Objectives

- Describe the approach to evaluating the risk of transmission in a Neonatal ICU setting for situations in which infants and adults are identified with TB disease.

- Identify characteristics that increase the risk of TB transmission in a Neonatal ICU setting.

Index Patient — Autopsy-Diagnosed Tuberculosis

- In July 2013, tuberculosis (TB) was diagnosed during autopsy of a post-partum Nevada resident (Patient A).
  - U.S.-born
  - 25 year-old female
  - Delivered premature twins in a Nevada hospital (Hospital 1) in May 2013

- Patient A’s twins (Patients B and C) remained in neonatal intensive care unit (NICU) following birth.
Patients B & C — Neonatal TB

- Patient C died in May before TB suspected
  - No specimens available for testing

- Patient B Testing and Results
  - Patient A’s post-mortem TB diagnosis prompted Patient B’s testing
  - Mycobacterium tuberculosis complex isolated from Patient B's tracheal & gastric aspirates
  - Mycobacterium bovis identified through further laboratory testing

- Prompted TB contact investigation

Mycobacterium tuberculosis complex and M. bovis

- Disease caused by Mycobacterium tuberculosis complex
  - M. tuberculosis
  - M. bovis
  - M. africanum
  - others

- M. bovis
  - During 2008–2012, M. bovis represented 1% (3/273) of all genotyped TB cases in Clark County, Nevada*

Transmission of M. bovis

*Source: Clark County via TB GIMS as of 4/1/2014.
Transmission of *M. bovis*

- Contact investigation did not reveal a person with active TB disease that could explain recent airborne transmission to Patient A
- Reported to have consumed unpasteurized cheese from Mexico

Cattle Isolates from Aguascalientes (Mexico) Matched Cluster Isolates

- Reported to have consumed unpasteurized cheese from Mexico

Transmission Among Cluster Cases

- Contact investigation did not reveal a person with active TB disease that could explain recent airborne transmission to Patient A
- Reported to have consumed unpasteurized cheese from Mexico
Transmission Among Cluster Cases

- Contact investigation did not reveal person with active TB disease that could explain recent airborne transmission to Patient A
- Reported to have consumed unpasteurized cheese from Mexico
- M. bovis possibly transmitted to Patient A via ingestion
Patient A: Timeline — 2013

May: Admitted to Hospital A and delivered Patients B & C

May-June: Visited Patients B & C in NICU

May: Admitted to Hospital A and delivered Patients B & C
Patient A: Timeline — 2013

May: Admitted to Hospital A and delivered Patients B & C

May-June: Visited Patients B & C in NICU

May: Admitted to Hospital A and delivered Patients B & C

June: Visited outpatient clinic with fevers

June: Visited outpatient clinic with fevers

June: Patient C expired

June: Admitted to Hospital A

June: Patient C expired

May-June: Visited Patients B & C in NICU

May: Admitted to Hospital A and delivered Patients B & C

June: Visited outpatient clinic with fevers

June: Patient C expired

May-June: Visited Patients B & C in NICU

May: Admitted to Hospital A and delivered Patients B & C
Patient A: Timeline — 2013

May
June
July
August

June: Transferred to Hospital B by air ambulance
June: Admitted to Hospital A
June: Visited outpatient clinic with fevers
June: Patient C expired
May-June: Visited Patients B & C in NICU
May: Admitted to Hospital A and delivered Patients B & C

Patient A: Timeline — 2013

May
June
July
August

July: Expired, diagnosed with TB on autopsy
June: Transferred to Hospital B by air ambulance
June: Admitted to Hospital A
June: Visited outpatient clinic with fevers
June: Patient C expired
May-June: Visited Patients B & C in NICU
May: Admitted to Hospital A and delivered Patients B & C

Patient A: Timeline — 2013

May
June
July
August

Infectious period: March 15–death
July: Expired, diagnosed with TB on autopsy
June: Transferred to Hospital B by air ambulance
June: Admitted to Hospital A
June: Visited outpatient clinic with fevers
June: Patient C expired
May-June: Visited Patients B & C in NICU
May: Admitted to Hospital A and delivered Patients B & C
Patient B: Timeline — 2013

May: Born at 24-weeks gestation and placed in Hospital A's level III neonatal intensive care unit (NICU)

June: Patient C expired

July: Patient B diagnosed with M. bovis, moved to a NICU respiratory isolation

July: Patient A expired, autopsy-diagnosed TB

August: Patient B expired

Objectives of TB Contact Investigation — Health Care Personnel (HCP)

- Identify and interrupt TB transmission through identification and treatment of contacts with active TB disease or TB infection
- Identify risk factors associated with transmission of TB in Hospital 1
Cluster Case Definitions

**Confirmed case:**
- TB disease in HCP at Hospital 1 with the outbreak strain of M. bovis reported during January 1, 2013–December 31, 2013

**Probable case:**
- TB disease in HCP at Hospital 1 without laboratory confirmation reported during January 1, 2013–December 31, 2013, with epidemiologic linkage to an already identified case.

Identification of HCP Contacts

- Interviews with Patient A’s family
- Interviews with hospital unit managers
- Medical records reviews
- Staff work schedule reviews

Evaluation for LTBI/TB Disease

**LTBI**
- No signs or symptoms of TB disease and
- Contacts with tuberculin skin tests (TSTs) ≥5 mm induration or
- Contacts with positive Quantiferon®-TB tests (QFTs)

**TB Disease**
- Clinical or
- Radiographic or
- Microbiologic
Conversion Definition and Calculating Conversion Rates

- Conversion is presumptive evidence of new TB infection and increased risk of progression to active disease; priority for LTBI treatment

- TB test conversion*
  - Same test performed within 2 years
  - **TST conversion** - increase of ≥10 mm, compared with previous TST
  - **QFT conversion** - positive QFT after a previous negative QFT

- Conversion rates for HCP were calculated as:

\[ \frac{\# \text{ HCP with test conversions (TST or QFT conversion)}}{\text{Total } \# \text{ HCP eligible for conversions}} \]


Risk Factor Analysis - Stratified TB Conversion Rates

- Patient A contact
  - May hospitalization
  - June hospitalization

- Work location

- Occupation

Hospital 1 Exposures — Patients A, B and C

- Patient A
  - March 15–July 1 (death)

- Patient B
  - May 15–July 8 (moved to isolation)

- Patient C
  - May 15–June 1 (death)
### Hospital 1 — Overall Testing Results

<table>
<thead>
<tr>
<th>Number of HCP Contacts Eligible for Testing*</th>
<th>Tested</th>
<th>Positive result</th>
<th>Conversion (TST/QFT)</th>
<th>TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>177</td>
<td>172</td>
<td>21 (12)</td>
<td>16/146 (11)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

* HCP with past positive TB tests were not eligible for testing and were evaluated with symptom screen and chest radiograph; none were found to have TB disease.
### Hospital 1 — Overall Testing Results

<table>
<thead>
<tr>
<th>Number of HCP Contacts Eligible for Testing*</th>
<th>Tested n (%)</th>
<th>Positive result n (%)</th>
<th>Conversion (TST/QFT) n (%)</th>
<th>TB Disease n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>177</td>
<td>172 (97)</td>
<td>21 (12)</td>
<td>16/146 (11)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*20 HCP with prior positive TB tests were not eligible for testing and were evaluated with symptom screen and chest radiograph; none were found to have TB disease.

### Stratified Conversion Rates

#### Exposure Grouping

- **May Hospitalization**: All, RN, RT, MD, Other
- **June Hospitalization**: RN, RT, MD, Other
- **Possible Contact with Patients A, R, and C**: NICU Contact RN, RT, MD, Other

#### Conversion Rates

- **Tested and Eligible for Conversion**
  - May Hospitalization
    - All: 14, RN: 19, RT: 4, MD: 3, Other: 18
  - June Hospitalization
    - RN: 42, RT: 15, MD: 22, Other: 9

- **Conversion Rates**
  - May Hospitalization
    - RN: 7 (37%), RT: 1 (25%), MD: 0, Other: 0
  - June Hospitalization
    - RN: 3 (7%), RT: 5 (33%), MD: 0, Other: 0

- **Total**: 146, Conversion: 16 (11%)
### Stratified Conversion Rates

<table>
<thead>
<tr>
<th>Exposure Grouping</th>
<th>Job Title</th>
<th>Tested and Eligible for Conversion</th>
<th>Conversion</th>
<th>Stratified</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>May Hospitalization</td>
<td>All</td>
<td>14</td>
<td>0 —</td>
<td>0 —</td>
<td>0/44 (18)</td>
</tr>
<tr>
<td>Patient A Contacts</td>
<td>RN</td>
<td>19</td>
<td>7 (37)</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>4</td>
<td>2 (50)</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>3</td>
<td>0</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>18</td>
<td>0 —</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td>June Hospitalization</td>
<td>RN</td>
<td>42</td>
<td>3 (7)</td>
<td>8/88 (9)</td>
<td></td>
</tr>
<tr>
<td>Possible Contact with Patients A, B, and C</td>
<td>RN</td>
<td>19</td>
<td>7 (37)</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>4</td>
<td>1 (25)</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>3</td>
<td>0</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>18</td>
<td>0 —</td>
<td>8/44 (18)</td>
<td></td>
</tr>
<tr>
<td>NICU Contact</td>
<td>RN</td>
<td>42</td>
<td>3 (7)</td>
<td>8/88 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>15</td>
<td>5 (33)</td>
<td>8/88 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>22</td>
<td>0 —</td>
<td>8/88 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>9</td>
<td>0 —</td>
<td>8/88 (9)</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>146</td>
<td>16 (11)</td>
<td>8/88 (9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• NICU respiratory therapists reported changing Patient B & C's ventilator tubing and being sprayed by mist from the tubing
• No masks worn during these procedures
Epidemic Curve of Hospital-Associated *M. Bovis* Cluster Cases (TB Disease) — Clark County, 2013

Conclusions

- Health-care-associated transmission of TB
  - Occurred in the NICU
  - Active TB in NICU respiratory therapist (with DNA match)
  - New TB infections in other HCP

- Probable airborne transmission in Hospital 1
  - From Patient A to staff caring for her in June
  - From Patients A, B, or C to staff in NICU

Conclusions

- Overall, RNs and RTs had a higher rates of TB infection than other HCP

- Among NICU staff, RTs had a higher rate of TB infection than nurses
Limitations

- Inability to interview Patient A
  - Symptoms and duration (cough, fevers, etc.)
  - Amount of time spent in the NICU and level of interaction with NICU staff (nurses and respiratory therapists)
- Contact with Patients A, B, and C difficult to quantify and delineate; work records used as proxy for contact

Recommendations

- HCP maintain a high index of suspicion of TB
  - Diagnose and treat active cases of TB disease
  - Diagnose and treat LTBI
- Educate the public of dangers of consuming unpasteurized milk products
- Strengthen standard precautions for health care workers

Recommendations

- Ensure adequate capacity for rapid TB evaluation in HCP after workplace exposures
- Further research of NICU-specific factors associated with TB transmission
Congenital Transmission of TB\(^1\)

- Hematogenous infection via umbilical vein
- Fetal aspiration of infected amniotic fluid
- Fetal ingestion of infected amniotic fluid


*M. bovis*

- Accounts for 1–2% of all genotyped TB cases in the United States (U.S.)*
- Of 165 cases in U.S. during 1995–2005, 35% were exclusively pulmonary cases suggesting possible infectiousness*


Standard Precautions

- "Minimum infection prevention measures that apply to all patient care, regardless of suspected or confirmed infection status of the patient"*
- Personal protective equipment (PPE) selected based on potential for exposure to infectious agents
  - Gloves
  - Gowns
  - Face masks (procedure or surgical)
  - Goggles
  - Respirators (N-95)
### Literature Review – Infant/Pediatric TB Cases Resulting in Hospital Exposures

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Exposure Setting</th>
<th>Testing Results (pos/total tested)</th>
<th>Subsequent Active TB Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crookette et al. (2004)</td>
<td>NICU</td>
<td>3/328 (1%) 1/79 (1%)</td>
<td>0/70</td>
</tr>
<tr>
<td>Winters et al. (2010)</td>
<td>NICU</td>
<td>2/15 (13%) 0/9</td>
<td>0/10</td>
</tr>
<tr>
<td>Maynard et al. (2004)</td>
<td>NICU</td>
<td>3/322 (10%) 0/91</td>
<td>0/93</td>
</tr>
<tr>
<td>Loerti et al. (2002)</td>
<td>NICU</td>
<td>Not reported 0/36</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sunthi et al. (2001)</td>
<td>NICU</td>
<td>3/144 (2%) 0/99</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lee et al. (1998)</td>
<td>NICU</td>
<td>2/260 (1%) 0/14</td>
<td>4/27 (19%)</td>
</tr>
<tr>
<td>Fadul et al. (1991)</td>
<td>NICU</td>
<td>1/20 (5%) 0/90</td>
<td>Not reported</td>
</tr>
<tr>
<td>Myers et al. (1991)</td>
<td>NICU</td>
<td>0/190 0/90</td>
<td>Not reported</td>
</tr>
<tr>
<td>Total 8 Studies</td>
<td>NICU, 2 other</td>
<td>0–2% 1 (0–1%)</td>
<td>Positive for unknown duration 1 infant case</td>
</tr>
</tbody>
</table>

### HCP Conversions Informed Further Investigation Activities

- High conversion rate among NICU staff resulted in recommendation to test and offer preventive treatment to all NICU infants

<table>
<thead>
<tr>
<th>Risk Grouping</th>
<th>Job Title</th>
<th>Number Tested</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible Contact</td>
<td>RN</td>
<td>42</td>
<td>3 (7)</td>
</tr>
<tr>
<td>with Patients A, B, and C</td>
<td>NICU Staff</td>
<td>22</td>
<td>2 (9)</td>
</tr>
<tr>
<td>RT</td>
<td>22</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>22</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

### NICU Infants Possibly Exposed

- We identified 142 infants possibly exposed: defined as residing in the NICU with Patient’s B or C (before Patient B was moved to respiratory isolation)

- Infant Evaluations
  - Due to immature immune system, need 3 rounds of evaluations
    - Immediately
    - 6 months (age-adjusted for prematurity)
    - 1 year (age-adjusted for prematurity)
  - Evaluations include physical exam, TST, and chest x-ray
### Infant Evaluation Results (n=133)

<table>
<thead>
<tr>
<th>Evaluation Type</th>
<th>Evaluation Round</th>
<th>TST</th>
<th>Chest X-ray</th>
<th>Physical Exam</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Round 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>No signs of TB</td>
<td>No signs of TB</td>
<td>66 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Incomplete</td>
<td>Incomplete</td>
<td>19 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>Incomplete</td>
<td>Incomplete</td>
<td>3 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>No signs of TB</td>
<td>Incomplete</td>
<td>4 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>No signs of TB</td>
<td>Incomplete</td>
<td>0 –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>No signs of TB</td>
<td>Incomplete</td>
<td>0 –</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At least negative TST = 93%

All 3 evals negative = 50%

### Hospital 1 – Annual Staff Testing Results 2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Workers tested</th>
<th>Conversions* ( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>781</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>2011</td>
<td>869</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2012</td>
<td>815</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>2013</td>
<td>499</td>
<td>11 (2.2)</td>
</tr>
</tbody>
</table>

*Defined by Hospital B as a negative TST result followed by a positive TST result using a 10mm cut-off for positivity. Data as of 9/30/13.
Hospital 1’s 2013 Annual TB Testing Data

<table>
<thead>
<tr>
<th>Department</th>
<th>Workers tested</th>
<th>Conversions* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Therapy</td>
<td>29</td>
<td>6 (24)</td>
</tr>
<tr>
<td>NICU</td>
<td>33</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Adult ICU</td>
<td>9</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>13</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Operating Room</td>
<td>36</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Rehab Unit</td>
<td>11</td>
<td>1 (9)</td>
</tr>
<tr>
<td>All Others</td>
<td>368</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Defined by exposed & up to a negative TST result followed by a positive TST result having a 10mm or greater response.

Hospital Exposures — Patients A, B and C

Patient A
Infectious Period: March 15–July 1 (death)

Patient B
Infectious Period: May 11–June 1 (death)

Patient C
Infectious Period: May 11–July 8 (moved to isolation)

Interpretations of TST and QFT Results – By Purpose of Testing in HCP

<table>
<thead>
<tr>
<th>Region of testing</th>
<th>TST</th>
<th>QFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reactor</td>
<td>Never seen in a positive result.</td>
<td>Any result (positive)</td>
</tr>
<tr>
<td>2. Active persistent disease</td>
<td>M. tuberculosis in a positive result (positive)</td>
<td></td>
</tr>
<tr>
<td>3. Known exposure</td>
<td>Any result (positive)</td>
<td>Any result (positive)</td>
</tr>
</tbody>
</table>

Genotyping and Other Laboratory Testing

- Genotyping G03483
- Spoligotype: 664073400007600
- 24-locus MIRU-VNTR: 232224251322 253473253214

What can we do at the program level?

- Draw Attention to TB
- Advocate for Improvements and Resources
- Conduct Research
- Share Lessons Learned
- Make Policy Changes
- Implement and Evaluate Changes