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Meta-Analysis of Antibiotics and the Risk of Community-Associated *Clostridium difficile* Infection

Kevin A. Brown,[a] Nagham Khanafer,[b] Nick Daneman,[c] David N. Fisman[a]

Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada[a]; Laboratoire de Biométrie et de Biologie Évolutive, Université de Lyon, Lyon, France[b]; Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada[c]

The rising incidence of *Clostridium difficile* infection (CDI) could be reduced by lowering exposure to high-risk antibiotics. The objective of this study was to determine the association between antibiotic class and the risk of CDI in the community setting. The EMBASE and PubMed databases were queried without restriction to time period or language. Comparative observational studies and randomized controlled trials (RCTs) considering the impact of exposure to antibiotics on CDI risk among nonhospitalized populations were considered. We estimated pooled odds ratios (OR) for antibiotic classes using random-effect meta-analysis. Our search criteria identified 465 articles, of which 7 met inclusion criteria; all were observational studies. Five studies considered antibiotic risk relative to no antibiotic exposure: clindamycin (OR = 16.80; 95% confidence interval [95% CI], 7.48 to 37.76), fluoroquinolones (OR = 5.50; 95% CI, 4.26 to 7.11), and cephalosporins, monobactams, and carbapenems (CMCs) (OR = 5.68; 95% CI, 2.12 to 15.23) had the largest effects, while macrolides (OR = 2.65; 95% CI, 1.92 to 3.64), sulfonamides and trimethoprim (OR = 1.81; 95% CI, 1.34 to 2.43), and penicillins (OR = 2.71; 95% CI, 1.75 to 4.21) had lower associations with CDI. We noted no effect of tetracyclines on CDI risk (OR = 0.92; 95% CI, 0.61 to 1.40). In the community setting, there is substantial variation in the risk of CDI associated with different antimicrobial classes. Avoidance of high-risk antibiotics (such as clindamycin, CMCs, and fluoroquinolones) in favor of lower-risk antibiotics (such as penicillins, macrolides, and tetracyclines) may help reduce the incidence of CDI.

Clostridium difficile, a toxin-producing bacterium that causes diarrhea, is the largest single cause of morbidity and mortality among hospital-acquired infections (1). In hospitals, *C. difficile* infection (CDI) is generally acquired when patients with predisposing factors such as advanced age and antibiotic use are exposed to *C. difficile* spores emanating from other hospitalized infected patients (2). With the emergence of increasingly virulent *C. difficile* strains have come reports of CDIs in patients previously considered to be at low risk of this infection, including those living in the community (3–5). Spore exposure may occur outside inpatient settings, since river water, soil, and foods can be contaminated (6, 7), outpatient exposures to the health care system are common, and transmission may occur within households (8). A recent study noted that the population-based incidence of community-acquired CDI (11.2 cases per 100,000 person-years) was on par with hospital-acquired CDI (12.1 cases per 100,000 person-years) (9).

One published meta-analysis and one systematic review have considered the impact of antibiotic exposure on CDI (10, 11) risk among hospital inpatients. The meta-analytic study noted that tetracyclines and penicillins were associated with the lowest risk, while fluoroquinolones, clindamycin, and expanded-spectrum cephalosporins were associated with the highest risk of CDI acquisition, despite considerable confidence interval overlap (10). The systematic review established that the strongest evidence of risk existed for penicillins and clindamycin and that effect estimates for other antibiotic classes were liable to bias (11).

In addition to yielding accurate adjusted effect estimates, a systematic review of the association between exposure to antibiotics and community-associated CDI is necessary, since the risk profile is different among nonhospitalized populations (younger, less frequent exposure to patients with symptomatic CDI, and different profile of underlying infections and antibiotic treatments). We conducted a systematic review of the association between antibiotic type and the risk of CDI in nonhospitalized populations. Our objective was to quantify the relative risks of specific antibiotics in order to better understand the risks of prescribing various antibiotics in the community setting.

MATERIALS AND METHODS

Search criteria. A literature search was conducted in March 2012 using the EMBASE and PubMed databases and included all articles without restriction to language or time period. The Reference sections of the articles were browsed, and content experts were approached to identify further relevant articles. Within each database, our search strategy was to use both key words and mapped subject headings as terms describing the exposure (i.e., antibiotic, antibacterial, antimicrobial, aminoglyosides, beta-lactams, cephalosporins, clindamycin, fluoroquinolones, macrolides, metronidazole, sulfonamides, and tetracyclines), outcome (*C. difficile* infection), and the detection of a community-acquired infection (community-acquired, community-associated, outpatient, ambulatory care, registry, and general practice). Exposure, outcome, and population terms were then combined using the Boolean "and" operator (12).

We included population-based studies of people with little to no health care system contact prior to the onset of disease (13); studies restricted to hospital-acquired or health care-associated disease (e.g., studies restricted to HIV and cancer outpatients) were excluded. The outcome of interest was incident CDI (collected at the individual level). We were interested in exposure to specific antibiotic classes. We excluded studies

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Address correspondence to Kevin A. Brown, kevin.brown@mail.utoronto.ca.

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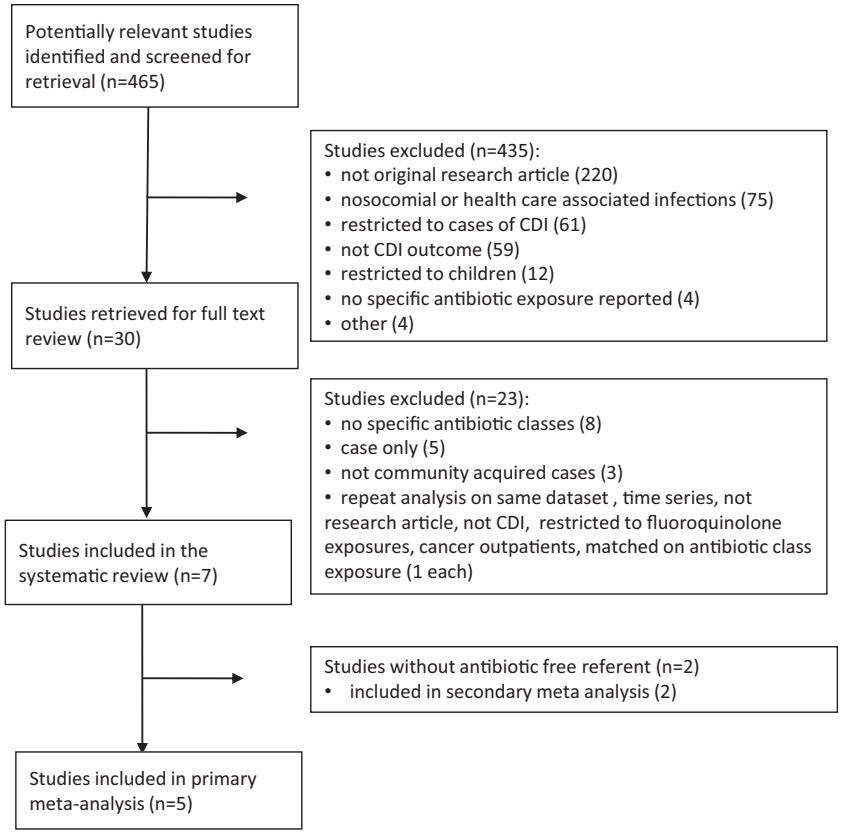

FIG 1 Flow chart of studies screened and included in this study.

considering risk factors for severe or relapsing CDI among individuals already diagnosed with *C. difficile*, time series analyses, and those not examining specific antibiotics or antibiotic classes.

Screening and data abstraction. One author (K. A. Brown) screened article titles and abstracts of the initial database search to identify those appropriate for full text review. The full text of identified articles was read; those articles eliminated in the initial screen of titles and abstracts were distinguished from articles eliminated in the full-text screen. Data on the numbers of cases and controls, unadjusted and adjusted effect sizes, and 95% confidence intervals corresponding to each antibiotic exposure group reported were abstracted and entered into a spreadsheet. When insufficient information was available to obtain the appropriate effect size standard errors, study authors were contacted by e-mail.

Quality assessment. Study quality was assessed using a six-criterion checklist (14–16) with certain elements of the checklist aimed at addressing specific concerns raised in previous systematic reviews on the topic (10, 11). The six study quality assessment questions follow. (Question 1 [Q1]) Did the study have a clearly stated study aim? (Q2) Was the study population clearly defined (i.e., was an appropriate method used to ensure that inpatients were excluded)? (Q3) Were the case counts of the antibiotic exposure groups reported, and if so, were they sufficiently large to statistically compare effect sizes? A study with 10 or more cases in each antibiotic exposure group was given a score of 2, <10 in some groups was given a score of 1, and a study not reporting case counts was given a score of 0. (Q4) Were the criteria for diagnosis of *C. difficile* clearly defined (e.g., statement of ICD [international classification of diseases] code for registry studies; clear description of microbiologic methods used for clinical studies)? (Q5) Was there an attempt to use statistical analyses to adjust for confounding or to standardize disease rates by age, duration of antibiotic exposure, and exposure to combinations of antibiotics? (Q6) Was there a discussion of study limitations? Each quality criterion identified except question 3 was scored as 0 (no) or 1 (yes); question 3 was graded on a scale from 0 to 2. Two authors (K. A. Brown and N. Khanafer) independently graded study quality; the results were compared, and disagreements were resolved through discussion. By summing up the points, the studies were classified as high quality (6 or 7 points), moderate quality (4 or 5 points), or poor quality (<4 points).

Variables. Antibiotics were classified into one of the following 7 groups from the articles included in this meta-analysis study: (i) tetracyclines; (ii) sulfonamides and trimethoprim; (iii) penicillins; (iv) macrolides; (v) cephalosporins, monobactams, and carbapenems (CMCs); (vi) fluoroquinolones; and (vii) clindamycin. The dependent variable of interest was the adjusted study-specific log odds ratio of a given antibiotic class relative to no antibiotic exposure; this variable and the standard error for each reported effect were usually transcribed directly from the publication Results section. In the study of Dial et al. (17), the effect sizes of levofloxacin, gatifloxacin, and moxifloxacin antibiotics were combined by taking the weighted average of the log odds ratios, with inverse variance weights; in the study of Kuntz et al. (9), the effect sizes for the CMCs were combined in a similar manner.

Statistical analysis. A pooled random-effects analysis was used to consider the impact of any antibiotic exposure irrespective of antibiotic class relative to no exposure, using the DerSimonian-Laird approach (18). A stratified analysis was then used to consider the risk associated with each antibiotic type compared to no antibiotic exposure. In a secondary analysis restricted to the 2 studies excluding antibiotic unexposed persons (19, 20), odds ratios were calculated from the number of CDI-positive cases and the total person-time within antibiotic exposure classes with 0.5 added to each cell (in order to estimate effects in the presence of zero cells) (21); for the odds ratio, penicillin-exposed persons were considered the referent category. Due to the low incidence of community-acquired CDI in contemporary populations (9), the odds ratios reported in this study

TABLE 1 Selected characteristics of the seven eligible articles

Characteristic	Delaney et al. (34)	Dial et al. (17)	Hirschhorn et al. (19)	Kuntz et al. (9)	Levy et al. (20)	Naggie et al. (36)	Wilcox et al. (27)
Publication yr	2007	2008	1994	2011	2000	2011	2008
Study design	Case control	Nested case control	Retrospective cohort	Nested case control	Nested case control	Case control	Case control
Data source(s)	UK General Practice Research Database (GPRD) and British National Formulary	Hospital discharge summary and medical insurance records of Quebec, Canada	Harvard Community Health Plan	University of Iowa Wellmark Data Repository (Iowa and South Dakota, USA)	United Health Group claims database	Duke University Medical Center, Durham Regional Hospital, Durham, Salisbury, and Asheville VAMCs[a]	UK laboratory test results and telephone questionnaire
Study period[b]	Jan. 1993 to Dec. 2004	Jan. 1996 to Dec. 2004	Apr. 1988 to Nov. 1990	Jan. 2004 to Dec. 2007	Jan. 1992 to Dec. 1994	Oct. 2006 to Nov. 2007	Jan. to Dec. 1999
Study population	Persons registered in GPRD not hospitalized in the last yr	Persons ≥ 65 yrs old, with at least one previous hospitalization, without hospital discharge in the previous 90 days	Enrollees not hospitalized in the last 42 days and with ≥1 antibiotic prescription in the previous 2 to 42 days	Enrollees with >12 mo of health coverage without discharge in the previous 12 wks	Enrollees with a *C. difficile* lab test and with exactly 1 antibiotic exposure in the previous 2 to 42 days	Outpatients ≥ 18 yrs old without history of diarrhea and without discharge in the previous 12 wks	Outpatients with a fecal sample sent for *C. difficile* toxin test
Case definition	Presence of an initial positive *C. difficile* toxin assay result and/or a clinical diagnosis recorded by their general practitioner (GP)	Primary hospital diagnosis of CDI (ICD coding)	Positive assay result for *C. difficile* toxin with documented diarrhea or colitis with onset within 48 h of admission	Primary or secondary CDI diagnosis on insurance claim. For hospital patients, it must be recorded at admission.	Documented diarrhea and a positive *C. difficile* laboratory test result in the medical record	Patients with diarrhea (onset in community or ≤72 h of hospital arrival) and a positive stool toxin assay result	Patients presenting to their GP with symptoms of diarrhea with positive stool toxin assay result
Matching	Age, clinic site, and index date[c]	Index date[c] and date of 1st hospitalization	None	Index date[c]	None	Index mo[c] and clinic site	Age, sex, and index period[c] (3 mo)
Antibiotic exposure	National claims database; 90-day window	Provincial claims database; 45-day window	Health maintenance organization (HMO) pharmacy records; 2- to 42-day window	Outpatient drug claims; 180-day window	HMO pharmacy records; 2- to 42-day window	Electronic medical records; 90-day window	Postal questionnaire; 4-wk window
Adjustment method	Conditional logistic regression	Conditional logistic regression	Stratification	Conditional logistic regression	Stratification	Logistic regression	Matching
No. of cases (*n*)/no. of controls (*N*)	1,233/12,330	836/8,360	51/175,275[d]	304/3,040	48/358,389[d]	66/114	40/112

[a] VAMC, Veterans Affairs Medical Center.
[b] Jan., January; Dec., December; Apr., April; Nov., November; Oct., October.
[c] The index date (or month) was defined as the date of diagnosis, symptom onset, or admission for cases and the date of health care facility visit for controls.
[d] *N* = person-days.

TABLE 2 Quality characteristics of eligible studies

Study (author, reference, and publication yr)	Quality score[a]						
	Total (0–7)	Q1	Q2	Q3[b]	Q4	Q5	Q6
Delaney et al. (34) (2007)	6	1	1	2	0	1	1
Dial et al. (17) (2008)	4	1	1	0	0	1	1
Hirschhorn et al. (19) (1994)	6	1	1	1	1	1	1
Kuntz et al. (9) (2011)	7	1	1	2	1	1	1
Levy et al. (20) (2000)	3	1	0	1	0	0	1
Naggie et al. (36) (2011)	4	1	0	0	1	1	1
Wilcox et al. (27) (2008)	3	1	0	0	1	0	1

[a] The six study quality assessment questions and scoring method are given in "Quality assessment" in Materials and Methods.
[b] Scored on a scale from 0 to 2.

may be interpreted as risk ratios (22). For the studies in the secondary analysis, a similar stratified meta-analysis measured the risk associated with each antibiotic type compared to penicillin exposure.

We assessed the heterogeneity of study results by use of the τ^2, Q (18), and I^2 statistics (23). Possible sources of heterogeneity were explored in sensitivity analyses in which certain subgroups were excluded, as well as through creation of meta-regression models (24). Analyses were conducted in R using the meta and metafor packages (25). Data and R code have been deposited in the Dryad repository (http://dx.doi.org/10.5061/dryad.g7b05).

RESULTS

Out of a total of 465 articles identified, only 7 fulfilled the eligibility criteria (Fig. 1). Three studies employed nested case control designs, 3 used nonnested case control designs, and one was a cohort study (Table 1). The studies monitored subjects from 1988 to 2007 and varied in size from as few as 40 to over 1,200 cases of CDI.

A total of 5 studies included controls without antibiotic exposure and could be included in the primary meta-analyses; the other 2 studies were included in a secondary meta-analysis limited to studies without antibiotic-free controls.

Of the studies in the primary analysis, two evaluated all 7 candidate antibiotic classes, two covered between 5 and 6 of the 7 classes, and one reported on only 4 of 7 classes. The two studies in the secondary analysis each reported exposures for all 7 antibiotic classes, but no patients exposed to clindamycin in either of these additional studies acquired CDI infection, so the odds ratios were not calculated for this agent.

Among the studies included in the primary meta-analyses, study quality (Table 2) was scored high for two studies, moderate for two studies, and low for one study. Among studies included in the secondary meta-analyses, one was scored as high quality, and the other was scored as low quality. Note that for three studies, the case definition did not properly exclude potentially hospital-acquired cases (17, 26, 27).

Pooled effects. The pooled impact of any antibiotic exposure (irrespective of antibiotic class) across all 29 antibiotic effects (Fig. 2) was to increase the risk of CDI by a multiple of 3 (OR = 3.55; 95% CI, 2.56 to 4.94). In this analysis, which ignored antibiotic class, effect heterogeneity was extremely high (I^2 = 90.6%; $P < 0.001$).

Antibiotic types. In the analyses stratified by antibiotic class, 6 of 7 antibiotic classes were associated with increased risk of CDI (Fig. 2). Specifically, clindamycin (OR = 16.80; 95% CI, 7.48 to 37.76), fluoroquinolones (OR = 5.50; 95% CI, 4.26 to 7.11), and CMCs (OR = 5.68; 95% CI, 2.12 to 15.23) were found to increase CDI risk the most, while macrolides (OR = 2.65; 95% CI, 1.92 to 3.64), sulfonamides and trimethoprim (OR = 1.81; 95% CI, 1.34 to 2.43), and penicillins (OR = 2.71; 95% CI, 1.75 to 4.21) were found to have a lesser, but nevertheless statistically significant impact. There was no evidence of the impact of tetracyclines on CDI risk (OR = 0.92; 95% CI, 0.61 to 1.40).

Between-study heterogeneity was largest in the CMC (I^2 = 93.8%; $P < 0.001$), penicillin (I^2 = 76.8%; $P = 0.002$), and clindamycin (I^2 = 66.7%; $P = 0.05$) drug classes. Conversely, heterogeneity was lowest for tetracyclines (I^2 = 0.0%; $P = 0.98$), sulfonamides and trimethoprim (I^2 = 0.0%; $P = 0.56$), and fluoroquinolones (I^2 = 10.9%; $P = 0.34$). Relative to the pooled meta-analysis ($\tau^2 = 0.62$), the stratified model reduced heterogeneity by 55% ($\tau^2 = 0.27$; $P < 0.001$).

Meta-regression. Meta-regression was used in order to investigate the factors influencing residual heterogeneity from the primary analysis. The five studies were associated with systematic differences in drug effects ($P = 0.001$ by the χ^2_4 test); in particular, the pooled odds ratios in one study (17) were twice those of the remaining studies (OR = 1.93; 95% CI, 1.30 to 2.87). The addition of study level effects to the meta-regression model reduced heterogeneity by 63% ($\tau^2 = 0.10$; $P < 0.001$). As a sensitivity analysis, we excluded the one study reporting larger effect sizes; the pooled odds ratio in the remaining 4 studies was 2.86 (95% CI, 2.86 to 3.81) and the between-study effects were no longer significant ($P = 0.12$ by the χ^2_3 test).

For the subset of high-quality studies ($n = 2$), the heterogeneity of between-study effects was below detectable limits ($P = 0.96$ by the χ^2_1 test). These two studies reported effect sizes for all antibiotic classes that were smaller than those of medium- and low-quality studies (OR = 2.50; 95% CI 1.80 to 3.47).

Publication bias. We tested for funnel plot asymmetry using the stratified model and found no evidence of an association between effect estimate precision and residual effect sizes ($z = 0.53$; $P = 0.59$).

Antibiotic-associated CDI risk (AACR) index. In a *post hoc* exploratory analysis, a simple 4 point index summarizing the meta-analysis results was developed; the index was equal to 1 for tetracyclines, 2 for sulfonamides and trimethoprim, macrolides, and penicillins, 3 for CMCs and fluoroquinolones, and 4 for clindamycin. Each one-point increase in the index was associated with a 2.41-fold increase (95% CI, 2.14 to 2.74) in the odds of acquiring CDI. Mean antibiotic class effect did not deviate significantly from the linear trend ($P = 0.30$ for sulfanomides to $P = 0.85$ for tetracyclines). The model fit is presented graphically in Fig. 3.

Secondary analysis. With this analysis, similar findings were noted; namely, tetracyclines (OR = 0.60; 95% CI, 0.14 to 2.61) were not associated with an increased risk of *C. difficile*; sulfonamides and trimethoprim (OR = 0.85; 95% CI, 0.29 to 2.52), and macrolides (OR = 0.60; 95% CI, 0.20 to 1.76) tended to have the smallest effect sizes with the least heterogeneity, while CMCs (OR = 4.12; 95% CI, 2.28 to 7.44) and fluoroquinolones (OR = 4.31; 95% CI, 1.46 to 12.70) had larger and more variable effect sizes. In both studies, clindamycin exposure was rare (<0.5% of total antibiotic exposures in each); neither reported any cases associated with clindamycin.

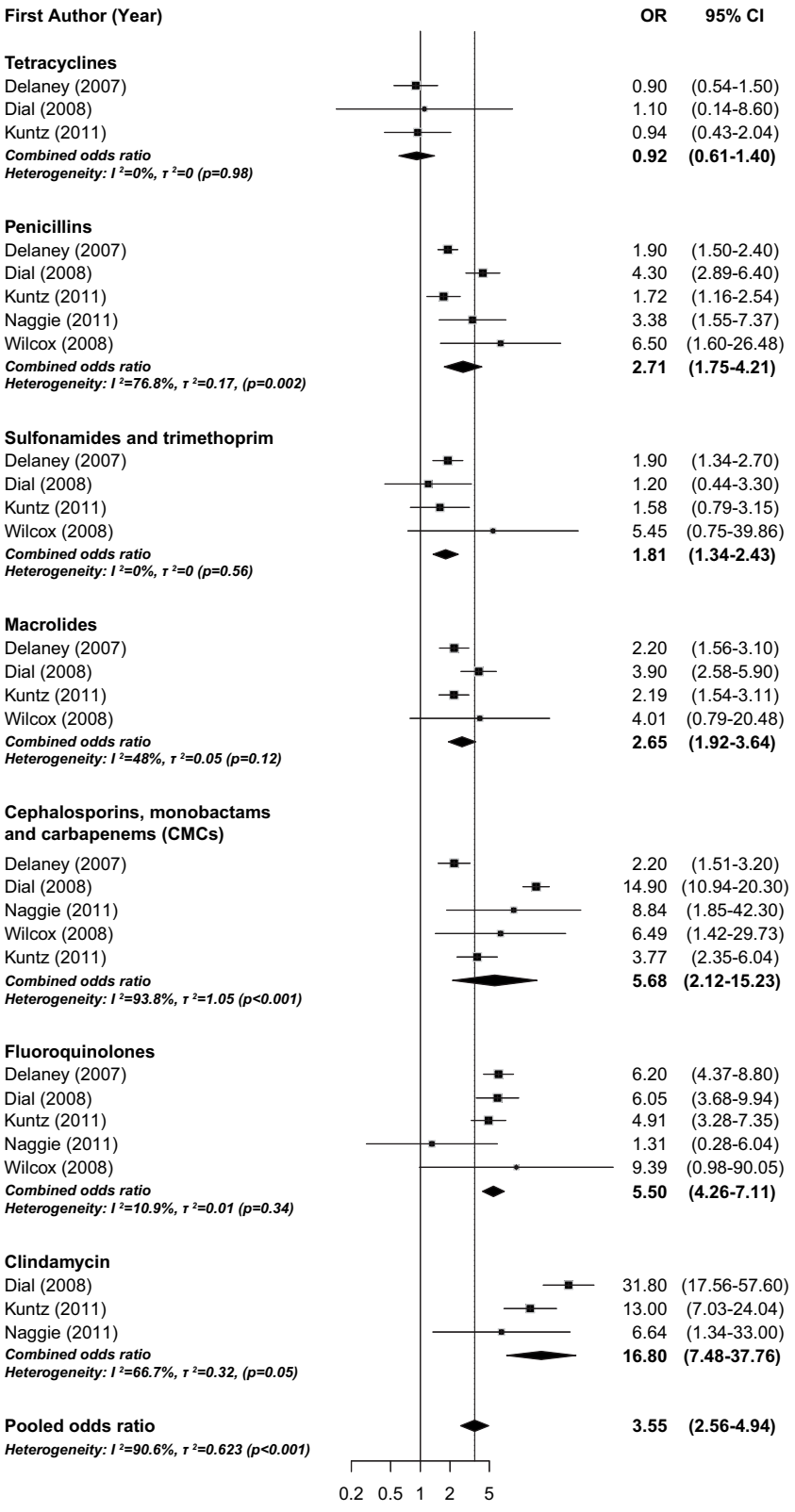

FIG 2 Pooled and study-specific risk estimates of community-associated CDI risk by antibiotic class.

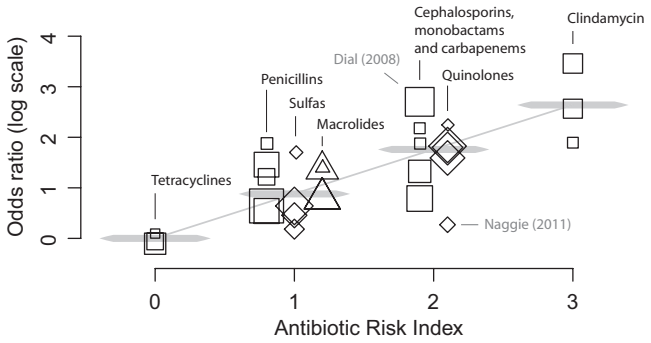

FIG 3 Linear association between a 4-point antibiotic risk index and community-associated CDI risks.

DISCUSSION

The emergence of *C. difficile* as an infection in individuals without prior hospitalization, and presumed community acquisition, represents a concerning development in the ongoing emergence of this pathogen. As any prescription of an antimicrobial agent to a patient in an outpatient setting requires a careful weighing of risks and benefits, we performed a systematic review to quantify the risks associated with individual antibiotic classes and to identify areas of heterogeneity in such risk. Overall use of antibiotic agents is associated with a 3-fold increased risk of community-acquired CDI, but we also detected substantial variation in risk associated with different antimicrobial classes, with fluoroquinolones, CMCs, and clindamycin associated with the greatest enhancement of risk.

This study largely corroborates the associations found for hospital-associated CDI risk (10, 11, 28). In keeping with many historic studies of CDI risk and outbreaks of the disease, clindamycin was found to have the strongest association with risk. One must note however, that clindamycin has not been associated with the greatest risk enhancement in every study (28); variability in effects may be due to true biological heterogeneity of effect (e.g., variable strain susceptibility to clindamycin [29], timing of inoculation relative to the end of antibiotic exposure), or it could be an artifact of the different methods used for outcome ascertainment (see below).

Our study found large effects for fluoroquinolones and CMCs. This could be expected given the broad spectrum of activity of these agents against intestinal microbes and the low susceptibility of *Clostridium difficile* to these classes of antibiotics (30). The risk associated with CMCs was highly variable across studies, in contrast to fluoroquinolones, which appeared to have more-consistent effects. This heterogeneity may be due to the greater activity of newer cephalosporins against anaerobic bacteria and Gram-negative bacilli (10). In contrast, one study limited to patients with fluoroquinolone exposures (31) found no differences in effect between levofloxacin, gatifloxacin, and moxifloxacin, notwithstanding the enhanced anti-anaerobic spectrum of the latter agents.

Our findings reaffirmed the finding of moderate effects for penicillins, macrolides, and sulfonamides and trimethoprim from a recent hospital-based study (28); this is in contrast to other hospital-based studies that have noted large effects for penicillins (11). The relatively low MICs for penicillins among common CDI strains (32) could help explain the observed modestly elevated risk level for the penicillin class, such that the enhancement of CDI risk resulting from elimination of normal enteric flora is somewhat counterbalanced by anti-*C. difficile* activity. These discrepancies may also result from wide variations in the antibiotic spectrum of penicillin subclasses (including broad-spectrum penicillins used more in the hospital setting such as piperacillin-tazobactam). Our meta-analysis noted that tetracycline antibiotics have little antibiotic-associated risk, which is in keeping with the only meta-analysis of inpatient CDI (10) risk.

Like any observational study, the findings of studies incorporated into this meta-analysis could have been biased by methodological flaws, including issues of control selection, misclassification of both outcomes and exposures, and residual confounding (33). Our quality checklist attempted to assess the overall risk of these biases in each study; we outline some specific observations below. With respect to the definition of the population, two studies did not exclude patients exposed to hospital settings during the risk period, and as such may actually represent studies of community-onset but hospital-acquired disease (20, 27) while two studies were restricted to patients who received a *C. difficile* assay, and as such, the controls did not represent the source population of cases (20, 27). With respect to ascertaining the outcome, all positive cases may have been subject to misclassification due to infection with another diarrhea-causing organism. Further, in two studies (17, 20), a lack of clinical detail meant that hospital-diagnosed cases with onset of symptoms ≥48 h after admission could not be separated from those with onset within 48 h. As such, unmeasured inpatient antibiotic exposures may have caused the disease outcome. Indeed, in the study of Dial et al. (17), outpatient antibiotic exposures were detected in only 47.1% of the cases. Of the studies included in this meta-analysis study, only one (34) considered the robustness of results to diagnostic suspicion bias by comparing effect sizes from clinical diagnoses to those with test-based confirmation; they found no significant differences in effect with the clinically diagnosed subgroup.

Other potential sources of bias in our meta-analysis could include a lack of consensus regarding the appropriate time window for identification of antibiotic exposure. As risk associated with antibiotic exposure decreases with increasing time, larger effect sizes are liable to be found in studies looking at the shorter time windows. Indeed, the study in our primary analyses with the shortest exposure window reported larger effect sizes for all antibiotics except tetracyclines (17). In fact, the appropriate time window may differ between antibiotic classes due to differing antimicrobial effect duration (35). In addition, simultaneous administration of multiple antimicrobial agents and confounding by indication (as individuals receiving antimicrobials may have underlying health conditions placing them at greater risk for CDI) may have biased results.

Finally, although we did not find evidence to suggest that our findings were influenced by publication bias, we did notice some selective reporting of antibiotic class exposures. Specifically, the smallest study meeting the inclusion criteria (36) failed to report effect estimates for 3 of the 7 antibiotic classes (tetracyclines, macrolides, and sulfonamides and trimethoprim), and none of the studies reported on the impact of oxalizidenones, glycopeptides, carbapenems, or aminoglycosides.

In summary, and on the basis of the best available evidence, we found that the risk profiles for antimicrobial classes as risk factors for community-acquired CDI are similar to those described for health care-associated disease. In particular, antimicrobial classes with broad-spectrum, and potent anti-Gram-negative and/or an-

tianaerobic bacterial activity, including cephalosporins, fluoroquinolones, and clindamycin, are most likely to cause CDI. In contrast, macrolides, penicillins, sulfonamides and trimethoprim, and particularly tetracyclines confer a lower risk of CDI. While community-acquired CDI remains fortunately less common than its health care-associated counterpart, we propose that CDI risk represents yet another factor that needs to be factored into the decision to prescribe antimicrobials (and the choice of antimicrobial) in the outpatient setting.

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