Making sense of antimicrobial use and resistance surveillance data: application of ARIMA and transfer function models

D. L. Monnet[1], *J.-M. López-Lozano*[2], *P. Campillos*[2], *A. Burgos*[2], *A. Yagüe*[2] *and N. Gonzalo*[2]

[1]Department of Microbiological Research and Development, Statens Serum Institut, Copenhagen, Denmark, [2]Investigation Unit, Pharmacy and Microbiology Laboratory, Hospital Vega Baja, Orihuela (Alicante), Spain

Clin Microbiol Infect 2001: 7 (Supplement 5): 29–36

INTRODUCTION

After years of attempts to generate regular data on bacterial resistance to antimicrobials using a sustainable methodology, several surveillance projects now collect and report such data at the regional, national or international level [1]. These projects rely mainly on two methodologies, i.e. centralized testing of isolates or electronic collection of local susceptibility data. On-going surveillance studies based on centralized testing have the advantage of providing very comparable susceptibility results but are costly and lack timeliness. However, with some initial investment, surveillance systems based on electronic collection of local data can provide timely results but certainly need careful evaluation of data through filter checks and external quality assessment of local susceptibility testing.

Antimicrobial consumption data can be obtained from various sources such as sales from pharmaceutical companies, pharmacy purchases, pharmacy issues, prescriptions or chart reviews. However, unlike resistance data, they are rarely made available for analysis. For hospitals, they generally consist of consumption data calculated by the pharmacy for the whole institution or at the hospitalization unit level. With a few exceptions, data on antimicrobial use at the patient level are only obtained through time-limited audits and therefore do not represent surveillance data.

While there has been a growing concern about increasing bacterial resistance worldwide, access to data concerning antimicrobial use remains limited, and could explain the small amount of literature on the relationship between antimicrobial use and resistance. In this paper, we will review previous attempts to study this relationship and present the application of time series analysis to antimicrobial use and resistance surveillance data.

Corresponding author and reprint requests: D.L. Monnet, Department of Microbiological Research and Development, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark
Tel.: +45 32688190
Fax: +45 32683887
E-mail: dom@ssi.dk

PRIOR APPROACHES TO UNDERSTANDING THE RELATIONSHIP BETWEEN ANTIMICROBIAL USE AND RESISTANCE AND THEIR LIMITATIONS

There is indirect evidence of a relationship between antimicrobial use and bacterial resistance. The various levels of evidence for this relationship, which include biological plausibility, consistent associations, demonstration of a dose–response relationship and concomitant variations, have been reviewed in detail by McGowan [2]. However, antimicrobial use is the major, but not the only, factor determining resistance in a defined ecologic system such as a hospital, which could explain why some studies failed to demonstrate a relationship. Failure to deal with these confounding factors, e.g. use of antibiotics other than the one studied, noncompliance with infection control practices, as well as selection biases and insufficient statistical power, are reasons for the difficulty in evaluating the impact of antimicrobial use on resistance [3].

Multicenter studies have been implemented to correct for selection biases and to increase the statistical power of analyses [4,5]. Unfortunately, these studies only identified associations or dose–effect relationships between antimicrobial use and resistance at the group level and did not study variations of these two variables over time. Such concomitant variations, i.e. changes in antimicrobial use followed by changes in resistance in the same direction, are probably the most convincing since they take into account the time sequence between the suspected cause and the observed effect. They have been reported from various single hospitals [6–13] or from single countries [14]. However, pooled data, covering one or several years, were used to analyse temporal associations observed between two time periods, which means that these studies could not measure the delay necessary to observe an effect of antimicrobial use on resistance. Because data were only available on a yearly basis, attempts to take this delay into account empirically considered a 1-year delay. For example, as shown in Figure 1b, Goossens et al found a correlation

between the percentage of gentamicin-resistant Gram-negative bacilli and gentamicin use during the previous year [15]. Interestingly, no correlation was observed when using gentamicin use from the same year (Figure 1a). Our experience at Hospital Vega Baja shows that there is often a 1-year delay, but not always. For example, as shown in Figure 2, we generally observed such variations of the percentage of ceftazidime-resistant Gram-negative bacilli following variations in ceftazidime use, except in 1996 when ceftazidime resistance increased following a decrease in ceftazidime use in 1995!

Similarly, there have been empiric attempts to take into consideration the use of several antimicrobials when modelling the relationship between use and resistance. Søgaard made the assumption that simultaneous occurrence of resistance traits or co-resistances were the result of the action of several antimicrobials, and that one should also take into account fractions of the use of these antimicrobials when studying the relationship with resistance [13]. He defined the coupling fraction cf_{BA} for an antimicrobial B (to explain resistance to antimicrobial A) as the percentage of isolates resistant to A that were also resistant to B. The corrected antimicrobial use $corrDDD_A$ was then calculated using the formula:

$$\text{corr } DDD_A = DDD_A + (DDD_B \times cf_{BA}) + (DDD_C \times cf_{CA}) + \ldots$$

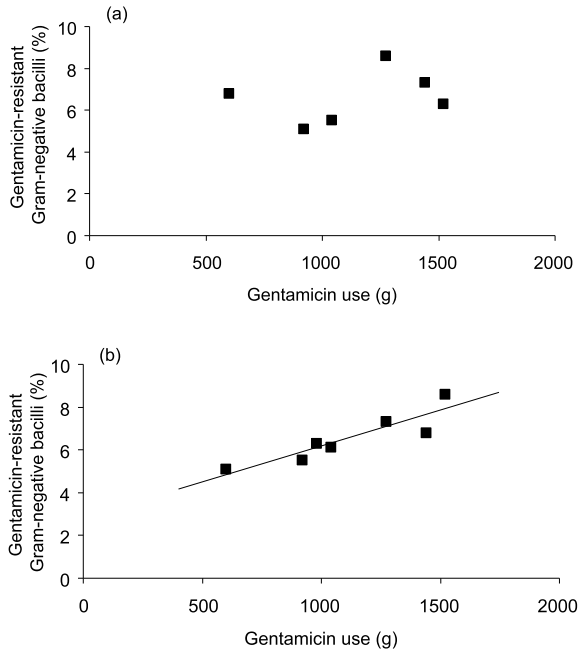

Figure 1 Percentage gentamicin-resistant Gram-negative bacilli and hospital gentamicin use, St Pieters University Hospital, Brussels, Belgium, 1979–86. Adapted from Goossens et al [15]. (a) Percentage gentamicin-resistant Gram-negative bacilli and hospital gentamicin use the same year (no correlation). (b) Percentage gentamicin-resistant Gram-negative bacilli and hospital gentamicin use the year before ($R = 0.90$, $P < 0.005$).

where DDD_A is the use of antimicrobial A expressed as a number of Defined Daily Doses per year, DDD_B is the use of antimicrobial B, cf_{BA} is the coupling fraction for B to explain resistance to A, etc. Usefulness of the method was later confirmed by Møller who found a higher degree of correlation with corrected antimicrobial use using coupling fractions than with use of a single antimicrobial [11]. Recently, Friedrich et al analyzed multiple-drug relationships in their hospital and identified numerous situations where a variation in the use of a single antimicrobial resulted in changes of susceptibility to other antimicrobials [16]. Finally, Crowcroft et al used a multiple linear regression model to show that several classes of antimicrobials were independent factors explaining a high percentage of methicillin-resistant *Staphylococcus aureus* in 50 Belgian hospitals [17].

APPLICATION OF TIME SERIES ANALYSIS TO ANTIMICROBIAL USE AND RESISTANCE SURVEILLANCE DATA

What is time series analysis?

Time series analysis corresponds to a group of techniques aimed at adjusting a mathematical model to a series of observations taken over time, or time series, for the purpose of predicting future behavior of the series based on its historical behavior, and trying to explain its characteristics as well as factors influencing the series. Unlike usual statistical methods that assume observed data to be realizations of independent random variables, time series analysis takes into account the possible relationship existing between consecutive observations [18]. This method is appropriate when data are measured repeatedly at equal intervals of time and when these intervals are much shorter than the period of observation.

In 1976, Box and Jenkins provided a practical method for modeling time series by use of so-called autoregressive integrated moving average (ARIMA) models that analyze the temporal behavior of a variable as a function of its previous values, its trends and its abrupt changes in the near past [19]. Since then this method has been used in various fields where data are collected at repeated intervals for long periods of time, such as econometry, engineering, meteorology and water resources research. More recently, it has been applied in medical specialties where such data are collected at the patient or population level, such as endocrinology, cardiology, environmental medicine and the study of chronic diseases [18,20]. Additionally, an extension of this method, called transfer function, allows the assessment of relationships between one or several time series [18]. In medicine, transfer function models have been used to study, for example, the relationship between weather parameters and mortality [21] or influenza and mortality [22].

Is time series analysis relevant to antimicrobial use and resistance data?

Time series analysis is clearly relevant to the analysis of data produced by surveillance activity, which consist of repeated measurements at regular intervals during long periods of time. Such data, e.g. monthly percentage of antimicrobial-resistant microorganisms or monthly number defined daily doses of antimicrobial per 1000 hospitalization days, can be produced by surveillance of antimicrobial use and resistance activity and correspond to the definition of time series. Observation of these time series shows short-term variations of both resistance and use levels, which could not be shown by using yearly data (Figures 2–4). Additionally, our experience shows that these consecutive measurements of resistance levels on the one hand, and of antimicrobial use on the other hand, are highly correlated from one period to one or several other periods (J. M. López-Lozano, unpublished data). This correlation should not be disregarded and classical statistical methods should not be used to analyze longitudinal antimicrobial use and resistance data since these methods necessitate independent observations. Instead one should make use of methods that take this correlation into account such as time series analysis.

What is needed to perform time series analysis?

We think that this type of analysis requires a minimum of 60 observations or time intervals, i.e. 15 years of trimester-level data, 5 years of monthly data or a little more than 1 year of weekly data. Resistance levels, expressed as a percentage (number resistant/number tested $\times$ 100) or as an incidence density (number resistant/1000 patient-days) must be calculated for each of these intervals during the whole period. These data are generally collected retrospectively to build the first models, then prospective surveillance is implemented to gather additional data. Although it would be interesting to use data collected at very short intervals, e.g. weeks, monthly data are generally preferred as a compromise between getting a maximum number of intervals using available data while keeping a sufficient number of isolates tested in each of these intervals. Additionally, antimicrobial use data (in g/1000 patient-days or in DDD/1000 patient-days) collected at the same intervals during the same period of time are needed to analyze the relationship between antimicrobial use and resistance.

As of now, we identified four software that perform time series analysis: SPSS Trends^{TM} 10.0 (SPSS Inc., Chicago, IL, USA), SAS/ETS 6.12 (SAS Institut Inc., Cary, NC, USA), SCA PC-UTS, PC-Expert and PC-MTS (Scientific Computing Associates Corp., Chicago, IL, USA) and Eviews 4.0 (Quantitative Micro Software, Irvine, CA, USA). All software operate in a Microsoft Windows environment; however, some procedures must still be performed using the software's programming language. The SCA modules offer fully automatized transfer function model construction. Each software has its preference regarding the method used for transfer function models, e.g. Haugh for SPSS Trends, Box–Jenkins for SAS/ETS, and Linear Transfer Function for SCA; however, SCA modules allow use of each of these methods when using programming language.

How to build ARIMA and transfer function models

The strategy for constructing an ARIMA model is based on a three-step iterative cycle of model identification, model estimation and diagnostic checks on model adequacy as described by Box and Jenkins [19]. Model identification consists in choosing a particular model of the ARIMA class from the observed time series. In some cases, differencing and other proper transformations, e.g. natural logs, are necessary to obtain a stationary series, i.e. a series with a constant mean and a constant variance through time. Once stationariness is achieved, the series autocorrelations (ACF) and partial autocorrelations (PACF) are examined to identify autoregressive (AR) behavior, i.e. related to the past values of the variable of interest, moving average (MA) behavior, i.e. related to abrupt changes in the near past, or mixed behavior (ARMA). At a second stage, parameters of the identified model are estimated by unconditional least squares or by likelihood functions. Goodness of fit is estimated and the determination coefficient R^2 is calculated. This coefficient corresponds to the percentage of the variance of the observed time series which is explained by the model. Finally, diagnostic checks are applied to determine whether or not the chosen model adequately represents the given time series. If not, the model must be modified and the three steps are repeated until an adequate model is achieved [18,19,22].

Transfer function allows modeling of the relationship between a target or output series (in our case, resistance) and one or several explanatory or input series (in our case, use of one or several antimicrobials). Several strategies have been proposed to build such models. We used the method proposed by Haugh [23] for Example 1 presented in this paper and the Linear Transfer Function (LTF) identification method proposed by Pankratz [24] for Example 2. In short, the method proposed by Haugh consists of identifying an adequate ARIMA model for both the output and the input time series, computing the cross-correlation function (CCF) between the residuals of each ARIMA model, identifying the systematic part of the transfer function model, i.e. the adequate lags between the output and input variables as a measure of how the input series is a leading indicator for the output series, introducing the lagged input series in the model, estimating

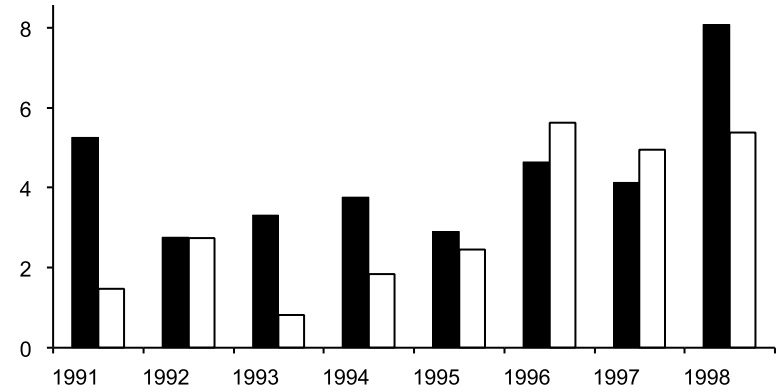

Figure 2 Yearly hospital ceftazidime use and percentage ceftazidime-resistant/intermediate Gram-negative bacilli, Hospital Vega Baja, Spain, 1991–98. ■ ceftazidime use (DDD/1000 patient-days); □, ceftazidime-resistant/intermediate Gram-negative bacilli (%).

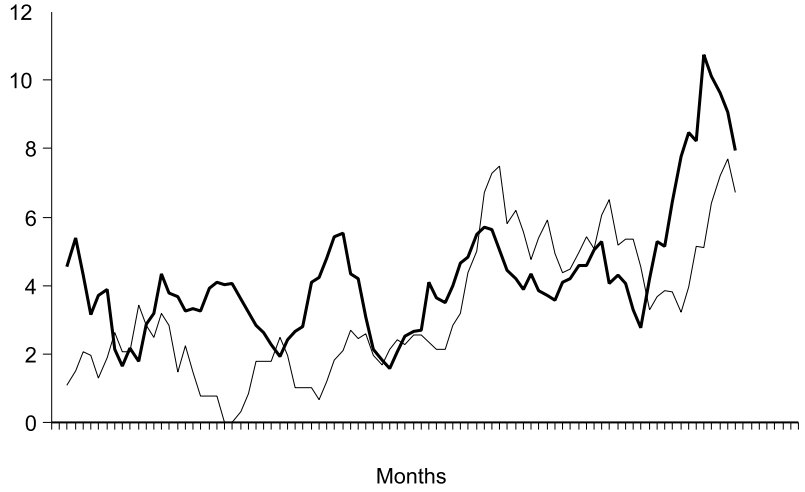

Figure 3 Smoothed monthly hospital ceftazidime use and percentage ceftazidime-resistant/intermediate Gram-negative bacilli (centered moving average of period 5), Hospital Vega Baja, Spain, 1991–98. Adapted from López-Lozano et al [26]. ▬, ceftazidime use (DDD/1000 patient-days); —, ceftazidime-resistant/intermediate Gram-negative bacilli (%).

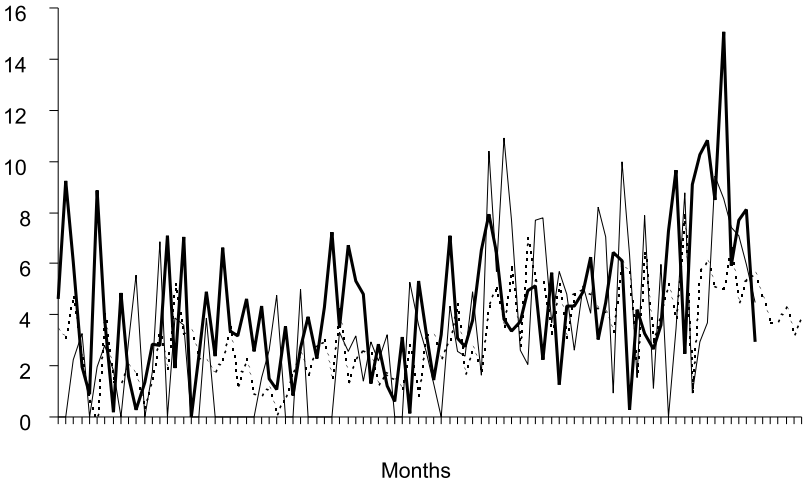

Figure 4 Monthly hospital ceftazidime use (observed) and monthly percentage ceftazidime-resistant/intermediate Gram-negative bacilli (observed and predicted by transfer function model, see Table 1), Hospital Vega Baja, Spain, 1991–98. Adapted from López-Lozano et al [26]. ▬, observed ceftazidime use (DDD/1000 patient-days); —, observed ceftazidime-resistant/intermediate Gram-negative bacilli (%); – – –, predicted ceftazidime-resistant/intermediate Gram-negative bacilli (%).

the parameters and performing diagnostic checks [18,23]. The LTF method consists in directly constructing a transfer function model with a reasonable number of lags for the input variable(s) approaching the stochastic part of the model using an autoregressive term of order 1 (AR1), then in eliminating nonsignificant terms and identifying an ARIMA model for the part of the model that is not explained, i.e. disturbances, and finally in estimating the parameters and performing diagnostic checks [24,25]. One advantage of the LTF method is that it allows multivariate transfer function modeling, i.e. the analysis of the effect of several input series on one output series.

Short-term forecasting of resistance, i.e. up to 6 months, can be obtained with ARIMA models (using past resistance data only) or transfer function models (using both past resistance and antimicrobial use data).

Example 1: Ceftazidime use and ceftazidime-resistant Gram-negative bacilli, Hospital Vega Baja, Spain, July 1991–December 1998 [26]

Figure 3 shows smoothed data on ceftazidime use and the percentage of ceftazidime-resistant Gram-negative bacilli. These curves were obtained using a 5-month MA transformation, i.e. the value plotted for a specific month is the average of the value observed this month, the previous 2 months and the next 2 months. Although these smoothed series have no statistical value, they give a better visual representation of the behavior of the two series and their possible relationship. To study this relationship, we used raw data as presented in Figure 4 and the methodology described above. The transfer function model is presented in Table 1 and can be interpreted as follows. The present percentage of ceftazidime-resistant Gram-negative bacilli is related to the percentage of the same resistance observed 3 and 5 months ago. An increase (or decrease) of 1 DDD/1000 patient-days of ceftazidime use results, with an average delay of 1 month, in an average increase (or decrease) of 0.42% of the percentage of resistance.

Table 1 Transfer function model for percentage ceftazidime-resistant/intermediate Gram-negative bacilli taking into account hospital ceftazidime use, Hospital Vega Baja, Spain, 1991–98 [26]

Term	Order[a]	Parameter[b] (SE)	T-ratio	*P*-value
Constant	0	1.354 (0.760)	1.78	0.078
Ceftazidime use	1	0.420 (0.096)	4.34	<0.0001
AR[c]	3	0.352 (0.096)	3.68	<0.001
AR	5	0.265 (0.098)	2.72	<0.01

[a]Delay necessary to observe the effect (in months).
[b]Size and direction of the effect.
[c]AR, autoregressive term representing past values of resistance.

The model can also be presented as the following equation:

$$\%R_{(t)} = 1.354 + 0.352\%R_{(t-3)} + 0.265\%R_{(t-5)} + 0.420U_{(t-1)}$$

where %R is the percentage of ceftazidime-resistant Gram-negative bacilli, t is the time in months, and U is the hospital ceftazidime use. The determination coefficient R^2 was 0.44. This means that this model, taking into account past antimicrobial use and past values of resistance, can explain 44% of the variations in the resistance series; the remaining 54% being due to other factors such as the use of other antimicrobials or infection control practices. Nevertheless, this model allowed us to predict the percentage of ceftazidime-resistant Gram-negative bacilli for the first 6 months of 1999 as 4.7, 3.9, 4.5, 4.2, 3.4 and 4.2, respectively (Figure 4). By using such transfer function models, similar results were obtained for imipenem use and imipenem-resistant *Pseudomonas aeruginosa* (Table 2) and various other antimicrobial–bacteria combinations in the same hospital.

Example 2: Use of aminoglycosides and third-generation cephalosporins and amikacin-resistant *P. aeruginosa*, Hospital Vega Baja, Spain, July 1991–September 1999 [27]

Figures 5 and 6 show smoothed data on the percentage of amikacin-resistant *P. aeruginosa* and use of various aminoglycosides and third-generation cephalosporins, respectively. Figure 5 clearly shows that, with one exception, there was no concomitant variation in amikacin use and the percentage of amikacin-resistant *P. aeruginosa*, suggesting that most variations of resistance were related to other factors. The transfer function model is presented in Table 3 and can be interpreted as follows. The present percentage of amikacin-resistant *P. aeruginosa* is related to the percentage of the same resistance observed 2 months ago. An increase (or decrease) of 1 DDD/1000 patient-days of amikacin use results, with an average delay of 7 months, in an average increase (or decrease) of

Table 2 Transfer function model for percentage imipenem-resistant/intermediate *P. aeruginosa* taking into account hospital imipenem use, Hospital Vega Baja, Spain, 1991–98 [26]

Term	Order[a]	Parameter[b] (SE)	T-ratio	*P*-value
Constant	0	4.388 (1.717)	2.56	<0.05
Imipenem use	1	0.400 (0.104)	3.83	<0.001
AR[c]	5	−0.247 (0.108)	−2.28	<0.05
MA[d]	1	−0.212 (0.106)	−2.00	<0.05
MA	6	−0.241 (0.105)	−2.29	<0.02

[a]Delay necessary to observe the effect (in months).
[b]Size and direction of the effect.
[c]AR, autoregressive term representing past values of resistance.
[d]MA, moving average term representing disturbances or abrupt changes of resistance.

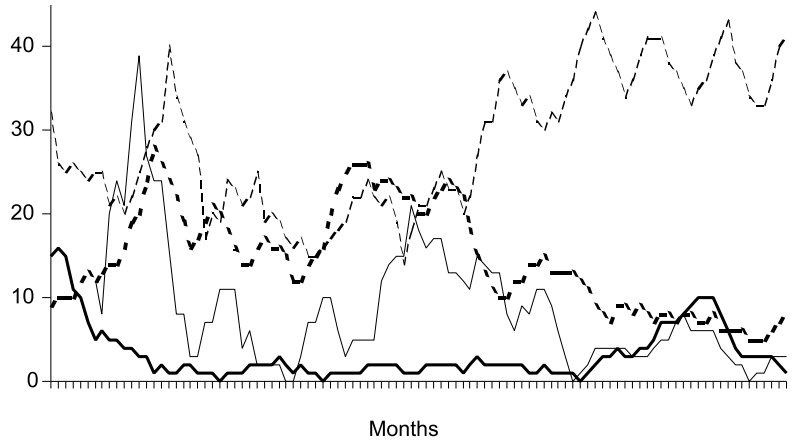

Figure 5 Smoothed monthly hospital use of various aminoglycosides and percentage amikacin-resistant/intermediate *P. aeruginosa* (centered moving average of period 5), Hospital Vega Baja, Spain, 1991–98. Adapted from López-Lozano et al [27]. ▬, amikacin use (DDD/1000 patient-days); ▪ ▪ ▪, gentamicin use (DDD/1000 patient-days); – – –, tobramycin use (DDD/1000 patient-days); —, amikacin-resistant/intermediate *P. aeruginosa* (%).

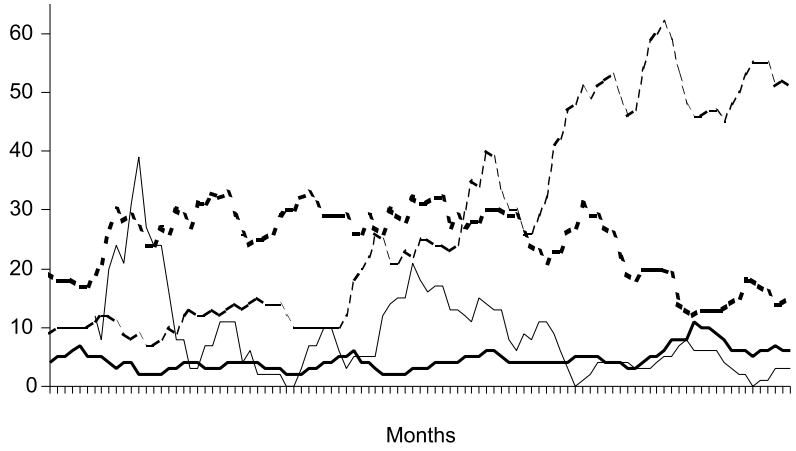

Figure 6 Smoothed monthly hospital use of various third-generation cephalosporins and percentage amikacin-resistant/intermediate *P. aeruginosa* (centered moving average of period 5), Hospital Vega Baja, Spain, 1991–98. Adapted from López-Lozano et al [27]. ▬, ceftazidime use (DDD/1000 patient-days); ▪ ▪ ▪, cefotaxime use (DDD/1000 patient-days); – – –, ceftriaxone use (DDD/1000 patient-days); —, amikacin-resistant / intermediate *P. aeruginosa* (%).

Table 3 Multivariate transfer function model for percentage amikacin-resistant/intermediate *P. aeruginosa* taking into account hospital aminoglycoside and third-generation cephalosporin use, Hospital Vega Baja, Spain, 1991–99 [27]

Term	Order[a]	Parameter[b] (SE)	T-ratio	*P*-value
Constant	0	−20.741 (4.516)	−4.59	<0.001
Amikacin use	7	0.973 (0.391)	2.49	<0.02
Gentamicin use	7	0.420 (0.153)	2.75	<0.01
Cefotaxime use	3	0.297 (0.112)	2.66	<0.01
Cefotaxime use	6	0.437 (0.110)	3.98	<0.001
AR[c]	2	0.295 (0.091)	3.24	<0.01

[a]Delay necessary to observe the effect (in months).
[b]Size and direction of the effect.
[c]AR, autoregressive term representing past values of resistance.

0.97% of the percentage of resistance. The same interpretation can be made for gentamicin use with an average delay of 7 months and an average effect on resistance of 0.42%, and for cefotaxime use with average delays of 3 and 6 months and an average effect on resistance of 0.73% (algebraic sum of both effects). No relationship with resistance was observed when we tried to include use of other aminoglycosides and other third-generation cephalosporins in the model.

As a verification, we examined co-resistance patterns among amikacin-resistant and amikacin-susceptible *P. aeruginosa* (Table 4). Resistance to amikacin in *P. aeruginosa* isolates was strongly associated with gentamicin resistance, less strongly, although significantly, associated with tobramycin and ceftazidime resistance, and not associated with cefotaxime resistance. However, one could read this table in another way and notice that more than 90% of amikacin-resistant *P. aeruginosa* isolates were also resistant to gentamicin and cefotaxime, whereas only 42.5% of isolates were resistant to tobramycin and 18.8% to ceftazidime. Data on ceftriaxone are difficult to interpret because only approximately half of the *P. aeruginosa* isolates were tested for susceptibility to this antimicrobial. Common sense suggests that within a population of bacteria an antibiotic selects for the bacteria that resist

Table 4 Antimicrobial co-resistance in amikacin-resistant/intermediate and amikacin-susceptible *P. aeruginosa* isolates, Hospital Vega Baja, Spain, 1991–99

Co-resistance	Amikacin-R/I[a] no. (%)	Amikacin-S[a] no. (%)	Risk ratio	*P*-value
Gentamicin-R/I	78 (97.5)	177 (17.5)	128.0	<0.0001
Cefotaxime-R/I	73 (91.3)	840 (83.0)	–	NS[b]
Ceftriaxone-R/I[c]	40 (81.6)	361 (74.7)	–	NS
Tobramycin-R/I	34 (42.5)	18 (1.8)	14.8	<0.0001
Ceftazidime-R/I	15 (18.8)	37 (3.7)	4.6	<0.0001

[a]R, resistant; I, intermediate; S, susceptible.
[b]NS, nonsignificant.
[c]Only 55.3% of isolates were tested for susceptibility to ceftriaxone.

this antibiotic. In our case, gentamicin use would select for gentamicin-resistant bacteria, including gentamicin-resistant Gram-negative bacilli that are almost all resistant to amikacin. This would result in an increase in the frequency of amikacin-resistant Gram-negative bacilli within this bacterial population. On the other hand, tobramycin use and ceftazdime use would select for a small percentage of amikacin-resistant Gram-negative bacilli isolates that would probably not result in an increase in their frequency within the bacterial population. These data on co-resistance are therefore consistent with the results obtained with the transfer function model.

CONCLUSION

During the past 20 years, there have been numerous attempts to study the relationship between antimicrobial use and resistance using surveillance data. The method presented here represents another of those attempts. It proved helpful to demonstrate a temporal relationship between antimicrobial use and resistance and, unlike most other methods, this method could take into account the use of several antimicrobials to explain one specific type of resistance, quantify the effect of use on resistance and estimate the delay between variations in use and subsequent variations in resistance. Additionally, it allowed us to predict future levels of resistance based on past antimicrobial use and resistance data. Our observations show that ecologic systems such as that within this hospital tend to react to changes in antimicrobial use much faster than previously thought, i.e. within a few months rather than several years. This finding has recently been confirmed by Corbella et al who reported rapid variations in the percentage of imipenem-resistant *Acinetobacter baumannii* following changes in carbapenem use in a Spanish hospital [28]. The recent application of time series analysis to antimicrobial use and resistance data from the primary health care sector in Denmark shows that this is probably also true outside hospitals [29]. In conclusion, time series analysis is a new tool that can help us make sense of antimicrobial use and resistance surveillance data, an area where modelling has proven difficult. Future developments must include confirmation of the usefulness of this method in other hospitals and in other countries. A multicenter project named ViResiST (Vigilancia de la Resistencia por medio del análisis de Series Temporales) is currently ongoing in several Spanish hospitals and hospitals in a few other countries.

REFERENCES

1. Monnet DL. Toward multinational antimicrobial resistance surveillance systems in Europe. *Int J Antimicrob Agents* 2000; **15**: 91–101.
2. McGowan JE Jr. Is antimicrobial resistance in hospitals related to antibiotic use? *Bull NY Acad Med* 1987; **63**: 253–68.
3. McGowan JE Jr. Ways and means to influence antimircobial prescribing in healthcare and its impact on resistance. In: Andremont A, Brun-Buisson C, McGowan JE Jr (eds). *Antibiotic Therapy and Control of Antimicrobial Resistance in Hospitals*, pp. 97–105. Amsterdam: Elsevier, 1999.
4. Monnet DL, Archibald LK, Phillips L *et al* Antimicrobial use and resistance in eight US hospitals: complexities of analysis and modeling. *Infect Control Hosp Epidemiol* 1998; **19**: 388–94.
5. Polk RE. Antibiotic use and resistance in US hospitals: MMIT/SCOPE network. In: *Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy*; 2000 September 17–20; Toronto, Canada, p. 527. Washington, DC: American Society for Microbiology, 2000.
6. Courcol RJ, Pinkas M, Martin GR. A seven year survey of antibiotic susceptibility and its relationship with usage. *J Antimicrob Chemother* 1989; **23**: 441–51.
7. Frank MO, Batteiger BE, Sorensen SJ. *et al* Decrease in expenditures and selected nosocomial infections following implementation of an antimicrobial-prescribing improvement program. *Clin Performance Quality Health Care* 1997; **5**: 180–8.
8. Gerding DN, Larson TA, Hughes RA, Weiler M, Shanholtzer C, Peterson LA. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. *Antimicrob Agents Chemother* 1991; **35**: 1284–90.
9. Ma MY, Goldstein EJ, Friedman MH, Anderson MS, Mulligan ME. Resistance of gram-negative bacilli as related to hospital use of antimicrobial agents. *Antimicrob Agents Chemother* 1983; **24**: 347–52.
10. Mouton RP, Glerum JH, van Loenen AC. Relationship between antibiotic consumption and frequency of antibiotic resistance of four pathogens–a seven-year survey. *J Antimicrob Chemother* 1976; **2**: 9–19.
11. Møller JK. Antimicrobial usage and microbial resistance in a University hospital during a seven-year period. *J Antimicrob Chemother* 1989; **24**: 983–92.

12. Natsch S, Conrad C, Hartmeier C, Schmid B. Use of amoxicillin-clavulanate and resistance in *Escherichia coli* over a 4-year period. *Infect Control Hosp Epidemiol* 1998; **19**: 653–6.
13. Søgaard P. The epidemiology of antibiotic resistance in three species of the *Enterobacteriaceae* and the relation to consumption of antimicrobial agents in Odense University Hospital. *Dan Med Bull* 1989; **36**: 65–84.
14. Seppälä H, Klaukka T, Vuopio-Varkila J *et al* The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N Engl J Med* 1997; **337**: 441–6.
15. Goossens H, Ghysels G, Van Laethem Y *et al* Predicting gentamicin resistance from annual usage in hospital. *Lancet* 1986; **2**: 804–5.
16. Friedrich LV, White RL, Bosso JA. Impact of use of multiple antimicrobials on changes in susceptibility of Gram-negative aerobes. *Clin Infect Dis* 1999; **28**: 1017–24.
17. Crowcroft NS, Ronveaux O, Monnet DL, Mertens R. Methicillin-resistant *Staphylococcus aureus* and antimicrobial use in Belgian hospitals. *Infect Control Hosp Epidemiol* 1999; **20**: 31–6.
18. Helfenstein U. Box-Jenkins modelling in medical research. *Stat Meth Med Res* 1996; **5**: 3–22.
19. Box GEP, Jenkins GM. *Time Series Analysis: Forecasting and Control*, 2nd edn. San Francisco (CA): Holden Day, 1976.
20. Crabtree BF, Ray SC, Schmidt PM, O'Connor PJ, Schmidt DD. The individual over time: time series applications in health care research. *J Clin Epidemiol* 1990; **43**: 241–60.
21. Saez M, Sunyer J, Castellsagué J, Murillo C, Antó JM. Relationship between weather temperature and mortality: a time series analysis approach in Barcelona. *Int J Epidemiol* 1995; **24**: 576–82.
22. Stroup DF, Thacker SB, Herndon JL. Application of multiple time series analysis to the estimation of pneumonia and influenza mortality by age 1962–83. *Stat Med* 1988; **7**: 1045–59.
23. Haugh LD. Checking the independence of two covariance-stationary time series: a univariate residual cross-correlation approach. *J Am Stat Assoc* 1976; **71**: 378–85.
24. Pankratz A. *Forecasting with Dynamic Regression Models*. New York, NY: Wiley 1991.
25. Liu LM, Hudak GB. *Forecasting and Time Series Analysis Using the SCA Statistical System*, Vol. 1. Oak Brook, IL: Scientific Computing Associated Corporation, 1992.
26. López-Lozano JM, Monnet DL, Yagüe A *et al* Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. *Int J Antimicrob Agents* 2000; **14**: 21–31.
27. López-Lozano JM, Monnet DL, Burgos Sanjose A, Gonzalo N, Campillos P, Yagüe A. Modelling the temporal relationship between use of amikacin and other antimicrobials and amikacin resistance in *Pseudomonas aeruginosa* isolates: a time series analysis. *Revista Española Quimioterapia-Spanish J Chemotherapy* 2000; **13 (Suppl. 2)**: 65.
28. Corbella X, Montero A, Pujol M *et al*. Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant *Acinetobacter baumannii*. *J Clin Microbiol* 2000; **38**: 4086–95.
29. Monnet DL. Antimicrobial use and resistance in Denmark. In: *Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 September 17–20; Toronto, Canada.* Washington, DC: *American Society for Microbiology*, 2000: p. 527.