

ORIGINAL ARTICLE

An Outbreak of Hepatitis A Associated with Green Onions

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ABSTRACT

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BACKGROUND

In November 2003, a large hepatitis A outbreak was identified among patrons of a single Pennsylvania restaurant. We investigated the cause of the outbreak and factors that contributed to its unprecedented size.

METHODS

Demographic and clinical outcome data were collected from patients with laboratory confirmation of hepatitis A, and restaurant workers were tested for hepatitis A. A case-control study was conducted among patrons who dined at the restaurant between October 3 and October 6, 2003. Sequence analysis was performed on a 315-nucleotide region of viral RNA extracted from serum specimens.

RESULTS

Of 601 patients identified, 3 died; at least 124 were hospitalized. Of 425 patients who recalled a single dining date at the restaurant, 356 (84 percent) had dined there between October 3 and October 6. Among 240 patients in the case-control study, 218 had eaten mild salsa (91 percent), as compared with 45 of 130 controls (35 percent) (odds ratio, 19.6; 95 percent confidence interval, 11.0 to 34.9) for whom data were available. A total of 98 percent of patients and 58 percent of controls reported having eaten a menu item containing green onions (odds ratio, 33.3; 95 percent confidence interval, 12.8 to 86.2). All restaurant workers were tested, but none were identified who could have been the source of the outbreak. Sequences of hepatitis A virus from all 170 patients who were tested were identical. Mild salsa, which contained green onions grown in Mexico, was prepared in large batches at the restaurant and provided to all patrons.

CONCLUSIONS

Green onions that were apparently contaminated before arrival at the restaurant caused this unusually large foodborne outbreak of hepatitis A. The inclusion of contaminated green onions in large batches that were served to all customers contributed to the size of the outbreak.

HEPATITIS A VIRUS IS TRANSMITTED BY the fecal–oral route, either by direct contact with a person who is infected with hepatitis A virus or by ingestion of food or water that has been contaminated with the virus. Contaminated food is identified as the source of transmission for less than 5 percent of cases reported in the United States.^{1,2} Recognized outbreaks of foodborne hepatitis A typically occur when food is contaminated by an infected food-service worker at the point of sale or service.³

In the United States, the incidence of hepatitis A has declined to historically low levels during the past several years.² However, even when transmission within communities is greatly reduced and food is prepared according to recommended hygienic standards, foods imported from communities where transmission of hepatitis A virus remains common can be sources of exposure. Hepatitis A virus can remain infectious on environmental surfaces for at least one month,⁴ and outbreaks of hepatitis A caused by foods contaminated during harvesting or processing have been reported.^{5–10}

On November 1, 2003, an alert clinician informed the Pennsylvania Department of Health of several cases of hepatitis A among residents of Beaver County, Pennsylvania. Only one case of hepatitis A had been reported in the county during the preceding year. Six persons who were ill recalled eating in two separate groups at a restaurant in Beaver County (Restaurant A). On November 1, an inspector for the Pennsylvania Department of Agriculture found no sanitary violations at the restaurant but did learn of food workers who were ill. On November 2, the restaurant voluntarily closed. By November 7, 111 cases of hepatitis A had been reported among persons who had dined at Restaurant A.

METHODS

CASE DEFINITION AND CASE FINDING

We undertook a public health investigation to control a communicable disease outbreak; as such, our study was not subject to approval by an institutional review board. The case definition was an acute illness consistent with hepatitis A with onset occurring between October 1 and December 1, 2003. In addition, patients had to have consumed food at Restaurant A during the two to six weeks before the onset of illness (consistent with the incubation period for hepatitis A) and have serologic confirmation of acute infection with hepatitis A virus (IgM antibody to hepatitis A virus).

In Pennsylvania, cases were identified through the state's electronic disease-surveillance system. An interview was attempted with every person who was reported to have hepatitis A in Beaver County in 2003, as well as with any other Pennsylvania resident with hepatitis A who reported eating at Restaurant A. Case reports for Restaurant A patrons who had traveled through Beaver County but resided in other states were requested. Estimated attack rates were calculated by dividing the number of patients who reported eating at Restaurant A on specific dates in early October (when most patients reported exposure) by the total number of meals served on the same dates. Persons who reported eating at Restaurant A multiple times during the incubation period were excluded from the numerator, but meals consumed by persons who may have eaten at the restaurant multiple times during the incubation period were not excluded from the denominator.

CASE–CONTROL STUDY

Patients who were Pennsylvania residents, who ate at Restaurant A only once during the incubation period (15 to 50 days), and who ate at Restaurant A between October 3 and October 6 were eligible for inclusion in the study. Beginning on November 8, patients were enrolled and interviewed as soon as they were reported to Pennsylvania's surveillance system. Included in the case–control study were as many reported patients as could be interviewed during the following two weeks of the investigation.

Controls included meal companions of patients or persons who were identified through credit-card receipts as having dined at Restaurant A between October 3 and October 6. Controls were excluded if they reported having had symptoms of acute hepatitis A, had a history of hepatitis A, or had received hepatitis A vaccine.

Patients and controls were interviewed by telephone with the use of a standard questionnaire between November 8 and November 29; all participants were asked about foods they had eaten at Restaurant A. The Restaurant A menu included 121 items made from 102 ingredients.

ASSESSMENT OF EMPLOYEES AND THE ENVIRONMENT

To determine whether contamination by ill restaurant employees could have been the source of the outbreak, employees who worked at any time between September 1 and November 2, 2003, were tested for IgM antibody to hepatitis A virus. Infor-

mation about food purchasing, storage, and preparation practices was obtained during interviews with Restaurant A food suppliers, management, and food-service workers. Officials from the Food and Drug Administration (FDA) and the Pennsylvania Department of Agriculture obtained shipping records from Restaurant A and its suppliers.

NUCLEIC ACID SEQUENCING

Serum specimens were requested from diagnostic laboratories, and all the specimens that could be obtained were used to conduct hepatitis A virus RNA sequence analysis. RNA of hepatitis A virus was amplified, and a 315-nucleotide segment of the VP1–P2A junction was sequenced with the use of published methods.¹¹ Viral sequences from these cases were compared with others in the sequence surveillance database at the Centers for Disease Control and Prevention (CDC) and with sequences from other outbreaks of foodborne hepatitis A.

STATISTICAL ANALYSIS

All statistical analyses were performed with the use of SAS software, version 9.1. Odds ratios and 95 percent confidence intervals were calculated for each menu item and food ingredient. Logistic regression was used to generate adjusted odds ratios and 95 percent confidence intervals for use in examining the association between infection with hepatitis A virus and demographic factors, menu items, and food items. Three logistic-regression models were constructed, including one for menu items, a second for ingredients, and a third in which exposure to mild salsa was considered separately from other exposures to green onions. In all three full models, variables with P values of more than 0.05 were removed to produce the final models. The variables in each final model were examined for first-order interactions. With the use of likelihood-ratio tests, we compared all three final models to assess the goodness of fit.

RESULTS

DESCRIPTIVE EPIDEMIOLOGY

A total of 527 patients with hepatitis A were identified among Pennsylvania residents, including 13 who were employees of Restaurant A (Table 1). An additional 74 persons with hepatitis A who had eaten at Restaurant A during early October 2003 were reported to the CDC from seven other states.

The median age of the Pennsylvania patients was 34 years (range, <1 to 82 years), and 59 percent were female. Dates of the onset of illness ranged from October 15 through November 27, 2003 (Fig. 1). Three men and one woman (age range, 38 to 57 years) had fulminant hepatitis A, including three (0.5 percent) who died; one man survived after receiving a liver transplant. Two of these four patients had an underlying illness (inflammatory bowel disease or diabetes). Among 485 patients whose hospitalization status was known, 124 (26 percent) were hospitalized.

Of 425 patients who reported having eaten food at Restaurant A only once during the 15-to-50-day incubation period, 356 (84 percent) ate there between October 3 and October 6 (Table 1), and 284 (67 percent) dined at Restaurant A on either October 4 or October 5. An estimated 1986 meals were served at Restaurant A on these four days (estimated attack rate for eating at Restaurant A, 17.9 percent), including 764 on October 4 (attack rate, 25 percent) and 339 on October 5 (attack rate, 29 percent).

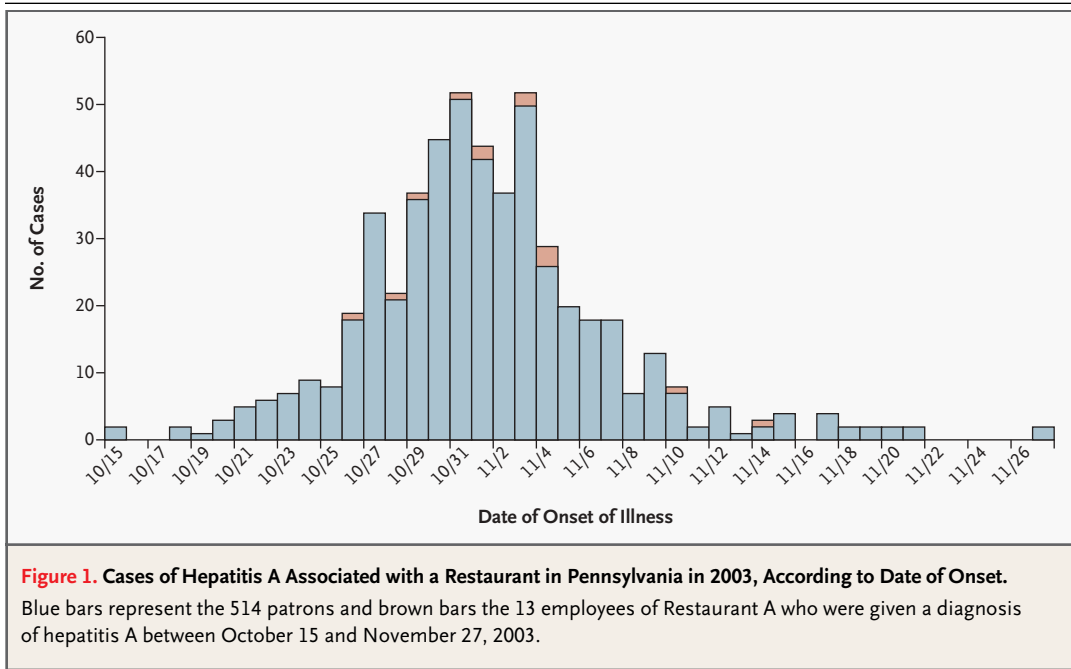
CASE-CONTROL STUDY

Participants in the case-control study included 240 patients with hepatitis A and 134 controls. Patients

Table 1. Demographic Characteristics, Clinical Characteristics, and Dates of Food Consumption in Restaurant A among Pennsylvania Residents with Hepatitis A, October and November 2003.*

| Variable | Value |
|---|--------------|
| Female sex — no./total no. (%) | 310/527 (59) |
| Age — yr | |
| Median | 34 |
| Range | <1–82 |
| Hospitalized for illness — no./total no. (%) | 124/485 (26) |
| Date of consumption of meal — no./total no. (%) | |
| Before October 3 | 23/425 (5) |
| October 3 | 20/425 (5) |
| October 4 | 187/425 (44) |
| October 5 | 97/425 (23) |
| October 6 | 52/425 (12) |
| After October 6 | 46/425 (11) |

* A total of 527 persons had hepatitis A, for 485 of whom hospitalization status was known; 425 patients reported eating at Restaurant A only once during the 15-to-50-day incubation period.



were significantly older than controls (median age, 34 years vs. 28 years; $P < 0.01$) but did not differ significantly according to sex.

Patients were significantly more likely than controls to have eaten at least one of five menu items—mild salsa, bar beverages, grilled chicken fajitas, ground beef burrito, and an enchilada platter (Table 2). Mild salsa, which was served to all patrons at seating, was consumed by 91 percent of patients and 35 percent of controls (odds ratio, 19.6; 95 percent confidence interval, 11.0 to 34.9). Besides mild salsa, no other menu item associated with illness was eaten by more than 25 percent of patients. Hot salsa, like mild salsa, was also served to all patrons at the time of seating but was not associated with illness. In a logistic-regression model (model 1) that initially included age and all five menu items associated with illness in the univariate analysis, only consumption of mild salsa (adjusted odds ratio, 19.7; 95 percent confidence interval, 11.0 to 35.5) and an age of more than 12 years (adjusted odds ratio, 2.8; 95 percent confidence interval, 1.4 to 5.6) remained significant in the final model (Table 3).

Of 102 ingredients examined, 13 had been eaten by at least 25 percent of the patients. Of these, seven were significantly associated with illness (Table 2). The two ingredients most strongly associated with illness were green onions (odds ratio, 33.3; 95 percent confidence interval, 12.8 to 86.2) and

diced white onions (odds ratio, 30.8; 95 percent confidence interval, 9.3 to 102.2). Green onions and diced white onions were the only two fresh produce ingredients in the mild salsa. Hot salsa contained white onions but not green onions.

In a logistic-regression model (model 2) that initially included age and the seven ingredients associated with illness in the univariate analysis, only consumption of green onions remained in the final model (Table 3). Because of the strong association between mild salsa and illness, a third model was constructed that included variables for age, consumption of mild salsa, and exposure to other menu items that contained green onions. Green-onion consumption in other menu items was independently associated with illness and showed a dose-response effect (model 3 in Table 3). Model 3 fit the data significantly better than did model 2 ($P < 0.001$).

ILLNESS OF EMPLOYEES

All 69 employees who worked at Restaurant A at any time between September 1 and November 2, 2003, were tested for IgM antibody to hepatitis A virus. Thirteen employees had positive results, and all were symptomatic, with dates of the onset of illness that were similar to those of restaurant patrons (range, October 26 to November 14). All had worked and eaten food at Restaurant A between October 3 and October 6. None reported recent travel to

Table 2. Consumption of Selected Food Items by 240 Patients with Hepatitis A and 134 Controls Who Ate One Meal in Restaurant A between October 3 and October 6, 2003.*

| Variable | Patients (N=240) | Controls (N=134) | Odds Ratio (95% CI) |
|--------------------------|------------------|------------------|---------------------|
| | <i>no. (%)</i> | | |
| Age >12 yr | 212 (88) | 97 (72) | 2.9 (1.7–5.0) |
| Menu items consumed | | | |
| Mild salsa† | 218 (91) | 45 (35) | 19.6 (11.0–34.9) |
| Grilled chicken fajitas‡ | 29 (12) | 8 (6) | 2.2 (1.0–4.9) |
| Bar beverage§ | 49 (21) | 16 (12) | 1.9 (1.0–3.5) |
| Ground beef burrito | 7 (3) | 0 | Indeterminate |
| Enchilada platter | 7 (3) | 0 | Indeterminate |
| Ingredients consumed¶ | | | |
| Green onions | 234 (98) | 76 (58) | 33.3 (12.8–86.2) |
| Diced white onions** | 237 (99) | 95 (72) | 30.8 (9.3–102.2) |
| Beans | 113 (47) | 35 (26) | 2.5 (1.6–4.0) |
| Mixed cheese | 181 (75) | 76 (57) | 2.3 (1.5–3.7) |
| Rice | 124 (52) | 46 (34) | 2.0 (1.3–3.2) |
| Sour cream | 92 (38) | 33 (25) | 1.9 (1.2–3.0) |
| Corn-cake mix | 124 (52) | 49 (37) | 1.9 (1.2–2.9) |

* Patients and controls who could not recall what they had eaten are not included in the calculations of percentages. CI denotes confidence interval.

† One patient and four controls could not recall whether they had eaten mild salsa.

‡ One patient could not recall whether she had eaten grilled chicken fajitas.

§ Two patients and one control could not recall whether they had consumed bar beverages.

¶ Ingredients that were consumed by fewer than 25 percent of patients are not listed.

|| One patient and four controls could not recall whether they had eaten items containing green onions.

** Two controls could not recall whether they had eaten items containing white onions.

a country where infection with hepatitis A virus is endemic.

PURCHASING AND PREPARATION OF MILD SALSA AND GREEN ONIONS

Mild Salsa

The mild salsa contained tap water, green onions, canned tomatoes, canned green chilis, a spice mix, and diced white onions. The latter four ingredients were all processed at various food-manufacturing facilities and were delivered to the restaurant packaged and ready to use. The spices were prepared in 635-kg (1400-lb) batches and delivered by a regional distributor in 394g (13.9-oz) packets. The white onions were washed with chlorinated water, machine-diced in 2268-kg (5000-lb) batches, and then packaged in 2-kg (5-lb bags) for shipment to

multiple restaurants. Preparation and handling of green onions are described below.

Restaurant A prepared up to two 38-liter (40-quart) batches of mild salsa each day. Each batch contained 170 g (6 oz) of diced green onions (equivalent to 10 to 16 whole onions). Ingredients were mixed in one large bowl, transferred into plastic containers, and stored for up to three days in a refrigerator. These containers were used to refill serving pans in the dining room. Salsa was ladled into bowls and served to all patrons. The ladles, dispensing pans, and plastic containers were washed each day.

Green Onions

Green onions were purchased by Restaurant A from a distributor, who purchased them from a produce supplier. Shipping boxes contained 4 kg (8.5 lb) of green onions packed on ice in bundles of six to eight onions each. Restaurant A workers placed bundles into 30-by-15-by-23-cm (12-by-6-by-9-in.) metal pans, which were stored in the refrigerator for up to five days.

Green onions were chopped as needed. Bundles were rinsed with tap water, the roots were cut, the rubber band around the bundle was removed, and the onions were chopped with the use of an electric dicer. Chopped onions were refrigerated in plastic containers for up to two days. The dicer was used solely for dicing green onions and was cleaned each day. The dicer was discarded before the investigation commenced.

NUCLEIC ACID ANALYSIS

All sequences of hepatitis A virus that were obtained from patients who had eaten at Restaurant A — including those from 136 patients from Pennsylvania and 34 from six other states — were identical; these sequences included those from the 3 patients who died. The outbreak sequence was similar (>96 percent) to sequences that have been commonly found among persons reporting travel to or residence in Mexico during the two to six weeks before illness and among patients with hepatitis A in Hispanic communities in the United States.^{11,12} Sequences from other outbreaks that were associated with green onions and that occurred during 1999, 2000, and 2003 were also part of this sequence cluster of hepatitis A virus.^{9,10,13} The sequence of the Pennsylvania outbreak was distinct from that of other outbreak sequences but most closely related to the sequences obtained from

Table 3. Multivariate Analysis of Demographic Characteristics and Food Exposures Associated with Hepatitis A among Patrons of Restaurant A, October 3 through October 6, 2003.*

| Variable | Case Patients (N=240) | Controls (N=134) | Model 1 | Model 2† | Model 3 |
|--|--------------------------|---------------------|--|------------------|------------------|
| | number (percent) | | adjusted odds ratio (95 percent confidence interval) | | |
| Age >12 yr | 212 (88) | 97 (72) | 2.8 (1.4–5.6) | NA | 2.3 (1.1–4.8) |
| Consumption of mild salsa‡ | 218 (91) | 45 (35) | 19.7 (11.0–35.5) | NA | 21.3 (11.5–39.7) |
| Consumption of green onions (any exposure)§ | 234 (98) | 76 (58) | NA | 33.3 (12.8–86.2) | NA |
| No. of menu items consumed, other than mild salsa, containing green onions | | | | | |
| None¶ | 82 (34) | 80 (60) | NA | NA | 1.0 |
| 1 other item | 131 (55) | 49 (37) | NA | NA | 1.7 (1.0–3.1) |
| 2 or more other items | 27 (11) | 5 (4) | NA | NA | 7.3 (2.1–24.7) |

* NA denotes that the variable was not included in the model.

† Only green onions were retained in the final model.

‡ One patient and four controls could not recall whether they had eaten mild salsa.

§ One patient and four controls could not recall whether they had eaten items containing green onions.

¶ The subjects in this category served as the reference group.

patients in separate foodborne outbreaks that occurred during September 2003 in Tennessee, North Carolina, and Georgia.¹³

FDA TRACE-BACK INVESTIGATION

An FDA trace-back investigation found that two farms in northern Mexico were the source of green onions shipped to Restaurant A in late September and early October 2003. No repacking occurred between the packing sheds on the farms and delivery to Restaurant A. At harvest, each onion's outer layer was stripped off and discarded. Green onions were hand-bundled with rubber bands, packed on ice in boxes at the farms, and imported into the United States; they passed through two or more distributors before being delivered to Restaurant A.

DISCUSSION

In this large foodborne outbreak of hepatitis A, illness was strongly associated with consumption of menu items containing green onions at a single restaurant in Beaver County, Pennsylvania. Food-service workers at the restaurant were tested for recent infection with hepatitis A virus, and infected workers were shown not to be the source of the outbreak. The implicated green onions were apparently contaminated with hepatitis A virus before or during packing into shipping boxes on farms in

northern Mexico during September 2003. In November 2003, the FDA issued an import ban on green onions from four farms (including the two that supplied green onions to Restaurant A) in Mexico¹⁴ and a consumer alert.¹⁵

The Pennsylvania outbreak was a very large outbreak of restaurant-associated hepatitis A. The estimates of attack rates (on the basis of the number of meals served) on October 4 and 5 were higher than attack rates observed among children who were served strawberries contaminated with hepatitis A virus (range, 0.2 to 14 percent)⁸ and the estimated attack rate among Shanghai residents exposed to contaminated clams (11.9 percent).¹⁶ Estimates of attack rates for hepatitis A outbreaks, and comparisons among various outbreaks, are subject to several limitations, including the presence of pre-existing immunity (due to previous infection or vaccination) among those exposed and focal or limited contamination within large food preparations.

A combination of factors probably contributed to the unprecedented size of the Pennsylvania outbreak and the high attack rate observed. First, nearly 2000 people were estimated to have dined at Restaurant A during the four days of the peak exposure period, and all were offered mild salsa, the food item most strongly associated with illness. Uncooked green onions were also used in more than 50 other menu items. Second, preparation practic-

es, such as rinsing green onions while they are still bundled, could have contributed to the size of the outbreak. Once contaminated onions were chopped, there were opportunities for the intermingling of uncontaminated and contaminated green onions stored in a common container; in addition, liquid on the surface of onions from rinsing or from melting ice might have facilitated diffusion of hepatitis A virus. Contaminated onions were then dispersed throughout the mild salsa.

None of the food-handling practices reported by Restaurant A employees were specifically linked to transmission. However, many of these preparation practices could result in cross-contamination and are probably used in other restaurants. The 2001 Food Code includes a requirement that vegetables that are not subsequently cooked must be washed, but it does not offer guidance about washing methods or other produce-preparation practices that might prevent cross-contamination.¹⁷ Methods for the routine detection of hepatitis A virus or the reduction of contamination of produce are not yet available. In laboratory settings, rinsing produce with chlorinated water, which should be done both after harvest¹⁸ and again before meal preparation,¹⁷ reduces but does not eliminate contamination with hepatitis A virus.¹⁹ Even a small amount of fecal contamination might result in many hundreds of infectious doses because concentrations of hepatitis A virus are estimated to reach 1 billion infectious doses per gram of stool and because the infectious dose, though unknown, is probably low.²⁰

Green onions were the source of restaurant-associated hepatitis A outbreaks in 1999 in Ohio, in 2000 in Kentucky and Florida, and earlier in 2003 in Tennessee, Georgia, and North Carolina.^{9,10,13} Trace-back investigations indicated that green onions that were implicated in these investigations were either definitely^{10,13} or probably⁹ grown in Mexico. As noted in the Pennsylvania investigation, the origin of the contaminated green onions was consistent with the sequence similarities in hepatitis A virus noted among patients involved in these outbreaks and among persons who acquired hepatitis A in Mexico or who live in communities in the United States where cases of hepatitis A are often epidemiologically linked with travel to Mexico or contact with travelers to Mexico (e.g., Hispanic communities).^{9,10,13}

Outbreaks of infection due to other enteric pathogens that are linked to imported green onions have

also been reported.²¹ Green onions require extensive handling during harvesting and preparation for packing, including the removal of outer skins and soil.^{9,22} Contamination of green onions could occur by contact with workers (or workers' children) who are infected with hepatitis A virus during harvesting and preparation or by contact with contaminated water during irrigation, rinsing, processing, cooling, and icing. In addition, viral particles or feces are especially difficult to wash off complex plant surfaces.²³

Green onions from the implicated farms were probably delivered to other restaurants. However, no other simultaneous restaurant-associated outbreaks of hepatitis A were identified despite public health alerts, extensive media coverage, and intensified surveillance activities nationwide. Contamination might have been confined to a small portion of the harvest, or contaminated produce might not have been recognized as the source of infection among persons who did not recall exposure. Foodborne outbreaks have been observed previously that were linked to produce but involved only a few food-serving institutions or cases scattered across a wide geographic area, despite widespread distribution of produce from the implicated farms.^{6-10,24-26}

An increasing proportion of reported foodborne outbreaks have been linked to fresh produce.^{17,20,27} Recommended control measures include ensuring that field workers are healthy and have access to adequate sanitary facilities and ensuring that water used to irrigate and rinse produce is not contaminated with feces. In food-service settings, consideration should be given to the possibility that contaminated produce might cause more widespread contamination of other produce and of the preparation area. Health care providers can assist in determining the source of foodborne outbreaks of hepatitis A by immediately notifying local and state health authorities when cases are identified. In many communities, especially in the developing world, children are the source of most transmission of hepatitis A virus.^{1,28} The reduction of the transmission of hepatitis A virus among children in areas where produce is grown and attempts to discourage the presence of children in areas where food is harvested will reduce opportunities for contamination with the virus.

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