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Tuberculosis Contact Investigations — United States, 2003–2012

Kai H. Young, MPH[1]; Melissa Ehman, MPH[2]; Randall Reves, MD[3]; Brandy L. Peterson Maddox, MPH[1]; Awal Khan, PhD[1]; Terence L. Chorba, MD[1]; John Jereb, MD[1]

Mycobacterium tuberculosis is transmitted through the air from an infectious patient (index patient) to other persons (contacts) who share space. Exposure to *M. tuberculosis* can result in tuberculosis (TB) disease or latent TB infection (LTBI), which has no clinical symptoms or radiologic evidence of disease. The cycle of transmission can be ended by isolating and treating patients with TB disease, examining contacts, and treating LTBI to prevent progression to TB disease. CDC systematically collects aggregate data on contact investigations from the 50 states, the District of Columbia (DC), and Puerto Rico. Data from 2003–2012 were analyzed for trends in yields from contact investigations, in terms of numbers of contacts elicited and examined and the estimated number of TB cases averted through treatment of LTBI among contacts in 2012. During 2003–2012, the number of TB cases decreased, while the number of contacts listed per index patient with contacts elicited increased. In 2012, U.S. public health authorities reported 9,945 cases of TB disease (*1*) and 105,100 contacts. Among these contacts, 84,998 (80.9%) were examined; TB was diagnosed in 532 (0.6%) and LTBI in 15,411 (18.1%). Among contacts with LTBI, 10,137 (65.8%) started treatment, and 6,689 (43.4% of all contacts with LTBI) completed treatment. By investigating contacts in 2012, an estimated 128 TB cases (34% of all potential cases) over the initial 5 years were averted, but an additional 248 cases (66%) might have been averted if all potentially contagious TB patients had contacts elicited, all contacts were examined, and all infected contacts completed treatment. Enhancing contact investigation activities, particularly by ensuring completion of treatment by contacts recently infected with *M. tuberculosis*, is essential to achieve the goal of TB elimination.

The reporting system for TB contact investigations is designed to document workload and productivity of state and local health departments (*2*). Contact classification and instructions for reporting are described in a user's manual and national guidelines (*3*,*4*). Data are collected based on the cascade of contact investigation activities, from eliciting contacts through completing treatment for LTBI. The reporting cycle lasts more than 2 years, reflecting the time required for investigation and completion of interventions (*2*–*4*). The data, aggregated at the reporting jurisdiction, are grouped into three categories based on the expected infectiousness of index patients: 1) sputum smear-positive pulmonary TB (i.e., presence of acid-fast bacilli on sputum-smear microscopy), 2) sputum smear-negative, but culture-positive pulmonary TB, and 3) all other cases and investigations (e.g., source-case investigations or investigations conducted to find persons who might have been infected from the same source as an index case) (*3*,*4*). The number and types of index patients investigated in the third category are not reported nationally because of jurisdictional variations in policy and practice (*3*).

For the period 2003–2012, data from 44 states and Puerto Rico were examined for trends; jurisdictions with gaps in

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annual reporting were excluded from this analysis. For 2012, data from all 50 states, DC, and Puerto Rico were summarized. To calculate the number of TB cases that were averted by treating LTBI diagnosed during contact investigations in 2012, an estimated 2.4% (95% confidence interval [CI] = 1.2%–4.7%) cumulative 5-year incidence without treatment (*5*) was used, discounted for an estimated 80% treatment effectiveness (based on findings of efficacy in clinical trials) (*6*). Incomplete treatment of LTBI was considered equivalent to no treatment. Missed opportunities for prevention were calculated by projecting the number of missed contacts from patients with no contact elicited or outcomes at each step of the contact investigation by the observed proportions. The projections for completing treatment were discounted by the observed proportions of patients not completing for reasons of death, adverse medication effects, health care provider decisions to discontinue treatment, and development of TB disease.

During 2003–2012, the 44 states and Puerto Rico reported 114,003 TB cases in surveillance, accounting for 90.2% of all TB cases reported in the United States and Puerto Rico (*1*). During this time, the number of index patients in the 44 states and Puerto Rico decreased while the number of contacts listed per index patient with contacts elicited increased from 14.9 to 21.3 contacts for sputum smear-positive index patients (Table 1). The percentage of index patients with no contact elicited decreased overall, from 7.2% in 2003 to 5.1% in 2012 for smear-positive patients and from 18.6% to 11.3% for smear-negative, culture-positive patients. The percentage of contacts who were fully examined remained stable at approximately 80%. The prevalence rates of both TB disease and LTBI decreased among contacts of smear-positive and smear-negative, culture-positive index patients. However, the yields of TB and LTBI diagnosed among contacts per index patient with contacts elicited remained stable, with an average of 0.11 contacts with TB disease and 3.13 contacts with LTBI per smear-positive index patient and 0.05 contacts with TB disease and 1.30 contacts with LTBI per smear-negative, culture-positive index patient with contacts elicited. Among contacts of smear-positive index patients who had a diagnosis of LTBI, the treatment completion rate remained stable as well, averaging 46.4% over the 10-year period. The pattern was similar for contacts of smear-negative, culture-positive index patients (Table 1).

During 2003–2012, the reason for not completing treatment was reported for 33,012 (78.8%) of 41,886 contacts who started, but did not complete treatment for LTBI, from all three categories of investigations. These reasons are mutually exclusive; if multiple factors were involved, the following hierarchy was applied: died (201; 0.6%), TB disease developed (215; 0.7%), adverse effect of treatment (2,263; 6.9%), health care provider decision (1,859; 5.6%), individual decision (15,173; 46.0%), moved and outcome was unavailable (3,240; 9.8%), or lost to follow-up (10,061; 30.5%).

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TABLE 1. Results of tuberculosis contact investigations — 44 states* and Puerto Rico, 2003–2012

Patient classification/ Year	No. of index patients for investigation	No. of patients with no contacts elicited (%†)	Total no. of contacts elicited	No. of contacts examined (%†)	No. of contacts with TB diagnosis (%†)	No. of contacts with LTBI diagnosis (%§)	No. with LTBI who initiated treatment (%†)	No. with LTBI who completed treatment (%¶)	Yields per patient with contacts elicited		
									Contacts elicited	TB diagnoses	LTBI diagnoses
Smear-positive**	**41,646**	**2,689 (6.5)**	**692,672**	**569,526 (82.2)**	**4,307 (0.8)**	**121,837 (21.4)**	**86,975 (71.4)**	**56,514 (46.4)**	**17.8**	**0.11**	**3.13**
2003	4,928	355 (7.2)	67,919	55,031 (81.0)	530 (1.0)	14,301 (26.0)	10,599 (74.1)	6,317 (44.2)	14.9	0.12	3.13
2004	5,020	356 (7.1)	78,322	64,953 (82.9)	491 (0.8)	15,396 (23.7)	10,851 (70.5)	6,669 (43.3)	16.8	0.11	3.30
2005	4,397	308 (7.0)	63,652	52,708 (82.8)	449 (0.9)	12,267 (23.3)	8,611 (70.2)	5,498 (44.8)	15.6	0.11	3.00
2006	4,619	353 (7.6)	70,103	56,483 (80.6)	371 (0.7)	12,241 (21.7)	8,952 (73.1)	5,931 (48.5)	16.4	0.09	2.87
2007	4,312	276 (6.4)	68,964	56,869 (82.5)	414 (0.7)	12,861 (22.6)	9,039 (70.3)	6,201 (48.2)	17.1	0.10	3.19
2008	4,326	325 (7.5)	75,759	62,270 (82.2)	438 (0.7)	12,400 (19.9)	8,793 (70.9)	5,625 (45.4)	18.9	0.11	3.10
2009	3,665	202 (5.5)	66,112	55,314 (83.7)	354 (0.6)	10,594 (19.2)	7,699 (72.7)	5,206 (49.1)	19.1	0.10	3.06
2010	3,532	178 (5.0)	63,795	53,068 (83.2)	485 (0.9)	10,495 (19.8)	7,702 (73.4)	5,257 (50.1)	19.0	0.14	3.13
2011	3,532	167 (4.7)	70,935	57,424 (81.0)	438 (0.8)	11,003 (19.2)	7,806 (70.9)	5,244 (47.7)	21.1	0.13	3.27
2012	3,315	169 (5.1)	67,111	55,406 (82.6)	337 (0.6)	10,279 (18.6)	6,923 (67.4)	4,566 (44.4)	21.3	0.11	3.27
Smear-negative, culture-positive††	**23,549**	**3,231 (13.7)**	**188,422**	**152,877 (81.1)**	**915 (0.6)**	**26,424 (17.3)**	**17,846 (67.5)**	**11,745 (44.4)**	**9.3**	**0.05**	**1.30**
2003	2,710	505 (18.6)	18,833	15,260 (81.0)	111 (0.7)	2,959 (19.4)	2,203 (74.5)	1,324 (44.7)	8.5	0.05	1.34
2004	2,672	392 (14.7)	21,425	16,979 (79.2)	108 (0.6)	3,386 (19.9)	2,405 (71.0)	1,504 (44.4)	9.4	0.05	1.49
2005	2,390	345 (14.4)	20,613	16,523 (80.2)	93 (0.6)	2,688 (16.3)	1,857 (69.1)	1,225 (45.6)	10.1	0.05	1.31
2006	3,137	362 (11.5)	19,909	16,051 (80.6)	92 (0.6)	2,933 (18.3)	1,998 (68.1)	1,336 (45.6)	7.2	0.03	1.06
2007	3,023	341 (11.3)	18,901	15,629 (82.7)	73 (0.5)	2,898 (18.5)	1,976 (68.2)	1,406 (48.5)	7.0	0.03	1.08
2008	2,261	414 (18.3)	22,082	18,037 (81.7)	103 (0.6)	2,808 (15.6)	1,805 (64.3)	1,169 (41.6)	12.0	0.06	1.52
2009	1,991	271 (13.6)	16,778	14,007 (83.5)	92 (0.7)	2,135 (15.2)	1,505 (70.5)	1,010 (47.3)	9.8	0.05	1.24
2010	1,937	220 (11.4)	17,850	14,631 (82.0)	90 (0.6)	2,220 (15.2)	1,445 (65.1)	990 (44.6)	10.4	0.05	1.29
2011	1,810	198 (10.9)	15,666	12,717 (81.2)	83 (0.7)	2,291 (18.0)	1,398 (61.0)	930 (40.6)	9.7	0.05	1.42
2012	1,618	183 (11.3)	16,365	13,043 (79.7)	70 (0.5)	2,106 (16.1)	1,254 (59.5)	851 (40.4)	11.4	0.05	1.47
Others§§	—	—	**163,150**	**135,404 (83.0)**	**1,013 (0.7)**	**21,071 (15.6)**	**14,329 (68.0)**	**9,005 (42.7)**	—	—	—
2003	—	—	19,941	16,914 (84.8)	100 (0.6)	2,831 (16.7)	2,004 (70.8)	1,212 (42.8)	—	—	—
2004	—	—	20,005	16,589 (82.9)	166 (1.0)	3,052 (18.4)	2,123 (69.6)	1,244 (40.8)	—	—	—
2005	—	—	18,761	16,053 (85.6)	89 (0.6)	2,148 (13.4)	1,459 (67.9)	908 (42.3)	—	—	—
2006	—	—	15,839	13,199 (83.3)	84 (0.6)	1,911 (14.5)	1,157 (60.5)	731 (38.3)	—	—	—
2007	—	—	16,431	12,339 (75.1)	103 (0.8)	1,894 (15.3)	1,345 (71.0)	872 (46.0)	—	—	—
2008	—	—	16,067	13,917 (86.6)	85 (0.6)	2,061 (14.8)	1,368 (66.4)	809 (39.3)	—	—	—
2009	—	—	12,210	10,349 (84.8)	82 (0.8)	1,618 (15.6)	1,133 (70.0)	735 (45.4)	—	—	—
2010	—	—	17,755	14,699 (82.8)	134 (0.9)	2,018 (13.7)	1,445 (71.6)	980 (48.6)	—	—	—
2011	—	—	14,477	11,985 (82.8)	107 (0.9)	2,002 (16.7)	1,338 (66.8)	902 (45.1)	—	—	—
2012	—	—	11,664	9,360 (80.2)	63 (0.7)	1,536 (16.4)	957 (62.3)	612 (39.8)	—	—	—

Abbreviations: LTBI = latent TB infection; TB = tuberculosis disease.

* Excludes Georgia, Louisiana, Pennsylvania, Washington, Wisconsin, Wyoming, and the District of Columbia because reports for some years were unobtainable.

† As percentages of the numbers in the preceding column.

§ As percentages of the number of contacts who were examined.

¶ As percentages of the number of contacts with LTBI.

** Smear-positive: pulmonary index patients with acid-fast bacilli reported from sputum-smear microscopy.

†† Smear-negative, culture-positive: pulmonary index patients without acid-fast bacilli reported from sputum-smear microscopy but with *Mycobacterium tuberculosis* isolated by culture.

§§ Others: TB patient contact investigations conducted for reasons determined by local policy, such as source-case investigations or investigations conducted to find persons who might have been infected from the same source as an index patient.

In 2012, health departments in all 50 states, DC, and Puerto Rico reported 105,100 contacts (Table 2). Contact investigations of sputum smear-positive index patients yielded higher numbers of contacts elicited (21.2), TB disease diagnoses (0.11), and LTBI diagnoses (3.26) per index patient with contacts elicited than did investigations of sputum smear-negative, culture-positive index patients (11.3 contacts elicited, 0.05 TB disease diagnoses, and 1.45 LTBI diagnoses per index patient with contacts elicited). Among sputum smear-negative, culture-positive index patients, 12.1% had no contacts elicited, compared with 5.5% of sputum smear-positive index patients. The number of contacts with TB disease and LTBI diagnoses per smear-positive index patient with contacts elicited was more than twice the number per smear-negative, culture-positive index patient with contacts elicited.

Based on TB contact investigations in 2012 in all 50 states, DC, and Puerto Rico, a projected estimate of 128 (CI = 64–252) TB cases were averted over a 5-year span by treating 6,689 contacts with LTBI (Table 3). An estimated additional 248 TB cases could have been averted by initiation and completion of LTBI treatment among missed contacts, contacts who were not examined, and those who did not start or complete treatment because the patient moved, was lost to follow-up, or chose to stop treatment. Overall, contact investigations resulted in the diagnosis of TB in 532 (76%) of 697 contacts projected to have TB disease and averted an estimated

TABLE 2. Results of tuberculosis contact investigations — United States* and Puerto Rico, 2012

Patient classification	No. of index patients for investigation	No. of patients with no contacts elicited (%†)	Total no. of contacts elicited	No. of contacts examined (%†)	No. of contacts with TB diagnosis (%†)	No. of contacts with LTBI diagnosis (%§)	No. with LTBI who initiated treatment (%†)	No. with LTBI who completed treatment (%¶)	Yields per patient with contacts elicited		
									Contacts elicited	TB diagnoses	LTBI diagnoses
Smear-positive**	3,681	201 (5.5)	73,602	60,120 (81.7)	380 (0.6)	11,337 (18.9)	7,668 (67.6)	5,052 (44.6)	21.2	0.11	3.26
Smear-negative, culture-positive††	1,840	223 (12.1)	18,233	14,311 (78.5)	83 (0.6)	2,340 (16.4)	1,384 (59.1)	945 (40.4)	11.3	0.05	1.45
Others§§	—	—	13,265	10,567 (79.7)	69 (0.7)	1,734 (16.4)	1,085 (62.6)	692 (39.9)	—	—	—
Total	—	—	**105,100**	**84,998 (80.9)**	**532 (0.6)**	**15,411 (18.1)**	**10,137 (65.8)**	**6,689 (43.4)**	—	—	—

Abbreviations: LTBI = latent TB infection; TB = tuberculosis disease.
* Includes all 50 states and the District of Columbia.
† As percentages of the numbers in the preceding column.
§ As percentages of the number of contacts who were examined.
¶ As percentages of the number of contacts with LTBI.
** Smear-positive: pulmonary index patients with acid-fast bacilli reported from sputum-smear microscopy.
†† Smear-negative, culture-positive: pulmonary index patients without acid-fast bacilli reported from sputum-smear microscopy but with *Mycobacterium tuberculosis* isolated by culture.
§§ Others: TB patient contact investigations conducted for reasons determined by local policy, such as source-case investigations or investigations conducted to find persons who might have been infected from the same source as an index patient.

128 (34%) of the 376 TB cases that could have been averted in the initial 5-year period, if every possible intervention had been completed.

Discussion

Although the number of TB cases in 44 states and Puerto Rico and the percentage of index patients with no contacts elicited declined from 2003 to 2012, the percentage of contacts who were examined did not change, and fewer than half of contacts who received a diagnosis of LTBI completed treatment. In 2012, contacts outnumbered TB cases almost 11 to 1 in the United States, which indicates a burden of public health work that is not evident from TB case counts alone, and is thus not apparent to the public or to policy makers. TB contact investigations are complex interventions, lasting more than 2 years and requiring specialized skills (*4*). For example, after public health authorities assess the contagious period of an index TB patient, a list of contacts is elicited by 1) interviewing the index patient or proxies, 2) reviewing administrative records in congregate settings (e.g., schools), and 3) visiting sites frequented by the index patient (*4*). The procedures required to confirm TB disease or LTBI can take up to 3 months. The most common regimen for treating LTBI has been daily isoniazid for 9 months, with monthly health care visits for monitoring treatment (*4*).

Because the rate of developing TB disease is highest in the first 2 years following infection, as are the opportunities for preventing TB (*4*–*8*), TB contact investigations are efficient for finding previously undiagnosed cases and detecting newly acquired LTBI. For the period 2003–2012, for every smear-positive TB patient with contacts elicited, an average of three contacts with LTBI were found, and for every 10 smear-positive TB patients with contacts elicited, one contact had TB disease. Among all contacts who were examined from 2003 to 2012, 0.7% received a diagnosis of TB disease, a percentage slightly smaller than the 1%–3% reported globally in epidemiologic studies (*7*). Since 2012, the World Health Organization has recommended contact investigations as part of the global TB control strategy, focusing on the most vulnerable contacts with the most intense exposure for low-resource settings (*8*). For settings with more resources, larger and more intensive contact investigations are recommended (*4*,*8*).

The estimate of 128 potential TB cases averted through treatment of LTBI in TB contact investigations in 2012 is conservative. The risk for TB developing without treatment extends for the lifetime of infected contacts, far beyond this estimate of cases averted during the first 5 years after infection. Further, this estimate does not include any projections of cases averted from secondary transmission or partial effectiveness of LTBI treatment among patients who started but did not complete treatment.

The findings in this report are subject to at least three limitations. First, the reports contain no information about whether all persons who were included as contacts had significant exposure to the index patient, or whether all persons who were exposed were included as contacts in the investigations. Second, the data are not linked to the index TB cases reported to the National Tuberculosis Surveillance System (*1*). Finally, data are not externally validated, and risk stratification (e.g., for HIV infection) is not possible nationally because the data are aggregated before they are sent to CDC. Nonetheless, the overall U.S. findings are similar to those from studies using a variety of methods (*1*,*4*,*6*).

Contact investigations in the United States are not achieving their full potential for preventing TB because of shortfalls at several junctures. First, contacts were not elicited for one in

TABLE 3. Projected number of tuberculosis cases averted by contact investigations and number of missed opportunities to avert additional cases — United States* and Puerto Rico, 2012

Patient classification	Reported counts	Total no. contacts elicited	No. of contacts examined	No. of contacts with TB diagnosis	No. of contacts with LTBI diagnosis	No. with LTBI who initiated treatment	No. with LTBI who completed treatment	Projected no. TB cases averted† (95% CI)
Smear-positive§								
Results from investigations	—	**73,602**	**60,120**	**380**	**11,337**	**7,668**	**5,052**	**97 (48–190)**
Missed opportunities, total¶	—	—	—	—	—	—	—	**177 (88–346)**
Patients with no contacts elicited	201	4,261	4,261	26	805	805	770	15 (7–29)
Contacts not examined	13,482	—	13,482	81	2,548	2,548	2,436	47 (23–92)
Contacts with LTBI, did not initiate treatment	3,669	—	—	—	—	3,669	3,508	67 (34–132)
Contacts with LTBI, initiated treatment, not completed**	2,616	—	—	—	—	—	2,501	48 (24–94)
Smear-negative, culture-positive††								
Results from investigations	—	**18,233**	**14,311**	**83**	**2,340**	**1,384**	**945**	**18 (9–36)**
Missed opportunities, total¶	—	—	—	—	—	—	—	**44 (22–85)**
Patients with no contacts elicited	223	2,520	2,520	15	413	413	387	7 (4–15)
Contacts not examined	3,922	—	3,922	24	643	643	603	12 (6–23)
Contacts with LTBI, did not initiate treatment	956	—	—	—	—	956	897	17 (9–34)
Contacts with LTBI, initiated treatment, not completed**	439	—	—	—	—	—	412	8 (4–15)
Others§§								
Results from investigations	—	**13,265**	**10,567**	**69**	**1,734**	**1,085**	**692**	**13 (7–26)**
Missed opportunities, total¶	—	—	—	—	—	—	—	**27 (14–53)**
Contacts not examined	2,698	—	2,698	19	442	442	418	8 (4–16)
Contacts with LTBI, did not initiate treatment	649	—	—	—	—	649	613	12 (6–23)
Contacts with LTBI, initiated treatment, not completed**	393	—	—	—	—	—	371	7 (4–14)
Total projected outcomes from investigations and estimated missed opportunities¶¶	—	**111,881**	**109,361**	**697**	**20,262**	**20,262**	**19,605**	**376 (189–737)**
Results from investigations	—	**105,100**	**84,998**	**532**	**15,411**	**10,137**	**6,689**	**128 (64–252)**
Total missed opportunities¶	—	**6,781**	**24,363**	**165**	**4,851**	**10,125**	**12,916**	**248 (125–486)**

Abbreviations: CI = confidence interval; LTBI = latent TB infection; TB = tuberculosis disease.

* Includes all 50 states and the District of Columbia.

† Number of TB cases averted = number of contacts with LTBI who completed treatment multiplied by 2.4% (cumulative 5-year incidence without treatment) and 80.0% (estimated treatment effectiveness).

§ Smear-positive: pulmonary index patients with acid-fast bacilli reported from sputum-smear microscopy.

¶ Missed opportunities for prevention: potential number of contacts elicited = number of patients with no contact elicited multiplied by the number of contacts elicited per index patient investigated (21.2 for smear-positive, 11.3 for smear-negative, culture-positive index patient investigated); potential number of contacts examined = number of contacts elicited (assuming all contacts elicited are examined); potential number of contacts with TB diagnosis = number of contacts not examined multiplied by 0.6% (proportion with TB diagnosis among contacts of smear-positive, or smear-negative, culture-positive patients) or 0.7% (among other contacts); potential number of contacts with LTBI diagnosis = number of contacts not examined multiplied by 18.9% (proportion with LTBI diagnosis among contacts of smear-positive patients) or 16.4% (among contacts of smear-negative, culture-positive patients, or other contacts); potential number contacts with LTBI who initiated treatment = number with LTBI diagnosis (assuming all contacts diagnosed with LTBI initiate treatment) or number with LTBI who did not initiate treatment; potential number of contacts with LTBI who completed treatment = number with LTBI who initiated treatment, or number of LTBI who initiated treatment, but did not complete, subtracting the proportion not completing for reasons of death, adverse effects, health care provider decisions to discontinue treatment, and TB disease developed (4.4% for contacts of smear-positive patients, 6.2% for contacts of smear-negative, culture-positive patients, and 5.5% for other contacts).

** Includes contacts who moved, were lost to follow-up, or decided to stop treatment.

†† Smear-negative, culture-positive: pulmonary index patients without acid-fast bacilli reported from sputum-smear microscopy but with *Mycobacterium tuberculosis* isolated by culture.

§§ Others: TB patient contact investigations conducted for reasons determined by local policy, such as source-case investigations or investigations conducted to find persons who might have been infected from the same source as an index patient.

¶¶ Projected outcomes from investigations are the sum of results from investigations and the estimated missed opportunities from each step of the contact investigation process.

13 potentially infectious (smear-positive or smear-negative, culture-positive) index patients in 2012. Although contact elicitation has improved over the years, and success could be attributed to the guidance encouraging prioritization of activities based on the infectiousness of index patients (*4*), efforts should be made to ensure that contacts are elicited from all potentially infectious patients. Second, one in five contacts were not examined. Third, more than half of infected contacts did not complete a regimen for preventing TB. Treatment is recommended for all contacts who have LTBI (*4*), but one third of persons with LTBI did not start treatment, possibly because of patient or health care provider misperceptions about

Summary

What is already known on this topic?

Tuberculosis (TB) disease is spread person-to-person by the airborne route. Investigating contacts of contagious TB patients, a globally recommended strategy, finds new TB cases. Additional cases can be prevented by treating contacts who have latent TB infection (LTBI).

What is added by this report?

From 2003 to 2012, the number of TB cases decreased, while the number of contacts listed per index patient with contacts elicited increased. For 2012, the United States reported an average of 11 contacts for every TB case counted (21 contacts for each of the most contagious TB patients with contacts elicited). Approximately 1% of contacts already had TB at the time of examination. An estimated 128 cases over 5 years were averted by treating LTBI among contacts in 2012. However, an additional 248 cases could have been prevented if all infectious TB patients had contacts identified, all contacts received a medical examination, and contacts with LTBI started and completed treatment.

What are the implications for public health practice?

TB contact investigations in the United States are productive. The workload and yield of TB contact investigations are not reflected in the number of cases that are routinely reported in TB surveillance. Increasing the number of contacts with LTBI diagnoses who start and complete treatment would considerably reduce the number of TB cases in the United States.

risks and benefits of treatment for LTBI (*4*,*6*,*8*). Furthermore, one third of all infected contacts who started treatment did not complete it.

A major barrier to completing treatment has been the 9-month isoniazid regimen. A briefer combination regimen of isoniazid-rifapentine administered once a week as directly observed therapy over 12 weeks, which some health departments began to implement in 2012, can increase treatment initiation and completion rates (*9*), and innovative case management strategies building on collaborations between health care systems could minimize loss to follow-up and ensure treatment completion. Increasing the treatment of LTBI for multiple risk groups, including contacts recently infected with *M. tuberculosis*, is essential for achieving TB elimination (*10*).

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[1]Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC; [2]Division of Communicable Disease Control, Center for Infectious Diseases, California Department of Public Health; [3]Denver Public Health Department.

Corresponding author: Kai H. Young, deq0@cdc.gov, 404-639-2217.

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Fatal Bacterial Meningitis Possibly Associated with Substandard Ceftriaxone — Uganda, 2013

Jason W. Nickerson, PhD[1]; Amir Attaran, DPhil[2]; Brian D. Westerberg, MD[3]; Sharon Curtis, PhD[2]; Sean Overton[2]; Paul Mayer, PhD[2]

The burden of disease from bacterial meningitis is highest in low-income countries (*1*). Early initiation of antibiotic therapy is important in reducing the risk for mortality. Current treatment guidelines recommend the use of an expanded-spectrum cephalosporin (cefotaxime or ceftriaxone) (*2*), but these therapies increasingly are limited by drug resistance, and are threatened by the proliferation of substandard and falsified medicines (*3*,*4*). In February 2013, a case of bacterial meningitis following a middle ear infection was diagnosed in an adolescent at the Mulago National Referral Hospital in Kampala, Uganda. Once-daily treatment with 2 g of intravenous ceftriaxone administered according to guidelines failed, and the patient died. To determine whether the patient's treatment failure and subsequent death might be related to the ceftriaxone product administered, a sealed vial similar to the one administered to the patient was analyzed at the University of Ottawa, Canada, and was found to contain only 0.455 g of the drug, not 1 g as stated by the manufacturer. This would have resulted in subtherapeutic dosing. Substandard medicines are a global problem that disproportionately affects low-income countries, leading to fatal consequences and promoting the emergence of drug resistance (*4*).

On February 7, 2013, a boy aged 13 years from central Kampala was evaluated at the Mulago National Referral Hospital in Kampala, Uganda. He had experienced 10 days of confusion, followed by fevers, chills, rigors, and intermittent vomiting. On otoscopic examination, pus was visible in the right ear canal, and there was tenderness over the right mastoid. Neither computed tomography nor lumbar puncture testing was available at the time of the patient's evaluation, and a presumptive diagnosis of otogenic bacterial meningitis was made. The patient was admitted to the hospital, and treatment with 2 g intravenous ceftriaxone once daily was initiated. Ceftriaxone is recommended as the primary drug for treatment of meningitis and is available in the public health system in Uganda (*2*).

On the fourth treatment day, the patient remained febrile and lethargic, and 500 mg of intravenous metronidazole given twice daily was added to the regimen. The following day, the patient had a worsening headache, and he became irritable and agitated. Antibiotic therapy was continued, and because of the failure of medical therapy, a mastoidectomy was planned for treatment day 7; however, the patient had seizures that day. Computed tomography, which became available only that day, demonstrated multiple small abscesses in the posterior cranial fossa. Neurosurgeons advised that these abscesses were likely to respond to antibiotics (*5*), and considering the risks associated with neurosurgery in a resource-constrained setting, recommended a conservative approach. Therefore, only the planned mastoidectomy was performed; no specimens were sent for culture. Postoperatively, the patient was admitted to the intensive care unit and started on second-line treatment with meropenem (1 g three times daily), phenytoin (500 mg daily), and tramadol (50 mg three times daily). On day 8, when the patient failed to respond to treatment, levofloxacin and clindamycin were added. On day 10, the patient experienced acute respiratory failure, requiring endotracheal intubation and mechanical ventilation. On day 11, peripheral and corneal reflexes were absent, and the patient was declared brain dead, presumably from elevated intracranial pressure. On day 12, treatment was withdrawn.

Suspecting that the patient's initial treatment failure might be related to the potency of the ceftriaxone product administered, physicians obtained a sealed vial of injectable ceftriaxone sodium (labeled 1 g), similar to that administered to the patient, from the hospital dispensary for testing. The sample was unexpired and stored according to manufacturer's guidelines. Upon examination of the vial, no obvious signs of falsification (such as spelling or typographical errors on the packaging or on the vial) were observed. It was unknown whether this vial was from the same lot as the one used to treat the patient.

Analysis of the sample was performed at the John L. Holmes Mass Spectrometry Facility at the University of Ottawa, Canada, using established laboratory methods (*6*). The presence and quantity of active ingredient was verified by mass spectrometry with an analytical standard of 92% ceftriaxone disodium salt and a vial of ceftriaxone sodium BP. The sample contained only 0.455 g of the drug, not 1 g as stated by the manufacturer and indicated on the label. If the vials administered to the patient were similarly compromised, the patient would have received a subtherapeutic dose of ceftriaxone, which might have contributed to treatment failure (*7*).

Summary

What is already known on this topic?

Falsified and substandard medicines, particularly antimalarial and antiretroviral drugs, are a major threat to global public health, and have been detected in markets around the world. The scope of this problem across different drug classes, including antibiotics, has not been adequately characterized.

What is added by this report?

A case of fatal bacterial meningitis was possibly associated with administration of substandard ceftriaxone containing less than half of the stated active pharmaceutical ingredient. Substandard or falsified ceftriaxone might be a cause of treatment failure in bacterial meningitis in Africa.

What are the implications for public health practice?

The presence and use of substandard medicines, particularly antibiotics, is likely to contribute to treatment failures and emergence of drug resistance. It is important for public health practitioners to be aware of both the potential harms and the large scale of these medicines. National and international pharmacovigilance is important to prospectively identify poor quality medicines.

Discussion

Although antibiotic resistance has been documented globally, and treatment failure can result from multiple factors related to limitations common in resource-poor environments, including complex or atypical disease progression, ceftriaxone is the recommended first-line treatment for bacterial meningitis in Africa (*2*). Substandard or intentionally adulterated medicinal products are a global problem that disproportionately affects low-income countries, where regulation of the pharmaceutical market is often limited. In addition to leading to treatment failures, these medicines also contribute to emerging antibiotic resistance in the community, and can erode confidence in health systems (*4*). Drugs containing little or no active ingredient, including first-line therapies for the treatment of tuberculosis, malaria, and human immunodeficiency virus, have been found in many low-income countries (*4*). A recent meta-analysis of 21 surveys of antimalarial drug quality in 21 sub-Saharan African countries revealed that, of 2,297 samples included, 796 (35%) failed chemical analysis, and 79 of 389 (20%) samples appeared falsified, and thus criminal in origin (*8*). A study from Pakistan highlighted similar quality concerns in injectable ceftriaxone, finding that 15.6% of 96 samples tested were outside acceptable quality ranges (*9*). In May 2015, the World Health Organization released a Medical Product Alert warning of falsified meningitis vaccines circulating in West Africa.* Substandard medicines can result from multiple supply chain factors, including manufacturing or handling problems, deliberate criminal fraud by drug manufacturers, or other criminal practices that exploit regulatory vulnerabilities in drug markets.

The findings in this report are subject to at least three limitations. First, because of a lack of reliable diagnostic tools (e.g., computed tomography, lumbar puncture, or bacterial culture), the specific pathogen present in this case was not identified, potentially resulting in the selection of an incorrect antimicrobial therapy. Second, it is not known whether the antibiotic that was tested came from the same lot that was used to treat this patient. Finally, because of delayed (10 days into the clinical course) or inadequate interventions, such as reliance on antibiotics as the sole therapy (e.g., no surgical treatment of the abscesses), and the possibility that the patient's disease could have progressed beyond a point where single antibiotic therapy might have been effective, it is not known whether higher quality medicines would have altered the progression of disease in this case. However, the lack of clinical response to first-line therapy prompted clinicians to question whether the antibiotic might have been substandard, and analysis found the sample to contain less than half of the stated amount of antibiotic.

This case highlights the problem of poor quality medicines and can alert practitioners in Africa to consider the possibility that substandard or falsified ceftriaxone might be a cause of treatment failure in bacterial meningitis. Averting a global public health crisis attributed to low-quality medicines requires coordinated international and national efforts to identify and remove these products at all levels of distribution. Establishment of product standards and robust pharmacovigilance systems, in tandem with stronger criminal legislation, are important for ensuring that patients have access to quality medications (*10*) and for enforcing penalties for those who intentionally produce or sell substandard or falsified medicines.

* More information available at http://www.who.int/medicines/publications/drugalerts/VF_MenomuneAlertENversion.pdf?ua=1.

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Eleanor Reimer, MD, British Columbia Children's Hospital, Vancouver, Canada.

[1]Bruyère Research Institute, Ottawa, Ontario, Canada; [2]University of Ottawa, Ottawa, Ontario, Canada; [3]University of British Columbia, Vancouver, British Columbia, Canada; St. Paul's Rotary Hearing Clinic, Vancouver, British Columbia, Canada.

Corresponding author: Jason W. Nickerson, Jason.Nickerson@uottawa.ca, 613-562-6262 ext. 2906.

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Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014

Rose A. Rudd, MSPH[1]; Noah Aleshire, JD[1]; Jon E. Zibbell, PhD[1]; R. Matthew Gladden, PhD[1]

On December 18, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

The United States is experiencing an epidemic of drug overdose (poisoning) deaths. Since 2000, the rate of deaths from drug overdoses has increased 137%, including a 200% increase in the rate of overdose deaths involving opioids (opioid pain relievers and heroin). CDC analyzed recent multiple cause-of-death mortality data to examine current trends and characteristics of drug overdose deaths, including the types of opioids associated with drug overdose deaths. During 2014, a total of 47,055 drug overdose deaths occurred in the United States, representing a 1-year increase of 6.5%, from 13.8 per 100,000 persons in 2013 to 14.7 per 100,000 persons in 2014. The rate of drug overdose deaths increased significantly for both sexes, persons aged 25–44 years and ≥55 years, non-Hispanic whites and non-Hispanic blacks, and in the Northeastern, Midwestern, and Southern regions of the United States. Rates of opioid overdose deaths also increased significantly, from 7.9 per 100,000 in 2013 to 9.0 per 100,000 in 2014, a 14% increase. Historically, CDC has programmatically characterized all opioid pain reliever deaths (natural and semisynthetic opioids, methadone, and other synthetic opioids) as "prescription" opioid overdoses (*1*). Between 2013 and 2014, the age-adjusted rate of death involving methadone remained unchanged; however, the age-adjusted rate of death involving natural and semisynthetic opioid pain relievers, heroin, and synthetic opioids, other than methadone (e.g., fentanyl) increased 9%, 26%, and 80%, respectively. The sharp increase in deaths involving synthetic opioids, other than methadone, in 2014 coincided with law enforcement reports of increased availability of illicitly manufactured fentanyl, a synthetic opioid; however, illicitly manufactured fentanyl cannot be distinguished from prescription fentanyl in death certificate data. These findings indicate that the opioid overdose epidemic is worsening. There is a need for continued action to prevent opioid abuse, dependence, and death, improve treatment capacity for opioid use disorders, and reduce the supply of illicit opioids, particularly heroin and illicit fentanyl.

The National Vital Statistics System multiple cause-of-death mortality files were used to identify drug overdose deaths.* Drug overdose deaths were classified using the *International Classification of Disease, Tenth Revision* (ICD-10), based on the ICD-10 underlying cause-of-death codes X40–44 (unintentional), X60–64 (suicide), X85 (homicide), or Y10–Y14 (undetermined intent) (*2*). Among the deaths with drug overdose as the underlying cause, the type of opioid involved is indicated by the following ICD-10 multiple cause-of-death codes: opioids (T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6); natural and semisynthetic opioids (T40.2); methadone (T40.3); synthetic opioids, other than methadone (T40.4); and heroin (T40.1). Some deaths involve more than one type of opioid; these deaths were included in the rates for each category (e.g., a death involving both a synthetic opioid and heroin would be included in the rates for synthetic opioid deaths and in the rates for heroin deaths). Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S standard population age distribution (*3*). Significance testing was based on the z-test at a significance level of 0.05.

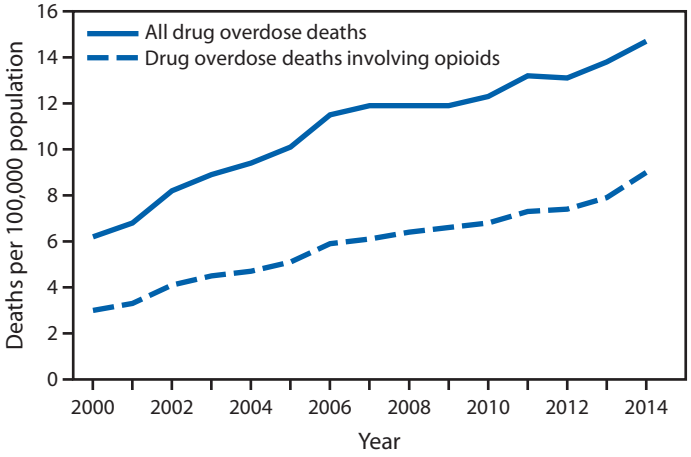
During 2014, 47,055 drug overdose deaths occurred in the United States. Since 2000, the age-adjusted drug overdose death rate has more than doubled, from 6.2 per 100,000 persons in 2000 to 14.7 per 100,000 in 2014 (Figure 1). The overall number and rate of drug overdose deaths increased significantly from 2013 to 2014, with an additional 3,073 deaths occurring in 2014 (Table), resulting in a 6.5% increase in the age-adjusted rate. From 2013 to 2014, statistically significant increases in drug overdose death rates were seen for both males and females, persons aged 25–34 years, 35–44 years, 55–64 years, and ≥65 years; non-Hispanic whites and non-Hispanic blacks; and residents in the Northeast, Midwest and South Census Regions (Table). In 2014, the five states with the highest rates of drug overdose deaths were West Virginia (35.5 deaths per 100,000), New Mexico (27.3), New Hampshire (26.2), Kentucky (24.7) and Ohio (24.6).† States with statistically significant increases in the rate of drug overdose deaths from 2013 to 2014 included Alabama, Georgia, Illinois, Indiana, Maine, Maryland, Massachusetts, Michigan, New Hampshire, New Mexico, North Dakota, Ohio, Pennsylvania, and Virginia.

In 2014, 61% (28,647, data not shown) of drug overdose deaths involved some type of opioid, including heroin. The age-adjusted rate of drug overdose deaths involving opioids increased significantly from 2000 to 2014, increasing 14% from 2013 (7.9 per 100,000) to 2014 (9.0) (Figure 1). From 2013 to 2014, the largest increase in the rate of drug overdose deaths involved synthetic opioids, other than methadone

* Additional information available at http://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm.

† Additional information available at http://www.cdc.gov/drugoverdose/data/statedeaths.html.

FIGURE 1. Age-adjusted rate* of drug overdose deaths† and drug overdose deaths involving opioids§,¶ — United States, 2000–2014



Source: National Vital Statistics System, Mortality file.

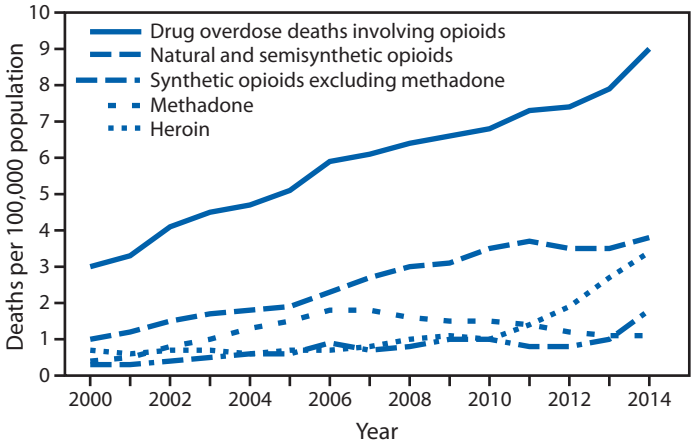
* Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S. standard population age distribution.

† Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

§ Drug overdose deaths involving opioids are drug overdose deaths with a multiple cause-of-death code of T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6. Approximately one fifth of drug overdose deaths lack information on the specific drugs involved. Some of these deaths might involve opioids.

¶ Opioids include drugs such as morphine, oxycodone, hydrocodone, heroin, methadone, fentanyl, and tramadol.

FIGURE 2. Drug overdose deaths* involving opioids,†,§ by type of opioid¶ — United States, 2000–2014



Source: National Vital Statistics System, Mortality file.

* Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S. standard population age distribution.

† Drug overdose deaths involving opioids are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14 with a multiple cause code of T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6.

§ Opioids include drugs such as morphine, oxycodone, hydrocodone, heroin, methadone, fentanyl, and tramadol.

¶ For each type of opioid, the multiple cause-of-death code was T40.1 for heroin, T40.2 for natural and semisynthetic opioids (e.g., oxycodone and hydrocodone), T40.3 for methadone, and T40.4 for synthetic opioids excluding methadone (e.g., fentanyl and tramadol). Deaths might involve more than one drug thus categories are not exclusive.

(e.g., fentanyl and tramadol), which nearly doubled from 1.0 per 100,000 to 1.8 per 100,000 (Figure 2). Heroin overdose death rates increased by 26% from 2013 to 2014 and have more than tripled since 2010, from 1.0 per 100,000 in 2010 to 3.4 per 100,000 in 2014 (Figure 2). In 2014, the rate of drug overdose deaths involving natural and semisynthetic opioids (e.g., morphine, oxycodone, and hydrocodone), 3.8 per 100,000, was the highest among opioid overdose deaths, and increased 9% from 3.5 per 100,000 in 2013. The rate of drug overdose deaths involving methadone, a synthetic opioid classified separately from other synthetic opioids, was similar in 2013 and 2014.

Discussion

More persons died from drug overdoses in the United States in 2014 than during any previous year on record. From 2000 to 2014 nearly half a million persons in the United States have died from drug overdoses. In 2014, there were approximately one and a half times more drug overdose deaths in the United States than deaths from motor vehicle crashes (*4*). Opioids, primarily prescription pain relievers and heroin, are the main drugs associated with overdose deaths. In 2014, opioids were involved in 28,647 deaths, or 61% of all drug overdose deaths; the rate of opioid overdoses has tripled since 2000. The 2014 data demonstrate that the United States' opioid overdose epidemic includes two distinct but interrelated trends: a 15-year increase in overdose deaths involving prescription opioid pain relievers and a recent surge in illicit opioid overdose deaths, driven largely by heroin.

Natural and semisynthetic opioids, which include the most commonly prescribed opioid pain relievers, oxycodone and hydrocodone, continue to be involved in more overdose deaths than any other opioid type. Although this category of opioid drug overdose death had declined in 2012 compared with 2011, and had held steady in 2013, there was a 9% increase in 2014.

Drug overdose deaths involving heroin continued to climb sharply, with heroin overdoses more than tripling in 4 years. This increase mirrors large increases in heroin use across the country (*5*) and has been shown to be closely tied to opioid pain reliever misuse and dependence. Past misuse of prescription opioids is the strongest risk factor for heroin initiation and use, specifically among persons who report past-year dependence or abuse (*5*). The increased availability of heroin, combined with its relatively low price (compared with diverted prescription opioids) and high purity appear to be major drivers of the upward trend in heroin use and overdose (*6*).

The rate of drug overdose deaths involving synthetic opioids nearly doubled between 2013 and 2014. This category includes both prescription synthetic opioids (e.g., fentanyl

TABLE. Number and age-adjusted rates of drug overdose deaths,* by sex, age, race and Hispanic origin,† Census region, and state — United States, 2013 and 2014

Decedent characteristic	2013		2014		% change from 2013 to 2014
	No.	Age-adjusted rate	No.	Age-adjusted rate	
All	**43,982**	**13.8**	**47,055**	**14.7**	**6.5§**
Sex					
Male	26,799	17.0	28,812	18.3	7.6§
Female	17,183	10.6	18,243	11.1	4.7§
Age group (yrs)					
0–14	105	0.2	109	0.2	0.0
15–24	3,664	8.3	3,798	8.6	3.6
25–34	8,947	20.9	10,055	23.1	10.5§
35–44	9,320	23.0	10,134	25.0	8.7§
45–54	12,045	27.5	12,263	28.2	2.5
55–64	7,551	19.2	8,122	20.3	5.7§
≥65	2,344	5.2	2,568	5.6	7.7§
Race and Hispanic origin†					
White, non-Hispanic	35,581	17.6	37,945	19.0	8.0§
Black, non-Hispanic	3,928	9.7	4,323	10.5	8.2§
Hispanic	3,345	6.7	3,504	6.7	0.0
Census region of residence					
Northeast	8,403	14.8	9,077	16.1	8.8§
Midwest	9,745	14.6	10,647	16.0	9.6§
South	15,519	13.1	16,777	14.0	6.9§
West	10,315	13.6	10,554	13.7	0.7
State of residence					
Alabama	598	12.7	723	15.2	19.7§
Alaska	105	14.4	124	16.8	16.7
Arizona	1,222	18.7	1,211	18.2	-2.7
Arkansas	319	11.1	356	12.6	13.5
California	4,452	11.1	4,521	11.1	0.0
Colorado	846	15.5	899	16.3	5.2
Connecticut	582	16.0	623	17.6	10.0
Delaware	166	18.7	189	20.9	11.8
District of Columbia	102	15.0	96	14.2	-5.3
Florida	2,474	12.6	2,634	13.2	4.8
Georgia	1,098	10.8	1,206	11.9	10.2§
Hawaii	158	11.0	157	10.9	-0.9
Idaho	207	13.4	212	13.7	2.2
Illinois	1,579	12.1	1,705	13.1	8.3§
Indiana	1,064	16.6	1,172	18.2	9.6§
Iowa	275	9.3	264	8.8	-5.4
Kansas	331	12.0	332	11.7	-2.5
Kentucky	1,019	23.7	1,077	24.7	4.2
Louisiana	809	17.8	777	16.9	-5.1
Maine	174	13.2	216	16.8	27.3§
Maryland	892	14.6	1,070	17.4	19.2§
Massachusetts	1,081	16.0	1,289	19.0	18.8§
Michigan	1,553	15.9	1,762	18.0	13.2§
Minnesota	523	9.6	517	9.6	0.0
Mississippi	316	10.8	336	11.6	7.4
Missouri	1,025	17.5	1,067	18.2	4.0
Montana	137	14.5	125	12.4	-14.5
Nebraska	117	6.5	125	7.2	10.8
Nevada	614	21.1	545	18.4	-12.8
New Hampshire	203	15.1	334	26.2	73.5§
New Jersey	1,294	14.5	1,253	14.0	-3.4
New Mexico	458	22.6	547	27.3	20.8§
New York	2,309	11.3	2,300	11.3	0.0
North Carolina	1,259	12.9	1,358	13.8	7.0
North Dakota	20	2.8	43	6.3	125.0§
Ohio	2,347	20.8	2,744	24.6	18.3§
Oklahoma	790	20.6	777	20.3	-1.5
Oregon	455	11.3	522	12.8	13.3

See table footnotes on the next page.

TABLE. (*Continued*) Number and age-adjusted rates of drug overdose deaths,* by sex, age, race and Hispanic origin,† Census region, and state — United States, 2013 and 2014

Decedent characteristic	2013		2014		% change from 2013 to 2014
	No.	Age-adjusted rate	No.	Age-adjusted rate	
Pennsylvania	2,426	19.4	2,732	21.9	12.9§
Rhode Island	241	22.4	247	23.4	4.5
South Carolina	620	13.0	701	14.4	10.8
South Dakota	55	6.9	63	7.8	13.0
Tennessee	1,187	18.1	1,269	19.5	7.7
Texas	2,446	9.3	2,601	9.7	4.3
Utah	594	22.1	603	22.4	1.4
Vermont	93	15.1	83	13.9	-7.9
Virginia	854	10.2	980	11.7	14.7§
Washington	969	13.4	979	13.3	-0.7
West Virginia	570	32.2	627	35.5	10.2
Wisconsin	856	15.0	853	15.1	0.7
Wyoming	98	17.2	109	19.4	12.8

Source: National Vital Statistics System, Mortality file.

* Deaths are classified using the *International Classification of Diseases, Tenth Revision* (ICD–10). Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S standard population age distribution.

† Data for Hispanic origin should be interpreted with caution; studies comparing Hispanic origin on death certificates and on census surveys have shown inconsistent reporting on Hispanic ethnicity.

§ Statistically significant change from 2013 to 2014.

and tramadol) and non-pharmaceutical fentanyl manufactured in illegal laboratories (illicit fentanyl). Toxicology tests used by coroners and medical examiners are unable to distinguish between prescription and illicit fentanyl. Based on reports from states and drug seizure data, however, a substantial portion of the increase in synthetic opioid deaths appears to be related to increased availability of illicit fentanyl (*7*), although this cannot be confirmed with mortality data. For example, five jurisdictions (Florida, Maryland, Maine, Ohio, and Philadelphia, Pennsylvania) that reported sharp increases in illicit fentanyl seizures, and screened persons who died from a suspected drug overdose for fentanyl, detected similarly sharp increases in fentanyl-related deaths (*7*).§ Finally, illicit fentanyl is often combined with heroin or sold as heroin. Illicit fentanyl might be contributing to recent increases in drug overdose deaths involving heroin. Therefore, increases in illicit fentanyl-associated deaths might represent an emerging and troubling feature of the rise in illicit opioid overdoses that has been driven by heroin.

The findings in this report are subject to at least three limitations. First, several factors related to death investigation might affect estimates of death rates involving specific drugs. At autopsy, toxicological laboratory tests might be performed to determine the type of drugs present; however, the substances tested for and circumstances under which the tests are performed vary by jurisdiction. Second, in 2013 and 2014, 22% and 19% of drug overdose deaths, respectively, did not include information on the death certificate about the specific types of drugs involved. The percent of overdose deaths with specific drugs identified on the death certificate varies widely by state. Some of these deaths might have involved opioids. This increase in the reporting of specific drugs in 2014 might have contributed to some of the observed increases in drug overdose death rates involving different types of opioids from 2013 to 2014. Finally, some heroin deaths might be misclassified as morphine because morphine and heroin are metabolized similarly (*8*), which might result in an underreporting of heroin overdose deaths.

To reverse the epidemic of opioid drug overdose deaths and prevent opioid-related morbidity, efforts to improve safer prescribing of prescription opioids must be intensified. Opioid pain reliever prescribing has quadrupled since 1999 and has increased in parallel with overdoses involving the most commonly used opioid pain relievers (*1*). CDC has developed a draft guideline for the prescribing of opioids for chronic pain to address this need.¶

In addition, efforts are needed to protect persons already dependent on opioids from overdose and other harms. This includes expanding access to and use of naloxone (a safe and effective antidote for all opioid-related overdoses)** and increasing access to medication-assisted treatment, in combination with behavioral therapies (*9*). Efforts to ensure access to integrated prevention services, including access to syringe service programs when available, is also an important

§ Additional information available at http://pub.lucidpress.com/NDEWSFentanyl/.

¶ Additional information available at http://www.cdc.gov/drugoverdose/prescribing/guideline.html.

** Additional information available at https://store.samhsa.gov/shin/content/SMA13-4742/Overdose_Toolkit_2014_Jan.pdf.

Summary

What is already known on this topic?

The rate for drug overdose deaths has increased approximately 140% since 2000, driven largely by opioid overdose deaths. After increasing since the 1990s, deaths involving the most commonly prescribed opioid pain relievers (i.e., natural and semisynthetic opioids) declined slightly in 2012 and remained steady in 2013, showing some signs of progress. Heroin overdose deaths have been sharply increasing since 2010.

What is added by this report?

Drug overdose deaths increased significantly from 2013 to 2014. Increases in opioid overdose deaths were the main factor in the increase in drug overdose deaths. The death rate from the most commonly prescribed opioid pain relievers (natural and semisynthetic opioids) increased 9%, the death rate from heroin increased 26%, and the death rate from synthetic opioids, a category that includes illicitly manufactured fentanyl and synthetic opioid pain relievers other than methadone, increased 80%. Nearly every aspect of the opioid overdose death epidemic worsened in 2014.

What are the implications for public health practice?

Efforts to encourage safer prescribing of opioid pain relievers should be strengthened. Other key prevention strategies include expanding availability and access to naloxone (an antidote for all opioid-related overdoses), increasing access to medication-assisted treatment in combination with behavioral therapies, and increasing access to syringe service programs to prevent the spread of hepatitis C virus infection and human immunodeficiency virus infections. Public health agencies, medical examiners and coroners, and law enforcement agencies can work collaboratively to improve detection of and response to outbreaks associated with drug overdoses related to illicit opioids.

consideration to prevent the spread of hepatitis C virus and human immunodeficiency virus infections from injection drug use.

Public health agencies, medical examiners and coroners, and law enforcement agencies can work collaboratively to improve detection of outbreaks of drug overdose deaths involving illicit opioids (including heroin and illicit fentanyl) through improved investigation and testing as well as reporting and monitoring of specific drugs, and facilitate a rapid and effective response that can address this emerging threat to public health and safety (*7*). Efforts are needed to distinguish the drugs contributing to overdoses to better understand this trend.

[1]Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC.

Corresponding author: Rose A. Rudd, rvr2@cdc.gov, 770-488-3712.

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Notes from the Field

Group A Streptococcal Pharyngitis Misdiagnoses at a Rural Urgent-Care Clinic — Wyoming, March 2015

Alexia Harrist, MD, PhD[1,2]; Clayton Van Houten, MS[2]; Stanford T. Shulman, MD[3]; Chris Van Beneden, MD[4]; Tracy Murphy, MD[2]

Group A *Streptococcus* (GAS) is the most common bacterial cause of pharyngitis, implicated in 20%–30% of pediatric and 5%–15% of adult health care visits for sore throat (*1*). Along with the sudden onset of throat pain, GAS pharyngitis symptoms include fever, headache, and bilateral tender cervical lymphadenopathy (*1*,*2*). Accurate diagnosis and management of GAS pharyngitis is critical for limiting antibiotic overuse and preventing rheumatic fever (*2*), but distinguishing between GAS and viral pharyngitis clinically is challenging (*1*). Guidelines for diagnosis and management of GAS pharyngitis have been published by the Infectious Diseases Society of America (IDSA)* (*1*). IDSA recommends that patients with sore throat be tested for GAS to distinguish between GAS and viral pharyngitis; however, IDSA emphasizes the use of selective testing based on clinical symptoms and signs to avoid identifying GAS carriers rather than acute GAS infections (*1*). Therefore, testing for GAS usually is not recommended for the following: patients with sore throat and accompanying symptoms (e.g., cough, rhinorrhea) that strongly suggest a viral etiology; children aged <3 years, because acute rheumatic fever is extremely rare in this age group; and asymptomatic household contacts of patients with GAS pharyngitis (*1*). IDSA recommends penicillin or amoxicillin as the treatment of choice based on effectiveness and narrow spectrum of activity. To date, penicillin-resistant GAS has never been documented (*1*).

In March 2015, a rural urgent-care clinic serving a population of 5,000–7,000 reported a substantial increase in GAS pharyngitis infections since November 2014, with some infections nonresponsive to penicillin and amoxicillin to the Wyoming Department of Health (WDH). By March 2015, the clinic reported diagnosing up to 90 cases of GAS pharyngitis per week. WDH started an investigation to verify this potential GAS pharyngitis outbreak, assess clinic testing and treatment practices, and implement control measures.

WDH reviewed a clinic-provided line list of 42 patients tested for GAS pharyngitis using rapid antigen detection tests (RADTs) during March 13–17 and two additional patients who had received diagnoses of GAS pharyngitis the previous week and returned with persistent symptoms. Patient characteristics stratified by age are provided (Table).

The line list revealed nonadherence to IDSA guidelines in testing and treatment procedures. Ten of 34 (29%) patients aged ≥3 years who were tested for GAS reported no sore throat, the symptom that should prompt evaluation for GAS pharyngitis in patients aged ≥3 years (*1*). Two of these 10 were asymptomatic adult contacts of patients with diagnosed GAS pharyngitis; both asymptomatic contacts had positive RADT results and were prescribed an antibiotic. Of the 24 tested patients aged ≥3 years with sore throat, 19 (79%) reported cough or rhinorrhea, symptoms that suggest a viral rather than bacterial etiology (*1*). Although diagnostic testing of patients aged <3 years is not routinely recommended, testing of symptomatic children who are household contacts of persons with laboratory-confirmed GAS pharyngitis can be considered (*1*). Among the seven patients aged <3 years who were tested for GAS pharyngitis, five (71%) had GAS-positive family members indicated by shared surname included in the line list; however, all seven (100%) had cough, and five (71%) had rhinorrhea.

Four of six patients with negative RADT results received an antibiotic. The clinic practice was to send throat swabs from patients with negative RADTs to a commercial laboratory for back-up culture, but it is unknown whether the clinic obtained any GAS-positive throat cultures from RADT-negative patients. All patients who were administered an antibiotic received a cephalosporin, clindamycin, or amoxicillin-clavulanate rather than penicillin or amoxicillin as the initial antibiotic therapy. Three patients were prescribed a second course of an antibiotic because of symptoms persisting >48 hours after the start of initial therapy; data provided did not indicate whether they were retested for GAS.

Because of the high positivity rate (38 of 44; 86%) among RADTs performed, including eight of 10 positive test results among patients aged ≥3 years without sore throat, WDH requested that the clinic perform oropharyngeal cultures on patients with positive RADTs. The clinic reported that four throat cultures collected from RADT-positive patients simultaneously with the RADT throat swab had no GAS isolated; the number of cultures submitted is unknown. Based on these results, WDH recommended that the clinic review testing procedures with the RADT manufacturer. The clinic subsequently reported to WDH that staff members were interpreting certain RADT results later than the recommended maximum incubation time of 5 minutes, a practice that can result in false-positives, according to the manufacturer.

WDH and CDC investigators reviewed IDSA guidelines for diagnosis and management of GAS pharyngitis with clinic practitioners. GAS cultured from throat swabs during

* Available at http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/2012%20Strep%20Guideline.pdf.

TABLE. Clinical characteristics of 44 patients evaluated for group A streptococcal pharyngitis (GAS) using a rapid antigen detection test (RADT) at a rural urgent-care clinic — Wyoming, March 2015

Characteristic	All patients (N = 44) No. (%)	Patients aged <3 yrs (n = 7) No. (%)	Patients aged ≥3 yrs (n = 34)		
			Patients aged ≥3 yrs (n = 34) No. (%)	With sore throat (n = 24) No. (%)	With no sore throat (n = 10) No. (%)
Age group (yrs)					
<3	7 (16)	7 (100)	—	—	—
3–19	18 (41)	—	18 (53)	14 (58)	4 (40)
20–61	16 (36)	—	16 (47)	10 (42)	6 (60)
Unknown	3 (7)	—	—	—	—
Symptom					
Sore throat	28 (64)	2 (29)	24 (71)	24 (100)	0 (0)
Cough	23 (52)	7 (100)	15 (44)	13 (54)	2 (20)
Rhinorrhea	19 (43)	5 (71)	13 (38)	11 (46)	2 (20)
Fever	15 (34)	4 (57)	9 (26)	6 (25)	3 (30)
Sinus congestion	14 (32)	3 (43)	11 (32)	9 (38)	2 (20)
Nausea	12 (27)	0 —	11 (32)	7 (29)	4 (40)
Ear pain	10 (23)	1 (14)	9 (26)	8 (33)	1 (10)
Headache	9 (20)	0 —	9 (26)	8 (33)	1 (10)
Fatigue	9 (20)	2 (29)	6 (18)	4 (17)	2 (20)
Vomiting	5 (11)	1 (14)	4 (12)	3 (13)	1 (10)
Lymphadenopathy	4 (9)	1 (14)	3 (9)	2 (8)	1 (10)
Rash	0 —	0 —	0 —	0 —	0 —
None (GAS exposure only)	2 (5)	0 —	2 (6)	0 —	2 (20)
Positive RADT result	38 (86)	6 (86)	29 (85)	21 (88)	8 (80)
Initial antibiotic therapy*					
1st gen. cephalosporin	6 (14)	0 (0)	6 (18)	4 (17)	2 (20)
2nd gen. cephalosporin	20 (45)	5 (71)	14 (41)	9 (38)	5 (50)
Amoxicillin-clavulanate	13 (30)	1 (14)	11 (32)	10 (42)	1 (10)
Clindamycin	3 (7)	1 (14)	1 (3)	1 (4)	0 —
None	2 (5)	0 —	2 (6)	0 —	2 (20)
Second antibiotic therapy†					
2nd gen. cephalosporin	1 (2)	0 —	1 (3)	1 (4)	0 —
Amoxicillin-clavulanate	2 (5)	0 —	2 (6)	2 (8)	0 —
None	41 (93)	7 (100)	31 (91)	21 (88)	10 (100)

Abbreviations: 1st gen. = first generation; 2nd gen. = second generation.
* Four patients with negative RADT results were prescribed antibiotics.
† Data are from March 13–17, 2015, only; it is unknown how many patients were prescribed a second antibiotic after March 17.

subsequent weeks was confirmed to be uniformly sensitive to penicillin and amoxicillin. Subsequently, the number of RADT-positive GAS pharyngitis cases declined, and the clinic returned to using penicillin or amoxicillin as first-line therapy.

Based on the available information, investigators determined that the clinic performed RADTs on patients unlikely to have GAS pharyngitis (e.g., no sore throat, or sore throat coincident with cough or rhinorrhea), which is inconsistent with IDSA guidelines. Possible reasons for RADT-positive results among these patients are GAS carriage (*1*) or RADT incubation periods exceeding manufacturer recommendations. Although RADTs are highly specific (*3*) and allow clinicians to make treatment decisions at the time of the patient visit, incorrect technique at the point of care can result in false-positives. As a result of these errors, patients likely to have viral illness were treated with antibiotics. The patients' failure to improve led to the assumption of bacterial resistance, which prompted use of broad-spectrum antibiotics as first-line therapy in subsequent patients. The clinic practitioners' recognition of their unusually high GAS incidence, request for assistance, and compliance with suggested interventions were critical in identifying and amending problematic practices.

Sore throat is one of the most common symptoms reported by outpatients (*4*,*5*), with viral infections responsible for the majority of cases (*1*). Correct diagnosis and treatment of GAS pharyngitis prevents acute rheumatic fever, shortens illness duration, and reduces person-to-person spread (*2*); however, antibiotic overuse for sore throat is common among both children and adults (*4*,*5*). This can result in unnecessary side effects and promote development of antibiotic resistance. Clinics should take steps to ensure practitioner understanding of and adherence to published guidelines, and to promote the use of good laboratory practices, such as periodic evaluation of competency in testing procedures (*6*).

[1]Epidemic Intelligence Service, CDC; [2]Public Health Sciences Section, Wyoming Department of Health; [3]Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital, Northwestern University School of Medicine, Chicago, Illinois; [4]Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC.

Corresponding author: Alexia Harrist, alexia.harrist@wyo.gov, 307-777-5532.

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Notes from the Field

Hepatitis C Outbreak in a Dialysis Clinic — Tennessee, 2014

Daniel Muleta, MD[1]; Marion A. Kainer, MBBS[1]; Loretta Moore-Moravian[1]; Andrew Wiese MPH[1]; Jennifer Ward MSc[1]; Sheila McMaster, MSN[2]; Duc Nguyen, MD[3]; Joseph C. Forbi, PhD[4]; Tonya Mixson-Hayden, PhD[4]; Melissa Collier, MD[4]

Outbreaks of hepatitis C virus (HCV) infections can occur among hemodialysis patients when recommended infection control practices are not followed (*1*). On January 30, 2014, a dialysis clinic in Tennessee identified acute HCV in a patient (patient A) during routine screening and reported it to the Tennessee Department of Health. Patient A had enrolled in the dialysis clinic in March 2010 and had annually tested negative for HCV (including a last HCV test on December 19, 2012), until testing positive for HCV antibodies (anti-HCV) on December 18, 2013 (confirmed by a positive HCV nucleic acid amplification test). Patient A reported no behavioral risk factors, but did have multiple health care exposures.

On April 16, 2014, the Tennessee Department of Health observed infection control practices at the clinic. Clinic officials reported that no changes to infection control protocols at the dialysis clinic had been made from the time patient A was identified to this date of observation. The health department observers noted that no visible blood was present on any surfaces, sinks were easily accessible, staff hand hygiene was performed consistently, and gloves and other personal protective equipment were used appropriately. Individual patient stations were disinfected after the previous patient left the station, with a 1:100 diluted household bleach solution, and surfaces were allowed to dry completely between patients. Medications were prepared for each patient in a separate, clean medication room at the time of administration; no multidose medication vials were carried into patient care areas. Blood for glucose testing was drawn from dialysis access sites with a syringe and tested by a glucometer in the laboratory. The glucometer was adequately disinfected between uses. Monthly trainings in infection control had been consistently provided to all staff members before the outbreak was identified.

Sixty-two dialysis patients were being treated at the clinic at the time of the investigation; all were retested for HCV. Nine (15%) patients, including patient A, were HCV-infected; specimens from patient A and five other chronically infected dialysis patients were positive for HCV genotype 1a (Figure), the remaining three were positive for genotype 1b. Genotype 1a is the most prevalent genotype in the United States (*2*). Patient B, who seroconverted in December 2010, had a history of injection drug use, which, at the time of diagnosis, was considered to be the source of exposure. Patient C was chronically infected and had tested positive for HCV upon admission at the dialysis clinic. Infection duration for all other HCV infected patients, including patient C, was unknown.

Quasispecies (HCV intra-genotype variants) analysis was performed from serum specimens collected from all nine patients found to be HCV positive. Patients A, B, and C were infected with genotype 1a; less than 5% nucleotide variation among intra-host HCV sequences was detected among the three patients, suggesting epidemiologic linkage of these infections (Figure). On separate occasions, patients A and B underwent dialysis on the same machine following patient C, during the most likely exposure periods (January–May 2013 for patient A and November 2009–June 2010 for patient B). Hospitalization events for patients A, B, and C during the likely exposure periods did not overlap in space and time. No other common exposures were identified.

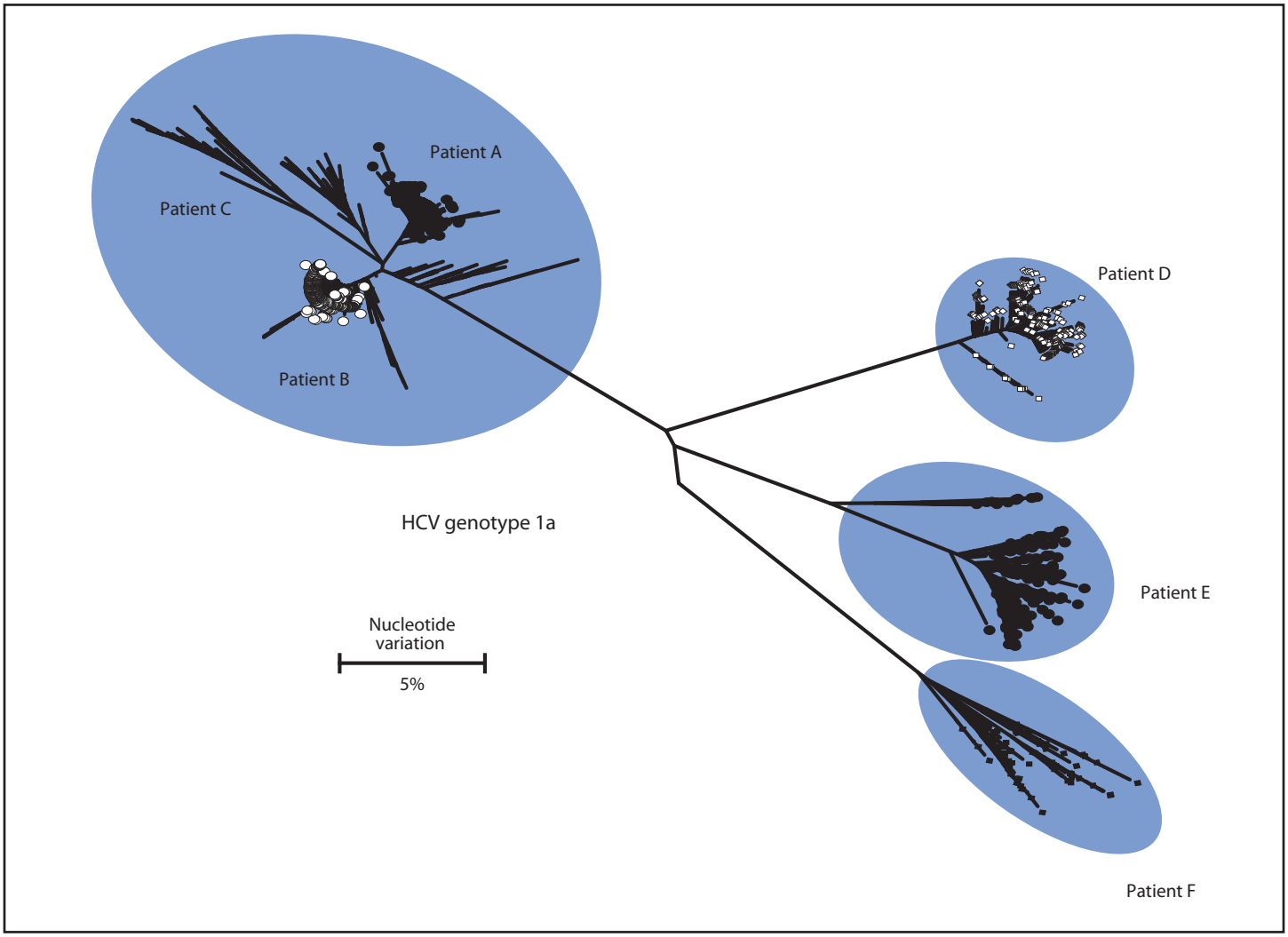
No specific event or practice was identified at the dialysis center that could have led to HCV transmission. However, the limited infection control practice observation time or unreported changes in practice between the transmission event and Tennessee Department of Health infection control observations might have affected these observations. The laboratory findings, the common station use, and the absence of other shared exposures support infection of patients A and B during dialysis at the clinic.

Following CDC recommendations (*3*) for HCV screening of dialysis patients by performing anti-HCV testing every 6 months and reporting new anti-HCV seroconversions (*4*) to local health departments are important practices for dialysis clinics. More rigorous HCV screening regimens, combined with timely reporting of seroconversions to public health officials, will facilitate investigation and infection control improvement recommendations to prevent future infections. Even a single reported case of acute HCV infection in a hemodialysis patient warrants health department investigation, because it might represent intra-facility transmission.

[1]Tennessee Department of Health; [2]End Stage Renal Disease Network 8, Ridgeland, Mississippi;[3]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Diseases, CDC; [4]Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC.

Corresponding author: Daniel Muleta, Daniel.Muleta@tn.gov, 615-532-6633.

FIGURE. Nucleotide variation in hepatitis C quasispecies (E1-HVR1 region, 306 base pairs in length) among six patients* at a dialysis clinic — Tennessee, 2014



* Patient C's hepatitis C test was positive on entry to the dialysis clinic; patients A and B seroconverted after beginning dialysis. Patients D, E, and F are other chronic hepatitis C-infected patients in treatment at the clinic, and were not genetically linked to the outbreak.

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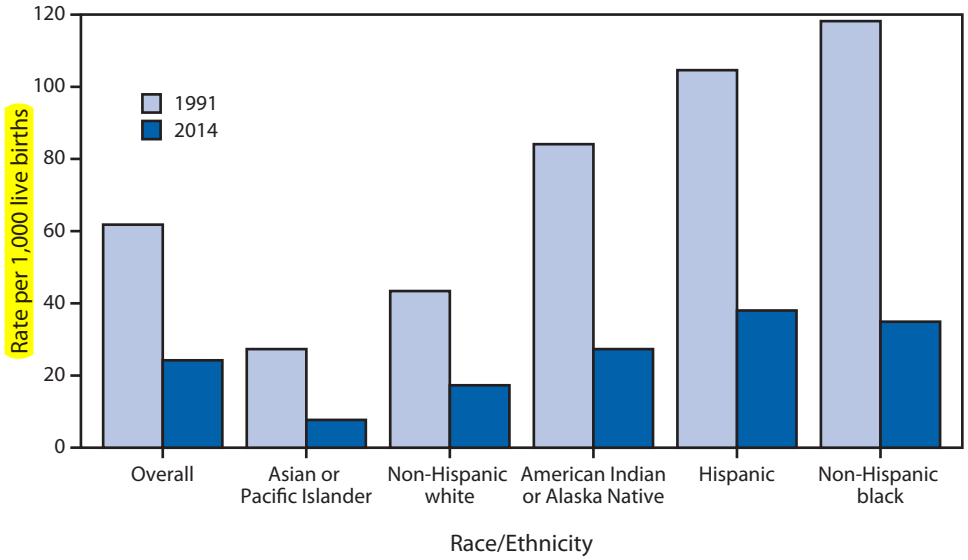
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Birth Rates Among Females Aged 15–19 Years, by Race/Ethnicity* — National Vital Statistics System, United States,† 1991 and 2014



* For American Indian or Alaska Natives and Asian or Pacific Islanders, includes persons of Hispanic and non-Hispanic origin.
† Data are for U.S. residents only.

From 1991 to 2014, the birth rate for females aged 15–19 years declined 61%, from 61.8 to 24.2 births per 1,000, the lowest rate ever recorded for the United States. Declines ranged from 60% for non-Hispanic white teens to 72% for Asian or Pacific Islander teens. Despite the declines among all groups, teen birth rates by race/ethnicity continued to reflect wide disparities. In 1991, rates ranged from 27.3 per 1,000 for Asian or Pacific Islanders to 118.2 for non-Hispanic blacks; in 2014, rates ranged from 7.7 for Asian or Pacific Islanders to 38.0 for Hispanics.

Source: Hamilton BE, Martin JA, Osterman MJ, et al. Births: final data for 2014. Natl Vital Stat Rep 2015;65(12). Available at http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_12.pdf.

Reported by: T.J. Mathews, MS, tmathews@cdc.gov; Brady E. Hamilton, PhD, bhamilton@cdc.gov.

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