Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis

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**Objectives:** Despite vigorous infection control measures, *Clostridium difficile* continues to cause significant disease burden. Antibiotic stewardship programmes (ASPs) may prevent *C. difficile* infections by limiting exposure to certain antibiotics. Our objective was to perform a meta-analysis of published studies to assess the effect of ASPs on the risk of *C. difficile* infection in hospitalized adult patients.

**Methods:** Searches of PubMed, Web of Science, Cumulative Index to Nursing and Allied Health Literature and two Cochrane databases were conducted to find all published studies on interventions related to antibiotic stewardship and *C. difficile*. Two investigators independently assessed study eligibility and extracted data. Risk of bias was assessed using the Downs and Black tool. Risk ratios were pooled using random effects models. Heterogeneity was evaluated using the $I^2$ statistic.

**Results:** The final search yielded 891 articles; 78 full articles were reviewed and 16 articles were identified for inclusion. Included articles used quasi-experimental (interrupted time series or before–after) or observational (case–control) study designs. When the results of all studies were pooled in a random effects model, a significant protective effect (pooled risk ratio 0.48; 95% CI: 0.38, 0.62) was observed between ASPs and *C. difficile* incidence.

When stratified by intervention type, a significant effect was found for restrictive ASPs (complete removal of drug or prior approval requirement). Furthermore, ASPs were particularly effective in geriatric settings.

**Conclusions:** Restrictive ASPs can be used to reduce the risk of *C. difficile* infection.

**Keywords:** healthcare-associated infections, antibiotic restriction, geriatrics

**Introduction**

*Clostridium difficile* is an enteric pathogen that may opportunistically colonize the human intestine following antibiotic therapy.1 Severe infections can progress to colonic perforation, sepsis and death. There are ~336,600 cases of *C. difficile* infection (CDI) per year in US hospitals, primarily affecting the elderly, with nearly 1 in 10 CDI stays ending in death.2 The estimated costs associated with *C. difficile* in the USA are ~$8 billion per year.2

Antibiotic exposure nearly always predates CDI.1 Broad-spectrum antibiotics have been particularly implicated, including third-generation cephalosporins, fluoroquinolones and clindamycin.3 Restriction of exposure to certain ‘high-risk’ antibiotics through antibiotic stewardship programmes (ASPs) is a potential method of preventing CDIs. ASPs may include physician education about the risks of certain drugs, prescription review by infectious disease-trained physicians and pharmacists, prior-approval policies for certain antibiotics and/or complete removal of a drug from the pharmacy stock. ASPs have been promoted by national associations around the world, not just for preventing CDIs, but also to slow the emergence of multidrug-resistant pathogens.4–7

Several observational studies have reported that restricting exposure to certain antibiotics can reduce the incidence of CDI, whereas others have reported no effect. This inconsistency may be attributed to differences in patient populations, ASP intervention methods or the drug classes restricted. The aim of this study was to use meta-analysis techniques to assess the effect of ASPs on the risk of CDI in hospitalized adult patients. Furthermore, we aimed to determine whether the patient population, the type of stewardship policy or the classes of antimicrobials targeted for restriction has an effect on the impact of an ASP on CDI. The results of this meta-analysis will provide support for evidence-based recommendations for the further development of guidelines and to guide the implementation of ASPs at hospitals interested in using antibiotic restriction to prevent CDIs.
Methods

Search strategy

This meta-analysis was conducted according to the MOOSE checklist for observational studies. Institutional review board approval was deemed unnecessary for this review of the literature. The systematic literature search was supervised by health science librarians. Searches of PubMed, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) were conducted. No special search software was used. The complete search strategy is available in Table S1 (available as Supplementary data at JAC Online). Briefly, terms related to ‘Clostridium difficile’/C. difficile/pseudomembranous colitis’, ‘antibiotic/antimicrobial’ and ‘restriction/stewardship/guideline/policy’ were used. No date limit was placed on the search. In addition, we reviewed the reference lists of included articles to identify studies that were not found by the primary search strategy. The final search for inclusion in the meta-analysis was completed on 8 August 2013.

The interventions of interest were policy changes and programmes that altered or restricted the use of antibiotics for adult inpatients. The primary outcome of interest was CDI incidence before and after an ASP introduction. The analysis included the following types of observational design: experimental (e.g. randomized trials), quasi-experimental (e.g. interrupted time series and before–after), case–control and cohort studies. No attempt was made to contact authors.

Inclusion and exclusion criteria

Inclusion criteria included reporting of CDI incidence in adult inpatients before and after an ASP was initiated. Exclusion criteria included non-hospital settings, paediatric populations, outbreak situations, lack of primary data, failure to report changes in CDI rates, failure to report incidence risk ratio/OR/Relative risk or insufficient data for a contingency table. The reasons for exclusion can be found in Table S2 (available as Supplementary data at JAC Online).

Selection, abstraction and quality

Reviewers abstracted data regarding study design, population, setting, intervention, antimicrobials and CDI incidence. ASPs were separated into ‘restrictive’ and ‘persuasive’ categories for subset analysis. Restrictive ASPs were defined as interventions that restricted the freedom of prescribers to select some antibiotics (i.e. complete removal from the pharmacy or requirement for prior approval from an infectious disease specialist). Persuasive ASPs aimed at changing prescriber behaviour without active restriction (i.e. education, post-prescription review and recommendations, and changes in guidelines). Titles and abstracts were screened to assess whether they met the inclusion criteria. Two of three independent reviewers (L. M. F., M. L. S. and A. M.) abstracted data from each article. Disagreements were resolved by consensus.

The Downs and Black quality score for observational studies was completed for each article by both reviewers and the two scores were averaged (Tables S3 and S4, available as Supplementary data at JAC Online). Of the 27 original questions, 8 were judged inapplicable to quasi-experimental study designs. We therefore excluded questions 8, 9, 14, 15, 22, 23, 24 and 26 on blinding, time of recruitment and loss to follow-up. Because the majority of included articles were quasi-experimental, two important components of controlling for confounding – randomization and blinding – were not possible, and four of these questions were excluded. Transparency of reporting was assessed by use of the ORION checklist. In general, studies with above-average quality scores were those with higher transparency (Table S4). Thus, only Downs and Black scores were used for stratified analyses.

Statistical analysis

We calculated the natural log of the risk ratio and variance for each study. Both fixed effects and random effects models were used. Pooled risk ratio estimates were constructed using Microsoft Excel 2007 and Cochrane Review Manager (RevMan) version 5.2. To assess heterogeneity we used the $I^2$ statistic, and the results of stratified analyses based on the following a priori categories: study design, population, setting and drug class. Publication bias was assessed by visual inspection of a funnel plot.

Results

Our search yielded a total of 891 non-duplicate potential articles, of which 875 were excluded (Figure 1 and Table S2). Sixteen studies met our inclusion criteria. Fifteen of the studies reported the number of patients, giving a total of 442 873. One additional study gave an incidence risk ratio, but did not report the total number of patients.

Details of the included studies can be found in Table 1. Eight articles reported on restrictive antibiotic stewardship (i.e. removal from formulary, requirement for prior approval), five reported persuasive stewardship policies (i.e. education, post-prescription review or guideline changes) and the methods of three studies were unclear. Furthermore, the ASPs varied in the specific drugs that were targeted for restriction, but common classes for restriction included cephalosporins and fluoroquinolones. Only one study reported changes in the use of clindamycin.

The average quality of the studies was low, as measured by the modified Downs and Black tool. Most studies suffered from poor internal validity, particularly with respect to bias (Figure 2). As a
<table>
<thead>
<tr>
<th>Author year</th>
<th>Study location</th>
<th>Study design; study duration</th>
<th>Study setting</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elligsen 2012</td>
<td>Toronto, Canada</td>
<td>quasi-ITS; 12/12 months</td>
<td>ICU/critical care</td>
<td>post-prescription review and recommendation (persuasive)</td>
<td>SOC</td>
<td>4697</td>
</tr>
<tr>
<td>Fowler 2007</td>
<td>London, UK</td>
<td>quasi-ITS; 21/21 months</td>
<td>geriatric acute care</td>
<td>education and post-prescription review and recommendation (persuasive)</td>
<td>SOC and earlier intervention: cephalosporin restriction</td>
<td>6129</td>
</tr>
<tr>
<td>Frank 1997</td>
<td>Indianapolis, IN, USA</td>
<td>quasi-ITS; 12/12 months</td>
<td>entire hospital</td>
<td>prior approval requirement (restrictive)</td>
<td>SOC</td>
<td>28 055</td>
</tr>
<tr>
<td>Gulihar 2009</td>
<td>Leicester, UK</td>
<td>quasi-ITS, retro case–control; 12/12 months</td>
<td>geriatric surgery, hip fractures only</td>
<td>formulary restriction/change in stocking (restrictive)</td>
<td>SOC and earlier intervention: hand washing and cleaning</td>
<td>1491</td>
</tr>
<tr>
<td>Jones 1997</td>
<td>Bristol, UK</td>
<td>before–after; 9/9 months</td>
<td>only chest infection patients included</td>
<td>‘change in our antimicrobial guidelines to replace cephalosporins’ (unclear)</td>
<td>unclear</td>
<td>1157</td>
</tr>
<tr>
<td>Ludlam 1999</td>
<td>Cambridge, UK</td>
<td>before–after, retro case–control; 12/12 months</td>
<td>geriatric acute care</td>
<td>‘antibiotic policy restricting the use of third-generation injectable cephalosporins’ (unclear)</td>
<td>SOC</td>
<td>4194</td>
</tr>
<tr>
<td>Malani 2013</td>
<td>Ann Arbor, MI, USA</td>
<td>retro cohort; 12/12 months</td>
<td>entire hospital</td>
<td>prior approval requirement (restrictive)</td>
<td>SOC</td>
<td>716</td>
</tr>
<tr>
<td>Miller 2009</td>
<td>Stoke on Trent, UK</td>
<td>before–after; 12/12 months</td>
<td>ICU/critical care</td>
<td>‘introduction of a restrictive antibiotic prescribing policy’ (unclear)</td>
<td>SOC</td>
<td>2132</td>
</tr>
<tr>
<td>O’Connor 2004</td>
<td>Cork, Ireland</td>
<td>before–after, retro cohort; 16/17 months</td>
<td>geriatric acute care</td>
<td>education and policy change (persuasive)</td>
<td>SOC</td>
<td>683</td>
</tr>
<tr>
<td>Price 2010</td>
<td>Brighton, UK</td>
<td>quasi-ITS; 4/4 months</td>
<td>entire hospital</td>
<td>formulary restriction/change in stocking (restrictive)</td>
<td>SOC</td>
<td>200 245</td>
</tr>
<tr>
<td>Reinoso 2002</td>
<td>Madrid, Spain</td>
<td>before–after; 4/4 months</td>
<td>endocrinology, vascular surgery</td>
<td>post-prescription review and recommendation (persuasive)</td>
<td>SOC</td>
<td>680</td>
</tr>
<tr>
<td>Schön 2011</td>
<td>Kalmer, Sweden</td>
<td>before–after, point prevalence survey; 12/15 months</td>
<td>entire hospital × 3</td>
<td>education, change in national guidelines (persuasive)</td>
<td>SOC</td>
<td>76 416</td>
</tr>
<tr>
<td>Starks 2008</td>
<td>Staffordshire, UK</td>
<td>retro case–control; 24/24 months</td>
<td>geriatric surgery, hip fractures only</td>
<td>‘change in antibiotic prophylaxis’ pre-operative protocol (restrictive)</td>
<td>SOC</td>
<td>1811</td>
</tr>
<tr>
<td>Stone 1998</td>
<td>London, UK</td>
<td>before–after; 6/6 months</td>
<td>geriatric acute care</td>
<td>formulary restriction/change in stocking (restrictive)</td>
<td>SOC</td>
<td>2467</td>
</tr>
<tr>
<td>Talpaert 2011</td>
<td>London, UK</td>
<td>quasi-ITS; 12/12 months</td>
<td>medical and surgical wards only</td>
<td>education, formulary restriction/change in stocking and post-prescription review and recommendation (restrictive)</td>
<td>SOC</td>
<td>NR</td>
</tr>
<tr>
<td>Thomas 2002</td>
<td>Perth, Australia</td>
<td>before–after; 12/12 months</td>
<td>entire hospital</td>
<td>formulary restriction/change in stocking and prior approval requirement (restrictive)</td>
<td>SOC</td>
<td>112 000</td>
</tr>
</tbody>
</table>

quasi-ITS, quasi-experimental interrupted time series; ICU, intensive care unit; retro, retrospective; SOC, standard of care; NR, not reported.

aNumber of months in pre-ASP/post-ASP periods of study.
whole, the included studies were particularly poor in matching of
time periods, their description of statistical methods, reporting of
compliance with the intervention and adjustment for confound-
ing. Visual inspection of a funnel plot of the included studies
(Figure 3) did not indicate a strong effect of publication bias.

**Impact on CDI incidence**

Implementation of ASPs had an overall protective benefit (pooled
risk ratio: 0.48; 95% CI: 0.38, 0.62), indicating a risk reduction for
CDI of 52%. However, a large amount of heterogeneity between
studies was apparent, $I^2 = 76\%$ (Figure 4).

The 16 studies were stratified into subgroups based on study
characteristics. The majority of tested subgroups showed signifi-
cant protective effects (Table 2). First, we tested whether the
study quality affected the outcome of the pooled result. Studies
were pooled by quality score above or below the mean (13.6 of
19 possible). Both higher and lower quality studies showed signifi-
cant protective benefit (Table 2); however, the higher quality stud-
ies had low heterogeneity ($I^2 = 0\%$), while the lower quality
studies were more heterogeneous ($I^2 = 84\%$).

Next, we investigated the role of study setting. ASPs were
applied in different hospital settings including the entire hospital
($n = 5$), geriatrics (i.e. acute care wards and hip fracture patients
>65 years old; $n = 6$), intensive care/critical care wards ($n = 2$)
and other patient populations (chest infections and medical/sur-
gical wards; $n = 3$). In two settings – the entire hospital and geri-
atries – ASP introduction had a significant protective impact
(Table 2). The most significant protective effect was among geri-
atries populations, which included four studies of geriatric acute
care wards and two studies of hip fracture surgical patients. For
geriatric patients, institution of an ASP resulted in a 56% reduction
in the risk of CDI, with low heterogeneity (pooled risk ratio: 0.44;
95% CI: 0.35, 0.56; $I^2 = 1\%$).

Then, we subanalysed the method and time period of anti-
biotic restriction. We first separated these into restrictive and per-
suasive policies. The restrictive ASPs had a statistically significant
protective effect (pooled risk ratio: 0.46; 95% CI: 0.38, 0.56; $n = 8$),
while the persuasive ASPs did not (pooled risk ratio: 0.49; 95% CI:
0.24, 1.01; $n = 5$). Restrictive policies instituted in entire hospitals
were beneficial and had low heterogeneity (pooled risk ratio: 0.51;
95% CI: 0.44, 0.59; $I^2 = 0\%$). Additionally, each of the three types
of active policy (complete removal, prior approval, post-
prescription review and recommendations) was found to be

![Figure 2. Downs and Black quality assessment. Averaged results of two independent reviewers. Eight questions from the Downs and Black quality assessment tool were excluded (see the Methods section). The total score possible was 19. The mean score for included studies was 13.6 (broken line).](https://academic.oup.com/jac/article-abstract/69/7/1748/2911036)

![Figure 3. Funnel plot of all included studies. RR, risk ratio.](https://academic.oup.com/jac/article-abstract/69/7/1748/2911036)
Figure 4. Forest plot of all included studies. IV, inverse variance.

Table 2. Subset analyses

<table>
<thead>
<tr>
<th>Study of subgroup</th>
<th>log [Risk ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Risk ratio IV, Random, 95% CI</th>
<th>Risk ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td>0.48 (0.38, 0.62)</td>
<td>💯 100.0% 0.48 [0.38, 0.62]</td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>entire hospital</td>
<td></td>
<td></td>
<td></td>
<td>0.63 (0.42, 0.95)</td>
<td>0.03 88% 0.63 [0.42, 0.95]</td>
</tr>
<tr>
<td>geriatrics</td>
<td></td>
<td></td>
<td></td>
<td>0.44 (0.35, 0.56)</td>
<td>&lt;0.00001 1% 0.44 [0.35, 0.56]</td>
</tr>
<tr>
<td>othera</td>
<td></td>
<td></td>
<td></td>
<td>0.42 (0.25, 0.71)</td>
<td>0.001 66% 0.42 [0.25, 0.71]</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>persuasive</td>
<td></td>
<td></td>
<td></td>
<td>0.49 (0.24, 1.01)</td>
<td>0.05 77% 0.49 [0.24, 1.01]</td>
</tr>
<tr>
<td>restrictive</td>
<td></td>
<td></td>
<td></td>
<td>0.46 (0.38, 0.56)</td>
<td>&lt;0.00001 31% 0.46 [0.38, 0.56]</td>
</tr>
<tr>
<td>restrictive – entire hospitals</td>
<td>0.51 (0.44, 0.59)</td>
<td>&lt;0.00001 1% 0.51 [0.44, 0.59]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>removal from pharmacy</td>
<td>0.46 (0.37, 0.58)</td>
<td>&lt;0.00001 33% 0.46 [0.37, 0.58]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>prior approval</td>
<td></td>
<td></td>
<td></td>
<td>0.50 (0.36, 0.68)</td>
<td>&lt;0.00001 7% 0.50 [0.36, 0.68]</td>
</tr>
<tr>
<td>post-prescription review</td>
<td>0.38 (0.88, 0.67)</td>
<td>0.0007 44% 0.38 [0.88, 0.67]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>higher (&gt;14)</td>
<td></td>
<td></td>
<td></td>
<td>0.49 (0.43, 0.55)</td>
<td>&lt;0.00001 0% 0.49 [0.43, 0.55]</td>
</tr>
<tr>
<td>lower (&lt;14)</td>
<td></td>
<td></td>
<td></td>
<td>0.48 (0.30, 0.76)</td>
<td>0.002 84% 0.48 [0.30, 0.76]</td>
</tr>
<tr>
<td>Drug class</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>cephalosporins</td>
<td></td>
<td></td>
<td></td>
<td>0.50 (0.39, 0.64)</td>
<td>&lt;0.00001 77% 0.50 [0.39, 0.64]</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td>0.45 (0.30, 0.67)</td>
<td>&lt;0.00001 58% 0.45 [0.30, 0.67]</td>
</tr>
<tr>
<td>ASP duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short (&lt;9 months)</td>
<td></td>
<td></td>
<td></td>
<td>0.55 (0.42, 0.73)</td>
<td>&lt;0.00001 42% 0.55 [0.42, 0.73]</td>
</tr>
<tr>
<td>medium (12 months)</td>
<td></td>
<td></td>
<td></td>
<td>0.49 (0.33, 0.73)</td>
<td>0.0004 83% 0.49 [0.33, 0.73]</td>
</tr>
<tr>
<td>long (&gt;16 months)</td>
<td></td>
<td></td>
<td></td>
<td>0.36 (0.23, 0.55)</td>
<td>&lt;0.00001 0% 0.36 [0.23, 0.55]</td>
</tr>
</tbody>
</table>

*Comprising intensive care/critical care (n = 2), medical/surgical wards (n = 1), chest infection (n = 1) and endocrine and vascular surgery patients only (n = 1).
protective (Table 2), although two studies used multiple active interventions, so the individual effect of each intervention could not be determined. The duration of each ASP also affected the magnitude of the effect, with longer studies resulting in a greater protective effect than shorter studies (Table 2).

Last, we tested the impact of restricting different classes of antibiotic. The antibiotics restricted by the ASPs varied between studies. The most common drug classes restricted were cephalosporins (n = 14 studies) and fluoroquinolones (n = 6). As shown in Table 2, the restriction of cephalosporins and the restriction of fluoroquinolones were effective methods of CDI prevention.

Discussion

ASPs effectively decrease the incidence of CDI. This finding was supported by subset analyses for entire hospitals and geriatric services. The greatest benefit was observed for geriatric patients, which is not surprising given that the majority of CDI cases occur among elderly populations. Furthermore, restrictive policies that modified physician prescription practices were more effective than persuasive policies.

Recent research has shown that CDI cases present a significant economic burden. Thus, restrictive ASPs would probably result in significant savings for hospitals, insurers and society. In addition, several studies reported significant savings in antibiotic expenses associated with ASPs.

Meta-analyses are only as valid as the studies that contribute to the pooled risk ratio. Most of the included studies were observational quasi-experimental studies. This study design is subject to many biases and can suffer from lower internal validity. Future studies should use designs with higher internal validity, either by using a cluster-randomized design or by the addition of non-equivalent control groups and multiple measurements.

Another limitation is high heterogeneity. Much of the heterogeneity resolved with stratified analysis, particularly for higher quality studies, geriatric populations and restrictive stewardship policies applied to entire hospitals. High heterogeneity indicates that the observed finding may be due to differences in study characteristics rather than an effect of the intervention. However, the fact that stratified analyses decreased heterogeneity adds reassurance to our finding of the protective impact of ASPs on CDI. Alternative explanations for our findings are also plausible, such as increased healthcare worker awareness about CDI and/or improved infection prevention precautions such as hand hygiene compliance. However, this explanation is not likely because our analysis showed active policies were more effective than policies aimed solely at increased awareness and education.

Further limitations of this meta-analysis include the lengthy timeframe and geographical distribution. Since 2002, the incidence and virulence of C. difficile has increased, particularly with the emergence of the NAP1 strain. Pooling studies that were published as early as 1998 with current studies may contribute to heterogeneity between studies. Lastly, the majority of the included studies were conducted in the UK. This limits the generalizability of this meta-analysis, particularly to North America, where more virulent strains of C. difficile are prevalent. Thus, given the apparent benefit of ASPs on reducing CDI, further research and implementation of active ASPs is needed in North America.

In conclusion, the current evidence supports implementing ASPs that actively modify prescription behaviour for high-risk antimicrobials (cephalosporins and fluoroquinolones) as an effective method for decreasing C. difficile incidence rates.

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Transparency declarations

None to declare.

The VA Office of Research and Development had no role in the design and conduct of the study.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Supplementary data

Tables S1 to S4 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References
