REVIEW ARTICLE
A systematic review of outbreak and non-outbreak studies of extraintestinal pathogenic *Escherichia coli* causing community-acquired infections

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SUMMARY

A systematic review of outbreak and non-outbreak studies of infections caused by extraintestinal pathogenic *Escherichia coli* (ExPEC) was conducted. This review examines the epidemiology, seasonality, source or mode of transmission, and temporal changes, based on *E. coli* serogroup, in ExPEC causing sporadic *vs.* outbreak-associated infections. Twelve outbreak and 28 non-outbreak studies were identified. The existence of ExPEC outbreaks was well supported. Three of four outbreak reports indicated peak periods during the winter months. Serogroups associated with outbreak infections ranged from 1% to 26% (average 11·4%) *vs.* (range 1–15%, average 3·5%) for serogroups associated with sporadic infections; the distribution of serogroups also differed for outbreak and non-outbreak infections. Study authors indicated that the outbreaks may have resulted from foodborne transmission, but direct evidence was unavailable. This review provides evidence that the epidemiology of endemic *vs.* epidemic ExPEC infections differs; however, study reporting quality limited epidemiological inferences.

Key words: Epidemiology, extraintestinal infections, *E. coli*, urinary tract infections (UTIs), outbreak.

INTRODUCTION

Extraintestinal pathogenic *Escherichia coli* (ExPEC), cause a wide spectrum of illnesses including cystitis, pyelonephritis, bacteraemia, prostatitis and other infections which occur outside the human intestine. The most common type of infection due to ExPEC is urinary tract infection (UTI); 70–95% of UTIs are caused by ExPEC [1–3]. It is estimated that 11% of women aged ⩾18 years are affected by UTIs annually, resulting in over 1 billion dollars of direct and indirect costs per year [2, 4, 5]. The increasing antibiotic resistance of the *E. coli* that commonly cause UTIs has complicated their management.

ExPEC colonize the human intestine and then are transferred to an extraintestinal site, such as the bladder, where they can cause infection [6, 7]. The most common risk factors for UTI in young women include sexual intercourse and spermicide use [8]. The mechanics of sexual intercourse aid in moving ExPEC from the intestine to the urethra, where the bacteria can ascend to the bladder, kidneys or move to the bloodstream [9–11]. ExPEC infections are thought to be sporadic in nature and caused by a diverse collection of *E. coli*, which tend to possess specific virulence genes [12].

Over the past few decades, clusters of community-acquired, extraintestinal infections arising from genetically related groups (or clonal groups) have been

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documented in several countries including England [13], Canada [14], Denmark [15] and the USA [16]. *E. coli* associated with these clusters or outbreaks were often recognized due to an unusual antimicrobial resistance phenotype or serogroup, not typically associated with such infections. The source and transmission routes for these strains have not been identified, but speculation has grown that these outbreaks may occur as the result of food or other environmental contamination [13–16]. Moreover, these outbreak-associated ExPEC strains tend to exhibit multidrug resistance and many have been associated with severe infections [17–19].

Increasing antimicrobial resistance in ExPEC isolates has been hypothesized to be due to the increased use of antimicrobials in human medicine. However, recent studies suggest that the development of and selection for antimicrobial-resistant *E. coli* may also result from the use of antimicrobial agents in food animal production for therapy, prevention and control of diseases, and to promote growth [20]. There is evidence to suggest that the increased selective pressure on the commensal microbiota of these animals has induced resistance that may be transferred to humans, potentially via consumption of contaminated meat [20]. Various studies have identified an abundance of antimicrobial-resistant strains of *E. coli* in retail meats, specifically poultry [21–24]. Some food isolates have been found to be indistinguishable from human clinical isolates [22, 24]. The existence of ExPEC-associated outbreaks and the new evidence linking ExPEC in food reservoirs to human infections suggests that the epidemiology of ExPEC infections may be characterized by two models: the endemic model, where infections are caused by a range of diverse, primarily human-adapted *E. coli* and the epidemic model, where specific strains of *E. coli* found in food animal reservoirs are transmitted via food to humans periodically, as in the case of the observed outbreaks. An examination of the scientific literature for epidemiological evidence for these two models motivated this systematic review.

In this review, two types of studies were identified: (i) reports of potential outbreaks of ExPEC infections over the past 30 years; and (ii) studies conducted from the 1950s to the present, which were primarily designed to characterize ExPEC isolates ('non-outbreak studies') causing infections including community-acquired UTIs and other extraintestinal infections. First, epidemiological details were summarized from all identified outbreak reports, including documentation of any evidence for a food or environmental source. The seasonality of the outbreaks was also examined. Second, *E. coli* serogroup was identified as a marker of temporal changes in the epidemiology and distribution of ExPEC over time since its application is standard and has been used consistently in many studies since the late 1940s.

METHODS

Outbreak studies

A systematic literature review was designed to retrieve published articles of ExPEC outbreak reports from Medline from 1950 to July 2009. Published articles concerning confirmed or suspected outbreaks, as defined by the authors, of extraintestinal infections emerging from the community in otherwise healthy individuals were reviewed. All searches were performed with the assistance of an experienced librarian. The data extracted from the articles included year of outbreak, location, whether the illness associated with the infection was acquired in the community, hospital or a combination of both, the diseases associated with the outbreak, the observation period, period of peak numbers of cases, number of people and isolates used in the study, age range, the sex of those studied and the serogroup, serotype and/or multilocus sequence type (MLST) of the epidemic strain. Where possible, a designation for an *E. coli* strain is provided, which includes the serogroup or serotype and MLST, for example *E. coli* serotype O25:H4-ST131. Structured interviews were conducted with the authors of some studies to complete missing information and to identify additional studies.

Exclusion criteria for outbreak studies

Studies were excluded if they (i) reported outbreaks occurring exclusively in a healthcare setting; (ii) reported outbreaks associated exclusively with gastroenteritis or involving pathogens other than *E. coli*; (iii) reported outbreaks associated with animals; (iv) involved only a few case-reports; and (v) reported in languages other than French and English.

Non-outbreak studies

A similar review of ExPEC non-outbreak studies was designed using 'human', and English and French language limits. These studies contained information on *E. coli* typically responsible for extraintestinal

infections occurring in the community in otherwise healthy individuals. The data extracted from the articles included study observation period, location, whether the infection was acquired in the community, hospital or both, infection type, the number of people and isolates included, age range, the sex of those studied, the number of O-antisera used and the identified *E. coli* serogroups. Studies that did not provide the number of antisera used for testing were included if a reference laboratory was cited, or if the number of non-typable isolates was low. This criterion was used to ensure that the isolates were completely characterized according to serogroup. The proportion of each serogroup was calculated using the total number of isolates in the study as the denominator, unless otherwise indicated. A weighted average for each serogroup was estimated using the inverse of the number of isolates in the study. In some cases, values were collapsed (e.g. if UTI and pyelonephritis serogroups were reported separately), and thus may differ from those reported in the articles.

Exclusion criteria for non-outbreak studies

Published articles were excluded if they (i) focused exclusively on complicated infections (i.e. pregnant women, children or infants, the institutionalized elderly, those with underlying conditions such as diabetes or, hospitalized patients, catheterized patients, patients with urological abnormalities and chronic UTIs [5]), (ii) reported serotyping results based on fewer than 50 O-antisera, (iii) included results from intervention studies or randomized control trials, (iv) focused exclusively on bacteriuria, or (v) were published in a language other than English or French. Only a single article was included if multiple articles based on the same study population were identified. In both searches, studies that did not clearly conform to our criteria were discussed and evaluated by both reviewers.

RESULTS

ExPEC outbreaks

Twelve ExPEC outbreaks studies were included in this review (see Fig. 1). ExPEC outbreaks were identified in UK, Denmark, USA, Spain, Canada, Croatia, and Portugal. The earliest outbreak detected occurred in 1986 and the latest in 2008. The illnesses associated with these outbreaks were primarily related to the urinary tract but were also associated with blood(+stream) and other infections. Both males and females, across a wide age range, were affected. The incidence of the outbreak strains in these reports varied from <1% to 26%, after excluding studies with exclusively antimicrobial-resistant isolate samples. The most common serogroups associated with ExPEC outbreaks included O15 and O25. The articles are summarized in Table 1 and below.

West Lambeth, London, 1986–1987, serogroup O15:K52:H1

An uncommon *E. coli* strain was responsible for a community outbreak between October 1986 and October 1987 in Southeast London, England, involving urinary, bloodstream and other infections [13]. The strain was first recognized due to the unusual antimicrobial pattern which included resistance to ampicillin, chloramphenicol, streptomycin, sulphonamide, tetracycline and trimethoprim. During the outbreak, this strain was associated with 15% of all urinary isolates observed over the year in the region. Moreover, 84/819 patients grew the epidemic *E. coli*, identified by serotyping, from stool samples. This *E. coli* serotype caused 29 cases of septicaemia during the outbreak, while it had caused only 16/674 septicaemia cases over the previous 17 years [13]. Following this reported outbreak in West Lambeth, similar findings were documented in Roehampton [25] and South London [26]. In addition, a study in Barcelona, Spain found the epidemic strain in 1·3% of more than 1000 urine and blood samples received between June 1994 and May 1995, nearly a decade after the London outbreak [27].

Ohio, serogroup O18:K1:H7

In a study of the nutritional and osmotic requirements of clinical *E. coli* isolates, a group of strains requiring nicotinamide for growth and exhibiting the O18:K1:H7 serotype was isolated from 16/101 consecutive urine samples from young women with cystitis and 5/100 stool samples from healthy subjects in Ohio [28]. The O18:K1:H7 serotype was found to be similar to that associated with neonatal meningitis and sepsis. Indistinguishable RAPD patterns were also observed between neonatal meningitis, urine and faecal isolates belonging to O18:K1:H7 [29]. This serotype of *E. coli* is suspected of colonizing the vagina or intestines of women and may
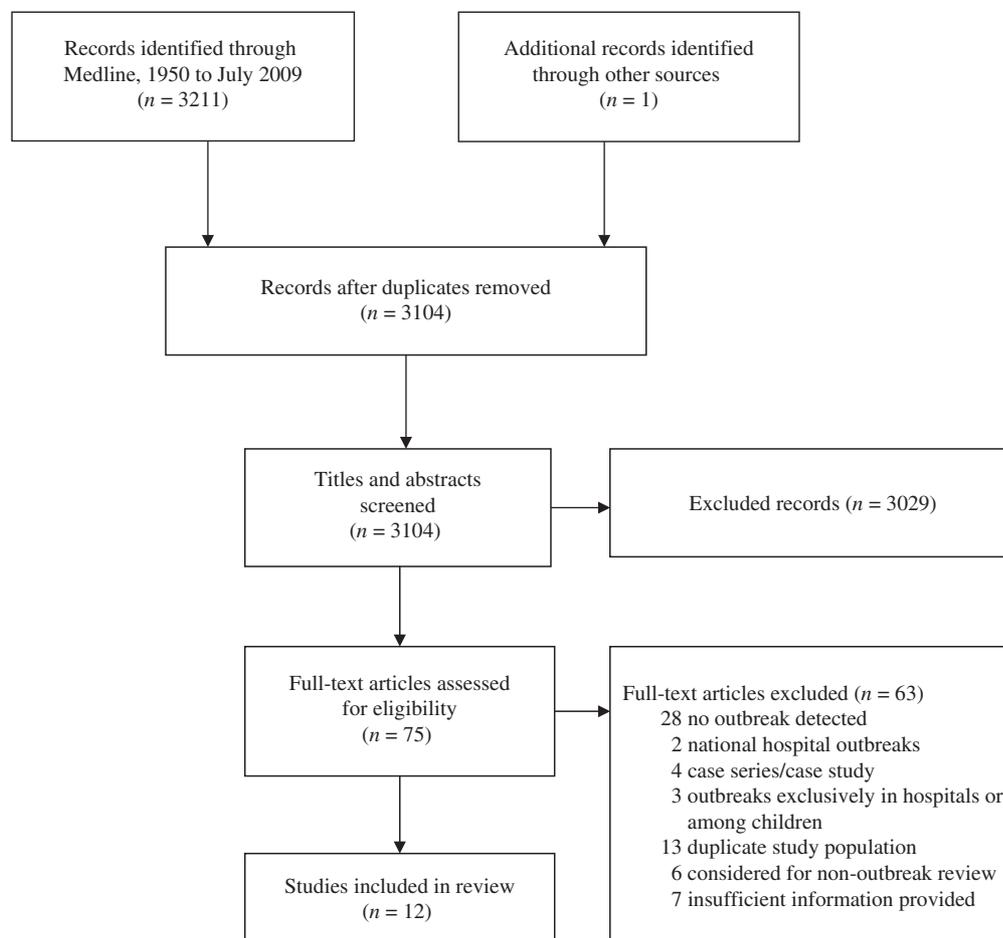
Fig. 1. The selection process of outbreak ExPEC articles into the review. Flow chart adapted from Moher *et al.* [77].

consequently enter the bladder, causing cystitis, or may be transferred to infants during or immediately following birth [28].

Copenhagen, 1991, serogroup O78:H10

In 1991, a year-long outbreak of multidrug-resistant *E. coli* O78:H10 occurred in the Greater Copenhagen region of Denmark [15]. Infections with the epidemic serotype occurred in 15 females and three males. All isolates were recovered from urine specimens and 13 cases were related to UTI. According to the authors, at least 14 cases were community-acquired infections [15]. The epidemic strain was resistant to ampicillin, chloramphenicol, tetracycline, strepto-mycin, sulphonamides and trimethoprim. A single O78:H10 outbreak isolate was identified from among 500 stool samples collected over an 8-month period. *E. coli* O78 was known to cause septicaemia in calves, but had not previously been reported to cause human disease. Only 30 O78:H10 isolates were identified during a retrospective study of isolates collected from

around the world between 1956 and 1990 by the WHO International *Escherichia* and *Klebsiella* Centre at the Statens Serum Institut. Although, epidemiological information was not available for this outbreak, the authors concluded that the outbreak was most likely associated with foodborne transmission; however, a vehicle was not identified.

Berkeley, California, 1999–2001, serogroup O11/O17/O73/O77:K52:H18-ST69

During a study analysing urine samples from women in three different communities in the USA, a multidrug-resistant *E. coli* clonal group, designated clonal group A (CgA), caused one-third to one-half of all TMP-SMZ-resistant [16] cases of UTI. Forty-one percent of the California CgA isolates were indistinguishable by *Xba*I PFGE fingerprinting. CgA members belonged to serotypes O11 and O77:K52:H18 at the California study site; and were later found to belong to serogroups O17 and O73 [17] and exhibit MLST ST69 [30]. In addition to

Table 1. *Reported outbreaks of community-acquired* Escherichia coli *causing human extraintestinal infections*

Ref.	Location	Infection*	Observation period	Peak period	No. isolates	No. epidemic strain	Proportion (%)	Sex‡	Age (yr)	Serotype/sequence type (ST)
[13]	London, UK	UTI, PY, B	1986–1987	Oct. 1986–Apr. 1987		>500		B	0–97	O15:K52:H1
[15]	Copenhagen, Denmark	UTI	1991–1992	Apr. 1991–Sept. 1991	72	19	26	B	0–87	O78:H10
[28]	Columbus, USA	UTI			101	16	16	F	≥18	O18:K1:H7
[27]	Barcelona, Spain		1994–1995		1871	25	1		0–83	O15:K52:H1
[16]	Berkeley, USA	UTI	1999–2000		255	28	11	F	18–45	O11/O17/O77:K52:H18
[14]	Calgary, Canada	UTI, PY, B	2000–2002	Oct.–Dec. 2000	232||	67	29	B	1–92§	
[37]	UK	UTI, PY, B	2003–2004	Oct. 1986–Apr. 1987	291||	110	38			O25
[35]	Zagreb, Croatia	U, UTI, PY	2004		2451	25	1	B	1–79	O4
[36]	UK	U, B	2004–2005		88	21	24			O25-ST131
[33]	Spain	UTI, B	2004–2005		525||	103	20	B	≤14 to ≥65	
[34]	Portugal	U, B†	2006–2008		119||	91	76	B		
[44]	Lugo, Spain	U			11343	77	1			O25(b):H4-ST131

* B, Isolates recovered from blood samples, bacteraemia cases or sepsis cases; U, Isolates recovered from urine samples; UTI, isolates recovered from cases of cystitis or UTIs; PY, isolates recovered from pyelonephritis cases.
† *E. coli* was also recovered from wounds, ascitic fluid, sputum, gastric fluids, bronchioaveolar lavage and secretions.
‡ M, male; F, female; B, both male and female.
§ Dr J. Pitout, personal communication.
|| Indicates that the proportion is estimated based on a sub-sample of ESBL-producing *E. coli* and therefore does not reflect the overall proportion.

TMP-SMZ, this clonal group also exhibited resistance to ampicillin, tetracycline, chloramphenicol, and streptomycin. A peak period could not be ascertained due to the 4 months' duration of the study. Dissemination throughout the community was observed through the recovery of CgA from stool samples from 15/41 healthy subjects during the same study period [16].

A second cross-sectional study was conducted 1 year later to evaluate the hypothesis that CgA was associated with an outbreak of UTI [31]. In the second study, only four (11%) TMP-SMZ-resistant CgA isolates were identified *vs.* 23 (49%) in the first study ($P<0.001$). The temporal decline in UTI cases associated with CgA provided further evidence that CgA may have caused a community outbreak of UTI. Alternatively, the decline may be indicative of a decrease in the endemicity of CgA in UTIs (J. R. Johnson, personal communication). Six other clonal groups were responsible for 32% of TMP-SMZ-resistant UTIs during the observation period [31]. As with CgA, members of these other clonal groups exhibited closely related PFGE patterns and were recovered from unrelated women [31]. The fluctuation of other *E. coli* clonal groups in this community suggested that a large proportion of community-acquired UTIs may be caused by *E. coli* disseminated from one or more point sources. However, epidemiological evidence indicating a source was not available.

Outbreaks associated with extended spectrum β-lactamase (ESBL)-producing *E. coli*

The production of β-lactamases by ExPEC has complicated the treatment of UTIs and other infections. These newly emerging pathogens have developed resistance to commonly used antibiotics, such as cephalosporins. Such organisms have been found in healthcare facilities since the 1980s, but are now of even greater concern due to the increase in incidence in the community, especially the CTX-M subtypes [32]. Dissemination of related ESBL-producing strains have also been documented in Canada [14], Spain [33], Portugal [34], Croatia [35] and the UK [36, 37]. ESBL-producing *E. coli* O25:H4-ST131 is one clone which appears to have spread widely and has been responsible for several outbreaks.

Calgary, Alberta, Canada, 2000–2001

Between April 2000 and December 2001, Pitout *et al.* reported a community-wide outbreak in Calgary,

Alberta of a CTX-M-14 β-lactamase-producing *E. coli* clonal group, with a peak in cases falling approximately between October and December 2000 [14]. This clonal group, designated CTX-M-14A and defined by closely related *Xba*I PFGE patterns, caused infections in 59 patients, predominately of community onset (80%), all identified from urine specimens. The epidemic strain was associated with phylogenetic group D [38]. This was the first reported outbreak associated with community-acquired ESBL-associated infections. The authors of this report also suggest the possibility of a common food or environmental source; however, epidemiological information to test this hypothesis was unavailable. An increase in CTX-M-14 isolates was also observed in the same region in 2003 [39] and had also spread to Edmonton, Canada (J. D. Pitout, personal communication).

Madrid, Spain, 2004–2005

During a surveillance study of ESBL-producing *E. coli* strains which were resistant to cefotaxime and ceftazidime, a multidrug resistant, epidemic strain was identified in 103/525 isolates collected from mostly urine, blood and wound samples from January 2004 to August 2005 [33]. The outbreak strain, identified by *Xba*I PFGE, most commonly exhibited resistance to ciprofloxacin, gentamicin, tobramycin, ampicillin, amoxicillin-clavulanic acid and TMP–SMX.

Portugal, 2004–2006, serogroup O25:H4-ST131

Of 181 ESBL-producing *E. coli* isolates collected and analysed from mainly urine specimens between March 2004 and March 2006 in Portugal, 91 comprised a group of related or indistinguishable isolates by *Xba*I PFGE [34]. The majority of this cluster produced CTX-M-15 enzymes and 58% of these isolates were recovered from outpatients. The predominant resistance profile included resistance to ampicillin ($\pm$ sulbactam), aztreonam, piperacillin, ticarcillin, ciprofloxacin, gentamicin and tobramycin. A small sample of these isolates were evaluated for serogroup, MLST (ST131) and phylogroup (B2) [40].

Zagreb, Croatia, 2004, serogroup O4

A 5-month study in Croatia, between January and May 2004, revealed a clonally related cluster defined by *Xba*I PFGE of 25 ESBL-producing *E. coli* isolates recovered from non-hospitalized patients [35]. These isolates belonged to serogroup O4 and exhibited a common pattern of resistance to gentamicin, amikacin, netilmicin and TMP-SMX.

United Kingdom, 2003–2004, serogroup O25-ST131

Two clonal groups A and D, responsible for a community and hospital outbreak, were identified during 2003–2004 in the UK from urine and blood samples from more than 200 cases [37, 41, 42]. Both strains were shown to be *E. coli* O25, most produced CTX-M enzymes [37] and were resistant to quinolones and trimethoprim [42]. Strains A and D belonged to phylogenetic B2 [43], were closely related by PFGE analysis and belonged to ST131. Faecal carriage of strains was found in community and hospital diarrhoeal samples [42]. Certain outpatients were interviewed but no association with food or retail outlets was noted [42].

A similar outbreak was identified in northwest England during October 2005 [36]. These isolates were recovered from blood and urine samples were also found to belong to ST131.

Lugo, Spain, 2006–2008 O25:H4-ST131

In a study involving ESBL-producing isolates from Lugo, Spain, a cluster of strains belonging to serogroup O25b:H4 and ST131 was identified between February 2006 and May 2008 [44]. All isolates in this group belonged to phylogenetic group B2 and demonstrated resistance to ciprofloxacin, TMP-SMX and tobramycin. The epidemic strain was isolated mainly from urine samples. CTX-M-15-producing isolates accounted for about 20% of all ESBL-producing isolates during 2006–2008.

ExPEC non-outbreak studies

After extracting information from full-article texts, 28 eligible non-outbreak studies were included in this review (see Fig. 2). A summary of the studies and serogroups identified in the ExPEC non-outbreak studies is presented in Table 2. These studies were conducted in USA, UK, Spain, Ireland, Denmark, The Netherlands, Australia, New Zealand, South Africa, China, Japan, and India between 1960 and 2001. The studies are presented from earliest sampling period to most recent period; if this information was not reported, publication date was used. Both men and women were included in the studies and a wide
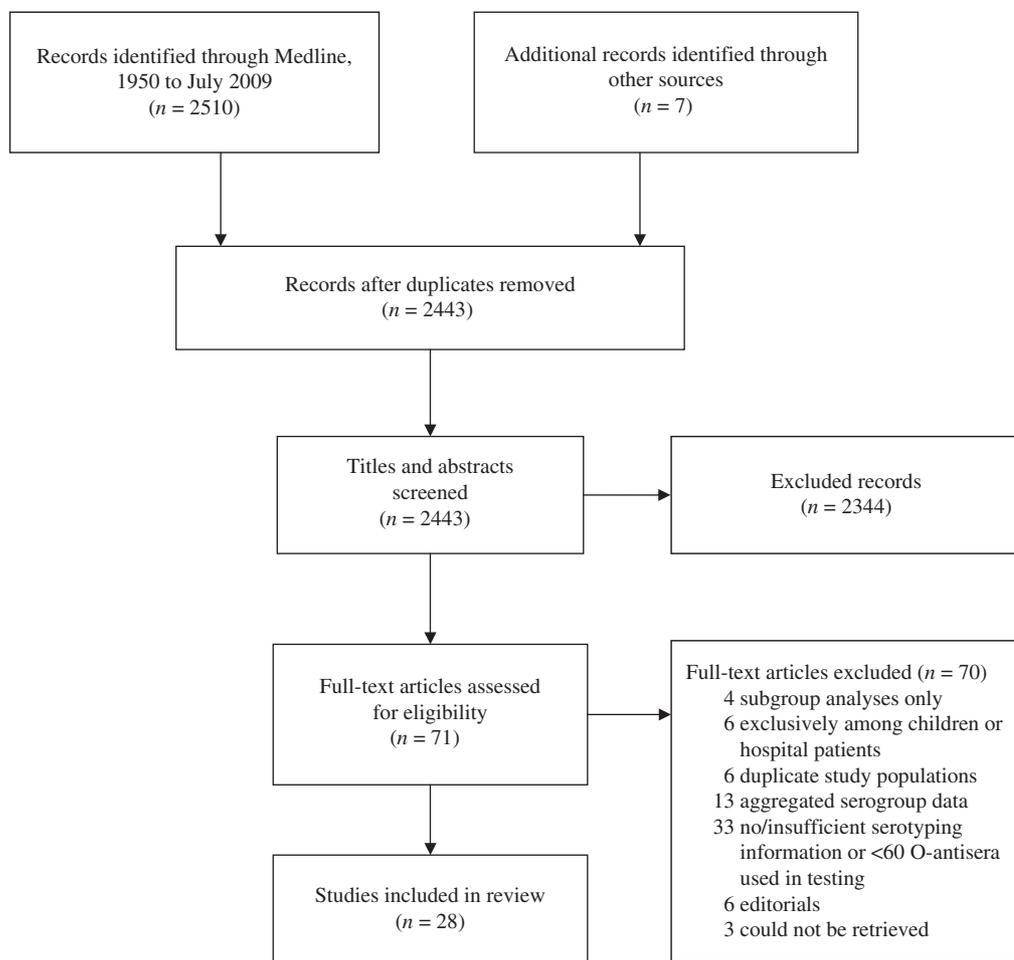
Fig. 2. The selection process of non-outbreak ExPEC articles into the review. Flow chart adapted from Moher *et al.* [77].

range of extraintestinal infections including cystitis, pyelonephritis, bacteraemia and prostatitis were observed. Eleven studies used samples from outpatients only, while eight used a combination of both in- and outpatient samples. Nine studies did not specify the population type. It is possible that some of the non-outbreak studies, particularly the earlier studies, contained unrecognized outbreaks. The serogroups most commonly associated with UTIs were O1, O2, O4, O6, O7, O8, O16, O18, O25, and O75 [7, 45]. The weighted proportion of these serogroups varied from 1% to 15%. Serogroup O6 occurred most frequently, ranging in incidence from 4% to 30%, and was identified in every study. Serogroups O2, O4, and O75 were the next most common serogroups reported and were identified in almost all studies (Table 2). Our results are consistent with the observed distribution of ExPEC recovered from infections from other studies [46, 47], although proportions may vary temporally and geographically [7, 48].

DISCUSSION

Extraintestinal infections caused by *E. coli* are believed to be sporadic, opportunistic infections. This notion, however, is being challenged by the recognition of clusters of infections caused by indistinguishable or closely related *E. coli*, occurring in specific geographic locations over short periods of time. This is the first epidemiological review and comparison of published reports describing ExPEC-associated outbreaks and reports describing community-acquired infections caused by endemic or sporadic ExPEC. The existence of ExPEC outbreaks appears well supported. It is likely that the occurrence of these outbreaks has been substantially under-reported; however, the availability of inexpensive genotyping assays has probably led to an increase in the number of ExPEC outbreak reports since the 1990s.

Apart from serogroups O4, O18 and O25, the ExPEC outbreak-related serogroups were relatively

Table 2. *Reported serogroups of* Escherichia coli *causing human extraintestinal infections: non-outbreak studies*

Ref.	Pop. Type*	Observation period	Location†	Sex‡	Infection§	Isolates	No. O-antisera¶	Common serogroups (%)							Epidemic serogroups (%)								
								O1	O2	O6	O7	O8	O16	O75	O4	O11	O15	O17	O18	O25	O73	O77	O78
[47]	1	1960–1981		F	UTI, PY, ABU	614||	131	2	0·3	22	5	2		10	10	0·7	0·8	1	4	5	0·8	0·8	
[53]	2		USA		U, UTI, PY	156	129	5	4	19	3	2		14	13				0·6	2	0·6			0·6
[7]	1	1965–1967	UK		UTI	395	147	5	6	16	6	0·8	0·3	13	6	2	0·3	1	5	1	0·3		
[48]	1	1966–1970	DK	F	PY, B	367	150		14	8				10	8								
[54]	2		AU	B	UTI	1008	143	2		20	4	0·7	0·3	11	5	0·9	0·6	1	2	4	0·4	0·5	
[55]	3	1972–1973	SA		U	222	±150	2	5	30	3			7	18	1			15				
[56]	2	1969–1976	CH		UTI	427	164	4	8	5	1	3			7		2		2	3			
[57]	2	1969–1987	UK	B	B	861||	RL	6	10	13				5	6		7		5				
[58]	3		USA		B	149	71	5	7	13	5	3	5	3	8	0·7	4	0·7	6	4			0·7
[59]	1	1973–1981	NZ	F	UTI	101	164	3	6	13	3	5		16	2				2	1			
[60]	1	1979	NE	F	UTI	30		7	17	17		7		10					3			10	
[61]	1	1980–1983	SW	F	UTI, PY	84||	165	11	5	6	5		13	6	6				4				
[62]	1	1980–1983	SW	F	PY, B	75||	165	15	7	5	7		16	5	8		4		3				
[63]	3		NE & UK		UTI, PY, ABU	119	181	6	4	14		5		10					3	4			4·2
[64]	1	1983–1992	SW	M	UTI, PY	88	171	1	7	26	1	2	5	7	7		9		5				
[65]	2	1986–1990	DK		B	172	171	6	7	12	3	5		8	2		6		5				
[66]	2	1987–1988	IN	B	U	56	RL	2	4	4	2				5		4						
[67]	2	1988–1991	USA & KE	B	B	187	173	5	8	19	1	2	2	4	5				6	3			
[68]	2	1989–1992	SP	B	UTI, PY, ABU	252	101	3	8	13	3	3		4	8	2	3	2	15	2	2		
[69]	1	1992–1993	IR	B	UTI	87	68	1	2	24	8	3			13		2	9	1				
[70]	3	1993–1996	SW	M	UTI	70		3	16	23		1		7	19				3	4			
[71]	1	1994–1999	USA	F	UTI, PY	329	RL	5	19	10	2		3	7					5				
[72]	1		SP	F	UTI, P	90	170	2	11	29	6	3		3	10								
[73]	3		JA	M	PR	107		4	16	11			3	5	9	0·9	0·9		14	5			
[73]	3		JA	F	UTI, PY	270		12	11	9	2	11		9	3		2		17	4		0·4	
[74]	3			F	UTI	74	RL	7	5	19				4	4				6				
[75]	3		DK	B	B	247	171	7	8	11	3	6		6			6			7	3		
[12]	3	1997–1997	IN		UTI	100	RL		2	5		2			12			1	2			2	
[76]	3	1998–2001	BR	B	B	60		3	13	10	3		2	5	2	3			12	3			2
Weighted average								4	7	15	3	2	1	8	6	1	1	1	5	2	0·2	0·3	0·1

* Population type: 1, community-acquired infections; 2, community- and hospital-acquired infections; 3, patient population type not reported.

† AU, Australia; CH, China; UK, England; DK, Denmark; SP, Spain; NE, The Netherlands; SW, Sweden; JA, Japan; FN, Finland; CR, Croatia; CA, Canada; PR, Portugal; IN, India; BR, Brazil; KE, Kenya; IR, Iran; SA, South Africa; NZ, New Zealand.

‡ M, male; F, female; B, both male and female.

§ B, Isolates recovered from blood samples, bacteraemia cases or sepsis cases; U, isolates recovered from urine samples; UTI, isolates recovered from cases of cystitis or UTIs; PY, isolates recovered from pyelonephritis cases; PR, isolates recovered from prostatitis cases; ABU, isolates recovered from asymptomatic bacteriuria cases.

\|\| The denominator used for calculations may differ from the number of isolates tested. For Vosti [47], the denominator is 614 due to missing information from 291 patients; for Grandsen *et al.* [57], the denominator is 861 which is the number of patients studied; for Sandberg *et al.* [61], the denominator is 84 (only non-pregnant PY and UTI patients included); for Otto *et al.* [62] the denominator is 75 (92 minus complicated cases, including diabetic patients).

¶ RL was used when serotyping was done at a reference laboratory and was assumed to use the entire set of O-antisera present at the time of the study.

uncommon in reports of sporadic ExPEC-associated infections. Moreover, the proportion of infection with an outbreak-associated serogroup was notably higher during the outbreak periods (1–26%, excluding reports with exclusively antimicrobial-resistant isolate samples) than during non-outbreak periods (weighted proportions <1–15%). Furthermore, serogroup O25, which was commonly associated with endemic ExPEC infections (weighted proportion 2%), has recently been associated with the emergence of ESBL-producing *E. coli*, and was responsible for several outbreaks [14, 33–35, 37, 42, 44]. Although some of the epidemic serogroups or serotypes were detected in the non-outbreak studies, the proportion of these serogroups during an epidemic was higher. Most outbreaks involved community-acquired UTIs, and females were disproportionately affected. The age range of infected persons was broad. The duration of the outbreaks was difficult to assess since many studies inadvertently discovered the outbreak or were retrospective in design.

ExPEC infections may follow a seasonal pattern, similar to sexually transmitted infections [49]. The frequency of UTIs and bloodstream infections have been shown to peak during the warmer seasons [50, 51]. It has been suggested that warmer temperatures may enhance growth of these types of *E. coli* in food or environmental sources, and may promote the expression of certain virulence factors [49]. Only four of the outbreak studies reported information on the timing of the peak period of infections; three of these four reports indicated an observed peak in the winter months. Due to limited data on reported peak periods, conclusions *vis-à-vis* seasonality could not be drawn.

The source of the *E. coli* involved in these outbreaks remains unclear, although several reports reviewed suggest a food or shared community exposure. Although no source was identified in any of the outbreaks, there has been evidence to support food as a potential reservoir for ExPEC. Isolates cultured from retail meats and other food items have been found to resemble human clinical isolates from urine and faeces [22, 24]. Further, during an outbreak involving gastroenteritis due to *Salmonella*, a bacterium known to be contracted via undercooked meat and other food items, at a camp in Girona, Spain, investigators detected genetically related extended-spectrum cephalosporin-resistant *E. coli*. Clones A and B were confined to those individuals with *Salmonella* infections. Those infected had no previous contact before

camp yet lived together and shared a water and food supply during camp [52]. Human contamination might also have contributed to the spread of the strains, yet food handlers surveyed during the camp outbreak did not possess the epidemic strains of *E. coli*, nor was any transmission detected in the households of those colonized [52]. Several of the outbreak studies also included a stool survey which allowed for the detection of the outbreak strains circulating in healthy community members [16, 28, 52]. Together, the evidence points to food as a potential reservoir of ExPEC, which would lead to intestinal colonization with these strains.

There are several limitations to this review. Incomplete data collection and reporting in the outbreak studies, particularly related to epidemiological information including complete dates, subject sample size, and precise sex and age distributions, was problematic. The outbreak studies reported were often conducted once the outbreak was underway and may not reflect the entire time the epidemic strain was circulating in the community; moreover, many reports did not continue surveillance or conduct repeated sampling over time. The outbreaks were identified primarily due to an unusual serogroup, antibiotic profile or growth conditions exhibited by the outbreak strain, suggesting that the characteristics of the outbreak strains are biased and outbreaks due, for example, to antibiotic-susceptible ExPEC, would be under-reported. The association between infection with an outbreak strain and the development of more severe disease may be biased as laboratory or diagnostic testing occurs more frequently with severe infections, treatment failures or recurrent infections. Serogroup was used a marker of *E. coli* dynamics over time in studies of extraintestinal infections. Serogroup has been consistently collected in many studies over time and therefore allows for temporal analysis of studies of extraintestinal infections from 1950 onwards. However, specific serogroups will encompass multiple genotypes; therefore serogroup is an imperfect biomarker for our comparisons. Only studies with O-antisera testing panels containing >50 serogroups were included to ensure representation of most circulating serogroups. Some studies may have included recurrent infections or collected multiple samples for a single person; this may have led to overestimation of certain serogroups in the non-outbreak studies.

Many questions remain unanswered about the epidemiology of ExPEC and their associated infections.

The origin and mode of transmission of these types of *E. coli* has not yet been confirmed but evidence suggests foodborne dissemination [16, 24, 52]. Despite limitations in reporting, this review highlights the existence of outbreaks associated with specific types of ExPEC and illustrates the differences in serogroup in ExPEC associated with outbreaks and ExPEC that have been responsible for sporadic disease over the past several decades. The frequency and magnitude of ExPEC outbreaks remains unclear, but their existence is strongly supported.

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DECLARATION OF INTEREST

None.

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