

What's new in TB?

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Wadsworth Center

New York State Department of Health

NLTN - December 14, 2005



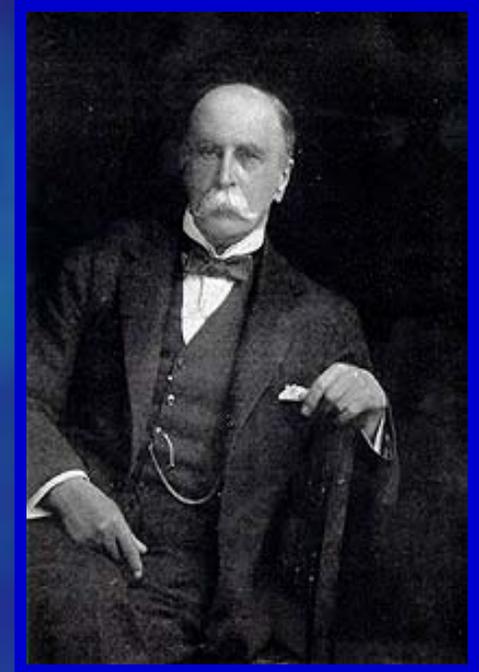
Axelrod Institute, Wadsworth Center, NYS Department of Health



'Science in the Pursuit of Health'



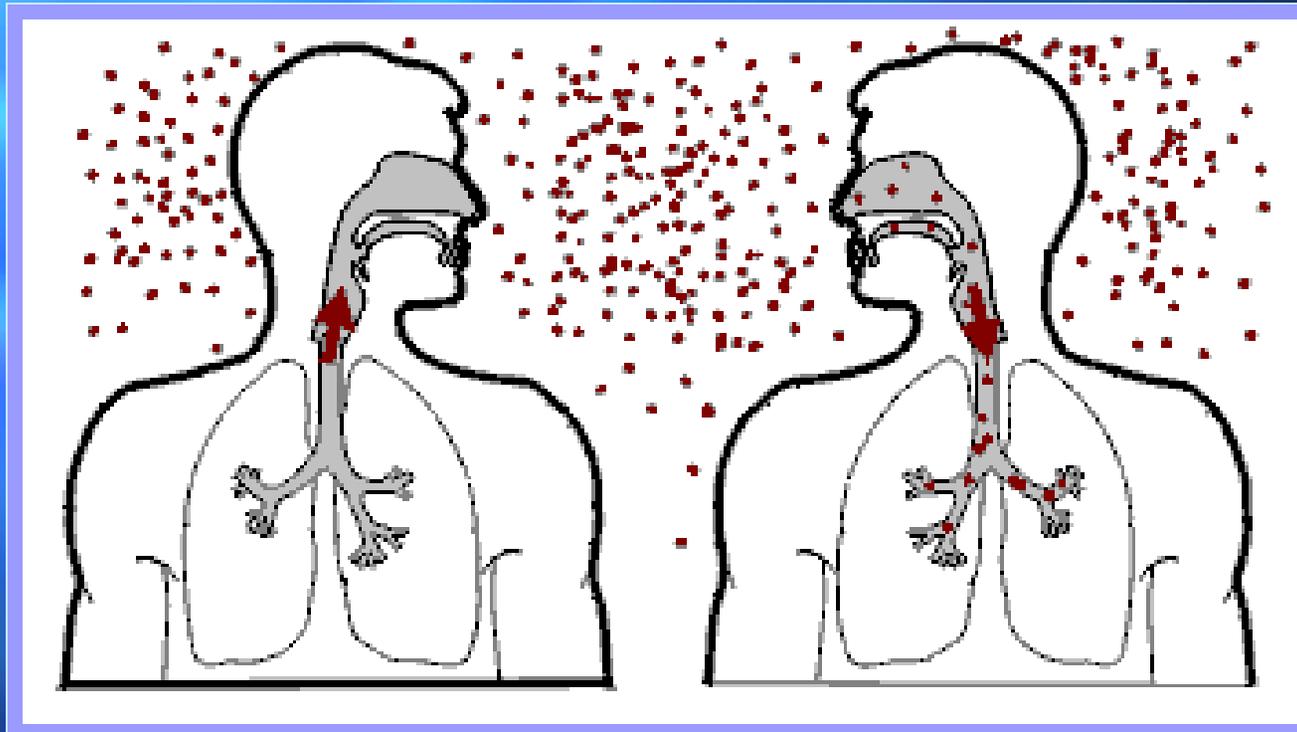
'Tuberculosis
is a social
disease with
a medical
aspect.'



Sir William Osler
1849-1919



Transmission



Sick



Infected



Healthy Persons



Natural History of TB

- **10%** of infected persons with normal immune systems develop TB at some point in life
- HIV strongest risk factor for development of TB if infected
 - Risk of developing TB disease **7% to 10% each year**
- Untreated TB, **50% will die**



Tuberculosis - WHO data

- One third of world's pop. infected
- 8 Million new cases each year
- 2 Million deaths each year



Cost of Caring for TB Patients in US

- Drug susceptible case:
\$ 22,000 [N=32, 1992 \$]
- Multidrug-resistant case (salvage therapy):
\$ 180,000 [N=35, 1990 \$]

Am J Infect Control 23:1-4(1995); JAMA 270:65-68(1995)



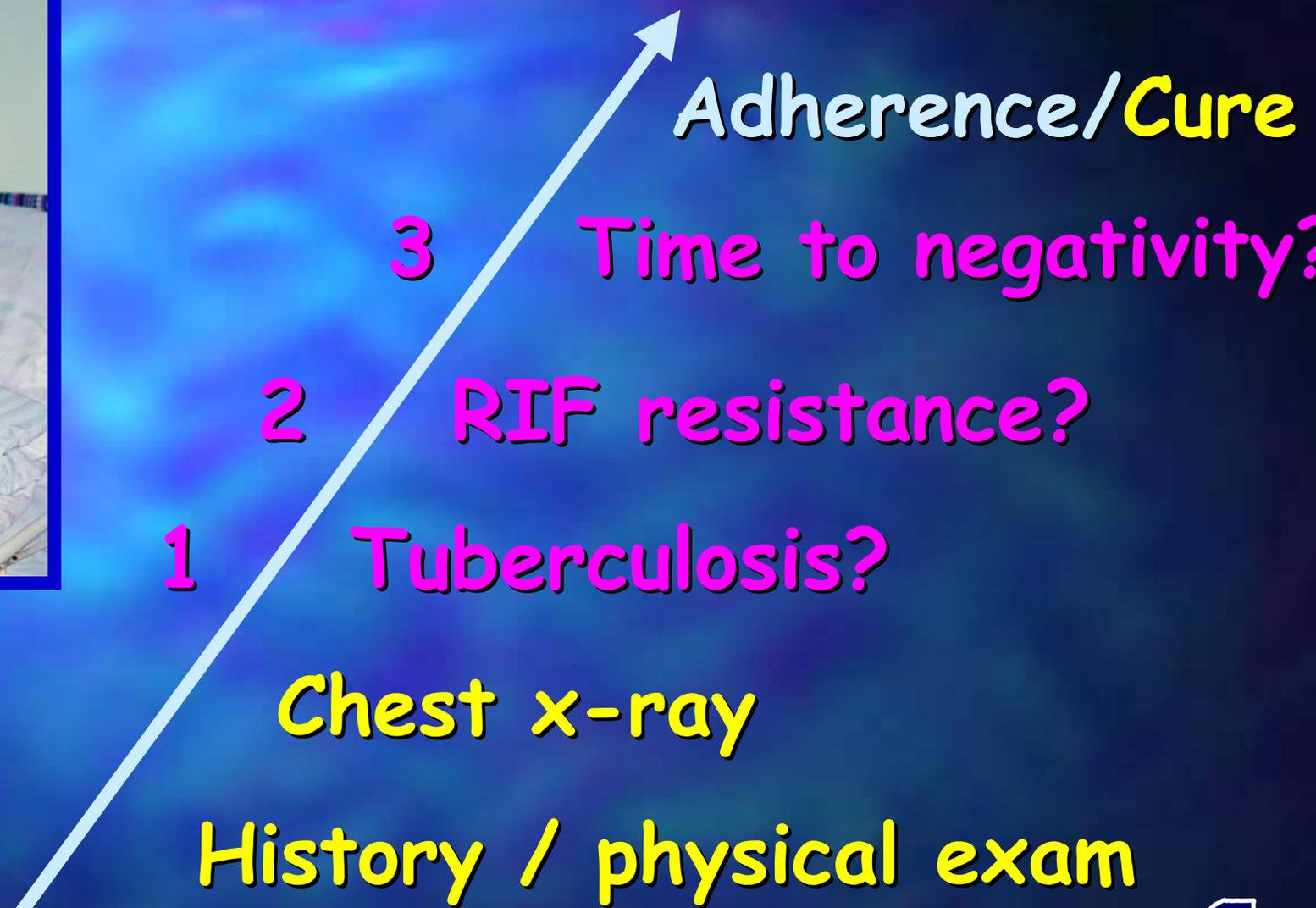
PHL Fast Track Programs since 90s

- State-of-the-art laboratory procedures
- Shortest turnaround time
- All patients with newly diagnosed AFB smear-positive sputum are eligible





sees
a
doctor



Follow up specimens



Follow up specimens I

- Follow up specimens until 2 consecutive specimens are culture negative:
- AFB smear negative: at least once a mo
- AFB smear positive: **bi-weekly**

2 sputum specimens per event (NYS)



Follow up specimens II

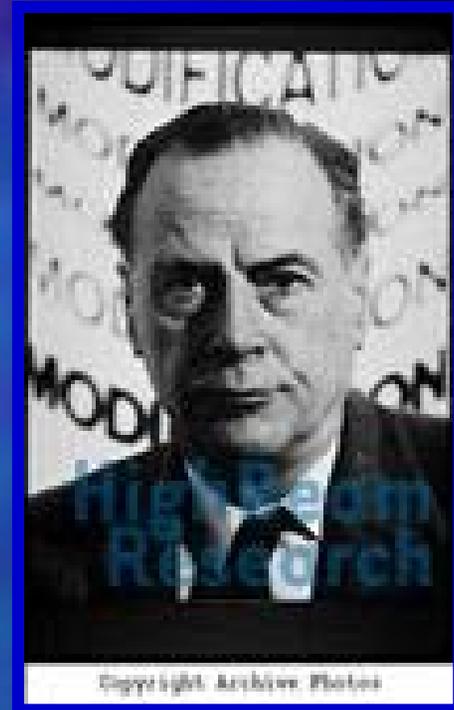
- Follow up specimens until 2 consecutive specimens are culture negative...
- Initial cavitation & mo-2 culture pos: extend INH/Rif from 4 to 7 months
- Repeat susceptibility testing after 3 mo
- Pos culture @ mo-4: Treatment failure





JAN 2 2005

'Global village'



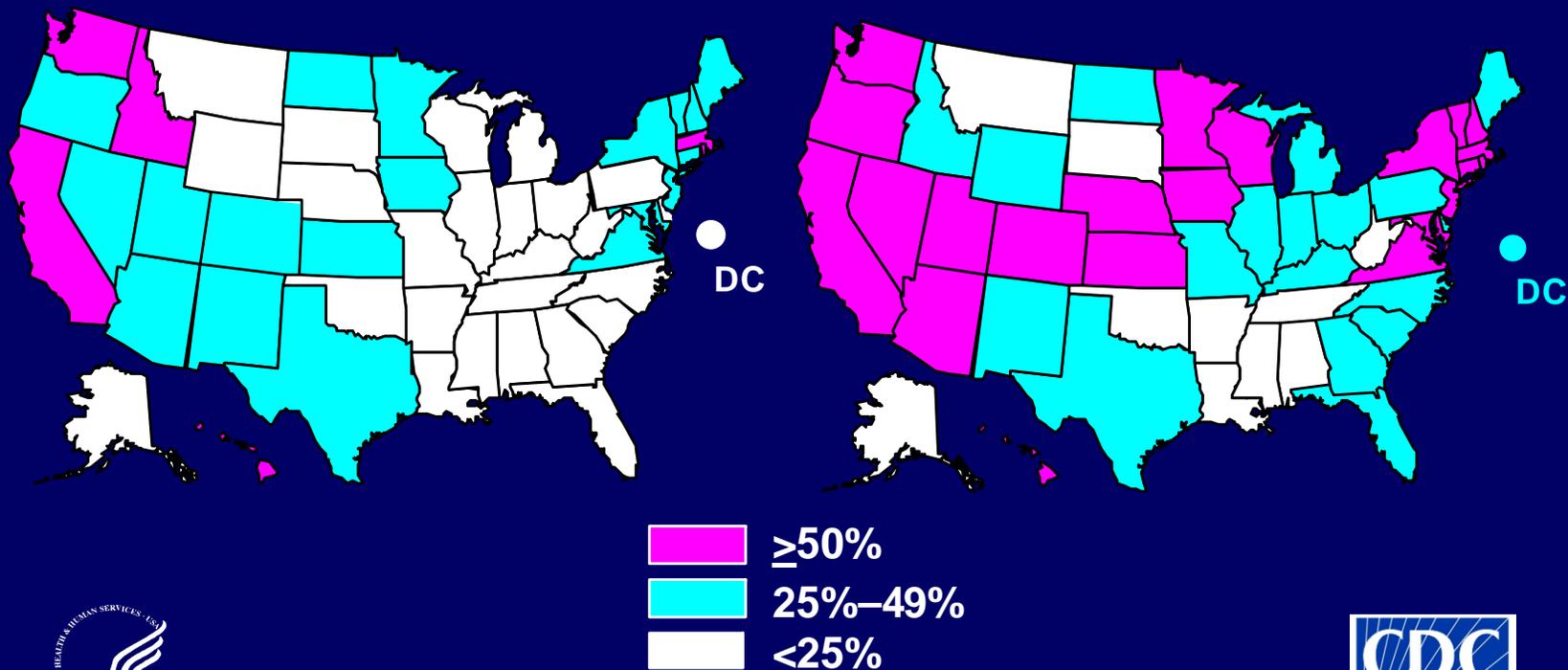
Marshall McLuhan, 1911-1980



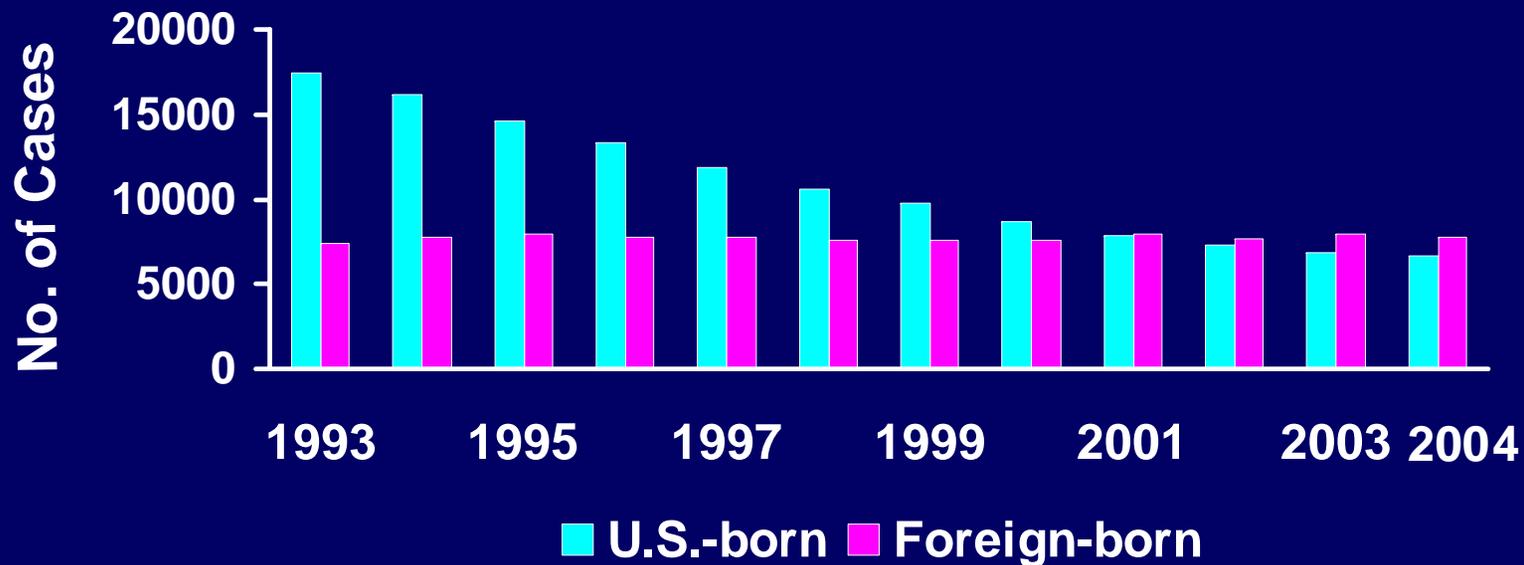
Percentage of TB Cases Among Foreign-born Persons, United States

1994

2004



Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1993–2004



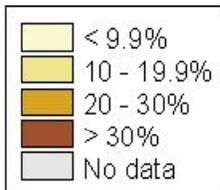
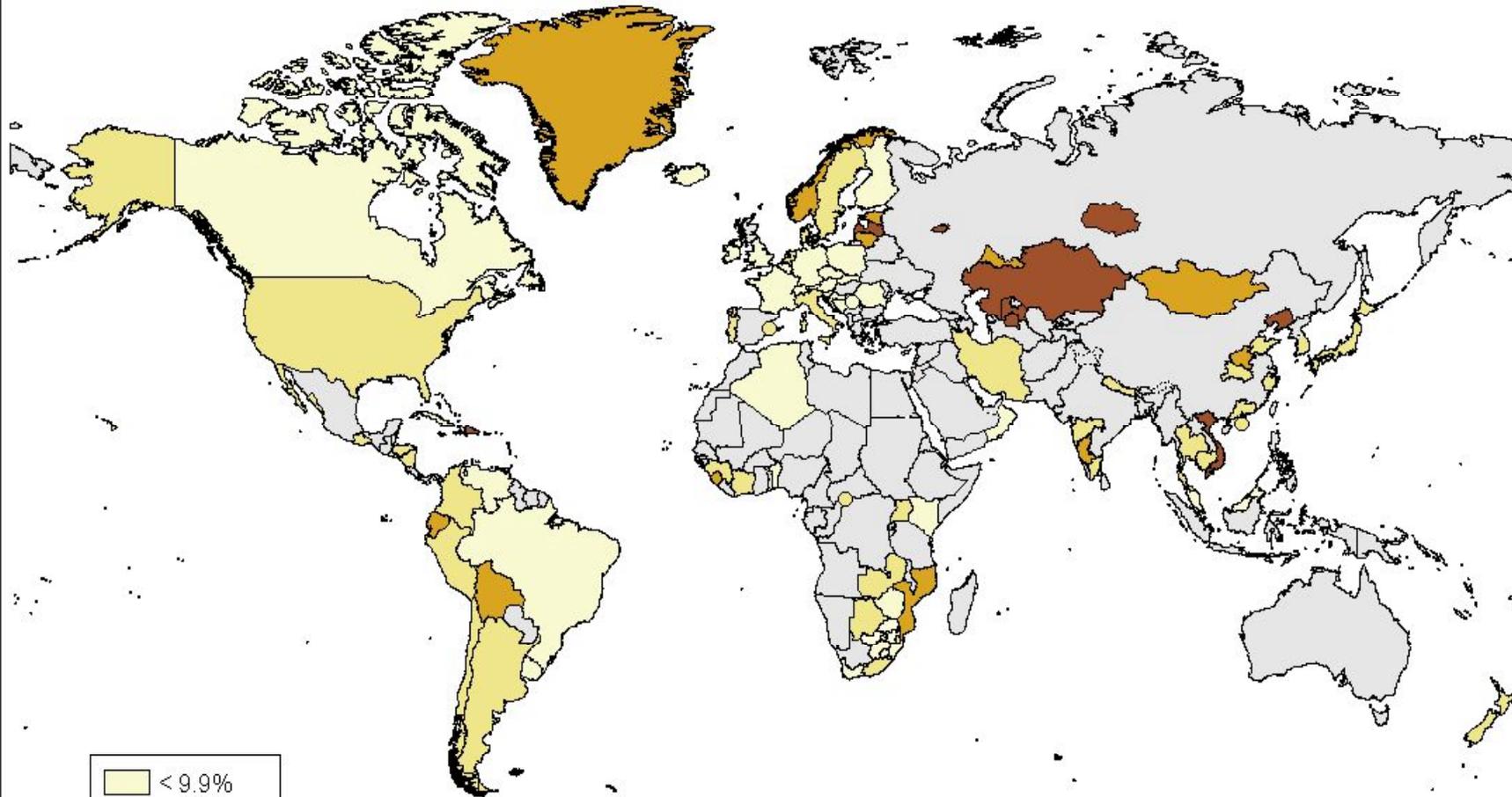
All case counts and rates for 1993–2003 have been revised based on updates received by CDC as of April 1, 2005.



DR TB



Prevalence of any drug resistance among new TB cases, 1994 - 2002



0 2000 4000 Kilometers

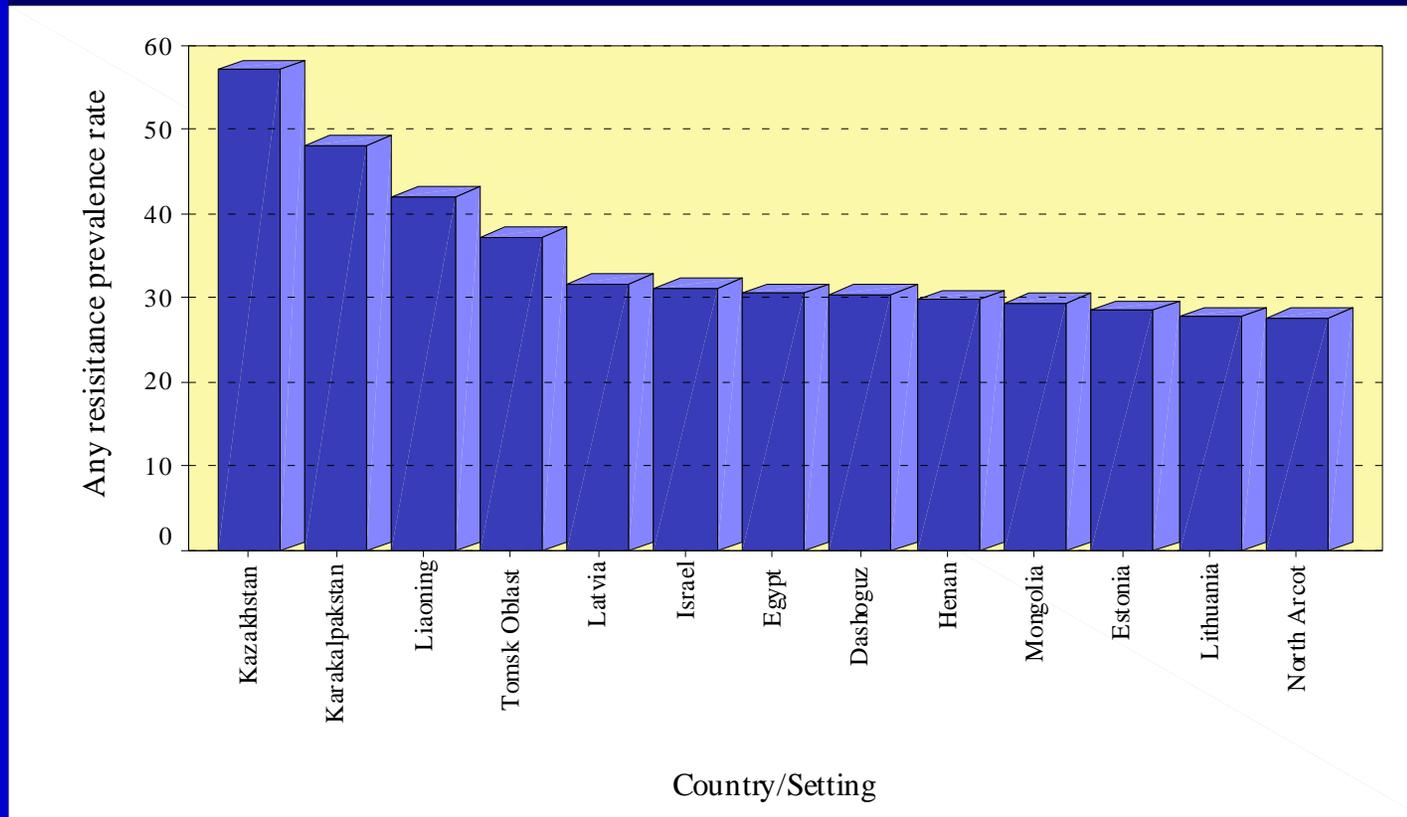
Data Source: WHO/IUALTD Global Project
Map Production:
Public Health Mapping Group
Communicable Diseases (CDS)
World Health Organization
© World Health Organization, October 2003



The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or of its authorities, or concerning the delineation of its frontiers or boundaries.



Countries/Settings with any resistance rates higher than 25% among New Cases (1999-2002)



Hot Spots: Eastern Europe,
Central & Southeast Asia



Treatment of MDR TB:

- A regimen of 3-4 drugs to which the isolate is susceptible
- 18 to 24 months beyond culture conversion

Am. J. Respir. Crit. Care Med.; 167:603-662(2003)



Florida MDR TB (1994 - 1997):

Chart Review [N=81]:	<u>Cured</u>
Community Care [N=31]	48%
A.G. Holley Hospital [N=39]	79%

Narita et al CHEST 120:343-348(2001)



***Faster
Turnaround
Times !***



RIF resistance

yes

or

no ?

Clinical course

Egg based AST

Agar based AST

Radiometric / Non-r.

rpoB analysis



rpoB analysis



Model 3100 _357_B01_IS241193-rpo95_03.ab1
Version 3.7 357-2 B1 dormanty
Basecaller-3100POP6SRSIS241193-rpo95
BC 1.5.0.0 Cap 3

Signal G:3121 A:1845 T:1818 C:2682
DT3100POP6{BDv3}v1.mob
3100
Points 1300 to 2800 Pk 1 Loc: 1300

Page 1 of 1
Wed, Nov 10, 2004 3:28 PM
Wed, Nov 10, 2004 12:47 PM
Spacing: 13.13{13.13}

A GTTC TTC GG CACCA GCCA GC TGAGCCAA TTCATGG ACCA GAACAACC CGC TGTGGGGT TGACC AAGCGCCGACTGTCGGCGCTGGGCCCGGCGGTCTGT CACGTGAGCN
10 20 30 40 50 60 70 80 90 100 110

GAC

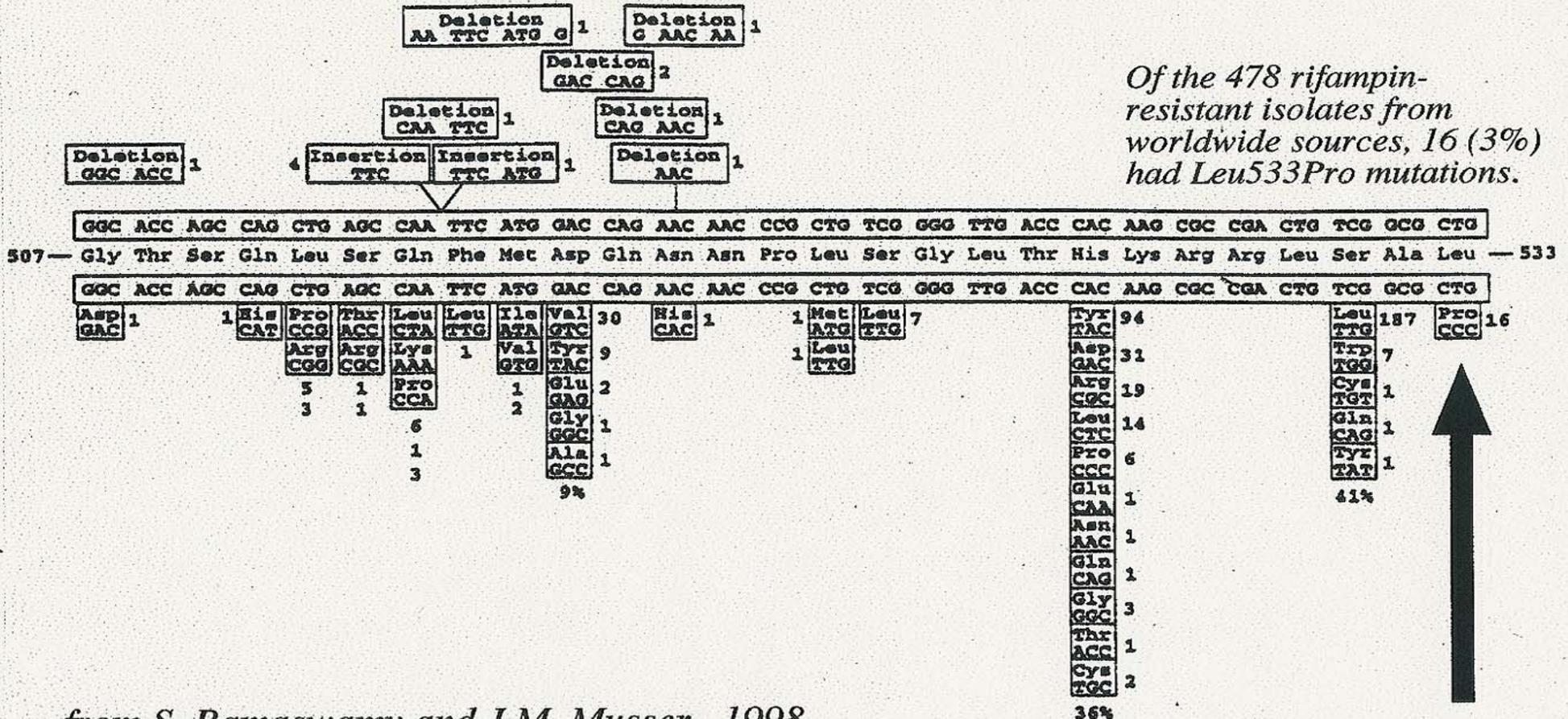


Codon 526 (CAC) encodes histidine in sus. strain
replaced with (GAC) aspartate in res. strain.



Mutations located in the 81 bp of *M. tuberculosis rpoB* associated with resistance to rifampin

Of the 478 rifampin-resistant isolates from worldwide sources, 16 (3%) had Leu533Pro mutations.



from S. Ramaswamy and J.M. Musser. 1998. *Tubercle and Lung Disease* 79:3-29

Challenge!

Molecular testing:

Drug	Gene	% mutations
RIF	<i>rpoB</i>	>96%
PZA	<i>pncA</i>	97%
INH	<i>katG</i>	40-60%
INH-ETH	<i>inhA</i>	15-43%
INH	<i>ahpC</i>	10%
INH	<i>kasA</i>	unknown



Drug-Resistant TB -

A Survival Guide For Clinicians

Francis J. Curry National Tuberculosis
Center, San Francisco, 263 p. (2005)

www.nationaltbcenter.edu



TBC

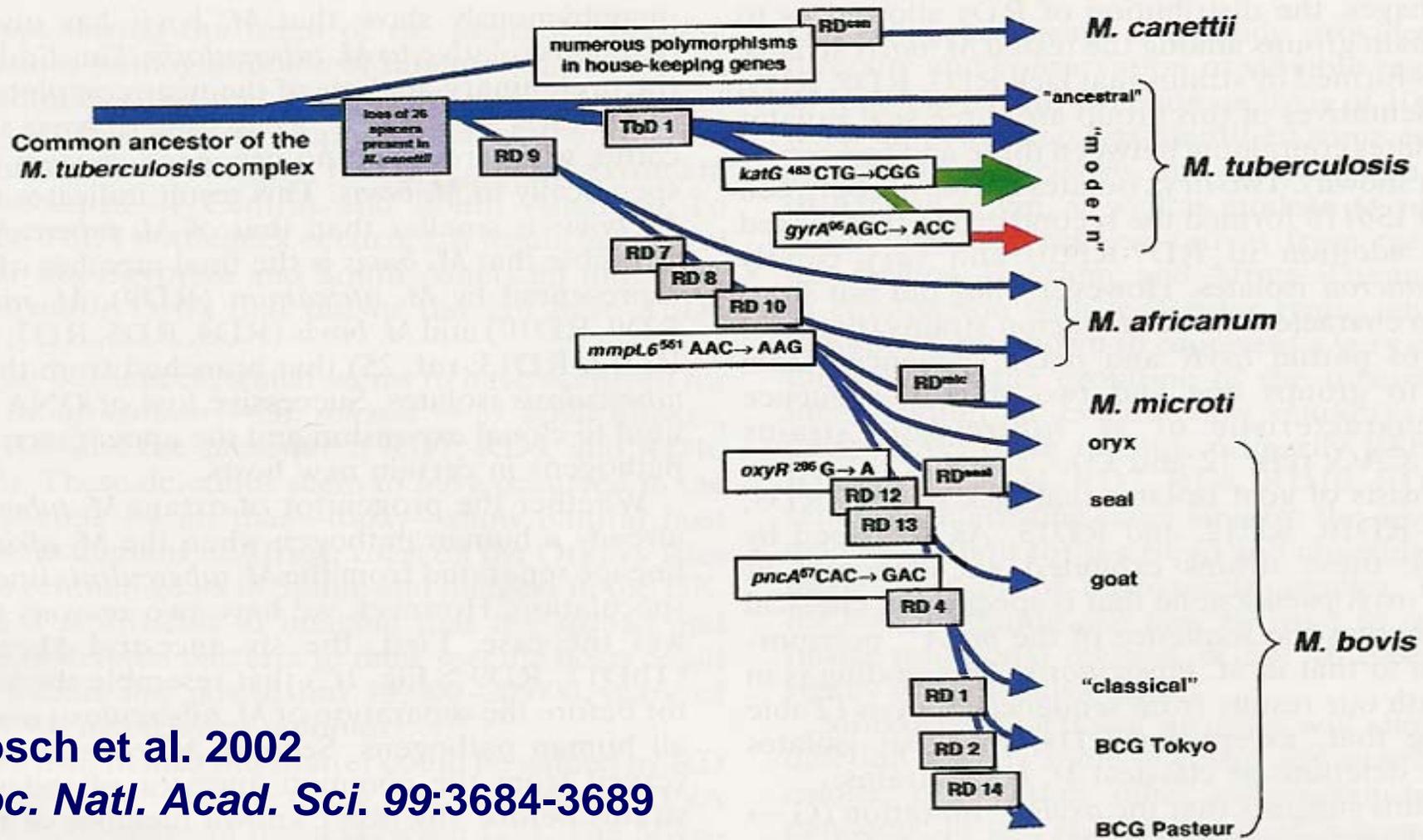


NAA, AccuProbe, and 16S sequencing detect all members of *M. tuberculosis* complex

- *M. tuberculosis*
- *M. bovis*
- *M. bovis* BCG
- *M. africanum*
- *M. caprae*
- *M. microti*
- *M. canettii*
- *M. pinnipedii*



Proposed Evolutionary Pathway of the Tubercle Bacilli (successive loss of DNA)



Brosch et al. 2002
 Proc. Natl. Acad. Sci. 99:3684-3689

**PCR based
genomic
deletion analysis
for TBC members**



Selected RD regions for Differentiation of the TBC

	RD1	RD9	RD10	RD4	RD5	RD12
<i>MTB</i>	+	+	+			
<i>AFR</i>	+	-	+/-	+	+/-	+
<i>CAP</i>	+	-	-	+	-	-
<i>BOV</i>	+	-	-	-	-	-
BCG	-	-	-			

Parsons et al. 2002
J. Clin. Microbiol. 40:2339-2345



Screening 1,685 Clinical Isolates belonging to the TBC (2001-2004)

	No.	(Percent)
■ <i>M. tuberculosis</i>	1,594	(94.6%)
■ <i>M. africanum</i>	31	(1.8%)
■ <i>M. bovis</i>	36	(2.1%)
■ <i>M. caprae</i>	1	(0.1%)
■ <i>M. bovis</i> BCG	23	(1.4%)



**Human tuberculosis
caused by
Mycobacterium bovis
- New York City
2001 - 2004**

Winters et al. 2005 *MMWR* 54:605-608



NAA



Nucleic acid amplification

- FDA approved:

Smear-pos (Dec 1995)

Smear-neg* (Sep 1999)

- MMWR July 7, 2000 [R]
- AFB-pos / NAA-neg
- AFB-neg* / NAA-pos



HEALTHY

PEOPLE

2010



14-14 Reduce TAT for laboratory Dx

Target: **2 d for 75%**

[21 d // '96]

U.S. Department of Health and Human
Services, January 2000



Errors



Review of false-positive cultures for Mtb and recommendations for avoiding unnecessary treatment

Burman & Reves, Clin Infect Dis 2000, 31:1390-1395



Results:

- 14 studies with 100+ patients (12 incl. DNA typing)
- Definitions for false-positive vary
- Median false-positivity rate: **3.1%**
(interquartile range 2.2% to 10.5%)



Pioneer from Harvard



'Errors must be accepted as evidence of systems flaws **not** character flaws. Until and unless that happens, it is unlikely that any substantial progress will be made in reducing medical errors.'

Leape, JAMA 1994, 272:1851-1857



TB

fingerprinting



Universal, real-time Genotyping

National TB Genotyping and Surveillance Network

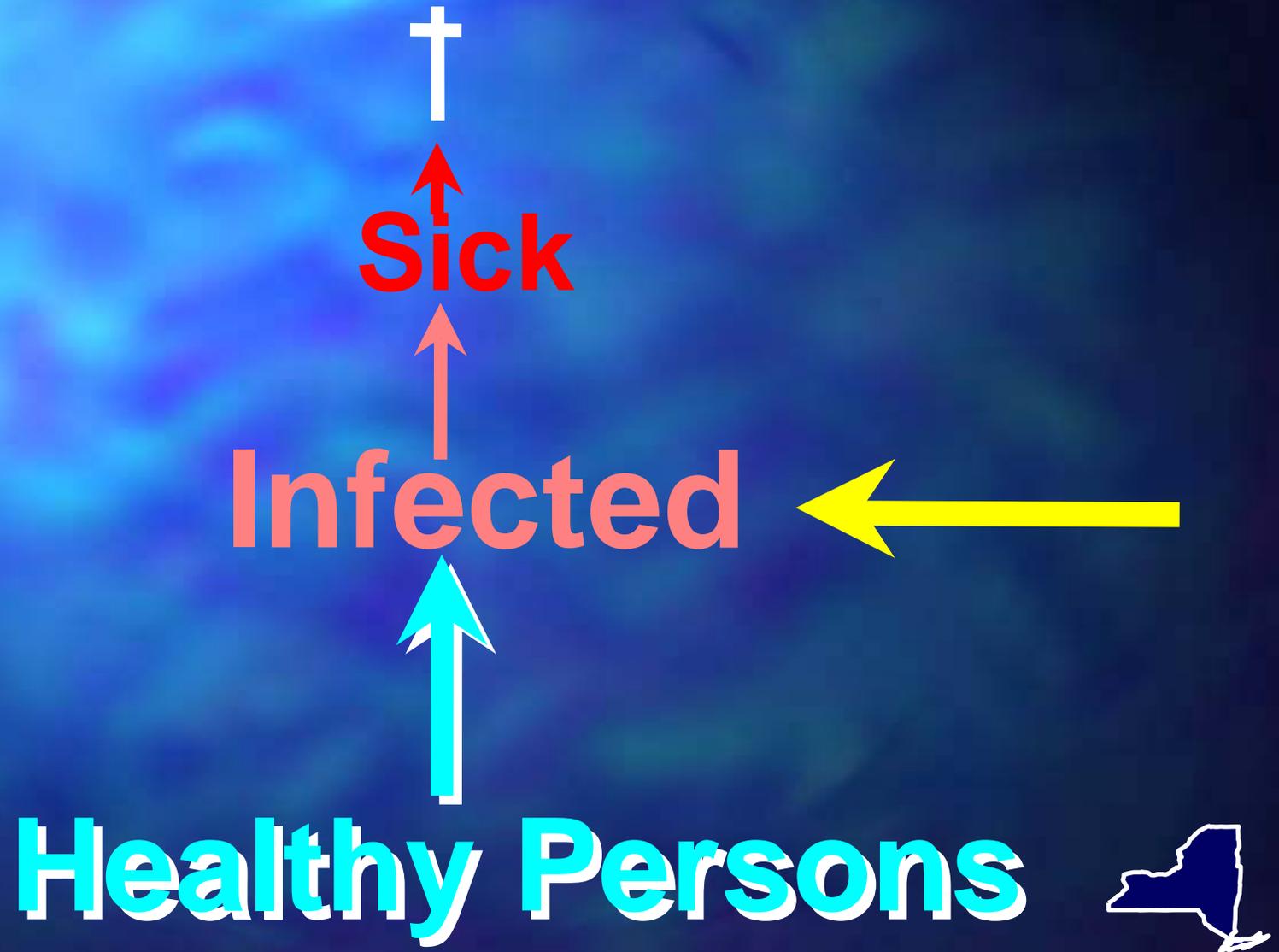
- Spoligotyping / MIRU
- Conventional RFLP



What have been the most useful aspects of universal DNA fingerprinting of M.tb?

- Detecting false positive cultures
- Uncovering previously unrecognized cases of transmission
- Assessing efficacy of TB Control programs





Tuberculin PPD-S



Dr. Florence B. Seibert,
1897-1991
Henry Phipps Institute
1959 retired, St. Petersburg

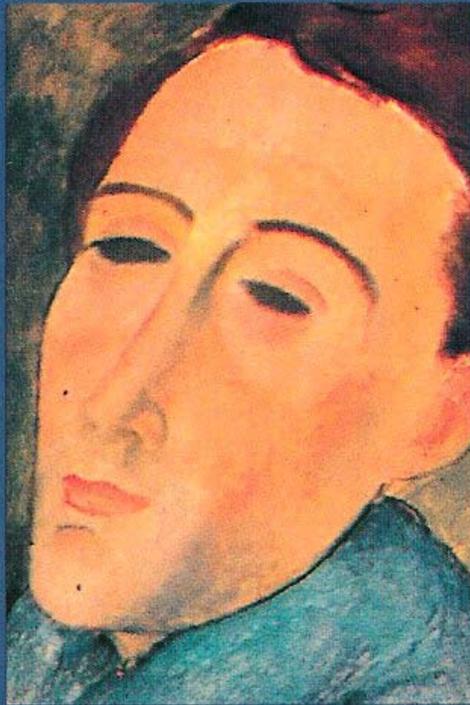
1940 Produced PPD-S (Standard)

1941 US Standard

1952 WHO Standard



Ending Neglect



The Elimination
of
Tuberculosis
in the
United States



Institute of Medicine 2000

**From TB
control to TB
elimination!**



Elimination:

< 1 case

per 1 million pop

per 1 year



'... the greatest needs in the US are new diagnostic tools for the more accurate identification of individuals who are **truly infected** and who are also **at risk of developing TB.**'

IOM Report 2000



Interferon Gamma assays

Pai et al. Lancet ID 4:761-776(2004)



• QuantiFERON-TB

FDA approval: November 2001

CDC guidelines: MMWR Vol 52
(RR-2) Jan 31, 2003 [R]

• T-SPOT.TB

Not FDA approved



Performing the assay:

- I Blood collection (heparin)
- II Incubation of blood with stimulating antigens (ESAT-6, CFP-10)
- III Interferon gamma ELISA
- IV Interpretation



QuantiferON Test:

Pros: 1) requires only one visit, 2) simple format, 3) more objective than TST

Cons: 1) antigens not TB-specific (*M. kansasii*; *M. szulgai*, *M. marinum*, 2) set up <12 hrs, 3) clinical experience limited



Interferon Gamma Assay





Unresolved TB lab issues:

Processing sputum

Left over sediment
used for molecular
work-up - can you
believe it?



Postmarketing surveillance

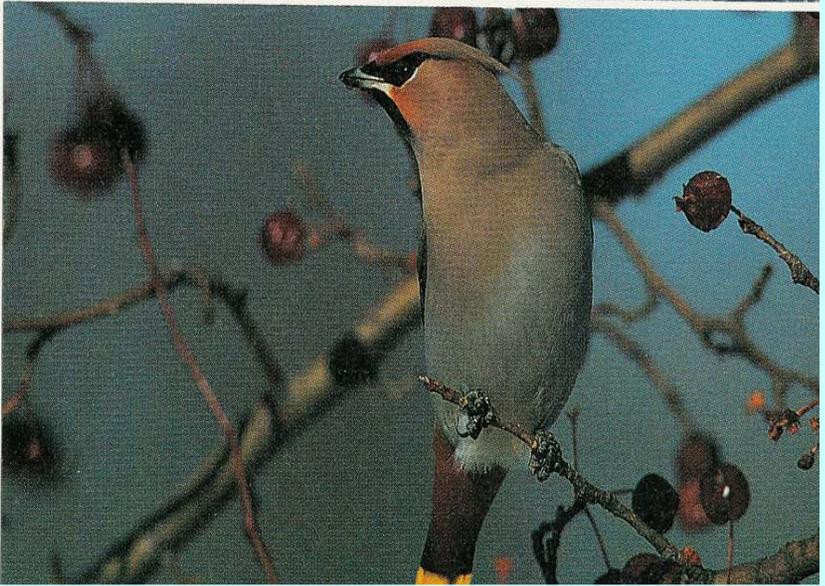
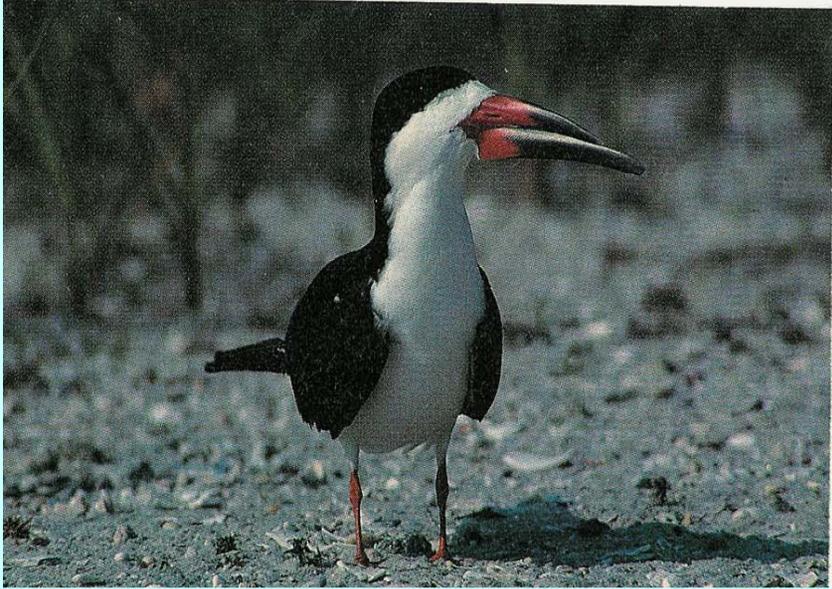
No systematic
postmarketing
surveillance for FDA
approved assays - can
you believe it?



TB meningitis

The sensitivity of laboratory assays is inversely proportional to the seriousness of the disease? - No improvement around the corner!





**'It is health
which is real wealth
not pieces of silver and gold'**

Mahatma Gandhi, 1869-1948



**Working
together**



PHL Fast Track Programs, 2005:

- State-of-the-art laboratory procedures
- Shortest turnaround time
- All patients with newly diagnosed AFB smear-positive* sputum
- All patients with suspected drug-resistant TB



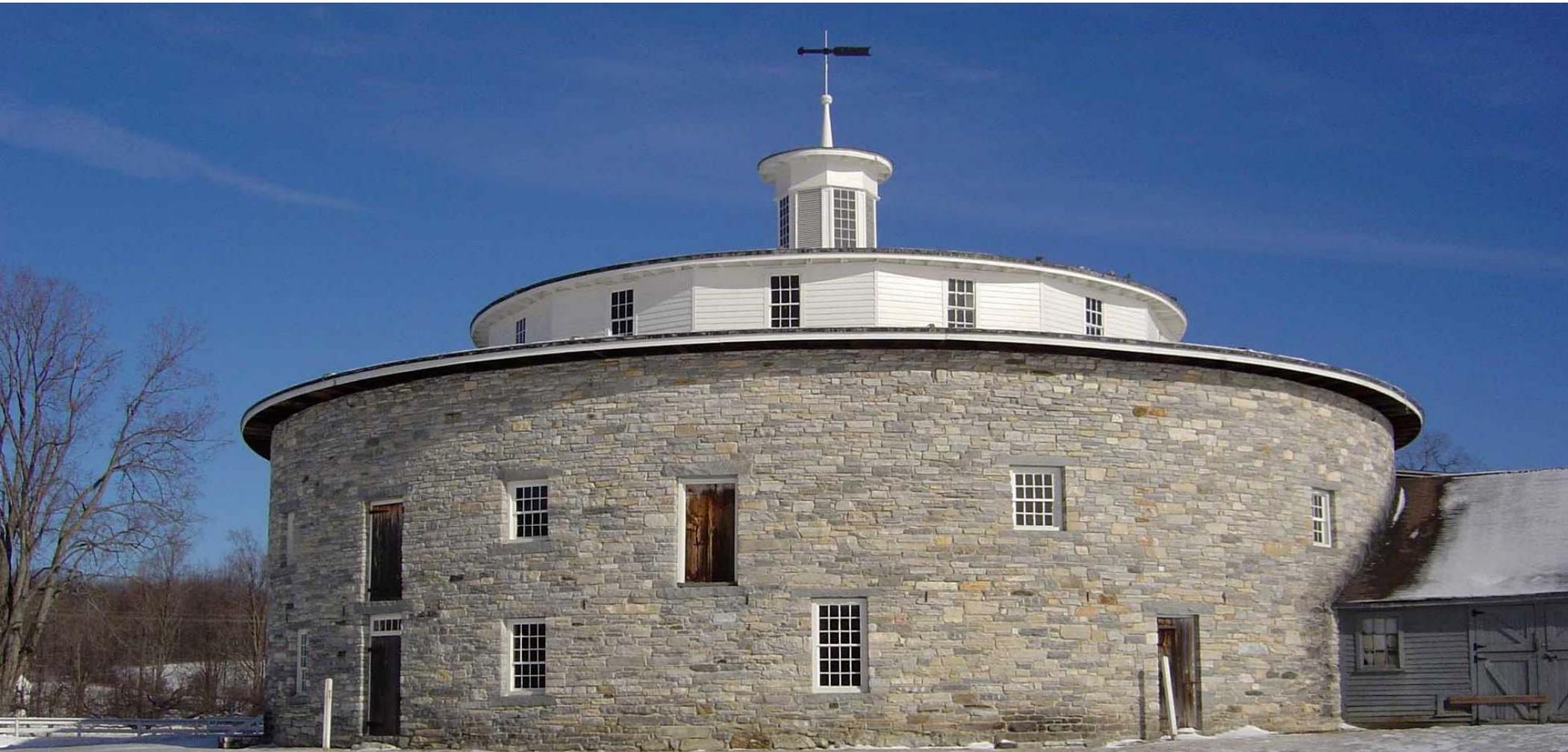
Never Give Up!



- Fighting TB
- Fighting poverty
- Standing up for

PEACE On Earth!





Thank you and Happy Holidays!