Multiple Modes of Hepatitis A Virus Transmission among Methamphetamine Users

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Methamphetamine users are at increased risk of hepatitis A, but modes of transmission are unclear. The authors conducted a case-control study among methamphetamine users during an outbreak in Iowa in 1997. Twenty-eight reported, laboratory-confirmed, hepatitis A cases did not differ from 18 susceptible controls with respect to age, sex, or number of doses used. When compared with controls in multivariate analysis, case-patients were more likely to have injected methamphetamine (odds ratio (OR) = 5.5, 95% confidence interval (CI): 1.1, 27), to have used methamphetamine with another case-patient (OR = 6.2, 95% CI: 0.95, 41), and to have used brown methamphetamine (OR = 5.5, 95% CI: 0.51, 59). Receptive needle sharing was reported by 10 of the 20 case-patients who injected. Methamphetamine use with another case-patient was also associated with hepatitis A in an analysis restricted to noninjectors (OR = 17, 95% CI: 1.0, 630). During this outbreak, hepatitis A may have been transmitted from person to person among methamphetamine users through the fecal-oral and the percutaneous routes. Methamphetamine users should be vaccinated against hepatitis A and should be given immune globulin if they used methamphetamine with a case-patient in the last 2 weeks. Persons who intend to continue using methamphetamine should be advised about safer practices. Am J Epidemiol 2000;152:186–92.

case-control studies; disease outbreaks; epidemiologic methods; equipment contamination; hepatitis A; methamphetamine; substance abuse, intravenous

Hepatitis A virus is usually transmitted though the fecal-oral route and occasionally transmitted through the percutaneous route (1, 2). Although rarely fatal, acute hepatitis A is associated with substantial morbidity among adults, and it remains one of the most frequently reported vaccine-preventable diseases in the United States. In 1997, 30,021 cases were reported to the Centers for Disease Control and Prevention (CDC)’s National Notifiable Disease Surveillance System (3). After correction for underreporting, it is estimated that approximately 80,000 cases occurred (CDC, unpublished data).

Most hepatitis A cases occur during communitywide outbreaks that are often prolonged and difficult to control (1). In published reports of several of these outbreaks (4–6), a high proportion of case-patients reported use of illicit drugs, mostly injected. An association between hepatitis A and injecting drug use has also been reported from other countries (7–12). In the United States, methamphetamine, a drug also known as “speed,” “crystal,” “crank,” and “ice,” which can be swallowed, smoked, snorted, or injected, has been commonly reported to be associated with hepatitis A outbreaks (4, 5, 13).

Among illicit drug users, hepatitis A virus could be transmitted from person to person or acquired during common source outbreaks caused by fecally contaminated batches of drug (14). The route of transmission from person to person could be fecal-oral, facilitated by poor hygienic practices (4). Among injectors, transmission could also occur through the percutaneous route (2, 15). Identification of modes of transmission among illicit drug users would help in formulating recommendations for the prevention of hepatitis A in this population.

Between December 1, 1996, and July 31, 1997, 158 hepatitis A cases were reported in Marion, Monroe, Polk, and Wapello counties in Iowa, compared with two cases during the same period in 1995 and 1996. Similar to an outbreak that occurred the previous year in western Iowa, a high proportion of cases (26.1 percent) occurred among persons who reported injecting drugs, mostly methamphetamine (13). On June 4, 1997, an investigation was initiated to identify modes of hepatitis A virus transmission among persons using methamphetamine and to formulate recommendations to control the outbreak.
MATERIALS AND METHODS

Descriptive epidemiology

A hepatitis A case was defined as an acute illness clinically compatible with hepatitis A, with laboratory confirmation (detectable immunoglobulin M antibodies to hepatitis A virus) or an epidemiologic link to a laboratory-confirmed case (16). Local health departments collected information on case-patients who could be interviewed using the Viral Hepatitis Surveillance Program questionnaire. Incidence rates were calculated using 1990 population denominators from the US Census Bureau.

Pilot study among case-patients

A convenience sample of case-patients was enrolled in a pilot study to generate hypotheses about potential modes of transmission. Data were collected on a questionnaire containing both open-ended and close-ended questions about demographic characteristics, use of health care and social services, methamphetamine use, practices associated with methamphetamine consumption, paraphernalia use, and injection practices.

Case-control study

A case-control study was conducted to identify risk factors for hepatitis A among residents of Polk and Wapello counties. Reported laboratory-confirmed hepatitis A cases with onset dates between April 1 and July 24, 1997, and a reported methamphetamine use in the 2–6 weeks prior to onset were included in the study. Cases reported before June 15, 1997 (date of the initiation of the case-control study), were included retrospectively while cases reported from June 15 were included prospectively.

Of the 13 case-patients who used methamphetamine included in the pilot study, 10 (76.9 percent) reported using the emergency room more than any other health care facility. Potential controls were therefore identified prospectively from patients seeking medical care at two emergency rooms in the area (one in each county) and at a public clinic adjacent to the emergency room of Polk County. During the study period, the triage nurse in each facility asked all patients between 15 and 45 years of age about methamphetamine use in the last 12 months. Patients who reported methamphetamine use during this time period were identified as potential controls.

The referent exposure period for cases was defined as the 2–6 weeks before illness onset, the incubation period of hepatitis A virus infection. Referent exposure periods of the controls were 4-week time periods chosen to match the distribution of the cases’ referent exposure periods.

Trained interviewers administered a questionnaire directly to case-patients and potential controls to collect data on demographic characteristics; education; living conditions; use of social and public assistance services; exposure to a day care center; contact with a hepatitis A case-patient; international travel; sexual activity; history of substance abuse; behaviors associated with methamphetamine usage; type, quantity, and route of administration of methamphetamine; and injection practices. Potential controls were asked to give a blood sample for serologic testing.

Potential controls who did not report methamphetamine usage during the referent exposure period or who were positive or not tested for total antibody to hepatitis A virus were excluded from the study.

Associations between potential exposures and hepatitis A were measured by the calculation of odds ratios. The Kruskall-Wallis nonparametric test was used to test the significance of the differences for quantitative variables, and confidence intervals for odds ratios were calculated using the exact method (crude analyses) or the method of Robins, Greenland, and Breslow (adjusted analyses) using Epi-Info, version 6 (17). Variables for which the p value in stratified analysis was 0.2 or less were tested in a stepwise forward logistic regression model using EGRET software (SERC, Seattle, Washington). For study participants who reported methamphetamine injection during the referent exposure period, the association between the circumstances of the injection events and hepatitis A was measured using generalized estimating equations (18), using SAS software (SAS Institute, Cary, North Carolina). For this purpose, the data were transposed to represent repeated measures on individuals where each injection was considered as an incident without an underlying distribution.

RESULTS

Descriptive epidemiology

A total of 158 cases were reported in the four counties between December 1, 1996, and July 31, 1997 (incidence rate, 39/100,000 population), with the number of reported cases increasing between January and June, 1997 (figure 1). The majority of cases (n = 137; 87 percent) were reported from Polk and Wapello counties.

The 15- to 44-year age group accounted for the majority of cases (82.3 percent) and had the highest attack rate (table 1). The attack rate was higher in males than in females (table 1). Substantial proportions of case-patients reported contact with another hepatitis A patient (33.3 percent) and injecting drug use (26.1 percent). Of male case-patients, 25.9 percent reported homosexual or bisexual preference. Among case-patients for whom the information was available, 9.7 percent reported both injecting drugs and homosexual or bisexual preference.

Pilot study among case-patients

A total of 13 case-patients who reported methamphetamine use were interviewed for the pilot study. Case-patients reported that both imported and locally produced methamphetamine types were available. While the imported methamphetamine was white or off-white in color, local producers dyed their methamphetamine with various other colors as a way of tracking their product. Numerous local production laboratories were located in a variety of settings under poor sanitary conditions, includ-
ing homes, motel rooms, trucks, and abandoned shelters in rural areas.

While methamphetamine can be swallowed, snorted, or smoked, a high proportion of the case-patients (n = 11; 84.6 percent) who used it reported injecting it. A common setting for injecting methamphetamine was a small group gathering (two or three people), with one person preparing for the others. Hand washing before preparation was reported to be uncommon. First, methamphetamine was diluted with tap water in a drug-mixing container (a spoon or a cup) and stirred with the tip of a needle. No heating was needed because methamphetamine dissolves well in water. Second, the solution was aspirated with the syringe through a cigarette filter (a “cotton”). Sharing of drug-mixing containers or “cottons” among patients was common. Eight (80 percent) of the 10 injecting case-patients for whom the information was available reported buying their syringes and needles without prescription from pharmacies. The same proportion of these case-patients (80 percent) reported reusing needles and syringes for themselves, but none reported sharing syringes and needles with other people.

Eating food, sharing a bowl of ice cubes, or having sex while gathered to use methamphetamine was reported by 20 percent, 33 percent, and 30 percent of case-patients who used methamphetamine, respectively. Drinking sodas while using methamphetamine was reported by 80 percent of case-patients. Two case-patients reported believing that brown methamphetamine was the source of their infection.

**Case-control study**

Of the 95 patients reported with laboratory-confirmed hepatitis A with onset dates after April 1, 1997, 19 could not be located, one refused to participate, and 75 (78.9 percent) were interviewed. Of the 75 interviewed, 40 (54.1 percent) reported methamphetamine use in the last 12 months, and 28 (37.3 percent) who reported methamphetamine use during the referent exposure period were included in the case-
control study. Of the 62 potential controls who had used methamphetamine in the last 12 months, 34 (54.8 percent) reported methamphetamine use during the referent exposure period. Serum was available from 24 (70.6 percent) of these 34 controls. Of these, 18 (75 percent) were negative for anti-hepatitis A virus and were included in the analysis.

All 18 controls and 14 (50.0 percent) cases were recruited prospectively, while the remaining 14 cases were included retrospectively. The proportion of case-patients who had sought medical care in the emergency room for their hepatitis symptoms did not differ from the proportion of controls recruited in the emergency room (table 2). Cases and controls did not differ with respect to age, sex, county of residence, and many indicators of socioeconomic status; however, case-patients were more likely than controls to have less than 12 years of schooling and to receive food stamps. A majority of case-patients and controls had attended a drug treatment center (table 2).

The majority of case-patients (74.1 percent) had injected methamphetamine during the referent exposure period, compared with 22.2 percent of controls (odds ratio (OR) = 10.0, 95 percent confidence interval (CI): 2.1, 54; table 2). This association was still observed when adjusted for the number of years of methamphetamine use (adjusted OR = 9.7, 95 percent CI: 2.3, 41) or for the number of methamphetamine doses used during the referent exposure period (adjusted OR = 26, 95 percent CI: 2.4, 280).

In an analysis restricted to the 24 study participants who reported injecting methamphetamine during the referent exposure period, there was no difference in the median number of methamphetamine doses injected (48 vs. 47, \( p = 0.84 \)). Ten of the 20 case-patients who had injected had used needles or syringes previously used by others (i.e., receptive needle sharing) versus none of the four injecting controls (OR undefined, exact lower limit of the CI: 0.51). When injection events of cases and controls were compared, injection events of cases were less likely to have occurred with a new syringe and needle (OR = 0.16, 95 percent CI: 0.01, 0.7). No other characteristics of injection events differed between cases and controls.

### Table 2. Selected characteristics of hepatitis A cases and controls, methamphetamine users, Polk and Wapello counties, Iowa, 1997

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 of 28 cases (53.6%)</td>
<td></td>
<td></td>
<td>0.73</td>
<td>0.18, 2.8</td>
<td></td>
</tr>
<tr>
<td>Age ≥30 years</td>
<td></td>
<td></td>
<td>1.9</td>
<td>0.50, 7.6</td>
<td></td>
</tr>
<tr>
<td>Household size &gt;3 persons</td>
<td></td>
<td></td>
<td>1.5</td>
<td>0.38, 6.3</td>
<td></td>
</tr>
<tr>
<td>Polk County residence</td>
<td></td>
<td></td>
<td>0.73</td>
<td>0.10, 4.1</td>
<td></td>
</tr>
<tr>
<td>Recruitment in the emergency room†</td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.20, 4.3</td>
<td></td>
</tr>
<tr>
<td>Having more than 12 years of schooling</td>
<td></td>
<td></td>
<td>0.21</td>
<td>0.0, 1.0</td>
<td></td>
</tr>
<tr>
<td>Receiving unemployment benefit</td>
<td></td>
<td></td>
<td>—‡</td>
<td>—</td>
<td></td>
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<tr>
<td>Being medically insured</td>
<td></td>
<td></td>
<td>1.3</td>
<td>0.0, 8.1</td>
<td></td>
</tr>
<tr>
<td>Being Medicaid eligible</td>
<td></td>
<td></td>
<td>0.86</td>
<td>—</td>
<td></td>
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<tr>
<td>WIC* voucher recipient in the household</td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.10, 13</td>
<td></td>
</tr>
<tr>
<td>Receiving food stamps</td>
<td></td>
<td></td>
<td>1.6</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Using methamphetamine</td>
<td></td>
<td></td>
<td>1.39</td>
<td>0.39, 6.4</td>
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</tr>
<tr>
<td>Using methamphetamine more than 5 years</td>
<td></td>
<td></td>
<td>1.2</td>
<td>0.30, 4.7</td>
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<tr>
<td>Household contact with a hepatitis A case§</td>
<td></td>
<td></td>
<td>2.2</td>
<td>0.33, 24</td>
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</tr>
<tr>
<td>Sexual contact with a hepatitis A case§</td>
<td></td>
<td></td>
<td>—</td>
<td>0.27, —</td>
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<tr>
<td>Sharing food with a hepatitis A case§</td>
<td></td>
<td></td>
<td>5.9</td>
<td>0.63, 280</td>
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<tr>
<td>Using having ≥20 methamphetamine doses§</td>
<td></td>
<td></td>
<td>1.8</td>
<td>0.47, 7.3</td>
<td></td>
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<tr>
<td>Methamphetamine injection§</td>
<td></td>
<td></td>
<td>10.0</td>
<td>2.1, 54</td>
<td></td>
</tr>
<tr>
<td>Methamphetamine partner with hepatitis A§</td>
<td></td>
<td></td>
<td>10.0</td>
<td>2.1, 54</td>
<td></td>
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<tr>
<td>Using brown methamphetamine§</td>
<td></td>
<td></td>
<td>11.8</td>
<td>1.3, 540</td>
<td></td>
</tr>
<tr>
<td>Using drinks with other methamphetamine users§</td>
<td></td>
<td></td>
<td>2.1</td>
<td>0.50, 8.9</td>
<td></td>
</tr>
<tr>
<td>Using drinks with other methamphetamine users§</td>
<td></td>
<td></td>
<td>3.0</td>
<td>0.70, 15.5</td>
<td></td>
</tr>
<tr>
<td>Using ice cubes with other methamphetamine users§</td>
<td></td>
<td></td>
<td>1.3</td>
<td>0.0, 8.0</td>
<td></td>
</tr>
<tr>
<td>Using sex with other methamphetamine users§</td>
<td></td>
<td></td>
<td>0.6</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* CI, confidence interval; WIC, Women, Infants, and Children clinic.
† Site where health care was sought on hepatitis onset for cases and site of recruitment for controls.
‡ —, undefined.
§ During the referent exposure period.
Case-patients were more likely than controls to have used methamphetamine during the referent exposure period with someone who currently had hepatitis A. This association persisted when the analysis was restricted to study participants who had not injected during that time (OR = 17, 95 percent CI: 1.0, 920) or to study participants who did not have household or sexual contact with a case-patient (OR = undefined, lower limit of the 95 percent CI: 1.1).

Case-patients were more likely than controls to have used brown methamphetamine (table 2), even when adjusted for recent methamphetamine use with a case-patient (adjusted OR = 9.5, 95 percent CI: 0.96, 95). Illness onset dates for case-patients who reported use of brown methamphetamine were clustered around the 19th and 20th week of 1997 (figure 2). Use of other specific colors of methamphetamine was not associated with illness.

In multivariate analysis, injecting methamphetamine and having used methamphetamine with a case-patient were the only two factors significantly associated with hepatitis A (OR = 5.5, 95 percent CI: 1.1, 27 and OR = 6.2, 95 percent CI: 0.95, 41, respectively). After adjustment for these two risk factors, the odds ratio measuring the association between use of brown methamphetamine and illness decreased, and its 95 percent confidence interval included one (OR = 5.5, 95 percent CI: 0.51, 59).

**DISCUSSION**

Although outbreaks of hepatitis A associated with illicit drug use are common in the United States, modes of transmission among drug users have not been determined. During this outbreak, 54.1 percent of the case-patients screened for the case-control study reported methamphetamine use. This high proportion suggested that methamphetamine users were at increased risk of hepatitis A and provided an opportunity to study modes of hepatitis A virus transmission among methamphetamine users. The results of the analysis suggest that hepatitis A virus was spread during this outbreak through various routes among persons who used methamphetamine together, and that a small common source cluster associated with a batch of methamphetamine may have occurred.

During communitywide outbreaks of hepatitis A, transmission by the fecal-oral route between household or sexual contacts is a major mode of transmission (1). In addition, facilitation of person-to-person transmission of hepatitis A virus via the fecal-oral route by social and environmental conditions associated with lower socioeconomic status has been hypothesized (4, 19, 20). Compared with controls, case-patients more frequently reported household or sexual contact with a case-patient, although these associations were not statistically significant, and by some indicators (e.g., level of education and receiving food stamps), case-patients were of lower socioeconomic status than controls. Using methamphetamine with a case-patient was associated with an increased risk of hepatitis A, even among users who did not report injections during the referent exposure period. This indicates that transmission by the fecal-oral route may also occur when people gather to swallow, smoke, or snort methamphetamine together.

Percutaneous transmission of hepatitis A virus has been reported among persons who received contaminated clotting factor concentrates or blood units (2, 21, 22). This mode of transmission has also been hypothesized to occur among injecting drug users who share needles (2), but it has been...
considered to be uncommon because of the short duration of the viremia during hepatitis A virus infection. In this study, 74.1 percent of the case-patients reported injecting methamphetamine during the referent exposure period, and there was a strong association between hepatitis A and methamphetamine injection compared with other routes of administration. In addition, injection events of cases were less likely to have occurred with a new syringe and needle. Thus, for the 10 injectors (50 percent) who reported receptive needle sharing, the source of the percutaneous transmission may have been contamination of the syringe or the needle by the blood of a viremic patient. For the 10 injectors (50 percent) who did not report receptive needle sharing, this source is unlikely. Five of these case-patients reported sharing drug-mixing containers, and five reported sharing of “cottons.” These practices, referred to as “indirect sharing” (23), are more common among injecting drug users than receptive needle sharing and are suspected to lead to transmission of bloodborne pathogens (24–26). In addition, in the absence of hand washing, sharing of drug-mixing containers and “cottons” may have facilitated fecal contamination of methamphetamine during the manipulation that preceded injection.

There was an association in univariate analysis between using brown methamphetamine and hepatitis A, and the onset dates of case-patients who reported using this product were clustered. These findings suggested that a small common source outbreak associated with a batch of brown methamphetamine contaminated with hepatitis A virus may have occurred. However, in multivariate analysis, this association was not statistically significant. One published report from Sweden is compatible with the occurrence of such a cluster (14). No information was available on the manufacturing process used for the brown methamphetamine, and no information was available to suggest a relation between the brown color of the methamphetamine and a hypothetical fecal contamination. An infected manufacturer could have contaminated a batch of methamphetamine through manipulation of the product during packing or distribution, after the manufacturing process, which would have inactivated hepatitis A virus. However, if a common source cluster associated with brown methamphetamine indeed occurred, the distribution of cases over time and the limited number of case-patients exposed to brown methamphetamine indicate that exposure to this contaminated drug could not have accounted for the majority of cases during the outbreak.

In addition to hepatitis A virus infection, injecting drug users are also at increased risk for infection with human immunodeficiency, hepatitis B, hepatitis C, and hepatitis D viruses (27, 28). Vaccines effective against hepatitis A and hepatitis B are available. The Advisory Committee on Immunization Practices has recommended hepatitis B vaccination for injecting drug users since 1982 and, since 1996, hepatitis A vaccination for users of illicit drugs (1, 29, 30). However, vaccination programs targeting these populations have encountered barriers, including the cost of vaccine and the difficulties in accessing injecting drug users (31, 32). The high proportion of case-patients and controls who had ever attended a drug treatment center in our study suggests that these facilities could be access points to methamphetamine users for long-term vaccination programs.

Our study had limitations. First, because of our small sample size, we had limited statistical power to find statistically significant associations between certain exposures, including brown methamphetamine and household contact with a case-patient. Second, the small number of susceptible controls who had injected methamphetamine limited our ability to study specific risk factors among injectors, such as different injection practices. Third, because controls were recruited among patients visiting certain health care facilities, the control group may not have been representative of all methamphetamine users in the study area. However, cases and controls were recruited from similar health care facilities, and their similarity with respect to demographic characteristics, total number of methamphetamine doses used, and duration of methamphetamine use suggests that they were recruited from the same secondary study base (33). Fourth, because they had hepatitis A, case-patients might have been more likely to recall using methamphetamine with someone who had hepatitis A at the time that they were likely to have been infected. Finally, potential controls who used methamphetamine may have denied it during the interview by the triage nurse. However, case-patients may also have denied methamphetamine use, and the failure to report methamphetamine use probably affected the recruitment of cases and controls in a nondifferential way, so that case-patients and controls were comparable in that they all used methamphetamine use.

In addition to the recommended vaccination of illicit drug users against hepatitis A (1, 13), other measures to prevent hepatitis A virus transmission among methamphetamine users can be proposed. Since transmission occurred from person to person among people who used drugs together, consideration should be given to recommending immune globulin in addition to hepatitis A vaccine for people who used methamphetamine in the previous 2 weeks with hepatitis A patients. Persons who intend to continue using methamphetamine should also be educated about the risk of hepatitis A associated with using drugs with other people. Hands should be washed before drug preparation, and drug-mixing containers, “cottons,” syringes, needles, and other injection works should not be shared. Although the effectiveness of needle exchange programs is unclear for the prevention of hepatitis B and C virus infection, they might provide useful settings for provision of safe equipment and education of injecting drug users about the dangers associated with direct and indirect sharing (26).

In many communitywide outbreaks, a high proportion of case-patients report illicit use of drugs (13). During such outbreaks, reducing hepatitis A virus transmission among drug users through behavior modification and vaccination early in the outbreak may prevent the extension to broader segments of the community (34). Routine vaccination of methamphetamine users may also help to prevent outbreaks and reduce the overall burden of hepatitis A. However, it is unlikely that sustained nationwide reductions in hepatitis A incidence will occur through short-term programs to control individual communitywide epidemics or vaccination of selected high-risk groups. The initiation of programs of rou-
tine vaccination of young children in states and communities with consistently elevated rates of hepatitis A as recommended in 1999 by the Advisory Committee on Immunization Practices will create a high level of population immunity that should produce sustained reductions of hepatitis A incidence over time (30).

ACKNOWLEDGMENTS

The authors thank Dean Austin, Karen B. Buechler, Dr. Russ Currier, Judith H. Goddard, and Janet Swick (Iowa Department of Public Health); Sue Boley, Pat Breckenridge, Janice Doggett, Marilyn Hart, Dr. Douglas Lesueur, and Chris Morphew (Polk County Department of Public Health); Lynelle Diers (Wapello County Department of Public Health); Kathy Kohler and Catherine Paulson (Broadlawood Medical Center, Des Moines); Dr. Randall Dielman and Dr. Edward Thompson (Ottumwa Regional Health Center, Medical Center, Des Moines); Kathy Hohler and Catherine Paulson (Broadlawood Medical Center, Des Moines); Dr. Richard Van Beneden (Centers for Disease Control and Prevention).

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