A Continuing Outbreak of Multidrug-Resistant Tuberculosis, with Transmission in a Hospital Nursery

Beth Nivin, Peter Nicholas, Mitchell Gayer, Thomas R. Frieden, and Paula I. Fujiwara

We investigated an increase in cases of multidrug-resistant tuberculosis (MDRTB) at a large urban facility where a prior nosocomial outbreak of MDRTB had occurred. Nosocomial transmission appeared to account for this outbreak as well, including a cluster of cases in a newborn nursery. Seven of 24 patients (29%) described in this investigation may have been exposed in the hospital nursery during an approximately 2-week period. We believe this to be the first documented outbreak of MDRTB in a hospital nursery. The transmission in the nursery demonstrates that the possibility of exposure to unrecognized active tuberculosis in nursery and hospital personnel is always present. Infection and active disease in the infants developed after a relatively short period of exposure. These findings underscore the need for adherence to published infection control guidelines in health care settings.

In the past decade, one of the most serious threats to tuberculosis control in the United States has been outbreaks of multidrug-resistant tuberculosis (MDRTB) in institutional settings [1–3]. From 1990 to 1992, the Centers for Disease Control and Prevention (CDC) investigated outbreaks of MDRTB in several hospitals and a state correctional system. Almost 300 cases of MDRTB were identified in these outbreaks; most patients were HIV-seropositive. The mortality rate was 80–90%, and the median intervals from diagnosis of tuberculosis to death ranged from 4 to 16 weeks [1–7].

One of these outbreaks occurred in an urban hospital in New York City (hospital A) [7]. From 1 January 1990 to 31 December 1992, MDRTB was diagnosed in 16 patients at this facility. All cases involved strains of Mycobacterium tuberculosis resistant to at least isoniazid, rifampin, and streptomycin. Investigators attributed the nosocomial spread to delayed diagnosis and treatment, a lack of negative air pressure in isolation rooms, and inadequately masked tuberculosis patients walking in the hospital wards [7]. Since the CDC investigation, additional MDRTB cases have been diagnosed in or associated with hospital A. This report summarizes the epidemiological investigation of this apparent continuation of the MDRTB outbreak, including the first documented transmission of MDRTB within a hospital nursery.

Methods

Medical record reviews were performed for all patients who (1) had an illness consistent with tuberculosis; (2) had an M. tuberculosis isolate resistant to at least isoniazid, rifampin, and streptomycin (defined as multidrug-resistant); and (3) had tuberculosis diagnosed at hospital A or were exposed to tuberculosis at hospital A between 1 January 1993 and 31 May 1994, after which their tuberculosis was diagnosed elsewhere. Criteria for case selection were consistent with those used in the previous investigation [7].

Information was collected on symptoms of tuberculosis, evidence on chest radiographs (CXRs), bacteriologic results, HIV serostatus, prior admissions at this or other hospitals, prior treatment for tuberculosis, isolation procedures, adherence to isolation, and cause of death, when applicable.

A computerized bed registry was used to identify the bed locations of all case patients hospitalized at this facility from 1990 (original outbreak) through 1994. This list was matched with the Bureau of Tuberculosis Control Case Registry to identify patients hospitalized at this facility whose tuberculosis may have been diagnosed elsewhere, as well as to provide further information on prior tuberculosis treatment, bacteriology, and current treatment outcome.

Tuberculin Skin Test Evaluation of Exposed Infants

Case patients included several infants born at this facility. To search for additional pediatric tuberculosis cases, medical records were reviewed for all infants born at hospital A during the period of suspected exposure and who were in the implicated nursery (29 December 1992 through 11 January 1993; n = 184). The parents or guardians of these infants were notified in June 1995 to have these infants evaluated for possible
Table 1. Cases of tuberculosis and multidrug-resistant tuberculosis (MDRTB) at hospital A during 1990–1994.

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>No. of cases of tuberculosis</th>
<th>No. (%) of cases of MDRTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>94</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>1991</td>
<td>116</td>
<td>13 (11.2)</td>
</tr>
<tr>
<td>1992</td>
<td>115</td>
<td>14 (12.2)</td>
</tr>
<tr>
<td>1993</td>
<td>104</td>
<td>16 (15.3)</td>
</tr>
<tr>
<td>1994</td>
<td>114</td>
<td>11 (9.6)</td>
</tr>
</tbody>
</table>

NOTE. $\chi^2$ for linear trend = 8.46; $P < .01$.

exposure to tuberculosis. When possible, staff from the New York City Department of Health (NYCDOH) contacted the parents or guardians of infants with no documented tuberculin skin test (TST) result; appointments were made for them to undergo TSTs at the hospital A pediatric clinic.

Laboratory Investigation

Mycobacterial isolates from all case patients were identified and processed in the hospital A mycobacteriology laboratory or at the NYCDOH mycobacteriology laboratory. Second-line susceptibility testing was performed at the NYCDOH laboratory, using both radiometric (BACTEC; Becton Dickinson, Sparks, MD) and conventional methods [8, 9]. Drugs tested included isoniazid, rifampin, ethambutol, streptomycin, pyrazinamide, ethionamide, capreomycin, kanamycin, cycloserine, ciprofloxacin, and para-aminosalicylic acid.

DNA fingerprinting was performed on each case patient’s first positive culture at the Public Health Research Institute TB Center [10]. All specimens were coded to ensure confidentiality.

Environmental Investigation

Qualitative analysis in the form of directional smoke testing was performed in randomly selected isolation rooms on two patient floors and in the emergency department. Supplemental disinfection devices, such as germicidal ultraviolet lights and high-efficiency particulate air filters, were inspected by one of the authors (M.G.) to assess whether they were functioning properly and to determine the frequency of maintenance.

Statistical Analysis

Data were analyzed with use of Epi-Info (version 5, CDC) [11]. Categorical variables were compared with the $\chi^2$ or Fisher’s exact two-tailed test.

Results

Epidemiological Studies

From 1 January 1993 through 31 May 1994, 23 patients met the case definition (figure 1). An additional patient had culture-negative, clinically confirmed tuberculosis.

Of the 24 patients, 17 had a documented prior admission to hospital A. For all but one patient, previous admissions overlapped temporally with hospitalizations of patients with MDRTB, whose $M. tuberculosis$ isolates had the same susceptibility patterns. In addition, three case patients had worked at this facility (health care workers [HCWs] 1, 2, and 3) during the period under investigation, but their tuberculosis was diagnosed elsewhere. Of the remaining four patients, two had community exposure from case patients who had been admitted at hospital A during this or the prior outbreak. The other two had no prior hospitalizations at this facility. One of these patients developed MDRTB 8 weeks into a 5-month-long hospitalization.

There were three separate clusters of nosocomial transmission. Figure 1 shows the transmission links identified among these patients.

Cluster A

A cluster of cases appears to have occurred in the nursery/maternity ward. In 1993 and 1994, a total of six cases of culture-confirmed MDRTB in infants were diagnosed in New York City. Three of these infants were born at hospital A within a 2-week period, between 29 December 1992 and 11 January 1993. Approximately 4,000 infants are delivered at this facility annually.

Among all infants born at this facility ($n = 184$) during this 2-week period, the median hospital stay was 2 days (range, 1–26 days). The three infants (median hospital stay, 5 days; range, 3–7 days) developed MDRTB between 4 and 15 months after birth. All three infants had a TST result of $>10$ mm (range, 11–18 mm); none had received BCG. Two infants had a CXR strongly suggestive of tuberculosis; gastric aspirates from both infants yielded $M. tuberculosis$. One infant had tuberculosis of the bone, and $M. tuberculosis$ was recovered from an abscess of the left hip.

All three infants had uneventful full-term deliveries (two vaginal and one cesarean section). All three infants roomed in with their mothers. One infant had neonatal jaundice that required treatment; this infant stayed in the nursery for an additional 2 days after the mother’s discharge. One infant stayed 7 days to be with the mother, who received treatment for post-partum fever.

In addition to these infants, one woman who had delivered at hospital A during this 2-week period went on to develop MDRTB ~1 year later. This woman’s infant was found to have a positive TST (6 mm) and an abnormal CXR, although $M. tuberculosis$ was not recovered from either sputum or gastric aspirate. The infant was treated for active tuberculosis with a regimen based on the susceptibility pattern of the mother’s isolate.
The mothers of the other three infants have no evidence of tuberculosis disease. One mother had delivered a child at this facility on four occasions between 1991 and 1994. Her TSTs were negative in 1991 and 1992. A TST done in September 1993 was recorded as positive (no millimeters recorded); the CXR was normal.

All four mothers were in proximity on the ward; two shared one room and the other two shared the adjacent room.

Two health care workers (HCW 1 and HCW 2) from the nursery, who worked during the period of exposure, developed MDRTB between 14 and 20 months after exposure; both cases were diagnosed at other hospitals. HIV status was not known in either case. TST status was negative for HCW 1 at the time of diagnosis; the medical history of HCW 2 included BCG vaccination and a positive TST.

Seven (29%) of the 24 patients described in this investigation (including the infant who was treated presumptively) may have been exposed in the hospital nursery.

A health care worker (HCW 3) with MDRTB diagnosed in January 1993 reportedly visited the nursery ward on several occasions during the period of exposure. It is not known if this HCW was symptomatic, but sputum was smear-positive for acid-fast bacilli (AFB) and culture-positive for *M. tuberculosis* from January through April 1993.

DNA fingerprint analysis showed that all six of the culture-confirmed cases, as well as that of HCW 3, involved identical *M. tuberculosis* strains.

Excluding the four infants in this cluster, 77 (43%) of the 180 infants present in the nursery during this period had a documented negative TST result; 107 infants could not be located. The names of all infants born at hospital A during this period were compared against the Tuberculosis Case Registry.

No other suspected or confirmed cases of tuberculosis had been reported among these 107 infants as of 31 December 1996.

**Cluster B**

A patient with MDRTB diagnosed during the initial 1991 outbreak was rehospitalized on three separate occasions from 11 December 1992 to 15 January 1993. During these hospitalizations, the patient’s sputum smears were positive for AFB, and *M. tuberculosis* grew in cultures. Although the patient was placed in isolation immediately upon each admission, nursing notes indicated that the patient was nonadherent to isolation protocols and often wandered the halls without wearing a mask.

Eight patients hospitalized in the same section of the ward during the period of 11 December 1992 through 15 January 1993 developed MDRTB within 2–14 months. Seven of the eight cases were diagnosed at hospital A; the eighth was diagnosed at another municipal hospital. Isolates from all eight patients had the same DNA fingerprint as the isolates from the presumed source case.

Two of these patients are believed to have infected other patients during subsequent hospitalizations at hospital A (figure 1).

**Cluster C**

The most recent instance of transmission occurred in December 1993. In November 1993, a 37-year-old HIV-seropositive man was admitted to hospital A; his sputum smear at that time was negative for AFB, but the culture later yielded *M. tuberculosis*. This patient was in cluster B.
The patient was rehospitalized in December 1993, while the November 1993 culture result was still pending. A CXR taken in the emergency department showed cavitation, reported as probably due to pulmonary tuberculosis. It is unclear when the radiograph report was placed in the medical record or was made known to the physician. However, this patient was placed in a room housing four other patients. Approximately 4 days after his admission, a sputum specimen was taken and found to be positive for AFB. The patient was then placed in respiratory isolation.

Three of the patients who had shared the room with this patient during the second admission developed MDRTB (4, 8, and 10 weeks later, respectively). *M. tuberculosis* isolates from all three patients had identical DNA fingerprints. One of these roommates had also been exposed to the source case of cluster B (figure 1) 1 year earlier and thus could have been infected by either source case. The fourth roommate developed MDRTB 14 months later; DNA fingerprint analysis was not performed on the isolate, but the drug susceptibility pattern was the same as that of the other roommates’ isolates.

**Discussion**

We believe this to be the first documented outbreak of MDRTB in a nursery setting. The possibility of exposure to unrecognized tuberculosis in newborn and hospital personnel is always present [13]. Newborn infants are thought to be particularly susceptible to infection with *M. tuberculosis* [13]. The paucity of alveolar macrophages in neonatal lungs and the diminished rates of phagocytosis and killing of bacteria by these cells may allow increased microbial replication by bacteria entering the respiratory tract [14].

Several investigations of exposure in nurseries to individuals with smear-positive, cavitary tuberculosis, involving hundreds of infants, have not revealed tuberculosis infection or disease in the exposed infants [13, 15, 16]. The only reported exposure in a nursery that caused active disease was investigated by Steiner et al. in 1975 [17]. Two infants with uneventful neonatal periods, born 4 days apart and housed in the same nursery, developed miliary tuberculosis at age 2.5 months and 5.5 months, respectively. After a futile attempt to discover a household source case, an epidemiological study of nursery personnel revealed a nurse’s aide with cavitary tuberculosis. None of the other (~1,600) infants exposed to this nurse were found to be infected.

Transmission of tuberculosis depends on many factors, such as the infectiousness of the source case, duration of exposure, condition of the individual infants, and air circulation in the nursery and within that particular wing of the hospital [13]. In this investigation, several of these factors were unknown, which limited our understanding of exposure in the nursery. We were unable to clearly identify a source case for this cluster. HCW 3, who may have been the source, had MDRTB diagnosed at the time of suspected exposure in the nursery and may himself have been exposed during the 1991 outbreak.

A second possibility, although impossible to document, is the source case of cluster B, hospitalized with AFB smear–positive MDRTB during this same period, one floor below the nursery. This patient was known to wander the hospital during his hospitalization, although his exact movements are unknown. It is difficult to speculate about the air movement between the nursery and the floor below because the state of the hospital ventilation system during the suspected period of exposure is not known. A third possibility is that another health care worker or a visitor to the nursery had undiagnosed tuberculosis.

There was a paucity of information regarding the infants born during the period in question. TST results were not available for more than half of the exposed infants, as they could not be located. It is also conceivable that additional cases of MDRTB did occur but were not reported or were reported to a health department other than that of New York City.
It has been recommended [17] that an investigation be carried out among nursery personnel and frequent visitors when any child aged 5 months or younger develops active tuberculosis and for whom a source case cannot be found in the household. Employee Health Services personnel monitor staff members working in high-risk areas for tuberculosis exposure; the nursery should be included in this list. This must apply to all levels of such staff, including those who enter the nursery on an intermittent basis. One possible source case for the nursery exposure, HCW 3, was reported as being in the nursery only to sign in for work assignments. It is important to be vigilant about obtaining information about both patients and visitors with regard to symptoms and history of tuberculosis. This report of MDRTB in four infants (three culture-confirmed and one culture-negative case) in a hospital nursery demonstrates that even a relatively brief period of exposure—in this case, an average hospital stay of 5 days—can lead to the development of active disease.

Implementation of measures recommended in the CDC tuberculosis control guidelines has been shown to be effective in halting transmission of MDRTB to both patients and health care workers [18–20]. Effective prevention includes both administrative and environmental controls, such as rapid identification and treatment of case patients with an expanded drug regimen, effective isolation capability, and ongoing surveillance of health care personnel for active tuberculosis and tuberculosis infection.

Acknowledgments

The authors acknowledge Sonal S. Munsiff, M.D., for her thoughtful review of this manuscript and Yuling Chen and Sharlette Cook for their assistance with graphic presentations.

References