Outbreak of Hepatitis A Associated with Frozen Pomegranate Arils Imported from Turkey—Multiple U. S. States

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Acknowledgments:

We would like to thank the following people for their contributions to the investigation:
Nicole Comstock, Alycia Downs, Kathleen Harriman, Cynthia Jorgensen, Bill Keene, Kenneth Komatsu, Paul Peterson, Devin Raman, and Phil Spradling

CDC Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Funding:

This study was funded by the Centers for Disease Control and Prevention, the Food and Drug Administration, and other state and local public health departments

Conflicts of interest:

None of the authors hepatitis A viruse any conflicts of interest

Author contribution: All authors made substantial contributions to the manuscript conception or design, helped in drafting or critically revising it for important intellectual content, had final approval of publication, and agreed to be accountable for all aspects.

Panel: Research in context

Systematic review

Outbreaks of infectious diseases are investigated with a combination of methods, including descriptive epidemiology, and for foodborne outbreaks, shopping data and product tracing once a food item is identified as a potential vehicle. We did not do a systematic review of methods. Case-control or cohort studies[5,12–14] are done if a specific food cannot be identified through descriptive epidemiology alone, which was not necessary for this investigation.

Interpretation

This investigation is the first to our knowledge in which a food item linked to hepatitis A infection from a common source was identified rapidly enough for effective post-exposure prophylaxis interventions, potentially preventing hepatitis A illnesses.

Abstract

Background In May 2013, an outbreak of symptomatic hepatitis A virus (HEPATITIS A VIRUS) infections occurred in the United States. Federal, state, and local public health officials investigated the cause of the outbreak and instituted actions to control its spread.

Methods We interviewed patients, obtained their shopping information, and performed genetic analysis of hepatitis A virus recovered from case-patient serum and stool specimens. We tested products for the virus and traced supply chains.

Findings Of 165 patients identified from ten states, 69 (42%) were hospitalized, two developed fulminant hepatitis, one required a liver transplant; none died. Illness onset dates were March 31 through August 12, 2013. Ages ranged from less than one to 84 years, and ninety-one (55%) were women; 153 patients reported consuming Product B from Retailer A. Forty patients had Product B in their freezers, and 113 patients purchased it according to Retailer A member card data. HEPATITIS A VIRUS genotype IB, uncommon in the Americas, was recovered from specimens from 117 persons with HEPATITIS A VIRUS illness. Pomegranate arils that were imported from Turkey, where HEPATITIS A VIRUS genotype IB is common, were identified in Product B. No HEPATITIS A VIRUS was detected in Product B specimens.

Interpretation Imported frozen pomegranate arils were identified as the vehicle early in the investigation by combining epidemiology – with data from several sources – HEPATITIS A VIRUS genetic analysis from patient specimens, and product tracing. Product B was removed from store shelves, the public were warned not to eat Product B, product recalls took place, and post-exposure prophylaxis with both hepatitis A vaccine and immunoglobulin was provided. Our findings show that modern public health actions can help rapidly detect and control hepatitis A virus illness caused by imported. Our findings

show that postexposure prophylaxis can successfully prevent hepatitis A illness when a specific product is identified. Imported food products combined with waning immunity in some adult populations might make this type of intervention necessary in the future.

Introduction

Infection with the hepatitis A virus causes an acute viral illness characterized by fever, abdominal pain, elevated levels of aminotransferase enzymes, and jaundice. Hepatitis A vaccine or immunoglobulin (IG) administered within two weeks of exposure can prevent disease.[1] In the USA, hepatitis A vaccination has been recommended for all children aged 12–23 months since 2006[2] and consequently a the number of acute cases has greatly fallen.[3] Hepatitis A virus is transmitted by person-to-person contact or ingestion of contaminated food or water, and is primarily a human pathogen. International travel is a risk factor for about one-half of all reported U·S·cases.[4] The most recent common source foodborne hepatitis A outbreak in the United States occurred in 2005.[5]

On May 13, 2013, the New Mexico Department of Health notified the Centers for Disease Control and Prevention (CDC) of two people in the same city who had shopped at retailer A and who had hepatitis A illness with symptoms onset dates within one week of each other. The Department contacted states in the same retailer A distribution area, and the Colorado Department of Public Health and Environment identified four additional retailer A shoppers with hepatitis A illness. None of these case-patients had typical risk factors for hepatitis A (e·g· international travel, injection drug use). Initial interviews using a hypothesis generating questionnaire, which asks about all possible food exposures, identified some similar eating patterns, including fruits and vegetables consumed in smoothies. Four patients from two states had product B, a frozen mix of cherries, strawberries, raspberries, blueberries, and pomegranate arils, in their freezers and used it in smoothies. Retailer A provided member card information confirming that persons with hepatitis A purchased product B from retailer A. This report describes the investigation of a multi-state outbreak of hepatitis A associated with product B and the public health actions taken to halt the outbreak.

Methods

Patients We defined acute hepatitis A as an acute illness with hepatitis symptoms (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), and either jaundice or elevated serum alanine aminotransferase or aspartate aminotransferase concentrations[6] and positive for IgM antibody to hepatitis A virus. An outbreak-related was confirmed if the patient met acute hepatitis A criteria with symptom onset between March 15, 2013 and August 12, 2013, and either reported consuming product B within their illness incubation period (15 – 50 days prior to symptom onset) irrespective of HEPATITIS A VIRUS genotype or who had HEPATITIS A VIRUS genotype IB isolated from a clinical specimen. Secondary cases had close contact with a confirmed case-patient but did not report consuming product B during the incubation period. State and local health departments collected demographic, clinical, and food exposure information and clinical specimens from persons with reported acute hepatitis A with symptom onset during March 15, 2013—September 5, 2013. This study was done in response to a public health emergency and was thus exempt from institutional review board approval

Procedures Serum or stool samples from potential outbreak-related cases were collected within 28 days of the date of symptom onset, frozen at -20 C as soon as possible after collection, and shipped overnight on dry ice to CDC's Division of Viral Hepatitis Laboratory for genetic sequencing. HEPATITIS A VIRUS RNA was extracted from serum specimens and used to amplify and sequence a 315 base pair fragment of the VP1/P2B region.[7] Preliminary sequence analysis was performed using DNAStar Lasergene 11 (DNASTAR, Inc·, Madison, WI). We did further sequence analysis with the Geneious 7·0·5 (Biomatters Ltd·, Auckland, New Zealand). We used Geneious Alignment to do sequence alignment. We constructed a final phylogenetic tree based on maximum likelihood algorithms.[8] To improve case-finding, in addition to outbreak-related laboratory activities, specimens were solicited nationwide through the CDC's Epidemic Information Exchange (Epi-X) on June 26, 2013 from people

with acute hepatitis A and no history of international travel during the incubation period. These data were used in a sensitivity analysis to assess the inclusion of hepatitis A virus genotype IB in our case definition by looking at how many genotype IB infections were detected among non-outbreak related cases. Samples of product B from patients' freezers were collected for hepatitis A virus testing, and tests with a method modified from the US Food and Drug Administration (FDA) bacteriological analytical manual for hepatitis A virus in green onions.[9]

The Food and Drug Administration (FDA) investigated the facility of manufacturer C, which made product B. All product B ingredients were traced back to their source, and frozen pomegranate arils from importer D were traced forward.

Information about the ongoing outbreak was sent through Epi-X, to notify all states about the potential outbreak on May 22, 2013. The public was notified of the outbreak on May 31, 2013 through state and local health department press releases and CDC's website.[10] Information from membership cards for retailer A was obtained to identify which patients bought product B from retailer A during December 21, 2012—May 31, 2013; patients were then contacted from May31, 2013, with information about the risk of hepatitis A associated with product B. Product B was removed from shelves of retailer A on May 30, 2013. CDC, state, and local health officials recommended that anyone who had eaten Product B in the previous 2 weeks be evaluated for HEPATITIS A VIRUS post-exposure prophylaxis (PEP), which included hepatitis A vaccine and immunoglobulin, either through state or local health departments or their private physician. CDC provided guidance to state and local health departments about who should receive what postexposure prophylaxis according to the Advisory Committee for Immunization Practices guidelines;[1] however, final decisions were made locally based on local resources.

Results

We identified 165 persons from ten states meeting the confirmed case definition; eight of whom met the secondary case definition. Illness onset dates ranged from March 31, 2013—August 12, 2013 (figure 1). 69 (42%) of 165 patients were admitted to the hospital, two (1%) developed fulminant hepatitis, and one secondary case-patient with fulminant hepatitis required liver transplant; no deaths were reported. Most patients were aged 40 – 64 years and 91 (55%) were female (table). Few patients were aged 18 years or younger, none of whom were vaccinated (two children were from one family that refused PEP).

Product B was a mixture of frozen strawberries, red raspberries, blueberries, cherries, and pomegranate arils. The workers processing product B wore gloves, limiting bare hand contact with the product, and no workers reported symptoms of acute hepatitis. Through lot numbers of product B recovered from 4 case-patients' freezers, the five ingredients that were in product B were traced back to their originating firms through investigation of purchasing and invoice documents.

Strawberries and blueberries came from multiple importers from more than one location, and so were not considered the likely vehicle. Cherries from the USA and strawberries from Argentina in product B came from a single supplier but in several different lots and so were unlikely to be the vehicle. The product B cherries and strawberries were also used in other widely distributed products made by manufacturer C and no other outbreak-associated cases were found among consumers of other manufacturer C products. Frozen pomegranate arils imported from Turkey by Importer D from a single lot were found in Product B recovered from case-patient freezers (Figure 2). The same lot of frozen pomegranate arils was also used in product E produced by manufacturer F, and one person who had consumed product E had an infection of hepatitis A virus IB matching the outbreak strain. The first lot to contain the Turkish arils was produced on January 24, 2013 and the bags had a shelf life of 2 years.

Of 157 primary case-patients, 152 (97%) reported consuming product B or had purchased it according to member card information. Of five persons who did not recall consuming product B, three

were members at retailer A but did not purchase product B, one person did not consume or purchase Product B but consumed Product E (which contained the same arils), and one person did not consume either product B or E. According to member card information, 113 patients (72%) bought product B, and 40 had product B in their freezers (of whom, we could not find purchase records for three). 71 (63%) of 113 patients bought product B more than once between January 24 and May 31, 2013. The person identified in New Jersey was a secondary case exposed to a primary case in Colorado, the two people from Wisconsin consumed product B while living in California before relocating to Wisconsin, and the person from New Hampshire traveled to Nevada during the illness incubation period but did not recall consuming product B.

Of the 165 patients, 120 had clinical specimens available for testing, including 119 serum and one stool specimen. 117 (98%) tested positive for hepatitis A virus genotype IB. Genotype IA virus was recovered from two patients who reported consuming product B, and one patient was hepatitis A virus negative. Phylogenetic analysis of the outbreak specimens showed that the sequences from 99 genotype IB specimens (85%) were identical in the 315 bp segment of VP1/P2B (figure 3); the remaining 18 outbreak specimens belonged to minor genotype IB strains. To ensure that other hepatitis A cases related to this outbreak were detected, CDC issued a national request through Epi-X for state and local health departments to submit specimens from people with hepatitis A symptom onset from March 1, to Sept 5, 2013. Specimens from an additional 131 people were submitted as a result; of these, 47 (36%) were PCR negative for hepatitis A virus, 82 (62%) were positive for genotype IA, of which 66 belonged to the subtype IA1 cluster, and two (2%) were positive for genotype IB. We could not isolate hepatitis A virus from product B.

Product B was purchased 283 times by 113 primary case-patients (an average of 2·5 purchases per person) between December 21, 2012, and May 31, 2013. 218 (77%) of these purchases were made between February 17, 2013, and May 12, 2013. Product B was distributed through retailer A in Alaska,

Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, and Washington between January 21, 2013, and May 30, 2013; however, no cases were reported from residents of Alaska, Idaho, Montana, Oregon, or Washington. During January 21, 2013–May 30, 2013 a total of 409,286 units were sold. Of those units, 364,076 (89%) were sold in the seven states from which the cases were reported and where product B was sold. The product also was distributed on a much smaller scale (1,616 units) in the northeastern USA with different packaging under brand G; no cases were reported from consumers of brand G.

On June 4, 2013, manufacturer C issued a voluntary recall of specific product B lots, including selected lots of brand G; this recall was expanded on June 28, 2013 to include additional lots.[11] Retailer A used automated phone calls to notify more than 250,000 members who bought product B about the link to hepatitis A. State and local health departments gave postexposure prophylaxis to thousands of persons. Retailer A paid for and administered vaccine to more than 10,000 people at more than 200 stores, which was done by licensed professionals. On June 26, 2013, a voluntary recall was issued by manufacturer F for product E, which FDA identified through traceforward activities to contain the same lot of frozen Turkish pomegranate arils as product B (Figure 1). Although product E was recalled, CDC did not recommend postexposure prophylaxis for people who had consumed the product; however, some states did offer PEP to their residents if they consumed the product. FDA placed Importer D on two separate Import Alerts on June 29, halting importer D shipments into the USA.

Discussion

This foodborne outbreak of hepatitis A virus was the first in the USA in almost 10 years, during an era of universal childhood vaccination. Its investigation and control were unique in several ways (panel): the implicated source originated from another continent, showing the international distribution of foods and associated food safety problems; genetic information from patient specimens suggesting infection with IB genotype was used to link cases; the product was sold by a single retailer with modern information systems, including itemized sales data, with exact purchase dates, and customer information; and the retailer had the willingness and resources give hepatitis A vaccine to those affected. Hepatitis A, unlike other foodborne pathogens, can be prevented if vaccination can be provided within two weeks of exposure; in one instance during this outbreak, parents refused vaccination for their children who then became ill.

Public health action was not delayed to wait for results of a case-control study because hepatitis A has a long incubation period (making patient recall of dietary exposures questionable), the shelf life of the implicated product was 2 years, and the continuing health risk. Although cherries and strawberries were also common among lots of product B, both the cherries and strawberries were used in many other products sold by product B's manufacturer and no outbreak-associated cases were recorded among people who had consumed those products. This finding, combined with the case of IB genotype infection matching the outbreak strain associated with product E (which contains no cherries or strawberries), supported the conclusion that the pomegranate arils were the source.

Product B was packaged in large bags (3 lb or 1.5 kg) and contained many servings. Hepatitis A virus is resistant to environmental conditions such as freezing[15] and can be infectious up to a month on environmental surfaces.[16] This persistence in the environment was shown in two previous outbreaks of hepatitis A in which frozen strawberries were harvested a year or more before causing illnesses, suggesting that these contaminated frozen foods can be a source of hepatitis A illnesses for a long period

if not recalled.[12,13] Hepatitis A virus is inactivated by heat, but needs high temperatures to be completely inactivated (up to 90°C for 180 seconds).[17]

To our knowledge, this is the first US multistate food borne hepatitis A outbreak in which vaccine and immunoglobulin were recommended and provided by local health departments and where vaccine was provided by a retailer. The infrastructure provided by retailer A (in-store pharmacies, vaccine administration staff, and automated calling system) enabled the vaccine to be delivered quickly and efficiently, and increased the uptake of postexposure prophylaxis, as evidenced by the large number of people vaccinated. These measures probably prevented additional cases: the number of new cases decreased soon after the public was notified May 31, 2013. Illness among unvaccinated children that occurred after one family declined postexposure prophylaxis could have been prevented. Postexposure prophylaxis, both active and passive, is an effective illness prevention strategy. However, the burden and cost of providing it must be balanced with the risk of disease. For this reason and lack of cases associated with product E, CDC did not recommend postexposure prophylaxis for product E consumers.

This outbreak primarily involved genotype IB, and very few specimens identified during the outbreak period were genotype IB. These findings assisted in the detection of the outbreak and show the potential of molecular typing techniques. Most cases of acute hepatitis A reported in the USA are genotype IA which is endemic in Mexico; genotype IB is predominant in the Middle East.[18–20] Several recent outbreaks of hepatitis A virus genotype IB illnesses associated with food from the Middle East hepatitis A virus been reported outside the USA: frozen strawberries from Egypt and Morocco were associated with illness in Europe,[21] frozen pomegranate seeds from Egypt were associated with illness in Canada in 2012,[22] and semidried tomatoes from Turkey were associated with illness in Europe and Australia in 2009 – 2011.[14,24,25] These outbreaks show the international nature of hepatitis A, the difficulties of identification and control of outbreaks related to foods of foreign origin,[26] and the importance of ensuring adequate hygiene during the production of imported foods.

The age-specific seroprevalence of antibody against hepatitis A virus among US adults has decreased since the mid-1990s because of herd immunity provided by universal vaccination of children.[27,28] In this outbreak, most patients were aged 40 – 64 years and of white ethnic origin, either because they were more likely to consume product B or because they were less likely to be immune to hepatitis A virus, or a combination of both. As more food is imported from distant areas of the world where adequate processing methods are difficult to verify, the effectiveness of vaccination for postexposure prophylaxis in people older than 40 years needs to be studied.

We encountered challenges during this investigation. First, we were unable to confirm pomegranate aril contamination through food testing due to the difficulty in isolating hepatitis A virus from food.[9,29] Second, public health surveillance for hepatitis A is passive and specimens are not routinely submitted for public health analysis. Cases could hepatitis A virus been missed if not reported or the outbreak link was not considered. Third, we were unable to inspect importer D due to political unrest in the region.

In conclusion, public notification, product recall, and hepatitis A postexposure prophylaxis within two weeks of exposure can prevent illnesses during outbreaks; these efforts are helped by retailers with reliable sales data who are willing to work with public health agencies. The foreign origin of the contaminated ingredient in this outbreak underscores the importance of the new import-related regulations in the Food Safety Modernization Act. Under this new law, importers are required to have a programme to verify food product safety, and will be required to implement risk-based preventive controls.

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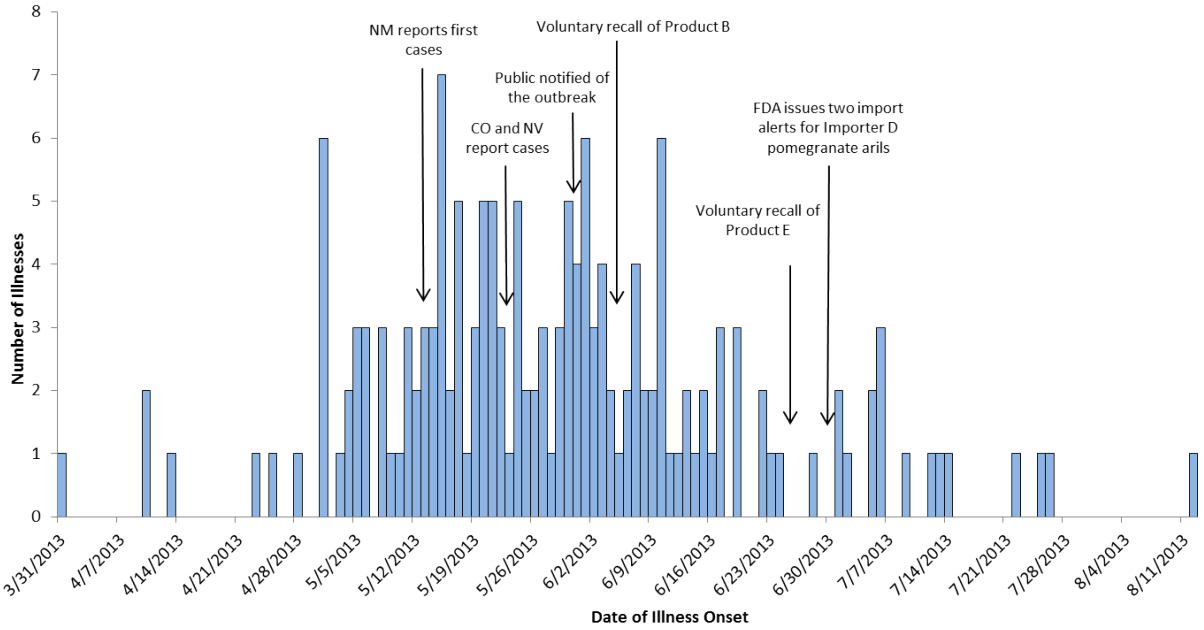
Figure 1. **Confirmed outbreak-related cases of hepatitis A.**

Abbreviations: NM = New Mexico, CO = Colorado, NV = Nevada

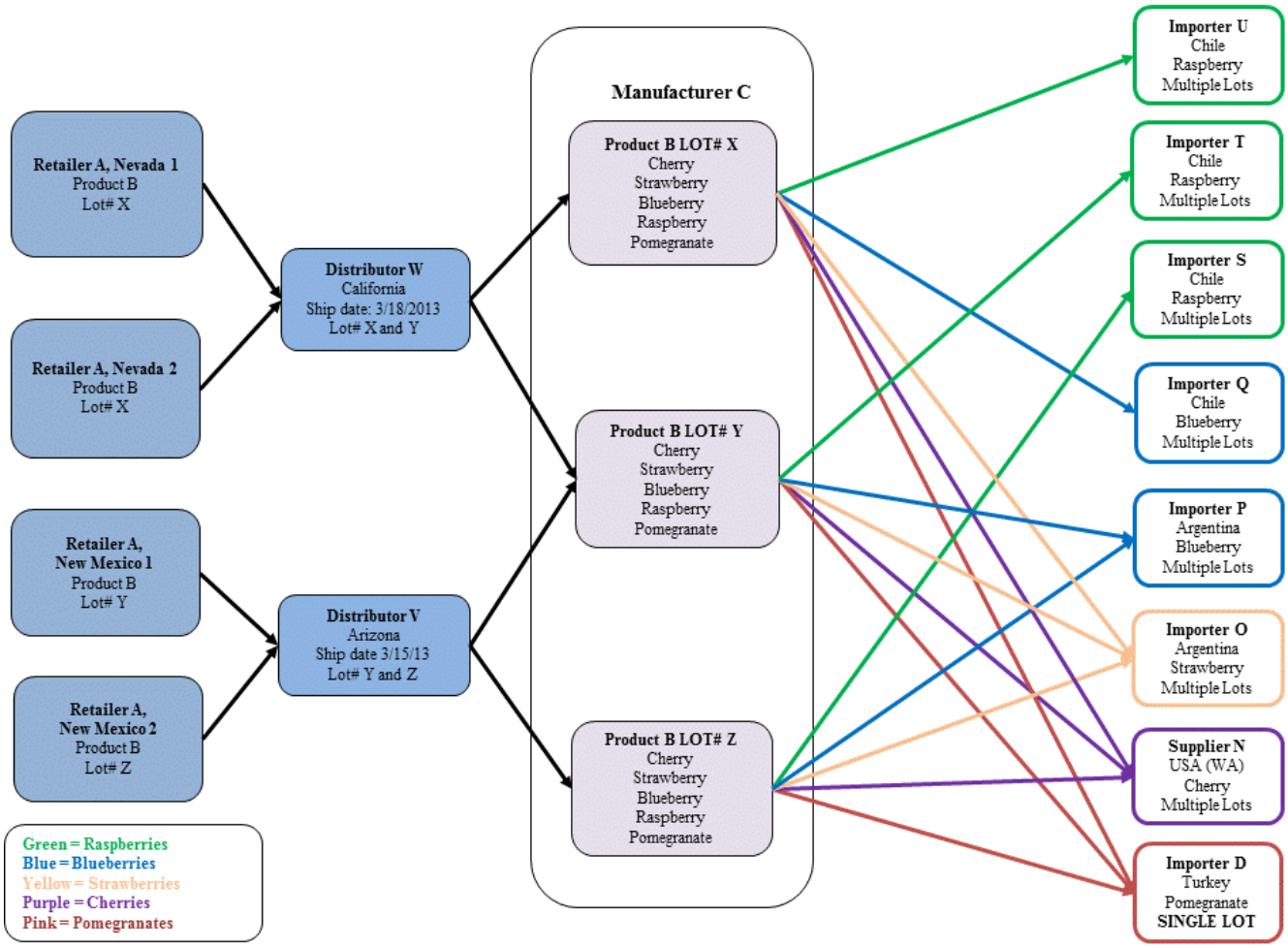
Figure 2. Tracing the ingredients of product B.

Figure 3. Hepatitis A virus genotype IB genetic analysis. Compares the sequence of the 315 bp segment (VP1/P2B) among outbreak related and non-outbreak related genotype IB specimens.


NM reports first cases
Voluntary recall of Product B
Public notified of the outbreak
CO and NV report cases
FDA issues two import alerts for Importer D pomegranate arils
Voluntary recall of Product E
Number of Illnesses
Date of Illness Onset
0
1
2
3
4
5
6
7
8
3/31/2013
4/7/2013
4/14/2013
4/21/2013
4/28/2013
5/5/2013
5/12/2013
5/19/2013
5/26/2013
6/2/2013
6/9/2013
6/16/2013
6/23/2013
6/30/2013
7/7/2013
7/14/2013
7/21/2013
7/28/2013
8/4/2013
8/11/2013

Characteristic	no· / total no· (%)
Female sex	91/165 (55)
Age — years	
Median (IQR)	47 (35–58)
0 - 18 years	11/165 (7)
18 - 39 years	42/165 (25)
40 - 64 years	95/165 (58)
65 + years	17/165 (10)
Race	
White	123/165 (74)
Hispanic or Latino	13/165 (8)
Asian	6/165 (4)
Black	2/165 (1)
Other	3/165 (2)
Unknown race	18/165 (11)
State of Residence	
Arizona	24 (15)
California	80 (48)
Colorado	29 (18)
Hawaii	8 (5)
New Hampshire	1 (<1)
New Jersey	1 (<1)
New Mexico	11 (7)
Nevada	6 (4)
Utah	3 (2)
Wisconsin	2 (1)

Table: Patient characteristics


Retailer A, Nevada 1
Product B
Lot# X
Retailer A, Nevada 2
Product B
Lot# X
Retailer A,
New Mexico 1
Product B
Lot# Y
Retailer A,
New Mexico 2
Product B
Lot# Z
Distributor W
California
Ship date: 3/18/2013
Lot# X and Y
Distributor V
Arizona
Ship date 3/15/13
Lot# Y and Z
Manufacturer C
Product B LOT# X
Cherry
Strawberry
Blueberry
Raspberry
Pomegranate
Product B LOT# Y
Cherry
Strawberry
Blueberry
Raspberry
Pomegranate
Product B LOT# Z
Cherry
Strawberry
Blueberry
Raspberry
Pomegranate
Importer U
Chile
Raspberry
Multiple Lots
Importer T
Chile
Raspberry
Multiple Lots
Importer S
Chile
Raspberry
Multiple Lots
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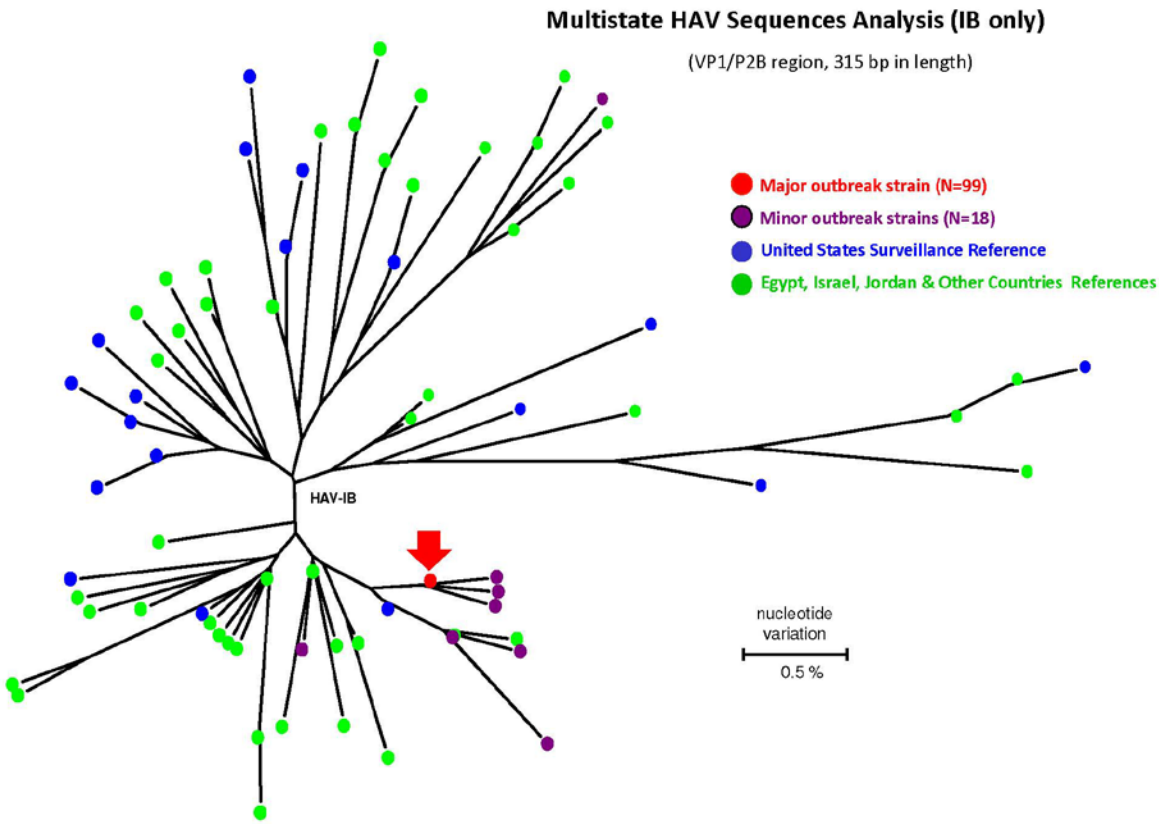
Multiple Lots
Importer P
Argentina
Blueberry
Multiple Lots
Importer O
Argentina
Strawberry
Multiple Lots
Supplier N
USA (WA)
Cherry
Multiple Lots
Importer D
Turkey
Pomegranate
SINGLE LOT
Green = Raspberries
Blue = Blueberries
Yellow = Strawberries
Purple = Cherries
Pink = Pomegranates


Multistate HAV Sequences Analysis (IB only)
(VP1/P2B region, 315 bp in length)
Major outbreak strain (N=99)
Minor outbreak strains (N=18)
United States Surveillance Reference
Egypt, Israel, Jordan & Other Countries References
HAV-IB
nucleotide variation
0.5 %