Addressing the increasing difference between TB rates in foreign-born and U.S.-born persons is critical for TB elimination. Most foreign-born persons with TB (78.8%) had their TB diagnosed after being in the United States for more than 2 years,¶ consistent with reactivation of LTBI acquired abroad. Therefore, treating LTBI will be critical for accelerating the TB decline among foreign-born persons.[5] In 2007, CDC published technical instructions for TB screening in prospective immigrants to the United States.[7] As more high-TB burden countries adopt these technical instructions, screening and treating immigrants should improve. Persons screened overseas and found to have LTBI should receive preventive TB treatment upon arrival in the United States. A new, shorter regimen for LTBI requiring just 12 once-weekly drug administrations has been recommended by CDC and might result in better adherence to LTBI treatment in foreign-born and U.S.-born populations.[8,9]

Approximately 81% of TB cases in 2011 had known HIV status at TB diagnosis. This increase (66.3% in 2010) is attributed to increased reporting from selected regions. The American Thoracic Society and the Infectious Disease Society of America recommend that all TB patients be counseled and tested for HIV.[10]

This analysis is limited to reporting provisional TB cases and case rates for 2011. Case rates are based on estimates of population denominators from either 2010 or 2011. CDC's annual TB surveillance report will provide final TB case rates based on updated denominators later this year.

Progress toward TB elimination in the United States will require ongoing surveillance and improved TB control and prevention activities. Sustained focus on domestic TB control activities and further support of global TB control initiatives is important to address persistent disparities between non-Hispanic whites and racial/ethnic minorities and between U.S.-born and foreign-born persons.

Acknowledgments

State and local TB control officials.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Reported tuberculosis in the United States, 2010. Atlanta, GA: US Department of Health and Human Services, CDC; 2011. Available at http://www.cdc.gov/tb/statistics/reports/2010/default.htm. Accessed February 21, 2012.
2. Centers for Disease Control and Prevention (CDC). Decrease in reported tuberculosis cases—United States, 2009. *MMWR Morb Mortal Wkly Rep*. 2010; 59(10):289-294.
3. US Census Bureau. Current estimates data. Available at http://www.census.gov/popest/data/national/totals/2011/index.html. Accessed February 2, 2012.
4. Dowdle WR; Centers for Disease Control (CDC). A strategic plan for the elimination of tuberculosis in the United States. *MMWR Morb Mortal Wkly Rep*. 1989;38(suppl 3):1-25.
5. Hill AN, Becerra JE, Castro KG. Modelling tuberculosis trends in the USA [published online ahead of print]. *Epidemiol Infect*. 2012:1-11.
6. Cegielski JP, Griffith DE, McGaha PK, et al. Eliminating tuberculosis, one neighborhood at a time. *Am J Public Health*. In press.
7. Centers for Disease Control and Prevention (CDC). CDC immigration requirements: technical instructions for tuberculosis screening and treatment. Using cultures and directly observed therapy. US Department of Health and Human Services, CDC; 2009. Available at http://www.cdc.gov/immigrantrefugeehealth/pdf/tuberculosis-ti-2009.pdf. Accessed February 16, 2012.
8. Sterling TR, Villarino ME, Borisov AS, et al; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155-2166.
9. Centers for Disease Control and Prevention (CDC). Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep*. 2011;60:1650-1653.
10. Centers for Disease Control and Prevention (CDC). Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR Recomm Rep*. 2003;52(RR-11):1-77.

*Available at http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/tuberculosis_current.htm.

†Additional information available at http://dataferrett.census.gov.

‡Vermont no longer reports HIV status of TB patients to CDC.

§Defined by the World Health Organization as a case of TB in a person with a *Mycobacterium tuberculosis* isolate resistant to at least isoniazid and rifampin. Additional information available at http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf.

‖Defined by the World Health Organization as a case of TB in a person with an *M. tuberculosis* isolate with resistance to at least isoniazid and rifampin among first-line anti-TB drugs, resistance to any fluoroquinolone (e.g., ciprofloaxacin or ofloxacin), and resistance to at least one second-line injectable drug (e.g., amikacin, capreomycin, or kanamycin). Additional information available at http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf

¶The percentage of foreign-born persons with TB residing in the United States for more than 2 years was based on provisional 2011 National Tuberculosis Surveillance System data accessed on February 22, 2012.

Severe Methemoglobinemia and Hemolytic Anemia From Aniline Purchased as 2C-E (4-ethyl-2, 5-dimethoxyphenethylamine), a Recreational Drug, on the Internet—Oregon, 2011

MMWR. 2012;61:85-88

In August 2011, two men in Oregon drank a liquid they believed to be 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), a psychoactive stimulant used as a recreational drug, after purchasing it on the Internet. Fifteen minutes after ingestion, the men became cyanotic and subsequently were treated for refractory methemoglobinemia and hemolytic anemia. The Oregon Poison Center, Oregon Public Health Division, Drug Enforcement Administration (DEA), and Food and Drug Administration (FDA) jointly investigated to determine the cause of the poisoning and identify other cases. The Oregon Poison Center and Oregon Public Health Division promptly alerted health-care providers and public health agencies and searched for additional cases. DEA confiscated all product remaining in the men's possession, and FDA identified the substance as aniline, an industrial solvent known to cause methemoglobinemia. One patient reported purchasing the substance from the Internet site of a Chinese chemical company. No additional cases were identified by investigators. Purchase of chemicals from unregulated Internet sources poses a serious risk to purchasers from product contamination and substitution.

Case Reports

Patient A. On August 19, 2011, a man aged 33 years was taken by ambulance to a local emergency department after he

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What is already known on this topic?

Psychoactive chemicals (including the phenethylamines 2C-B, 2C-E, or 2C-I) are sold on unregulated Internet sites as "research chemicals."

What is added by this report?

This is the first published report of unintentional exposure to aniline among persons attempting to purchase psychoactive drugs sold online for recreational use from an international manufacturer. Two men in Oregon experienced methemoglobinemia and hemolytic anemia after ingesting a substance intended for misuse as a stimulant. The methemoglobinemia that developed in both proved refractory to usual doses of methylene blue, and one of the two patients required blood transfusions, multiple cycles of plasmapheresis, and exchange transfusion.

What are the implications for public health practice?

Recognition of the health danger of contaminated or adulterated ingestible products purchased on the Internet is important to the public's health. Collaboration is essential among health-care providers, poison control centers, public health officials, and law enforcement agencies to identify, treat, and trace potentially toxic substances purchased on the Internet.

collapsed in a fast food restaurant. He reported feeling lightheaded and nauseated 15 minutes after consuming a soft drink with his friend (patient B). When questioned, patient A initially said he had not ingested medications or illicit drugs. On physical examination, he appeared cyanotic with altered mental status, and his blood oxygen saturation measured by pulse oximetry was 86% on 100% supplemental oxygen by nonrebreather mask. Blood drawn for laboratory testing was chocolate-brown. Arterial blood pH was 7.43, the pCO was 35 mm Hg, and the pO was 222 mm Hg. His methemoglobin concentration was 66.7% (normal: 1%-3%), his hemoglobin concentration was 14.3 g/dL (normal: 13.8-17.2 g/dL), and his platelet count was 338,000/mm^3 (normal: 150,000-400,000/mm^3). The Oregon Poison Center was consulted and recommended administration of 1 mg/kg body weight methylene blue intravenously. The patient was admitted to the hospital intensive-care unit.

After the initial dose of methylene blue, a repeat methemoglobin concentration was 67.2%. A second 1 mg/kg dose was administered 4 hours after arrival. Patient A's methemoglobin concentration peaked at 79.6% at 6 hours after ingestion. The patient ultimately received a total of five 1 mg/kg doses of methylene blue during the next 2 days. By hospital day 3, his methemoglobin concentration had decreased to 11%, and his hemoglobin concentration had decreased to 10.1 g/dL.

On hospital day 5, the patient's hemoglobin concentration was 5.7 g/dL, and he reported fatigue. His blood oxygen saturation measured by pulse oximetry remained at 70%-80% despite supplemental oxygen administration. He received 2 units of packed red blood cells. Other laboratory assessment was significant for haptoglobin <30 mg/dL (normal: 41-165 mg/dL), lactate dehydrogenase (LDH) 2,005 U/L (normal: 105-333 U/L), and platelets 73,000/mm^3. Acute oxidant stress-induced hemolysis was suspected, and the patient was transferred to a tertiary-care intensive-care unit.

The patient received an additional unit of packed red blood cells and underwent plasmapheresis, after which his hemoglobin concentration was 5.8 g/dL. During the following 2 days, daily plasmapheresis was performed, as well as one complete exchange transfusion.[1] During this process, serum LDH concentration decreased to 428 U/L, and the patient's hemoglobin concentration stabilized at 9.5 g/dL. On hospital day 8, a fourth plasmapheresis was performed; hemoglobin concentration remained stable, and his serum LDH concentration decreased to 158 U/L, suggesting resolution of hemolysis. Glucose-6-phosphate dehydrogenase concentrations were normal (deficiency is a risk factor for hemolytic anemia). On hospital day 12, the patient was discharged home. Subsequently, results of comprehensive toxicology screening of urine by gas chromatography/mass spectroscopy were positive for p-aminophenol, an aniline metabolite.

Patient B. A man aged 34 years (patient B) who had accompanied patient A to the emergency department also appeared cyanotic, but said he had no symptoms. When questioned, patient B also initially said he had not ingested medications or illicit drugs. However, he later reported having consumed the same soft drink as patient A. Patient B's initial blood oxygen saturation measured by pulse oximetry was 80% on 40% supplemental oxygen by nonrebreather mask, and peripheral venous blood drawn for laboratory testing was dark brown. His methemoglobin concentration drawn 45 minutes after ingestion was 49.5%, and his hemoglobin concentration was 16.4 g/dL. Methylene blue 1 mg/kg was administered intravenously, and a repeat methemoglobin concentration was 47.8%. The patient received a second dose of methylene blue, and was admitted to the intensive-care unit overnight. His methemoglobin concentration peaked at 74.4% 8 hours after ingestion.

Patient B received a total of 4 doses of methylene blue and then left the hospital against medical advice 19.5 hours after ingestion. His last methemoglobin concentration was 10%. His glucose-6-phosphate dehydrogenase concentration was not tested.

After patient A was transferred to tertiary care for chemical-induced hemolytic anemia on postexposure day 5, multiple attempts were made to contact patient B. He returned for repeat evaluation on postexposure day 6 and reported fatigue and dyspnea. His hemoglobin concentration had decreased to 10 g/dL at follow-up. A repeat methemoglobin concentration was 1.1%. Despite plans for repeat hemoglobin testing in 1-2 days, he did not return for further evaluation.

Multi-Agency Investigation

During evaluation in the emergency department, the physician questioned pa-

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tient A and patient B because of concern for possible consumer product contamination of their soft drink by a methemoglobin-inducing substance. After initial denials, they reported buying 2C-E as a recreational chemical from an Internet site. They described ingesting 4 mL of a bitter, yellow-tinted liquid that they had mixed with a soft drink to mask the taste. This description was inconsistent with 2C-E, which is available typically as a capsule or white powder.

Further questioning implicated a company based in Nanjing, China, that produces and sells 2C-E and industrial products manufactured using aniline. Consultation with FDA confirmed that 2C-E was a federally controlled substance, and that, since the product was purchased from an international distributor, the incident was under federal jurisdiction. DEA was notified. DEA obtained the leftover product that the patients had purchased, and FDA determined the liquid was pure aniline, with no evidence of 2C-E. Aniline is a common solvent used in manufacturing processes. Ingestion of aniline can cause methemoglobinemia and hemolytic anemia through the action of its metabolites, phenylhydroxylamine and aminophenol, both strong oxidizing agents.[1-4]

The patients said they had not shared the product with others. Nonetheless, public health and poison control investigators conducted active case-finding because of concern that aniline might have been mislabeled and sold to other buyers seeking 2C-E. A case was defined as unexplained methemoglobinemia in a person who had ingested a chemical purchased through the Internet since January, 2011. The Oregon Poison Center queried poison center directors nationally and searched for reports of aniline poisoning in the National Poison Data System. CDC was notified, and investigators conducted supplemental symptom-based case-finding using the Oregon Health Alert Network and CDC's Epidemic Information Exchange (Epi-X)* to query for cases of unexplained methemoglobinemia. No additional cases were identified.

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CDC Editorial Note: Strong oxidizing agents, such as aniline metabolites, can cause methemoglobinemia or, at higher concentrations, acute red blood cell hemolysis. Symptoms related to increased methemoglobin concentrations reflect declining oxygen delivery. Concentrations above 50% can cause syncope. Concentrations above 70% can be lethal. During venipuncture, the blood usually appears chocolate brown, a clue to the presence of methemoglobin. Standard noninvasive pulse oximetry typically shows a reading of 85% that does not change despite administration of 100% oxygen or the antidote methylene blue.

Hydroxylamine compounds (e.g., aniline metabolites phenylhydroxylamine and aminophenol) often produce methemoglobin that is refractory to conversion back to normal hemoglobin by administration of methylene blue, and can precipitate acute hemolytic anemia.[1-4] Paradoxically, methylene blue can be a source of oxidant stress and, in high doses, can cause hemolytic anemia. However, this is more likely with glucose-6-phosphate dehydrogenase deficiency, and patient A's concentrations were normal, whereas patient B's concentrations were not tested.

Use of novel psychoactive chemicals has continued to increase in the United States despite passage of the 1986 Controlled Substances Analogue Enforcement Act (CSAEA).[5,6] The phenethylamines (e.g., 2C-B, 2C-E, and 2C-I), their isomers, and their salts are illegal substances under CSAEA.[7] To circumvent such laws, manufacturers produce substances that have chemical structures distinct from regulated substances, yet still produce psychoactive effects. These products pose challenges to both surveillance and regulation because they frequently are advertised for sale as "research chemicals" through international and domestic Internet sites.

Purchase of psychoactive chemicals and other ingestible products from the Internet places the public at risk for obtaining products that are inherently toxic or have been made toxic by adulteration, either inadvertently or deliberately. Persons reporting emergencies involving ingested substances purchased from the Internet should telephone FDA at the 24-hour, toll-free number (1-888-INFO-FDA). Persons reporting nonemergencies should contact the FDA district office consumer complaint coordinator for their geographic area during regular business hours.† Communication and collaboration among health-care, public health, poison control, and law enforcement agencies are crucial to identify adverse events associated with Internet-purchased toxic chemicals and coordinate health messages for health-care providers.

This is the first published report of unintentional aniline intoxication in persons attempting to purchase psychoactive chemicals for recreational use. Whether this potentially lethal incident represents deliberate ingredient substitution or a packaging error by a vendor not subject to industry standards is unknown. This case highlights the danger to the public and the challenges facing public health agencies in an era in which virtually any chemical produced in any country is available through Internet sales.

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REFERENCES

7 Available.

*Available to participating officials designated by their public health agencies at http://www.cdc.gov/mmwr/epix/epix.html.

†Available at http://www.fda.gov/safety/reportaproblem/consumercomplaintcoordinators/default.htm.

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