

Epidemiology of a Tuberculosis Outbreak in a Rural Missouri High School

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ABSTRACT. *Objectives.* 1) Demonstrate the importance of maintaining a tuberculosis (TB) control program even in low-incidence areas by studying a TB-contact investigation of a highly infectious high school student in rural Missouri, and 2) discuss factors that perpetuated or contained this school-based outbreak.

Methods. A case review of the index patient, a 15-year-old high school student, established estimates of his level and duration of infectiousness. Contact investigations of his household ($n = 5$), high school ($n = 781$), and school bus ($n = 67$) were administered according to guidelines established by the Centers for Disease Control and Prevention. High school students were stratified further based on classroom exposure, and relative risks were calculated for each risk group.

Results. The case review revealed that the index patient had evidence of a pulmonary cavity on chest radiograph 6 months before his TB diagnosis. Of the 5 household contacts, all were infected and 3 (60%) had developed active TB disease. Of the 781 high school students sought for TB screening, 559 (72%) completed testing, and 58 (10%) were PPD-positive. Sixty-seven bus riders were sought for testing and 7 (19%) were purified protein derivative (PPD)-positive, with 1 bus rider subsequently diagnosed with active disease.

Risks were calculated based on classroom and bus exposure to the patient. The relative risks for a positive PPD were 3.2 for attending any class with the patient ($n = 25$), 4.2 for classes with less ventilation ($n = 21$), and 5.7 for ≥ 3 classes ($n = 7$) with the patient. A total of 62 students started treatment for latent TB infection, and 49 have completed it. Forty-two of these students received directly observed therapy through the local public health agency and the high school.

Conclusion. This investigation demonstrated widespread adult-type transmission from a pediatric TB case with a 6-month delay in diagnosis. Several actions contributed to the success of this investigation, including rapidly mobilizing the public health system, centralizing follow-up, and on-site testing and treatment with directly observed therapy. Pediatricians need to maintain awareness of TB and risk factors in children, even in low-incidence areas. Prompt diagnosis would have reduced the severity of illness in the patient and potentially prevented widespread school-based transmission. Public health authorities must maintain an infrastructure to respond to large TB outbreaks. *Pediatrics* 2004; 113:e514–e519. URL: <http://www.pediatrics.org/cgi/>

content/full/113/6/e514; tuberculosis disease, latent tuberculosis infection, directly observed therapy, school-based outbreak, contact investigation.

ABBREVIATIONS. TB, tuberculosis; LTBI, latent TB infection; MO DHSS, Missouri Department of Health and Senior Services; CXR, chest radiograph; PPD, purified protein derivative; DOT, directly observed therapy; AFB, acid-fast bacilli; LPHA, local public health agency; HIV, human immunodeficiency virus; RR, relative risk.

Pediatric tuberculosis (TB) is rare in many parts of the United States, particularly in low-incidence areas.¹ The rate and/or number of pediatric TB cases can serve as a barometer of a TB-control program. A state or area with effective TB-control and -contact investigations should have little or no pediatric TB. Since 1994, Missouri has had <18 cases of active disease and ~250 cases of latent TB infection (LTBI) in children reported per year. The overall rate of TB in Missouri has declined from 4.9 in 100 000 in 1994 to 2.4 in 100 000 in 2002. Missouri receives ~5000 to 7000 LTBI reports per year.² Two thirds of diagnosed active-disease cases were reported from Missouri's 3 major metropolitan areas (St Louis, Kansas City, and Springfield) in 2002. In rural areas of Missouri, TB is rare and generally occurs more in the ≥ 65 age group (Missouri Department of Health and Senior Services [MO DHSS], unpublished data from the Tuberculosis Information Management System, MO DHSS TB Control Program, 2002). In young children, TB is rarely infectious. They are much less likely to have a cough forceful enough to aerosolize infectious bacilli. Sputum specimens must be obtained by gastric wash or bronchoscopy. In contrast, older children and adolescents with TB can be very effective transmitters.^{3,4} The following describes a pediatric TB case in rural Missouri and the subsequent school-based outbreak.

In May 2001, a case of highly infectious TB was diagnosed in a 15-year-old high school student in rural Missouri. The student had presented to his primary care provider in December 2000 with upper respiratory symptoms and a frequent cough. The chest radiograph (CXR) revealed a right upper lobe infiltrate and small cavitory lesion. He was diagnosed with pneumonia and treated with a 10-day course of a broad-spectrum antibiotic. Between December 2000 and May 2001, his symptoms (fatigue, fever, cough, hemoptysis, and weight loss) progressively worsened. His medical records indicate 10 visits to area health clinics. Diagnoses included up-

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PEDIATRICS (ISSN 0031 4005). Copyright © 2004 by the American Academy of Pediatrics.

per respiratory infection, bronchitis, depression, and anemia. He was ultimately referred to a pediatric hematologist in May 2001, who noted a positive purified protein derivative (PPD) of 25-mm induration. He then was referred to an area pediatric pulmonologist. The pulmonologist, based on CXR and physical examination, suspected active TB and prescribed 4 drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) and directly observed therapy (DOT). Sputum specimens showed numerous acid-fast bacilli (AFB) on smear. This initial information was reported to the local public health agency (LPHA) nurse and triggered an investigation of contacts at both home and school. Cultures subsequently revealed *Mycobacterium tuberculosis* sensitive to all first-line antibiotics. His human immunodeficiency virus (HIV) test was negative.

METHODS

Case Review

On May 23, 2001, the regional TB nurse case manager for the MO DHSS began coordinating the investigation with the LPHA nurse, including the medical record review, case interview, and history. The patient's CXR on May 15, 2001, showed a large, right upper lobe cavity and infiltrates in the right lower lobe and left upper lobe (Fig 1). Based on the initial review, the index patient was believed to be highly contagious. Evidence of contagiousness included abundant AFB on sputum smear, hemoptysis, cavitary CXR, and frequent cough. Other symptoms included fever, night sweats, and a weight loss of 25 pounds over 6 months. To suspend additional transmission, the index patient was instructed to remain isolated at home and to not attend school until 3 consecutive AFB-smear-negative sputa were obtained. His dosages of isoniazid, rifampin, pyrazinamide, and ethambutol were being directly observed by nursing staff at the LPHA.

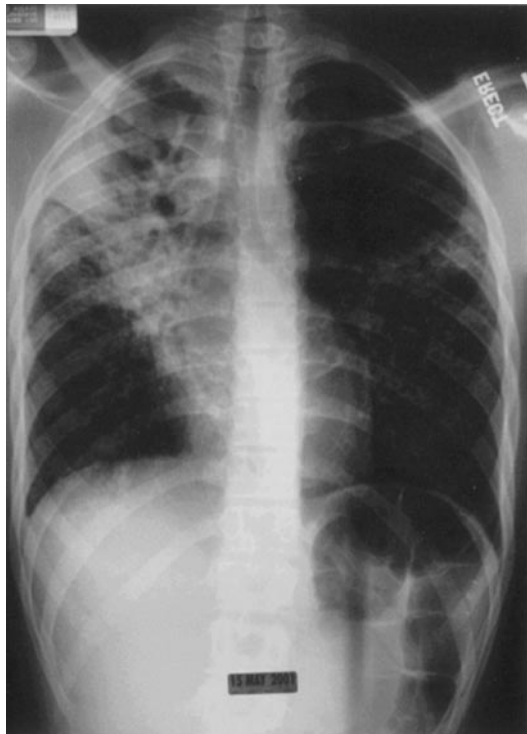


Fig 1. CXR of the patient in May 2001, at the time of diagnosis.

Contact Investigations

Home

MO DHSS and LPHA nurses collaborated on an investigation of all household contacts. The household comprised the patient's mother, father, and 3 younger siblings (ages 12 years, 9 years, and 5 months). All the household members were screened for signs and symptoms of active TB. The parents and all siblings received Mantoux skin tests. Household contacts with induration of at least 5 mm were considered positive. Any household member with a positive skin test was referred for a CXR and physical examination. Although asymptomatic, the infant was immediately referred for CXR and examination per Centers for Disease Control and Prevention recommendations.³ LPHA and MO DHSS conducted a lengthy interview of the index patient to identify 1) contacts and 2) a possible source case.

School

Interview of the index patient indicated that his schoolmates were his primary social contacts. Because of the severity of his illness, he had had poor attendance, missing ~48 days of school during the 2000-2001 school year. The timing of the student's diagnosis allowed just enough time to conduct widespread testing during the last week of the school year. A database of all students and faculty including names, guardian names, addresses, and telephone numbers was obtained from the technology director at the high school. This database was merged with a template from the statewide infection registry and provided the tracking mechanism used in this investigation. The names and class schedules of all students sharing a class with the index patient were obtained. All students were provided with permission slips to be signed by their guardians, a TB fact sheet regarding TB disease and the potential for transmission, and a symptom-review checklist to be completed. Every student was considered a potential contact, and any person with an induration measured at ≥ 5 mm were evaluated for LTBI. For students with PPD readings between 5 and 10 mm, additional detailed information on exposure to the index patient was considered in their LTBI diagnosis to rule out the possibility of a false-positive. LPHA and hospital infection-control nurses skilled in administering and reading skin tests participated in the screening. The regional MO DHSS nurse was also on site to assist with skin tests, coordinate evaluation of positive skin tests and/or positive symptoms, and participate in public/media-relations activities. Sputum kits were available on site as needed and distributed to persons with positive symptoms and a productive cough.

School Bus

The patient used school bus transportation. A bus contact list was obtained from the school. All children and drivers were notified for testing in the same manner described above. This testing was held separately at the LPHA.

Treatment of Infected Contacts: School and School Bus

A pediatric pulmonologist and pediatric nurse practitioner evaluated all student contacts with a positive PPD identified during initial testing. These students were referred for CXRs either through their primary care physician or under standing orders from this pulmonologist. CXRs were provided through MO DHSS diagnostic services program for those without the ability to pay. All CXRs were obtained and reviewed by the nurse practitioner and physician. The clinical evaluation included baseline liver enzymes, pregnancy tests for females, and HIV counseling and testing. Those diagnosed with LTBI were placed on isoniazid, 15 mg/kg (maximum: 900 mg) twice weekly (DOT) for 9 months. Plans for DOT were arranged through the LPHA during the summer and on site at the high school (or elementary school for school bus contacts) once school resumed. All information resulting from clinic testing was entered into the tracking database.

Follow-up

The contact investigation included follow-up testing at least 3 months after the last exposure to the index patient. The process for the initial testing was repeated in mid-September to correspond with resumption of the fall school session. Graduating seniors were instructed at the time of initial testing of the need for fol-

low-up testing and then contacted by mail 3 months later. School bus riders were notified by mail and telephone and offered testing at the LPHA. Results also were entered into the tracking database. The MO DHSS arranged for all CXRs to be reviewed by the pediatric pulmonologist. New positives were offered DOT during school hours.

Other Contacts

Additional tested contacts included potentially exposed teachers, health care workers, neighbors, friends of siblings, and other concerned community members requesting tests. The index patient did not participate in any sports, after-school clubs or organizations, church groups, or other extracurricular activities because of his poor health.

Analysis

School and school bus contacts were stratified into risk groups. School exposures were stratified based on class attendance. Students in ≥ 3 classes with the index patient were considered at greatest risk. Students in typical classroom settings were considered at greater risk than those with enhanced ventilation (ie, gym and art classes). Study hall was considered a lower risk also, because attendance was optional. Risks to students in any class with the index patient were compared with the rest of the school. Two students were both on the bus and in school with the index patient. These 2 were evaluated as part of the bus risk group. We estimated the relative risk (RR) of TB infection according to estimated exposure to the index patient: riding the bus with the index patient; sharing any class; sharing class in rooms with standard ventilation; and sharing ≥ 3 classes. RRs were calculated by comparing positivity rates for exposed students with rates for those without exposure. Taylor-series 95% confidence intervals were calculated to assess the statistical significance of RRs. Fisher's exact test was used if any risk group total was ≤ 5 . Numbers of students with and without risk and the number with and without positive skin tests were entered into the Epi Info 6 program for automated calculations of RRs and confidence intervals.⁵

RESULTS

Source-Case Investigation

Initially, the index patient had no obvious risk factors for TB. After several interviews, LPHA nurses learned that during the summer of 1999 he had stayed in another state with an aunt who was ill. Through interstate communication, MO DHSS discovered that this aunt had active TB during his stay but was not diagnosed until after he left. The aunt's name was obtained and her diagnosis verified through the TB disease registry. Both the aunt's and the index patient's organisms were sensitive to all first-line antibiotics. Had the aunt's isolate been preserved, the epidemiologic link could have been confirmed through genotyping. However, with no other known contact to a TB case and little or no TB in his hometown, we surmised that his aunt was the likely source case. The MO DHSS had no record of interstate communication from 1999 indicating that this boy had been a contact to an active case of TB.

Household Contacts

All household members were tuberculin-skin-test-positive except the infant. As discussed earlier, the infant immediately received a CXR, which showed right middle lobe infiltrates. Gastric aspirates were obtained and found to be AFB-positive on smear and subsequently grew *M tuberculosis*. He was placed on isoniazid, rifampin, and pyrazinamide. He received systemic steroid therapy for severe endobronchial disease during his course of treatment for TB. The

9-year-old had a 20-mm PPD, and his CXR revealed lymphadenopathy. He also was placed on isoniazid, rifampin, and pyrazinamide. Typically, TB cases are started on a 4-drug regimen including ethambutol in the event that the organism is drug-resistant. However, because the index patient was pansensitive at the time of diagnosis, the pediatric pulmonologist started them on a 3-drug regimen. The 12-year-old brother had a 20-mm PPD with a normal CXR. He was placed on isoniazid for 9 months. The mother had a 16-mm PPD with a CXR revealing a fibrotic area in the left apex. She was not symptomatic; however, a sputum specimen was obtained through sputum induction. She was smear-negative but culture-positive for *M tuberculosis*. Although susceptibility results were available on the index patient, her physician conservatively started her on the standard regimen of 4 drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) until her isolate was confirmed to be pansensitive. The father had a 15-mm PPD and a normal CXR. He was placed on isoniazid for 6 months.

School and School Bus RRs

Southwest Missouri is a primarily rural area. The high school has a population of 781 students and 87 faculty. There are 7 periods in the day in addition to a lunch hour. All students were sought for testing. See Table 1 for results of the screening.

All students were classified into mutually exclusive risk groups based on their class schedule and exposure. A total of 106 students were in ≥ 1 class with the index patient and completed testing. Of these, 24% ($n = 25$) had a positive PPD. Period 3 was art class the first semester and gym class the second semester. These classes were in rooms with enhanced ventilation. Period 4 was study hall (with optional attendance). After excluding the students that were in only periods 3 and 4, there were 66 students who shared at least one class with the index patient during periods 1, 2, 5, 6, and 7 and completed testing. Thirty-two percent ($n = 21$) had a positive PPD. Thirteen students shared ≥ 3 classes with the index patient and completed testing. Fifty-four percent ($n = 7$) of those students had a positive PPD. A total of 27 students rode the bus with the index patient and completed testing. Twenty-six percent ($n = 7$) had positive PPDs. RRs and confidence intervals are shown in Table 2.

Treatment of LTBI

Of the 65 infected school and school bus contacts, 95% ($n = 62$) agreed to treatment of their LTBI. The

TABLE 1. Results of the Initial and Follow-up Screening of High School Students and Staff

	Initial Testing (May 2001)	Follow-up Testing (September 2001)
No. sought for testing (students and bus riders)	848	798
No. tested	740	586
No. with disease	1	0
No. with LTBI	49	16

TABLE 2. RRs and Confidence Intervals for Results of High School Students and Bus Riders

Persons Tested	No. Sought for Testing	No. Completing Testing	Induration >5 mm	RR	95% Confidence Interval
All students*	781	559	58	NA	NA
All bus riders	67	27	7	2.5†	1.26–4.93
Students in ≥1 class	137	106	25	3.2	2.0–5.18
Students in periods 1, 2, and 5–7	80	66	21	4.2	2.6–6.75
Students in ≥3 classes	14	13	7	5.7	3.26–10.13

NA indicates not applicable.

* Two students rode the bus and attended school but were not in class with the index patient. The 2 were counted as bus riders when calculating RRs.

† RR compares risk of riding the bus with the index patient versus attending school with index patient.

3 that refused treatment were encouraged to reconsider treatment both by letter and telephone contact. Their pediatricians were also notified of their PPD results. One contact from the bus had an abnormal CXR but was asymptomatic. This contact was treated for active disease. During the summer, students under treatment came to the LPHA twice a week. Once school resumed, LPHA nurses directly observed treatment at the high school. Children infected on the school bus were directly observed through the LPHA during the summer. The LPHA nurse went to the elementary school once classes resumed. Table 3 summarizes the results of treatment of LTBI for the 65 positive contacts.

CONCLUSIONS

There is great potential for extensive transmission of TB in a high school setting by an adolescent index patient. Schools are the most common site reported for community-based outbreaks. Contributing factors include delay in diagnosis, sustained contact, and inadequate ventilation or overcrowding.⁶ Despite evidence that sustained contact and classroom ventilation played a role in transmission, the most significant contributing factor in this outbreak was the delay in diagnosis of active TB. Medical record review indicates that this patient had a CXR on December 20, 2000, that showed a small cavitory lesion in the right upper lobe. However, this patient was not diagnosed with active TB at that time. Subsequently, the patient had at least 10 clinic visits at various sites in the community and was diagnosed with upper respiratory infections, depression, anemia, and pneumonia. The school nurse notes conversations with the family and medical community regarding this patient's continuing decline in health status. The diagnosis ultimately was not made until May 2001, which represents a 6-month delay in diagnosis after the initial cavitory CXR. This delay likely contributed to transmission of TB, particularly among classmates during the second semester of the

school year. The infant sibling, born during this 6-month period, also could have completely avoided exposure and disease had the patient been diagnosed with the first cavitory CXR. To assist area pediatricians in familiarizing themselves with TB during this outbreak, the LPHA distributed the latest Centers for Disease Control and Prevention TB diagnosis and LTBI treatment recommendations. This outbreak demonstrated that, even in low-incidence areas in which pediatric TB is rare, pediatricians must remain cognizant of TB, continue to screen all children for risk factors for TB, and test those at risk (see Table 4).⁷ By promptly diagnosing active TB and preventing TB in children with LTBI, pediatricians will continue to have a key role in preventing school-based outbreaks.

The delay of diagnosis likewise impacted the severity of his illness. The index patient was not able to return to school until October 2001, when sputum cultures were negative. In the United States, most patients' smears and cultures convert to negative in <2 months. This patient remained smear-positive until August 2001 (4 months) and culture-positive until October 2001 (6 months). Clinical trials for 6-month TB treatment regimens have shown that cavitation on initial CXR and positive cultures after completion of 2 months of therapy are associated with a nearly 22% rate of failure/relapse, compared with 2% rate of failure/relapse in HIV-negative patients when neither factor exists. Guidance since has changed to recommend extending treatment at least 3 months for delayed culture conversion to prevent relapse or future reactivation.⁸ The index patient in this outbreak was ultimately treated for 12 months.

The transmission of TB followed a predictable pattern at the high school. Students with the most exposure, those in ≥3 classes with the patient, were most at risk (RR: 5.7). Documented previous school-based outbreaks have revealed similar findings. In South Carolina, an outbreak among junior high students found 74% with LTBI if sharing 1 class, 91% if sharing 2 classes, and 100% if sharing 3 classes.⁹ In this outbreak, the risk of transmission was reduced in classes that were in rooms with increased ventilation (art and gym). These findings are consistent with other outbreaks during which confined air space promoted transmission, such as those aboard ships, in factories, and in bars.^{4,10}

Testing the entire high school led to the identifica-

TABLE 3. Results of LTBI Treatment for Infected Contacts

	Directly Observed	Self-Administered
Started treatment	42/65 (65%)	20/65 (31%)
Completed treatment	36/42 (86%)	13/20 (65%)
Stopped treatment	4/42 (10%)	2/20 (10%)
Still on medication	2/42 (5%)	1/20 (5%)
Unknown completion status	0/42 (0%)	3/20 (15%)

TABLE 4. American Academy of Pediatrics Recommendations for Pediatric Screening for TB⁶

Children for whom immediate skin testing is indicated	Contacts of persons with confirmed or suspected infectious TB (contact investigation), including children identified as contacts of family members or associates in jail or prison in the last 5 years. Children with radiographic or clinical findings suggesting TB. Children immigrating from endemic countries (eg, Asia, Middle East, Africa, or Latin America). Children with travel histories to endemic countries and/or significant contact with indigenous persons from such countries.
Children who should be tested annually for TB	Children infected with HIV.
Children who should be tested every 2–3 years	Incarcerated adolescents. Children exposed to HIV-infected people, homeless people, residents of nursing homes, institutionalized adolescents or adults, users of illicit drugs, incarcerated adolescents or adults, and migrant farm workers (includes foster children with exposure to adults in these high-risk groups).
Children who should be considered for TB skin testing at 4–6 and 11–16 years of age	Children whose parents immigrated (with unknown tuberculin skin-test status) from regions of the world with a high prevalence of TB; continued potential exposure by travel to the endemic areas and/or household contact with persons from endemic areas (with unknown TB skin-test status) should be an indication for repeat TB skin testing. Children without specific risk factors who reside in high-prevalence areas; in general, a high-risk neighborhood or community does not mean that an entire city is at high risk; it is recognized that rates in any area of the city may vary by neighborhood or even from block to block; physicians should be aware of these patterns in determining the likelihood of exposure; public health officials or local TB experts should help clinicians identify areas that have appreciable TB rates.

tion of infected students that may otherwise have been missed; however, it presented challenges in tracking the results of hundreds of tests. A key factor in the success in the tracking and treatment of the infected contacts was our single medical resource for care of all of them. Tracking and case management would have been greatly complicated if all the infected contacts obtained follow-up from an assortment of private providers with varying levels of expertise in TB treatment. Because one pulmonologist/nurse practitioner team agreed to see all infected contacts, the continuity of treatment and communication among the parents and students was enhanced greatly, and the LPHA could implement a DOT program (MO DHSS memorandum, "After Action Review/Lessons Learned," February 21, 2002). Public health workers and pediatricians must work closely in outbreaks involving children to maintain continuity of care among infected contacts.

Overall, 84% of contacts completed initial testing, and 67% completed follow-up testing (Table 1), which exceeds the national average of 55%.¹¹ On-site testing significantly increased compliance with follow-up testing. The school bus testing results, when compared with the school's results, were less encouraging at 40% (Table 2). For high school students tested on site, contacts were 3.7 times more likely to present for retesting than school bus contacts ($P < .01$), indicating that off-site testing was a significant barrier to completing follow-up testing. After the results of the second round of testing, the students who had not received the second test were contacted by telephone on multiple occasions. If contact could not be made with an adult in the home, a letter was sent stressing the need for follow-up. The students at highest risk for infection, identified through the risk gradient shown in Table 2, received a letter from the

MO DHSS. After these efforts, an additional 87 students were tested; none were positive.

In rural Missouri, 75% of contacts typically complete LTBI treatment.¹² DOT is the standard of care for active TB disease and is often used for high-risk contacts with LTBI. Advantages of DOT are increased completion of treatment rates and assurance that all doses are remembered and taken appropriately.¹³ The patient needs to take medication only twice weekly, as opposed to daily for 9 months; a ready link to a nurse is maintained throughout, which helps in maintaining both motivation (a "buddy" system) and consistent clinical monitoring. In this outbreak, 86% of school and school bus contacts receiving DOT completed treatment, whereas only 65% of those self-administering therapy completed treatment. Having centralized care for the infected students through one pediatrician familiar with the advantages of DOT certainly facilitated increased completion rates. Pediatricians with patients involved in an outbreak of TB need to work closely with public health authorities to coordinate DOT treatment and assure completion.

Because of the low incidence of TB in rural Missouri, the LPHA had previously designated only 20% of one nurse's time to handle TB-control activities. This finding is consistent with a survey of LPHA nurses in low-incidence areas of Missouri, in which 78% of public health nurses surveyed devote <25% of their time to TB activities.¹⁴ Most LPHA nurses are skilled in administering Mantoux skin tests. However, mobilizing a response to this event involved most of the staff of the LPHA, including all nurses and most of the clerks, for several months. Additionally, the MO DHSSs regional TB nurse case manager and several staff members from the central office were extensively involved. Even in low-incidence

areas, provisions at state health departments must be made to respond to outbreaks and assist LPHAs. As a result of this outbreak, the TB-control program at MO DHSS has developed a TB-outbreak-response plan specific for school outbreaks. The plan contains a list of essential steps and contacts plus ready-made templates of parental consents, information letters, fact sheets, etc. The plan will help optimize efficiency and rapid response, particularly in low-incidence areas in which resources are scarce.

ACKNOWLEDGMENTS

This investigation and subsequent manuscript were a team effort; we thank the staff at the local public health agency, including B. Hollier, J. Berry, and D. Gold. We also thank E. Simoes, S. Denny, D. Oeser, J. Evans, J. Wieberg, L. Tennison, V. Tomlinson, and K. Hadlock at the Missouri Department of Health and Senior Services; J. Gibson and J. Jereb at the Centers for Disease Control and Prevention; and A. Harden and the rest of the staff at the Springfield Missouri Pediatric Speciality Clinic.

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Pediatrics 2004;113:e514

DOI: 10.1542/peds.113.6.e514

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