BCG vaccine update

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BCG

History
Strains
Recommendations
Efficacy
Safety
Heterologous effects
Worldwide shortage
Pragmatics
BCG: History

• named after the French investigators who developed the vaccine from an attenuated strain of *Mycobacterium bovis*.
• Isolated from a cow with TB
• They presented their results to the Academie de Sciences in 1908
• Subcultured every 3 weeks for 13 years..
BCG Strain History

Disseminated throughout world in the late 1920s
Each country maintained its own supply propagated in the same conditions as at the Pasteur Institute
Next few decades each of these laboratories developed its own sub strains, or “daughter strain” of BCG.

– called by the laboratory, country or person’s name with which they were associated
Oils aint oils- from WHO website:

“The BCG vaccines that are currently in use are produced at several (seven?) sites throughout the world. These vaccines are not identical. To what extent they differ in efficacy and safety in humans is not clear at present...”
Figure 1. Cohorts of vaccinated and non-vaccinated children in Kazakhstan, 2002–2006.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0032567
Table 2. BCG vaccine prevention effectiveness for clinically defined, radiologically confirmed TB cases, Kazakhstan, 2002–2008.

<table>
<thead>
<tr>
<th>Cohort (BCG product)</th>
<th>BCG Vaccinated</th>
<th>Non-vaccinated (Cohort A)</th>
<th>RR†</th>
<th>95% CI† for RR</th>
<th>PE† (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># births</td>
<td># cases</td>
<td>Risk per 1000*</td>
<td># births</td>
<td># cases</td>
<td>Risk per 1000*</td>
</tr>
<tr>
<td>B Russian</td>
<td>138,059</td>
<td>207</td>
<td>1.50</td>
<td>160,970</td>
<td>310</td>
<td>1.93</td>
</tr>
<tr>
<td>C Serbian</td>
<td>150,938</td>
<td>165</td>
<td>1.09</td>
<td>160,970</td>
<td>310</td>
<td>1.93</td>
</tr>
<tr>
<td>D Japanese</td>
<td>168,664</td>
<td>102</td>
<td>0.60</td>
<td>160,970</td>
<td>310</td>
<td>1.93</td>
</tr>
</tbody>
</table>

*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

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0032567
Differing antimicrobial sensitivity

TABLE 1. Susceptibilities of different BCG vaccine strains to antituberculous drugs

<table>
<thead>
<tr>
<th>Antituberculous drug</th>
<th>Conc (µg/ml)</th>
<th>BCG-Bulgaria (SL 222 Sofia)</th>
<th>BCG-Connaught (SSI 1331)</th>
<th>BCG-Denmark (Tokyo 172)</th>
<th>BCG-Medac (RIVM from 1173-P2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>0.1</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>0.4</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1.0</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.5</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>100.0</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>5.0</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Ritz et al AAC 2009
BCG should be specifically considered for the following:

- ATSI neonates living in regions of high TB incidence
- Neonates born to parents with leprosy/ FHx of leprosy
- Infants of migrant parents from high incidence settings
- Children who will be travelling to high TB incidence settings
  - Esp children <5 years of age who will be travelling longer than 3 m

Occupational:
- embalmers, HCW performing autopsies
State and Territory guidelines should be consulted for the following groups

- healthcare workers who may be at high risk of exposure to drug-resistant cases,
- neonates weighing <2.5 kg,
- children ≥5 years and <16 years of age who will be travelling or living for extended periods in countries with a high prevalence of tuberculosis.
BCG effective in preventing severe TB in children

Protection

• Consistent 60-80% protection against disseminated tuberculosis (TBM, miliary TB) in HIV-negative and unexposed young children

• Variable protection: pulmonary TB, limited impact transmission

• Revaccination: no benefit

Limited efficacy data in HIV-infected infants

• High TB incidence HIV-infected infants (small subpopulation): 25 fold higher in HIV-infected infants

• HAART: reduces risk of TB in HIV-infected infants

~50% effective in preventing both infection and disease

In children and young adults
BCG Safety

REVISED PAEDIATRIC BCG DISEASE CLASSIFICATION

Local disease
Abscess

Regional disease
Adenitis

Disseminated disease
Beyond regional

Dual disease
M. tb and BCG

BCG IRIS
Following HAART

Hesseling et al, Clin Infect Dis 2006
BCG Safety

Disseminated BCG disease (dBCCG)

Pre-HIV era: incidence 1 -5 per million vaccinees (Fine, 1997)

BCG poses a risk of disseminated BCG disease in infants vertically infected with HIV  


Risk quantification?
<table>
<thead>
<tr>
<th>Complication</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local hypersensitivity reaction</td>
<td>None, or topical dressing</td>
</tr>
<tr>
<td>Abscess or ulcer at injection site</td>
<td>Drainage or needle aspiration if indicated. Isoniazid or erythromycin</td>
</tr>
<tr>
<td>Regional lymphadenitis</td>
<td>Surgical if there is excessive enlargement, overt suppuration, or sinus formation</td>
</tr>
<tr>
<td>Distant lesion, eg osteitis</td>
<td>Chemotherapy*</td>
</tr>
<tr>
<td>Disseminated BCG infection (‘BCG-osis’)</td>
<td>Chemotherapy*</td>
</tr>
<tr>
<td>Disseminated BCG infection with cardiovascular effects following intravesical instillation of BCG</td>
<td>Chemotherapy* plus intravenous corticosteriods</td>
</tr>
</tbody>
</table>
Revised BCG vaccination guidelines for infants at risk for HIV infection

WHO, 2007
“SAGE agreed that the BCG position paper should be updated to reflect this change and provide guidance to national policy-making bodies, recognizing the complexity of the decision-making process and the lack of information as well as the necessary infrastructure to perform adequate risk assessment in individual children.

Among HIV-infected children, the benefits of potentially preventing severe TB are outweighed by the risks associated with the use of BCG vaccine. GACVS therefore advised WHO to change its recommendation such that children who are known to be HIV-infected, even if asymptomatic, should no longer be immunized with BCG vaccine.”
“Since not vaccinating an infant who is exposed to HIV but remains uninfected may increase the risk of disseminated tuberculosis, BCG vaccination should continue in settings where HIV infection and tuberculosis are both highly endemic until it is feasible to implement a policy of selective vaccination.
December 1929 and April 1930

- 251 of 412 infants born in Lübeck, Germany, received three doses of BCG vaccine by the mouth during the first ten days of life.

Within 12 months

- 72 died of tuberculosis
- 135 clinical TB but recovered
BCG History: The Lübeck disaster

44 became TST-positive but remained well

Strain from Pasteur institute but propagated locally: contaminated with a virulent strain of *M. tuberculosis*
BCG and TST

TST response post-BCG not predictive of efficacy

Koch phenomenon within 48-72h

GW Comstock. CID 2000; 30:S250
SAEFVIC: BCG AEFI

SAEFVIC BCG Reports by year

N=130
SAEFVIC: BCG AEFI

Primary reaction

- Abscess: 49%
- Lymphadenopathy: 27%
- Rash: 3%
- Injection site reaction - minor/common/expected: 7%
- Hypotonic–hypo-responsive episode - HHE: 2%
- Urticaria/Hives/Allergic Rash: 5%
- Drug error (Program error): 2%
- Nodule at injection site: 2%

[Image of a person's neck with a reaction at the injection site]
Pragmatics: BCG in Oz

2013 BCG Connaught strain replaced with BCG Denmark strain
  – Denmark higher rate disseminated disease in HIV
  – 100 dose vials rather than 10 dose

2015 BCG Connaught strain

2016 World wide shortage: NTAC
  – BCG Moreau strain made in Poland
    • Not TGA licensed
Pragmatics: BCG in Victoria

Not TGA licensed: approved prescriber by TGA plus informed consent from parents

Public clinics:
RCH Immunisation
Monash Immunisation
Geelong Hospital

TST not required <2yo if no contact or direct epidemiology of risk

Need referral
Heterologous effects of BCG

Appears to reduce mortality from infections other than TB

• Guinea-Bissau; US/UK 1940-50s

Revaccination no effect

?differ by strain

Affects immune response hep B vaccine

?affects risk allergy: MISBAIRS

TB vaccines: the future?

Strategies for TB Vaccine Development

- **Pre-infection**: to prevent infection
  - Improved priming vaccines
  - Novel booster vaccines

- **Post-infection**: to prevent disease
  - Develop novel booster vaccines to extend and enhance immune protection

- **Immunotherapeutic**: treatment
  - Shorten the course of chemotherapy for active TB
  - Improve efficacy of MDR/XDR/TDR-TB treatment
“Although the trial raised no concerns about safety, the absence of any detectable efficacy presents the tuberculosis vaccine community with a serious challenge”
Thank you
Schematic representation of infection profiles in naive and BCG-vaccinated hosts.