A MULTISTATE, FOODBORNE OUTBREAK OF HEPATITIS A

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ABSTRACT

Background We investigated a large, foodborne outbreak of hepatitis A that occurred in February and March 1997 in Michigan and then extended the investigation to determine whether it was related to sporadic cases reported in other states among persons who had consumed frozen strawberries, the food suspected of causing the outbreak.

Methods The cases of hepatitis A were serologically confirmed. Epidemiologic studies were conducted in the two states with sufficient numbers of cases, Michigan and Maine. Hepatitis A virus RNA detected in clinical specimens was sequenced to determine the relatedness of the virus from outbreak-related cases and other cases.

Results A total of 213 cases of hepatitis A were reported from 23 schools in Michigan and 29 cases from 13 schools in Maine, with the median rate of attack ranging from 0.2 to 14 percent. Hepatitis A was associated with the consumption of frozen strawberries in a case–control study (odds ratio for the disease, 8.3; 95 percent confidence interval, 2.1 to 33) and a cohort study (relative risk of infection, 7.5; 95 percent confidence interval, 1.1 to 53) in Michigan and in a case–control study in Maine (odds ratio for infection, 3.4; 95 percent confidence interval, 1.0 to 14). The genetic sequences of viruses from 126 patients in Michigan and Maine were identical to one another and to those from 5 patients in Wisconsin and 7 patients in Arizona, all of whom attended schools where frozen strawberries from the same processor had been served, and to those in 2 patients from Louisiana, both of whom had consumed commercially prepared products containing frozen strawberries from the same processor.

Conclusions We describe a large outbreak of hepatitis A in Michigan that was associated with the consumption of frozen strawberries. We found apparently sporadic cases in other states that could be linked to the same source by viral genetic analysis. (N Engl J Med 1999;340:595-602.)

SURVEILLANCE data suggest that foodborne outbreaks account for less than 5 percent of reported cases of hepatitis A in the United States.[1] Most outbreaks occur in a single food establishment and result from contamination of uncooked or previously cooked food by an infected food handler.[2] Occasionally, more widespread foodborne outbreaks are associated with uncooked or fresh food contaminated before distribution, including shellfish,[3,4] lettuce,[5] and frozen raspberries and strawberries.[6-9] In approximately 40 percent of reported cases of hepatitis A, the source of infection cannot be identified.[1] Some of these cases may be caused by the ingestion of contaminated food, but small clusters of foodborne disease are unlikely to be recognized with current methods of investigation.

METHODS

Background

From February 24 to March 26, 1997, 126 cases of hepatitis A were reported in Calhoun and Saginaw counties in Michigan. Most cases were among schoolchildren and school employees. No cases had been reported in these counties during 1996.

From January 1 to March 31, 1997, 19 cases of hepatitis A were reported to the Maine State Bureau of Health. Seventeen of these cases occurred among schoolchildren or employees in eight schools throughout the state. In comparison, 28 cases had been reported in Maine in 1996.

Epidemiologic Studies

A case of hepatitis A was defined as an acute illness with clinical symptoms compatible with the disease in association with the presence of IgM antibody to the hepatitis A virus (HAV). Cases were identified on the basis of reports by laboratories and physicians. Cases for which there was no history of household or close contact with a person with hepatitis A during the 50 days before the onset of illness were considered primary.

Calhoun County, Michigan

In Calhoun County, Michigan, primary cases reported from February 24 to March 26, 1997, among schoolchildren and employees of the school district with the highest rate of attack of hepatitis A were eligible for enrollment in a case–control study. In each school, unaffected control subjects were randomly selected from the affected children's classrooms or from among other staff members; in each case, the numbers of control subjects equaled the numbers of patients. Information was collected regarding how often a subject ate a school lunch and which items were eaten during 7 school days, beginning 32 days before the peak incidence of disease. Patients and control subjects were compared with respect to the reported frequency with which they ate school lunch, whether they ate school lunch on specific days, and whether they ate specific foods.

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Saginaw County, Michigan

In Saginaw County, Michigan, all children in the fifth grade or higher and all staff members of the one school where cases of hepatitis A were reported were included in a retrospective cohort study. Information was collected regarding food served at the school during 10 school days, beginning 35 days before the day of the peak incidence of disease.

Maine

In Maine, a preliminary study was conducted in the schools in which primary cases of hepatitis A were reported through April 4, 1997, with all unaffected classmates used as controls. A second case–control study included all students or staff members with primary cases in whom the onset of symptoms began between January 1 and May 15, 1997, and who had not traveled outside Maine in the 50 days before the onset of symptoms. Four control subjects were matched to each patient according to classroom and the frequency with which school lunch was eaten. All participants in each school answered a questionnaire about their use of the school cafeterias during 10 school days beginning 35 days before the onset of illness in the patient. Data from school-specific questionnaires were recoded according to the consumption of foods made with ingredients common to the various schools, and all sets of patients and controls were analyzed with the use of identical variables.

Other States

Sporadic cases of hepatitis A that were reported in other states among persons who had potentially consumed the food suspected of causing the outbreak in Michigan were investigated to rule out other sources of infection, but no controlled epidemiologic studies were conducted.

Distribution of Frozen Strawberries

After frozen strawberries were identified as a suspected source of the outbreak on March 28, 1997, we identified the source of the fruit, the lot numbers shipped to Michigan and Maine, and the growing fields. The processing plant and the growing fields were surveyed to identify conditions that might have contributed to contamination of the strawberries.

Amplification of Hepatitis A Virus RNA

The polymerase chain reaction (PCR) was used to amplify HAV RNA, and products suitable for sequence analysis in two genomic regions were available for 118 patients from Michigan, 10 patients from Maine, and 16 patients from other states who had eaten frozen strawberries from the same processor. Specimens from patients with hepatitis A in other locations were examined to determine the background frequency of the HAV sequence associated with the outbreak of infection. A total of 98 patients were tested who had no history of travel to areas in which HAV was endemic. Of these patients, 21 were living in Michigan counties other than Calhoun and Saginaw in 1997, 7 were living in northern California between 1995 and 1997, 16 were living in Salt Lake City in 1996, and 54 were living in one of six sentinel surveillance counties — Pierce County, Washington; Jefferson County, Alabama; Multnomah County, Oregon; Pinellas County, Florida; Denver County, Colorado; and Contra Costa County, California — from 1996 through 1997.[10] A second group consisted of 61 patients who had presumably acquired HAV infection in Mexico. Five of these patients were identified during a serologic survey in Mexico in 1995, and 56 were residents of one of the six sentinel counties who had traveled in Mexico during 1996 and 1997.

HAV RNA was amplified from serum or stool specimens by reverse-transcription PCR (RT-PCR) followed by second-round PCR (Table 1). The regions of the VP3–VP1 junction and the VP1–P2A junction of the HAV genome were amplified.[12] HAV RNA was extracted from serum specimens positive for IgM antibodies to HAV that were obtained during the acute phase of the disease with the use of methods for the detection of hepatitis C virus RNA.[13] Briefly, 100 μl of serum was mixed with Tri-pure Isolation Reagent (Boehringer Mannheim, Indianapolis) and incubated at room temperature, after which 200 μl of chloroform was added. The mixture was chilled on ice and centrifuged. RNA was precipitated from the aqueous phase by mixing the sample with an equal volume of ice-cold isopropanol and 40 μg of glycogen as a carrier (Boehringer Mannheim), followed by incubation and centrifugation at 4°C. The RNA pellet was washed once with 70 percent ethanol, dried, and resuspended in 10 μl of RNase-free water. RT-PCR and nested PCR were performed as described previously. Stool specimens were converted to 10 percent suspensions,[14] HAV was immunologically isolated from a 100-μl aliquot, RNA was released, and RT-PCR was performed as described previously.[15,16]

TABLE 1. OLIGONUCLEOTIDE PRIMERS USED FOR THE AMPLIFICATION OF HEPATITIS A VIRUS RNA FROM CLINICAL SPECIMENS.

LOCATION AND PRIMERS*	NUCLEOTIDE NO.†	NUCLEOTIDE SEQUENCE
VP3–VP1 junction (N terminal)		
External	2132	5′GTTAATGTTTATCTTTCAGCAAT3′
	2451	5′GATCTGATGTATGTCTGGATTCT3′
Internal	2172	5′GCTCCTCTTTATCATGCTATGGAT3′
	2415	5′CAGGAAATGTCTCAGGTACTTTCT3′
VP1–P2A junction (C terminal)		
External	2870	5′GACAGATTCTACATTTGGATTGGT3′
	3381	5′CCATTTCAAGAGTCCACACACT3′
Internal	2897	5′CTATTCAGATTGCAAATTACAAT3′
	3288	5′AACTTCATTATTTCATGCTCCT3′

*External primers were used for first-round amplification, and internal primers were used for second-round nested amplification.

†Nucleotides are numbered according to the wild-type hepatitis A virus HM 175 sequence.[11]

Nucleic Acid Sequencing

PCR products were purified with QuiQuick PCR purification kits (Qiagen, Chatsworth, Calif.), sequencing reactions were performed with the Prism Dye Terminator Cycle-Sequencing kit (Applied Biosystems, Foster City, Calif.), reaction products were purified (Centri Sep spin columns, Princeton Separations, Adelphia, N.J.), and electrophoresis was performed with an automated sequencer (model 373 or 377, Applied Biosystems) for 14 hours according to the manufacturer's instructions. Preliminary sequence analysis was performed with Applied Biosystems software, with further analysis performed with Wisconsin package 9.1 (Genetics Computer Group).[17]

Statistical Analysis

Odds ratios were used to measure the strength of the association in the case–control studies, and relative risks were used for the cohort study. Confidence intervals for the measures of association were calculated with Epi Info software, version 6,[18] with use of the exact method and the method of Robins, Breslow, and Greenland. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Epidemiologic Studies

From January 1 to May 18, 1997, 198 primary cases of hepatitis A were reported in Calhoun County,

Michigan, 21 primary cases were reported in Saginaw County, Michigan, and 39 primary cases were reported in Maine. Of these 258 cases, 242 (94 percent) occurred among students or school employees. In Michigan, 213 of the cases were reported from 23 schools in the two counties, with a median attack rate of 2.2 percent (range, 0.2 to 14 percent) in affected schools. The incidence peaked during the week starting March 3, 1997, and declined rapidly thereafter, suggesting a common source (Fig. 1), but no common event, food-handling facility, or water supply was identified to account for the distribution of cases. In contrast, 29 of the cases in Maine were reported from 13 schools scattered in 12 counties, with a median attack rate of 0.3 percent (range, 0.2 to 1.7 percent) and onset dates from January through May 1997.

Calhoun County, Michigan

Of the 78 patients with primary cases of hepatitis A who were reported by March 26, 1997, in the district in Calhoun County that was chosen for study, 65 (83 percent) were included in the case–control study, as were 65 control subjects. The median age of the participants was nine years, and 31 (48 percent) were male. Of the participants for whom information was available, 60 of 62 case patients (97 percent) ate food prepared at the school cafeteria at least once a week, as compared with 47 of 63 controls (75 percent; odds ratio, 10.0; 95 percent confidence interval, 2.2 to 94). Among those who ate at the school cafeteria at least once a week, eating the school lunch on February 11 or 12, 1997, was significantly associated with hepatitis A (respective odds ratios adjusted for the frequency of eating at school, 6.7 and 9.1; and respective 95 percent confidence intervals, 1.6 to 29 and 1.9 to 45). Among participants who ate the school lunch on these two days, consumption of the strawberry shortcake served on February 12 was the only factor significantly associated with hepatitis A (Table 2).

Saginaw County, Michigan

Of the 51 children in the fifth grade or higher and the 13 staff members in the study in Saginaw County, the median age was 13 years, 32 (50 percent) of the participants were male, 43 (67 percent) ate at school five days a week, and hepatitis A developed in 15 (23 percent). Of 43 foods examined, the strawberry shortcake served on February 10, 1997, was the only food significantly associated with hepatitis A (relative risk, 7.5; 95 percent confidence interval, 1.1 to 53).

Maine

The preliminary study in Maine included 14 case patients and 329 control subjects and indicated that the frequency of eating school lunch was associated

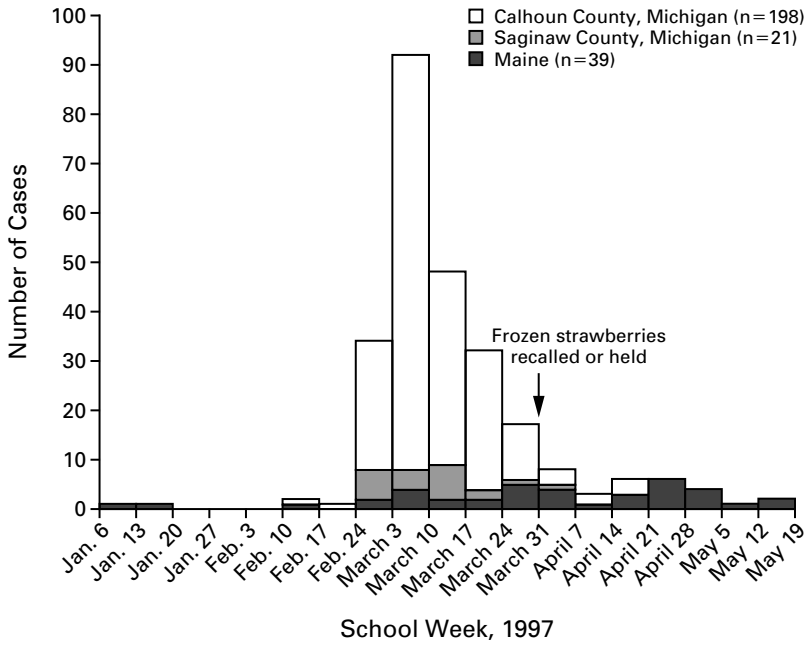

Figure 1. Serologically Confirmed Primary Cases of Hepatitis A in Maine and Calhoun and Saginaw Counties, Michigan, in 1997, According to the Week of Onset.

Frozen strawberries were identified as the suspected source of the outbreak, and the strawberries were withdrawn from use on March 28, 1997. Each school week starts on a Monday.

TABLE 2. CONSUMPTION OF FOOD ON FEBRUARY 11 AND 12, 1997, BY CASE PATIENTS AND CONTROL SUBJECTS WHO ATE AT SCHOOL ON THOSE DAYS IN CALHOUN COUNTY, MICHIGAN.

FOOD	CASE PATIENTS (N=52)	CONTROL SUBJECTS (N=32)	ODDS RATIO (95% CI)†
	no. who ate the food/ total no. (%)*		
Food served on February 11			
Soft taco	25/46 (54)	19/31 (61)	0.83 (0.3–2.3)
Baked potato and toppings	22/49 (45)	8/31 (26)	2.2 (0.77–6.5)
Lettuce	22/50 (44)	12/31 (39)	1.6 (0.57–4.6)
Seasoned rice	12/48 (25)	5/32 (16)	2.3 (0.64–8.3)
Chilled fruit	25/48 (52)	15/31 (48)	1.2 (0.36–3.8)
Sack lunch	4/49 (8)	4/31 (13)	1.1 (0.22–5.2)
Food served on February 12			
Toasted-cheese sandwich	24/51 (47)	13/30 (43)	1.3 (0.45–3.8)
Hot dog	22/50 (44)	13/31 (42)	1.3 (0.43–4.2)
Salad	22/48 (46)	8/30 (27)	3.5 (0.88–14)
Strawberry shortcake	40/52 (77)	11/31 (35)	8.3 (2.1–33)
Sack lunch	1/50 (2)	3/31 (10)	0.28 (0.03–2.3)

*The total number of study participants varied depending on whether or not they recalled eating the food.

†Odds ratios were adjusted for the classroom by the method of Robins, Breslow, and Greenland. CI denotes confidence interval.

with the likelihood of hepatitis A (chi-square for trend=4.5, P=0.03). Nineteen patients and 59 control subjects in 13 schools were included in the second case–control study. Eating items at the school cafeteria that contained frozen strawberries was the only factor associated with hepatitis A (Table 3).

Distribution of Frozen Strawberries

The strawberries implicated in this outbreak were grown in Mexico, processed and frozen in a California plant, and distributed through the Department of Agriculture for school-lunch programs and through distributors for commercial use. The processor shipped 13 lots of frozen strawberries processed on April 19, May 8, and May 9, 1996, to the Michigan school-lunch programs, and 9 lots processed on April 29, April 30, and May 3, 1996, to the Maine school-lunch programs. In each state, the sealed 30-lb (14-kg) containers of frozen strawberries were opened in the school kitchens, thawed, and incorporated into shortcakes or served in cups. The risk of illness associated with specific lot numbers could not be examined because no records were kept of which local kitchens received which lots.

TABLE 3. CONSUMPTION OF FOODS BY CASE PATIENTS AND CONTROL SUBJECTS IN 13 MAINE SCHOOLS, FEBRUARY–APRIL 1997.

FOOD	CASE PATIENTS (N=19)	CONTROL SUBJECTS (N=59)	MATCHED ODDS RATIO (95% CI)*
	no. eating food (%)		
Items containing frozen strawberries	13 (68)	26 (44)	3.4 (1.0–14)
Items containing ham	10 (53)	33 (56)	0.73 (0.24–2.3)
Hamburger	11 (58)	36 (61)	0.95 (0.28–3.4)
Items containing fresh celery	8 (42)	19 (32)	2.3 (0.58–11)
Items containing carrots	10 (53)	37 (63)	0.65 (0.17–2.7)
Fresh kiwi	4 (21)	9 (15)	0.94 (0.21–3.8)
Items containing peanut butter	1 (5)	14 (24)	0.24 (0.01–2.4)
Fresh pineapple	4 (21)	14 (24)	0.88 (0.19–3.7)

*CI denotes confidence interval.

Officials of the California Department of Health Services, the Food and Drug Administration (FDA), and the Department of Agriculture surveyed the plant where the strawberries had been processed, packed, and frozen. The investigation did not identify any record of illness consistent with hepatitis A among the employees during the time the strawberries were processed. Strawberries were carried on a conveyor belt, washed in a chlorine solution of 12 parts per million, mechanically sliced, combined with a sucrose solution, packed, and frozen. Hand contact with the berries was limited to the rejection of unacceptable berries as they passed on the conveyor belt.

Officials from the FDA also visited three of the four growing fields in Mexico. Water for drip irrigation was piped from a river and filtered in sand tanks. Few slit latrines were available for use by pickers. The only hand-washing facilities were on trucks

that circulated through the fields. The pickers did not wear gloves and removed the strawberry stems with their fingernails. No records were kept of illnesses among the pickers.

Follow-up

On March 28, 1997, the 13 lots of frozen strawberries shipped to Michigan were withdrawn from use nationwide (Fig. 1), and surveillance for hepatitis A was heightened.[19] Testing of strawberries from these lots for coliform bacteria was negative. Frozen strawberries from other lots processed in 1996 and distributed to school-lunch programs were put on hold on April 1 and then withdrawn after the final results of the investigation in Maine.

Of the 13 states that received frozen strawberries from the same processor for their school-lunch program, cases of hepatitis A in schools where the product had been served were reported in Tennessee (two cases), Arizona (nine cases), and Wisconsin (five cases). In Louisiana, four cases of hepatitis A were reported in persons who had eaten a commercially prepared drink ("smoothie") made from frozen strawberries that were traced back to the same processor.

Genetic Relatedness of Hepatitis A Virus

All PCR products from the patients in Calhoun and Saginaw counties had identical sequences in the two genomic regions examined (approximately 500 nucleotides). Eight of the 10 PCR products from Maine were identical to the 1 identified in Michigan. Only one of the two patients who had a different HAV RNA sequence attended a school where strawberries from the same processor had been served. However, it was not possible to determine whether the child had eaten the strawberries. Of the PCR products obtained from five patients in Wisconsin, two in Louisiana, seven in Arizona, and two in Tennessee, all but the one from the two patients in Tennessee were identical to the PCR product identified in Michigan (Fig. 2).

Viral sequences from 4 of the 98 background cases (4 percent) in patients who presumably acquired HAV infection in the United States were identical to the sequence involved in the outbreak. Two of these four cases were reported in Pierce County, Washington, in 1996, and one each was reported in Jefferson County, Alabama, in 1996 and Multnomah County, Oregon, in 1997 (Fig. 2). Of the 61 PCR products obtained from persons suspected of having acquired HAV infection in Mexico, none were related to the sequence involved in the outbreak.

DISCUSSION

Epidemiologic studies indicated that the outbreaks of hepatitis A in Michigan were associated with the consumption of frozen strawberries. No other common event or food could explain the distribution of cases. The investigation also indicated that the strawberries were contaminated before they were distributed, since the sealed containers were not opened before being used in the various school kitchens. The genetic identity of the HAV sequences from Michigan patients confirmed the epidemiologic evidence indicating that the outbreak originated from a common source.

In Maine, the association between hepatitis A and the consumption of frozen strawberries was suspected on the basis of the epidemiologic evidence, but in Arizona, Louisiana, Tennessee, and Wisconsin, there were too few reported cases to perform epidemiologic studies. The genetic sequencing of HAV from the patients in those states linked most cases to the Michigan outbreak. In contrast, in only a small proportion of the background cases of hepatitis A was the genomic sequence identical to the outbreak sequence.

Fecal contamination of foods that are not subsequently cooked is a potential source of HAV, and the virus remains infectious for long periods under a variety of environmental conditions, including freezing.[20] Consumption of frozen raspberries and strawberries has been associated with outbreaks of hepatitis A.[6-9] Fecal contamination of fresh fruit and vegetables could occur during irrigation, harvesting, sorting or shipping, and processing. Because the fruits implicated in this outbreak had been picked and processed approximately one year earlier, it was not possible to identify the point at which contamination occurred. The strawberries could have been contaminated by spray irrigation with contaminated water, but the plants in Mexico were drip irrigated. It is unlikely that contamination occurred during the short time the fruit was held in the fields and transported for processing. In the plant, workers did not handle the fruit, and fecal contamination of the water used to wash the fruit or to prepare the sucrose slurry would most likely have resulted in the detection of coliform bacteria in the final product. Contamination may have occurred during harvest, because of the poor toilet and hand-washing facilities in the fields and because of the hand contact required to remove the stem from each berry.

In a previous outbreak associated with the consumption of frozen strawberries, cases were restricted to one school in Georgia and one institution for the developmentally disabled in Montana, despite wide distribution of the implicated lot of berries.[9] In the current outbreak, large quantities of frozen strawberries were widely distributed to school-lunch programs and in retail products, but the number of cases attributable to the consumption of the uncooked product was limited. This finding suggests that during both outbreaks, contamination occurred at a low level and was not uniform. In addition, dur-

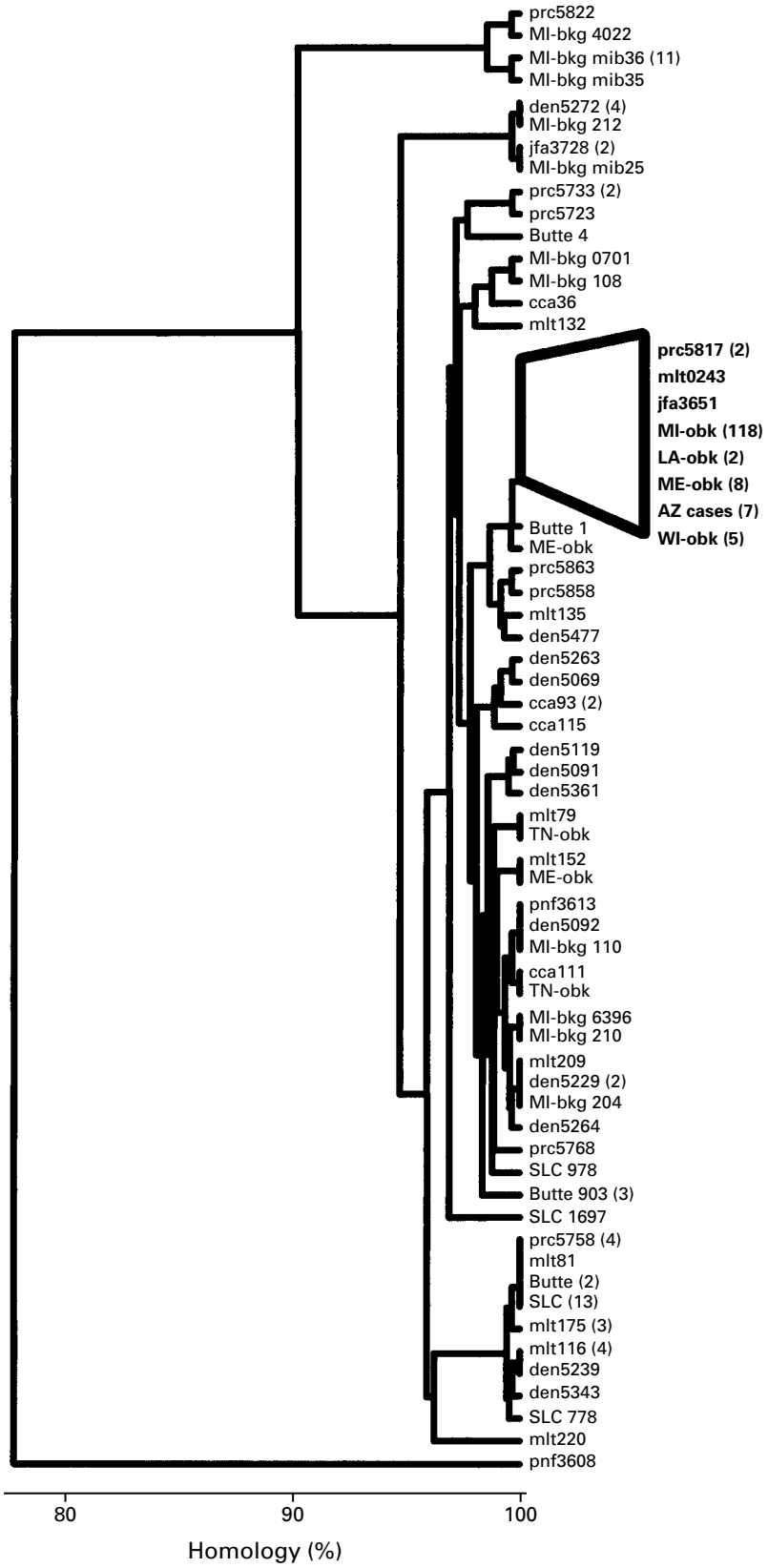

Figure 2. Genetic Relatedness of the Hepatitis A Virus Identified in the Outbreak and the Hepatitis A Virus Identified in Background Cases, as Shown by a Pairwise Comparison of 315 Nucleotide Sequences in the Region of the VP1–P2A Junction.

Cases related to the outbreak were identified in Michigan (MI-obk), Louisiana (LA-obk), Maine (ME-obk), Arizona (AZ cases), and Wisconsin (WI-obk). Background cases were identified in Michigan (MI-bkg), northern California (Butte), Salt Lake City (SLC), and the six sentinel surveillance counties — Pierce County, Washington (prc); Jefferson County, Alabama (jfa); Multnomah County, Oregon (mlt); Pinellas County, Florida (pnf); Denver County, Colorado (den); and Contra Costa County, California (cca). Sequences identical to the outbreak one are shown in boldface. The numbers of PCR products with identical sequences are shown in parentheses.

ing this outbreak, we were able to demonstrate with the use of genetic-sequencing analysis a link between apparently sporadic cases and the outbreak in Michigan.

With strain-characterization techniques it has been possible to identify bacterial pathogens such as salmonella,[21] *Listeria monocytogenes,*[22] and *Escherichia coli* O157:H7[23] as the cause of common-source foodborne outbreaks that mimicked sporadic cases of disease. A determination of the extent of foodborne outbreaks of hepatitis A in the United States will require the use of genetic sequencing to identify linkage between small clusters of disease. This task may be more difficult than for bacterial pathogens, because the incubation period of HAV infection is longer.

Foodborne hepatitis A will require specific prevention strategies until high levels of immunity are achieved in all age groups as a result of routine vaccination during childhood. Since there were several steps at which the strawberries could have been contaminated, a hazard analysis and critical-control-points program or other systematic quality-control programs are needed to prevent contamination during strawberry production.[24] Persons infected with HAV who handle food products that are not subsequently cooked can be a source of contamination, even if this handling occurs before retail distribution. Adequate toilet and hand-washing facilities must be provided to such workers, and proper hand-washing techniques taught. Current national food-safety activities are beginning to address the issues raised by this outbreak, including the need for a coordinated response by local, state, and federal agencies, as occurred during this episode.[25]

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APPENDIX

Other members of the National Hepatitis A Investigation Team included the following: *Calhoun County Department of Health* — J. Carver, D. Kalnins, P. Makoski, P. Somsel, S. Spieldenner, H. Thawnghmung, T. Wanner, R. Wetters, S. Williams; *Saginaw County Department of Health* — S. Gottlieb; *Michigan Department of Public Health* — J.V. Altamirano, W. Hall; *Michigan Department of Agriculture* — P. Kirkwood, J.D. Park, J. Tilden; *Maine State Bureau of Health* — G. Beckett, R. Pyler, E. Sidman, D. Williams; *Wisconsin Department of Public Health* — J.P. Davis, J.J. Kazmierczak, K.M. Labby, M.J. Trepka, D.L. Zernicke; *Louisiana Department of Public Health* — D.E. Berg, L. McFarland, S. Wilson; *Tennessee Department of Public Health* — A.S. Craig, V. Kegerise, C. Meade, D. Oliver, C. Riviere, R. Taylor, Jr.; *Arizona Department of Public Health* — R. England, C. Kioski, D. Vertz; *Centers for Disease Control and Prevention* — C. Arcari, M. Baron, K.S. Byun, F.-X. Gao, X. Han, S. Lambert, L. Li, E. Mast, K. Sabin, C. Whittier, G. Xia; *Food and Drug Administration* — M. Fow, L.A. Jackson, J. Kozick, E. Morrison, J. Oliver, F. Shank; *California Department of Health Services* — J. Farrar, S. Richardson, Jr., J. Waddell.

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