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Objectives: Making valid comparisons of antimicrobial utilization between hospitals requires risk adjustment for each hospital’s case mix. Data on individual patients may be unavailable or difficult to process. Therefore, risk adjustment for antimicrobial usage frequently needs to be based on a hospital’s services. This study evaluated such a strategy for hospital antimicrobial utilization.

Methods: Data were obtained on five broad subclasses of antibiotics [carbapenems, β-lactam/β-lactamase inhibitor combinations (BLBLIs), fluoroquinolones, glycopeptides and third-generation cephalosporins] from the Queensland pharmacy database (MedTrx) for 21 acute public hospitals (2006–11). Eleven clinical services and a variable for hospitals from the tropical region were employed for risk adjustment. Multivariable regression models were used to identify risk and protective services for these antibiotics. Funnel plots were used to display hospitals’ antimicrobial utilization.

Results: Total inpatient antibiotic utilization for these antibiotics increased from 130.6 defined daily doses (DDDs)/1000 patient-days in 2006 to 155.8 DDDs/1000 patient-days in 2011 (P<0.0001). Except for third-generation cephalosporins, the average utilization rate was higher for intensive care, renal/nephrology, cardiac, burns/plastic surgery, neurosurgery, transplant and acute spinal services than for the respective reference group (no service). In addition, oncology, high-activity infectious disease and coronary care services were associated with higher utilization of carbapenems, BLBLIs and glycopeptides.

Conclusions: Our model predicted antimicrobial utilization rates by hospital services. The funnel plots displayed hospital utilization data after adjustment for variation among the hospitals. However, the methodology needs to be validated in other populations, ideally using a larger group of hospitals.

Keywords: antibiotic use, benchmarking, hospital services

Introduction

The choice of antimicrobials in hospitals is usually governed by formal guidelines and protocols. There is often variation in utilization within and between institutions that results from the specific patient case mix, geographical variation among certain organism strains, and individual prescribing practices that may include failure to implement guidelines correctly.

Antimicrobial use that deviates from published guidelines remains a primary and potentially preventable initiating factor in the emergence and spread of antibiotic-resistant organisms, including Clostridium difficile.

Monitoring antimicrobial consumption is an approach used to encourage compliance with antimicrobial guidelines. Because hospital services and case mix vary, risk adjustment is necessary to ensure such monitoring is unbiased. In addition, infection transmission and the varying microbiological environments in hospitals can result in clustering and breakdown of independence, resulting in heightened variation. Thus, in order to analyse aggregated among-institution antimicrobial utilization data, it is necessary to use methods suitable for the analysis of data that are highly variable (over-dispersed). This over-dispersion may involve both hospitals and the services they provide. It needs to be accommodated both in risk adjustment based on a hospital’s services that depend on the characteristics of its patient population, and also for among-hospital comparisons.

It is important that antibiotic utilization is measured in a standardized manner, e.g. using state-wide data aggregated at a hospital
level. The availability of these data in Queensland makes it possible to measure, track and provide feedback on antimicrobial use.

Methods

Study design

The study was an observational, retrospective analysis of antimicrobial use among 21 public Queensland Health (QH) facilities. These hospitals were large (tertiary teaching and referral hospitals) to medium (general hospitals) in size. Table 1 shows the range of clinical services for each hospital.

Data source

Within Queensland public hospitals, drug transactions are captured in the MedTrx database system. This receives data from the QH Pharmacy Information System (iPharmacy) introduced in 2005. All prescribing and distribution information and in and out of pharmacies in all QH facilities is recorded in iPharmacy. Antimicrobial transactions are extracted from iPharmacy into the MedTrx system and converted into defined daily doses (DDDs) using the WHO Anatomical Therapeutic Chemical (ATC)/DDD classification system.3 This system allows standardization of drug groupings and provides accurate quantitative data to enable comparison of drug use among hospitals.

Antimicrobial utilization data were obtained from 2006 to 2011 for the 21 participating hospitals. We used the following groups of antibiotics available on the QH list of approved medicines as outcome variables:

(i) Carbapenems: meropenem, doripenem, ertapenem and imipenem with enzyme inhibitor
(ii) β-Lactam/β-lactamase inhibitor combinations (BLBLIs): ticarcillin with clavulanate and piperacillin with tazobactam
(iii) Fluoroquinolones: ciprofloxacin, moxifloxacin and norfloxacin
(iv) Glycopeptide antibacterials: vancomycin and teicoplanin (liquid oral preparations are excluded) and
(v) Third-generation cephalosporins: cefixime, cefotaxime, ceftazidime and ceftriaxone.

Fractional accrued patient-days obtained from the QH statistics centre were used as the denominator data in order to estimate usage rates. These are the total number of days that inpatients spent in hospital during the reported time period, measured in daily and hourly increments. Antimicrobial utilization was expressed as the number of DDDs/1000 patient-days.

Clinical services and geographical data for each hospital were used as explanatory variables. Clinical service data were extracted from the QH Clinical Services Capability Framework, Health Statistics Centre and hospital web pages. Three clinical services (intensive care, oncology and infectious disease services) were classified into three groups (no service, small/medium-level service and high-level service) based on the number of episodes of care from the specific unit of service. The remaining variables were classified into two groups (no service, dedicated wards/units) based on whether hospitals had dedicated wards or units, as shown in Table 1. The additional variable derived for hospitals in the tropical northern region of Queensland (Cairns, Townsville, Mount Isa and Mackay) was based on expert microbiology advice from infectious diseases physicians regarding the unique bacterial flora present in the tropical environment.

Statistical analysis

Stata Version 11.0 (Stata Corporation, College Station, TX, USA) and R software (R Development Core Team, 2012) were used. The methodology for this analysis was based on a previous report by Tong et al.4 Descriptive analyses were performed for each antimicrobial agent and for all explanatory factors. We used generalized estimating equation (GEE) negative binomial regression models to identify risk and protective

Table 1. Clinical services and details of level of service for each hospital

<table>
<thead>
<tr>
<th>Hospital ID</th>
<th>Intensive care</th>
<th>Coronary care</th>
<th>Oncology</th>
<th>Infectious disease</th>
<th>Renal/nephrology</th>
<th>Cardiac surgery</th>
<th>Burns/plastic surgery</th>
<th>Neurosurgery</th>
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<sup>a</sup>0, no service; 1, small/medium-level service; 2, high-level service.

<sup>b</sup>0, no service; 1*, dedicated wards/units.
services for the outcome variables because of the marked variability of antimicrobial use. This model is appropriate for rates that show moderate to high variability collected from the same institutions over time.

Results for these models are reported using a rate ratio and 95% CI for each level of each factor. Predicted values were obtained for each hospital – antibiotic combination.

Funnel plots were used to present hospital aggregated data incorporating predicted values from the models. Because among-institution over-dispersion remained after regression analysis, a correction described by Mohammed and Laney was employed together with winsorizing, as described by Spiegelhalter. The results for individual hospitals can be evaluated in relation to the average of the risk-adjusted values. The observed-to-expected (O/E) ratio was used for displaying each hospital’s outcomes. A ratio >1.0 indicated higher than expected usage and if any point fell outside the upper two standard deviation (SD) control limit then there was statistical evidence that the hospital may have had higher than expected usage compared with the risk-adjusted average usage of all the hospitals.

Technical details of the regression, funnel plot and winsorizing methods are available as Supplementary data, available at JAC Online.

Results

Descriptive analysis

The total rate of inpatient utilization of the five antimicrobial groups for the 21 participating hospitals in 2006 was 130.6 DDDs/1000 patient-days and in 2011 it was 155.8 DDDs/1000 patient-days, an increase of 16%. The rate increased steadily between 2006 and 2011 for all antimicrobial groups except fluoroquinolones (Table 2).

Table 3 shows that, with the exception of third-generation cephalosporins, the average rate of antimicrobial usage was higher for intensive care services, renal/nephrology, cardiac, burns/plastic surgery, neurosurgery, transplant and acute spinal services than the respective reference group (no service). Third-generation cephalosporin utilization was higher in non-specialized clinical services. In addition, the mean rate of use of carbapenems, BLBLIs and glycopeptides was higher in oncology, infectious diseases and coronary care, and higher utilization was observed in tropical Queensland for fluoroquinolones.

Regression analysis

The results of the regression models for usage of the 2006–10 data for all five antimicrobial groups are shown in Table 4. The use of carbapenems, BLBLIs, glycopeptides and third-generation cephalosporins increased by 14%, 7%, 11% and 7% per year from 2006 to 2010, respectively. In addition, hospitals with high-level infectious disease and solid organ transplantation services had increased use of carbapenems; those with high-level infectious disease services also had increased use of BLBLIs. The hospital with acute spinal services was associated with less frequent use of carbapenems, fluoroquinolones and third-generation cephalosporins. Hospitals with intensive care services (level 1 and level 2) were associated with high usage of glycopeptide antibiotics whereas hospitals with cardiac services and those from the tropical north were associated with higher usage of fluoroquinolones. High-level oncology services were associated with lower usage of third-generation cephalosporins.

The goodness-of-fit statistics indicated that the models fit the data adequately for carbapenems, BLBLIs, fluoroquinolones and glycopeptides. They could therefore be used for generating expected rates of antibiotic use so that valid hospital risk-adjusted comparisons could be made. For third-generation cephalosporins, the goodness-of-fit measures of the validation sample indicated a model that fit the data adequately; however, goodness of fit for the development model was less satisfactory, hence expected rates would be determined with less assurance for this outcome.

Hospital usage displays

To illustrate how the model can be used to facilitate valid comparison of the data for multiple hospitals, further analysis was conducted on all five antimicrobial groups with the O/E ratios displayed in funnel plots. As we have indicated, the plots required modification to deal with remaining among-hospital over-dispersion using the methods described by Mohammed and Laney and Spiegelhalter. They are summarized in the Supplementary data, available at JAC Online. Figure 1 shows the funnel plot for each antimicrobial group after modification for over-dispersion. Hospitals with rates outside the funnel plot’s modified 2 SD control limits are considered to be potential outliers; they have increased antimicrobial usage and therefore require further investigation (e.g. hospitals A and D in Figure 1 for carbapenem usage).

Discussion

Risk adjustment of antimicrobial utilization is an emerging field, and methods are being developed based on the hospital services, indices of patient severity or combinations of both. Also,

Table 2. Yearly and summary statistics of inpatient antimicrobial utilization rate (number of DDDs/1000 patient-days) for each antimicrobial group and total usage

<table>
<thead>
<tr>
<th>Year</th>
<th>Carbapenems</th>
<th>BLBLIs</th>
<th>Fluoroquinolones</th>
<th>Glycopeptide antibacterials</th>
<th>Third-generation cephalosporins</th>
<th>Total use</th>
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<tbody>
<tr>
<td>2006</td>
<td>9.6</td>
<td>28</td>
<td>40.6</td>
<td>18.9</td>
<td>33.5</td>
<td>130.6</td>
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<tr>
<td>2007</td>
<td>10.4</td>
<td>29.4</td>
<td>38.5</td>
<td>18</td>
<td>40.9</td>
<td>137.2</td>
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<tr>
<td>2008</td>
<td>12</td>
<td>32.7</td>
<td>39.5</td>
<td>19.9</td>
<td>43.8</td>
<td>147.9</td>
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<tr>
<td>2009</td>
<td>13.5</td>
<td>34.4</td>
<td>37.1</td>
<td>22.2</td>
<td>41.9</td>
<td>149.1</td>
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<tr>
<td>2010</td>
<td>14.7</td>
<td>34.7</td>
<td>38.5</td>
<td>22.2</td>
<td>40.2</td>
<td>150.3</td>
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<tr>
<td>2011</td>
<td>16.1</td>
<td>37.4</td>
<td>37.5</td>
<td>22.3</td>
<td>42.4</td>
<td>155.8</td>
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<tr>
<td>Mean</td>
<td>8.76</td>
<td>26.25</td>
<td>35.95</td>
<td>14.92</td>
<td>52.85</td>
<td>138.7</td>
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<tr>
<td>Variance</td>
<td>73.02</td>
<td>143.04</td>
<td>261.80</td>
<td>84.47</td>
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</table>
although DDDs and patient-days are employed here, days of therapy and length of therapy are alternative measures.\textsuperscript{11,12} We used negative binomial regression to model the data, owing to substantial over-dispersion. The validation results and goodness of fit indicated, with the possible exception of third-generation cephalosporins, that the model was a good fit for the data. Hence, expected rates could be determined and used for presenting the observed and expected usage for each hospital. However, substantial over-dispersion remained after regression analysis, and unadjusted prediction limits were therefore

\begin{table}[htb]
\centering
\caption{Average yearly rate (DDDs/1000 bed-days) of usage of each antibiotic by clinical services in 21 CHRISP participating hospitals in Queensland, 2006–11} 
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Medical services/levels & Carbapenems, mean (95\% CI) & BLBLIs, mean (95\% CI) & Fluoroquinolones, mean (95\% CI) & Glycopeptides, mean (95\% CI) & Third-generation cephalosporins, mean (95\% CI) \\
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\hline
Intensive care services
\textit{no services} & 1.8 (1.2–2.4) & 12.2 (10.4–14.0) & 22.2 (17.5–26.9) & 5.2 (4.2–6.2) & 67.3 (46.9–87.7)
\textit{small/medium level} & 7 (6.2–7.8) & 25.8 (24.1–27.5) & 35.2 (32.6–37.8) & 12.7 (11.5–13.8) & 56.9 (47.9–61.9)
\textit{highest level} & 18.5 (14.3–22.8) & 38.6 (34.1–43) & 48.8 (41.7–55.9) & 28.1 (25.0–31.2) & 36.3 (30.1–42.5)

\hline
Coronary care services
\textit{no service} & 5 (3.9–6.0) & 21.7 (18.9–24.5) & 33.3 (29.7–36.8) & 9.8 (8.1–11.6) & 71.6 (58.7–84.4)
\textit{dedicated wards/units} & 11.1 (8.9–13.3) & 29.1 (26.3–31.8) & 37.6 (33.6–41.6) & 18.0 (15.8–20.3) & 41.3 (37.5–45.1)

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Oncology services
\textit{no service} & 4.5 (3.5–5.4) & 20 (17.6–22.4) & 31.5 (27.9–35.1) & 9.4 (7.7–11.1) & 71.9 (60.6–83.3)
\textit{small/medium level} & 11.1 (7.8–14.4) & 26.3 (23.5–29) & 41.2 (34.7–47.8) & 16.9 (14.5–19.3) & 44.7 (40.2–49.2)
\textit{highest level} & 13.2 (10.4–16.1) & 37.8 (33.2–41.9) & 36.6 (33.4–39.7) & 22.1 (18–26.2) & 29.9 (26.4–33.3)

\hline
Infectious diseases services
\textit{no services/ambulatory} & 7.3 (5.8–8.9) & 23.4 (21.5–25.3) & 36.1 (32.6–39.6) & 12.4 (10.9–13.9) & 58.8 (51.9–65.7)
\textit{medium level} & 7.9 (6.1–9.8) & 26.4 (23.3–29.5) & 31.8 (29.7–34.0) & 15.9 (14.1–17.8) & 31.9 (30.2–33.7)
\textit{highest level} & 21.6 (18.9–24.3) & 50.5 (46.9–53.9) & 38.9 (36.0–41.9) & 35.3 (32.9–37.6) & 23.3 (20.4–26.1)

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Renal/nephrology services
\textit{no service} & 7.2 (5.5–8.9) & 22.2 (20.4–23.9) & 32.4 (29.7–35.0) & 11.6 (10.3–13.0) & 59.4 (52.1–66.7)
\textit{dedicated wards/units} & 13.8 (11.1–16.5) & 39.4 (35.1–43.6) & 47.4 (40.2–54.6) & 25.5 (21.8–29.2) & 32.0 (28.6–35.4)

\hline
Cardiac surgery services
\textit{no service} & 6.5 (5.5–7.4) & 23.9 (21.9–25.8) & 32.1 (29.8–34.4) & 12.3 (10.9–13.7) & 54.8 (48.1–61.5)
\textit{dedicated wards/units} & 22.5 (16.7–28.3) & 40.4 (35.0–45.9) & 59.0 (50.1–68.0) & 30.8 (28.1–33.6) & 41.1 (31.3–50.9)

\hline
Burns/plastic surgery services
\textit{no service} & 7.1 (5.4–8.9) & 21.7 (19.9–23.5) & 32.8 (30.0–35.6) & 11.5 (10.0–12.9) & 61.6 (54.1–69.2)
\textit{dedicated wards/units} & 12.8 (10.5–15.2) & 37.7 (33.8–41.6) & 43.8 (37.2–50.4) & 23.5 (20–26.9) & 31 (27.8–34.2)

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Neurosurgery services
\textit{no service} & 7.5 (5.9–9.1) & 22.7 (21.0–24.5) & 33.0 (30.5–35.6) & 11.8 (10.5–13.1) & 58.5 (51.6–65.5)
\textit{dedicated wards/units} & 14.3 (10.9–17.6) & 41.2 (36.2–46.1) & 48.4 (39.6–57.2) & 28.3 (24.6–32.1) & 28.6 (25.7–31.6)

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Transplant services
\textit{no service} & 6.6 (5.7–7.5) & 24.7 (22.7–26.7) & 34.8 (31.8–37.9) & 13.1 (11.6–14.6) & 53.9 (47.5–60.3)
\textit{dedicated wards/units} & 29.4 (24.3–34.5) & 40.7 (32.6–48.9) & 46.4 (42.6–50.3) & 32.1 (28.3–35.8) & 43.1 (28.5–57.7)

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Acute spinal
\textit{no service} & 8.0 (6.6–9.5) & 24.9 (23.0–26.8) & 35.6 (32.7–38.6) & 13.8 (12.3–15.4) & 54.5 (48.4–60.7)
\textit{dedicated wards/units} & 23.3 (18.6–27.9) & 53.4 (47.8–58.9) & 42.2 (38.8–45.6) & 37.0 (33.3–40.8) & 19.2 (16.8–21.6)

\hline
Hospice care
\textit{no service} & 7.9 (6.2–9.7) & 25.7 (22.4–29.0) & 33.9 (31.0–36.8) & 14.4 (11.8–17.1) & 55.6 (46.1–65)
\textit{dedicated wards/units} & 9.4 (7.2–12.5) & 26.9 (24.8–29.1) & 38.7 (33.3–44.0) & 15.6 (13.6–17.6) & 49.2 (43.2–55.2)

\hline
Tropical regions
\textit{no} & 8.8 (6.9–10.7) & 25.9 (23.4–28.3) & 31.6 (29.2–33.9) & 14.2 (12.3–16.2) & 50.6 (44.1–57.2)
\textit{yes} & 8.5 (7.1–9.9) & 27.9 (23.9–31.9) & 54.6 (47.1–62.1) & 17.9 (14.5–21.3) & 62.3 (48.0–76.6)

\hline
\end{tabular}
\end{table}
unsuitable for obtaining funnel plot control limits for these antibiotic usage data.

This over-dispersion is possibly due to the changing bacterial populations within and between the hospitals, and the breakdown in independence due to bacterial transmission. In addition, there are factors that may influence antimicrobial prescribing that cannot be attributed to case mix. For example, there is anecdotal evidence that overseas-trained doctors in the Queensland Public Health System continue to prescribe according to usual practice in their country of origin and do not rigorously adhere to local prescribing guidelines. There is considerable variation in the services provided, particularly among the tertiary referral and larger general hospitals. Also, there is variability in the level of specialist infectious disease and microbiology support provided to regional hospitals, which can result in different prescribing practices. MacDougall and Polk found that variables (bed numbers and hospital characteristics) previously recommended for risk adjustment in benchmarking rates of antimicrobial use in among-hospital comparisons were weak predictors of rates of antibacterial use after normalization for total number of patient-days. It was therefore necessary in our study to use additional measures for dealing with over-dispersion.

A number of options for handling this over-dispersion have been suggested by Spiegelhalter and Mohammed and Laney, and z-score and winsorizing options were used in creating the funnel plots shown in Figure 1. The results of our study do not provide definitive evidence of inappropriate overuse of antimicrobials in hospitals. These data should be used as part of a broader antimicrobial stewardship programme to monitor antimicrobial utilization. The identification of outliers, as such as seen in Figure 1, should be used only to identify institutions requiring further investigation. As Mohammed et al. have indicated, outlier status does not prove poor compliance, and their outline for performing further analysis should be followed. Conversely, if a hospital is not an outlier for a particular drug it should not be interpreted as problem free. This methodology should be considered as a signal for further investigation using more specific methods such as audits and point prevalence surveys.

The study has some limitations. First, we restricted it to the 21 medium to large acute public hospitals in Queensland, with each hospital contributing only five yearly data points for a total of 105 observations in the analysis. We believe this approach was justified as these 21 hospitals contribute ~80% of the hospital activity in the Queensland Public Health System. We compensated for the limited sample size by employing the bootstrap method to estimate standard errors and a stringent criterion for ultimate inclusion of predictor variables in the models. Second, we did not use individual patient-level case-mix data to perform the risk adjustment. To obtain such patient-level data would be time-consuming and resource intensive. Our method provides a convenient approach to risk adjustment with readily available data. Third, we did not evaluate every clinical service provided in each hospital in our model. We included only those services where there is a large patient throughput and heavy use of antimicrobials. There may be additional services across hospitals, such as orthopaedic services, that could influence antimicrobial utilization.

Our results are not directly comparable to other studies that benchmark antimicrobial use with case mix, owing to methodological differences in the choice of parameters for risk-adjustment models. Kuster et al. defined a case-mix index using the cost weights of diagnostically related groups, whereas Kanerva et al. used individual patient risk factors to rank hospital

### Table 4. Rate ratios of all five antimicrobial usage groups for services provided by 21 public hospitals in Queensland, Australia

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Significant medical services</th>
<th>GEE negative binomial with a log link and AR(1) correlation structure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>incident ratio</td>
</tr>
<tr>
<td>Carbapenem usage</td>
<td>transplant (dedicated service)</td>
<td>6.17</td>
</tr>
<tr>
<td></td>
<td>acute spinal (dedicated service)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>infectious disease (high level)</td>
<td>3.70</td>
</tr>
<tr>
<td></td>
<td>year</td>
<td>1.14</td>
</tr>
<tr>
<td>BLB/L usage</td>
<td>infectious disease (high level)</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td>year</td>
<td>1.07</td>
</tr>
<tr>
<td>Fluoroquinolone usage</td>
<td>tropical region (yes)</td>
<td>1.58</td>
</tr>
<tr>
<td></td>
<td>cardiac services (dedicated service)</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>acute spinal (dedicated service)</td>
<td>0.84</td>
</tr>
<tr>
<td>Glycopeptide usage</td>
<td>intensive care service level 1 (small/medium-level service)</td>
<td>2.42</td>
</tr>
<tr>
<td></td>
<td>intensive care service level 2 (high-level service)</td>
<td>5.75</td>
</tr>
<tr>
<td></td>
<td>year</td>
<td>1.11</td>
</tr>
<tr>
<td>Third-generation cephalosporin usage</td>
<td>oncology (high level)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>acute spinal</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>year</td>
<td>1.07</td>
</tr>
</tbody>
</table>

*a* Compared with the reference group ‘no service’.
antimicrobial use. Future research into meaningful comparisons of antimicrobial utilization among institutions within and between jurisdictions should only be undertaken when there are consistent definitions and indices of case mix.

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Transparency declarations
None to declare.

Supplementary data
Technical details of the regression, funnel plot and winsorizing methods are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References