Specific control measures for antibiotic prescription are related to lower consumption in hospitals: results from a French multicentre pilot study

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Background: In France, antibiotic consumption (ABC) is dramatically high in parallel with the high rate of multidrug-resistant bacteria. For the last few years, a nationwide policy has been implemented at the national level to control and monitor ABC. Since 2002, surveillance networks have been set up with voluntary hospitals to evaluate the antibiotic policy and consumption. The present study was conducted to identify whether specific control measures of the antibiotic policy could reduce ABC in hospitals.

Methods: Based on the data from the Northern France surveillance system, local recommendations and antibiotic use were collected annually on a standardized questionnaire that had 21 items. ABC was expressed in defined daily doses (DDDs) per 1000 patient-days (PDs). The ABC indicator was the overall antibiotic consumption. A multivariate logistic regression analysis was performed using low (≤75th percentile) and high (>75th percentile) ABC as the dependent variable.

Results: A total of 83/111 hospitals were included in the study. In 75% of the hospitals, total ABC was ≤669.5 DDDs/1000 PDs. The less frequent practices were educational antibiotic programmes (17%), authorization from an antibiotic specialist for selected antibiotics (26%) and systematic reassessment of AB treatment after 72 h (27%). In the multivariate analysis, three variables remained significantly and independently associated (P < 0.05) with ABC: the type of hospital, the proportion of non-acute-care beds and the nominative delivery form as the only antibiotic control measure. Total ABC was lower in hospitals having a nominative delivery form, compared with hospitals not having it. Conversely, ABC was significantly higher in public teaching hospitals compared with non-teaching hospitals. Similarly, ABC was higher in hospitals with a lowest proportion (i.e. ≤25%) of non-acute-care beds compared with hospitals where this proportion was >25%.

Conclusions: Specific control measures could lower ABC. Sustained control efforts should focus on antibiotics with the highest potential for emerging bacterial resistance.

Keywords: hospital antibiotic consumption, antimicrobial practice, infection control measures

Introduction

In the last decades, the high use of antimicrobial agents has been recognized as an important public health challenge. Their widespread use has been linked to the development of bacterial resistance responsible for increases in morbidity, mortality, hospital stay duration and healthcare costs associated with untreatable infections.1–3 Many studies have shown that

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unjustified or inappropriate antibiotic consumption (ABC) in hospitals can reach up to 50% of the antibiotic prescriptions.4–6 These findings concern both intravenous and prophylactic therapies, which are often unnecessarily prolonged. In France, hospital and community ABC is dramatically high,7–9 in parallel to the high rate of multiresistant bacteria,10 which highlights the need for an antibiotic policy and antimicrobial stewardship programmes.

To cope with this issue, the professional medical societies and public health authorities of many countries11–14 published recommendations and consensus statement guidelines highlighting good practices on ABC. They aim at balancing optimal patient outcomes while working towards maintaining their future efficacy, improving cost-effectiveness therapy and reducing antimicrobial resistance. Most of the antimicrobial stewardship programmes insist on surveillance and monitoring systems, regulation of the interactions between pharmacists and physicians, the need for effective infection control policy and a strategy to influence prescribing patterns and to improve antimicrobial use.11–14 Basically, the latter includes training the prescriber to make the correct choice at the time of prescribing (education and guidelines), reviewing antibiotic prescription and attempting to persuade prescribers to change undesirable prescriptions (review and feedback), and controlling prescribing options by dictating which antibiotics a clinician may or may not prescribe, e.g. antimicrobial formulary and restrictions for controlled dispensation [written justification for specific antimicrobial agents or prior approval by an infectious diseases (ID) specialist or any specially trained physician], automatic stop-orders or checking of the microbial susceptibility reports.

A growing body of research has examined the effectiveness of strategies that have been used in antimicrobial stewardship programmes.12,15–17 However, to date, there is no consensus about the best approach, and the strategy combining multiple interventions conducted simultaneously remains difficult to assess. The present study aimed at identifying whether specific control measures could influence ABC based on annual data collected in a network of volunteer hospitals in northern France.

**Methods**

The Antimicrobial Surveillance Network of northern French hospitals was set up in 2002. It is coordinated by the regional centre for nosocomial infection control in northern France (CCLIN-Paris Nord). This area covers four administrative regions, as described elsewhere.18 All 772 public and private hospitals in the region were contacted, via their infection control physician or nurse, and invited to participate in the study.

Annual data on ABC and antibiotic policies were collected for all participating hospitals at the beginning of each year, following monitoring. Data were then entered into a Microsoft Excel application (Microsoft Corporation, Redmond, WA, USA), designed separately for each data group by CCLIN Paris-Nord. Antibiotic policy data were collected annually using a standardized closed questionnaire. The questionnaire included two sections: in the first section, hospital characteristics such as hospital size (number of beds), hospital ownership (public/private) and teaching status were recorded. The second section requested data concerning antimicrobial control practices. The items of this section, listed in Table 1, were based on the recommendations issued by the French National Agency for Accreditation and Evaluation in Health (ANAES)19 and the French Society of Infectious Diseases (SPILF).20

Hospitalization days and all ABC (including oral, parenteral, emergency room, surgical antibiotic prophylaxis, rehabilitation and long-term care prescriptions) were considered in this study. ABC was entered in the Excel spreadsheet as the number of administered units (vials, pills or bottles) and was converted into defined daily doses (DDDs)/1000 patient-days (PDs), following the 2003 version of the World Health Organization recommendations.20 The spreadsheet automatically calculated the DDDs/1000 PDs. This application was derived from the ABC Calc software developed by the Danish Statens Serum Institut (http://www.escmid.org/). All data were transmitted to the regional centre by a local correspondent (an ID or infection control physician or a hospital pharmacist). Collected data were checked for missing or incorrect values and then merged in a database for overall analysis.

A cross-sectional analysis was performed on the data collected in the cohort of hospitals that participated at least once during the 2 year surveillance network (2002–03) and answered the antibiotic policy and ABC sections of the questionnaire. For hospitals that participated twice, only the first year of participation was taken into account. The antibiotic consumption indicator was the overall ABC. For all calculations, statistical significance was defined as P < 0.05.

In the univariate analysis, overall ABC mean values were compared for the 21 dichotomous variables related to an antibiotic policy using the Wilcoxon test. The Kruskal–Wallis test was used for comparison between classes of hospital characteristics: hospital size (<400, 401–800, >800 beds), type of hospital (public teaching, public non-teaching and private) and the proportion of non-acute-care beds (i.e. long-term care, rehabilitation units or psychiatric wards in two classes: ≤25% or >25%). In the cases in which the Kruskal–Wallis test was significant, pairwise comparisons were performed to identify specific differences. The Bonferroni correction was used to adjust the alpha level for multiple testing and to maintain an alpha value of 0.05.

A multivariate logistic regression analysis was performed using a dichotomous dependent variable by splitting total ABC into two categories according to the 75th percentile (p75): highest (> p75) ABC and a lowest (≤ p75) ABC. Multivariate logistic regression was computed using a manual backward-stepwise variable-selection procedure. Only variables that showed a statistical association with ABC on univariate analysis were included as candidate variables for the full model. Variables that were thought to correlate with each other were investigated, and in the case of multicolinearity, the variable that led to the best predictive model based on the −2 log likelihood was retained. Non-significant variables were removed one at a time until all those remaining in the final model had a significant contribution (P < 0.05). At each step, the variable with the smallest contribution to the model (or the largest P value) was removed. Qualities of the final model were calculated using the −2 log likelihood ratio test and the area under the receiver operating characteristic curve for discriminative accuracy. The whole analysis was performed using STATA Statistics/Data Analysis 8.0 software (Stata Corporation, College Station, TX, USA).

**Results**

Over the study period, a total of 111 volunteer hospitals participated for the first time in the network. However, only 83 hospitals completed both the ABC and the antibiotic policy sections (68 in 2002 and 15 in 2003) and were included in the analysis. More than two-thirds of the participating hospitals were public, and only 15.7% had teaching status (Table 2). Median hospital size was 442 beds [interquartile range (IQR) = 257–675, min = 62, max = 1906] and varied significantly according to the type of hospital (median test, P < 0.0001). The hospital size was
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Table 1. Requested data concerning antibiotic policy practices

<table>
<thead>
<tr>
<th>Question</th>
<th>Possible answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your hospital have a local multidisciplinary Drugs and Therapeutics Committee (DTC)?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have a multidisciplinary Local Antimicrobial Committee?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Has your hospital carried out training/educational programmes of healthcare staff on ABC?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have one or several antibiotic specialist consultants?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have a written antibiotic formulary including a list of restricted use antibiotics?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Which antibiotics are concerned with the controlled dispensation?</td>
<td></td>
</tr>
<tr>
<td>Which are the prescription characteristics for these antibiotics?</td>
<td></td>
</tr>
<tr>
<td>Written prescription</td>
<td></td>
</tr>
<tr>
<td>The duration of the delivery is limited in the time</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Which are the dispensation conditions for these antibiotics in first intention?</td>
<td></td>
</tr>
<tr>
<td>The dispensation of certain antibiotics is limited to certain indications</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>A written justification, based on clinical or microbiological evidence, is necessary</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have implemented a systematic reassessment of antibiotic treatments after 72 h?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have computerized antibiotic prescribing?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have computerized antibiotic dispensing?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have a nominative delivery form?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have a standard prescription protocol on the use of antibiotics by clinical diagnosis?</td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Does your hospital have a written guideline on good ABC?</td>
<td>(yes/no)</td>
</tr>
</tbody>
</table>

‘Nominative prescription’ is different from ‘nominative delivery form’. Nominative prescription is equivalent to a nominative antibiotic order form that is completed by the physician for dispensing antimicrobials that have a controlled dispensation. The nominative delivery form is a special form that is completed by the pharmacist. This form is used in an individualized drug dispensing system, by which the hospital pharmacy delivers drugs separately per patient in a package that is ready to be administered to the patient, according to the medical prescription. The nominative delivery form allows traceability of each delivered patient’s medications.

lower in private hospitals (median = 292, IQR = 120–382), higher in public non-teaching hospitals (median = 546, IQR = 385–817) and even higher in public teaching hospitals (median = 593, IQR = 408–761).

The most frequent antibiotic policy practices were the presence of a ‘Drugs and Therapeutics Committee’ (DTC) and a written antibiotic formulary (Figure 1). In contrast, the following practices were less frequently observed: educational programmes on ABC, prior approval from an ID or a specially trained physician for selected antibiotics, systematic reassessment of antibiotic treatment after 72 h and computerized prescription and dispensation.

The median of total ABC was 461 DDDS/1000 PDs (IQR = 277.3–669.5). Univariate analyses (Table 2) identified hospital characteristic and antibiotic policy variables, for which mean values of ABC were statistically significantly different. As shown in Table 2, mean values of ABC were significant according to the type of hospital: ABC seems to be higher in both public teaching and private hospitals in comparison with non-teaching hospitals. However, the pairwise comparisons using a Bonferroni-adjusted alpha level of 0.017 (i.e. 0.05 divided by three pairwise tests) revealed only significant differences among public non-teaching and private hospitals ($P = 0.004$). The comparison between teaching and non-teaching hospitals had a limited statistical significance ($P = 0.019$). There was no significant difference according to the hospital size. However, hospitals with a proportion of non-acute-care beds ≤25% were more likely to have a high ABC compared with hospitals where this proportion was higher ($P < 0.0001$). Among the antibiotic policies, five control measures were significantly related to ABC, and two of them were associated with a lower ABC (Table 2): the restriction of selected antibiotic dispensation to limited indications and the nominative delivery form.

In the multivariate analysis, three variables remained significantly and independently associated ($P < 0.05$) with ABC: the type of hospital, the proportion of non-acute-care beds and the nominative delivery form as the only antibiotic control measure (Table 3). After adjusting for the effect of the other variables in the model, total ABC was lower in hospitals having a
nominative delivery form compared with hospitals that do not implement this measure. Conversely, overall ABC was significantly higher in public teaching hospitals, compared with non-teaching hospitals. Similarly, ABC was higher in hospitals with a lowest proportion (i.e. ≤25%) of non-acute-care beds compared with those with a proportion >25% of these beds. Overall, ABC did not remain significantly different between private and public non-teaching hospitals.

Discussion

Our study identified the nominative delivery form as the most significant and independent antibiotic control measure associated with a lower ABC. The nominative delivery form is a special form used by the pharmacist in an individualized drug dispensing system by which the hospital pharmacy delivers drugs separately per patient in a package that is ready to be administered.
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Written guidelines on good AB use
Standard prescription protocol
Written AB formulary
Nominative delivery form
Computerized AB dispensing
Computerized AB prescribing
Systematic reassessment after 72 h
Written justification (clinical or microbiological)
Request for an AB specialist
Dispensation is limited to certain indications
Detailed dosage has to be provided
Duration of treatment has to be provided
Nominative prescription
Dispensation is limited to certain indications
Controlled dispensation for specific ABs
Microbiologist or ID physician as AB specialist consultant
Educational sessions on AB use
Local Antimicrobial Committee (LAC)
Drugs and Therapeutics Committee

Figure 1. Proportion of hospitals having implemented antibiotic (AB) policy practices (n = 83). ID, infectious diseases physician.

Table 3. Multivariate logistic regression analysis to identify independent relationships between antibiotic policy and antibiotic consumption

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominate delivery form</td>
<td>0.3 (0.07–0.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Proportion of non-acute-care beds ≤25%</td>
<td>5.6 (1.2–27.3)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Type of hospital public non-teaching</td>
<td>reference</td>
<td>—</td>
</tr>
<tr>
<td>public teaching</td>
<td>10 (1.4–69.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>private</td>
<td>2.3 (0.4–14.5)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Model validation results

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<table>
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<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitals</td>
<td>80</td>
</tr>
<tr>
<td>Hospitals with AB consumption &gt;p75</td>
<td>20</td>
</tr>
<tr>
<td>Area under the ROC curve</td>
<td>0.85</td>
</tr>
<tr>
<td>−2 log likelihood ratio test</td>
<td>χ² = 4.03 (df = 3, P = 0.26)</td>
</tr>
</tbody>
</table>

AB, antibiotic; OR, odds ratio; CI, confidence interval; ROC, receiver operating curve; df, degrees of freedom. P values less than 0.05 are in bold font.

†Output models obtained by retaining the significant variables (P < 0.05).

*Total antibiotic consumption is the dependent variable and was categorized as a 0/1 variable according to low (<75th percentile or p75) and high consumption (>p75).

The independent variables were dichotomous (yes/no) and coded 1 or 0, respectively. The full model also included the following variables: antimicrobial committee meets more often than twice per year, microbiologist or ID physicians; dispensation of select antibiotics is limited to certain indications.
to the patient, according to the medical prescription. When a hospital has declared that it uses nominative delivery forms, it means that an individualized drug dispensing system is in place and the traceability of each patient’s medications is ensured. This control measure, frequently associated with an antimicrobial formulary for restricted drugs, nominative prescriptions or with automatic stop-orders, has been used in several French studies that showed a reduction in both ABC and drug cost.21–24 A recent study in Southwestern France reported a lack of ABC reduction for the nominative delivery form unless associated with automatic stop-orders.24

In our study, only the nominative delivery form remained associated with an overall lowest ABC after adjustment for the other factors included in the multivariate logistic model. However, the results found in the univariate analysis should be discussed. Three control measures were significantly associated with higher ABC: the presence of a local antimicrobial committee (LAC), an LAC that meets more often than twice per year, and the presence of a microbiologist or an ID physician as an antibiotic specialist consultant. Two main issues could explain this positive association: the effect of an incomplete or inefficient response to an overwhelming ABC and the fact that hospitals with high ABC have probably been motivated to create antimicrobial committees with more frequent meetings, as also reported in the Southwestern France network.24

Our findings also showed that ABC was higher in public teaching hospitals than in public non-teaching or private hospitals. Similarly, total ABC was higher in hospitals with the lowest proportion (i.e. \( \leq 25\% \)) of non-acute-care beds compared with those with a proportion \( > 25\% \) of these beds. This finding was expected, because teaching hospitals generally have more settings where ABC is known to be high, such as intensive care units and specialized tertiary care wards including ID, burn care, shock trauma or haematology—oncology units. Conversely, hospitals with a stronger proportion of non-acute-care beds have an overall lower antibiotic consumption. Indeed, the patients in long-term care facilities often spend a longer period without any antibiotic treatment. In contrast, it is quite surprising that we did not find a relationship between hospital size and ABC. Indeed, variations in the ABC according to hospital size, hospital ownership and teaching status have been reported previously by other studies.24,25

Several antibiotic control measures were not associated with ABC in our study. For instance, the implementation of written guidelines for better antibiotic use, the impact of an ID specialist on prescription practices, the rotation and antibiotic cycling strategy or the use of a restricted list of antibiotics to be prescribed was reported by others to be effective strategies,26–30 but turned out to have no significant effect on ABC in our work. Several factors could explain these differences, including weakness of statistical power analysis, heterogeneity of participating hospitals and cross-sectional measurement, which alter causal inferences. In addition, there was a potential risk of selection bias, given that participation to the ASN is non-compulsory. Indeed, hospitals that have chosen to participate in the ASN might be different from non-participating ones. However, although hospital participation was self-selecting, participation was also anonymous. Therefore, there was no motivation to deliver false or invalid data to the surveillance system. Furthermore, it should be noted that, in the absence of a ‘gold standard’ to define a high or low ABC, we chose the 75th percentile as an indicator of the ABC level. Therefore, definitions of ‘low and high ABC’ were specific to the hospitals included in the analysis. Nevertheless, the selection of this threshold seemed to us appropriate because it allowed us to evaluate the situation in the group of hospitals having the highest (\( > p75 \)) ABC and to compare them with the 75\% having a lower (\( \leq p75 \)) ABC according to explanatory variables.

Although our study has some limitations involving some findings that should be interpreted with caution, it also has several important strengths that should be emphasized. First, our approach allowed us to identify individual antimicrobial policies that were associated with ABC due to robust statistical analysis. To date, efforts to evaluate the efficacy of individual control measures aiming to reduce ABC in hospitals have been undermined by the absence of robust published evidence. Indeed, in several studies (actually, most of the monocentric studies), multiple interventions have been conducted simultaneously, making it difficult to assess the benefit attributable to each intervention. Furthermore, the relationship between antibiotic policy and ABC was examined by adjusting for hospital characteristics such as the type of hospital and the proportion of long-stay beds. In conclusion, antibiotic guidelines are crucial in high-risk settings, and regulators should insist on the use of particular strategies that have been proven to effectively improve prescription quality and reduce the costly and unsafe antibiotic consumption.

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Transparency declarations

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References


