Development of standardized methods for analysis of changes in antibacterial use in hospitals from 18 European countries: the European Surveillance of Antimicrobial Consumption (ESAC) longitudinal survey, 2000–06

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Objectives: Our objective was to develop and test standardized methods for collection and statistical analysis of longitudinal data on hospital antibacterial use from different countries.

Methods: We collected data on monthly supply of antibiotics from pharmacies in one hospital from each of 18 European countries. We applied a standardized method to classify drugs, measure use in defined daily doses and compare the effect of using occupied bed-days (OBDs) or admissions as denominators for longitudinal analysis.

Results: Antibiotic use increased in 14 (78%) hospitals and decreased in 4 hospitals. For 16 (89%) hospitals, adjustment of antibiotic use with OBDs resulted in larger changes over time than adjustment with admissions. Inclusion of all hospital clinical activity variables (admissions, length of stay and OBDs) in multivariate time series analysis identified distinct hospital groups. Nine (50%) hospitals had statistically significant changes in antibiotic use (six increasing and three decreasing) that were not explained (n=3) or only partially explained (n=6) by change in clinical activity. Three (17%) hospitals had no significant change in antibiotic use. In the remaining six hospitals, apparent changes in antibiotic use were largely explained by changes in clinical activity.

Conclusions: This is the first study to use a standardized method for data collection and longitudinal analysis of antibiotic use in different hospitals. These data suggest that determination of changes in antibiotic exposure of hospital patients over a period of time is unreliable if only one clinical activity variable (such as OBDs) is used as the denominator. We recommend inclusion of admissions, OBDs and length of stay in statistical, time series analysis of antibiotic use. This model is also relevant to longitudinal analysis of infections in hospitals.

Keywords: antibiotics, drug utilization, statistics, time series analysis

Introduction

The European Surveillance of Antimicrobial Consumption (ESAC) was established in 2000. In the first phase of the ESAC project, data collection was limited to national sources of information about antibacterial use. Data on antibacterial use in ambulatory care were available from 26 countries, whereas only 15 countries could provide data on hospital antibacterial use. Moreover, the data did not include reliable information about the number of occupied bed-days (OBDs) or admissions for the hospitals, so the results were expressed as defined daily doses (DDDs) per 1000 inhabitants. This is a reasonable measure of antibacterial use at the regional level, but does not provide useful information for comparison of hospitals. In the second phase of the ESAC project, from 2004 to 2007, a hospital subproject was established to collect more detailed information from individual hospitals through longitudinal analysis of antibacterial consumption and point prevalence survey. The results of the first European point prevalence survey have been published.

Reports on hospital antibiotic use have lacked detail about definitions of the units of measurement, which makes it difficult to compare results between hospitals or countries. Longitudinal
studies with well-defined units of measurement have been published from multiple hospitals within the Netherlands\(^5\) and Germany.\(^6\) Both of these studies compared adjustment of antibiotic use for clinical activity with admissions versus OBDs and reported that total systemic antibacterial use increased when measured as DDDs per 100 patient-days, whereas it remained constant when expressed in DDDs per 100 admissions. A possible explanation is that these hospitals had increasing numbers of admissions with shorter length of hospital stay (LOS) over time.\(^4\)–\(^6\) However, it is not clear whether these results can be generalized to other countries. The aim of the ESAC longitudinal survey was to develop and test standardized methods for collection and statistical analysis of longitudinal data on hospital antibacterial use from different countries. We had two research questions. First, what is the change in hospital antibiotic use in the participating hospitals over the study period? Second, what effect do different denominators (OBDs or admissions) have on longitudinal analysis of hospital antibiotic use?

**Methods**

ESAC national representatives were invited to participate in the study and recruit one hospital to the longitudinal survey. One hospital was selected from 18 countries (Austria, Belgium, Croatia, the Czech Republic, Denmark, England, Estonia, Finland, France, Greece, Latvia, the Netherlands, Norway, Scotland, Slovenia, Sweden, Turkey and Wales). With the exception of Turkey and Wales, the same hospitals also participated in the ESAC point prevalence study in June 2006.\(^3\) Participants were asked to send data samples, and to attend a workshop for discussion of the pilot data samples and for agreement on uniform databases, which was organized in January 2006. Data were submitted during February to June 2006. We asked hospitals to provide monthly data for 6 years, starting from January 2000 until December 2005; 15 hospitals provided 6 years of data, 1 hospital provided 5 years of data and 2 hospitals provided 4 years of data. According to the project protocol, we collected total antibacterials dispensed only to inpatient destinations and clinical activity (OBDs or patient-days, and admissions) data for all inpatient destinations. Hospitals were not requested to separate their data by clinical groups and specialties, because it was not possible for many participants and these data were not required to answer the study question.

The study only used aggregated data on consumption of antibiotics from hospital pharmacies and did not require approval from a research ethics committee.

**Measurement of drug use**

The study focused on systemic antibacterials in the J01 subclass according to Anatomical Therapeutic Chemical (ATC) classification by the WHO Collaborating Centre for Drug Statistics Methodology plus oral metronidazole, oral vancomycin and colistin.\(^7,8\) There were three minimum database requirements: first, a list of all drugs, preferably by generic name and translated into English; second, a dosage form with complete information on the strength, package and route of administration; and, third, identification of antibacterials that were dispensed to inpatient destinations. The amounts of each product were converted into WHO DDDs at the Health Informatics Centre in Dundee. DDDs were those that were current when processing of the data began in 2006.\(^7,8\)

**Adjustment of drug use for clinical activity**

Clinical activity data included all inpatients and excluded outpatients or day cases. The project compared two denominators; OBDs and admissions. Participants sent their monthly bed-days (daily census of the number of occupied beds at a specified time) or patient-days (duration of stay minus 1 day to count the day of admission and the day of discharge as 1 OBD) and admissions (excluding transfers between wards and clinical groups).

**Statistical analysis**

**Trends of use and clinical activity**

We used a stock adjustment process to estimate two additional clinical activity variables (number of discharges and LOS) from the data on admissions and OBDs. A stock adjustment process is an accounting mechanism that shows how a certain stock accumulates over time, given its net flow over time. Further explanation and the equation used are provided in the Supplementary data (available at JAC Online).

For two hospitals, we could obtain the actual LOS for the study period to compare each of two datasets with estimated values. There was no statistically significant difference between actual and estimated values.

The level of antibacterial use and clinical activity variables differed widely across the hospitals. We needed a method to compare the change over time between similar variables and between different variables for each of the hospitals. Simple comparison of the slopes of regression lines was misleading. For example, a slope of 0.5 DDDs per 100 OBDs (DDDs)/month for a hospital with average or baseline use of 200 DDDs is a change of 0.25% per month. In contrast, the same slope for a hospital with 50 DDDs is a 1% change. Consequently, the slope of the regression line did not distinguish between a hospital with a higher level of baseline use but shallower slope versus a hospital with lower use but steeper slope. Therefore, the result was the product of the intercept (baseline) values and the gradient of the slope (trend). In order to compare the change in each variable over time, we scaled the slopes with their intercepts to produce the mean annual change using the following formula:

\[
\% \Delta \text{Variable} = (\text{slope} \times 12)/\text{intercept} \times 100
\]

For each hospital, we calculated the mean annual change with 95% confidence intervals (CIs). Changes were considered significant if the 95% CIs for the percentage difference did not cross zero.

**Time series and dynamic regression analysis**

For each hospital, we investigated the extent to which the change in clinical activity explained the change in antibacterial use. Moreover, we assessed whether there was an inherent predictable component of antibiotic use due to exogenous trends and seasonal fluctuations not captured by clinical activity variables, and compared the results across the hospitals. We used regression analysis with DDDs as the dependent variable to construct a dynamic regression model (Supplementary data, available at JAC Online) with autoregressive moving average, in order to analyse the temporal behaviour of antibiotic use (DDDs) as a function of its previous values, its trends and its abrupt changes in the near past. Dynamic regression analysis is a form of multivariate analysis that is used to examine the relationship among two or more time series.\(^9\)

We used standard time series regression methods\(^10,11\) to identify the best-fitted model for each of the hospitals and restricted the number of variables to include only those that contributed to the model for each hospital.

We used Eviews version 6 for analysis of time series.

**Interpretation of results**

From a public health perspective, the key question is ‘is there evidence that the exposure of patients to antibiotics in this hospital may have
increased or decreased over time? The term ‘exposure of patients to antibiotics’ encompasses any or all of the factors ‘number of patients treated’, ‘unit doses administered’ or ‘duration of treatment’, because they could all influence the measure of antibiotic use (DDDs). We separated the hospitals into five groups based on the likelihood that change in exposure of patients to antibiotics had occurred: very likely, statistically significant changes in DDDs that were not explained by changes in clinical activity; likely, statistically significant changes in DDDs that were related to changes in clinical activity; possible, no significant change in DDDs, but significant change in the same direction for DDDs per 100 admissions (DADs) or DBDs; unlikely, change in the opposite direction for DDDs and either DADs or DBDs; and very unlikely, no significant change in DDDs, DBDs or DADs.

**Results**

**Description of participating hospitals**

The 18 participating hospitals had a total of 13664 beds (mean 759, range 242–2459). Detailed information about case mix was returned from 16 hospitals with 12411 beds, of which 12 were teaching hospitals with 11164 beds (82% of the total) and seven were tertiary care hospitals with 7572 beds (55% of the total). At least one intensive care unit (ICU) was present in each hospital, 12 hospitals had paediatric units and 7 had a paediatric ICU, 13 hospitals had haematology units, 11 hospitals had renal dialysis units and 10 hospitals had infectious diseases departments. Hospitals 5 and 17 were infectious diseases hospitals. Sixteen hospitals also participated in the ESAC point prevalence survey3 and were identified by the same numbers in both surveys.

**Changes in antibacterial use**

Mean monthly total use was 14190 DDDs and ranged from 2791 DDDs in Hospital 12 to 53195 DDDs in Hospital 17. Total antibacterial use measured in DDDs increased in 14 of the 18 hospitals and decreased in four (Figure 1). The changes were statistically significant for eight hospitals with increasing use (Hospitals 2, 6, 7, 11, 12, 14, 15 and 18) and for three hospitals with decreasing use (Hospitals 1, 8 and 9) (Figure 1). Mean annual changes in DDDs, DBDs and DADs with 95% CIs for each individual hospital are provided in Table S1 (available as Supplementary data at JAC Online).

**Adjustment for clinical activity**

**Changes in clinical activity**

The mean number of admissions was 2928 (range 659–7269) per month. Admissions increased in 10 hospitals and decreased in 8 hospitals. Changes were significant in five hospitals (Figure 2). Mean monthly OBDs was 18222 (range 6435–49567). OBDs increased in 5 hospitals and decreased in 13 hospitals (Figure 2).

Comparing changes in admissions with OBDs, only Hospital 12 had a statistically significant increase in admissions and OBDs. Of the remaining nine hospitals with significant increases in admissions, five had no significant change in OBDs (Hospitals 2, 6, 8, 16 and 18) and three had significant decreases in OBDs (Hospitals 4, 9 and 11).

Mean LOS was 6.65 days (range 3.0–10.8 days). LOS decreased in 11 hospitals and the change was significant in 11 hospitals (Figure 2). Hospitals 3, 12 and 17 had small increases in LOS that were not statistically significant (Figure 2). These changes in LOS probably explain most of the discrepancies between changes in admissions and OBDs. The hospital with significant increases in both admissions and OBDs (Hospital 12) had a small, non-significant increase in LOS (Figure 2). In contrast, LOS decreased in all of the eight hospitals with increases in admissions, but either no change or a decrease in OBDs. Mean annual changes in OBDs, admissions and LOS with 95% CIs for each individual hospital are provided in Table S2 (available as Supplementary data at JAC Online).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Mean annual percentage change in DDDs of total antibacterials with 95% CIs. Hospitals are ranked in descending order of change in use.
There was considerable variation between hospitals in both measures of adjusted antibiotic use. Ranking of individual hospitals by mean change in use and clinical activity variables is shown in Figure S1 (available as Supplementary data at JAC Online). Mean monthly use in DBDs was 83.7 (range 16.5–351), and the ratio between the highest and the lowest hospital was 21.3. Mean monthly use in DADs was 505 (range 171–1499), and the ratio between the highest and the lowest hospital was 8.8. With only two exceptions (Hospitals 12 and 13), adjustment of DDDs by OBDs resulted in larger changes over time than adjustment by admissions (Figure 3).

For most hospitals, adjustment for either bed-days or admissions made little difference to the scale or statistical significance of changes in DDDs (Figure 3). For Hospitals 5 and 10, the changes were in the same direction with DDDs, DBDs and DADs, but only statistically significant for DBDs. However, in three hospitals, changes in DDDs, DBDs and DADs were not in the same direction. Hospital 12 had a significant change in the opposite direction to DDDs for both DBDs and DADs (Figure 3). This hospital had a large (25%) increase in admissions with no significant change in LOS; consequently, adjustment of change in DDDs for either admissions or OBDs gave similar results—in this case, a reversal of the trend in DDDs because of the large increase in clinical activity measured with either admissions or OBDs. For Hospitals 4 and 16, there was a non-significant increase in DDDs with a statistically significant increase in DBDs, but a statistically significant decrease in DADs (Figure 3). These discrepancies probably occurred because both hospitals had statistically significant increases in admissions with statistically significant decreases in LOS.
Changes in hospital antibacterial use

Regression analysis of time series

The results of time series analysis suggested that, in general, hospitals behaved differently in their antibacterial usage, and that the clinical activity variables did not always play a significant role in explaining changes in use. In six (33%) of the hospitals (4, 7, 8, 13, 14 and 17), there was no significant relationship between antibiotic use and the clinical activity variables. Three hospitals (Hospitals 7, 8 and 14) had a statistically significant change in DDDs, DADs and DBDs, whereas Hospitals 4, 13 and 17 had no significant change in DDDs, DADs or DBDs. In the remaining 12 hospitals, changes in DDDs were related to change in clinical activity. In three hospitals (5, 9 and 15), all of the clinical activity variables (bed-days, admissions, discharges and LOS) influenced DDDs. Considering the two main clinical activity variables, OBDs and admissions, both directly explained change in antibiotic use in six (33%) of the hospitals (3, 5, 9, 10, 12 and 15) and neither of them were explanatory factors in seven (41%) of the hospitals (4, 7, 8, 11, 13, 14 and 17). Full results of the regression analyses of time series are in Table S3 (available as Supplementary data at JAC Online).

Discussion

This is the first study to use a standardized method to collect data on antibacterial use from hospitals in different countries. Previous studies have focused on individual hospitals or on multiple hospitals from single countries. The collection of data from hospitals in 18 different countries has provided a wide range of antibiotic use and of changes in clinical activity over time. Measurement of drug use in DDDs is the foundation of the WHO Collaborating Centre for Drug Statistics Methodology. It is especially important for international studies when drugs have different trade names and strengths in different countries. In the ESAC Hospital Care Subproject, ATC/DDD was assigned by a central team. This required considerable time and effort, because we found that many hospitals did not assign ATC/DDD correctly. Furthermore, in some hospitals we had several trade names for one product, including a few that were manufactured for use in countries outside Europe. Further research is required to understand the importance of these errors and improve the reliability of alternative methods for data collection, such as web-based methods for assisting hospitals with ATC classification and the calculation of DDDs. Central processing of the data is unlikely to be sustainable in all countries.

The use of antibacterials increased over time in 14 hospitals and decreased in 4 hospitals. The change was statistically significant in 11 hospitals (Figure 1). However, there were marked changes in clinical activity with decreasing LOS in 15 hospitals and increasing admissions in 9 hospitals (Figure 2). Analysis of changes in clinical activity is therefore critical for the final interpretation of results.

Changes in clinical activity

The WHO-recommended method for the surveillance of drug use in hospitals is to divide DDDs by OBDs. However, OBDs is itself a complex measure determined by the number of admissions, LOS and the hospital’s occupancy rate. Our results show the importance of a clear, stepwise approach to the interpretation of the data. Overall, our results supported the hypothesis that DBDs would show greater annual change than DADs due to an underlying reduction in LOS. However, this trend was not universally present. Moreover, there were four hospitals with extreme results that clearly demonstrated the potential complexity of changes in admissions and LOS that are not obvious from the measurement of OBDs alone (Figure 3; Hospitals 4, 9, 12 and 16). Our results support the recommendations to include both admissions and OBDs in the surveillance of antimicrobials, but we propose that interpretation is facilitated by the calculation of LOS from admissions and OBDs (Figure 3). Regression analysis results for each individual hospital are provided in Table S3.

Interpretation of results

In addition to allowing multivariate adjustment for clinical activity, the time series analysis accounted for outlier, extreme results and for structural breaks (step change) in the data. The combination of analysis of mean annual change with time series analysis allowed us to separate the hospitals into five groups based on the likelihood of change in exposure of patients to antibiotics (Table 1). Further research is required to assess the clinical importance of these distinctions. In order to test the hypothesis that likelihood of change in exposure of patients to antibiotics is related to changes in antimicrobial resistance, ESAC is currently collecting data from a larger sample of hospitals that have participated in the European Antimicrobial Resistance Surveillance Scheme. In addition to the analysis of total antibiotic use, the time series model will also be used to analyse changes in the use of classes of drugs such as quinolones or third-generation cephalosporins that have been previously linked with changes in antimicrobial resistance and Clostridium difficile infection. Our time series model will also facilitate the evaluation of interventions to change antibiotic use, by identifying step changes or progressive changes that cannot be explained by change in clinical activity.

Strengths and weaknesses

The strengths of this study are that we have used standardized methods to collect and analyse longitudinal data from multiple countries with a wide range of antibiotic use and clinical activity. We have addressed several of the weaknesses identified in previous studies by using a standardized method for the conversion of drug use into DDDs, clearly defined definitions of bed-days and admissions, and collection of monthly data. In this study, we have further explored the effects of the additional denominator of clinical activity. Furthermore, we have estimated discharges and LOS. In future studies these estimates should be replaced with actual data. We have also established a new method for statistical analysis of trends over time and for the regression of time series analysis of antibacterial use (Supplementary data, available at JAC Online). The combination of analysis of mean change in antibiotic use per year with time series analysis enabled the identification of hospitals in which exposure of patients to antibiotics probably has or has not changed over time. Having established the model for the impact of clinical activity variables on total use and identified differences in changes over time using different denominator of clinical activity, we suggest further studies to describe more explanatory factors in seven (41%) of the hospitals (4, 7, 8, 11, 13, 14 and 17). Full results of the regression analyses of time series are in Table S3 (available as Supplementary data at JAC Online).
factors for changes in antibiotic use. For example, in future studies, it would be helpful to have data on changes in antibiotic policy and case mix over time. Changes in antibiotic policy can affect the total use in DDDs, e.g., a shift in prescribing for intra-abdominal infection from a combination of amoxicillin plus gentamicin plus metronidazole to monotherapy with piperacillin/tazobactam would reduce the associated DDDs by two-thirds. We were able to collect information about hospital characteristics in the final year of data collection, but found that hospitals were unable to provide data on changes in case mix (e.g., proportion of pediatric beds) throughout the study period.

Our study does have some potentially important weaknesses. It was impossible for a number of hospitals to exclude dispensing at discharge from their pharmacy supply data. However, none of the hospitals had changed their dispensing system over the study period, so this should not have had a major influence on our longitudinal analysis. Nonetheless, LOS did reduce over the study period in most hospitals and, therefore, the number of patients with length of antibiotic treatment greater than LOS is likely to be increasing. It would be helpful for future studies to document the impact of dispensing at discharge. We only included 18 hospitals in total and the period of the longitudinal survey did not include the year of the point prevalence survey so we have no concurrent information about prescribed daily doses. Having established the methodology, ESAC is currently conducting a larger study with 50 hospitals that will provide longitudinal data linked with point prevalence data on prescribed doses and details about hospital characteristics.

**Recommendations**

Our results provide further evidence that both admissions and OBDs should be used to adjust for changes in clinical activity when comparing antibiotic use between hospitals or in analysis of changes over time. These data suggest that the determination of changes in antibiotic exposure of hospital patients over a period of time is unreliable if only one clinical activity variable (such as OBDs) is used as the denominator. Furthermore, we recommend that the calculation of LOS from admissions and OBDs facilitates the interpretation of results.

We recommend that admissions, LOS and OBDs should also all be used in the surveillance of infection. The presentation of data (e.g., methicillin-resistant *Staphylococcus aureus* bacteraemia) adjusted for admissions or OBDs provides an estimate of the average risk of infection per patient or per day in hospital. However, for comparison of infection rates between hospitals or within a hospital over time, we believe that it is more informative to use all available clinical activity data in multivariable and time series analysis, with number of infections as the dependent variable.

Centralized, standardized data entry is the most reliable method for comparison of use of antibiotics between hospitals, but this is unlikely to be a sustainable method for all healthcare organizations. Further research is required to improve the reliability of sustainable, web-based solutions.

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**Table 1. Overall interpretation of change in antibiotic exposure in the 18 hospitals from the results of statistical analysis of mean annual change and time series analysis of antibiotic use**

<table>
<thead>
<tr>
<th>Likelihood of change in antibiotic exposure</th>
<th>Change in DDDs</th>
<th>Hospitals</th>
<th>Mean change in antibiotic use</th>
<th>Time series analysis of antibiotic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very likely decrease</td>
<td>8 and 14</td>
<td>statistically significant change in the same direction for DDDs, DADs and DBDs</td>
<td>change in DDDs independent of clinical activity in all hospitals</td>
<td></td>
</tr>
<tr>
<td>Likely decrease 1 and 9</td>
<td>2, 6, 11 and 15</td>
<td>statistically significant change in the same direction for DDDs and either DADs or DDBs</td>
<td>change in DDDs related to change in clinical activity in all hospitals</td>
<td></td>
</tr>
<tr>
<td>Possible decrease 5 and 10</td>
<td>no hospitals</td>
<td>no significant change in DDDs; significant change in the same direction for DADs or DBDs</td>
<td>change in DDDs related to change in clinical activity for Hospitals 5 and 10</td>
<td></td>
</tr>
<tr>
<td>Unlikely decrease 4, 12, 16 and 18</td>
<td>no hospitals</td>
<td>opposite change in direction for DDDs and either DADs or DBDs</td>
<td>change in DDDs related to change in clinical activity in Hospitals 12, 16 and 18, but not in Hospital 4</td>
<td></td>
</tr>
<tr>
<td>Very unlikely decrease 17</td>
<td>3 and 13</td>
<td>no significant change in DDDs, DADs or DBDs</td>
<td>change in DDDs related to change in clinical activity in Hospital 3, but not in Hospital 13 or 17</td>
<td></td>
</tr>
</tbody>
</table>

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Supplementary data
Supplementary data, including Tables S1 to S3 and Figure S1, are available at JAC Online (http://jac.oupjournals.org/).

References