Effect of Substance Abuse on the Treatment of TB Along the Border

Lisa Armitige, MD, PhD
Medical Consultant
Heartland National TB Center

Associate Professor of Medicine and Pediatrics
UT Health Northeast
It starts with.....

The Patient Suspected of Having TB

NOT a TB Suspect!
Pathogenesis of TB
Progression to Disease

Exposure → TB Infection

- 5% First Year
- 2-3% Second Year
- ~0.1% per year thereafter

No Disease (90%)
Who Should be Tested for TB Infection?

- Contacts of persons with active TB
- HIV positive individuals
- Persons with medical risk factors that increase risk of progression to disease
- Targeted testing of high risk persons to identify those at risk of recent infection
Populations at High Risk for TB

- Contacts of infectious persons
- HIV-infected persons
- Foreign-born persons
- Homeless persons
- Those in congregate living situations
- Persons who inject illicit drugs
- Detainees and prisoners
Populations at High Risk for TB

- Contacts of infectious persons
- HIV-infected persons
- Foreign-born persons
- Homeless persons
- Those in congregate living situations
- Persons who inject illicit drugs
- Detainees and prisoners
ORIGINAL INVESTIGATION

Tuberculosis and Substance Abuse in the United States, 1997-2006

John E. Oeltmann, PhD; J. Steve Kammerer, MBA; Eric S. Pevzner, PhD; Patrick K. Moonan, DrPH
Tuberculosis and Substance Abuse in the United States, 1997-2006

Oeltmann et al. Arch Intern Med. 2009;169(2):189-197
TB Rates in U.S.-born, by Race/Ethnicity, United States, 1993–2004

- Black, non-Hispanic
- White, non-Hispanic

Kenneth G. Castro, MD
Stop TB in the African-American Community
May 16-17, 2006, Atlanta, Georgia
Percent of TB Cases in Persons with History of Substance Abuse,* 1993–2004

*Injecting drug, non-injecting drug, or excess alcohol use in year prior to TB diagnosis

**U.S.-born non-Hispanic

Kenneth G. Castro, MD
Stop TB in the African-American Community
May 16-17, 2006, Atlanta, Georgia
# Tuberculosis Outbreak Investigations in the United States, 2002–2008

Kiren Mitruka, John E. Oeltmann, Kashif Ijaz, and Maryam B. Haddad

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 3, March 2011

## Table 2. Tuberculosis risk factors for patients in CDC-investigated TB outbreaks, United States, 2002–2008*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. (%) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>398 (100)</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
</tr>
<tr>
<td>HIV co-infection</td>
<td>46 (12)‡</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Immunosuppression (not HIV associated)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>History of TB</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Incomplete treatment</td>
<td>7 (44)</td>
</tr>
<tr>
<td><strong>Social</strong></td>
<td></td>
</tr>
<tr>
<td>Any substance abuse</td>
<td>233 (58)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>204 (51)</td>
</tr>
<tr>
<td>Nonintravenous drug use</td>
<td>117 (29)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Incarceration history§</td>
<td>126 (32)</td>
</tr>
<tr>
<td>Homelessness</td>
<td>78 (20)</td>
</tr>
</tbody>
</table>

## Table 3. Predominant characteristics of CDC-investigated TB outbreaks, United States, 2002–2008†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) outbreaks†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>27 (100)</td>
</tr>
<tr>
<td><strong>US born</strong></td>
<td>24 (89)</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>22 (81)</td>
</tr>
<tr>
<td>Substance abuse (alcohol/drugs)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Acid-fast bacilli smear positive</td>
<td>17 (63)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>16 (59)</td>
</tr>
<tr>
<td>Incarceration history</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Cavitary disease on chest radiograph</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Homelessness</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (11)</td>
</tr>
<tr>
<td>HIV co-infection</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*TB, tuberculosis; CDC, Centers for Disease Control and Prevention.
†Outbreak had >50% of patients with the select characteristic.
Systematic Reviews and Meta-analyses evaluating tuberculosis and cigarette smoking

- **Slama et al, Int J Tuberc Lung Dis 2007, 11; 1049**
  - “Tobacco and tuberculosis: a qualitative systematic review and meta-analysis”

- **Lin et al, PLoS Med 2007, 4; e20**
  - “Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis”

- **Bates et al Arch Intern Med 2007**
  - “Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis”

- **Conclusions:**
  - Smokers almost twice as likely to be infected with TB and to progress to active disease
  - 2 of 3 studies suggest smokers almost twice as likely to die from TB
Systematic Reviews and Meta-analyses evaluating tuberculosis and cigarette smoking

- Approximately 13% of the TB cases in the world each year may be attributable to tobacco exposure.

- “Tobacco cessation must become an integral part of all TB control programs.”
People who live with HIV and inject drugs have a 2–6-fold increased risk of developing TB compared with non-injectors, and commonly have comorbidities with hepatitis B (HBV) and C viral (HCV) infection.

They are also at increased risk of criminalization and incarceration.

The risk of TB disease in prisons is on average 23 times higher than the level in the general population.
How do we approach the problem?

- Identify cases and get them into care (stop transmission in my community)
- Identify contacts, screen them for infection or disease and get them into care
- Complete the screening/treatment process on all individuals brought into care
TB control measures

Patient diagnosed as having TB disease

Investigation conducted to identify all contacts of person with TB disease

Screen contacts for TB disease and latent infection

Substance abuse–related barriers

Substance abuse is associated with sputum smear–positive disease (ie, infectious) and delayed care seeking (ie, prolonged infectiousness)

Patients who abuse substances are often unwilling or unable to recall names of their contacts

Contacts of patients with TB disease who abuse substances are more difficult to locate and less likely to get screened for TB disease and latent infection

Oelmann et al. Arch Intern Med. 2009;169(2):189-197
Substance abuse in TB patients

- **Tuberculosis Outbreak in Southern Mississippi, 2005-2007**
  - All US-born, all HIV negative, 92% black, 82% substance abuse, 100% pulmonary disease, 170 contacts (45% TST+)

- **Crack Cocaine and Infectious Tuberculosis**
  - Story et al. 2008. EID 14 (9):1466
  - 64% UK-born, 64 % white or black Caribbean, crack use associated with 2.4X higher rate of smear positivity

- **Tuberculosis and Drug Users in Iran**
  - Shamaei et al. IJ STD & AIDS. 2009. 20:320
  - 91% Iranian, 98% men, heroin/opium, 89% sputum smear positive

- **Tuberculosis Outbreak in Nevada and Arizona**
  - Mitrucha et al. Public Health Reports 129: 78
  - 100% Hispanic (born in Mexico), index case deported by ICE (returned), 130 contacts (54.6% TST positive), methamphetamines
Alcohol and TB Disease

Table 2  Differences in disease characteristics between North Carolina tuberculosis cases reporting excess alcohol use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Excess alcohol use</th>
<th>No/unknown</th>
</tr>
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<tbody>
<tr>
<td>Pulmonary (±extrapulmonary)</td>
<td>1227 (92.5%)</td>
<td>3266 (77.2%)</td>
</tr>
<tr>
<td>Extrapulmonary only</td>
<td>99 (7.5%)</td>
<td>964 (22.8%)</td>
</tr>
<tr>
<td>Chest radiographic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavitary</td>
<td>452 (36.8%)</td>
<td>920 (28.2%)</td>
</tr>
<tr>
<td>Non-cavitary</td>
<td>775 (63.2%)</td>
<td>2346 (71.8%)</td>
</tr>
<tr>
<td>Sputum smear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>809 (65.9%)</td>
<td>1495 (45.8%)</td>
</tr>
<tr>
<td>Negative</td>
<td>418 (34.1%)</td>
<td>1771 (54.2%)</td>
</tr>
<tr>
<td>Sputum culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1038 (84.6%)</td>
<td>2270 (69.5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>189 (15.4%)</td>
<td>996 (30.5%)</td>
</tr>
</tbody>
</table>

Chest radiographic, sputum smear, and sputum culture data are for cases with pulmonary involvement only.

Pulmonary Disease
92.3% vs 61.1%

Smear positive
74% vs 57.6%

IV drug use
4.2% vs 0.8%

Tobacco and Treatment Delay

• 605 TB patients
  – 44.8% current smokers,
  – 5.5% ex-smokers,
  – 49.8% never smokers

• Median total delay in seeking treatment was 103 days
  current smokers 133 days,
  ex-smoker 103 days and
  never smokers 80 days.

• Longer delay was more common among current smokers (aOR 2.03, 95%CI 1.24–3.31).
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Oelmann et al. Arch Intern Med. 2009;169(2):189-197
Limited Utility of Name-Based Tuberculosis Contact Investigations among Persons Using Illicit Drugs: Results of an Outbreak Investigation

Rana Jawad Asghar, David E. Patlan, Mark C. Miner, Halsey D. Rhodes, Anthony Solages, Dolly J. Katz, David S. Beall, Kashef Ijaz, and John E. Oelmann

- 18 patients (64% crack use, 78% any drug use)
- INH-resistant
- 187 contacts were evaluated
  - 91 named (8.8% TST positive)
  - 16 church (12.5% TST positive)
  - 61 dialysis center (10% TST positive)
  - 19 ‘observed’ (68% TST positive)
TB control measures

Patient diagnosed as having TB disease

Investigation conducted to identify all contacts of person with TB disease

Screen contacts for TB disease and latent infection

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Oeltmann et al. Arch Intern Med. 2009;169(2):189-197
Treatment of contacts with TB disease and latent infection

Contacts who abuse substances are less likely to initiate, adhere to, and complete treatment

Treatment cure for people with TB disease and complete preventive therapy for contacts with latent infection

Oeltmann et al. Arch Intern Med. 2009;169(2):189-197
Effect of Substance Abuse on Treatment of TB
ANTITUBERCULOSIS DRUGS
(ATS/CDC/IDSA)

• First-Line drugs
  – Isoniazid
  – Rifampin
  – Rifapentine
  – Rifabutin*
  – Ethambutol
  – Pyrazinamide

• Second-Line Drugs
  – Cylcoserine
  – Ethionamide
  – Levofloxacin*
  – Moxifloxacin*
  – PAS
  – Streptomycin
  – Amikacin/Kanamycin
  – Capreomycin

*Not FDA approved for TB
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  – PAS
  – Streptomycin
  – Amikacin/Kanamycin
  – Capreomycin

*Not FDA approved for TB
Regimens for Treating TB Infection

- 9-months of isoniazid (INH) is the preferred regimen
- 6-month regimen of INH is less effective but may be used if unable to complete 9 months
- Rifampin (RIF) daily for 4 months is an acceptable alternative when treatment with INH is not feasible.
- In situations where Rifampin cannot be used, rifabutin for 4 months may be substituted (e.g., HIV-infected persons receiving protease inhibitors, patients receiving methadone).
- INH/rifapentine weekly for 12 weeks by directly observed therapy
Treatment of Patients with TB Disease

• Initiation phase of therapy
  – 8 weeks
  – INH, Rifampin and PZA +/- EMB

• Continuation phase of therapy
  – At least 18 weeks
  – INH and Rifampin
Tobacco and Culture Conversion

Smoking and 2-month culture conversion during anti-tuberculosis treatment


*† Núcleo de Doenças Infecciosas, Centro de Ciências da Saúde, Universidade Federal do Espírito Santo, Vitória, Espírito Santo; †Programa de Pós-graduação em Saúde Coletiva, Centro de Ciências da Saúde, Universidade Federal do Espírito Santo, Vitória, Espírito Santo, Brazil; *†Tuberculosis Research Unit, Department of Medicine, Division of Infectious Diseases, Case Western Reserve University, Cleveland, Ohio, USA

- 714 patients in Brazil
- 2 months daily HRZE then 2 or 4 months daily HR, all evaluated after 2 months
- Excluded if co-morbid conditions: DM, asthma, rheum dz, HIV

➢ Patients who smoked had three-fold greater odds of remaining sputum culture-positive after 2 months of treatment than non-smokers
➢ *Alcohol consumption did not affect culture conversion
Alcohol and LTBI treatment

- **Isoniazid**
  - Alcohol consumption appeared to more than double the rate of probable isoniazid hepatitis
  - Abnormal results were associated with alcohol use, but not with race, age, chronic hepatitis B infection, or HIV infection
  - A study in Spain found that only excessive alcohol consumption and a high baseline ALT concentration were independently associated with isoniazid hepatotoxicity

- **Rifampin**
  - Hong Kong Chest Service study with 49 individuals, 20% of whom used alcohol and 8% of whom used injection drugs, treated with rifampin for 6 months had no symptomatic liver injury
Alcohol and LTBI treatment

- For those with chronic alcohol consumption, or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI may outweigh benefits.

- If LTBI treatment is undertaken, close monitoring is indicated.

- The decision to treat LTBI, or more likely defer, should be carefully made on a case-by-case basis, weighing the risk of progression to TB disease against the risk of INH or rifampin-related DILI.
Alcohol and Hepatotoxicity in the Treatment of TB Disease

Table 5  Dichotomous variables in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=86)</th>
<th>Controls (n=406)</th>
<th>$\chi^2$†</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High alcohol intake</td>
<td>19.8%</td>
<td>4.9%</td>
<td>20.4</td>
<td>4.76 (2.25 to 10.05)*</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>14.0%</td>
<td>3.5%</td>
<td>13.6</td>
<td>4.5 (1.88 to 10.93)*</td>
</tr>
<tr>
<td>Slow acetylator</td>
<td>82.9%</td>
<td>64.2%</td>
<td>5.60</td>
<td>2.72 (1.16 to 6.57)**</td>
</tr>
<tr>
<td>Jaundice in past</td>
<td>11.6%</td>
<td>10.8%</td>
<td>0.001</td>
<td>1.08 (0.49 to 2.35)</td>
</tr>
<tr>
<td>Pyrazinamide in regimen</td>
<td>62.8%</td>
<td>25.1%</td>
<td>44.78</td>
<td>5.03 (2.99 to 8.47)**</td>
</tr>
</tbody>
</table>

*p<0.001; **p<0.01; ***p<0.1 x 10^-7.
†Yates’ corrected $\chi^2$. 

Pande Thorax 1996;51:132-136
Other Substances of Abuse
Rifampin and Opioids

• Methadone
  – Rifampin lowers the serum concentration of methadone by 33-66%  
  – Administration of rifampin to patients on methadone has led to opioid withdrawal in patients on methadone replacement therapy  
  – Need to increase methadone dose and monitor carefully to prevent withdrawal with co-administration of rifampin and methadone

Rifampin and Opioids

- **Codeine**
  - Administration with rifampin leads to decreased biotransformation to morphine (which is responsible for most of the analgesic effects)
  - Decreased serum concentration with rifampin

- **Morphine**
  - 28% decrease in serum levels when given with rifampin
  - Loss of analgesic effect

Rifampin and Benzodiazepines

• **Diazepam**
  - Reduction of half-life by 76%
  - Enhanced total body clearance by 300%
  - May require a 2-3 fold increase in dose for effect

• **Midazolam and Triazolam**
  - Decreased serum concentration to 2-4% of controls
  - Ineffective during co-administration with rifampin

Rifampin and Benzodiazepines

Rifampin Drug Interactions

• It is imperative to be aware of all medications a patient is taking when that patient is placed on rifampin.
Rifabutin

- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.

- Adverse effects: Less severe induction of hepatic microsomal enzymes, therefore, less effect on the metabolism of other drugs.
Rifampin, but not rifabutin, may produce opiate withdrawal in buprenorphine-maintained patients

Elinore F. McCance-Katz, David E. Moody, Sudha Prathikanti, Gerald Friedland, Petrie M. Rainey

\(^a\) University of California San Francisco, San Francisco, CA, United States
\(^b\) University of Utah, Salt Lake City, UT, United States
\(^c\) Yale University School of Medicine, New Haven, CT, United States
\(^d\) University of Washington, Seattle, WA, United States

\(\pm\) Rifampin

\(\pm\) Rifabutin

Fig. 3. Effect of rifampin or rifabutin on ratings of opiate withdrawal severity.
US-Mexico border and TB
# 2014 TB Cases and Substance Abuse

<table>
<thead>
<tr>
<th></th>
<th>Injecting Drug Use</th>
<th>Non-injecting Drug Use</th>
<th>Excessive Alcohol Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td>137 (1.5%)</td>
<td>661 (7.5%)</td>
<td>954 (10.8%)</td>
</tr>
<tr>
<td>Arizona</td>
<td>6 (3.6%)</td>
<td>13 (7.7%)</td>
<td>21 (12.4%)</td>
</tr>
<tr>
<td>Colorado</td>
<td>1 (1.6%)</td>
<td>1 (1.6%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>New Mexico</td>
<td>0</td>
<td>2 (4.3%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Utah</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>California</td>
<td>29 (1.4%)</td>
<td>144 (7.1%)</td>
<td>162 (8%)</td>
</tr>
<tr>
<td>Texas</td>
<td>45 (3.8%)</td>
<td>127 (10.6%)</td>
<td>209 (17.5%)</td>
</tr>
</tbody>
</table>
Risk Factors per RVCT*, New Mexico 2013

n=50

- RVCT*= Report of Verified Case of Tuberculosis
- Other Category unspecified = 10/50 (20%)
- No risk factors identified = 23/50 (46%)

Diana Fortune, TB Program manager
## Border counties - Arizona

<table>
<thead>
<tr>
<th>County</th>
<th>Alcohol Abuse</th>
<th>Injecting Drug Use</th>
<th>Non-Injecting Drug Use</th>
<th>Unemployed</th>
<th>Co-infected with HIV</th>
<th>Homeless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maricopa</td>
<td>6.0%</td>
<td>3.6%</td>
<td>9.5%</td>
<td>19.1%</td>
<td>4.8%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Pima</td>
<td>8.7%</td>
<td>0.0%</td>
<td>4.4%</td>
<td>17.4%</td>
<td>8.7%</td>
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<tr>
<td>Pinal</td>
<td>12.5%</td>
<td>15.6%</td>
<td>25.0%</td>
<td>9.4%</td>
<td>6.3%</td>
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<tr>
<td>Yuma</td>
<td>18.2%</td>
<td>22.7%</td>
<td>45.5%</td>
<td>18.2%</td>
<td>13.4%</td>
<td>4.6%</td>
</tr>
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<td>Border* Counties</td>
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Amanda Baker, Surveillance Epidemiologist
# Border counties – Arizona
(Demographics of TB patients)

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<tr>
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</tr>
</tbody>
</table>

Amanda Baker, Surveillance Epidemiologist
# Border Counties – Texas

(Demographics of TB patients)

<table>
<thead>
<tr>
<th>2011</th>
<th>Alcohol Abuse</th>
<th>IDU</th>
<th>Non-IDU</th>
<th>Diabetes</th>
<th>Unemployed</th>
<th>HIV Co-Infection</th>
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## Border Counties – Texas

**(Demographics of TB patients)**

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# Border Counties – Texas

(Demographics of TB patients)

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Goals in TB Elimination

• Identify cases and get them into care

• Identify contacts, screen them for infection or disease and get them into care

• Complete the screening/treatment process on all individuals brought into care
Barriers to Care Unique to the Border

• Disproportionately on the US-Mexico border:
  – Higher poverty rates
  – Poor access to care (fewer providers, treatment programs)
  – High unemployment (poor insurance coverage) rates
  – Homelessness
  – Legal status concerns

• Stigma and hesitation to seek care
Biggest Barrier to care:
What is important to you? Your patient?

• Difference in focus between care providers and substance abuser
  – Providers are focused on
    • Compliance
    • Co-morbid conditions
    • Pill counts
  – Patient is frequently focused on
    • Avoiding withdrawal
    • Avoiding drugs that make me feel bad or ‘kill my buzz’
    • Next ‘fix’
    • Next meal, a place to sleep
    • Avoiding incarceration
How do we help the patient?

• See addiction as another co-morbidity to be addressed

• Let go of stigma and focus on walking with the patient to care

• Answer the question: “What’s in it for me?”
  – A meal?
  – A bed?
Use of Incentives

CLINICAL RESEARCH STUDY

Financial Reinforcers for Improving Medication Adherence: Findings from a Meta-analysis
Nancy M. Petry, PhD, Carla J. Rash, PhD, Shannon Byrne, PhD, Shehryar Ashraf, MD, William B. White, MD
Cathleen Cardiology Center, University of Connecticut School of Medicine, Farmington.

*The American Journal of Medicine (2012) 125, 888-896*

- Interventions that were
  - longer in duration,
  - provided an average reinforcement of **$50 or more per week**, and
  - reinforced patients **at least weekly**

resulted in larger effect sizes than those that were shorter, provided lower reinforcers, and reinforced patients less frequently.
Acknowledgements
(and my sincerest gratitude for sharing their data)

• Texas
  – Douglas Schuster, Epidemiologist/Program Specialist
  – Jonathon Poe, Epidemiology and Supplemental Projects Group Manager

• Arizona,
  – Amanda Baker, Surveillance Epidemiologist

• New Mexico,
  – Diana Fortune, TB Program Manager (and Nurse Extraordinaire)
Thank you for your attention

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Lisa.Armitige@dshs.state.tx.us
1-800-TEX-LUNG
www.HeartlandNTBC.org