
The etiology of tuberculosis: *Mycobacterium tuberculosis*

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TB etiology: overview

- ◆ Top-down exploration:
 - Genus: *Mycobacteria*
 - Species: *Mycobacterium tuberculosis* complex
 - Subspecies: *Mycobacterium tuberculosis*
 - Strains: *M. tb* around the world
- ◆ Pending questions

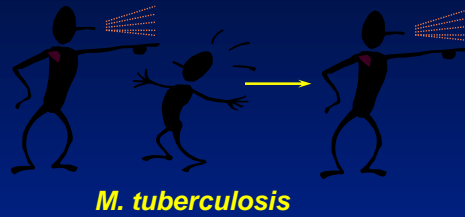
The genus *Mycobacteria*

- ◆ *Mycobacteria* named for mycolic acids
 - Very long fatty acids in the cell wall
 - Affect their staining properties for microscopy
- ◆ Currently ~ 150 species
 - More named each year (sampling, naming)
- ◆ Vast majority of *mycobacteria* are non-pathogenic:
 - soil & water organisms
- ◆ Small number of pathogens

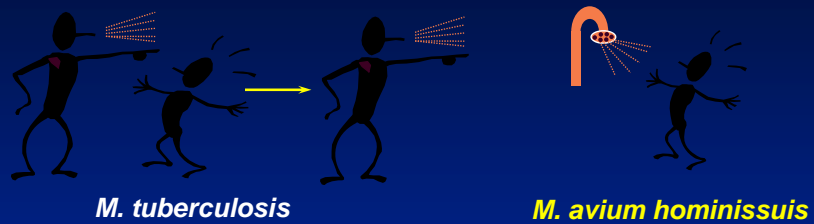
Pathogenic *Mycobacteria*

- ◆ Subset of *mycobacteria* that can cause disease in a eukaryotic host
- ◆ Some naturally live in the environment, e.g. *M. avium*
- ◆ Some have evolved to live with their eukaryotic host, e.g. *M. tuberculosis*
- ◆ Place of residence conceptually affects how we approach disease control

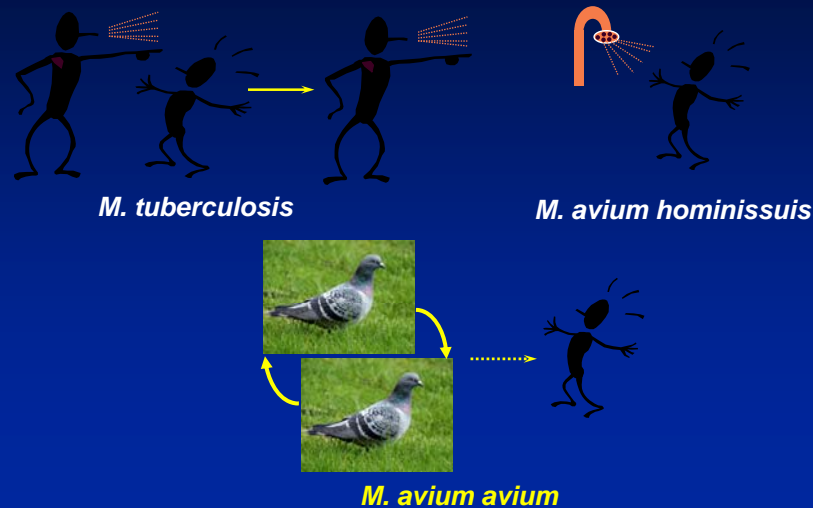
Mycobacterial species Human pathogen, e.g. TB



Mycobacterial species Pure environmental, e.g. 'M. avium'



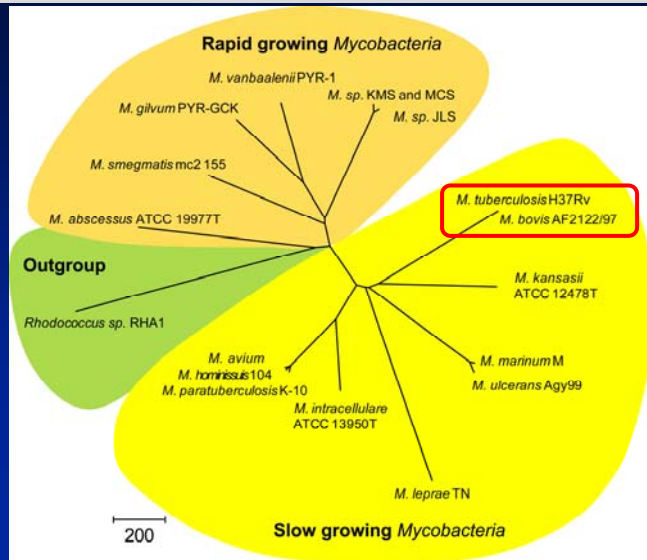
Mycobacterial species Zoonotic pathogens



Non-tubercuous Mycobacteria pathogenic to humans

- ◆ Cause disease in humans
- ◆ Are not spread from person to person
 - *Mycobacterium avium*
 - » Disseminated disease in AIDS
 - » Lymph node disease in children
 - *M. avium* subsp. *paratuberculosis*:
 - » Hypothesized role in Crohn's disease
 - *M. kansasii*
 - » TB-like disease in coal miners
 - *M. ulcerans*
 - » Cause of Buruli ulcer (Bairnsdale ulcer)

Mycobacteria sequenced, 2010 Phylogeny by analysis of 16 genes



Veyrier, BMC
Evol. Biol, 2009

Mycobacterium tuberculosis complex

- ◆ *M. tuberculosis*, *M. bovis*, *M. caprae*,
M. microti, *M. africanum*...
 - Agents of TB in mammalian hosts
- ◆ Identical by 16s rRNA sequence
- ◆ Homology in other genes > 99%
 - Thus, one species (MTC)
 - But, each retains name by convention

M. tuberculosis complex (MTC)

M. tuberculosis



M. africanum

M. microti



M. bovis



M. tuberculosis



M. africanum

M. microti



M. bovis



Oryx bacillus



M. caprae



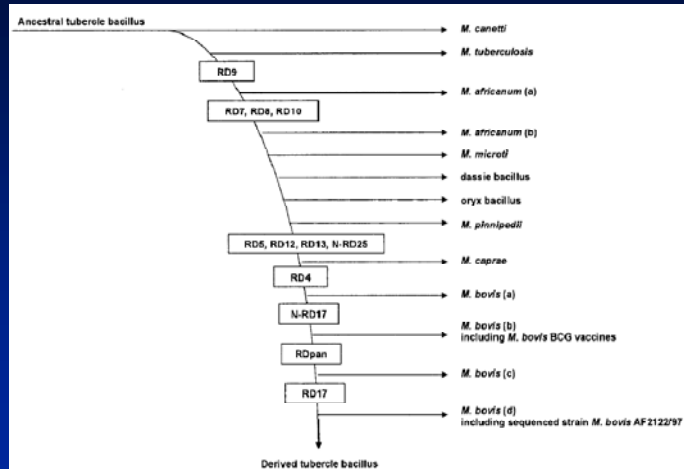
Dassie bacillus



M. pinnipedii



MTC phylogeny based on genomic differences (deletion analysis)



Mostowy et al., J Bact, 2005

MTC variability

- ◆ Two types of variability
- ◆ Host adapted strains
 - E.g. *M. tuberculosis* vs. *M. bovis* vs. *M. caprae*, etc.
- ◆ Lab adapted vaccine
 - Virulent *M. bovis* vs. *M. bovis* BCG vaccine

Host-adapted members of MTC

- ◆ People can get TB due to *M. bovis*
- ◆ However, MTC organisms only spread efficiently in their particular host
 - E.g. When livestock TB is controlled, *M. bovis* disease is eliminated from human population
- ◆ The basis of host adaptation is not well understood
 - *In vivo* co-evolution
 - *M. tuberculosis* first used as vaccine in cows
 - The human vaccine was derived from *M. bovis*

Lab-adapted BCG vaccine

- ◆ BCG = Bacillus of Calmette and Guerin
- ◆ Derived during studies on bovine TB
 1. Intestinal inoculation with *M. bovis* caused pulmonary TB via lymphatic spread
 2. Hard to infect animals, need to grind bacteria into a fine emulsion
 3. Try to grow bacteria in presence of bile to get rid of clumps
 4. Observe for a strain that was less virulent
 5. Voila! A vaccine candidate

BCG vaccines: Controversy and opportunity

Facts:

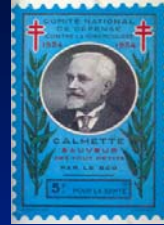
- ◆ > 100 million doses/year
- ◆ Less virulent than *M. bovis*

Major unknowns:

- ◆ Policy: Do they prevent TB? Which forms? How long?

Opportunity:

- ◆ Bacterial pathogenesis: Why are they of attenuated virulence?
- ◆ How genetics: Why do some people get sick from BCG vaccine?



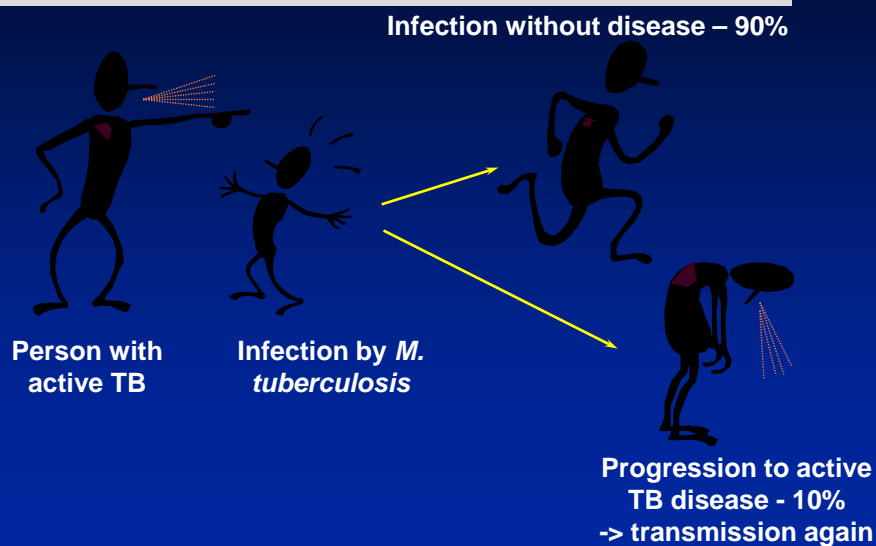
M.tb. vs. BCG: Tale of two bacilli

| Attribute | <i>M. tuberculosis</i> | <i>M. bovis</i> BCG |
|-------------|------------------------|---------------------------------|
| Birthplace | Africa | France |
| Birthdate | Paleolithic | 3 rd Republic (1908) |
| Home | Host macrophage | Vaccine lab |
| Job | Cause disease | Prevent disease |
| Infected | 2 billion people | 100 million / year |
| Disease | 1 in 10 | 1 in 100,000 |
| Relatedness | >99% genetic identity | |

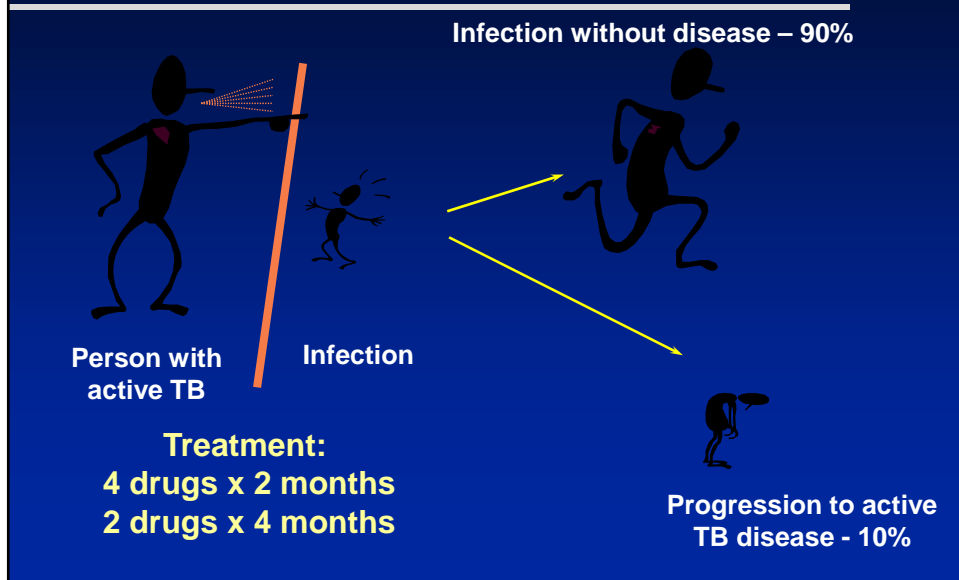
MTC variants in Montreal

- ◆ In Mtl., > 98% of TB due to *M. tuberculosis*
 - Less data in places where livestock TB has not been controlled
- ◆ Some cases of *M. caprae*, *M. africanum* since LSPQ began testing for these
 - Clinical importance of distinction not yet clear
- ◆ *M. bovis* is pyrazinamide resistant
- ◆ *M. bovis* BCG:
 - » In child: HIV test and an immunology consult
 - » In adult: associated with treatment of bladder cancer

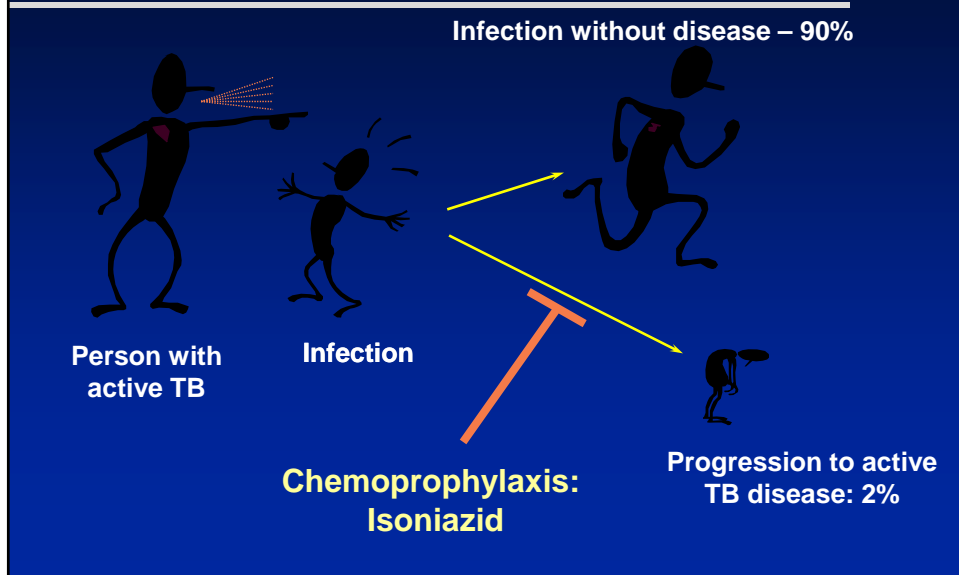
Natural history: Can ignore other members of the MTC



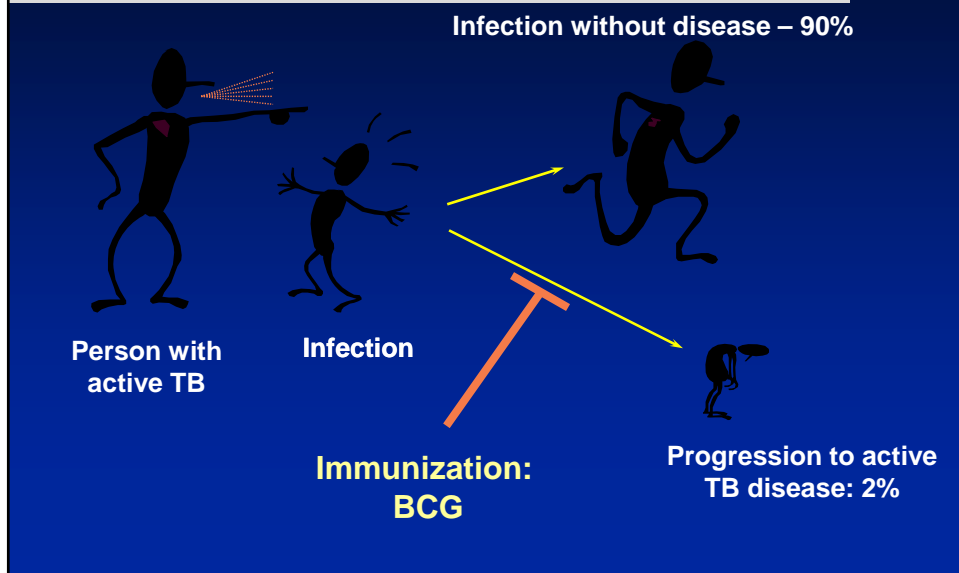
TB disease and infection: Effect of treatment



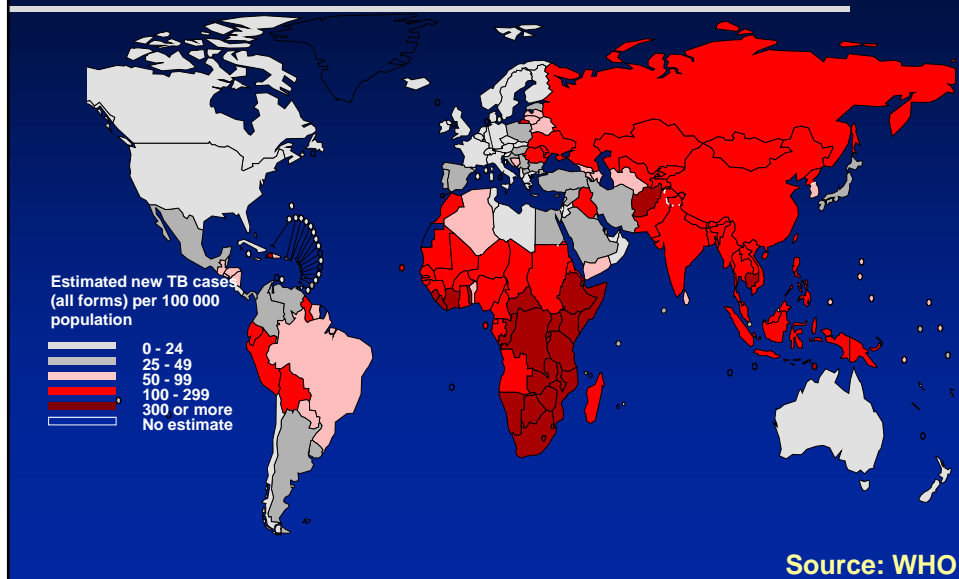
TB disease and infection: Effect of chemoprophylaxis



TB disease and infection: Goal of pre-exposure vaccination



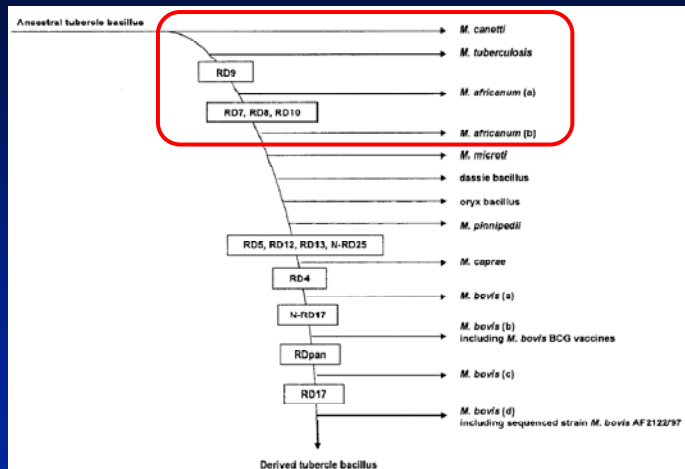
TB: More than Montreal



MTC variants around the world

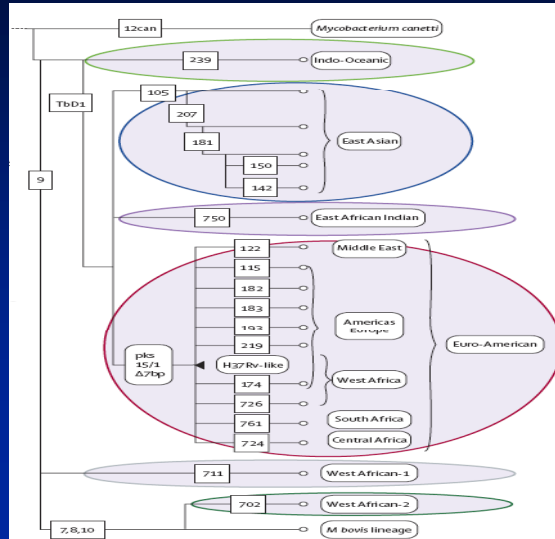
- ◆ In post-genomic era, now apparent that there are different strains that pre-dominate in different parts of the world
- ◆ Two questions:
 - Are these real associations?
 - » As opposed to artifacts of study populations
 - Are these meaningful?
 - » Can we envision different management

Deletion-based MTC phylogeny



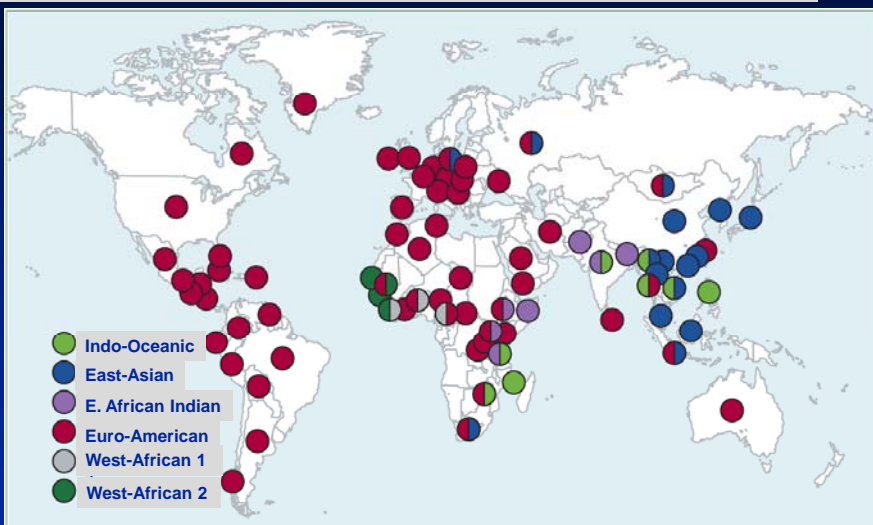
Mostowy et al., J Bact, 2005

M. tb sensu stricto phylogeny 2006



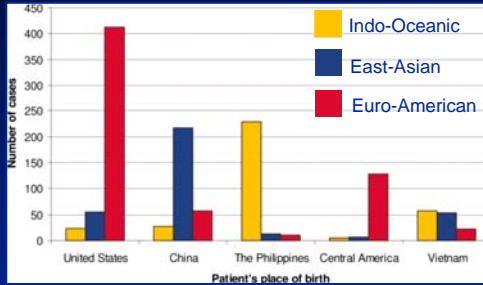
Gagneux et al, 2006

M. tuberculosis strains & place of birth



Gagneux et al, 2006

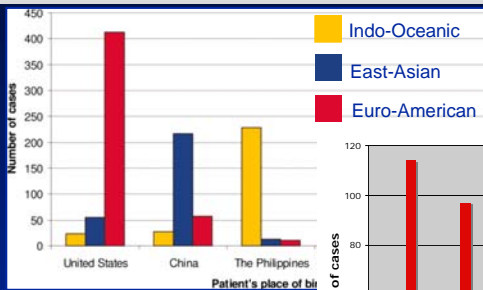
Patient/strain associations: Is this for real?



San Francisco

71% of TB cases
- 5 countries

Patient/strain associations: Montreal

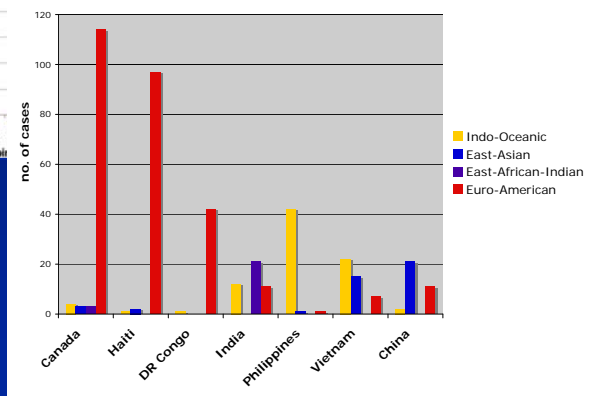


Montreal

60% of TB cases
- 7 countries

San Francisco

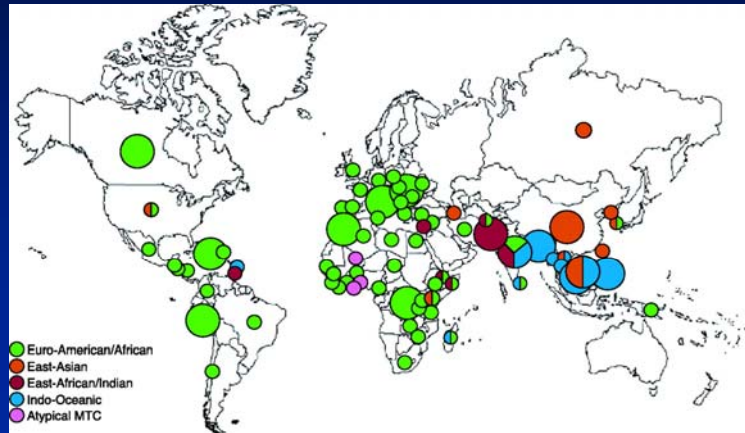
71% of TB cases
- 5 countries



Reed et al, J. Clin Micro, 2009

Selected contributions

What strains of bacteria cause TB in Montreal?



Reed et al, JCM, 2009

MTC variants around the world

◆ Two questions:

- Are these real associations?
 - » Yes.
 - » You do not have to leave Montreal to study the global diversity of *M. tb*.
- Are differences meaningful?
 - » Can be used for epidemiology / strain tracking
 - » In the clinic, all strains cause TB
 - » For immunodiagnosis, all strains have virtually identical antigenic proteins

TB etiology: overview

- ◆ Genus: *Mycobacteria*
 - Many organisms, few pathogenic
- ◆ Species: *Mycobacterium tuberculosis* complex
 - Host-associated agents of TB
- ◆ Subspecies: *Mycobacterium tuberculosis*
 - Rarely *M. africanum*, *M. caprae*, *M. bovis*
- ◆ Strains: Mostly Euro-American strains here in Mtl.
 - We have the Beijing strain, but it does nothing remarkable in our community

TB etiology: pending questions

- ◆ Bacterial genetic variability
 - Importance for antibiotic resistance
 - » Are some strains more likely to become DR, MDR?
 - Host-associated pathogen
 - » Genetics of adaptation to a particular host
 - » Ultimately, is this a dead-end strategy for the bacteria?
 - Host-pathogen fits
 - » Is the genetic predisposition of the host linked to the bacterial profile?
 - We have had TB for thousands of years
 - » Is it only bad? Is there some benefit?

Thank you

◆ Questions:
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