Reduction of fluoroquinolone use is associated with a decrease in methicillin-resistant *Staphylococcus aureus* and fluoroquinolone-resistant *Pseudomonas aeruginosa* isolation rates: a 10 year study

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Objectives: High rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and fluoroquinolone-resistant *Pseudomonas aeruginosa* may be related, in part, to the overuse of fluoroquinolones. The objective was to analyse and correlate long-term surveillance data on MRSA and fluoroquinolone-resistant *P. aeruginosa* rates and antibiotic consumption after implementation of an institution-wide programme to reduce fluoroquinolone use.

Methods: An interrupted time series/quasi-experimental study of monthly fluoroquinolone use and MRSA and fluoroquinolone-resistant *P. aeruginosa* isolation rates was carried out in a tertiary hospital during three periods: pre-intervention (January 2000–August 2005), intervention (September 2005–March 2006), and post-intervention (March 2006–March 2010). The effect of the intervention on the consumption of fluoroquinolones and bacterial resistance was assessed using segmented regression analyses.

Results: Mean monthly fluoroquinolone consumption dropped by 29.1 defined daily doses per 1000 patient-days (DDD/1000 PD) (95% CI 13.1–45.9; *P*= 0.0005) from a mean of 148.2 to 119.1 DDD/1000 PD during the intervention period. A sustained and significant decrease in fluoroquinolone consumption of 2.095 DDD/1000 PD/month was also observed during the post-intervention period (*P*= 0.0002). During the post-intervention period the rate of fluoroquinolone-resistant *P. aeruginosa* continuously decreased, from a mean of 42% to 26%, with a constant relative change rate of −213%/year (95% CI −19 to −5, *P*= 0.001). A decrease in the MRSA rate was observed during the intervention period, from a mean resistance rate of 27% to 21% (*P*< 0.0001).

Conclusions: We showed the sustained impact of a fluoroquinolone control programme on the reduction of fluoroquinolone use with a significant decrease in fluoroquinolone-resistant *P. aeruginosa* and MRSA rates over 4 years.

Keywords: antibiotic stewardship, interrupted times series, resistance

Introduction

The increasing prevalence of antimicrobial-resistant organisms is a major public health issue and is of particular concern in hospitals. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are two major nosocomial pathogens that both express multidrug resistance. Rates of antimicrobial resistance in hospitals are affected by various factors, including local epidemiology, infection control practices and usage patterns for antibiotics. The use of antibiotic therapy to treat individuals has an ecological impact on all the patients hospitalized in the same facility, and the correlation between the use of antibiotics and the development of antibiotic resistance is widely accepted.¹⁻³ Indeed, the relationship between increasing fluoroquinolone (FQ) use and decreasing susceptibility to FQs has been shown in Gram-negative bacteria and *S. aureus*.⁴⁻⁷ Among Gram-negative bacilli, a notable reduction in ciprofloxacin susceptibility, correlated to the increase in use of FQs, was reported with *P. aeruginosa*.¹⁸⁻²² Bacterial resistance leads not only to longer and more costly hospital stays, but also to increased morbidity.
Fluoroquinolone use decrease and MRSA and *P. aeruginosa* resistance reduction

and death rates.\(^5\) Whether resistance is reversible and a reduction in antimicrobial use would result in a parallel reduction in bacterial resistance is still to be determined. Studies addressing the effect of the reduction of antibiotic use on bacterial resistance have reported conflicting results.\(^{13-16}\) Few studies have analysed the impact of a specific reduction of FQ consumption on resistance in the community or in hospitalized patients.\(^{15}\)

The long-term impact of FQ use reduction has been rarely addressed.\(^17\) The purpose of this study was to analyse antibiotic consumption in our hospital after implementation of an institution-wide programme to reduce FQ use and correlate it to the incidence of antimicrobial resistance among *S. aureus* and *P. aeruginosa* isolates.

**Methods**

**FQ control programme**

Saint-Louis hospital is a 600-bed acute care university hospital with great activity in haematology and oncology. A programme aimed at reducing FQ use was implemented in 2005 and consisted of:

(i) Audit of FQ use (February 2005): prescriptions of FQs were studied with a focus on the indication for FQ prescription, doses, route of administration and justification for intravenous infusion. The prevalence of inappropriate FQ use was evaluated, with appropriateness of use judged according to established institutional guidelines.

(ii) Feedback to the hospital community on the results of the audit (September 2005–March 2006): a 1 h slide conference was led by the head of the antimicrobial stewardship programme in all wards of the hospital.

(iii) Written guidelines (pocket-size leaflet) on FQ use (September 2005): the staff was advised against the empirical use of FQs. These recommendations were provided to all prescribing physicians.

(iv) A procedure of individualized therapeutic recommendations was subsequently implemented. This on-going activity consisted of daily counseling by the antimicrobial stewardship team physician on antibiotic prescriptions, prompted by microbiological results (positive blood cultures, isolation of resistant bacteria or any serious infection) and/or initiated by the prescribers.

**Study design**

We conducted an interrupted times series/quasi-experimental study in which three periods were defined. The first period was the pre-intervention period (January 2000–August 2005). The second period was the intervention period (September 2005–March 2006) \([(iii) and (ii), see above]\). The third period was the post-intervention period (April 2006–March 2010) \][(iv), see above].

During the three periods we measured FQ and alcohol-based hand-rub (ABHR) solution use and also studied bacterial resistance. The monthly FQ consumption in our hospital was retrieved from the computerized database of pharmacy records. FQs available for oral and intravenous administration were analysed (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and norfloxacin). The total antibiotic use rate per year in our institution was also recorded by the central pharmacy during the same period. All antibiotics prescribed for inpatients were collected. FQ use was also studied, on a yearly basis, in the regional Coordinating Centres for Nosocomial Infection Control (CCLIN-Nord) network and compared with our hospital data. CCLIN-Nord is a network whose main missions cover healthcare-associated infections and antimicrobial resistance prevention and control, encompassing 700 healthcare facilities (including our institution) in the north of France. The application we used included all antibacterial drugs marketed in France for systemic use [J01 class of the WHO Anatomical Therapeutic Chemical (ATC) classification] in defined daily doses per 1000 patient-days (DDD/1000 PD).

As the effect of ABHR solution use on methicillin-resistant *S. aureus* (MRSA) rate has been reported, the monthly ABHR solution use in Saint-Louis hospital was also recorded and expressed in litres (L) per 1000 PD using the data provided by the central pharmacy.\(^{18}\)

To evaluate the impact of the programme on antimicrobial resistance, we chose to study two nosocomial pathogens, i.e. *S. aureus* and *P. aeruginosa*. A retrospective observational study on MRSA and FQ-resistant *P. aeruginosa* isolation rates was carried out from January 2000 through to March 2010. All non-duplicate strains isolated from clinical specimens in patients hospitalized were analysed, including blood, urine, skin and respiratory specimen cultures. Susceptibility tests were performed using national guidelines. Duplicate strains, defined as strains with the same antibiotic susceptibility pattern already counted for the same patient, regardless of the site from which they were isolated, were excluded. The results were given as the proportion (expressed as a percentage) of MRSA among clinical isolates of *S. aureus* and FQ-resistant *P. aeruginosa* strains among clinical isolates of *P. aeruginosa*. Relative changes in resistance rates were calculated as a percentage over all the study period and per month.

**Statistical analysis**

The effect of the intervention on the use of FQs and bacterial resistance was assessed using segmented regression analyses.\(^{19}\) For FQ consumption, segmented linear regression was used, while segmented Poisson regression was used for counts of resistant isolates. Models included an intercept (mean value at the beginning of the study) and linear time trends for each study period (before intervention, during intervention and after intervention). Whenever necessary, non-linear polynomial effects were added to the model to improve the fit of observed data. The model formulation was then selected by minimization of Akaike's information criterion (AIC). Study period main effects were also included to avoid constrained models. Seasonal effects were investigated by adding yearly and bi-yearly periodic effects to the models. Once a model was fitted, the model fit was examined by residual versus fitted plots. For segmented linear regression, quantile-to-quantile plots of residuals and the Breusch–Pagan test for heteroskedasticity were also used. For segmented Poisson regression, models with overdispersion were used. Additionally, generalized additive models with splines were also used to investigate non-linear time trends within the study periods. The independence of residuals was investigated using their autocorrelation and partial autocorrelation functions that showed no significant autocorrelation, thus justifying the independence assumption. \(P\) values of <0.05 were considered to be statistically significant for all tests. Analyses were performed using R statistical software version 2.10.1.

**Results**

**Impact of the programme on antibiotic use**

During the pre-intervention period, a constant and significant overall increase in FQ (essentially ofloxacin and ciprofloxacin) consumption was observed (on average, \(+0.37\) DDD/1000 PD/month; \(P=0.006\) \[(Figure 1]\), starting from an average 123.1 DDD/1000 PD. The monthly FQ consumption then dropped by 29.1 DDD/1000 PD (95% CI 13.1–45.9; \(P=0.0005\)), from a mean of 148.2 to 119.1 DDD/1000 PD (i.e. 19.6%) during the intervention period. A sustained and significant decrease in FQ consumption was also observed during the post-intervention...
period, from a mean of 118.2 to 77.5 DDD/1000 PD (20.95 DDD/1000 PD/month; $P = 0.0002$).

A statistically significant change in slope of yearly consumption of antibiotics other than FQs was also found during the post-intervention period as compared with the pre-intervention period ($P = 0.001$) (data not shown). This decrease was significantly lower than that of FQ use, with an average decrease by 6.0%/year for non-FQ antibiotics as compared with 10.1% for FQs ($P < 0.0001$).

The study of yearly FQ use in CCLIN-Nord hospitals showed a much lower FQ use rate compared with our hospital, but that did not change during the study period (average non-significant increase 0.4 DDD/1000 PD/year, 95% CI $-1.4$ to $+2.1$, $P = 0.62$) (Figure 2).

**ABHR solution use**

The monthly ABHR solution consumption from January 2000 to January 2010 is reported in Figure 3. The use of ABHR solution remained low until September 2002. From October 2002 it began to increase non-linearly in time ($P < 0.0001$). Consumption of ABHR solution gradually increased until September 2006, stabilized for about 15 months, then showed a sharp and sustained increase through to January 2010.

**Changes in antibiotic resistance**

Overall, 2239 specimens of *P. aeruginosa* and 3760 specimens of *S. aureus* were isolated during the study period and tested for FQ and methicillin resistance, respectively. The number of monthly analysed isolates of *P. aeruginosa* increased from a mean of 18.5 (SD 5.4) at the beginning of the study period to 28.2 (SD 8.0) at the end, while the monthly number of *S. aureus* specimens remained stable—on average, 37.6 (SD 10.2) throughout the study period.

During the pre-intervention period, the rate of FQ-resistant *P. aeruginosa* isolates did not vary linearly with time ($P = 0.008$ in the Poisson model) (Figure 4). The mean observed resistance rate was 42% (SD 13) in the first 6 months of 2002 and 42% (SD 9) in the last 6 months before implementation of the intervention. During the intervention period, the FQ-resistant *P. aeruginosa* rate did not vary significantly ($P = 0.60$). In the post-intervention period; however, the time trend for FQ
resistance of *P. aeruginosa* was significantly modified as compared with pre-intervention (*P*=0.011). The FQ resistance rate of *P. aeruginosa* continuously decreased to 26%, with a constant relative change rate of −13%/year (95% CI −19 to −5, *P*=0.001).

The rates of *S. aureus* isolates resistant to methicillin are depicted in Figure 5. On average, 26% (SD 7) of isolates were resistant to methicillin in the first 6 months of the pre-intervention period, 26% (SD 9) during the last 6 months of the pre-intervention period, and 14% (SD 3) during the last 6 months of the post-intervention period (Figure 5). The model best fitting the data showed a significantly lower rate of resistance in the post-intervention period, with a decrease during the intervention period from a mean resistance rate of 27% to 21% (95% CI 9 to 9), whereas a non-significant decrease was observed in the post-intervention period (relative change rate per year −7%, 95% CI −15 to 2).

Changes in FQ-resistant *P. aeruginosa* and MRSA rates were confirmed when adjusting the analysis on the consumption of ABHR solution.

**Discussion**

In this study we demonstrated the sustained efficacy of a programme aimed at decreasing the use of FQs; their use decreased significantly over almost 4 years following the implementation of this intervention. The durability of the effect of an intervention on physician antibiotic-prescribing behaviour has been evaluated in a few studies. The long-lasting effect of our programme on FQ use may be due, in part, to the continuous educational outreach visits by the antimicrobial stewardship infectious diseases-trained physician to providers after the intervention period. Of note, no formulary restriction was used, although this would contribute significant reductions in antimicrobial use. When analysing data from institutions in the CCLIN-Nord network as a control, we observed that FQ use during the pre-intervention period at Saint-Louis hospital was much higher. This may be explained by the major clinical activities in HIV, haematology and oncology in our hospital. However, we showed that, unlike Saint-Louis hospital, FQ use did not decrease in other hospitals. This reinforced the assertion that FQ use decreased in our hospital was a direct result of the programme we implemented.

We also assessed whether the reduction in FQ use translated into a decrease in antimicrobial resistance. We observed a significant decrease in FQ-resistant *P. aeruginosa* and MRSA rates. We should be cautious, however, before concluding that there is a causal association with the decrease in FQ use, particularly if we look at three factors. First, a decrease in the MRSA rate was also observed in other French hospitals of the Assistance Publique–Hôpitaux de Paris, hospitals that are closed to Saint-Louis hospital in terms of location, structure and recruitment. However, the reduction of the MRSA rate in our hospital was shifted in time, with a delay of 5 years (2000 versus 2005) as compared with other hospitals, suggesting that this evolution was an independent event and was not related to a regional effect. Second, the decrease of total antibiotics use, other than FQs, during the study period also could have led to the decrease in antimicrobial resistance rates. However, the decrease in total antibiotic use was significantly lower than that of FQs alone, suggesting that this was not the main trigger of resistance improvement. Third, the constant increase in ABHR solutions use during the pre-intervention period and thereafter also may have
contributes to the decrease in antibiotic resistance rates. However, the MRSA rate was not significantly modified during the pre-intervention period, although ABHR solutions use increased up to 20 L/1000 PD and there is no demonstrated benefit of ABHR solution use on \( P. \text{aeruginosa} \) FQ resistance.

Regression analyses used in our study allow the estimation of associations between the intervention and microbial resistance and FQ use.\(^{19} \) The strength of our analysis is that we used data from multiple pre- and post-intervention time intervals (i.e. months) to estimate the slope. The use of at least 10 observations per model parameter is usually suggested to avoid overfitting.\(^{19} \) A number of studies looking at the relationship between antibiotic consumption and microbial resistance used one point of measurement per year; that is too few to allow a time series analysis.\(^{24} \)

Few intervention studies have attempted to decrease antimicrobial resistance by active antibiotics policies, with most studying MRSA rates only.\(^{17,25–29} \) A Cochrane review, published in 2005, did not present strong evidence to support MRSA control by antibiotic stewardship interventions.\(^{16} \) As for \( P. \text{aeruginosa}, \) studies looking at the effects of a decrease in FQ use on FQ resistance rates are scarce and provide little evidence.\(^{30,31} \)

However, our study has a number of limitations. The design was not a randomized controlled trial. Consequently, statistical association between a decrease in FQ use and a favourable impact on resistant pathogens could not be formally demonstrated. Furthermore, rates of antimicrobial resistance and the isolation of resistant bacteria in hospitals are affected by various factors, including infection control practices, usage patterns for antibiotics, local epidemiology and the medical and surgical procedures performed at the hospital. Our study was not designed to look at all these aspects. However, we did ascertain that neither outbreaks of MRSA or \( P. \text{aeruginosa} \) nor infection control policy changes occurred during the study time frame. We could also not discriminate between cross-transmission and antimicrobial selection pressure in the levels of bacterial resistance observed.

Thus, we demonstrated the long-lasting impact of a FQ control programme on FQ use by combining several types of action maintained over time. If our study could not demonstrate that decreasing FQ use led to reduced FQ-resistant \( P. \text{aeruginosa} \) and MRSA rates, it suggests nevertheless the positive impact of FQ use reduction on antimicrobial resistance.

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