Associating sporadic, foodborne illness caused by Shiga toxin-producing *Escherichia coli* with specific foods: a systematic review and meta-analysis of case-control studies

SUPPLEMENTARY MATERIALS

Section A. Additional Details of the Systematic Review Methods

Development of the search terms

Search filters provided by the University of Texas (http://libguides.sph.uth.tmc.edu/search_filters) informed development of the study design terms for case control studies. When possible, case control term synonyms in each database's thesaurus were combined with other chosen study design terms using the Boolean term 'OR'. Where possible, a population term for 'humans' was included, specific to the database (e.g., in Medline we excluded articles with the tag 'animals'), to exclude studies conducted solely in animal populations.

We searched PROSPERO for studies on STEC to determine search terms commonly included in systematic reviews on STEC. Synonyms of STEC (e.g., verotoxigenic *E. coli*, Shiga toxigenic *E. coli*) were identified via relevant literature, expert consulation, and via a PubMed literature search on STEC. To identify and include all potentially relevant STEC serogroups as search terms, we consulted with the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Core Expert Group on STEC/VTEC, and compiled a list of serogroups that have been found in humans (see below); serogroups "O", "OR", "ON", and "OUT" were excluded from the list of search terms because, as stand-alone words, their inclusion generated a substantial number of irrelevant results. These serogroups were combined with the

term “coli” during the search, to ensure results were relevant to *E. coli*. Serogroups were also searched with “*Escherichia coli*” as a prefix (e.g., “*Escherichia coli* O157”) to ensure sensitivity in the search.

Comprehensive list of STEC serogroups* that have been associated with human infection, identified from the references below, and in consultation with the Joint FAO/WHO Expert Group on Shiga toxin-producing *Escherichia coli***

O1	O17	O38	O58	O77	O98
O2	O18	O39	O59	O78	O100
O3	O19	O40	O60	O79	O101
O4	O20	O41	O61	O80	O102
O5	O21	O42	O62	O81	O103
O6	O22	O43	O63	O82	O104
O7	O23	O44	O64	O83	O105
O8	O24	O45	O65	O84	O106
O9	O25	O46	O66	O86	O107
O9ab	O26	O48	O68	O87	O108
O10	O27	O49	O69	O88	O109
O11	O28	O50	O70	O89	O110
O12	O29	O51	O71	O90	O111
O13	O30	O52	O73	O91	O112
O14	O32	O54	O74	O92	O112ab
O15	O36	O55	O75	O93	O113
O16	O37	O57	O76	O96	O114

O115	O128	O141	O156	O171	O186
O116	O128ab	O142	O157	O172	O187
O117	O128ac	O143	O158	O173	O188
O118	O129	O145	O159	O174	O189
O119	O130	O146	O160	O175	OgC4-O118-
O120	O131	O147	O161	O176	O151
O121	O132	O148	O162	O177	OX3
O123	O133	O149	O163	O178	OX7
O123-O186	O134	O150	O164	O179	OX177
O124	O135	O151	O165	O180	OX178
O125	O136	O152	O166	O181	O-Dys1
O125ac	O137	O153	O168	O182	O-Rough
O126	O138	O153-O178	O169	O183	O-Untypeable
O127	O139	O154	O169-O183	O185	

*serogroups “O”, “OR”, “ON”, “OUT” were identified as associated with human infection, but were excluded from the list of search terms because they are also stand-alone words that returned substantial numbers of irrelevant results.

**members of the Joint FAO/WHO Expert Group on Shiga toxin-producing *Escherichia coli* can be found at: http://www.fao.org/3/ca0032en/CA0032EN.pdf

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Screening processes

For initial screening, titles and abstracts were screened by two independent reviewers per reference (LN, SEM), with a third reviewer (SMP) to resolve any conflicts. First, the two reviewers screened 25 references together to establish agreement on how to apply the screening criteria; additional subsets were then independently screened, and then discussed, until kappa agreement of 0.75 or greater was obtained. Then, reviewers independently screened the remaining references using standardized instructions. Citations that fulfilled the inclusion criteria, or for which there was not sufficient information to determine whether the citation fulfilled the inclusion criteria, were advanced to full text screening.

For full text screening, each complete article was screened by two independent reviewers per reference (BND, DT, SEM), with a third reviewer to resolve any conflicts (SMP, BD), using standardized instructions. To ensure clarity and consistency in the application of the instructions, the two reviewers first screened five references together to establish agreement on how to apply the instructions; additional subsets were then independently screened, and then discussed, until kappa agreement of 0.75 or greater was obtained. Studies that passed the second stage of screening advanced to data extraction.

Details on data extraction

Data were extracted by two reviewers (BND, SC, DT), with a third reviewer (SEM) to resolve any conflicts, using standardized forms and instructions.

Extracted variables were: author; year published; study country and timeframe; age of the study population; information on cases (case definition, laboratory confirmation, how cases were identified), and controls (how controls were identified and whether controls were matched to cases); case and control exclusion cirteria (prior international travel, co-infection, secondary cases or individuals with ill family members); STEC serotype (O157 and non-O157) and laboratory methods used; the sample size of cases and controls; the statistical methods used (including those employed to control confounding); and the specific food exposures assessed, including the numbers of cases and controls exposed (and unexposed) and the measure of association with 95% confidence interval (CI) and p-value (if reported). Because there was heterogeneity in age group definitions across studies, we used three broad age categories: at the level of each food item, age groups were classified as "children" if the majority of the included

individuals were below 18 years of age, as "adults" if the majority of the included individuals were 18 years or older, and as "all" if the individuals spanned all ages.

For papers where the description of the laboratory methods given in the Methods section was insufficient to determine the appropriateness for identifying STEC, an expert in STEC laboratory identification (AG) assessed the full text articles, and used information implicit in other parts of the paper, such as the representation of results, and historical knowledge of the standard laboratory methods used or available to the authoring institutions at time of the study.

Risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf), modified to address critical items for case-control studies using relevant questions from the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center Item Bank and its modifications [9-10]. Overall study quality was captured using the RTI Overall Assessment question ("are the results of the study believable taking study limitations into consideration?"), as well as a modified version of ROBINS-I, relevant to case-control studies [11]. Finally, we determined that the most important confounder given the study design and the topic (STEC infection related to food) was age. Thus, we assessed whether age was adequately controlled as part of our quality assessment by assessing the combined impact of the study's design and analyses.

Section B.

Results of the meta-analysis using our alternate method (i.e., using the reported univariate OR for all instances where such values were reported, and then used the reported number of cases and controls who were either exposed or unexposed to a given food category for instances where ORs were not given).

Table B1. ***Alternate method results for Table 4: pooled univariate odds ratios (ORs) per food category (significant values shown in bold), ranked in descending order by the number of food items in the category.***

Food Category (no. items within category; no. studies)	**Odds ratio (95% confidence interval)**	**P-value**	**P-value Regression test**	**P-value Rank test**	**I^2**	**Trim and Fill Method**	
						Odds ratio (95% confidence interval)	**p-value**
Beef (80*; 18)	**1.650 (1.399, 1.947)**	**<0.001**	**<0.001**	**0.023**	68%	**1.436 (1.212, 1.701)**	**<0.001**
Meat - unspecified (60*; 13)	**1.194 (1.020, 1.397)**	**0.027**	**0.001**	**0.029**	56%	1.017 (0.867, 1.192)	0.839
Produce (38; 11)	**0.645 (0.514, 0.810)**	**<0.001**	**0.024**	0.083	71%	**0.618 (0.490, 0.780)**	**<0.001**
Dairy (23*; 9)	**0.719 (0.548, 0.942)**	**0.017**	0.202	0.497	64%		
Chicken (9*, 8)	0.795 (0.356, 1.775)	0.576	0.681	0.612	79%		
Seafood (8; 4)	0.700 (0.467, 1.050)	0.084	0.254	0.905	52%		
Pork (7; 5)	1.036 (0.625, 1.716)	0.892	0.297	0.239	64%		
Eggs (5; 2)	**0.646 (0.491, 0.851)**	**0.002**	0.852	0.817	0%		
Lamb (3; 1)	1.899 (0.570, 6.330)	0.296	0.083	0.333	45%		
Turkey (2; 2)	1.038 (0.112, 9.590)	0.974	N/A	N/A	60%		
Poultry/Game - unspecified (2; 2)	**0.386 (0.179, 0.834)**	**0.015**	N/A	N/A	34%		

* This number is less than in Table 3 because some food items as reported did not have sufficient useable data

Table B2. Alternate method results for Table 5: results for each World Health Organization (WHO) Sub- Region, showing pooled univariate odds ratios (ORs) per food category (significant values shown in bold)

Food Category	WHO Subregion AMR A[1] (10 studies)			WHO Subregion AMR B[2] (1 study)			WHO Subregion EUR A[3] (7 studies)			WHO Subregion WPR A[4] (3 studies)		
	No. items per category (No. studies)	**OR (95% C.I.)**	I^2	**No. items per category (No. studies)**	**OR (95% C.I.)**	I^2	**No. items per category (No. studies)**	**OR (95% C.I.)**	I^2	**No. items per category (No. studies)**	**OR (95% C.I.)**	I^2
Beef	22 (9)	1.420 (0.993, 2.031) †	79%	32 (1)	**1.573 (1.199, 2.063)** †	67%	19 (6)	**1.374 (1.018, 1.855)**	57%	7 (2)	1.303 (0.782, 2.170)	49%
Meat - unspecified	9 (4)	**1.392 (1.067, 1.815)**	12%	8 (1)	**0.461 (0.369, 0.576)** †	0%	38 (5)	**1.207 (1.045, 1.394)** †	16%	5 (3)	1.268 (0.846, 1.900)	0%
Produce	9 (3)	**0.515 (0.356, 0.745)**	64%	0 (-)	N/A	N/A	17 (5)	0.938 (0.713, 1.233)†	50%	12 (3)	0.617 (0.310, 1.227)†	87%
Dairy	1 (1)	9.774 (0.981, 97.360)	0%	0 (-)	N/A	N/A	20 (7)	**0.653 (0.498, 0.855)**	61%	2 (1)	1.221 (0.696, 2.141)	0%
Chicken	4 (4)	**0.322 (0.202, 0.515)**	0%	0 (-)	N/A	N/A	2 (2)	1.146 (0.104, 12.606)	90%	3 (2)	**2.677 (1.264, 5.671)**	0%
Seafood	2 (1)	0.683 (0.417, 1.118)	0%	0 (-)	N/A	N/A	5 (2)	0.688 (0.227, 2.085)	79%	1 (1)	**0.480 (0.309, 0.747)**	0%
Pork	2 (2)	1.469 (0.863, 2.500)	0%	2 (1)	1.107 (0.320, 3.830)	76%	0 (-)	N/A	N/A	3 (2)	0.685 (0.361, 1.301) †	46%

Eggs	0 (-)	N/A	N/A	0 (-)	N/A	N/A	1 (1)	**0.600 (0.398, 0.905)**	0%	4 (1)	**0.686 (0.474, 0.993)**	0%
Lamb	0 (-)	N/A	N/A	0 (-)	N/A	N/A	3 (1)	1.899 (0.570, 6.330)	45%	0 (-)	N/A	N/A
Turkey	1 (1)	0.400 (0.088, 1.815)	0%	0 (-)	N/A	N/A	0 (-)	N/A	N/A	1 (1)	4.000 (0.361, 44.277)	0%
Poultry/Game - unspecified	0 (-)	N/A	N/A	0 (-)	N/A	N/A	2 (2)	**0.386 (0.179, 0.834)**	34%	0 (-)	N/A	N/A

[1] AMR A includes the following countries: Canada; Cuba; United States of America.

[2] AMR B includes the following countries: Antigua and Barbuda; Argentina; Bahamas; Barbados; Belize; Brazil; Chile; Colombia; Costa Rica; Dominica; Dominican Republic; El Salvador; Grenada; Guyana; Honduras; Jamaica; Mexico; Panama; Paraguay; Saint Kitts and Nevis; Saint Lucia; Saint Vincent and the Grenadines; Suriname; Trinidad and Tobago; Uruguay; Venezuela (Bolivarian Republic of).

[3] EUR A includes the following countries: Andorra; Austria; Belgium; Croatia; Cyprus; Czech Republic; Denmark; Finland; France; Germany; Greece; Iceland; Ireland; Israel; Italy; Luxembourg; Malta; Monaco; Netherlands; Norway; Portugal; San Marino; Slovenia; Spain; Sweden; Switzerland; United Kingdom.

[4] WPR A includes the following countries: Australia; Brunei Darussalam; Japan; New Zealand; Singapore.

† Using trim and fill method

Section C.

Results of the analysis of univariate moderating effects of study characteristics, using our alternate method (i.e., using the reported univariate OR for all instances where such values were reported, and then used the reported number of cases and controls who were either exposed or unexposed to a given food category for instances where ORs were not given).

Table C. ***Alternate method results for Table 6: Univariate moderating effects of study characteristics, by food category, with significant values shown in bold (food categories with <20 results are not shown)***

Study Characteristic	Characteristic level (no. items)	OR	95% C.I.	p-value	I^2	Adjusted R^2
Beef (n=80)						
WHO subregion	AMR A (22; reference)	—	—	—	69%	0%
	AMR B (32)	1.135	0.752, 1.713	0.546		
	EUR A (19)	0.820	0.514, 1.308	0.405		
	WPR A (7)	0.758	0.391, 1.470	0.412		
Publication year	(80)	1.021	0.997, 1.045	0.084	67%	6.5%
Study population age	All (37; reference)	—	—	—	67%	2.5%
	Adults (5)	1.295	0.692, 2.424	0.419		
	Children (38)	1.364	0.969, 1.921	0.075		
Food item status	Not raw (1; reference)	—	—	—	44%	62%
	Raw or undercooked (33)	2.372	0.961, 5.855	0.061		
	Unknown (46)	1.011	0.412, 2.481	0.982		
Robin's I	1 (14; reference)	—	—	—	67%	3.5%
	2 (61)	1.451	0.947, 2.222	0.087		
	4 (4)	1.036	0.474, 2.268	0.929		
	6 (1)	4.193	0.769, 22.868	0.098		
Believeable findings	Yes (79; reference)	—	—	—	68%	2%
	No (1)	3.155	0.596, 16.700	0.177		
Meat–unspecified (n=60)						
WHO subregion	AMR A (9; reference)	—	—	—	9%	92%
	AMR B (8)	**0.333**	**0.233, 0.475**	**<0.001**		
	EUR A (38)	0.961	0.717, 1.289	0.792		
	WPR A (5)	0.915	0.556, 1.505	0.727		
Publication year	(60)	1.001	0.980, 1.021	0.952	56%	0%
Study population age	All (24; reference)	—	—	—	47%	26%
	Adults (10)	1.410	0.949, 2.094	0.089		
	Children (26)	0.795	0.575, 1.101	0.167		
Food item status	Not raw (10; reference)	—	—	—	54%	4.4%
	Raw or undercooked (13)	1.501	0.909, 2.479	0.112		
	Unknown (37)	1.157	0.761, 1.760	0.495		
Robin's I	1 (24; reference)	—	—	—	55%	0%
	2 (29)	0.781	0.553, 1.103	0.160		
	4 (7)	0.929	0.561, 1.537	0.773		
	6 (0)	N/A	N/A	N/A		

Believeable findings	Yes (59; reference)	—	—	—	56%	0%
	No (1)	1.683	0.336, 8.432	0.526		
Produce (n=38)						
WHO subregion	AMR A (9; reference)	—	—	—	64%	22%
	AMR B (0)	N/A	N/A	N/A		
	EUR A (17)	1.636	0.972, 2.755	0.064		
	WPR A (12)	1.050	0.598, 1.844	0.864		
Publication year	(38)	0.978	0.941, 1.017	0.270	70%	4.7%
Study population age	All (26; reference)	—	—	—	72%	0%
	Adults (4)	1.040	0.491, 2.200	0.919		
	Children (8)	1.117	0.608, 2.054	0.721		
Food item status	Not raw (0)	N/A	N/A	N/A	71%	0%
	Raw or undercooked (16; reference)	—	—	—		
	Unknown (22)	1.065	0.669, 1.694	0.792		
Robin's I	1 (12; reference)	—	—	—	69%	6.6%
	2 (26)	0.778	0.488, 1.238	0.289		
	4 (0)	N/A	N/A	N/A		
	6 (0)	N/A	N/A	N/A		
Believeable findings	Yes (38; reference)	—	—	—	71%	N/A
	No (0)	N/A	N/A	N/A		
Dairy (n=23)						
WHO subregion	AMR A (1; reference)	—	—	—	55%	35%
	AMR B (0)	N/A	N/A	N/A		
	EUR A (20)	0.067	0.006, 0.752	0.028		
	WPR A (2)	0.126	0.010, 1.583	0.109		
Publication year	(23)	0.958	0.911, 1.007	0.089	66%	0%
Study population age	All (9; reference)	—	—	—	58%	24%
	Adults (3)	0.937	0.395, 2.224	0.883		
	Children (11)	0.610	0.354, 1.053	0.076		
Food item status	Not raw (2; reference)	—	—	—	60%	0%
	Raw or undercooked (9)	1.116	0.455, 2.736	0.810		
	Unknown (12)	0.531	0.234, 1.205	0.130		
Robin's I	1 (7; reference)	—	—	—	65%	0%
	2 (15)	0.637	0.351, 1.157	0.138		
	4 (1)	10.326	0.827, 128.858	0.070		
	6 (0)	N/A	N/A	N/A		
Believeable findings	Yes (22; reference)	—	—	—	61%	16%

	No (1)	**14.054**	**1.210, 163.205**	**0.035**		

Figure C. Forest plots of the log odds ratio (OR) of the risk of human STEC infection from beef (left) and meat-unspecified (right), showing the overall pooled OR together with the 95% confidence interval (CI).