

Climbing the Fence: Effective TB Treatment in 2012 and Beyond

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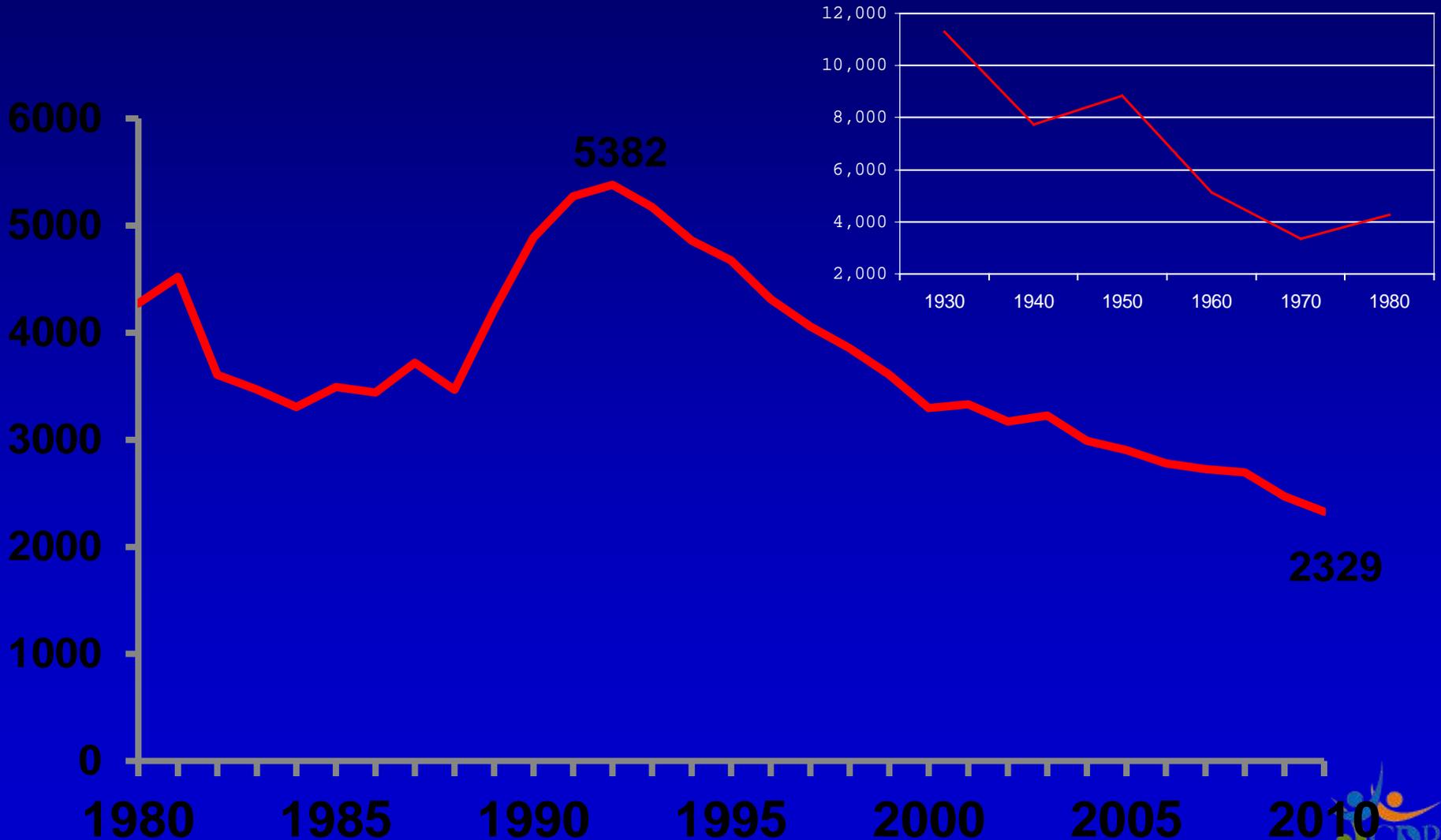
Tuberculosis Control Branch

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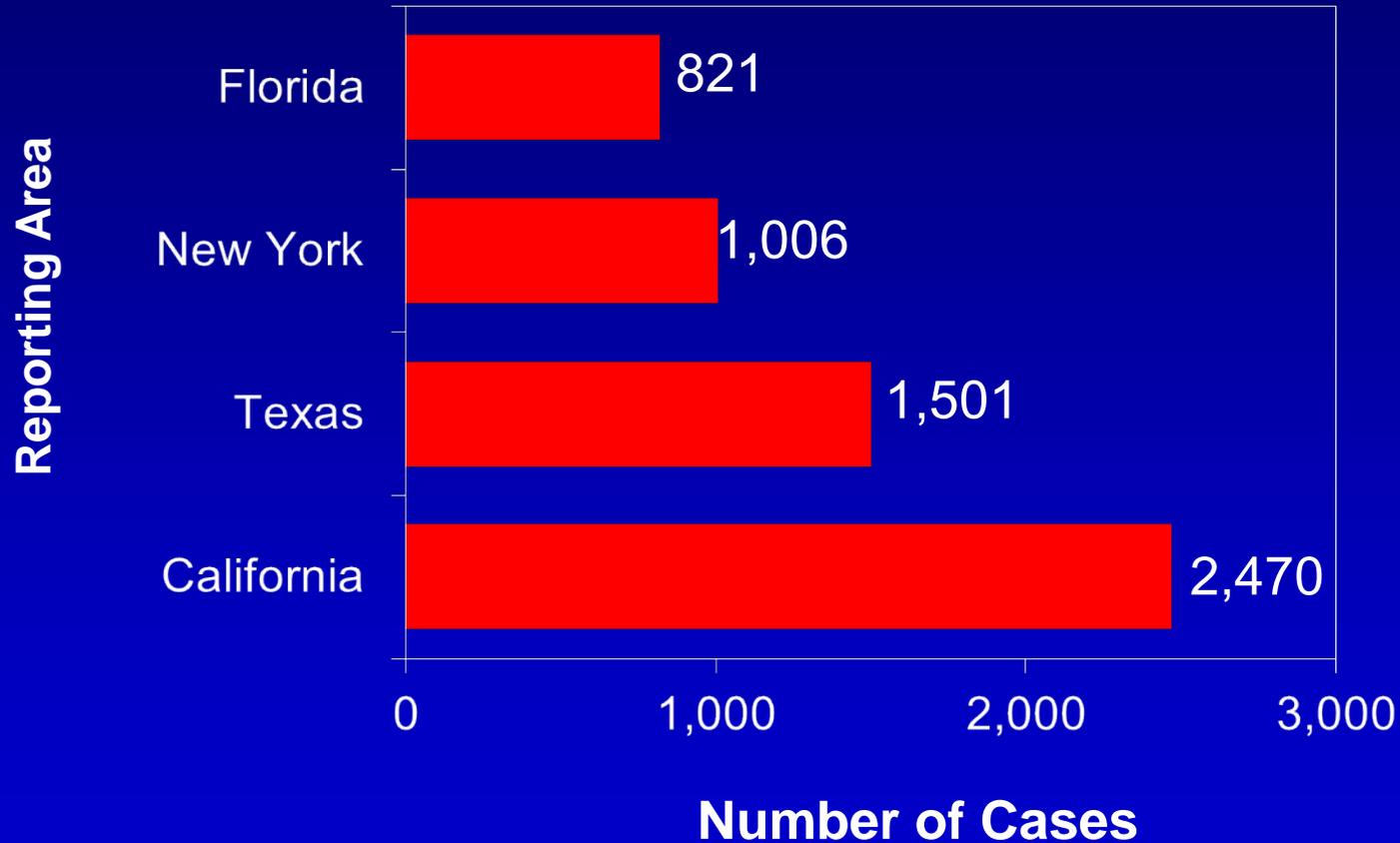
Outline

- Truly short course LTBI regimens
- TB drug access in 2012
- TMC207: the newest drug on the block

Number of Tuberculosis Cases California, 1930-2010



Magnitude of Tuberculosis, 2009



Latent TB Pool in California

TB Infrastructure- going forward

- >100 positions lost
- Case manager case load increased
- Priorities shifted toward....

Too busy fighting alligators to drain the swamp?



Prevention:

Can we afford it?

Can we afford not to do it?

Treatment of Latent TB Infection: 2000 ATS/CDC Guidelines

- INH daily X 9 months A(III)
- Rifampin Daily X 4 months B (II)
- INH/rifampin X 4 months not rated

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- A Preferred: should be generally offered
 - B Alternative: acceptable to offer
 - C Offer when preferred or alternative regimens cannot be given

Rifampin X 4 months

- Randomized controlled trial
- Rifampin 4 mos vs INH 9 mos

RESULTS

- Higher completion rates and lower hepatitis in 4 month rifampin arm

Menzies. Resp Crit Care Med

Evidence: INH x 6,9 or 12 months?

- 28,000 with fibrotic lesions on CXR
- followed for 5 years
- Received 12, 24, 52 weeks or placebo
- 52 weeks prevented the most TB
- but 24 weeks prevented more TB cases /case of hepatitis caused

IUAT Bull WHO 60:1982

Rifapentine

- Rifamycin with
 - High peak serum level
 - Long half-life
 - More bactericidal than rifampin
 - Activity enhanced with INH
 - Meal increases absorption
 - Biliary excretion

Rifapentine Toxicities

- Thrombocytopenia/TTP
- Flu like syndrome (intermittent administration)
- Hepatic injury
- Rare: hemolysis, intestinal nephritis, acute renal failure, dyspnea, shock
- Induces cytochromes P4503A4 and P4502C8/9 (less than rifampin)

PREVENT TB Study:

TB Trials Consortium Study 26

Study design

- Daily INH x 9 months
 - Vs. Once weekly Rifapentine + INH x 12 weeks (DOT)
- Randomized open-label
- 33 months follow-up

Study population

- Contacts and TST converters
- Small group of HIV+, children, TB4s

Findings

- 3RPT/INH is noninferior to 9INH
- Completion rate of 3RPT/INH (81.9%) is significantly higher than 9INH (69.5%)

Source: Sterling et al. International Union Meeting, presented
November 2011

The NEW ENGLAND JOURNAL of MEDICINE

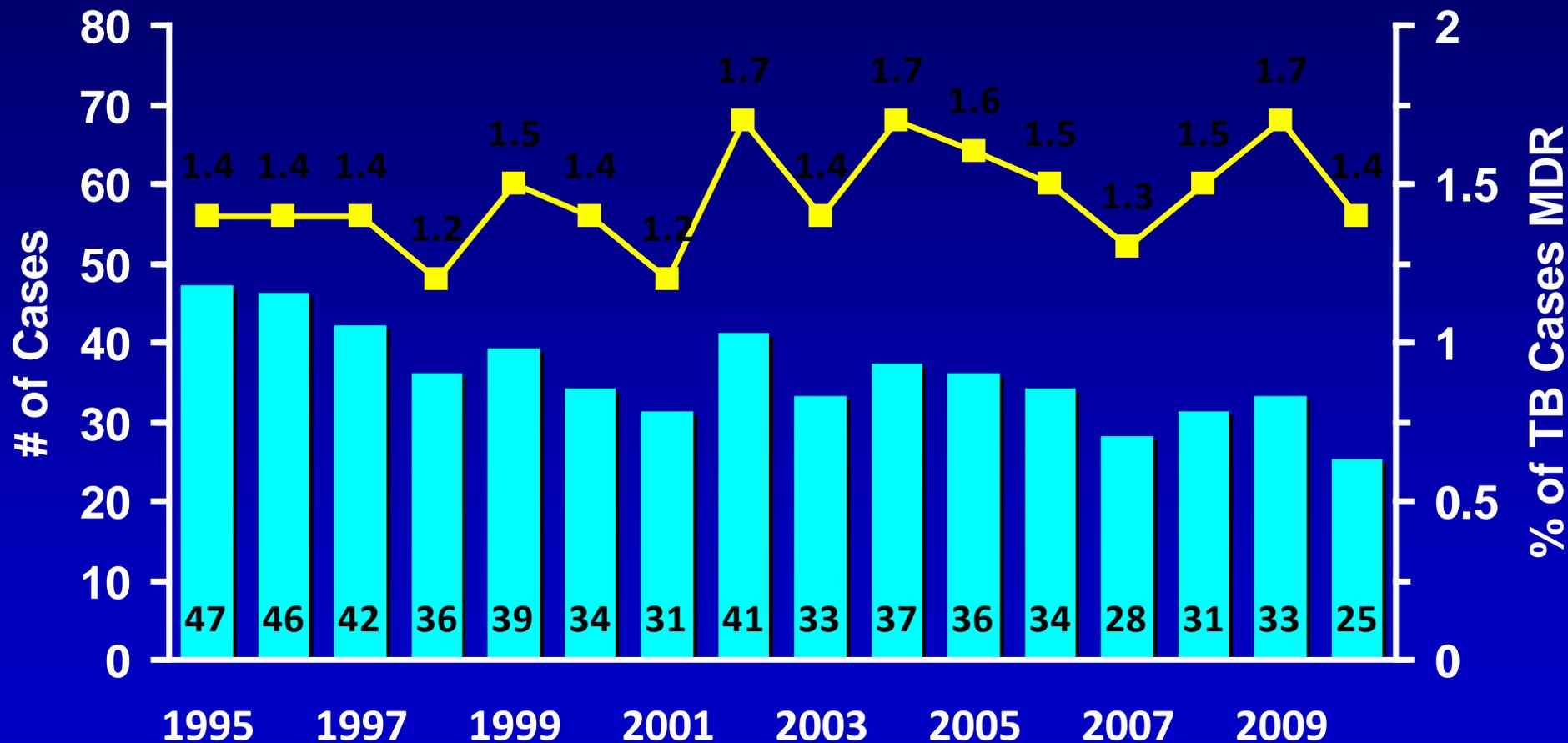
CLINICAL PRACTICE

Latent Tuberculosis Infection in the United States

C. Robert Horsburgh, Jr., M.D., and Eric J. Rubin, M.D., Ph.D.

Horsburgh CR Jr, Rubin EJ. Clinical Practice: Latent Tuberculosis Infection in the United States.
NEJM 2011;364 (15):1441-8.

Tuberculosis Cases with MDR-TB California, 1995-2010



Note: Prevalence \approx 2x incidence

Rifapentine/INH in HIV positive

(Martinson, et al. NEJM July 2011)

Study Design

- Randomized trial in South Africa
- 4 LTBI regimens
- Primary outcome measure: TB or death
- 4 years median follow up

Study Population

- HIV positive with CD4 > 200, not on HAART
- TST positive

Table 2. Rates of Study End Points According to Treatment Group.*

End Point	Rifapentine with Isoniazid Weekly for 12 Wk (N=328)	Rifampin with Isoniazid Twice Weekly for 12 Wk (N=329)	Isoniazid Daily for ≤6 Yr (N=164)	Isoniazid Daily for 6 Mo (N=327)	All Patients (N=1148)
Death or tuberculosis					
No. of cases	37	35	15	41	128
Person-yr of follow-up	1187.5	1219.7	561.0	1143.9	4112.1
Incidence rate per 100 person-yr	3.1	2.9	2.7	3.6	3.1
Crude incidence-rate ratio (95% CI)	0.87 (0.54–1.39)	0.80 (0.50–1.29)	0.75 (0.38–1.38)	Reference 1.0	
P value	0.54	0.34	0.34		

Case Prevention: Which Regimen for Whom?

Problem

INH x 9 months: limited by poor completion

Purpose

Evaluated cost and cost-effectiveness of 4 LTBI regimens

Regimens

- Rifampin x 4 months (SAT)
- Rifapentine and INH x 12 doses weekly (DOT)
- INH daily (SAT) x 9 months
- INH twice-weekly (DOT) x 9 months

Findings

- Rifampin is less costly, increased benefits, cost-saving
- INH and rifapentine is cost-saving for extremely high risk patients and cost-effective for lower risk patients

Source: Holland et al. *Am J Respir Crit Care Med* 2009;179

Who to evaluate and treat?

What is the evidence?

Evaluation of individuals with B-notification
(abnormal CXR)

Percent of
active cases

COST-SAVING

3% and above

COST-EFFECTIVE

4% - 1.5%

Source: Porco et al. *BMC Public Health* 2006;6

Case Prevention

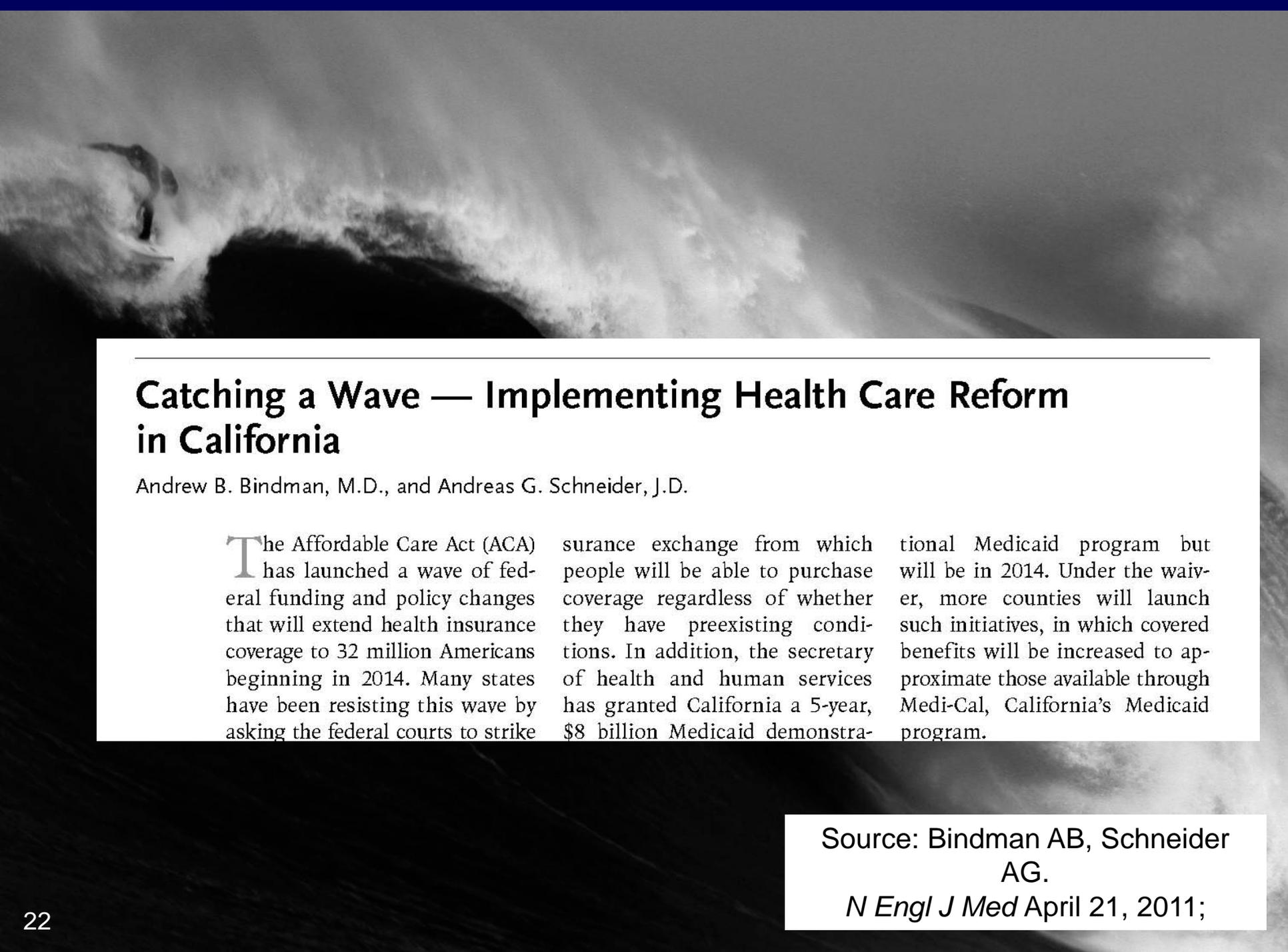
Who should be tested and treated?

- Contacts: all, close, highest risk
- TB4
- Homeless
- School entrants with specific risk
- New arrivers:
 - immigrants
 - refugees
 - student visas
 - worker visas
 - undocumented
- Remote arrivers
- Persons with medical risk factors
- Health care workers
- Others

How can this be accomplished?

What Strategic Direction is Under Consideration?

- Adopt cost-effective diagnostic and treatment approaches
- Abandon ineffective unproven approaches
- Tackle case prevention as cases decline



Catching a Wave — Implementing Health Care Reform in California

Andrew B. Bindman, M.D., and Andreas G. Schneider, J.D.

The Affordable Care Act (ACA) has launched a wave of federal funding and policy changes that will extend health insurance coverage to 32 million Americans beginning in 2014. Many states have been resisting this wave by asking the federal courts to strike

insurance exchange from which people will be able to purchase coverage regardless of whether they have preexisting conditions. In addition, the secretary of health and human services has granted California a 5-year, \$8 billion Medicaid demonstra-

tional Medicaid program but will be in 2014. Under the waiver, more counties will launch such initiatives, in which covered benefits will be increased to approximate those available through Medi-Cal, California's Medicaid program.

Source: Bindman AB, Schneider AG.

N Engl J Med April 21, 2011;

When Drugs are Hard to Come By: Obstacles for Patients Receiving TB Treatment in the United States

Anti-TB Drugs in the United States

First-line

Isoniazid

Rifampin

Rifapentine

Rifabutin*

Ethambutol

Second-line

PAS

Cycloserine

Ethionamide

Levofloxacin*

Moxifloxacin*

Amikacin/kanamycin*

Pyrazinamide Capreomycin

Streptomycin

Third-line

Linezolid

Clofazamine

Imipenem

Clarithromycin

Augmentin

** Not approved by the United States Food and Drug*

Essential Components of a National TB Program

Essential Components of a Tuberculosis Prevention and Control Program, ACET

- Ensure patients who have TB receive appropriate treatment until they are cured
- Treat patients without consideration of their ability to pay

International Standards for TB Control programs

- An uninterrupted supply of good quality anti-TB drugs

Background

Why are we discussing in 2011?

- TB patients and programs have experienced recurring difficulty accessing MDR TB drugs

Issues:

- Drug shortages
- Climbing costs
- Multi-step processes for procurement
- Out-of-reach for uncovered patients

2010 NTCA Survey:

Interruptions in TB Drug Supply

- 21 of 33 (64%) faced challenges obtaining MDR drugs
- 95% experienced nationwide shortage
- 62% indicated drugs too expensive for program

TB Drug Shortages since 2005

- INH
 - Rifabutin
 - Rifapentine
 - Amikacin
 - Capreomycin
 - Kanamycin
 - Streptomycin
- cycloserine
ethionamide
cycloserine

What factors impede the MDR TB drug supply?

The Short List:

- FDA inspection overseas pending
- Materials to make drug in short supply
- Not FDA approved, requires lengthy IRB investigational drug (IND) process
- Drugs have very short time to expiration
- Cost of drugs puts drug out of reach

Which drugs have a tenuous supply?

Drugs

Reason for supply barriers

Amikacin

materials short for production
overseas FDA inspection pending

Capreomycin

company change → huge cost increase

Cycloserine

shortages and cost increase

Clofazimine

manufacturing halted;
restricted to Hansen's disease
requires IND /IRB for each patient

How much does an MDR TB treatment regimen cost?

Drug	Cost per dose	No. doses	Total cost
Capreomycin	\$137.00	137*	\$23,975
Linezolid	\$39.00	790	\$49,770
Levofloxacin	\$4.80	790	\$15,721
Cycloserine	\$12.50	790	\$9876
PZA	\$1.40	790	\$2212

- 8 months of above multidrug regimen with injectable
- Followed by regimen without injectable X 18 months
- Assumes culture conversion at 3 months (treatment: 24 mos. post conversion)

TOTAL MDR TB DRUG COSTS:

\$ 64,352 (340 B clinic) or

\$101,553

(common hospital)

*Injectable given 5 days/week X 3.5 months; 3 days/week X 4.5 months

Less expensive regimen*

Amikacin	\$630
Levofloxacin	\$15,721
Ethionamoide	\$6,952
Ethambutol	\$2048
PZA	\$2212
<hr/>	
TOTAL:	\$27,490

*No linezolid or capreomycin; common hospital cost

Who cannot afford TB treatment?

Patients with MDR TB:

- Working with co-pay or limit
- Not covered: students, temp workers, undocumented
- Indigent non-medicaid eligible

Programs:

- Drug costs larger than many TB program's budget

Who pays? Impact of interrupted supply of MDR TB Drugs

- Impact felt by patient, programs, providers
- TB programs lose credibility; can't meet core functions
- Patient's disease may worsen, acquire further drug resistance, or TB may spread
- Failed response to outbreaks: perfect storm – short on drugs, overwhelmed with disease
- TB not controlled

Case example 1

- 26 yo female on work visa from European country with high MDR/XDR incidence
- Smear negative, culture-positive cavitary MDR TB diagnosed 2 wks prior to travel
- Given 10 day supply of medications through Green Light Committee
- Told by physician- not to worry because “TB medications are free everywhere in the world”

Case example 1 -continued

- On arrival smear positive, 2nd line DST not initially known
- Patient had employer insurance but payment disallowed given pre-existing condition
- Prescribed initial regimen but capreomycin cost to program = \$140.00/dose
- Patient on MDR drugs without injectable > 10 days
- Receiving jurisdiction reports ~10 TB cases/year
- Unable to afford drug regimen, in addition to MD, nurse care, DOT, isolation
- Through diplomatic channels arranged delivery of GLC medications from originating country

Example 2: County X and the perfect storm

- Country X reports ~6-10 MDR TB cases/year
- All MDR TB patients need injectable agent
- Given price of capreomycin, this county changed regimen and pharmacy contract to amikacin
- When amikacin had protracted shortage, TB controller became concerned

Response to Drug Shortages

- Not a new problem (ref. 1994 IUATLD)
- Multiple agencies, programs, individuals exert effort to resolve
- Response has been case by case
- Time from shortage detection to drug reaching patient is long

Possible Solutions

- Drug stockpile (eg. antitoxin)
- CDC to work with FDA and federal partners to establish simple mechanism for accessing drugs
- Patient eligibility unrestricted- all TB patients can access needed drugs
- Centralized IRB mechanism for compassionate use for new or old drugs
- NTCA proposal for partnering with HRSA for funds for MDR TB drugs
- Other proactive solutions

What is on the horizon?

New TB Drugs

TMC207

- Diacon AH, et.al. “The Diarylquinoline TMC207 for MDR TB” NEJM, Vol.360; 2009
- TMC207 400 mg daily X 2 weeks, then 200 mg 3X weekly for 6 weeks vs placebo, added to 5 drug background regimen.
- Negative culture achieved in 48% vs 9% with TMC207 vs placebo
- Reductions in the log CFU count in TMC207 group exceeded placebo group at all time points
- No serious adverse events attributable to the study drug

TMC207

- Inhibits mycobacterial ATP synthase
- Inhibits drug-sensitive and drug-resistant M.tb in vitro
- Exhibits bactericidal activity in vivo in patients with drug-susceptible pulmonary TB

TMC207

- Update at ICAAC 2010
- Median culture conversion 11 weeks vs 18 weeks in placebo group
- 81% in TMC207 group culture (–) at end of trial or last observation vs 57% with placebo

END

World Health Organization

Element 4: AN EFFECTIVE DRUG SUPPLY AND MANAGEMENT SYSTEM

- An uninterrupted and sustained supply of quality assured anti-TB drugs is fundamental to TB control
- A reliable system of procurement and distribution of all essential anti-TB drugs to all relevant health facilities should be in place
- Anti-TB drugs should be available free of charge to all TB patients, both because many patients are poor and may find them difficult to afford, and because treatment has benefits that extend to society as a whole (cure prevents transmission to others)

Questions

- What factors impede supply of MDR TB drug supply to patients in the US?
 - Which drugs have been in short supply?
 - Which drugs are really expensive?
 - Who cannot afford TB treatment?
- What is the impact on patients and programs?
- What are potential solutions for a continuous drug supply in the United States in 2012?

Clofazimine – Special case with implications for new drugs

Indications:

- Intolerant to other second line drugs
- extensive drug resistance (3rd line option)

Time from recommendation to drug supplied in California:

- 8-10 weeks

Clofazimine

- **Lamprene** (generic name clofazimine) manufactured by Novartis, has not been available through traditional pharmaceutical distribution since 2004
- An international compassionate care program with Novartis, WHO and the U.S.
- Clofazimine available for Hansen's Disease and under special circumstances for use in treatment of MDR TB

Procedure to obtain Clofazimine

- Patients to fill out a “simple form “
- Provider completes application through hospital IRB
- Submits individual IND to FDA for patient requiring drug
- **Required Documents**
- FDA Forms:
 - [Form FDA 1571 \(PDF\)](#) | [Form FDA 1571 Instructions](#)
 - [Form FDA 1572 \(PDF\)](#) | [Form FDA 1572 Instructions](#)
 - [Form FDA HFD-590 \(DOC\)](#)
 - [Download forms from the FDA's Official Website](#)
- Doctor's CV
- Current lab results for patient (CBC, chem, sensitivity data)
- Signed informed consent document
- IRB approval letter
 - **For your information -** [Clofazimine Treatment Protocol](#)
- Once IRB approved
- send forms to FDA
- Once approved, clofazamine provided to patient through Hansen's Division/Novartis free of cost
- Usually takes about 10-14 days from time FDA receives fax to arrival of clofazimine