American Journal of Infection Control 47 (2019) 180–185

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Cohorting to prevent acquisition of multidrug-resistant bacteria: An interrupted time series study

Micheli Coral Arruda MSc [a*], Raquel Souza de Aguiar BSc [a], Wagner Mariano Jardim [b], Luiz Henrique Melo MD [a], Tiago Mendonça MSc [c], Alexandre Biasi Cavalcanti MD, PhD [a], Paulo Henrique Condeixa de França PhD [b]

[a] *Dona Helena Hospital, Joinville, Brazil*
[b] *University of Region of Joinville (Univille), Joinville, Brazil*
[c] *Insper Teaching and Research Institute, São Paulo, Brazil*

Key Words:
Patient isolation
Infection control
Bacterial infections
Microbial drug resistance

A B S T R A C T

Background: Grouping patients who acquired resistant microorganisms within a single area (cohorting) has been used to prevent cross-transmission. We aimed to assess cohorting effectiveness in the absence of an outbreak.

Methods: An interrupted time series study was performed in a general hospital considering patients admitted to wards. In the first year, patients who acquired multidrug-resistant (MDR) bacteria were isolated without physical transfer. In the second year, cohorting was implemented, and patients with mixed MDR bacteria were transferred to individual rooms in a specific isolation unit. Cultures were requested upon clinician orders, and surveillance or routine cultures were not performed. The effect of cohorting on the incidence density of MDR bacteria acquisition was assessed using segmented regression analysis.

Results: In the first and second years, 2.0 and 2.8 cases per 1,000 patient-days acquired MDR bacteria. The length of hospitalization and mortality rate were similar between phases. There was a linear increase of the monthly incidence densities of MDR bacteria acquisition in the first year (β_1: 0.11; 95% confidence interval [CI]: −0.02 to 0.24), though without an immediate impact of cohorting (β_2: −1.32; 95% CI: −3.81 to 1.16) or a change in the temporal trend (β_3: 0.04; 95% CI: −0.14 to 0.23) from the first to second phase.

Conclusion: Cohorting may not reduce the incidence density of MDR bacteria acquisition in the absence of an outbreak.

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The incidence of infections associated with multidrug-resistant (MDR) bacteria has increased worldwide. It is estimated that 700,000 deaths per year are caused by MDR bacteria, with projections of this number reaching 10 million in 2050, surpassing diseases and conditions such as cancer, diabetes, and trauma.[1] The presence of MDR bacteria, particularly in highly complex hospital environments, significantly affects morbidity and mortality, length of hospitalization, and expenditures on diagnostics and therapeutic procedures.[1]

Given the significant potential of causing outbreaks, hospitals have implemented policies to prevent the spread of MDR bacteria. One of these policies is cohorting, which is defined as the action of grouping patients who acquired the same organism in specific areas or units to avoid cross-transmission to other patients.[2,3] However, studies evaluating the effect of cohorting have yielded conflicting results.[4] Additionally, most of the studied initiatives implemented cohorting during outbreaks, complicating results interpretation given that the phenomenon of regression to the mean might totally or partly account for the observed decrease in the rates of MDR bacteria acquisition.[2,5-8] Indeed, guidelines by medical societies suggest the use of cohorting of patients and health staff only during outbreaks.[9]

In August 2015, a private general hospital in Brazil adopted the policy of cohorting in the absence of MDR bacteria outbreaks, transferring adult patients who acquired MDR bacteria and were hospitalized in units other than the intensive care unit (ICU) to a specific

*Address correspondence to Micheli Coral Arruda, MSc, Dona Helena Hospital, Blumenau Street, 123, Joinville 89204-250, Brazil.
E-mail address: micheli.c@donahelena.com.br (M.C. Arruda).
Conflicts of Interest: None to report.

https://doi.org/10.1016/j.ajic.2018.07.025
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inpatient unit. The aim of this study was to assess whether this intervention reduced the incidence density of MDR bacteria acquisition compared to simple isolation in the patient's room of origin.

METHODS

Study design and setting

This was an observational, interrupted time series study. Retrospective data collection was aimed at comparing the incidence densities of MDR bacteria acquisition before and after the implementation of a specific inpatient unit to isolate patients who acquired MDR bacteria at the Dona Helena Hospital in Joinville, SC, in southern Brazil. The institution is a private tertiary general hospital with 188 beds. The study was conducted between August 2014 and July 2016.

The research was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study was approved by the Research Ethics Committee of the University of Joinville Region (CAAE no. 60242016.5.0000.5366), which dismissed the use of informed consent forms.

Patients

All patients older than 18 years were included in the study. Patients with cultures positive for MDR bacteria that were collected during hospitalization were considered cases of MDR bacteria acquisition. These cases were identified among patients under contact isolation. Patients from whom MDR bacteria were identified initially in the ICU or another health unit or those who were under isolation for other reasons, such as viral disease or transfer from another institution, were not included. Cultures were requested only upon doctors' orders (ie, surveillance or routine cultures were not performed at the institution).

Data collection

Collection of demographic, clinical, and laboratory data was performed by consulting electronic medical records. Collected data included age, gender, type of hospital admission (emergency or elective), whether a surgery procedure was performed during admission, origin before admission, culture results, reason of contact precaution, date of hospitalization, and date of discharge and hospital death.

Phases of the study and intervention

The first phase of the study comprised the period between August 2014 and July 2015, during which patients who acquired MDR bacteria were isolated without their physical transfer from the original hospital unit. The second phase comprised the period between August 2015 and July 2016. Starting in August 2015, patients who acquired MDR bacteria were transferred to a specific isolation unit (cohorting).

In the first phase, patients were assisted in rooms for 2 patients or individual rooms equipped with a bathroom. Only patients colonized or infected with the same MDR bacteria could share a room. In the second phase, patients were cared for in individual rooms equipped with a bathroom.

In both phases, the policy of relative and friend visitation to patients was the same. The number of persons visiting the patient was limited to 2. In addition, visitors were instructed to use gowns and gloves. During the second phase, both equipment and staff (nurses) were dedicated to the cohorting area. Conversely, physicians and other health care assistants (respiratory therapists, psychologists, and others) were not exclusive to the cohorting area.

Outcomes

The primary outcome was the incidence density of MDR bacteria acquisition. The MDR bacteria definition adopted in the institution and used in this study was an adaptation of the definition recommended by the National Healthcare Safety Network, which considers MDR bacteria as those resistant to 1 key antimicrobial agent.[10] The following microorganisms were considered MDR bacteria: *Staphylococcus aureus* resistant to oxacillin; *Pseudomonas aeruginosa* resistant to 1 of these antibiotics: ceftazidime or cefepime or ciprofloxacin or carbapenems; *Acinetobacter baumannii* complex resistant to ceftazidime or carbapenems; *Escherichia coli*, *Klebsiella* spp, and *Proteus mirabilis* resistant to third-generation cephalosporins and/or producers of extended-spectrum beta-lactamases (ESBL); bacteria within the *Citrobacter* spp, *Enterobacter* spp, *Serratia* spp, *Providencia* spp, and *Morganella* spp (CESP) group, *Burkholderia cepacia*, bacteria from the *Ralstonia* spp complex, and *Stenotrophomonas maltophilia* exhibiting intrinsic resistance to several antimicrobials; *Enterococcus* spp resistant to vancomycin; *Klebsiella* spp resistant to carbapenems; and other enterobacteria producers of carbapenemases.

Statistical analysis

The study sample size was defined by convenience. Categorical variables were expressed as absolute numbers and percentages, and continuous variables were expressed as means and standard deviations (mean ± standard deviation). The t test was used to compare quantitative variables, and the χ^2 test was used to compare qualitative variables.

We assessed the effect of the intervention on the monthly incidence densities of MDR bacteria acquisition with segmented regression analysis performed with a generalized estimating equation model.[11] Month and cohorting were explanatory variables. In addition, a first-order autoregressive structure of correlation among the observations was considered. In the model, β_0 estimates the base level of the incidence density of MDR bacteria acquisition, β_1 estimates the linear trend of incidence-density variation along the preintervention period, β_2 estimates the immediate effect of the intervention, and β_3 estimates the change in linear trend of incidence-density variation along the postintervention period in relation to the preintervention period. As a sensitivity analysis, the cases of MDR bacteria acquisition who stayed in the ICU before being admitted to an inpatient unit were disregarded due to the possibility that the MDR bacteria initially detected in the inpatient unit was potentially acquired in the ICU.

The incidence densities of MDR bacteria acquisition were calculated per 1,000 patient-days, and the comparison among the incidence densities was accomplished through Poisson regression with a logarithmic link function.[12] The results were presented as incidence-density ratios, 95% confidence intervals (CIs), and *P* values. The results were considered significant when the *P* values were less than .05. We did not adjust *P* values or 95% CIs for multiplicity of hypothesis testing; thus, all analyses of secondary outcomes must be interpreted as exploratory only. R software (R Core Team, 2017, Vienna, Austria) was used for the analyses.

RESULTS

Patient features

During the study, 23,293 patients were hospitalized in inpatient units. In total, 11,677 were hospitalized in the first phase (with no isolation unit), and 11,616 were hospitalized in the second phase (with an isolation unit) (Fig 1). The demographic and

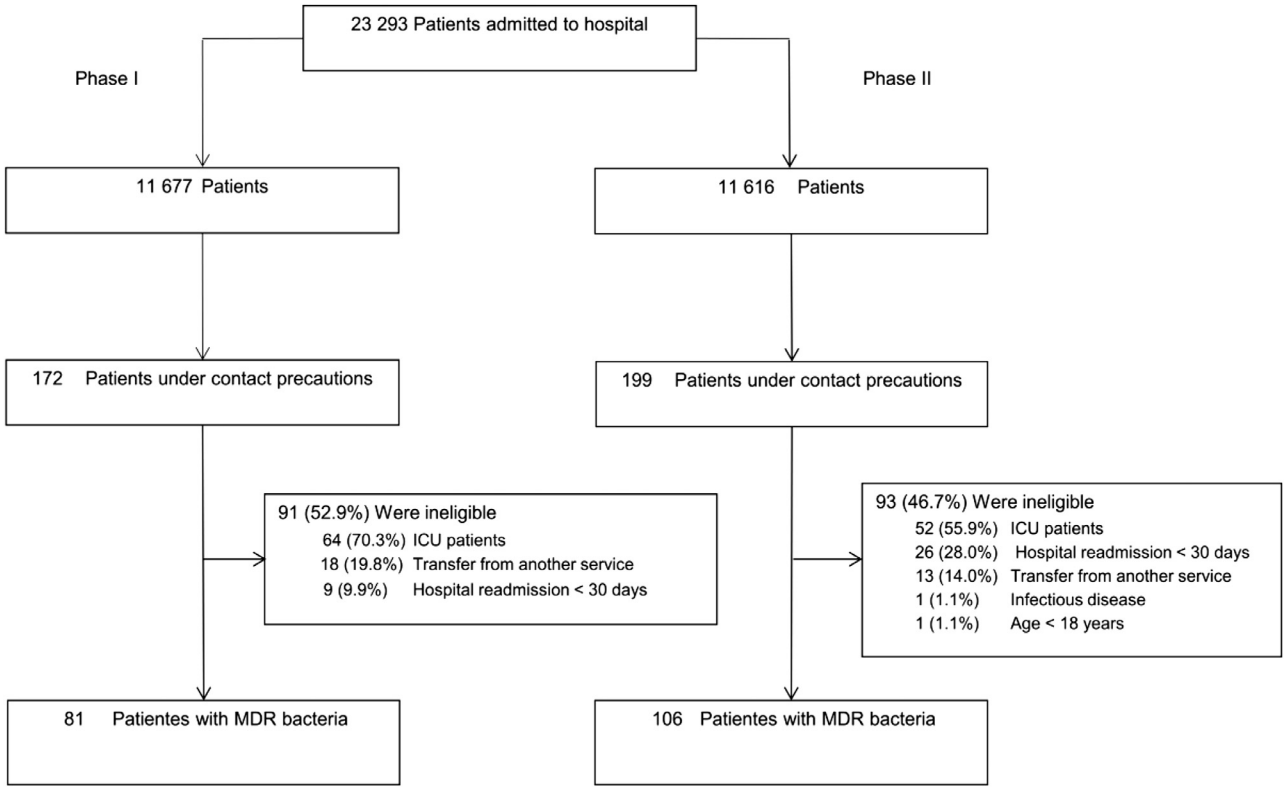

Fig 1. Patient flow before and after the implementation of cohorting.

clinical characteristics of the patients hospitalized in the study periods are presented in Table 1. Significant differences were noted between the first and the second phases for age (37.6 ± 19.3 years and 38.4 ± 19.8 years; $P = .002$) and gender (65.8% and 64.5% of females; $P = .04$). Most patients underwent surgeries, without differences between the 2 phases (74.5% and 73.9%; $P = .26$). The duration of hospitalization (4.3 ± 8.8 days and 4.2 ± 9.0 days; $P = .45$) and hospital mortality (1.6% and 1.9%; $P = 0.23$) were also similar between the 2 phases.

Effect of the implementation of a specific inpatient isolation unit

A total of 172 patients were isolated in the first phase and 199 in the second phase. Among these, respectively, 81 and 106 patients acquired MDR bacteria in the inpatient unit. The demographic and clinical characteristics of the patients were similar between the 2 phases (Table 2).

The incidence densities of MDR bacteria acquisition were 2.0 and 2.8 cases per 1,000 patient-days in the first and second phases of the study, respectively, with an incidence-density ratio of 1.35 (95% CI: 1.01-1.81; $P = .04$) (Table 3). The incidence densities of acquisition of specific bacteria were similar between the phases for most microorganisms except *E. coli*, which exhibited an increased incidence in the second phase ($P = .03$). Similarly, no difference was noted between the phases when the incidence densities were assessed based on the resistance mechanisms except for the CESP group, which exhibited an increased incidence in the second phase ($P = .04$).

In the segmented regression analysis model (Fig 2), used to evaluate the interrupted time series, a nonsignificant trend toward increase in the monthly incidence densities of MDR bacteria acquisition was identified starting in the first phase (β_1: 0.11; 95% CI: −0.02 to 0.24; $P = .10$). However, there was no immediate effect of cohorting on the incidence density of MDR bacteria acquisition (β_2: -1.32; 95% CI: −3.81 to 1.16; $P = .28$). Additionally, the trend of variation in the

Table 1
Characteristics of patients hospitalized in the study periods

Characteristic* mean ± sd are mean and standard deviation	Phase I, before cohorting ward (n = 11,677)	Phase II, after cohorting ward (n = 11,616)	*P* value
Age, y*	37.6 ± 19.3	38.4 ± 19.8	.002
Female sex, n (%)	7,684 (65.8)	7,496 (64.5)	.04
Admission type, n (%)			
Emergency	6,727 (57.6)	6,643 (57.2)	.53
Elective	4,950 (42.4)	4,973 (42.8)	
Surgical procedures, n (%)			
Surgery on hospital day 1	6,980 (59.8)	6,819 (58.7)	.10
Surgery during any day of hospital stay	8,702 (74.5)	8,581 (73.9)	.26
Length of hospital stay, d*	4.3 ± 8.8	4.2 ± 9	.45
In-hospital death, n (%)	192 (1.6)	216 (1.9)**	.23

*Values are mean ± standard deviation.

Table 2
Characteristics of patients who acquired multidrug-resistant bacteria in the study periods

Characteristic	Phase I, before cohorting ward (n = 81)	Phase II, after cohorting ward (n = 106)	*P* value
Age, y*	59.2 ± 21.8	61.2 ± 21.2	.54
Female sex, n (%)	38 (46.9)	50 (47.2)	1.00
Admission type, n (%)			
Emergency	76 (93.8)	97 (91.5)	.75
Elective	5 (6.2)	9 (8.5)	
Surgical procedures, n (%)			
Surgery on hospital day 1	9 (11.1)	12 (11.3)	1.00
Surgery during any day of hospital stay	48 (59.3)	57 (53.8)	.55
Length of hospital stay, d*	25.4 ± 27.8	28.9 ± 30.9	.43
In-hospital death, n (%)	7 (8.5)	17 (16.2)	.18

*Values are mean ± standard deviation.

incidence density of MDR bacteria acquisition over time also did not change after the implementation of the isolation unit (β_3: 0.04; 95% CI: −0.14 to 0.23; *P* = .64).

In the segmented regression analysis excluding cases that passed through the ICU before admission to inpatient units (13 and 20 cases of the first and second phases, respectively), the estimated effects were similar to those of the main analysis (Figure 2).

DISCUSSION

In a general hospital, the transfer of patients with MDR bacteria to a specific isolation inpatient unit did not reduce the overall risk of acquiring these microorganisms compared to patients isolated in their unit of origin. Segmented regression analysis revealed a temporal trend toward increase in the incidence densities of MDR bacteria acquisition. However, no immediate effect of cohorting or a change in the trend over time were observed. Similarly, no reductions were noted in the incidence densities of specific species of bacteria classified according to resistance mechanisms. Actually, the incidences of some specific microorganisms were higher in the second phase, probably reflecting a subjacent secular trend.

In contrast to these results, other studies have reported a reduction in MDR bacteria incidence densities after the implementation of cohorting. In all clinical studies identified, the intervention was implemented during outbreaks; thus, a reduction in MDR bacteria incidence densities might have been explained by the phenomenon of regression to the mean rather than a specific effect of cohorting.[2,5-8] None of these studies assessed the cohorting of

Table 3
Incidence densities (per 1,000 patient-days) of multidrug-resistant bacteria acquisition during the study periods according to the microorganism and type of resistance

Microorganism	Phase I, before cohorting ward (n = 81)		Phase II, after cohorting ward (n = 106)		Incidence-density ratio (95% CI)	*P* value
	n	Incidence density	n	Incidence density		
Any antibiotic resistant-microorganism	81	2.0	106	2.8	1.35 [1.01-1.81]	.04
Specie						
Acinetobacter baumannii	1	0.0	2	0.1	2.06 [0.2-44.35]	.56
Acinetobacter lwoffi	1	0.0	0	0.0	—	—
Burkholderia cepacia	2	0.1	0	0.0	—	—
Citrobacter amalonaticus	1	0.0	0	0.0	—	—
Citrobacter freundii	1	0.0	1	0.0	1.03 [0.04-26.06]	.98
Citrobacter koseri	0	0.0	3	0.1	—	—
Enterobacter aerogenes	11	0.3	16	0.4	1.5 [0.7-3.32]	.30
Enterobacter cloacae	9	0.2	8	0.2	0.92 [0.34-2.4]	.86
Enterobacter gergoviae	0	0.0	2	0.1	—	—
Escherichia coli	10	0.3	22	0.6	2.27 [1.1-5.01]	.03
Klebsiella ozaenae	1	0.0	0	0.0	—	—
Klebsiella pneumoniae	14	0.4	10	0.3	0.74 [0.32-1.65]	.46
Morganella morganii	3	0.1	6	0.2	2.06 [0.54-9.77]	.31
Proteus mirabilis	2	0.1	0	0.0	—	—
Pseudomonas aeruginosa	11	0.3	12	0.3	1.12 [0.49-2.59]	.78
Pseudomonas fluorescens	1	0.0	0	0.0	—	—
Pseudomonas spp	0	0.0	1	0.0	—	—
Serratia liquefaciens	3	0.1	6	0.2	2.06 [0.54-9.77]	.31
Serratia marcescens	8	0.2	12	0.3	1.55 [0.64-3.95]	.34
Staphylococcus aureus	3	0.1	8	0.2	2.75 [0.79-12.55]	.14
Type of resistance						
Nonfermenting Gram-negative bacilli resistant to carbapenems	1	0.0	3	0.1	3.09 [0.4-62.5]	.33
CESP	35	0.9	53	1.4	1.56 [1.02-2.41]	.04
ESBL	18	0.5	21	0.5	1.2 [0.64-2.28]	.57
Enterobacteriaceae resistant to carbapenems	5	0.1	3	0.1	0.62 [0.13-2.52]	.51
MRSA	3	0.1	8	0.2	2.75 [0.79-12.55]	.14
Gram-negative bacilli resistant to 3rd- or 4th-generation cephalosporins	4	0.1	0	0.0	—	—

CI, confidence interval; *CESP*, *Citrobacter* spp, *Enterobacter* spp, *Serratia* spp, *Providencia* spp, and *Morganella* spp; *ESBL*, extended-spectrum beta-lactamase; *MRSA*, methicillin-resistant *Staphylococcus aureus*.

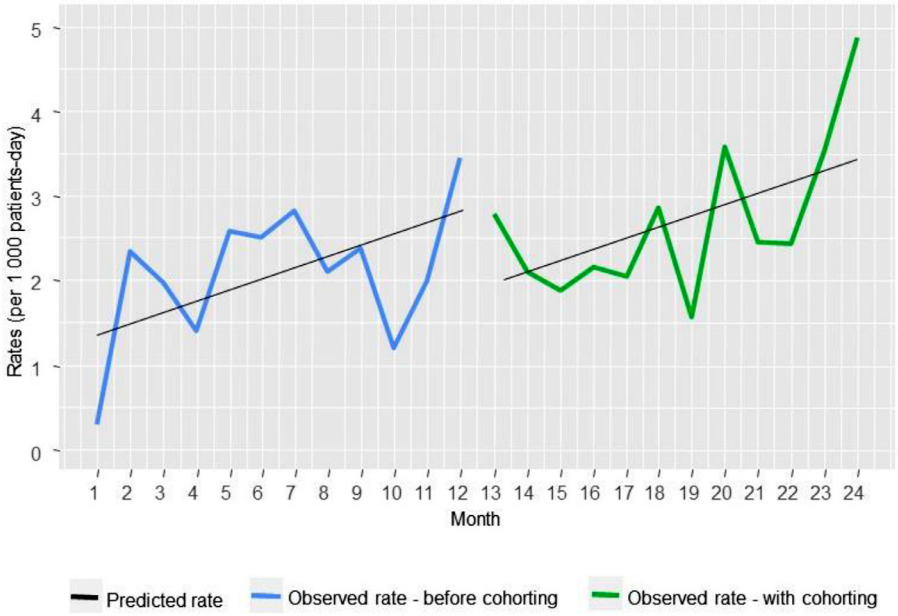

Fig 2. Observed and predicted incidence densities of MDR bacteria acquisition before and after the implementation of cohorting. The results of the generalized estimating equation model are as follows:

β_0 (baseline incidence density): 1.43; 95% CI: 0.59-2.28; $P = .002$;

β_1 (temporal trend prior to intervention): 0.11; 95% CI: −0.02 to 0.24; $P = .10$;

β_2 (immediate effect of intervention): −1.32; 95% CI: −3.81 to 1.16; $P = .28$;

β_3 (temporal trend after the intervention): 0.04; 95% CI: −0.14 to 0.23; $P = .64$.

patients and health workers as an isolated intervention in endemic scenarios.[9] A key feature of our study that may explain the observed differences compared to the results of other studies is that cohorting was implemented in periods of endemic MDR bacteria rates (ie, there was no ongoing outbreak).

Additionally, other differences that limit the comparison of our study and others include focusing on patients admitted to ICUs, children, and the implementation of an intervention package (rather than cohorting only).[2,4,13,14] However, a study in which the use of contact precautions and cohorting were used as the measures to reduce the epidemic spread of *K pneumoniae* resistant to carbapenems suggests that cohorting alone was effective.[15]

A few studies observed a positive effect of cohorting on specific microorganisms. For instance, a unicentric study in Puerto Rico demonstrated that, in a high-risk unit, the cohorting of patients with *K pneumoniae* in an ICU rapidly controlled the outbreak.[16] Cohorting of patients in a unicentric study with patients of a surgical unit and medical clinic in New York (USA) helped reduce the infection rate by methicillin-resistant *Staphylococcus aureus* acquired in the hospital and the length of stay in the unit.[17] In our study, we did not observe reductions in infection incidence densities of specific microorganisms.

Our study had limitations. The main limitation was the absence of a properly randomized control group. Confounding variables, particularly temporal trends, may introduce bias and limit the interpretation of results of studies with historical control.[18] The generalized estimating equation considering a correlation structure among the measures aims to minimize this issue; however, it is possible that residual biases exist. Second, a major limitation was that periodic surveillance cultures are not conducted in the institution, which may be associated with an inadequate sensitivity for the detection of cases colonized with MDR bacteria, leading to increased random error and reduced precision of the estimated effects. Thus, even if a true beneficial effect in the rates of MDR bacteria occurred, the study might have missed it. Third, patients colonized or infected with different bacteria were grouped in the same cohorting floor in the second phase, potentially raising the risk of a patient acquiring an MDR bacteria that they did not have from a neighbor. However, it must be reinforced that patients were always cared for in individual rooms in the cohorting area. Fourth, patients colonized with ESBL are systematically put at contact precautions in our institution. It is possible that some of those patients acquired these bacteria in the community. That fraction of ESBL rate could not have been prevented by an in-hospital intervention such as cohorting—only further spreading would. Fifth, an intervention evaluated in a single hospital limits the potential of generalizing the results of the study. Finally, it is possible that some patients acquired MDR bacteria in the ICU; however, the detection occurred only after the patient was discharged from the ICU and during admission to an inpatient unit. Obviously, as the intervention would affect only patients in the inpatient unit, this condition would reduce the ability of the study to estimate the effect of the intervention. Nevertheless, results of a sensitivity analysis excluding cases that were hospitalized in the ICU before being transferred to the ward were consistent with the main analysis.

CONCLUSIONS

In this interrupted time series conducted in a single general hospital in the absence of an MDR outbreak, the transfer of non-ICU adult inpatients with MDR bacteria to a specific inpatient unit (cohorting) did not reduce the incidence density of MDR bacteria acquisition compared to simple isolation in the patient's room of origin. Nevertheless, our study had several limitations; thus, further studies on this issue are warranted. Those studies should consider methodological aspects, such as the existence conduction of periodic surveillance cultures and expansion of the study sample size. In addition, robust design with cluster randomization and a sufficient number of participating institutions are desirable.

ACKNOWLEDGMENTS

We thank the directors and the staff of Hospital Dona Helena who provided support for conducting this study.

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