Controversial topics:
BCG vaccination in low incidence settings

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Unevenly distributed risk

- Sweden general population: 5.5/100k
- EU average: 17/100k
- Romania: 118/100k
- Prison: Spain: 226/100k
- Sierra Leone migrants (screened): 500/100k
3 Progress towards Elimination

- 23 countries
- 10% of MDR/TB out of all cases
- 4 countries
- 3 countries
- Notification rate all cases

% of MDR/TB out of all cases
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

Sweden
Cyprus
Malta
Italy
Denmark
Germany
Finland
Ireland
Netherlands
United Kingdom
France
Belgium
Austria
Czech Republic
Greece
Slovenia
Spain
Slovakia
Hungary
Portugal
Poland
Bulgaria
Estonia
Lithuania
Latvia
Romania
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
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
### Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Romanus 93, Sweden</th>
<th>Trnka 93 (2), Czech Rep</th>
<th>INSERM 2004, France</th>
<th>KTL 2001, Finland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppurative lymphadenitis</td>
<td>0.9 per 1,000</td>
<td>-</td>
<td>0.4 per 1,000</td>
<td>3.0 per 1,000</td>
</tr>
<tr>
<td>Osteitis</td>
<td>1.4 per 100,000</td>
<td>1.3 per 100,000</td>
<td>-</td>
<td>1.4 per 100,000</td>
</tr>
<tr>
<td>Disseminated BCG</td>
<td>4 per 100,000</td>
<td>0.3 per 100,000</td>
<td>1.6 per 100,000</td>
<td>1.3 per 1,000,000</td>
</tr>
</tbody>
</table>
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

\[ \text{Tb}_{prev} = \text{Tb}_{not} \times \left(\frac{1}{1 - \text{Eff}_{BCG} \times \text{Cov}_{BCG}}\right) - 1 \]

\text{Tb}_{pre} = \text{TB Cases prevented by BCG}
\text{Tb}_{not} = \text{TB cases notified in a given year}
\text{Eff}_{BCG} = \text{Efficacy of BCG}
\text{Cov}_{BCG} = \text{BCG vaccination coverage}
ARI method

- 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

\[ Tb_{men-prev} = 5 \ B \ \lambda \ \rho_{men} \ \rho_v \ \epsilon_{men} \]

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

\( B = \) births in a given year

\( \lambda = \) Annual Risk of Infection

\( \rho_{men} = \) proportions of infections leading to \( Tb_{men} \)

\( \rho_v = \) proportion vaccinated (BCG coverage)

\( \epsilon_{men} = \) BCG efficacy against TBmen
Comparison between the two methods

<table>
<thead>
<tr>
<th>Model</th>
<th>Expected cases TBM</th>
<th>Prevented cases TBM (^a)</th>
<th>Methods/source</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI based (cohort 2004)</td>
<td>15 (95% CI: 8.4–24.7)</td>
<td>12 (95% CI: 6.2–20.9)</td>
<td>ARI based model</td>
</tr>
<tr>
<td>Italy(^b)</td>
<td>5.6</td>
<td>NA</td>
<td>Hospital records</td>
</tr>
<tr>
<td>ARI based (cohort 2004)</td>
<td>4.6 (95% CI: 1.4–10.9)</td>
<td>NA</td>
<td>ARI based model</td>
</tr>
</tbody>
</table>

\(^a\) Under universal BCG coverage.
\(^b\) Average of hospitalised cases during the period 1999/2003.
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

Romania
Latvia
Lithuania
Estonia
Poland
Bulgaria
Hungary
Portugal
Slovakia
Spain
Slovenia
Greece
Czech Republic
Austria
Belgium
France
United Kingdom
Ireland
Luxembourg
Germany
Netherlands
Denmark
Italy
Malta
Cyprus
Sweden
BCG lymphadenitis per one prevented severe TB case

- Romania
- Latvia
- Lithuania
- Poland
- Bulgaria
- Hungary
- Portugal
- Slovakia
- Spain
- Slovenia
- Greece
- Czech Republic
- Austria
- Belgium
- France
- United Kingdom
- Ireland
- Luxembourg
- Finland
- Germany
- Netherlands
- Denmark
- Italy
- Malta
- Cyprus
- Norway
- Sweden
- Iceland
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
Effect of discontinuation in the presence of high risk groups

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

<table>
<thead>
<tr>
<th>Setting</th>
<th>Percentile</th>
<th>% of cases belonging to high-risk groups$^a$</th>
<th>Severe TB cases prevented under <em>universal</em> BCG vaccination</th>
<th>Severe TB cases prevented under <em>selective</em> BCG vaccination</th>
<th>Number of BCG vacc. per severe TB prevented under <em>universal</em> BCG vaccination</th>
<th>Number of BCG vacc. per severe TB prevented under <em>selective</em> BCG vaccination (under three different assumptions of proportion of population belonging to high-risk groups 20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5th</td>
<td>50</td>
<td>0.6</td>
<td>0.3</td>
<td>161,499</td>
<td>64,599</td>
</tr>
<tr>
<td>B</td>
<td>25th</td>
<td>50</td>
<td>1</td>
<td>0.5</td>
<td>95,785</td>
<td>38,314</td>
</tr>
<tr>
<td>C</td>
<td>50th</td>
<td>50</td>
<td>1.7</td>
<td>0.8</td>
<td>59,102</td>
<td>23,641</td>
</tr>
<tr>
<td>D</td>
<td>75th</td>
<td>15</td>
<td>5.4</td>
<td>0.8</td>
<td>18,519</td>
<td>24,691</td>
</tr>
<tr>
<td>E</td>
<td>95th</td>
<td>1</td>
<td>12</td>
<td>1.2</td>
<td>8,317</td>
<td>16,633</td>
</tr>
</tbody>
</table>

$^a$ 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 assumptions have been used namely, 5%, 10% and 20%)
Conclusions

Importance to assess epidemiological heterogeneity in low incidence setting

Model possibly underestimating risk of severe TB in high risk cohort given that an average contact rate and smear prevalence 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)