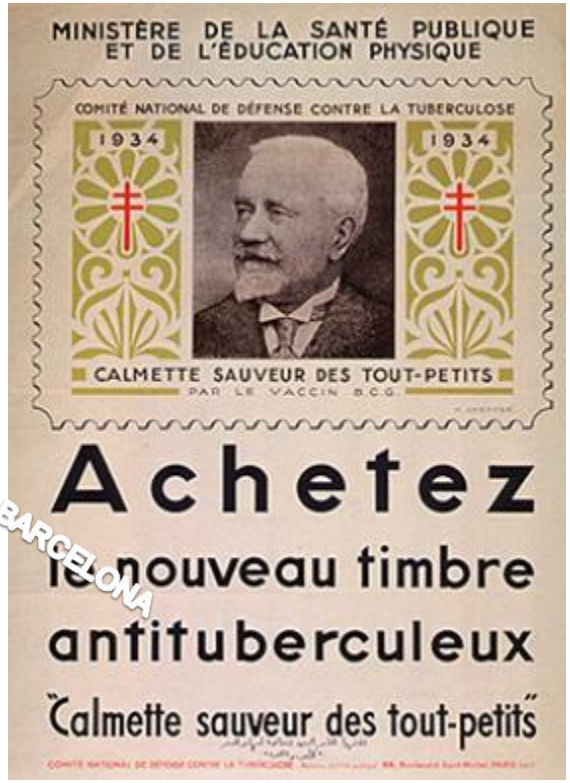
Developement of BCG

After the 39th passage the strain was unable to kill experimental animals

13 years (1909-1921), 231 passages

June 21 in 1921 first oral vaccine on a newborn (mother died from TB and to be transfered to grandmother with TB)

1921-1924 vaccination of 300 children in France at high risk for TB



Calmette A, 1927, La Vaccination Preventive contre la Tuberculose, Masson et Cie, Paris

History of BCG (Bacille-Calmette-Guérin)

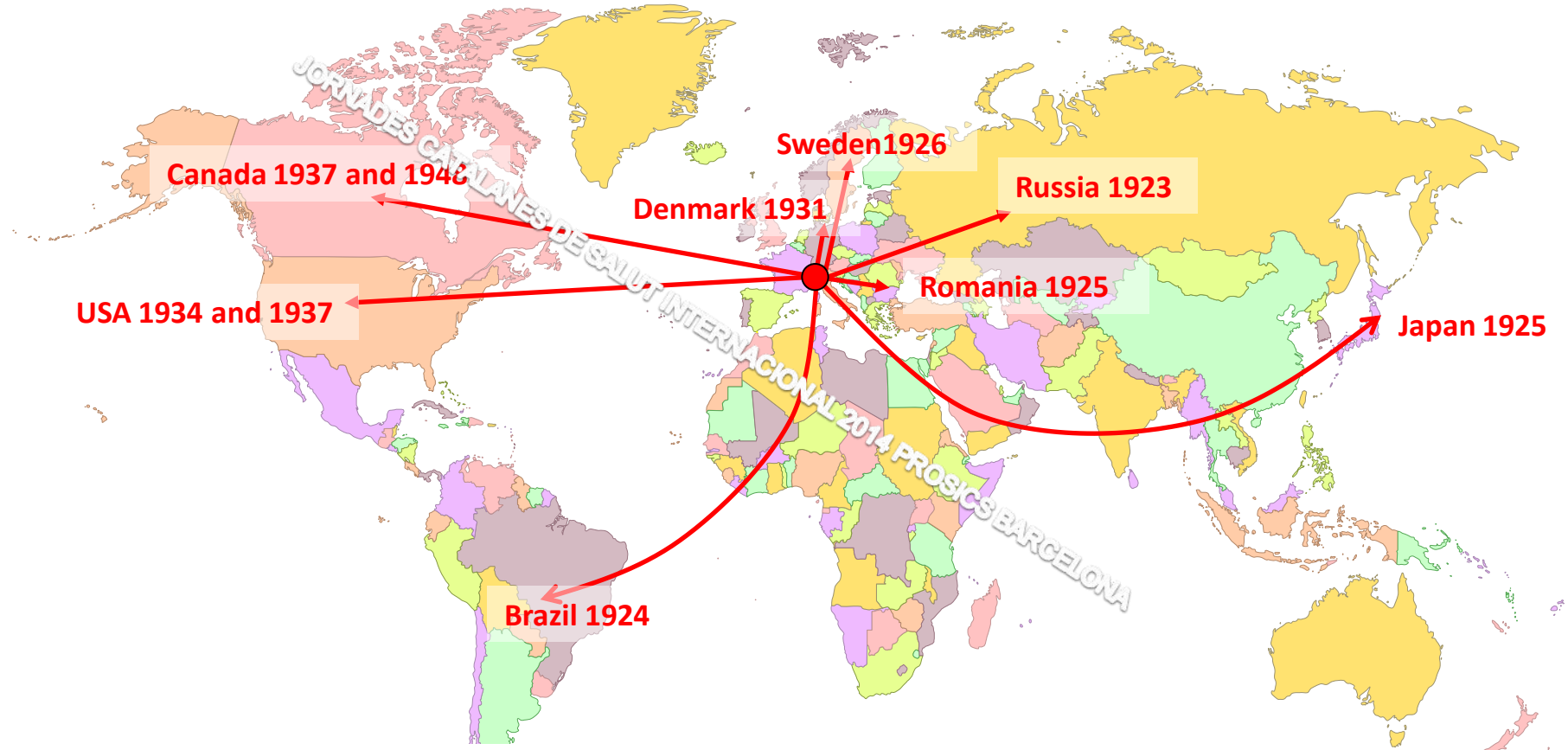
1924
- Efficacy and safety established (motality among vaccinated 1.9%)
- „massproduction“ of BCG began
- vaccine also given to adults
- samples of BCG distributed to 34 countries

1929 subcutaneous route more popular (especially in Scandinavian countries)

1956 lyophilisation

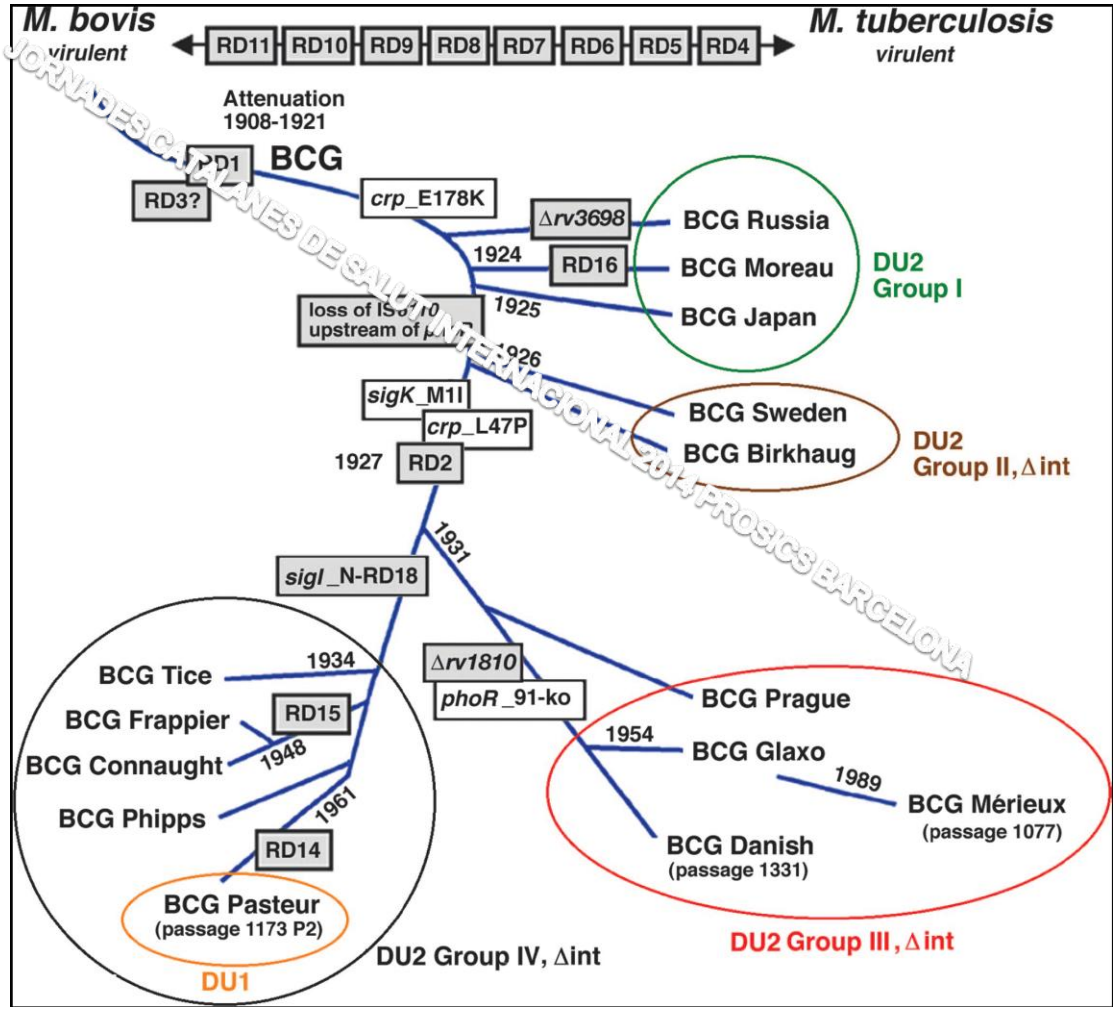
1974 BCG was introduced in WHO immunisation programme

BCG strains



1900	1909-1921	1930s	1950s	1998
Original *M. bovis* strain isolated	Attenuation of *M. bovis*	Phenotypic differences	First BCG lyophilisation	Genomic differences of BCG strains

Family tree of BCG immunisations

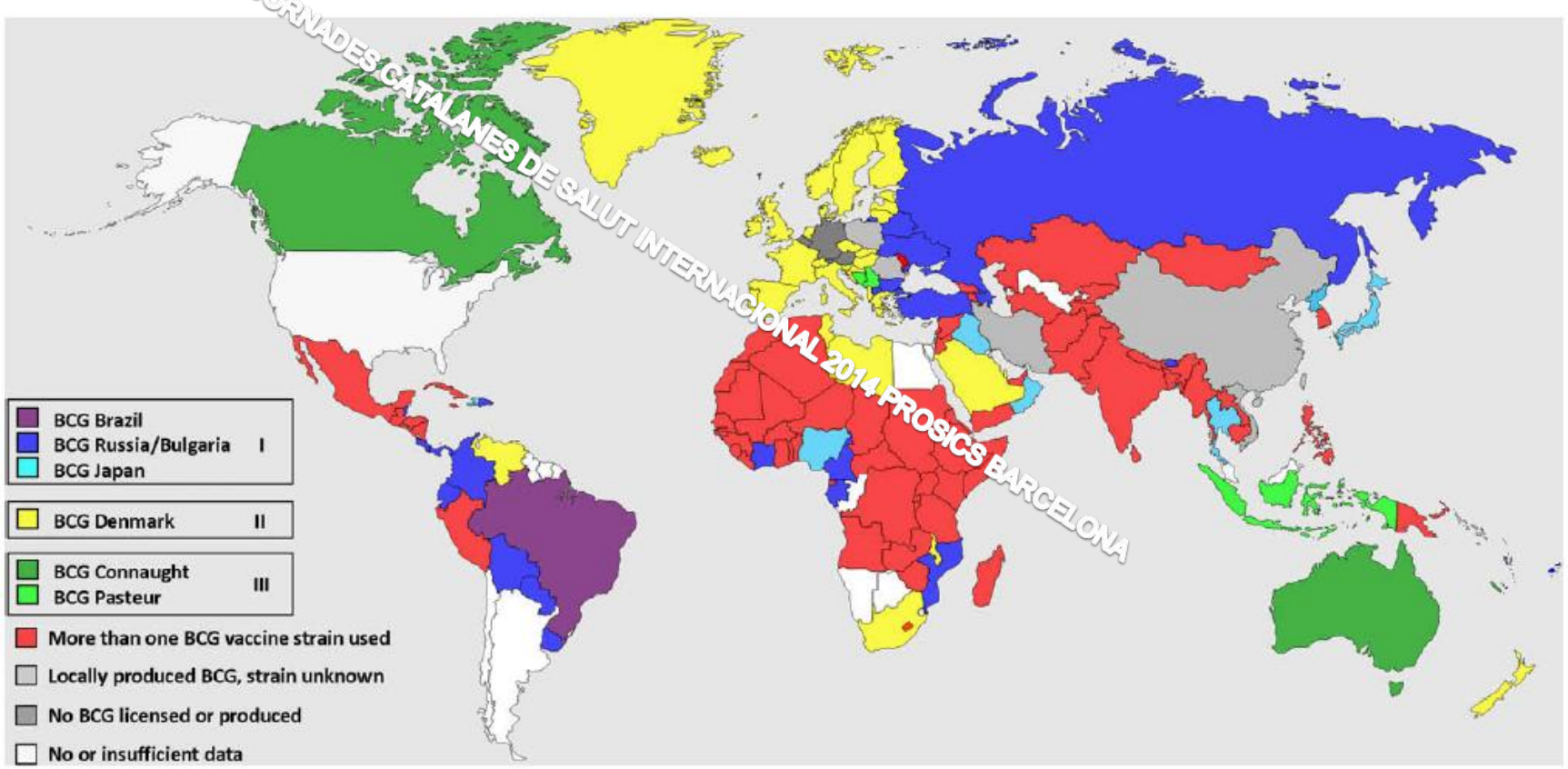


Brosch R, PNAS 2007

BCG vaccine strains in Europe (up to 2007)

Ritz N, FEMS Microbiol Rev 2008

BCG vaccine strains globally (2003 – 2007)



Ritz N,Tuberculosis 2009

BCG in Europe today

Web-based survey including all members of the paediatric-tuberculosis-network-European-trials group (pTBnet) and tuberculosis network (TBnet)

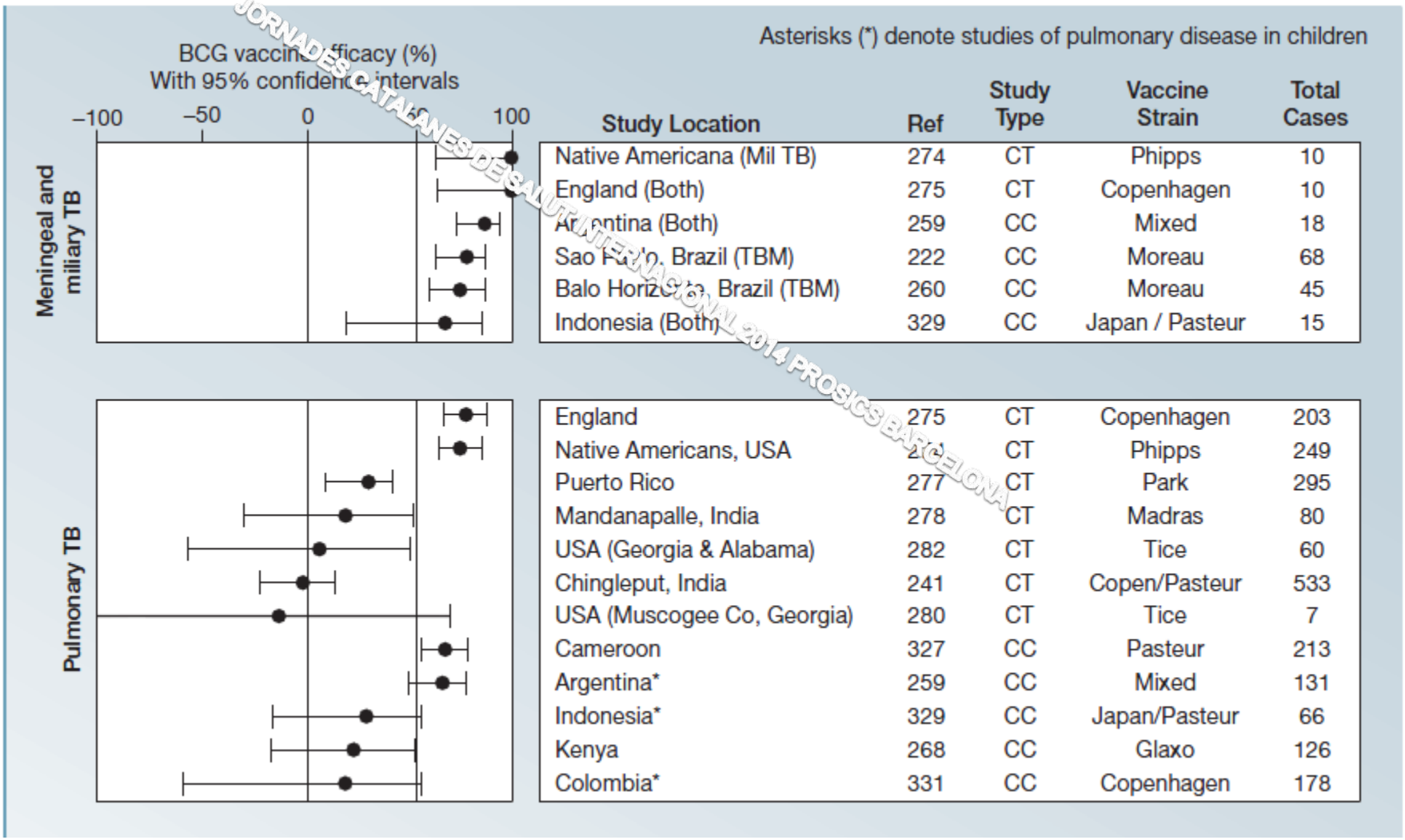
Anonymous survey between Oct 2012 – May 2013

27/31 (87%) countries have national BCG immunisation policy/guidelines

BCG used: 77 % BCG Denmark, 19 % other strains, 32 % did not know the strain used in their country

Dierig A, ESPID 2014

Protective efficacy of BCG according to TB form



Asterisks (*) denote studies of pulmonary disease in children

Study Location	Ref	Study Type	Vaccine Strain	Total Cases
Native Americana (Mil TB)	274	CT	Phipps	10
England (Both)	275	CT	Copenhagen	10
Argentina (Both)	259	CC	Mixed	18
Sao Paulo, Brazil (TBM)	222	CC	Moreau	68
Balo Horizonte, Brazil (TBM)	260	CC	Moreau	45
Indonesia (Both)	329	CC	Japan / Pasteur	15
England	275	CT	Copenhagen	203
Native Americans, USA	276	CT	Phipps	249
Puerto Rico	277	CT	Park	295
Mandanapalle, India	278	CT	Madras	80
USA (Georgia & Alabama)	282	CT	Tice	60
Chingleput, India	241	CT	Copen/Pasteur	533
USA (Muscogee Co, Georgia)	280	CT	Tice	7
Cameroon	327	CC	Pasteur	213
Argentina*	259	CC	Mixed	131
Indonesia*	329	CC	Japan/Pasteur	66
Kenya	268	CC	Glaxo	126
Colombia*	331	CC	Copenhagen	178

Vaccines 6th edition 2013

Protective efficacy of BCG against disseminate forms of TB

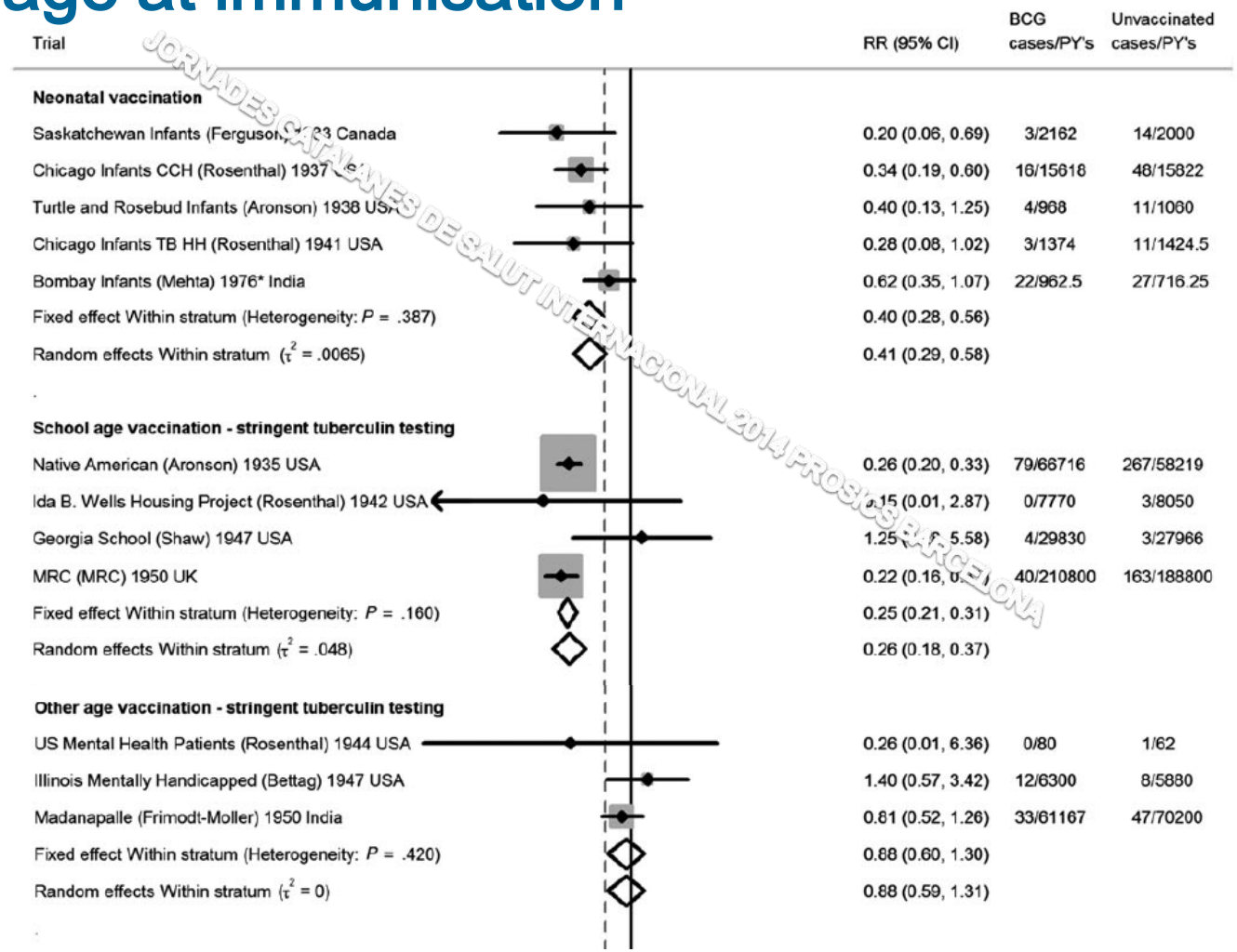
	Publication date	Efficacy (%, 95% CI)	Reference
Tuberculous meningitis			
Buenos Aires, Argentina	1988	98% (70 to 100)	48
Bahia, Brazil	1991	1% (78 to 97)	49
São Paulo, Brazil	1990/93	87% (7 to 94)	50,51
São Paulo, Brazil	1990/93	92% (65 to 9	50,51
Belo Horizonte, Brazil	1988	81% (47 to 93)	52
Belo Horizonte, Brazil	1988	65% (17 to 86)	52
Yangon, Burma	1987	52% (13 to 73)	53
Nagpur, India	1996	87% (70 to 94)	54
Chennai, India	1996	77% (63 to 86)	55
Delhi, India	1996	64% (30 to 81)	56
Delhi, India	1989	84% (69 to 97)	57
Lucknow, India	1999	47% (−6 to 74)	58
Papua New Guinea*	1980	58% (−36 to 87)	59
Delhi, India	1993	56% (−49 to 87)	60
Summary efficacy		73% (67 to 79)	
Miliary tuberculosis			
Buenos Aires, Argentina	1988	78% (28 to 93)	48
Yangon, Burma	1987	80% (45 to 92)	53
Papua New Guinea*	1980	70% (0 to 91)	59
Djakarta, Indonesia	1983	75% (5 to 94)	61
Summary efficacy		77% (58 to 87)	

*Not designed as a case-control study.

Table 3: Meta-analysis of BCG efficacy against tuberculous meningitis and miliary tuberculosis from case–control studies

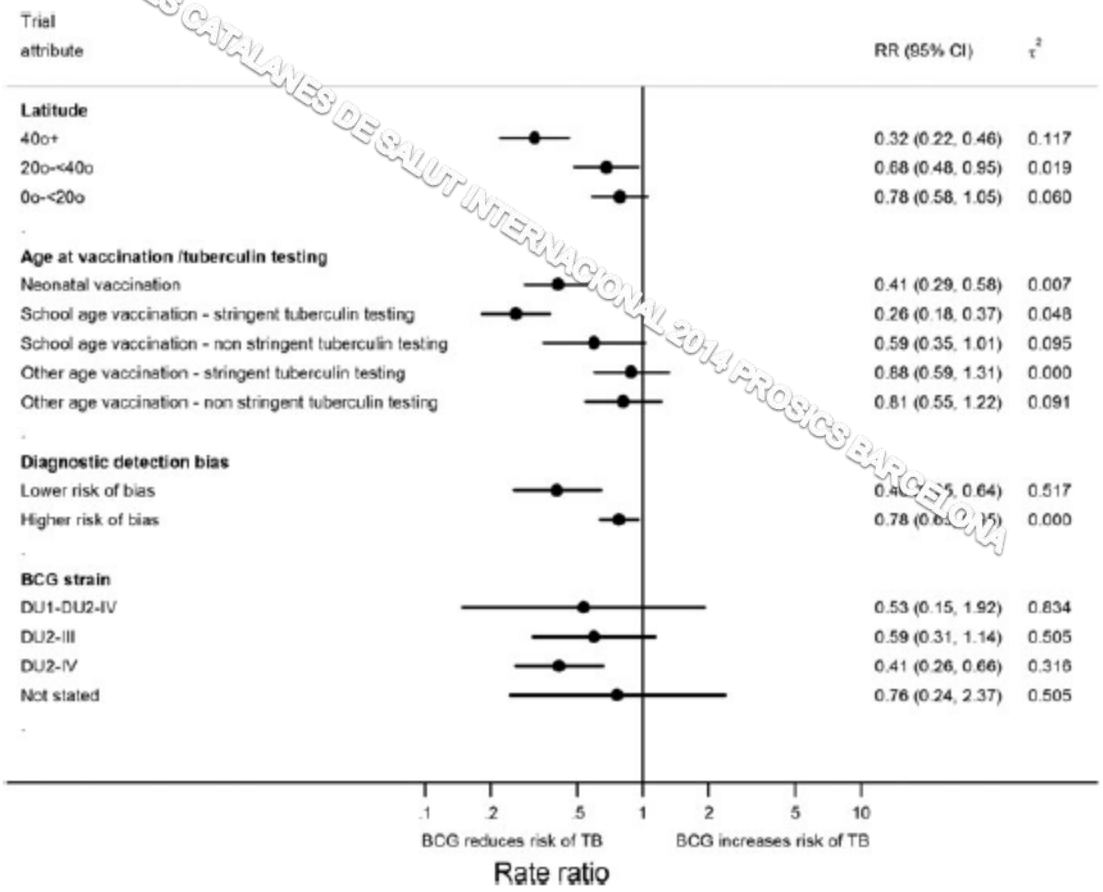
Trunz BB, Lancet 2006

Protective efficacy of BCG on pulmonary TB: age at immunisation



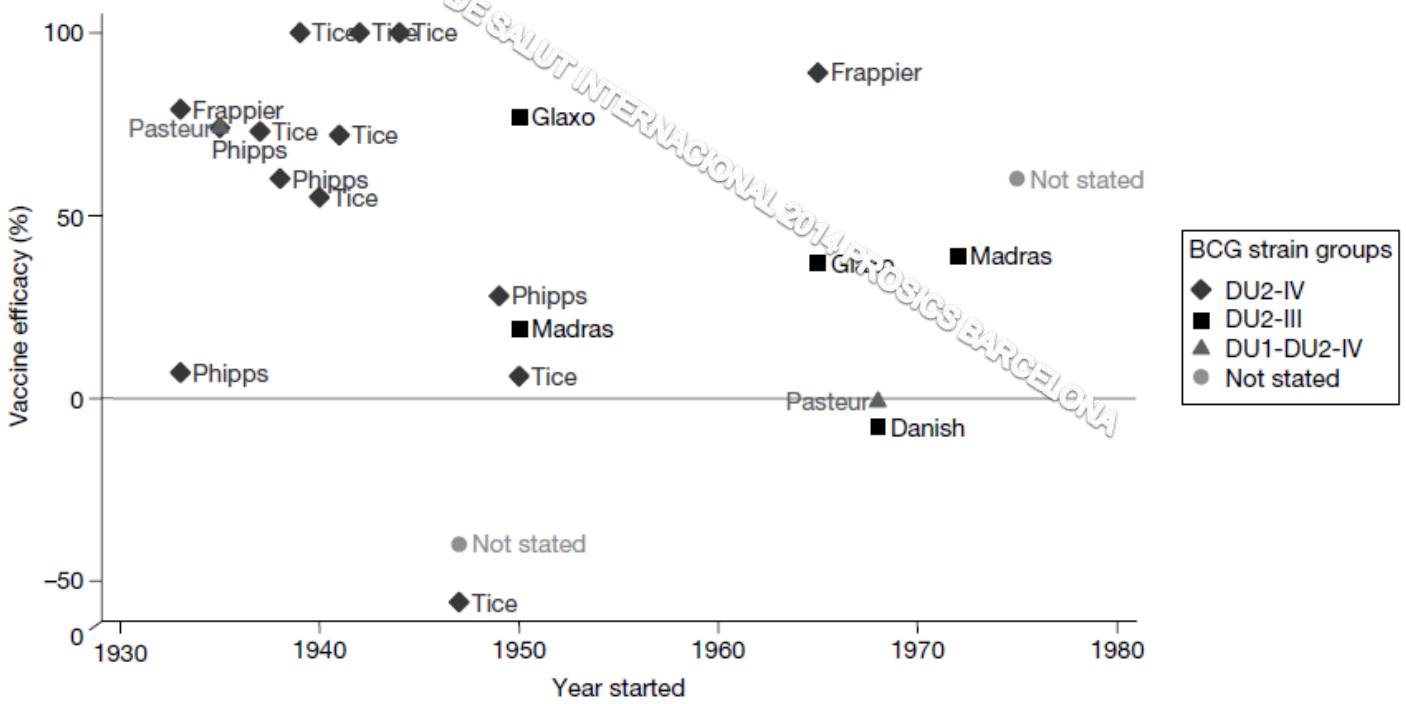
Mangtani P, CID 2014

Protective efficacy of BCG on pulmonary TB: latitude of the study



Mangtani P, CID 2014

Protective efficacy of BCG on pulmonary TB: BCG vaccine stain used



Abubakara I, Health Tech Assess 2013
Mangtani P, CID 2014

Protective efficacy of BCG on pulmonary TB: BCG vaccine stain used

REVIEW ARTICLE

Influence of BCG vaccine strain on the immune response and protection against tuberculosis

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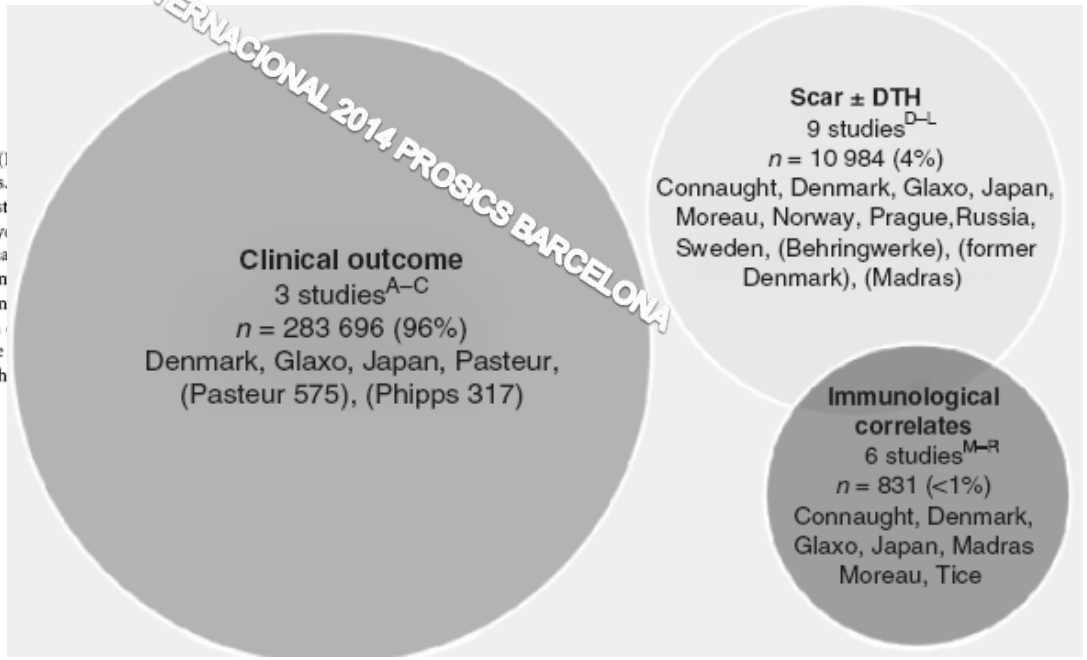
DOI:10.1111/j.1574-6976.2008.00118.x

Editor: Neil Fairweather

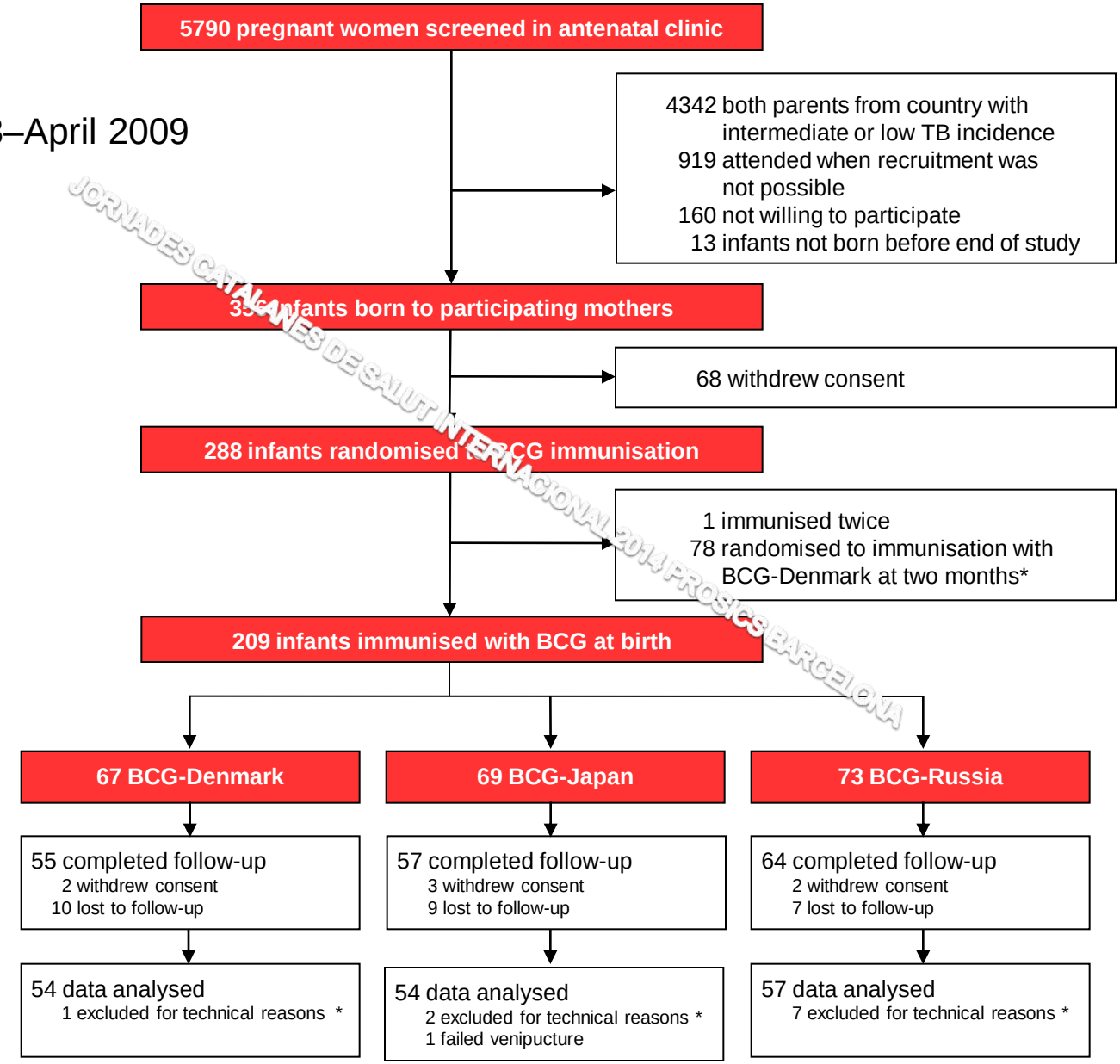
Abstract

The Bacille Calmette–Guérin (
to protect against tuberculosis.
with BCG, making it the most
120 million doses used each y
investigation, BCG will rema
worsening tuberculosis panden
of genetic differences between
influence of the vaccine strain
review critically examines the
BCG vaccine strains. Although



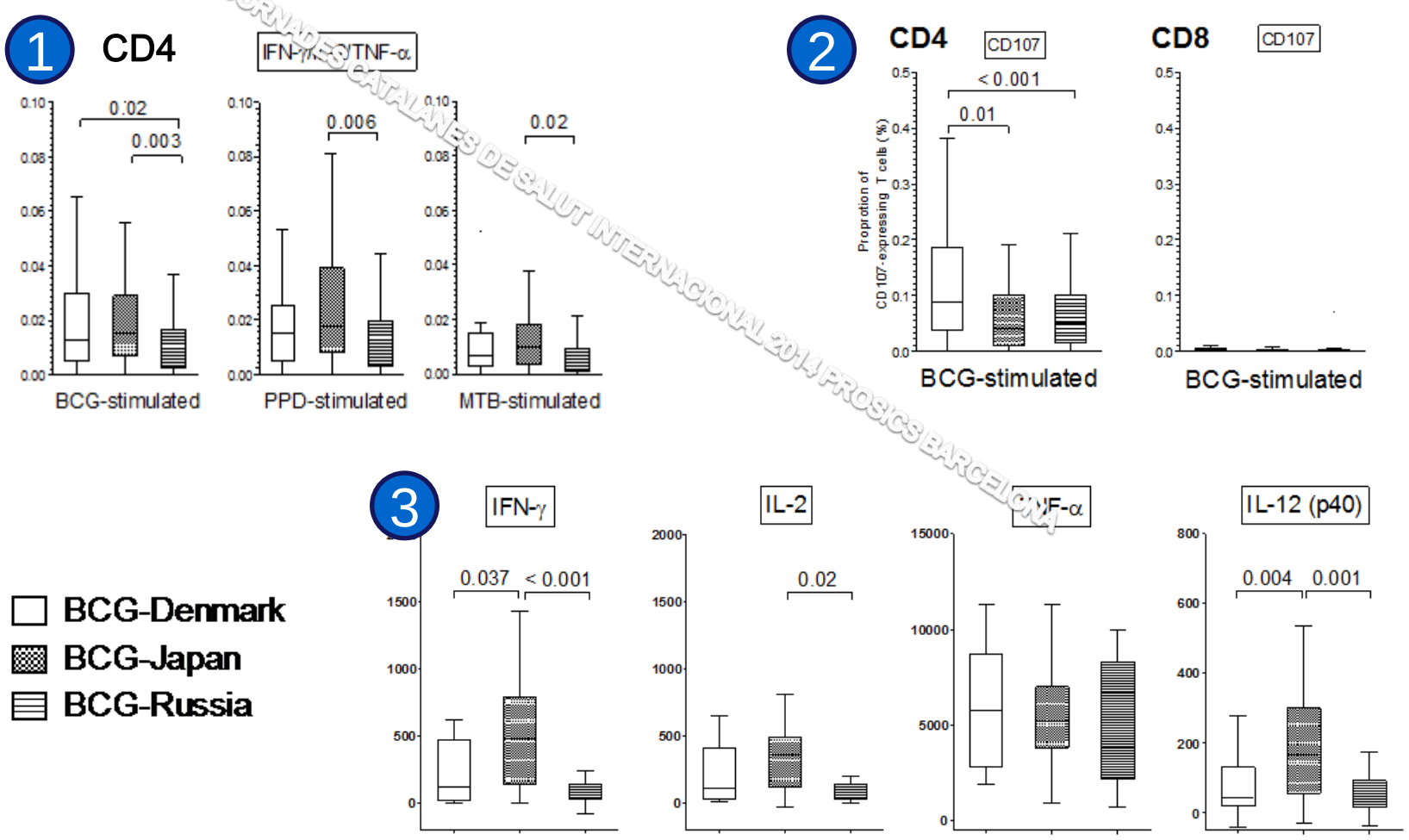
Ritz N, FEMS Microbiol Rev 2008

March 2008–April 2009



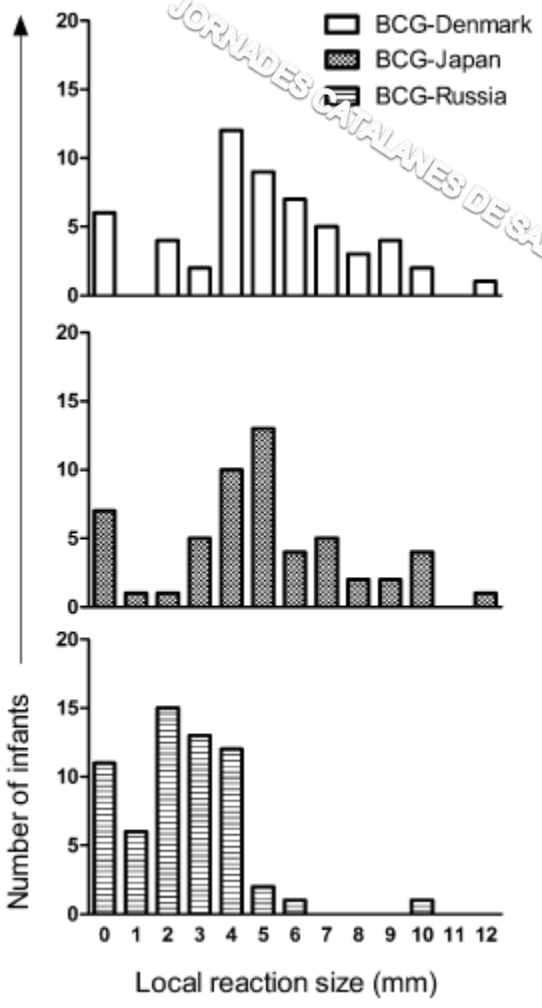
Ritz N, AJRCCM 2012

Immune response to different BCG vaccine strains



Ritz N, AJRCCM 2012

In vivo reaction to different BCG vaccine strains



Ritz N, AJRCCM 2012

Protective efficacy of BCG: 3 BCG vaccine strains in Kazakhstan

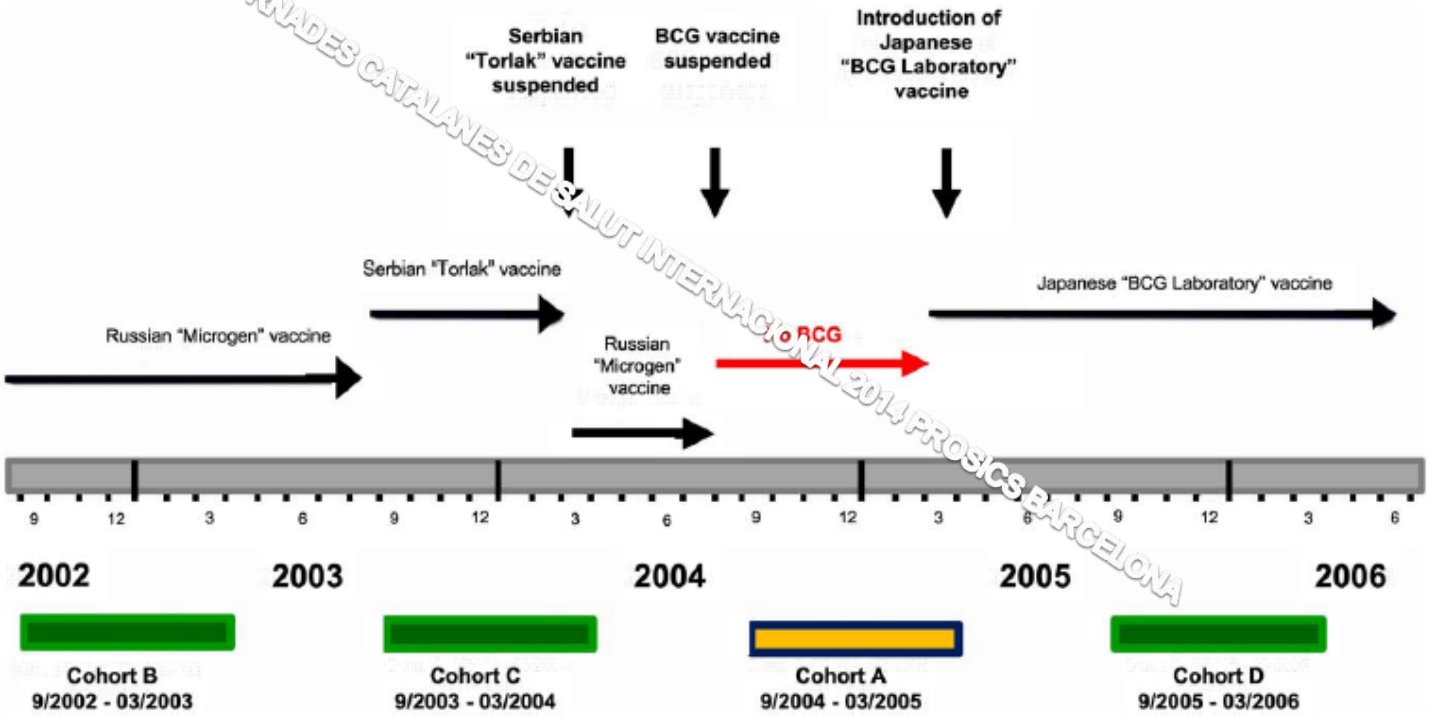


Figure 1. Cohorts of vaccinated and non-vaccinated children in Kazakhstan, 2002–2006.
doi:10.1371/journal.pone.0032567.g001

Favorov M, PloS ONE 2012

Protective efficacy of BCG: 3 BCG vaccine strains in Kazakhstan

Table 2. BCG vaccine prevention effectiveness for clinically defined, radiologically confirmed TB cases, Kazakhstan, 2002–2008.

Cohort (BCG product)	BCG Vaccinated			Non-vaccinated (Cohort A)			RR†	95% CI† for RR		PE† (%)	p-value
	# births	# cases	Risk per 1000*	# births	# cases	Risk per 1000*					
B Russian	138,059	207	1.50	160,970	310	1.93	0.78	0.65	0.93	22	0.005
C Serbian	150,938	165	1.09	160,970	310	1.93	0.57	0.47	0.69	43	<0.001
D Japanese	168,664	102	0.60	160,970	310	1.93	0.31	0.25	0.39	69	<0.001

*Risk calculated for the entire follow-up period (3 years).
†RR, relative risk; CI, confidence interval; PE, prevention effectiveness.
doi:10.1371/journal.pone.0032567.t002

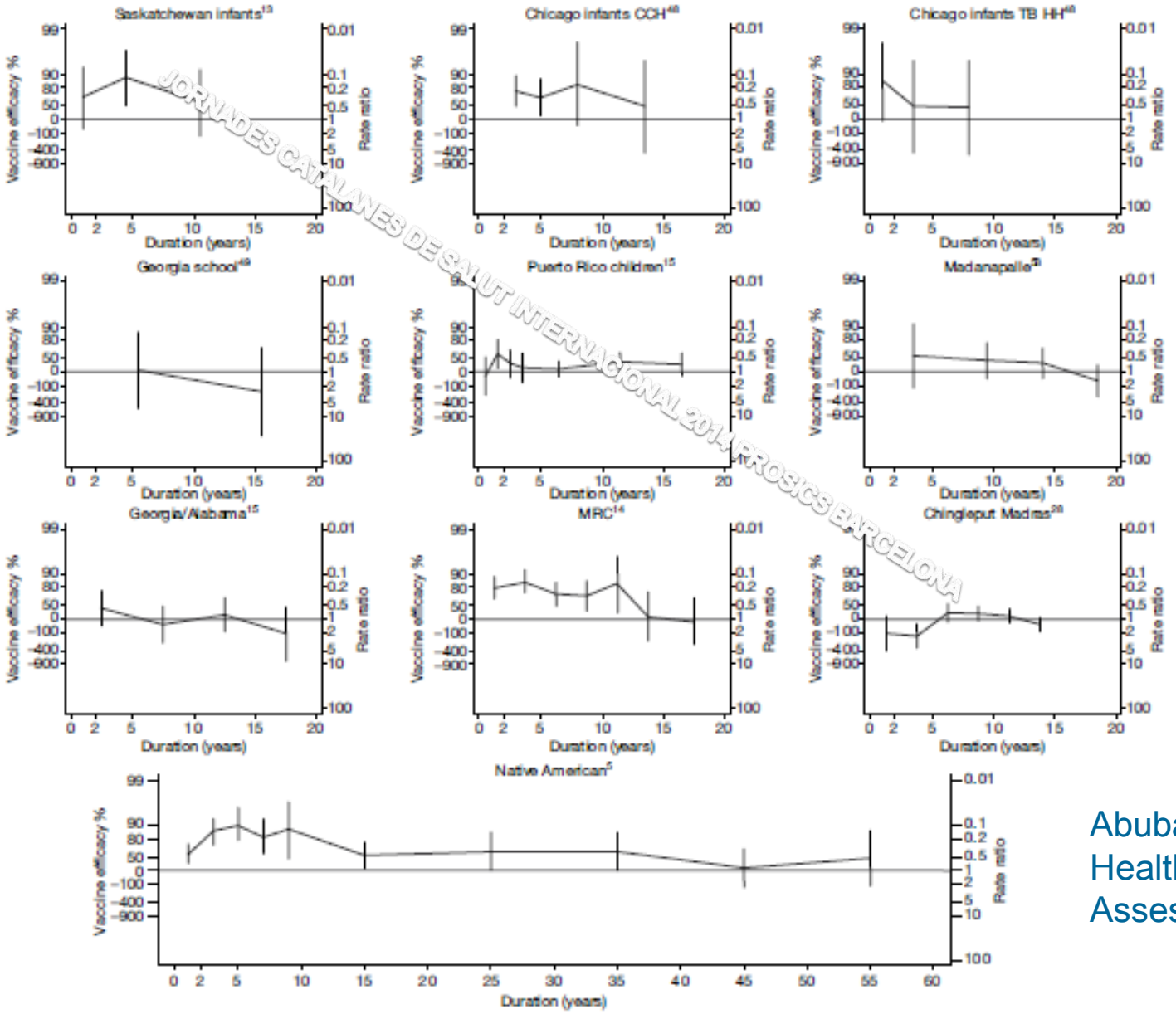
Table 3. BCG vaccine prevention effectiveness for culture positive TB cases, Kazakhstan, 2002–2008.

Cohort (BCG product)	BCG Vaccinated			Non-vaccinated (Cohort A)			RR†	95% CI† for RR		PE† (%)	p-value
	# births	# cases	Risk per 1000*	# births	# cases	Risk per 1000*					
B Russian	138,059	5	0.04	160,970	12	0.07	0.49	0.17	1.38	51	0.166
C Serbian	150,938	2	0.01	160,970	12	0.07	0.18	0.04	0.79	82	0.011
D Japanese	168,664	1	0.01	160,970	12	0.07	0.08	0.01	0.61	92	0.002

*Risk calculated for the entire follow-up period (3 years).
†RR, relative risk; CI, confidence interval; PE, prevention effectiveness.
doi:10.1371/journal.pone.0032567.t003

Favorov M, PloS ONE 2012

Duration of protection by BCG



Abubakara I, Health Tech Assess 2013

Summary: Protection from BCG against TB

Best protection for disseminated forms of TB

Homing of the immune cells induced by BCG

Better protection of younger individuals (birth – school age)

Better protection further away from the equator

Prior exposure to TB or NTM reduces protective efficacy

Better protection with certain BCG vaccine strains

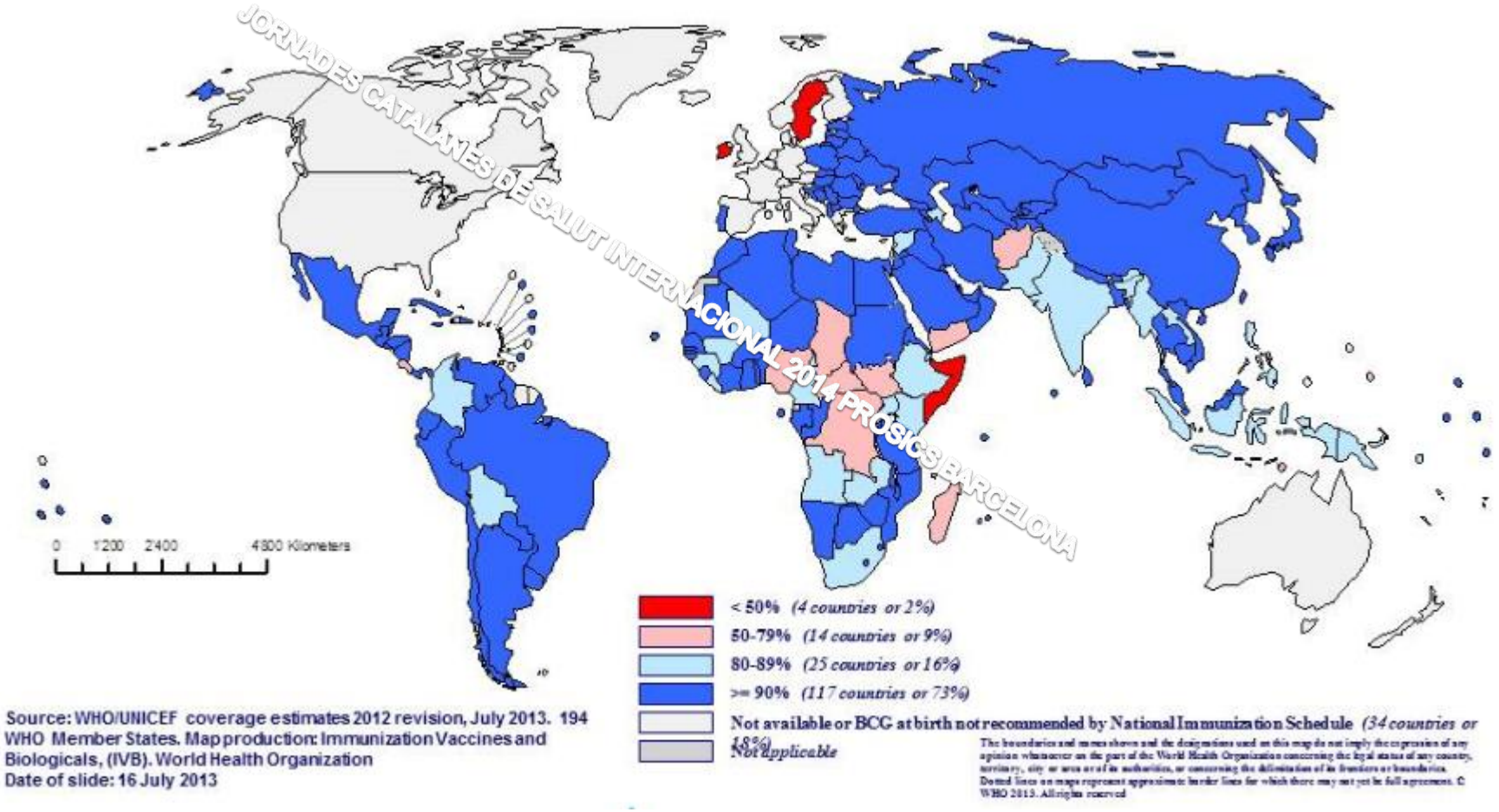
Strain influences immune response and protection

Protection from BCG wanes over time

Loss of memory cells

Non immunised become protected

BCG immunisation coverage worldwide



WHO 2014

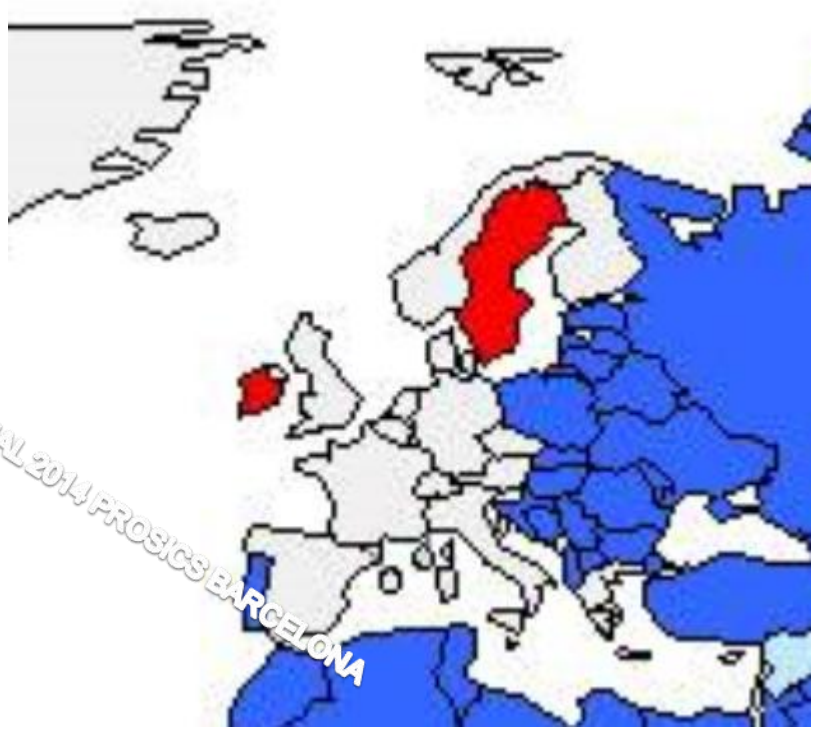
BCG immunisation in Europe

Routine at birth:
Basque counry, Portugal, Ireland, Hungary, Croatia, Albania, Poland

At birth to high risk groups
Switzerland, France, UK, Sweden

Routine at later age: Greece,
Finnland, Greece, Malta

Never
Germany



BCG a travel immunisation?

Source	Pre-travel BCG immunisation	Age limit	Definition of risk country	Duration of travel
National immunisation guidelines				
Australia [24]	Recommended	<5 years	>100/100,000 TB incidence	>3 months
Canada [25]	"To be considered"	Not specified	"High"	"Extended"
France [26]	Recommended	Not specified	"High prevalence"	"Prolonged"
Germany [27]	Not recommended	–	–	–
Ireland [28]	Recommended	Not specified	"High incidence"	>1 month
New Zealand [29]	Recommended	Neonatal	All but 25 named countries[a]	>3 months during first 5 years of life
Sweden [30]	Recommended for "travel involving close contact with local population"	Not specified	"High prevalence"	Not specified
Switzerland [31]	Not recommended	–	–	–
United Kingdom [15]	Recommended for "those who are going to live and work with local people"	<35 years	>40/100,000 TB incidence	>3 months
United States of America [32]	Not recommended	–	–	–

Ritz N, Vaccine 2008

WHO BCG recommendations

BCG should be given to all infants as soon as possible after birth in countries with a high burden of TB

Contraindications: individuals with HIV or other immunosuppressive conditions (in settings with adequate HIV services, delay BCG until infant is tested)

BCG revaccination not recommended

World Health Organization

The debate about revaccination

A number of countries recommend revaccination: eg Bulgaria, Russia, Ukraine ect

Table 2
BCG-VE from TB for school age (first and second dose) and neonatal vaccination, separately for Salvador and Manaus.

	Vaccinated	Cases in vaccinated	Crude incidence rate per 100,000 person years in vaccinated (95% CI)	Not vaccinated	Cases in not vaccinated	Crude incidence rate per 100,000 person in not vaccinated years (95% CI)	VE (95% CI)	*p* value
First dose, neonatal								
Salvador	46,762	217	5.13 (4.49–5.86)	9530	74	8.56 (6.81–10.75)	40% (22–54%)	<0.001
Manaus	49,938	170	3.77 (3.24–4.38)	8856	47	5.86 (4.41–7.81)	36% (11–53%)	0.008
First dose, school age								
Salvador	12,015	62	5.71 (4.44–7.31)	9530	74	8.56 (6.81–10.75)	34% (7–53%)	0.017
Manaus	8505	40	5.21 (3.81–7.09)	8856	47	5.86 (4.41–7.81)	8% (−39 to 40%)	0.686
Second doses, school age (first dose neonatal)								
Salvador	60,820	236	4.29 (3.78–4.88)	46,762	217	5.13 (4.49–5.86)	19% (3–33%)	0.022
Manaus	42,520	142	3.69 (3.14–4.36)	49,520	170	3.77 (3.25–4.38)	1% (−27 to 23%)	0.932

Estimate of vaccine efficacy (VE) adjusted for age, sex, socio-economic status (in Salvador), incidence of leprosy and incidence of tuberculosis before the start of the trial in Manaus.

Baretto I, Vaccine 2014 (in press)

Risks from BCG immunisation

Short communication

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

Anneke C. Hesseling [a,b,*], Ben J. Marais [a], Robert P. Gie [a], H. Simon Schaaf [a], Paul E.M. Fine [b], Peter Godfrey-Faussett [b], Nulda Beyers [a]

[a] *Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, P.O. Box 19063, Tygerberg, 7505, South Africa*

[b] *Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, UK*

Received 16 May 2006; received in revised form 15 July 2006; accepted 16 July 2006
Available online 1 August 2006

Nature of adverse event	Description	Rate/doses
Mild	Injection site papule (onset 2–4 weeks)	
	Mild ulceration (1–2 months)	Almost all vaccinees
	Scar (2–5 months)	
Severe	Local	
	Local abscess	
	Keloid	
	Lymphadenitis	
	Suppuration (onset 2–6 months)	1 per 1000–10 000
	Systemic (onset 1–12 months)	
	Cutaneous skin lesions	Case reports only
	Osteitis	1 per 3333–10^8
	Disseminated BCG	1 per 230 000–640 000
	Immune reconstitution syndrome	1 per 640 000

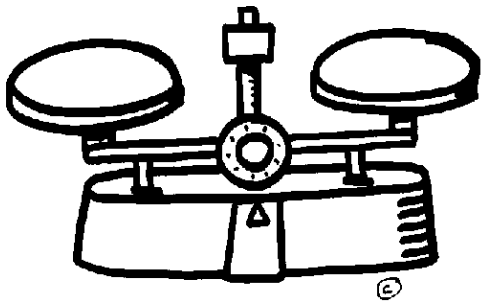
Dara M, ERJ 2014

When to stop general BCG immunisation?

Balance between risk of adverse effects and protective efficacy

IUTLD recommends to stop general BCG immunisation when TB incidence is < 5 / 100 000
(based on expert opinion)

“It is noteworthy that even in low-incidence countries, there may be a subset of the population with a higher risk of TB»



IUTLD, Tuberc Lung Dis
Dara M, ERJ 2014

Summary

BCG is one of the oldest vaccine in use

Protective efficacy depends on age at immunisation, form of TB, prior exposure to mycobacteria and BCG vaccine strain

BCG recommendations considerable vary across Europe

BCG is a safe vaccine but severe adverse effects can occur in immunocompromised