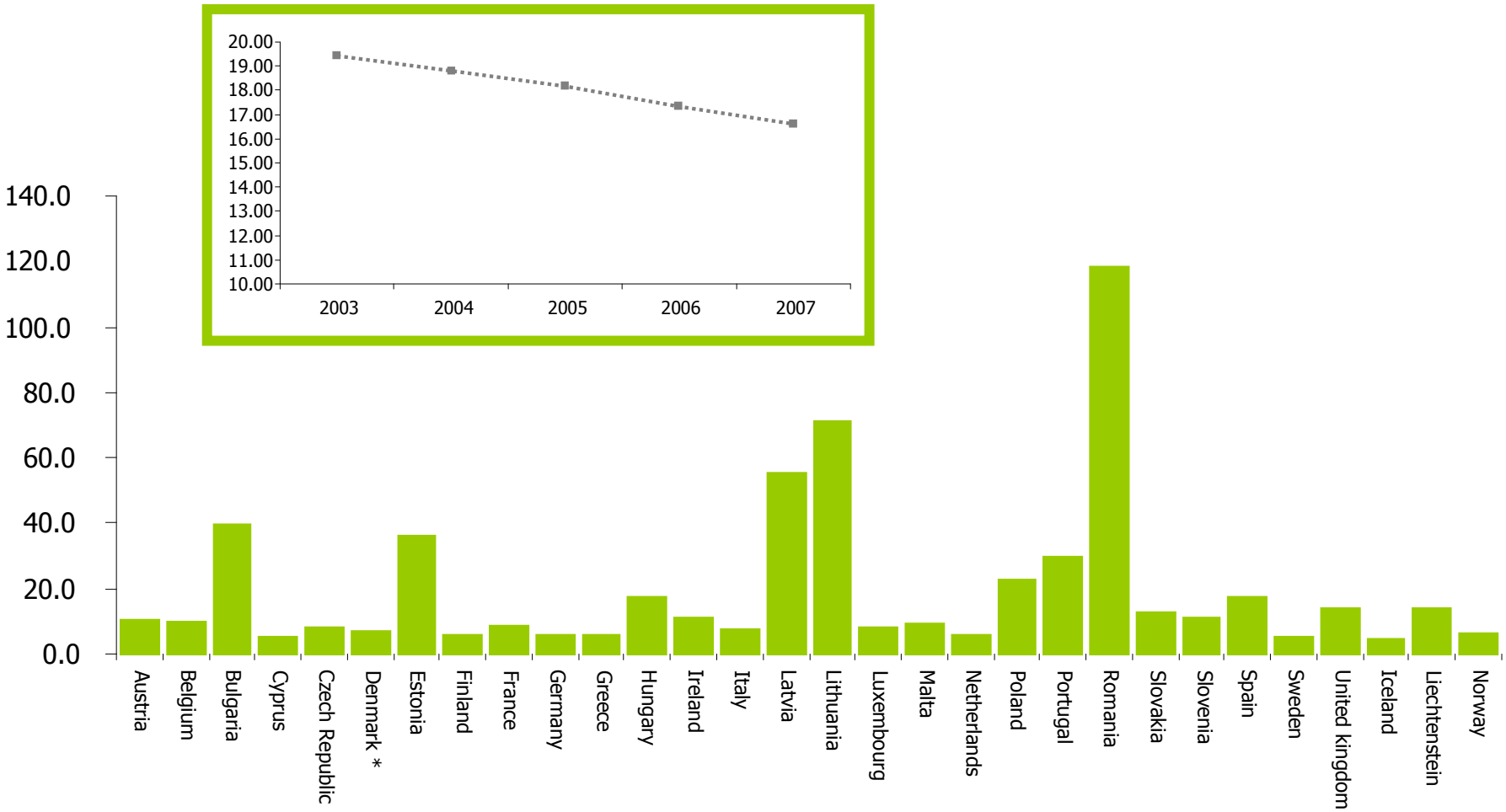
Controversial topics: BCG vaccination in low incidence settings

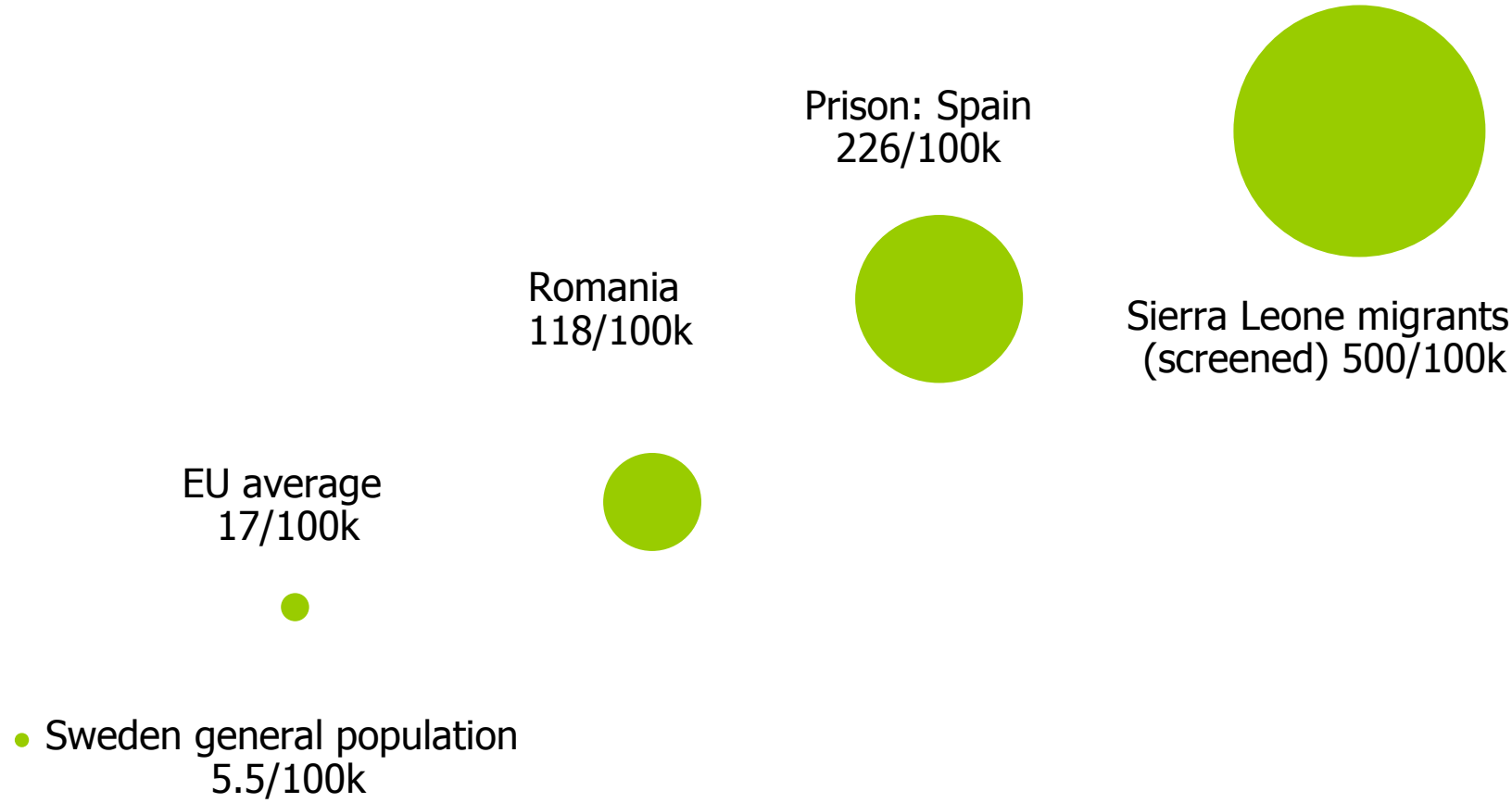
Davide Manissero

Children with TB sleeping outside in Clapham, November 1932

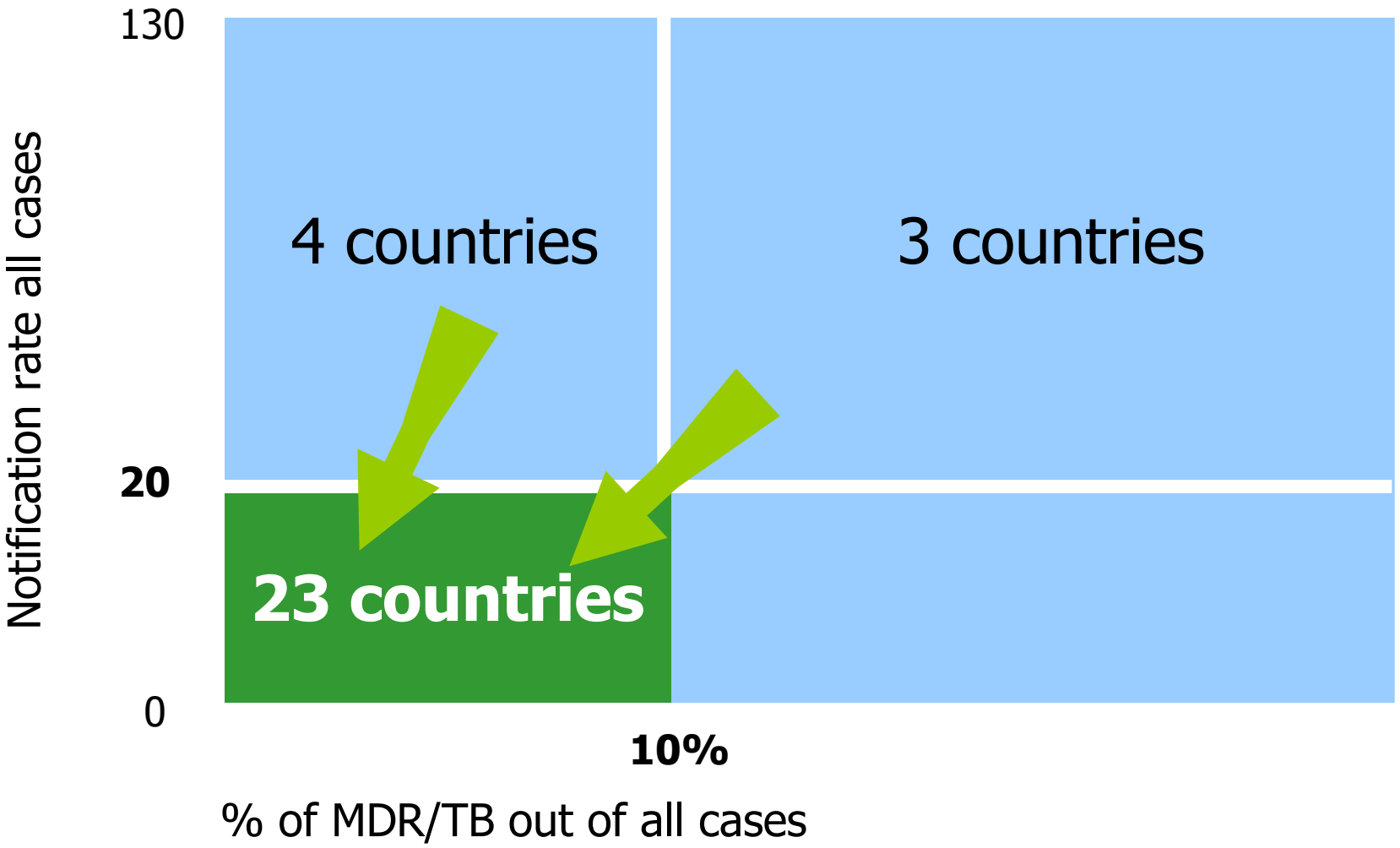
TB trends and rates in the EU and EEA/EFTA



Unevenly distributed risk



3 Progress towards Elimination



Background

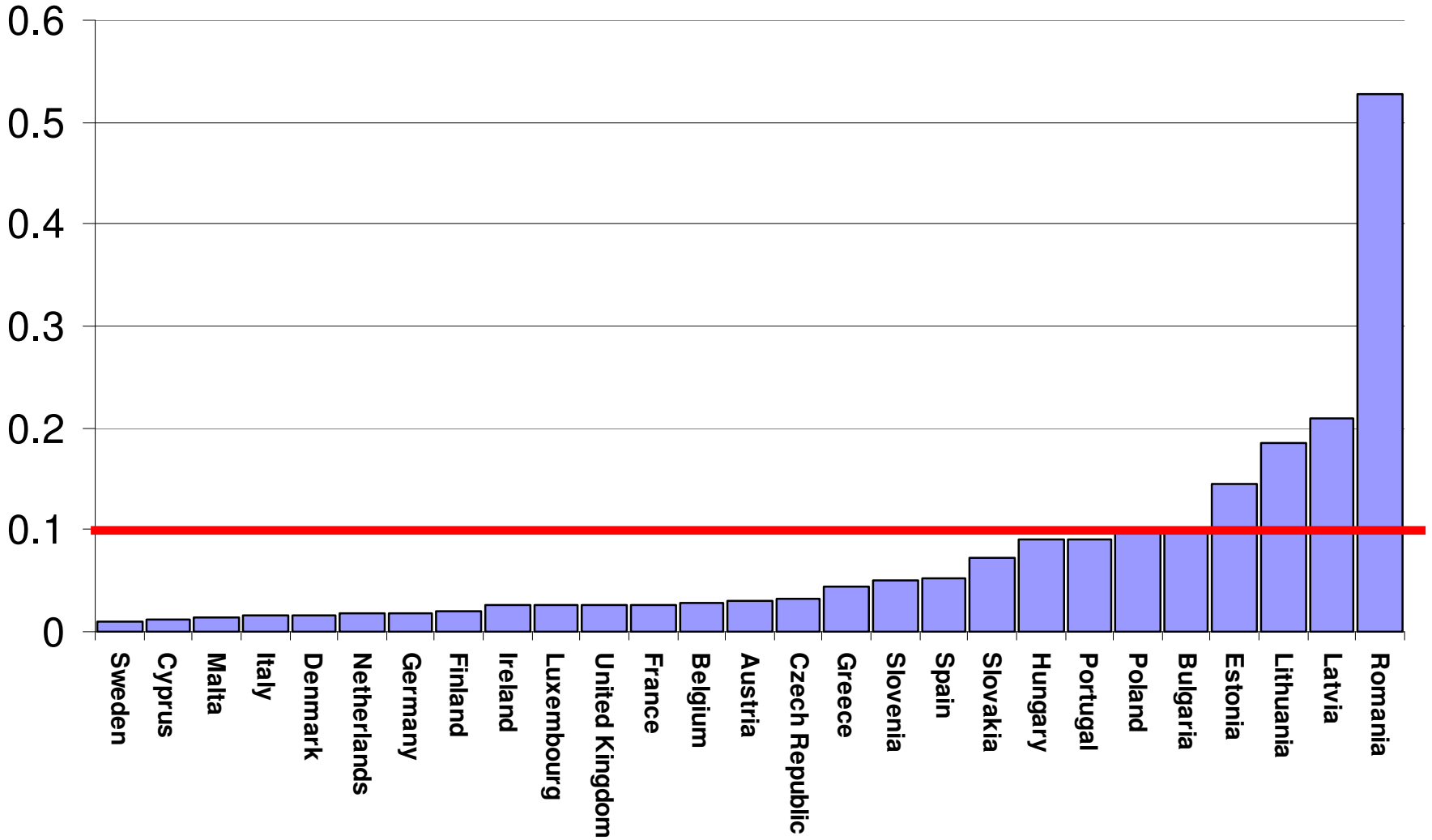
In a situation where the present national BCG vaccination policy is universal vaccination at birth what is the evidence for changing this policy to:

Selective vaccination of newborns belonging to high risk groups for TB

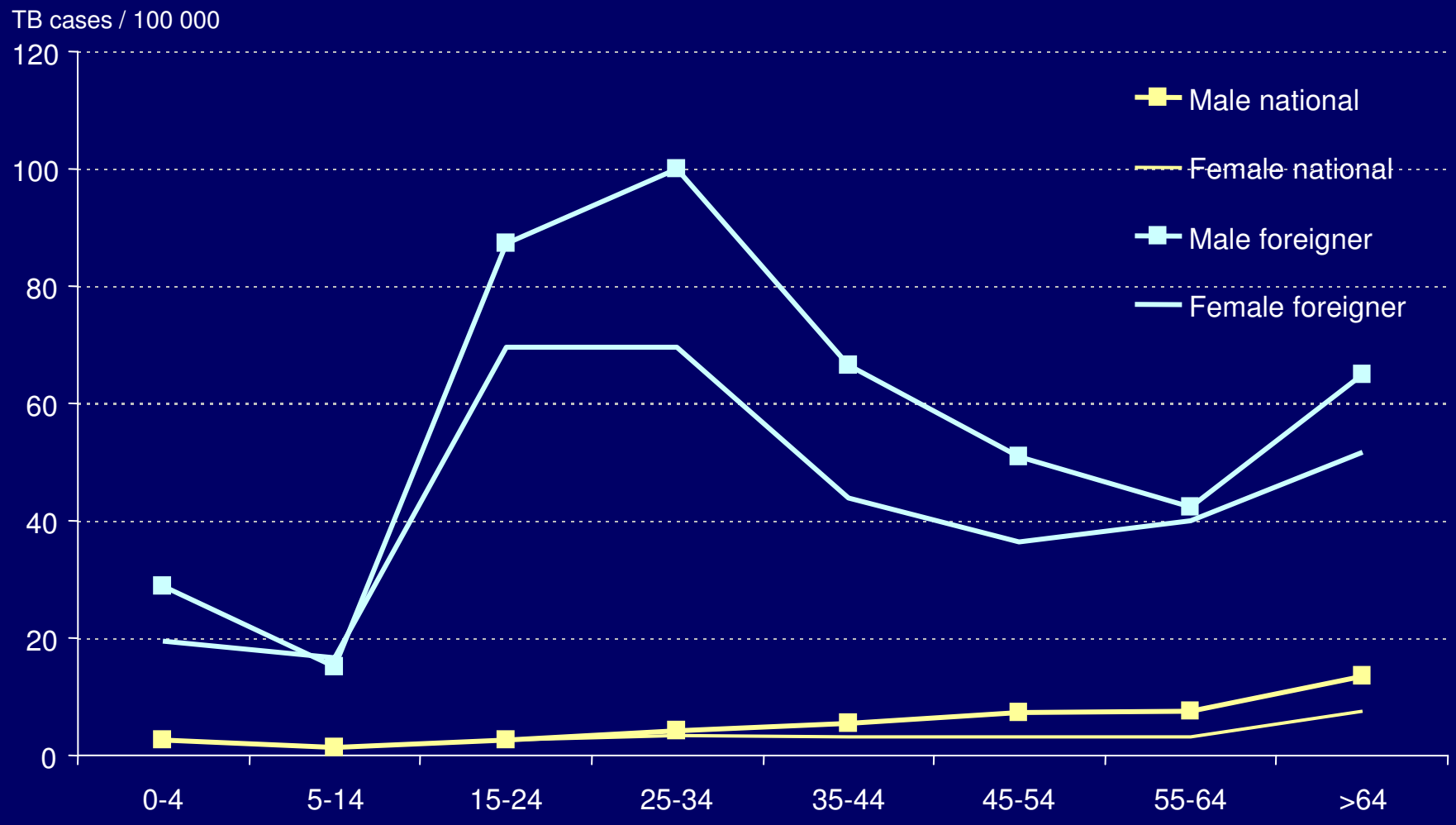
IUATLD guidelines for discontinuation of BCG 1994

- Efficient TB notification system in place
- Annual notification rate of ss+ TB cases below 5 per 100,000;or
- Annual notification rate of tuberculous meningitis in children aged under five years below 1 per 10 million during previous 5 years; or
- ARI below 0.1%

Range of estimated ARI in EU 25 + 2



TB notification rates by age-group, sex and geographic origin, EU & West*, 2004



* Countries submitting population data by geographic origin: Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Netherlands, Norway, Slovenia, Sweden, Switzerland, United Kingdom

EuroTB

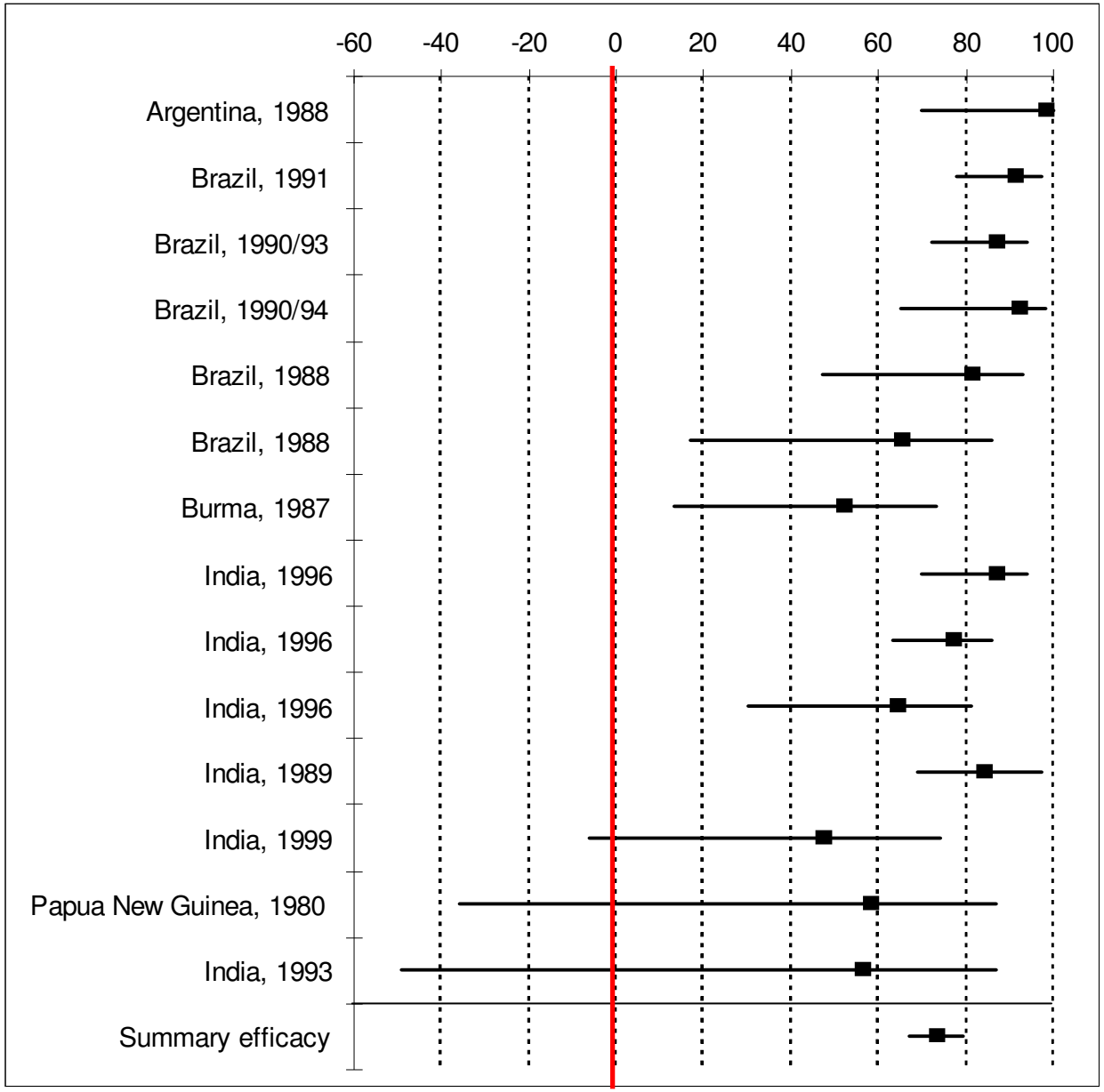
Developing a tool for decision making

- What is BCG efficacy ?
- Effects of suspension of BCG ?
- What is the occurrence of BCG side effects ?
- Assess universal vs selective vaccination strategy taking into account the heterogeneity of the population in terms of TB risk

Efficacy of BCG

- Childhood tuberculosis and tuberculous meningitis – consistent protection in the range of 80%
- Adult pulmonary TB – highly controversial with ranges from 0% to 80%
- Booster doses – no evidence of increased protection
- Leprosy and other mycobacteriosis

***Colditz GA, Berkey CS, Mosteller F, et al**. The efficacy of Bacillus Calmette Guerin vaccination of newborns and infants in the prevention of tuberculosis:meta-analysis of the published literature. Pediatrics 1995; 96: 29-35.*



Adverse events

	Romanus 93, Sweden	Trnka 93 (2), Czech Rep	INSERM 2004, France	KTL 2001, Finland
Suppurative lymphadenitis	0.9 per 1,000	-	0.4 per 1,000	3.0 per 1,000
Osteitis	1.4 per 100,000	1.3 per 100,000	-	1.4 per 100,000
Disseminated BCG	4 per 100,000	0.3 per 100,000	1.6 per 100,000	1.3 per 1,000,000

Measurable outcomes

- Estimated number of TB meningitis, miliary TB cases prevented in a cohort of children born in 2004 for the first 5 years of life
- Estimated number of primary TB cases prevented in a cohort of children born in 2004 for the first 15 years of life
- Estimated number of BCG vaccinations required to prevent one case of TB meningitis, miliary TB or primary TB.
- Number of BCG adverse event per case prevented

Two methods

- *Fine et al 1999 ; Bourdin Trunz et al 2006*
- *Based on historical assumption on the ratio between prevalence of SM+ disease and annual risk of TB infection (TB)*
- *Based on contact rate number of infected contacts per infectious case*
- *Contact rate historically 10 but can vary*

- *Institut De Veille Sanitaire 2005; Rahamn et al 2001*
- *Based on surveillance*
- *Notifications of severe form of TB and paediatric notifications need to be known along BCG coverage*
- *More accurate as not based on assumptions*
- *Requires optimal surveillance*
- *Severe TB is a rare disease*

Surveillance method

$$\mathbf{Tb_{prev} = Tb_{not} * (1/(1- Eff_{BCG} * Cov_{BCG})-1)}$$

Tb_{pre} = TB Cases prevented by BCG
Tb_{not} = TB cases notified in a given year
Eff_{BCG} = Efficacy of BCG
Cov_{BCG} = BCG vaccination coverage

ARI method

- Adaptation and update of work by Bourdin B, Dye C and Fine P, Lancet 2006)
- ARI derived from estimated prevalence using average contact rate of <6>
- Predicted cases of meningitis calculated using pre-chemotherapy data (1% of infected under fives contracts tuberculous meningitis)
- Miliary TB estimated through known ratio of 0.5 cases of MTB per case of TBM
- No cases of TBM or MTB assumed to be occurring in over 5s

ARI methods

$Tb_{men\text{-}prev} = 5\ B\ \lambda\ \rho_{men}\ \rho_{v}\ \epsilon_{men}$

$Tb_{men\text{-}prev}$ = TB meningitis cases prevented in a birth cohort for first five years of life

B = births in a given year

λ = Annual Risk of Infection

ρ_{men} = proportions of infections leading to Tb_{men}

ρ_{v} = proportion vaccinated (BCG coverage)

ϵ_{men} = BCG efficacy against TBmen

Comparison between the two methods

Model	Expected cases TBM	Prevented cases TBM[a]	Methods/source
INVS 2000/2002	11–16	9–13	Surveillance based method/notifications
ARI based (cohort 2004)	15 (95% CI: 8.4–24.7)	12 (95% CI: 6.2–20.9)	ARI based model
Italy[b]	5.6	NA	Hospital records
ARI based (cohort 2004)	4.6 (95% CI: 1.4–10.9)	NA	ARI based model

[a] Under universal BCG coverage.
[b] Average of hospitalised cases during the period 1999/2003.

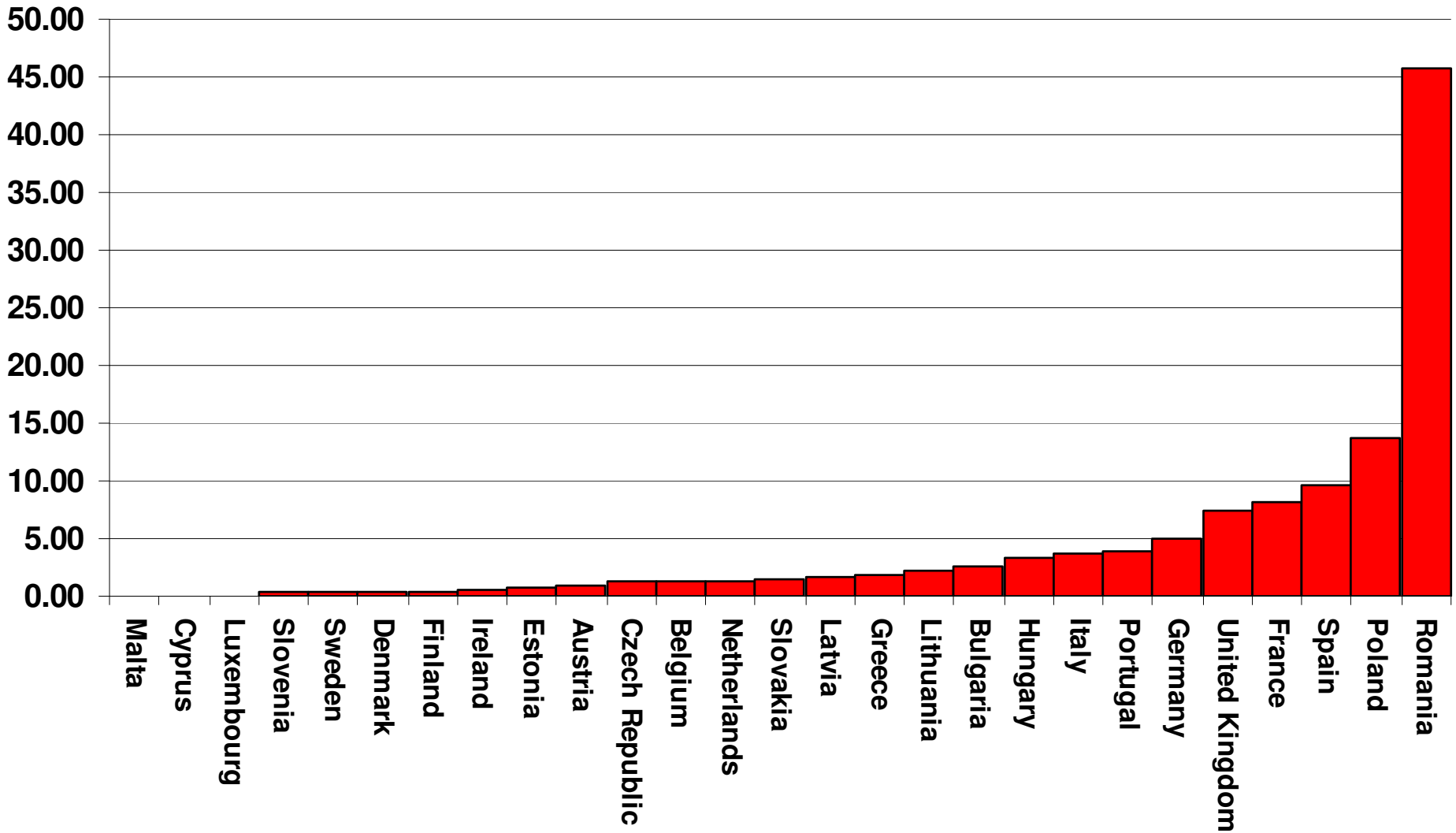
Table 1 Outcomes for the 5 selected settings from the ARI model applied for a cohort of 100,000 children

Setting	Percentile	TB Prevalence[a]	ARI (%)	Expected severe TB cases (TB meningitis)[b]	Prevented severe TB cases (TB meningitis)	Number of BCG vacc. per severe TB prevented	Expected disseminated BCG-itis per severe TB case prevented	Expected supp. Lymphadenitis per severe TB case prevented	Prevented primary TB cases (children under 15 years)
A	5th	1.7	0.01	0.8 (0.5)	0.6 (0.4)	161,499	6.5	161	3.8
B	25th	2.9	0.02	1.3 (0.9)	1.0 (0.7)	95,785	3.8	96	6.5
C	50th	4.7	0.03	2.1 (1.4)	1.7 (1.1)	59,102	2.4	59	10.6
D	75th	15.0	0.09	6.8 (4.5)	5.4 (3.6)	18,519	0.7	19	33.8
E	95th	33.4	0.20	15.0 (10.0)	12.0 (8.0)	8,317	0.3	8	75.2

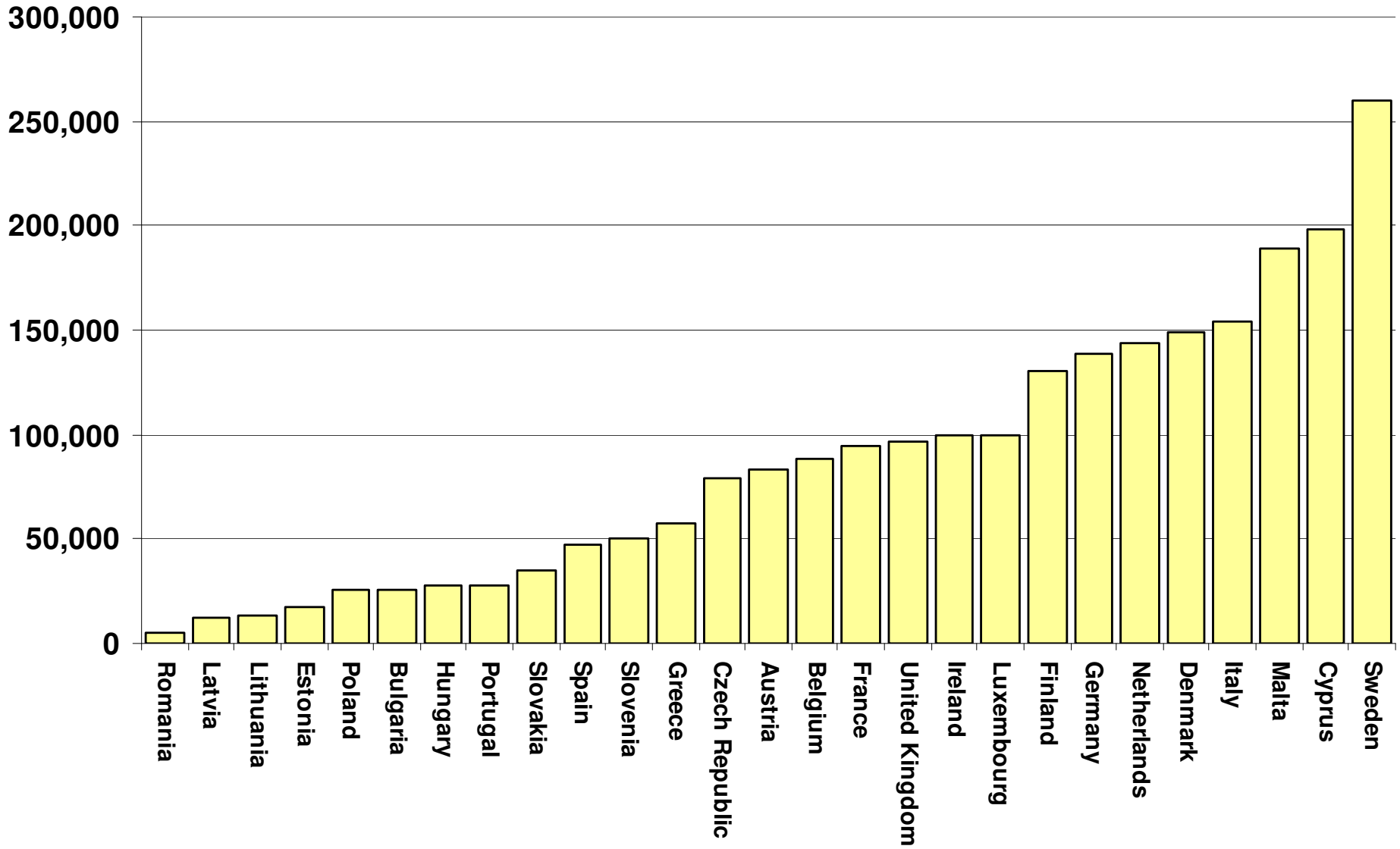
[a] Prevalence of sputum smear positive TB per 100,000 population.
[b] Calculated from $Tb_{sev\text{-}exp} = (1+k)\,(5B\beta\,\rho_{sm} + \rho_{men})$ and $Tb_{men\text{-}exp} = (5B\beta\,\rho_{sm} + \rho_{men})$ extrapolated from formula in Box 1.

TB prevalence (SS + per 100,000 population) ranges from 1.7 (setting A, 5th percentile) to 33.4 (setting E, 95th percentile), corresponding to ARI values ranging from 0.01 to 0.20 per 100,000 population.

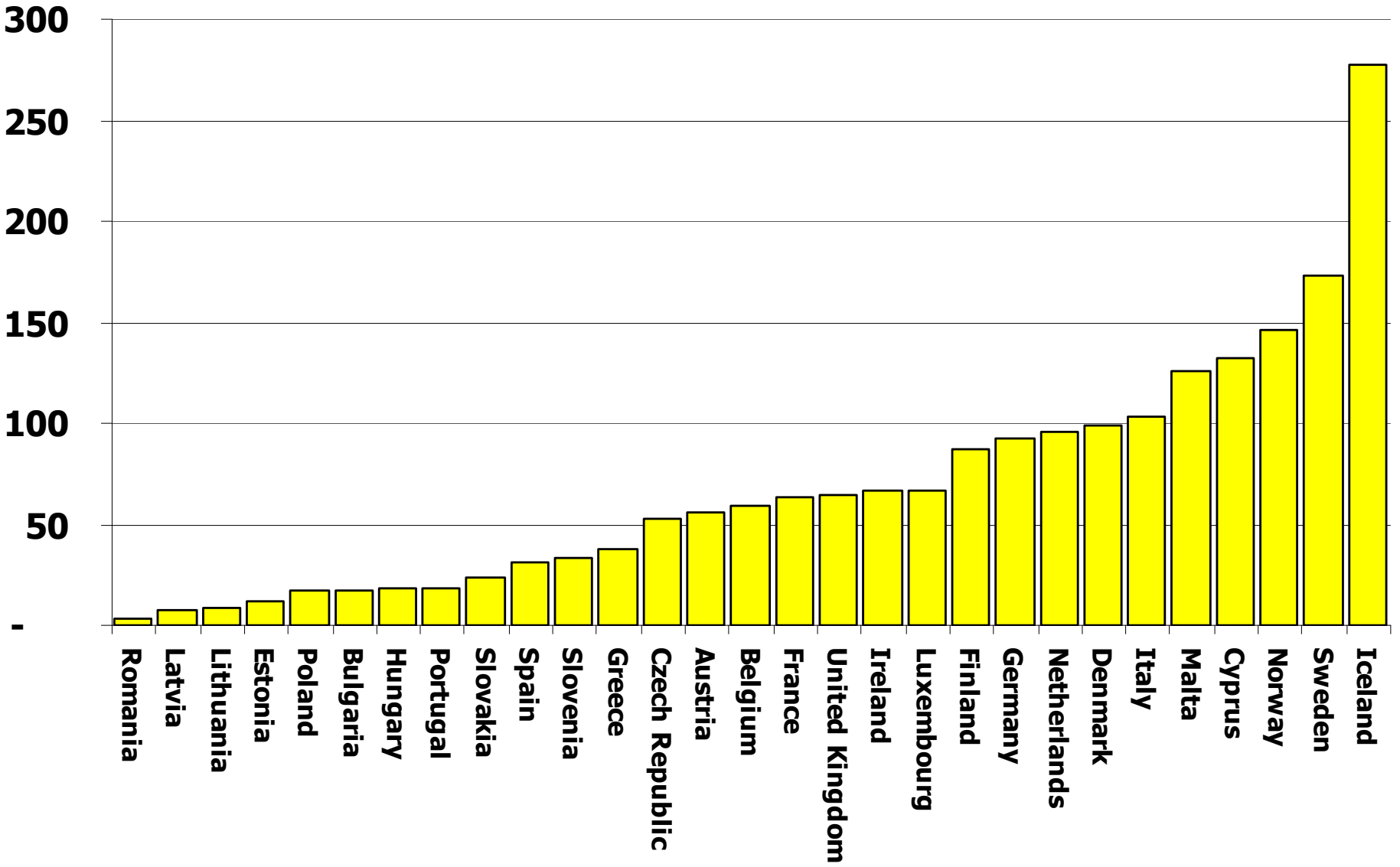
TBM prevented in the birth cohort 2004



BCG vaccinations required to prevent one case of TBM



BCG lymphadenitis per one prevented severe TB case



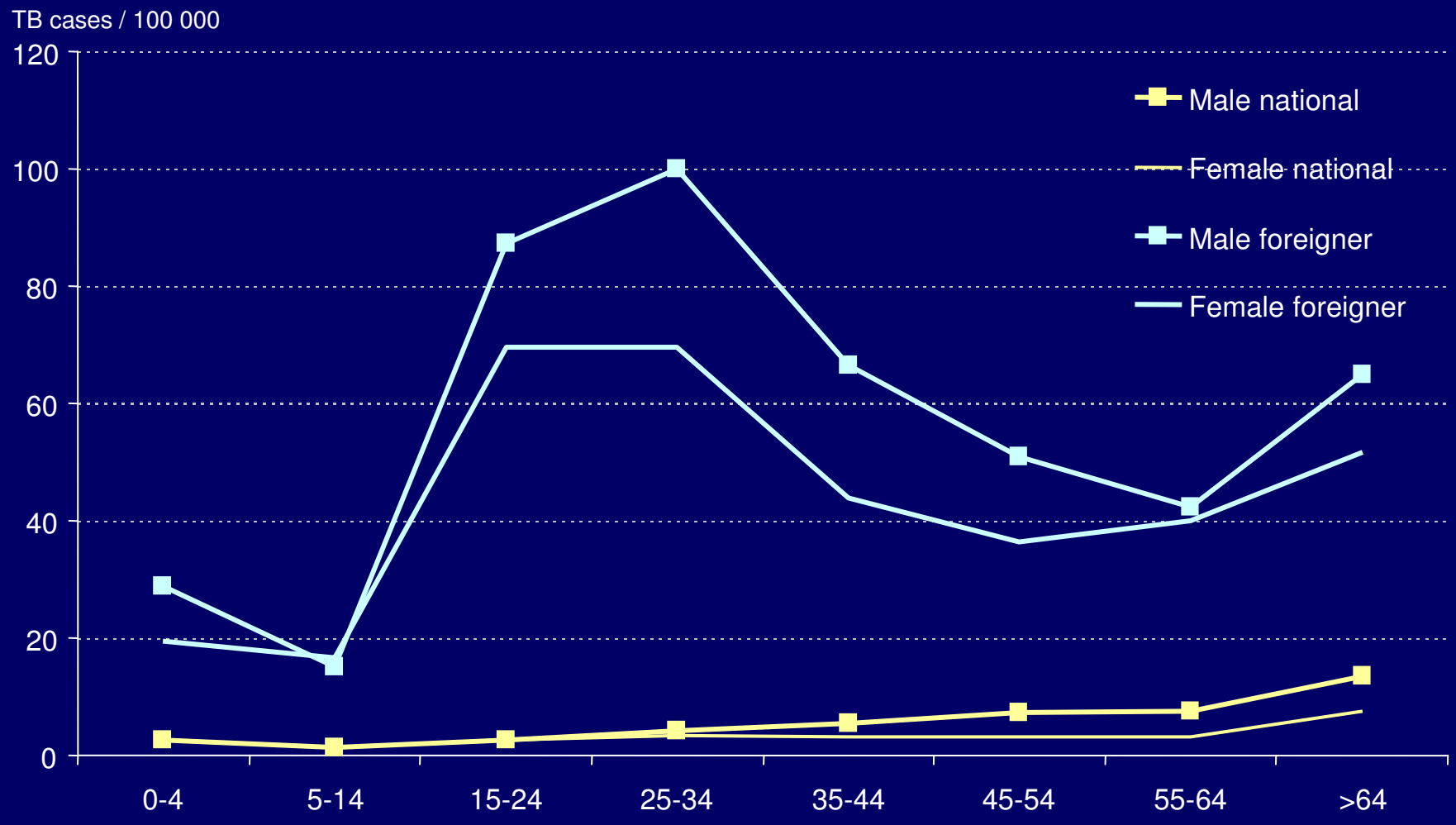
Conclusions

Universal BCG programme could be beneficial in settings with prevalence levels around 30 sputum smear positive per 100,000.

In settings with prevalence levels below 15 per 100,000 the benefit of universal BCG vaccination should be carefully assessed, particularly where prevalence is below 5 per 100,000 and universal vaccination might lead to an excess of adverse events per case prevented.

Selective vaccination

TB notification rates by age-group, sex and geographic origin, EU & West*, 2004



* Countries submitting population data by geographic origin: Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Netherlands, Norway, Slovenia, Sweden, Switzerland, United Kingdom

EuroTB

Effect of discontinuation in the presence of high risk groups

‘’***The discontinuation of BCG in Sweden was associated with demonstrable increases in childhood tuberculosis’’***

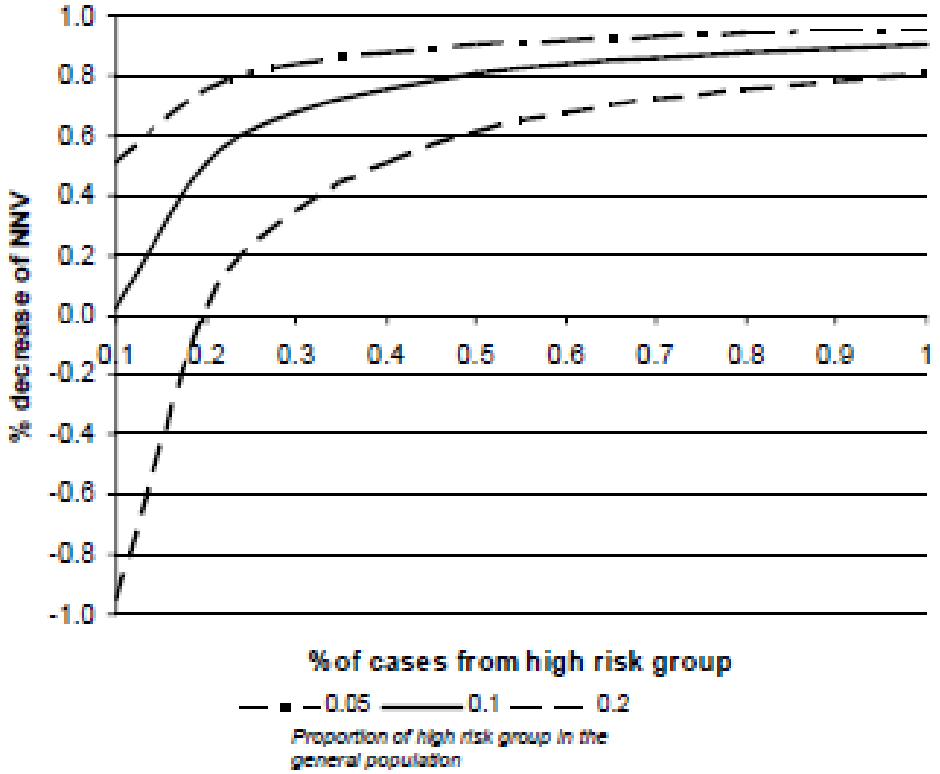
Romanus V, Svensson A, Hallander HO. The impact of changing BCG coverage on tuberculosis incidence in Swedish-born children between 1969 and 1989. Tubercle and Lung Disease 1992; 73: 150 -161.

Table 3 Comparison of universal vs. selective high-risk groups BCG vaccination under different assumptions in settings A–E

Setting	Percentile	% of cases belonging to high-risk groups[a]	Severe TB cases prevented under *universal* BCG vaccination	Severe TB cases prevented under *selective* BCG vaccination	Number of BCG vacc. per severe TB prevented under *universal* BCG vaccination	Number of BCG vacc. per severe TB prevented under *selective* BCG vaccination (under three different assumptions of proportion of population belonging to high-risk groups 20%)		
						20%	10%	5%
A	5th	50	0.6	0.3	161,499	64,599	32,300	16,150
B	25th	50	1	0.5	95,785	38,314	19,157	9,579
C	50th	50	1.7	0.8	59,102	23,641	11,820	5,910
D	75th	15	5.4	0.8	18,519	24,691	12,346	6,173
E	95th	1	12	1.2	8,317	16,633	8,317	4,158

[a] Average % of cases belonging to high-risk groups in EU countries in the range of prevalence A–E, according to the EURO TB report 2005 [24].

Figure 1. Percentage decrease in number needed to vaccinate (switching from universal to selective vaccination) under different assumptions of proportion of cases belonging to high risk groups, and proportion of high risk group individuals in the general population. (three assumption have been used namely, 5%, 10% and 20%)



Conclusions

Importance to assess epidemiological hetereogenity in low incidence setting

Model possibly underestimating risk of sever TB in high risk cohort given that an average contact rate and smear prevelance is being used

ARI likely to be much higher in cohort of children from vulnerable populations

The model assumes 100% coverage of the high risk group (extremely difficult in real life situation)