Epidemic of Gastrointestinal Tract Infection Including Hemorrhagic Colitis Attributable to Shiga Toxin 1-producing *Escherichia coli* O118:H2 at a Junior High School in Japan

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ABSTRACT. *Background.* **An epidemic of gastrointestinal disturbances related to food ingestion occurred at a junior high school in Komatsu, Japan, and was caused by specifically Shiga toxin (Stx) 1-producing *Escherichia coli* O118:H2, which has not been reported previously in humans. No outbreak of *E coli*-producing Stx 1 alone had occurred.**

Methods. **A total of 526 students and 35 adult staff members who ate the same food at lunch in the school were investigated. Questionnaires about food consumption at lunch were given to all 561 subjects as well as to clinics and hospitals that had treated 79 patients. Stool specimens from 525 subjects, and food, water, and environmental specimens, including cooking utensils, were collected in an attempt to identify the pathogen.**

Results. **A total of 126 subjects (22.5%) developed a diarrheal illness. The pathogen was isolated from the stool in 131 subjects, 49 of which were asymptomatic, and from a dipper. Salads served over several days were identified as high-risk from food analysis. Gastrointestinal symptoms resembled those associated with previous infections of Stx-producing *E coli*, but were mild. No cases of the hemolytic–uremic syndrome developed. Headache was present in 87 patients. Three patients underwent surgery for acute appendicitis during this epidemic. Four of five carriers had received an antibiotic effective against the pathogen.**

Conclusions. **This outbreak of *E coli* O118:H2 demonstrated the clinical and epidemiologic features of infection by *E coli* that produces Stx 1 alone. Infections with such organisms are being recognized increasingly, and the pattern of disease observed may differ from the pattern observed with *E coli* O157:H7. *Pediatrics* 1999;103(1). URL: http://www.pediatrics.org/cgi/content/full/103/1/e2; *Escherichia coli O118:H2, Shiga-toxin 1, outbreak.***

ABBREVIATIONS. HUS, hemolytic–uremic syndrome; Stx, Shiga toxin; RPLA, reversed passive latex agglutination.

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In Japan from 1990 to 1995, seven outbreaks of gastrointestinal tract infection caused by *Escherichia coli* O157:H7 were reported.[1] In contrast, during the very short period from May to October 1996, 22 outbreaks of *E coli* O157:H7 occurred over a large area in Japan, and many people suffered from hemorrhagic colitis and hemolytic–uremic syndrome (HUS).[1] Although *E coli* O157:H7 is the most common source of Shiga toxin (Stx) 1 and 2, there are many other serotypes that also produce this toxin in vitro and in vivo. Four outbreaks of non-O157 Stx-producing *E coli* were confirmed in Japan from 1984 to 1995,[1] with the pathogen belonging to the serotypes O145:H-, O111:H-, and Out:H19. In other countries, only two previous outbreaks of infection by non-O157 Stx-producing *E coli*, such as O104:H21 in the United States [2] and O111:H- in Italy,[3] have been reported. All these isolates produced both Stx 1 and Stx 2, or Stx 2 alone.[1–3] Until the outbreak reported here, an outbreak of *E coli*-producing Stx 1 alone had not occurred. In July 1996, a large outbreak of exclusively Stx 1-producing *E coli* O118:H2 occurred in a junior high school in Komatsu city. This appears to be the first report in the world of clinical infection caused by this organism, and we describe here the clinical and epidemiologic features of the gastrointestinal infection caused by *E coli*-producing Stx 1, but not by Stx 2.

METHOD

Epidemiologic Investigation

An outbreak of a diarrheal illness occurred at R Junior High School between July 8 and July 21, 1996. This outbreak was first reported to the Minami Kaga Public Health Center, Ishikawa Prefectural Government, on July 15, 1996. Students and adult members of the school staff, all whom ate the same foods at lunch, were considered to be at risk and were investigated in detail. The food was prepared in the kitchen of the R Junior High School by professional cooks. Students and staff members ate lunch in an assigned classroom. A person was defined as a symptomatic subject if he or she developed at least one of the following symptoms: diarrhea (one or more watery or bloody stools in 24 hours or at least two loose stools in a 24-hour period), abdominal pain, vomiting, or headache.

A questionnaire was distributed to each student and adult staff member on July 15 and 19, 1996. It sought information about the foods eaten at lunch between July 4 and July 12, 1996; the symptoms; the date they appeared; and whether a physician was consulted. Information on the sequential changes of patients and the students who developed a gastrointestinal illness after July 20, 1996, was obtained from the teachers. A questionnaire also was

mailed to the 19 clinics and hospitals that were consulted by patients. It included questions about the date of onset of symptoms; date of consultation; specific symptoms; physical findings; results of laboratory tests used to evaluate the blood, urine and stool; and treatment administered. Of 79 such medical questionnaires, 75 were available for analysis.

Microbiologic Investigation

Between July 15 and 23, 1996, stool specimens were collected and examined for *Salmonella, Vibrio*, and *Staphylococcus*, using standard procedures. Representative stool specimens from 20 patients with diarrheal illness, including 5 patients with bloody diarrhea, also were examined for *Shigella*, *Campylobacter*, and *Yersinia*, using standard procedures. The first five colonies of *E coli* selected from MacConkey agar were serotyped using *E coli* O and H antisera, and sorbitol–MacConkey agar also was used in the routine screening for *E coli* O157:H7. These colonies of *E coli* also were examined for Stx 1 and Stx 2, using a reversed passive latex agglutination (RPLA) kit (Denka Seiken Co, Ltd, Tokyo, Japan).[4] Isolates of *E coli* were inoculated onto 10 mL of brain–heart infusion broth (Denka Seiken Co, Ltd) containing 900 μg of lincomycin. After overnight incubation at 37°C, colonies were inoculated to 1 mL of saline containing 5000 U of polymyxin B and shaken at 37°C for 30 minutes. The culture was centrifuged for 30 minutes at 3000 rpm. The supernatant was tested using an RPLA kit. This kit could detect 2 ng/mL of purified Stx. Representative specimens were reexamined for Stx by the polymerase-chain reaction procedure described previously.[5] Isolates were sent to the National Institute of Health (Tokyo, Japan) for serotyping. Asymptomatic subjects exhibited Stx-producing *E coli* in their stools were defined as healthy shedders. Immunoglobulin M antibody for O118 lipopolysaccharide in the serum of two patients with appendicitis was measured at the National Children's Medical Research Center (Tokyo, Japan).[6–9] Thirty samples of the foods served as lunch between July 8 and July 12, 1996, were stored at 4°C to investigate for pathogens in the event of an outbreak of gastrointestinal illness, and 9 samples of water and 29 environmental specimens obtained from utensils and other sources in the kitchen on July 15, 1996, also were examined by culture. Approximately 1 month after the onset of the present outbreak, stool culture studies were performed using the same method. Subjects exhibiting Stx-producing *E coli* in the reexamination of stools were defined as carriers. We inquired of carriers whether their family members developed gastrointestinal symptoms, and stools of family members were examined to isolate the Stx-producing *E coli*.

Statistical Analysis

Data are reported as means ± 1 standard deviation unit. The student's *t* test was used to compare laboratory values. The χ^2 test was used to test for differences in frequency distribution and proportion. The Yates' corrected χ^2 test was applied when the expected value for a cell was <5. A level of $P < .05$ was accepted as statistically significant.

RESULTS

The findings obtained from this outbreak are summarized in Table 1. Of 561 subjects who were at risk for the infection, 241 (43.0%) were defined as symptomatic and 126 (22.5%) developed a diarrheal illness. Of these patients, 9 were hospitalized with severe symptoms (6 patients with bloody diarrhea and 3 patients with acute appendicitis). The number of students with symptoms significantly exceeded that of the adult staff members (239/526 [45.4%] vs 2/35 [5.7%]; $P < .005$), and the number of students with diarrheal illness also significantly exceeded that of the adult staff members (125/526 [23.8%] vs 1/35 [2.9%]; $P < .01$). A characteristic of this outbreak was the surprisingly high number of patients who complained of headache, but there was no significant difference in the frequency of headache in the culture-positive versus culture-negative subjects (23/131 [17.6%] vs 59/394 [15.0%]). The majority of patients with abdominal discomfort complained of cramping in the periumbilical area. Only 5 (4.0%) of the 126 patients with diarrheal illness experienced vomiting. The average number of nonbloody diarrhea episodes per day was 3.3 ± 2.2 (ranging from 1 to 15 stools per day), and that of bloody diarrhea was 6.4 ± 2.6 (ranging from 3 to 10 stools per day). A watery diarrhea of 1.6 ± 0.9 days of duration (ranging from 0 to 3 days of duration) was antecedent to the onset of bloody diarrhea, and their peak body temperature was <38.0°C. No adult staff members developed bloody diarrhea.

TABLE 1. Summary of Findings: Epidemic of Gastrointestinal Illness at a Junior High School in Japan

	No.	*(%)*
People at risk	561	
Students (12 3/12 to 15 3/12 y)	526/561	93.8
Staff	35/561	6.2
Symptoms or signs	241/561	43.0
Asymptomatic	320/561	57.0
Symptomatic with nonbloody diarrhea*	117/561	20.9
Symptomatic with bloody diarrhea†	9/561	1.6
Symptomatic without diarrhea‡	115/561	20.5
Headache	87/241	36.1
With diarrhea	44/87	50.6
With abdominal pain only	34/87	39.1
Without other symptom	9/87	10.3
High temperature (>38.0°C)	5/241	2.1
Confirmed pathogen by RPLA	131/525‖	25.0
Asymptomatic	49/303	16.2
Symptomatic with nonbloody diarrhea	53/106	50.0¶
Symptomatic with bloody diarrhea	4/5	80.0¶
Symptomatic without diarrhea‡	25/111	21.6

* Nonbloody diarrhea with vomiting in 4 patients, headache in 40, and high temperature in 5.
† Bloody diarrhea with headache in 4 patients.
‡ Abdominal pain, vomiting, and/or headache without diarrhea.
‖ Stool culture was performed in 525 of 561 subjects at risk.
¶ $P < .005$ compared with the asymptomatic and symptomatic subjects without diarrhea.

Table 2 shows a comparison of laboratory findings during the acute phase in patients with bloody and nonbloody diarrhea. A mild but significant increase of the absolute neutrophil count and decrease of the platelet count were noted in patients with bloody diarrhea. Serum C-reactive protein value and leukocyte count were normal to slightly elevated in the majority of these patients. No fragmentation of erythrocytes was observed on the blood smears. Urinalysis revealed hematuria and/or proteinuria in 6 of the 29 patients tested. No cases of the HUS developed during the epidemic.

Two patients underwent surgery for acute appendicitis on July 16 and July 18, 1996. These patients exhibited previous watery diarrhea and a change from abdominal cramping to continuous pain in the right lower quadrant. Fever was absent in these patients. Their respective laboratory values were maximum leukocyte, 9.1×10^3 and $10.0 \times 10^3/\mu$L (9.1×10^9 and 10.0×10^9/L); and maximum C-reactive protein, <0.24 and 0.47 mg/dL (<2400 and 4700 μg/L). Macroscopic examination confirmed a hyperemic and swollen appendix in both patients. The ileocecal region also was involved in 1 patient, whereas serous ascites was seen in the other. Micro-

TABLE 2. Laboratory Findings During Acute Phase of Disease in Patients With and Without Bloody Diarrhea

	Bloody Diarrhea	Nonbloody Diarrhea	*P* Value
Leukocyte ($\times 10^3/\mu L$)	7.3 ± 1.4 (9)	6.4 ± 2.0 (15)	.254
Neutrophil ($\times 10^3/\mu L$)	5.5 ± 1.7 (8)	4.0 ± 1.1 (11)	.028
Hemoglobin (g/dL)	14.3 ± 1.1 (9)	13.6 ± 2.2 (15)	.388
Platelet ($\times 10^4/\mu L$)	23.2 ± 6.7 (9)	28.9 ± 5.9 (15)	.039
CRP (mg/dL)	0.6 ± 0.3 (9)	0.5 ± 1.1 (11)	.784
Blood urea nitrogen (mg/dL)	10.7 ± 4.7 (9)	12.0 ± 2.7 (10)	.450
Creatinine (mg/dL)	0.8 ± 0.2 (8)	0.6 ± 0.1 (10)	.035
LDH (U/L)	348.8 ± 59.3 (9)	354.4 ± 38.3 (10)	.807
AST (U/L)	19.8 ± 7.6 (8)	17.5 ± 3.9 (11)	.401
ALT (U/L)	16.9 ± 18.2 (8)	11.2 ± 2.6 (11)	.315

The number of patients is noted in the parentheses. CRP indicates C-reactive protein; LDH, lactate dehydrogenase; AST, asparate aminotransferase; ALT, alanine aminotransferase. For conversion to SI units: leukocyte count, $1/\mu L = 1 \times 10^6/L$; hemoglobin, 1 g/dL = 0.155 mmol/L; platelet count, $1/\mu L = 1 \times 10^6/L$; CRP, 1 mg/dL = 1×10^4 μg/L; blood urea nitrogen, 1 mg/dL = 0.375 mmol urea/L; creatinine, 1 mg/dL = 88.4 μmol/L; LDH, AST, and ALT, 1U/L = 1U/L.

scopic examination revealed hemorrhage and necrosis of an edematous appendicular mucous membrane. Slight infiltration of the appendix by neutrophils was present in only 1 of the 2 patients. Although no pathogen was isolated in cultures of the specimens of resected appendix, immunoglobulin M antibody for O118 lipopolysaccharide was present in the serum of both patients. In another 1 patient who underwent appendectomy on July 20, 1996, close examinations for pathologic changes of the appendix and causal relationship between Stx-producing *E coli* and appendicitis were not conducted.

As confirmed by the examination of 10 representative samples using the polymerase-chain reaction procedure, exclusively Stx 1-producing *E coli* was isolated by RPLA from stool specimens of 131 (25%) of 525 subjects whose stools were examined by culture, and the incidence of pathogen isolated from subjects with diarrheal illness was significantly higher than that for asymptomatic and symptomatic subjects without diarrhea (Table 1). Of 131 subjects found to be positive for Stx-producing *E coli*, 57 (43.5%) developed a diarrheal illness, 25 (19.1%) were symptomatic without diarrhea, and 49 (37.4%) were asymptomatic. There was no significant difference in the incidence of detection of this pathogen in the students versus the adult staff members (127/490 [25.9%] vs 4/35 [11.2%]). The isolate was identified as *E coli* serotype O118:H2. This isolate fermented sorbitol. Additional characterization of the strain, such as the ability to adhere to epithelial cells or possession of the eae gene, was not performed in this study.

Although Stx-producing *E coli* was not isolated from the samples of food and water, it was isolated from a dipper and identified as O118:H2. The analysis of the food eaten by the culture-positive versus culture-negative subjects revealed that high-risk food items served as lunch were coleslaw salad (July 5, 1996; $P < .005$), chicken and cucumber with cold mustard sauce (July 8, 1996; $P < .05$), sour sauce salad (July 9, 1996; $P < .025$), egg salad (July 10, 1996; $P < .005$), and corn salad (July 11, 1996; $P < .01$). Other food items served as lunch were rice; bread; soup; packed sterile milk; and thoroughly cooked meat, fish, eggs, and vegetables. No subjects developed the infection at the 11 other schools that had served the same vegetables and other foods and used the same menu. Five cooks developed no gastrointestinal symptoms, and Stx-producing *E coli* was not isolated from their stools.

Of 75 symptomatic patients who consulted a hospital or clinic, 56 received antimicrobial agents. New quinolones were used in 33 patients (norfloxacin, 17; enoxacin, 5; lomefloxacin, 4; levofloxacin, 4; tosufloxacin, 2; and ciprofloxacin, 1); fosfomycin in 27; macrolides in 3 (clarithromycin 2 and josamycin 1); cephems in 3 (cefaclor, cefteram piroxil, and cefuroxime axetil); and tetracyclines in 1 (minocycline). Eleven patients received two antibiotics in combination. Duration of antibiotic therapy was 4.5 ± 2.4 days. *E coli* O118:H2 was susceptible to these antibiotics. Table 3 shows the relationship between the isolation of pathogen from the stool and the duration of antibiotic treatment. Although effective agents were used in treating this pathogen, 9 of 15 patients still exhibited it 1 day after the administration of antibiotics. In fact, the pathogen was detected even after the administration of antibiotics for 2 or 3 days.

Table 4 shows the results of reexamination of stools from 470 students and 32 adult staffs for Stx-producing *E coli.* In the 49 asymptomatic subjects identified as healthy shedders by the first stool culture, the pathogen disappeared from their stools without treatment on days 28.6 ± 5.1 after the first culture. However, reexamination of the stools of symptomatic subjects on days 26.0 ± 5.4 after the

TABLE 3. Detection of Stx1-producing *E coli* in Stool Cultures After the Administration of Antibiotics

Days after Administration		No. of Cases	Antibiotics Used
1 (15 Cases)	Pathogen (+)	9	N4, F3, N + F2
	Pathogen (−)	6	F2, M2, N1, N + F1
2 (4 Cases)	Pathogen (+)	2	N1, C1
	Pathogen (−)	2	N2
3 (2 Cases)	Pathogen (+)	1	N1
	Pathogen (−)	1	N1
4 (2 Cases)	Pathogen (+)	0	
	Pathogen (−)	2	N1, M + N1

Pathogen (+) indicates confirmed pathogen in stool; pathogen (−), no confirmed pathogen in stool; C, cephems (cefteram piroxil); F, fosfomycin; M, macrolides (clarithromycin and josamycin); N, new quinolones (norfloxacin, levofloxacin, lomefloxacin, and enoxacin). Numbers to the right of these capital letters are the number of the patients using these antibiotics.

TABLE 4. Results of the Reexamination of Stools for Stx 1-producing *E coli* by RPLA

Result of First Stool Culture	No. of Cases† (502)	Confirmed Pathogen‡ (5)	(%) (1.0)
Asymptomatic subjects			
Pathogen (+)	49	0	
Pathogen (−)	236	0	
Total	285	0	0.0
Symptomatic subjects without antibiotic therapy			
Pathogen (+)	56	0	
Pathogen (−)	103	1	
ND	3	0	
Total	162	1	0.6
Symptomatic subjects with antibiotic therapy			
Pathogen (+)	25	2	
Pathogen (−)	17	2	
ND	13	0	
Total	55	4	7.3*

† The number of subjects whose stools were reexamined approximately 1 month after the onset of this outbreak.
‡ Confirmed pathogen by the reexamination of stools.
Pathogen (+) indicates confirmed pathogen by the first stool culture; pathogen (−), no confirmed pathogen by the first stool culture; ND, the first stool culture studies not performed.
* $P < .025$ compared with the symptomatic subjects without antibiotic therapy.

first examination showed that 5 subjects, 4 of whom had received effective antibiotics, exhibited Stx-producing *E coli.* These carriers were clinically healthy at the second stool culture. The pathogen disappeared from the stools of 5 carriers after the readministration of antibiotics. Stx-producing *E coli* was not isolated from stools of 22 family members of 5 carriers. Reexamination of stools showed that the incidence of pathogen from 55 symptomatic subjects treated with antibiotics significantly exceeded that of the 162 symptomatic subjects who did not receive antibiotics (Table 4).

In the present outbreak, although we could not identify patients with secondary infection, and we did not investigate whether the families of subjects at risk (except for 5 carriers) had gastrointestinal symptoms, 2 fathers of carriers were confirmed to develop a diarrheal illness on June 17 and 19, 1996.

DISCUSSION

There is no previous report of an epidemic or a sporadic occurrence of infection by *E coli* O118:H2. Furthermore, no outbreak of non-O157 *E coli* that produced a single toxin, Stx 1, had been reported previously in Japan[1] or in other countries.[2,3] We consider that infections caused by only Stx 1-producing *E coli* are becoming increasingly important because a small outbreak (the number of patients was 6) of *E coli* O26:H11-producing only Stx 1 occurred in Toyama prefecture, Japan, approximately 1 month after the present outbreak.[1] Attention has focused recently on Stx-producing *E coli* isolated from animals, because they are considered to be the primary source of this pathogen.[10–12] Fukui and associates isolated *E coli* O118:H16, which produced only Stx 1, from 2 of 7 calves with fatal infections in Shiga prefecture, Japan, between 1991 and 1993.[11] Garabal and co-workers also isolated *E coli* O118 from piglets with diarrhea.[12] Findings suggest that *E coli* O118:H2 may originate in domestic animals. On the other hand, *E coli* O118:H2, like other non-O157 Stx-producing *E coli*,[13] is not recognized by sorbitol–MacConkey agar used in the routine screening for *E coli* O157:H7, which does not ferment sorbitol.

In this outbreak, gastrointestinal symptoms were the same as those of the infections of Stx producing-*E coli* that were reported previously,[14–16] except that they were mild. Approximately 40% of the infected subjects became healthy shedders. Although mild abnormalities of urinalysis were observed, there were no signs and symptoms of HUS. This could be explained by the fact that the 50% lethal dose for mice of Stx 2 was 28-fold less than that of Stx 1,[17] and subjects had low susceptibility for Stx because they were not infants or elderly persons, but junior high school students and adult staff members. Although a case of HUS attributable to *E coli*-producing Stx 1 alone had been reported,[13] it can be expected that the prevalence of HUS attributable to exclusively Stx 1-producing *E coli* infection may be much lower than that of *E coli*-producing both Stx 1 and 2 or Stx 2 alone in infants or in the elderly. On the other hand, although the prevalence of diarrheal illness and other symptoms was significantly higher in the students than in the adult staff members, there was no significant difference in the incidence of isolation of *E coli* O118:H2 in those groups. This suggests that young people of junior high school age are more susceptible to Stx-producing *E coli* than are adults.

This outbreak was unusual in that many patients complained of headache. Because of Stx being referred to as a neurotoxin, headache is considered to be an effect of Stx. However there is a possibility that the headaches were not related to the infection of this organism, because there was no significant difference in the frequency of headache in the culture-positive versus culture-negative subjects. Another interesting feature of this outbreak was the finding of 2 patients with acute appendicitis. The diagnosis was verified surgically in both patients. However, additional discussion about the indication for operation is necessary, because the pathologic findings of the appendix in these patients resembled those seen with hemorrhagic colitis caused by infection of Stx-producing *E coli*.[14,18,19] Suppurative appendicitis was absent. Swelling of the appendix caused by Stx led to the symptoms of appendicitis. Appendicitis has likely occurred in other outbreaks and sporadic infections caused by Stx-producing *E coli*.

Although the apparent source of the primary infection was not identified, salad was considered to be a high-risk food in the analysis of the food eaten by the subjects. However, no subjects developed the gastrointestinal symptoms at the 11 other schools that had served the same vegetables as salad. The pathogen was isolated from a dipper used in this school. It was suspected that the infection may have been transmitted by placing uncooked, uncontaminated food in contaminated utensils. Undercooked, contaminated food was excluded as a source. Although the subjects affected in this outbreak were

not infants or the elderly, and *E coli* O118:H2 produced Stx 1 alone, the prevalence of the infection was distinctly high. This pathogen might have been consumed repeatedly in contaminated salads over several days.

The use of antibiotics for treating Stx-producing *E coli* infection is controversial. Carter and colleagues reported that antibiotic therapy was associated with an increased risk of secondary infection and a poor prognosis.[16] Karch and researchers demonstrated that incubating *E coli* O157:H7 with subinhibitory concentrations of trimethoprim-sulfamethoxazole resulted in a 4-fold increase in intracellular Stx and up to a 256-fold increase in extracellular Stx.[20] In the present outbreak, there was no evidence that the clinical course was exacerbated by the administration of antibiotics. However, it is questionable whether the antibiotics could eradicate the pathogen. Although this strain was susceptible to the antibiotics used in many clinics and hospitals, the pathogen was isolated from the stool of many patients even after the initiation of antibiotic therapy. Stool cultures performed ~1 month after the onset of outbreak indicated that the incidence of pathogen isolated from symptomatic subjects treated with antibiotics exceeded significantly that of symptomatic subjects not receiving antibiotic therapy. We consider that the number of carriers may be increased by antibiotic administration. However, Karch et al reported that 13% of patients with *E coli* O157 infection who received no antibiotic treatment became carriers.[21] These questions need to be answered to establish the appropriate treatment for Stx-producing *E coli* infections.

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REFERENCES

1. Takeda Y. Epidemic of infections caused by enterohemorrhagic *Escherichia coli* in Japan. *Nippon Rinsho.* 1997;55:631–633 [in Japanese]
2. Outbreak of acute gastroenteritis attributable to *Escherichia coli* serotype O104:H21—Helena, Montana, 1994. *JAMA.* 1995;274:529–530
3. Caprioli A, Luzzi I, Rosmini F, et al. Communitywide outbreak of hemolytic-uremic syndrome associated with non-O157 verocytotoxin-producing *Escherichia coli. J Infect Dis.* 1994;169:208–211
4. Yamada S, Matsushita S, Kai A, et al. Detection of verocytotoxin from stool and serologic testing of patients with diarrhea caused by *Escherichia coli* O157:H7. *Microbiol Immunol.* 1993;37:111–118
5. Saiki RK, Gelfand DH, Stoffel S, et al. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science.* 1988; 239:487–491
6. Chart H, Blanco JE. Serologic identification of infection by Vero cytotoxine producing *Escherichia coli* in patients with haemolytic uraemic syndrome. *Serodiag Immunotherapy Infect Dis.* 1990;4:413–418
7. Greatorex JS, Thorne GM. Humoral immune responses to Shiga-like toxins and *Escherichia coli* O157 lipopolysaccharide in hemolytic-uremic syndrome patients and healthy subjects. *J Clin Microbiol.* 1994;32: 1172–1178
8. Ludwig K, Bitzan M, Zimmermann S, Kloth M, Ruder H, Müller-Wiefel DE. Immune response to non-O157 Vero-toxin producing *Escherichia coli* in patients with hemolytic uremic syndrome. *J Infect Dis.* 1996;174: 1028–1039
9. Reymond D, Johnson RP, Karmali MA, et al. Neutralizing antibodies to *Escherichia coli* Vero cytotoxin 1 and antibodies to O157 lipooplysaccharide in healthy farm family members and urban residents. *J Clin Microbiol.* 1996;34:2053–2057
10. Wells JG, Shipman LD, Green 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;29:985–989
11. Fukui H, Sueyosi M, Naitoh S, Uda Y, Tsukamoto T. Bacteriology and pathology of natural infection in calves with attaching and effacing *Escherichia coli. J Jpn Vet Med Assoc.* 49:517–522 [in Japanese]
12. Garabal JI, Gonzalez EA, Vazquez F, Blanco J, Blanco M, Blanco JE. Serogroups of *Escherichia coli* isolated from piglets in Spain. *Vet Microbiol.* 1996;48:113–123
13. Tarr PI, Fouser LS, Stapleton AE, et al. Hemolytic-uremic syndrome in a six-year-old girl after a urinary tract infection with Shiga-toxin-producing *Escherichia coli* O103:H2. *N Engl J Med.* 1996;335:635–638
14. Riley LW, Remis RS, Helgerson SD, et al. Hemorrhagic colitis associated with a rare *Escherichia coli* serotype. *N Engl J Med.* 1983;308:681–685
15. Spika JS, Parson JE, Nordenberg D, Wells JG, Gunn RA, Blake PA. Hemolytic uremic syndrome and diarrhea associated with *Escherichia coli* O157:H7 in a day care center. *J Pediatr.* 1986;109:287–291
16. Carter AO, Borczyk AA, Carlson JAK, et al. A severe outbreak of O157:H7-associated hemorrhagic colitis in a nursing home. *N Engl J Med.* 1987;317:1496–1500
17. Takeda Y, Kurazono H, Yamasaki S. Verotoxins (Shiga-like-toxins) produced by enterohemorrhagic *Escherichia coli* (Verocytotoxin-producing *E. coli*). *Microbiol Immunol.* 1993;37:591–599
18. Sakurai Y, Tsuchiya H, Ikegami F, Funatomi T, Takasu S, Uchikoshi T. Acute right-sided hemorrhagic colitis associated with oral administration of ampicillin. *Dig Dis Sci.* 1979;22:910–915
19. Richardson SE, Rotman T, Jay V, et al. Experimental verocytotoxemia in rabbits. *Infect Immunol.* 1992;60:4154–4167
20. Karch H, Goroncy-Bermes P, Opferkuch W, Kroll HP, O'Brien A. Subinhibitory concentrations of antibiotics modulate amount of Shiga-like toxin produced by *Escherichia coli.* In: Adam D, Hahn H, Opferkuch W, eds. *The Influence of Antibiotics on the Host–Parasite Relationship*. Vol II. Berlin, Germany: Springer Vering; 1985:239–245
21. Karch H, Rüssmann H, Schmidt H, Schwarzkopf A, Heesemann J. Long-term shedding and clonal turnover of enterohemorrhagic *Escherichia coli* O157 in diarrheal diseases. *J Clin Microbiol.* 1995;33:1602–1605

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Epidemic of Gastrointestinal Tract Infection Including Hemorrhagic Colitis Attributable to Shiga Toxin 1-producing *Escherichia coli* O118:H2 at a Junior High School in Japan

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