



12th Annual Conference IUATLD-NAR

Dr. Marcel Behr has no financial relationship with companies who have provided support to this meeting that suggests a personal conflict of interest in relations to the planning for the above captioned CME Event.

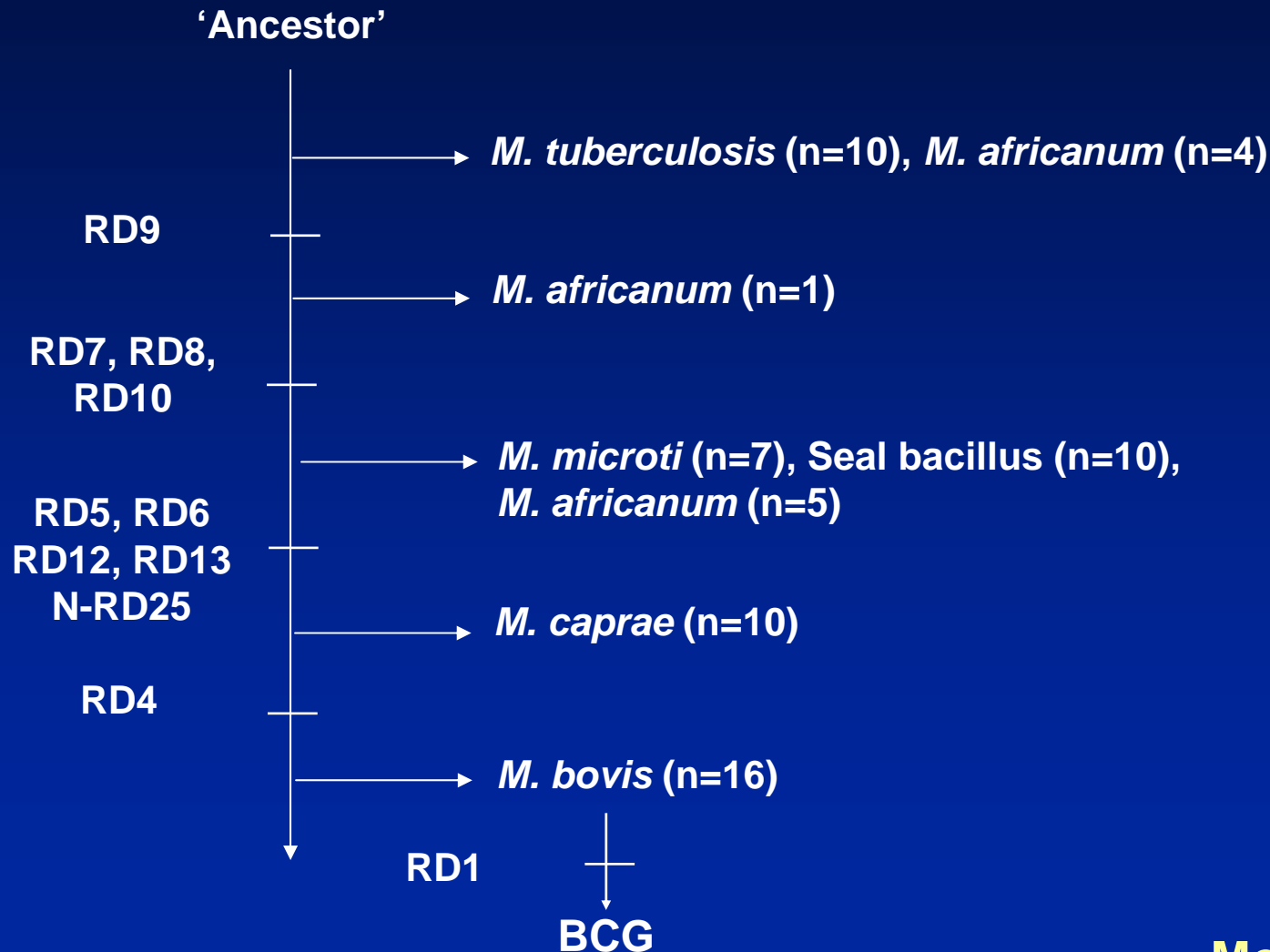
***M. tuberculosis* genetic variability:
So what?**

**Marcel A. Behr
McGill University
marcel.behr@mcgill.ca
www.molepi.mcgill.ca**

Overview

- ◆ *M. tuberculosis* phylogeny
- ◆ Phenotypic consequence
 - Diagnosis
 - Treatment
 - Outcome
- ◆ Future challenges

M. tuberculosis complex phylogeny



Atypical hosts

VOLE



DASSIE



ORYX



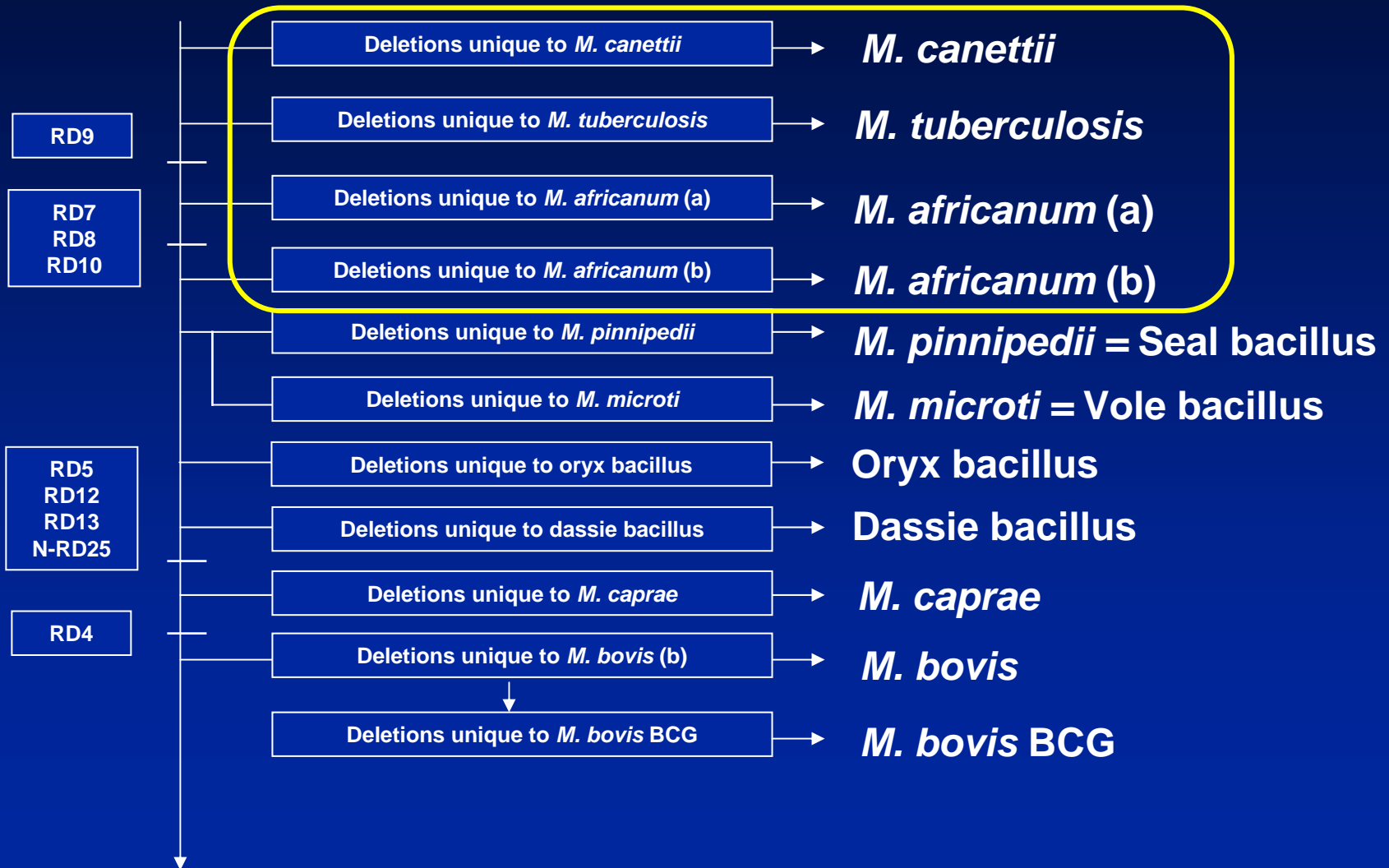
GOAT



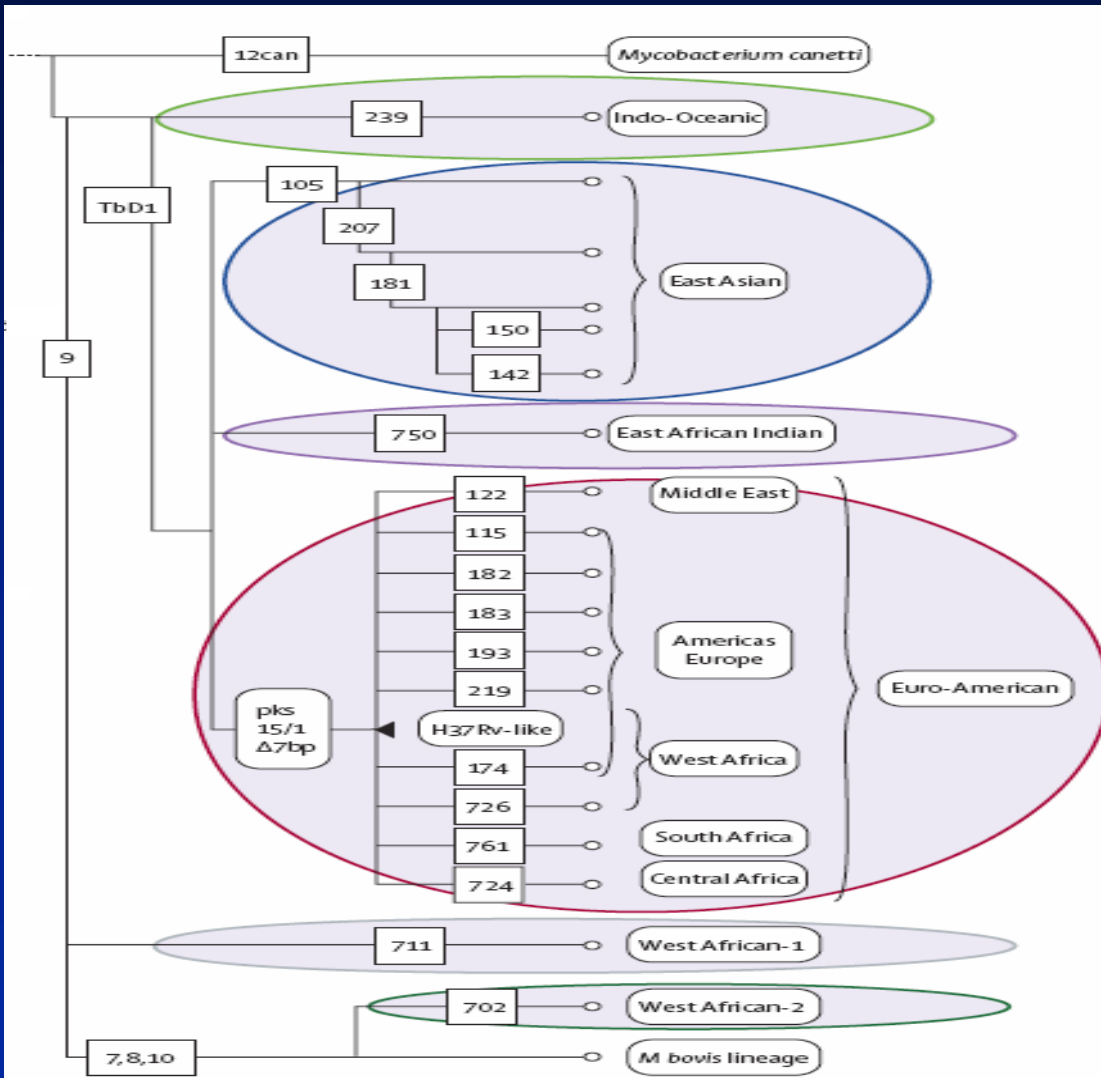
SEAL



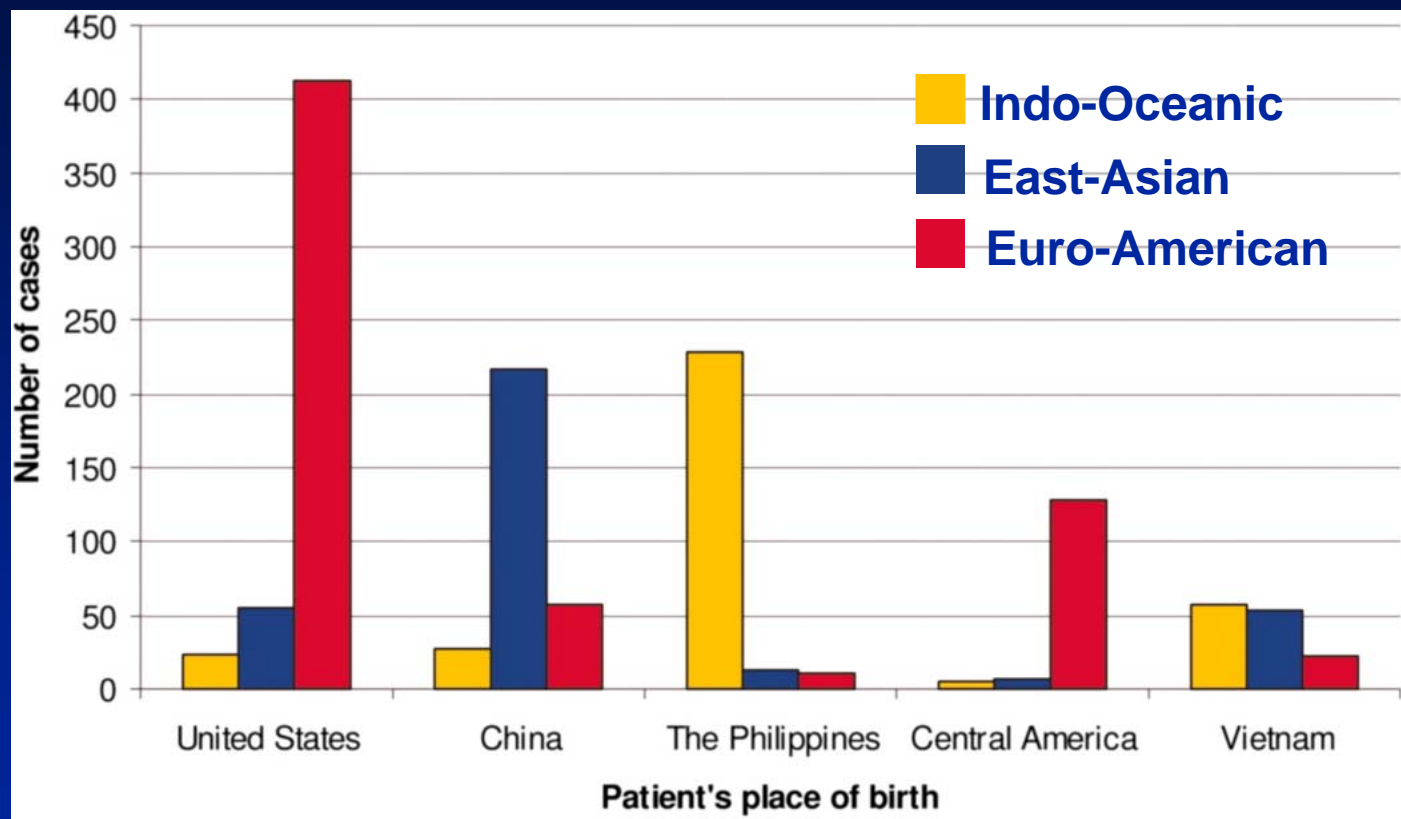
M. tb complex phylogeny 2005



M. tb sensu stricto phylogeny 2006

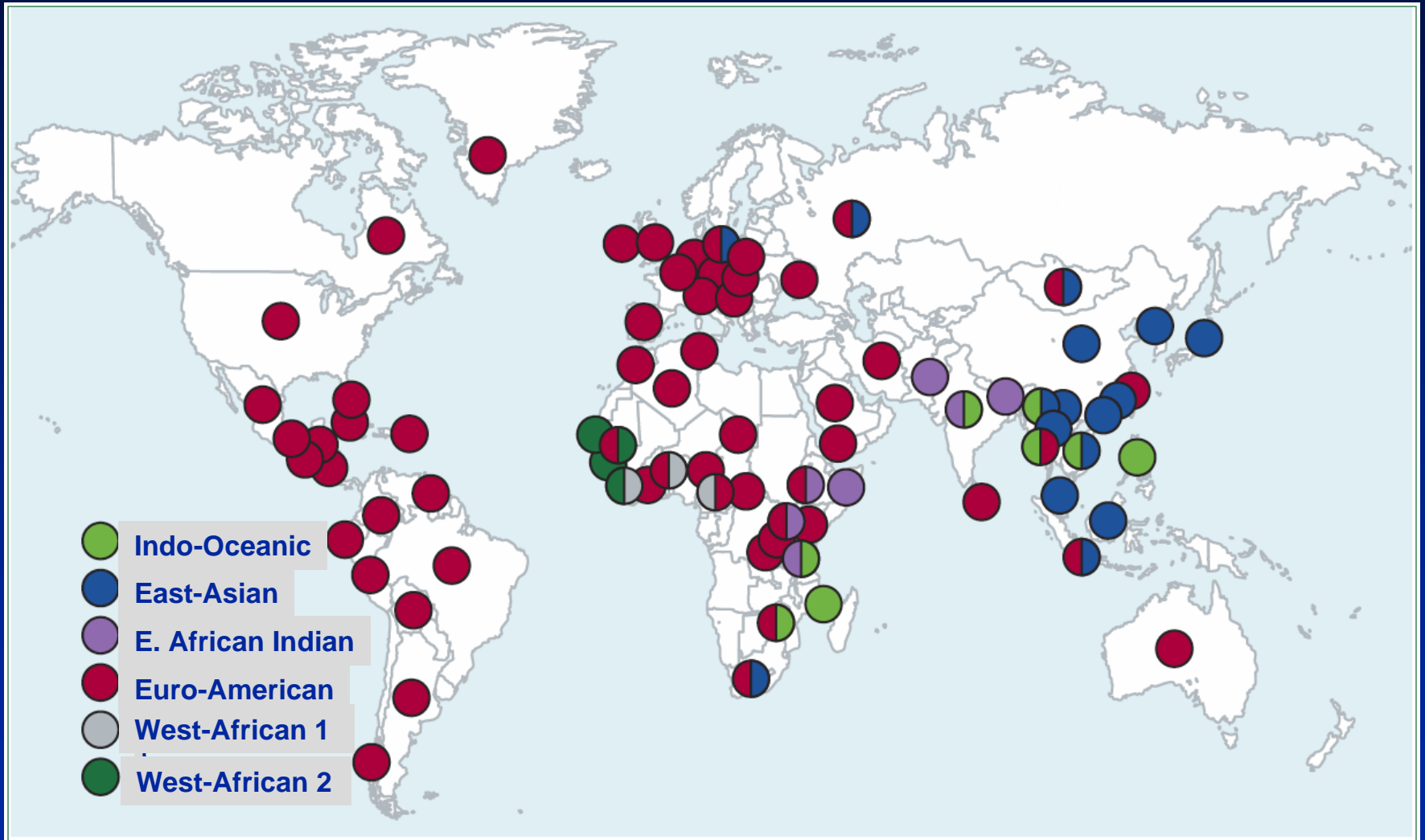


Patient/strain associations: San Francisco

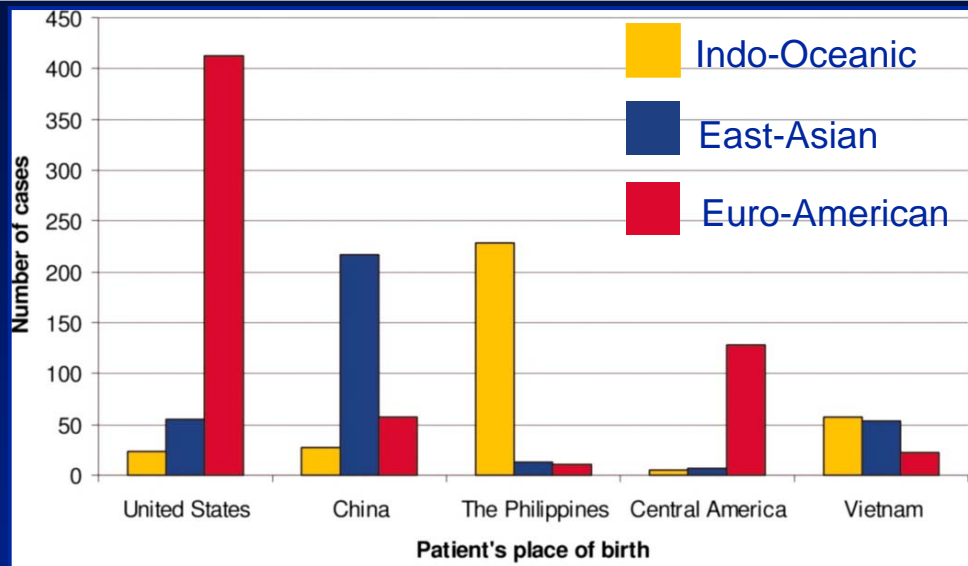


Strong association between place of birth and TB lineage

M. tuberculosis strains & place of birth



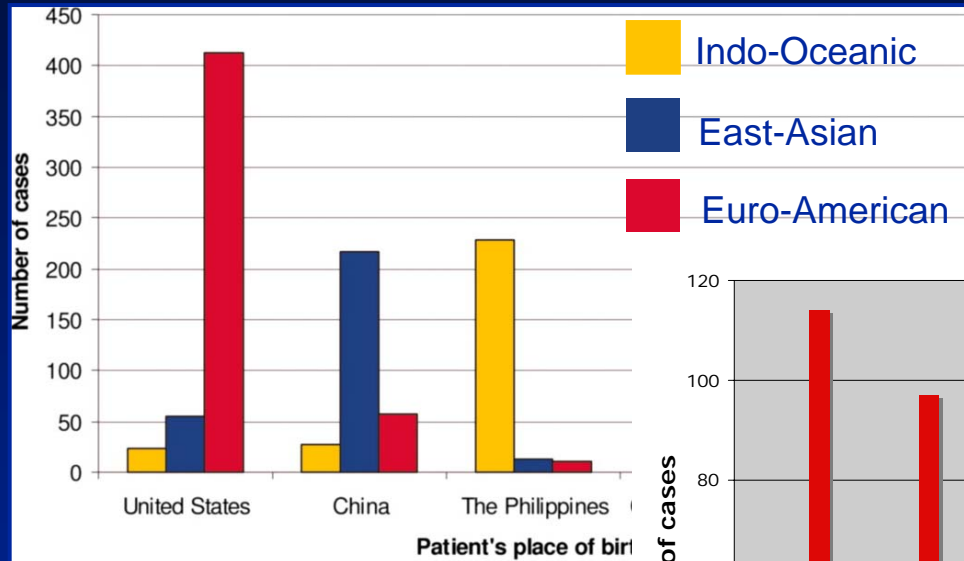
Patient/strain associations: Is this for real?



San Francisco

71% of TB cases
- 5 countries

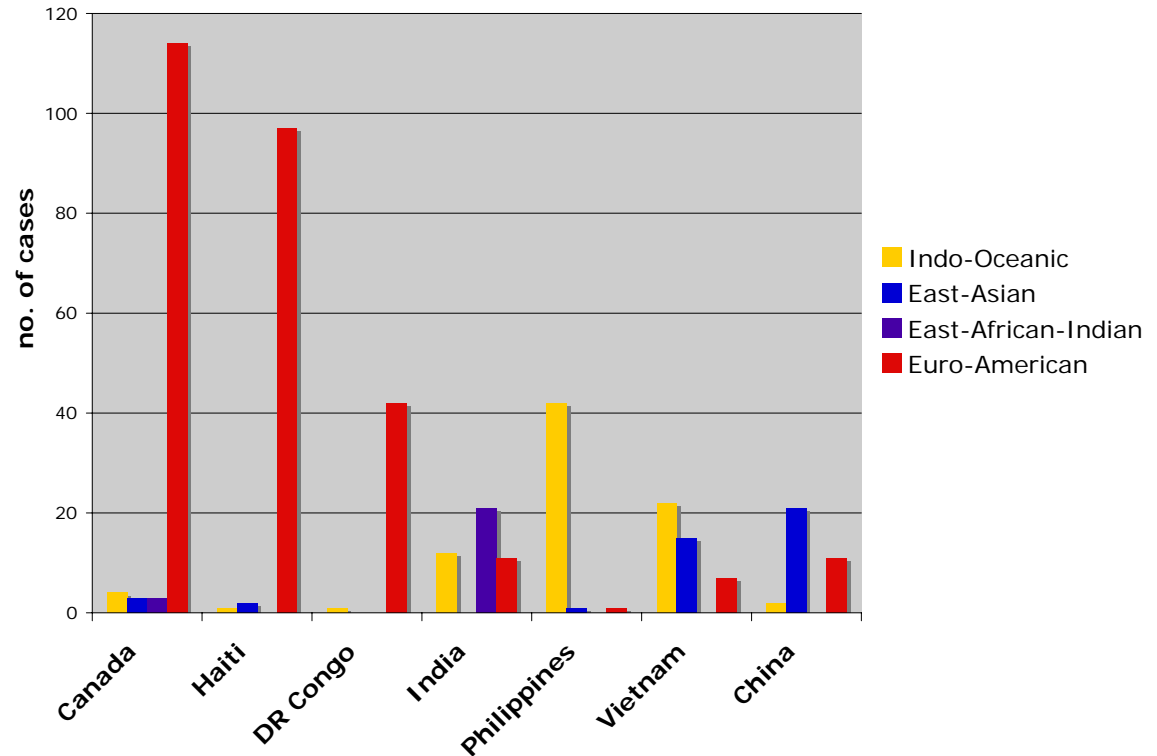
Patient/strain associations: Montreal



Montreal
60% of TB cases
- 7 countries

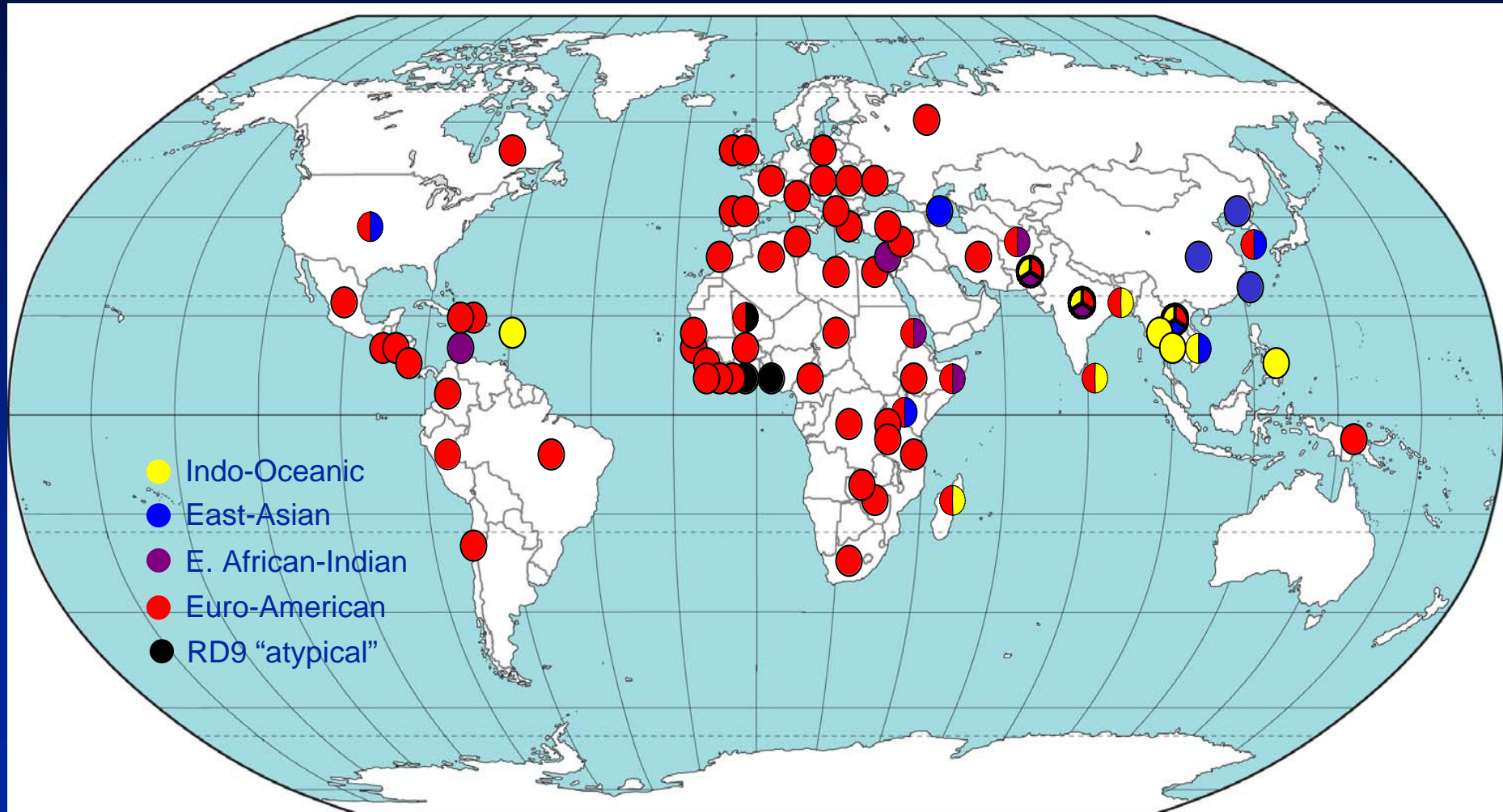
San Francisco

71% of TB cases
- 5 countries



Reed and Behr, unpublished

M. tuberculosis strains & place of birth: Montreal



Overview

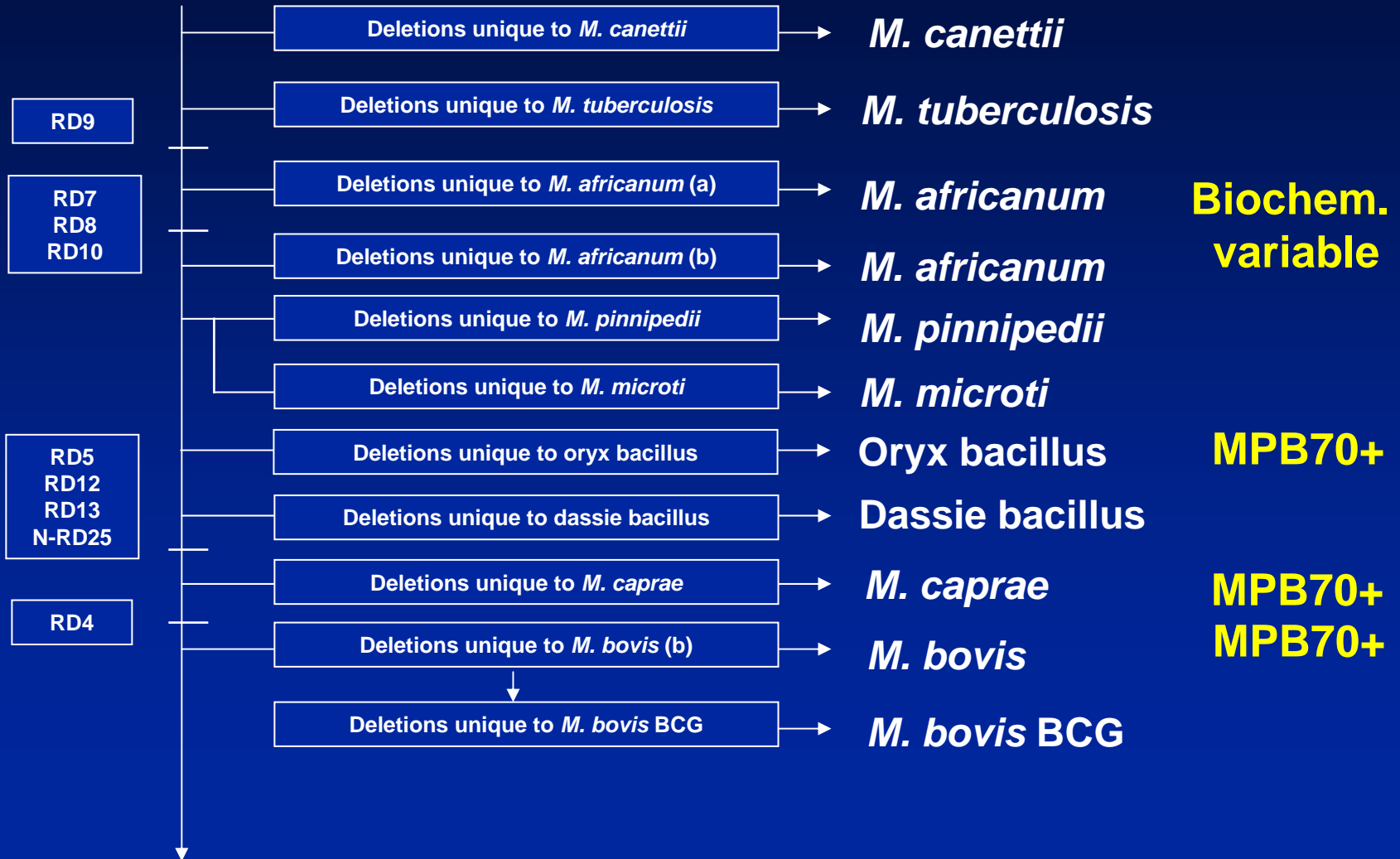
- ◆ *M. tuberculosis* phylogeny
 - It's for real
- Phenotypic consequence
 - Diagnosis
 - Treatment
 - Outcome

***M. tuberculosis* diagnosis: Microbiology laboratory**

- ◆ **Prior to 2000:**
 - Mostly phenotypic assays
 - Catalase, Niacin, Nitrate, MPB70 production
- ◆ **More recently:**
 - PCR for deleted segments
 - Higher specificity than old tests

Parsons, 2001

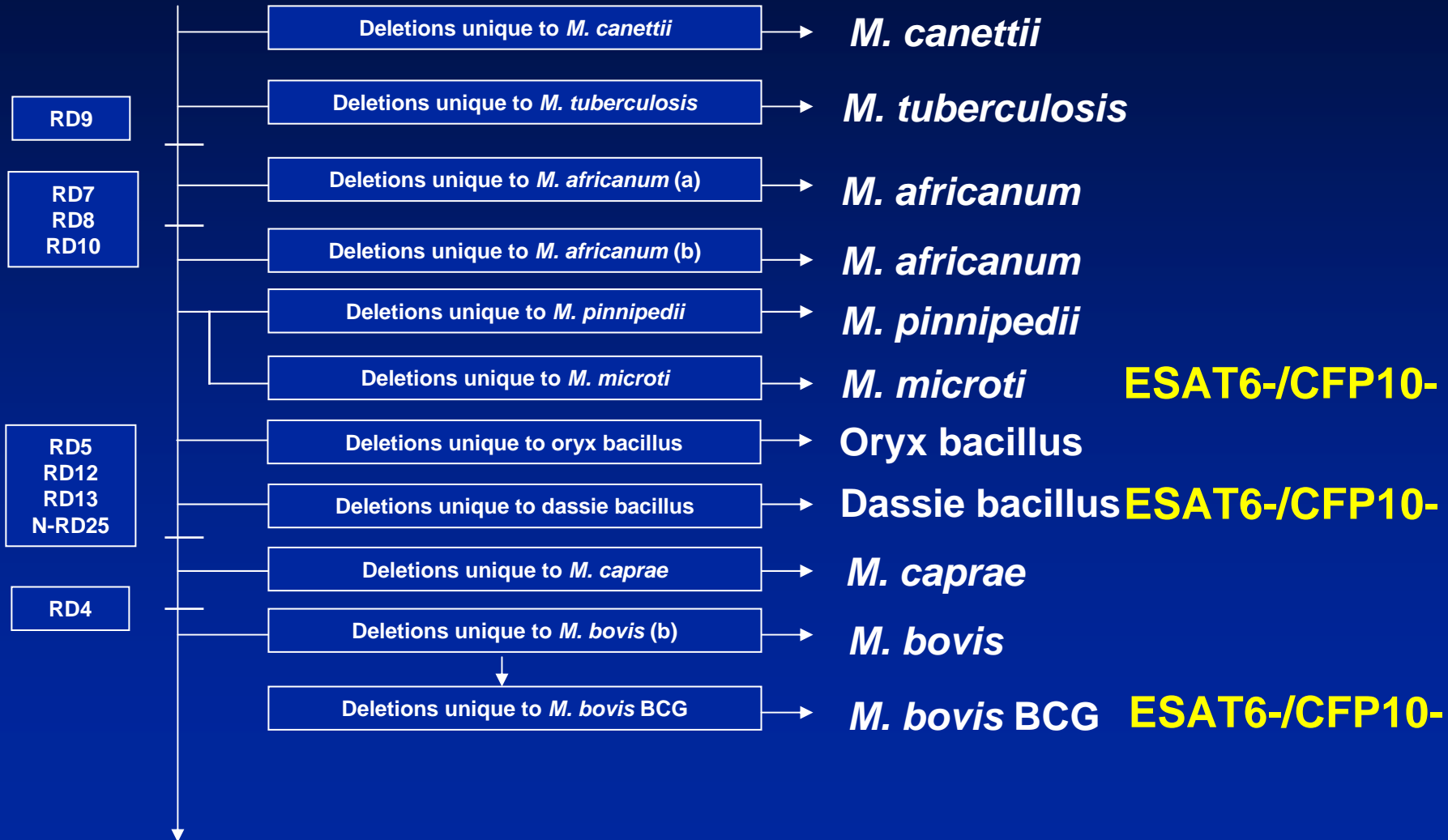
M. tb phylogeny: microbiology



***M. tuberculosis* diagnosis: Immunodiagnosics**

- ◆ **Prior to 2000:**
 - Tuberculin skin testing
 - » PPD
 - » Atypical PPDs, such as PPD avian, PPD-B
- ◆ **More recently:**
 - Interferon-gamma release assays
 - Higher specificity than old tests
 - Based on recognition of ESAT-6, CFP-10

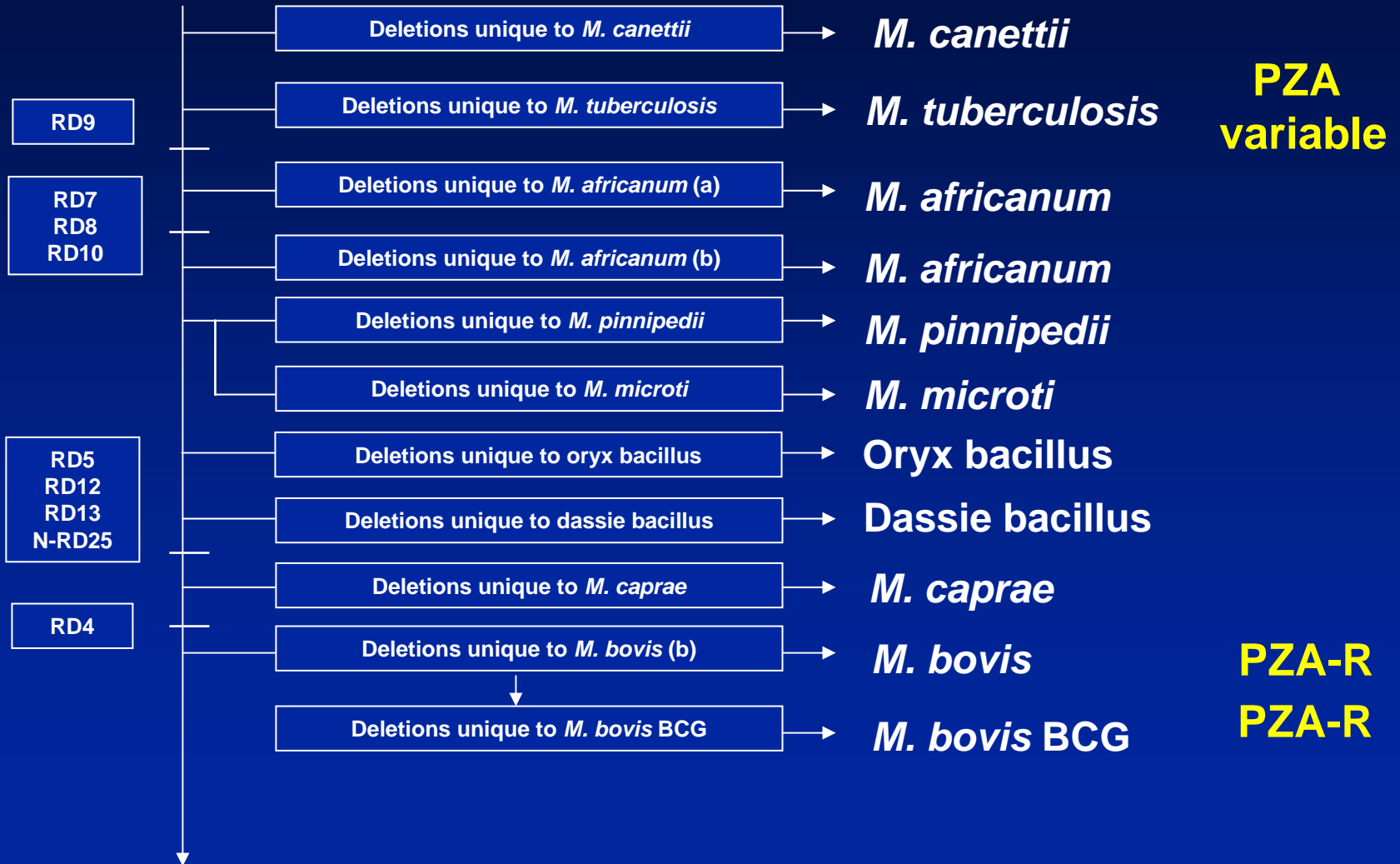
M. tb phylogeny: immune testing



***M. tuberculosis* treatment: Antibiotic susceptibility**

- ◆ Pyrazinamide activity depends on mycobacterial gene:
 - Called pyrazinamidase
- ◆ PZAse+ organisms are PZA sens.
- ◆ *M. bovis* is PZAse-
- ◆ Also, 7% of isolates in Quebec
 - Poorer outcomes of Rx

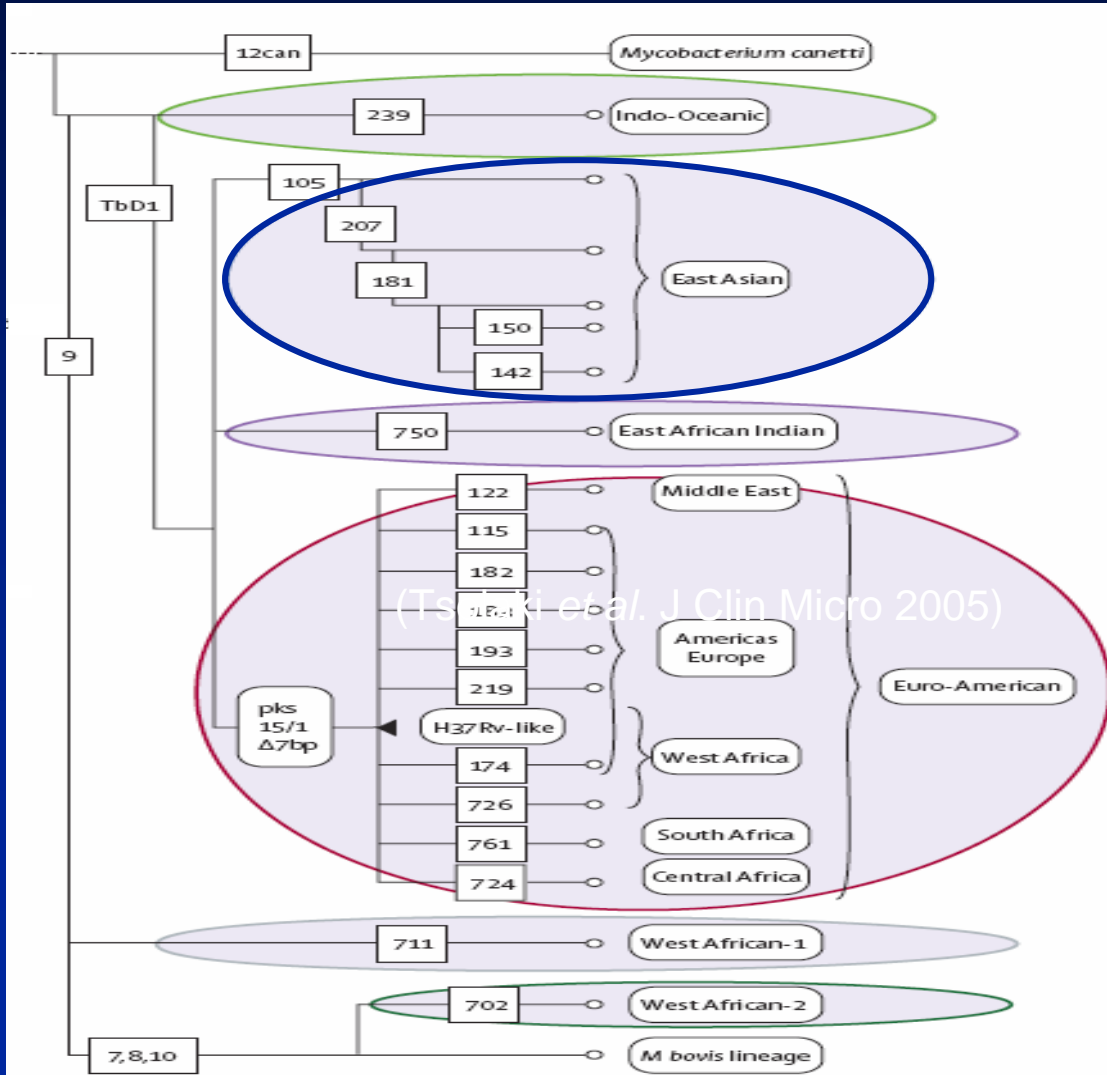
M. tb phylogeny: antibiotics



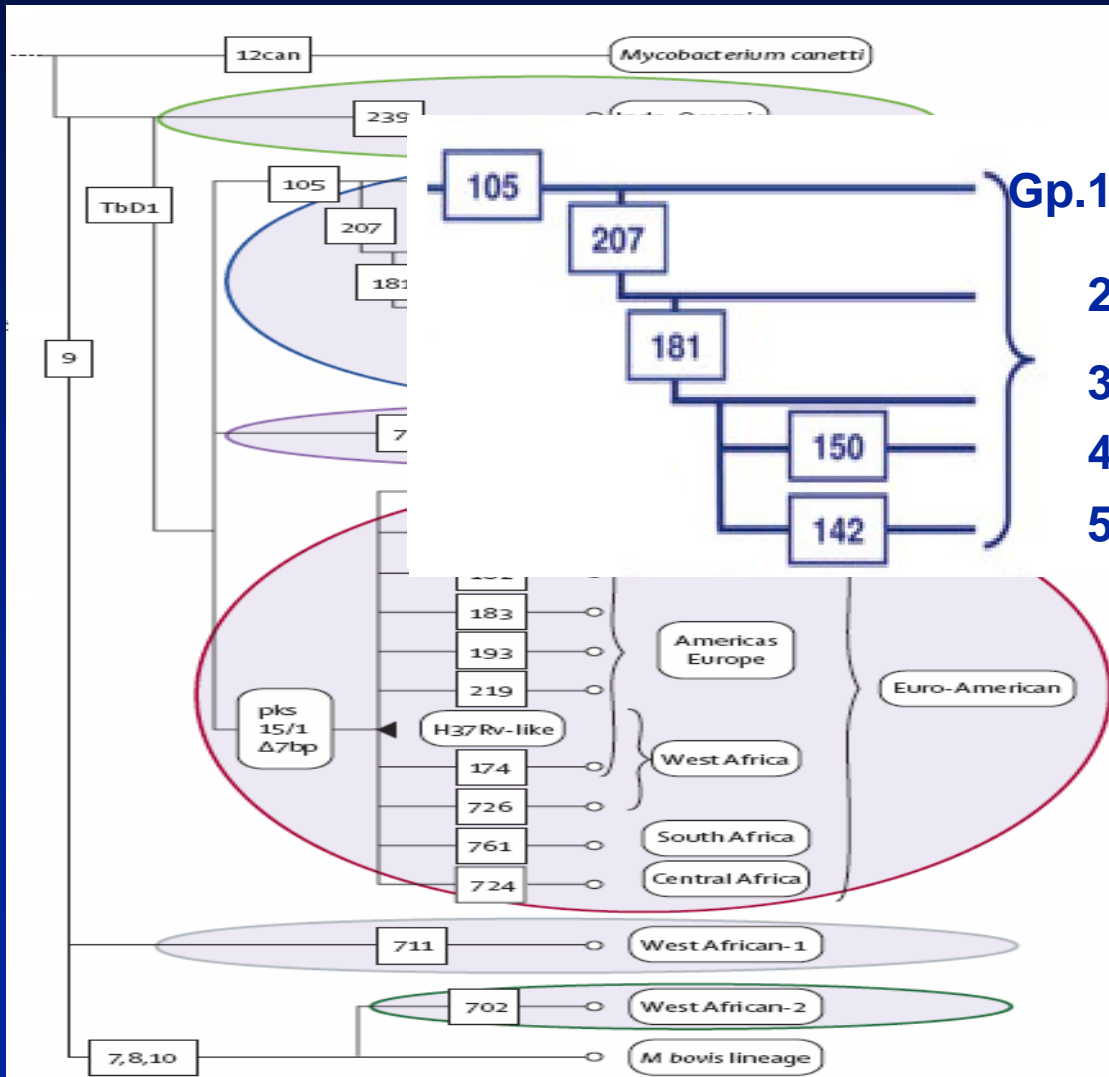
***M. tuberculosis* outcomes: Does strain matter?**

- ◆ **Beijing strain associated with:**
 - Drug resistance
 - Clustering
 - BCG resistance
 - Disseminated disease
- ◆ **Can Beijing strain do all these things?**
- ◆ **How?**

How do we define Beijing strain?



How do we define Beijing strain?



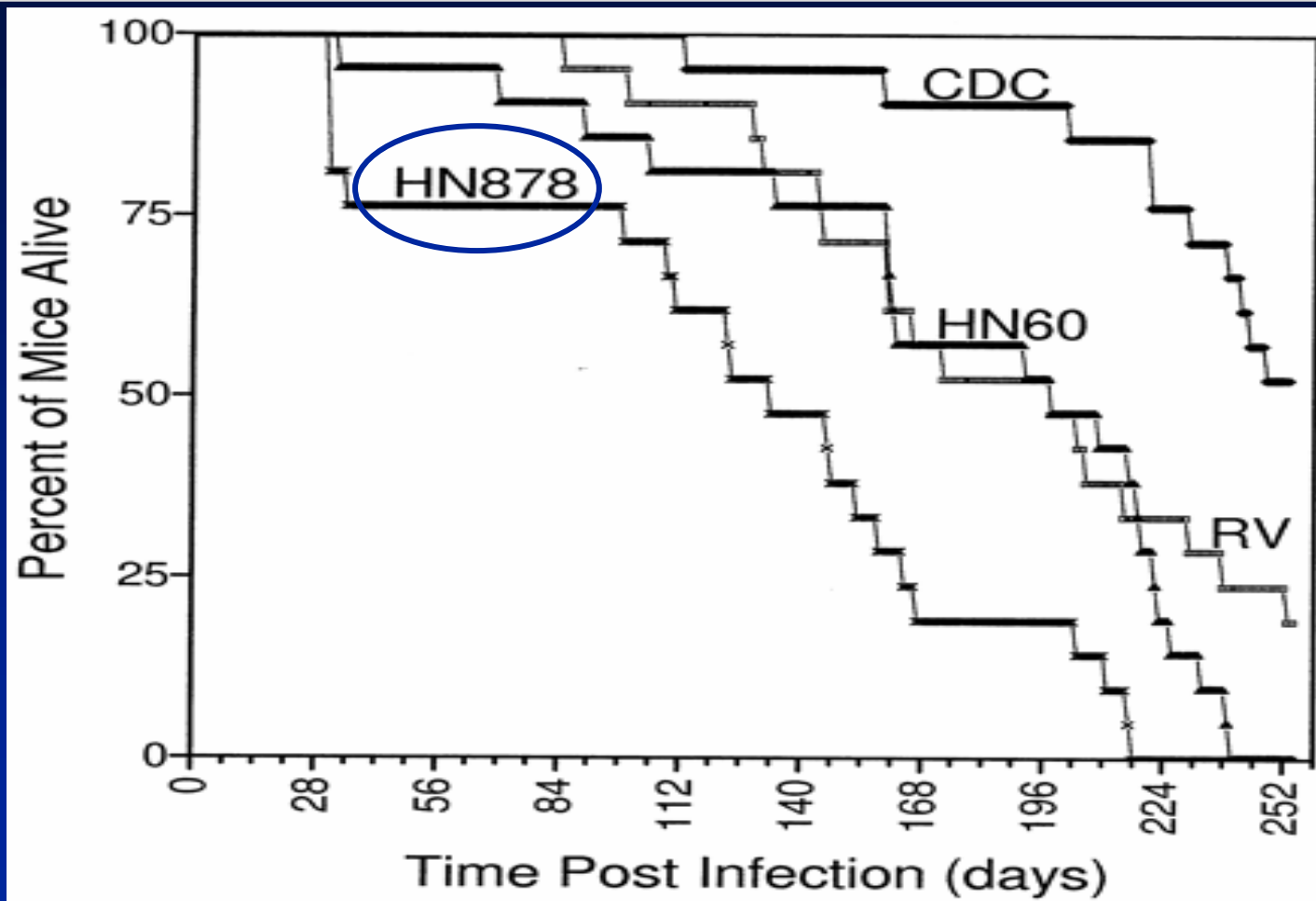
Beijing strain is defined by the RD105 deletion

- 5 sub-lineages
- Some have 'Beijing' spoligotype

Tsolaki, 2007

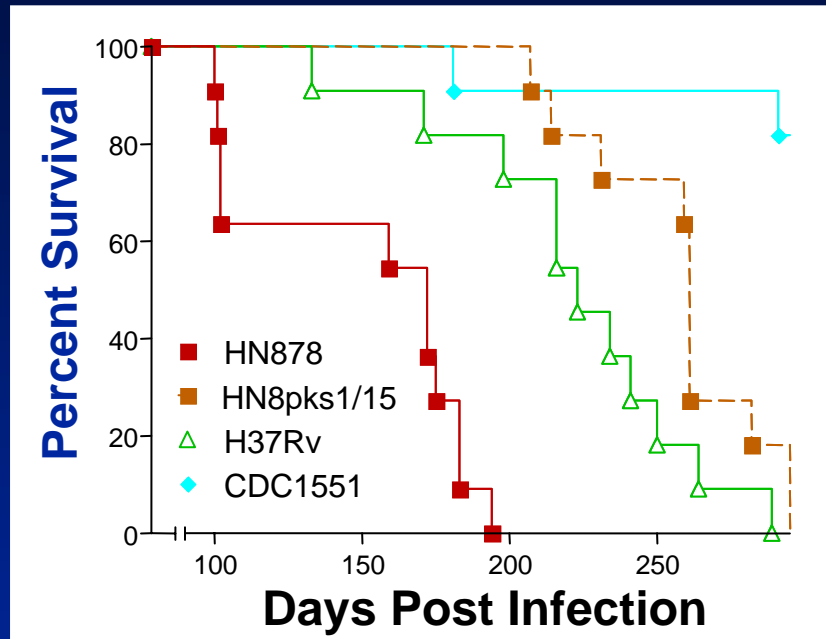
HN878

Do strains differ in lab outcomes?



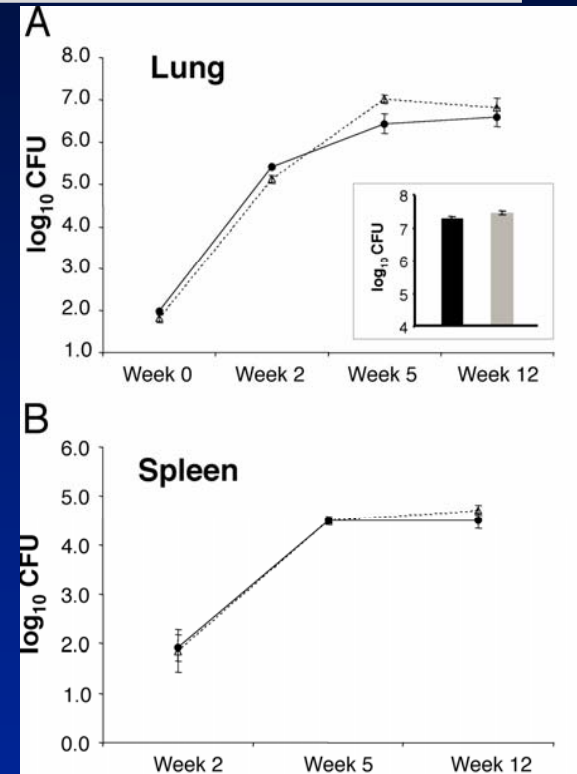
Beijing more lethal in a mouse

Virulence linked to specific lipids



Mouse Strain: C57BL/6 x DBA2 F1

($P < 0.0001$, HN878 vs. $\Delta pks1-15$; $P = 0.07$, H37Rv vs. $\Delta pks1-15$)



Summary: strain variability

- ◆ **Rare animal sub-types:**
 - Vary in ESAT-6
 - Can be PZA-R
- ◆ **Common human strains:**
 - Different survival in mice
 - Beijing strain and lipids
- ◆ **Cup is half full, twice**

Future challenges: research

- ◆ **More strains being sequenced**
 - **More genetic variants being catalogued**
- ◆ **Rate-limiting step:**
 - **Phenotype**
 - » **Microbiology lab**
 - » **Clinical presentation**
 - » **Public health**
- ◆ **Challenge: those who see and manage TB to ask when something unusual happens**

Future challenges: practice

- ◆ Patient diagnosed with smear-positive pulmonary TB
- ◆ Currently on 4 drugs, in isolation

Future challenges: practice

- ◆ Patient diagnosed with smear-positive pulmonary TB
- ◆ Currently on 4 drugs, in isolation
- ◆ What do you do if:
 - Isolate is *M. africanum*
 - Isolate is *M. caprae*
 - Isolate is *M. bovis*
 - Isolate is Beijing strain of *M. tuberculosis*

Acknowledgements

www.molepi.mcgill.ca

- ◆ Serge Mostowy
- ◆ Battouli Saïd-Salim

Michael Reed

Kevin Schwartzman

Alice Zwerling

Paul Brassard

Dick Menzies

Funding:

TB genomics:

CIHR

TB molepi:

CIHR to Schwartzman

CIHR to Menzies

National Sanitorium Association