

## Hospitalizations for Crohn's Disease — United States, 2003–2013

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In 2009, an estimated 565,000 Americans had Crohn's disease (1), an inflammatory bowel disorder that can affect any part of the gastrointestinal tract. Symptoms include persistent diarrhea, abdominal cramps and pain, constipation leading to bowel obstruction, and rectal bleeding.\* Symptoms sometimes intensify in severity and require hospitalization and surgeries of the small intestine, colon, or rectum (2). Hospital discharge data from the National Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP) were used to estimate U.S. hospitalizations<sup>†</sup> for Crohn's disease as both the first-listed and any-listed<sup>§</sup> discharge diagnosis and common surgical procedures during hospitalizations with Crohn's disease as first-listed diagnosis from 2003 to 2013, the most recent decade of data. Despite new therapies that were expected to improve remission and reduce hospitalizations, estimated numbers (and age-adjusted rates per 100,000 U.S. population) of hospitalizations for Crohn's disease as the first-listed diagnosis did not change significantly from 2003 to 2013. The proportion of these hospitalizations during which small bowel resection was performed decreased from 4.9% in 2003 to 3.9% in 2013 ( $p < 0.05$ ); however, colorectal resection and fistula repair rates remained stable. Hospital stays for any-listed Crohn's disease increased from >120,000 (44.2 per 100,000) in 2003 to >196,000 (59.7 per 100,000) in 2013 ( $p < 0.05$ ). Patient education initiatives should focus on increasing awareness of exacerbating factors and medication compliance to prevent hospitalizations.

NIS hospital discharge data, which were obtained from the Agency for Healthcare Research and Quality (AHRQ),

represent an annual stratified sample of 7–8 million hospital records collected by 37–44 participating states from approximately 20% of U.S. community hospitals.<sup>¶</sup> Records are weighted for hospital characteristics as well as for patient diagnoses, age, and admission month, so that analyses can produce reliable national estimates. Because the NIS implemented a new systematic sampling design in 2012, revised sampling weights were used for all analyses. Crohn's disease was defined for a first-listed diagnosis field and for any of 15 diagnosis fields during 2003–2008 and 25 fields during 2009–2013 with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) disease codes 555.0–555.9. For states, the number of hospitalizations in 2013 with any diagnosis of Crohn's disease was obtained using the online query tool\*\* from 35 states

<sup>¶</sup> <https://www.hcup-us.ahrq.gov/db/nation/nis/NISIntroduction2012.pdf>.

\*\* <https://www.hcup-us.ahrq.gov/sidoverview.jsp>. A list of the HCUP Data Partners that contribute to HCUP is available at <https://www.hcup-us.ahrq.gov/db/hcupdatapartners.jsp>.

\* <http://www.crohnscolitisfoundation.org/what-are-crohns-and-colitis/what-is-crohns-disease>.

<sup>†</sup> Hospitalizations or hospital stays refer to a patient being admitted to a hospital for one or more days.

<sup>§</sup> First-listed Crohn's disease diagnosis indicates that Crohn's disease was the principal reason for the hospitalization. Any-listed Crohn's disease diagnosis indicates that patients had Crohn's disease, but Crohn's disease was not necessarily the main reason they were being hospitalized.

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participating in the State Inpatient Databases, HCUP, AHRQ. Denominators for all annual hospitalization rates by age, sex, and state were obtained from the U.S. Census intercensal estimates for 2003–2009<sup>††</sup> and 2010–2013.<sup>§§</sup> Direct age-adjustment to the projected 2000 U.S. population was performed using five age groups (<18, 18–44, 45–64, 65–84, and ≥85 years) to calculate age-adjusted hospitalization rates per 100,000 U.S. population and 95% confidence intervals (CIs). Because race/ethnicity was not reported for 26% of hospital records in 2003 and 6% in 2013, these analyses do not include estimates by race/ethnicity. The percentages of first-listed hospitalizations that included small bowel resection, colorectal resection, or fistula repair were also obtained from any of up to 15 procedure fields.<sup>¶¶</sup> SAS-callable SUDAAN was used to account for the complex sampling design of NIS. For comparisons of rates from 2003 to 2013 and between males and females, statistical significance ( $p < 0.05$ ) was determined by the Z-test.

<sup>††</sup> Intercensal Estimates of the Resident Population by Sex and Age for the United States: April 1, 2000 to July 1, 2010. <https://www2.census.gov/programs-surveys/popest/tables/2000-2010/intercensal/national/us-est00int-01.xls>.

<sup>§§</sup> Annual Estimates of the Resident Population: April 1, 2010 to July 1, 2014. 2014 Population Estimates. [https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP\\_2016\\_PEPANNRES&src=pt](https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP_2016_PEPANNRES&src=pt).

<sup>¶¶</sup> ICD-9-CM procedure codes: small bowel resection (45.61–45.63), colorectal resection (17.3, 45.71–45.79, 45.81–45.83, 48.40–48.49, 48.50–48.59, or 48.61–48.69), fistula repair (46.74, 46.76, 48.73, 48.93, 49.11, 49.12, 49.73, 57.83, 58.43, or 70.72–70.74).

Hospitalization rates for any-listed diagnosis of Crohn's disease were two times higher than those for a first-listed diagnosis from 2003 to 2007 and three times higher from 2008 to 2013 (Figure 1). Potential reasons for the sharp increase in hospitalization rates from 2007 to 2008 are unknown; however, there were no changes in NIS methodology, states reporting data, or diagnosis codes at that time. Age-adjusted hospitalization rates were higher among females than among males for both first-listed and any-listed diagnosis of Crohn's disease ( $p < 0.05$ ).

From 2003 to 2013, there was no significant change in the estimated number of hospitalizations for Crohn's disease as a first-listed diagnosis; however the age-adjusted hospitalization rate for Crohn's disease as any-listed diagnosis increased 35.1% from 44.2 per 100,000 (120,209 hospitalizations) in 2003 to 59.7 per 100,000 (196,480 hospitalizations) in 2013 (Table). As a first-listed diagnosis, there was a significant increase in the hospitalization rate in 2013 relative to 2003 (+14.5%), only among males ( $p < 0.05$ ). In contrast, hospitalization rates for any-listed Crohn's disease increased from 2003 to 2013 for all groups defined by age and sex. In both 2003 and 2013, hospitalization rates for Crohn's disease as a first-listed diagnosis were higher among persons aged 18–44 years than among other age groups, whereas, hospitalization rates with any-listed Crohn's disease increased among successive age groups until age 65–84 years.

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Geographic variations were observed in tertiles of age-adjusted hospitalization rates with any-listed Crohn's disease in 2013 among participating HCUP states (Figure 2), with age-adjusted hospitalization rates per 100,000 ranging from 19.2 in Hawaii to 91.6 in Rhode Island. States with the lowest hospitalization rates were clustered in the Southwest and Rocky Mountain states.

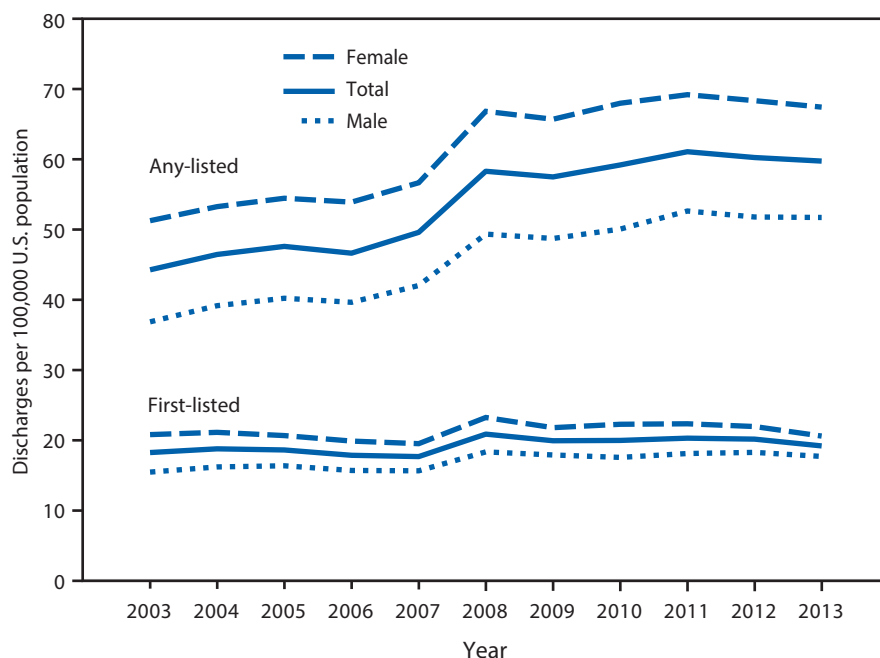
Among hospitalizations for a first-listed diagnosis of Crohn's disease in 2013, 3.9% were for small bowel resection, 12.8% for colorectal resection, and 2.0% for fistula repair. The decline in the percentage of hospitalizations for small bowel resection from 2003 (4.9%) was significant ( $p < 0.05$ ), but the percentages of 2003 hospitalizations for colorectal resections (14.8%) or fistula repairs (1.8%) were similar to those in 2013.

### Discussion

Stable trends for a first-listed Crohn's disease diagnosis from 2003 to 2013 suggest that the 4.3% annual increase reported for a first-listed diagnosis from 1998 to 2004 (3) has not continued. Although this result suggests that the available treatments have not increased clinical remissions or reduced hospitalizations, it is possible that these trends indicate the beginning of a reversal of the increased hospitalizations and surgical procedures observed in the years leading up to the study period. The proportion of hospitalizations with small bowel resection declined from 2003 to 2013, with no significant change in colorectal resections and fistula repairs. These trends contrast with the period from 1993 to 2004, when rates of small bowel and right colon resection did not change and fistula repairs increased significantly (4). Resections are only performed on an inpatient basis and the decline cannot be explained by increases in outpatient procedures; therefore, the declines in small bowel resection during hospitalizations might represent a decrease in clinical severity, possibly related to newer therapies. Hospitalizations with any-listed diagnosis of Crohn's disease continued to increase in the most recent decade. This increase might represent greater physician awareness and diagnosis of Crohn's disease or more complete coding of secondary diagnoses by physicians.

State variations in any-listed hospitalization for Crohn's disease are similar to findings in earlier reports showing state-specific first- and any-listed hospitalization rates during 2001–2006 (5). Previous studies found lower first-listed hospitalization rates in

**FIGURE 1. Age-adjusted\* hospitalization rate (per 100,000 population) for a first-listed or any-listed diagnosis† of Crohn's disease, by sex — National Inpatient Sample, United States, 2003–2013**



\* Age-adjusted to the 2000 projected U.S. population.

† First-listed Crohn's disease diagnosis indicates that Crohn's disease was the principal reason for the hospitalization. Any-listed Crohn's disease diagnosis indicates that patients had Crohn's disease, but Crohn's disease was not necessarily the main reason they were being hospitalized.

western U.S. regions during 1998–2004 (3), lower prevalence of Crohn's disease among insured adults in the South and West, and higher prevalence in the Midwest during 2008–2009 (1). Whether this consistent regional pattern is the result of variations in physician awareness and diagnosis of Crohn's disease or variations in risk factors for Crohn's disease is unknown.

The findings in this report are subject to at least five limitations. First, information on hospital diagnosis and procedures is based solely on ICD-9-CM codes that are reported in the hospital record, which cannot be validated in this study and should not be interpreted as new incident cases. Second, severity of the condition cannot be determined for most cases, other than that surgical procedures were performed during some hospitalizations. Third, the surveillance estimates for surgical procedures in this study only represent hospital inpatient records and do not include procedures performed in outpatient clinics, or small bowel resections and colon resections conducted for first-listed diagnosis codes other than Crohn's disease. It is also likely that the number of hospital discharges for Crohn's disease includes an undetermined number of repeat hospital stays for some persons. Fourth, although the reporting of race/ethnicity on hospital records has improved during the

TABLE. Hospitalizations for Crohn's disease, by selected characteristics — National Inpatient Sample, United States, 2003 and 2013

Characteristic	2003		2013		Relative change (%) <sup>§</sup>
	No.*	Hospitalization rate (95% CI) <sup>†</sup>	No.*	Hospitalization rate (95% CI) <sup>†</sup>	
<b>First-listed diagnosis</b>					
<b>Total</b>					
Unadjusted	52,855	18.2 (16.4–20.0)	60,255	19.1 (18.3–19.8)	+4.6
Age-adjusted		18.2 (16.8–19.5)		19.1 (18.5–19.7)	+5.2
<b>Age group (yrs)</b>					
<18	3,384	4.6 (3.4–5.8)	4,410	6.0 (5.0–7.0)	+29.4
18–44	29,666	26.4 (23.4–29.4)	33,149	28.9 (27.5–30.2)	+9.4
45–64	13,938	20.2 (18.2–22.3)	15,745	19.0 (18.0–19.9)	-6.4
65–84	5,333	17.0 (15.3–18.7)	6,370	16.5 (15.5–17.5)	-3.0
≥85	533	11.9 (9.3–14.6)	580	9.6 (7.8–11.4)	-19.6
<b>Sex</b>					
Male	21,931	15.4 (14.1–16.6)	27,330	17.6 (16.9–18.3)	+14.5 <sup>¶</sup>
Female	30,751	20.7 (19.2–22.2)	32,920	20.5 (19.7–21.3)	-1.0
<b>Any-listed diagnosis</b>					
<b>Total</b>					
Unadjusted	120,209	44.5 (41.1–47.9)	196,480	62.1 (60.1–64.2)	+39.5 <sup>¶</sup>
Age-adjusted		44.2 (41.9–46.5)		59.7 (58.3–61.1)	+35.1 <sup>¶</sup>
<b>Age group (yrs)</b>					
<18	5,005	6.8 (5.2–8.5)	7,115	9.7 (8.2–11.2)	+41.2 <sup>¶</sup>
18–44	56,303	50.1 (45.3–54.9)	77,220	67.3 (64.4–70.2)	+34.2 <sup>¶</sup>
45–64	41,144	59.8 (55.3–64.2)	63,175	76.0 (73.2–78.8)	+27.0 <sup>¶</sup>
65–84	23,666	75.4 (69.8–81.0)	42,495	109.9 (105.9–113.9)	+45.8 <sup>¶</sup>
≥85	3,090	69.2 (60.9–77.5)	6,475	107.2 (100.1–114.3)	+54.9 <sup>¶</sup>
<b>Sex</b>					
Male	51,454	36.8 (34.7–38.9)	82,035	51.7 (50.3–53.1)	+40.5 <sup>¶</sup>
Female	77,514	51.2 (48.5–53.9)	114,425	67.4 (65.7–69.1)	+31.6 <sup>¶</sup>

Abbreviation: CI = confidence interval.

\* Estimated number of hospitalizations.

† Hospitalization rate (per 100,000 U.S. population) and 95% CI. Age-adjusted to the 2000 projected U.S. population, except for age groups.

§ Change in 2013 relative to 2003.

¶ Statistically significant difference ( $p < 0.05$ ) in rates from 2003 to 2013 using the Z-statistic.

past decade, the continued absence of such sociodemographic information from a significant proportion of records constrains assessment of possible disparities in this low prevalence chronic disease. Finally, the lack of data for every state limits the ability to detect geographic clustering of hospital discharge rates.

Diagnosis of Crohn's disease is based on a combination of gastrointestinal endoscopy, imaging, and pathologic studies (2). Progression of treatment for a patient usually proceeds from aminosalicylates and corticosteroids to immunomodulators and other biologic therapies, and to surgery in severe cases (2). From 1994 to 2005, prescriptions declined for corticosteroids and increased for immunomodulatory or biologic therapies during office visits involving a diagnosis of either Crohn's disease or ulcerative colitis (6).

Risk factors for Crohn's disease are not clearly established. Cigarette smoking has been suggested as a risk factor and is recognized to increase disease severity among patients with Crohn's disease (7). Upper respiratory or enteric infections, nonsteroidal anti-inflammatory drugs, and possibly stress might initiate and exacerbate symptoms and lead to hospitalizations

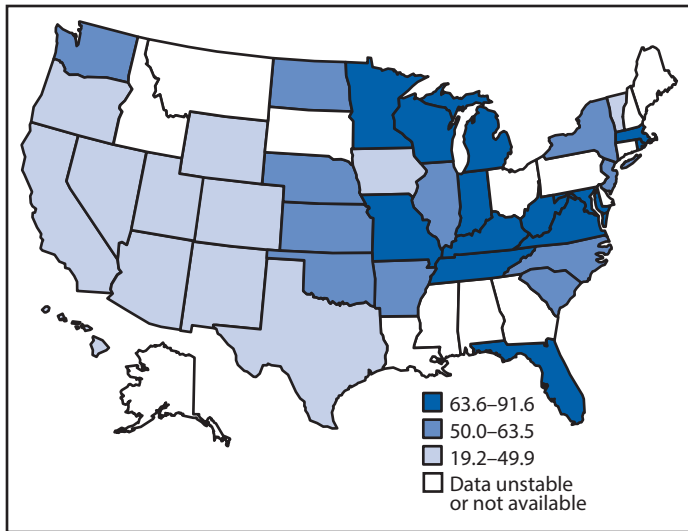
(2). A major deterrent in identifying risk factors is that Crohn's disease is assumed to be a low prevalence chronic disease. Large sample size studies, which would be prohibitively expensive, would be required for national surveillance systems to collect reliable information on the prevalence of existing cases and the incidence of new cases in the general U.S. population and in subgroups, such as children and minorities (8).

Because the cause of Crohn's disease is unknown, it is difficult to determine what changes in public health practice could help prevent it. Patient education initiatives could focus on increasing awareness of exacerbating factors such as cigarette smoking and stress, and medication compliance to prevent hospitalizations. Professional education should continue to increase awareness of the signs and symptoms of Crohn's disease and improve diagnosis and management.

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**FIGURE 2. Age-adjusted\* hospitalization rate† (per 100,000 population) for any-listed diagnosis‡ of Crohn's disease — State Inpatient Databases, 2013**



\* Age-adjusted to the 2000 projected U.S. population.

† Estimates considered unstable if relative standard error >30%.

‡ Any-listed Crohn's disease diagnosis indicates that patients had Crohn's disease, but Crohn's disease was not necessarily the main reason they were being hospitalized.

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## Summary

### What is already known about this topic?

Hospital discharges for a first-listed diagnosis of Crohn's disease increased from 1993 to 2004, despite new therapies that were expected to improve remission and reduce hospitalizations.

### What is added by this report?

Hospitalizations for a first-listed diagnosis of Crohn's disease did not change from 2003 to 2013. In addition, inpatient surgical procedures for small bowel resection declined, whereas those for colorectal resection or fistula repairs remained stable. It is unclear whether these trends indicate the beginning of a reversal of the increases in hospitalizations and surgical procedures observed in the years leading up to study period. The increase in hospitalizations for any-listed diagnosis of Crohn's disease might represent greater physician awareness and diagnosis of the condition. State-specific estimates suggest geographic variation in hospitalizations.

### What are the implications for public health practice?

Because the risk factors are not known, public health prevention programs are not possible. However, stress reduction and smoking cessation might be beneficial in ameliorating disease severity among patients with Crohn's disease. Professional education should continue to increase awareness of the signs and symptoms of Crohn's disease, and improve diagnosis and management of the disease.

## Characteristics of Fentanyl Overdose — Massachusetts, 2014–2016

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Opioid overdose deaths in Massachusetts increased 150% from 2012 to 2015 (1). The proportion of opioid overdose deaths in the state involving fentanyl, a synthetic, short-acting opioid with 50–100 times the potency of morphine, increased from 32% during 2013–2014 to 74% in the first half of 2016 (1–3). In April 2015, the Drug Enforcement Agency (DEA) and CDC reported an increase in law enforcement fentanyl seizures in Massachusetts, much of which was believed to be illicitly manufactured fentanyl (IMF) (4). To guide overdose prevention and response activities, in April 2016, the Massachusetts Department of Public Health and the Office of the Chief Medical Examiner collaborated with CDC to investigate the characteristics of fentanyl overdose in three Massachusetts counties with high opioid overdose death rates. In these counties, medical examiner charts of opioid overdose decedents who died during October 1, 2014–March 31, 2015 were reviewed, and during April 2016, interviews were conducted with persons who used illicit opioids and witnessed or experienced an opioid overdose. Approximately two thirds of opioid overdose decedents tested positive for fentanyl on postmortem toxicology. Evidence for rapid progression of fentanyl overdose was common among both fatal and nonfatal overdoses. A majority of interview respondents reported successfully using multiple doses of naloxone, the antidote to opioid overdose, to reverse suspected fentanyl overdoses. Expanding and enhancing existing opioid overdose education and prevention programs to include fentanyl-specific messaging and practices could help public health authorities mitigate adverse effects associated with overdoses, especially in communities affected by IMF.

Barnstable, Bristol, and Plymouth counties in Massachusetts were investigated because of high opioid overdose death rates (estimated 29.8–34.5 per 100,000 population in 2015), and feasibility of interviewee recruitment through existing harm reduction programs in these counties (5).<sup>\*</sup> To rapidly obtain a cross section of persons misusing opioids for semistructured, in-person interviews, a nonrandom sample of approximately 20 knowledgeable respondents per county was recruited with the help of harm reduction programs. Eligible persons were aged ≥18 years, lived in Massachusetts, had used illicit opioids during the previous 12 months, and had witnessed or

experienced an opioid overdose during the previous 6 months. Equal numbers of men and women were recruited. Trained interviewers asked respondents about their experiences, knowledge, attitudes, and beliefs regarding opioid overdose. Interviews were audio recorded, transcribed, and thematically coded by multiple investigators.

Opioid overdose death data were abstracted from medical examiner charts, which included autopsy and toxicology reports, death scene reports, and emergency medical service logs. Abstracted charts met the following criteria: the death occurred during October 1, 2014–March 31, 2015; the decedent overdosed or resided in Barnstable, Bristol, or Plymouth counties; and opioids were listed as a contributing cause of death. Postmortem toxicology tests were used to categorize deaths as involving fentanyl (regardless of presence of other drugs), heroin or morphine (i.e., no fentanyl),<sup>†</sup> or other opioids (e.g., prescription opioids). Fentanyl deaths were further categorized using death scene evidence as suspected IMF, suspected prescription fentanyl, or unknown source of fentanyl. Rapidity of overdose death was determined from available evidence, including needles inserted in decedents' bodies, syringes found in hand, tourniquets still in place, and bystander reports of rapid unconsciousness after drug use. Demographic and overdose characteristic frequencies were examined by drug type.

Among 64 interview respondents, 52% were women, 61% were aged 25–44 years, and 81% were non-Hispanic white. Ninety-one percent reported that they were trained by a Massachusetts Department of Public Health-supported overdose education and naloxone distribution program in the use of naloxone for reversing an opioid overdose; trainees are taught that opioid overdose is defined by unresponsiveness and decreased respirations (6). During the 6 months before the interview, 95% of respondents witnessed an overdose and 42% overdosed themselves. Eighty-eight percent of respondents attributed the increase in opioid overdose deaths to suspected fentanyl, and 69% reported that suspected fentanyl

<sup>†</sup> There is no toxicology test specifically for heroin. Heroin metabolizes into 6-monoacetylmorphine (6-MAM), which in turn is rapidly metabolized to morphine. Deaths in which the decedent tested positive for 6-MAM or morphine were classified as heroin- or morphine-involved. Recent evidence from Massachusetts indicates that a majority of morphine-positive toxicology test results are due to heroin metabolism. <http://www.mass.gov/eohhs/gov/departments/dph/stop-addiction/chapter-55-overdose-assessment.html>.

<sup>\*</sup> County-specific rates were calculated using the number of deaths listed in this reference and population counts from CDC WONDER (<https://wonder.cdc.gov/>).

was now available for purchase in powdered form (consistent with IMF preparation), and not as diverted prescription medications, (e.g., Duragesic transdermal fentanyl patch) (Box). Respondents reported that suspected fentanyl could be obtained alone or mixed with heroin, and persons using heroin often did not know whether fentanyl was mixed into the heroin they purchased. Respondents' reactions to the addition of fentanyl to the illicit drug market varied. Although some persons sought out fentanyl and others attempted to avoid it, a majority of respondents reported that opioid-seeking behaviors were not altered in response to the emergence of fentanyl. A majority of respondents who witnessed a suspected fentanyl overdose (75%) described symptoms as occurring rapidly, within seconds to minutes. Twenty-five percent reported witnessing or experiencing an overdose when fentanyl was insufflated (snorted), and the remainder reported the overdose always involved injecting fentanyl. Atypical overdose characteristics described by respondents during suspected fentanyl overdose included immediate blue discoloration of the lips (20%), gurgling sounds with breathing (16%), stiffening of the body or seizure-like activity (13%), foaming at the mouth (6%), and confusion or strange affect before unresponsiveness (6%). Seventy-five percent of respondents reported witnessing naloxone administration, administering naloxone themselves, or receiving naloxone to successfully reverse an opioid or fentanyl overdose. Among these events, 83% of respondents reported that  $\geq 2$  naloxone doses (typical nasally administered dose in Massachusetts is 2 mg/2 mL<sup>§</sup>) per suspected fentanyl overdose were used before the person responded. Thirty percent of respondents reported using heroin or fentanyl with others present to help protect themselves from a fatal overdose.

Among 196 opioid overdose decedents whose records were reviewed, 73% were men, 50% were aged 15–34 years, and 91% were non-Hispanic white. Demographics of fentanyl overdose decedents were similar to those of the overall opioid overdose decedents (Table). Among all opioid overdose decedents 64% tested positive for fentanyl on postmortem toxicology; this proportion increased from 44% in October 2014 to 76% in March 2015 (Figure). Eighty-two percent of fentanyl deaths were suspected to involve IMF, 4% were suspected to involve prescription fentanyl, and 14% involved an unknown source of fentanyl. Thirty-six percent of fentanyl deaths had evidence of an overdose occurring within seconds to minutes after drug use, and 90% of fentanyl overdose decedents were pulseless upon emergency medical services arrival (Table). Ninety-one percent of fatal fentanyl overdoses occurred in a hotel, motel, or private residence. Only 6% of fentanyl overdose deaths had evidence

<sup>§</sup> <http://prescribeprevent.org/pharmacists/formulations>.

**BOX. Sample quotations from persons who reported using opioids and who had witnessed or experienced an opioid overdose — Barnstable, Bristol, and Plymouth counties, Massachusetts, April 2016\***

### **Illicitly manufactured fentanyl (IMF) responsible for opioid overdose deaths**

“So, now what they [people selling illicit drugs] are doing is they're cutting the heroin with the fentanyl to make it stronger. And the dope [heroin] is so strong with the fentanyl in it, that you get the whole dose of the fentanyl at once rather than being time-released [like the patch]. And that's why people are dying—plain and simple. You know, they [people using illicit drugs] are doing the whole bag [of heroin mixed with fentanyl] and they don't realize that they can't handle it; their body can't handle it.”

### **Overdoses involving IMF are acute and rapid**

“A person overdosing on regular dope [heroin] leans back and drops and then suddenly stops talking in a middle of a conversation and you look over and realize that they're overdosing. Not like with fentanyl. I would say you notice it [a fentanyl overdose] as soon as they are done [injecting the fentanyl]. They don't even have time to pull the needle out [of their body] and they're on the ground.”

### **Naloxone reverses overdoses involving IMF; multiple doses often required**

“So he put half [one dose] up one nose [nostril] and half [one dose] up the other nose, like they trained us to do, and she didn't come to. So he put water on her face and kind of slapped her, which doesn't really make you come to [regain consciousness]. It doesn't. So he pulled out another thing of Narcan [brand of naloxone] and he put half of it [another dose] up one nose and then she came to...She just didn't remember anything. She said, ‘What happened? I remember washing my hands and, like, what happened?’ We said, ‘You just overdosed in this room!’ So yeah, it was wicked scary.”

### **Self-protective measures often employed**

“Like I will do a very, very, very little bit of fentanyl... and if I don't feel it, I will do that little bit plus half. I'm just not going to throw the whole thing in the cooker and then do it, no way. I just know better.”

### **Co-use of opioids and benzodiazepines**

“My daughter's mother had benzos. And when she did one bag of heroin she already had done four or five Klonopin [brand of clonazepam] and she just died. That was it. She went into a coma for the night and she was dead in the morning.”

\*Categories are not mutually exclusive; all respondents reported using opioids in the past 12 months and had witnessed or experienced an overdose, or both.

**TABLE. Demographic characteristics and overdose precipitating circumstances of fentanyl overdose decedents (N = 125) — Barnstable, Bristol, and Plymouth counties, Massachusetts, October 1, 2014–March 31, 2015**

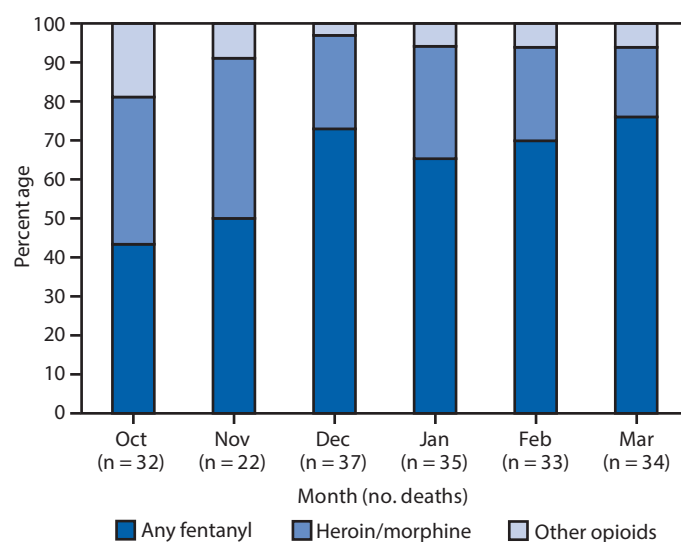
Characteristic	No. (%)
<b>Sex</b>	
Male	100 (80)
Female	25 (20)
<b>Age group (yrs)</b>	
15–24	15 (12)
25–34	52 (42)
35–44	24 (19)
≥45	34 (27)
<b>Race/Ethnicity</b>	
White, non-Hispanic	111 (89)
Other	14 (11)
<b>Location of overdose</b>	
Decedent's home	85 (68)
Other private residence	22 (18)
Hotel or motel	7 (6)
Other	11 (9)
<b>Overdose onset, pulselessness, and bystander naloxone administration</b>	
Evidence of rapid onset of overdose symptoms	45 (36)
Pulseless upon emergency medical services arrival	112 (90)
Evidence of bystander naloxone administration	7 (6)
<b>Barriers to bystander response</b>	
No bystander present	23 (18)
Decedent spatially separated from any bystander*	73 (58)
Bystander unaware of decedent's drug use	30 (24)
Bystander also using drugs or alcohol	15 (12)
Bystander reported symptoms of intoxication or overdose (snoring, falling asleep, or nodding), but did not realize decedent was overdosing	14 (11)
Decedent was thought to have gone to sleep	19 (15)
<b>Route of drug administration†</b>	
Evidence of injection	83 (66)
Evidence of insufflation (snorting)	11 (9)
No evidence of route of administration	26 (21)

\* Spatial separation defined as having a bystander nearby, either during or shortly preceding the overdose, who potentially had an opportunity to intervene and respond to the overdose, but who was not in the same room or physical space as the decedent.

† Categories were not defined as mutually exclusive, but all records with evidence of injection had no evidence of insufflation, and all records with evidence of insufflation had no evidence of injection. Any evidence of route of administration was coded but not linked to specific drugs.

of lay bystander-administered naloxone, which is available from pharmacies and harm reduction programs in Massachusetts. In addition to the limited use of naloxone by laypersons, rapid bystander response to fentanyl overdose was inhibited by lack of bystanders (18%), spatial separation of decedents from bystanders (e.g., person was in another room of the house [58%]), lack of awareness of decedent's drug use by bystanders (24%), intoxication of bystanders who were present (12%), failure of bystanders to recognize overdose symptoms (11%), or bystander assumption that the decedent had gone to sleep (15%). Clear evidence that a bystander was unimpaired, witnessed the drug consumption, and was present during an overdose (i.e., able to respond immediately) was reported in 1% of the fentanyl overdose decedent charts.

**FIGURE. Percentage of opioid overdose deaths involving fentanyl, heroin/morphine (without fentanyl), and other opioids (without fentanyl, heroin/morphine) — Barnstable, Bristol, and Plymouth counties, Massachusetts, October 2014–March 2015**



## Discussion

Introduction of fentanyl into the illicit drug market has been a major contributing factor to the rapid increase in opioid overdoses in southeastern Massachusetts and reflects a growing national public health issue (7). Previous DEA reports (4) and the findings of this investigation indicate that IMF is widely available through illicit drug markets in southeastern Massachusetts, and that the majority of fentanyl linked to fatal overdoses is suspected IMF rather than diverted prescription fentanyl. Taken together, these data highlight the need to integrate fentanyl testing into standard substance use toxicology tests employed by the medical, criminal justice, and treatment communities in Massachusetts areas with high levels of fentanyl use and overdose.

Evidence from over one third of medical examiner charts and reports from 75% of interview respondents demonstrated that fentanyl overdose can begin suddenly, progress to death rapidly, and manifest atypical physical symptoms. Timely administration of a sufficient naloxone dose by a trained layperson or emergency medical services responder can reverse fentanyl overdose. Although bystanders were frequently present in the general location of overdose death, timely bystander naloxone administration did not occur because bystanders did not have naloxone, were spatially separated or impaired by substance use, or failed to recognize overdose symptoms. Findings indicate that persons using fentanyl have an increased chance of surviving an overdose if directly observed by someone trained and equipped with sufficient



**Summary****What is already known about this topic?**

Fentanyl has a growing presence in the illicit drug market and is involved in an increasing proportion of opioid overdose deaths.

**What is added by this report?**

Approximately two thirds of investigated opioid overdose deaths in southeastern Massachusetts during October 1, 2014–March 31, 2015 involved fentanyl, a majority of which was suspected illicitly manufactured fentanyl (IMF), reported to be widely available in the illicit drug market. Fentanyl overdose can progress rapidly, and a majority of decedents were physically separated from bystanders. Naloxone can reverse fentanyl overdose if administered in sufficient dosage immediately upon recognition of overdose symptoms.

**What are the implications for public health practice?**

A comprehensive public health response is needed to address overdoses related to IMF. First, fentanyl should be included on standard toxicology screens to facilitate early identification. Second, existing harm reduction strategies to identify likely fentanyl exposure should be adapted, such as training for bystanders that includes direct observation of anyone injecting or insufflating illicit opioids, ensuring that trained bystanders are equipped with sufficient doses of naloxone, expanding layperson training, and providing access to naloxone. Third, access and linkages to medication for opioid use disorders need to be enhanced in fentanyl-affected areas.

doses of naloxone. In some countries, including Canada and Australia, overdose morbidity and mortality rates have decreased in areas near supervised injection facilities where personnel are available to observe overdose onset, if it occurs, and administer naloxone as needed (8). Because multiple doses might be required to reverse a fentanyl overdose, emergency medical services and community naloxone distribution programs might need to ensure that appropriate numbers of doses are distributed.

The findings in this report are subject to at least three limitations. First, toxicology reports in medical examiner charts cannot distinguish between prescription fentanyl and IMF; therefore, categorization was completed using death scene evidence, which varied and sometimes was inconclusive. In addition, samples were not tested for emerging fentanyl analogs, such as carfentanil. Overdose deaths were also categorized broadly as involving fentanyl, heroin or morphine, or other opioids, although in many cases other drugs also contributed to the death. Atypical symptoms reported during fentanyl overdose may be attributable to other drugs or drug combinations and not fentanyl. Second, circumstances or events preceding death (e.g., rapid onset of overdose symptoms) can be inferred from death scene evidence, but absence of

evidence cannot be interpreted as evidence of absence; numbers presented therefore likely underestimate the actual prevalence of circumstances. Finally, interview respondents were recruited with the help of community-based harm reduction programs in which overdose prevention education and naloxone rescue kits were offered. Thus, this sample population was potentially more informed about and experienced with fentanyl, naloxone, overdose prevention and treatment, and rescue efforts than are all persons who use illicit opioids. In addition, interview comparability is limited because not all respondents were asked uniform questions.

Adaptation of harm reduction practices designed to reduce health-related consequences of unsafe drug use, including the addition of warnings about fentanyl's characteristics and toxicity, could mitigate the fentanyl-related impact of the U.S. opioid epidemic in communities affected by fentanyl. Population-based strategies to prevent and reduce opioid use and opioid use disorders, such as expansion of access to evidence-based treatment, are likely to be effective in preventing fentanyl overdose and death. The high percentage of fatal overdoses occurring at home with no naloxone present, coupled with the rapid onset of overdose symptoms after using fentanyl through injection or insufflation, underscores the urgent need to expand initiatives to link persons at high risk for overdose (such as persons using heroin, persons with past overdoses, or persons recently released from incarceration) to harm reduction services and evidence-based treatment (2,8).

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## Use of Video Directly Observed Therapy for Treatment of Latent Tuberculosis Infection — Johnson County, Kansas, 2015

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Tuberculosis (TB) is caused by the bacterium *Mycobacterium tuberculosis* and is spread from person to person through the air. TB can be spread in congregate settings, such as school environments, to varying degrees, based on factors including duration of contact and air ventilation (1); therefore, evaluating potential contacts and exposures can be challenging. In February 2015, a student at a Kansas high school received a diagnosis of active pulmonary TB disease. Screening of 385 (91%) school contacts, four (100%) household contacts, and 19 (90%) social contacts resulted in the identification of 50 persons with latent TB infection. Johnson County Department of Health and Environment (JCDHE) Public Health Emergency Preparedness personnel used their experience with points of distribution logistics to optimize testing clinic layouts and implement the incident command structure. Open communication with students, school staff members, the public, and the media about the investigation from the outset was imperative to reduce rumors and unease that can accompany a large communicable disease investigation. The large number of persons needing treatment for latent TB overwhelmed JCDHE's two TB nurses. As a result, JCDHE developed a policy and procedure to allow persons who met eligibility requirements to complete 12 weekly doses of isoniazid and rifampentine treatment using video directly observed therapy (VDOT) rather than traditional in-person directly observed therapy (DOT). This procedure facilitated treatment compliance and completion; among the eligible 15 persons who chose the 12-week VDOT option, 14 (93%) completed treatment. State and local health departments might consider use of VDOT to monitor treatment of persons with latent TB infection.

### Index Patient

On February 27, 2015, JCDHE received notification from an area physician who suspected TB disease in a high school student. The patient had a 3-month history of cough, fatigue, night sweats, 25-pound weight loss, and an abnormal chest x-ray. The patient was immediately placed in home isolation and started on the standard four-drug therapy of isoniazid, rifampin, ethambutol, and pyrazinamide, pending confirmation and susceptibility testing. Sputum specimens were collected from the patient and tested by acid-fast bacilli (AFB)

microscopy and culture confirmed at the Kansas Health and Environmental Laboratories. The patient's sputum was AFB positive, grading 4+, indicating a potentially high level of infectiousness. The specimen was confirmed as TB through nucleic acid amplification testing on March 3, and reported as pansensitive (i.e., sensitive to all antibiotics usually administered in TB treatment) on March 30. Treatment was completed in August 2015.

### Contact Investigation

Contacts of the index patient were identified through interviews with the patient and review of the patient's class schedule. All four household members tested positive for TB infection by interferon-gamma release assays (IGRAs) and were medically evaluated and determined to have latent TB infection. Twenty-one social contacts were identified, and 19 completed testing, five (26%) of whom had a positive IGRA result and were found to have latent TB infection.

The index patient's high school has an enrollment of approximately 2,000 students who are predominantly non-Hispanic white (77%) and Hispanic (10%). Initially, JCDHE recommended testing for 345 staff members and students who had at least one class with the index patient. Before the first school clinic, multiple information sessions led by JCDHE TB nurses and the state TB controller were conducted, allowing staff members, students, and parents to ask questions and voice concerns. Joint press releases from JCDHE and the high school were issued. Health department staff members and the school nurse coordinator were available for media interviews.

The first school testing clinic was held on March 11. Local and state health department personnel performed IGRA tests on 282 (81%) students and staff members for whom testing was recommended; all laboratory analyses were performed at the Kansas Health and Environmental Laboratories. After 26 (9%) persons tested positive for likely TB infection, it was learned that nine of the students who tested positive had a weight lifting class with the index patient. Further investigation revealed that 79 students in a second weight lifting class held in the same location had not been identified for the initial testing because the class had a different instructor; this increased the total number of contacts from 345 to 424. The additional 79 students were contacted for testing, information sessions were

held, and a second school clinic was conducted on April 8. A third school clinic was conducted on May 5 to ensure that all students and staff members were tested at least 8 weeks after their last exposure to the index patient, to allow sufficient time for seroconversion. During the second and third testing clinics, 15 students were found to have latent TB infection, five of whom were in the second weight lifting class. Overall, among the 424 students and staff members identified for testing, 385 (91%) completed testing, 27 (6%) were tested once but did not complete testing at least 8 weeks following their last exposure to the index patient, and 12 (3%) were never tested. A total of 50 (12%) contacts, including 41 (11%) students and staff members, four household contacts, and five social contacts had positive IGRA results (Table 1).

### Use of Video Daily Observed Therapy

Medical evaluation ruled out active TB disease in all of the 50 persons who had a positive IGRA result. Therefore, all 50 latent TB patients were offered three treatment options: 1) 9 months of daily isoniazid, self-monitored, with monthly visits to the health department; 2) 4 months of daily rifampin, self-monitored, with visits to the health department every 2 weeks for the first month, and once per month thereafter; or 3) 12 weekly doses of rifapentine and isoniazid administered under DOT.

Sixteen persons selected and completed the 4-month daily rifampin treatment. Seven persons initiated 9-month daily isoniazid treatment, and six completed all 9 months of treatment; one person discontinued treatment for unknown reasons. Twenty-seven of the infected students opted for treatment with the 12 weekly doses of rifapentine and isoniazid under DOT (Table 2).

Because the investigation took place in the spring, treatment needed to occur over the summer, making it impossible for JCDHE to partner with the school to manage DOT for

**TABLE 1. Testing results and treatment among contacts of a high school student with tuberculosis (TB) disease — Johnson County, Kansas, 2015**

Testing results, treatment initiation, and completion	Identified contacts			
	Students and staff members (n = 424)	Household contacts (n = 4)	Social contacts (n = 21)	Total (N = 449)
	No. (%)	No. (%)	No. (%)	No. (%)
Completed testing*	385 (91)	4 (100)	19 (90)	408 (91)
Latent TB infections†	41 (11)	4 (100)	5 (26)	50 (12)
Initiated treatment‡	41 (100)	4 (100)	5 (100)	50 (100)
Completed treatment¶	40 (98)	4 (100)	4 (80)	48 (96)

\* Among identified contacts.

† Among contacts who completed testing.

‡ Among contacts who tested positive for TB.

¶ Among patients who initiated treatment.

students. As a consequence, the number of patients would make it difficult for the two JCDHE TB nurses to provide DOT. Therefore, JCDHE, in consultation with the state TB controller, developed a procedure to implement VDOT. To be eligible for VDOT, patients had to meet specific eligibility requirements (Box).

Fifteen of the 27 persons opted for VDOT over conventional DOT. One of the persons being monitored via VDOT discontinued treatment because of an adverse medication reaction.\* The remaining 14 persons completed treatment with 100% compliance. Use of VDOT saved JCDHE an estimated \$2,066 in mileage and staff time and allowed patients to continue treatment during international travel and family relocation. All 12 students undergoing conventional DOT completed treatment.

### Discussion

The successful investigation and treatment of identified latent TB infection cases can be attributed to extensive collaboration with the school and community. Before laboratory confirmation of TB in the index patient on March 3, 2015, JCDHE developed an incident action plan in partnership with the high school and the state TB controller. JCDHE staff members involved included department leadership, Public Health Emergency Preparedness staff members, public information officers, an epidemiologist, and two TB nurses. The Public Health Emergency Preparedness unit provided expertise in risk communication strategies that were employed throughout the investigation. Communication with the media, high school, and community about the investigation was prioritized, with the first joint press release occurring on March 4. The same day, letters were sent home with all students indicating whether

\* Reported adverse events from treatment included migraine, abdominal pain, hip pain, muscle pain, shortness of breath, and subjective fever.

**TABLE 2. Treatment regimens and completion rates among latent tuberculosis (TB) infection contacts (N = 50) of a student with tuberculosis (TB) disease — Johnson County, Kansas, 2015**

Treatment options for latent TB infection	No. who chose a treatment option	No. (%) who discontinued treatment	No. (%) who completed treatment
Daily isoniazid for 9 months, self-monitored	7	1 (14)	6 (86)
Daily rifampin for 4 months, self-monitored*	16	0 (—)	16 (100)
Weekly rifapentine and isoniazid for 12 weeks, DOT	27	1 (4)	26 (96)
Conventional DOT	12	0 (—)	12 (100)
VDOT	15	1 (7)	14 (93)
<b>Total</b>	<b>50</b>	<b>2 (4)</b>	<b>48 (96)</b>

**Abbreviations:** DOT = directly observed therapy; VDOT = video directly observed therapy.

\* With visits to the health department every 2 weeks for the first month, and once per month thereafter.

**BOX. Monitoring and eligibility requirements for patients with latent tuberculosis infection choosing video directly observed therapy (VDOT) with a 12-dose regimen of weekly rifapentine and isoniazid — Johnson County, Kansas, 2015**

**Monitoring requirements**

- Obtain baseline laboratory testing before initiation.
- Complete the first 4 doses at the health department, with no complications.
- Have specimens collected at fourth appointment, and receive medication for future VDOT doses.
- Agree to return to the clinic for the eighth and twelfth doses, for clinical evaluation and routine laboratory testing.

**Eligibility requirements**

- No likely risk factors for poor adherence (homelessness, substance abuse, psychiatric illness, reduced mental capacity, or memory impairment).
- Motivated to complete treatment.
- Speak a language that VDOT staff members can accommodate.
- Able to accurately identify medication.
- Access to VDOT device and demonstrate proper use.\*
- Physical setting for confidential communication available.

\*All of the eligible patients who participated had their own devices; however, iPads would have been provided if any patients needed them. VDOT was conducted live via FaceTime.

**Summary**

**What is already known about this topic?**

Tuberculosis (TB) is a contagious airborne disease that can spread in congregate settings such as a school environment. Recommendations for testing contacts in these settings are to test those at highest risk for exposure, followed by evaluation of findings and expanding testing as needed. Persons who test positive for latent TB infection should be treated with an antibiotic course ranging from 12 weeks to 9 months to prevent the development of active TB disease.

**What is added by this report?**

Following identification of a case of infectious TB in a high school student in February 2015, 23 (92%) of 25 household and social contacts and 385 (91%) of 424 high school students and staff members who shared at least one class with the index patient completed TB testing. Among 50 persons who tested positive, all were medically screened, and started on treatment for latent TB infection; 48 (96%) completed treatment. Approximately half (54%) of the infected persons opted for 12 weekly doses of isoniazid and rifapentine treatment, which require directly observed therapy. A procedure was developed to allow these persons to use video directly observed therapy (VDOT) to successfully complete their treatment.

**What are the implications for public health practice?**

VDOT, which previously had only been used during treatment of persons with active TB disease, is a viable option that can reduce costs and the time involved for both TB staff members and patients, while maintaining high compliance and completion rates.

testing was needed. Social media posts and four additional joint press releases informed the public as well as national and international media about the progress of the investigation.

On March 5, state and JCDHE personnel delivered a presentation at the high school to inform students, staff members, and parents about tuberculosis, the investigation process, the importance of being tested, the science behind not testing the entire school, and treatment options if test results were positive. On March 10, an informational forum was held for the public and the media. Throughout the investigation, JCDHE's TB nurses were available to provide information to concerned school and community members.

The layout of the testing clinic was designed based on points of distribution principles. The incident command structure

was implemented during each of the mass testing clinics. After each clinic, volunteers were debriefed and identified successes and opportunities for improvement. This feedback was used to refine the layout and flow of future testing clinics. As of March 2017, no persons had developed TB disease that could be linked to the index patient or the high school.

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## Notes from the Field

### Complications of Mumps During a University Outbreak Among Students Who Had Received 2 Doses of Measles-Mumps-Rubella Vaccine — Iowa, July 2015–May 2016

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During July 2015–May 2016, a mumps outbreak occurred at the University of Iowa, which is located in Johnson County (1). A total of 301 cases of mumps were diagnosed among students. To characterize the outbreak, the Johnson County Public Health Department, the Iowa Department of Public Health, and the University of Iowa, with assistance from CDC, conducted an investigation through telephone interviews, medical chart abstractions, and review of immunization records. Among 287 (95%) students with mumps for whom clinical information was available, 20 (7%) patients with complications were identified (16 self-reported and four clinician-diagnosed). The 20 cases included 15 (5%) cases of orchitis, three (1%) of transient hearing loss, two of mastitis, and one of meningitis (one patient had both orchitis and transient hearing loss). All 20 patients had documentation of receipt of at least 2 doses of measles-mumps-rubella vaccine. Because data are limited regarding the presentation and clinical course of mumps complications in persons who have received 2 doses of mumps-containing vaccine, three illustrative cases of complications (orchitis, transient hearing loss, and meningitis) in students with mumps are presented.

#### Patient A

On November 17, 2015, a man aged 21 years developed right jaw pain and swelling and received a clinical diagnosis of mumps parotitis; the diagnosis occurred 2 weeks after his roommate had received a mumps diagnosis. By the ninth day after symptom onset, the patient's parotitis had resolved, but he reported a fever of 101.0°F (38.8°C), and 2 days later, he developed left testicular pain and swelling. Orchitis was diagnosed and he was prescribed nonsteroidal anti-inflammatory drugs and ice packs and had no further follow-up care.

#### Patient B

On October 13, 2015, a woman aged 21 years developed progressive right ear pain, cough, and shortness of breath. Two days later, she was treated in a hospital emergency department where she received a diagnosis of right otitis

externa and left otitis media, for which she was prescribed amoxicillin and analgesics. Later that day, she went to the University of Iowa Student Health Center because of worsening respiratory symptoms. During that encounter, she was also noted to have right bullous myringitis (purulent inflammation of the tympanic membrane), right parotitis suspected to be mumps, and suspected pneumonia. Azithromycin was prescribed empirically to treat both the bullous myringitis and atypical pulmonary pathogens. A polymerase chain reaction (PCR) test for mumps was performed on a buccal swab specimen and was negative. However, her symptoms and epidemiologic link to the outbreak met the Council of State and Territorial Epidemiologists case definition for a probable case of mumps. One day later, she noticed tinnitus and diminished hearing in her right ear; on day 8, she had audiology testing and was evaluated by an otolaryngologist, at which time she received a diagnosis of moderate right sensorineural hearing loss, attributed to mumps, and conductive hearing loss, attributed to otitis media and myringitis. She was treated for 1 week with prednisone, and all her symptoms resolved by the thirteenth day after onset of parotitis. No repeat audiology testing was performed.

#### Patient C

On November 2, 2015, a man aged 21 years developed left facial pain and swelling and tested positive for mumps by PCR on a buccal swab specimen. Twenty-two days after onset of symptoms, he was treated at an emergency department for neck stiffness, fever, and tachycardia. A lumbar puncture was performed, and he was empirically treated for meningitis with acyclovir and ceftriaxone. Volume of cerebrospinal fluid was inadequate for performing PCR testing for mumps, but Gram stain and bacterial culture were negative, and analysis was consistent with viral meningitis (40 lymphocytes/mm<sup>3</sup>, 60 mg/dL of protein, and 67 mg/dL of glucose). Because the onset of mumps-related meningitis has been described as ranging from 4 days before the onset of parotitis until 3 weeks after (2), the patient's viral meningitis diagnosis was attributed to mumps. He was discharged with recommendations for symptomatic care, and meningeal symptoms resolved within 1 week.

Complications of mumps have been reported less frequently since licensure and widespread use of mumps-containing vaccines. However, this case series demonstrates that complications still occur, even in persons who have received the recommended 2 doses of measles-mumps-rubella vaccine. In

addition, complications can occur at varying times throughout the course of the illness and in the absence of parotitis (2,3). Health officials should remain vigilant for these complications and their relation to mumps, and when mumps is suspected, conduct PCR testing on a buccal swab specimen and serology on a serum specimen (4,5).

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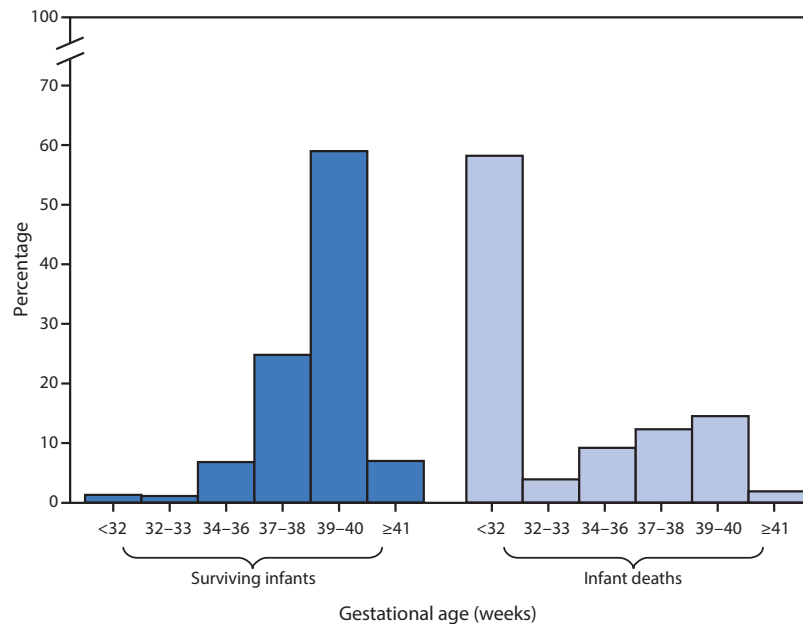
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## QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

### Percentage Distribution of Gestational Age in Weeks for Infants Who Survived to Age 1 Year and Infants Who Died Before Age 1 Year — National Vital Statistics System, United States, 2014



Infants who do not survive the first year of life are more likely to be born at earlier gestational ages. In 2014, 66% of infants who survived to age 1 year were delivered at full term or later ( $\geq 39$  completed weeks) compared with 16% of infants who died before reaching age 1 year. Fifty-eight percent of infants who died before age 1 year were delivered at  $< 32$  weeks gestation compared with only 1% of infants who survived to age 1 year.

Source: National Vital Statistics System, Linked Birth and Infant Death Data. <https://www.cdc.gov/nchs/nvss/linked-birth.htm>.

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