SEMINAR
ON
BCG
Contents

1. HISTORY
2. CHARACTERISTICS
3. VACCINATION
Introduction

Tuberculosis remain world wide public health problem and especially major public health problem in India.

**Tuberculosis Control** – (WHO definition)

Control is said to be achieved when the prevalence of natural infection in age group of 0-14 yrs is in order of 1%. 40% in India.

Control has two components:-

1. **Curative**
   - Case finding & treatment *(Most powerful weapon)*

2. **Preventive**
   - BCG vaccination & chemoprophylaxis
Ever since Koch discovered M. tuberculosis in 1882, attempts were made to prepare prophylactic vaccine against tuberculosis.

1906  Albert Calmette (Bacterologist) & Camille Gurein (Veterianarian)  
Began Attenuating a highly virulent strain of Tubercle Bacilli of Bovine origin (M. bovis).

1908  Observation of Beef Bile dividing aggregates of these Bacilli  
resulting lost of virulence.  
Cultivation of Bacilli in potato-glycerol-Bile medium for further attenuation.
Subcultured every three weeks for next 13 years

After 231 subcultures (lost its virulence)

1921 Strain was described as completely harmless even in highly susceptible guinea pigs, yet its antigenicity unimpaired.

1924 Calmette declared it incapable of reverting to Virulent form.

1928 League of Nations declared BCG strains harmless to animals & man.
1948

- 1st INTERNATIONAL CONGRESS on BCG confirmed its absolute effectiveness in man as preventive measure.
- BCG vaccine program started at Madanapalle.
- BCG vaccine Laboratory established in Madras.

1960

Mass BCG vaccine program – 1st round completed

Biggest Health Program ever undertaken anywhere in the world.
**BCG**

**Characteristics:-**
- Attenuated strain of *M. bovis*
- Regular cell membrane
- Rarely branching
- Cytoplasm with dense granules

**Colony Morphology:-**
- No differentiation w.r.t virulent bacilli
- On solid media colonies flat, smooth, moist, white and break up easily when touched.
Morphological variation:-

- Under repeated Cultures are within normal limits and present Constant characteristics under uniform conditions.
BCG VACCINATION

AIM:-
To induce Benign \textit{artificial} primary infection which stimulate acquired resistance to possible subsequent infection with \textit{virulent} tubercle Bacilli & reduce the morbidity & mortality from primary tuberculosis among those at risk.

Vaccine:-
BCG is the only widely used Live attenuated bacterial vaccine.
Substrains :-

many substrains have evolved of the original descendant ‘Calmette’ strain of BCG.

Four Strains:-
1. Pasteur - 1173 p2
2. Tokyo - 172
3. Copenhagen - 1331
4. Glaxo – 1077 strains

Studies fail to differentiate protective efficacy among these strains.

Quality control of BCG vaccine by WHO

*Bull. WHO 1989;68;93-108*
WHO Recommendations

“Danish 1331” strain for the production of BCG vaccine.

Since Jan 1967, BCG Lab. at Guindy Chennai has been using it for production of BCG vaccine.

Quality control ensured by International Reference Centre for BCG Quality control at Copenhagon.
FORMS OF VACCINE –

1. Freeze dried –
   - used in all countries now
   - more stable preparation.

2. Liquid form – (no more used)

Each dose contain 0.1 – 0.4 million viable bacilli of attenuated BCG strain.
Storage:-

-20 °C (subzero)  2 years.
+2-8 °C (middle component of refrigerator)  6 month.
2 – 8 °C (at peripheral level)  1 week

Requirements for Storage:-

- Maintenance of cold chain (centre to peripheral)
- Protected from exposure to light.
  - Supplied in dark colored ampules.
  - Wrapped in Black paper/cloth.
• Reconstitution – Normal Saline is recommended as a diluent, as distilled water may cause irritation

Diluent is also kept at similar temperature, in cold part of refrigerator.

Reconstituted vaccine

• used in 3 hrs
• left over vaccine discarded.
Dosage:-

- STANDARD DOSAGE of vaccine 0.1 mg in 0.1 ml volume
- For New Born (< 4 weeks) dosage 0.05ml

*WHO (1981) Tech resp series*

- RCT (1.3%) incidence of lymphadenitis w.r.t 1% incidence with lower dose.
- Doubts on adequate efficacy with low dose exits.
Administration

1. WHO Recommendation
   - Intradermal administration as standard procedure.
   - Tuberculin syringe (Omega microstat syringe fitted with 1cm steel 26 gauge intradermal needle).
   - Most precise way of administration with respect to other methods (Bifurcated Needles, dermojets, Multipuncture technique).
   - If given S/C, abscess formation more likely.
Site -

- Conventionally, Lt. upper arm, just above the insertion of deltoid muscle.
- Vaccine must not be contaminated with an antiseptic or detergent. If alcohol is used to swab the skin allow it to evaporate.
- A satisfactory injection should produce a wheal of 5 mm in diameter.
3. **Age of Vaccination**:–

National policy for vaccination differ from country to country.

National policy in India:– *(Current Status)*

- BCG given - early in infancy
  - at birth (for institutional deliveries) or
  - at 6 weeks (with other immunizing agents DPT & Polio, preferable before 9 months)
- effective in preterm infants, however they show poor rate of post vaccination conversion.
Global Immunization 1980-2005, BCG coverage at birth

Global coverage at 83% in 2005

% coverage


Date of slide: 11 September 2006
Revaccination

Much controversy over the effectiveness of repeated doses.
Although European countries have used repeated vaccination
but increase in efficacy has not been documented.

Not included in Official Immunization Schedule in India under (expanded program of immunization).
Phenomenon after vaccination

0.1ml vaccine

2-3 weeks papule development

4-8 mm by 5 weeks

Subsides / Break into shallow ulcer, rarely open, usually covered with crust

Heals by 10–12 weeks with permanent tiny round scar 4-8 mm

Normally Montoux test become +ve after period of 8 weeks but some times take 14 weeks.
<table>
<thead>
<tr>
<th>Dissemination (non fatal)</th>
<th>Fatal generalized lesions (Very rare)</th>
</tr>
</thead>
<tbody>
<tr>
<td>otitis</td>
<td></td>
</tr>
<tr>
<td>Retropharyngeal abscess</td>
<td></td>
</tr>
<tr>
<td>cut. Lesions</td>
<td></td>
</tr>
<tr>
<td>mesenteric adenitis</td>
<td></td>
</tr>
<tr>
<td>lesions of bone, joints &amp; Synovium</td>
<td>(Less than 1 per million vaccination)</td>
</tr>
</tbody>
</table>
To Avoid these untoward reactions:

1. Inject – intradermally

2. No other injection to be given for at least 6 months into the same arm.
Contraindications

Immunological Response

Impaired
- Congenital immunodeficiency
- Symptomatic HIV infection
- Leukemia
- Lymphoma
- Generalized Maligancy

Suppressed Immunization
- Steroids
- Alkylating agents
- Antimetabolites
- Radiation
Avoid vaccination following:

1. After Viral Infections for 4-6 weeks.
2. Neonates TORCH infections.

Note:

INH chemoprophylaxis (5-10 mg/Kg/Day) in infants who develop Measles / whooping cough within 4-6 weeks of BCG vaccination.
Protective Efficacy of BCG vaccine

Matter of Dispute & still being debated.

Ever since BCG vaccination started there were uncertainties about the efficacy – Lobeck disaster in 1930 in which all 240 children vaccine developed serious disease & 72 of them died, though later vaccine administered to them was found contaminated with virulent Tubercle Bacilli.

Best method for determining Efficacy is by prospective, randomized, double-blind, placebo-controlled trials, though...
### Series of controlled trials begun since, 1930

<table>
<thead>
<tr>
<th>Trial and age-group</th>
<th>Period</th>
<th>Duration of Observation (Years)</th>
<th>% of protection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. American Indian (1-18)</td>
<td>1935-38</td>
<td>9-11</td>
<td>80</td>
<td>Aronson (15)</td>
</tr>
<tr>
<td>Chicago (infants)</td>
<td>1937-48</td>
<td>12-23</td>
<td>75</td>
<td>Rosenthal (16)</td>
</tr>
<tr>
<td>Georgia (6-17)</td>
<td>1947</td>
<td>20</td>
<td>Nil</td>
<td>Comstock (17)</td>
</tr>
<tr>
<td>Puerto Rico (below 20)</td>
<td>1949-51</td>
<td>51/2-71/2</td>
<td>31</td>
<td>Palmer (6)</td>
</tr>
<tr>
<td>UK (14-15)</td>
<td>1950-52</td>
<td>15</td>
<td>78</td>
<td>MRC (7)</td>
</tr>
<tr>
<td>Madanapalle (all ages)</td>
<td>1950-55</td>
<td>9-14</td>
<td>30</td>
<td>F. Moller (18)</td>
</tr>
<tr>
<td>Chingelput (all ages)</td>
<td>1968-71</td>
<td>71/2</td>
<td>Nil</td>
<td>ICMR (14)</td>
</tr>
</tbody>
</table>

**Protection Observed in Various Controlled Trials of BCG Vaccination**
Trials in South India
(Controlled double blind Community trial)

- Study started in Chingleput, South India
  - attempt to avoid methodological errors that might have affected previous trials.

- Organized by ICMR in collaboration with WHO & CDC, US public Health services.

- Intake included 2.6 lakh participants out of 3.6 lakh population.
All ages were eligible & tuberculin reactors were not excluded (as with previous trails).

Two BCG strains – Copenhagen & Paris.

Follow up – 7.5 years period.

Report presented showed:

- No protective Efficacy Of BCG vaccination.
- Incidence of T.B was seen more among Tuberculin +ve people.
- Incidence of infection high in population studied.
(WHO – Scientific Committee Conclusion)

- Highly scientific quality of Chingelput trial.
- Evidence indicates BCG did not protect against Bacillary pul. TB & results are not applicable to other parts of world.
- Not provide information about the effect of vaccine in infants & children, & further studies needed to assess Efficacy against development of meningeal or miliary TB.
Follow up should be continued & regularly monitored.

Further intensive research needed to detect the role of Indian variant of M. tuberculosis and its epidemiological, bacteriological, immunological problems related to BCG vaccine & TB.
Documents two year case - control study in Sao-Paulo, Brazil has shown 75-86% protection against tubercular bacterial meningitis and miliary TB after BCG vaccination.

Postulated – Quick mobilization of CMI in vaccinated children w.r.t non - vaccinated when exposed to natural infection (as it prevents lymphohaemotogenous dissemination following primary complex formation)
Global advisory group of EPI (1990)

Proposed vaccination to be given as soon as possible after birth in all population at higher risk of developing tuberculosis.

In case of Infants born to sputum positive mothers chemoprophylaxis for six months duration with INH, tuberculin test should be performed at the end of six months and if infants is tuberculin negative BCG vaccine is administered.
Explanations for variable Efficacy of BCG

- Most popular explanation – due to interactions with immune responses of the individual to other Mycobacterial infections.
  
  \textbf{(Palmer et al)}

- In 1980 – Rook, Stanford and Associates
  Proposed to CMI responses on exposure to Non-tuberculous Mycobacterium
    1. Listeria type
    2. Koch’s type

\textbf{(Bull. Int. Union Tubercle, 1983)}
<table>
<thead>
<tr>
<th>Listeria Type</th>
<th>Koch’s Type</th>
</tr>
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<tbody>
<tr>
<td>Enhances protective effect of subsequent vaccination with BCG</td>
<td>Opposes the protective effect and also blocks recognition of further species by listeria like responses.</td>
</tr>
<tr>
<td>Vaccination with this type fail to produce protection (likely</td>
<td></td>
</tr>
</tbody>
</table>
Although attempts to demonstrate prior infection with any mycobacterium induces a suppressive effect against BCG have failed, later study says that modulation may take place during later course.

Difference between BCG preparations.

More Recently proposed that Subgroup of population may have weak tuberculin sensitivity because of:
1. Environmental mycobacterium infection.
2. Infection with mycobacterium tuberculosis.
Former has decreased Efficacy with BCG vaccination and latter have risk of reactivation of TB soon after vaccination, perhaps From focal reactions due to enhancement of their weak sensitivity (South India Trial broadly consistent with this hypothesis)
Indication of BCG Vaccination

AJRCC 1994;149:1359-74
(Treatment of Tuberculosis in Adult & Children)

1. Infants and children with *tuberculin* –ve *skin test*
   a. At **high risk** of intimate
      - Prolonged exposure to persistently untreated or ineffectively treated patient with infectious pul.TB
      - Who cannot be removed from source of exposure
      - Who cannot be placed on long term preventive therapy
   b. Exposure to person who have bacilli resistant to INH & Rmp

2. Where rate of new infection **exceeds** 1% per year
   - who have no regular access with health care.
BCG – Response of Tuberculin Skin Test

- BCG vaccination usually produces a reaction to tuberculin skin test.

- No way to distinguish tuberculin sensitivity caused by vaccination with BCG from natural infection of M. TB.

- Reactivity wanes over with time and in absence of infection with mycobacterium tuberculosis, not likely to persist over 10 year after vaccination.
Diagnosis of M. TB in BCG vaccinated persons with +ve skin test is considered if

1. Size of skin test induration is large.
2. History of contact with a person of tuberculosis.
3. +ve family history of tuberculosis.
4. High prevalence of TB in the area.
BCG Vaccination & HIV infection

1987 WHO special program on AIDS and Expanded Program of Immunization statement

“Although a theoretical risk exists, evidence for an increased rate of adverse reactions after BCG immunization amongst symptomatic HIV infected individuals remains inconclusive.”

(there has been no report of disseminated BCG disease in areas where HIV infection is prevalent and BCG vaccination is widely used)
WHO Expert Committee recommends:

1. BCG vaccination at birth or as soon as possible after birth as for non-HIV infected children.

2. With held BCG vaccination in symptomatic HIV infected individuals (AIDS).
BCG – Other Uses

1. BCG provides potent immunogenicity.

2. BCG and its cell wall components act as highly effective adjuvants.
   a. Mixtures of BCG and schistosomosomal antigen have been successfully demonstrated to provide protection in mice model of schistosomiasis (SM 97, S. Paramycin with BCG).
   b. Adjuvant with killed SIV – partial protection against SIV infection in monkeys.
c. Single BCG vaccination affords 50% or more protection against leprosy and second vaccination enhances it (interpretation from 5 year RCT of single BCG, repeat BCG or combine BCG and killed M.leprae vaccine for prevention of leprosy and TB in Malawi)

(Lancet 1996;348;17-24)

3. Report of decreased incidence of leukemia (long standing effect on immune mechanism)

(Lancet 1971;238:1314)
4. Intralesional BCG used as an immunomodulator especially in **Bladder Cancer** (stage T0 & T1)

Intravesical instillation – well tolerate

(6% cases with fever, malaise and migratory polyarthritis)

BCG is suggested to be used as VECTOR (carrier) against various diseases .eg.CA-Bladder,CA-Lung for giving immunotherapy
What’s new in Tuberculosis Vaccines

Over the last 10 years TB vaccine development is enjoying renaissance and resurged as an active area of investigation

Suggested 3 possible vaccination strategies:

1. Pre – infective vaccination
2. Post – infective vaccination
3. Adjunctive immunotherpy (speed up and enhance standard TB treatment in those already ill from TB)
Recent Progress

Bull. WHO 2002;80:483-488

A. Development and screening of candidate vaccines

Four basic vaccines:-

1. **Subunit vaccine** —
   - consists of one or more myc.components, proteins
   - subunits (majority)

2. **Naked DNA vaccine** —
   - used in immunocompromised people
Recent Progress

*Bull. WHO* 2002;80:483-488

3. Live attenuated myc., including Rec. BCG, attenuated strains of M.TB and non pathogenic myc. (M.Vaccae, M.Smegmatis)

4. Non mycobacterial vectors (live attenuated) e.g. salmonella or vaccinia virus

REC .BCG STRAINS expressing antigen-85B and Two proteins clones-213 and 65 of M.TB have performed better than BCG in animal models and hold very good promise for future.
Lessons from screening in animal models:-

1. Well and **consistent** protection in animal models who closely mimic primary tuberculosis in naïve host.

2. Some subunits vaccines however provided **better** protection than control BCG.

3. Evaluated for long term protection.

**Note:-**

*First human safety and immunogenicity study of novel candidate vaccine has already begin.*
Recent Progress

*Bull. WHO 2002;80:483-488*

B. Complete genomic sequence of strain of M.TB has been deciphered.

(Nature 1998;396:190)

1. Provide insight into virulence factors.

2. Improving BCG to increase efficacy at lower dose and in prime – boost protocol
Remaining Questions, Ongoing Challenges

1. Asymptomatic persistence of M.TB for long periods in human host.

2. Surrogate markers of protective efficacy.

3. Role of coinfections and comorbidities in TB.

4. Effective vaccinations in immunocompromised population.

5. Ethical issues:
   a. Withholding BCG vaccine till new vaccine proven to be safe and effective.
   b. To test vaccines safely where HIV infection is prevalent.
All the best..