American Journal of Epidemiology

Vol. 150, No. 8
Printed in U.S.A.

Invited Commentary: Public Health in Crisis: Outbreaks of *Escherichia coli* O157:H7 Infections in Japan

Jonathan H. Mermin[1,2] and Patricia M. Griffin[1]

In July 1996, Sakai City, Japan, experienced the largest outbreak of *Escherichia coli* O157:H7 infections ever reported, involving over 7,000 persons. Michino et al. (1) have convincingly demonstrated through a review of school absentee records, a cohort study of over 47,000 schoolchildren, product traceback, and molecular subtyping that illness was due to consumption of contaminated white radish sprouts served through a centralized lunch program. Multiple other outbreaks of *E. coli* O157:H7 infections occurred in Japan during the same summer (2). Investigations of these outbreaks as well as the one in Sakai City highlight some of the problems that face public health officials worldwide and illustrate lessons to be learned for investigating foodborne disease outbreaks.

SAKAI CITY

The cohort study conducted by Michino et al. of all elementary school students in Sakai City was a massive undertaking. The health infrastructure in Japan showed a remarkable ability to mobilize itself: Almost 50,000 children were questioned, more than 180,000 stool samples were cultured, and over 1,600 food items were analyzed (1, 3). Because of the scale of the study, the investigation and analysis required 4 weeks to complete—a very short time considering its size. However, the investigation might have been streamlined and resources directed differently. A smaller initial case-control study using a subset of cases and controls from the cohort might have yielded results more quickly.

The authors do not mention training interviewers in administering the questionnaire. This is particularly important when teachers, who are generally not experienced in epidemiologic methods, are used as interviewers, as was done in this investigation. In Japan, students are expected to eat all food served in their lunch, so they may have been reluctant to tell their teachers they had not consumed a particular item (1). If ill children were more likely to be affected by this reporting bias, this would increase the likelihood that food items other than radish sprouts would be statistically associated with illness. This may be one reason that significant odds ratios were found for several different foods. Additionally, if unexposed children reported eating radish sprouts, this would lead to an underestimation of the association with illness. In either case, the investigators would have more difficulty implicating radish sprouts as the food vehicle.

The investigators were ultimately able to implicate radish sprouts by combining information from several sources. The usual incubation period for *E. coli* O157:H7 infection is 3 to 4 days, with a range of 1–8 days (4). Thus, food items served before July 3 (8 days before July 11, the first peak for infections) were not a likely source for infection. If a contaminated food item were served at schools on only one day, students who did not attend school that day would be expected not to report illness from *E. coli* O157:H7 infection. Examination of absentee records supports the implication of a food item served on July 8 in the North-East District and on July 9 in the Middle-South District. Of all food items served within the incubation period, two served on July 8 were significantly associated with illness in the North-East District: radish sprouts, served with chicken and lettuce, and milk. In the Middle-South District, three items were significantly associated with illness: cold noodles on July 4, milk on July 8 and 9, and radish sprouts served with noodles on July 9. If information from both districts is combined, only radish sprouts and milk are potential sources for infection, served on July 8 in the North-East District and on July 9 in the Middle-South District. Thus, the results of the cohort study and absentee records alone show that milk and radish sprouts would be equally likely vehicles for transmission of infection.

Received for publication January 13, 1999, and accepted for publication May 7, 1999.

Abbreviation: PFGE, pulsed-field gel electrophoresis.

[1] Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.

[2] Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, GA.

Reprint requests to Dr. Patricia M. Griffin, Foodborne and Diarrheal Diseases Branch, MS-A38, Centers for Disease Control and Prevention, Atlanta, GA 30333.

Because bovine products are well-established vehicles for *E. coli* O157:H7 infection and milk has been associated with previous outbreaks (5, 6), many investigators might have stopped at this point and mistakenly implicated milk. However, Michino et al. looked beyond Sakai City. They noted two outbreaks of *E. coli* O157:H7 infections during the same period as the Sakai City outbreak: one at a local factory and one at a nursing home. Both facilities served white radish sprouts obtained from the same producer who supplied the Sakai City lunch program, and stools of patients in both outbreaks yielded *E. coli* O157:H7 with the same pulsed-field gel electrophoresis (PFGE) pattern as that in the Sakai City outbreak. The investigators of the Sakai City outbreak used traceback and molecular subtyping data from these other outbreaks to support their implication of white radish sprouts. The spurious association between drinking milk and illness may have occurred because milk was consumed at the same meals as the radish sprouts. Controlling for milk consumption through stratification or multivariable logistic regression analysis of the cohort data might also have assisted in more specifically associating consumption of sprouts with illness.

Why was the rate of illness in the North-East District half that in the Middle-South District? The most plausible answer relates to the shipments of radish sprouts, further strengthening implication of this food item. Examination of the data as a cohort study shows a rate of 1 percent for hospitalization and 15 percent for symptoms among children who ate radish sprouts in the North-East District compared with 3 percent for hospitalization and 35 percent for symptoms among children who ate radish sprouts in the Middle-South District (1, 7). The different rates of illness may be due to the fact that only half of the shipments to schools in the North-East District were contaminated. This hypothesis, suggested by the authors, is supported by the observation that only 52 percent of schools in the North-East District reported hospitalized children, whereas 97 percent of the schools in the Middle-South District did. The percentage of students hospitalized was approximately the same for schools that reported any ill children (7), suggesting that the degree of contamination of sprouts was about the same for all contaminated shipments. The North-East District served sprouts received from the implicated producer on July 5 and 7, and the Middle-South District served sprouts received on July 8–10. If sprouts were not contaminated at the producer until after July 5th, the North-East District would have received an uncontaminated shipment on July 5 and a contaminated shipment on July 7 and served both on July 8; this may be the reason that only half the schools reported hospitalized children. Further examination of production records and shipment invoices might clarify this issue.

OTHER SPROUT-RELATED OUTBREAKS

Michino et al. (1) report the first recognized sprout-related outbreak of *E. coli* O157:H7 infections. Recognizing a new food vehicle for a pathogenic organism can be extremely difficult. Because *E. coli* O157:H7 infections have most frequently been associated with consumption of cattle products (4, 8), the association with radish sprouts was treated with skepticism (9). However, at least six outbreaks of *Salmonella* infections related to alfalfa sprouts and one related to mung bean sprouts have been reported in the past 10 years (10–15). In addition, since the investigation in Japan, one outbreak of *E. coli* O157:H7 infections (16) and one of *E. coli* O157:NM infections (California Department of Health Services, unpublished data) have been reported from the United States. The germination and sprouting process provides an environment conducive to the growth of *Salmonella* (17) and *E. coli* O157:H7 (18).

The mechanism of radish sprout contamination in Japan was not determined. Because different retail facilities were associated with Sakai City cases of *E. coli* O157:H7 infection and other sprout-associated cases in Japan, contamination at retail facilities is unlikely. Sprouts could have been contaminated by using contaminated seeds for sprouting, during growth at the sprouting facility, or during transport to retail establishments. Possible sources for contamination at the sprouting facility or during transport include an infected worker or animal feces in the environment or water. *E. coli* O157:H7 can be carried in the intestines of healthy cattle and deer, and consuming food that could have been contaminated with their feces has been associated with illness (4, 19–21). Water, presumably contaminated with animal or human feces, has caused outbreaks of *E. coli* O157:H7 infection in Japan (22) and the United States (23). Although cultures of well water from the radish sprout producer did not yield *E. coli* O157:H7, the report did not state whether the water was tested for the presence of fecal coliforms, a measure of contamination by animal or human feces.

The most likely source of contamination is the seeds. At least five sprout-related outbreaks of salmonellosis (10–14) and one of *E. coli* O157:H7 infections (16) have been traced to contaminated seed. Additionally, 8 months after the Sakai City outbreak, an increase in the number of *E. coli* O157:H7 infections was reported from several prefectures in Japan (24). *E. coli* O157:H7 was isolated from samples of radish sprouts taken from patients' homes, and the

PFGE patterns of isolates from patients and sprouts were indistinguishable both from each other and from isolates from the Sakai City outbreak (25, 26). The radish sprouts were traced to a different sprouting facility than the one associated with the Sakai City outbreak; however, both facilities had purchased their seeds in 1995 from the same distributor in the United States (26, 27). Although cultures of seed samples from the lot used for sprouts consumed in Sakai City did not yield *E. coli* O157:H7 (1), this does not mean the seeds were not the source. Sensitive methods for culturing seeds have not been established, and the contamination of the lot may not have been uniform. Prevention of illness from contaminated seeds is difficult; soaking alfalfa seeds in chlorine bleach greatly reduces but does not eliminate *Salmonella* populations (10), and viable *E. coli* O157:H7 organisms have been demonstrated in the inner tissues of radish sprouts grown from experimentally contaminated seed (28).

EPIDEMIOLOGY CAN HELP DIRECT MICROBIOLOGIC INVESTIGATIONS

Massive outbreaks of foodborne illness require a well-coordinated and rapid response so that fears can be allayed, contaminated products can be removed from the marketplace, and measures can be identified to prevent illnesses from the same product or by the same mechanism of contamination in the future. The combination of careful epidemiology and good microbiologic assessment, when possible, is the most effective method of determining the vehicle for foodborne outbreaks. In Japan, significant resources were spent gathering and culturing the 1,626 food samples taken from lunches served on 10 days. Instead, the epidemiologic data could have been used to target particular lunches and food items for culturing. In addition, when PFGE patterns of *E. coli* O157:H7 isolates from sporadic cases in Osaka Prefecture and from patients in three outbreaks at homes for the aged in neighboring Wakayama Prefecture were found to be indistinguishable from Sakai City isolates, a case-control study of the sporadic cases and epidemiologic investigations of these smaller outbreaks could have been conducted. This would have been an efficient way to strengthen the data implicating radish sprouts as a vehicle.

The emphasis on microbiology instead of epidemiology resulted in the failure to identify food vehicles for most of the *E. coli* O157:H7 outbreaks in the summer of 1996 and difficulty implementing effective control programs. These other outbreaks affected more than 1,800 persons and resulted in several deaths (2, 3, 29). In four clusters in June 1996, involving a total of 825 cases, PFGE subtyping of *E. coli* O157:H7 isolates revealed patterns indistinguishable from each other and distinct from that in the Sakai City outbreak (2), suggesting a common source for these infections. In one of these clusters, *E. coli* O157:H7 was isolated from vegetable salad that did not contain radish sprouts (2), but no epidemiologic investigation was reported linking illness to a particular food item in this or the other three clusters, which together appear to represent the second largest outbreak of *E. coli* O157:H7 infections ever reported. The opportunity to learn from these outbreaks about other potentially preventable sources of *E. coli* O157:H7 infection was lost.

Even with the available epidemiologic evidence implicating radish sprouts in the Sakai City outbreak, an official in Osaka Prefecture stated that "as long as we don't find *E. coli* O157:H7 at the [radish sprout] producer, we can't order the company to stop operations" (30). The reliance on microbiology is understandable; it is increasingly being used for quality control at food production facilities (31), and in some countries, it has been the mainstay of foodborne outbreak investigations. Microbiologic data often provide key information linking a particular product to illness. However, use of microbiologic methods alone to either implicate or exonerate a food product can limit the success of an investigation of a foodborne outbreak. Often, food items are no longer available for testing, laboratory techniques are not perfectly sensitive for detecting organisms, or products are not uniformly contaminated.

Some recent investigations provide examples of public health actions based on strong epidemiologic data. For example, in the United States in 1993, more than 700 persons became ill and four died during an outbreak of *E. coli* O157:H7 infections (4, 32). A rapidly conducted case-control study implicated premade hamburger patties from a restaurant chain, and recall of the contaminated meat prevented several hundred infections. After the recall, laboratory testing confirmed contamination of the meat by *E. coli* O157:H7. Epidemiologic data, including product traceback information, often provide the only evidence for the source of outbreaks caused by perishable products that are consumed or disposed of by the time an investigation is conducted. For example, in the United States in 1997, at least 64 persons from two states became ill during an outbreak of *E. coli* O157:H7 infections (16). When case-control studies in both states implicated alfalfa sprouts produced from the same lot of seeds by two different sprouters, the implicated sprouts and seeds were recalled even though cultures of sprouts and seeds did not yield *E. coli* O157:H7. Similarly, in 1996, epidemiologic studies in the United States and Canada linked consumption of Guatemalan raspberries with 55 clusters of *Cyclospora cayetanensis* infec-

tions, involving 725 cases (33). Because no method for culturing *Cyclospora* is available, epidemiology was the only tool available to investigators. In 1997, another multistate outbreak of cyclosporiasis was associated with Guatemalan raspberries (34, 35). In response to these outbreaks, the US Food and Drug Administration restricted importation of Guatemalan raspberries, and no further outbreaks associated with raspberries occurred in the United States. However, in Canada, 13 clusters of *Cyclospora* infections associated with Guatemalan raspberries occurred in 1998, indicating a persistent source of contamination (35).

PUBLIC RESPONSE

Public health officials, health care providers, and the press should be aware of the intense anxiety that outbreaks can cause, especially those that involve deaths of children. Throughout Japan, restaurants, hotels, and public baths experienced a decrease in business. Pools and water fountains in Osaka Prefecture, in which Sakai City is located, were closed (36). In Osaka, restaurant meals, meat, and fish sales decreased by between 40 and 60 percent. Hotels and inns in other parts of Japan rejected some guests after finding out that they lived in Sakai City. Children were reported to have shouted "You are a germ," at students just released from the hospital (37), and bullying of children who had been infected became a serious concern for teachers and parents (38). The director of the school lunch program in Sakai City committed suicide after the outbreak (39). Such broad-reaching psychologic trauma related to *E. coli* O157:H7 infection is not unique to Japan. Despite the emphasis by public health officials on the need for industry to provide safer food products (40), parents often feel responsible when their children become ill after eating contaminated food. In the United States in 1995, the father of a 2-year-old girl who died of hemolytic uremic syndrome after eating hamburger at a family cookout committed suicide (41). The impact of illnesses and deaths on family, friends, and the larger community must be considered when evaluating the societal costs of *E. coli* O157:H7 infections.

GOVERNMENTAL EMERGENCY RESPONSE

Considerable pressure was felt by Japanese public health and governmental authorities to control the spread of infections, even when sources were not definitively identified. The central government issued educational materials and held media conferences about the outbreaks. Posters recommending that people wash their hands appeared on buildings throughout the country, and in Sakai City, people in cars with loud speakers recommended that citizens eat only cooked food.

During a large outbreak, it is often difficult to coordinate efforts among academicians and central, prefectural, and local-level officials. A complex public health response and the lack of a known food vehicle for most of the outbreaks resulted in several policy actions that were probably not cost-effective, including widespread screening of stool specimens from asymptomatic students before school enrollment, administration of antimicrobial agents to persons with asymptomatic infection, and routine random sampling and culturing for *E. coli* O157:H7 in the agriculture industry. The Sakai City Board of Education announced that all students in kindergartens and elementary and junior high schools in the city should be tested for *E. coli* O157:H7; those who did not submit a stool sample might be suspended from school. Six weeks after the outbreak, the Ministry of Education allowed school doctors to prevent asymptomatic students infected with *E. coli* O157:H7 from attending school and required the nation's 90,000 school cooks and nutritionists to undergo medical examinations for bacterial infections (42). Screening of asymptomatic persons can be important for controlling acute outbreaks in settings where person-to-person transmission is common, such as child care centers (43). However, screening of asymptomatic elementary school students and food handlers for diarrhea-causing pathogens is expensive, time consuming, and unlikely to be a cost-effective method for preventing secondary infections (44, 45).

Assuring collaboration between local and central health officials, timely communication, and appropriate action is a challenge for public health officials throughout the world. In Japan, difficulties with coordination and emergency response have been reported in connection with two other public health disasters: the Great Hanshin earthquake in 1995, which displaced 342,000 persons and caused 5,502 deaths (46, 47), and the Tokyo subway sarin gas attack in 1995, which affected approximately 5,000 persons and caused 12 deaths (48, 49). These events, as well as recent publicity regarding the administration of human immunodeficiency virus-contaminated blood products to persons with hemophilia in the early 1980s, may have eroded the public's trust in the public health system (50) and encouraged skepticism of the report by the Ministry of Health and Welfare that contaminated radish sprouts were the cause of the Sakai City outbreak (7, 51). The establishment of a central governmental agency responsible for coordinating the investigation of outbreaks of illness, staffed by experienced epidemiologists and laboratory personnel and invested with authority to collect data and interview patients

throughout the country, would probably improve response to future foodborne disease outbreaks as well as to other public health emergencies.

EFFECTS OF CENTRALIZED FOOD DISTRIBUTION

The outbreak in Sakai City is an extreme example of the potential dangers of centralized food distribution. Many school lunch-related disease outbreaks have been reported in Japan, and they tend to affect a large number of persons because the same food is distributed to many schools (1, 52, 53). Outbreaks of foodborne illness can be extremely large and cross national boundaries. In 1994, for example, more than 2,000 culture-confirmed cases of *Salmonella* serotype Agona infection associated with consumption of a prepackaged snack food occurred in Israel, Great Britain, and North America (54, 55). Also in 1994, an estimated 224,000 persons in the United States were infected with *Salmonella* serotype Enteritidis from eating contaminated ice cream (56). Because of the potential for large outbreaks, special efforts are needed to reduce pathogen contamination in food production facilities (31). There are also benefits to centralized food production. Improvements in practices at large producers can have far-reaching effects that may be more easily instituted than at multiple smaller facilities. In both of the outbreaks mentioned above, recall of the implicated food prevented more cases, and changes were instituted in the production of the food items to reduce the chance of contamination.

Contaminated seeds shipped internationally were the most likely source of the Sakai City outbreak as well as previous outbreaks of sprout-related *Salmonella* infections (10, 14). Yet, we know of no efforts by industry or government to determine the ways that seeds become contaminated. These outbreaks should strengthen our resolve to find ways to decrease the chance for contamination of seeds and, more generally, to reduce the contamination of human food with pathogens from animal feces.

CONCLUSIONS

The investigators of the Sakai City outbreak provided convincing evidence that the cause was radish sprouts. They and their colleagues have served the world community well by presenting their epidemiologic, laboratory, and clinical data in peer-reviewed journals (1, 29, 57, 58), in other reports (3, 59), and on the Internet (58). They implicated a widely distributed food product that is eaten raw, emphasizing the need for control measures directed at farms and other food production establishments because consumers can do little to protect themselves. The possibility that the contamination originated from seeds grown in the United States underscores the need for improved global surveillance, communication, and control measures.

Central governments are ideally positioned to respond to national emergencies such as major foodborne outbreaks, especially those that may be due to products consumed in more than one jurisdiction. The investigation of the Sakai City outbreak by Michino et al. might have been easier if funding and personnel resources in Japan were specifically directed toward health-related emergencies. The source of some of the other outbreaks of *E. coli* O157:H7 infections might also have been identified if responsibility for responding to foodborne disease outbreaks were assigned to a group of epidemiologists who could be freed from other responsibilities to travel to sites of outbreaks to collaborate with local officials in designing, conducting, and analyzing epidemiologic studies. Ministry of Health and Welfare investigators would also benefit by having emergency legal authorization to investigate outbreaks, including the collection of data and the interviewing of ill and well persons, without the need for institutional clearances usually necessary in nonemergency settings.

To address these issues, the Japanese National Institute of Health has recently reorganized communicable disease surveillance (60). In addition, it has assigned two physicians to positions outside Japan to gain experience in communicable disease control and outbreak investigation, one at the Division of Emerging Diseases at the World Health Organization and the other at the Epidemic Intelligence Service at the Centers for Disease Control and Prevention. The outbreaks of *E. coli* O157:H7 infections in Japan emphasize the need for central governments to design strategies to rapidly detect and respond to outbreaks and to adjust public health structures to improve emergency response, just as the Japanese government has done.

ACKNOWLEDGMENTS

The authors appreciate comments on the paper by Drs. Eric Noji, Robert Hyams, Laurence Slutsker, Paul Mead, and Robert Tauxe and editorial assistance from Lynne McIntyre.

REFERENCES

1. Michino H, Araki K, Shunsaku M, et al. Massive outbreak of *Escherichia coli* O157:H7 infection in schoolchildren in Sakai

City, Japan, associated with consumption of white radish sprouts. Am J Epidemiol 1999;150:787–96.
2. Ministry of Health and Welfare. Enterohemorrhagic *Escherichia coli* (verocytotoxin-producing *E. coli*) infection, 1996-April 1998. Infectious Agents Surveillance Report 1998; 19:122–3.
3. Task force on the mass outbreak of diarrhea in schoolchildren of Sakai City. Report on the outbreak of *E. coli* O157 infections in Sakai City. Sakai City, Japan: Sakai City Government, 1997.
4. Griffin PM. *Escherichia coli* O157:H7 and other enterohemorrhagic *Escherichia coli*. In: Blaser MJ, Smith PD. eds. Infections of the gastrointestinal tract. New York, NY: Raven Press, Ltd., 1995:739–61.
5. Keene WE, Hedberg K, Herriott DE, et al. A prolonged outbreak of *Escherichia coli* O157:H7 infections caused by commercially distributed raw milk. J Infect Dis 1997;176:815–18.
6. Mechie SC, Chapman PA, Siddons CA. A fifteen month study of *Escherichia coli* O157:H7 in a dairy herd. Epidemiol Infect 1997;118:17–25.
7. Ministry of Health and Welfare, Japan. Study report on the cause of the outbreak of diarrhea due to *E. coli* O157:H7 among primary school students in Sakai City. (In Japanese). Tokyo, Japan: Food Sanitation Division, Environmental Health Bureau, Ministry of Health and Welfare, 1996.
8. Boyce TG, Swerdlow DL, Griffin PM. *Escherichia coli* O157:H7 and the hemolytic-uremic syndrome. N Engl J Med 1995;333:364–8.
9. Swinbanks D. Japan shuns radishes after 'possible link' to *E. coli*. Nature 1996;382:567.
10. Mahon BE, Ponka A, Hall WN, et al. An international outbreak of *Salmonella* infections caused by alfalfa sprouts grown from contaminated seeds. J Infect Dis 1997;175:876–82.
11. O'Mahony M, Cowden J, Smyth B, et al. An outbreak of *Salmonella saint-paul* infection associated with beansprouts. Epidemiol Infect 1990;104:229–35.
12. Ponka A, Andersson Y, Siitonen A, et al. *Salmonella* in alfalfa sprouts. Lancet 1995;345:462–3.
13. Glynn MK, Patrick S, Wuhib T, et al. When health food isn't so healthy—an outbreak of *Salmonella* serotypes Anatum and Infantis associated with eating contaminated sprouts, Kansas and Missouri, 1997. Abstract presented at the 47th Annual Epidemic Intelligence Service Conference, Centers for Disease Control and Prevention, Atlanta, Georgia, April 20–24, 1998:16.
14. Van Beneden CA, Keene WE, Werker DH, et al. A health food fights back: an international outbreak of *Salmonella* Newport infections due to alfalfa sprouts. Abstract presented at the 36th Annual Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, New Orleans, Louisiana, September 15–18, 1998:258.
15. Mouzin E, Werner SB, Bryant RG, et al. When a health food becomes a hazard: a large outbreak of salmonellosis associated with alfalfa sprouts—California. Abstract presented at the 46th Annual Epidemic Intelligence Service Conference, Centers for Disease Control and Prevention, Atlanta, Georgia, April 14–18, 1998:15.
16. Centers for Disease Control and Prevention. Outbreaks of *Escherichia coli* O157:H7 infection associated with eating alfalfa sprouts—Michigan and Virginia, June-July 1997. MMWR Morbid Mortal Wkly Rep 1998;46:741–4.
17. Jaquette CB, Beuchat LR, Mahon BE. Efficacy of chlorine and heat treatment in killing *Salmonella stanley* inoculated onto alfalfa seeds and growth and survival of the pathogen during sprouting and storage. Appl Environ Microbiol 1996; 62:2212–15.
18. Hara-Kudo Y, Konuma H, Iwaki M, et al. Potential hazard of radish sprouts as a vehicle of *Escherichia coli* O157:H7. J Food Prot 1997;60:1125–7.
19. Wells JG, Shipman LD, Greene KD, et al. Isolation of *Escherichia coli* serotype O157:H7 and other Shiga-like-toxin-producing *E. coli* from dairy cattle. J Clin Microbiol 1991;29:985–9.
20. Keene WE, Sazie E, Kok J, et al. An outbreak of *Escherichia coli* O157:H7 infections traced to jerky made from deer meat. JAMA 1997;277:1230–1.
21. Cieslak PR, Barrett TJ, Griffin PM, et al. *Escherichia coli* O157:H7 infection from a manured garden. (Letter). Lancet 1993;342:367.
22. Akashi S, Joh K, Tsuji A, et al. A severe outbreak of haemorrhagic colitis and haemolytic uraemic syndrome associated with *Escherichia coli* O157:H7 in Japan. Eur J Pediatr 1994; 153:650–5.
23. Swerdlow DL, Woodruff BA, Brady RC, et al. A waterborne outbreak in Missouri of *Escherichia coli* O157:H7 associated with bloody diarrhea and death. Ann Intern Med 1992;117: 812–19.
24. O-157 detected in radish sprouts in Yokohama. Daily Mainichi. 1997 April 26.
25. MHW to request U.S. to test seeds in line with detections of O-157 from kaiware. Nihon Keizai Shinbun. 1997 May 3.
26. Radish sprouts contaminated by O-157 *E. coli* bacteria: Health and Welfare Ministry to examine U.S.-grown radish sprouts that were used in Kanagawa and Osaka. Asahi Shimbun. 1997 April 26.
27. O-157 probe looks at radish seeds. Asahi Evening News. 1997 April 26.
28. Itoh Y, Sugita-Konishi Y, Kasuga F, et al. Enterohemorrhagic *Escherichia coli* O157:H7 present in radish sprouts. Appl Environ Microbiol 1998;64:1532–5.
29. Higami S, Nishimoto K, Kawamura T, et al. Retrospective analysis of the relationship between HUS incidence and antibiotics among patients with *Escherichia coli* O157 enterocolitis in the Sakai outbreak. (In Japanese). Kansenshogaku Zasshi 1998;72:266–72.
30. Daikon sprouts fingered in Sakai food poisonings. Japan Times. 1996 August 8.
31. Pathogen reduction; hazard analysis and critical control point (HACCP) systems. Federal Register July 25, 1996;61: 38806–7.
32. Bell BP, Goldoft M, Griffin PM, et al. A multistate outbreak of *Escherichia coli* O157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers: the Washington experience. JAMA 1994;272:1349–53.
33. Herwaldt BL, Ackers M-L. An outbreak in 1996 of cyclosporiasis associated with imported raspberries. Cyclospora Working Group. N Engl J Med 1997;336:1548–56.
34. Centers for Disease Control and Prevention. Outbreaks of cyclosporiasis—United States, 1997. MMWR Morbid Mortal Wkly Rep 1997;46:451–2.
35. Centers for Disease Control and Prevention. Outbreak of cyclosporiasis—Ontario, Canada, May 1998. MMWR Morbid Mortal Wkly Rep 1998;47:806–9.
36. MITI: O-157 hurting smaller firms. Mainichi Daily News. 1996 August 6.
37. *E. coli* food poisoning leads to dismissals, discrimination. Japan Times. 1996 August 20.
38. For Japan's children, a Japanese torment. New York Times. 1996 September 8.
39. School aide a suicide over Japan food deaths. New York Times. 1996 November 2.
40. Griffin PM, Bell BP, Cieslak PR, et al. Large outbreak of *Escherichia coli* O157:H7 infections in the western United States: the big picture. In: Karmali MA, Goglio AG. eds. Recent advances in verocytotoxin-producing *Escherichia coli* infections. Amsterdam, the Netherlands: Elsevier Science B.V. 1994:7–12.
41. Grief swallows dead girl's dad. The Morning Journal. 1995 September 14.
42. Schools get OK to ban O-157 students. Asahi Shimbun. 1996 August 25.
43. Belongia EA, Osterholm MT, Soler JT, et al. Transmission of *Escherichia coli* O157:H7 infection in Minnesota child day-care facilities. JAMA 1993;269:883–8.
44. Vugia DJ, Griffin PM. Asymptomatic hospital foodhandlers should not be screened routinely for intestinal parasites. Infect Control Hosp Epidemiol 1993;14:457–8.

45. de Wit JC, Rombouts FM. Faecal micro-organisms on the hands of carriers: *Escherichia coli* as model for *Salmonella*. Zentralbl Hyg Umweltmed 1992;193:230–6.
46. Baba S, Taniguchi H, Nambu S, et al. The Great Hanshin earthquake. Lancet 1996;347:307–9.
47. Ross C. Mental spring cleaning after Kobe. Lancet 1995;345:245–6.
48. Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management. Part 1: community emergency response. Acad Emerg Med 1998;5:613–17.
49. Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management. Part 3: national and international responses. Acad Emerg Med 1998;5:625–8.
50. Swinbanks D. Blood scandal and *E. coli* raise questions in Japan. Nature 1997;385:9.
51. Tokuda Y. Unscientific speculation. (Letter). Nature 1996;383:381.
52. Ministry of Health and Welfare, Japan. *Vibrio parahaemolyticus*, Japan, 1994–1995. Infect Agents Surveillance Rep 1996;17:1–2.
53. Review central procurement of school meal materials. Asahi Shimbun. 1996 August 23.
54. Shohat T, Green MS, Merom D, et al. International epidemiological and microbiological study of outbreak of *Salmonella agona* infection from a ready to eat savoury snack. II: Israel. BMJ 1996;313:1107–9.
55. Killalea D, Ward LR, Roberts D, et al. International epidemiological and microbiological study of outbreak of *Salmonella agona* infection from a ready to eat savoury snack. I. England and Wales and the United States. BMJ 1996;313:1105–7.
56. Hennessy TW, Hedberg CW, Slutsker L, et al. A national outbreak of *Salmonella enteritidis* infections from ice cream. N Engl J Med 1996;334:1281–6.
57. Watanabe H, Wada A, Inagaki Y. Outbreaks of enterohaemorrhagic *Escherichia coli* O157:H7 infection by two different genotype strains in Japan, 1996. Lancet 1996;348:831–2.
58. Yukioka H, Kurita S. *Escherichia coli* O157 infection disaster in Japan, 1996. Eur J Emerg Med 1997;4:165.
59. Ministry of Health and Welfare J. Verocytotoxin-producing *Escherichia coli* (enterohemorrhagic *E. coli*) infections, Japan, 1996-June 1997. Infect Agents Surveillance Rep 1997;18:1–3.
60. Anti-disease effort takes shape. Asahi Evening News. August 23, 1996.