Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis

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Objectives: To update the evidence for associations between antibiotic classes and hospital-acquired *Clostridium difficile* infection (HA-CDI).

Methods: Electronic databases of journal articles, scholarly theses and conference proceedings using subject headings and keywords related to CDI and antibiotic exposure were searched. Observational epidemiological studies measuring associations between antibiotic classes and HA-CDI were eligible for inclusion. Pooled ORs and 95% CIs were calculated using a random effects model. Study factors identified a priori were examined as sources of heterogeneity. The quality of the studies was assessed using the Newcastle-Ottawa Scale.

Results: Of 569 citations identified, 13 case–control and 1 cohort study (15,938 patients) were included. The strongest associations were found for third-generation cephalosporins (OR = 3.20, 95% CI = 1.80–5.71; n = 6 studies; $I^2 = 79.2\%$), clindamycin (2.86, 2.04–4.02; n = 6; $I^2 = 28.5\%$), second-generation cephalosporins (2.14, 1.30–3.52; n = 2; $I^2 = 0.0\%$), carbapenems (1.84, 1.26–2.68; n = 6; $I^2 = 0.0\%$), trimethoprim/sulphonamides (1.78, 1.04–3.05; n = 5; $I^2 = 70\%$), fluoroquinolones (1.66, 1.17–2.35; n = 10; $I^2 = 64\%$) and penicillin combinations (1.45, 1.05–2.02; n = 6; $I^2 = 54\%$). The study population and the timing of measurement of antibiotic exposure were the most common sources of heterogeneity. Study quality scored high for seven studies, moderate for six studies and low for one study.

Conclusions: The risk of HA-CDI remains greatest for cephalosporins and clindamycin, and their importance as inciting agents should not be minimized. The importance of fluoroquinolones should not be overemphasized, particularly if fluoroquinolone-resistant epidemic strains of *C. difficile* are absent.

Keywords: diarrhoea, antimicrobials, risk factors, healthcare facilities

Introduction

*Clostridium difficile* is the leading cause of healthcare facility (HCF)-associated diarrhoea, estimated to cost the USA more than $3 billion per year.1 Susceptibility to infection with *C. difficile* is induced by exposure to factors that disrupt gut microflora, most usually antibiotics that are commonly used in HCFs. Our earlier systematic review of the published literature up to 2001 found that clindamycin and third-generation cephalosporins were most strongly associated with HCF-associated *C. difficile* infection (HA-CDI).2

The rates of CDI in industrialized countries have risen with the emergence of the NAP1/RT027 strain in 2002, responsible for outbreaks of severe disease in North America and Europe.3,4 Although rates of community-associated CDI (CA-CDI) are also increasing worldwide, 70%–80% of cases are associated with exposure to an HCF.5 The aim of this study was to evaluate the associations between antibiotic classes and the risk of HA-CDI over the period January 2002 to December 2012.

Methods

A systematic review was conducted in March 2013. The PRISMA statement was used to guide the methodology and reporting of the study.6

Search strategy and selection criteria

Searches of the primary literature were conducted using Medline (PubMed, OvidSP) and Embase (OvidSP). Dissertations and theses were searched using WorldCat (www.worldcat.org), ProQuest Dissertations and Theses (PQDT; www.proquest.com), Electronic Theses Online Service (EthOS), Networked Digital Library of Theses and Dissertations (NDLTD; www.ndltd.org) and the National Library of Australia (Trove; www.trove.nla.gov.au). The Conference Proceedings Citation Index was searched using the Web of Science.
Science (incorporated 2003). The reference lists of the articles were examined.

All the searches were limited to studies published from 1 January 2002 to 31 December 2012 that reported on human participants. Primary literature searches were conducted using MeSH and Emtree terms and keywords in all fields: *Clostridium difficile*, diarrhea, diarrhoea, colitis, antibacterial agents, anti-infective agents, antibiotic, antimicrobial, case–control studies, cohort studies, retrospective studies and prospective studies (see the full search strategy in the Supplementary data at JAC Online). Searches of theses and dissertations used the terms *Clostridium difficile*, epidemiology and public health. Conference abstracts were searched using the terms *Clostridium difficile*, antibiotic, antimicrobial and risk factors.

Inclusion and exclusion criteria were developed using the Patients, Interventions, Comparisons and Outcomes approach. Studies were included in the review if they met the following criteria: observational studies conducted among hospital inpatients, measurement of antibiotic exposure, inclusion of a comparison group and outcome of HA-CDI. We

#### Figure 1. PRISMA flow diagram.
Table 1. Characteristics of 14 case–control and 1 cohort study assessing HA-CDI

<table>
<thead>
<tr>
<th>Study citation</th>
<th>Data source</th>
<th>Study period</th>
<th>Study population</th>
<th>Case definition</th>
<th>Control definition</th>
<th>Matching</th>
<th>Adjustment method</th>
<th>Antibiotic exposure</th>
<th>Definition of HCF-acquisition</th>
<th>N cases/ non-cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asha 2006 19</td>
<td>Leeds Teaching Hospitals, UK</td>
<td>Jun 2001 – Apr 2002</td>
<td>Inpatients &gt;2 years</td>
<td>N/A</td>
<td>N/A</td>
<td>Diarrhoea and positive test for C. difficile toxin (cell culture cytototoxicity)</td>
<td>age, gender, ward location</td>
<td>conditional logistic regression</td>
<td>source not stated; 28 days prior to index date</td>
<td>≥3 days after admission</td>
</tr>
<tr>
<td>Baxter 2008 15</td>
<td>Kaiser Permanente of Northern California, USA</td>
<td>Jan 1998 – Dec 2005</td>
<td>Inpatients; antibiotics previous 60 days</td>
<td>Diarrhoea and positive test for C. difficile toxin; no history of CDI for 1 y (toxin A/B EIA (Meridian Premier))</td>
<td>Inpatients with no positive test result for C. difficile</td>
<td>hospital, ward, date</td>
<td>conditional logistic regression</td>
<td>Age, sex; community</td>
<td>Pharmacy database; 60 days prior to index date</td>
<td>≥3 days after admission</td>
</tr>
<tr>
<td>Hensgens 2012 22</td>
<td>9 hospitals, Netherlands</td>
<td>Mar 2006 – May 2009</td>
<td>Inpatients</td>
<td>Diarrhoea and positive test for C. difficile toxin (various EIA)</td>
<td>Hospital, ward, date</td>
<td>Conditional logistic regression</td>
<td>Age, sex, comorbidity, other antibiotics</td>
<td>Electronic medical information system; 3 months prior to diagnosis</td>
<td>≥2 days after admission or physician’s request</td>
<td>337/337a</td>
</tr>
<tr>
<td>Kallen 2009 34</td>
<td>Community hospital, USA</td>
<td>Jun 2005 – May 2007</td>
<td>Inpatients; antibiotics previous 3 months</td>
<td>Diarrhoea and positive test for C. difficile toxin (toxin A/B EIA (Meridian Premier))</td>
<td>Patients hospitalized for at least 48 h, no CDI up to 30 days post discharge</td>
<td>Logistic regression</td>
<td>Age, comorbidity, LOS, PPI use, NG tube use, tube feeding, other antibiotics</td>
<td>Pharmacy records; 3 months prior to index date</td>
<td>≥48 h after admission</td>
<td>100/100</td>
</tr>
<tr>
<td>Loo 2005 17</td>
<td>12 hospitals, Quebec, Canada</td>
<td>Jan – Jun 2004</td>
<td>Inpatients</td>
<td>Diarrhoea and positive test for C. difficile toxin and/or a clinical diagnosis (various EIA and culture cytotoxicity)</td>
<td>Patients admitted and discharged during the same period, no known history of CDI</td>
<td>Age, Charlab Index, date, ward, length of time at risk</td>
<td>Conditional logistic regression</td>
<td>Age, sex, other antibiotics, no. of days at risk of CDI, comorbidity, chemotherapy, PPIs, histamine H2-blockers, enteral feeding</td>
<td>Source not reported; 6 weeks prior to diagnosis</td>
<td>≥72 h after admission or within 1 month of previous admission</td>
</tr>
<tr>
<td>McCusker 2003 35</td>
<td>Veterans Affairs Maryland Healthcare System, USA</td>
<td>Jan – Jun 2001</td>
<td>Inpatients</td>
<td>Diarrhoea and positive test for C. difficile toxin (toxin A EIA (Wampole))</td>
<td>Patients admitted for at least 48 h during the same 6 month period as the cases; no history of CDI and no receipt of oral metronidazole</td>
<td>Conditional logistic regression</td>
<td>Other antibiotics, days at risk</td>
<td>Electronic medical records; 6 weeks prior to index date</td>
<td>≥72 h after admission</td>
<td>30/60</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Study citation</th>
<th>Data source</th>
<th>Study period</th>
<th>Study population</th>
<th>Age, years cases/controls, mean (SD)</th>
<th>Male, %</th>
<th>Case definition</th>
<th>Control definition</th>
<th>Matching</th>
<th>Adjustment method</th>
<th>Antibiotic exposure</th>
<th>Definition of HCF-acquisition</th>
<th>N cases/ non-cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minsen 2007²⁰</td>
<td>615 bed non-academic urban medical facility, Nashville, USA</td>
<td>Oct 2005 – Mar 2006</td>
<td>inpatients</td>
<td>&gt; 18 years</td>
<td>69/63</td>
<td>41</td>
<td>Diarrhoea and a positive test for C. difficile toxin A/B EIA (Meridian Premier)</td>
<td>inpatients with no history of CDI (or metronidazole/vancomycin use during admission)</td>
<td>age, gender, length of time at risk, LOS in ICU</td>
<td>none</td>
<td>source not reported; previous 8 weeks</td>
<td>≥ 72 h after admission</td>
</tr>
<tr>
<td>Modena 2005¹⁷</td>
<td>Temple University Hospital, Philadelphia, USA</td>
<td>Aug 2003 – Jun 2004</td>
<td>inpatients; ≥ 5 days antibiotics</td>
<td>57 (18/60 17)</td>
<td>47</td>
<td>Diarrhoea and positive test for C. difficile toxin (no history of CDI) (toxin A/B EIA (Wampole))</td>
<td>inpatients with other infections</td>
<td>none</td>
<td>logistic regression. ICU, LOS</td>
<td>medical and pharmacy records during index admission</td>
<td>antibiotics &gt;5 days</td>
<td>50/200</td>
</tr>
<tr>
<td>Muta 2005¹⁵</td>
<td>600 bed tertiary care teaching hospital, Pittsburg, USA</td>
<td>Jan 2000 – Apr 2001</td>
<td>inpatients</td>
<td>64 (17 - 95)/ 59 (16 - 93)¹⁹</td>
<td>52</td>
<td>signs and symptoms of CDI and positive test for C. difficile toxin (cell culture cytotoxicity)</td>
<td>inpatients with no positive test for C. difficile</td>
<td>date of admission, service, LOS</td>
<td>conditional logistic regression. age, diabetes mellitus, transplantation, H2 blockers, PPIs</td>
<td>electronic medical records; 28 days prior to diagnosis</td>
<td>≥ 72 h after admission</td>
<td>203/203</td>
</tr>
<tr>
<td>Polgreen 2007¹⁵</td>
<td>Small, rural hospital, Iowa, USA</td>
<td>Jan 2004 – Apr 2004</td>
<td>inpatients</td>
<td>81³⁵</td>
<td>39</td>
<td>Diarrhoea and positive test for C. difficile toxin (toxin A EIA (Becton Dickinson))</td>
<td>inpatients admitted during the study period</td>
<td>age, sex</td>
<td>conditional logistic regression. LOS</td>
<td>medical records; 6 weeks prior to admission</td>
<td>≥ 48 h after admission</td>
<td>15/45</td>
</tr>
<tr>
<td>Sundram 2009¹¹</td>
<td>520 bed district general hospital, Surrey, England</td>
<td>Mar 2006 – Mar 2007</td>
<td>inpatients (excluding paediatric)</td>
<td>81(9)/ 80 (9)</td>
<td>49</td>
<td>Diarrhoea and positive test for C. difficile toxin (toxin A/B EIA (Meridian Premier))</td>
<td>inpatients without diarrhoea and no history of CDI</td>
<td>age, sex, ward, ASA score, LOS</td>
<td>conditional logistic regression. Enteral feeding, any antibiotic exposure</td>
<td>medical records; 6 weeks prior to onset</td>
<td>≥ 48 h after admission</td>
<td>97/97</td>
</tr>
<tr>
<td>Thomas 2003¹¹</td>
<td>560 bed tertiary teaching hospital, Perth, Australia</td>
<td>Jan 1996 – Oct 1998</td>
<td>inpatients</td>
<td>72 (15 - 97)²⁰</td>
<td>46</td>
<td>Diarrhoea and positive test for C. difficile toxin (cell culture cytotoxicity or culture)</td>
<td>inpatients without diarrhoea and no history of CDI</td>
<td>age, gender, date</td>
<td>conditional logistic regression. GI procedures, comorbidity, LOS, other antibiotics</td>
<td>medical records; index admission</td>
<td>≥ 48 h after admission (or &lt;48 h if previous admission within 7 days)</td>
<td>149/310</td>
</tr>
</tbody>
</table>
# Results

A total of 569 non-duplicate records were screened for eligibility, 14 met the inclusion criteria, covering 15,958 patients (Figure 1).

## Statistical analyses

- **A pooled random effects meta-analysis** was used to assess the risk associated with antibiotic exposure. The meta-analysis was performed using the DerSimonian-Laird method, which is a random-effects model that takes into account the variability in effect sizes across studies. The DerSimonian-Laird method is generally preferred over the fixed-effects model because it provides a more conservative estimate of the overall effect size. It is particularly useful when there is significant heterogeneity among the studies.

## Screening and data abstraction

The quality of included studies was assessed based on the Newcastle-Ottawa Scale (see Table S1, available as Supplementary data at JAC online). The authors performed a meta-analysis using the DerSimonian-Laird random-effects model. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). The NOS is a tool used to assess the quality of non-randomized studies (such as case-control studies) by considering three broad domains: selection, comparability, and outcome. Each domain is assigned a maximum score of 3, and the overall quality score ranges from 0 to 9. Studies with a score of 6 or more are generally considered to have a lower risk of bias.

## Data extraction

Data were extracted from each included study using a standard form. The form included information on study design, population, interventions, outcomes, and results. The data were then entered into a statistical software program (such as STATA) for analysis. This model is generally preferred over the fixed-effects model because it allows for greater flexibility in the assumptions about the sources of variation in effect sizes across studies. It is particularly useful when there is significant heterogeneity among the studies.
Figure 2. Antibiotic classes and the risk of hospital-acquired CDI.
There were 13 case–control studies and one cohort study (Table 1). Ten studies were conducted in North America, three in Europe and one in Australia, spanning the period 1996–2009; eight studies were conducted after 2002 and three of these were conducted during CDI outbreaks.4,14,15 The studies varied in size from 15 to 1142 cases of CDI. Most studies used hospital inpatients as their study population; four studies used an antibiotic exposed subpopulation.14,16–18 Although studies specifically based on paediatric populations were excluded, one study included patients aged 2 years.20

All studies included symptomatic cases with a positive C. difficile assay. The most common diagnostic test was toxin A/B EIA in six studies.14,16–18,20,21 Definitions of HCF acquisition were 48 h (n = 6)14,15,18,21–23 and >72 h after admission (n = 7).4,16,19,20,24–26 Two studies incorporated previous contact with an HCF in their definition.24,25

Most studies (12/14) used asymptomatic controls. Three studies measured exposure during admission only,17,18,23 while the remainder measured antibiotics received prior to and during the admission (28 days to 3 months). Only two studies evaluated all nine main antibiotic classes of interest.16,25 Ten studies reported various associations for subclasses of penicillins (n = 4),14,19,21,24 cephalosporins (n = 1)22 or both (n = 5).4,16,20,23,25

Study quality was scored high for seven studies14,16,18,22–25 (see Table S2 available as Supplementary data at JAC Online). Studies with low to moderate scores experienced limitations across all three domains. All studies took into account at least some important confounders. Six studies addressed four or more confounders but not for every association examined.4,14,16,22,23,25 The most common confounders assessed were age, sex, length of stay and exposure to other antibiotics. Only five studies considered co-morbidities.4,16,18,22,23 Studies commonly failed to report details of a priori sample size calculations, and six studies either had insufficient power to detect any differences or did not report sufficient information to allow calculation.

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### Pooled effects

Figure 2 presents the pooled effects for exposure to the nine main antibiotic classes from case–control studies using non-diarrhoal
Overall exposure to antibiotics was associated with a 60% (95% CI = 1.31–1.87) increased risk of CDI, but there was a substantial variation between antibiotic classes. The strongest associations were seen for clindamycin (OR = 2.86, 95% CI = 2.04–4.02), cephalosporins (OR = 1.97, 95% CI = 1.21–3.23), carbapenems (1.84, 95% CI = 1.26–2.68), quinolones (fluoroquinolones, OR = 1.66, 95% CI = 1.17–2.35) and trimethoprim/sulphonamides (OR = 1.78, 95% CI = 1.04–3.05). There was no association with aminoglycosides, tetracyclines or macrolides.

There was evidence of heterogeneity in the pooled ORs for all classes except clindamycin ($I^2 = 28.5\%, P = 0.22$), carbapenems ($I^2 = 0.0\%, P = 0.45$) and tetracyclines ($I^2 = 48.5\%, P = 0.14$).

**Stratification by antibiotic subclass**

There was a 50% (95% CI = 1.05–2.24) increased risk of CDI associated with penicillin combination antibiotics but not for other penicillin subgroups (Figure 3). Second-, third- and fourth-, but not first-generation cephalosporins were also associated with two to three times the risk of CDI (Figure 4); however,
heterogeneity persisted, particularly for third-generation cephalosporins ($I^2 = 79.2\%$, $P < 0.001$).

**Meta-regression and sensitivity analyses**

The study population was the most common source of heterogeneity (Table 2), seen for trimethoprim/sulphonamides, third-generation cephalosporins and macrolides. Excluding studies based on antibiotic-exposed inpatients reduced the heterogeneity, except for macrolides, for which further analysis indicated that studies conducted after 2002 or those using antibiotic-exposed participants had ~30% smaller effect sizes than other studies.

The timing of antibiotic exposure measurement was a significant heterogeneity source for fluoroquinolones and aminoglycosides. The risk associated with fluoroquinolones fell from 66% to 39% after excluding one study that measured antibiotic exposure during hospital admission only.

The strongest predictor of heterogeneity for penicillin combinations was the definition of hospital acquisition: there was no significant association when analyses were restricted to 4/6 studies that used a definition of >72 h compared with studies using a definition of >48 h (Table 2).

The choice of diagnostic test was weakly associated with heterogeneity for first-generation cephalosporins, where studies that used toxin EIA tests had smaller effect sizes (OR $= 1.04$, 95% CI $= 0.88–1.24$) than studies using other methods (2.08, 1.37–3.17, $n=2$ studies). For second-generation cephalosporins, there were higher associations for studies conducted after 2002 (4.08, 2.27–7.34).

**Diarrhoea controls**

Three studies included symptomatic patients who tested negative for *C. difficile* as controls. A calculation of crude effect sizes found smaller associations for the toxin-negative than the non-diarrhoeal control group in one study.22 Asha et al.19 reported a 4-fold increased risk associated with ‘broad-spectrum’ cephalosporins (OR $= 3.8$, 95% CI $= 3.0–4.6$). Vesta et al.26 provided descriptive information only and, due to the matched design, precluded the calculation of effect estimates.

**Cohort studies**

One cohort study, consisting of ~8000 adult inpatients exposed to antibiotics and followed up until 60 days post-discharge, was included.18 Independent associations for fluoroquinolones [hazard ratio (HR) $= 4.05$, 95% CI $= 2.75–5.97$], third-/fourth-generation cephalosporins (HR $= 3.12$, 95% CI $= 1.85–5.25$) and trimethoprim/sulphonamides (HR $= 2.03$, 95% CI $= 1.19–3.47$) were reported. Weak associations were observed for clindamycin (HR $= 1.92$, 95% CI $= 0.84–4.40$) and macrolides (HR $= 1.56$, 95% CI $= 0.75–3.25$), and no association was apparent for aminoglycosides (HR $= 0.88$, 95% CI $= 0.26–2.95$).

**Non-English-language studies**

Five out of 27 non-English language studies were eligible for inclusion at abstract screening (Table S3 available as Supplementary data at JAC Online).27–31 Of these, full texts of three articles were available, and two were eligible for inclusion following a full text review. The findings were generally consistent with those of studies published in English, with the strongest associations reported for clindamycin32 and third-generation cephalosporins.

**Publication bias**

For studies reporting results for the main antibiotic classes, the funnel plot (Figure S1 available as Supplementary data at JAC Online) showed little evidence of publication bias. The result of Egger’s test of small-study effects was not significant ($P = 0.57$).

**Discussion**

A systematic review and meta-analysis was undertaken to summarize the evidence for associations between antibiotic classes and the risk of HA-CDI. The findings indicate that third-generation cephalosporins remain the strongest antibiotic risk factor. The modest association seen for fluoroquinolone antibiotics is not surprising as they are more specifically related to *C. difficile* infections with the NAP1/RT027 fluoroquinolone-resistant epidemic strain.22

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**Table 2. Sensitivity analysis to explore heterogeneity**

<table>
<thead>
<tr>
<th>Study subgroup</th>
<th>Exposure</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>OR (95% CI)</th>
<th>Heterogeneity ($I^2$, % (P value))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population: all inpatients</td>
<td>Third-generation cephalosporins</td>
<td>5</td>
<td>1757</td>
<td>4.04 (2.81–5.81)</td>
<td>0.00% (0.72)</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/sulphonamides</td>
<td>4</td>
<td>1283</td>
<td>2.22 (1.53–3.23)</td>
<td>0.00% (0.59)</td>
</tr>
<tr>
<td></td>
<td>Macrolides</td>
<td>6</td>
<td>2378</td>
<td>1.64 (0.91–2.93)</td>
<td>77% (0.001)</td>
</tr>
<tr>
<td>Antibiotic exposure assessment: prior to hospitalization</td>
<td>Fluoroquinolones</td>
<td>9</td>
<td>6335</td>
<td>1.39 (1.09–1.76)</td>
<td>29% (0.19)</td>
</tr>
<tr>
<td>HA-CDI definition &gt;72 h</td>
<td>Aminoglycosides</td>
<td>5</td>
<td>5791</td>
<td>0.89 (0.70–1.14)</td>
<td>0.00% (0.72)</td>
</tr>
<tr>
<td>HA-CDI definition &gt;48 h</td>
<td>Penicillin combinations</td>
<td>4</td>
<td>5635</td>
<td>1.20 (0.99–1.47)</td>
<td>0.00% (0.74)</td>
</tr>
<tr>
<td>Toxicity EIA test</td>
<td>Penicillin combinations</td>
<td>2</td>
<td>659</td>
<td>3.20 (1.75–5.91)</td>
<td>0.00% (0.72)</td>
</tr>
<tr>
<td>Studies conducted post-2002</td>
<td>First-generation cephalosporins</td>
<td>3</td>
<td>4911</td>
<td>1.04 (0.88–1.24)</td>
<td>0.00% (0.90)</td>
</tr>
<tr>
<td>Studies conducted up to 2002</td>
<td>Second-generation cephalosporins</td>
<td>3</td>
<td>892</td>
<td>4.08 (2.27–7.34)</td>
<td>0.00% (0.68)</td>
</tr>
<tr>
<td>Post-2002 and all inpatients</td>
<td>Second-generation cephalosporins</td>
<td>3</td>
<td>5358</td>
<td>1.72 (1.27–2.31)</td>
<td>7.8% (0.34)</td>
</tr>
</tbody>
</table>

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Since our earlier review, the quality of studies has improved, reducing the threat of bias. However, four studies restricted their study populations to inpatients with recent antibiotic exposure, which are not representative of all HA-CDI cases,\textsuperscript{14,16–18} and one study used toxin-negative controls, which do not represent the source population of cases.\textsuperscript{26} Bias relating to diagnostic suspicion remains problematic if those exposed to antibiotics are more likely to be tested for \textit{C. difficile}; guidelines that recommend testing all hospitalized patients who develop diarrhea should be followed.\textsuperscript{33} There was a variation in the definition of HA-CDI, with only a small number of studies including recent contact with HCFs,\textsuperscript{5,23} according to guidelines,\textsuperscript{34} and 27 studies were excluded from the review due to insufficient information regarding the acquisition of CDI.

There is a lack of consensus regarding the appropriate time window to measure antibiotic exposure giving rise to heterogeneity. Recent studies suggest the greatest risk is in the first 30 days but that it remains increased for up to 90 days.\textsuperscript{22,35} Furthermore, the number of antibiotics, dosage and duration of antibiotic exposure have all been previously identified as risk factors for CDI.\textsuperscript{36} Residual confounding remains a potential issue as only a few studies took into account a sufficient number of confounding factors.

This study provides the most up-to-date and systematic synthesis of the literature in relation to the risk of HA-CDI associated with antibiotics. However, the results should be interpreted with caution as the number of studies contributing to any one analysis ranged from three to 10. Our study is limited by the availability of a single reviewer to select, extract and analyse the data. Continued improvements in the conduct of observational studies of CDI would be gained by following recommendations from the STROBE initiative.\textsuperscript{37} The adoption of recently developed guidelines for the diagnosis and surveillance of CDI in future studies will also improve the quality of CDI epidemiological research.

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The study was investigator-driven and was carried out as part of our routine work.

**Transparency declarations**
None to declare.

**Author contributions**
C. S. designed and planned the study, undertook the literature searches, data collection, data analysis, data interpretation and prepared the manuscript. T. V. R. contributed to the design of the study, interpreted the data and contributed to the writing of the manuscript.

**Supplementary data**
The full search strategy, Figure S1 and Tables S1 to S3 are available as Supplementary online-only data at JAC Online (http://jac.oxfordjournals.org/).

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