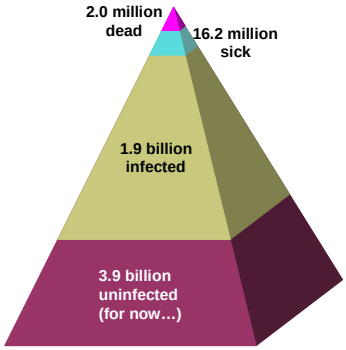
TB latency: the iceberg of pathogenesis



TOOLS FOR TB CONTROL

BCG VACCINE (1921)

DRUG THERAPY (1952)

Bacille Calmette-Guérin (BCG) vaccine

1902:
Edmond Nocard isolates virulent *Mycobacterium bovis* from a tuberculous cow

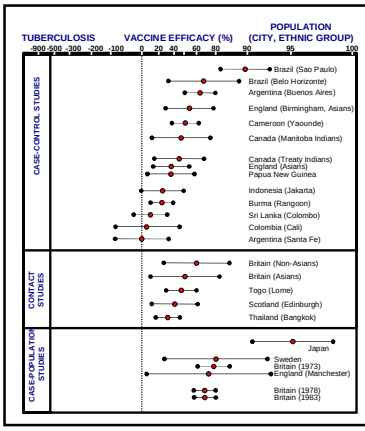
1908-1919:
Albert Calmette and Camille Guérin attenuate the virulent isolate by serial passage in pure culture

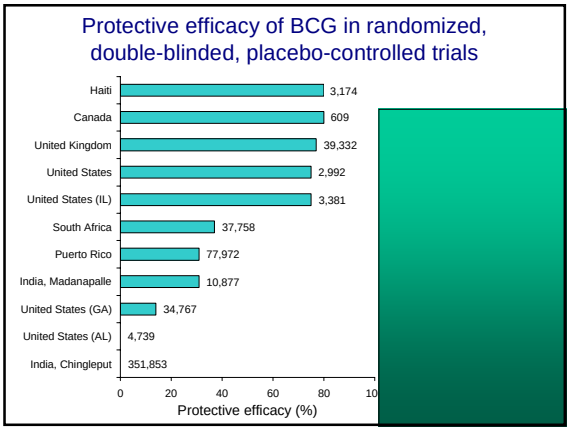
1921:
Benjamin Weill-Hallé and Raymond Turpin vaccinate a newborn child with the attenuated BCG strain

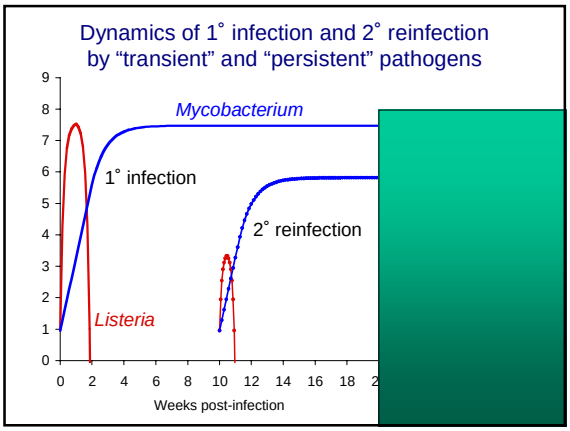
1921-2003:
BCG administered to >3 billion individuals worldwide

Bacille Calmette-Guérin (BCG) vaccine

- BCG can be GIVEN AT BIRTH or any time thereafter
- BCG is SAFE (adenitis in infants 370 per million; case fatality rate 0.19 per million)
- BCG is INEXPENSIVE to produce ("a dime a dose")
- BCG is the most STABLE live vaccine in current use
- BCG can be ADMINISTERED ORALLY
- BCG elicits CELL-MEDIATED & HUMORAL responses
- BCG elicits SYSTEMIC and MUCOSAL responses
- BCG gives LONG-LIVED MEMORY without boosting







TOOLS FOR TB CONTROL

BCG VACCINE (1921)

DRUG THERAPY (1952)

1947 Streptomycin

1952 Isoniazid

1952 Pyrazinamide

1958 Ethambutol

1967 Rifampin

"The ancient foe of man, known as consumption, the great white plague, tuberculosis, or by whatever other name, is on the way to being reduced to a minor ailment of man. The future appears bright indeed, and the complete eradication of the disease is in sight."

Selman Waksman (1964) *The Conquest of Tuberculosis*

Short-course chemotherapy for TB

M.M.W.R. (1998) 47RR-20: 1-58

Induction phase (2 months)

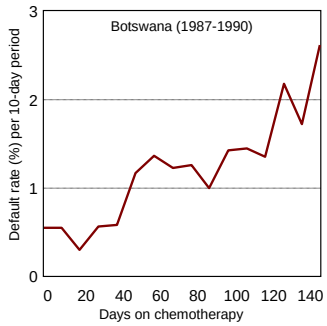
Isoniazid	→ Cell wall biogenesi
Rifampin	→ RNA synthesis
Pyrazinamide	→ Opinions vary…
Ethambutol	→ Cell wall biogenesi
Streptomycin	→ Protein synthesis

Continuation phase (4-7 month

Isoniazid	→ Cell wall biogenesi
Rifampin	→ RNA synthesis

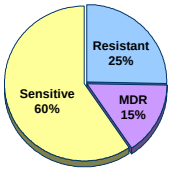
Non-compliance: the Achilles heel of chemotherapy

Murray, C.J.L. (1994) In *Tuberculosis: Pathogenesis, Protection, and Control* (ASM Press)

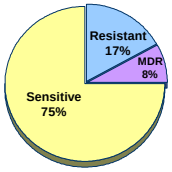


(Multi)Drug-resistant tuberculosis

World Health Organization (2004) *Anti-TB Drug Resistance in the World*

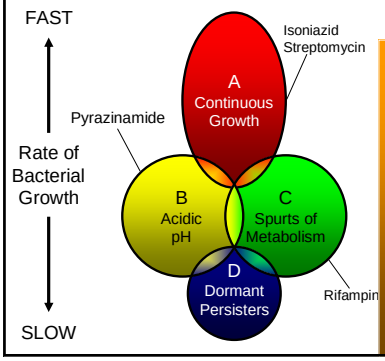


China (Henan Province)
Population: 1.265 billion
TB incidence: 100/100K



India (Tamil Nadu State)
Population: 1.002 billion
TB incidence: 400/100K

The "Mitchison Hypothesis"



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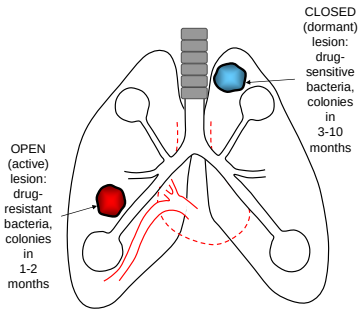
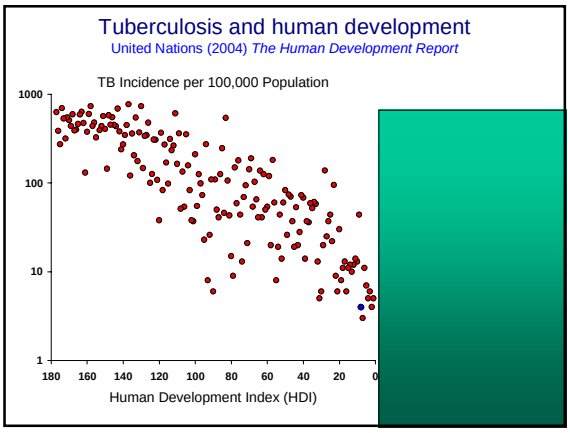
Persistence of *M. tuberculosis* in patients undergoing drug therapy

Vandiviere et al. (1956) *Am. J. Med. Sci.* 232: 30-37





95% of TB cases are in developing countries

99% of TB deaths are in developing countries