

Cyclosporiasis: Detecting, Investigating, and Preventing Cases and Outbreaks of this Foodborne Parasitic Disease

**Clinician Outreach and
Communication Activity (COCA)**

Webinar

June 18, 2015

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Objectives

At the conclusion of this session, the participant will be able to:

- ❑ Discuss what is known about how and where *Cyclospora cayetanensis* is transmitted
- ❑ Describe the available approaches for diagnosing, treating, and preventing *Cyclospora* infection, including the limitations of the approaches
- ❑ Explain why timely reporting of *Cyclospora* cases to public health authorities is essential
- ❑ Discuss the reported U.S. foodborne outbreaks of cyclosporiasis, including the findings and constraints of the outbreak investigations

TODAY'S PRESENTER



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CAPT, US Public Health Service

Medical Epidemiologist

Division of Parasitic Diseases and Malaria
Centers for Disease Control and Prevention

Cyclosporiasis is an enteric illness
caused by *Cyclospora cayetanensis*,
an enigmatic emerging parasite,
which was named
as recently as the early 1990s
& has repeatedly caused
U.S. foodborne outbreaks



Cyclospora's timeline*

Outbreaks

Other occurrences

What type of microbe?

1st documented U.S. outbreak (Chicago)

Waterborne outbreak (Pokhara, Nepal)

Many
~~Multiple~~ foodborne
outbreaks in North
America linked to various
types of fresh produce

'77 1st 3 documented cases of infection with "undescribed coccidian" diagnosed in
'78 Papua New Guinea

'79

'80

'81

'82

'83 1st documented cases in Haiti ("Big Crypto"), in patients with AIDS

'84

'85 1st documented case in Peru ("*Cryptosporidium muris*-like object")

'86 1st documented U.S. cases, in 4 travelers returning from Haiti and Mexico

'87

'88

'89 1st documented cases in Nepal, in 55 foreigners

'90

'91 Name "cyanobacterium-like or coccidian-like body (CLB)" used

'92

'93 Organism confirmed to be a coccidian parasite

'94 Name *Cyclospora cayetanensis* proposed

'95 Trimethoprim-sulfamethoxazole shown to be effective

'96 Phylogenetic relationship to *Eimeria* species shown

'97

'98

'99 →... 2015 (It's not "going away")



Cyclospora cayetanensis: **Knowns & unknowns**

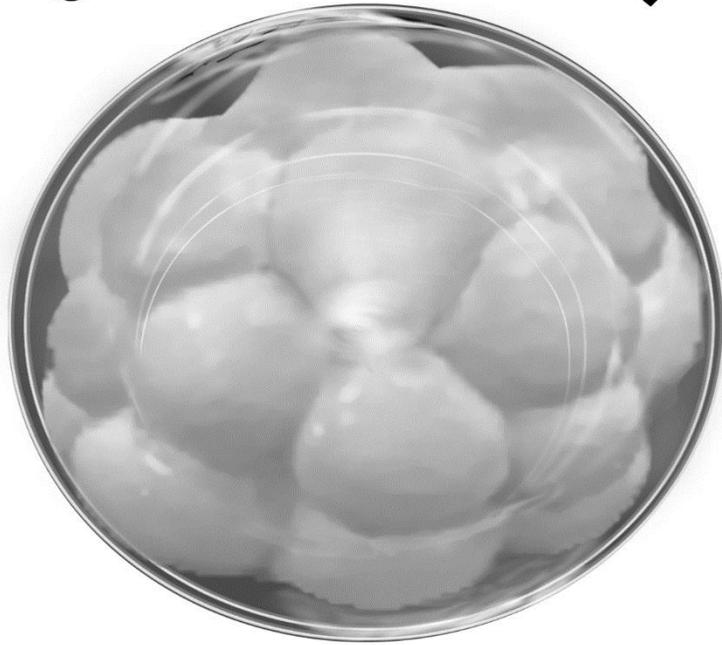
	Now known	Still unknown
Pathogen	Parasite (<u>not</u> an alga or fungus) – Protozoan (ie, unicellular) – Coccidian (oocysts <u>not</u> cysts)	Do <u>other</u> <i>Cyclospora</i> species infect humans?
Host	Humans – Gastrointestinal tract – Asexual & sexual stages	Are there any <u>nonhuman</u> hosts of <i>C. cayetanensis</i>?
Extrinsic maturation	<u>Not</u> infective when shed in stool – Requires days to weeks to sporulate & become infective	How quickly can the parasite sporulate under optimal environmental conditions?
Transmission	Fecally contaminated food / H₂O – <u>No</u> risk if ingest <u>un</u> sporulated oocysts, even if large inoculum	What accounts for seasonality of cases, which varies among <i>Cyclospora</i>-endemic regions?



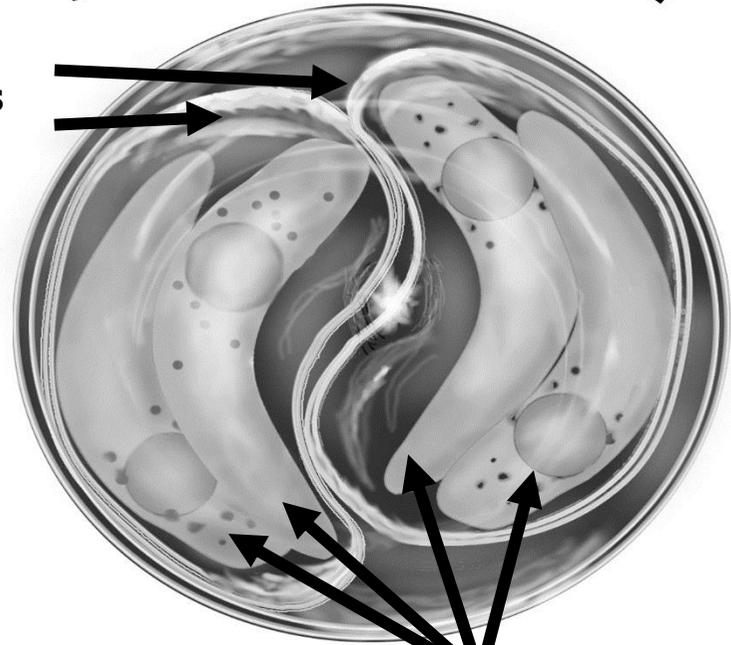
unsporulated

sporulated

Graphic illustration



2 sporocysts



4 sporozoites

Microscopy
(DIC)

sporulation



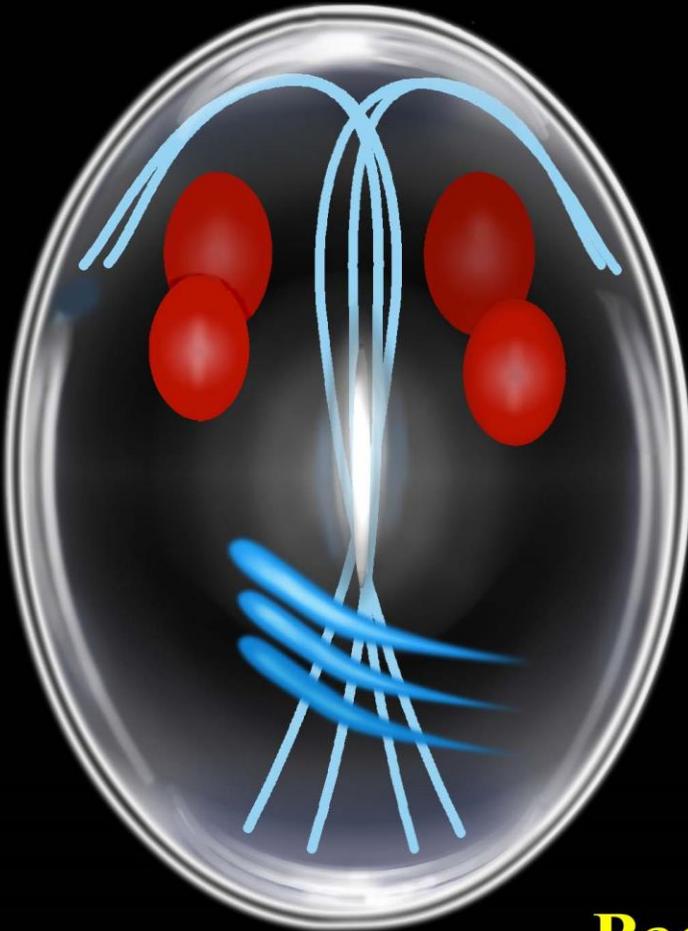
(undifferentiated cytoplasm)



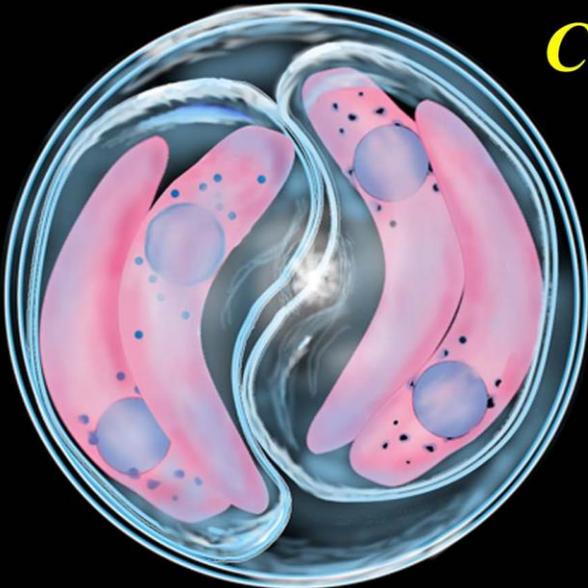
(fully differentiated)

Relative sizes of microbes

Giardia



Cyclospora



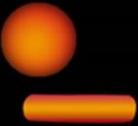
Cryptosporidium



8 - 10 micrometers

Bacteria

Virus



(Herwaldt BL. Clin Infect Dis 2000;31:1040-57.)

Cyclospora: Transmission & risk factors

- **Infected people shed an immature form of the parasite in their feces, which has to mature (*sporulate*) to become infective**
 - Environmental conditions conducive to oocyst sporulation & survival are poorly understood
 - Direct person-to-person transmission is highly unlikely
- **Two well-established risk factors for U.S. cases:**
 - International travel to cyclosporiasis-endemic regions (eg, in parts of the tropics & subtropics)
 - Domestic consumption of contaminated fresh produce imported from such regions



Prevention of *Cyclospora* infection

- Persons planning to travel to the tropics or subtropics should be told that **food & water precautions** for *Cyclospora* are similar to those for other intestinal pathogens—except that:
 - *Cyclospora* is not likely to be killed by routine chemical disinfection or sanitizing methods (eg, with chlorine or iodine)
- No *Cyclospora* vaccine is available



Clinical features of symptomatic *Cyclospora* infection

- **The incubation period typically is ~1 week** (range, ~2 days to 2+ weeks)—which adds to delays in detecting & investigating cases & outbreaks
- **The most common symptom is watery diarrhea, which can be profuse**
 - Other common abdominal symptoms include anorexia, weight loss, bloating/gas, cramps/pain, & nausea
 - Body aches & low-grade fever may be noted
- **If untreated, the illness may last for days to weeks to months, with remitting-relapsing symptoms—ie, not a brief, trivial illness**
 - Substantial weight loss & prolonged fatigue commonly occur



Symptoms of *Cyclospora* infection

(1996 US outbreak*; N = 760 case-patients with available data†)

Symptom	Percentage
Diarrhea (<i>watery; <u>not</u> bloody</i>)	99%
Anorexia	93%
Fatigue	92%
Weight loss	91%
Bloating / gas	84%
Abdominal cramps / pain	75%
Nausea	71%
Aches	66%
Fever (<i>typically, low grade</i>)	54%
Vomiting	27%

* Herwaldt BL, et al. N Engl J Med 1997;336:1548–56.

† The number with available data differed for the various symptoms.



Diagnosis of *Cyclospora* infection

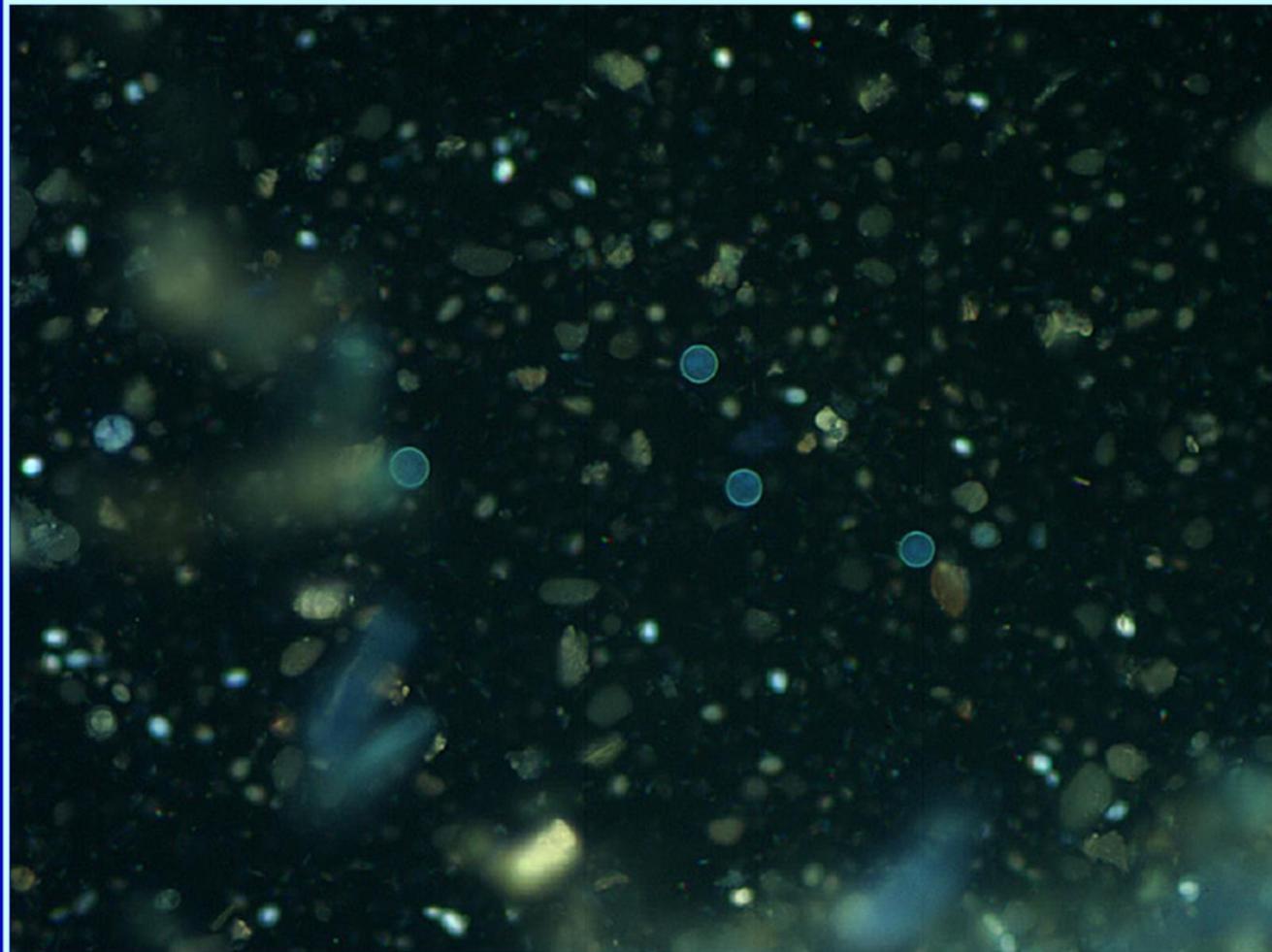
If indicated, consider the diagnosis & request testing:

- Stool specimens examined for ova & parasites (O & P) usually are not examined for *Cyclospora* unless such testing is requested *explicitly*
- *Even persons with profuse diarrhea might not shed enough *Cyclospora* oocysts to be readily detectable*
 - Several specimens, from different days, may need to be examined
 - The lab should use sensitive recovery & detection methods
- CDC & other reference labs can provide diagnostic assistance & confirmatory testing, using microscopic & molecular techniques

Not available: methods to culture (or propagate / maintain) the parasite, molecular tools for strain differentiation, serologic assays,



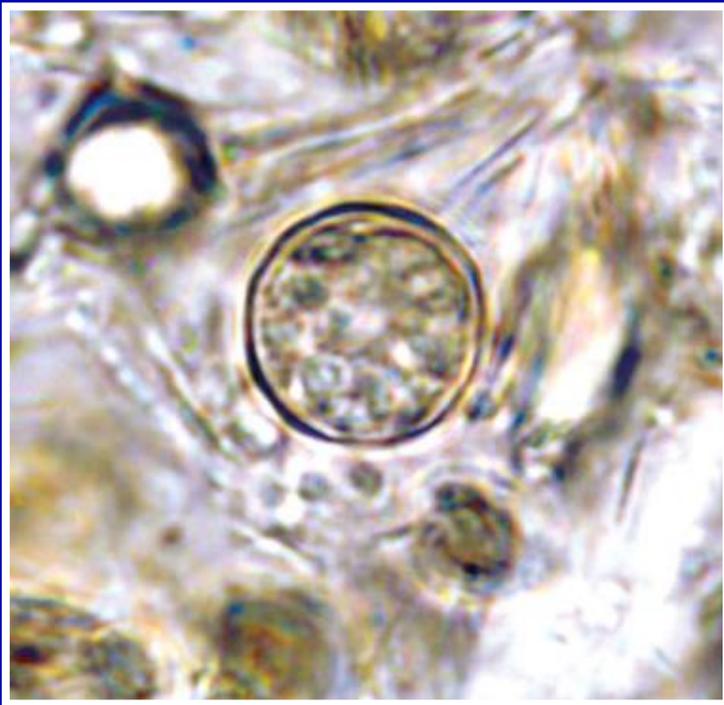
Cyclospora oocysts are autofluorescent (UV fluorescence microscopy)



Detection of *Cyclospora* oocysts by microscopy

Easy to miss

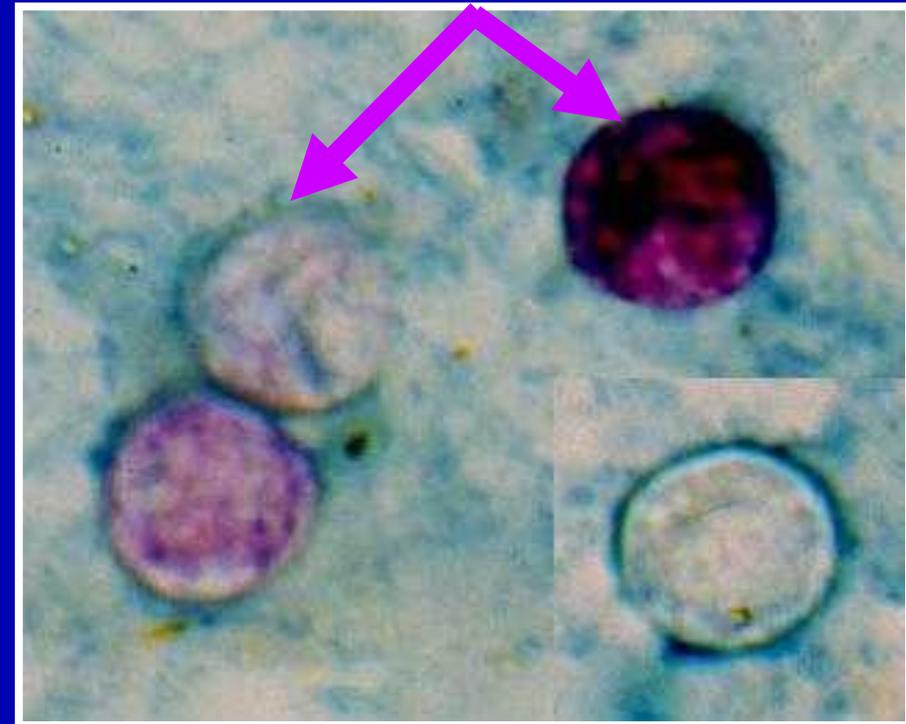
(blends in with background
on an unstained slide)



Easy to spot
(autofluorescent)



Variably acid fast
(not all oocysts retain the stain)



Treatment of *Cyclospora* infection

- **The treatment of choice is trimethoprim-sulfamethoxazole (TMP/SMX)***
 - Typical regimen for immunocompetent adults is 1 double-strength tablet (*TMP 160 mg; SMX 800 mg*), twice a day, for 7 to 10 days
- **No *highly effective* alternatives to TMP/SMX have been identified yet for persons who are allergic to or cannot tolerate TMP/SMX**
- **The fact that the therapy (ie, TMP/SMX) differs from the medications used for most other enteric protozoan infections (eg, giardiasis, amebiasis, cryptosporidiosis) highlights the importance of diagnosing infection rather than treating empirically**

* Off-label use (not an FDA-approved indication)



Cyclospora's timeline: what was known & what occurred in & since the mid-1990s*

Outbreaks

Other occurrences

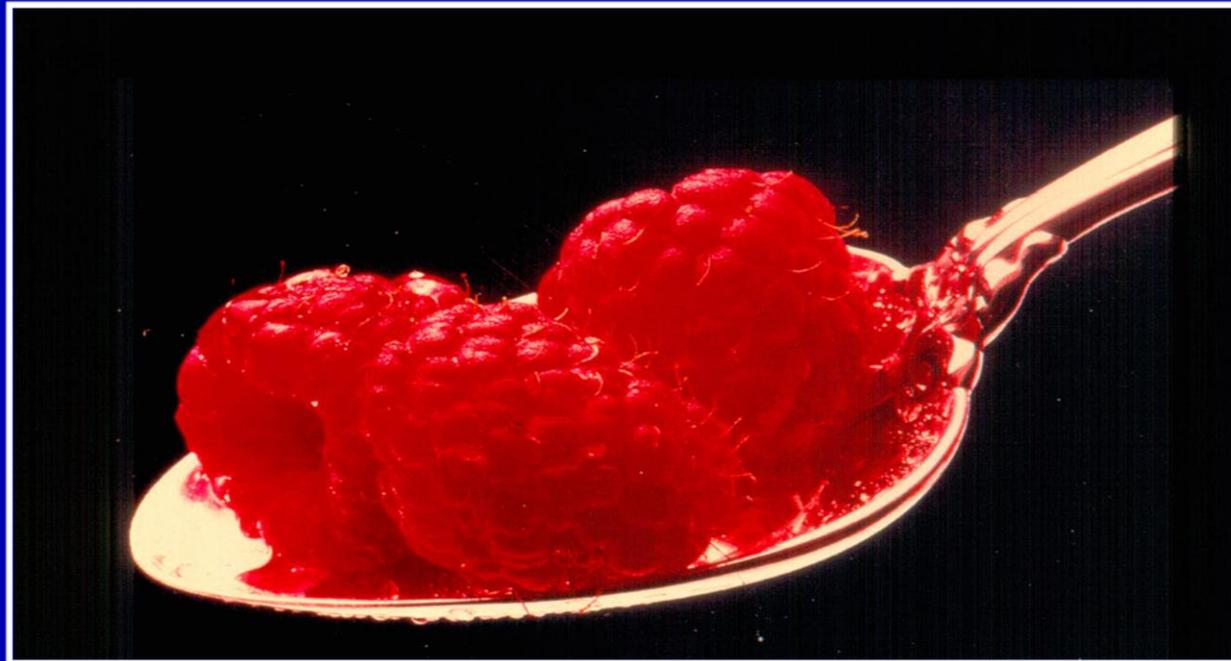
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**Who would have predicted that a
protozoan parasite
would repeatedly cause
large foodborne outbreaks?**



The series of spring outbreaks of cyclosporiasis
linked to **Guatemalan raspberries**
underscores recurring themes & challenges



The beginning (1995–1997): *From small harbinger outbreaks to large raspberry-associated outbreaks*

1,465 reported cases

(20 states, Wash DC,
2 provinces)

1,012 reported cases

(17 states, Wash DC,
2 provinces)

(harbingers)

(70 reported cases;
2 eastern states)

1995

1996

1997

1998

1999

2000



***Cyclospora* oocysts, cases, & outbreaks are easily missed**
— 1 oocyst, 1 tech, 1 case, 1 call ... can make a difference —

In the large, multistate outbreaks in **1996 & 1997**

- **1996:** Index cases were detected in 2 states that had lab personnel with unusual expertise regarding *Cyclospora*
- **1997:** Several index cases/clusters were detected because of unusual circumstances (eg, case-patients were health professionals who knew to consider the diagnosis of *Cyclospora* infection)



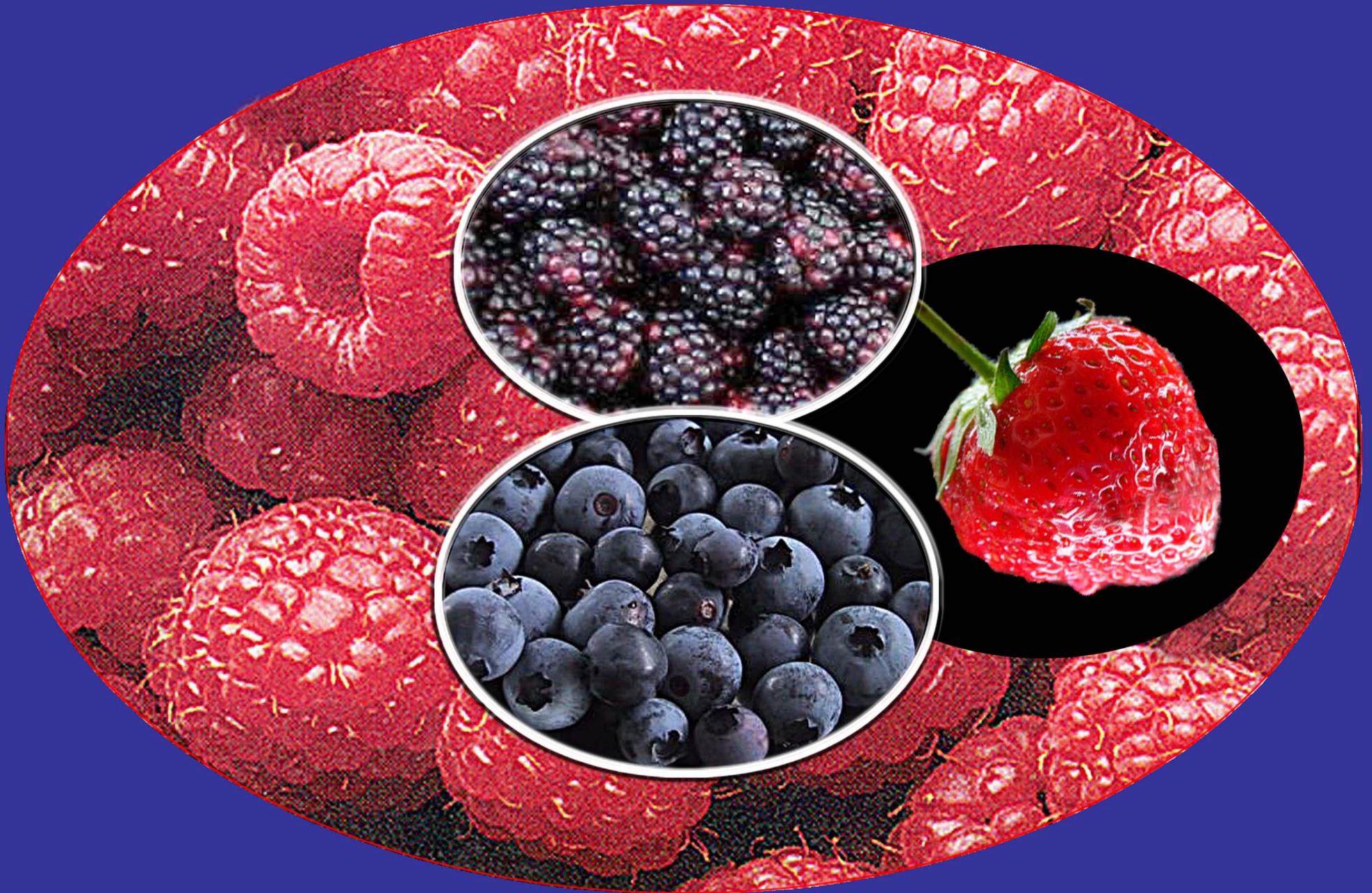
Fresh produce often is served in mixtures & inconspicuous ways (eg, garnishes)

- Look for commonalities among different case clusters & for epidemiologic associations with illness —**

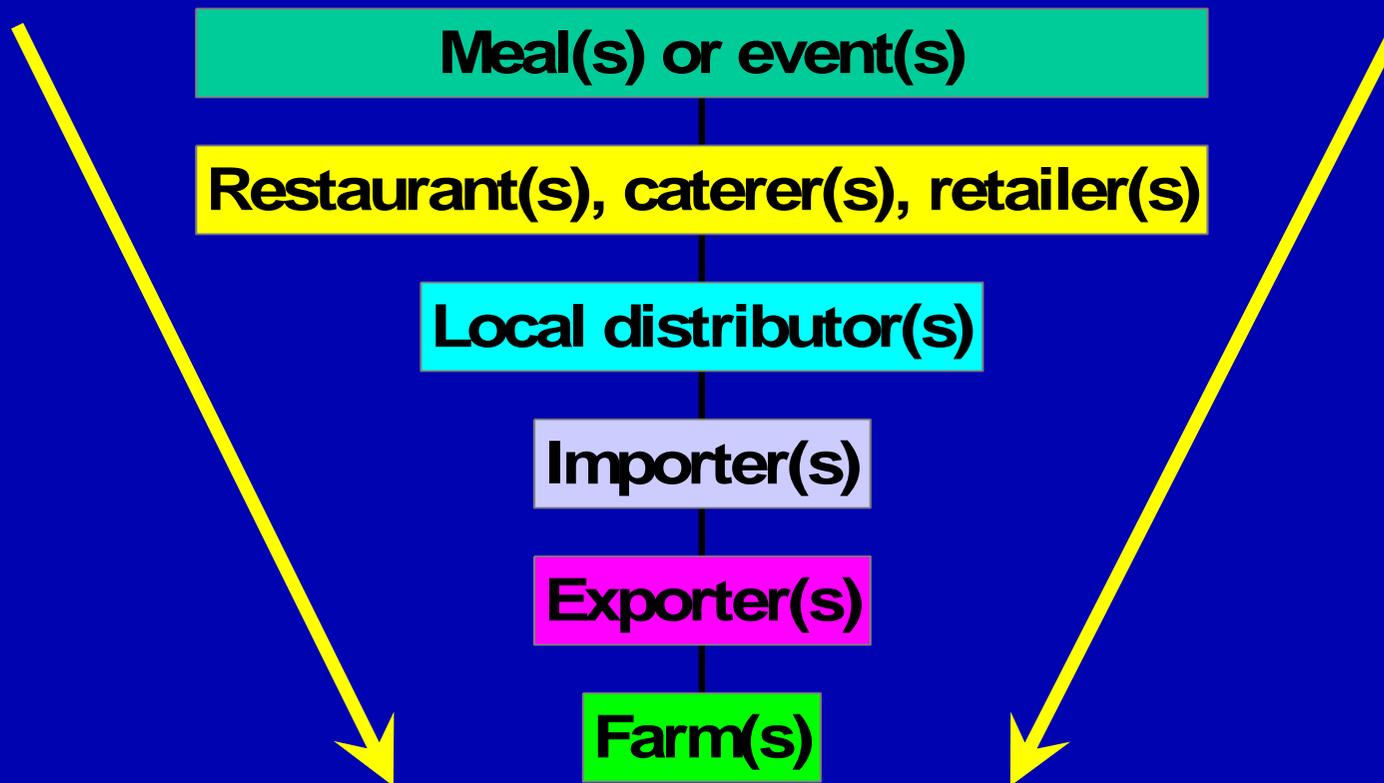


**Would you even remember this garnish?
Would the chef? Would the details be
specified on the menu or other records?**

Raspberries were the common theme



Traceback investigations for fresh produce often are very challenging



Compelling, aggregate, multi-cluster traceback data
linked the implicated raspberries to Guatemala



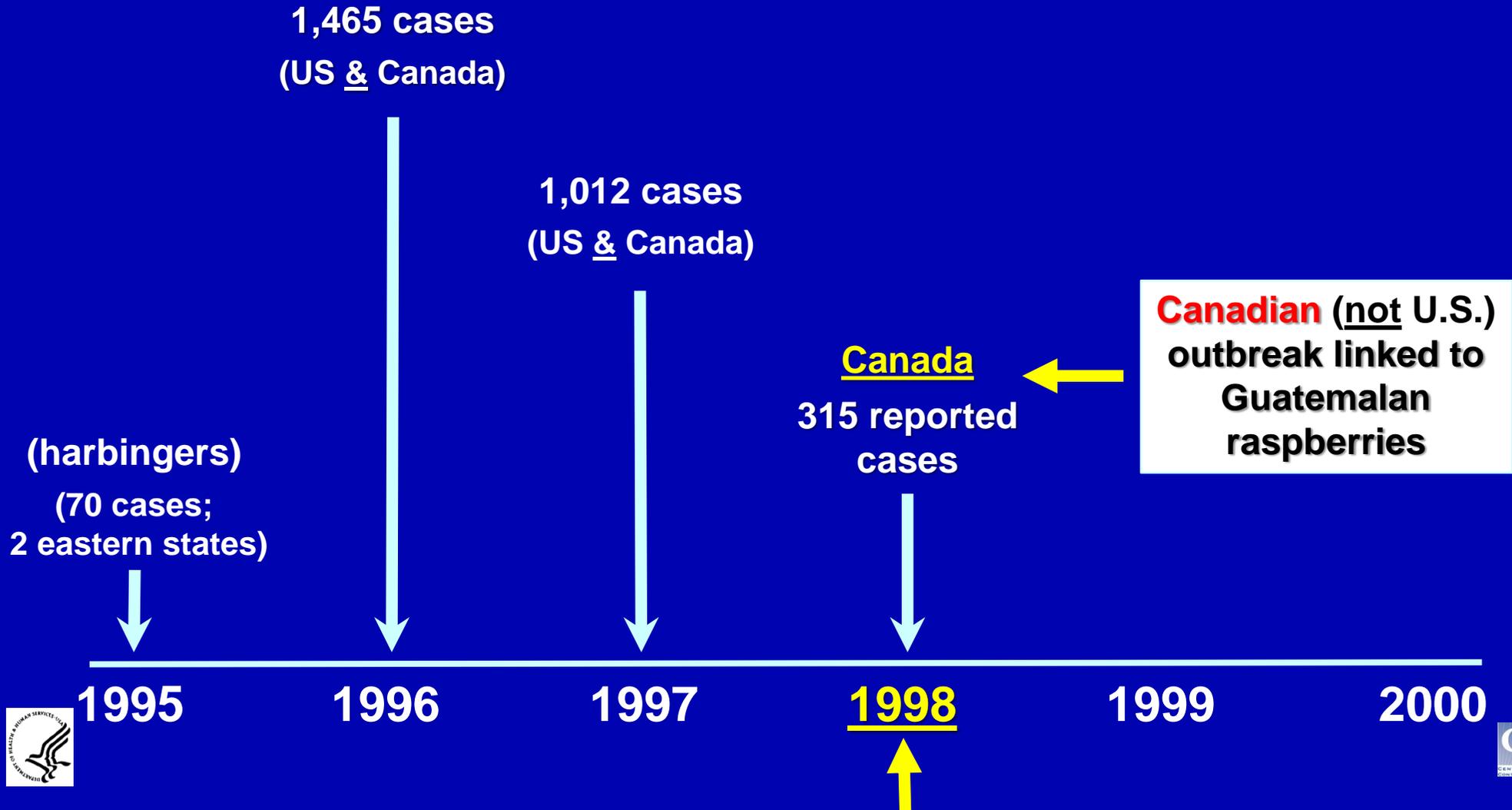
Guatemalan raspberries: suspension of exports

- On **May 30, 1997**—*at FDA's request*—the government of Guatemala & the Guatemalan Berry Commission announced their decision to voluntarily suspend exports of fresh raspberries to the United States
- Shipments could resume in mid-**August 1997**
- In **1998**, as planned, shipments were suspended from mid-**March** through mid-**August**
 - ***But*** this applied only to the United States—**not** to *Canada*



Spring 1998: evidence from an inadvertent intervention trial

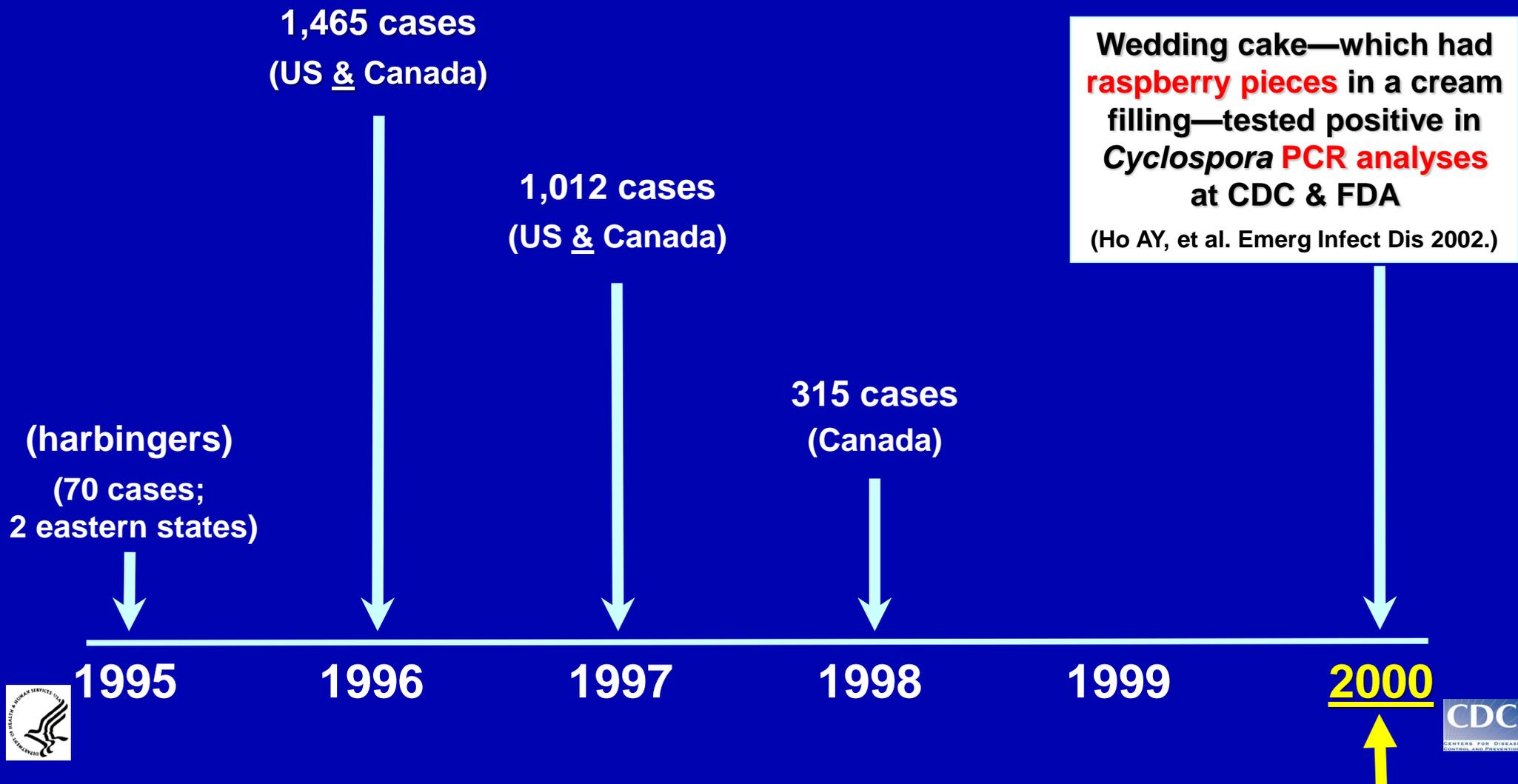
— **Canada (not USA)** imported Guatemalan raspberries & had an outbreak —



It is **very** unusual to have
implicated produce items
still available for *Cyclospora* testing



Spring 2000: Evidence regarding Guatemalan raspberries was strengthened further by detection of *Cyclospora* DNA in frozen leftovers of an epidemiologically implicated food item

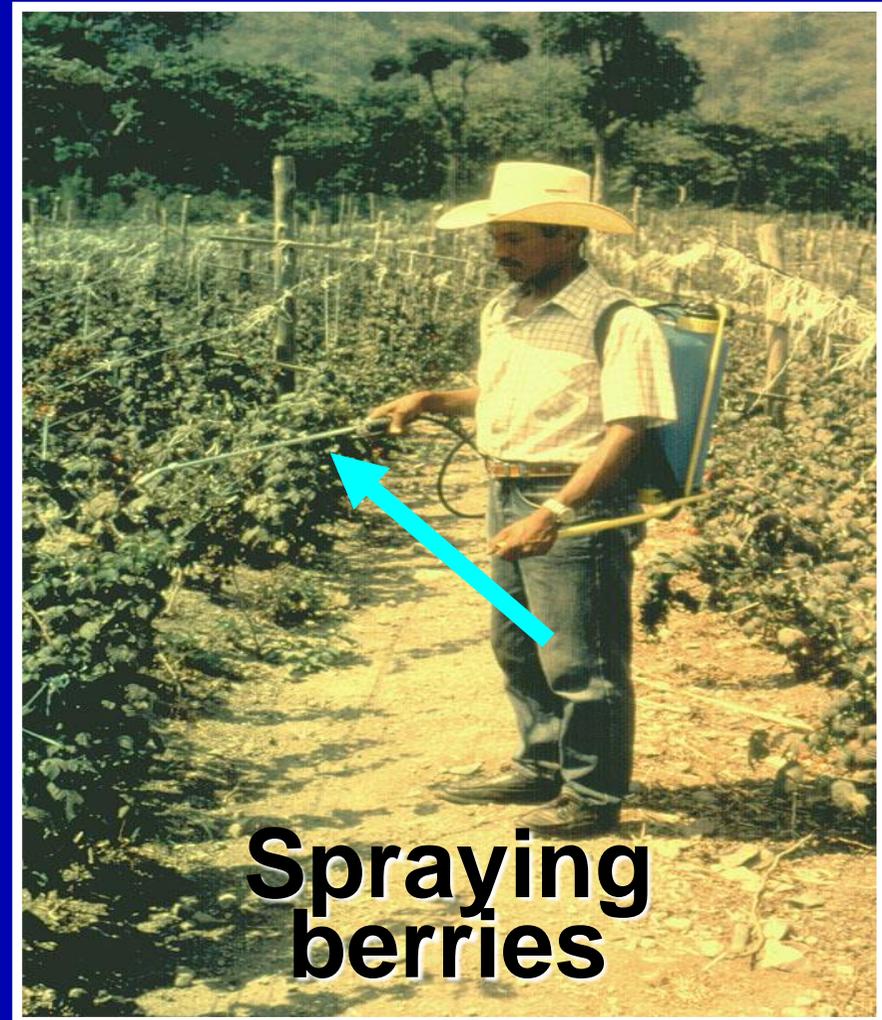
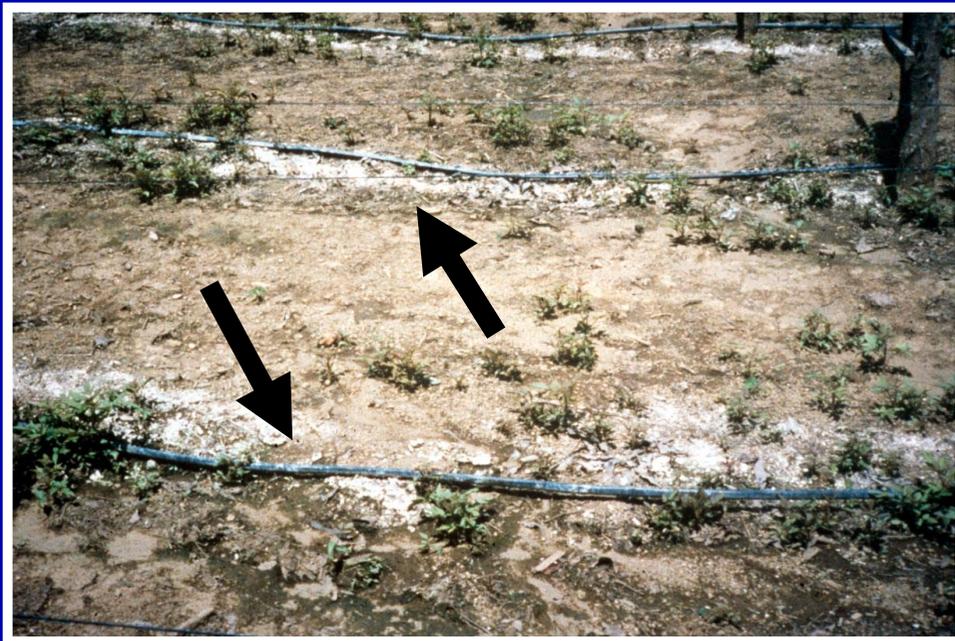


Route(s) of contamination of the raspberries unknown

— Unproven hypothesis: via contaminated **water** —

Pesticides, fungicides, insecticides, etc, were mixed in **water** & **sprayed** on the raspberries

Drip irrigation
(on ground; not near berries)



Spraying
berries

Not just raspberries

Not just Guatemala

Not just spring

Not just 1 vehicle per year

Not just 1 source per vehicle



1997: a series of 5 outbreaks of cyclosporiasis

— by month(s) of exposure (eg, social events)

- **March & April: Florida**
 - Mesclun lettuce from Peru (see *Dec 1997; aggregate evidence*)
- **April & May: USA & Canada**
 - Raspberries from Guatemala
- **June & July: Washington DC / Baltimore metro area**
 - Basil (*multiple possible sources*)
- **September: Virginia**
 - Fruit plate (*which ingredient?—only 1 cluster of cases was identified; no opportunities to triangulate*)
- **December: Florida**
 - Salad (mesclun lettuce; *aggregate evidence*)



The series of U.S. foodborne outbreaks of cyclosporiasis

- **Large outbreaks in the mid-1990s**
 - **1996:** multistate outbreak linked to fresh raspberries from Guatemala
 - **1997:** multistate outbreak linked to Guatemalan raspberries; *also*, outbreaks linked to mesclun lettuce (Peru) & basil (>1 possible source)
- **Outbreaks detected almost every year thereafter**
 - Food vehicles/sources not always identified; *but examples* include raspberries & snow peas (Guatemala), basil (Peru), & cilantro (Mexico)
 - To date, no *commercially* frozen produce implicated
- **Route(s) of produce contamination not definitively established**
- **Some outbreak investigations led to interventions & prevention measures**



... 2013–2014 ...

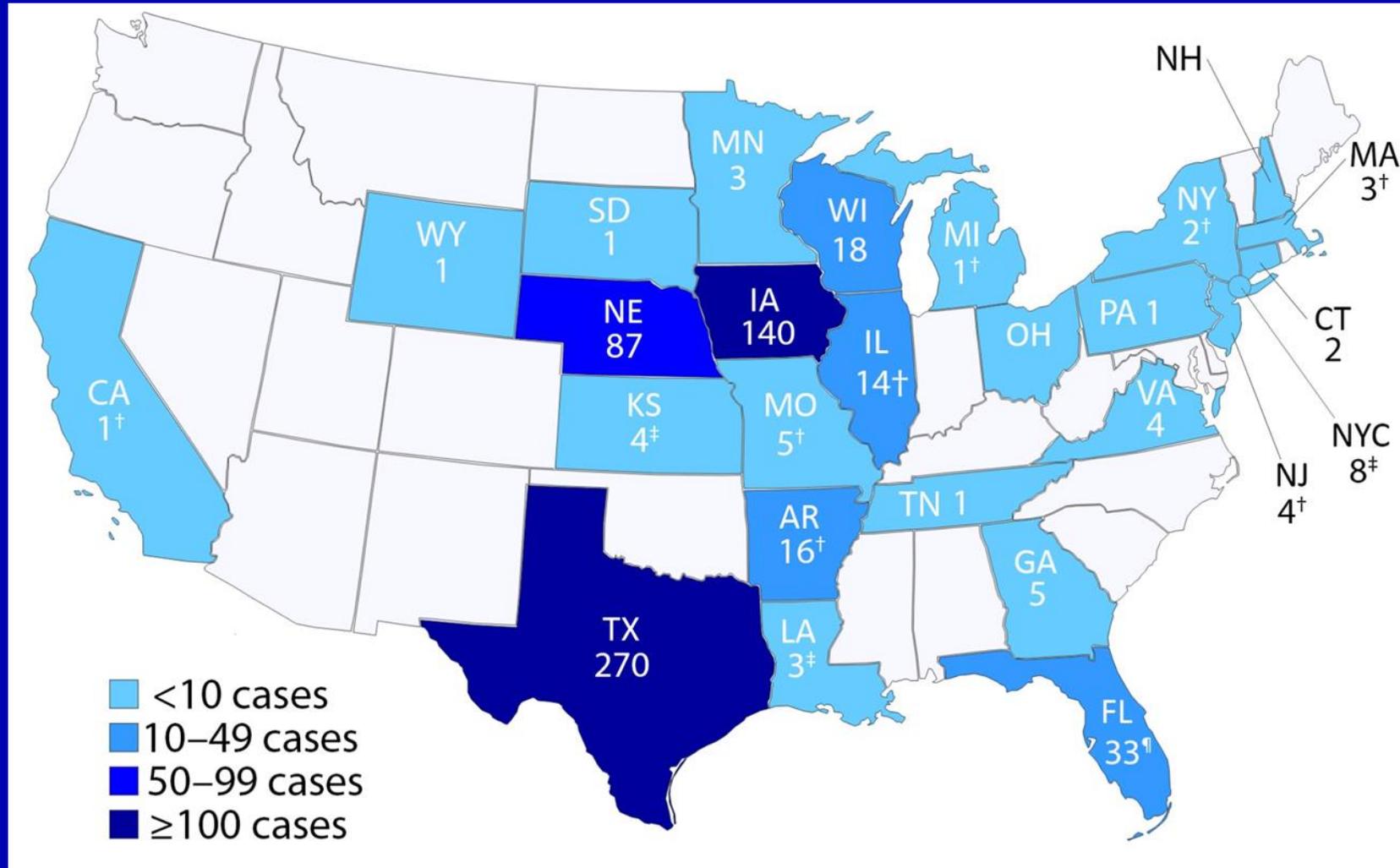


2013: U.S. outbreaks of cyclosporiasis

- In late June 2013, public health officials in Iowa & Nebraska began receiving reports of lab-confirmed *Cyclospora* cases not associated with international travel (during 2-week period before symptom onset)
- Overall, a total of 631 such cases, with onset dates during June–August, were reported by 25 states
 - 497 cases (79%) were from 3 states: Texas, Iowa, & Nebraska



2013: Laboratory-confirmed U.S. cases of cyclosporiasis (N = 631*), by state



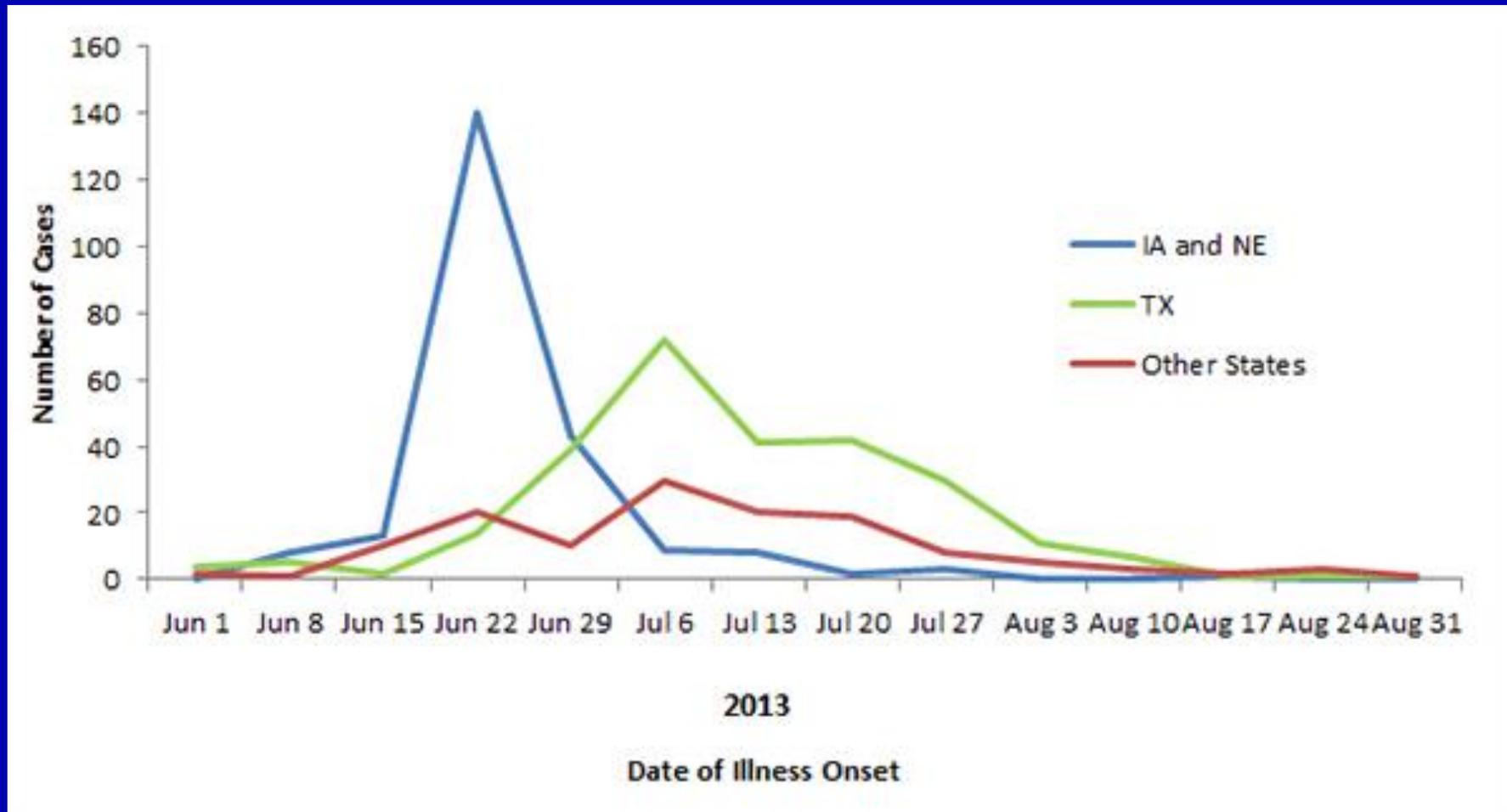
* Lab-confirmed infection in a person with illness onset during **June–August**, without known travel outside USA/Canada in 14-day period before onset.

† Includes 1 case that may have been acquired out of state. ‡ Includes 2 cases that may have been acquired out of state.

¶ Might include an international travel-associated case.



2013: Laboratory-confirmed U.S. cases of cyclosporiasis — by groups of states & week of illness onset (N = 631*)



* Lab-confirmed infection in a person with illness onset during **June–August**, without known travel outside USA/Canada in 14-day period before onset



Recent **U.S. outbreaks of cyclosporiasis** underscore recurring themes & challenges

In **2013**, *at least 2* distinct outbreaks occurred—linked by epi & traceback data to different types of fresh produce from different parts of Mexico (MX)

- **Iowa & Nebraska**: Restaurant-associated cases were linked to a **bagged salad mix** (*iceberg/romaine lettuces, carrots, red cabbage*) from Taylor Farms in **Guanajuato, MX**
 - What was pertinent ingredient(s) in the mix?
- **Texas**: Some case clusters were associated with **cilantro** from **Puebla, MX**
 - In **2014**, another *Cyclospora* outbreak in Texas was linked to **cilantro** from **Puebla**, which strengthened the evidence

The bulk of the reported domestically acquired *Cyclospora* cases in **2013 & 2014** were not *directly* linked to food vehicle(s)



C. cayetanensis: **Advanced Molecular Detection**

- No molecular tools are available yet that can distinguish among strains of the parasite
- Development of such tools is a high priority
- Availability of such tools in the future could help public health investigators **determine if cases are linked to each other & to particular food items & sources**



Cyclosporiasis is a nationally notifiable disease

*Prompt reporting & investigations
of cases & outbreaks are essential*

The fastest
surveillance
system



As discussed

- Consider the diagnosis of *Cyclospora* infection for persons with persistent or remitting-relapsing diarrheal illness
 - *regardless* of whether they have a history of international travel
 - *regardless* of the time of year—*but especially* during spring & summer
- *If indicated, explicitly* request laboratory testing for this parasite per se
- *Promptly* report confirmed & suspected cases to public health authorities
 - *Even* seemingly isolated cases could be part of outbreaks



Whither *Cyclospora*?

... 2015 ...?



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