FOODBORNE PATHOGENS AND DISEASE
Volume 11, Number 2, 2014

DOI: 10.1089/fpd.2013.1572

Review

Chronic Sequelae of *E. coli* O157: Systematic Review and Meta-analysis of the Proportion of *E. coli* O157 Cases That Develop Chronic Sequelae

Jessica Keithlin,[1,2] Jan Sargeant,[1,2] M. Kate Thomas,[3] and Aamir Fazil[4]

Abstract

Objective: This was a systematic review and meta-analysis to determine the proportion of *Escherichia coli* O157 cases that develop chronic sequelae.
Data Sources: We conducted a systematic review of articles published prior to July 2011 in Pubmed, Agricola, CabDirect, or Food Safety and Technology Abstracts.
Study Selection: Studies were selected that reported the number of *E. coli* O157 cases that developed reactive arthritis (ReA), hemolytic uremic syndrome (HUS), irritable bowel syndrome, inflammatory bowel disease, or Guillain Barré syndrome.
Methods: Three levels of screening and data extraction of articles were conducted using predefined data fields. Meta-analysis was performed on unique outcome measures using a random-effects model, and heterogeneity was assessed using the I^2 value. Meta-regression was used to explore the influence of nine study-level variables on heterogeneity.
Results: A total of 82 studies were identified reporting 141 different outcome measures; 81 reported on HUS and one reported on ReA. Depending on the number of cases of *E. coli* O157, the estimate for the proportion of *E. coli* O157 cases that develop HUS ranged from 17.2% in extra-small studies (<50 cases) to 4.2% in extra-large studies (>1000 cases). Heterogeneity was significantly associated with group size ($p<0.0001$); however, the majority of the heterogeneity was unexplained.
Conclusions: High unexplained heterogeneity indicated that the study-level factors examined had a minimal influence on the variation of estimates reported.

Introduction

Escherichia coli O157 (*E. coli* O157) have been linked to gastrointestinal disease in humans, including numerous food and waterborne outbreaks worldwide. (Yoshioka *et al.*, 1999; Garg *et al.*, 2006a; Karmali *et al.*, 2010). The O157 serogroup of *E. coli* is of particular concern as it is associated with severe symptoms such as hemolytic uremic syndrome (HUS), the leading cause of acute renal failure in children. In addition, chronic sequelae such as reactive arthritis (ReA), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and Guillain Barré syndrome (GBS) have potential links to infection by foodborne pathogens such as *E. coli* O157 (Thabane *et al.*, 2007; Garg *et al.*, 2008; Havelaar *et al.*, 2012).

The World Health Organization introduced the Global Burden of Disease effort to expand disease burden estimates beyond mortality rates. Diarrheal disease is estimated to be the fifth leading cause of morbidity worldwide, causing an estimated 2.2 million deaths per year (World Health Organization, 2008). As diarrheal disease can be caused by many pathogens, the exact number of cases attributed to *E. coli* O157 is uncertain. An increased understanding of disease progression and the sequelae associated with *E. coli* O157 infection could assist efforts to develop more accurate burden of disease (BOD) estimates for *E. coli* O157.

Understanding the true BOD is an important aspect of evidence-informed decision making and can help guide policy related to foodborne disease prevention, interventions,

[1]Centre for Public Health and Zoonoses, University of Guelph, Guelph, Ontario, Canada.
[2]Department of Population Medicine, Ontario Veterinary College, Guelph, Ontario, Canada.
[3]Centre for Food-borne, Environmental, and Zoonotic Infectious Diseases, Public Health Agency of Canada, Guelph, Ontario, Canada.
[4]Laboratory for Foodborne Zoonoses, Public Health Agency of Canada, Guelph, Ontario, Canada.

and cost estimates. However, the accuracy of current BOD estimates is limited by minimal knowledge of the long-term health effects. Development of measures such as Disability Adjusted Life Years (World Health Organization, 2008) and Health Adjusted Life Years (Public Health Agency of Canada, 2005) have attempted to incorporate the long-term health effects of an illness into disease burden estimates. Although the association between *E. coli* O157 infection and HUS is accepted (Karmali *et al*., 1985; Palermo *et al*., 2009; Zoja *et al*., 2010; Melton-Chelsa *et al*., 2012), the frequency of cases that go on to develop HUS and other potential chronic sequelae is less well known.

Systematic review is an established way to identify and summarize the body of literature associated with a subject area in a transparent, reproducible manner (Liberati *et al*., 2009; Higgins and Green, 2011). Meta-analysis (the formal statistical pooling of results from multiple studies) allows for the development of summary estimates, which can be used to inform BOD estimates. Meta-regression can be used to explore variables that may influence the range in reported outcomes (Higgins and Green, 2011). This review was conducted as part of a broader literature search, which also investigated the proportion of cases of *Salmonella* and *Campylobacter* that develop chronic sequelae. The purpose of this systematic review and meta-analysis was to estimate the proportion of cases of *E. coli* O157 that develop HUS, IBS, IBD, ReA, or GBS and to explore which variables contribute to differences between studies.

Materials and Methods

Literature search

A keyword search was performed between July 19 and July 25, 2011 using Pubmed, Agricola, CabDirect, and Food Safety and Technology Abstracts to identify information on *E. coli* O157, *Salmonella*, and *Campylobacter*. The search terms were constructed iteratively by exploring the addition of new search terms. No limitations on date, country of publication, or language were used. Studies specific to *E. coli* O157 were identified at the final stages of data extraction and are included in this review. The search strategy included any combination of the terms ('*Escherichia coli* O157,' or, 'O157,' 'VTEC,' 'STEC,' 'O157:H7' or *Salmonella* or *Campylobacter)* and ('sequel*,' 'long-term,' 'long term,' 'chronic,' 'Guillain*,' 'HUS,' 'hemolytic uremic syndrome,' 'haemolytic uraemic syndrome,' 'hemorrhagic uremic syndrome,' 'haemorrhagic uraemic syndrome,' 'Reiter*,' 'complication*,' 'arthritis,' 'irritable bowel syndrome,' 'IBS,' 'post infectious irritable bowel syndrome,' or 'inflammatory bowel disease'). Additional references were located through a search of the reference lists of all studies that met the inclusion criteria. All references were imported into RefWorks Reference Management Software (ProQuest LLP, 2012), where duplication removal occurred using the exact and close match functions.

Inclusion and exclusion criteria for systematic review

Three levels of screening were performed (for details, see Supplementary Data S1; Supplementary Data are available online at www.liebertpub.com/fpd). The first two levels of screening were based on title and abstract only. The final level was applied to full-text articles. The first round excluded studies that did not focus on *E. coli* O157, *Salmonella*, or *Campylobacter* or did not include information on chronic disease in humans. Level two screening narrowed down results to specific species of pathogens associated with foodborne transmission routes, study designs, and chronic sequelae. A third level of screening of the full- text for articles passing the first two levels of relevance screening identified studies that provided the information necessary to meet the research objectives. Studies where full-text articles were not available in English or French were excluded. Data were extracted from studies that provided details on the number of cases of *E. coli* O157, *Campylobacter,* or *Salmonella* that developed one or more of the chronic sequelae of interest. Case–control studies reporting the number of cases of sequelae with evidence of past pathogen exposure were excluded. After data extraction, studies on outcomes specific to *E. coli* O157 were identified for inclusion in this review.

Data collection process

Relevance screening and data extraction were conducted using a standardized form created in Microsoft Excel (Version 2007) (available from the authors upon request). Training for the first level of screening was performed using 200 test articles that were assigned to each reviewer. Consensus of >95% was achieved between reviewers for the test articles. Due to the high agreement and resource constraints, each article was subsequently reviewed by a single reviewer.

The second level of screening was performed independently by two reviewers per reference. Inclusion/exclusion results for the articles were compared and conflicts were resolved via consensus, with included references moving on to the third level of screening.

The third level of screening was performed by four different reviewers, with two reviewers independently reviewing each article. The screening questions and data extraction tool were refined through a pilot test of 50 articles. Once refined, data were extracted using the data extraction tool described in the following section. Conflicts were resolved via consensus; any remaining disagreements were resolved by a third reviewer.

Data variables

Information on population (dates for data collection, country, age range, and gender distribution of *E. coli* O157 cases), disease status (related to the sequelae) prior to illness with *E. coli* O157, season of data collection, outbreak source (where applicable), study directionality (retrospective versus prospective), source of data (surveillance versus outbreak versus hospitalized cases of *E. coli* O157), categories describing *E. coli* O157 diagnosis and sequelae diagnosis, the length of time between *E. coli* O157 infection and sequelae diagnosis (follow-up time) and outcomes (number of participants with *E. coli* O157, number of participants who developed chronic sequelae) was extracted. Categorization of season, outbreak source, data source, study design, pathogen diagnosis, and sequelae diagnosis was performed after data extraction for inclusion in the meta-regression. In the northern hemisphere, seasons were classified as fall (September–November), winter (December–February), spring (March–May), and summer (June–August). In the southern hemisphere they were classified as fall (March–May), winter (June–August), spring

(September–November), and summer (December–February). Outbreak source was classified as food, water, animal contact, day care, nursing home, or other. Data source was classified as surveillance (which included laboratory and notifiable disease registries, sporadic cases, and other population surveillance), associated with an outbreak or as hospitalized cases of *E. coli* O157. Study directionality was classified as prospective (cases of *E. coli* O157 were identified and the assessment for sequela occurred in the future), retrospective (both identification as a case of *E. coli* O157 and sequelae diagnosis had already occurred when data collection for the study was initiated), or other (for hospitalized cases where directionality could not be determined). Pathogen diagnosis was classified as confirmed (through culture, serology, or DNA based tests), probable (based on case definition from study or associated with an outbreak), or other (which included studies where cases of HUS were included in the case definition for *E. coli* O157). Sequelae diagnosis was categorized as taken from medical records/diagnosed by physician, other (which included self-reported questionnaires, or studies that reported multiple outcomes using a variety of definitions for HUS), or not reported. For studies that identified both full and partial cases (met some but not all criteria used to assess HUS) of HUS, only full cases were included as an outcome measure for the analysis.

As some studies reported multiple methods of diagnosis for both the sequelae (e.g., both medically diagnosed and self-reported cases) and *E. coli* O157 (e.g., both probable and culture-confirmed cases) as well as multiple data sources (e.g., both outbreak associated and hospitalized cases), each combination of *E. coli* O157 and sequelae diagnosis was considered a separate outcome measure. As it was possible to create multiple estimates from the same study for the proportion of cases of *E. coli* O157 that developed sequelae, the term "outcome measure" was used to describe these unique proportion estimates.

Assessment of reporting of factors related to internal and external validity

Information on reporting of factors related to internal validity (risk of bias) and external validity (generalizability) were extracted to allow for further exploration. Ten criteria were extracted. Factors related to internal validity were study directionality, the source of data, method of diagnosis for both the pathogen and sequelae, follow-up time, and reporting the

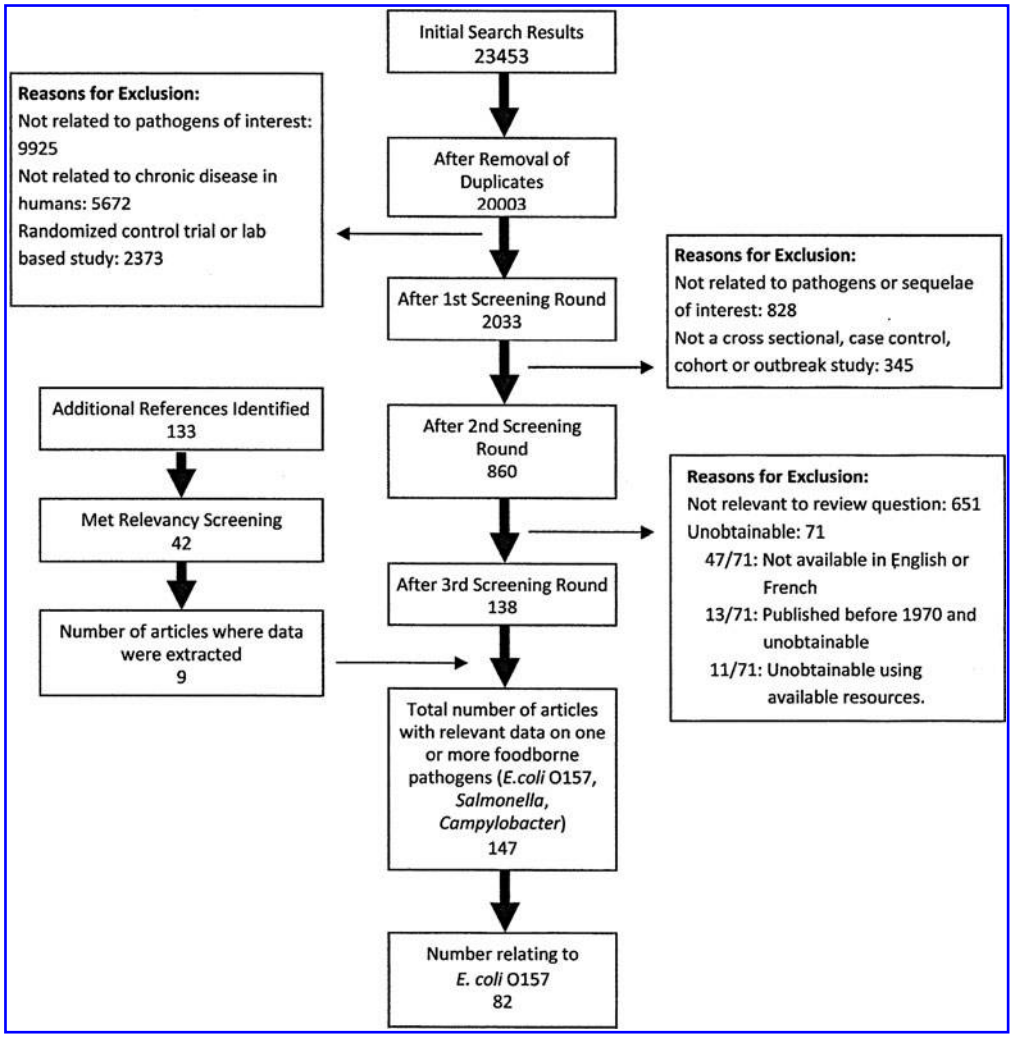

FIG. 1. Results from the literature search for studies relating to chronic sequelae associated with *Escherichia coli* O157 published prior to July 2011.

specific criteria used for the sequelae diagnosis. The definitions for sequelae diagnosis were divided into two categories: the method of diagnosis (physician versus self-reported versus other) and whether specific diagnostic criteria were provided (e.g., a description of the laboratory criteria used in diagnosis of HUS). Factors related to external validity were reporting of relevant population information (country, gender distribution, and age range of *E. coli* O157 cases).

Statistical analysis

The primary outcome was the proportion of people with *E. coli* O157 who developed a specific chronic sequela. This was calculated as the number of persons developing a sequela divided by the total number of cases of *E. coli* O157. Standard errors and confidence intervals for a single proportion were derived. Prior to analysis adjusted proportions were calculated using a logit transformation (Sanchez *et al*., 2007).

All statistical analyses were performed in Stata Version 12 (Statacorp 2012). Meta-analysis for each sequela was performed using a random-effects model and the DerSimonian and Laird method to derive the summary estimate (Egger *et al*., 2001). Heterogeneity was assessed using the I^2 value, where values closer to 100% indicate that heterogeneity is due to actual differences between studies and values closer to 0% indicate that heterogeneity is due to chance (Higgins and Thompson, 2002). For studies reporting on the same populations (for example, multiple reports from the same outbreak using the same outcome measure), the publication that provided the most complete ancillary information was included. A count of 0.5 was added (to those reporting 0%) or subtracted (from those reporting 100%) to allow for inclusion in the meta-analysis (Borenstein *et al*., 2007). Meta-regression was used to explore sources of heterogeneity if the I^2 value was higher than 25% and if >10 outcome measures were available. The source of data, method of pathogen diagnoses, age group, country (England and Wales were combined into a single category), decade of data collection, season, outbreak source, group size, and whether the design was retrospective or prospective were factors considered. Meta-regression was performed using logit transformed outcomes and logit transformed within-study standard errors, and factors were only included if there was variation in the factor among studies. Significance tests were performed using univariable analysis where those presenting a p-value ≤ 0.05 were considered significant. Significant variables were then entered into a backwards multivariable model, and those that remained significant ($p \leq 0.05$) were explored with subgroup meta-analysis.

Categorical variables representing group size and age group were generated prior to meta-regression. For group size, the studies were classified based on the number of cases (extra small <50 cases, small = 51–200 cases, medium = 201–500 cases, large = 501–1000 cases, and extra-large >1000 cases). Age group was classified as all ages, adults (≥ 18 years), or youth (<18 years). A separate category for children was generated to acknowledge and explore those studies that reported on children only (<10 years).

Results

Systematic review

Study selection. The results of the search are summarized in Figure 1. The screening process included three foodborne pathogens until the final step, which was specific to *E. coli* O157. After final screening of full text articles and evaluation of the reference lists of relevant studies, there were 82 studies containing relevant information on *E. coli* O157.

Study descriptions. The 82 studies reported on 121 different populations from 18 different countries (Table 1). All but two studies were from North America ($n=44$), Europe ($n=26$) and Japan ($n=10$). Seventy-nine studies related to *E. coli* O157 and HUS, two evaluated *E. coli* O157 and HUS or thrombotic thrombocytopenic purpura (TTP), and one study investigated *E. coli* O157 and ReA. No studies on the other chronic sequelae were found.

Of the 121 populations reported, 90 were based on outbreaks. Of those outbreak-based populations that reported seasonality, 63% (54/86) of outbreaks occurred in the spring and/or summer. Only 41% (37/90) of those reported the source of the outbreak, of which 57% (21/37) were foodborne. Of the remaining study designs (surveillance and hospital-based), 26 were based on population surveillance, of which 16 were prospective, six focused on hospitalized cases of *E. coli* O157, and a single study looked at sporadic cases in the community.

E. coli *O157 and HUS*

Outcome measures. There were 141 different outcome measures for the probability of developing HUS following *E. coli* O157 infection from the 120 different populations (Table 2 and Fig. 2). The proportion of cases of *E. coli* O157 was variable across studies, and estimates for development of HUS ranged from 0% to 100% (Fig. 2). In the outbreak studies, *E. coli* O157 case numbers ranged from 2 to 2311 persons. Of the population surveillance studies, *E. coli* O157 case numbers ranged from 25 to 3464 persons, and the hospitalized cases of *E. coli* O157 ranged in size from 2 to 2313 persons. For diagnosis of *E. coli* O157, 63% (90/141) reported "confirmed" cases of E. *coli* O157, with the proportion of cases that developed HUS ranging from 0% to 100%. Of the 39 outcomes reporting probable cases of *E. coli* O157, the probability of developing HUS ranged from 0% to 67%. There were 10 studies that assumed all cases of HUS were positive for *E. coli* O157 and therefore included them as a case (classified as "other" for pathogen diagnosis). In these studies, the number of cases developing HUS ranged from 1.8% to 50%.

Assessment of internal and external validity. Thirty percent (25/82) of studies reported the length of time between diagnosis as a case and assessment for HUS. No studies reported on sequelae status prior to the study. All studies reported study directionality and source of data. Two studies did not provide information on how the pathogen was diagnosed. Due to the severity associated with HUS symptoms, all sequelae were physician diagnosed. However, 37% (30/82) of the studies did not provide a definition for the diagnosis of HUS. For population variables, 26% (22/82) did not report age range, and 44% (36/82) did not report gender distribution. Country was specified for all populations.

Meta-analysis/meta-regression. Prior to analysis, duplicate reports from the same outbreak or reports that presented on a subset of the same data were identified as "duplicate

Table 1. Population Characteristics for Studies Relating to Selected Chronic Sequelae of *Escherichia coli* O157 Published Before July 2011

First author, date of publication	*Country*	*Age category*[a] *(for* E. coli *cases)*	*% Female (for* E. coli *cases)*	*Source of data*	*Study directionality*	*Outbreak source*	*Date for data collection*	*Season*
HUS								
Afza, 2006	UK	All ages	89	Outbreak in community	Prospective	Nursing home	2001	Summer
Al-Jader, 1999	Wales	Adult	38	Outbreak in community	Retrospective	Day care	1995	Summer/Fall
Ammon, 1997	Austria	NR	NR	Population surveillance[b]	Retrospective	Various	1992	NR
Ammon, 1997	England/ Wales	NR	NR	Population surveillance	Retrospective	Various	1992–1994	NR
Ammon, 1997	Germany	NR	NR	Population surveillance	Retrospective	Various	1992,1995–1996	NR
Ammon, 1997	Ireland	NR	NR	Population surveillance	Retrospective	Various	1995	NR
Ammon, 1997	Scotland	NR	NR	Population surveillance	Retrospective	Various	1992–1996	NR
Ammon, 1997	Sweden	NR	NR	Population surveillance	Retrospective	Various	1995–1996	NR
Bell, 1994	USA	All ages	49	Outbreak in community	Prospective	Food–meat	1992–1993	Winter
Bell, 1997	USA	Youth	52	Outbreak in community	Retrospective	Food–meat	1993	Winter
Belongia, 1993	USA	Youth	31	Outbreak in community	Prospective	Food–meat	1988	Fall
Besser, 1993	USA	All ages	83	Outbreak in community	Retrospective	Food–vegetable	1991	Fall
Blackwell, 2002	Scotland	NR	NR	Outbreak in community	Prospective	NR	1996	NR
Buteau, 2000	Canada	Youth	51	Hospitalized cases	other[a]	NA	1987–1997	All
CDC, 2005 (report on multiple outbreaks, indicated by superscript)	USA–Florida[1] Arizona[2]	All ages[1] NR[2]	56[1] NR[2]	Outbreak in community[1/2]	Prospective[1] Retrospective[2]	Animal contact[1/2]	2005[1/2]	Winter/Spring[1] Summer[2]
CDC, 2002	USA	All ages	NR	Outbreak in community	Prospective	Food–meat	2002	Summer
CDC, 1996[a]	USA	All ages	30	Outbreak in community	Prospective	Food–meat	1995	Summer
CDC, 1996[b]	Canada/ USA	All ages	46	Outbreak in community	Prospective	Food–other	1996	Fall
CDC, 2006	USA	NR	NR	Outbreak in community/ hospitalized cases	Prospective	Food–vegetable	2006	Summer/Fall
Cimolai, 1994	Canada	NR	54	Hospitalized cases	Other	NA	1984–1989	All
Cornick, 2002	USA	Children	38	Population surveillance	Prospective	NA	1997–2000	All
Davies, 2005[c] (report on multiple outbreaks, indicated by superscript)	USA[1/2]	NR[1] All ages[2]	NR[1] 56[2]	Hospitalized cases[1] Outbreak in community[2]	Other[1] Prospective[2]	Animal Contact[1/2]	2005[1/2]	Summer[1] Spring[2]
Davis, 1993 (report on multiple outbreaks, indicated by superscript)	USA Washington[1] Idaho[2] Nevada[3] California[4]	All ages[1/2/4] NR[3]	NR[1–4]	Outbreak in community[1–4]	Prospective[1/2] Retrospective[3/4]	Food–meat[1–4]	1992–1993[1–4]	Winter[1–3] Fall/Winter[4]
Diallo, 2011	USA	All ages	64	Outbrhak in community/ hospitalized cases	Prospective	Food–vegetable	1999	Fall
Duncan, 1987	Canada	NR	NR	Outbreak in community	Prospective	Daycare	1986	Spring
Dundas, 2001	Scotland	All ages	66	Outbreak in community	Retrospective	Food–meat	1996	Fall/Winter
Espie, 2006	France	All ages	33.3	Outbreak in community	Prospective	Food–dairy	2004	Summer
Ethelberg, 2004	Denmark	NR	NR	Population surveillance	Prospective	NA	1997–2003	All

(*continued*)

TABLE 1. (CONTINUED)

First author, date of publication	Country	Age category[a] (for E. coli cases)	% Female (for E. coli cases)	Source of data	Study directionality	Outbreak source	Date for data collection	Season
Farquhar, 2000	USA	Children	NR	Population surveillance	Prospective	NA	Pre-2000	NR
Fukushima, 1999	Japan	Youth	51	Hospitalized cases	Prospective	Food–other	1996	Summer
Gammie, 1996	England	All ages	73	Outbreak in community	Prospective	Food–meat	1995	Fall
Goode, 2009	USA	All ages	59	Outbreak in community	Prospective	Animal contact	2004	Fall
Gould, 2009	USA	All ages	61	Population surveillance	Prospective	NA	2000–2006	All
Gouveia, 1998 (report on outbreak & sporadic cases,indicated by superscript)	USA[1/2]	Youth[1] All ages[2]	60[1] 44[2]	Outbreak in community[1] Population surveillance[2]	Prospective[1] Retrospective[2]	Day care[1/2]	1994[1/2]	Summer[1] Spring/Summer[2]
Gransden, 1986	Canada	Adults	53	Population surveillance	Prospective	NA	1983–1985	All
Griffin, 1988[c] (report on multiple outbreaks, indicated by superscript)	USA[1–4] Canada[5]	All ages[1–3] Children[4] Adults[5]	NR[1–5]	Outbreak in community	Retrospective	Food–meat[1–3] Day care[4] Nursing home[5]	1982[1,2] 1986[3] 1984[4] 1985[5]	NR[1/2/4/5] Fall[3]
Hamano, 1993	Japan	Youth	NR	Outbreak in community	Prospective	Waterborne	1990	Fall/Winter
HPA, 1997[b]	England	NR	NR	Outbreak in community	Prospective	Food–other	1997	Winter
HPA, 1997[a]	Canary Islands	NR	NR	Outbreak in community	Prospective	Other[d]	1997	Spring
Hedican, 2009	USA	All ages	57	Population surveillance	Prospective	NA	2000–2006	All
Honda, 1999[c]	Japan	All ages	NR	Outbreak in community	Retrospective	Food–vegetable	1996	NR
Ikeda. 1999[c]	Japan	Youth	52.1	Hospitalized cases	Retrospective	Food–other	1996	NR
Ikeda, 2000[c]	Japan	Youth	51.7	Outbreak in community	Retrospective	Food–other	1996	Summer
Ishikawa, 2000	Japan	Youth	55	Hospitalized cases	Prospective	NA	NR	NR
Jelacic, 2002	USA	Children	56	Population surveillance	Prospective	NA	1997–2001	All
Karch, 1997	Germany	NR	NR	Hospitalized cases	Prospective	NA	1991–1995	All
Karmali, 1988	Canada	Adults	40	Outbreak in community	Prospective	Other	1985	Summer
Kawano, 2008	Japan	All ages	NR	Population surveillance	Other	NA	2001–2003	All
King, 2009	France	All ages	45	Outbreak in community	Prospective	Food–meat	2005	Fall
Kitajima 2002[c]	Japan	NR	NR	Outbreak in community/ Hospitalized cases	Retrospective	Food–other	1996	NR
Lerman, 1992	Israel	Youth	NR	Outbreak in community	Prospective	Day care	1990	Spring
Liptakova, 2004	Slovakia	All ages	56	Outbreak in community	Prospective	Food–dairy	Pre-2004	Fall
Ludwig, 1997	Bavaria	Adults	NR	Outbreak in community	Prospective	Other	1993	Summer
MacDonald, 1996	Scotland	All ages	50	Population surveillance	Prospective	NA	1988–1990	All
MacDonald, 1988	USA	All ages	44	Population surveillance/ hospitalized cases	Prospective	NA	1985–1986	All
McCarthy, 2001	USA	All ages	55	Outbreak in community	Prospective	Waterborne	1999	Summer
McDonnell, 1997 (report on adults and children, indicated by superscript)	England[1/2]	All ages[1] Adults[2]	73[1] 25[2]	Outbreak in community[1/2]	Prospective[1/2]	Food–meat[1/2]	1995[1/2]	Spring/ Summer[1/2]
Milne, 1999	UK	Adults	33	Outbreak in community	Prospective	Animal contact	1997	Spring/summer

(*continued*)

Table 1. (Continued)

First author, date of publication	Country	Age category[a] (for E. coli cases)	% Female (for E. coli cases)	Source of data	Study directionality	Outbreak source	Date for data collection	Season
Murray, 2000[c]	USA	NR	NR	Outbreak in community/ hospitalized cases	Retrospective	NR	1993	Winter
O'Donnell, 2002	Ireland	All ages	50	Outbreak in community	Prospective	Day care	1998	Winter
Olsen, 2002	USA	All ages	51	Outbreak in community	Prospective	Waterborne	1998	Summer
Orr, 1994	Canada	All ages	52	Outbreak in community	Prospective	Food–other	1991	Summer/Fall
Pai, 1988	Canada	All ages	58	Population surveillance	Prospective	NA	1984–1986	All
Payne, 2003	Wales	All ages	NR	Outbreak in community	Prospective	Animal contact	1999	Summer
Pebody, 1999	Canary Islands	All ages	60	Outbreak in community	Prospective	Waterborne	1997	Spring
Pierard, 1997	Belgium	All ages	59	Population surveillance	Retrospective	NA	1990–1995	All
Pollock, 2010	Scotland	NR	NR	Outbreak in community	Prospective	Day care	2006	Spring
Raffaelli, 2007	USA	Children	42	Outbreak in community	Prospective	Day care	2004	Summer
Remis, 1984	USA	All ages	46	Population surveillance	Prospective	NA	1982–1984	All
Roberts, 2000	Scotland	All ages	59	Outbreak in community	Retrospective	Food–dairy	1994	Spring
Rowe, 1991	Canada	Adults	60	Hospitalized cases	Prospective	NA	1985 – 1988	All
Rowe, 1998	Canada	Children	58	Population surveillance	Prospective	NA	1991–1994	All
Rowe, 1994[c]	Canada	Children	NR	Outbreak in community	Prospective	Other	1991	Summer/Fall
Salmon, 1989	England	All ages	NR	Outbreak in community	Prospective	Food–other	1987	Summer
Shimazu, 2000[c]	Japan	NR	NR	Outbreak in community	Retrospective	Food–other	1996	Summer
Shiomi, 1999[c]	Japan	Children	41	Outbreak in community	Prospective	Food–other	1996	Summer
Takeda, 1998	Japan	All ages	NR	Population surveillance	Prospective	NA	1996–1997	All
Tserenpuntsag, 2005	USA	All ages	62	Population surveillance	Prospective	NA	1998–1999	All
Varma, 2003	USA	All ages	57	Outbreak in community	Prospective	Other	2001	Summer/Fall
Wall, 1996	England/ Wales	All ages/ Children	NR	Population surveillance	Retrospective	Various	1992–1994	All
Willshaw, 1994	Wales	All ages	50	Outbreak in community	Prospective	Food–meat	1993	Summer
Wong, 2000	USA	Children	49	Population surveillance	Prospective	NA	1997–1999	All
Wood, 2001	Scotland	All ages	NR	Outbreak in community	Prospective	Food–meat	1996	All
Yoshioka, 1999	Japan	NR	NR	Outbreak in community	Retrospective	Food–other	1996	NR
HUS & TTP								
Guh, 2008	USA	All ages	57	Outbreak in community	Retrospective	Food–dairy	2008	Summer
Ostroff, 1990	USA	All ages	64	Population surveillance	Prospective	NA	1987	All
ReA								
Townes, 2008	USA	All ages	50	Population surveillance	Prospective	NA	2002–2004	All

[a]Other denotes studies using hospitalized cases of *E. coli* O157 where it was not possible to determine directionality.
[b]Surveillance included laboratory and notifiable disease registries, sporadic cases, and other population surveillance.
[c]Indicates publications identified as duplicate populations, excluded from meta-analysis.
[d]Other includes person to person transmission, environmental (non-water) contamination or unidentified source.
HUS, hemolytic uremic syndrome; NR, not reported; NA, not applicable; TTP, thrombotic thrombocytopenic purpura; ReA, reactive arthritis.

Table 2. Outcome Variables for Studies Relating to Selected Chronic Sequelae of *Escherichia coli* O157 Published Before July 2011

First author, date of publication	*Time from* E. coli *O157 illness to evaluation for chronic sequelae (days)*	*Sequelae diagnosis*	E. coli *O157 diagnosis*	*Number of people with* E. coli *O157*	*Number of people who developed sequelae*	*Outcome measure estimate (%)*
HUS						
Afza, 2006	NR	Medical records/physician	Probable[a]	95	1	1.05
	NR		Confirmed[a]	20	1	5.00
Al-Jader, 1999	50	Medical records/physician	Other[a]	31	2	6.45
Ammon, 1997 (Austria)	NR	Multiple approaches used[b]	Confirmed	9	0	0.00
Ammon, 1997 (England/Wales—18 different populations)	NR	Multiple approaches used	Confirmed	5	0	0.00
				19	0	0.00
				37	5	13.51
				3	0	0.00
				4	0	0.00
				2	0	0.00
				5	5	100.00
				3	1	33.30
				4	1	25.00
				6	1	16.67
				7	3	42.86
				7	3	42.86
				7	4	57.14
				9	6	66.67
				9	2	22.22
				12	2	16.67
				17	1	5.88
				17	3	17.65
Ammon, 1997 (Scotland—11 different populations)	NR	Multiple approaches used	Confirmed	5	1	20.00
				5	0	0.00
				5	0	0.00
				8	0	0.00
				16	0	0.00
				100	9	9.00
				24	1	4.17
				22	1	4.55
				8	3	37.50
				5	3	60.00
				4	1	25.00
Ammon, 1997 (Germany)	NR	Multiple approaches used	Confirmed	41	3	7.32
Ammon, 1997 (Ireland)	NR	Multiple approaches used	Confirmed	15	1	6.67
HPA, 1997b (England)	NR	Medical records/physician	Confirmed	10	3	30.00

(*continued*)

TABLE 2. (CONTINUED)

First author, date of publication	*Time from* E. coli *O157 illness to evaluation for chronic sequelae (days)*	*Sequelae diagnosis*	E. coli *O157 diagnosis*	*Number of people with* E. coli *O157*	*Number of people who developed sequelae*	*Outcome measure estimate (%)*
HPA, 1997a (Canary Island)	NR	Medical records/physician	Probable	32	1	3.13
Bell, 1994	NR	Medical records/physician	Confirmed	501	45	8.98
Bell, 1997	60–120	Medical records/physician	Other	278	33	11.87
Belongia, 1993	NR	Medical records/physician	Probable	54	0	0.00
			Confirmed	15	0	0.00
Besser, 1993	NR	Medical records/physician	Confirmed	23	4	17.39
Blackwell, 2002[c]	365	Medical records/physician	Confirmed	186	28	15.05
Buteau, 2000	NR	Medical records/physician	Confirmed	221	27	12.22
CDC, 2006	NR	Medical records/physician	Confirmed	183	29	15.85[1]
(report on outbreak[1] and hospitalized cases[2])				95	29	30.53[2]
CDC, 2005	21[1]	Medical records/physician[1]	Probable[1]	63	7	11.11[1]
(report on multiple outbreaks, Florida[1]/ Arizona[2])	NR[2]	NR[2]	Confirmed[2]	2	0	0.00[2]
CDC, 2002	NR	Medical records/physician	Probable	10	1	10.00
CDC, 1996[a]	NR	NR	NR	28	5	17.86
CDC, 1996[b]	NR	Medical records/physician	Other	45	12	26.67
Cimolai, 1994	NR	Medical records/physician	Confirmed	118	28	23.73
Cornick, 2002	14	Medical records/physician	Confirmed	68	6	8.82
Davies, 2005[c]	NR[1/2]	Medical records/physician[1]	Confirmed[1/2]	22	7	31.82[1]
(report on outbreak[1] and hospitalized cases[2])		NR[2]		2	0	0.00[2]
Davis, 1993	NR	Medical records/physician	Confirmed	477	30	6.29[1]
(report on multiple outbreaks, Washington[1,] Idaho[2,]				14	1	7.14[2]
				58	3	5.17[3]
Nevada[3], California[4])				34	7	20.59[4]
Diallo, 2011	NR	Medical records/physician	Probable	16	3	18.75[1]
(report on outbreak[1] and			Confirmed	11	3	27.27[1]
hospitalized cases[2])			Probable	6	3	50.00[2]
Duncan, 1987	NR	Medical records/physician	Probable	47	3	6.38
Dundas, 2001	14	Medical records/physician	Confirmed	120	34	28.33
Espie, 2006	Other	Medical records/physician	Probable	3	2	66.67
			Confirmed	2	2	100.00
Ethelberg, 2004	NR	Multiple approaches used	Confirmed	81	11	13.58
Farquhar, 2000	14	Medical records/physician	Confirmed	71	10	14.08
Fukushima, 1999	NR	Medical records/physician	Probable	425	12	2.82
			Confirmed	57	4	7.02
Gammie, 1996	NR	Medical records/physician	Probable	11	4	36.36
Gammie, 1996	NR	Medical records/physician	Probable	7	4	57.14

(*continued*)

TABLE 2. (CONTINUED)

First author, date of publication	*Time from* E. coli *O157 illness to evaluation for chronic sequelae (days)*	*Sequelae diagnosis*	E. coli *O157 diagnosis*	*Number of people with* E. coli *O157*	*Number of people who developed sequelae*	*Outcome measure estimate (%)*
Goode, 2009	NR	NR	Probable	108	15	13.89
Gould, 2009	NR	Multiple approaches used	Confirmed	3464	218	6.29
Gouveia, 1998	NR	NR	Confirmed	20	0	0.00
Gouveia, 1998	NR	NR	Confirmed	18	0	0.00
Gransden, 1986	NR	Medical records/physician	Confirmed	34	9	26.47
Griffin, 1988[c]	NR[1–5]	Medical records/physician[1–5]	Probable[1–5]	55[1]	22[1]	40.00[1]
(report on multiple outbreaks, indicated by superscript)				21[2]	0[2]	0.00[2]
				26[3]	0[3]	0.00[3]
				37[4]	1[4]	2.70[4]
				36[5]	8[5]	22.22[5]
Guh, 2008	58	Medical records/physician	Probable	14	3	21.43
Hamano, 1993	NR	Medical records/physician	Probable	106	5	4.72
Hedican, 2009	14	Medical records/physician	Confirmed	98	7	7.14
Honda, 1999[c]	NR	Medical records/physician	NR	182	51	28.02
Ikeda, 1999[c]	219[1]	Medical records/physician	Probable	605	36	5.95[1]
(report on outbreak[1] and hospitalized cases[2])	13[2]		Confirmed	300	16	5.33[2]
Ishikawa, 2000	NR	Medical records/physician	Confirmed	22	9	40.91
Jelacic, 2002	NR	Medical records/physician	Confirmed	131	25	19.08
Karch, 1997	NR	NR	Confirmed	2313	2	0.09
Karmali, 1988	NR	Medical records/physician	Confirmed	5	5	100.00
Kawano, 2008	14	Medical records/physician	Confirmed	98	7	7.14
King, 2009	NR	Medical records/physician	Confirmed	63	17	26.98
King, 2009	NR	Medical records/physician	Probable	69	17	24.64
Kitajima, 2002[c]	NR	Medical records/physician	Confirmed	2311	107	4.63[1]
(report on outbreak[1] and hospitalized cases[2])				614	107	17.43[2]
Lerman, 1992	21	NR	Confirmed	4	0	0.00
Liptakova, 2004	NR	Medical records/physician	Confirmed	14	3	21.43
Ludwig, 1997	35	Medical records/physician	Other	6	1	16.67
MacDonald, 1996	21	Medical records/physician	Confirmed	25	0	0.00
MacDonald, 1988	NR	Medical records/physician	Confirmed	95	8	8.42[1]
(report on surveillance[1] and hospitalized cases[2])				30	8	26.67[2]
McCarthy, 2001	NR	Medical records/physician	Confirmed	11	3	27.27
McDonnell, 1997	NR	Medical records/physician	Other	22	0	0.00[1]
(report on adults[1] and children[2])				4	2	50.00[2]
McDonnell, 1997	NR	Medical records/physician	Other	4	2	50.00
Milne, 1999	NR	Medical records/physician	Confirmed	3	2	66.67

(*continued*)

Table 2. (Continued)

First author, date of publication	*Time from* E. coli *O157 illness to evaluation for chronic sequelae (days)*	*Sequelae diagnosis*	E. coli *O157 diagnosis*	*Number of people with* E. coli *O157*	*Number of people who developed sequelae*	*Outcome measure estimate (%)*
Murray, 2000[c]	NR	NR	Probable	602	30	6.29[1]
(report on outbreak[1] and			Other	477	30	20.83[1]
hospitalized cases[2])			Confirmed	144	30	4.98[2]
O'Donnell, 2002	NR	Medical records/physician	Confirmed	11	0	0.00
Olsen, 2002	NR	NR	Probable	157	4	2.55
Orr, 1994	NR	Medical records/physician	Other	152	22	14.47
			Probable	521	22	4.22
Ostroff, 1990	NR	Medical records/physician	Confirmed	93	9	9.68
Pai, 1988	Other	Medical records/physician	Confirmed	137	2	1.46
Payne, 2003	NR	NR	Other	24	3	12.50
Pebody, 1999	NR	Medical records/physician	Probable	15	3	20.00
Pierard, 1997	NR	Medical records/physician	Confirmed	29	3	10.34
Pollock, 2010	NR	Medical records/physician	Probable	18	8	44.44
Raffaelli, 2007	10	Medical records/physician	Probable	45	2	4.44
			Confirmed	11	2	18.18
Remis, 1984	NR	Medical records/physician	Confirmed	28	1	3.57
Roberts, 2000	NR	Medical records/physician	Probable	71	10	14.08
Rowe, 1991	NR	Medical records/physician	Confirmed	72	6	8.33
Rowe, 1998	30	Medical records/physician	Confirmed	739	157	21.24
Rowe, 1994[c]	NR	Medical records/physician	Probable	84	19	22.62
			Confirmed	80	15	18.75
Salmon, 1989	7	Medical records/physician	Probable	26	1	3.85
Shimazu, 2000[c]	NR	NR	Probable	9523	121	1.27
Shiomi, 1999[c]	NR	Medical records/physician	Confirmed	42	4	9.52
Takeda, 1998	NR	Medical records/physician	Confirmed	1271	107	8.42
Tserenpuntsag, 2005	NR	Medical records/physician	Confirmed	238	36	15.13
Varma, 2003	42	Medical records/physician	Other	111	2	1.80
			Probable	23	2	8.70
Wall, 1996	NR	NR	Probable	173	36	20.81[1]
(report on all ages[1]			Confirmed	69	31	44.93[2]
andchildren[2])						
Willshaw, 1994	NR	Multiple approaches used	Confirmed	8	1	12.50
Wong, 2000	14	Medical records/physician	Confirmed	71	10	14.08
Wood, 2001	NR	Medical records/physician	Probable	245	9	3.67
Yoshioka, 1999	NR	Medical records/physician	Probable	758	121	15.96
TTP						
Guh, 2010	58	Medical records/physician	Probable	14	1	7.14
Ostroff, 1990	NR	Medical records/physician	Confirmed	93	2	2.10
ReA						
Townes, 2008	42	Multiple approaches used	Confirmed	395	1	0.25

[a]Pathogen diagnosis: Confirmed included those confirmed for *E. coli* O157 by culture, serology, or DNA-based tests. Probable included cases of *E. coli* O157 that met clinical case definition of study or were associated with an outbreak. Other included those where a case of HUS was considered positive for *E. coli* O157 in case definition.

[b]Sequelae diagnosis: Medical records/physician included those hospitalized for sequelae or diagnosed by a physician.

[c]Indicates publications identified as duplicate populations, excluded from meta-analysis.

HUS, hemolytic uremic syndrome; NR, not reported; TTP, thrombotic thrombocytopenic purpura; ReA, reactive arthritis.

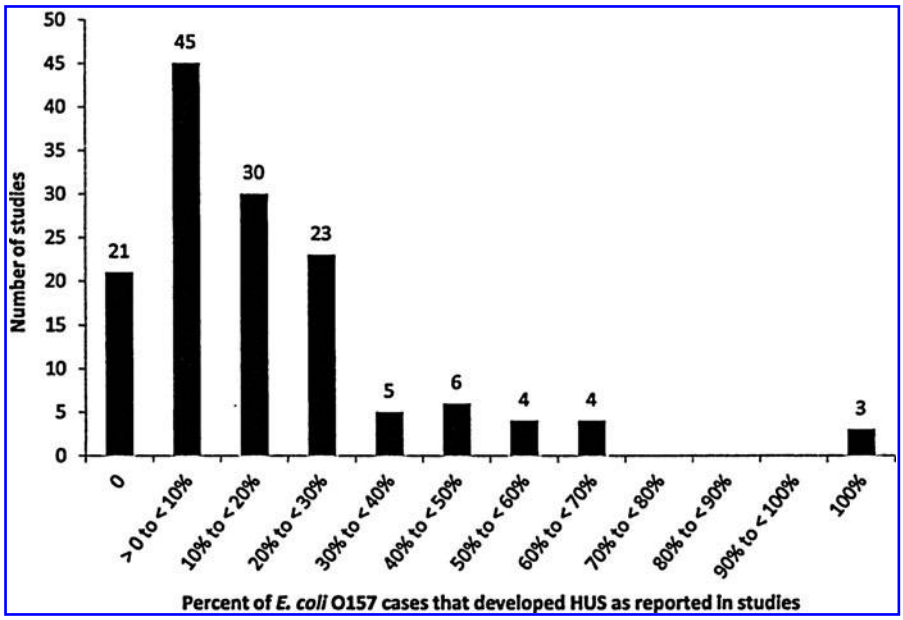

FIG. 2. Distribution of outcome estimates of the proportion of *Escherichia coli* O157 cases that developed hemolytic uremic syndrome (HUS) from studies published prior to July 2011.

populations." Removal of information on duplicate populations resulted in the exclusion of nine studies, for a total of 131 outcome measures included in the meta-analysis. The overall estimate for the proportion of cases of *E. coli* O157 that developed HUS was 13.1% (95% confidence interval 10.1%–17.1%, $I^2 = 91.3\%$). Due to the large amount of heterogeneity, meta-regression was performed.

The influence of age group, country, season, outbreak source, decade of data collection, study directionality, source of data, pathogen diagnosis, and group size was explored using meta-regression. Individually, all variables except for group size ($p < 0.0001$) and season ($p = 0.016$) were nonsignificant. After multivariable analysis, only group size remained significant ($p < 0.0001$). Subgroup analysis demonstrated large variability between summary estimates, with extra-small groups (<50 cases) having a higher proportion of cases developing HUS (17.2%) with less heterogeneity ($I^2 = 48.9\%$), and extra-large groups (>1000 cases) having a significantly lower proportion of cases developing HUS (4.2%) with extremely high heterogeneity ($I^2 = 94.8\%$) (Table 3).

Table 3. Results of Subgroup Random Effects Meta-analysis for *Escherichia coli* O157 and Hemolytic Uremic Syndrome from Studies Published Prior to July 2011

Variable	*Summary estimate (%)*	*Lower 95% CI*	*Upper 95% CI*	I^2 *(%)*	*Number of outcome measures*
Overall estimate	13.1	10.1%	17.1%,	91.3	131
Group size					
Extra small (<50 cases)	17.18	13.90%	21.03%	48.90	83
Small (51–200 cases)	13.33	10.38%	16.97%	85	32
Medium (201–500 cases)	7.80	5.09%	11.78%	87	7
Large (501–1000 cases)	10.02	5.59%	17.31%	96.50	5
Extra large (>1000 cases)	4.25	2.60%	6.88%	94.80	4

CI, confidence interval.

E. coli *O157 and ReA or TTP*

In the single study on *E. coli* O157 and ReA, the number of culture-confirmed cases that developed reactive arthritis was 0.25%. For TTP, proportions were reported as 2% for culture-confirmed cases and 7% in probable cases.

Discussion

This study used the results of a systematic literature search and meta-analysis to provide an estimate for the proportion of cases of *E. coli* O157 that developed chronic sequelae. Although there is a large body of literature available on *E. coli* O157, information on chronic sequelae was primarily limited to those studies that investigated the relationship with HUS. Within this body of research, the proportion of *E. coli* O157 cases developing HUS varied greatly. The large variation between studies makes developing a single summary estimate for the proportion of cases of *E. coli* O157 that develop HUS difficult. Group size was the only characteristic that had a significant effect on heterogeneity. All but three of the 102 outbreak-related outcome measures presented less than 100 cases of *E. coli* O157. The high proportion of HUS estimated from these smaller groups is concerning, considering the high number of small outbreaks that were located during the search. Previous studies have indicated as many as 12% of HUS cases result in death or end-stage renal disease, and 25% of HUS cases develop long-term renal sequelae (Karmali,

2004). In contrast, for larger populations those proportions were significantly lower, which may have more implications in the development of BOD estimates for *E. coli* O157 as they could be more representative of the incidence of HUS at the population level. The biggest concern, however, with interpreting these estimates is the high heterogeneity in the data even after subgroup meta-analysis, as this indicates that the study-level variables considered in this review were potentially not as influential as other host, pathogen, and environmental factors.

Some potential explanations and areas for further investigation could be virulence differences between *E. coli* O157 strains, severity of acute illness in cases, dose of *E. coli* O157 received, immune status of cases prior to infection, and age range of HUS cases. Although an association between HUS and age is generally accepted (Karmali *et al*., 2010), age was not found to be a significant contributor to heterogeneity in this review. This may be a factor of categorization as opposed to a true lack of association. In this study, the population was categorized based on the age range for *E. coli* O157 cases, not HUS cases. For those categorized as "all ages," the occurrence of HUS could have been limited to children; however, this was not captured by our approach due to data-reporting limitations in the primary studies. The difficulty with capturing the effects of the other potential sources of heterogeneity is that this level of detail was often not reported within the primary studies. In order for these areas to be addressed in future meta-analyses, more detailed descriptions of the characteristics of HUS cases and identification of the *E. coli* O157 strains should be reported.

In addition, the inter-relatedness among variables and lack of variation between studies could explain why no associations were found. Due to the nature and severity of HUS, all of the sequelae cases were considered "medically diagnosed," follow-up time was not reported in most studies, and most of the publications were small-outbreak studies. Differences in the case definitions for HUS and for cases of *E. coli* O157 could also be potential factors explaining the large amount of unexplained heterogeneity between studies. Additionally, there were no consistent criteria used to identify "probable cases of *E. coli* O157" between studies, contributing to the difficulties in comparing results between studies. The potential for misclassification as a case of *E. coli* could bias the results and increase or decrease prevalence estimates, depending on whether the case definition used had a high number of false positives or false negatives. Although the exploration of confirmed versus probable cases in the meta-regression attempted to explore the effects of this issue, clear and consistent case definitions for both *E. coli* O157 and HUS should be implemented and reported in future studies to allow further exploration of potential sources of heterogeneity.

An important issue identified by this systematic review was the lack of data pertaining to all other potential chronic sequelae. There are a few explanations for why these relationships may not have been evaluated in the available literature. The timing between illness and the assessment for chronic sequelae was short, or not reported, in the majority of studies, which may prevent the detection of illnesses that take longer to develop (for example, HUS typically manifests with severe symptoms in days versus ReA or IBS, which can take months to develop.) Another potential reason is that the studies themselves did not consider sequelae other than HUS, so their development would not have been captured. Finally, there is the possibility that other sequelae do not occur after *E. coli* O157 infection. Whether this relationship exists or not was not possible to determine given the available data. Developing accurate BOD estimates for *E. coli* O157 is limited until a better understanding of all chronic sequelae is known.

A number of long-term studies have looked at the sequelae associated with the Walkerton Outbreak of *E. coli* O157 and *Campylobacter* in Ontario, Canada in 2000 (Garg *et al*., 2003, 2005, 2006a, b, 2008, 2008a, b). The outbreak included cases infected with either or both pathogens. Due to the scale of the outbreak, confirming pathogen diagnosis was not conducted throughout the outbreak. The case definition for these studies was based on symptoms and potential exposure (Garg *et al*., 2006b). Because of this, distinguishing between cases of *E. coli* O157 and *Campylobacter* was not possible. Although these studies provide valuable insight into the issue of sequelae development after infection, the inability to distinguish between *E. coli* O157 and *Campylobacter* cases prevented their inclusion in this review. As a comparison, however, there were 27 confirmed cases of HUS in the Walkerton Health Study (Garg *et al*., 2006b). Based on the 995 cases of confirmed gastrointestinal illnesses included in the study, the proportion from this study is estimated at approximately 2.71%, on the lower end of our estimate for an extra-large group. However, when considering laboratory-confirmed cases of *E. coli* O157 or *Campylobacter* ($n = 188$), the proportion was 14.9%, well within the *confidence interval* estimated in this study for a small group.

There are some additional limitations to the available data. Although efforts were made to remove outcomes on duplicate populations from the meta-analysis, due to the minimal information provided on each outbreak included in the overview study by Ammon *et al*. (1997), there is the possibility that some of the populations were also included in other studies. In addition, there was variation in outcomes reported from the same outbreak as demonstrated in the studies from Japan regarding the Sakai School Outbreak. The studies on this outbreak reported different outcomes for their subpopulations, and it appeared the overall estimates for the outbreak itself changed over time (Fukushima *et al*., 1999; Ikeda *et al*., 1999; Ikeda *et al*., 2000). Under-reporting for cases of foodborne disease, such as *E. coli* O157, is difficult to estimate and it is also possible that only the more severe cases of infection were captured during these studies. Together these could bias the summary estimates by inflating the reported prevalence of HUS.

Limitations specific to this systematic review and meta-analysis also need to be considered. A truly international perspective was not possible due to inaccessible articles and language restrictions. It is difficult to predict how the exclusion of 71 potentially relevant articles would affect the final outcome estimate. Considering the amount of unexplained heterogeneity and the lack of significance of the study-level factors explored in this review, further research into population-level effects is needed, and the exploration of results from countries such as those excluded from this review could be insightful. In addition, as multiple outcomes were taken from some studies, the assumption of independence of estimates for the meta-analysis was not met, which could lead to narrowing of confidence intervals. Post-hoc categorization of age group and group size should also be acknowledged as a limitation when interpreting the results and could potentially have contributed to the nonsignificant findings. Additionally,

the use of a single reviewer for the first round of screening increased the potential to inappropriately exclude studies from this review; however, this round of screening was purposively designed to remove only the obvious irrelevant articles, and thus there was likely minimal impact. Finally, the methodological approach of using a logit transformation for the meta-analysis and regression introduces limitations to the resultant summary estimates, as the methodology may not be the most appropriate for low case counts. Currently, no formal methods exist to evaluate the potential impact of using the logit transform in this situation. Additional research comparing methodological approaches for prevalence estimates in a meta-analysis and meta-regression is required to clarify their effects on outcome estimates and the significance of these differences.

Conclusions

In conclusion, it was estimated that the number of cases of *E. coli* O157 that develop HUS ranged from 4% in groups with >1000 cases to 17% in groups with <50 cases. Although these proportions must be interpreted with caution due to the large amount of unexplained heterogeneity between studies, the high proportion of cases developing HUS indicates the need for further research to develop more accurate estimates of disease burden, as HUS is associated with severe or even fatal complications. Future studies are encouraged to report the following:

1. The follow-up between diagnosis as a case and sequelae diagnosis.
2. Detailed case definitions for the sequelae and probable cases of the pathogen.
3. Details of the diagnostic methods used to assess sequelae development.
4. Categorization of the sequelae by age categories to correspond to those used in international burden of illness studies.
5. Investigate potential sequelae following infection with non-O157 *E. coli* serogroups.

In addition, for accurate BOD estimates to be developed, a better understanding of additional chronic sequelae associated with *E. coli* O157 infection is required.

Acknowledgments

The authors thank Mai Pham, Ashley Whiteman, Dianna Wolfe, Tyler O'Neil, and Theresa Procter for technical assistance with this study. Funding for this research was received from a Canadian Institutes of Health Research (CIHR) Institute of Population and Public Health/Public Health Agency of Canada Applied Public Health Research Chair (awarded to J.M. Sargeant). In addition, financial and in-kind support was provided by the Public Health Agency of Canada.

Disclosure Statement

No competing financial interests exist.

References

Afza M, Hawker J, Thurston H, *et al*. An outbreak of *Escherichia coli* O157 gastroenteritis in a care home for the elderly. Epidemiol Infect 2006;134:1276–1281.

Al-Jader L, Salmon RL, Walker AM, *et al*. Outbreak of *Escherichia coli* O157 in a nursery: Lessons for prevention. Arch Dis Child 1999;81:60–63.

Ammon A. Surveillance of enterohaemorrhagic *E. coli* (EHEC) infections and haemolytic uraemic syndrome (HUS) in Europe. Euro Surveill 1997;2:91–96.

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. J Am Med Assoc 1994;272:1349–1353.

Bell BPB, Griffin PMP, Lozano PP, *et al*. Predictors of hemolytic uremic syndrome in children during a large outbreak of *Escherichia coli* O157:H7 infections. Pediatrics 1997;100:E12–E12.

Belongia EA, Osterholm MT, Soler JT, *et al*. Transmission of *Escherichia coli* O157:H7 infection in Minnesota child day-care facilities. J Am Med Assoc 1993;269:883–888.

Besser RE, Lett SM, Weber JT, *et al*. An outbreak of diarrhea and hemolytic uremic syndrome from *Escherichia coli* O157:H7 in fresh-pressed apple cider. J Am Med Assoc 1993; 269:2217–2220.

Blackwell CC, Dundas S, James VS, *et al*. Blood group and susceptibility to disease caused by *Escherichia coli* O157. J Infect Dis 2002;185:393–396.

Borenstein M, Hedges L, Rothstein H. *Introduction to Meta-analysis.* West Sussex, UK: John Wiley & Sons, 2009.

Buteau C, Proulx F, Chaibou M, *et al*. Leukocytosis in children with *Escherichia coli* O157:H7 enteritis developing the hemolytic-uremic syndrome. Pediatr Infect Dis J 2000;19:642–647.

[CDC] Centers for Disease Control and Prevention. Outbreak of *Escherichia coli* O157:H7 infection—Georgia and Tennessee, June 1995. Morb Mortal Wkly Rep 1996a;45:249–251.

CDC. Outbreak of *Escherichia coli* O157:H7 infections associated with drinking unpasteurized commercial apple juice: British Columbia, California, Colorado, and Washington, October 1996. Mortal Wkly Rep 1996b;45:975.

CDC. Multistate outbreak of *Escherichia coli* O157:H7 infections associated with eating ground beef: United States, June–July 2002. Morb Mortal Wkly Rep 2002;51:637–639.

CDC. Outbreaks of *Escherichia coli* O157:H7 associated with petting zoos: North Carolina, Florida, and Arizona, 2004 and 2005. Morb Mortal Wkly Rep 2005;54:1277–1280.

CDC. Ongoing multistate outbreak of *Escherichia coli* serotype O157:H7 infections associated with consumption of fresh spinach—United States, September 2006. Morb Mortal Wkly Rep 2006;55:1045–1046.

Cimolai N, Basalyga S, Mah DG, *et al*. A continuing assessment of risk factors for the development of *Escherichia coli* O157:H7-associated hemolytic uremic syndrome. Clin Nephrol 1994;42:85–89.

Cornick NA, Jelacic S, Ciol MA, *et al*. *Escherichia coli* O157:H7 infections: Discordance between filterable fecal shiga toxin and disease outcome. J Infect Dis 2002;186:57–63.

Davies M, Engel J, Griffin D, *et al*. Outbreaks of *Escherichia coli* O157:H7 associated with petting zoos—North Carolina, Florida, and Arizona, 2004 and 2005. JAMA 2006;295:378–380.

Davis M, Osaki C, Gordon D. Update: Multistate outbreak of *Escherichia coli* O157:H7 infections from hamburgers—Western United States, 1992–1993. Morb Mortal Weekly Rep 1993; 42:258–263.

Diallo MO, Bradley KK, Crutcher JM, *et al*. An outbreak of *Escherichia coli* O157:H7 infection linked to unpasteurized apple cider in Oklahoma, 1999. Food Prot Trends 2011;31:88–92.

Duncan L, Mai V, Carter A, *et al*. Outbreak of gastrointestinal disease—Ontario. Can Dis Weekly Rep 1987;13:5–8.

Dundas S, Todd WT, Stewart AI, *et al*. The central Scotland *Escherichia coli* O157:H7 outbreak: Risk factors for the hemolytic uremic syndrome and death among hospitalized patients. Clin Infect Dis 2001;33:923–931.

Egger M, Davey Smith G, Altmand DG. *Systematic Reviews in Health Care: Meta-Analysis in Context.* 2nd ed. London: Brit Med J, 2001.

Espie E, Vaillant V, Mariani-Kurkdjian P, *et al*. *Escherichia coli* O157 outbreak associated with fresh unpasteurized goats' cheese. Epidemiol Infect 2006;134:143–146.

Ethelberg S, Olsen KE, Scheutz F, *et al*. Virulence factors for hemolytic uremic syndrome, Denmark. Emerg Infect Dis 2004; 10:842–847.

Farquhar D. *E. coli*, antibiotics and hemolytic–uremic syndrome in children. CMAJ 2000;163:438.

Fukushima H, Hashizume T, Morita Y, *et al*. Clinical experiences in Sakai city hospital during the massive outbreak of enterohemorrhagic *Escherichia coli* O157 infections in Sakai city, 1996. Pediatr Int 1999;41:213–217.

Gammie AJ, Mortimer PR, Hatch L, *et al*. Outbreak of verocytotoxin-producing *Escherichia coli* O157 associated with cooked ham from a single source. PHLS Microbiol Digest 1996;13:142–145.

Garg AX, Clark WF, Salvadori M, *et al*. Absence of renal sequelae after childhood *Escherichia coli* O157:H7 gastroenteritis. Kidney Int 2006a;70:807–812.

Garg AX, Salvadori M, Moist LM, *et al*. Renal prognosis of toxigenic *Escherichia coli* infection. Kidney Int Suppl 2009;112: S38–S41.

Garg AX, Pope JE, Thiessen-Philbrook H, *et al*. Arthritis risk after acute bacterial gastroenteritis. Rheumatology 2008a;47:200–204.

Garg AX, Macnab J, Clark W, *et al*. Long-term health sequelae following *E. coli* and campylobacter contamination of municipal water: Population sampling and assessing non-participation biases. Can J Public Health 2005;96:125–130.

Garg AX, Suri RS, Barrowman N, *et al*. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: A systematic review, meta-analysis, and meta-regression. J Am Med Assoc 2003;290:1360–1370.

Garg AX, Marshall J, Salvadori M, *et al*. A gradient of acute gastroenteritis was characterized, to assess risk of long-term health sequelae after drinking bacterial-contaminated water. J Clin Epidemiol 2006b;59:421–428.

Garg AX, Salvadori M, Okell JM, *et al*. Albuminuria and estimated GFR 5 years after *Escherichia coli* O157 hemolytic uremic syndrome: An update. Am J Kidney Dis 2008b;51:435–444.

Goode B, O'Reilly C, Dunn J, *et al*. Outbreak of *Escherichia coli* O157. Arch Pediatr Adolesc Med 2009;163:42–48.

Gould LH, Demma L, Jones TF, *et al*. Hemolytic uremic syndrome and death in persons with *Escherichia coli* O157:H7 infection, foodborne diseases active surveillance network sites, 2000–2006. Clin Infect Dis 2009;49:1480–1485.

Gouveia S, Proctor ME, Lee MS, *et al*. Genomic comparisons and shiga toxin production among *Escherichia coli* O157:H7 isolates from a day care centre outbreak and sporadic cases in southeastern Wisconsin. J Clin Microbiol 1998;36:727–733.

Gransden WR, Damm MA, Anderson JD, *et al*. Further evidence associating hemolytic uremic syndrome with infection by verotoxin-producing *Escherichia coli* O157:H7. J Infect Dis 1986;154:522–524.

Griffin PM, Ostroff SM, Tauxe RV, *et al*. Illnesses associated with *Escherichia coli* O157:H7 infections. Ann Intern Med 1988; 109:705–712.

Guh A, Quyen Phan, Nelson R, *et al*. Outbreak of *Escherichia coli* O157 associated with raw milk, Connecticut, 2008. Clin Infect Dis 2010;51:1411–1417.

Hamano S, Nakanishi Y, Nara T, *et al*. Neurological manifestations of hemorrhagic colitis in the outbreak of *Escherichia coli* O157:H7 infection in Japan. Acta Paediatr 1993;82:454–458.

Havelaar AH, Haagsma JA, Mangen MJ, *et al*. Disease burden of foodborne pathogens in the Netherlands, 2009. Int J Food Microbiol 2012;156:231–238.

[HPA] Health Protection Agency. European collaboration identifies an outbreak of *Escherichia coli* O157 infection in visitors to Fuerteventura, Canary Islands 1997. CDR Weekly 1997a; 7:127.

[HPA]. *Escherichia coli* O157 outbreak in Lincolnshire 1997. CDR Weekly 1997b;7:101.

Hedican EB, Medus C, Besser JM, *et al*. Characteristics of O157 versus non-O157 shiga toxin-producing *Escherichia coli* infections in Minnesota, 2000–2006. Clin Infect Dis 2009;49:358–364.

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558.

Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* 2011;5.1.0. http://handbook.cochrane.org/, accessed December 2011.

Honda T. Factors influencing the development of hemolytic uremic syndrome caused by enterohemorrhagic *Escherichia coli* infection: From a questionnaire survey to in vitro experiment. Pediatr Int 1999;41:209–212.

Ikeda K, Ida O, Kimoto K, *et al*. Effect of early fosfomycin treatment on prevention of hemolytic uremic syndrome accompanying *Escherichia coli* O157:H7 infection. Clin Nephrol 1999;52:357–362.

Ikeda K, Ida O, Kimoto K, *et al*. Predictors for the development of haemolytic uraemic syndrome with *Escherichia coli* O157:H7 infections: With focus on the day of illness. Epidemiol Infect 2000;124:343–349.

Ishikawa N, Kamitsuji H, Murakami T, *et al*. Plasma levels of granulocyte elastase-alpha1-proteinase inhibitor complex in children with hemolytic uremic syndrome caused by verotoxin-producing *Escherichia coli*. Pediatr Int 2000;42: 637–641.

Jelacic S, Wobbe CL, Boster DR, *et al*. ABO and P1 blood group antigen expression and stx genotype and outcome of childhood *Escherichia coli* O157:H7 infections. J Infect Dis 2002; 185:214–219.

Karch H, Huppertz HI, Bockemuehl J, *et al*. Shiga toxin-producing *Escherichia coli* infections in Germany. J Food Prot 1997;60:1454–1457.

Karmali MA. Infection by shiga toxin-producing *Escherichia coli*: An overview. Mol Biotechnol 2004;26:117–122.

Karmali MA, Gannon V, Sargeant JM. Verocytotoxin-producing *Escherichia coli* (VTEC). Vet Microbiol 2010;140:360–370.

Karmali MA, Petric M, Lim C, *et al*. The association between idiopathic hemolytic uremic syndrome and infection by verotoxin-producing *Escherichia coli*. J Infect Dis 1985;151: 775–782.

Karmali MA, Arbus GS, Ish-Shalom N, *et al*. A family outbreak of hemolytic-uremic syndrome associated with verotoxin-producing *Escherichia coli* serotype O157:H7. Pediatr Nephrol 1988;2:409–414.

Kawano K, Okada M, Haga T, *et al*. Relationship between pathogenicity for humans and stx genotype in shiga toxin-producing *Escherichia coli* serotype O157. Eur J Clin Microbiol Infect Dis 2008;27:227–232.

King LA, Mailles A, Mariani-Kurkdjian P, *et al*. Community-wide outbreak of *Escherichia coli* O157:H7 associated with consumption of frozen beef burgers. Epidemiol Infect 2009; 137:889–896.

Kitajima H, Ida S, Fujimura M. Daily bowel movements and *Escherichia coli* O157 infection. Arch Dis Child 2002;87: 335–336.

Lerman YY, Cohen DD, Gluck AA, *et al*. A cluster of cases of *Escherichia coli* O157 infection in a day-care center in a communal settlement (kibbutz) in Israel. J Clin Microbiol 1992; 30:520–521.

Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluation health care interventions. BMJ 2009;6:1–28.

Liptakova A, Siegfried L, Rosocha J, *et al*. A family outbreak of haemolytic uraemic syndrome and haemorrhagic colitis caused by verocytotoxigenic *Escherichia coli* O157 from unpasteurised cow's milk in Slovakia. Clin Microbiol Infect 2004;10:576–578.

Ludwig K, Ruder H, Bitzan M, *et al*. Outbreak of *Escherichia coli* O157:H7 infection in a large family. Eur J Clin Microbiol Infect Dis 1997;16:238–241.

Melton-Celsa A, Mohawk K, Teel L, O'Brien A. Pathogenesis of Shiga-toxin producing *Escherichia coli*. Curr Top Microbiol Immunol 2012;357:67–103.

MacDonald IA, Gould IM, Curnow J. Epidemiology of infection due to *Escherichia coli* O157: A 3-year prospective study. Epidemiol Infect 1996;116:279–284.

MacDonald KL, O'Leary MJ, Cohen ML. *Escherichia coli* O157:H7, an emerging gastrointestinal pathogen: Results of a one-year, prospective, population-based study. J Am Med Assoc 1988;259:3567–3570.

McCarthy TA, Barrett NL, Hadler JL, *et al*. Hemolytic-uremic syndrome and *Escherichia coli* O121 at a lake in Connecticut, 1999. Pediatrics 2001;108:991–992.

McDonnell RJ, Rampling A, Crook S, *et al*. An outbreak of vero cytotoxin producing *Escherichia coli* O157 infection associated with takeaway sandwiches. CDR Rev 1997;7: R201–R205.

Milne LM, Plom A, Strudley I, *et al*. *Escherichia coli* O157 incident associated with a farm open to members of the public. Commun Dis Public Health 1999;2:22–26.

Murray KF, Patterson K. *Escherichia coli* O157:H7-induced hemolytic-uremic syndrome: Histopathologic changes in the colon over time. Pediatr Dev Pathol 2000;3:232–239.

O'Donnell JM, Thornton L, McNamara EB, *et al*. Outbreak of vero cytotoxin-producing *Escherichia coli* O157 in a child day care facility. Commun Dis Public Health 2002;5:54–58.

Olsen SJ, Miller G, Breuer T, *et al*. A waterborne outbreak of *Escherichia coli* O157:H7 infections and hemolytic uremic syndrome: Implications for rural water systems. Emerg Infect Diseases 2002;8:370–375.

Orr P, Lorencz B, Brown R, *et al*. An outbreak of diarrhea due to verotoxin-producing *Escherichia coli* in the Canadian northwest territories. Scand J Infect Dis 1994;26:675–684.

Ostroff SM, Griffin PM, Tauxe RV. A statewide outbreak of *Escherichia coli* O157:H7 infections in Washington state. Am J Epidemiol 1990;132:239–247.

Pai CH, Ahmed N, Lior H, *et al*. Epidemiology of sporadic diarrhea due to verocytotoxin-producing *Escherichia coli*: A two-year prospective study. J Infect Dis 1988;157:1054–1057.

Palermo MS, Exeni RA, Fernández GC. Hemolytic uremic syndrome: Pathogenesis and update of interventions. Expert Rev Anti Infect Ther 2009;7:697–707.

Payne CJ, Petrovic M, Roberts RJ, *et al*. Vero cytotoxin-producing *Escherichia coli* O157 gastroenteritis in farm visitors, North Wales. Emerg Infect Dis 2003;9:526–530.

Pebody RG, Furtado C, Rojas A, *et al*. An international outbreak of vero cytotoxin-producing *Escherichia coli* O157 infection amongst tourists; a challenge for the European infectious disease surveillance network. Epidemiol Infect 1999;123:217–223.

Pierard D, Stevens D, Moriau L, *et al*. Isolation and virulence factors of verocytotoxin-producing *Escherichia coli* in human stool samples. Clin Microbiol Infect 1997;3:531–540.

Pollock KGJ, Locking ME, Beattie TJ, *et al*. Sorbitol-fermenting *Escherichia coli* O157, Scotland. Emerg Infec Dis 2010;16:881–882.

Public Health Agency of Canada. Population health impact of disease in canada: Canadian summary measures. Available at: http://www.phac-aspc.gc.ca/phi-isp/summary_measures-eng.php. Updated 2005, accessed August 24, 2012.

Raffaelli RM, Paladini M, Hanson H, *et al*. Child care-associated outbreak of *Escherichia coli* O157:H7 and hemolytic uremic syndrome. Pediatr Infect Dis J 2007;26:951–953.

Remis RS, MacDonald KL, Riley LW, *et al*. Sporadic cases of hemorrhagic colitis associated with *Escherichia coli* O157:H7. Ann Intern Med 1984;101:624–626.

Roberts JA, Upton PA, Azene G. *Escherichia coli* O157:H7; an economic assessment of an outbreak. J Public Health Med 2000;22:99–107.

Rowe PC, Walop W, Lior H, MacKenzie AM. Haemolytic anaemia after childhood *Escherichia coli* O157:H7 infection: Are females at increased risk? Epidemiolog Infect 1991;106: 523–530.

Rowe PC, Orrbine E, Lior H, *et al*. Risk of hemolytic uremic syndrome after sporadic *Escherichia coli* O157:H7 infection: Results of a canadian collaborative study. J Pediatr 1998;132:777–782.

Rowe PC, Orrbine E, Ogborn M, *et al*. Epidemic *Escherichia coli* O157:H7 gastroenteritis and hemolytic-uremic syndrome in a Canadian Inuit community: Intestinal illness in family members as a risk factor. J Pediatr 1994;124:21–26.

Salmon RL, Farrell ID, Hutchison JGP, Coleman DJ, Gross RJ, Fry NJ, Bowe B, Palmer SR. A christening party outbreak of haemorrhagic colitis and haemolytic uraemic syndrome associated with *Eschericia coli* O157:H7. Epidemiolog Infect 1989;103:249–254.

Sanchez J, Dohoo IR, Christensen J, *et al*. Factors influencing the prevalence of Salmonella spp. in swine farms: A meta-analysis approach. Prev Vet Med 2007;81:148–177.

Shimazu T, Shimaoka M, Sugimoto H, *et al*. Does blood type B protect against haemolytic uraemic syndrome? An analysis of the 1996 Sakai outbreak of *Escherichia coli* O157:H7 (VTEC O157) infection. J Infect 2000;41:45–49.

Shiomi M, Togawa M, Fujita K, *et al*. Effect of early oral fluoroquinolones in hemorrhagic colitis due to *Escherichia coli* O157:H7. Pediatr Int 1999;41:228–232.

Takeda T. Strategy to prevent the progression of enterohemorrhagic *Escherichia coli* O157 infection to hemolytic uremic syndrome. Jpn J Med Sci Biol 1998;51:S124–S128.

Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. Aliment Pharmacol Ther 2007;26: 535–544.

Townes JM, Deodhar AA, Laine ES, *et al*. Reactive arthritis following culture-confirmed infections with bacterial enteric pathogens in Minnesota and Oregon: A population-based study. Ann Rheum Dis 2008;67:1689–1696.

Tserenpuntsag B, Chang HG, Smith PF, *et al*. Hemolytic uremic syndrome risk and *Escherichia coli* O157:H7. Emerg Infec Dis 2005;11:1955–1957.

Varma JK, Greene KD, Reller M, *et al*. An outbreak of *Escherichia coli* O157 infection following exposure to a contaminated building. JAMA 2003;290:2709–2712.

Wall PG, McDonnell RJ, Adak GK, *et al*. General outbreaks of vero cytotoxin producing *Escherichia coli* O157 in England and Wales from 1992 to 1994. Commun Dis Rep CDR Rev 1996;6:R26–R33.

Willshaw GA, Thirlwell J, Jones AP, *et al*. Vero cytotoxin-producing *Escherichia coli* O157 in beefburgers linked to an outbreak of diarrhoea, haemorrhagic colitis and haemolytic uraemic syndrome in Britain. Lett Appl Microbiol 1994;19: 304–307.

Wong CS, Jelacic S, Habeeb RL, *et al*. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med 2000;342:1930–1936.

Wood R, Donaghy M, Dundas S. Monitoring patients in the community with suspected *Escherichia coli* O157 infection during a large outbreak in Scotland in 1996. Epidemiol Infect 2001;127:413–420.

World Health Organization. Global burden of disease 2004 update. Geneva, 2008.

Yoshioka K, Yagi K, Moriguchi N. Clinical features and treatment of children with hemolytic uremic syndrome caused by enterohemorrhagic *Escherichia coli* O157:H7 infection: Experience of an outbreak in Sakai city, 1996. Pediatr Int 1999;41:223–227.

Zoja C, Buelli S, Morigi M. Shiga toxin-associated hemolytic uremic syndrome: Pathophysiology of endothelial dysfunction. Pediatr Nephrol 2010;25:2231–2240.

Address correspondence to:
Jessica Keithlin, MSc
Centre for Public Health and Zoonoses
University of Guelph
50 Stone Rd. East
Guelph, Ontario N1G 2W1, Canada

E-mail: jkeithli@uoguelph.ca

This article has been cited by:

1. Mohamed O. Ahmed, Yousef M. Abouzeed. 2014. Enterohaemorrhagic Escherichia coli O157: a survey of dairy cattle in Tripoli, Libya. *Libyan Journal of Medicine* **9**. . [CrossRef]