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Congenital Transmission of Chagas Disease — Virginia, 2010

Chagas disease, caused by infection with the parasite *Trypanosoma cruzi*, affects 8–11 million persons globally (*1*). In the endemic areas of Mexico, Central America, and South America, most infections are transmitted by triatomine insect (kissing bug) vectors. However, infection also can be acquired congenitally or through blood transfusion, organ transplantation, consumption of triatomine-contaminated food or drink, or laboratory accident (*2*). Early detection and treatment are highly effective; however, acute infection often is subclinical, and most persons are unaware of their infection. If left untreated, the infection is lifelong. The majority of persons with chronic infection remain without signs or symptoms, but 20%–30% eventually develop disease manifestations, most commonly, cardiomyopathy. Migration from endemic areas has led to an estimated 300,000 persons in the United States with chronic Chagas disease (*3*), including women of reproductive age who risk transmitting the infection to their children. This report describes the first case of congenital Chagas disease in the United States confirmed by CDC and highlights the importance of raising awareness of Chagas disease among health-care providers.

Case Report

In August 2010, a boy was born to a mother, aged 31 years, who recently had moved to the United States from Bolivia. A cesarean delivery was performed at 29 weeks gestation because of fetal hydrops. The mother reported no chronic medical conditions. The newborn's Apgar scores were 6 at 1 minute and 9 at 5 minutes (normal: 7–10 at 5 minutes). His birth weight was 1,840 grams. He was noted to have ascites, pleural effusion, and pericardial effusion. Diagnostic paracentesis revealed that the ascites fluid was nonexudative. The child had direct hyperbilirubinemia, but electrolytes and glucose were normal. Serologic tests for *Toxoplasma gondii*, rubella virus, and cytomegalovirus were negative. Herpes simplex virus (HSV) immunoglobulin G was positive; however, HSV cultures and a polymerase chain reaction (PCR) test for HSV nucleic acid were negative. Cytomegalovirus PCR, enterovirus PCR, malaria smear, and hepatitis panel also were negative. Acyclovir was administered, and the child received ampicillin and gentamicin for 5 days for presumed sepsis. Antibiotics were stopped after his clinical status improved and blood cultures were negative.

In the child's second week of life, his physicians learned from the mother that, at the time of her previous pregnancy in Bolivia, she had been told that she had Chagas disease. She had not received antitrypanosomal treatment. The child's peripheral blood again was examined, and a blood smear revealed *T. cruzi* trypomastigotes (the extracellular form of the parasite). Serologic tests for anti–*T. cruzi* antibodies were positive, and *T. cruzi* PCR was strongly positive. An echocardiogram showed no abnormality other than pericardial effusion, no rhythm disturbances were noted during cardiac monitoring, and the child's neurologic examination was normal. He was treated with a 60-day course of benznidazole. His ascites and effusions resolved. Follow-up laboratory testing performed at age 10 months showed that the boy had been cured, based on negative results of *T. cruzi* PCR and negative serologic tests for anti–*T. cruzi* antibodies.

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Serologic testing of the child's mother confirmed that she had Chagas disease. A complete history and physical examination revealed no signs or symptoms of the infection, and her electrocardiogram was normal. She was advised to complete a course of antitrypanosomal therapy after her child was weaned. Her other children, who remain in Bolivia, have been referred to a local physician to determine if they are infected.

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Editorial Note

Congenital *T. cruzi* infection has no specific clinical signs. Infected newborns often are asymptomatic or have subtle manifestations. The 10%–40% of newborns who are symptomatic might have low birth weight, low Apgar scores, hepatosplenomegaly, respiratory distress, anasarca, cardiac failure, or meningoencephalitis (*4*). Severe congenital Chagas disease carries a high risk for neonatal death. However, even severe disease might not be recognized because of the lack of defining clinical features and because the diagnosis is not considered. The diagnosis can be made by detecting *T. cruzi* in cord blood or peripheral blood from the newborn by examination of Giemsa-stained blood smears or buffy coat by light microscopy (*5*). Molecular methods are the most sensitive, but a positive PCR should be confirmed with a second specimen, because low levels of DNA occasionally are found at birth in uninfected children born to infected mothers. If all results are initially negative, testing of the child should be repeated at 4–6 weeks to confirm lack of infection, because the level of parasitemia increases in the month after birth. Results of serologic testing of uninfected children should be negative at age 9–12 months, after maternal antibodies have waned.

Treatment of congenital infection is highly effective, with cure rates >90% when instituted in the first few weeks of life. Benznidazole and nifurtimox, the antitrypanosomal drugs used to treat Chagas disease, are not Food and Drug Administration–approved in the United States, but they are available through CDC for use under investigational protocols.

The case presented in this report is the first documented congenital transmission of *T. cruzi* in the United States. Additional, but unrecognized, cases likely exist. Congenital transmission occurs in 1%–10% of children born to infected mothers (*6*–*8*). Data about the prevalence of chronic Chagas disease in the United States among women of reproductive age are limited, and the risk for transmission in nonendemic areas is unknown. However, by using country-specific seroprevalence and birth

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What is already known on this topic?

Untreated Chagas disease is a lifelong parasitic infection that eventually can cause cardiomyopathy or other disease manifestations. Chagas is acquired through contact with triatomine insect (kissing bug) vectors or through other routes, including congenital transmission. Congenital transmission occurs in 1%–10% of children born to infected mothers.

What is added by this report?

A child delivered at 29 weeks gestation in the United States was diagnosed with Chagas disease at age 2 weeks when *Trypanosoma cruzi* trypomastigotes were detected in his peripheral blood. His mother, from Bolivia, was in apparent good health, but later mentioned that she had been diagnosed with Chagas disease in Bolivia. The child was cured with a 60-day course of benznidazole. This first reported case of congenital transmission of Chagas disease in the United States illustrates that congenital Chagas disease, even when severe, might not be recognized or diagnosis might be delayed because of the lack of defining clinical features or because the diagnosis is not considered.

What are the implications for public health practice?

Chagas disease affects an estimated 300,000 persons in the United States; most have emigrated from endemic areas of Latin America where the infection was acquired. Increased awareness of Chagas disease is needed among health-care providers so that pregnant women potentially at risk for Chagas disease can be screened serologically and infected offspring identified and treated. Data about the prevalence of Chagas disease in pregnant women are needed to guide decisions and recommendations for screening.

rates among immigrants from endemic areas who now live in the United States, and assuming a risk for transmission of 1%–5%, the annual incidence of congenital Chagas disease in the United States recently was estimated to be 65–315 cases (*3*). Other reports estimate the annual incidence at 166–638 cases (*4*). Data about the prevalence of *T. cruzi* infection in pregnant women are needed to guide decisions about the utility of and approaches to screening.

Obstetrician-gynecologists in the United States have limited knowledge of Chagas disease (*9*). Increased awareness of Chagas disease is needed among health-care providers so that pregnant women who have emigrated from Mexico, Central America, and South America, and who might have been at risk for infection with *T. cruzi* can be identified and screened serologically. If the mother is known to have chronic Chagas disease, the newborn should be tested and, if infected, given prompt treatment. All children previously born to seropositive mothers should be screened serologically and offered treatment, if needed. Although treatment is most effective when provided early in infection, treatment of chronic infection might prevent or slow disease progression (*10*). The safety of antitrypanosomal drug use in pregnancy has not been studied; however, treatment of the mother after delivery and when she has finished breastfeeding is recommended (*10*) and might reduce the incidence of transmission of *T. cruzi* among future offspring.

CDC provides assistance for questions about laboratory diagnosis, management, and treatment of Chagas disease by telephone (404-718-4745) and e-mail (parasites@cdc.gov). Additional information about Chagas disease is available at http://www.cdc.gov/chagas.

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Unexplained Respiratory Disease Outbreak Working Group Activities — Worldwide, March 2007–September 2011

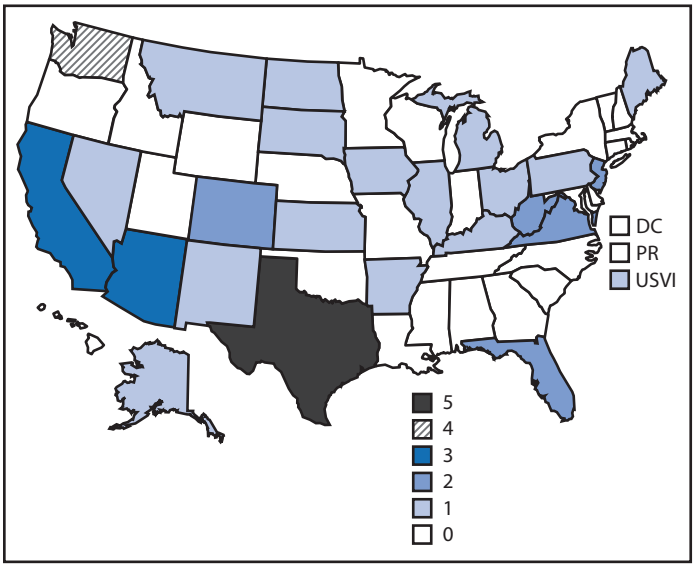
The Unexplained Respiratory Disease Outbreak (URDO) working group is a multidisciplinary team composed of approximately 40 scientists from across CDC with expertise in infectious and noninfectious respiratory diseases. The URDO working group was formed in 2004 to streamline CDC response efforts to assist local, state, and international public health officials in investigations of unexplained respiratory disease outbreaks. This report summarizes URDO working group activities from March 2007 through September 2011. During that period, the URDO working group was notified of 57 investigations and facilitated consultations with subject matter experts (in all 57 investigations), laboratory testing at CDC (in 42 investigations), and on-site field investigation support (in eight investigations). Of these 57 investigations, 41 occurred domestically, and 16 occurred internationally. An etiology was identified in 29 (51%) investigations; among these, the most commonly implicated pathogens were non-influenza respiratory viruses (41%), influenza viruses (17%), *Mycoplasma pneumoniae* (14%), and *Bordetella pertussis* (14%). Notification occurred a median of 33 days after illness onset in the first case, which might have limited the ability to collect early laboratory specimens or epidemiologic data. Reducing delays in sample collection, epidemiologic investigations, and consultation with the URDO working group might increase the ability to identify etiologies and lead to more rapid control of these unexplained respiratory disease outbreaks.

The objectives of this analysis were to describe the investigations reported to the URDO working group from March 2007 through September 2011 and identify opportunities to improve the URDO working group's public health response. The URDO working group might be notified of unexplained respiratory disease outbreaks before the initiation of an investigation or during an ongoing investigation if uncertainty exists regarding the etiology or co-etiologies. Notifications were tracked beginning in March 2007, and correspondence from URDO working group investigators was collected. Because these materials often contained preliminary information from evolving investigations, this information was supplemented with field investigation final reports and publications, when available (*1*–*6*). Investigations were classified by the level of support provided, affected age group (children, adults, or both), setting, and whether the etiology was determined. Medians and ranges for the number of days from illness onset in the first case to notification were calculated, as were numbers of cases, hospitalizations, and deaths.

During March 2007–September 2011, the URDO working group was notified by state or international public health officials of 57 investigations. Of these, 41 occurred in the United States and its territories, and 16 occurred internationally (Figure). Notifications per year ranged from eight to 15 (Table 1). The median time from illness onset in the first case to notification (available for 37 investigations) was 33 days (range: 4–218 days). For all investigations, the URDO working group provided input through either telephone or e-mail consultation. Depending on the specific needs of the requestor, additional assistance ranged from advice given via conference calls with the working group (in 70% of investigations), to laboratory testing at CDC (74%), to on-site epidemiologic investigation assistance (14%) (Table 1). Once an etiology was identified or highly suspected, laboratory testing and investigation assistance were provided by CDC divisions with relevant subject matter expertise. Laboratory testing included molecular diagnostics for respiratory pathogens using polymerase chain reaction (PCR), serology, culture, histopathology, immunohistochemistry, and urine antigen testing. Additionally, in 13 investigations, the URDO working group provided laboratory support with TaqMan Array Cards (Life Technologies, Grand Island, New York), a PCR-based technology that tests simultaneously for approximately 20 respiratory pathogens (*7*).

Fifty-one investigations involved two or more cases. Of the other six investigations, one involved a pseudo-outbreak caused by clinical specimen contamination (*4*), and five involved single case consultations. The exact case count was available for 49 investigations; the median case number was 15 (range: one to 409 cases). The number of hospitalizations was available in 32 (56%) investigations (median: three; range: zero to 18). Among 26 (46%) investigations with two or more cases and numbers of cases and hospitalizations reported, the median percentage of cases resulting in hospitalization was 23% (range: zero to 100%). A total of 36 (63%) investigations had the number of deaths reported (median: zero, range: zero to 12, with one outlier from a wild-type poliovirus outbreak with 169 deaths reported) (*3*). The URDO working group was notified of this outbreak because it appeared initially to have a respiratory component. Age ranges of affected persons were reported in 52 (91%) investigations; adults were affected most commonly (Table 2). Communities (i.e., noninstitutional settings) and long-term–care facilities were the most common settings for outbreaks (Table 2).

FIGURE. Number of notifications received by the Unexplained Respiratory Disease Outbreak working group, by state/territory — United States, March 2007–September 2011*



Abbreviations: PR = Puerto Rico; USVI = U.S. Virgin Islands.
* International notifications: Mexico (four) and one each for Australia, Brazil, Guatemala, Honduras, Kenya, Nepal, Nicaragua, Panama, Republic of Congo, Rwanda, Taiwan, and United Kingdom.

The etiology was determined in 29 (51%) investigations, based on the interpretation of laboratory results with clinical and epidemiologic information. The most commonly identified etiologies were influenza viruses, *Mycoplasma pneumoniae*, *Bordetella pertussis*, and noninfluenza respiratory viruses (e.g., respiratory syncytial virus, adenovirus, and parainfluenza virus) (Table 2). Five (9%) investigations involved multiple etiologies. CDC provided laboratory support for 24 (83%) of 29 investigations with confirmed etiologies and for 18 (64%) of 28 that remained unexplained. Among 13 investigations involving TaqMan Array Cards, the etiology was identified for six (e.g., parainfluenza virus 3, *Streptococcus pneumoniae*, *Chlamydophila pneumoniae*, human parechovirus, human metapneumovirus, rhinovirus, and human enterovirus 68) (*6*). Of the seven investigations involving TaqMan Array Cards for which the etiology remained unclear, two or more pathogens were identified in five.

What is already known on this topic?

Respiratory disease outbreaks can present investigation challenges, especially because of the many potential etiologies with overlapping clinical presentations.

What is added by this report?

The Unexplained Respiratory Disease Outbreak (URDO) working group provided varying forms of support, ranging from telephone consultation to laboratory testing to on-site field investigation assistance for 57 domestic and international investigations during March 2007–September 2011. A cause was found for 51% of the outbreaks investigated. The most common causes were influenza viruses, *Mycoplasma pneumoniae*, *Bordetella pertussis*, and noninfluenza respiratory viruses.

What are the implications for public health practice?

Reducing delays in sample collection, epidemiologic investigations, and consultation with the URDO working group might increase the ability to identify etiologies and lead to more rapid control of these unexplained respiratory disease outbreaks.

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TABLE 1. Number and percentage of notifications received by the Unexplained Respiratory Disease Outbreak working group, by year and type of support provided — worldwide, March 2007–September 2011

	2007*		2008		2009		2010		2011*		Total	
Notifications/Type of support	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total no. of notifications†	**8**	**(100)**	**14**	**(100)**	**15**	**(100)**	**9**	**(100)**	**11**	**(100)**	**57**	**(100)**
Epidemiologic consultation via conference call	6	(75)	11	(79)	9	(60)	7	(78)	7	(64)	**40**	**(70)**
Laboratory testing§	6	(75)	13	(93)	9	(60)	8	(89)	6	(55)	**42**	**(74)**
Field epidemiologic investigation§	4	(50)	1	(7)	1	(7)	1	(11)	1	(9)	**8**	**(14)**

* Not full years (i.e., March–December for 2007 and January–September for 2011).
† All outbreak notifications resulted in at least a telephone or e-mail consultation.
§ Laboratory testing and field epidemiologic investigation support was provided by CDC teams from divisions with subject matter expertise in the identified or suspected etiologies.

TABLE 2. Number (N = 57) and percentage of notifications received by the Unexplained Respiratory Disease Outbreak (URDO) working group, by selected characteristics — worldwide, March 2007–September 2011

Characteristic	Notifications*	
	No.	(%)
Information on age of affected persons available	52	(91)
Principal age group affected		
Children	12	(23)
Adults	30	(58)
Children and adults	10	(19)
Information on setting available	51	(89)
Community†	21	(41)
Long-term–care facility	10	(20)
School/Child care facility/College	5	(10)
During travel	8	(16)
Prison	3	(6)
Acute-care facility§	2	(4)
Other¶	2	(4)
Consultation for nonoutbreak situations	6	(11)
Consultation on single severe case**	5	(83)
Pseudo-outbreak††	1	(17)
No. of investigations with etiologies determined	29	(51)
Multiple pathogens identified	5	(17)
Specific etiologies identified§§		
Influenza viruses¶¶	5	(17)
Mycoplasma pneumoniae	4	(14)
Bordetella pertussis	4	(14)
Streptococcus pneumoniae	2	(7)
Noninfluenza respiratory viruses***	12	(41)
Other†††	7	(24)

* Numbers as reported to the URDO working group; final outbreak case report numbers included only if provided to the URDO working group.
† Includes investigations that occurred in noninstitutional settings.
§ Hospital (one notification) and psychiatric treatment facility (one).
¶ Refugee camp (one notification) and workplace (one).
** Case of severe community-acquired pneumonia (one notification); cases of severe respiratory disease in single travelers (four).
†† Determined to be caused by contamination of clinical specimens and not a disease outbreak.
§§ Includes investigations with multiple pathogens identified.
¶¶ Influenza A (H1N1)pdm09 (four notifications) and influenza A (H3N2) (one).
*** Respiratory syncytial virus (three notifications), parainfluenza virus 3 (two), adenovirus (two), adenovirus 14 (one), and one each for human metapneumovirus, parechovirus, enterovirus 68, and rhinovirus.
††† One notification each for *Chlamydophila pneumonia*, human herpesvirus 2, *Legionella*, *Bordetella parapertussis*, *Bordetella pertussis* pseudo-outbreak, *Rickettsia rickettsii*, and wild poliovirus type 1.

Editorial Note

Respiratory disease outbreak investigations present several challenges. Clinical presentation alone usually is insufficiently distinct to permit identification of an etiology. Respiratory specimens of good quality can be difficult to obtain in a timely manner, and local laboratory capability to test for multiple potential causes often is limited. Furthermore, rapid identification of the etiology is important for timely implementation of control measures (e.g., appropriate infection control, vaccination, and chemoprophylaxis). To enhance public health responses to unexplained respiratory outbreaks, CDC integrated epidemiologic and laboratory expertise from across the agency to form the URDO working group to advise, conduct laboratory testing, and facilitate CDC assistance for these outbreaks. During the evaluation period (March 2007–September 2011), the URDO working group was notified of 57 investigations, 29 (51%) of which resulted in the identification of the etiology. Common respiratory pathogens, such as influenza viruses, *Mycoplasma pneumoniae*, *Bordetella pertussis*, and noninfluenza respiratory viruses, were identified as the etiology for several outbreaks. Additionally, the URDO working group assisted with investigations of illnesses with respiratory symptoms that were determined to be primarily nonrespiratory (e.g., *Rickettsia rickettsii* infection and polio). The URDO working group has capacity to provide rapid, multipathogen testing with TaqMan Array Cards for investigations in which several etiologies are under consideration.

Information is available to guide investigations of unexplained respiratory disease outbreaks. These materials include documents that can assist public health officials with establishing case definitions, forming line lists, and generating epidemic curves, as well as a sample respiratory illness questionnaire and instructions for specimen collection (*8*). Of particular importance are disease outbreaks that 1) might be interrupted by timely vaccination (*5*), environmental interventions, or other control methods; 2) occur in institutional settings or among vulnerable populations; 3) might involve bioterrorism agents; 4) are severe, large, or rapidly progressive; or 5) cause public concern (*8,9*). Such outbreaks might warrant notification of the URDO working group and further investigation.

The findings in this report are subject to at least three limitations. First, the fraction of unexplained respiratory outbreaks that are reported is not known; reported outbreaks might not represent the distribution of etiologies among all unexplained respiratory outbreaks. Second, the URDO working group is provided information while investigations are under way but does not systematically collect final reports from local public health officials. Therefore, the data in this report likely underestimate case counts, hospitalizations, and deaths. Finally, information was not collected about unexplained respiratory disease investigations occurring before March 2007, so determining whether the URDO working group has improved identification of etiologies or outbreak mitigation is not possible.

An etiology was identified in only about half of all investigations by the URDO working group. This might result, in part, from delays in clinical specimen collection because many pathogens (e.g., influenza) only can be detected for a short time after illness onset (*10*). The URDO working group was notified of each outbreak a median of 33 days after illness onset in the first case. These delays might have resulted from delayed outbreak recognition or because local investigators waited until local testing failed to identify the etiology. Reducing the time

between outbreak recognition and notification might increase the likelihood that optimal respiratory specimens are collected. However, even when timely specimens are obtained, sensitive and specific laboratory diagnostic tests might not be available locally or at CDC for some known pathogens and for new pathogens. Finally, gaps in available clinical and epidemiologic information might decrease the URDO working group's ability to determine plausible etiologies and to recommend appropriate diagnostics.

Health-care providers and facilities are encouraged to report suspected outbreaks early to local public health officials, and health officials are invited to consult the URDO working group early in the course of any unexplained respiratory disease investigation. Additionally, CDC recommends that public health officials collect and store clinical specimens as an investigation evolves for potential future testing. The URDO working group provides an example of a successful, interdisciplinary approach to providing assistance to public health professionals in the United States and abroad. The URDO working group can be contacted through CDC's Emergency Operations Center by telephone, at 770-488-7100. Additional information and resources are available at http://emergency.cdc.gov/urdo.

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Members of the URDO working group: Sasha Klimov, Mike Jhung, Ashley Fowlkes, Greg Armstrong, Larry Anderson, David Shay, Gayle Fischer Langley, Nicole Alexander, Barry Fields, Marc Fischer.

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CDC Grand Rounds: the TB/HIV Syndemic

Since Robert Koch's 1882 discovery of *Mycobacterium tuberculosis*, substantial progress has been made in tuberculosis (TB) control. Nevertheless, in the latter part of the 20th century, a long period of neglect of both quality program implementation and research led to persistently high TB incidence rates and failure to develop new tools to adequately address the problem. Today, most of the world continues to rely on the same diagnostic test invented by Koch approximately125 years ago and on drugs developed 40 years ago. The world now faces a situation in which approximately 160 persons die of TB each hour (1.45 million died in 2009), in which a quarter of all deaths in persons with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (PWHA) are caused by TB, and in which the evolution of the bacteria has outpaced the evolution of its treatment to such an extent that some forms of TB are now untreatable (*1*). More recently, renewed attention has been given to reducing the global burden of TB (*2*), but much remains to be done.

Misconceptions Regarding TB

Misconceptions about TB infection and disease impede patient care, program implementation, and policy innovation. The first misconception is that TB infection and TB disease are the same. For TB disease prevention and control purposes, the global population can be divided into three discrete groups: those without TB infection, those with TB infection, and those whose TB infection has developed into TB disease. The lifetime risk that a person with TB infection will develop TB disease is 5%–10%; that risk is much higher among PWHA (*3,4*). A successful control strategy must, therefore, address each group.

A second misconception about TB is that it is no longer a major public health problem. In fact, of the 7 billion persons in the world, 2.3 billion are already infected with TB, and about 9 million develop TB disease each year. Furthermore, TB causes about 1.4–2 million deaths annually (Figure 1) (*1*).

A third misconception is that TB can be diagnosed easily by a physician or laboratory. To diagnose TB infection, only two tests are validated currently: the tuberculin skin test (TST) and the interferon gamma blood test. Unfortunately, TST is neither sensitive nor specific for TB infection, and both tests can be difficult to implement in resource-limited settings. To diagnose TB disease, most laboratories examine sputum with a microscope to look for TB bacilli, the same approach that Koch invented. In PWHA, the sensitivity of microscopic examination is low, approximately 40% (*5–7*). Given the high risk for death in PWHA who have untreated TB, this low sensitivity is a critical challenge that must be addressed. Culture of sputum for *M. tuberculosis* is considered the gold standard test, but it is difficult to use and, in resource-limited settings, challenging to implement. Culturing *M. tuberculosis*, a slow-growing airborne pathogen, requires laboratories that employ high levels of biosafety and specialized technicians. In 2010, the Xpert MTB/Rif assay, a sensitive, easy-to-use, polymerase chain reaction (PCR)–based test was validated. With no need for sophisticated biosafety or specialized technicians and a turnaround time of 2 hours for both TB diagnosis and detection of drug resistance, this assay has the potential to improve TB control in the developing world (*8*). Limiting its current use is the relatively high cost of the necessary equipment and supplies, a lack of evidence that the assay's use is feasible in routine practice, and the fact that it has not yet been demonstrated to improve patient outcomes in resource-limited settings.

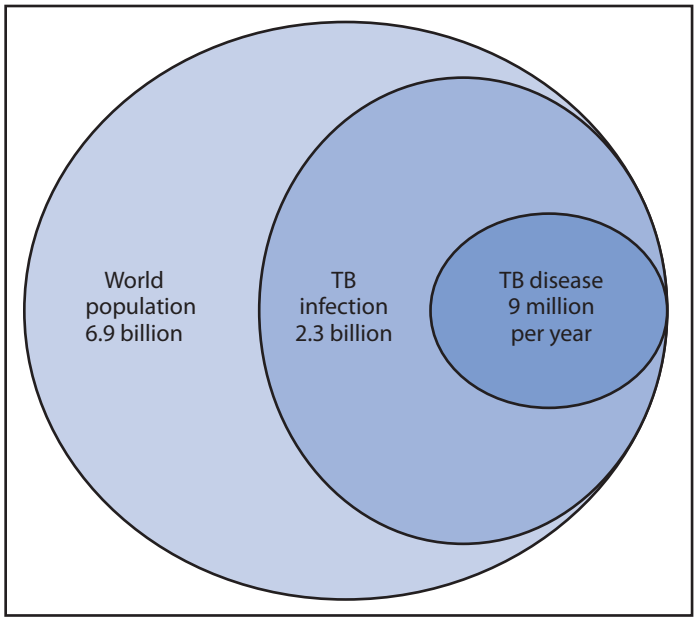
This is another in a series of occasional MMWR *reports titled CDC Grand Rounds. These reports are based on grand rounds presentations at CDC on high-profile issues in public health science, practice, and policy. Information about CDC Grand Rounds is available at http://www.cdc.gov/about/grand-rounds.*

TB/HIV Syndemic*

TB and HIV act synergistically within a population to cause excess morbidity and mortality. PWHA are more likely to develop TB disease because of their immunodeficiency; HIV infection is the most powerful risk factor for progressing from TB infection to disease (*4*). Diagnosing TB disease among PWHA is particularly challenging because PWHA who have pulmonary TB frequently have negative sputum smears and up to one third might have completely normal chest radiographs (*5*). Furthermore, TB in PWHA often occurs outside the lungs, evading traditional diagnostic tests. Because TB is both common and difficult to diagnose, many PWHA feel ill but are unaware that they have TB. A recent review found that when systematic efforts were undertaken to diagnose TB, approximately 8% of patients who went to HIV care and treatment facilities were found to have TB disease (*9*), although the exact proportion varies substantially depending on the epidemiology of TB in the area. Finally, TB is a frequent cause of death for PWHA, particularly if HIV disease is advanced and antiretroviral therapy (ART) has not yet been initiated. Persons with both diseases must adhere to complex

*Additional information available at http://www.cdc.gov/nchhstp/programintegration/definitions.htm.

FIGURE 1. Estimated number of persons infected with TB and number who will develop TB disease each year — worldwide, 2010



Abbreviation: TB = tuberculosis.
Source: World Health Organization. Global tuberculosis control: WHO global report 2010. Geneva, Switzerland: World Health Organization; 2011. Available at http://www.who.int/tb/publications/global_report/archive/en/index.html.

drug regimens that might interact with each other and might have overlapping toxicities.

Combating the Dual Burden of Disease

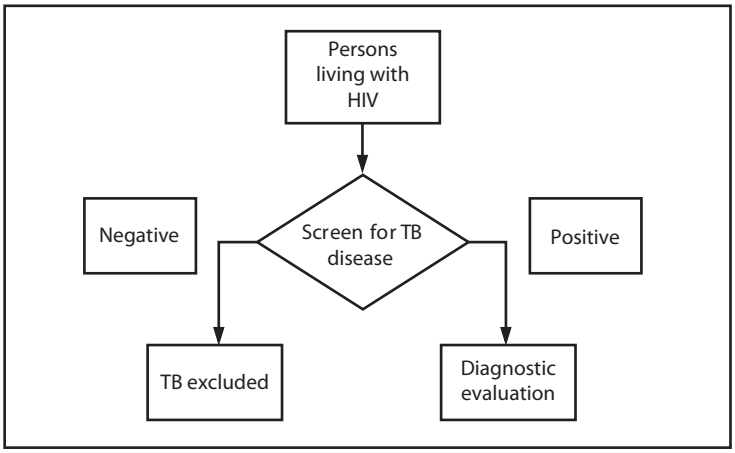
TB disease and death can be prevented in PWHA by early TB diagnosis and effective treatment of both diseases. Early diagnosis and treatment ensure that TB treatment is provided before the illness reaches an advanced stage, thereby decreasing mortality, and ensures that the duration of infectiousness is limited, thereby reducing transmission of TB to others. TB disease also can be prevented by treating persons with TB infection. Treatment of TB infection requires reliably excluding the presence of TB disease to avoid the development of drug resistance; drug resistance could emerge if a patient receives a single drug to treat TB infection when the patient, in fact, requires a multidrug regimen to treat TB disease.

Until recently, no internationally accepted, evidence-based, sensitive approach existed to screen PWHA for TB disease, although some preliminary data had begun to suggest that commonly used approaches were inadequate. CDC investigators partnered with the U.S. Agency for International Development (USAID), ministries of health, and nongovernmental organizations in three Southeast Asian countries to derive a TB screening algorithm that would solve this problem. This study concluded that asking patients about three symptoms (i.e., cough, fever of any duration, or night sweats lasting longer than 3 weeks) accurately categorized PWHA for targeted interventions. Patients with none of these three symptoms can be considered free of TB disease and offered treatment to prevent TB disease, if indicated; patients with at least one of these symptoms should have further diagnostic tests performed for TB disease (*5,6*) These criteria mark a significant improvement over the 2007 World Health Organization (WHO) guidelines in which screening was based primarily on the presence of chronic cough (*10*). Screening for cough lasting more than 2 weeks was only 33% sensitive for TB disease in this study; screening for the combination of symptoms increased sensitivity to 93% (Figure 2) (*5*). The increased sensitivity under the new criteria will lead to fewer missed diagnoses of TB disease, at the cost of requiring TB diagnostic evaluation for more people.

Although this approach simplifies TB screening, a comparable approach for simplifying diagnosis of TB disease remains elusive. In the same study, investigators learned that adding liquid culture of two sputum specimens more than doubled the yield of TB case detection among PWHA, compared with microscopic examination alone of the same two sputum specimens, as recommended by WHO at the time (76% versus 31% sensitivity) (*6*). Unfortunately, liquid culture is not widely available in resource-poor settings and requires high levels of training, biosafety, and supervision. It is hoped that introduction of the Xpert MTB/Rif assay, which is more sensitive than smear but less sensitive than liquid culture, along with other emerging diagnostic techniques, will improve diagnostic accuracy in PWHA who have symptoms of TB (*8*).

In persons who screen negative for TB disease, treatment of TB infection should be considered. The tuberculin skin test (TST) identifies persons with TB infection who can benefit from isoniazid preventive therapy (IPT), a regimen that involves ingesting isoniazid daily for at least 6 months. In the pre-ART era, clinical trials confirmed that IPT was effective in reducing the development of TB disease in TST-positive PWHA by 64% (*11*). Subsequently, in 1998, WHO recommended that all PWHA living in TB-endemic countries receive 6 months of IPT, and that TST screening generally was not needed in countries with a high burden of TB. Follow-up studies found that the benefit of IPT waned as early as 6 months after completion of IPT. In 2009, only 0.3% of PWHA globally received IPT (*1*). ART also can reduce the risk for TB disease in PWHA by 54%–92% and might have a synergistic effect when used with IPT (*12*). In collaboration with the Botswana Ministry of Health, and with funding from CDC and USAID, CDC conducted a clinical trial in Botswana to evaluate how much better TB could be prevented with a 36-month regimen of IPT in PWHA who had access to government-provided ART. This study found that among those with positive TSTs, 36 months of IPT reduced TB incidence by 74%, compared

FIGURE 2. Performance of symptom-screening criteria identified in a Southeast Asia study, compared with 2007 World Health Organization recommendations — Cambodia, Thailand, and Vietnam, 2006–2008



Predictor	Misclassified as not having TB	
	%	No. of patients
Cough ≥2 wks	67	179 (of 267)
Cough, fever, or night sweats ≥3 wks	7	18 (of 267)

Abbreviations: HIV = human immunodeficiency virus; TB = tuberculosis.
Sources: World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: recommendations for HIV-prevalent and resource-constrained settings. Geneva, Switzerland: World Health Organization; 2007. Available at http://www.who.int/hiv/pub/tb/pulmonary/en/index.html.
Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. N Engl J Med 2010;362:707–16.

with persons receiving only 6 months IPT. When the analysis was limited to TST-positive trial participants randomized to the 36-month IPT arm who successfully completed the initial 6 months of IPT, the reduction in TB was 92%. As with previous studies, no significant benefit from IPT was observed for TST-negative participants (Figure 3). ART provided an added benefit to IPT's protective effect, reducing TB risk a further 50% in all groups (*13*).

These findings have enormous implications for controlling the TB epidemic in countries with a high burden of HIV. If 36 months of IPT were provided to all TST-positive PWHA in Botswana, countrywide TB incidence would decline 45%[†] (Figure 4). A cost-effectiveness model of 10,000 PWHA in Botswana demonstrated that providing 36 months of IPT for PWHA with a positive TST result, in addition to ART for those with CD4 <250 cells/μL, could avert more incident TB cases with fewer resources than increasing the threshold for ART initiation alone (CD4 <350 or 500), suggesting any cost-effective TB prevention strategy should include the provision of IPT for TST-positive PWHA.

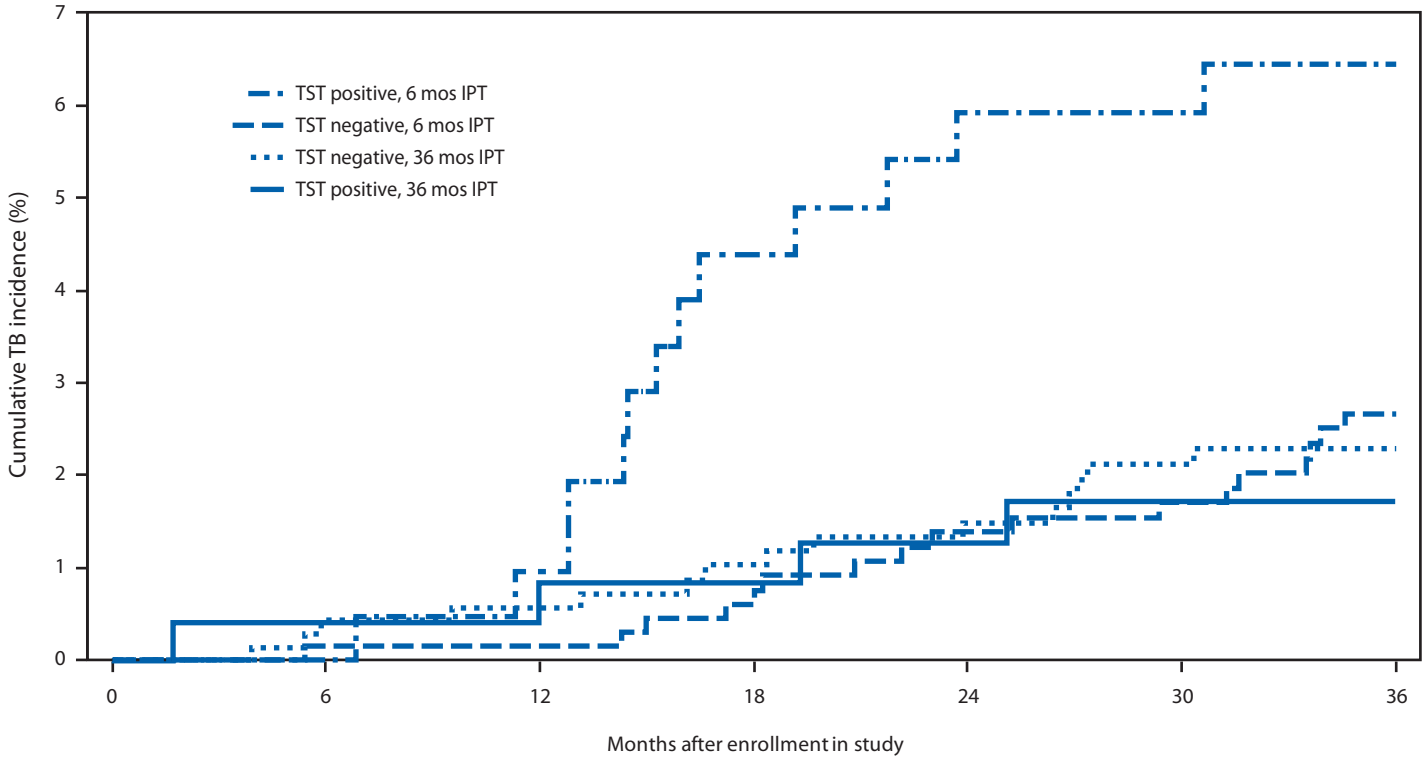
From Evidence to Guidance to Global TB Control

The strong evidence provided by the studies described above has been combined with results from other studies to update the global guidelines for TB screening and prevention (*14*). A recent WHO publication outlines four updated recommendations for resource-constrained settings: 1) PWHA should be screened with the new symptom-based algorithm, and those who do not report current cough, fever, weight loss, or night sweats are unlikely to have active TB and should be offered IPT (a minor modification to the algorithm developed in the CDC Southeast Asia study); 2) PWHA who report any of the aforementioned symptoms are considered suspects for TB disease and should be evaluated further for TB and other diseases as clinically indicated; 3) PWHA who are TST positive or have unknown TST status and are unlikely to have TB disease based on symptom screening should receive IPT for at least 6 months; and 4) in settings where feasible, PWHA should receive IPT for at least 36 months, or even lifelong. Where feasible, TST should be used to help identify those who would benefit most from IPT (*15*).

TB control relies on an international strategy known as "DOTS" (directly observed treatment, short course) that includes finding as many highly infectious patients with TB as possible, initiating effective treatment, directly observing drug ingestion to ensure adherence, and standardized monitoring, evaluation, and reporting. DOTS has saved approximately 7 million lives globally since 1990 (*1*). In the United States, the experience in New York City provides an example of the progress that can be made through full implementation of the DOTS strategy (*16*). However, although TB prevalence and deaths around the world did fall in the period after widespread global DOTS implementation, treatment programs generally have not resulted in a rapid reduction in global TB incidence

[†] Assuming provision of antiretroviral therapy to all PWHA if CD4 <200 cells/μL.

FIGURE 3. Cumulative incidence of TB disease in persons with HIV infection treated with 36 months of IPT compared with 6 months of IPT, by TST result — Botswana, 2004–2009



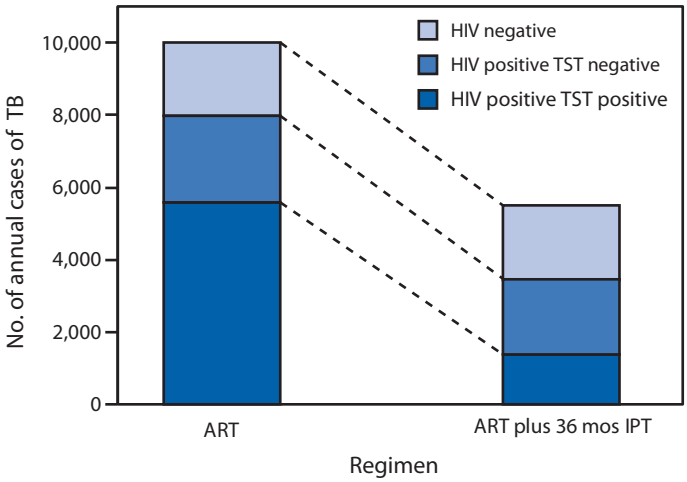
Abbreviations: HIV = human immunodeficiency virus; TB = tuberculosis; TST = tuberculin skin test; IPT = isoniazid preventive therapy.
Source: Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet 2011;377:1588–98.

(*17*). Multiple factors explain this phenomenon: insufficient resources and commitment to implement DOTS, in part because TB occurs predominantly in the poorest populations; a focus entirely on treatment of TB disease but not TB infection; the HIV epidemic; the emergence of multidrug resistant TB strains; and limited attention to the social determinants of sustained TB transmission and reactivation. Modeling studies suggest that detecting more infectious TB cases and successfully treating them will, on its own, be insufficient to drive down TB incidence and prevalence quickly and that the global TB strategy must address the large burden of latent TB infection that exists globally (*18*). The simplified symptom-based screening approach derived in the Southeast Asian study and the effective approach to chemoprophylaxis documented in the Botswana clinical trial help address this need.

The Way Forward

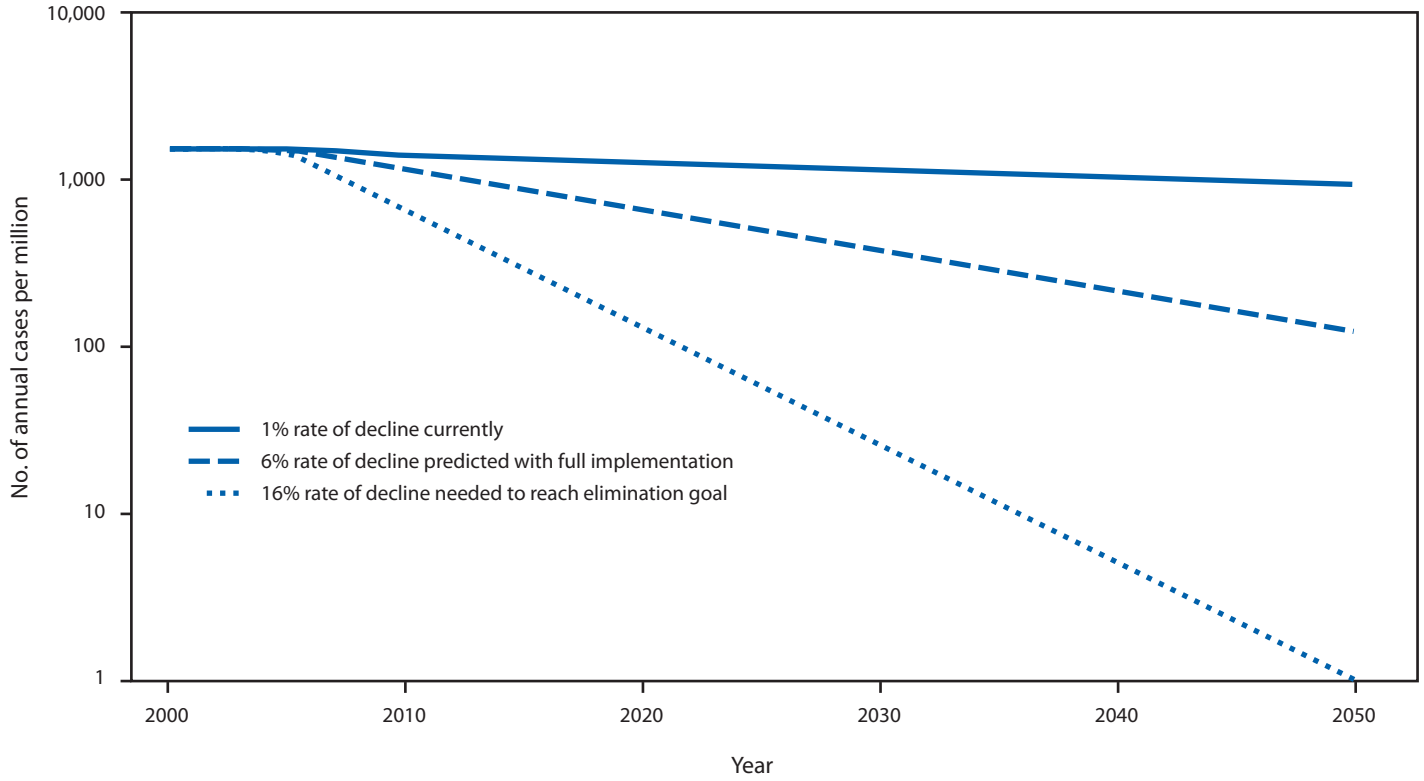
In a 2010 "call to action," global leaders in TB control outlined crucial areas that must be addressed to accelerate the decline in global TB incidence to more than 1% per year and to meet the target for the 2015 Millennium Development Goal (Figure 5) (*19*). Achieving this will require fully implementing

FIGURE 4. Potential reduction in TB cases in entire country if 36-month regimen of IPT and ART* is used to treat persons with HIV infection who have a positive TST result — Botswana, 2004–2009



Abbreviations: TB = tuberculosis; IPT = isoniazid preventive therapy; ART = antiretroviral therapy; HIV = human immunodeficiency virus; TST = tuberculin skin test.
* Provided to all HIV-infected persons if CD4 <250 cells/μL.

FIGURE 5. Current rate of decline in TB incidence compared with rate of decline with full implementation of STOP TB strategy, and rate of decline needed to reach elimination goal — worldwide, 2000–2050



Abbreviation: TB = tuberculosis.
Source: Marais BJ, Raviglione MC, Donald PR, et al. Scale-up of services and research priorities for diagnosis, management, and control of tuberculosis: a call to action. Lancet 2010;375:2179–91.

the DOTS strategy globally, and it will also require going far beyond that to address the limited impact that would be expected with DOTS alone, as outlined in WHO's latest STOP TB strategy (*20*). WHO calls for improvements in TB screening and diagnosis, including the use of newer TB diagnostic assays. In addition to these steps, treatment of latent TB infection also is needed (*18*). In settings with a high prevalence of HIV infection, implementing IPT can reduce TB incidence greatly. Finally, scientific advances are needed in three key areas to develop 1) an effective TB vaccine; 2) a shorter, simpler anti-TB drug regimen with efficacy against both drug-susceptible and drug-resistant TB; and 3) new diagnostic tests that can simply and accurately diagnose both TB infection and disease (*21*).

The fundamentals of TB control are early and accurate TB diagnosis, effective treatment, and prevention. The gap between what we know and what we need to know is large, but the gap between what we know and what we are implementing in practice is both larger and more harmful. By closing both our knowledge gap and our implementation gap, we can eliminate this deadly syndemic.

Reported by

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Injuries from Ingestion of Wire Bristles from Grill-Cleaning Brushes — Providence, Rhode Island, March 2011–June 2012

On July 3, 2012, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

Foreign object ingestion is a common reason for visiting an emergency department (ED), particularly for children (*1–3*). In recent years, internal injuries have been reported following unintentional ingestions of wire grill-cleaning brush bristles by both children and adults (*4–6*). A series of six cases from a single hospital system with two EDs during July 2009–November 2010 was reported previously (*4*). This report describes a series of six more cases identified at the same hospital system during March 2011–June 2012. The six patients ranged in age from 31 to 64 years; five were men. Like the patients in the previous series (*4*), all six reported outdoor residential food grilling and use of commercially available wire grill-cleaning brushes. The severity of injury ranged from puncture of the soft tissues of the neck, causing severe pain on swallowing, to perforation of the gastrointestinal tract requiring emergent surgery. Awareness of this potential injury among health-care professionals is critical to facilitate timely diagnosis and treatment. Additionally, awareness among the public, manufacturers who make wire grill-cleaning brushes, and retailers who sell these products can reduce exposures and decrease the likelihood of further occurrences. Before cooking, persons should examine the grill surface carefully for the presence of bristles that might have dislodged from the grill brush and could embed in cooked food. Alternative residential grill-cleaning methods or products might be considered.

The first of the six most recent cases was identified on March 14, 2011, and the latest on June 3, 2012. Medical staff members continue to conduct surveillance for additional cases of injury from ingested wire grill-cleaning brush bristles treated in the hospital system.

Case Reports

A man aged 50 years arrived at the ED with abdominal pain that had begun after eating steak at a backyard barbeque. Computed tomography (CT) scan of the abdomen and pelvis revealed a linear object extending through the wall of a loop of small intestine into the omentum (Figure). Laparotomy was performed to remove the foreign body, which appeared to be a wire bristle from a grill-cleaning brush. The patient fully recovered and was discharged the next day.

Five more patients visited the ED during August 2011–June 2012 after inadvertent ingestion of a wire bristle that had become dislodged from a grill-cleaning brush and embedded in food. In all of the cases, the bristles were initially identified by radiographs of the neck or CT scans of the abdomen and pelvis, and their origin was confirmed after removal (Table). Patient interviews revealed a common history of recent ingestion of grilled meat. After definitive treatment, all six patients recovered fully.

Severe pain on swallowing was the chief symptom in three of the six patients. In all three of these patients, a wire bristle from a grill-cleaning brush was found in the neck. The three included a woman aged 46 years and two men aged 50 and 64 years (Table). The three initially were evaluated with plain radiography, which identified the foreign object in each patient. One who was initially evaluated with plain radiography then underwent CT for precise localization. All three were treated successfully with laryngoscopic removal of the wire bristle.

Severe abdominal pain was the chief symptom of the other patients, who were three men aged 31, 35, and 50 years (Table). These patients were evaluated primarily with intravenous contrast-enhanced CT of the abdomen and pelvis. In two patients, the wire bristle was noted lodged within the omentum adjacent to a loop of small intestine. In one patient, the wire bristle was located within the sigmoid colon, indenting the bladder. Two patients underwent emergency abdominal surgery to retrieve the foreign object and repair the intestine. In one patient, the wire had not perforated the intestine and was removed via colonoscopy.

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Editorial Note

Foreign object ingestion resulted in approximately 80,000 ED visits in 2010 (*1*); the vast majority occurred in children (*1,2*). Serious morbidity from foreign object ingestion occurs in <1% of ED cases (*3*). Prior to 2012, two case reports described perforation of the upper gastrointestinal tract secondary to ingestion of a wire bristle from a grill-cleaning brush. In both patients, perforation resulted in abscess formation, one in a sublingual and one in a paraesophageal location (*5,6*). This report, like an earlier report from the same hospital system (*4*), suggests that such incidents might be more common than previously suspected. The continued occurrence of injuries from ingested wire bristles warrants further investigation and action.

FIGURE. Axial and coronal images (A, B) from intravenous contrast-enhanced computed tomography show a wire grill-cleaning brush bristle in the omentum (arrows), surrounded by soft tissue stranding (inflammation); a specimen radiograph (C) from omental resection confirms complete foreign object retrieval (arrow).

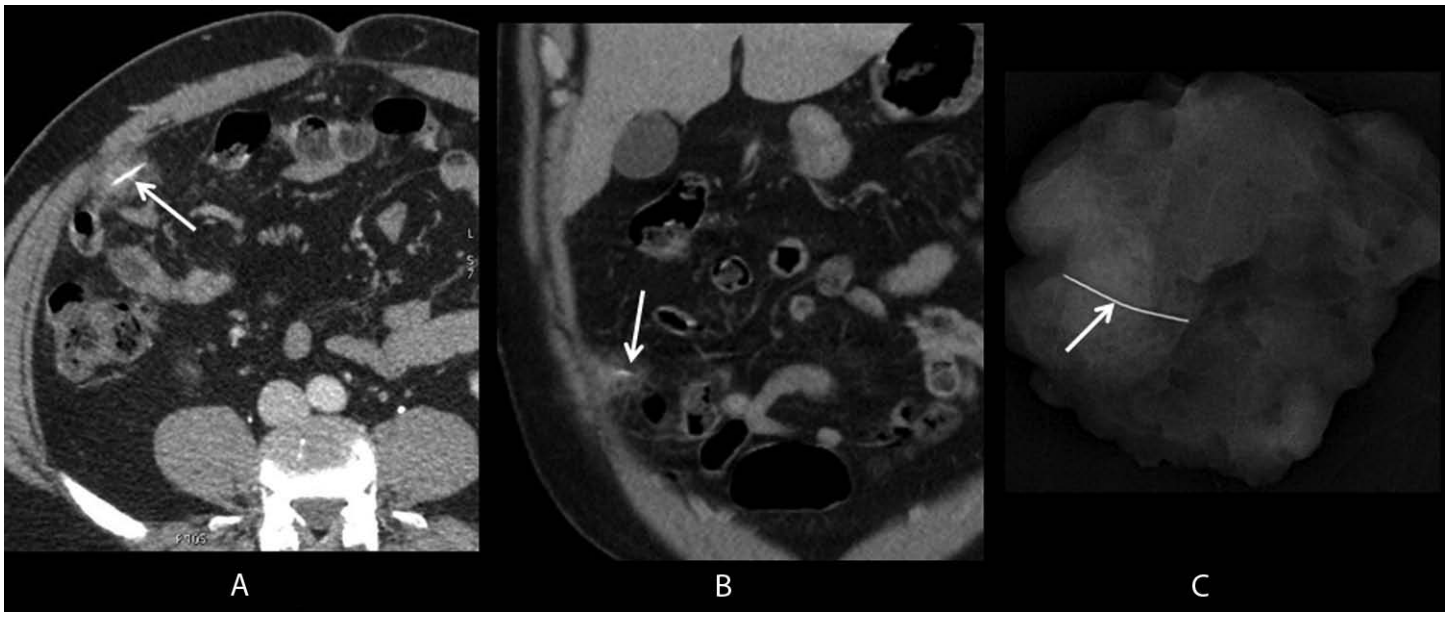

TABLE. Clinical characteristics of six patients with injuries after unintended ingestion of wire grill-cleaning brush bristles — Providence, Rhode Island, March 2011–June 2012

Month of onset	Age (yrs)	Sex	Diagnostic method	Anatomic site	Removal procedure
March 2011	50	Male	XR	Oropharynx	Laryngoscopy
August 2011	64	Male	XR, CT	Base of tongue	Laryngoscopy
November 2011	35	Male	CT	Greater omentum	Laparoscopy
April 2012	31	Male	CT	Sigmoid colon	Colonoscopy
May 2012	50	Male	CT	Greater omentum	Laparotomy
June 2012	46	Female	XR	Oropharynx	Laryngoscopy

Abbreviations: XR = radiograph; CT = computed tomography.

Actions to prevent these injuries include increasing awareness among consumers, manufacturers, retailers, and medical professionals to promote prevention, timely diagnosis, and appropriate treatment. Additionally, the Consumer Product Safety Commission (CPSC) currently is reviewing available grill-cleaning brush–related injury data to determine if an identifiable pattern of product defect could pose an unreasonable risk for injury or death, necessitating a consumer warning, product recall, or other regulatory action.

With the summer grilling season under way, broad awareness of the risk will help ED physicians, internists, and radiologists to quickly and appropriately diagnose this injury. These bristles are small, and can be quite difficult to visualize on plain radiographs and CT. If necessary, CT scans of the abdomen and pelvis should be performed without oral contrast, which can obscure the wire bristle. Clinical history is critical so that radiologic evaluation can be tailored to pinpoint the location of the wire (and potential complications) for the appropriate intervention. Additionally, public awareness might result in careful examination of any grill surface before use or use of alternative grill-cleaning methods or products. Awareness by manufacturers and retailers might encourage alteration of current products or development of safer ones for consumer use. Finally, those in the food services industry should examine whether their patrons are at risk for this injury.

Detailed information on the types and brands of grill-cleaning brushes was not available; therefore, recommendations regarding which brands might be safer overall or less likely to lose their bristles could not be made. Questions remain regarding whether different brands or designs of grill-cleaning brushes, different grill types (e.g., uncoated cast iron versus porcelain-coated cast iron), different types of food (e.g., whole cuts of meat versus patties), or different health conditions (e.g., dentures or other oral conditions) make a difference in the risk for ingestion of wire bristles.

Physician awareness of this potential injury is critical to facilitate timely diagnosis and treatment. Awareness of this potential injury by the general population, manufacturers, and retailers can reduce exposures and decrease the likelihood of occurrence. Careful examination of the grill surface before grilling or use of alternative grill-cleaning methods or products are advisable. To improve monitoring of this injury mechanism, medical professionals or consumers should report these injuries to CPSC at http://www.saferproducts.gov.

What is already known on this topic?

Case reports and one case series have been published describing the risk from unintentional ingestion of wire bristles from grill-cleaning brushes.

What is added by this report?

This case series presents an additional six cases during a 17-month period from a single hospital system. The two case series together document that this risk continues and suggest that this injury mechanism might be more common than suspected previously.

What are the implications for public health practice?

Persons who grill should be aware of the risk for ingestion of wire bristles from grill-cleaning brushes. They should examine their grills or consider alternative methods or products for grill cleaning to reduce exposure and potential injury. Medical professionals need to be aware of this injury to facilitate appropriate diagnosis and treatment.

Acknowledgment

Julie Gilchrist, MD, Div of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC.

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Vital Signs: Risk for Overdose from Methadone Used for Pain Relief — United States, 1999–2010

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Abstract

Background: Vital statistics data suggest that the opioid pain reliever (OPR) methadone is involved in one third of OPR-related overdose deaths, but it accounts for only a few percent of OPR prescriptions.

Methods: CDC analyzed rates of fatal methadone overdoses and sales nationally during 1999–2010 and rates of overdose death for methadone compared with rates for other major opioids in 13 states for 2009.

Results: Methadone overdose deaths and sales rates in the United States peaked in 2007. In 2010, methadone accounted for between 4.5% and 18.5% of the opioids distributed by state. Methadone was involved in 31.4% of OPR deaths in the 13 states. It accounted for 39.8% of single-drug OPR deaths. The overdose death rate for methadone was significantly greater than that for other OPR for multidrug and single-drug deaths.

Conclusions: Methadone remains a drug that contributes disproportionately to the excessive number of opioid pain reliever overdoses and associated medical and societal costs.

Implications for Public Health Practice: Health-care providers who choose to prescribe methadone should have substantial experience with its use and follow consensus guidelines for appropriate opioid prescribing. Providers should use methadone as an analgesic only for conditions where benefit outweighs risk to patients and society. Methadone and other extended-release opioids should not be used for mild pain, acute pain, "breakthrough" pain, or on an as-needed basis. For chronic noncancer pain, methadone should not be considered a drug of first choice by prescribers or insurers.

Introduction

U.S. physicians have used the synthetic opioid methadone as a treatment for heroin addiction since the 1960s and increasingly as a treatment for chronic noncancer pain since the mid-1990s (*1*). Individual states began to report increasing numbers of overdose deaths involving methadone in 2003 (*2*). Subsequently, rates of deaths and emergency department (ED) visits involving methadone have increased nationwide (*3,4*). Studies using medical examiner data suggested that more than three quarters of methadone overdoses involved persons who were not enrolled in programs treating opioid addiction with methadone and that most persons who overdosed were using it without a prescription (*3*). In November 2006, the Food and Drug Administration (FDA) issued a warning regarding careful prescribing of methadone because of the sharp rise in overdose deaths among patients receiving methadone for pain (*5*). FDA also revised the interval for the recommended starting dosage from 2.5–10 mg every 3–4 hours to 2.5–10 mg every 8–12 hours. In January 2008, on request of the Drug Enforcement Administration (DEA), manufacturers voluntarily limited distribution of the largest (40 mg) formulation of methadone to authorized opioid addiction treatment programs and hospitals only, because this formulation was not approved for the treatment of pain (*6*).

Recent analyses have shown that methadone was involved in one in three opioid-related deaths in 2008 (*7*). Moreover, the involvement of methadone in drug overdose deaths, in toxic exposures quantified by poison centers, and in diversion to nonpatients is disproportionate to the number of methadone prescriptions for pain when compared with other opioid pain relievers (*3,8*). Analysis of ED data indicates that the estimated number of ED visits resulting from nonmedical use of methadone alone or in combination with other drugs in 2009 (n = 63,031) was significantly greater than the estimated number in 2004 (n = 36,806) (*4*). CDC reviewed national data on trends in methadone use and mortality and data from medical examiners on methadone mortality to determine whether additional recommendations for its safe use for pain treatment are necessary.

Methods

For this report, national death rates during 1999–2009 are based on the National Vital Statistics System multiple cause of death files (*9*). Methadone-related deaths were defined as those with an underlying cause of death classified by the *International*

Classification of Diseases, 10th Revision (ICD-10) external cause of injury codes as X40-X44, X60-X64, X85, or Y10-Y14 and an ICD-10 code (T40.3) for methadone poisoning. Methadone might have been listed alone or in combination with other drugs.

The amounts of opioid pain relievers distributed for 1999–2010 nationally and by state were obtained from the DEA's Automation of Reports and Consolidated Orders System (ARCOS).* Distributions of methadone to opioid treatment programs were not included. Annual numbers of prescriptions dispensed for methadone and other opioids in outpatient settings for 1999–2009 came from an analysis conducted by FDA in 2010 using a commercial prescription and patient measurement service (Vector One: National [VONA]) that can estimate the number of prescriptions for drugs dispensed by outpatient retail pharmacies in the United States (*10*).

Population-based counts of drug-related deaths for methadone and other opioids in 2009 came from 13 states in the Medical Examiner component of the Drug Abuse Warning Network (DAWN): Delaware, Massachusetts, Maryland, Maine, New Hampshire, New Mexico, Oklahoma, Oregon, Rhode Island, Utah, Virginia, Vermont, and West Virginia.† State medical examiners provided information on all drug-related deaths, and CDC analyzed the deaths involving an opioid, whether in combination with other drugs or by itself. Opioid distribution data for these states were available from the ARCOS system and converted to morphine milligram equivalents (MME) using a standard reference (*11*).

Comparison of methadone to other major opioids in DAWN data was based on rates of death per 100 kg of opioid analgesic in MME. Drug-specific rates were compared using rate ratios and 95% confidence intervals with the rates for methadone as the referents.

Results

The rate of overdose deaths involving methadone in the United States in 2009 was 5.5 times the rate in 1999 (Figure 1). The mortality rate peaked at 1.8 deaths per 100,000 persons in 2007 and then declined in parallel with the amount of methadone being distributed nationally in 2008 and 2009. The annual rate of methadone prescriptions for pain rose to 1.5 per 100 persons by 2008 and did not increase further in 2009. Methadone accounted for 4.4 million (1.7%) of the 257 million opioid prescriptions in 2009. However, in 2010, methadone accounted for 9.0% of all the MME of all major opioids tracked by ARCOS other than buprenorphine. This proportion varied by state from 4.5% in New Jersey to 18.5% in Washington (Figure 2).

Among the 13 DAWN Medical Examiner states, methadone accounted for 9.8% of the MME tracked by ARCOS. Methadone was involved in 31.4% of the 3,294 deaths involving these opioids, more than any opioid other than oxycodone in 2009 (Table). Among the 748 single-drug deaths, methadone was involved in 298 (39.8%), twice as many as any other opioid. The rate of methadone deaths per 100 kg sold in MME was significantly higher than that for any other opioid for both all deaths and single-drug deaths. The difference between methadone and other opioids was more pronounced in the analysis of single-drug deaths. Even if some of these deaths (e.g., 25%) had been attributable to methadone dispensed from opioid treatment programs, the differences between methadone and other opioids would remain significant. The methadone death rate was still significantly higher than the rate for any other opioid in both comparisons.

Conclusions and Comment

The primary advantages of using methadone over other opioids for pain treatment are its long duration of action, relatively low cost, and availability in liquid formulation for oral use. Its primary disadvantages are its long and unpredictable half-life and associated risk for accumulating toxic levels leading to severe respiratory depression; its multiple interactions with other drugs, including frequently abused drugs such as antianxiety agents; and its ability to cause major disturbances of cardiac rhythm (*12*).

Increased use of methadone since 1999 might have been prompted by growing costs of treating pain with opioids and increasing reports of abuse of other, more expensive, extended-release opioids (*1*). Overdose reports and interventions by FDA and DEA might have resulted in declines in the amount of methadone distributed and methadone-related fatal overdoses in 2008, although the number of methadone prescriptions did not decline. The parallel trends in the amount of methadone distributed for use as a pain reliever and in the methadone mortality rate are consistent with methadone prescribed as a pain reliever being the primary determinant of methadone mortality rates (*1,3*).

Data suggest that some of the current uses of methadone for pain might be inappropriate. According to an analysis conducted by FDA, the most common diagnoses associated with methadone use for pain in 2009 were musculoskeletal problems (such as back pain and arthritis) (46%), headaches (17%), cancer (11%), and trauma (5%). Most methadone prescriptions were written by primary care providers or mid-level practitioners (e.g., nurse practitioners) rather than pain specialists. Nearly a third of prescriptions appear to have been dispensed to patients with no opioid prescriptions in the previous month (i.e., opioid-naïve patients) (*10*).

* Information about the DEA's ARCOS system is available at http://www.deadiversion.usdoj.gov/arcos.

† Information about the DAWN Medical Examiner system is available at http://www.samhsa.gov/data/2k11/dawn/2k9dawnme/html/dawn2k9me.htm.

FIGURE 1. Rates of methadone distribution for pain, methadone-related overdose deaths, and methadone prescriptions for pain — United States, 1999–2010

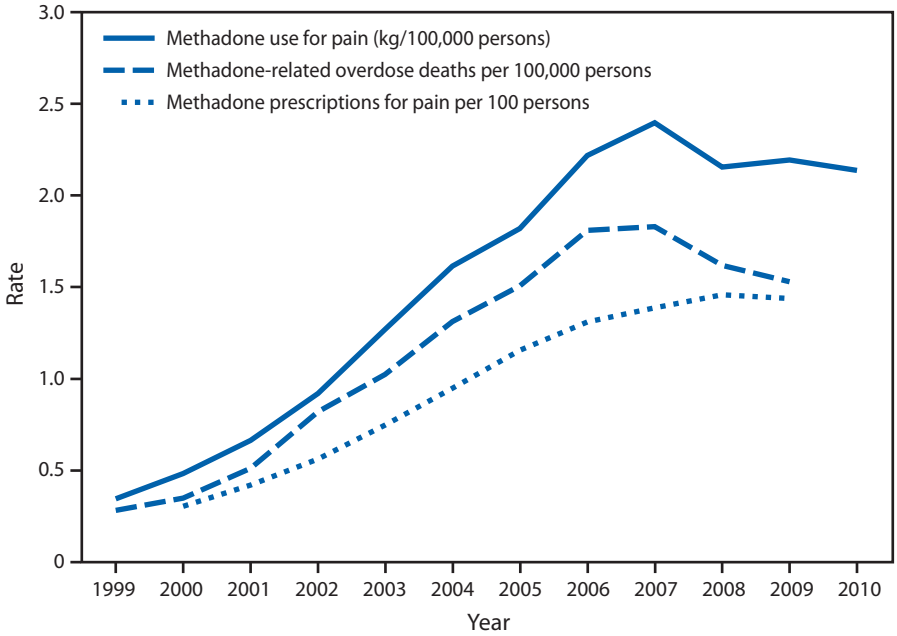
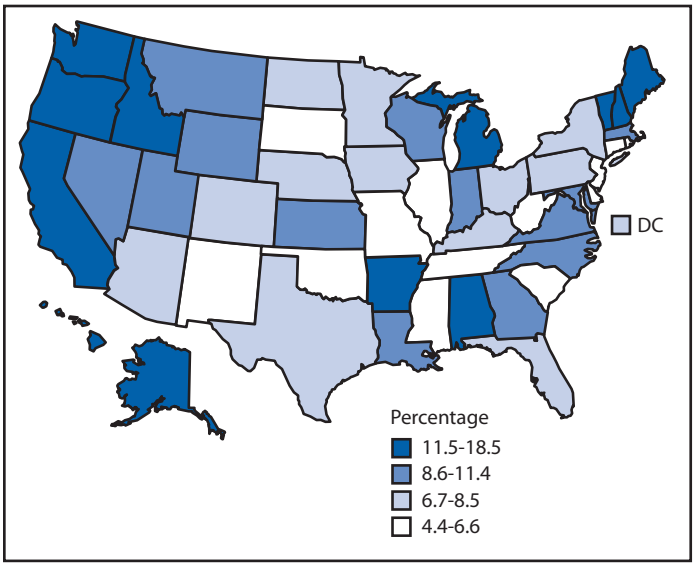


FIGURE 2. Percentage of opioid distribution accounted for by methadone prescribed for pain, by state — United States, 2010



The findings in this report are subject to at least five limitations. First, vital statistics underestimate the number of overdose deaths from specific drugs because the type of drug is not specified on many death certificates. Second, medical examiners in the DAWN system might have varying definitions of drug-related deaths. However, individual medical examiners likely apply the same definitions to all types of opioid analgesics. Third, assigning responsibility to any single drug in multidrug overdoses is difficult. However, this is not an issue in single-drug deaths, among which the highest risks for methadone were observed. Fourth, some deaths might have resulted from methadone provided in take-home doses by opioid treatment programs, but adjusting for such deaths in this analysis did not change the overall results. Finally, ARCOS data reflect distributions to retail outlets by state, but some drugs might have been used by residents of neighboring states.

This study and others suggest that methadone remains a drug that contributes disproportionately to opioid pain reliever overdoses and associated medical and societal costs. Additional warnings to prescribers about dosage are likely to have limited effect, given the high prevalence of use without a prescription among persons who overdose. The public health goal now should be to mount a concerted effort to reserve methadone for those pain-related conditions for which the benefits likely outweigh the risks to patients and society, such as use for cancer-related pain or palliative care. This will reduce the amount of methadone available for diversion and nonmedical use.

Methadone and other, extended-release opioids should not be used for mild pain, acute pain, "breakthrough" pain, or on an as-needed basis. For chronic noncancer pain, methadone should not be considered a drug of first choice. This is especially true for conditions for which the benefits of opioids have not been demonstrated, such as headache and low back pain. Only a small fraction of patients with intractable chronic headache treated with opioids experience long-term pain reduction or functional improvement (*13*). Evidence that any opioids are effective in chronic low back pain is limited (*14*). Additionally, methadone should not be prescribed to opioid-naïve patients, and, whenever possible, should not be prescribed to patients taking benzodiazepine antianxiety agents because of an increased risk for severe respiratory depression. Health-care providers who choose to prescribe methadone should have substantial experience with its use and follow consensus guidelines for appropriate opioid prescribing (*15*). Providers should instruct patients about the potential risks of methadone and how to store and dispose of it properly.

Public and private insurers and health-care systems can ensure that prescribers of methadone follow dosage guidelines by requiring authorization for starting doses for pain that exceed the recommended upper limit of 30 mg per day (*5*). Insurance formularies should not list methadone as a preferred drug for the treatment of chronic noncancer pain. Pharmaceutical companies

TABLE. Drug-related deaths involving opioids, by type of opioid — Drug Abuse Warning Network Medical Examiner System, 13 states, 2009

Opioid	No.	Death rate per 100 kg MME	RR	(95% CI)
All deaths				
Buprenorphine	20	0.8	0.02	(0.01–0.04)
Fentanyl	364	7.7	0.28	(0.25–0.32)
Hydrocodone	550	14.3	0.42	(0.38–0.47)
Hydromorphone	74	9.1	0.27	(0.21–0.34)
Morphine	824	20.2	0.64	(0.58–0.70)
Oxycodone	1,097	8.7	0.26	(0.24–0.28)
Methadone	1,034	33.6	1.00	referent
Total*	**3,294**	**10.4**		
Single-drug deaths				
Buprenorphine	2	0.1	0.01	(0.00–0.03)
Fentanyl	99	2.1	0.26	(0.21–0.33)
Hydrocodone	42	1.1	0.11	(0.08–0.16)
Hydromorphone	4	0.5	0.05	(0.02–0.14)
Morphine	153	3.8	0.41	(0.34–0.50)
Oxycodone	150	1.2	0.12	(0.10–0.15)
Methadone	298	9.7	1.00	referent
Total	**748**	**2.4**		

Abbreviations: MME = morphine milligram equivalent; RR = rate ratio; CI = confidence interval.

* Counts for each opioid might not sum to the total shown for all deaths because some deaths involved more than one opioid.

should introduce a 2.5-mg formulation of methadone to facilitate treatment with the lowest recommended dosage.

Although interventions related to methadone use are urgently needed, government agencies, health-care providers, insurers, and other stakeholders must combine these interventions with measures that will address the problems of misuse and abuse of all opioid pain relievers. Interventions such as the use of prescription drug monitoring programs, appropriate screening and monitoring before prescribing opioid pain relievers, regulatory and law enforcement efforts, and state policies (e.g., "pill mill" laws) aimed at providers and patients involved in diversion of these drugs continue to be essential elements in addressing this public health emergency.

Reported by

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Key Points

- Between 1999 and 2009, the rate of fatal overdoses involving methadone increased more than fivefold as its prescribed use for treatment of pain increased.
- Methadone is involved in approximately one in three opioid-related overdose deaths. Its pharmacology makes it more difficult to use safely for pain than other opioid pain relievers.
- Methadone is being prescribed inappropriately for acute injuries and on a long-term basis for common causes of chronic pain (e.g., back pain), for which opioid pain relievers are of unproven benefit.
- Insurance formularies should not list methadone as a preferred drug for the treatment of chronic noncancer pain. Methadone should be reserved for use in selected circumstances (e.g., for cancer pain or palliative care), by prescribers with substantial experience in its use.

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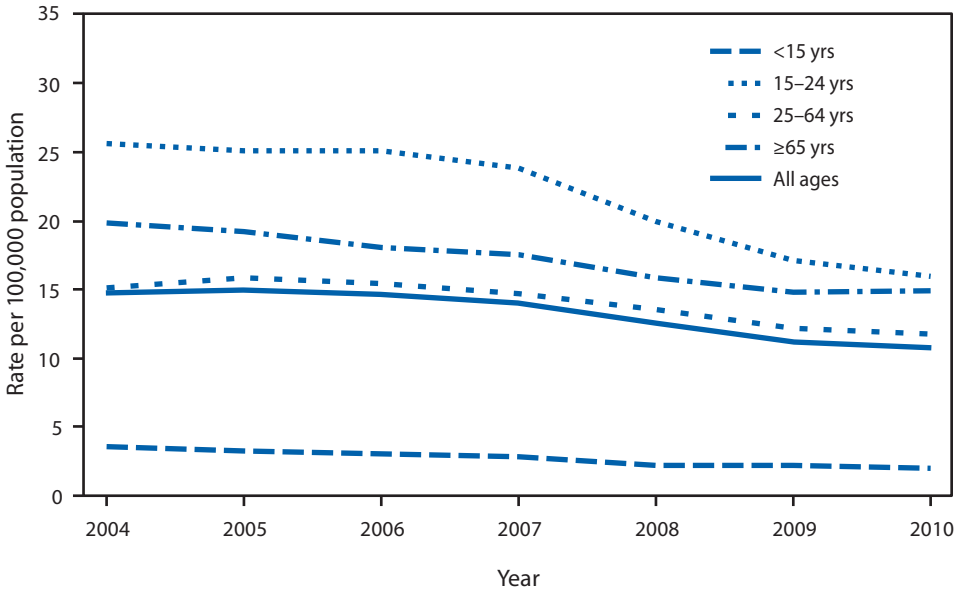
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Rate of Unintentional Motor Vehicle Traffic Deaths, by Age Group — United States, 2004–2010*



* Data for 2010 are preliminary.

During 2004–2010, the rate of unintentional motor vehicle traffic deaths declined for the total U.S. population by 27% (4.0 percentage points). The death rate decreased 44% (1.6 percentage points) for persons aged <15 years, 38% (9.6 percentage points) for those aged 15–24 years, 22% (3.3 percentage points) for those aged 25–64 years, and 25% (4.9 percentage points) for those aged ≥65 years.

Source: National Vital Statistics System. Mortality public use data files, 2004–2010. Available at http://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm.

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