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Effect of individual- and group-level antibiotic exposure on MRSA isolation: a multilevel analysis

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Objectives: To observe the relative role of individual and group-level antimicrobial selective pressure on subsequent methicillin-resistant *Staphylococcus aureus* (MRSA) isolation in a university hospital.

Methods: For this purpose, 18 596 patients were included in a retrospective statistical analysis, applying multilevel modelling with discrete time intervals at the lowest level. Individual-level and hospital group variables on antimicrobial exposure and MRSA colonization pressure were collected from computerized databases.

Results: The simultaneous hospital group- and individual-level analysis showed individual exposure to fluoroquinolones and collective exposure to penicillins to be associated with MRSA isolation after adjustment for colonization pressure and other potential confounders.

Conclusions: These results support efforts to reduce prescriptions of selected antimicrobial drug classes such as fluoroquinolones and show the added value of multilevel analysis for research on the adverse outcomes of antibiotic prescribing.

Keywords: methicillin-resistant *Staphylococcus aureus*, antimicrobial use, individual exposure, ecological bias

Introduction

Recent studies have highlighted the importance of antibiotic exposure as a significant risk factor for the acquisition and transmission of methicillin-resistant *Staphylococcus aureus* (MRSA).[1] However, the effect of this individual-level antibiotic exposure can be decreased or amplified as a result of an interaction between the individual and the group effect.[2] This group-level effect (also called ecological effect) may be particularly important for Gram-positive pathogens, such as MRSA. In a recent article, Monnet *et al.*[3] have reported that, at a hospital level, use of antimicrobial drugs may be an important factor in perpetuating a hospital-wide MRSA outbreak. We have also demonstrated a relationship between antimicrobial use and MRSA spread at the hospital unit (HU) level.[4] Notwithstanding their many pitfalls, ecological studies provide a potentially useful function in studies of infectious agents, because they allow measurement of the global effect of an exposure. This is important, because the global effects of antibiotics encompass not just the direct effects on the individual who receives the antibiotic but also the indirect effects mediated by effects on transmissibility or on the likelihood of transmission of susceptible organisms.[5] The present study was specifically designed to determine the relative part of individual- and group-level (HU) antimicrobial pressure on subsequent MRSA isolation. For this purpose, we used advanced statistical multilevel modelling, which takes account of factors at the individual and group level simultaneously.

Materials and methods

Setting, study period and patients

The Besançon Hospital is a French university-affiliated hospital. Data for year 2001 were collected for the following departments: medicine, surgery and adult intensive care. Psychiatric, paediatric and gynaecology-obstetric units were excluded. All patients admitted for

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more than 48 h were included in the study. For each patient, only the first hospitalization during the study period and only the time spent in the HU where the patient was present 48 h after admission were retained for the analysis.

MRSA status

MRSA-positive patients were defined as patients who had a clinical specimen (requested for diagnostic work-up) that yielded MRSA and who were not known to be positive for MRSA during the previous 12 months. Screening samples were not considered for ascertainment of the MRSA status. Patients in whom MRSA was isolated within 48 h after admission (imported MRSA cases) were excluded.

Data structure

Level 1: Time. The lowest level was that of discrete 24 h time periods nested within individual patients. The history of each patient in the HU was treated as a series of discrete 24 h periods, excluding the first 2 days of hospitalization. For individual colonization pressure and antibiotic exposure variables, each day of hospitalization was coded as negative before occurrence and as positive from the first day it occurred to the last day of the follow-up. Patients without MRSA isolation were censored at the time of HU discharge or in-hospital death.

Level 2: Individual. Individual patients constituted the second level of the data. Individual-data variables on age (> or ≤ 60 years), sex and individual MRSA colonization pressure (presence or absence in the HU of at least one patient known to be positive for MRSA during the hospitalization) were collected from computerized databases. Individual exposure to each of the four antimicrobial classes of interest defined (see below) was expressed as a binary, time-varying covariate (exposed/non-exposed on a given day).

Level 3: Hospital unit (HU). The highest level of data was at the HU level. The HUs were classified into three types: medicine ($n = 31$), surgery ($n = 17$) and intensive care ($n = 2$). The average antibiotic use was 718.5 DDD per 1000 patient-days, ranging from 535.4 in surgical units to 808.6 in medical units and 1517.7 in ICUs. Antibiotics were grouped into five classes: penicillins, cephalosporins, fluoroquinolones (96% inactive against MRSA), glycopeptides (100% active against MRSA) and other antibiotics (including macrolides, lincosamides, aminoglycosides) with variable activity against MRSA. The distribution of antibiotic use by class was penicillins, 51.3%; cephalosporins, 10.9%; fluoroquinolones, 18.6%; glycopeptides, 3.6%; and other antibiotics, 15.6%. We only retained penicillins, cephalosporins, fluoroquinolones and glycopeptides for the analysis. The HUs were divided into two categories using the median cut-point for each of the four retained antimicrobial classes (weak versus high consumer). In addition, the mean colonization pressure was calculated for each unit from the ratio of the number of patient-days of MRSA patients to the total number of patient-days.

Statistical analysis

We analysed data using a multilevel discrete-time logistic regression model with MRSA ascertainment as binary outcome.[6] This approach allowed us to consider a nested hierarchical structure of the data. Initially, each variable was tested in a univariate model adjusted for the time at risk. Second, a reference model was built by introducing the variables with $P < 0.20$ in the univariate analysis, with the exception of antimicrobial exposure. Both individual and collective antimicrobial exposure variables were simultaneously forced into the reference model. Modelling was performed using MlwiN V2.0 software.

Results

In 2001, 41 790 patients (excluding re-admissions) were admitted, of whom 18 596 were included in our study. We identified 59 MRSA-positive patients according to our selection criteria. Characteristics of the patients are shown in Table 1. In univariate analysis, group-level MRSA colonization pressure ($P = 0.002$), group-level penicillin use ($P = 0.001$) and individual fluoroquinolone exposure ($P < 0.001$) were associated with MRSA isolation. In Figure 1, MRSA isolation is plotted by individual antibiotic exposure and level of antibiotic use in the HU. Figure 1(a) suggests a unique increase with the individual fluoroquinolone exposure regardless of the level of fluoroquinolone use in the HU. Conversely, Figure 1(b) suggests a unique increase with high level of penicillin use in the HU regardless of the individual penicillin exposure.

The simultaneous hospital group- and individual-level analysis showed individual exposure to fluoroquinolones and collective exposure to penicillins to be associated with MRSA isolation after adjustment for colonization pressure and other potential confounders (Table 2). For fluoroquinolones, the effect of individual exposure was not modified when adjusted on collective exposure. Conversely, for penicillins, the observed collective effect was not influenced by individual exposure.

Discussion

The results reported here demonstrate a significant association between antibiotic exposure and subsequent isolation of MRSA in our hospital. This relationship persists when other identified risk factors such as age, sex, MRSA colonization pressure and the type of unit are taken into account. The advanced multilevel analysis fits the complex structure of the data and allows differentiation between individual and collective antibiotic exposure for each antimicrobial class.

Table 1. Characteristics of the patients

Variables	MRSA-negative patients	MRSA-positive patients
Number of patients	18 537	59
Mean (SD) age	58 years (20.91)	72 years (16.37)
Percentage of patients who were men	54.4%	57.6%
Mean (SD) hospitalization duration in the first unit	7.4 days (9.84)	35.3 days (23.89)
Mean (SD) delay between admission and MRSA isolation		16.2 days (4.73)
Percentage of patients who received at least one antimicrobial	23.6%	64.4%
Percentage of patients simultaneously hospitalized with at least one other MRSA-positive patient in the same unit.	48.2%	74.6%

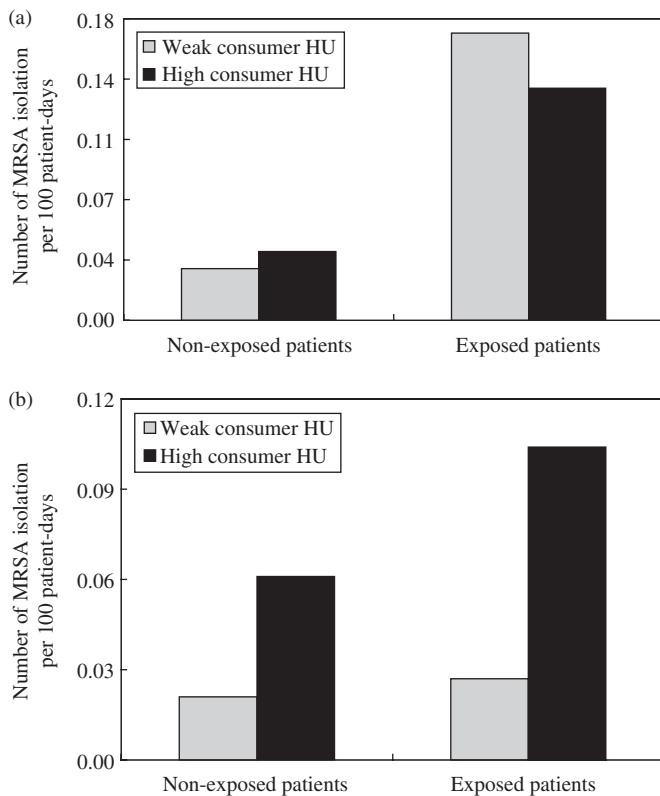MRSA, methicillin-resistant *Staphylococcus aureus*.

(a)

(b)

Figure 1. Distribution of patient-days with MRSA isolation among total patient-days, comparison of individual and collective exposure to antibiotics. (a) Fluoroquinolones; (b) penicillins.

Table 2. Multilevel (including time) multivariate analysis for each antimicrobial variable adjusted for sex, individual, MRSA colonization pressure and type of hospital unit

	Individual exposure		Group-level exposure	
Antibiotic class	OR (95% CI)	*P* value*	OR (95% CI)	*P* value*
Penicillins	0.89 (0.49–1.62)	0.79	2.52 (1.15–5.51)	**0.03**
Fluoroquinolones	2.63 (1.44–4.80)	**0.01**	0.85 (0.37–1.96)	0.64
Cephalosporins	0.83 (0.38–1.83)	0.71	0.85 (0.39–1.86)	0.61
Glycopeptides	2.01 (0.62–6.53)	0.25	0.99 (0.45–2.20)	0.98

*Wald test.

Regarding the fluoroquinolone effect, our results are concordant with those of Weber *et al.*,[1] who demonstrated that this class has a specific individual effect on MRSA. Our multilevel model shows that this effect is observed regardless of the amount of fluoroquinolones used at the HU level. It suggests that the ecological effect of fluoroquinolones reported by previous studies may just reflect the sum of individual effects.[3,4,7] Fluoroquinolones, which are frequently ineffective against nosocomial MRSA,[8] have an excellent tissue diffusion, which could promote the acquisition of MRSA by eradicating susceptible microorganisms, such as methicillin-susceptible

Staphylococcus aureus (MSSA). Moreover, Bisognano *et al.*[9] have demonstrated that exposure to subinhibitory levels of ciprofloxacin results in increased expression of adherence factors promoting host colonization. It seems that the combination of the two mechanisms gives a plausible explanation for the specific effect of fluoroquinolones on MRSA: fluoroquinolone exposure would promote *Staphylococcus aureus* colonization while selectively eradicating MSSA strains.

We observed a group-level effect of penicillin use on MRSA isolation and this could not be explained by an ecological fallacy because both individual- and group-level antibiotic exposure was considered using adequate statistical modelling. Thus, an ecological effect purely explained by the aggregated effect of individual exposures can be excluded. The observed ecological effect could be due either to a confounding factor or to a real effect. Penicillins are the most frequently prescribed antibiotic class in our hospital, making it possible that an ecological effect would only manifest above a certain threshold of use.

Some limitations of our study have to be addressed. First, our findings are supported by data collected in a single hospital. It would be of interest to apply our multilevel model to other settings. Second, due to statistical complexity, we used a nested multilevel model which implies that one level is related to only one upper level. So, we only retained the first unit-stay for analysis and consequently did not consider the entire spectrum of MRSA colonization occurring in our hospital. Third, our microbiological data, i.e. isolation of MRSA from clinical sample, were laboratory-based. We did not collect clinical information to confirm MRSA infection. MRSA screening on admission was performed for 15% of the patients admitted. So, we have not evidenced a specific association of antibiotic exposure with MRSA acquisition or with progression from MRSA colonization towards infection but an association between antibiotic exposure and a mix of these two stages.

Finally, our results are consistent with several studies, supporting a relationship between antimicrobial use, particularly individual exposure to fluoroquinolones, and MRSA spread.[3,4] Interestingly, hospitals in Nordic European countries, with very low MRSA incidence, use the least fluoroquinolones.[10] Our findings support efforts to further study the effect of implementing programmes to control antibiotic use. To conclude, our multilevel analysis shows that exploring the problem of antimicrobial resistance at the individual level or at the collective level alone will miss either of these aspects of the problem.

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Transparency declarations

Conflicts of interests: none.

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