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Outbreaks of enterotoxigenic *Escherichia coli* infection in American adults: a clinical and epidemiologic profile

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SUMMARY

Because enterotoxigenic *Escherichia coli* (ETEC) is not identified by routine stool culture methods, ETEC outbreaks may go unrecognized, and opportunities for treatment and prevention may be missed. To improve recognition of adult ETEC outbreaks, we compared them with reported outbreaks of viral gastroenteritis. During 1975–95, we identified 14 ETEC outbreaks in the United States and 7 on cruise ships, caused by 17 different serotypes and affecting 5683 persons. Median symptom prevalences were: diarrhoea 99%, abdominal cramps 82%, nausea 49%, fever 22%, vomiting 14%. The median incubation period was 42 h, and for 8 of 10 outbreaks, the mean or median duration of illness was > 72 h (range 24–264). For 17 (81%) ETEC outbreaks, but for only 2 (8%) viral outbreaks, the prevalence of diarrhoea was $\geqslant 2{\cdot}5$ times the prevalence of vomiting. ETEC outbreaks may be differentiated from viral gastroenteritis outbreaks by a diarrhoea-to-vomiting prevalence ratio of $\geqslant 2{\cdot}5$ and a longer duration of illness.

INTRODUCTION

Enterotoxigenic *Escherichia coli* (ETEC) is an important cause of diarrhoeal illness in the developing world and of 'travellers' diarrhoea' [1]. The organism was first recognized as a cause of severe human illness in Calcutta in 1968, when strains of *E. coli* that produced a heat-labile enterotoxin (LT) similar in structure to cholera toxin were isolated from patients with cholera-like disease [2]. Subsequent studies demonstrated that some strains of enterotoxigenic *E. coli* produce a heat-stable enterotoxin (ST) that also causes diarrhoea [3].

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Since 1990, foodborne outbreaks of ETEC have become increasingly recognized in the United States and on cruise ships that dock in US ports [4, 5]. While ETEC is not identified by routine stool culture methods, it can be identified by specific animal assay, cell culture, enzyme-linked immunosorbent assay, DNA probing, and polymerase chain reaction techniques [6–13]. These techniques are not widely used because they require special equipment, supplies, reagents and specialized training. The available commercial test kits for LT and ST detection are impractical because of their cost and limited shelf life [14, 15]. Consequently, most clinical and public health laboratories cannot identify ETEC.

When stool cultures from patients with diarrhoeal illness do not yield routine bacterial enteric pathogens, physicians and public health officials may attribute

the illness to a viral cause, although confirmatory tests for Norwalk virus and other agents of viral gastroenteritis are rarely obtained. As a result, sporadic cases and outbreaks of gastroenteritis due to ETEC infection may be misclassified as viral gastroenteritis, and opportunities for appropriate treatment and prevention may be missed. To improved recognition of ETEC outbreaks, we describe their clinical and epidemiologic parameters and compare these with data from published reports of 27 outbreaks of viral gastroenteritis.

METHODS

For the 21-year period 1975–95, we reviewed all outbreaks solely or jointly investigated by the Foodborne and Diarrheal Diseases Branch, Centers for Disease Control and Prevention (CDC), in which ETEC was identified by CDC in a stool specimen from an ill person. Stool specimens collected during these investigations were routinely cultured for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia* and *Vibrio* spp. At CDC, ETEC was generally sought when other bacterial pathogens were not detected; when available, stool specimens were referred for electron microscopy to look for agents of viral gastroenteritis.

We included in the analysis those outbreaks in which ETEC isolates of the same serotype were isolated from $\geqslant 3$ ill persons and no other bacterial or viral pathogens were identified, and those in which ETEC isolates of the same serotype were isolated from $\geqslant 10$ ill persons, and no more than one other bacterial or viral pathogen was identified in a single stool specimen. Three outbreaks that occurred in neonatal nurseries and predominantly involved infants < 1 year old were excluded.

Laboratory methods evolved over the study period, but typically involved characterization of at least 5 lactose-positive and 2 lactose-negative isolates of *E. coli* from each of 10 patient specimens. Methods used for the identification of ETEC included Y-1 adrenal cell assay (for LT detection), infant mouse assay (for ST detection), ELISA, DNA probes, and PCR from 1994 onward [6-13]. Isolates identified as ETEC by any of these methods were serotyped for O and H antigens according to standard procedures [16]. Antimicrobial sensitivities to ampicillin, amoxicillin-clavulinic acid, carbenicillin, cephalothin, chloramphenicol, streptomycin, sulphisoxazole, tetracycline and trimethoprim-sulphamethoxazole were determined by using standard disk-diffusion methods [17].

Clinical data from ETEC outbreaks were abstracted from epidemiologic reports generated by state and local health departments, CDC, and the US Air Force. Data on clinical manifestations of viral gastroenteritis were culled from published reports from 1969 to 1991 cited in two comprehensive reviews [18, 19]. The authors of both reviews were consulted when clarification was necessary. Because viral gastroenteritis produces a different symptom profile in children (relatively more frequent vomiting), only the 27 outbreaks that occurred predominantly among adults were included.

RESULTS

Epidemiologic and clinical characteristics

During the 21-year study period, CDC participated in 159 outbreak investigations in which stool specimens were examined for ETEC. Of the 87 outbreaks investigated between 1975 and 1995 involving cruise ships that docked in US ports, stools were examined for ETEC in 66 outbreaks, ETEC was isolated from 1 or more ill persons in 22 outbreaks, however, only 7 outbreaks met the case definition for an ETEC outbreak. During 1975–95, there were 93 outbreaks investigated within the United States in which stools were examined for ETEC. ETEC was isolated from 1 or more ill persons in 14. All 14 outbreaks met the case definition for an ETEC outbreak. The 21 outbreaks affected a total of 5683 persons (Table 1).

For the 92 outbreaks in the United States in which CDC screened the initial stool specimens for ETEC (in one outbreak the initial stool specimens were screened by another agency), ETEC was the aetiologic agent in 6 of 74 (8%) outbreaks during 1975–89 compared to 7 of 18 (39%) outbreaks during 1990–5. For cruise ship outbreaks screened for ETEC, ETEC was the aetiologic agent in 3 of 55 (6%) outbreaks during 1975–89 compared to 4 of 11 (36%) during 1990–5. For all outbreaks, both in the United States and on cruise ships, there was a mean of 0·6 ETEC outbreaks per year during 1975–89 and a mean of 1·8 ETEC outbreaks per year during 1990–5.

The range, median, and interquartile (25th to 75th percentile) symptom prevalences in outbreaks of ETEC and viral gastroenteritis are shown in Figure 1. For ETEC outbreaks, diarrhoea was the most common symptom, reported by 83–100% of patients (median 99%). The prevalence of bloody diarrhoea was ascertained in 13 ETEC outbreaks; it ranged from 0% (in 4 outbreaks) to 7%. Other median

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Table 1. *Epidemiologic and clinical characteristics of enterotoxigenic* Escherichia coli *outbreaks, United States, 1975–95*

No.	Month/ year	Location	Setting [reference]	Presumed source	No. ill	Per cent of cases with symptoms				Median illness duration (days)
						Diarrhoea	Vomiting	Nausea	Fever	
1	6/75	Oregon	National Park [36]	Water	2666	100	80	75	50	11
2	12/75	Caribbean	Cruise ship [24]		64	100	39	81	33	
3	12/75	Caribbean	Cruise ship [24]	Crabmeat	285	100	21	49	22	
4	5/77	Caribbean	Cruise ship		95	100	17	43	17	
5	3/80	Wisconsin	Restaurant [22]		452	95	8	39	16	7
6	4/81	Texas	Hospital [37]		282	98	74	—	25	
7	9/83	Multistate	Multiple [21]	Brie cheese	45	91	2	38	20	4*
8	4/84	Maine	Country club	Scallops	44	100	14	43	19	7*
9	10/85	Tennessee	Boxed lunch	Devilled eggs	97	91	10	58	37	
10	7/88	Florida	Nursing home		65	83	65	39	5	1*
11	1/90	Caribbean	Cruise ship	Scallops	283	96	38	58	16	
12	1/90	Caribbean	Cruise ship	Scallops	210	100	10	46	15	
13	4/91	Caribbean	Cruise ship	Pasta	183	94	70	84	50	2*
14	3/93	Rhode Island	Airline [4]	Salad	47	100	13	70	13	
15	4/93	New Hampshire	Restaurant [4]	Salad	121	100	11	59	22	
16	7/93	Washington, DC	Restaurant	Shrimp	15	93	14	46	33	
17	9/93	Georgia	Pot luck	Turkey	17	94	6	35	41	
18	8/94	Louisiana	Church fete	Dressing	28	100	11	50	14	4
19	9/94	Wisconsin	Banquet [20]	Potatoes	220	99	13	50	27	6
20	1/95	Costa Rica	Cruise ship [23]	Zucchini	431	94	25	48	33	4
21	6/95	Virginia	Luncheon		33	100	6	42	48	6

* Mean illness duration.

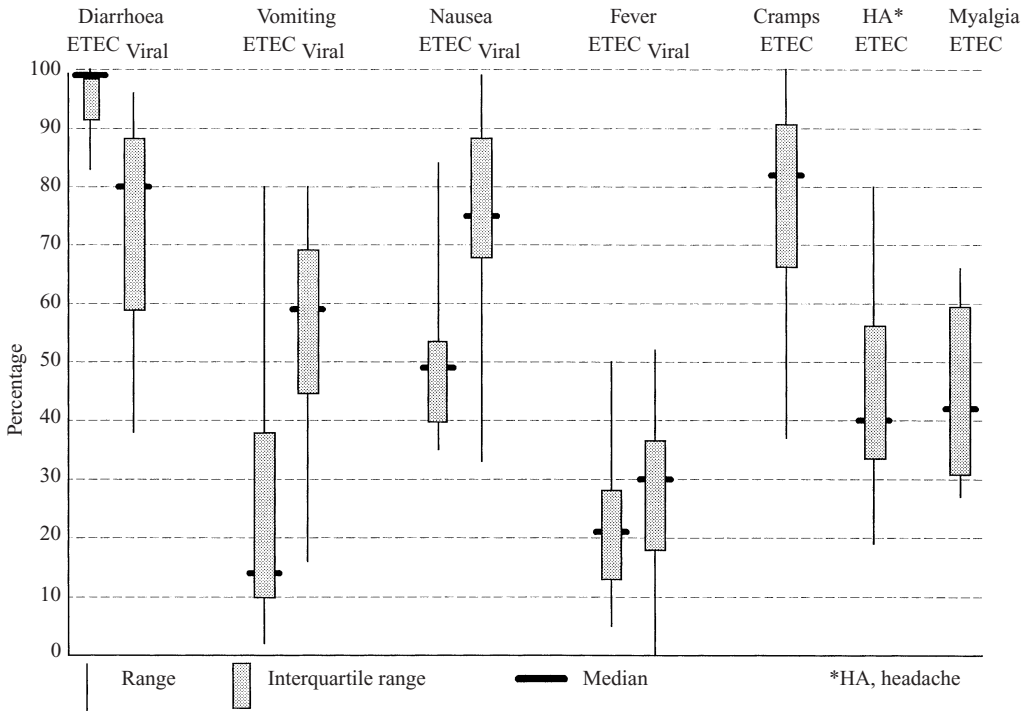

Fig. 1. Range, median, and interquartile symptom prevalence in outbreaks of gastroenteritis caused by ETEC ($n = 21$) and viral agents ($n = 27$), United States, 1975–95.

symptom prevalences included abdominal cramps 82%, nausea 48%, myalgias 42%, headache 40%, vomiting 14%, and fever 22% (Table 1, Fig. 1). Vomiting was reported by $\leqslant 50\%$ of patients in 17 (81%) outbreaks; fever was reported by $\leqslant 50\%$ of patients in all 21 outbreaks.

In every ETEC outbreak, diarrhoea was more frequent than vomiting. The diarrhoea-to-vomiting

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prevalence ratio (D/V ratio), obtained by dividing the percentage of patients who reported diarrhoea by the percentage who reported vomiting, ranged from 1·3 to 45·5 (median 7·1). In 17 (81%) ETEC outbreaks, the D/V ratio was $\geqslant$ 2·5. In contrast, the prevalence of vomiting was much higher in outbreaks of viral gastroenteritis (median 59%) (Fig. 1). Vomiting was more commonly reported than diarrhoea in three (12%) viral outbreaks, and the D/V ratio for outbreaks of viral gastroenteritis ranged from 0·6 to 5·5 (median 1·4). In 23 (92%) of 25 viral gastroenteritis outbreaks for which the prevalence of both diarrhoea and vomiting were known, the D/V ratio was $<$ 2·5.

Patients with ETEC reported nausea and fever less frequently than patients with viral gastroenteritis, but the relative prevalence of these symptoms did not differentiate the two causes as clearly as the D/V ratio (Fig. 1). Although outbreak-specific prevalences of abdominal cramps, headaches, and myalgias were not examined for outbreaks of viral gastroenteritis, the published range and median values suggest that both abdominal cramps and myalgias are reported with slightly greater frequency, and headaches with approximately equal frequency, by patients with ETEC infection than by patients with viral gastroenteritis [18, 19].

Median incubation periods could be calculated for 9 ETEC outbreaks; they ranged from 21 to 68 h, with a median of 42 h. In 2 other outbreaks, mean incubation periods of 35 and 44 h were reported. The median (or mean) incubation period was between 24 and 48 h for 8 (73%) of 11 ETEC outbreaks for which a median or mean could be calculated. Incubation periods for viral gastroenteritis are also typically 24–48 h [18, 19]. The minimum incubation period reported for any individual from any ETEC outbreak was 1 h and the maximum was 10 days.

Median illness duration was reported for 6 ETEC outbreaks as 4, 4, $>$ 4, 6, 7 and 11 days. Four other investigations reported mean illness duration of 1, 2, 4 and 7 days. The median (or mean) duration was $>$ 3 days in 8 (80%) of 10 ETEC outbreaks for which it could be calculated. In contrast, the median duration of illness is typically 24–48 h and virtually always $\leqslant$ 60 h in viral gastroenteritis outbreaks [18, 19]. In only 6 (21%) of 28 outbreaks of Norwalk gastroenteritis did patients report illness lasting for $\geqslant$ 3 days, and in each outbreak this was a minority ($<$ 15%) of patients [18]. The minimum duration of illness for any individual reported from any ETEC outbreak was 12 h. The maximum duration of illness for any individual with ETEC infection often exceeded the interval for which patients were followed; for 9 outbreaks it was reported as $>$ 6, 8, 11, $>$ 13, 14, 14, $>$ 14, $>$ 30 and 63 days [4, 20–23].

A food vehicle was epidemiologically implicated in 14 (67%) of the 21 ETEC outbreaks (Table 1), however, ETEC was not isolated from any of the implicated foods. Seafood was the most commonly implicated vehicle. Five (36%) of 14 outbreaks in which a food vehicle was implicated were reported due to contaminated seafood (crabmeat in 1975 [24], scallops in 1984, scallops twice in 1990, and shrimp in 1993). Salads and other foods served cold were also commonly implicated. Although in three outbreaks, imported food was implicated (brie cheese in 1983 [21], and scallops twice in 1990), associations with imported food or with food workers who have travelled have not been evident in more recent investigations of ETEC outbreaks occurring in the United States [4, 5, 20], indicating that ETEC may have emerged in the domestic food production chain.

Microbiologic characteristics

In total, 35 strains representing 17 different ETEC serotypes were identified in specimens from the 21 ETEC outbreaks (Table 2). In five outbreaks more than one ETEC serotype was isolated. The most common serotype was O6:H16, which carried the genes for both LT and ST. It was the only serotype isolated from patients in 5 outbreaks, and it was also isolated from patients in 3 outbreaks where multiple serotypes were detected. The next most common serotypes were O25:non-motile/LT (3 single-serotype outbreaks), O153:H45/ST and O148:H28/LT/ST (2 single-serotype outbreaks and 1 multiple-serotype outbreak each).

The implicated serotype(s) carried the gene for LT only in 4 outbreaks, for ST only in 6 outbreaks, and for both LT and ST in 11 outbreaks. The relative symptom prevalence, incubation period and duration did not differ significantly for illnesses caused by ST only, LT only and LT/ST strains (data not shown).

Resistance to antimicrobial agents was common among outbreak isolates. Nineteen (54%) of 35 isolates were resistant to tetracycline, 11 (31%) were resistant to sulphisoxazole, 8 (23%) were resistant to ampicillin, and 4 (11%) were resistant to trimethoprim-sulphamethoxazole. Multidrug resistance appears to have become increasingly frequent. Resistance to $\geqslant$ 3 antimicrobial agents was found in only

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Table 2. *Microbiologic characteristics of enterotoxigenic* Escherichia coli *outbreaks, United States, 1975–95*

No.	Month/ year	Number ill	Number isolates	Serotype/ toxin type	Antimicrobial resistance*
1	6/75	2666	20	O6:H16/LT, ST	Sensitive
2	12/75	64	12	O25:NM/LT	Su, Tc
3	12/75	285	16	O25:NM/LT	Su, Tc
4	5/77	95	11	O148:H28/LT, ST	Tc
5	3/80	452	20	O6:H16/LT, ST	Tc
6	4/81	282	41	O25:NM/LT	Tc
7	9/83	45	9	O27:H20/ST	Sensitive
8	4/84	44	6	O49:NM/ST	Sensitive
			3	O27:NM/ST	Sensitive
			2	O6:H16/LT, ST	Sensitive
			1	O6:NM/LT, ST	Sensitive
9	10/85	97	15	O27:H7/ST	St, Su, Tc
10	7/88	65	8	O6:H16/LT, ST	Sensitive
11	1/90	283	13	O153:H45/ST	Ap, Ca, St, Su, Tc
			2	O27:H7/ST	St, Su, Tc
12	1/90	210	5	O-:H7/LT	Sensitive
			1	O-:H32/LT	Ap, Ca
13	4/91	183	3	O6:H16/LT, ST	Sensitive
14	3/93	47	3	O6:NM/LT, ST	Sensitive
15	4/93	121	7	O6:NM/LT, ST	Sensitive
			5	O63:H12/ST	Ap, Cp
			2	O6:H16/LT, ST	Sensitive
			1	O128:H27/ST	Tc
			1	O6:H10/LT, ST	Sensitive
16	7/93	15	5	O159:NM/ST	(Ap), St, Su, TmS
17	9/93	17	6	O148:H28/LT, ST	Tc
18	8/94	28	7	O153:H45/ST	Ap, Cp, St, Su, Tc, TmS
19	9/94	220	5	O153:H45/ST	Ap, St, Su, Tc
20	1/95	431	6	O27:H7/ST	St, Su, Tc
			1	O169:H41/ST	Tc
			1	O169:H41/ST	Ap, St, Su, Tc, TmS
			1	O6:H16/LT, ST	Ap, St, Su, Tc, TmS
			1	O8:H9/LT	Ap, AmC, Ch, Tc
			1	O148:H28/LT, ST	Tc
21	6/95	33	5	O6:H16/LT, ST	Tc

* Ap, ampicillin; Amc, Amoxicillin/clavulinic acid; Ca, carbenicillin; Ch, Chloramphenicol; Cp, cephalothin; Su, sulphasoxazole; St, streptomycin; Tc, tetracycline; TmS, trimtethoprim/sulphamethoxazole, ( ), intermediate resistance; NM, non-motile; LT, heat-labile toxin; ST, heat-stable toxin.

1 (8%) of 13 outbreak strains identified before 1990, but in 9 (41%) of 22 outbreak strains identified from 1990 on.

DISCUSSION

CDC surveillance suggests that ETEC may be an increasingly common cause of outbreaks of gastroenteritis in the United States and on cruise ships docking in US ports with annual rates of reported outbreaks increasing three-fold in the 1990s compared to the 15 years prior to 1990 [4, 5]. While CDC laboratory methods evolved over the study period, the increased rate of outbreaks reported cannot be explained solely by the use of increasingly sensitive methods. Newer methods resulted in simpler and more efficient processes and the introduction of more sensitive methods, such as PCR in 1994, occurred only late in the study period. For infected patients to receive timely and appropriate antimicrobial therapy, and for effective prevention measures to be developed and implemented, ETEC outbreaks must be recognized early and confirmed by suitable laboratory methods.

ETEC cannot be distinguished from non-toxigenic *E. coli* by culture on selective media nor by bio-

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chemical tests. Serotyping may be of some value, but it is time-consuming, depends on the availability of reagents, and is neither sensitive nor specific. Thirty-five serotypes of *E. coli* that have been repeatedly isolated from patients with diarrhoea or associated with an outbreak and confirmed as ETEC by appropriate laboratory methods have been documented [25]. However, these serotypes do not always possess the enterotoxin genes, whereas other serotypes that do are occasionally encountered [26].

Because identification of ETEC requires special methods, this organism is not routinely tested for and is likely to be under-recognized and under-reported. ETEC is reported to cause $< 1\%$ of foodborne disease outbreaks reported to CDC [27]. However, 62% of reported foodborne outbreaks are of undetermined aetiology. In approximately 20% of these outbreaks, reported incubation periods are 24–48 h, compatible with either Norwalk-like viral gastroenteritis or ETEC [27]. Some of these undiagnosed outbreaks may have been caused by ETEC, but not identified as such because appropriate laboratory methods were not applied.

Several characteristics of outbreaks of gastroenteritis caused by ETEC may help differentiate them from outbreaks due to other causes and indicate a need for appropriate laboratory studies. We have shown that ETEC outbreaks may be distinguished from outbreaks of viral gastroenteritis by a greater prevalence of diarrhoea relative to vomiting and by a longer duration of illness.

Kaplan and colleagues proposed criteria in 1982 for considering an outbreak to be caused by a Norwalk-like virus: stool cultures negative for routine bacterial pathogens; median incubation period of 24–48 h (if known); median or mean duration of illness of 12–60 h; and vomiting in $\geqslant 50\%$ of patients [28]. In 1993, Hedberg and Osterholm proposed substituting greater frequency of vomiting relative to fever as an alternative to an absolute frequency of vomiting in $>$ 50% of cases [19]. By either of these criteria, 2 (22%) of 9 ETEC outbreaks for which this information is available would have been respectively misclassified as being due to Norwalk-like virus.

We suggest the D/V ratio as a more readily available, more sensitive and more specific indicator for distinguishing ETEC outbreaks from outbreaks of viral gastroenteritis. A reported D/V ratio of $\geqslant 2{\cdot}5$ had a sensitivity of 82% and specificity of 92% for ETEC versus viral outbreaks. In 1 of 4 ETEC outbreaks with a D/V ratio of $< 2{\cdot}5$, the median duration of illness exceeded 60 h; information on the duration of illness could potentially improve the specificity of this indicator, when available. Our proposed criteria for suspecting ETEC as the cause of an outbreak of gastroenteritis would therefore be as follows: stool cultures negative for routine bacterial pathogens; median incubation period 24–48 h (if known); D/V ratio $\geqslant 2{\cdot}5$; median duration > 60 h (if known). Because sufficient age-specific data were unavailable to determine whether ETEC causes a higher prevalence of vomiting and a lower prevalence of diarrhoea in children than in adults, as has been reported for Norwalk-like viruses [18, 19], the D/V ratio criterion of 2·5 should be interpreted with caution in outbreaks that primarily involve children.

Routine cultures of stool specimens or rectal swabs will differentiate ETEC outbreaks from those caused by *Salmonella*, *Campylobacter* and *Shigella* spp., all of which are generally characterized by a greater prevalence of subjective fever. Infection with ETEC may be difficult to distinguish from mild *V. cholerae* infection (perhaps because of the close homology of cholera toxin and the heat-labile toxin of ETEC); however, *Vibrio* spp. can readily be identified by culture on thiosulphate–citrate–bile salts-sucrose medium. ETEC infection may be distinguished from infections with other enterotoxin-producing organisms, such as *Staphylococcus* spp., *Bacillus cereus* and *Clostridia perfringens*, by its longer incubation period and/or lower prevalence of vomiting and longer duration of illness. This appears to be true regardless of whether the ETEC strain carries the gene for LT, ST or both toxins. In a previous study from Bangladesh, infections with strains carrying both toxin genes tended to produce more copious diarrhoea of a longer duration [29]. Data from the current study did not confirm this observation.

Seafood was the most frequently implicated vehicle in ETEC outbreaks. Contamination of seafood with ETEC is common in South American market places [30]. As with other bacterial enteric pathogens, proper food preparation and handling practices will reduce the opportunities for ETEC transmission.

Appropriate antimicrobial therapy can shorten the duration of illness and discomfort from ETEC infection and diminish the duration of excretion of organisms [29, 31]. Tetracycline, trimethoprim-sulphamethoxazole, and ciprofloxacin are among the agents that have been recommended for treatment [29, 31] and for prophylaxis of travellers' diarrhoea [32]. The emerging multi-drug resistance observed in

this review is consistent with that reported from around the world [33, 34] and may be associated with over-the-counter sales of antimicrobial agents in developing countries and inappropriate prophylaxis or incomplete treatment of travellers' diarrhoea.

Because many clinical laboratories do not test for ETEC, large geographically dispersed ETEC outbreaks associated with consumption of contaminated domestic or imported foods could easily go unrecognized [35]. Recognition or ETEC outbreaks depends on physician awareness and on the application of appropriate laboratory techniques. Physicians may be unlikely to suspect ETEC infection in patients who have not travelled and are not associated with a recognized outbreak. Nonetheless, such cases certainly occur. Until a simple, reliable, and inexpensive laboratory test for ETEC is widely available, solitary suspect cases of ETEC infection will be difficult to confirm. However, outbreaks of gastroenteritis in which illness is characterized by an incubation period of 24–48 h, a D/V ratio of $\geqslant 2{\cdot}5$, and a duration > 60 h should be considered as possibly caused by ETEC. For outbreaks that meet this clinical profile, and in which routine stool cultures have been unrewarding, arrangements should be made to send *E. coli* isolates to reference laboratories. Recognition and investigation of ETEC outbreaks are the first steps towards developing specific effective prevention measures.

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