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Thrombotic Thrombocytopenic Purpura (TTP)–Like Illness Associated with Intravenous Opana ER Abuse — Tennessee, 2012

On August 13, 2012, a nephrologist reported to the Tennessee Department of Health (TDH) three cases of unexplained thrombotic thrombocytopenic purpura (TTP), a rare but serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia. The annual incidence is approximately 1 per 100,000 population (*1,2*). Known risk factors for TTP include infection with Shiga toxin–producing *Escherichia coli* (STEC) and the use of drugs, including platelet aggregation inhibitors, quinine, and cocaine (*1,3,4*). The three patients were intravenous (IV) drug users who resided in a rural county in northeast Tennessee. To identify other cases of TTP-like illness that might be associated with injection-drug use, TDH conducted a statewide investigation. By the end of October, a total of 15 such cases had been reported; none were fatal. A case-control study was conducted, and investigators determined that the cases of TTP-like illness were associated with dissolving and injecting tablets of Opana ER (Endo Pharmaceuticals), a recently reformulated extended-release form of oxymorphone (an opioid pain reliever) intended for oral administration. Fourteen of the 15 patients reported injecting reformulated Opana ER. Seven of the 15 were treated for sepsis in addition to TTP-like illness. Twelve patients reported chronic hepatitis C or had positive test results for anti-HCV antibody. Health-care providers who prescribe Opana ER and pharmacists who dispense it should inform patients of the risks from the drug when used other than as prescribed. Health-care providers should ask patients with TTP-like illness of unknown etiology about any IV drug abuse. Suspected cases can be reported to public health officials.

Clinical Characteristics

Following report of the initial three cases, TDH contacted infectious disease specialists, dialysis centers, and the regional poison center in Tennessee seeking additional cases. A case of TTP-like illness was defined as microangiopathic hemolytic anemia (hemolytic anemia based on haptoglobin and lactate dehydrogenase and the presence of schistocytes) and thrombocytopenia in a person with a hospital admission platelet count ≤50,000/μL, in the absence of certain known causes of TTP. By the end of October 2012, a total of 15 cases had been reported in Tennessee. TDH interviewed patients in person and reviewed medical charts. Among the 15 patients, 13 were women. All were white; none were pregnant. The 15 patients ranged in age from 22 to 49 years (median: 34 years). The earliest diagnosis of TTP-like illness was April 16, 2012 (Figure). Seven of the 15 patients were from the same rural county in northeast Tennessee; five were from nearby counties, and three were from counties in middle Tennessee.

The 15 patients were further categorized by presence or absence of a concurrent infection (as evidenced by sepsis) as a possible etiology. Clinical characteristics were similar among patients with and without infection (Table). Patients reported symptoms typical of TTP-like illness, including nausea (11 patients) abdominal pain (11), fatigue (10), and fever (six). Seven patients were treated for sepsis. Twelve were treated with plasmapheresis. The median admission platelet counts for patients without and with infection were 20,000/μL (range: 9,000–40,000/μL) and 26,000/μL (range: 9,000–49,000/μL),

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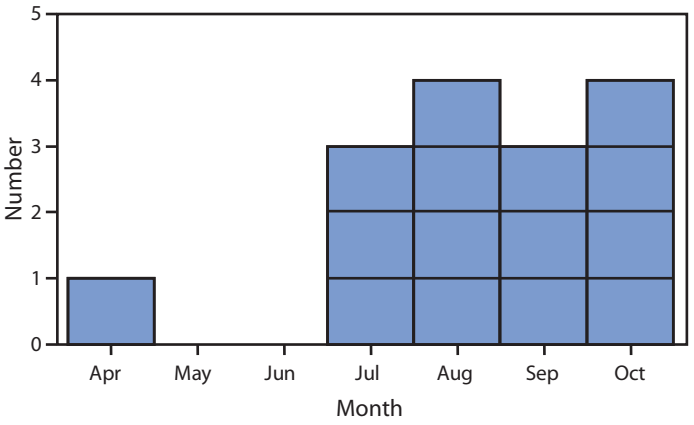
FIGURE. Number of cases (N = 15) of thrombotic thrombocytopenic purpura (TTP)–like illness, by month of first presentation — Tennessee, 2012



respectively. Activity levels of the von Willebrand factor–cleaving protease (ADAMTS13), which is involved in blood clotting, were available for eight of the 15 patients. ADAMTS13 median activity level among patients without infection was 90% (range: 84%–131%) and among patients with infection was 64% (range: 42%–100%). Twelve of the 15 patients reported chronic hepatitis C or had positive results for anti-HCV antibody testing performed during hospital admission (Table). None were HIV-positive. TDH conducted serologic testing on six patients to assess exposure to STEC O157; one had evidence of prior infection.

Case-Control Study

To test for an association between TTP-like illness and injection of reformulated Opana ER, TDH conducted a case-control study. Controls were recruited from patients in a methadone clinic in eastern Tennessee and had to meet the inclusion criterion of injection-drug abuse in the previous 6 months. Only drug abuse reported during TDH interviews was used in the analysis. All 15 case-patients and 28 controls participated in the case-control study. No case-patients or controls eligible for the study refused to participate.

Among the 28 controls, median age was 31 years (range: 19–52 years); 13 were female, and all were white. None of the controls received a diagnosis of TTP–like illness. Nine reported injecting Opana ER in the preceding 6 months, including seven who reported injecting reformulated Opana ER. One control was unsure of the formulation and was categorized in the analysis as injecting reformulated Opana ER. Therefore, eight of the 28 controls, compared with 14 of the 15 case-patients, reported recent injection of reformulated Opana ER (odds ratio [OR] = 35.0; 95% confidence interval [CI] = 3.9–312.1). Thirteen of the 14 case-patients who reported reformulated Opana ER abuse injected intravenously; one reported subcutaneous injection. Case-patients reported a first injection of reformulated Opana ER 21–120 days before hospital admission (median: 60 days). The last reported injection of reformulated Opana ER occurred 0–2 days before admission (median: 1 day). None of the case-patients reported

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using quinine, either alone or as part of the preparation process. Five case-patients also reported IV abuse of hydromorphone or oxycodone; one reported cocaine use. Twenty-two of the 28 controls reported injecting oxycodone, and 18 reported injecting morphine.

Seven of the eight case-patients without infection (as evidenced by sepsis) compared with eight of the 28 controls reported recent injection of reformulated Opana ER (OR = 17.5; CI = 1.8–166.0). One case-patient without infection did not report Opana ER use during the TDH interview but did report use to health-care providers. The odds ratio for case-patients with infection was undefined because all seven with infection reported recent injection of reformulated Opana ER.

Public Health Response

TDH submitted an alert via CDC's Epidemic Information Exchange (Epi-X) on August 23, 2012. The Food and Drug Administration (FDA) released a statement regarding the association of IV abuse of reformulated Opana ER and TTP-like illness on October 11. TDH submitted a second alert to Epi-X on October 24, and CDC released a Health Advisory on October 26 to warn against injection of Opana ER and to aid in case finding.

TABLE. Clinical characteristics of patients with thrombotic thrombocytopenic purpura (TTP)–like illness, by infection status (as evidenced by sepsis) — Tennessee, 2012

Characteristic	TTP-like illness without infection (n = 8)		TTP-like illness with infection (n = 7)	
	Median	Range	Median	Range
Test result				
Platelet count (per μL)	20,000	9,000–40,000	26,000	9,000–49,000
Hematocrit (%)	18.7	15.3–20.7	19.3	16.6–20.1
Hemoglobin (g/dL)	6.0	5.2–7.3	6.5	5.5–6.7
Creatinine (mg/dL)	1.1	0.5–11.4	2.5	1.2–4.2
BUN (mg/dL)	28	8–84	52	21–59
LDH (units/L)	1,080	131–3,007	768.5	395–1,191
ADAMTS13 activity level (%)	90*	84–131	64*	42–100
Schistocytes present (no. patients)	8	—	7	—
	No.	**(%)**	**No.**	**(%)**
Symptom				
Nausea	6	75	5	71
Abdominal pain	5	63	6	86
Fever	1	13	5	71
Fatigue	5	63	5	71
Treatment				
Plasmapheresis	6	75	6	86
Dialysis	2	25	0	0
Other illness				
Hepatitis C	5	63	7	100
Sepsis	0	0	7	100
Endocarditis	0	0	3	43
Renal failure	4	50	7	100

Abbreviations: BUN = blood urea nitrogen; LDH = lactate dehydrogenase; ADAMTS13 = the von Willebrand factor–cleaving protease.
* Data not available for seven of the 15 cases.

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Editorial Note

TTP is a one of the thrombotic microangiopathies, conditions characterized by thrombosis in arterioles and capillaries that manifest clinically with thrombocytopenia and microangiopathic hemolytic anemia (*3*). Patients with TTP require hospitalization and usually plasmapheresis. Without treatment, TTP is associated with a high mortality rate (*2*). TTP is more common among women (*1,2*). In addition to platelet aggregation inhibitors, other toxic chemotherapeutic and immunosuppressive drugs have been associated with TTP (*1,3*).

Hepatitis C and systemic infections often are associated with IV drug abuse as well as with thrombocytopenia, hemolytic anemia, and deficiency of the ADAMTS13 enzyme. Therefore, whether TTP was caused by infection or some noninfectious exposure has been unclear in certain previous cases (*5,6*). However, in the cases described in this report, injection of reformulated Opana ER was strongly associated (OR = 35.0; CI = 3.9–312.1) with the illness of the case-patients.

FDA approved Opana ER for oral use in 2006. However, like other opioid analgesics, the drug has been abused by some persons seeking its euphoria-inducing effects, including some who have crushed the tablets to snort them or dissolved them for injection (*7,8*). The new formulation, designed to inhibit crushing and dissolving tablets, was released into the market in February 2012. The new formulation contains inactive ingredients not found in the original formulation, including polyethylene oxide (PEO) and polyethylene

What is already known on this topic?

Thrombotic thrombocytopenic purpura (TTP) is a rare but serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia and has not been associated previously with intravenous abuse of Opana ER, an extended-release form of oxymorphone intended for oral administration. In February 2012, a new formulation of Opana ER was released with the intent to inhibit crushing and dissolving the tablets.

What is added by this report?

In 2012, 15 cases of TTP-like illness were identified among intravenous drug users in Tennessee, including 14 who reported injecting reformulated Opana ER. A case-control analysis identified a strong association (odds ratio = 35.0; 95% confidence interval = 3.9–312.1) between TTP-like illness and injection of reformulated Opana ER.

What are the implications for public health practice?

The disease mechanism and extent of the problem with Opana ER abuse are unknown. Health-care providers should ask patients with TTP-like illness of unknown etiology about injection-drug abuse. Additionally, health-care providers who prescribe Opana ER and pharmacists who dispense it should inform persons using it of the risks involved when used other than as prescribed.

glycol. Of note, in October 2010, the makers of OxyContin, another extended-release opioid analgesic, also launched a reformulated product designed to deter abuse that contained PEO. No cases of TTP-like illness following injection of reformulated OxyContin have been reported.

It is unclear what component or components of reformulated Opana ER might trigger TTP-like illness when injected and whether different methods of preparing the drug can increase or decrease the risk from injection. No human studies have evaluated the risk from injecting this new formulation, although in one study in rats, intravenously injected PEO caused thrombocytopenia (*9*). It is also possible that the pills in the Tennessee cases were adulterated by a drug dealer. However, at least two patients obtained the drugs directly from a licensed pharmacy with prescriptions, and the involved communities are far enough apart to make a single nonmedical source for other cases unlikely. In general, injection of any opioid pain reliever formulated for oral use presents risks for fatal toxicity and bloodborne infection, but this is the first report of TTP-like illness associated with abuse of an opioid pain reliever by injection.

FDA has warned* that Opana ER is meant to be taken orally and should only be taken when prescribed and as directed. CDC has recommended† that clinicians treating patients with TTP-like illness with unknown etiology ask about IV drug abuse, perform a urine drug test to look for oxymorphone, and request a copy of the patient's prescriptions for controlled substances from state prescription drug monitoring programs. Clinicians should counsel patients who report injection of reformulated Opana ER of the risk for recurrent TTP, bloodborne infections, and overdose with continued use; refer them to substance abuse treatment programs, and notify other clinicians who have prescribed the patient Opana ER. Cases can be reported to state or local health departments. A standardized case report form is available at e-mail, lbp4@cdc.gov.

* Available at http://www.fda.gov/drugs/drugsafety/ucm322432.htm.
† Available at http://www.bt.cdc.gov/han/han00331.asp.

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Published Reports of Delayed Hemolytic Anemia After Treatment with Artesunate for Severe Malaria — Worldwide, 2010–2012

Artesunate has been recommended by the World Health Organization (WHO) as the first-line treatment for severe malaria since 2010. It is not licensed in the United States but is available from CDC under an investigational new drug (IND) protocol. During 2010–2012, a total of 19 cases of delayed hemolytic anemia after treatment of severe malaria with artesunate were published in the peer-reviewed medical literature, but no such cases have been reported in the United States. CDC Malaria Branch staff reviewed each published report of delayed hemolysis after artesunate use. Based on the pathogenesis of malaria, the hemolysis likely is a result of severe malaria and not the treatment itself. However, artesunate used in the United States is produced by the U.S. Army Medical Materiel Development Activity, and artesunate used outside of the United States is not. An unrecognized difference might exist between the U.S. artesunate and the artesunate used elsewhere. Alternatively, cases of artesunate-associated hemolysis might have occurred in the United States but were not reported. To better assess these possibilities, CDC has amended the artesunate IND protocol and now recommends that persons treated for severe malaria with artesunate be followed for 4 weeks after treatment and evaluated for hemolytic anemia.

A literature search was performed using the terms "artesunate" and either "hemolytic anemia" or "delayed anemia." All reports were reviewed, and additional case reports referenced in these reports also were obtained and reviewed. Case reports were considered relevant if the patient had received artesunate therapy for the treatment of severe malaria and then experienced worsening hemolytic anemia after initial clinical improvement and resolution of parasitemia. In total, six articles (describing 19 cases) fit these requirements. One incident of hemolytic anemia was reported in two different articles, one published in 2002 and the other in 2010. Only the 2010 report is included in this summary.

All cases except one were in adults (median age: 50 years; age range: 5–71 years) (Table). Eighteen patients had traveled to sub-Saharan Africa, and one to India. All 12 patients with documentation of parasitemia were hyperparasitemic (>5% of red blood cells [RBCs] infected), with a mean highest parasitemia reported of 22% (range: 7%–45%). Seven of the patients also received artemether-lumefantrine, an oral drug similar to artesunate, for either initial treatment or to complete the treatment regimen. Ten patients received nonartemisinin antimalarials before or after artesunate therapy. All 14 patients for whom multiple hemoglobin measurements were available had a reduction in hemoglobin within the first week of treatment, from a mean of 12.3 g/dL on admission to 8.8 g/dL on follow-up. Seven patients received transfusions with either packed RBCs or platelets during their initial presentation, including three who received exchange transfusions. All patients responded well to artesunate therapy, and complete parasite clearance was documented on average by day 5.

For all patients, hemolysis and worsening anemia were described after parasite clearance, 8–32 days after completion of artesunate therapy. The mean hemoglobin nadir was 6.2 g/dL (range: 4.4–8.6 g/dL) (n = 18). Other reported laboratory measurements supported the diagnosis of hemolysis including elevated lactate dehydrogenase, low or absent haptoglobin, elevated bilirubin, and/or elevated reticulocyte count (n = 12). Twelve patients required transfusions, ranging from 2–24 units, after artesunate treatment. The hemolysis resolved, and hemoglobin improved in all patients within 4–8 weeks after artesunate therapy. Two patients had documented moderate anemia more than 30 days after treatment.

Two studies included information on patients with severe malaria both with and without delayed hemolysis. One reported that the six patients with hemolysis had received a higher mean cumulative dose of artesunate than the 19 patients without hemolysis (12.8 mg/kg versus 7.6 mg/kg) (*1*). However, the mean cumulative dose in patients with hemolysis in the other article was 7.2 mg/kg, and no correlation between dose and hemolysis was observed (*2*). Although not specifically discussed, the reported parasitemia in the patients with delayed hemolysis was higher in both studies (mean parasitemia of 16% versus 11%, and median parasitemia of 27% versus 5%, respectively).

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Editorial Note

This review of published cases found reports of 19 cases of delayed hemolysis after artesunate therapy for severe malaria in nonendemic countries outside of the United States. Thus far, no published studies have assessed whether artesunate actually causes or increases the risk for delayed hemolysis; therefore, it remains unknown whether the hemolysis described

TABLE. Articles and cases reported in the literature involving delayed hemolytic anemia after treatment with artesunate, by selected characteristics — worldwide, 2010–2012

Case	Location	Case description	Peak parasitemia reported	Initial treatment	Artesunate total dose	Follow-up treatment	Parasite clearance time	Initial Hgb (g/dL)	Hgb nadir (g/dL)	Day of nadir*	Other laboratory findings
Rolling T, Schmiedel S, Wichmann D, et al. Post-treatment haemolysis in severe imported malaria after intravenous artesunate: case report of three patients with hyperparasitaemia. Malar J 2012;11:169.											
Case 1	Germany	German female aged 19 yrs with hypotension and hyperparasitemia	14%	Mefloquine	8 mg/kg	Mefloquine	5 days	12.0	8.6	14	LDH 1,010
Case 2	Germany	German male aged 54 yrs with somnolence, hypotension, hyperbilirubinemia, hyperparasitemia, and acute renal failure	21%	Artesunate	9 mg/kg	Atovaquone/ proguanil	7 days	NA	5.7	14	LDH increased Haptoglobin absent DAT IgG+
Case 3	Germany	German male aged 55 yrs with fever, acute renal failure, hyperbilirubinemia, and hyperparasitemia	20%	Artesunate	9 mg/kg	Atovaquone/ proguanil	NA (<1% on day 3)	14.7	6.6	15	LDH increased Haptoglobin absent DAT negative
Kreeftmeijer-Vegter AR, van Genderen PJ, Visser LG. Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium. Malar J 2012;11:102.†											
Case 4	Netherlands/ Belgium	Male aged 53 yrs with jaundice, impaired consciousness, and hyperparasitemia	34%	Quinine	NA	Atovaquone/ proguanil	4 days	12.9	6.9	20	DAT C3d+
Case 5	Netherlands/ Belgium	Female aged 50 yrs with impaired consciousness, jaundice, acidosis, renal impairment, and hyperparasitemia	19%	Artesunate	NA	Atovaquone/ proguanil	3 days	14.0	7.0	30	NA
Case 6	Netherlands/ Belgium	Female aged 50 yrs with jaundice and hyperparasitemia	11%	Artesunate	NA	Atovaquone/ proguanil	3 days	11.4	4.5	13	DAT negative
Case 7	Netherlands/ Belgium	Female aged 44 yrs with hyperparasitemia	37%	Quinine	NA	Artemether-lumefantrine	4 days	9.7	6.1	15	DAT C3d+ IgG+
Case 8	Netherlands/ Belgium	Male aged 5 yrs with shock, impaired consciousness, and hyperparasitemia	12%	Quinine	NA	Artemether-lumefantrine	4 days	9.8	6.1	8	DAT negative Hemacult negative
Case 9	Netherlands/ Belgium	Female aged 50 yrs with jaundice, hemoglobinuria, and hyperparasitemia	30%	Artesunate	NA	Artemether-lumefantrine	10 days	11.6	6.9	13	DAT IgG+ IgM+ Hemacult negative G6PD normal
Case 10	Netherlands/ Belgium	Female aged 71 yrs with impaired consciousness, acidosis, hypoglycemia, respiratory distress, renal impairment, and hyperparasitemia	20%	Quinine	NA	Artemether-lumefantrine	7 days	8.1	6.0	13	DAT negative
Zoller T, Junghanss T, Kapaun A, et al. Intravenous artesunate for severe malaria in travelers, Europe. Emerg Infect Dis 2011;17:771–7.											
Case 11	Europe	Female aged 30 yrs with hyperparasitemia	20%	Artesunate + doxycycline	12 mg/kg	None	79 hrs	11.3	5.7	15	LDH 1,437 Reticulocytes 10.2% DAT negative G6PD normal
Case 12	Europe	Female aged 54 yrs with HIV, admitted with hyperparasitemia and cerebral malaria	20%	Artesunate + doxycycline	12 mg/kg	None	158 hrs	13.2	6.1	32	LDH 805
Case 13	Heidelberg, Germany	Male aged 32 yrs with hyperparasitemia	30%	Artesunate	12 mg/kg	Atovaquone-proguanil	104 hrs	13.4	5.3	19	LDH 672
Case 14	Helsingborg, Sweden	Male aged 46 yrs with diabetes mellitus admitted with malaria, renal failure, and jaundice	4%	Artesunate	20 mg/kg	None	48 hrs	13.4	7.8	15	LDH 660 Reticulocytes increased
Case 15	Bergen, Norway	Male aged 49 yrs with renal failure, jaundice, disseminated intravascular coagulation, and hyperparasitemia	9%	Artesunate + doxycycline	12 mg/kg	Artemether-lumefantrine	35 hrs	15.5	5.7	15	LDH 1,489 Reticulocytes increased Haptglobin <0.1
Case 16	Europe	Female aged 34 yrs with renal failure, shock, and hyperparasitemia	10%	Artesunate + doxycycline	10 mg/kg	Artemether-lumefantrine	NA	14.2	5.8	16	LDH 444 Reticulocytes increased Haptoglobin <0.8 G6PD normal
Caramello P, Balbiano R, De Blasi T, et al. Severe malaria, artesunate and haemolysis. J Antimicrob Chemother 2012;67:2053–4.											
Case 17	Italy	Italian woman aged 22 yrs with fever, splenomegaly, jaundice, and hyperparasitemia	7%	Artemether-lumefantrine	NA	NA	4 days	NA	5.6	13	LDH 2,406 DAT negative G6PD normal
Kano S. Artemisinin-based combination therapies and their introduction in Japan. J Infect Chemother 2010;16:375–82.											
Case 18	Japan	Japanese woman aged 68 yrs	45%	Artesunate	NA	NA	1 day	NA	NA	11	NA
Case 19	Japan	Japanese man aged 54 yrs	NA	Artesunate	NA	NA	1 day	NA	4.4	15	LDH 1,483

Abbreviations: Hgb = hemoglobin; LDH = lactate dehydrogenase (in U/L); DAT = direct antiglobulin test; G6PD = glucose-6-phosphate dehydrogenase; NA = not available; IgG = immunoglobulin G; IgM = immunoglobulin M.

* Day of nadir = days after first dose of artesunate.

† Initial Hgb, for this article only, interpreted from published graphs of hemoglobin over time.

is a direct effect of the treatment or simply a consequence of severe malaria itself.

In 2010, a total of 176 cases of severe malaria in the United States were reported to CDC, 39 (22%) of which were in patients who received artesunate through the CDC IND protocol (*3*). Thus far, delayed hemolytic anemia has not been reported in patients treated with artesunate in the United States. Artesunate has been recommended by WHO as first-line treatment for severe malaria since 2010. It has been shown to be superior to quinine, with increased survival and decreased adverse events (*4*). Recently, many nonendemic countries have begun to use artesunate in patients with travel-associated severe malaria. The United States is the only country where the artesunate used has been certified as meeting good manufacturing practice (GMP) standards. In all other countries, the only form of artesunate available has not been certified as having been produced according to GMP standards, but has been prequalified by WHO as an essential drug (*1,5*). WHO prequalification involves a review of safety data and a manufacturing site assessment but is not thought to be as stringent as GMP certification. Various authors have expressed concern that these delayed hemolytic events might be a direct toxicity of the non-GMP artesunate that is currently used outside of the United States (*1,2*). However, based on this review on malaria and hemolysis, there appear to be more compelling mechanisms that might explain these delayed hemolytic events related to the pathogenesis of severe malaria itself.

There have been multiple published reports of hemolytic anemia in malaria not associated with artesunate. These include reports of "blackwater fever" (dark red or black urine associated with acute malaria) and prolonged hemolytic anemia in severe malaria patients treated with older antimalarial medications. In 1979, one study showed that circulating RBCs in patients with acute malaria continued to have a decreased life-span for up to 4–5 weeks after parasite clearance. Patients in this study treated with chloroquine experienced a mean 9% decline in their hemoglobin, occurring 3–22 days after completion of their treatment. Researchers also detected mild suppression of RBC production and complement-containing immune complexes on RBC surfaces after infection, likely promoting increased splenic removal of RBCs (*6*). A study conducted in The Gambia showed that patients with severe malaria, but without severe anemia, experienced an initial drop in hemoglobin when started on treatment. In addition, in a subset of children without hemoglobinopathies or glucose-6-phosphate dehydrogenase deficiency (n = 17), 16 were direct antiglobulin test (DAT)–positive, and nine were positive for immunoglobulin G autoantibodies, with higher parasitemia being associated with increased DAT positivity (*7*). In 1993, researchers in Germany detected immunoglobulin M antiglycolytic antibodies in patients with severe malaria and prolonged hemolysis after parasite clearance. These antibodies were only present in patients with severe malaria from *Plasmodium falciparum*, persisted up to >40 days after treatment, and resolved as hemolysis resolved. The typical hemoglobin nadir in this study occurred 6–12 days postdiagnosis (*8*).

What is already known on this topic?

Recent reports of delayed hemolytic anemia after artesunate treatment for severe malaria in nonendemic countries other than the United States have generated concern that this phenomenon might be related to the treatment.

What is added by this report?

Published reports describing prolonged hemolytic anemia in severe malaria not associated with artesunate treatment suggest multiple possible causes related to the pathogenesis of severe malaria infection itself.

What are the implications for public health practice?

Additional data are needed. Clinicians treating patients for severe malaria with artesunate should monitor the patient for 4 weeks after treatment, assess for hemolysis if anemia is present, and report any episodes of delayed hemolysis to CDC.

In 1997, a study using antibodies against ring-infected erythrocyte surface antigens (RESA) to label *P. falciparum*–infected cells found that RBCs with the RESA antigen, but without parasites, could be detected if labeled in vivo. This led to the hypothesis that the spleen or another organ removed or killed the parasites without destroying the RBCs (*9*). A follow-up study found that, in patients with severe malaria, artesunate treatment generated a much higher number of unparasitized RESA-positive RBCs than quinine. It also noted that artesunate-treated RBCs were more deformable then quinine-treated or parasitized RBCs, likely further extending their lifespan (*10*). This increase in RBCs surviving after parasitemia, albeit with a shorter lifespan than healthy RBCs, might explain the delayed postartesunate treatment decrease in hemoglobin observed in the cases reported.

Further comparative data would be required to determine how artesunate influences the risks for this complication, both in travelers and in the increasing proportion of patients receiving artesunate for severe malaria in highly endemic countries. There is insufficient evidence at present to attribute these few reported hemolytic events directly to artesunate treatment itself, and these events should not reduce confidence in artesunate, which has many other benefits for patients with severe malaria. In addition, all patients with reported delayed hemolysis have recovered without long-term complications. However, to further understand the relationship between delayed hemolysis and artesunate use, CDC is requesting that patients treated with artesunate in the United States be

evaluated and have their hemoglobin assessed 4 weeks after treatment. Significant declines in hemoglobin should be reported to CDC's Malaria Branch and should prompt an evaluation for hemolysis and closer monitoring.

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Vital Signs: Binge Drinking Among Women and High School Girls — United States, 2011

On January 8, 2013, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

Abstract

Background: Excessive alcohol use accounted for an estimated average of 23,000 deaths and 633,000 years of potential life lost (YPLL) among women and girls in the United States each year during 2001–2005. Binge drinking accounted for more than half of those deaths and YPLL. Binge drinking also is a risk factor for many health and social problems among women and girls, including unintended and alcohol-exposed pregnancy, sexually transmitted diseases, and breast cancer.

Methods: To describe the prevalence, frequency, and intensity of binge drinking (four or more drinks on an occasion in the last 30 days) among U.S. women aged ≥18 years, CDC analyzed data from the 2011 Behavioral Risk Factor Surveillance System. Data were also analyzed from the 2011 national Youth Risk Behavior Survey on the prevalence of current alcohol use (one or more drinks during the past 30 days) and binge drinking (five or more drinks in a row during the past 30 days) among U.S. high school girls in grades 9–12.

Results: Among adult women, the prevalence of binge drinking was 12.5%, and among those who binge drank, the frequency of binge drinking was 3.2 episodes per month and the intensity was 5.7 drinks on occasion. Binge drinking was most prevalent among women aged 18–24 years (24.2%) and 25–34 years (19.9%), and among those from households with annual incomes of ≥$75,000 (16.0%). Among those who binge drank, women aged 18–24 years had the highest frequency (3.6 episodes) and intensity (6.4 drinks) of binge drinking. Among high school girls, the prevalence of current alcohol use was 37.9%, the prevalence of binge drinking was 19.8%, and the prevalence of binge drinking among girls who reported current alcohol use was 54.6%.

Conclusions: Binge drinking is reported by one in eight U.S. adult women and one in five high school girls. Women who binge drink tend to do so frequently and with high intensity. Most high school girls who reported current alcohol use also reported binge drinking.

Implications for Public Health Practice: More widespread implementation of evidence-based interventions, such as those recommended by the Guide to Community Preventive Services and the U.S. Preventive Services Task Force, would be expected to reduce the frequency and intensity, and ultimately the prevalence of binge drinking among women and girls, and the harms related to it.

Introduction

Excessive alcohol use* among women and girls accounted for an estimated average of 23,000 deaths† and 633,00 years of potential life lost (YPLL)§ in the United States each year during 2001–2005. Binge drinking was responsible for more than half of those deaths and YPLL (*1*). Binge drinking is a risk factor for many health and social problems that affect women, including unintentional injuries, violence, liver disease, hypertension, heart disease, stroke, breast and other cancers, reduced cognitive function, and alcohol dependence (*2*). Binge drinking also can affect women's reproductive health by increasing the risk for acquiring human immunodeficiency virus and other sexually transmitted infections, unintended pregnancy, miscarriage, and low birth weight (*3*). A woman who binge drinks might unintentionally expose a developing fetus to high blood alcohol concentrations, increasing the risk for sudden infant death syndrome, fetal alcohol spectrum disorder, and attention-deficit/hyperactivity disorder (*3*). At the state level, binge drinking by women correlates strongly with binge drinking by high school girls (*4*).

Reducing the prevalence of binge drinking among adults and youths¶ is a leading health indicator in *Healthy People 2020*

* Excessive alcohol use includes binge drinking (defined by CDC as consuming four or more drinks per occasion for women or five or more drinks per occasion for men), heavy drinking (defined as consuming more than one drink per day on average for women or more than two drinks per day on average for men), any alcohol consumption by pregnant women, and any alcohol consumption by youths aged <21 years.

† Alcohol-attributable deaths for 2001–2005 were estimated using the Alcohol-Related Disease Impact (ARDI) application. Additional information is available at http://apps.nccd.cdc.gov/dach_ardi/default/default.aspx.

§ YPLL for 2001–2005 were estimated using the ARDI application using death and life expectancy data from the National Vital Statistics System.

¶ Objective SA-14.3 (adults) and SA-14.4 (youth). Objective MICH-11.2 (pregnant women).

(*5*). To assess measures of binge drinking nationwide among women and girls, CDC analyzed data from the 2011 Behavioral Risk Factor Surveillance System (BRFSS) to determine the prevalence, frequency, and intensity of binge drinking among adult women, and data from the 2011 national Youth Risk Behavior Survey (YRBS) to determine measures of current alcohol use and binge drinking among high school girls.

Methods

BRFSS

BRFSS is an annual, state-based, random-digit–dialed telephone survey of noninstitutionalized, civilian, U.S. adults aged ≥18 years that collects information on many leading health conditions and health risk behaviors, including binge drinking. In 2011, all 50 states and the District of Columbia (DC) conducted the BRFSS by landline and cellular telephones. The median proportion of all BRFSS interviews completed by cellular telephones was approximately 11%. In 2011, the median survey response rate was 49.7%, ranging from 33.8% to 64.1%.** BRFSS data were weighted to adjust for several demographic variables (e.g., education levels, marital status, home ownership, and telephone source). A total of 278,243 women respondents were included in the analysis. A more detailed description of BRFSS methods has been published (*6*).

For women, binge drinking was defined as consuming four or more alcoholic drinks per occasion during the past 30 days. Among women who binge drank, binge drinking frequency was defined as the total number of episodes of binge drinking during the past 30 days. Binge drinking intensity was defined as the average largest number of drinks consumed during the past 30 days by respondents who reported one or more episodes of binge drinking. Respondents who refused to answer, had a missing answer, or who answered "don't know/not sure" were excluded from the analyses involving those variables.

YRBS

The biennial national YRBS, a component of CDC's Youth Risk Behavior Surveillance System, measures the prevalence of health risk behaviors among U.S. high school students. The 2011 national YRBS obtained cross-sectional data representative of public- and private-school students in grades 9–12 in all 50 states and DC. Students completed an anonymous, self-administered questionnaire that included questions about alcohol use. Students from 158 schools completed 15,503 questionnaires. The school response rate was 81%, the student response rate was 87%, and the overall response rate was 71%. After quality control measures were taken, data from 15,425 students were available for analysis, of which data from 7,536 student girls were included in the analysis. Data were weighted to adjust for school and student nonresponse and oversampling of black and Hispanic students. A more detailed description of YRBS methods has been published (*7*).

Current alcohol use was defined as having had at least one drink of alcohol on at least 1 day during the 30 days before the survey. Binge drinking was defined for girls and boys as having had five or more drinks of alcohol in a row (i.e., within a couple of hours) on at least 1 day during the 30 days before the survey. T-tests were used to test for significant ($p<0.05$) differences between subgroups. Respondents who did not respond to one or both questions were excluded from the analysis.

Results

BRFSS

In 2011, the overall prevalence of binge drinking among women aged ≥18 years was 12.5% (Table 1). Among women who binge drank, the frequency of binge drinking was 3.2 episodes per month and the intensity was 5.7 drinks on occasion. Binge drinking was most prevalent among women aged 18–24 years (24.2%) and 25–34 years (19.9%), and then gradually decreased with increasing age. The highest frequency (3.6 episodes) and intensity (6.4 drinks) of binge drinking was reported by women aged 18–24 years. The prevalence of binge drinking was highest among non-Hispanic white women (13.3%), but the frequency and intensity of binge drinking was similar across racial and ethnic groups. Women who did not graduate from high school had the lowest prevalence of binge drinking (8.5%), but those who binge drank had the highest frequency (4.2 episodes) and intensity (6.2 drinks) relative to women with higher educational levels. Binge drinking prevalence increased with household income, and was highest among women with annual household incomes of $75,000 or more (16.0%).

YRBS

In 2011, the prevalence of current alcohol use and of binge drinking among high school girls in grades 9–12 was 37.9% and 19.8%, respectively (Table 2). Hispanic (22.4%) and non-Hispanic white (21.7%) high school girls had a higher prevalence of binge drinking than non-Hispanic black girls (10.3%). Binge drinking prevalence among high school girls increased with grade, and was twice as high among 12th grade girls (27.0%) as among 9th grade girls (13.0%).

** Response rates for BRFSS are calculated using standards set by the American Association of Public Opinion Research (AAPOR) response rate formula no. 4, available at http://www.aapor.org/standard_definitions2.htm. The response rate is the number of respondents who completed the survey as a proportion of all eligible and likely eligible persons. Additional information is available at http://www.cdc.gov/brfss/technical_infodata/quality.htm.

TABLE 1. Binge drinking* prevalence, frequency, and intensity, by sociodemographic characteristics among women — Behavioral Risk Factor Surveillance System, United States,† 2011

Characteristic	Prevalence			Frequency§			Intensity¶		
	No.	Weighted %	(95% CI)	No.	No. of episodes	(95% CI)	No.	No. of drinks	(95% CI)
Total	**278,243**	**12.5**	**(12.2–12.8)**	**24,681**	**3.2**	**(3.1–3.3)**	**23,352**	**5.7**	**(5.6–5.8)**
Age groups (yrs)									
18–24	10,378	24.2	(22.7–25.6)	2,535	3.6	(3.3–3.9)	2,381	6.4	(6.1–6.6)
25–34	26,042	19.9	(19.0–20.7)	5,023	3.0	(2.8–3.2)	4,786	6.0	(5.9–6.2)
35–44	35,290	14.5	(13.8–15.1)	5,049	3.0	(2.8–3.2)	4,808	5.5	(5.4–5.6)
45–64	112,529	9.5	(9.2–9.9)	9,957	3.3	(3.2–3.5)	9,427	5.1	(5.0–5.2)
≥65	94,004	2.5	(2.3–2.7)	2,117	3.4	(3.0–3.8)	1,950	4.2	(4.1–4.4)
Race/Ethnicity									
White, non-Hispanic	219,519	13.3	(13.0–13.7)	19,969	3.3	(3.2–3.4)	19,033	5.7	(5.6–5.8)
Black, non-Hispanic	24,521	10.1	(9.3–10.9)	1,670	3.2	(2.9–3.5)	1,524	5.2	(5.0–5.4)
Hispanic	17,089	11.0	(10.1–11.9)	1,545	2.8	(2.5–3.1)	1,414	5.8	(5.5–6.1)
Other, non-Hispanic**	14,625	10.9	(9.7–12.2)	1,369	3.4	(2.8–4.0)	1,272	6.0	(5.6–6.4)
Education Level									
Less than high school diploma	24,036	8.5	(7.7–9.3)	1,335	4.2	(3.6–4.8)	1,186	6.2	(5.8–6.6)
High school diploma	82,247	10.9	(10.4–11.4)	6,136	3.4	(3.2–3.7)	5,720	5.9	(5.7–6.1)
Some college	78,925	14.3	(13.7–14.9)	7,636	3.3	(3.2–3.5)	7,237	5.7	(5.6–5.8)
College graduate	92,528	14.1	(13.6–14.6)	9,552	2.7	(2.6–2.8)	9,189	5.3	(5.2–5.4)
Income									
<$25,000	78,723	11.4	(10.8–11.9)	5,533	3.4	(3.2–3.6)	5,155	6.0	(5.9–6.2)
$25,000–$49,999	63,946	12.0	(11.5–12.6)	5,546	3.3	(3.1–3.6)	5,261	5.8	(5.7–6.0)
$50,000–$74,999	35,840	13.0	(12.2–13.7)	3,690	2.9	(2.7–3.1)	3,567	5.4	(5.3–5.6)
≥$75,000	57,364	16.0	(15.4-16.7)	7,547	3.0	(2.8–3.2)	7,261	5.4	(5.2–5.5)

Abbreviation: CI = confidence interval.
* For women, binge drinking was defined in the BRFSS as consuming four or more alcoholic drinks per occasion during the past 30 days.
† Respondents were from 50 states and the District of Columbia.
§ Binge drinkers only; average number of binge-drinking episodes per month.
¶ Average largest number of drinks consumed by binge drinkers on any occasion in the past month.
** Other, non-Hispanic includes Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native, other race, and multiracial.

The prevalence of binge drinking among high school girls who reported current alcohol use was 54.6% (Table 2). Non-Hispanic white (57.8%) and Hispanic (55.4%) high school girls who reported current alcohol use had a higher prevalence of binge drinking than non-Hispanic black (35.0%) high school girls who reported current alcohol use. The prevalence of binge drinking among high school girls who reported current alcohol use increased with grade, from 45.2% among girls in grade 9 to 61.7% among girls in grade 12.

Conclusions and Comment

The results in this report indicate that in 2011, binge drinking was common among U.S. adult women, and women who binge drank tended to do so frequently (average of three times per month) and intensively (average of six drinks on occasion), placing themselves and others at a greater risk for alcohol-attributable harms (*1,2*). The prevalence of binge drinking was similar among high school girls (especially in grades 11 and 12), women aged 18–24 years, and women aged 25–34 years. Binge drinking was most prevalent among women living in households with annual incomes of $75,000 or more.

At the state level, alcohol consumption by high school girls is strongly correlated with alcohol consumption by adult women (*4*). This probably reflects the influence of adult drinking behavior on youths, including the fact that youths often obtain alcohol from adults (*8*) and that youths often aspire to behave like young adults. The drinking behavior of youths and adults also is affected by the price and availability of alcoholic beverages (*9*) and religious and cultural factors (*10*). Additionally, binge drinking, unlike other leading risk behaviors, has not been subjected to intense prevention efforts (*11*). Underage girls are overexposed to alcohol marketing relative to women to an even greater extent than underage boys are overexposed to alcohol marketing relative to men (*12*), thereby increasing the risk that girls will initiate alcohol consumption and consume more alcohol when they drink (*13*). New alcoholic beverages also have been developed and marketed (e.g., flavored malt beverages) that are known to appeal to underage girls (*14*).

Although binge drinking is more prevalent among men (*15*), women who binge drink are at high risk for alcohol-attributable harms, in part because they differ from men in their physiologic response to alcohol consumption. Women tend to reach higher blood alcohol levels than men at the same consumption level, even

TABLE 2. Prevalence of current alcohol use and binge drinking* by race/ethnicity and grade among high school girls — National Youth Risk Behavior Survey, United States, 2011

Characteristic	Current alcohol use (N = 7,032)		Binge drinking (N = 7,536)		Binge drinking among students reporting current alcohol use (N = 2,745)	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
Total	**37.9**	**(36.1–39.8)**	**19.8**	**(18.6–21.1)**	**54.6**	**(52.6–56.5)**
Race/Ethnicity						
White, non-Hispanic	38.8	(36.1–41.6)	21.7	(20.0–23.5)	57.8	(55.0–60.4)
Black, non-Hispanic	31.6	(28.0–35.3)	10.3	(8.3–12.6)	35.0	(28.6–42.1)
Hispanic	42.4	(39.4–45.5)	22.4	(20.5–24.5)	55.4	(52.4–58.4)
Other, non-Hispanic†	31.7	(27.1–36.6)	16.7	(13.7–20.1)	55.4	(46.8–63.8)
Grade						
9	30.3	(27.2–33.6)	13.0	(10.9–15.3)	45.2	(40.5–50.0)
10	37.1	(33.9–40.3)	17.8	(15.9–19.9)	50.4	(46.0–54.8)
11	40.1	(36.9–43.3)	22.6	(19.9–25.4)	58.4	(53.9–62.8)
12	45.4	(41.6–49.4)	27.0	(23.8–30.6)	61.7	(57.2–66.0)

Abbreviation: CI = confidence interval.

* Defined in the YRBS for girls and boys as having had five or more drinks of alcohol in a row (i.e., within a couple of hours) on at least 1 day during the 30 days before the survey.

† Other, non-Hispanic includes Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native, and multiracial.

after taking into account differences in body size, food consumption, and other factors (*16*). In addition, binge drinking increases the risk for unintended pregnancy, and women with unintended pregnancies tend to have delayed pregnancy recognition (*3*), increasing the risk for alcohol-exposed pregnancy and adverse reproductive health outcomes, such as fetal alcohol spectrum disorder, among women who binge drink, and further emphasizing the need to prevent binge drinking in women.

The findings in this report are subject to at least five limitations. First, BRFSS and YRBS data are self-reported. Among adults, alcohol consumption generally, and excessive drinking in particular, are underreported in surveys because of recall bias and social desirability bias (*17*). A recent study using BRFSS data found that self-reports identify only 22%–32% of presumed alcohol consumption in states, based on alcohol sales (*18*). Second, BRFSS does not collect information from persons living in institutional settings (e.g., on college campuses and military bases); therefore, BRFSS data might not be representative of these populations. Third, the BRFSS median response rate in 2011 was 49.7%. Fourth, the YRBS data apply only to youths who attend school, and thus are not representative of all persons in this age group. Nationwide, in 2009, of persons aged 16–17 years, approximately 4% were not enrolled in a high school program and had not completed high school.†† Finally, the YRBS definition of binge drinking (five or more drinks in a row), is not gender-specific, and studies among women have shown that reducing the threshold for defining binge drinking from five drinks to four drinks increases the relative prevalence of binge drinking by more than one third (*19*).

†† Information is available at http://nces.ed.gov/pubs2012/2012006.pdf.

The Guide to Community Preventive Services has recommended several population-level, evidence-based strategies to effectively reduce binge drinking and related harms. These include 1) limiting alcohol outlet density, 2) holding alcohol retailers liable for harms related to the sale of alcoholic beverages to minors and intoxicated patrons (dram shop liability), 3) maintaining existing limits on the days and hours when alcohol is sold, 4) measures increasing the price of alcohol, 5) avoiding further privatization of alcohol sales in states with government-operated or contracted liquor stores, 6) electronic screening and brief interventions in the clinical setting, and 7) maintaining and enforcing age 21 years as the minimum age for legal drinking (*20*). The U.S. Preventive Services Task Force also recommends screening and behavioral counseling interventions for alcohol misuse, including binge drinking, among adults (*21*). The findings of this study also support the need to monitor binge drinking routinely among women and girls (*11,15*) to characterize the public health impact of this behavior, and to evaluate the effect of evidence-based strategies to prevent it.

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Key Points

- Binge drinking is responsible for more than half of the estimated 23,000 deaths and 633,000 years of potential life lost among women and girls because of excessive alcohol consumption in the United States.
- In 2011, more than 13.6 million (12.5%) U.S. adult women binge drank (prevalence) an average of three times a month (frequency), and consume on average six drinks on occasion (intensity).
- The prevalence and intensity of binge drinking was highest among women aged 18–24 years.
- Women with household incomes ≥$75,000 had the highest binge drinking prevalence.
- In 2011, more than one in three high school girls reported drinking and one in five reported binge drinking; most high school girls who drank reported binge drinking.
- More widespread implementation of evidence-based interventions, such as those recommended by the Guide to Community Preventive Service and by the U.S. Preventive Services Task Force, would reduce binge drinking in states, as well as the health and social harms related to it.
- Additional information is available at http://www.cdc.gov/vitalsigns.

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Announcement

National Birth Defects Prevention Month and Folic Acid Awareness Week — January 2013

January is National Birth Defects Prevention Month. Each year, birth defects affect approximately one in 33 newborns in the United States (*1*). Birth defects are a leading cause of infant mortality, accounting for approximately 20% of infant deaths (*2*). Babies who survive and live with birth defects are more likely to have life-long physical and cognitive challenges. In the United States each year, the total hospital costs of children with birth defects exceed $2.6 billion (*3*).

Evidence suggests that use of tobacco or alcohol (*4,5*), uncontrolled diabetes (*6*), failure to consume 400 μg of folic acid daily (*7*), and failure to achieve and maintain a healthy weight before and during pregnancy (*8*) might be associated with birth defects. Health-care professionals can help prevent birth defects by encouraging women of childbearing age to manage health conditions and adopt healthy behaviors before becoming pregnant. Additional information is available at http://www.cdc.gov/birthdefects.

January 6–12, 2013, is National Folic Acid Awareness Week. CDC urges all women of childbearing age who are capable of becoming pregnant to consume 400 μg of folic acid every day, before becoming pregnant and during pregnancy, to help reduce the risk for neural tube defects (major birth defects of the brain and spine) (*7*). Health-care providers should encourage women to consume folic acid in fortified foods or supplements, or a combination of the two, in addition to a varied diet rich in folate. Additional information about folic acid is available at http://www.cdc.gov/folicacid.

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Erratum

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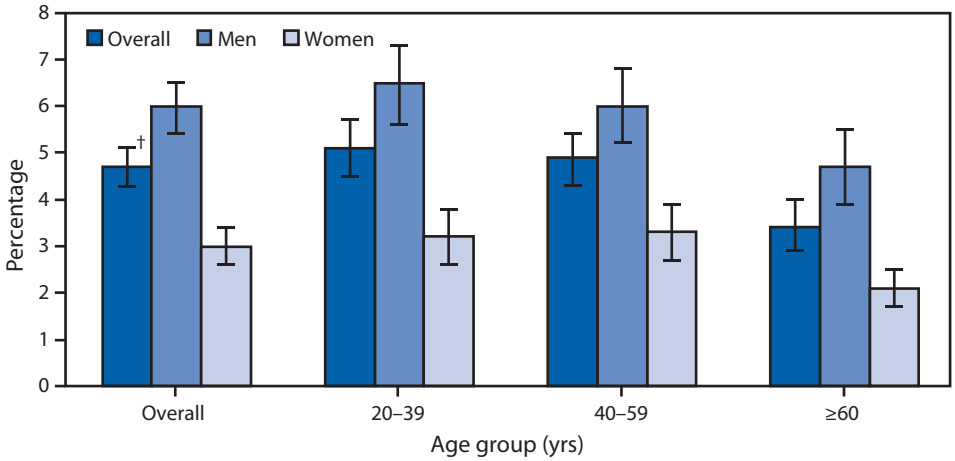
In the report, "Cervical Cancer Screening Among Women by Hysterectomy Status and Among Women Aged ≥65 Years — United States, 2000–2010," an error occurred on page 1045, in the third sentence of the first paragraph of the Editorial Note. The sentence should read as follows: "Despite consistent guidelines by three national organizations (USPSTF, ACS, and ACOG) recommending against routine screening for cervical cancer posthysterectomy, the proportion of women aged **≥30** years who have had a hysterectomy and recently have been screened declined only 15 percentage points, and approximately 59% of these women still reported recent (in the past 3 years) Pap testing in 2010."

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Average Percentage of Daily Calories from Alcoholic Beverages* Among Adults Aged ≥20 Years, by Age Group — National Health and Nutrition Examination Survey, United States, 2007–2010



* Alcoholic beverages include beer, wine, liquor, and mixed drinks (cocktails). Data on consumption are based on in-person, 24-hour dietary recall interviews.
† 95% confidence interval.

During 2007–2010, on average, 4.7% of the daily calories consumed by U.S. adults aged ≥20 years came from alcoholic beverages. The percentage of daily calories from alcohol ranged from 6.5% for men aged 20–39 years to 2.1% for women aged ≥60 years. Across age groups, the percentage of calories from alcohol was higher among men; among both men and women, the percentage declined with age.

Sources: National Health and Nutrition Examination Survey, 2007–2010. Available at http://www.cdc.gov/nchs/nhanes.htm.

Nielsen SJ, Kit BK, Fakhouri T, Ogden CL. Calories consumed from alcoholic beverages by U.S. adults, 2007–2010. NCHS data brief, no. 110. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2012. Available at http://www.cdc.gov/nchs/data/databriefs/db110.htm.

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Data presented by the Notifiable Disease Data Team and 122 Cities Mortality Data Team in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. Address all inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop E-90, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333 or to *mmwrq@cdc.gov.*

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