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Current Marijuana Use by Industry and Occupation — Colorado, 2014–2015

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The effects of marijuana use on workplace safety are of concern for public health and workplace safety professionals. Twenty-nine states and the District of Columbia have enacted laws legalizing marijuana at the state level for recreational and/or medical purposes. Employers and safety professionals in states where marijuana use is legal have expressed concerns about potential increases in occupational injuries, such as on-the-job motor vehicle crashes, related to employee impairment. Data published in 2017 by the Colorado Department of Public Health and Environment (CDPHE) showed that more than one in eight adult state residents aged ≥18 years currently used marijuana in 2014 (13.6%) and 2015 (13.4%) (*1*). To examine current marijuana use by working adults and the industries and occupations in which they are employed, CDPHE analyzed data from the state's Behavioral Risk Factor Surveillance System (BRFSS) regarding current marijuana use (at least 1 day during the preceding 30 days) among 10,169 persons who responded to the current marijuana use question. During 2014 and 2015, 14.6% of these 10,169 Colorado workers reported current marijuana use, with the highest reported prevalence among workers in the Accommodation and Food Services industry (30.1%) and Food Preparation and Serving (32.2%) occupations. Understanding the industries and occupations of adults with reported marijuana use can help direct and maximize impact of public health messaging and potential safety interventions for adults.

The Colorado BRFSS is a CDC-sponsored, state-based, random-digit–dialed telephone survey of the noninstitutionalized U.S. population aged ≥18 years. The survey collects information on health risk factors, preventive health practices, and disease status (*2*). In 2012, 2014, and 2015, two standardized employment questions were included in the Colorado BRFSS survey (*3*). Respondents who indicated that their current employment status was employed for wages, self-employed, or out of work for less than 1 year were asked 1) "What kind of business or industry do you work in?" (industry classification), and 2) "What is your job title?" (occupation classification). In 2014 and in 2015, questions that collected information on marijuana use during the past 30 days were added to the Colorado survey. Respondents who replied "yes" when asked if they had ever used marijuana or hashish were then asked how many days during the past 30 days they had used marijuana or hashish as well as subsequent questions on use frequency and methods. Current use of marijuana was defined as having used marijuana or hashish on at least 1 day in the past 30 days.

Using the 2014 and 2015 BRFSS data combined, state-weighted percentages were calculated, and bivariate analyses using a Rao-Scott chi-square test were performed to compare the prevalence of marijuana use by age group, sex, and race/ethnicity. In addition, prevalence and 95% confidence intervals (CIs) were calculated to compare the prevalence of marijuana use by industry and occupation. Overall BRFSS industry and occupation data, representing current Colorado employment, were added to illustrate the percentage of employees working in the industries and occupations identified within the state.

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Percentages of employed persons reporting current marijuana use in the industry and occupation comparisons were age-adjusted based on the 2000 U.S. standard population. The overall response rate for the Colorado BRFSS was 57.0% in 2014 and 55.2% in 2015.

Among the combined 26,936 respondents* in the BRFSS 2014 and 2015 surveys, 18,848 (70.0%) were given the opportunity to answer the question of whether they had ever used marijuana or hashish, and 18,674 (99.1%) responded (either positively or negatively) to the question. Of those respondents, 10,169 (54.5%) indicated that they were employed or had been out of work for less than 1 year. Among the 10,169 workers responding, 14.6% reported using marijuana during the preceding 30 days (Table 1). The prevalence of current marijuana use was higher among persons aged 18–25 years (29.6%) than among persons aged 26–34 years (18.6%) and persons aged ≥35 years (11.0%), and higher among men (17.2%) than among women (11.3%). By race/ethnicity, prevalence of current marijuana use was highest among non-Hispanic whites (15.3%), followed by Hispanics (15.1%) and non-Hispanic blacks (14.5%) (Table 1).

Among the 10,169 workers, the industry with the highest prevalence of current marijuana use (30.1%) was Accommodation and Food Services (Table 2). Among occupations, Food Preparation and Serving had the highest prevalence of current marijuana users (32.2%), although the age-adjusted prevalence was 19.1% (Table 3).

Among safety-sensitive occupations (those in which workers have responsibility for their own safety or the safety of others), prevalences of current marijuana use among workers who acknowledged using marijuana or hashish in the preceding 30 days and were employed in Construction and Extraction (16.5%);

TABLE 1. Self-reported current marijuana use among eligible employed adults (N = 10,169*), by selected characteristics — Behavioral Risk Factor Surveillance System, Colorado, 2014 and 2015

Characteristic	No.†	Current marijuana use % (95% CI)	p-value§
Total	**10,169**	**14.6 (13.6–15.7)**	—
Age group (yrs)			
18–25	625	29.6 (24.9–34.2)	<0.001
26–34	1,251	18.6 (15.7–21.4)	
≥35	8,187	11 (10–12)	
Sex			
Men	5,138	17.2 (15.7–18.7)	<0.001
Women	5,031	11.3 (9.9–12.8)	
Race/Ethnicity			
White, non-Hispanic	7,823	15.3 (14–16.5)	0.025
Black, non-Hispanic	259	14.5 (9–20)	
Other, non-Hispanic	194	5.7 (1.6–9.8)	
Multiracial, non-Hispanic	1,416	12.7 (10.2–15.3)	
Hispanic	270	15.1 (9.1–21.1)	

Abbreviation: CI = confidence interval.
* Respondents who indicated that they were employed or had been out of work for less than 1 year and who responded to the question of ever using marijuana or hashish.
† Age group missing for 106 (1.0%) respondents; race/ethnicity missing for 207 (2.0%).
§ By Rao-Scott chi-square test.

* Included adults who were students, retirees, and homemakers, in addition to those employed.

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TABLE 2. Prevalence of current marijuana use among eligible employed adults (N = 10,169*), ranked by industry, and overall percentage of state workers employed in the industry — Behavioral Risk Factor Surveillance System, Colorado, 2014 and 2015

Industry	Prevalence of current marijuana use, % (95% CI)	Age-adjusted prevalence of current marijuana use, % (95% CI)	Overall percentage of workers employed in the industry, % (95% CI)
Accommodation and Food Services	30.1 (23.4–36.7)	25.6 (17.3–34.0)	6.4 (5.7–7.1)
Arts, Entertainment, and Recreation	28.3 (19–37.6)	14.8 (7.7–22.0)	2.3 (1.9–2.8)
Other Services (except Public Administration)	20.9 (15.4–26.4)	21.2 (13.2–29.2)	4.3 (3.8–4.8)
Construction†	19.7 (16–23.4)	15 (10.4–19.6)	11.3 (10.4–12.2)
Real Estate, Rent, Lease	19.6 (13.6–25.7)	18.6 (9.1–28.0)	2.8 (2.4–3.2)
Retail Trade	18.9 (14.4–23.5)	18.0 (12.8–23.3)	9.4 (8.6–10.2)
Administration, Support, Waste Management, and Remediation Services	18.8 (13–24.7)	22.4 (14.4–30.5)	4.0 (3.4–4.5)
Information	18.2 (11.7–24.8)	18.1 (9.2–26.9)	3.2 (2.7–3.6)
Manufacturing†	16.3 (12–20.5)	17.3 (11.3–23.3)	6.9 (6.2–7.6)
Agriculture, Forestry, Fishing/Hunting†	14.4 (6.8–21.9)	18.3 (5.7–30.9)	2.1 (1.8–2.5)
Professional, Scientific, Technical Services	14.0 (10.4–17.7)	14.2 (8.7–19.8)	6.4 (5.8–7)
Finance and Insurance	13.5 (9–18.1)	8.9 (4.4–13.4)	4.0 (3.5–4.4)
Management of Companies and Enterprises	13.1 (0.0–30.3)	—§	0.2 (0.1–0.3)
Wholesale Trade	11.4 (4.8–17.9)	12.5 (3.4–21.7)	1.7 (1.3–2)
Transport and Warehousing†	10.2 (6–14.4)	10.7 (3.9–17.4)	4 (3.5–4.5)
Health Care and Social Assistance†	7.4 (5.5–9.4)	7.4 (4.3–10.5)	12.8 (11.9–13.6)
Education	5.8 (3.5–8.1)	6.1 (3.1–9.1)	7.4 (6.8–8.1)
Public Administration	5.8 (3.4–8.2)	5.6 (0.6–10.6)	7.1 (6.4–7.8)
Utilities†	5.8 (0.6–11.1)	3.2 (0.0–8.9)	1.4 (1–1.7)
Mining, Oil, and Gas†	5.2 (1.6–8.7)	6.9 (1.1–12.7)	2.3 (1.9–2.7)

Abbreviation: CI = confidence interval.
* Respondents who indicated that they were employed or had been out of work for less than 1 year and who responded to the question of ever using marijuana or hashish.
† Industries that typically perform routine employee drug testing.
§ Not computed because of limited sample size.

TABLE 3. Prevalence of current marijuana use among eligible employed adults (N = 10,169*), ranked by occupation, and overall percentage of state workers employed in the occupation — Behavioral Risk Factor Surveillance System, Colorado, 2014 and 2015

Occupation	Prevalence of current marijuana use, % (95% CI)	Age-adjusted prevalence of current marijuana use, % (95% CI)	Overall percentage of workers employed in the occupation, % (95% CI)
Food Preparation and Serving	32.2 (23.8–40.5)	19.1 (11.9–26.3)	4.5 (3.9–5.2)
Arts, Design, Entertainment, Sports and Media	27.5 (19.6–35.3)	25.3 (16.5–34.0)	2.2 (1.8–2.5)
Production	20.8 (14–27.6)	21.3 (13–29.5)	3.8 (3.2–4.3)
Life, Physical, and Social Science	20.6 (12–29.3)	22.7 (10.6–34.8)	1.7 (1.4–2)
Sales and Related	19.4 (15–23.7)	19.1 (14–24.2)	10.0 (9.1–10.8)
Installation, Maintenance, and Repair	19.2 (12.3–26.1)	20.3 (8.3–32.3)	3.0 (2.5–3.5)
Personal Care and Service	16.8 (11–22.7)	16.6 (8.7–24.5)	3.4 (3–3.9)
Farming, Fishing, and Forestry†	16.5 (1.5–31.4)	17.3 (0.0–36.2)	0.7 (0.5–1)
Construction and Extraction†	16.5 (12.6–20.4)	12.2 (8–16.4)	9.1 (8.2–10)
Building and Grounds Cleaning and Maintenance	16.0 (10.6–21.4)	17.0 (9.8–24.3)	4.6 (4–5.2)
Legal	15.9 (8.5–23.3)	10.0 (0.0–20.1)	1.3 (1.1–1.6)
Healthcare Support†	15.8 (8.3–23.3)	15.5 (7.5–23.6)	2.4 (1.9–2.8)
Management	15.2 (12.2–18.2)	17.9 (11.7–24.1)	12.3 (11.4–13.1)
Computer and Mathematical	13.2 (7.8–18.6)	19.1 (7.7–30.4)	4.2 (3.7–4.8)
Office and Administrative Support	12.7 (9.9–15.5)	13.9 (9.1–18.7)	9.7 (9–10.5)
Architecture and Engineering	11.1 (6.3–15.9)	11.7 (3.4–20.0)	3.1 (2.6–3.5)
Business and Financial Operations	10.4 (6.8–14.1)	7.6 (3.3–12)	4.5 (4–4.9)
Transportation and Material Moving†,§	10.3 (6.1–14.4)	10.4 (3.2–17.7)	5.2 (4.6–5.8)
Community and Social Services	6.7 (1.9–11.5)	7.6 (0.0–16.4)	1.2 (1–1.5)
Education, Training, and Library	6.3 (3.2–9.5)	6.8 (2.9–10.7)	5.1 (4.6–5.6)
Protective Service	6.2 (0.8–11.6)	0.1 (0.0–0.4)	2.3 (1.9–2.7)
Healthcare and Technical†	3.1 (1.5–4.8)	1.9 (0.0–3.7)	5.6 (5–6.1)

Abbreviation: CI = confidence interval.
* Respondents who indicated that they were employed or had been out of work for less than 1 year and who responded to the question of ever using marijuana or hashish.
† Safety-sensitive occupations in which workers have responsibility for their own safety or the safety of others.
§ Subject to federal drug testing requirements.

Farming, Fishing, and Forestry (16.5%); and Healthcare Support (15.8%) were higher than the overall state prevalence of 14.6% among employed adults. However, the prevalences of current marijuana use among workers in Transportation and Material Moving (10.3%) and Healthcare and Technical (3.1%) were lower than the overall state prevalence (Table 3)

Reported current use of marijuana was lower in industries that are known to perform routine drug testing on employees such as the Healthcare and Social Assistance (7.4%); Utilities (5.8%); and Mining, Oil, and Gas industries (5.2%) (Table 2). Current use also was lower than the overall state prevalence in Transportation and Material Moving occupations (10.2%), which are subject to federal drug testing requirement (Table 3).

Discussion

This is the first study to use BRFSS data to describe self-reported current marijuana use among adults working in various industries and occupations. Although reported past-month marijuana use does not necessarily indicate use or impairment on the job, there is some evidence that marijuana use in general might increase the risk for nondriving workplace injuries (*4*) Motor vehicle crashes are the leading cause of work-related

deaths in the United States (*5*), and studies have linked recent marijuana use to an increased risk for motor vehicle crashes (*6*,*7*). However, although marijuana negatively affects skills needed for safe driving, limitations related to roadside and toxicology testing, marijuana detection time, and co-use of substances contribute to uncertainty about risk. A 2006 study using 2000–2001 data from the National Household Surveys on Drug Abuse and the 2002 National Survey on Drug Use and Health found that workers who were subject to frequent workplace drug testing and severe penalties were less likely to report past month marijuana use (*8*). Because BRFSS is a public health survey, reporting marijuana use might be more representative of actual use by industry and occupation than if this information had been collected through an employer-sponsored survey.

Analysis of age-adjusted prevalences among workers who acknowledged ever using marijuana or hashish highlighted the impact of younger workers in various industries and occupations on prevalence rates. In industries that tend to attract younger workers, such as food services, the marijuana use prevalence decreased with age-adjustment. For example, whereas the unadjusted prevalence of marijuana use among adults employed in Food Preparation and Serving occupations was 32.2%, the age-adjusted prevalence was 19.1%. Similarly, there were large differences in adjusted and unadjusted prevalences in the Arts, Entertainment, and Recreation industry, which might have a large proportion of younger workers.

The findings in this report are subject to at least six limitations. First, data were collected from adults in Colorado who reported being employed at the time of the survey and might not be representative of all employed adults in Colorado. Second, among respondents to the marijuana question, not all responded to the question regarding which industry or occupation they were employed in or recorded an industry or occupation that could be coded to an existing industry or occupation. This resulted in missing data for the 10,169 workers analyzed. Third, industry and occupation information were reported by respondents who were currently employed for wages, self-employed, or out of work for less than 1 year. A respondent might not have been actively working in the industry or occupation recorded, and that could influence the prevalence of marijuana use. Fourth, data are self-reported and thus are subject to the limitations for such survey data, including recall and response bias. Fifth, self-reported data might be subject to interviewer and recording errors leading to misclassification. These estimates might differ from other nationally representative behavior surveillance systems because of differences in survey methods, survey type, and topic. Finally, current use of marijuana was defined as having used marijuana or hashish on at least 1 day in the past 30 days. An employee who uses marijuana every day versus one that uses only once a month might present different considerations for impairment in a workplace. It is also important to note that these data do not directly measure working under the influence of marijuana.

This analysis provides important data for employers considering or implementing workplace marijuana policies and highlight those industries where marijuana use among workers might reflect a higher proportion of younger workers, such as Accommodation and Food Services and Arts, Entertainment, and Recreation. Awareness of possible employee recreational marijuana use can inform employer policies regarding drug use and workplace impairment. For example, safety-sensitive industries that have higher prevalences of self-reported marijuana use could consider evaluating their current drug testing programs, drug panels used for preemployment screening, and testing frequencies, and develop policies regarding tolerance of drug use. Drug testing policies need to be explained clearly, including expectations around protocols when injuries occur. Age-adjusted employment data can help to potentially target responsible use education campaigns to particular occupations and industries that employ younger workers.

Summary

What is already known about this topic?

Eight states, including Colorado, have legalized recreational marijuana use among persons aged ≥21 years. The association between marijuana use and occupational injury is of public health concern.

What is added by this report?

During 2014–2015, 14.6% of 10,169 Colorado adult workers reported using marijuana in the past 30 days. The highest prevalences of current use were among young adults and men, and among adults working in the Accommodation and Food Services industry (30.1%) and Food Preparation and Serving occupation (32.2%).

What are the implications for public health practice?

By understanding the occupations and industries of workers who report recreational marijuana use, employers can develop appropriately targeted workplace marijuana policies and safety awareness campaigns.

Conflict of Interest

No conflicts of interest were reported.

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References

1. Colorado Department of Public Health and Environment. Marijuana use trends and health effects. Denver, CO: Colorado Department of Public Health and Environment; 2018. https://www.colorado.gov/cdphe/marijuana-health-report
2. CDC. About the Behavioral Risk Factor Surveillance System (BRFSS). Atlanta, GA: US Department of Health and Human Services, CDC; 2014. https://www.cdc.gov/brfss/about/index.htm
3. Towle M, Tolliver R, Bui AG, Warner A, Van Dyke M. Adding industry and occupation questions to the Behavioral Risk Factor Surveillance System: new opportunities in public health surveillance. Public Health Rep 2015;130:153–60. https://doi.org/10.1177/003335491513000208
4. Goldsmith RS, Targino MC, Fanciullo GJ, et al. Medical marijuana in the workplace: challenges and management options for occupational physicians. J Occup Environ Med 2015;57:518–25. https://doi.org/10.1097/JOM.0000000000000454
5. Bureau of Labor Statistics. Table A-1. Fatal occupational injuries by industry and event or exposure, all United States, 2016. Washington, DC: US Department of Labor, Bureau of Labor Statistics; 2018. https://stats.bls.gov/iif/oshcfoi1.htm#other
6. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ 2012;344:e536. https://doi.org/10.1136/bmj.e536
7. Phillips JA, Holland MG, Baldwin DD, et al. Marijuana in the workplace: guidance for occupational health professionals and employers: joint guidance statement of the American Association of Occupational Health Nurses and the American College of Occupational and Environmental Medicine. Workplace Health Saf 2015;63:139–64. https://doi.org/10.1177/2165079915581983
8. Carpenter CS. Workplace drug testing and worker drug use. Health Serv Res 2007;42:795–810. https://doi.org/10.1111/j.1475-6773.2006.00632.x

Acute Metam Sodium Poisoning Caused by Occupational Exposure at a Flower Farm — Uganda, October 2016

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On October 25, 2016, media reports alerted the Uganda Ministry of Health to an outbreak of >80 cases of vomiting, syncope, and acute diarrhea among workers at a flower farm in central Uganda; 27 workers were hospitalized. On November 1, an investigation was undertaken by the Uganda Public Health Fellowship Program.* A case-control study found that working inside greenhouse 7, which had been fumigated with the organosulfur compound metam sodium the night of October 13, was strongly associated with illness. Employees who worked in this greenhouse during October 14–21 reported a strong "suffocating" smell in the greenhouse. Investigation revealed that, in violation of safety protocols, workers did not properly cover the soil after fumigation, allowing vapors to become trapped inside the greenhouse. The farm management, unaware of the lapse, failed to inform workers to avoid the vicinity of the fumigation. Respiratory protective measures were not routinely available for workers, which likely contributed to the severity and extent of the outbreak. Although metam sodium is generally considered to be of low risk when used according to manufacturer's instructions (*1*), occupational exposure in the absence of recommended safety measures can have serious health consequences. The investigation highlighted the importance of identifying potential occupational hazards to workers, as well as establishing safety protocols in occupational settings, training workers at risk, such as pesticide sprayers and flower pickers,† and ensuring enforcement of safety protocols. After this outbreak, the farm management reviewed, revised, and trained the workers on safety protocols to prevent future outbreaks.

Epidemiologic Investigation and Findings

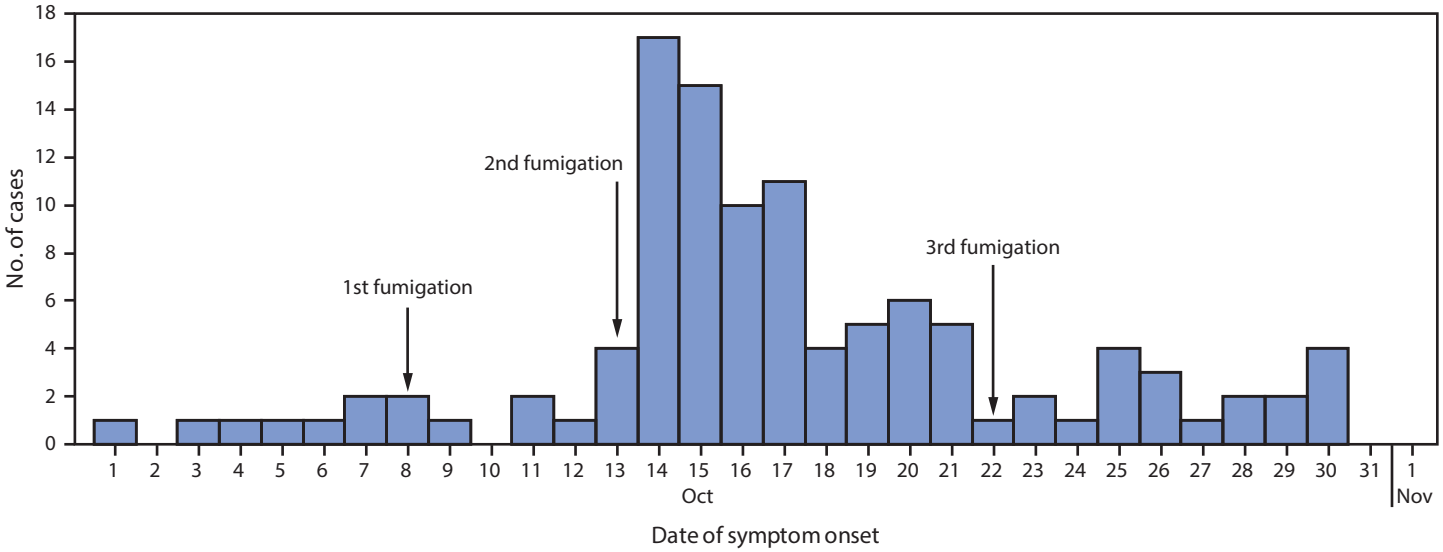
A case of greenhouse-associated poisoning was defined as the acute onset of shortness of breath, dizziness, syncope, or vomiting in a farm employee during October 2016. Medical records at the farm's clinic and nearby hospitals were reviewed. Active case finding was conducted among employees, with the assistance of the farm administrators. Descriptive epidemiologic analyses were performed, which informed hypothesis generation regarding potential exposures. From October 1 to 13, approximately one case of illness had been reported daily; the number of cases increased sharply on October 14, when 17 cases were reported. During the next 16 days, the number of cases declined to an average of two per day (Figure).

During the environmental assessment, inspection of the chemical warehouse and review of fumigation protocols and procedures revealed that metam sodium (sodium N-methyldithiocarbamate) had been used to fumigate greenhouse 7 on October 13, the day preceding the sharp increase in the number of reported cases. A Uganda Ministry of Internal Affairs analytical laboratory conducted toxicology testing using triple liquid chromatography mass spectrometry in the recently calibrated triple quadrupole liquid chromatograph mass spectrometer (*2*) for traces of metam sodium or methyl isothiocyanate (a metam sodium degradation product) in the blood of nine symptomatic patients. A case-control study was conducted to compare the exposure histories of 65 case-patients who worked during October 14–21 and 101 controls, selected from asymptomatic employees who had jobs similar to those of case-patients and who worked during the same period. Logistic regression was used to generate odds ratios comparing the odds of exposure to greenhouse 7 for case-patients and controls. The differences in attack rates by sex and occupation were assessed using Pearson's chi-square test, and statistical significance was defined as $p<0.05$.

Among the farm's 562 employees, 110 cases were identified (attack rate = 20%); 104 (95%) cases occurred in women. The mean age of patients was 25 years (range = 17–46 years). The attack rate was higher among women (22%; 104 of 465) than among men (6%; 6 of 97) (chi-square = 13.35; $p<0.001$), and varied by the nature of work, ranging from 5% among supervisors to 28% among flower pickers, (chi-square = 17.02; $p = 0.03$) (Table). Overall, 27 (25%) patients were hospitalized and treated with supportive care; no deaths were reported, and all patients fully recovered. The sharp increase in the number of cases on October 14, followed by a gradual decline over the ensuing weeks suggested a continuous common-source toxic exposure. After October 21, incident cases declined to approximately two per day (Figure). The most commonly reported symptoms included dizziness (74%; 81 of 110), shortness of breath (45%; 50 of 110), eye irritation (45%; 50 of 110), and headache (34%; 37 of 110). In the case-control study, 83% (54 of 65) of the case-patients and 34% (34 of 101) of controls

* Uganda Public Health Fellowship Program, a collaboration between the Uganda Ministry of Health, Makerere University School of Public Health and CDC is based in the Ministry of Health with the main function of investigating disease outbreaks as part of the National Rapid Response Team.
† https://www.cdc.gov/niosh/topics/hierarchy/.

FIGURE. Cases of acute metam sodium poisoning in flower farm employees (N = 110), by date of symptom onset and dates of fumigation of greenhouse 7 — Uganda, October 2016



reported working in greenhouse 7 during October 14–21 (odds ratio = 9.7; 95% confidence interval = 4.5–21).

Environmental and Laboratory Investigations

According to management staff members, the farm's greenhouses were fumigated with two rounds of metam sodium annually for pest, fungal, and weed control. Each round consisted of fumigation on 3 separate days, approximately 1 week apart. The farm's safety protocol mandated that the soil be completely covered with plastic sheeting after fumigation, that supervisors double-check to ensure adherence to the protocol, and that the greenhouse be closed for at least 24 hours before anyone could reenter. During the round associated with this outbreak, greenhouse 7 was fumigated on October 8, 13, and 22 (Figure).

Interviews with farm management staff members revealed that after fumigating greenhouse 7 on October 13, workers did not adhere to the safety protocol, poorly covering the fumigated area; this permitted vapors to escape from the soil and become trapped inside the greenhouse. In addition, the mandated postfumigation double-checking by supervisors was not conducted. Also, the requirement for greenhouse closure for at least 24 hours before reentry was not implemented. No environmental testing or air sampling were conducted in greenhouse 7 during the investigation. Interviews of flower pickers revealed that, apart from rubber boots and aprons, no respiratory, ocular or other personal protective equipment was provided by management for use during routine work, although hand-washing facilities were available. Toxicology testing of nine blood samples collected 2–9 days after symptom onset (median = 4 days) did not detect traces of methyl isothiocyanate probably because of chemical degradation over time.

The recommendations to the farm management were to review and revise the safe fumigation protocol, conduct training of workers and supervisors on the protocol, enforce strict adherence to the protocol, and institute mitigation measures should there be an exposure (such as eliminating the hazards promptly and warning workers to stay away from the exposed area). In addition, farm management is currently exploring alternative, less toxic methods for soil treatment, including steaming and biologic methods.

Discussion

Metam sodium (sodium N-methyldithiocarbamate), a liquid dithiocarbamate, is widely used as a soil fumigant, pesticide, herbicide, and fungicide in agricultural practices (*3*), with relatively low acute toxicity (*4*). However, upon exposure to the environment, the chemical degrades to methyl isothiocyanate, a low melting and powerful lachrymator (*5*). Although toxicology testing of ill patients in this outbreak did not detect traces of methyl isothiocyanate,[§] the signs and symptoms reported by patients and the sharp increase in the number of cases immediately after fumigation of the greenhouse in violation of the recommended safety protocol suggest that this outbreak was caused by exposure to metam sodium vapors, which escaped from the soil into greenhouse 7.

Respiratory, neurologic, and ocular symptoms have been reported in persons exposed to metam sodium. After

[§] A highly sensitive spectrometer that can detect up to 100 ng/mL was used for toxicology testing.

TABLE. Cases of illness associated with occupational exposure to metam sodium (N = 110) among flower farm workers and attack rates, by sex and job description — Uganda, October, 2016

Characteristic	Total no. of employees	No. of cases (% of all cases)	Attack rate, %
Sex			
Male	97	6 (5)	6
Female*	465	104 (95)	22
Job description			
Flower picker†	323	89 (81)	28
Steam boiler attendant	4	1 (1)	25
Scout	10	2 (2)	20
General worker	56	10 (9)	18
Transporter	6	1 (1)	17
Sprayer	15	2 (2)	13
Flower packer	19	2 (2)	11
Quality checker	35	2 (2)	6
Supervisors	20	1 (1)	5
Total	**562**	**110 (100)**	**20**

* Chi-square (degrees of freedom = 1) = 13.35, p<0.001.
† Chi-square (degrees of freedom = 8) = 17.02, p = 0.03.

Summary

What is already known about this topic?

Metam sodium (sodium N-methyldithiocarbamate) is widely used in agriculture as a soil fumigant, pesticide, herbicide, and fungicide. Acute health effects of metam sodium exposure have been rarely described.

What is added by this report?

In October 2016, an outbreak of vomiting, fainting, and diarrhea occurred among employees of a flower farm in central Uganda; 27 employees were hospitalized. Illness was associated with working inside a greenhouse recently fumigated with metam sodium. Safety protocol violations led to this outbreak.

What are the implications for public health practice?

This outbreak highlights the importance of establishing, training workers on, and enforcing safety protocols in occupational settings and ensuring that workers are provided with appropriate personal protective equipment.

19,000 gallons of metam sodium were spilled into the Sacramento River in northern California in 1991, an outbreak of respiratory and neurologic symptoms was reported in the surrounding community (*6*). In 2002, after a soil-incorporated application of metam sodium, a community outbreak of acute ocular and respiratory illnesses occurred in Arvin, California (*7*). Respiratory effects of metam sodium exposure have been shown to persist for up to 13 months after the initial acute poisoning (*8*). Teratogenicity studies have demonstrated maternal and fetal toxicity in experimental animals such as rats and rabbits after metam sodium exposure (*9*). The U.S. Environmental Protection Agency has identified metam sodium as a B2 (probable human) carcinogen (*9*).

Compared with the outbreak after the Sacramento River spill (*6*,*10*), a higher percentage of patients in this outbreak experienced neurologic symptoms, such as dizziness (74% versus 30%), and syncope (15% versus 0%). This difference might have been because the metam sodium vapors were trapped inside a greenhouse, and the workers, whose typical work shift was 8 hours, were exposed in an enclosed space, whereas after the Sacramento River spill, vapors reached residents in their homes after being dispersed in the wind. After the Sacramento River spill, some persons reported symptoms more than 1 week after the incident (*10*). During the current outbreak, some patients developed symptoms several days after their exposure.

The findings in this report are subject to at least three limitations. First, toxicologic testing did not find evidence of methyl isothiocyanate in the blood samples of the patients tested. Laboratory studies in rats have shown that >85% of orally administered metam sodium was excreted within 24 hours (*9*). However, no published data are available on human metabolism of metam sodium. It is possible that any metam sodium inhaled or absorbed by the patients was fully metabolized by the time the samples were collected. Second, the case definition was broad and included nonspecific symptoms, which might account for the high background rate. On the other hand, because employees were not provided with appropriate personal protective equipment such as masks, the high background rate might represent ongoing chronic exposure to various chemicals, including metam sodium, used in flower farming. Also, the flower farm routinely applied other chemicals for pest control in addition to the seasonal fumigation, including thiovit (micronised sulfur),¶ copper oxychloride,** and trigard,†† all of which can cause eye, skin, and respiratory tract irritation. These chemicals were not used in greenhouse 7 during the exposure period; however, the effects of these chemicals and their degradants might partially explain the relatively high number of background cases. Finally, air testing was not conducted to assess the level of metam sodium in greenhouse 7 during the outbreak period.

The flower industry is among Uganda's top income generators. Uganda's flowers are exported to European Union countries, the United States, and other countries. In 2015, Uganda exported 7,500 tons of flowers, generating $34 million in revenue; a quarter of those flowers were sold to the United States (Uganda Flowers Exporters Association, Performance Statistics, unpublished data, 2015). Ensuring implementation and enforcement of safety protocols for application of fumigants and other pest controls is important in protecting the safety and health of workers in this growing industry.

¶ http://www.herbiguide.com.au/MSDS/MSULP800_53904-0605.pdf.
** http://www.uap.ca/products/documents/2011-CopperSprayPCP19146.pdf.
†† https://www.msdsdigital.com/trigard%C2%AE-msds.

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Conflict of Interest

No conflicts of interest were reported.

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References

1. Carlock LL, Dotson TA. Metam-sodium [Chapter 107]. In: Krieger R, ed. Hayes' handbook of pesticide toxicology. 3rd ed. Amsterdam, Netherlands: Elsevier; 2010:2293–306.
2. Pitt JJ. Principles and applications of liquid chromatography-mass spectrometry in clinical biochemistry. Clin Biochem Rev 2009;30:19–34.
3. US Environmental Protection Agency. Safety information for handlers participating in a field fumigant application for metam sodium and metam potassium products. Washington, DC: US Environmental Protection Agency; 2009. https://www.epa.gov/sites/production/files/2013-11/documents/metam-handler-safety-info-11-2010.pdf
4. Lam WW, Kim JH, Sparks SE, Quistad GB, Casida JE. Metabolism in rats and mice of the soil fumigants metham, methyl isothiocyanate, and dazomet. J Agric Food Chem 1993;41:1497–502. https://doi.org/10.1021/jf00033a027
5. Pruett SB, Myers LP, Keil DE. Toxicology of metam sodium. J Toxicol Environ Health B Crit Rev 2001;4:207–22.
6. Bowler RM, Mergler D, Huel G, Cone JE. Aftermath of a chemical spill: psychological and physiological sequelae. Neurotoxicology 1994;15:723–9.
7. O'Malley M, Barry T, Ibarra M, Verder-Carlos M, Mehler L. Illnesses related to shank application of metam-sodium, Arvin, California, July 2002. J Agromed 2005;10:27–42. https://doi.org/10.1300/J096v10n04_06
8. Cone JE, Wugofski L, Balmes JR, et al. Persistent respiratory health effects after a metam sodium pesticide spill. Chest 1994;106:500–8. https://doi.org/10.1378/chest.106.2.500
9. California Environmental Protection Agency. Metam sodium (sodium N-methyldithiocarbamate) risk characterization document. Sacramento, CA: California Environmental Protection Agency; 2004. http://www.cdpr.ca.gov/docs/risk/rcd/metam.pdf
10. California Department of Health Care Services, Environmental Epidemiology and Toxicology Program. Acute health effects of the Cantara metam sodium spill: an epidemiological assessment. Sacramento, CA: California Department of Health Care Services; 1992.

Surveillance to Track Progress Toward Polio Eradication — Worldwide, 2016–2017

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Global efforts to eradicate polio began in 1988, and four of the six World Health Organization (WHO) regions currently have achieved poliofree certification. Within the remaining two regions with endemic poliomyelitis (African and Eastern Mediterranean), Afghanistan, Nigeria, and Pakistan have never interrupted transmission of wild poliovirus (WPV). The primary means of detecting poliovirus transmission is surveillance for acute flaccid paralysis (AFP) among children aged <15 years, combined with collection and testing of stool specimens for detection of WPV and vaccine-derived polioviruses (VDPVs)* in WHO-accredited laboratories within the Global Polio Laboratory Network (GPLN) (*1*,*2*). AFP surveillance is supplemented by environmental surveillance for polioviruses in sewage from selected locations. Genomic sequencing of isolated polioviruses enables the mapping of transmission by time and place, assessment of potential gaps in surveillance, and identification of the emergence of VDPVs (*3*). This report presents poliovirus surveillance data from 2016–2017, with particular focus on six countries in the Eastern Mediterranean Region (EMR) and 20 countries in the African Region (AFR) that reported WPV or circulating VDPVs (cVDPVs) during 2011–2017. Included in the 20 AFR countries are the three most affected by the 2014–2015 Ebola virus disease (Ebola) outbreak (Guinea, Liberia, and Sierra Leone), even though only one (Guinea) reported WPV or cVDPVs during the surveillance period. During 2017, a total of 14 (70%) of the 20 AFR countries and five (83%) of the six EMR countries met both surveillance quality indicators at the national level; however, provincial-level variation was seen. Surveillance strengthening activities are needed in specific countries of these regions to provide evidence supporting ultimate certification of the interruption of poliovirus circulation.

Acute Flaccid Paralysis Surveillance

Two principal indicators measure the quality of AFP surveillance. The first is the nonpolio AFP (NPAFP) rate (i.e., the number of NPAFP cases per 100,000 children aged <15 years per year); an NPAFP rate ≥2 is considered sufficiently sensitive to detect WPV or VDPV cases if poliovirus is circulating. The second indicator is the collection of adequate stool specimens from ≥80% of patients with AFP (*2*). Adequacy refers to collection of two stool specimens ≥24 hours apart, within 14 days of paralysis onset, and arrival at a WHO-accredited laboratory in good condition.†

Among all 47 AFR countries evaluated, 31,759 AFP cases were reported in 2016 and 30,889 in 2017. No WPV type 1 (WPV1) cases were reported in AFR in 2017. The four WPV1 cases that occurred in AFR in 2016 were reported from Borno state in Nigeria (*4*). Although no AFP cases or environmental isolates of WPV1 have been detected in Borno for >1 year, it is difficult to determine if transmission of WPV1 persists in pockets of the population where polio surveillance is infeasible or limited (e.g., in insurgent-controlled and inaccessible areas) (*5*). One cVDPV case was reported in AFR during 2016, a cVDPV type 2 (cVDPV2) case from Nigeria. During 2017, a total of 22 cVDPV cases were reported in AFR, all cVDPV2 cases from the Democratic Republic of the Congo (Table 1). Among the 20 countries evaluated in AFR, 14 (70%) met both national surveillance indicators in 2017, compared with 12 (60%) in 2016. All three Ebola-affected countries had NPAFP rates ≥2 during 2016 and 2017. In 2016 only Guinea also achieved ≥80% stool adequacy; however in 2017, Guinea and Liberia both achieved ≥80% stool adequacy.

Among the 21 EMR countries, 15,951 AFP cases were reported in 2016, and 19,035 in 2017. Two EMR countries (Afghanistan and Pakistan) reported WPV1 cases in 2016 (33) and 2017 (22). The number of WPV1 cases reported by Afghanistan remained constant (13 in 2016 and 14 in 2017); the number reported from Pakistan declined from 20 (2016) to eight (2017). In 2016, one cVDPV2 case was reported in EMR, in Pakistan. In contrast, during 2017, 74 cVDPV cases were reported from EMR. All cases were type 2 and occurred in Syria; the most recent case occurred in September 2017 (Table 1), resulting in the largest cVDPV2 outbreak since the synchronized global cessation of use of type 2 oral poliovirus vaccine in April 2016 (*6*). Among the six countries evaluated in EMR, five met both national surveillance indicators in 2017, compared with all six in 2016 (Table 1). Although overall performance improved in 2017, national-level surveillance indicators masked suboptimal surveillance performance at subnational levels in both regions, (Table 1) (Figure).

* Viruses that differ genetically from vaccine viruses and can emerge in areas with low vaccination coverage and cause paralysis.

† Reverse cold chain maintained and received without leakage or desiccation at a WHO-accredited laboratory. Reverse cold chain is maintained when stool specimens are stored immediately after collection at 4–8°C (32–39°F), frozen at -20°C (-4°F) when received for processing, and shipped to a WHO-accredited laboratory in dry ice or cold packs. Freezing of specimens is unnecessary if specimens can be received at a WHO-accredited laboratory within 72 hours of collection.

TABLE 1. National and subnational acute flaccid paralysis surveillance indicators and number of confirmed wild poliovirus and circulating vaccine-derived poliovirus cases, by country, for all countries with poliovirus transmission during 2011–2017 and those that were affected by the Ebola virus disease outbreak in West Africa — World Health Organization African Region and Eastern Mediterranean Region, 2016–2017*

WHO Region/ Country	No. of AFP cases (all ages)	Regional/ National NPAFP rate†	% Subnational areas with NPAFP rate ≥2§	% Regional or national AFP cases with adequate specimens¶	% Subnational areas with ≥80% adequate specimens	% Population living in areas meeting both indicators**	No. of confirmed WPV cases*	No. of confirmed cVDPV cases*,††
2016								
AFR (all 47 countries)§§	31,759	7.4	NA	92	NA	NA	4	1
Angola	392	3.5	94	94	100	84	—¶¶	—¶¶
Cameroon	868	7.8	100	87	90	82	—	—
Central African Republic***	143	7.0	100	73	29	25	—	—
Chad	484	7.2	87	85	65	78	—	—
Côte d'Ivoire	371	4.2	85	94	85	74	—	—
DRC***	1,819	5.1	100	78	50	56	—	—
Equatorial Guinea	3	0.6	0	0	0	0	—	—
Ethiopia***	1,048	2.5	82	79	46	9	—	—
Gabon***	43	6.1	100	26	10	3	—	—
Guinea	1,061	20.1	100	88	88	85	—	—
Kenya	554	2.8	89	89	79	70	—	—
Liberia	69	3.6	100	75	53	43	—	—
Madagascar	791	7.6	96	86	77	80	—	—
Mali	307	3.8	89	90	78	96	—	—
Mozambique	425	3.2	90	82	40	59	—	—
Niger***	366	3.5	75	62	13	3	—	—
Nigeria	17,867	20.7	97	99	97	99	4	1
Republic of the Congo	82	3.6	83	82	67	78	—	—
Sierra Leone	68	2.6	100	77	50	45	—	—
South Sudan	323	6.3	90	91	80	70	—	—
EMR (all 21 countries)†††	15,951	7.6	NA	90	NA	NA	33	1
Afghanistan	2,905	20.1	100	92	97	100	13	—
Iraq	605	4.2	90	81	58	44	—	—
Pakistan	7,848	12.6	100	87	88	99	20	1
Somalia	316	5.9	100	99	100	100	—	—
Syria	246	3.2	57	81	64	33	—	—
Yemen	715	7.1	100	91	100	100	—	—
2017								
AFR§§	30,889	7.1	NA	92	NA	NA	—	22
Angola	411	3.6	94	97	100	84	—	—
Cameroon	973	8.9	100	85	90	82	—	—
Central African Republic	167	8.3	100	80	43	48	—	—
Chad***	702	10.2	100	79	52	62	—	—
Côte d'Ivoire	334	3.6	60	91	75	58	—	—
DRC***	2,113	5.8	100	79	46	42	—	22
Equatorial Guinea	12	3.7	57	17	14	0	—	—
Ethiopia	1,096	2.6	73	86	100	90	—	—
Gabon***	51	6.9	100	59	50	35	—	—
Guinea	453	8.4	100	87	100	100	—	—
Kenya	463	2.2	66	84	72	53	—	—
Liberia	81	4.1	100	82	60	76	—	—
Madagascar	701	6.6	100	93	96	99	—	—
Mali	256	3.1	100	88	89	95	—	—
Mozambique	374	2.9	100	86	70	80	—	—
Niger***	681	6.4	100	70	0	0	—	—
Nigeria	15,967	18.5	97	98	97	99	—	—
Republic of the Congo	118	5.5	83	84	58	66	—	—
Sierra Leone***	75	2.8	100	77	75	77	—	—

See table footnotes on page 420.

TABLE 1. (*Continued*) National and subnational acute flaccid paralysis surveillance indicators and number of confirmed wild poliovirus and circulating vaccine-derived poliovirus cases, by country, for all countries with poliovirus transmission during 2011–2017 and those that were affected by the Ebola virus disease outbreak in West Africa — World Health Organization African Region and Eastern Mediterranean Region, 2016–2017*

WHO Region/ Country	No. of AFP cases (all ages)	Regional/ National NPAFP rate†	% Subnational areas with NPAFP rate ≥2§	% Regional or national AFP cases with adequate specimens¶	% Subnational areas with ≥80% adequate specimens	% Population living in areas meeting both indicators**	No. of confirmed WPV cases*	No. of confirmed cVDPV cases*,††
South Sudan	388	7.3	90	85	70	67	—	—
EMR†††	19,035	9.0	NA	88	NA	NA	22	74
Afghanistan	3,090	21.3	100	94	100	100	14	—
Iraq	699	4.8	95	87	79	74	—	—
Pakistan	10,196	16.3	100	86	100	100	8	—
Somalia	345	6.3	100	99	100	100	—	—
Syria***	348	3.6	57	70	57	28	—	74
Yemen	713	7.0	100	82	70	68	—	—

Abbreviations: AFP = acute flaccid paralysis; AFR = African Region ; cVDPV = circulating vaccine-derived poliovirus; DRC = Democratic Republic of the Congo; Ebola = Ebola virus disease; EMR = Eastern Mediterranean Region; NA = not available; NPAFP = nonpolio AFP; WHO = World Health Organization; WPV = wild poliovirus.

* Data current as of February 22, 2018.

† Per 100,000 persons aged <15 years per year.

§ For all subnational areas regardless of population size.

¶ Standard WHO target is adequate stool specimen collection from ≥80% of AFP cases, assessed by timeliness and condition. For this analysis, timeliness was defined as two specimens collected ≥24 hours apart (≥1 calendar day in this data set), and both within 14 days of paralysis onset. Good condition was defined as arrival of specimens in a WHO-accredited laboratory with reverse cold chain maintained and without leakage or desiccation.

** Percentage of the country's population living in subnational areas which met both surveillance indicators (NPAFP rates ≥2 per 100,000 persons aged <15 years per year and ≥80% of AFP cases with adequate specimens).

†† cVDPV was associated at least one case of AFP with evidence of transmission and genetically linked. Guidelines for classification of cVDPV can be found at http://polioeradication.org/wp-content/uploads/2016/09/Reporting-and-Classification-of-VDPVs_Aug2016_EN.pdf.

§§ Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cabo Verde, Central African Republic, Chad, Comoros, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Republic of the Congo, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, South Sudan, Swaziland, Togo, Uganda, Tanzania, Zambia, and Zimbabwe.

¶¶ Dashes indicate that no confirmed cases were found.

*** Stool adequacy dropped to <80% when stool condition was included with timeliness.

††† Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, and Yemen.

Environmental Surveillance

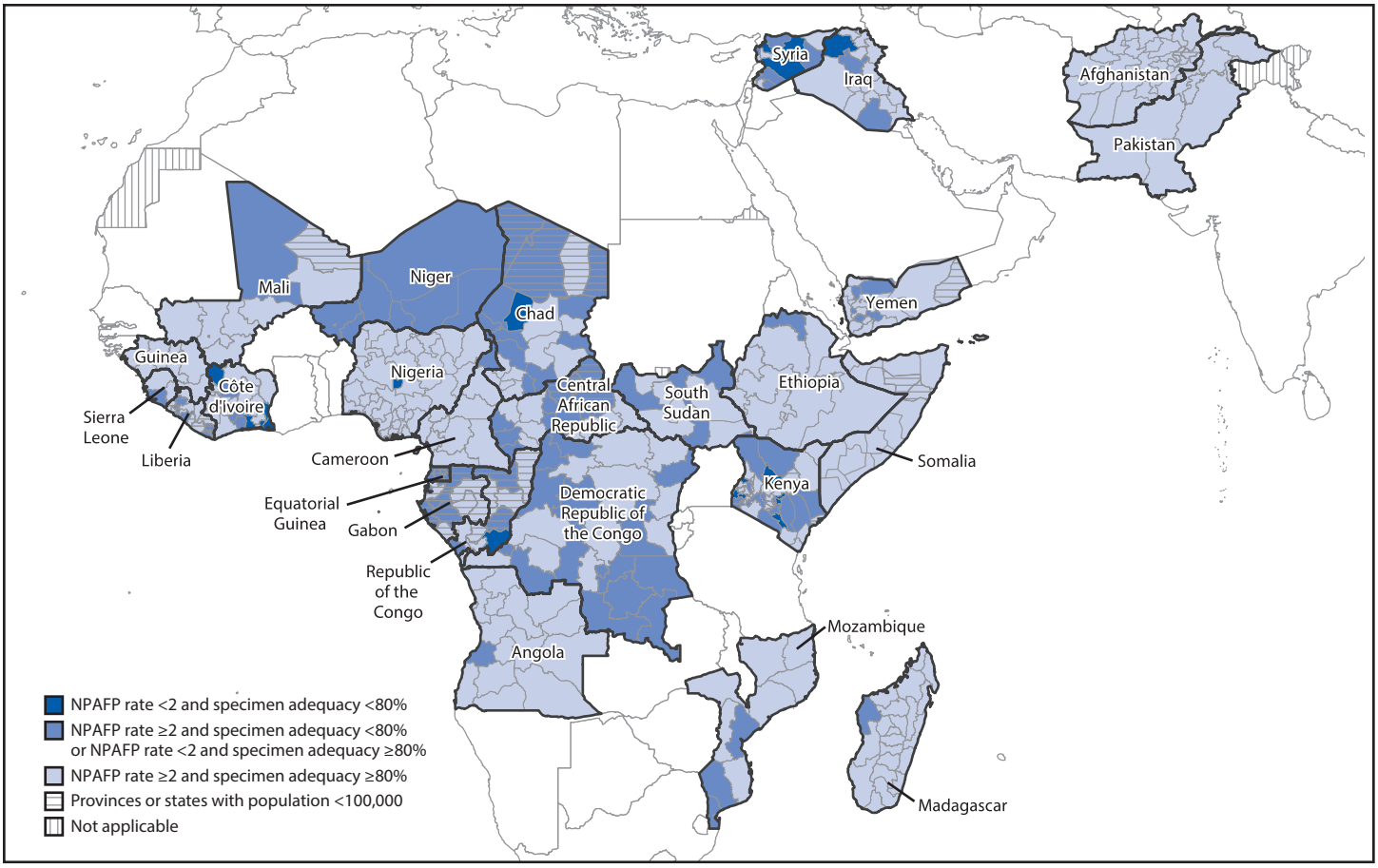
Sewage sample testing supplements AFP surveillance by identifying poliovirus transmission that might occur in the absence of detected AFP cases (*3*,*6*). Environmental surveillance collection sites increased in Afghanistan, Nigeria, and Pakistan, from 21 in 2011 to 143 in 2017. As part of the Global Polio Eradication Initiative's global environmental surveillance expansion plan, environmental surveillance is conducted in 91 sites in 38 countries without recent active WPV transmission, including 16 countries on the African continent.

In Nigeria, sewage sampling is currently conducted at 70 sites in 18 states and the Federal Capital Territory. No WPV has been isolated since May 2014, and cVDPV2 was last detected in Borno state in March 2016. In Afghanistan, environmental sampling is conducted at 20 sites in nine provinces; five of the 20 sites were added in 2017. WPV1 from four genetic clusters was detected in samples collected among five provinces in 2017. In Pakistan, sampling is conducted at 53 sites in five provinces, including the Islamabad Capital Territory; two of the 53 sites were added in 2017. In 2017, 13% of samples were positive for WPV1, compared with 11% in 2016. WPV1 was detected in all five provinces in 2017. Environmental sampling was established in Mogadishu, Somalia, in October 2017, and two of the first three samples collected yielded cVDPV2 isolates.

Global Polio Laboratory Network

GPLN consists of 146 poliovirus laboratories located in the six WHO regions that are subject to a WHO-led quality assurance program. GPLN member laboratories follow standardized protocols to 1) isolate and identify poliovirus, 2) conduct intratypic differentiation (ITD) to identify WPV or screen for Sabin (vaccine) poliovirus and VDPV (*7*), and 3) conduct genomic sequencing. Sequencing results help monitor pathways of poliovirus transmission by comparing the nucleotide sequence of the VP1-coding region of poliovirus isolates. To meet standard laboratory timeliness indicators for processing a stool specimen, laboratories should report ≥80% of poliovirus isolation results within 14 days of specimen receipt, ≥80% of ITD results within 7 days of isolate receipt, and ≥80% of sequencing results within 7 days of ITD result. The standard combined field and laboratory performance indicator is to report ITD results for ≥80% of isolates within 60 days of paralysis onset in AFP cases. This indicator considers the entire interval from paralysis onset to specimen testing (EMR countries use a 45-day timeliness standard).

FIGURE. Combined performance indicators for the quality of acute flaccid paralysis surveillance in subnational areas (states and provinces) of 26 countries that had poliovirus transmission during 2011–2017 or were affected by the Ebola outbreak in West Africa during 2014–2015 — World Health Organization African and Eastern Mediterranean Regions, 2017*,†



Abbreviations: AFP = acute flaccid paralysis; NPAFP = nonpolio AFP.

* The Global Polio Eradication Initiative has set the following targets for countries with current or recent wild poliovirus transmission and their states/provinces: 1) NPAFP detection rate of ≥2 cases per 100,000 persons aged <15 years per year and 2) adequate stool specimen collection from ≥80% of AFP cases, with specimen adequacy assessed by timeliness and condition. Timeliness was defined as two specimens collected ≥24 hours apart (≥1 calendar day) and both within 14 days of paralysis onset. Good condition was defined as specimens arriving without leakage or desiccation in a maintained reverse cold chain at a World Health Organization–accredited laboratory.

† Data are for AFP cases with onset during 2017, reported as of February 22, 2018.

The accuracy and quality of testing at GPLN laboratories is monitored through an annual accreditation program of onsite reviews and proficiency testing. During 2017, an accreditation checklist, including standard laboratory timeliness indicators for sewage sample processing, was implemented for laboratories conducting environmental surveillance.

GPLN tested 218,478 stool specimens from patients with AFP in 2016 and 201,546 in 2017. WPV1 was isolated from 37 AFP case samples in 2016 and 22 AFP case samples in 2017. In addition, cVDPV was detected from 11 AFP cases in 2016 and 96 in 2017. GPLN laboratories met timeliness indicators for poliovirus isolation in all regions (Table 2). The overall timeliness indicator for onset to ITD results was met in all regions in both years.

Overall genetic diversity declined among WPV1 isolates in 2017. In 2017, South Asia (SOAS) genotype was the only WPV1 genotype circulating globally and was detected in Afghanistan and Pakistan. West Africa B1 (WEAF-B1) genotype was last detected in Nigeria in 2016. Sequence analysis associated with the SOAS genotype indicates that WPV1 cases might have been missed by AFP surveillance in 2017; orphan WPV1 isolates (those with less genetic relatedness [≤98.5% in VP1 gene] to other circulating viruses) were associated with three of 22 WPV1 cases reported from Afghanistan and Pakistan, indicating possible gaps in AFP surveillance. In 2017, cVDPV viruses with extended divergence from the parental Sabin strain were also isolated from stool specimens of AFP cases and from environmental samples in three countries.

TABLE 2. Number of poliovirus isolates from stool specimens of persons with acute flaccid paralysis and timeliness of virus isolation and intratypic differentiation* reporting, by World Health Organization region — worldwide, 2016–2017†

WHO region/Year	No. of specimens	No. of poliovirus isolates			% Poliovirus isolation results on time**	% ITD results within 7 days of laboratory receipt††	% ITD results within 60 days of paralysis onset
		Wild	Sabin§	cVDPV¶			
African							
2016	65,520	4	4,771	4	95	94	97
2017	65,245	0	1,663	22	97	80	98
Americas							
2016	1,920	0	18	0	84	92	91
2017	1,755	0	14	0	83	100	100
Eastern Mediterranean							
2016	31,928	33	1,612	1	94	98	98
2017	35,602	22	2,521	74	98	99	97
European							
2016	3,606	0	71	0	82	100	86
2017	3,480	0	73	0	83	92	90
South-East Asia							
2016	101,550	0	5,247	2	98	99	99
2017	82,292	0	2,251	0	91	96	99
Western Pacific							
2016	14,196	0	253	4	96	98	96
2017	13,370	0	140	0	96	97	90
Total§§							
2016	**218,478**	**37**	**11,972**	**11**	**96**	**97**	**98**
2017	**201,546**	**22**	**6,662**	**96**	**94**	**91**	**98**

Abbreviations: cVDPV = circulating vaccine-derived poliovirus; ITD = intratypic differentiation; PV = poliovirus; PV1 = PV type 1; PV2 = PV type 2; VDPV = vaccine-derived poliovirus; WHO = World Health Organization.

* ITD is used to identify Sabin (vaccine) and non–Sabin-like poliovirus and screen for VDPV.

† Data current as of February 28, 2018.

§ Either 1) concordant Sabin-like results in ITD test and VDPV screening or 2) ≤1% VP1 nucleotide sequence difference compared with Sabin vaccine virus (≤0.6% for VP2).

¶ For poliovirus types 1 and 3, ≥10 VP1 nucleotide differences from the respective poliovirus; for poliovirus type 2, ≥6 VP1 nucleotide differences from Sabin PV2.

** Results reported within 14 days of receipt of specimen.

†† Results of ITD reported within 7 days of receipt of specimen.

§§ For the last three indicators, total represents weighted mean percentage of regional performance.

Discussion

The number of reported WPV cases declined to the lowest point ever in 2017; however, reported cVDPV cases increased from 2016 to 2017 because of major cVDPV2 outbreaks in the Democratic Republic of the Congo and Syria. Although most national-level surveillance quality indicators improved in 2017, considerable variation exists at subnational levels, particularly in inaccessible areas, and timely detection of circulating polioviruses can be hampered if active surveillance efforts are not rigorous. Repeated detection of WPV and cVDPV from sewage samples in locations where poliovirus cases have not been detected or where sewage detections have preceded detection in persons can provide early evidence of viral circulation within a community (e.g., WPV isolation in Pakistan during 2017) (*8*). Strategies to strengthen AFP surveillance in areas where conflict occurs have included increased AFP case searches among camps for internally displaced persons, engagement of community members in inaccessible areas, and active case searches in newly accessible areas (*5*). Although conflict might limit access to standard health facility–based surveillance, community-based surveillance has been effective in finding AFP cases, providing some assurance of the absence of poliovirus circulation in critical areas. For example, in Somalia, community volunteers have been instrumental in reporting AFP cases in inaccessible and partially accessible areas (*9*).

The findings in this report are subject to at least two limitations. First, security-related issues, issues associated with mobile and difficult-to-access populations, or other factors that affect surveillance performance could affect interpretation of AFP surveillance indicators. Second, high NPAFP rates do not necessarily imply sensitive surveillance, because a proportion of reported AFP cases might not be actual AFP cases, and not all actual AFP cases might be detected.

Certification of poliofree status requires at least 3 years of timely and sensitive poliovirus surveillance (*10*), including timely stool specimen collection and timely and appropriate transport of specimens to the laboratory. In 2017, specimen condition was a concern in Chad, DRC, Gabon, Niger, Sierra Leone, and Syria. Use of mobile technologies to improve timeliness and accuracy of AFP reporting in geographically hard-to-reach areas might be useful in some countries when linked with vigorous specimen collection (*5*). Strong supervision and monitoring of surveillance performance, especially at

Summary

What is already known about this topic?

Surveillance is the cornerstone of polio eradication efforts.

What is added by this report?

In 2017, 22 wild poliovirus cases were reported from two countries (Afghanistan and Pakistan), the fewest number ever reported globally. Polio cases caused by circulating vaccine-derived polioviruses increased from four in 2016 to 96 in 2017 because of large outbreaks in Syria and the Democratic Republic of the Congo. Although surveillance performance indicators are improving at the national level, gaps remain, including at subnational levels.

What are the implications for public health practice?

As polio cases decline, sensitive and timely surveillance becomes even more important. As long as polioviruses circulate in any country, all countries remain at risk.

subnational levels, is important to achieve high-quality surveillance that can detect poliovirus transmission. Environmental surveillance has been an important supplement to AFP surveillance and, when carefully conducted in populations covered by sewage networks, can improve detection of circulating virus, particularly in high-risk areas with suboptimal AFP surveillance (*3*). Polio surveillance efforts need to reach geographically difficult-to-access and security-compromised areas and mobile and migrant populations. Surveillance data should be assessed routinely to identify suboptimal data quality. The need for strong poliovirus surveillance will continue beyond certification of eradication, until well after the use of all oral poliovirus vaccine has stopped globally. Poliovirus surveillance will need to be integrated with surveillance of other vaccine-preventable diseases to sustain capacity and maintain sufficient performance quality. As long as polioviruses continue to circulate in any country, all countries remain at risk.

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Conflict of Interest

No conflicts of interest were reported.

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References

1. Maes EF, Diop OM, Jorba J, Chavan S, Tangermann RH, Wassilak SG. Surveillance systems to track progress toward global polio eradication—worldwide, 2012–2013. MMWR Morb Mortal Wkly Rep 2017;66:359–65. https://doi.org/10.15585/mmwr.mm6613a3
2. World Health Organization. WHO-recommended surveillance standard of poliomyelitis. Geneva, Switzerland: World Health Organization; 2015. http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/poliomyelitis_standards/en/
3. Asghar H, Diop OM, Weldegebriel G, et al. Environmental surveillance for polioviruses in the Global Polio Eradication Initiative. J Infect Dis 2014;210(Suppl 1):S294–303. https://doi.org/10.1093/infdis/jiu384
4. Nnadi C, Damisa E, Esapa L, et al. Continued endemic wild poliovirus transmission in security-compromised areas—Nigeria, 2016. MMWR Morb Mortal Wkly Rep 2017;66:190–3. https://doi.org/10.15585/mmwr.mm6607a2
5. Bolu O, Nnadi C, Damisa E, et al. Progress toward poliomyelitis eradication—Nigeria, January–December 2017. MMWR Morb Mortal Wkly Rep 2018;67:253–6. https://doi.org/10.15585/mmwr.mm6708a5
6. Hampton LM, Farrell M, Ramirez-Gonzalez A, et al.; Immunization Systems Management Group of the Global Polio Eradication Initiative. Cessation of trivalent oral poliovirus vaccine and introduction of inactivated poliovirus vaccine worldwide, 2016. MMWR Morb Mortal Wkly Rep 2016;65:934–8. https://doi.org/10.15585/mmwr.mm6535a3
7. Kilpatrick DR, Yang CF, Ching K, et al. Rapid group-, serotype-, and vaccine strain-specific identification of poliovirus isolates by real-time reverse transcription-PCR using degenerate primers and probes containing deoxyinosine residues. J Clin Microbiol 2009;47:1939–41. https://doi.org/10.1128/JCM.00702-09
8. Elhamidi Y, Mahamud A, Safdar M, et al. Progress toward poliomyelitis eradication—Pakistan, January 2016–September 2017. MMWR Morb Mortal Wkly Rep 2017;66:1276–80. https://doi.org/10.15585/mmwr.mm6646a4
9. Polio Global Eradication Initiative. Poliovirus risk analysis for conflict-affected polio-free countries. EMRO—December 2016. Geneva, Switzerland: Polio Global Eradication Initiative; 2017. http://polioeradication.org/wp-content/uploads/2017/04/Risk-Assessment_Specific_EMR_Countries_2017.pdf
10. World Health Organization. Report of the 1st meeting of the Global Commission for the Certification of the Eradication of Poliomyelitis. Geneva, Switzerland: World Health Organization; 1995. http://polioeradication.org/wp-content/uploads/2016/07/10Report.pdf

Updated CDC Recommendations for Using Artemether-Lumefantrine for the Treatment of Uncomplicated Malaria in Pregnant Women in the United States

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Malaria infection during pregnancy is associated with an increased risk for maternal and fetal complications. In the United States, treatment options for uncomplicated, chloroquine-resistant *Plasmodium falciparum* and *P. vivax* malaria in pregnant women are limited to mefloquine or quinine plus clindamycin (*1*). However, limited availability of quinine and increasing resistance to mefloquine restrict these options. Strong evidence now demonstrates that artemether-lumefantrine (AL) (Coartem) is effective and safe in the treatment of malaria in pregnancy. The World Health Organization (WHO) has endorsed artemisinin-based combination therapies (ACTs), such as AL, for treatment of uncomplicated malaria during the second and third trimesters of pregnancy and is currently considering whether to add ACTs, including AL, as an option for malaria treatment during the first trimester (*2*,*3*). This policy note reviews the evidence and updates CDC recommendations to include AL as a treatment option for uncomplicated malaria during the second and third trimesters of pregnancy and during the first trimester of pregnancy when other treatment options are unavailable. These updated recommendations reflect current evidence and are consistent with WHO treatment guidelines.

Background

Each year, approximately 1,700 cases of imported malaria occur in the United States; approximately 630 (37%) of these cases occur in women, including 5%–6% who are pregnant at the time they are infected (*4*). Treatment options for uncomplicated, chloroquine-resistant *P. falciparum* and *P. vivax* malaria infections in pregnant women in the United States are threatened by the spread of mefloquine resistance in Southeast Asia. Having only one quinine and mefloquine manufacturer in the United States can adversely affect access. In 2009, the Food and Drug Administration (FDA) approved AL for the treatment of uncomplicated malaria. At that time, this combination was not approved for use in pregnancy because animal research data indicated a potential association with poor pregnancy outcomes, and insufficient human data were available. Since then, global experience has contributed substantial evidence of the safety and efficacy of AL throughout pregnancy. Given the need for an additional option to treat uncomplicated malaria in pregnant women in the United States, a systematic review of the literature was performed to evaluate the safety and efficacy of AL use during pregnancy, and findings were used to update CDC recommendations.

Methods

A systematic review of English-language research articles listed in PubMed was conducted using the keywords "artemether," "lumefantrine," "Coartem," and "malaria in pregnancy." Clinical trials, observational studies, meta-analyses, and case reports of uncomplicated malaria treatment during pregnancy were included. Studies that did not include treatment or pregnancy outcomes were excluded, as were studies that did not identify the trimester of treatment. Review article and meta-analysis references were examined for additional primary source articles for inclusion. Online search results were compiled and deduplicated. Two independent reviewers determined the relevance of each article to the research objective based first on title, then abstract, then full text. If reviewers had discordant findings from title or abstract review, the article was included in the next review phase. The following data were abstracted and reviewed: participant age; geographic location; parity; reason for drug treatment (uncomplicated versus severe malaria); trimesters during which treatment occurred; medication dose administered; treatment duration; treatment outcomes; and pregnancy outcomes, which included miscarriage (pregnancy loss at <28 weeks' gestation), stillbirth (pregnancy loss at ≥28 weeks' gestation), preterm birth (<37 weeks' gestation), low birth weight (<2,500 g), congenital abnormalities, and any maternal adverse events reported.

Rationale and Evidence

Systematic review results. In the initial search, 1,726 articles were identified. After excluding four articles during deduplication, 1,534 during title review, 94 during abstract review, and 73 after full text review, 21 articles remained and were included in the review.

Efficacy. One meta-analysis (*5*) and five randomized open-label controlled trials performed in Uganda and Thailand examined the efficacy of ACTs for uncomplicated *P. falciparum* in women during their second and third trimesters of pregnancy and found cure rates ≥94.9%, with ACTs performing equal to or better than quinine-based regimens (Table 1) (*6*–*10*). A meta-analysis of African and Asian studies found lower but statistically similar treatment failure rates by days 28–63 in

TABLE 1. Findings of randomized trials of artemisinin-based regimens for treatment of malaria in pregnancy

Author, publication year	Country	Indication for treatment	Drug regimen	No. of participants	Follow-up time (days)	Treatment outcome, % (95% CI)
McGready, et al., 2000*	Thailand	Uncomplicated *P. falciparum*, second and third trimesters	1. MQ 25 mg/kg x 1 and As 4 mg/kg/d x 3d	66	63	Cure 98.2 (94.7–100)†
			2. Q 10 mg/kg q8hr x 7d	42	63	Cure 67.0 (43.3–90.8)†
McGready, et al., 2001§	Thailand	Uncomplicated *P. falciparum*, second and third trimesters	1. As 2 mg/kg/d x 7d	64	42	Cure 100
			2. Q 10 mg/kg q8hr x7d and CL 5 mg/kg q8hr x7d	65	42	Cure 100
McGready, et al., 2005¶	Thailand	Uncomplicated *P. falciparum*, second and third trimesters	As 4 mg/kg/d x 3d and A 20 mg/kg/d x 3d and P 8 mg/kg/d x 3d	39	63	Cure 94.9 (81.37–99.11)†,**
			Q 10 mg/kg q8hr x 7d	42	63	Cure 63.4 (46.9–77.4)†,††
Piola, et al., 2010§§	Uganda	Uncomplicated *P. falciparum*	1. AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d	152	42	Cure 99.3 (96.0–99.9)†,¶¶
			2. Q 10 mg/kg q8hr x 7d	152	42	Cure 97.6 (93.1–99.5)†,***
Kaye, et al., 2008†††	Uganda	Uncomplicated *P. falciparum*, second and third trimesters	1. AL 20/120 mg 4 tabs at 0 and 8hr x1d, then BID x 2d	57	28	Cure 100
			2. LapDap x 3d	57	28	Cure 100

Abbreviations: A = atovaquone; AL = artemether-lumefantrine; AQ = amodiaquine; As = artesunate; BID = twice daily; CI = confidence interval; d = days; hr = hour(s); kg = kilogram; LapDap = chlorproguanil-dapsone; mg = milligram; MQ = mefloquine; P = proguanil; PCR = polymerase chain reaction; Q = quinine; qd = once daily; q8hr = every 8 hours.

* McGready R, Brockman A, Cho T, et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 2000;94:689–93.

† PCR-adjusted.

§ McGready R, Cho T, Keo NK, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. Clin Infect Dis 2001;33:2009–16.

¶ McGready R, Ashley EA, Moo E, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. J Infect Dis 2005;192:846–53.

** 37 of 39 participants.

†† 26 of 41 participants.

§§ Piola P, Nabasumba C, Turyakira E, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated *Plasmodium falciparum* malaria: an open-label, randomised, non-inferiority trial. Lancet Infect Dis 2010;10:762–9.

¶¶ 137 of 139 participants.

*** 122 of 125 participants.

††† Kaye DK, Nshemerirwe R, Mutyaba TS, Ndeezi G. A randomized clinical trial comparing safety, clinical and parasitological response to artemether-lumefantrine and chlorproguanil-dapsone in treatment of uncomplicated malaria in pregnancy in Mulago hospital, Uganda. J Infect Dev Ctries 2008;2:135–9.

women taking ACTs versus non-ACTs to treat uncomplicated malaria in the second and third trimesters of pregnancy (pooled risk ratio random effects = 0.41; 95% confidence interval (CI) = 0.16–1.06; six trials) (*5*). With respect to AL efficacy during the second and third trimesters of pregnancy, a concern existed that a reduction in relative bioavailability of lumefantrine in pregnant women might affect treatment success later in pregnancy (*11*–*15*). However, the evidence presented indicates that treatment in pregnancy is efficacious at the doses currently recommended for nonpregnant women.

Second and third trimester safety. Data evaluating pregnancy outcomes in women taking ACTs during the second or third trimesters of pregnancy were available from 16 studies (Table 2). No differences in pregnancy outcomes were identified in four trials comparing ACTs with quinine-based regimens in Uganda and Thailand (*6*,*7*,*9*,*10*), one of which used AL (*9*), and in four other trials comparing AL with other ACTs in Nigeria (two studies), Thailand, and multiple sites in Africa (*16*–*19*). A Zambian cohort study comparing treatment of uncomplicated malaria using AL with treatment using sulfadoxine-pyrimethamine found similar pregnancy outcomes between groups (*20*). In addition, two meta-analyses of women with malaria in the second and third trimester of pregnancy found no association between ACT treatment and congenital malformations or miscarriage (*5*,*21*). Overall, fewer maternal adverse events occurred among women taking ACTs than among those taking non-ACTs (Table 2). One trial in Thailand found a relatively higher proportion of day 7 anemia among those treated with mefloquine-artesunate (67%) than among those treated with a quinine-based regimen (42%) (*6*). Four trials and one meta-analysis comparing ACTs with quinine-based regimens found that pregnant women taking quinine had higher rates of tinnitus, dizziness, and vomiting than did pregnant women taking ACTs (*5*–*9*). The three trials comparing AL with other ACTs found no differences in rates of serious adverse maternal effects between groups (*9*,*16*,*18*).

First trimester safety. No randomized trials evaluating AL use during the first trimester of pregnancy were found (Table 3). However, a meta-analysis of observational and other studies from six sub-Saharan African countries and the Thai-Burmese border included data from a total of 717 women taking ACTs during the first trimester of pregnancy (*22*). Comparisons of pregnancy outcomes between women taking ACTs and those receiving a quinine-based regimen

TABLE 2. Summary of studies using artemisinin-based treatment for malaria in second and third trimesters of pregnancy and safety outcomes

Author, publication year	Indication (country)	Drug(s)	No. of participants	Pregnancy outcomes, n/N (%)*	Congenital anomalies, n/N (%)	Maternal adverse events, n/N (%)
Randomized trials (all open label) using nonartemisinin drug in comparison group						
McGready, et al., 2000[†]	Uncomplicated *P. falciparum* (Thailand)	MQ 25 mg/kg x 1 and As 4 mg/kg/d x 3d	66	Miscarriage, 2 (3) Stillbirth, 0 (0) Low birth weight, 9/53 (17)	0 (0)	Anemia day 7, 32/48 (67)[§] Dizziness, (45)[§] Tinnitus, (17)[§]
		Q 10 mg/kg q8hr x 7d	42	Miscarriage, 0 (0) Stillbirths, 0 (0) Low birth weight, 6/33 (18)	0 (0)	Anemia day 7, 14/33 (42)[§] Dizziness, (87)[§] Tinnitus, (66)[§]
McGready, et al., 2001[¶]	Uncomplicated *P. falciparum* (Thailand)	As 2 mg/kg/d x 7d	64	Stillbirth, 1 (2)**	Minor, 1 (2)	Tinnitus, (9)[§]
		Q 10 mg/kg q8hr x 7d and CL 5 mg/kg q8hr x 7d	65	Stillbirth, 1 (2)**	Major, 1(2)	Tinnitus, (45)[§]
McGready, et al., 2005[††,§§]	Uncomplicated *P. falciparum* (Thailand)	As 4 mg/kg/d x 3d and A 20 mg/ kg/d x 3d and P 8 mg/kg/d x 3d	39	Preterm, 4/34 (12) Low birth weight, 6/23 (26)	Polythelia and cleft lip and palate, 2/34 (6)**	Tinnitus, (24)[§]
		Q 10 mg/kg q8hr x 7d	42	Stillbirth, 1 (2) Preterm, 6/38 (16) Low birth weight, 4/30 (13)	Left aural atresia, 1/38 (3)**	Tinnitus, (79)[§]
Piola, et al., 2010[¶¶]	Uncomplicated *P. falciparum* (Uganda)	AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d	152	Miscarriage, 2/144 (1) Intrauterine fetal death, 1/144 (1) Stillbirth, 2/144 (1) Preterm, 12/143 (1) Low birth weight, 12/120 (10)	Polydactyly, 2 (1)** Acyanotic heart disease, 1 (1)	Tinnitus, 0 (0)[§] Headache, 26 (17)[§] Nausea, 8 (5)[§] Vomiting, 6 (4)[§] Anorexia, 6 (4)[§]
		Q 10 mg/kg q8hr x 7d	152	Miscarriage, 2/137 (2) Intrauterine fetal death, 2/137 (2) Stillbirth, 3/137 (2) Preterm, 17/137 (3) Low birth weight, 16/137 (13)	Polydactyly, 2 (1)**	Tinnitus, 111 (73)[§] Headache, 9 (6)[§] Nausea, 26 (17)[§] Vomiting, 28 (18)[§] Anorexia, 16 (11)[§]
Kaye, et al., 2008[***]	Uncomplicated *P. falciparum* (Uganda)	AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d	57	Not assessed	Not assessed	Palpitations, 4 (7) Dizziness, 1 (2) Drowsiness, 1 (2) Rash, 1 (2)
		LapDap x 3d	57	Not assessed	Not assessed	Vomiting, 1 (2) Diarrhea, 1 (2) Palpitations, 1 (2)
Randomized trials (open label unless otherwise noted) using artemisinin in comparison group						
Sowunmi, et al., 1998[†††]	Failed CQ, SP or CQ-SP treatment for *P. falciparum* (Nigeria)	Ar 3.2 mg/kg IM x 1 then 1.6 mg/kg IM qd x 4d	23	IUGR, 1	None	None
		Ar 3.2 mg/kg IM x 1 then MQ 7.5 mg/kg qd x 2d	22	None	None	Abdominal discomfort, 2 (9) Dizziness, 2 (9)
McGready, et al., 2008[§§§]	Uncomplicated *P. falciparum* (Thailand)	AL 20/120 mg 4 tabs BID x 3d	124	Miscarriage, 0 (0) Stillbirth, 1/119 (1)	None	Vomiting, 2 (2)
		As 2 mg/kg qd x 7d	125	Miscarriage, 1/122 (1)** Stillbirth, 1/119 (1)	None	Vomiting, 1 (1) Rash, 1 (1)
Ukah, et al., 2015[¶¶¶]	Uncomplicated *P. falciparum* (Nigeria, double-blind)	AL (80 mg/480 mg) BID x 3d	75	Miscarriage, 1/71 (1) Stillbirth, 2/71 (3)	Not assessed	Body weakness 2 (3) Pruritis 0 (0)
		Ar-AQ (100 mg/270 mg) BID x 3d	75	Miscarriage, 1/65 (2) Stillbirth, 1/65 (2)	Not assessed	Body weakness, 26 (35) Pruritis, 4 (5)

See table footnotes on page 428.

TABLE 2. (*Continued*) Summary of studies using artemisinin-based treatment for malaria in second and third trimesters of pregnancy and safety outcomes

Author, publication year	Indication (country)	Drug(s)	No. of participants	Pregnancy outcomes, n/N (%)*	Congenital anomalies, n/N (%)	Maternal adverse events, n/N (%)
PREGACT, 2016****	*P. falciparum* (four African countries)	AL	880	Miscarriage, 1 Stillbirth, 16/856 (2) Preterm, (10)	Any defect, 17/832 (2)	
		AQ-As	842	Miscarriage, 4 (<1) Stillbirth, 17/815 (2) Preterm, (3)	Any defect, 8/776 (1)	Anemia, 2 (<1 Abdominal pain, 1 (<1) Malaise, 2 (<1)
		MQ-As	848	Miscarriage, 4 Stillbirth, 23/821 (3) Preterm, (8)	Any defect, 13/780 (2)	Abdominal pain, 1 (<1) Vomiting, 2 (<1) Malaise, 1 (<1)
		DHA-PIP	853	Miscarriage, 4 (<1) Stillbirth, 22/818 (3) Preterm, (10)	Any defect, 6/767 (1)	Headache/weakness, 1 (<1)
Cohort study						
Manyando, et al., 2010††††,§§§§	Uncomplicated *P. falciparum* (Zambia)	AL 20 mg/120 mg 4 tabs BID x 3d	495	Miscarriage, 7/504 (1) (all first trimester exposures) Stillbirth, 9/504 (2) Preterm, 71/504 (14)	Any defect, 29/449 (7)	Not reported
		SP (1500 mg/75 mg)	506	Miscarriage, 8/516 (2) (in 5 women, including one with twins and one with triplets) Stillbirth, 13/516 (3) Preterm, 90/516 (17)	Any defect, 18/444 (4)	Not reported
Descriptive studies (includes pharmacokinetic studies and case series)						
McGready, et al., 2001¶ (includes data published 1998)¶¶¶¶	*P. falciparum* or mixed, primary and recrudescent, uncomplicated and severe (Thailand)	As given 2–4 mg/kg up to 7 days (varies by indication) or As 4 mg/kg qd x 3d and AP or As 4 mg/kg qd x 3d and MQ	461	Miscarriage, 20/414 (5) Stillbirth, 7/386 (2)	Any defect, 3/386 (1) Major 1/386 (0)	No serious adverse events
		Community (no treatment)		Miscarriage, 1003/8154 (12) Stillbirth, 114/7058 (2) Low birth weight, 866/6418 (14)	Any defect, 866/6418 (14)	
Mosha, et al., 2014*****	Uncomplicated *P. falciparum* (Tanzania)	AL 20/120 mg 4 tabs at 0 and 8hr x1d, then BID x 2d	35	Not assessed, (follow-up to 42 days only)	Not assessed	No serious adverse events
Nyunt, et al., 2015††††	Uncomplicated *P. falciparum* (Uganda)	AL 20/120 mg 4 tabs at 0 and 8hr x 1d, then BID x 2d	30	Not assessed, (follow-up to 42 days only)	Not assessed	No serious adverse events
Adam, et al., 2004§§§§§,¶¶¶¶¶	*P. falciparum* (Sudan)	Ar 80 mg IM BID x1d then qd x 2d	28	Miscarriage, 0 (0) Stillbirth, 0 (0) Premature, 1 (4)**	Not assessed	Not assessed
Adam, et al., 2009******,¶¶¶¶¶	*P. falciparum* (Sudan)	Ar IM As and SP AL	62	Miscarriage, 2 (3)** (both had received artemether injections early in pregnancy and miscarried while receiving quinine infusions for a second malaria infection)	Not assessed	Not assessed
Wang, 1981††††††	*"Plasmodium"* (China)	Ar in oil 500–900 mg IM qd x 3d or Ar 600 mg IM qd x 3d	6	Miscarriage, 0 (0) Stillbirth, 0 (0) Premature, 0 (0)	Any defect, 0 (0)	Not assessed

See table footnotes on page 428.

Abbreviations: A = atovaquone; AL = artemether-lumefantrine; AQ = amodiaquine; Ar = artemether; As = artesunate; BID = twice daily; CL = clindamycin; CQ = chloroquine; d = day(s); DHA-PIP = dihydroartemisinin-piperaquine; hr = hour(s); IM = intramuscular; IUGR = intrauterine growth retardation; kg = kilogram; LapDap = chlorproguanil-dapsone; mg = milligram; MQ = mefloquine; P = proguanil; Q = quinine; qd = once daily; q8hr = every 8 hours; SP = sulfadoxine pyrimethamine.

* In studies with incomplete outcome data, denominators are provided.
† McGready R, Brockman A, Cho T, et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 2000;94:689–93.
§ Significant difference between comparison groups.
¶ McGready R, Cho T, Keo NK, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. Clin Infect Dis 2001;33:2009–16.
** Considered not related to drug.
†† McGready R, Ashley EA, Moo E, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. J Infect Dis 2005;192:846–53.
§§ 1-year follow-up of infants indicated no differences in development.
¶¶ Piola P, Nabasumba C, Turyakira E, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated *Plasmodium falciparum* malaria: an open-label, randomised, non-inferiority trial. Lancet Infect Dis 2010;10:762–9.
*** Kaye DK, Nshemerirwe R, Mutyaba TS, Ndeezi G. A randomized clinical trial comparing safety, clinical and parasitological response to artemether-lumefantrine and chlorproguanil-dapsone in treatment of uncomplicated malaria in pregnancy in Mulago hospital, Uganda. J Infect Dev Ctries 2008;2:135–9.
††† Sowunmi A, Oduola AMJ, Ogundahunsi OAT, et al. Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sufadoxine-pyrimethamine-resistant falciparum malaria during pregnancy. J Obstet Gynaecol 1998;18:322–7.
§§§ McGready R, Tan SO, Ashley EA, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated *Plasmodium falciparum* treatment in pregnancy. Rogerson S, editor. PLoS Med 2008; 5:e253.
¶¶¶ Ukah M, Badejoko O, Ogunniyi S, Loto O, Aboderin O, Fatusi A. A randomized trial of artesunate-amodiaquine versus artemether-lumefantrine for the treatment of acute uncomplicated malaria in pregnancy. Int J Gynaecol Obstet 2015;131:41–4.
**** PREGACT Study Group. Four artemisinin-based treatments in African pregnant women with malaria. N Engl J Med 2016;374:913–27.
†††† Manyando C, Njunju EM, Virtanen M, Hamed K, Gomes M, Van Geertruyden JP. Exposure to artemether-lumefantrine (Coartem) in first trimester pregnancy in an observational study in Zambia. Malar J 2015;14:77.
§§§§ Included women at all trimesters.
¶¶¶¶ McGready R, Cho T, Cho JJ, et al. Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 1998;92:430–3.
***** Mosha D, Mazuguni F, Mrema S, Sevene E, Abdulla S, Genton B. Safety of artemether-lumefantrine exposure in first trimester of pregnancy: an observational cohort. Malar J 2014;13:197.
††††† Nyunt MM, Nguyen VK, Kajubi R, et al. Artemether-lumefantrine pharmacokinetics and clinical response are minimally altered in pregnant Ugandan women treated for uncomplicated falciparum malaria. Antimicrob Agents Chemother 2016;60:1274–82.
§§§§§ Adam I, Elwasila E, Mohammed Ali DA, Elansari E, Elbashir MI. Artemether in the treatment of falciparum malaria during pregnancy in eastern Sudan. Trans R Soc Trop Med Hyg 2004;98:509–13.
¶¶¶¶¶ Included women in first and second trimesters.
****** Adam I, Elhassan EM, Omer EM, Abdulla MA, Mahgoub HM, Adam GK. Safety of artemisinins during early pregnancy, assessed in 62 Sudanese women. Ann Trop Med Parasitol 2009;103:205–10.
†††††† Wang TY. Follow-up observation on the therapeutic effects and remote reactions of artemisinin (Qinghaosu) and artemether in treating malaria in pregnant woman. J Tradit Chin Med 1989;9:28–30.

anytime during the first trimester and treatment with ACTs versus quinine-based regimen during 6–12 weeks' gestational age demonstrated no differences in miscarriage, stillbirth, or pregnancy loss (miscarriage and still birth combined) for women treated with ACTs versus quinine-based regimens during either period. Although limited by sample size, the pooled prevalences of congenital anomalies in infants born to mothers taking ACTs versus quinine-based regimens in the first trimester were similar (1.5%, 95% CI = 0.6–3.5 versus 1.2%, 95% CI = 0.6–2.4, respectively) (*22*).

Recommendation

Malaria infection during pregnancy can result in serious maternal and fetal complications. On the basis of the strength and quality of this evidence, CDC recommends AL as an additional option for treatment of uncomplicated malaria in pregnant women in the United States during the second and third trimesters of pregnancy at the same doses recommended for nonpregnant women. Women in the United States with uncomplicated malaria during the first trimester of pregnancy should be treated with the currently recommended options of either mefloquine or quinine plus clindamycin. However, when neither of these options is available, AL should be considered for treatment.

Discussion

This update of CDC recommendations based on accumulated evidence of the safety of AL in pregnancy is in line with the malaria treatment guidelines of other countries without endemic malaria and WHO (*3*,*23*,*24*). On the basis of the current strength and quality of the first trimester safety and efficacy evidence, the addition of ACTs, including AL, as a first-line treatment option for uncomplicated malaria during the first trimester of pregnancy is being considered by WHO after the Malaria Policy Advisory Committee's review (*2*,*3*). Women seeking care in the United States will now have a third treatment option for uncomplicated malaria during the second and third trimesters of pregnancy, and during the first trimester of pregnancy when other treatment options are unavailable, that is safe and effective for treating *P. falciparum* infections acquired in regions with chloroquine resistance. To assess the implementation and impact of these updated recommendations in the United States, data from the National Malaria Surveillance System will be used to examine how antimalarials

TABLE 3. Summary of safety outcomes in studies using artemisinin-based treatment for malaria in first trimester of pregnancy

Author, publication year	Description or indication (country)	Drug or regimen (no.)	Pregnancy outcomes, no. (%) (unless otherwise indicated)*	Congenital anomalies, no. (%) (unless otherwise indicated)	Maternal adverse events, no. (%) (unless otherwise indicated)
Meta-analysis					
Dellicour, et al., 2017†	Included five observational studies (individual participant data from six sub-Saharan African countries, and aggregate data from Thailand)	Areg (717) Q (947) No antimalarials (28,954)	Miscarriage: Areg versus Q: aHR = 0.73 (95% CI = 0.44–1.21) Areg versus none: aHR = 1.16 (95% CI = 0.81–1.66) Stillbirth: Areg versus Q: aHR = 0.29 (95% CI = 0.08–1.02) Areg versus none: aHR = 0.65 (95% CI = 0.34–1.23) Stillbirth and miscarriage: Areg versus Q: aHR = 0.58 (95% CI = 0.36–1.02)	As 1.5% (95% CI = 0.6–3.5); Q 1.2% (95% CI = 0.6–2.4)	Not assessed
Observational studies					
Any anomaly, 1 (1) Any anomaly, 1 (1) Any anomaly, 2 (3)	Identified women with inadvertent use of AL, other antimalarials, or none, then followed to birth outcome (Tanzania)	AL (164)	Miscarriage, 5 (3) and stillbirth, 6 (3.7); aOR = 1.4 (95% CI = 0.8–2.5, p = 0.295) Low birth weight, 8 (5.2); aOR = 1.2 (95% CI = 0.6–2.5, p = 0.573) Preterm, 8 (5.2); aOR = 0.9 (95% CI = 0.5–1.8, p = 0.865)		Not assessed
		Q (70)	Miscarriage, 3(4.3) and stillbirth, 5 (7.1); aOR = 2.5 (95% CI = 1.3–5.1, p = 0.009) Low birth weight, 1 (1.6); aOR = 0.6 (0.1–2.4, p = 0.461) Preterm, aOR = 2.6 (95% CI = 1.3– 5.3, p = 0.007)		Not assessed
		SP (66)	Miscarriage, 0 and stillbirth, 2 (3.0); aOR = 0.5 (95% CI = 0.1–2.0, p = 0.312) Low birth weight, 2 (3.1); aOR = 0.7 (95% CI = 0.2–3.0, p = 0.639) Preterm, 7 (10.9); aOR = 1.8 (95% CI = 0.8–4.1, p = 0.160)		Not assessed
		AQ (11)	Miscarriage, 0 and stillbirth, 0 Low birth weight, 0 Preterm, 0	Any anomaly, 0 (0)	Not assessed
		No antimalarials (1,464)	Miscarriage, 34 (2.3) and stillbirth, 49 (3.3); aOR = 0.8 (95% CI = 0.5–1.2, p = 0.260) Low birth weight, 69 (5.0); aOR = 1.2 (95% CI = 0.6–2.3, p = 0.564) Preterm, 88 (6.4); aOR = 0.7 (95% CI = 0.5–1.1, p = 0.168)	Any anomaly, 19 (1)	Not assessed
Dellicour, et al., 2015**,¶	Identified women with inadvertent use of AL, other antimalarials, or none, then followed to birth outcome (Kenya)	Confirmed ACT (77) Unconfirmed ACT (222) Q (13) No ACT exposure (835)	Miscarriage: Confirmed ACT exposure only: ACT 6/77 versus no antimalarial 57/793 aHR = 1.72 (95% CI = 0.66–4.45, p = 0.266) Q 0/3 versus no antimalarial 57/793 ACT 5/72 versus Q 1/13; aHR = 0.48 (95% CI = 0.12–1.89, p = 0.297) Confirmed and unconfirmed ACT: ACT 29/299 versus no antimalarial 57/793; aHR = 1.66 (95% CI = 1.04–2.67, p = 0.034) Q 1/13 versus no antimalarial 57/793; aHR = 4.27 (95% CI = 0.53–34.33, p = 0.172) ACT 28/286 versus Q 1/13; aHR = 0.64 (95% CI = 0.08–4.91, p = 0.665)	Not assessed	Not assessed
Moore, et al., 2016††,¶	Data from antenatal clinics analyzed (Thai-Myanmar border)	Areg (183) MQ (25) Q or Q and CL (971)	Miscarriage: when compared with Q or Q and CL, Areg, 92 (11): aHR = 0.78 (95% CI = 0.45–1.34, p = 0.3645) MQ 2 (8): aHR = 0.54 (95% CI = 0.13–2.31, p = 0.4082) When comparing malaria with no malaria in first trimester, miscarriage: aHR = 1.61 (95% CI = 1.32–1.97, p<0.0001)	Any malformation: Uncomplicated Pf treated with Areg, 2/109 (2), Q, 9/641 (1), Severe Pf treated with: Areg, 2/22 (9); Q, 0/8 (0)	Not assessed

See table footnotes on page 430.

TABLE 3. (*Continued*) Summary of safety outcomes in studies using artemisinin-based treatment for malaria in first trimester of pregnancy

Author, publication year	Description or indication (country)	Drug or regimen (no.)	Pregnancy outcomes, no. (%) (unless otherwise indicated)*	Congenital anomalies, no. (%) (unless otherwise indicated)	Maternal adverse events, no. (%) (unless otherwise indicated)
Manyando, et al., 2015[§§,¶]	Data analyzed from previous prospective cohort, women with inadvertent first trimester exposure (Zambia)	AL (135)	Miscarriage not assessed Stillbirth, 2 (1.5) (95% CI = 0.4–5.2) Low birth weight, 13 (10.2)	Any malformation, 9 (7)	Not assessed
		AL and SP (7)	Miscarriage not assessed Stillbirth, 0 (0) (95% CI = 0–39.0) Low birth weight, 1 (14.3)	Any malformation, 8/121 (7)	Not assessed
		SP and/or Q (129)	Miscarriage not assessed Stillbirth, 3 (2.3) (95% CI = 0.8–6.6) Low birth weight, 8 (6.7)		Not assessed
		No antimalarial (644)	Miscarriage not assessed Stillbirth, 17 (2.6) (95% CI = 1.7–4.2) Low birth weight, 52 (8.7)	Not assessed	Not assessed
Descriptive studies					
McGready, et al., 2001[¶¶] (includes data from McGready et al., 1998)[***]	P for mixed infection, both primary and recrudescent, uncomplicated and severe (Thailand)	Areg (19 primary treatment, 25 for retreatment)	Miscarriage, 7 (18.9)[†††]	Any malformation, 0	Not assessed
		Community (no treatment)	Miscarriage, 1,003/8,154 (12.3)	Any malformation, 56/3,707 (2)	Not assessed

Abbreviations: A = atovaquone; aHR = adjusted hazard ratio; AL = artemether-lumefantrine; aOR = adjusted odds ratio; AQ = amodiaquine; Ar = artemether; Areg = artemisinin regimen; As = artesunate; BID = twice daily; CI = confidence interval; CL = clindamycin; CQ = chloroquine; DHA-PIP = dihydroartemisinin-piperaquine; LapDap = chlorproguanil-dapsone; MQ = mefloquine; P = proguanil; Pf = *Plasmodium falciparum*; Q = quinine; SP = sulfadoxine pyrimethamine.

* In studies with incomplete outcome data, denominators are provided.

† Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: a meta-analysis of observational studies. Krishna S, editor. PLOS Med 2017;14:e1002290.

§ Mosha D, Mazuguni F, Mrema S, Sevene E, Abdulla S, Genton B. Safety of artemether-lumefantrine exposure in first trimester of pregnancy: an observational cohort. Malar J 2014;13:197.

¶ Study included in Dellicour 2017 meta-analysis.

** Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: a meta-analysis of observational studies. Krishna S, editor. PLOS Med 2017;14:e1002290.

†† Moore KA, Simpson JA, Paw MK, et al. Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study. Lancet Infect Dis 2016;16:576–83.

§§ Manyando C, Njunju EM, Virtanen M, Hamed K, Gomes M, Van Geertruyden JP. Exposure to artemether-lumefantrine (Coartem) in first trimester pregnancy in an observational study in Zambia. Malar J 2015;14:77.

¶¶ McGready R, Cho T, Keo NK, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*.

*** McGready R, Cho T, Cho JJ, et al. Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 1998;92:430–3.

††† Not different from overall community rate p = 0.211.

are used to treat uncomplicated malaria in pregnant women, as well as population-specific disease burden; in addition, the FDA Adverse Event Reporting System maintains adverse event and medication error data, which can be used to monitor adverse events associated with AL use during pregnancy.

Conflict of Interest

No conflicts of interest were reported.

[1]Epidemic Intelligence Service, CDC; [2]Division of Parasitic Diseases and Malaria, Center for Global Health, CDC; [3]Hubert Department of Global Health, Emory University, Atlanta, Georgia.

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References

1. CDC. Guidelines for treatment of malaria in the United States. Atlanta, GA: US Department of Health and Human Services, CDC; 2013. https://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf
2. World Health Organization Malaria Policy Advisory Committee. Intermittent screening and treatment in pregnancy and the safety of ACTs in the first trimester. Geneva, Switzerland: World Health Organization; 2015. http://www.who.int/malaria/publications/atoz/istp-and-act-in-pregnancy.pdf?ua=1
3. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. Geneva, Switzerland: World Health Organization; 2015.
4. Mace KE, Arguin PM. Malaria surveillance—United States, 2014. MMWR Surveill Summ 2017;66 (No. SS-12). https://doi.org/10.15585/mmwr.ss6612a1
5. Burger RJ, van Eijk AM, Bussink M, Hill J, Ter Kuile FO. Artemisinin-based combination therapy versus quinine or other combinations for treatment of uncomplicated *Plasmodium falciparum* malaria in the second and third trimester of pregnancy: a systematic review and meta-analysis. Open Forum Infect Dis 2015;3:ofv170. https://doi.org/10.1093/ofid/ofv170
6. McGready R, Brockman A, Cho T, et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 2000;94:689–93. https://doi.org/10.1016/S0035-9203(00)90235-9

7. McGready R, Cho T, Keo NK, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. Clin Infect Dis 2001;33:2009–16. https://doi.org/10.1086/324349
8. McGready R, Ashley EA, Moo E, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. J Infect Dis 2005;192:846–53. https://doi.org/10.1086/432551
9. Piola P, Nabasumba C, Turyakira E, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated *Plasmodium falciparum* malaria: an open-label, randomised, non-inferiority trial. Lancet Infect Dis 2010;10:762–9. https://doi.org/10.1016/S1473-3099(10)70202-4
10. Kaye DK, Nshemerirwe R, Mutyaba TS, Ndeezi G. A randomized clinical trial comparing safety, clinical and parasitological response to artemether-lumefantrine and chlorproguanil-dapsone in treatment of uncomplicated malaria in pregnancy in Mulago hospital, Uganda. J Infect Dev Ctries 2008;2:135–9. https://doi.org/10.3855/T2.2.135
11. Mosha D, Guidi M, Mwingira F, et al. Population pharmacokinetics and clinical response for artemether-lumefantrine in pregnant and nonpregnant women with uncomplicated *Plasmodium falciparum* malaria in Tanzania. Antimicrob Agents Chemother 2014;58:4583–92. https://doi.org/10.1128/AAC.02595-14
12. Nyunt MM, Nguyen VK, Kajubi R, et al. Artemether-lumefantrine pharmacokinetics and clinical response are minimally altered in pregnant Ugandan women treated for uncomplicated falciparum malaria. Antimicrob Agents Chemother 2016;60:1274–82. https://doi.org/10.1128/AAC.01605-15
13. McGready R, Stepniewska K, Lindegardh N, et al. The pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. Eur J Clin Pharmacol 2006;62:1021–31. https://doi.org/10.1007/s00228-006-0199-7
14. Tarning J, McGready R, Lindegardh N, et al. Population pharmacokinetics of lumefantrine in pregnant women treated with artemether-lumefantrine for uncomplicated *Plasmodium falciparum* malaria. Antimicrob Agents Chemother 2009;53:3837–46. https://doi.org/10.1128/AAC.00195-09
15. Price RN, Uhlemann A-C, van Vugt M, et al. Molecular and pharmacological determinants of the therapeutic response to artemether-lumefantrine in multidrug-resistant *Plasmodium falciparum* malaria. Clin Infect Dis 2006;42:1570–7. https://doi.org/10.1086/503423
16. PREGACT Study Group. Four artemisinin-based treatments in African pregnant women with malaria. N Engl J Med 2016;374:913–27. https://doi.org/10.1056/NEJMoa1508606
17. Ukah M, Badejoko O, Ogunniyi S, Loto O, Aboderin O, Fatusi A. A randomized trial of artesunate-amodiaquine versus artemether-lumefantrine for the treatment of acute uncomplicated malaria in pregnancy. Int J Gynaecol Obstet 2015;131:41–4. https://doi.org/10.1016/j.ijgo.2015.05.009
18. McGready R, Tan SO, Ashley EA, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated *Plasmodium falciparum* treatment in pregnancy. PLoS Med 2008;5:e253.
19. Sowunmi A, Oduola AMJ, Ogundahunsi OAT, et al. Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sufadoxine-pyrimethamine-resistant falciparum malaria during pregnancy. J Obstet Gynaecol 1998;18:322–7. https://doi.org/10.1080/01443619867038
20. Manyando C, Mkandawire R, Puma L, et al. Safety of artemether-lumefantrine in pregnant women with malaria: results of a prospective cohort study in Zambia. Malar J 2010;9:249. https://doi.org/10.1186/1475-2875-9-249
21. Kovacs SD, van Eijk AM, Sevene E, et al. The safety of artemisinin derivatives for the treatment of malaria in the 2nd or 3rd trimester of pregnancy: a systematic review and meta-analysis. PLoS One 2016;11:e0164963.
22. Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: a meta-analysis of observational studies. PLoS Med 2017;14:e1002290.
23. Askling HH, Bruneel F, Burchard G, et al.; European Society for Clinical Microbiology and Infectious Diseases Study Group on Clinical Parasitology. Management of imported malaria in Europe. Malar J 2012;11:328. https://doi.org/10.1186/1475-2875-11-328
24. Lalloo DG, Shingadia D, Bell DJ, Beeching NJ, Whitty CJM, Chiodini PL; PHE Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines 2016. J Infect 2016;72:635–49. https://doi.org/10.1016/j.jinf.2016.02.001

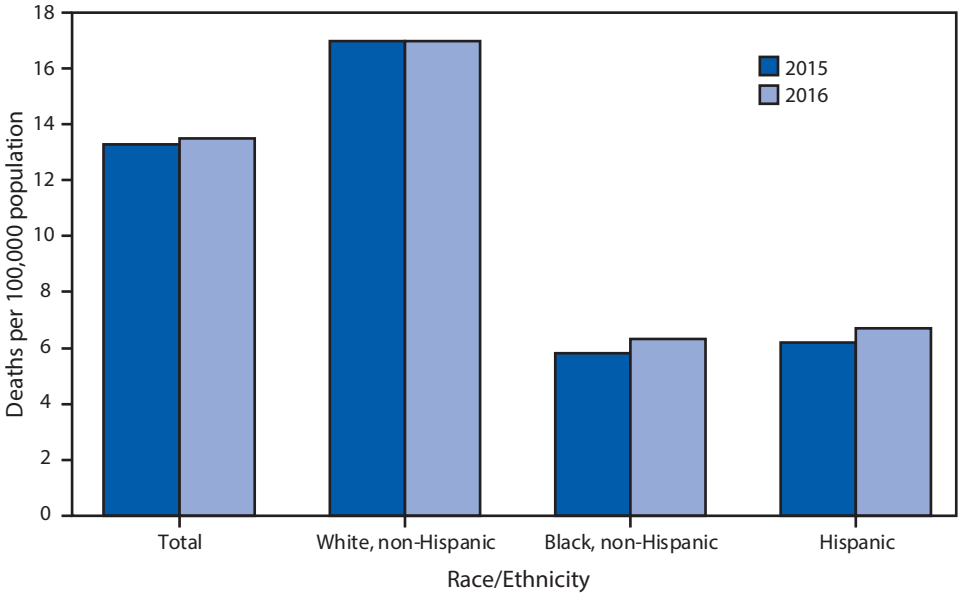
Erratum: Vol. 66, No. 29

In the report "Outbreak of Septic Arthritis Associated with Intra-Articular Injections at an Outpatient Practice — New Jersey, 2017," the type of container was misstated. The container should have been described as **a single-dose container** instead of a pharmacy bulk packaged (PBP) product. Single-dose containers can only be repackaged for multiple patients by qualified health care personnel in accordance with standards in United States Pharmacopeia General Chapter <797> Pharmaceutical Compounding — Sterile Preparations.

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Age-Adjusted Suicide Rates,*,† by Race/Ethnicity — National Vital Statistics System, United States, 2015–2016



* Deaths per 100,000 population are age-adjusted to the 2000 U.S. standard population.
† As underlying cause of death, suicide is identified with *International Classification of Diseases, 10th Revision* codes X60–X84, Y87.0, and also code U03.

From 2015 to 2016, the age-adjusted suicide rate for the total U.S. population increased from 13.3 per 100,000 standard population to 13.5 (an increase of 1.5%). The rate increased from 5.8 to 6.3 (8.6%) for non-Hispanic blacks and from 6.2 to 6.7 (8.1%) for Hispanics; it remained unchanged for non-Hispanic whites. In both 2015 and 2016, the non-Hispanic white rate was nearly three times the non-Hispanic black rate and 2.5 times the rate for the Hispanic population.

Source: National Vital Statistics System. Underlying cause of death data, 1999–2016. https://wonder.cdc.gov/ucd-icd10.html.

Reported by: Jiaquan Xu, MD, jiaquanxu@cdc.gov, 301-458-4086.

For more information on this topic, CDC recommends the following link: https://www.cdc.gov/violenceprevention/suicide/index.html.

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