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Antimicrobial drug use, alcohol-based hand disinfection and the burden of methicillin-resistant Staphylococcus aureus – A time series approach at a German University Medical Center

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Antimicrobial drug use, alcohol-based hand disinfection and the burden of methicillin-resistant *Staphylococcus aureus* – A time series approach at a German University Medical Center

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Keywords: antibiotic use; alcohol-based hand rub; hand hygiene; MRSA; time series

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Abstract

Background: The objective of our study was to identify the impact of antibiotic consumption and alcohol-based hand rub solution use on the incidence of nosocomial infections with methicillin-resistant *Staphylococcus aureus* (MRSA).

Methodology: A multivariate time series approach using the monthly incidence of nosocomial MRSA infections (infections per 1000 patient days, 01/2003 – 10/2007) as the dependent variable was carried out at Freiburg University Medical Center, a 1600 bed tertiary care hospital. The volume of alcohol-based hand rub solution used per month was quantified in liters per 1000 patient days. Antibiotic consumption was defined as monthly defined daily doses (DDD) per 1000 patient days. A multivariate regression model was built using a polynomial distributed lag (PDL) model.

Results: A mean of 0.074 nosocomial MRSA infections was identified per 1000 patient days. Alcohol-based hand rub was found to have a significant influence on the incidence of nosocomial MRSA infections (p<.0001). The multivariate analysis showed that a higher volume of use of alcohol-based hand rub is associated with a lower incidence of nosocomial MRSA infections. Conversely, a higher level of consumption for selected antimicrobial agents was followed by a higher incidence of nosocomial MRSA infections. In detail, the analysis showed this same relationship for the use of second-generation cephalosporins (p=0.003), third-generation cephalosporins (p=0.0077), fluoroquinolones (p=0.0013), lincosamides (p=0.076) and tetracyclines (p=0.0011). Furthermore, temporal relationships were observed between the incidence of patients admitted with MRSA and the incidence of nosocomial MRSA infections (p=0.06), i.e. a higher incidence of patients admitted with MRSA was associated with a higher incidence of nosocomial MRSA infections. The final model explained 76 % of the monthly variations in the incidence of nosocomial MRSA.

Conclusion: In a multivariate time-series analysis, we were able to demonstrate that both hand hygiene and rational use of antibiotics are the keys for prevention of nosocomial MRSA infections.

Introduction

The emergence and spread of methicillin-resistant *Staphylococcus aureus* (MRSA) is still an unresolved problem both in Germany and worldwide.[1, 2]

Prevention strategies for healthcare-associated MRSA can generally be divided into the following groups: (1) screening programs for early detection of MRSA, (2) decontamination strategies for sustained reduction of MRSA carriage; (3) improved compliance with hand disinfection to decrease transmission dynamics and (4) reduction of antibiotic selection pressure through the implementation of antibiotic control policies.[3]

In particular, stepping up efforts to improve hand disinfection and reduce antibiotic consumption are considered to be strategies for sustained control of MRSA.[4-8] The purpose of this study was to use a time series analysis to verify the impact of hand disinfection and antimicrobial use on MRSA at a German University Medical Center. Therefore, a multivariate regression model was built to identify the dynamic relationship between the use of different antimicrobial agents and alcohol-based hand rub and the incidence of nosocomial MRSA infections. The time series analysis methodology has been demonstrated to be a suitable method for investigation of the relationship between antibiotic consumption, infection control practices and the emergence and spread of antimicrobial resistance in general and MRSA, in particular.[9-12]

Methods

Setting

The analysis took place at University Medical Center Freiburg, a 1600 bed tertiary care hospital covering all the medical specialties and with approximately 54 000 inpatient admissions annually.

Data Collection

For each month of the study period (January 2003 to October 2007), data were collected on antimicrobial consumption, the volume of alcohol-based hand rub used, the number of hospitalization days and the number of nosocomial infections with MRSA.

Monthly quantities of all antimicrobial drugs and alcohol-based antiseptics for hand disinfection delivered to each in-patient unit were extracted from the pharmacy accounting system. Antimicrobial consumption was expressed in defined daily doses (DDD) following the definition of the WHO ATC index, while the use of antiseptics was expressed in liters. At the University Medical Center Freiburg only alcohol-based antiseptics are used for hand disinfection.

The number of monthly nosocomial MRSA infections was extracted from an existing database that registers MRSA cases for the Department of Infection Control, and for the German Nosocomial Infection Surveillance System. An MRSA infection was defined as being nosocomial if MRSA were detected more than 48 h after hospital admission. Finally, the number of hospitalization days was used to express all variables in values per 1000 patient days.

Study design

A time-series analysis using the incidence of nosocomial MRSA infections (infections per 1000 patient days) as the dependent variable was carried out to explore the influence of antimicrobial use and the volume of alcohol-based hand rub used on the burden of MRSA.

To increase the explanatory content of the analysis, we used nosocomial MRSA infections rather than nosocomial MRSA colonizations as the dependant variable, and thus only considered the hardest parameter for the burden of MRSA.

Besides standard precautions, at University Medical Center Freiburg barrier precautions are generally recommended for all patients colonized or infected with MRSA. These include single room placement or cohorting, wearing of gloves and gowns and screening of room-mates. However, in daily practice, recommendations are not always followed.

All the variables were logarithmically transformed. All the antimicrobials were included in the first analysis with the exception of glycopeptides, linezolid, daptomycin, tygecycline and fosfomycin because their application may be a result rather than a cause of MRSA, which fact could bias the analysis, the aim of which is to model MRSA as a result of antimicrobial consumption.

As a first step, the relationship between each independent variable (antimicrobial agents; alcohol-based hand rub) and dependent variable (MRSA incidence) was explored by computing ordinary least squares regressions. The purpose of single regressions was to quantify the relationship between the independent and the dependent variables and to identify lag structures for the final multivariate regression model.[14]

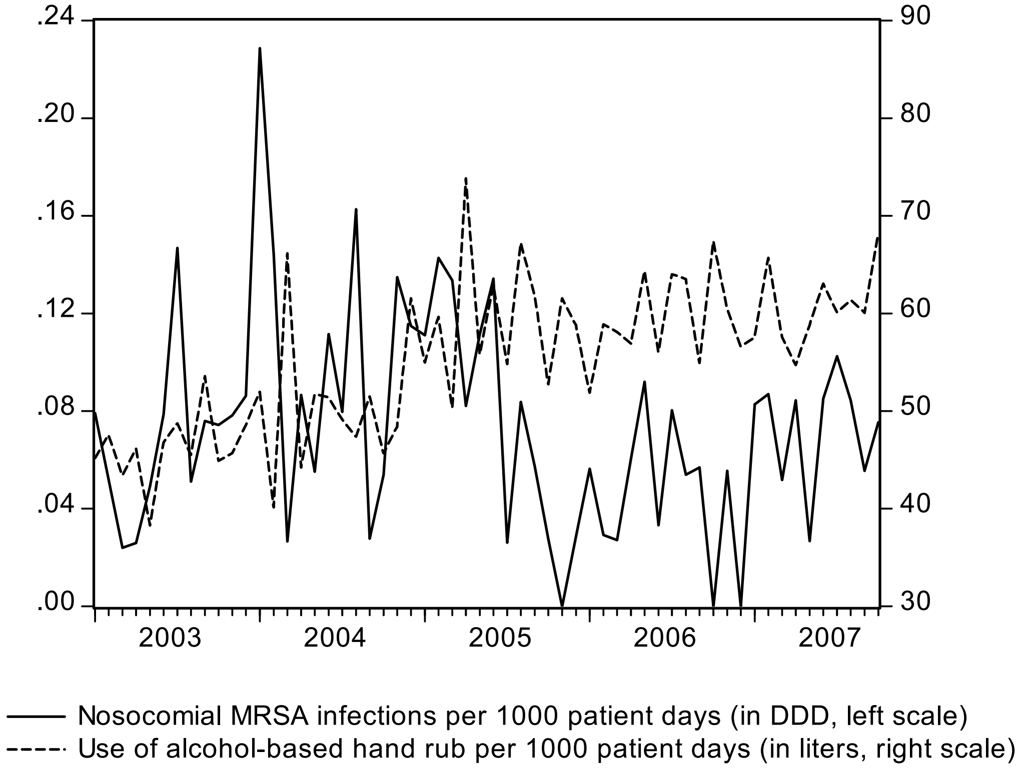
Next, we built a multivariate model to explain MRSA incidence by the selected independent variables. Additionally, the incidence of patients admitted with MSRA (both colonizations and infections) was integrated as an independent variable. To address the fact that for some variables more than one lag was identified as being statistically significant, a polynomial distributed lag (PDL) modelling approach was used for the multivariate regression analysis. The whole analysis was performed using Eviews 5.0 (Quantitative Micro Software, Irvine, California, USA). See appendix for a detailed description of the statistical model.

Results

Incidence of MRSA

From January 2003 to October 2007, a mean incidence of 0.48 MRSA cases, 0.16 nosocomial MRSA cases and 0.074 cases of nosocomial MRSA infection per 1000 patient days was documented at Freiburg University Medical Center. Our data show a mean incidence of 0.32 for patients admitted with MRSA (both infections and colonizations) over the same period. Whereas there was a slight increase in the incidence of all MRSA cases (based on regressions of the series on time, $p<0.001$) and in the incidence of patients admitted with MRSA ($p<0.001$), a descending trend was seen in the incidence of nosocomial MRSA cases ($p=0.02$). No trend was observed in the incidence of nosocomial MRSA infections ($p=0.122$). For the dependent variable of the regression analysis, a peak was observed in January 2004 and in three periods (11/2005, 10/2006 and 12/2006) no cases of nosocomial MRSA infections were observed at all (Figure 1).

Figure 1. The number of nosocomial MRSA infections and the volume of alcohol-based hand rub used per 1000 patient days at Freiburg University Medical Center, January 2003 to October 2007



Antibiotic consumption and use of alcohol-based hand rub

The trends in the use of each class of antimicrobials and in alcohol-based hand rub are presented in Table 1. The overall monthly consumption of antimicrobials amounted to 595.3 DDD/1000 patient days and showed an ascending trend ($p<0.001$). Significant ($p<0.05$) increasing trends were observed for the use of fluoroquinolones, macrolides, third-generation cephalosporins, carbapenems, lincosamides, combinations of sulfonamides and trimethoprim and use of alcohol-based hand rub. A descending trend was observed in the use of penicillins with extended spectrum.

Table 1. Characteristics of the estimators and transfer function models explaining the monthly number of nosocomial MRSA infections per 1000PDs

Possible explanatory variables	Average monthly use[a]	Trend[b]	p value[b]
All antimicrobials[b]	595.3 (472–693.6)	Upward	<0.001
Second-generation cephalosporins	177.7 (113.1–242.7)	No	0.463
Penicillins with extended spectrum	70.9 (30.5–102.9)	Downward	<0.001
Fluoroquinolones[c]	64.5 (39.9–92.4)	Upward	<0.001
Macrolides	47.4 (29–73.8)	Upward	<0.001
Combinations of penicillins with β-lactamase inhibitors	44.3 (27.7–58)	No	0.243
Third-generation cephalosporins	44.1 (26.4–66.9)	Upward	<0.001
β-lactamase-sensitive penicillins	41.1 (26.5–63.3)	No	0.178
Imidazoles	30.4 (21.2–68.2)	No	0.623
Lincosamides	23.1 (10.6–41.8)	Positive	0.08
Carbapenems	17.2 (1.5–47.2)	Upward	<0.001
Combinations of sulfonamides and trimethoprim	14.5(0–56.7)	Upward	<0.001
Tetracyclines	10.8 (1–31.3)	No	0.817
Aminoglycosides	9.1 (3.7–15.3)	No	0.225
Alcohol-based hand rub	55.1 (38.3–73.8)	Upward	<0.001

[a]Quantities of antimicrobials are expressed in DDD per 1000 patient days, those of Alcohol-based hand rub in liters per 1000 patient days.
[b]Based on regressions of the series on time.
[c]The use of glycopeptides, linezolid, daptomycin, tygecycline and fosfomycin is not present in the table.
[c]Including all fluoroquinolones except moxifloxacin.

According to the Augmented Dickey-Fuller Unit Root Test, the series of both fluoroquinolones and carbapenems were initially non-stationary. Stationarity was attained for fluoroquinolnes by taking moxifloxacin use out of the series. Moxifloxacin was introduced in late 2005 and showed a strongly ascending trend. The series of carbapenem use could not be modified to obtain stationarity, and therefore was not integrated into the final model.

Final model

The estimated multivariate model included seven statistically significant explanatory variables, i.e. second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones, licosamides, tetracyclines, alcohol-based hand rub and the incidence of patients admitted with MRSA. To construct the final model we started integrating variables that showed a significant relationship according to the results of the single regression analyses (see methods above), but in the end tested all variables for relevance.

Positive coefficients were estimated for all antimicrobial classes integrated into the final model. This shows that temporal increases/decreases in the volume of antimicrobial consumption are followed by a temporal increase/decrease in the incidence of nosocomial MRSA infection. Since all the variables were normalized due to logarithmical transformation, a one percentage increase of, say, the use of fluoroquinolones is associated with a 1.16 percent increase in the incidence of nosocomial MRSA infections after a time lag of four months (Table 2). Thus, all coefficients estimated for antimicrobial consumption equal the average percentage change in the incidence of nosocomial MRSA infections after a one percent change in the use of the selected antimicrobials, with a varying lag of time (Table 2).

Table 2. Multivariate model to explain the monthly number of nosocomial MRSA infections (R^2=0,76)

Explanatory variable	Lag	Coefficient	T-statistic	P-value
Second-generation cephalosporins	1	1.61	3.21	0.003
Third-generation cephalosporins[a]	3-4	1.15	2.79	0.0077
Fluoroquinolones[a]	4	1.16	3.53	0.0013
Lincosamides[a]	2	0.32	1.83	0.076
Tetracyclines[a]	7	0.22	3.59	0.0011
Alcohol-based hand rub[b]	3-7	-5.41	-7.43	<.0001
Patients admitted with MRSA[c]	0	0.33	1.95	0.06
Autoregressive term[d]	1	-0.48	-3.13	0.0037

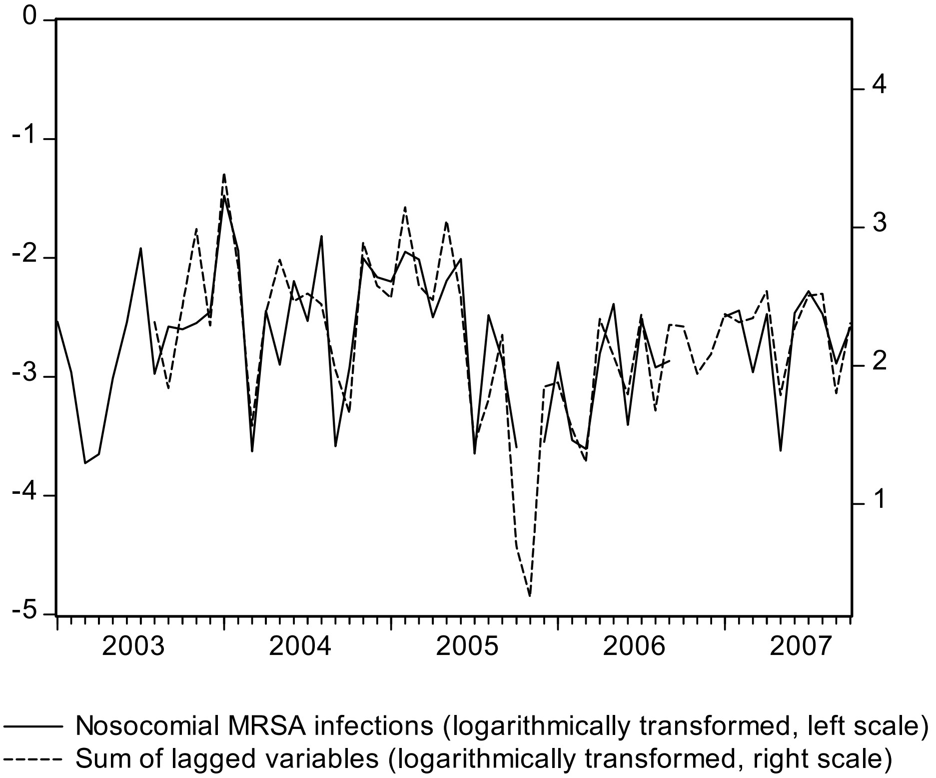
[a]In DDD/1000 patient days.
[b]In liters/1000 patient days.
[c]Patients admitted with MRSA infections or colonisations/1000 patient days.
[d]The autoregressive term represents the past incidence of MRSA.

Furthermore, the incidence of patients admitted with MRSA (both colonized and infected) was also included in the multivariate analysis. According to the estimated coefficient each change in the incidence of patients admitted with MRSA was followed by a 0.33 percent change in the incidence of nosocomial MRSA infections.

Conversely, the algebraic sign of the coefficient estimated for the use of alcohol-based hand rub was negative, which shows that a temporal increase in the use of alcohol-based hand rub used is followed by a temporal decrease in the incidence of nosocomial MRSA infections. Graphical representations between the monthly use of independent variables and the monthly incidence of nosocomial MRSA infections are displayed in Figure A-1 (see Appendix).

The model included an autoregressive term of order (lag) one and had a R^2 of 0.76 and an adjusted R^2 of 0.67. This means that the model fits the data relatively well, since up to 76 % of the monthly variations in MRSA are explained by the included variables (Figure 2).

Figure 2. The monthly number of MRSA cases and monthly sum of lagged independent variables as identified in the model



Discussion

The main objective of this study was to demonstrate the temporal relationship between certain classes of antimicrobials, hand disinfection and the incidence of MRSA. The final model allows to quantify the impact of antimicrobial consumption on the MRSA incidence and demonstrates the efficiency of hand disinfection. Third-generation cephalosporin and fluoroquinolone consumption was positively correlated with MRSA incidence. Apparently, uses of these kinds of antibiotics have stimulating effects on MRSA in hospital settings. In contrast, use of alcohol-based hand rub has a negative effect on the MRSA incidence and is, therefore, able to prevent the transmission of these pathogens.

Hand disinfection prevents cross-transmission of MRSA pathogens and has been proven to decrease the frequency of MRSA isolates.[4-6, 8] For instance, Mahamat et al. found the introduction of alcohol gel for hand disinfection to be associated with a 21%, respectively 30% decrease in the MRSA incidence at two Scottish hospitals.[15]

Other comprehensive time series approaches have shown a relationship between antimicrobial consumption and the varying incidence of MRSA, and have identified fluoroquinolone, macrolides and third-generation cephalosporins as having a positive impact on MRSA.[11, 16] Antibiotic consumption imposes selective pressure on resistant micro organisms and therefore directly affects the incidence of MRSA. Two recent studies analyzed the dynamic relationship between antibiotic consumption, alcohol-based hand rub use and the incidence of nosocomial MRSA in hospitals in Switzerland and Northern Ireland using time series analysis.[9, 12] The two studies enrolled both colonized and infected patients as the MRSA incidence in their analysis. In our study, however, the MRSA incidence only includes infections. Thus, the estimated interrelations between antimicrobial consumption, alcohol-based hand rub use and the incidence of MRSA directly affected the major burden of MRSA, i.e. the number of infections.

Especially the relationship between fluoroquinolone use and MRSA has previously been attested by time-series analysis.[11, 16, 17] Additionally, a number of other studies using different methodologies have linked fluoroquinolone use with MRSA colonizations and infections.[15, 18-22] A matched case-control study in a German hospital, for instance, identified fluoroquinolone use to be an independent risk-factor for MRSA carriage.[19]

In vitro studies have demonstrated that fluoroquinolone use has unique effects on the expression of resistance determinants and on fibronectin binding proteins in MRSA.[23] Besides fluoroquinolones, antimicrobials such as cephalosporins, clindamycin and tetracyclines, which are ineffective against MRSA, but have good tissue diffusion, could promote the acquisition of MRSA by increasing patient receptiveness to colonization and infection.

In conclusion, the analysis shows that selective pressure (antibiotic consumption) and transmission by hand are the two major driving parameters for the occurrence of MRSA in the hospital setting.

Appendix

To develop the final model, we followed a two-step approach. In the first step, we identified the relevant (significant) types of antimicrobials and their lag structure using OLS and the Akaike information criterion. We tested for stationarity using the Augmented Dickey Fuller test which is provided by the Eviews statistical package. All the relevant variables (the dependent and independent variables) are stationary at the ten percent level.

In the second step, we developed a multivariate model of the MRSA level with the selected antimicrobials and the variable alcohol-based hand rub. Because the series of alcohol-based hand rub and third-generation cephalosporins had more than one significant lag and as our sample has only 58 observations, we impose a smoothness condition on the lag coefficients using an Almon polynomial distributed lag (PDL) model. In contrast to unconstrained (classical) PDL models, the Almon approach puts a constraint on the coefficients i.e. that the estimators $\beta_0, \beta_1, \ldots \beta_q$ are situated on a polynomial of a low degree:

$$\beta_i = \upsilon_0 + \upsilon_1 \cdot i + \upsilon_2 \cdot i^2 + \ldots + \upsilon_d \cdot i^d = \sum_{k=0}^{d} \upsilon_k \cdot i^k \qquad (1)$$

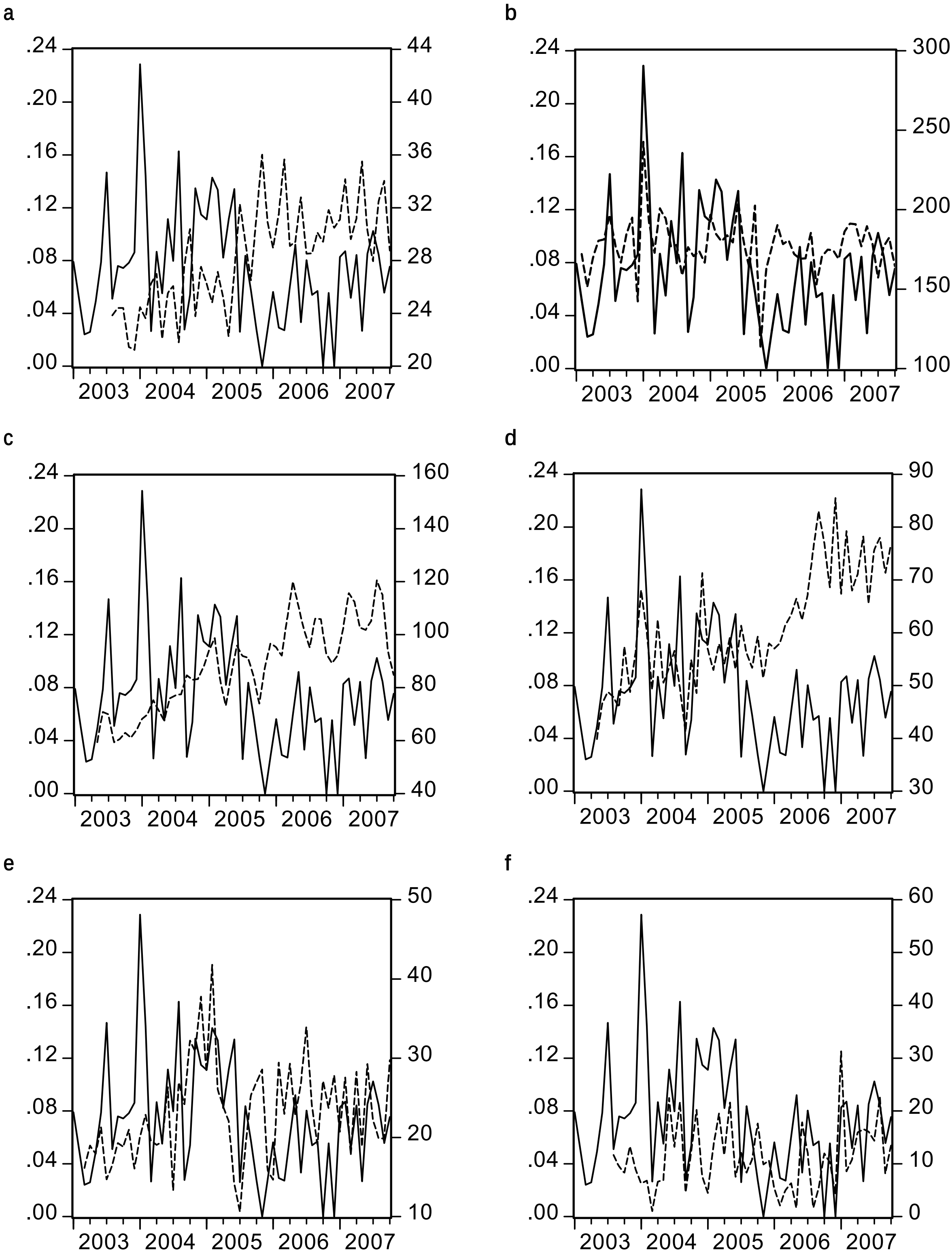
This leads to our final model which can be described as follows

$$\begin{aligned} HA-MRSA_t = \alpha + \beta_{2GC} 2GC_{t-1} + \sum_{i=3}^{4} \beta_{3GC,i} 3GC_{t-i} + \beta_{FQ} FQ_{t-4} + \beta_{LIN} LIN_{t-2} + \\ \beta_{TEt} TET_{t-7} + \sum_{i=3}^{7} \beta_{AHD,i} AHD_{t-i} + CA-MRSA_t + u_t \end{aligned} \qquad (2)$$

where HA-*MRSA* stands for the incidence of nosocomial MRSA infections, 2*GC* for second-generation cephalosporins, 3*GC* for third-generation cephalosporins, *FQ* for fluoroquinolones, *LIN* for lincosamides, *TET* for tetracyclines, *AHD* for alcohol-based hand rub and CA-MRSA for the incidence of patients admitted with MRSA. As usual, the error term is labelled u_t. Furthermore, the model is fitted by a normal least squares approach.

Our model fits the data relatively well with a R-squared of 0.76 and an adjusted R-squared of 0.67. Also, the F-statistic shows its significance (F=9.05). We can reject the null hypothesis of serial correlation with the Breusch-Godfrey Test and the null hypothesis of heteroscedacity with the White Heteroskedacity Test.

Figure A-1. Graphical explorations of the monthly number of nosocomial MRSA infections and lagged values of explanatory variables.



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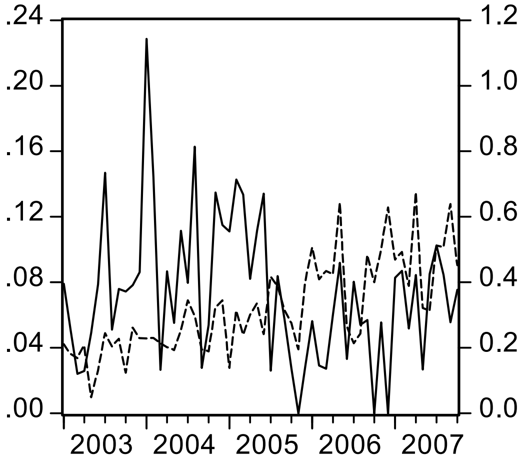

——— Nosocomial MRSA infections (left scale)
-------- Independent variables used for the final model (right scale); **a**) Use of alcohol-based hand rub (in liters, cumulated lags 3-7); **b**) Second generation cephalosporin use (in DDD, lag 1); **b**) Third generation cephalosporin use (in DDD, cumulated lags 3-4); **d**) Fluoroquinolone use (in DDD, lag 4); **e**) Lincosamide use (in DDD, lag 2); f) Tetracycline use (in DDD, Lag 7); **g**) Patients admitted with MRSA.

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