

## AN OUTBREAK IN 1996 OF CYCLOSPORIASIS ASSOCIATED WITH IMPORTED RASPBERRIES

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### ABSTRACT

**Background** *Cyclospora cayetanensis* is a parasite that causes gastroenteritis. Until last year most of the documented cases of cyclosporiasis in North America were in overseas travelers. In 1996, a large outbreak of cyclosporiasis occurred in North America. We investigated this outbreak.

**Methods** Health departments solicited information from clinicians and laboratories on cases of cyclosporiasis, which were then reported to the Centers for Disease Control and Prevention and to Health Canada. We conducted retrospective cohort studies for the cases associated with events (e.g., luncheons) and attempted to identify the sources of the implicated food.

**Results** A total of 1465 cases of cyclosporiasis were reported by 20 states, the District of Columbia, and 2 provinces. Of these cases, 978 (66.8 percent) were laboratory confirmed and 725 (49.5 percent) were associated with 55 events that were held from May 3 through June 14. Raspberries were definitely served at 50 events and may have been served at 4 events. For 27 of the 41 events for which adequate data were available (65.8 percent), the associations between the consumption of berries (raspberries with or without other berries) and cyclosporiasis were statistically significant ( $P < 0.05$ ). For all 29 events for which there were good data, the raspberries definitely came from Guatemala (21 events, 72.4 percent) or may have come from Guatemala (8 events, 27.6 percent). As few as five Guatemalan farms could have accounted for the 25 events for which the raspberries could be traced to a single exporter per event. The mode of contamination of the raspberries remains unclear.

**Conclusions** This large outbreak of cyclosporiasis in North America in 1996 was associated with the consumption of Guatemalan raspberries. The outbreak illustrates the need to consider that a local cluster of foodborne illness may be part of a widespread outbreak and to pursue investigations of the source of the implicated vehicle. (N Engl J Med 1997;336:1548-56.)

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**C**YCLOSPORA *cayetanensis*, previously called cyanobacterium-like body, was recently established to be a coccidian parasite.<sup>1,2</sup> Cyclospora oocysts do not multiply outside the host. After fecal excretion they do not sporulate and become infectious for days to weeks.<sup>1</sup> The parasite's natural ecology, infective dose, and host range

are unknown. It is also not known whether all human isolates belong to the same species (i.e., *C. cayetanensis*), or why in some countries most cases of cyclosporiasis occur from April through August.<sup>1-3</sup>

Cyclosporiasis has a median incubation period of one week, is associated with invasion of enterocytes of the small intestine,<sup>4,5</sup> is manifested by protracted and relapsing gastroenteritis, and is treatable with trimethoprim-sulfamethoxazole.<sup>6</sup> The oocysts of *C. cayetanensis* are 8 to 10  $\mu\text{m}$  in diameter, about twice the size of *Cryptosporidium parvum* oocysts, and are identified in stool specimens by the use of modified acid-fast and other stains, the examination of wet mounts under phase-contrast microscopy, and the demonstration of autofluorescence.<sup>1,2,7,8</sup> Sporulation of oocysts (i.e., the development of two internal sporocysts, each with two internal sporozoites) definitively establishes the diagnosis,<sup>1</sup> and techniques based on the polymerase chain reaction<sup>9,10</sup> may also prove useful.

Before 1996, most documented cases of cyclosporiasis in North America were in overseas travelers, and only three small U.S. outbreaks (with a maximum of 45 laboratory-confirmed cases) had been reported.<sup>11-13</sup> In May 1996, several health departments reported cases of cyclosporiasis to the Centers for Disease Control and Prevention (CDC). Ultimately, 978 laboratory-confirmed cases occurring in the spring and summer of 1996 were reported to the CDC and to Health Canada.<sup>14-20</sup>

Although early in the investigation various berries, including strawberries, were considered as possible vehicles of infection, Guatemalan raspberries were ultimately implicated. Raspberries were introduced in Guatemala in 1987 and first exported in 1988. In the past few years, exports have markedly increased, with the United States being the primary market for fresh raspberries; exports peak in May and June (during the rainy season) and October through December (the dry season). The possibility of foodborne transmission of cyclospora has been

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considered in previous cases and outbreaks,<sup>21-25</sup> including an outbreak that occurred in Florida in 1995, which may also have been associated with Guatemalan raspberries<sup>12</sup> (and Koumans E: personal communication). Our investigation of the large 1996 outbreak of cyclosporiasis definitively established that cyclospora can be a foodborne pathogen.

**METHODS**

**Epidemiologic Investigation**

In the spring of 1996, after an increase in the numbers of cases of cyclosporiasis was recognized, health departments solicited clinicians and laboratories for reports of cases, which were then reported to the CDC and to Health Canada. The CDC encouraged health departments to have reference laboratories (e.g., the CDC) reexamine stool specimens to reconfirm the diagnosis and to submit stool specimens in 2.5 percent potassium dichromate to the CDC for the demonstration of oocyst sporulation.<sup>1</sup>

A cluster of cases of cyclosporiasis was defined as a group of two or more cases among persons who, during May 1 through August 31, 1996, shared at least one meal or food item at an event (e.g., a luncheon or conference) and began to have at least one gastrointestinal symptom 12 hours to 14 days later. At least one case per cluster had to be laboratory confirmed; clinical case definitions for probable cases varied (Table 1). Health departments investigated clusters by conducting retrospective cohort studies or, for the cluster in Maryland, a case-control study (Table 2). Persons who attended the events associated with cases of cyclosporiasis were interviewed about symptoms and their consumption of food and beverages at the event. Univariate relative risks and odds ratios (for the Maryland cluster) were calculated for exposure variables, and two-tailed P values were computed with the chi-square test or, if appropriate, Fisher's exact test.

Sporadic cases were not associated with identified clusters, were laboratory confirmed, were characterized by the development of gastrointestinal symptoms during May 1 through August 31, and occurred in persons who had not traveled outside the United States or Canada during the two weeks before the onset of symptoms (the exposure period of interest).

**TABLE 1. NUMBER OF LABORATORY-CONFIRMED AND PROBABLE CASES OF CYCLOSPORIASIS IN THE UNITED STATES AND CANADA IN 1996, ACCORDING TO THE MOST LIKELY SITE OF THE ACQUISITION OF INFECTION.\***

LOCATION	CLUSTER-ASSOCIATED CASES			LABORATORY-CONFIRMED SPORADIC CASES	TOTAL	
	LABORATORY-CONFIRMED	PROBABLE†	TOTAL		LABORATORY-CONFIRMED	LABORATORY-CONFIRMED + PROBABLE
United States						
Colorado	4	10	14	0	4	14
Connecticut	0	0	0	38	38	38
District of Columbia	11	8	19	2	13	21
Florida	18	42	60	160	178	220
Georgia	0	0	0	5	5	5
Illinois	15	39	54	6	21	60
Iowa	0	0	0	1	1	1
Maine	0	0	0	2	2	2
Maryland	2	29	31	6	8	37
Massachusetts	21	67	88	82	103	170
New Hampshire	1	8	9	1	2	10
New Jersey	20	21	41	62	82	103
New York	29	87	116	191	220	307
Ohio	35	34	69	9	44	78
Pennsylvania	5	16	21	8	13	29
Rhode Island	0	0	0	9	9	9
South Carolina	11	25	36	7	18	43
Texas	22	27	49	48	70	97
Vermont	4	4	8	0	4	8
Virginia	1	15	16	1	2	17
Wisconsin	0	0	0	1	1	1
Subtotal	199	432	631	639	838	1270
Canada						
Ontario	36	55	91	98	134	189
Quebec	3	0	3	3	6	6
Subtotal	39	55	94	101	140	195
Total	238	487	725	740	978	1465

\*Cases are categorized according to the most likely site of acquisition of infection rather than according to the place of residence.

†The number of cluster-associated probable cases equals the total number of cluster-associated cases minus the number of laboratory-confirmed cases. For 21 of the 52 clusters with probable cases (40.4 percent), the definition of infection was strict (minimal criteria, three or more loose or watery stools for three or more days); for the other clusters, less strict definitions were used.

**TABLE 2.** EVENTS ASSOCIATED WITH CLUSTERS OF CASES OF CYCLOSPORIASIS IN 1996, ACCORDING TO THE STATE OR PROVINCE IN THE UNITED STATES AND CANADA.\*

LOCATION	EVENTS			MEDIAN ATTACK RATE†		MOST STRONGLY IMPLICATED BERRY ITEM CONTAINED ONLY RASPBERRIES‡	NO BERRIES BESIDES RASPBERRIES SERVED‡	P VALUE FOR ASSOCIATION OF BERRY ITEM WITH CYCLOSPORIASIS§				
	TOTAL NO. OF EVENTS	NO. WITH WELL-DOCUMENTED SOURCE DATA	DATES¶	TOTAL NO. OF ATTENDEES (MEDIAN % INTERVIEWED)	AMONG ALL ATTENDEES INTERVIEWED			AMONG THOSE WHO ATE BERRY-CONTAINING ITEM	<0.05	UN-DEFINED	NOT DETERMINED	≥0.05
						percent	number of events					
United States												
Colorado	1	1	5/25	80 (42.5)	41.2	80.0	1	1	1	0	0	0
District of Columbia	2	1	5/28-6/1	64 (44.6)	76.2	93.3	0	0	1	0	1	0
Florida	9	6	5/5-6/14	108 (100)	66.7	100	4	2	3	1	0	5
Illinois	3	1	5/10-6/8	95 (100)	78.6	95.7	1	0	3	0	0	0
Maryland	1	0	5/18-6/1	200 (28.0)	55.4	81.0	1	0	1	0	0	0
Massachusetts	4	2	5/11-6/13	165 (87.4)	76.4	100	2	2	2	1	0	1
New Hampshire	1	0	6/1	40 (22.5)	100	ND**	0	0	0	0	1	0
New Jersey	2	1	5/25-6/1	122 (61.6)	42.7	53.2	0	0	1	0	1	0
New York	7	3	5/4-6/14	1292 (77.1)	58.9	85.0	3	2	5	0	1	1
Ohio	6	3	5/18-6/1	259 (74.4)	66.0	91.3	4	1	2	1	0	3
Pennsylvania	2	2	5/10	39 (98.4)	61.5	77.1	2	2	1	0	0	1
South Carolina	1	1	5/23	64 (100)	56.3	88.6	1	0	1	0	0	0
Texas	5	5	5/9-5/30	105 (100)	52.6	100	1	0	4	1	0	0
Vermont	2	1	5/20-5/23	14 (100)	75.0	80.0	1††	1††	0	1	0	1
Virginia	1	0	5/3	72 (93.1)	23.9	31.3	0	0	0	0	0	1
Canada												
Ontario	7	2	5/11-6/9	313 (80.0)	54.5	70.0††	0	0††	2	0	3	1††
Quebec	1	0	6/5	3 (100)	100	100	0	0	0	1	0	0
Total	55	29	5/3-6/14	3035 (93.1)§§	56.3§§	93.3††§§	21¶¶	11††	27	6	7	14††¶¶

\*See NAPS document no. 05398 for 5 pages of supplementary material. Order from NAPS, c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) \$11.65 for photocopies or \$5 for microfiche. Outside the U.S., add postage of \$4.50 for up to 20 pages, \$5.50 for over 20 pages, or \$1.50 for microfiche. There is a \$15 invoicing charge on all orders filled before payment.

†The values are the medians of the event-specific rates, which are the percentages of persons in a particular category who were case patients (in the first subgroup the denominator includes all attendees interviewed, irrespective of exposure; in the second subgroup the denominator includes all persons who ate a berry item that contained or may have contained raspberries and was most strongly implicated). Attack rates were available for all events except one in the District of Columbia (for both subgroups), one in New Hampshire (for the second subgroup), one in New Jersey (for the second subgroup), one in New York (for both subgroups), and four in Ontario (for the second subgroup).

‡It is unclear whether raspberries were served at four events (if served, they were in fruit mixtures): one event in New Hampshire (some guests reported that raspberries were served), two events in Texas (Guatemalan raspberries were in the establishments on the days of the events and may have been served), and one event in Ontario (the fruit flan may have included raspberries).

§The four categories of P values are mutually exclusive. A P value was classified as undefined if a row or column total in the two-by-two table was zero and as not determined if a formal epidemiologic investigation of the exposures was not conducted.

¶For each multiday event, the starting date is shown. In a case-control study of a cluster in Maryland (at an independent living facility), ill persons were questioned about the two-week period before the onset of illness and control subjects (well persons in the facility) were questioned about the period from May 18 to June 1.

||Data provided are the total number of attendees for all events in a location (the number of attendees was approximated for 15 events) and the median event-specific interview rates (percentages of attendees who were interviewed).

\*\*ND denotes not determined.

††Strawberries may have been served at this event but probably were not.

‡‡No data are provided for one event in Ontario because no raspberries were served; blackberries from Guatemala were served in a fruit mixture, but it is not known whether they were fresh.

§§The value is the median of the event-specific rate, not of the location-specific medians provided in this column.

¶¶For 2 of the 21 events, consumption of the berry item that included only raspberries was highly correlated with consumption of one or more other items that included other berries.

|||The relative risks (an odds ratio for the Maryland event) for berry items of interest for 54 events at which raspberries were or could have been served included 16 values that were ≥2.0 (8 of which were ≥6.0), 6 that were <2.0, 19 that were infinite (attack rate >0 among exposed persons but 0 among those who were not exposed; no row or column total in the two-by-two table was zero), 6 that were undefined (a row or column total in the two-by-two table was zero), and 7 that were not determined (there was no formal epidemiologic investigation of the exposures).

### Tracing of the Sources of the Raspberries and Environmental Investigation

To identify the sources of implicated raspberries, we obtained dates of purchase and shipment. We used airway bill numbers supplied by importers to identify shipments and exporters and then farms that contributed to shipments. A well-documented tracing of the source was one in which each step from consumers back to farms was confirmed verbally and in writing (e.g., through copies of invoices). We visited farms and exporters in Guatemala to investigate the ways in which raspberries were grown and handled. We also investigated the way in which berries were inspected in the Miami airport. The epidemiologic and source data provided here are those available to the CDC by October 31, 1996.

## RESULTS

### General Epidemiologic Investigation

A total of 1465 cases of cyclosporiasis — 725 cluster-associated cases (49.5 percent) and 740 sporadic cases (50.5 percent) — were reported by 20 states, the District of Columbia, and 2 provinces (Table 1). All sites were east of the Rocky Mountains except the one in Colorado. A little more than half the cases were in females (772, 52.7 percent), 41 (2.8 percent) were in children under 18 years of age, and 3 (0.2 percent) were in persons known to be infected with the human immunodeficiency virus. Twenty-two hospitalizations (1.5 percent of cases) but no deaths were reported.

Overall, 978 cases (66.8 percent) were confirmed by various laboratories. At the CDC, quality-control examination of stained slides of stool specimens from 324 persons reconfirmed 159 of 176 as positive (90.3 percent) and 145 of 148 as negative (98.0 percent). The CDC also demonstrated oocyst sporulation in specimens from 11 persons from five sites. Most laboratory-confirmed cases (>90 percent) were associated with diarrhea, loss of appetite and weight, and fatigue (Table 3).

### Epidemiologic Investigation of Clusters of Cases

Fifty-five clusters of cases associated with attendance at a specific event were reported (Table 2). The events occurred from May 3 through June 14 (Fig. 1A): 22 (40.0 percent) were in private residences; 22 took place in restaurants, clubs, or hotels; and 11 (20.0 percent) occurred elsewhere. A total of 3035 persons attended (median, 28 per event; range, 2 to 1000), 1339 (44.1 percent) of whom were interviewed; of these, 772 had an event-associated illness, 725 (54.1 percent of 1339) were designated as case patients, and 238 (32.8 percent of 725) had laboratory-confirmed cases. The median event-specific attack rate among the persons interviewed was 56.3 percent (range, 19.0 to 100 percent; information was available for 53 events). Incubation periods for cases ranged from 1 to 14 days (by definition, <15); the median of the event-specific median incubation periods was 7 days.

The only type of exposure consistently associated

with cyclosporiasis was the consumption of raspberries; they were definitely served at 50 events and may have been served at 4 events (Table 2). Whereas raspberries were definitely not served at only 1 event (an event in Ontario at which Guatemalan blackberries were included in a fruit mixture), strawberries, blackberries, and blueberries were not served at a minimum of 13 (23.6 percent), 30 (54.5 percent), and 32 (58.2 percent) events, respectively. Although investigations of three May events had initially implicated strawberries, on reevaluation of the menus raspberries either were included (at an event in Ontario) or may have been included (at two events in Texas) among the implicated berry items. For at least 10 and probably 11 (20.0 percent) of the 55 events, raspberries were the only berry served; for at least 3 other events, other berries but no strawberries were also served.

The median of the event-specific attack rates among persons who ate the berry items that contained or may have contained raspberries, with or without other berries, was 93.3 percent (range, 29.6 to 100 percent; information was available for 47

**TABLE 3.** SYMPTOMS ASSOCIATED WITH 760 LABORATORY-CONFIRMED CASES OF CYCLOSPORIASIS IN THE UNITED STATES AND CANADA IN 1996.\*

SYMPTOM	No. WITH SYMPTOM/ No. WITH AVAILABLE DATA (%)†
Diarrhea‡	750/759 (98.8)
Loss of appetite	471/507 (92.9)
Fatigue	608/658 (92.4)
Weight loss§	584/644 (90.7)
Abdominal bloating or gas	236/282 (83.7)
Abdominal cramps or pain	519/695 (74.7)
Nausea	509/713 (71.4)
Muscle, joint, or body aches	204/310 (65.8)
Fever¶	348/649 (53.6)
Chills	124/252 (49.2)
Headache	106/224 (47.3)
Constipation	47/148 (31.8)
Vomiting	187/697 (26.8)

\*Data on symptoms were available for 760 case patients, including 643 with sporadic cases and 117 with cluster-associated cases. The median duration of illness was  $\geq 14$  days (range, 1 to 60) among 417 case patients for whom this information was available (at least 24 [5.8 percent] were still ill when interviewed); the duration of diarrheal illness was used for 202 case patients for whom the duration of the entire illness was unknown.

†The denominators for the various symptoms vary because not all sites collected data on all symptoms.

‡The median number of stools per day was 6 (range, 1 to 48) among the 536 case patients for whom this information was available. The median duration of diarrheal illness was 10 days (range, 1 to 60) among the 209 case patients for whom this information was available. Ten case patients noted bloody stools.

§The median weight loss was 3.6 kg (range, 0.9 to 18.2) among the 384 case patients for whom this information was available.

¶The median self-reported temperature was 38.3°C (range, 37.2° to 39.4°) among the 106 case patients for whom this information was available.

events). When we excluded from the 55 events the 1 event at which raspberries were definitely not served, the 6 events for which the P value was undefined, and the 7 events for which the P value was not determined, the associations between these berry items and cyclosporiasis were statistically significant ( $P < 0.05$ ) for 27 of the remaining 41 events (65.8 percent) (Table 2). When the events at which only mixtures of berries were served or the con-

sumption of various berries was highly correlated were also excluded, raspberries could be specifically implicated in 10 events.

Raspberries were served fresh, except perhaps at two events (at which their status was unknown or they were stored briefly in a freezer). They reportedly had been rinsed at 33 of 41 events (80.5 percent) for which such information was available. Raspberries were used as garnishes (e.g., for a lemon tart) at 14 or more events, with an estimated median number of raspberries per serving of 2.5 (range, 1 to 7.5 for 7 events), and were included in sauces at 4 or more events, including 2 at which garnishes were used.

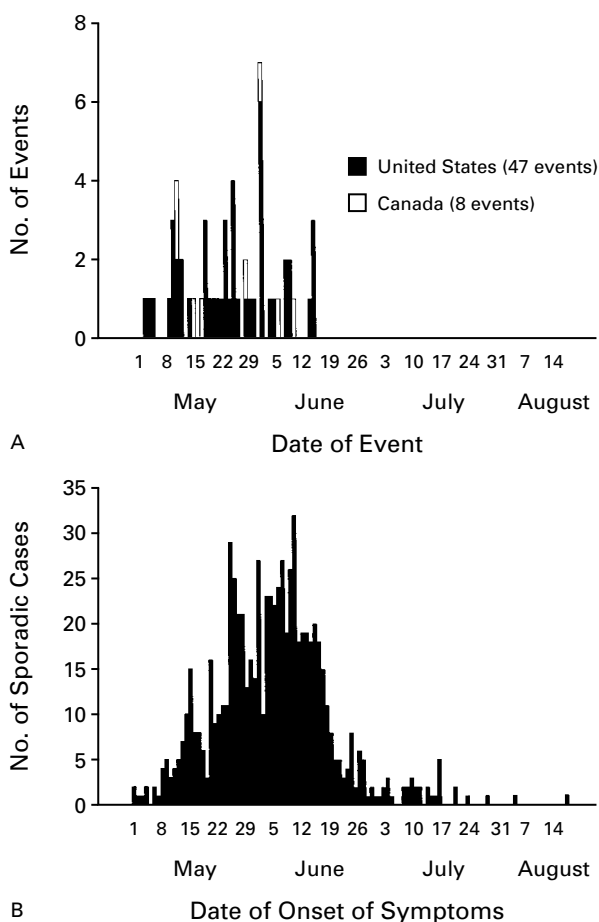
#### Sporadic Cases

The 740 sporadic cases occurred among persons whose median age was 49 years (range, 1 to 92; age was known for 717 case patients), were distributed approximately equally between the sexes (383 of 739 occurred in females; 51.8 percent), and developed from May 1 through August 17 (Fig. 1B). The proportions of sporadic cases in which fresh strawberries, raspberries, blueberries, and blackberries were reportedly eaten were 79.4 percent (501 of 631), 57.8 percent (365 of 632), 32.2 percent (138 of 429), and 19.3 percent (111 of 576), respectively. Among the 130 cases in which strawberries were not eaten, raspberries were eaten in 65 (50.0 percent); among the 267 cases in which raspberries were not eaten, strawberries were eaten in 200 (74.9 percent).

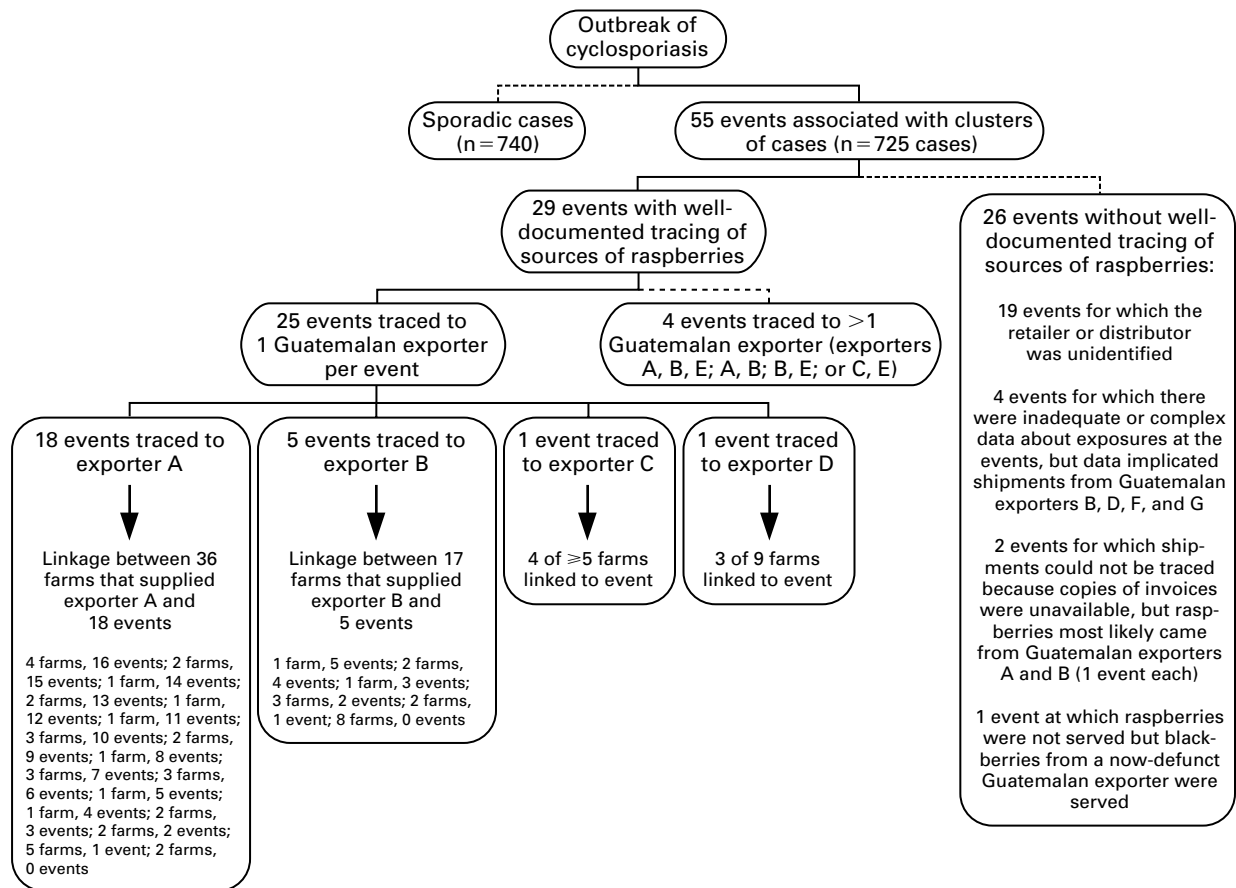
#### Tracing of Sources and Environmental Investigation

We attempted to trace the sources of raspberries for the 54 events at which raspberries were or may have been served. Those served at all 29 events for which we had well-documented data on the source (Fig. 2 and Table 2) either definitely were from Guatemala (21 events, 72.4 percent) or could have originated there (8 events, 27.6 percent, for which at least one of the raspberry shipments that could have been used came from Guatemala). The raspberries served at these events, which occurred from May 5 through June 14, were shipped from Guatemala from May 1 through June 5; seven exporters, of which A and B were the largest, shipped to the United States throughout this period.

The raspberries for 25 of the 29 events (86.2 percent) were traceable to one (vs. more than one) Guatemalan exporter per event: 18 of 25 (72.0 percent) to exporter A, 5 (20.0 percent) to exporter B, 1 (4.0 percent) to exporter C, and 1 (4.0 percent) to exporter D (Fig. 2). The raspberries at 11 of these 25 events (44.0 percent) were traceable to one (vs. more than one) shipment per event (median interval from shipment to consumption, 7 days; range, 3 to 15). Overall, the implicated raspberries for these 25 events could have been obtained from 39 shipments (May 1 through June 4) to eight importers. The ship-



**Figure 1.** Dates of Events Associated with 55 Clusters of Cases of Cyclosporiasis (Panel A) and Dates of the Onset of Symptoms of 737 Laboratory-Confirmed Sporadic Cases of Cyclosporiasis (Panel B) in the United States and Canada in 1996. In Panel A, the dates of events ranged from May 3 through June 14. For multiday events, the first day is indicated. For the cluster in Maryland, the first day of the two-week period about which control subjects in the case-control study were questioned is indicated (May 18). In Panel B, the dates of the onset of symptoms ranged from May 1 through August 17. The dates were known or approximated for 737 of the 740 case patients who reportedly became ill on or after May 1; 50 percent became ill by June 5, and 90 percent by June 20. An additional 39 patients with possible cyclosporiasis were excluded from the investigation because of uncertainty about whether they became ill on or after May 1.



**Figure 2.** Flow Chart Tracing the Sources of Raspberries Served at Events Associated with Clusters of Cases of Cyclosporiasis in the United States and Canada in 1996.

With respect to the 25 events traced to one Guatemalan exporter per event, 2 events in Texas were included at which it is not certain that raspberries were served; Guatemalan raspberries were in the establishments on the days of the events. Exporter E, a possible supplier for three events, exported raspberries only from the one farm it owned. A farm was linked to an event if it contributed to a shipment of raspberries that could have been used at the event. For example, for exporter A, each of four farms could have been the source of raspberries served at each of 16 events (not necessarily the same 16 events for each farm). For the 18 events for which exporter A was the sole possible Guatemalan supplier, 27 shipments (of 92 from exporter A from May 1 to June 5, the period of interest) were potentially implicated, to which 34 farms contributed raspberries (of 36 farms that sold to exporter A throughout the period of interest). A median of 11 farms contributed to each shipment (range, 3 to 28), which contained a median of 854 kg of raspberries (range, 182 to 2467). For the five events for which exporter B was the sole possible Guatemalan supplier, 10 shipments (of 100 possible for exporter B during the period of interest) were potentially implicated, to which 9 farms contributed (of 17 that sold to exporter B throughout the period of interest). A median of 2 farms contributed to each shipment (range, 1 to 6), which contained a median of 624 kg of raspberries (range, 454 to 1342).

ments arrived on five airline carriers at four U.S. ports of entry: Miami (33 shipments, 84.6 percent), the District of Columbia (3, 7.7 percent), Houston (2, 5.1 percent), and Los Angeles (1, 2.6 percent). In Miami, which was the port of entry for at least one shipment per event for all events except one, shipments were inspected in four cargo-clearance areas. Because exporters typically combined raspberries from multiple farms in a shipment, even a well-documented tracing of the source could identify only a group of contributing farms (median, 10 farms per event; range, 2 to 30) rather than one source farm.

However, as few as five farms — two for exporter A and one each for exporters B, C, and D — could have accounted for all 25 events (Fig. 2).

Thirty-four of the 36 farms that sold raspberries to exporter A throughout the period May 1 through June 5 were potential source farms for at least 1 of the 18 events linked solely to this exporter. Various combinations of 2 of the 34 farms could have accounted for all 18 events; each of 4 farms could have supplied raspberries for 16 of the 18 events (88.9 percent), and each of 2 other farms to 15 events (Fig. 2). The six most commonly implicated farms

are in the same region of Guatemala, began harvesting simultaneously in 1996, and often had raspberries in the same shipments. Five of the farms obtained agricultural water from wells, which varied in construction, depth, and quality; two of the five farms also stored well water in reservoirs constructed of concrete blocks and covered with concrete. The sixth farm used river water.

Nine of the 17 farms that sold to exporter B were potential source farms for at least one of the five events linked solely to this exporter. One of these nine farms could have supplied raspberries to all five events. This farm, which is 25 km from the closest of the six most implicated farms that sold raspberries to exporter A, used well water, which also was stored in a mesh-covered, plastic-lined, dug reservoir.

Agricultural water on the seven most commonly implicated farms that sold raspberries to exporter A or B and on Guatemalan raspberry farms in general is filtered to remove debris but not microbes. In the late summer of 1996, testing of agricultural-water samples from the seven farms indicated at least intermittent bacterial contamination, including fecal coliforms or *Escherichia coli* (data not shown). To avoid direct contact between berries and water, ground-level drip irrigation is used (primarily during the dry season). However, agricultural water is also used to mix insecticides and fungicides that are sprayed directly onto raspberries, sometimes as late as the day they are picked. Berries are picked and sorted by hand, packed on the farms in plastic "clamshells," usually kept cool thereafter, and flown to the United States within 36 hours of picking.

## DISCUSSION

Our investigation of a large outbreak of cyclosporiasis implicated Guatemalan raspberries. The strength of the investigation was in the collective evidence from clusters of cases associated with 55 events, at virtually all of which raspberries were served; hundreds of sporadic cases; and 29 events for which there was well-documented tracing of the sources of raspberries. We could not assess the true magnitude of the outbreak; most cases were probably undetected and unreported. For salmonellosis, a more familiar and easily diagnosed condition than cyclosporiasis, the number of cases reported to the CDC probably represents only 1 to 5 percent of all cases of infection in a year.<sup>26</sup> During routine testing for ova and parasites, stool specimens are not usually examined for cyclospora, and many laboratories do not yet have the expertise to identify it (CDC: unpublished data). Experienced personnel in a few sites were instrumental in detecting the outbreak of cyclosporiasis at its inception in May 1996, and subsequent media coverage most likely facilitated the identification of cases.

Data on the sporadic cases, like the data that we

presented on the events, support the association between raspberries and cyclosporiasis. The dates of the events associated with the clustered cases and the dates of the onset of symptoms in sporadic cases were similarly distributed (Fig. 1), which suggests that both types of cases were attributable to the same type of exposure. Data from matched case-control studies of sporadic cases in New York City, New Jersey, and Florida demonstrated strong associations with raspberries<sup>15,17,18</sup> (and New York City Department of Health: unpublished data). Although not all case patients recalled eating raspberries, explanations include poor recall, which is expected for foods served as garnishes and in sauces, and other vehicles or modes of transmission for some background cases. A case-control study in Canada showed similarly strong, independent associations with both raspberries and strawberries,<sup>19</sup> but it was the latest case-control study conducted and may have had the most potential for recall bias.

The data tracing the sources of raspberries served at the events consistently implicated Guatemalan raspberries; this finding is especially noteworthy since raspberries from other countries were readily available during the outbreak period. In April, May, June, and July 1996, Guatemalan raspberries represented only 3.8 percent (14,000 of 368,000 kg), 19.8 percent (109,000 of 550,000 kg), 8.7 percent (155,000 of 1,786,000 kg), and 5.1 percent (27,000 of 532,000 kg), respectively, of fresh raspberries (domestic and imported) shipped within the United States (figures calculated on the basis of government data<sup>27-29</sup>). For example, in May 1996, only 36.6 percent and 37.5 percent of raspberries at market sites in New York City and Newark and in Baltimore and the District of Columbia, respectively, were grown in Guatemala; for Los Angeles and for San Francisco and Oakland, western sites that did not report cases, the respective percentages were 6.7 and 5.3.

Given that there were many differences in various aspects of the distribution systems for the implicated raspberries, simultaneous and persistent contamination on multiple farms is the most likely explanation for the outbreak. We do not know whether the contaminating oocysts came from humans or animals. Likewise, we do not know whether the oocysts were unsporulated (e.g., on workers' hands), in which case they would have required at least several days to sporulate, or had already sporulated (e.g., in soil or water). The prevalence of human cyclospora infection in Guatemala is being investigated by the CDC. Despite some suggestive evidence,<sup>9,11,30-32</sup> to date no animals, including chickens and other birds, have been identified as reservoirs of infection for cyclospora isolates that infect humans.

Postulating a role for contaminated water is appealing because waterborne transmission of cyclospora has been implicated previously.<sup>3,11,33</sup> One hypothesis is

that raspberries became contaminated through spraying with insecticides and fungicides that had been mixed with contaminated water. Although we have not determined how water supplies on different farms could have become contaminated with oocysts during the same period, many water supplies were vulnerable to contamination because, for example, they were suboptimally constructed or maintained wells near deep pit latrines or seepage pits. They may have been particularly vulnerable during the rainy season (e.g., from surface-water runoff), which is when the 1996 outbreak occurred. No oocysts were found in samples of water and raspberries that were tested (data not shown), but the samples were obtained after the outbreak period, and the testing methods are insensitive. Once contaminated, by whatever means, fresh raspberries may remain contaminated until eaten because they are too fragile and replete with crevices<sup>34</sup> to be washed thoroughly. The high attack rates noted for most events, sometimes despite the consumption of only a few raspberries, suggest that the infectious dose of oocysts is low or the number of oocysts per berry was high, or both.

Although the mode of contamination remains unclear, our ability to pursue the investigation to the source of the raspberries resulted from the cooperation of the Guatemalan berry industry. The industry is now implementing a Hazard Analysis and Critical Control Point system; in such systems, selected points in production at which preventive and control measures can minimize or eliminate hazards are closely monitored.<sup>35,36</sup> We have recommended that potable water (e.g., water from a properly constructed and monitored deep well or water treated in ways that eliminate chlorine-resistant cyclospora oocysts) be used for drinking, hand washing, cleaning surfaces that touch berries, and mixing substances sprayed onto berries. Provision of better sanitary facilities for workers will decrease the potential for direct or indirect contamination of berries. Efforts to decrease the risk of cross-contamination should focus on the identification of the types of surfaces and cleaning solutions to use where berries are sorted and inspected. The effect of gamma irradiation on cyclospora oocysts is being investigated (Dubey JP: personal communication). Investigations of the source of the berries would have been easier if clamshell containers and invoices had been identified according to the source farm (e.g., with bar codes).

In summary, cyclospora has now been established to be a foodborne pathogen. This outbreak is a reminder that our supply of fresh produce has become increasingly international<sup>37-39</sup> and underscores the need to identify and investigate foodborne outbreaks promptly, to consider that a local cluster of cases could be part of a widespread outbreak, and to pursue investigations to the source of the implicated vehicle.<sup>39</sup> For imported vehicles, international collabo-

ration is critical to the success of the investigation and to the identification of appropriate measures of prevention and control.

## APPENDIX

The Cyclospora Working Group included the following (asterisks denote members of the Epidemic Intelligence Service, Epidemiology Program Office, CDC): California Department of Health Services, Food and Drug Branch — J. Farrar and S. Richardson, Jr.; Connecticut Department of Public Health and Addiction Services — R. Nelson; District of Columbia Department of Health — M. Fletcher and M. Levy; Florida: Florida Department of Health — D. Katz,\* and Palm Beach County Health Department — S. Kumar, J. Malecki, and M. Lowdermilk; Illinois: Lake County Health Department — L. Mackey and J. Bell; Maryland: Maryland Department of Health and Mental Hygiene — D. Portesi, and Montgomery County Department of Health and Human Services — C. Lacey; Massachusetts: Massachusetts Department of Public Health — L. Letendre, D. Hamlin, and R. Knowlton, and Boston Department of Health and Hospitals — A. Barry; New Jersey Department of Health and Senior Services — D. Chew,\* L. Finelli, and C. Genese; New York: New York City Department of Health — J. Miller and M. Layton, and New York State Department of Health — J. Guzewich; Ohio Department of Health — E. Salehi; Pennsylvania Department of Health — A. Weltman; South Carolina Department of Health and Environmental Control — V. Caceres\* and R. Ball; Texas: Texas Department of Health — B. Barnett,\* K. Hendricks, and J. Taylor, and Houston Department of Health and Human Services — R. Bell; Vermont Department of Health — S. Schoenfeld; Food Safety Consultation and Training — F. Bryan; Canada: Health Canada — S. Neamatullah and D. Werker, North York Public Health Department — D. Manuel, Ontario Ministry of Health — C. Le Ber, Montreal Children's Hospital — M. Arrieta, and Agriculture and Agri-Food Canada — D. Morrison; Medical Entomology Research and Training Unit, Guatemala — R. Klein; National Center for Infectious Diseases, CDC: Division of Parasitic Diseases — S. Wahlquist, E. Alfano, M. Eberhard, M. Arrowood, K. Hannak-Donaldson, M. Beach,\* M. Kramer,\* and A. Hightower, Division of Bacterial and Mycotic Diseases — D. Swerdlow, J. Winickoff, and R. Shapiro,\* and Epidemiology Program Office — M. Messonnier.

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