BCG and New Vaccines Against TB

Ford von Reyn MD
DARDAR International Programs
Dartmouth Medical School
USA
Bacille-Calmette Guerin (BCG)

1. Live attenuated *M. bovis* (subcultures every 3 weeks for 13 years = 231 passages, “Nocard” strain), first given 1921

2. Six substrains in use (Tokyo, Danish, Connaught, Glaxo, Tice etc)

3. Four billion doses given throughout the world for TB prevention (except US, Netherlands), routine ID or SC immunization at birth in endemic areas, avg $10^5$ cfu

4. Replicates locally and disseminates, causes local scar and parenchymal granulomata, induces cross protection to TB, converts tuberculin skin test to positive

5. Economical
BCG Trials
Rodrigues and Smith
Trans Royal Society Trop Med Hygiene 1990;84:739-744
Efficacy of BCG

1. Meta-analysis of 14 prospective trials and 12 case control studies concluded overall efficacy ~ 50% (Colditz, JAMA 1994).

2. However, re-examination suggests these trials often included adults or adolescents who were partly immune from NTM or prior TB (in vitro tests more sensitive than PPD).

3. Subset of 3 prospective trials in newborns (mycobacteria naïve) show efficacy of 73% for TB disease (esp meningal and disseminated) and 87% for death.

4. Protects against NTM, leprosy, Buruli ulcer (M. ulcerans).

5. Duration of immunity controversial (assumed to be 10-15 years; one recent f/u suggests 20 years).

6. No prospective data on efficacy in HIV-infected persons.
BCG: side effects and adverse events

1. Prolonged drainage and inflammation at vaccine site
2. Local ulceration and regional adenitis in <1% (strain)
3. Osteomyelitis in 3/10,000
4. Disseminated BCG rarely (<100 total): reported in cancer, malnutrition, bladder Ca, SCID, CGD, AIDS (infants and adults)

2006 WHO Recommendation on BCG: Advises against BCG for children with known HIV infection. If HIV testing of mother and ART available, then hold BCG if mother HIV-positive until infant known HIV-negative.
Limitations of BCG

1. Variation in potency?
2. Limited efficacy in adults, unknown in HIV
3. Side effects significant
4. Adds to burden of numerous childhood vaccines
5. Absence of booster effect (environmental mycobacteria or prior BCG limit replication)
6. Parenteral
7. Effect on tuberculin skin test (but no effect on new IFN-γ release assays)
New TB vaccine: desirable features

- Safe (including safe in HIV)
- Effective after single or small number of doses (non-injection route preferred)
- Long-lasting protection/immunologic memory
- Economical
- Heat stable/long shelf-life
- Compatible with current childhood immunization schedule
- (Note: Not likely to be more effective for infants and children than BCG)
Natural history: 3 types of TB vaccines

Exposure → Infection

- Preventive

Infection: PPD positive (8-12 weeks)

Post exposure

Disease: 10% lifetime risk of active disease

- Progressive TB
- Reactivation TB

- 5% in first 2 years
- 5% over remainder of lifetime

Therapeutic
TB vaccine development

1. Discovery
   - laboratory (dominant epitopes, genomics)
   - epidemiology/vaccine history

2. Animal models
   - mouse: relatively resistant, cfu in lung, spleen, reagents
   - guinea pig: 100% disease, survival, cfu
   - primates: analogy to human disease

3. Human Phase I and II trials: safety and immunogenicity in healthy adults and children, HIV positives

4. Human Phase III efficacy trials (BCG pos): possible designs include TB family contacts, HIV positives
Immunologic protection against TB in humans

- Prior infection/disease with MTB
- Prior infection with environmental non-tuberculous mycobacteria (NTM)
- Immunization with live BCG
- Immunization with live *M. microti* (vole bacillus)
- Immunization with inactivated whole cell mycobacterial vaccines: MTB, combination of MAC/MB/MTB (cfu > BCG, mult doses)
New vaccines against tuberculosis

- Subunit vaccines (including peptides, proteins)
- DNA vaccines
- Live vaccines
- Inactivated vaccines
Subunit TB vaccines

- **Examples:** ESAT-6 / Ag 85B (State Serum Institute)  
  *Mtb* 72f (GSK)

- **Rationale:** combinations (not single proteins) of purified or recombinant Ags protective in animal models

- **Animal studies:** protective in mouse model, *Mtb* 72f shows memory at 30 days

- **Human studies:** *Mtb* 72f in early human trials

- **Comments:** require adjuvants, multiple doses, expensive, predict low rate of side effects, ? immunogenic in HIV
Live TB vaccines

• Example: attenuated MTB (e.g. auxotrophs), recombinant (r) BCG overexpressing Ag 85, adenovirus 35 Ag85 (Aeras 402), modified vaccinia Ankara (MVA) 85 A

• Rationale: replication enhances immune response, auxotrophs cease replication, Ag 85 protective

• Animal studies: rBCG (Ag 85) superior to BCG in GP

• Human studies: Phase I of rBCG30 (Ag85) in 2004, Phase I of Aeras 402 in 2006 Kansas and 2007 Capetown, Phase II of MVA 85 underway

• Comments: possible efficacy > BCG, live mycobacterial vaccines may not replicate in BCG primed, safety issues in HIV positive for some live vaccines
Live TB vaccines

- **Example:** attenuated MTB (e.g. auxotrophs), recombinant (r) BCG overexpressing Ag 85, adenovirus 35 Ag85 (Aeras 402) modified vaccinia Ankara (MVA) 85 A

- **Rationale:** replication enhances immune response, auxotrophs cease replication, Ag 85 protective

- **Animal studies:** rBCG (Ag 85) superior to BCG in GP

- **Human studies:** Phase I of rBCG30 (Ag85) in 2004, Phase II of Aeras 402 in 2006 Kansas and 2007 Capetown, Phase II of MVA 85 underway

- **Comments:** possible efficacy > BCG, live mycobacterial vaccines may not replicate in BCG primed, safety issues in HIV positive for some live vaccines
Whole cell inactivated TB vaccines

- **Example:** *M. vaccae*

- **Rationale:** Inactivated mycobacterial vaccines effective in humans, NTM infection protects against TB

- **Animal studies:** Protects in M model, induces CTL

- **Human studies:** Phase I and II complete and show safety and immunogenicity, II/III efficacy in 2001

- **Comments:** Safe and immunogenic in HIV, reactogenic (<BCG), boosts responses in BCG primed, inexpensive, “adjuvant” included, multiple doses required
Prime boost strategies

- Many new TB vaccines are first being studied in adults who received BCG at birth.
- In this case the "prime" is BCG and the new vaccine is the "boost."
- Some vaccines might only be used as boosters, others are also being studied as the "prime" in children (e.g. MVA 85 from Oxford).
Conclusions: new TB vaccines

1. Main needs are:
   - booster for BCG in adults
   - safer vaccine for infants (esp HIV) as effective as BCG

2. Multiple dose *M. vaccae* in Phase III as BCG booster in HIV positives (Phase III results early 2009)

3. Several vaccines capable of boosting or replacing BCG in early Phase II (Phase III results expected 2015)

4. BCG booster may be available in next several years, but likely >10 years for BCG replacement
DARDAR Study (Dartmouth/Dar es Salaam, Tanzania)
Double blind, RCT of a prime-boost strategy to prevent TB in persons with HIV infection

2000 HIV-positive persons
CD4>200
BCG scar

Randomize 1:1

1000 placebo x5
(0,2,4,6,12 mos)

1000 M. vaccae x5
(0,2,4,6,12 mos)

Hypothesis: 50% reduction in disseminated TB
Endpoints: 1°-disseminated TB (blood), 2°-pulmonary TB
Study duration: 2001-2009
All subjects are followed every 3 months for routine care of HIV and for detection and treatment of new cases of tuberculosis
All subjects have LPAs and IFNγ assays to mycobacterial Ags at baseline and after 5 doses of vaccine.
DARDAR Study
October 2001-March 2002

Screened: 250+ subjects referred by word of mouth or from HIV testing centers

Randomized: 100+

Previously undiagnosed tuberculosis: 15% with CD4>200

PPD positive (Rx with INH): 60-70%
DNA TB vaccines

- **Example:** HSP 60, Ag 85
- **Rationale:** efficient method of delivering specific antigens, bias toward CTL response
- **Animal studies:** protection in M model less than BCG, HSP adverse (necrotizing pneumonia), less immunogenic in primates than rodents
- **Human studies:** on hold
- **Comments:** attractive but safety a concern and likely to be expensive; single proteins unlikely to be effective