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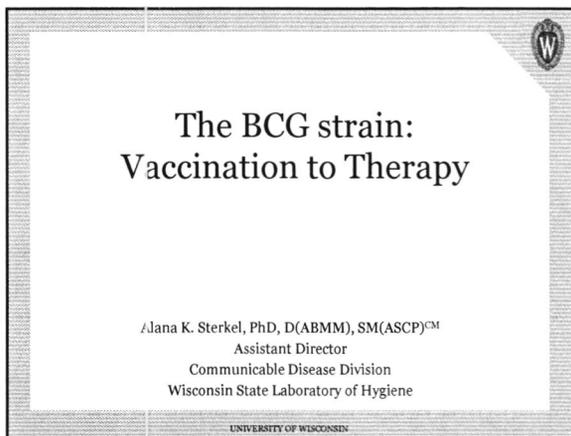
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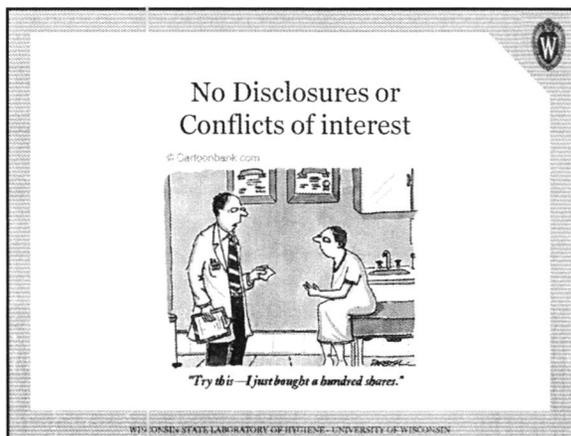
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### Contents

- Section 1: Vaccination
  - Case Study
  - History of BCG Vaccine
  - Lab identification of BCG
  - Treatment methods
- Section 2: Therapy
  - Case study
  - History of BCG therapy

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### Objectives

After seeing this talk audience members should be able to:

1. Recognize BCG adverse reactions
2. Discuss treatment options for disseminated BCG infections
3. Order and interpret laboratory results related to BCG
4. Discuss the history and development of the BCG strains

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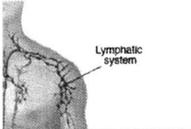
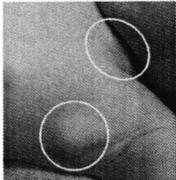
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### Case 1: Patient Presentation

- 14 month old male presents with a mass in his armpit (2.4 cm) and on his clavicle (2.7 cm).
- The armpit mass was noted at 1 month old and has been slowly growing.
- Clavicular mass has developed over the past month



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### Travel and Family History

- Born in Vietnam to a Vietnamese mother and US military father.
- Moved to the US at 1 month old
- Currently lives with father and paternal grandmother here in Wisconsin.
- Older half brother and Mother still live in Vietnam.



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### Clinical Presentation

- Overall well child with no fever and or other systemic symptoms.
- Good appetite, and has been gaining weight and developing normally.
- Development of second mass and some irritation of the masses prompted medical care
- Elevated WBC of 12.4 indicates possible infection



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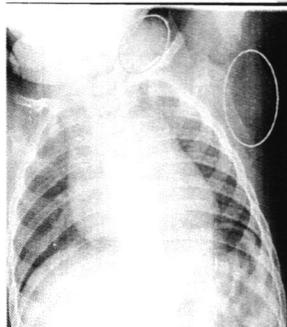
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### Imaging

- Necrotic lymph nodes with granulomas and calcifications
- PPD 18mm (+)
- Clear chest x-ray



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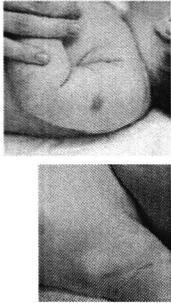
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### Putting the pieces together

- His skin exam was noteworthy for a left deltoid BCG scar that is well healed



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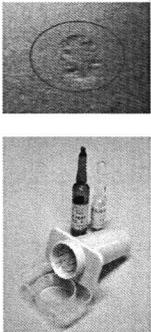
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### BCG Vaccine

- Purpose is to protect against **active TB**
- The WHO Expanded Programme on Immunization recommends vaccination at birth in certain countries (including Vietnam)
- Live attenuated strain of *Mycobacterium bovis*



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### *M. bovis* as a vaccine

- After success with the use of cowpox to prevent smallpox in the 18<sup>th</sup> century it was thought *Mycobacterium bovis* could protect against TB.
- Disastrous human trials in Italy found *M. bovis* to be just as virulent as TB.



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## Vaccine Development

### Bacille Calmette-Guerin (BCG)



Albert Calmette  
(1864-1934)



Camille Guérin  
(1872-1961)

- In the early 1900's at the Institut Pasteur de Lille (France)
  - Albert Calmette, a French physician and bacteriologist
  - Camille Guérin, a veterinarian
- Attempted to attenuate *M. bovis* through extensive passage
  - Glycerine potato medium with cow bile.
- Virulence periodically tested in research animals.
- In 1919, after 13 years and 239 passages an avirulent and protective strain was finally isolated.
- In 1921 the first BCG vaccine was used in humans.

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## Bumps in the road

- Slow to be adopted
- Vaccine disaster
  - The summer of 1930 in Lubeck, Germany
    - Infants were vaccinated in the first 10 days of life
    - Of 240 babies almost all developed acute tuberculosis and 72 infants died.
  - It was later discovered that the vaccine had been contaminated with a virulent strain that was being stored in the same incubator

IMMUNITY FROM TUBERCULOSIS

with Prof. von Behring's BOVOVACCINE

7,500 inoculations performed. Record proto-culture success, and Berlin Tuberculin, the "great white danger" finally conquered!

BOVOVACCINE

is easy of application and within the scope of every teacher, physician, etc. - Write for details. - Best prepared by

C. BISCHOFF & CO., 411 6th Washington St., NEW YORK.

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## Vaccine is most effective in children

- 1938 study: mortality rate reduced by 75% in children from a highly endemic region.
  - Adult mortality was not reduced.
- 1941 study: Vaccination reduced mortality in infants living in tuberculosis households by 66%.



WHO image, US National Library of Medicine History

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### BCG Vaccine Efficacy

- Meta-analysis in children (2014)
  - Against infection 19-27%
  - Against active TB 71%
- Best protection against miliary TB and TB meningitis
- Length of protection varied from 15-60+ years

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### Possible Reasons for Differences in Efficacy

- Genetic variation in the human population
- Sensitization by non-tuberculous mycobacteria
- Concurrent parasite infection (Th2 response)
- Vaccine frequency
- Dosing differences
- Malnutrition
- Age at vaccination
- Strain differences

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### How the Strain has Mutated

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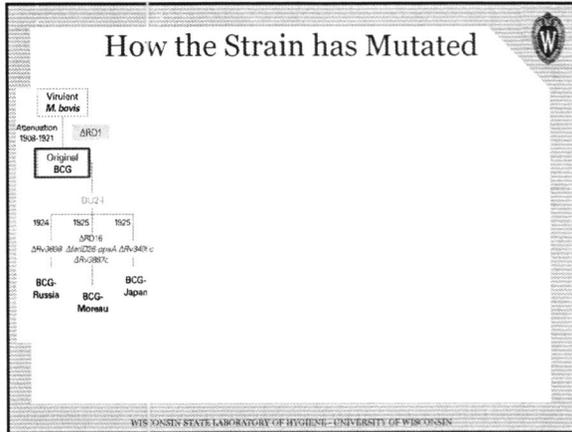
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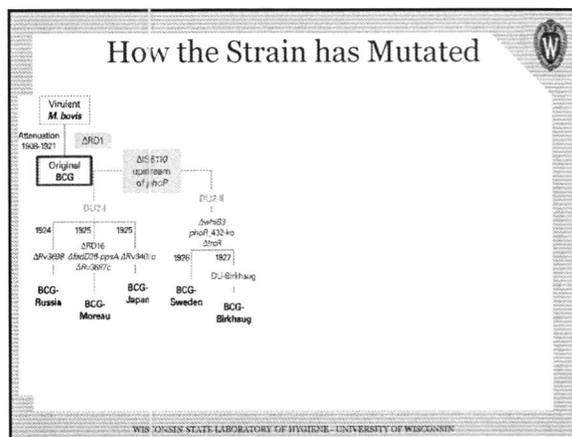
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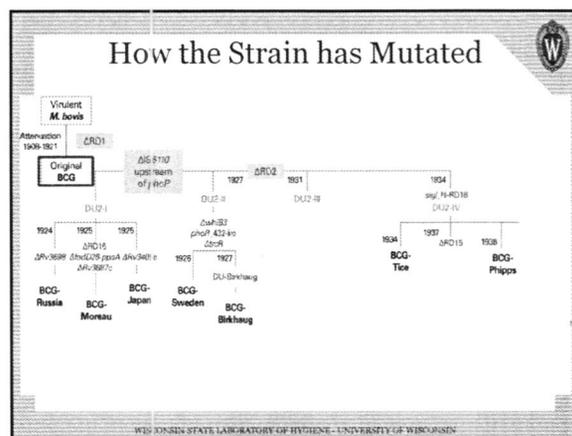
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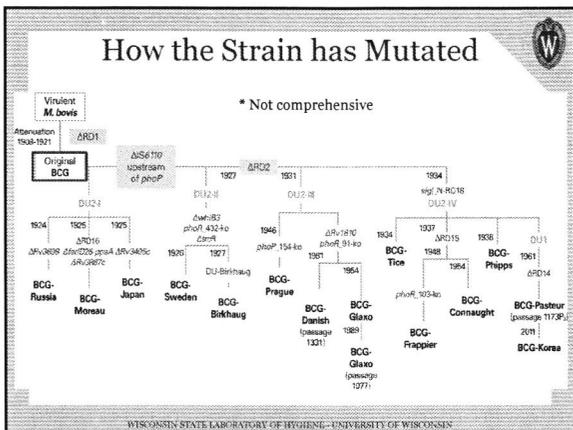
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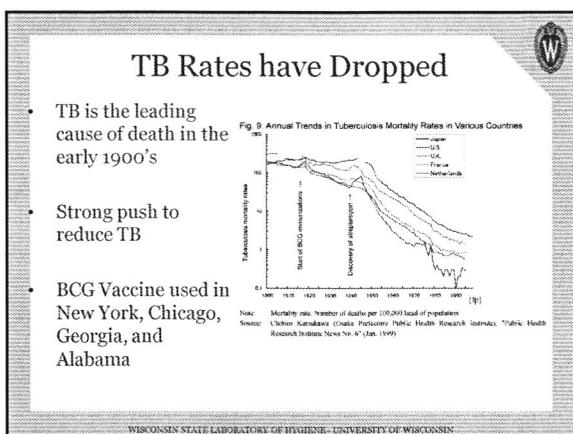
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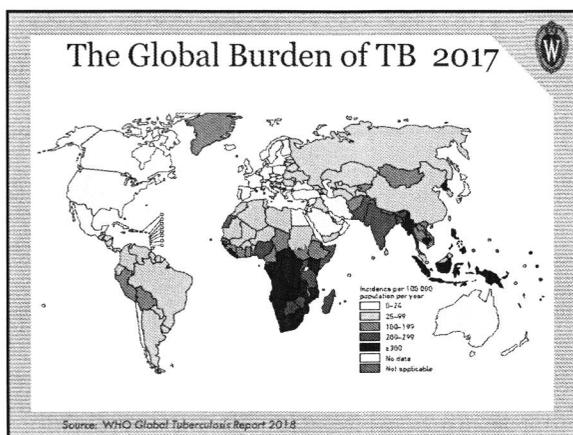
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### Why Doesn't the US Vaccinate?

- Low vaccine efficacy with unpleasant side effects
- Low TB rates in US make TB controllable by other means
- **PPD screening would no longer be an option**



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### Impact on Surveillance Testing

- The BCG vaccine can cause a false-positive reaction to the tuberculin skin test.
- Interferon gamma release assays (IGRA) are not affected

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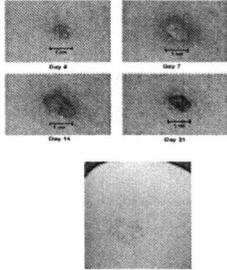
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### Normal BCG Vaccination Response

- A papule develops within a few days to a week
- It may be red and tender for 2-4 weeks
- It may become ulcerated and heals within 2-5 months
- Leaves an indurated scar

Primary Vaccination Site Reactions



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### BCG Complications

Adverse reactions are uncommon (1%–2%)  
(Median age at presentation 2.5 months)

- Ulcer, abscess, or wart at site of inoculation
- Regional lymphadenopathy
- Osteitis of the long bones
  - can occur up to several years later
- Fatal infection
  - very rare (2 per 1 million people)
  - primarily in immunocompromised

Severity ↑  
Frequency ↓



Morone et al. Clinical Management of Localized BCG Adverse events in Children. *Rev Inst Med Trop Sao Paulo*. 2002; 38: 84.

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### Current Vaccination Guidelines

- Not recommended for people with burns, skin infections, and primary or secondary immunodeficiencies, including HIV infection.
  - Our patient tested HIV negative
  - Routine immunological work-up was normal
- Skin test recommended prior to vaccination of older patients



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### Treatment

- BCG lymphadenopathy is usually self-limiting- wait and see
- Needle aspiration
- Surgical resection of the infected tissue
- Anti-Tb meds
  - Isoniazid with or without rifampicin, or ethambutol
  - Pyrazinamide is not effective against BCG and should not be included in treatment regimens.

Cuello-Garcia CA, Perez-Jacobs G, Romero-Gutierrez C. Treating BCG Induced Disease in Children. Cochrane. 2013

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### Case Continued

- The child was vaccinated the day after birth (National policy)
- Older half brother in Vietnam had similar lymphadenopathy in response to BCG vaccine
  - Resolved on its own
- IGRA comes back negative for Tuberculosis
- Patient sent home to heal on his OWN.



Chan WM, Kwan YW, Leung CW. HK J Paediatr 2011, 16, 85-91

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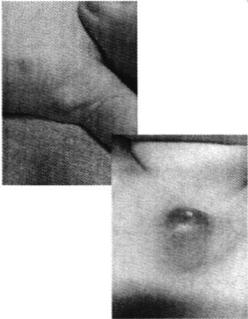
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### Case Continued

- Patient returns with worsening symptoms
- Sent home to wait and see again
- Clavicular lymph node spontaneously bursts open and leaks puss like fluid
- Culture positive for *Mycobacterium tuberculosis* complex



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### How to Identify BCG in the Laboratory



M. tuberculosis complex:  
*M. tuberculosis*, *M. bovis*, *M. bovis* BCG, *M. caprae*, *M. microti*, *M. africanum*, *M. canettii*, *M. pinnipedii*, and *M. mungi*

- Most TB PCRs will be positive regardless of species
- Similar colony morphology and growth rate
- Indistinguishable by MALDI-TOF
- Species within the complex are not routinely identified further by most labs

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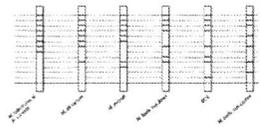
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### Species ID



1. PCR panels (Wadsworth)
2. Commercially available probes (National Jewish)
3. Sequencing (Michigan)
  - Results are used for epidemiology
  - Testing is not performed in a regulated environment
  - Results can not be reported clinically
  - Maybe in the future?

Organism	PCR results for target:				
	RD1	RD4	RD9	RD12	est RD9
<i>M. tuberculosis</i>	+	+	+	+	+
<i>M. bovis</i>	+	-	-	-	-
<i>M. bovis</i> BCG	-	-	-	-	-
<i>M. africanum</i>	+	+	-	+	+
<i>M. microti</i>	-	-	-	+	+
<i>M. magerit</i>	+	+	-	+	+
NTM <sup>2</sup>	-	-	-	-	-



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### Case Conclusion



- No clear immune disorder was found. However, it was thought to be genetic based of similar symptoms in the older brother.
- Over the course of about 3 months the clavicular abscess grew and drained 3 times causing pain and irritation for the child and making the father and grandmother very upset.
- Clinicians drained both masses and treated with isoniazid at the fathers request.
- At the last visit the masses were resolving.

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**Section 1: Take Home Points**

1. BCG vaccination can give false positive PPD.
2. IGRAs are recommended for patients that have received the BCG vaccine.
3. The BCG vaccine is used world wide but not in the USA.
4. Vaccine efficacy is highly variable but can prevent severe disease.
5. BCG is not routinely differentiated from TB in the lab but it can be done by special request
6. In rare cases this live vaccine can disseminate and cause disease.
7. All BCG are resistant to Pyrazinamide

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