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Shiga Toxin–Producing *Escherichia coli* Infection, Antibiotics, and Risk of Developing Hemolytic Uremic Syndrome: A Meta-analysis

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(See the Editorial Commentary by Mody and Griffin on pages 1259–61.)

Background. Antibiotic administration to individuals with Shiga toxin–producing *Escherichia coli* (STEC) infection remains controversial. We assessed if antibiotic administration to individuals with STEC infection is associated with development of hemolytic uremic syndrome (HUS).

Methods. The analysis included studies published up to 29 April 2015, that provided data from patients (1) with STEC infection, (2) who received antibiotics, (3) who developed HUS, and (4) for whom data reported timing of antibiotic administration in relation to HUS. Risk of bias was assessed; strength of evidence was adjudicated. HUS was the primary outcome. Secondary outcomes restricted the analysis to low-risk-of-bias studies employing commonly used HUS criteria. Pooled estimates of the odds ratio (OR) were obtained using random-effects models.

Results. Seventeen reports and 1896 patients met eligibility; 8 (47%) studies were retrospective, 5 (29%) were prospective cohort, 3 (18%) were case-control, and 1 was a trial. The pooled OR, including all studies, associating antibiotic administration and development of HUS was 1.33 (95% confidence interval [CI], .89–1.99; $I^2 = 42\%$). The repeat analysis including only studies with a low risk of bias and those employing an appropriate definition of HUS yielded an OR of 2.24 (95% CI, 1.45–3.46; $I^2 = 0\%$).

Conclusions. Overall, use of antibiotics was not associated with an increased risk of developing HUS; however, after excluding studies at high risk of bias and those that did not employ an acceptable definition of HUS, there was a significant association. Consequently, the use of antibiotics in individuals with STEC infections is not recommended.

Keywords. Shiga toxin; *Escherichia coli*; antibiotics; hemolytic uremic syndrome; meta-analysis.

Shiga toxin–producing *Escherichia coli* (STEC) infections frequently prompt consideration of antibiotic treatment, prior to or after culture results are known. However, such treatment may increase the risk of developing hemolytic uremic syndrome (HUS). HUS consists of nonimmune hemolytic anemia, thrombocytopenia, and renal insufficiency and is believed to be caused by circulating Shiga toxins [1]. An association between antibiotic administration and HUS is plausible: in vitro, a variety of antibiotics increase Shiga toxin production by *E. coli* [2, 3].

Two systematic reviews [4, 5] assessing HUS risk after antibiotic antibiotic administration to STEC-infected patients concluded that they neither decreased nor increased the likelihood of this complication. The first meta-analysis reported a pooled odds ratio (OR) of 1.15 (95% confidence interval [CI], .79–1.68), but had methodological limitations. These include use of a fixed-effects model for data with a bimodal distribution, the treatment of studies with increased ORs as outliers [6], and the heavy weighting given to a study in which 100% of patients who developed HUS and 99% of those who did not were given antibiotics [7]. The second described 19 studies but did not perform a meta-analysis. The inconclusive nature of these reviews has contributed to practice variation despite Centers for Disease Control and Prevention urgings against antibiotic use in these infections [8]. Nonetheless, approximately one-third of HUS patients in a 2007–2008 multicenter study of US and Scottish institutions [9] and in a nationwide survey of childhood HUS [10] received antibiotics prior to the development of HUS.

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Given the ongoing administration of antibiotics to STEC-infected individuals, the inconclusiveness of prior reviews, and recently published data, we conducted a meta-analysis to quantify the risk of developing HUS associated with antibiotic administration during the diarrheal phase of disease.

METHODS

We followed an a priori drafted protocol and published guidelines for conducting and reporting findings of systematic reviews and meta-analyses (MOOSE). Data sources and searches are provided in the Supplementary Text 1 and Supplementary Table 1.

Study Selection

Three trained study reviewers (J. X., M. S. N., W. L. H.) independently screened all identified publications for potential inclusion; those relevant by title and abstract were retrieved in full text. Eligible studies contained (1) a series of patients with documented STEC infection (confirmed by toxin assay, culture, or molecular techniques); (2) development of HUS; and (3) antibiotic administration prior to development of HUS (Table 1). Studies were excluded if they (1) were reviews; (2) contained data that were reported more comprehensively in prior or subsequent reports; (3) provided insufficient information to determine the proportions who received/did not receive antibiotics and who developed/did not develop HUS; or if they described a series of cases in which (4) all participants received antibiotics or developed HUS or (5) antibiotics were administered after HUS developed.

Review processes and data extraction are described in the Supplementary Text 2.

Outcome Measures

The primary outcome was the development of HUS according to study definitions (Supplementary Table 3). Subanalyses were performed including only subjects meeting commonly used criteria for diagnosing HUS—namely, presence of microangiopathic hemolytic anemia, thrombocytopenia (ie, platelet count <150 000 cells/μL), and renal insufficiency defined as a creatinine level greater than the upper limit of normal for age [34].

Table 1. Studies Included in Meta-analysis

Study	Design	Year	Country	Age Range (Mean or Median)	No. Eligible With STEC Infection	No. Eligible With HUS	Quality Score (NOS)[a]	Outbreak, Sporadic, or Mixed
Bell et al [11][b]	RC	1997	United States	0–15 y (median = 6 y)	268	36	6	Outbreak
Cadwgan et al [12]	RC	2002	United Kingdom	16–93 y (median = 48 y)	32	6	7	Sporadic
Cimolai et al [13]	RC	1994	Canada	Mean = 49 mo (HUS group); Mean = 82 mo (non-HUS)	118	28	6	Sporadic
Dundas et al [14]	RC	2001	United Kingdom	18 mo–94 y (median = 63 y)	119	33	7	Outbreak
Geerdes-Fenge et al [15]	PC	2013	Germany	4–81 y (mean = 36 ± 25)	24	19	6	Outbreak
Ikeda et al [16][c]	RC	1999	Japan	6–11 y	272	16	5	Outbreak
Ohnishi et al [17]	PC	2012	Japan	Mean = 41 ± 19 y (ABX group); 32 ± 10 y (No ABX)	15	1	5	Sporadic
Ostroff et al [18]	PC	1989	United States	11 mo–78 y (median = 14 y)	75	10	6	Mixture
Pavia et al [19]	RC	1990	United States	6–29 y (HUS group); 11–39 y (non-HUS)	23	8	6	Outbreak
Piercefield et al [20]	RC	2010	United States	1–88 y (median = 57)	72	26	7	Outbreak
Prats et al [21]	RC	1996	Spain	11 mo–70 y (median = 13 y)	9	2	6	Sporadic
Proulx et al [22]	RCT	1992	Canada	Mean = 64 ± 52 mo	47	6	High risk of bias[d]	Sporadic
Rivero et al [23]	PC	2010	Argentina	1–75 mo (median = 18 mo)	44	16	6	Sporadic
Slutsker et al [24]	CC	1998	United States	4 mo–87 y (median = 22 y)	93	7	7	Sporadic
Smith et al [25]	CC	2012	United States	0–19 y	188	63	9	Sporadic
Tserenpuntsag et al [26]	CC	2005	United States	Children & adults	238	36	6	Sporadic
Wong et al [27]	PC	2012	United States	0–10 y	259	36	9	Sporadic

No. eligible reflects those with condition (STEC infection), exposure (antibiotic), and outcome (HUS) data available.

Abbreviations: ABX, antibiotics; CC, case-control; HUS, hemolytic uremic syndrome; NOS, Newcastle-Ottawa scale; PC, prospective cohort; RC, retrospective cohort; RCT, randomized controlled trial; STEC, Shiga toxin–producing *Escherichia coli*.

[a] For itemized scores, please see Supplementary Table 5.

[b] Bell et al included in their study any HUS case, whether or not *E. coli* O157:H7 was isolated, if HUS was diagnosed in a Washington State resident aged <16 years, in January or February 1993 [11] during a massive *E. coli* O157:H7 outbreak [28]. There were 37 cases of HUS, and each was considered to be culture positive caused by *E. coli* 0157:H7, and outbreak related. Dr Bell was contacted to provide the number of HUS cases that were culture positive, but the data were unavailable for review because of the time that has elapsed since the publication. Based on the following reasons, it was decided that the study and all cases should be considered as STEC positive: (1) *E. coli* O157:H7 was the overwhelming cause of HUS in Washington State in the 1980s and 1990s [29, 30]; (2) inability to recover *E. coli* O157:H7 from a patient in Seattle with HUS is not uncommon if no antecedent stool culture is performed [29]; (3) intense analysis of 37 children with HUS at a single pediatric hospital in Seattle, during the outbreak (and included in the report) reported by Bell et al, failed to identify an STEC pathogen in only 5 children [31]; (4) endemic HUS and *E. coli* O157:H7 infections rarely occur in Washington State in January and February [18, 29, 30, 32, 33].

[c] Ikeda et al included in their study some cases of HUS in the absence of the identification of an STEC pathogen. However, this study was conducted during a massive localized *E. coli* outbreak, so the patients reported have been included in the summary estimates and analyses conducted [16].

[d] Composite measure is not available for clinical trials; itemized scores are provided in Supplementary Table 5.

For all included studies, study definitions were extracted and compared with the aforementioned criteria.

Risk of Bias

The same reviewers independently (ie, blinded to other reviewers' scores) assessed the risk of bias (RoB) using the Newcastle-Ottawa scale (NOS) [35], which assesses the quality and potential bias of nonrandomized studies in 3 domains: (1) cohort selection, (2) comparability, and (3) outcome assessment using 8 multiple-choice questions. However. reviewers were not blinded to study authors' identities. A study is deemed to be of good, fair, or poor quality if the score is ≥7, 6, and ≤5 (out of 9), respectively [36]. We used the Cochrane RoB (hereafter "RoB") tool to assess randomized trials. We used information pertaining to RoB to explore sources of heterogeneity.

Two reviewers classified the quality of the body of evidence into categories (very low, low, moderate, high) according to domains of study limitations, inconsistency, indirectness, imprecision, and other considerations (eg, evidence of publication bias) using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [37].

Data Synthesis and Analysis

Evidence tables included design features, methodologic quality, study populations, sample size, settings, outcomes, and potential covariates. For each study, the raw data were extracted regarding antibiotic administration and occurrence of HUS as dichotomous variables. Two-by-two tables were constructed to enable calculation of crude ORs and 95% CIs. Pooled OR estimates and 95% CIs were obtained using random-effects models of Mantel and Haenszel. Evidence of statistical heterogeneity (I^2 test), reporting bias (Begg and Egger tests and funnel plot inspection), and publication bias (Duval and Tweedie trim-and-fill method) were also sought. Too few studies reported adjusted ORs, and the level of detail provided was inadequate to conduct preplanned analyses (eg, adjusting for white blood cell count). Consequently, studies reporting adjusted ORs were explored qualitatively.

The following subanalyses were planned a priori: (1) children (ie, <18 years of age); (2) low RoB according to the NOS; (3) intermediate antibiotic use (ie, 25%–75% of patients received antibiotics); (4) moderate proportions developing HUS (ie, <20%); and (5) substantial numbers of subjects (ie, >100). Analyses were repeated when original reports included exposure data at varying time points (eg, antibiotics at 3 and 7 days after symptom onset); results were reported for both intervals only if there were significant differences. Additional analyses were performed at the request of peer reviewers. Two-sided P values were calculated with significance set at .05, using Review Manager (RevMan, Cochrane Collaboration), version 5.3.3.

RESULTS

We identified 2489 potentially relevant studies; 17 studies of 1896 infected individuals, of whom 349 (18.4%) developed HUS (Figure 1; Table 1), met all criteria and were subsequently analyzed. Eight (47%) were retrospective cohort studies, 5 (29%) were prospective cohort studies, 3 (18%) were case-control studies, and 1 was a clinical trial. Sample sizes ranged from 11 to 304. The proportion of participants who developed HUS was lower among studies that included only individuals >19 years of age (201/1196 [16.8%]) than among all others (148/700 [21.1%]; difference, 4.3% [95% CI, .7%–8.1%]). Twelve (71%) studies addressed only *E. coli* O157:H7 infections (Supplementary Table 2). HUS occurred more frequently in studies including non-O157:H7 (70/242 [28.9%]) compared with O157:H7 (279/1654 [16.9%]) infections (difference, 12.1% [95% CI, 6.4%–18.3%]).

Fifteen (88%) of the studies provided a definition of HUS (Supplementary Table 3). Thirteen required evidence of anemia and 14 required hemolysis. Ten and 3 studies employed platelet cut-points of <150 000 cells/μL and <100 000 cells/μL, respectively; 2 required "thrombocytopenia." A variety of definitions of renal impairment were employed, including elevated blood urea nitrogen (n = 2) or creatinine (n = 12) concentrations, "renal impairment/failure" without further definition (n = 2), and proteinuria and/or hematuria (n = 2). When the definitions of microangiopathic hemolytic anemia, thrombocytopenia, and serum creatinine level greater than the upper limit of normal for age are employed, 10 studies and 1309 subjects met eligibility criteria, and 7 studies and 587 subjects did not.

Main Pooled Analyses

The pooled OR of all studies regardless of their definition of HUS was 1.33 (95% CI, .89–1.99; $I^2 = 42\%$; Figure 2). When evaluating the association between antibiotic administration and development of HUS using studies meeting the a priori definition of HUS, the OR (1.45 [95% CI, .91–2.32]; $I^2 = 49\%$); Supplementary Figure 1) increased. We graded the strength of the evidence for this result as very low based on domains (Supplementary Table 4). The funnel plot (Supplementary Figure 2*A*) was symmetric; there was no evidence of small sample bias from any tests performed (Begg, $P = .71$; Egger, $P = .81$). No studies were added by the trim-and-fill method.

Subgroup Analyses

Subanalyses using studies focusing on children or adults produced similar ORs (1.40 [95% CI, .72–2.74]; $I^2 = 63\%$ and 1.54 [95% CI, .73–3.25]; $I^2 = 44\%$, respectively; Supplementary Figure 3). To account for the impact of extensive or very limited antibiotic use, the analysis was repeated including the 9 studies where antibiotic use was between 25% and 75% (OR, 1.13 [95% CI, .67–1.92]; $I^2 = 38\%$; Supplementary Figure 4). To reflect commonly reported rates of HUS among infected children, the overall prevalence of HUS within studies was accounted for by limiting analysis to the 8 studies where the proportions of HUS were <20%; in this subset, the pooled OR was 1.29 (95% CI, .73–22.6; $I^2 = 37\%$; Supplementary Figure 5). Restricting analysis to

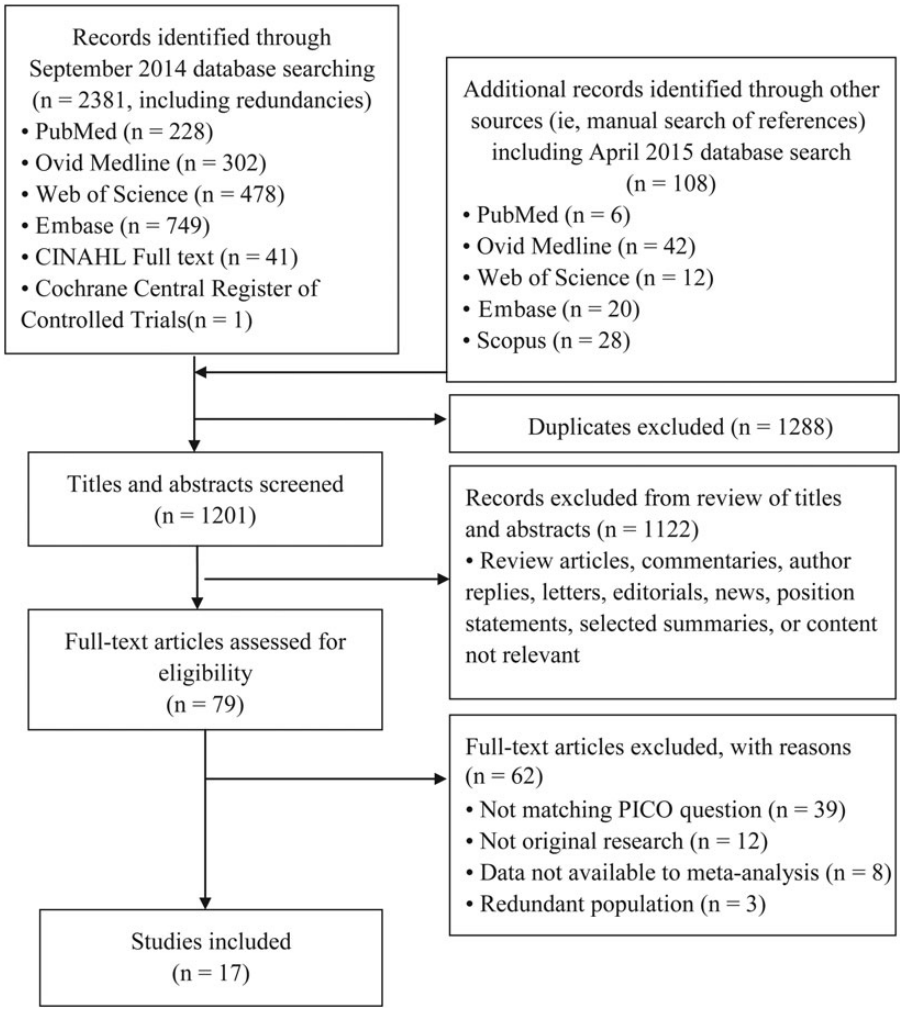

Figure 1. Selection of studies for inclusion in the meta-analysis. Abbreviations: CINAHL, Cumulative Index of Nursing and Allied Health Literature; PICO, P - patient, problem or population, I - intervention, C - comparison, control or comparator, O - outcomes.

the 7 studies reporting outcomes in >100 individuals yielded a pooled OR of 1.40 (95% CI, .83–2.34; $I^2 = 58\%$; Supplementary Figure 6). Meta-analysis including the 6 outbreak studies yielded an OR of 1.32 (95% CI, .54–3.25; Supplementary Figure 7), similar to that of the 11 sporadic case studies (OR, 1.31 [95% CI, .83–2.06]; Supplementary Figure 8). Country of study was also considered, but the United States was the only country with >2 eligible publications. Analysis restricted to the United States (n = 8) had an OR of 1.62 (95% CI, .95–2.77; Supplementary Figure 9). Analyses were also performed by antibiotic class when the data were available: trimethoprim-sulfamethoxazole (5 studies: OR, 1.95 [95% CI, .63–5.99]; Supplementary Figure 10); β-lactams (2 studies: OR, 6.10 [95% CI, .62–59.98]; Supplementary Figure 11); fluoroquinolones (3 studies: OR, 1.83 [95% CI, .70–4.75]; Supplementary Figure 12).

The median study RoB score was 6 (range, 5–9; Supplementary Table 5). The criterion that most studies failed to meet was "comparability," which requires that cases and controls be matched in the design and/or confounders adjusted for in the analysis.

When analysis was restricted to studies of low RoB (NOS score ≥7) the OR of developing HUS after antibiotic treatment increased to 1.95 (95% CI, 1.25–3.04; 6 studies; $I^2 = 13\%$; Supplementary Figure 13). Heterogeneity was reduced and association between antibiotics and HUS increased when analyzing only studies with low RoB and that used a stringent HUS definition (OR, 2.24 [95% CI, 1.45–3.36]; 5 studies; $I^2 = 0$; Figure 3). We repeated our quality assessment for this estimate and found it to be moderate (Supplementary Table 4; Supplementary Figure 1*B*). A sensitivity analysis around the RoB assessment was performed by repeating the analysis including studies with NOS scores ≥6 and lowered the estimate of association to an OR of 1.58 (95% CI, .96–2.59; 10 studies), but the I^2 increased to 55% (Supplementary Figure 14).

The ORs for infections caused by O157:H7 (OR, 1.44 [95% CI, .78–2.66]; 9 studies; $I^2 = 61\%$) and non-O157:H7 (OR,

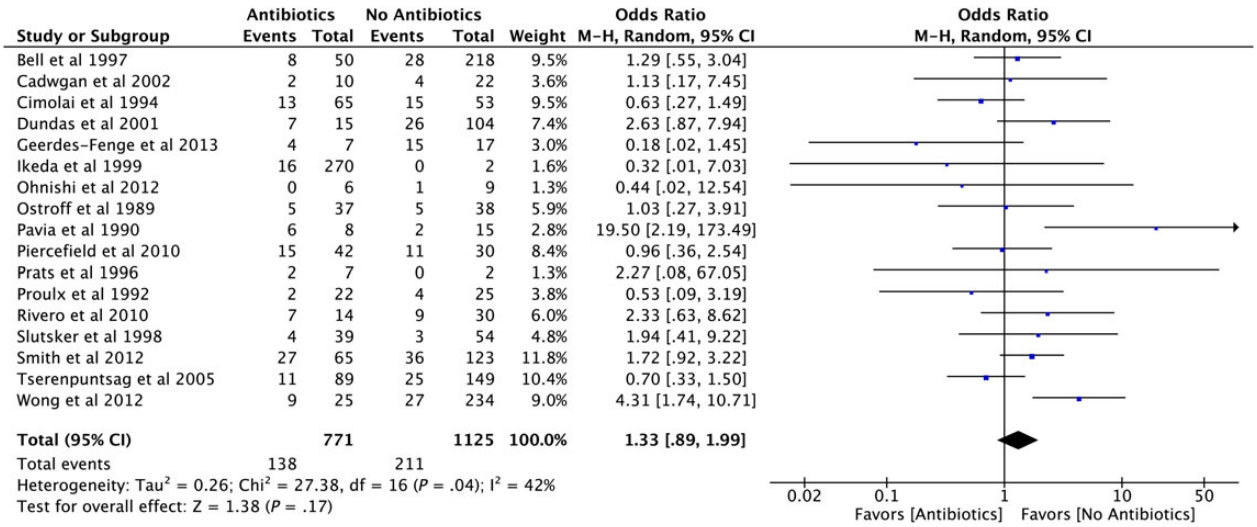

Figure 2. Random-effects meta-analysis of studies comparing odds of developing hemolytic uremic syndrome (HUS) in patients with *Escherichia coli* infection treated with antibiotics compared to those who did not receive antibiotics. The term "favors no antibiotics" implies that when antibiotics were given to the patients with Shiga toxin–producing *Escherichia coli* (STEC) infection, we observed increased odds of developing HUS, and the term "favors antibiotics" implies that when antibiotics were given to the patients with STEC infection, we observed decreased odds of developing HUS. Abbreviations: CI, confidence interval; M-H, Mantel–Haenszel.

0.93 [95% CI, .29–2.95]; 3 studies; $I^2 = 52\%$) were similar (Supplementary Figure 15). Studies reporting antibiotic administration within 3 days of diarrhea onset had an OR of 1.83 (95% CI, .99–3.40; 5 studies; $I^2 = 26\%$; Supplementary Table 2; Supplementary Figure 16). Publications since 2005 had an OR of 1.30 (95% CI, .68–2.49; 7 studies; $I^2 = 60\%$).

Qualitative Review of Results Adjusting for Covariates

Dundas et al found that infected individuals <15 and >65 years of age had greatest risk of developing HUS and adjusted for age in their analysis [14], lowering the OR of developing HUS if antibiotics were administered from 5.07 (95% CI, 1.5–16.8) to 4.71 (95% CI, 1.4–16.5). Piercefield et al used admission white blood cell count >20 000 cells/μL as a proxy for illness severity; however, adjustment did not change their results (adjusted values not provided) [20]. Smith et al adjusted for vomiting, fever, bloody diarrhea, and sex [25]. This minimally changed the ORs (1.8 [95% CI, .9–3.7] to 1.5 [95% CI, .5–4.5]). Last, after adjustment for vomiting and initial leukocyte count, Wong et al reported a slightly reduced strength of association (OR, 4.3 [95% CI, 1.7–10.7] to 3.5 [95% CI, 1.3–9.7]) [27].

DISCUSSION

Antibiotic administration to individuals with STEC infection has remained a controversial topic for 2 decades, with reports claiming increased risk of [38] or protection from [16] HUS. Indeed, this risk was suggested in the first description linking STEC to HUS [39]. Controversy was furthered by a meta-analysis that reported no association between antibiotic administration and development of HUS [4]. When all identified studies are included in our meta-analysis, there is no definite association

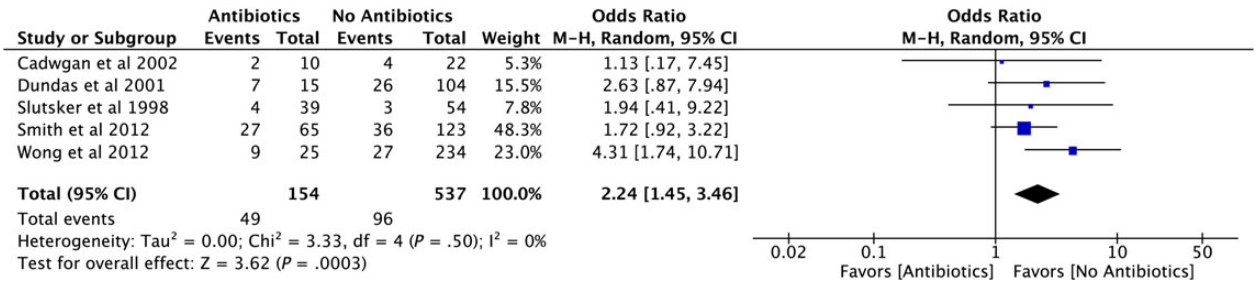

Figure 3. Random-effects meta-analysis of studies comparing odds of developing hemolytic uremic syndrome (HUS) including only studies deemed to be of low risk of bias and meeting HUS definition. The term "favors no antibiotics" implies that when antibiotics were given to the patients with Shiga toxin–producing *Escherichia coli* (STEC) infection, we observed increased odds of developing HUS, and the term "favors antibiotics" implies that when antibiotics were given to the patients with STEC infection, we observed decreased odds of developing HUS. Abbreviations: CI, confidence interval; M-H, Mantel–Haenszel.

between antibiotic administration and the development of HUS. However, the nature of the association changes after a priori planned sources of heterogeneity are explored. Restricting the analysis to studies with low RoB and using the accepted HUS definition, the association strengthens (OR, 2.24 [95% CI, 1.45–3.36]) and the I^2 value becomes 0%, implying that this analysis reflects the true estimate of association.

Since the publication of the first and only meta-analysis on this topic [4], standards for conducting and reporting such studies have advanced. Although the pooled OR reported by Safdar et al (1.15 [95% CI, .79–1.68]) [4] is similar to what we found, they did not refine results by incorporating RoB or scrutinizing the definition of HUS employed. Also, in that study, data extraction from the Ikeda et al report [16] was problematic, as the protective effect of antibiotics (OR, 0.12 [95% CI, .02–.74]) reported is not readily reproducible [7] and appears to be based on the inclusion of a subgroup of patients from the original manuscript [40].

Our meta-analysis benefited from a larger sample size (2245 vs 1121 infections) because of post-2002 publications. The prior analysis employed a fixed-effects model, which is inappropriate given the heterogeneity of included studies (I^2 not reported but $P < .001$), and it controlled for heterogeneity by removing 2 studies [19, 38] that strongly associated antibiotic administration and HUS; a pooled OR including them was not provided.

Although our primary analysis found no significant association between antibiotic administration and HUS, its point estimate (OR, 1.33) leans toward an association, and the associations strengthened in all subsequent analyses. The studies included in the overall analysis are heterogeneous. Heterogeneity was eliminated by including only low-RoB studies and the generally accepted criteria for HUS (Figure 3). After applying more rigorous criteria (ie, low RoB and low RoB plus tight HUS definition), the point estimate further increased. These findings illustrate the importance of considering such elements in guiding future research.

Ideally an adjusted OR would be calculated, but this was not possible because of the lack of detailed reported by the individual studies. Of the 4 studies adjusting for illness severity, 3 found only small reductions in the measure of association and none found changes in direction or significance of findings. While clinical severity in individuals with bloody diarrhea might prompt antibiotic treatment prior to culture results, emerging nucleic acid amplification technologies could potentially identify etiologies of disease and influence care, thereby eliminating such ambiguity. This evolution in diagnostics highlights the importance of understanding the link between antibiotic administration and HUS, and our results will be helpful in response to rapid identification of infected individuals.

One major limitation of this analysis is that it is built on observational studies. The single randomized controlled trial included, which did not influence the results, was of limited utility because the treatment was provided late (day 7), which is close to the median day of onset of HUS in many North American series [9, 27]. We attempted to mitigate this weakness by addressing publication and selection biases and broadening our search criteria to identify all publications, even when antibiotic use and development of HUS was not the focus. We included non-English publications to increase the generalizability of our findings and both outbreak and sporadic infections to reduce the likelihood that different STEC clones, and their propensity to lead to HUS, would influence our findings.

Our work had additional strengths. The subanalyses we conducted reduced heterogeneity and strengthened the relationship between antibiotic use and HUS. We analyzed studies employing a stringent case definition of the outcome to hone in on key studies that accurately addressed the issue being evaluated while minimizing selection bias. This strategy excluded many potentially useful studies that did not include the data required to answer our research question. Most notably, data from the 2011 *E. coli* O104:H4 outbreak in Germany were not included as reports of antibiotic use included primarily patients with established HUS and asymptomatic/postsymptomatic carriers. Although neither of these groups were among our study's target population, we do believe that they provide evidence that treatment during HUS, or during convalescence, may not result in recurring HUS, or late HUS after symptoms have resolved [41]. By also not including the work of Carter et al [42], who reported that antibiotic therapy early in illness was associated with increased fatalities, we might have understated our conclusions. Finally, data extractors were not blinded to our hypothesis, and 1 member of our team has previously published in the field [11, 27, 38]; however, literature screening and data extraction were conducted independently by 3 individuals who had neither met, nor discussed manuscripts with the study's senior author (P. I. T.).

The intrinsic weakness and significant heterogeneity of the included studies, and their suboptimal designs, limit our ability to assign causality to antibiotic use. Although the lack of detail relating exposures to outcomes at a patient level limited some of our subanalyses, we did explore the relationships between country and acquisition (ie, outbreak vs sporadic). We additionally explored antibiotic class as a risk factor in our meta-analysis; no antibiotic/antibiotic class emerged as protective from the development of HUS, compared with nontreatment [25, 27]. Although there are intra- and interserotype differences in the release of Shiga toxin from STEC after exposure to antibiotics in vitro [43], the decision to treat must be made at the time of initial presentation; hence, the variable release of toxin by an infecting strain cannot, for the foreseeable future, be entered into clinical decisions. Moreover, when O157:H7 is analyzed separately from non-O157:H7 strains, the OR CIs are overlapping.

In conclusion, after excluding studies at high RoB and those that did not employ an acceptable definition of HUS, there was a significant positive association between antibiotic administration

and the risk of developing HUS. Given the lack of literature support for the value of early-in-illness antibiotics in STEC infections, and the potential for harm associated with their administration in such instances, these results can be used to promote a more unified public health recommendation against using antibiotics in individuals infected with STEC.

Supplementary Data

Supplementary materials are available at "http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Author contributions. S. B. F., J. X., M. S. N., W. L. H., L. H., and P. I. T. designed the study. S. B. F., J. X., M. S. N., and W. L. H. screened titles and abstracts for inclusion. S. B. F., J. X., M. S. N., and W. L. H. selected full texts for inclusion and extracted data from eligible studies. S. B. F. and J. X. designed the electronic database. S. B. F., J. X., L. H., and P. I. T. did the analyses. S. B. F., L. H., and P. I. T. drafted the report. All authors edited and approved the final version of this report. S. B. F. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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APPENDIX

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