SEMINAR

ON

BCG

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Untoward Reactions with BCG Vaccination

•Side effects with normal Evaluation of BCG

. simple local reaction

swelling / pain at site.

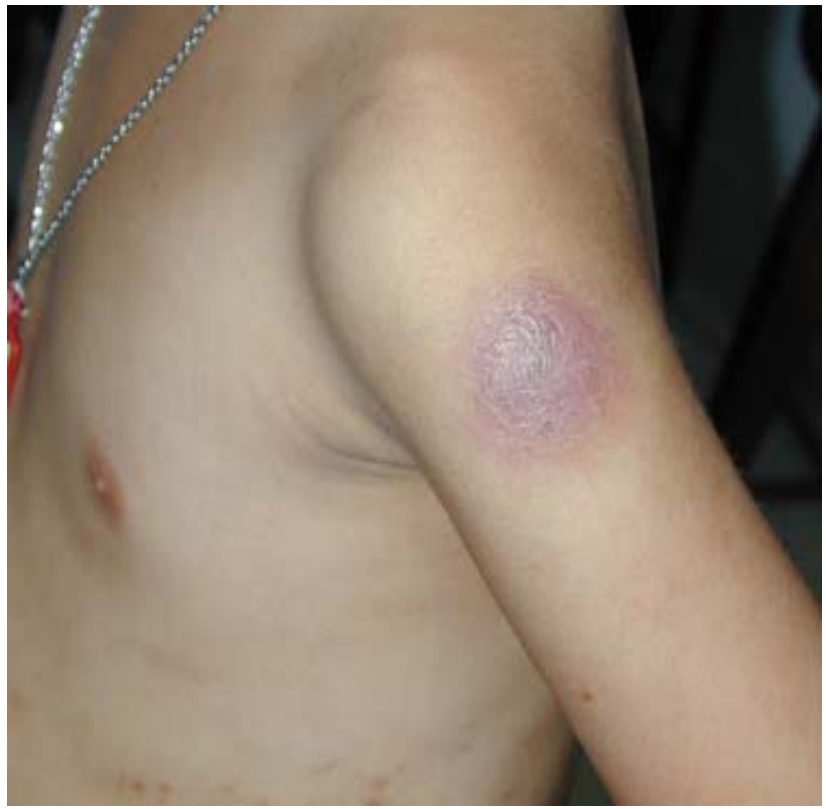
. temporary swelling of

lymph node

- Abnormal BCG-primary complex

  Local-Regional complications-

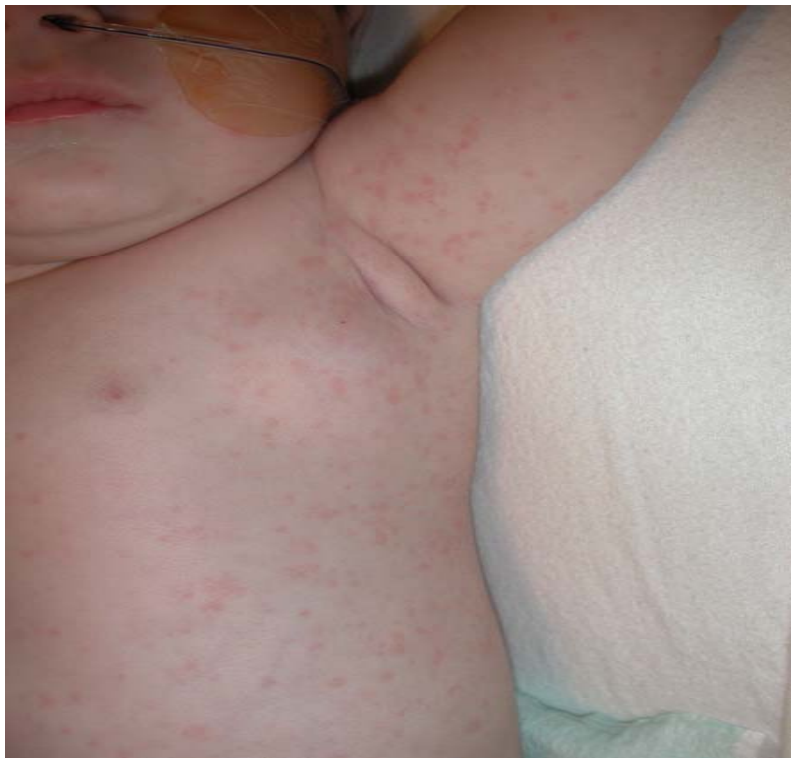
  .Abcess/Ulcers



.Indolent ulcers

.Keloid

.Tuberculides



.Regional lymphadenitids

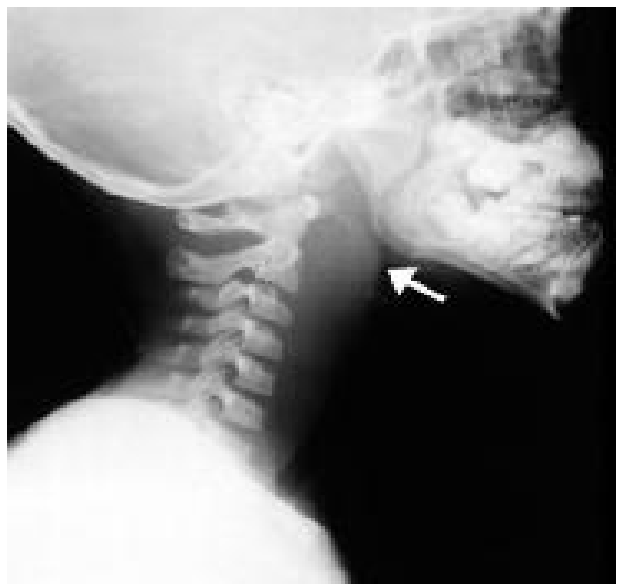
.Lupus vulgaris

.Koch’s phenomenon

- Generalized complications-

.Erythema nodosum

.Retropharangeal abcess



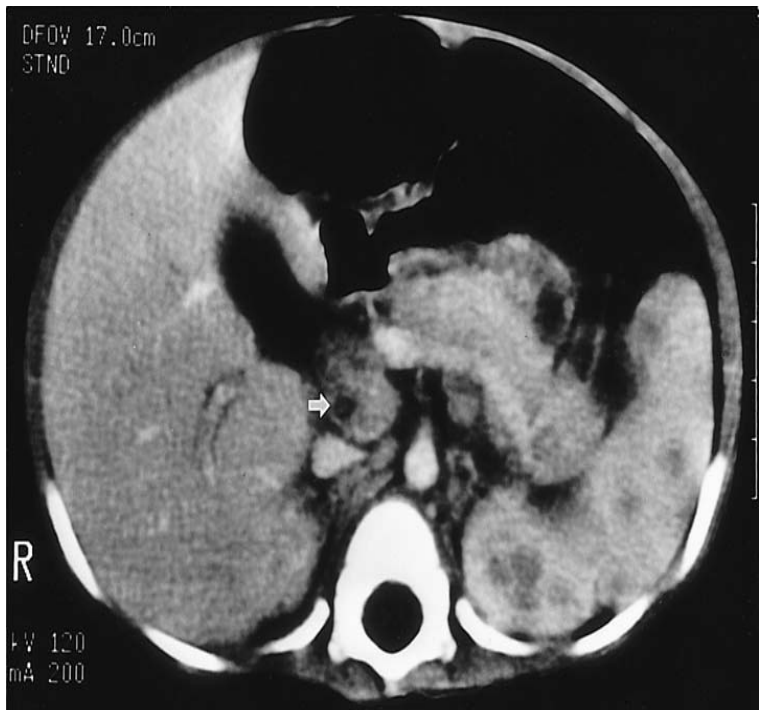
.Otitis media

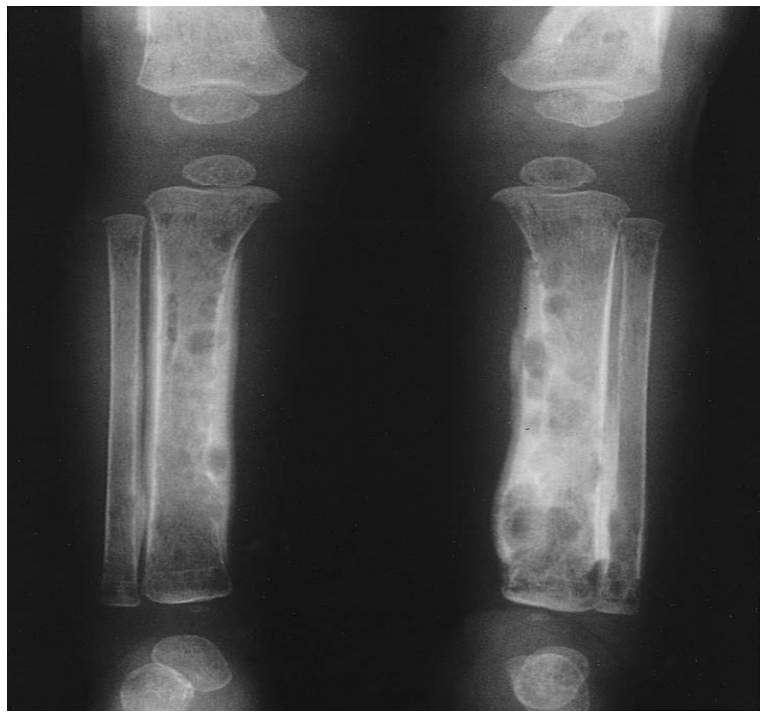
.Cutaneous lesions

.Mesentric adenitis

.Lesions of bone,joints and synovium

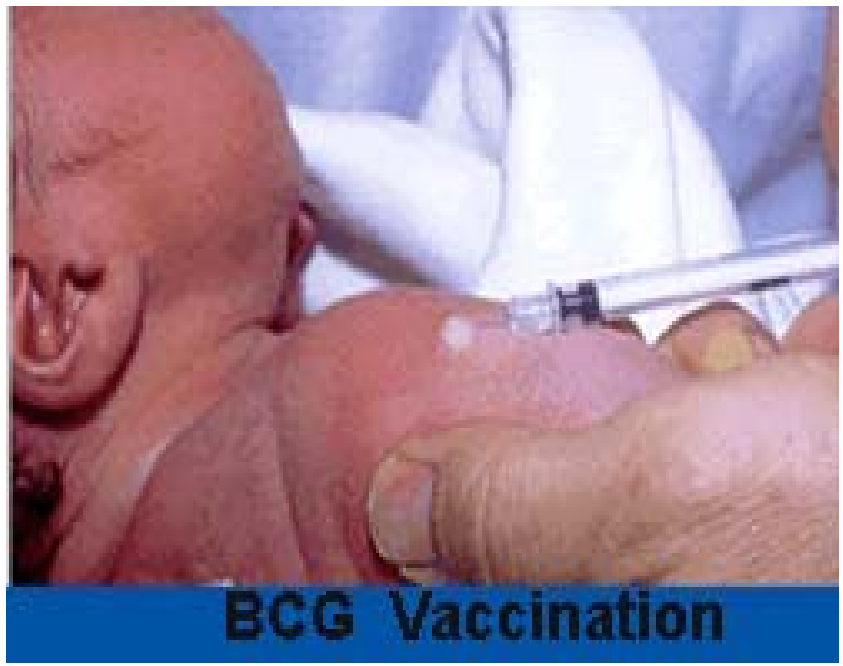
.Fatal generalized lesions [very rare]





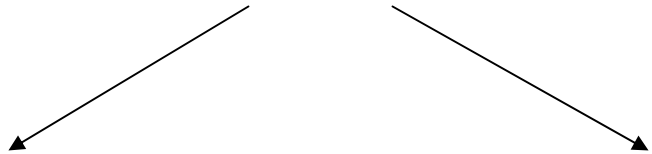
To Avoid these untoward reactions:-

1. Inject – intradermally
2. No other injection to be given for at least 6 months into the same arm.



Contraindications

Immunological Response



<u>Impaired</u>

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

<u>Suppressed Immunization</u>

- 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 wer
uncertainties

about the efficacy – **Lobeck disaster in 1930** in which a
240

children vaccine developed serious disease & 72 of ther
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 difficult to perform and very expensive.

Series of controlled trials begun since,1930

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

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 in 1980–Tech. Report Series

(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 epidemological, bacteriological, immunological problems related to BCG vaccine & TB.

Bulletin WHO, 1990

- 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.

  (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

  (*Bull. Int.Union Tubercle, 1983*)

Listeria Type

- Enhances protective effect of subsequent vaccination with BCG

Koch's Type

- Opposes the protective effect and also blocks recognition of further species by listeria like responses.
- vaccination with this type fail to produce protection (likely

- 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

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 schistomosomal antigen have been successfully demonstrated to provide protection in mice model of **schistomosomiasis** (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)

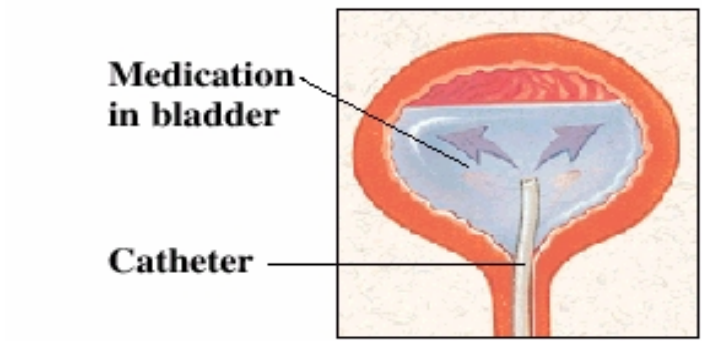
4. Intralesional BCG used as an immunomodulator especially in

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

Bull. WHO 2002;80:483-488

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

2. **Naked DNA vaccine** –

used in immunocompromised people

Recent Progress

Bull. WHO 2002;80:483-488

3. Live attenuated myc. , including Recombinant 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.

Recent Progress

Bull. WHO 2002;80:483-488

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

- Trials for Improving BCG

1. By testing double vaccination statergy.

   Double vaccinnation delivered as a prime followed in a

   few weeks by booster dose.

2. By testing human response to BCG by alternating its

   delivery method.

3. By attempting to improve on BCG by using prime-boost

   stratergies that combine BCG with novel candidate

   vaccine.

All the best…