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Modelling the impact of antibiotic use and infection control practices on the incidence of hospital-acquired methicillin-resistant *Staphylococcus aureus*: a time-series analysis

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***Objectives*: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen worldwide. A wide range of factors have been suggested to influence the spread of MRSA. The objective of this study was to evaluate the effect of antimicrobial drug use and infection control practices on nosocomial MRSA incidence in a 426-bed general teaching hospital in Northern Ireland.**

***Methods*: The present research involved the retrospective collection of monthly data on the usage of antibiotics and on infection control practices within the hospital over a 5 year period (January 2000–December 2004). A multivariate ARIMA (time-series analysis) model was built to relate MRSA incidence with antibiotic use and infection control practices.**

***Results*: Analysis of the 5 year data set showed that temporal variations in MRSA incidence followed temporal variations in the use of fluoroquinolones, third-generation cephalosporins, macrolides and amoxicillin/clavulanic acid (coefficients = 0.005, 0.03, 0.002 and 0.003, respectively, with various time lags). Temporal relationships were also observed between MRSA incidence and infection control practices, i.e. the number of patients actively screened for MRSA (coefficient = −0.007), the use of alcohol-impregnated wipes (coefficient = −0.0003) and the bulk orders of alcohol-based handrub (coefficients = −0.04 and −0.08), with increased infection control activity being associated with decreased MRSA incidence, and between MRSA incidence and the number of new patients admitted with MRSA (coefficient = 0.22). The model explained 78.4% of the variance in the monthly incidence of MRSA.**

***Conclusions*: The results of this study confirm the value of infection control policies as well as suggest the usefulness of restricting the use of certain antimicrobial classes to control MRSA.**

Keywords: hospital-acquired MRSA, antibiotic resistance, *S. aureus*

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a major nosocomial pathogen worldwide. In the UK, the proportion of *S. aureus* bacteraemia caused by MRSA has increased from 2% in 1990 to 43% in 2002.[1] Attempts to control the spread of MRSA have concentrated principally on transmission-based control policies such as active surveillance to identify colonized patients, patient isolation, environmental decontamination, hand hygiene and the use of barrier precautions, i.e. aprons or gowns and gloves.[2] These practices have been considered central to most national guidelines;[3–5] however,

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despite increased awareness, the incidence of hospital-acquired (HA) MRSA continues to rise, probably due to poor adherence to infection control practices.[2,6] The Society for Healthcare Epidemiology of America (SHEA) guidelines have reported that low adherence rates to hand hygiene practices of healthcare workers, averaging ~40%,[2] give rise to the increased MRSA incidence. In addition, guidelines for controlling MRSA in hospitals pay much less attention to controlling antibiotic use, although there is increasing evidence of a relationship between antibiotic use and the spread of MRSA.[7–10] There have been no studies to date which have combined data on both antibiotic use and infection control practices in order to comprehensively evaluate temporal relationships between these factors and MRSA incidence over time.

The objective of this study was to model the impact of antibiotic use and infection control practices on MRSA incidence in a medium-sized general hospital in Northern Ireland, using a time-series analysis. Unlike the classical statistical methods that assume that the observed data are independent random variables, time-series analysis takes into account the relationships existing between consecutive observations, a phenomenon known as autocorrelation.[11] This methodology has been proposed by López-Lozano *et al.*[12] as a suitable method to investigate the relationship between antibiotic use and the emergence of antimicrobial resistance.

Methods

The study was carried out in the Antrim Area Hospital in Northern Ireland, UK, a 426-bed district general teaching hospital serving a population of 420 000. The present retrospective investigation involved collecting data on a monthly basis on antibiotic use, infection control practices and the incidence of MRSA within the hospital over a 5 year period (January 2000–December 2004).

A retrospective review of the identified MRSA-positive patients' medical records was conducted using the clinical microbiology department standardized MRSA data collection form. Patients were classified as being HA-MRSA cases if they tested negative for MRSA on admission to the hospital but became MRSA-positive during subsequent testing >48 h after admission.[13] HA-MRSA cases included both infected and colonized patients. This means that HA-MRSA from both clinical and active screening samples were included. It was impossible to retrospectively assess whether cases were infected or colonized. However, each patient was counted only once, i.e. the first time MRSA was isolated, and repeat isolates during the same hospital stay were excluded.

Clinical samples were processed according to routine microbiology procedures. Gram-positive cocci were tested for catalase production, and catalase-positive colonies were then tested for coagulase, using the slide coagulase test. Slide coagulase-negative colonies were re-tested for coagulase using the tube coagulase test. Any coagulase-positive colony was subcultured onto non-selective blood agar for identification and susceptibility testing the next day using the Vitek 2 system (bioMérieux, Marcy l'Étoile, France). Antimicrobial susceptibility to a range of other antibiotics was then determined using the Vitek 2 method in accordance with the CLSI (formerly the NCCLS). Antimicrobial susceptibility patterns for MRSA isolates were obtained monthly from the clinical laboratory information system.

Additionally, a hospitalwide MRSA screening policy, followed by patient isolation if positive, was in place at the hospital throughout the study period. All patients (i) admitted with a previous history of MRSA, (ii) admitted from a residential or a nursing home, (iii) admitted from another hospital, or (iv) admitted to the intensive care unit, the neonatal unit or the renal unit were systematically screened for MRSA at hospital admission. Additional screening tests were performed in the case of MRSA outbreak. MRSA-positive patients were placed under contact isolation precautions. Active screening swabs were inoculated into Robertson's cooked meat broth at 30°C for 18–24 h. The broth was then subcultured onto oxacillin resistance screening agar (ORSA) and incubated at 35–37°C for 24 h. Colonies appearing blue on ORSA were tested for catalase production and catalase-positive colonies were then tested for coagulase, using the slide coagulase test. Slide coagulase-negative colonies were re-tested for coagulase using the tube coagulase test. The same procedure as for coagulase-positive colonies from clinical samples was then followed.

Bed occupancy data were obtained at monthly intervals during the study period to calculate the incidence of HA-MRSA per 100 bed-days.

The monthly quantities of each antibiotic delivered for patient care to each ward of the hospital were obtained from the pharmacy information system. These quantities were converted into a number of defined daily doses (DDDs) following the recommendations of the World Health Organization (WHO).[14] The numbers of DDDs of individual antibiotics were then grouped into classes belonging to group J01, i.e. antibacterials for systemic use, of the Anatomical Therapeutic Chemical (ATC) classification system from the WHO Collaborating Centre for Drug Statistics Methodology and were finally expressed as the number of DDDs per 100 bed-days.[14]

The total number of individual patients screened for MRSA every month and the results of these screening tests (positive or negative) were obtained from the clinical microbiology laboratory information system. Data were also collected on the monthly dispensed quantities of chlorhexidine (litres), alcohol-impregnated wipes (number), gloves (number of pairs), mupirocin (grams) and alcohol-based handrub (litres) from the hospital pharmacy information system. Data on each of these parameters were available monthly over the 5 year study period (January 2000–December 2004), with the exception of alcohol-based handrub which was introduced into the hospital from February 2002. The total number of individual patients screened for MRSA, as well as the quantities of chlorhexidine, alcohol-impregnated wipes, gloves, alcohol-based handrub and mupirocin, was finally expressed as a rate per 100 bed-days.

Linear regression was used to determine if there were significant changes in antibiotic use and infection control practices over the study period, using SPSS (version 14) for Windows.

Finally, dynamic regression (DR) models were used to study the relationships between antimicrobial use, infection control practices and incidence of HA-MRSA. Alcohol-based handrub use was modelled as an intervention variable coded '1' for the months of October 2002 and April 2004, and '0' for other months during the study period, thus reflecting bulk orders by the wards following hospitalwide promotion of hand hygiene.

DR models were developed as regression models, in which ARIMA models are used as disturbance. Construction of an ARIMA model for both the output and the input series was suggested before attempting to build a DR model by transfer functions. Linear transfer function (LTF) is one of several strategies used to build DR models and we used the approach proposed by Pankratz.[15,16] LTF shows how an output series (in the present case, HA-MRSA incidence) is related to the input series (use of various antimicrobial classes and infection control variables) by taking into account the possible time lags (delay for observing an effect of antimicrobial

use and infection control practices). It also takes into consideration the time structure (autocorrelation pattern) of the disturbance series. In building ARIMA and DR models, a three-stage model-building strategy was used, based on model identification, model estimation and model checking. In the DR model identification stage, LTF enabled a direct transfer function with a moderate number of lags for the input series to be built, approaching the stochastic part of the model using an autoregressive (AR) term with a low order. The augmented Dickey–Fuller test for unit roots was used for transformations and differentiation diagnosis series (Eviews 3.0, Quantitative Micro Software, Irvine, CA, USA). An appropriate tentative model from the DR family models that summarized these patterns and an ARIMA model for the disturbance were identified. In the second stage, parameters of the identified tentative model were estimated using a maximum-likelihood estimation method. Regression-type coefficients that represent the input–output relationship and ARIMA model coefficients that represent the disturbance series autocorrelation pattern were the parameters estimated with their approximated standard errors, tests of hypothesis and confidence intervals. The Akaike Information Criterion of the goodness of fit was estimated, together with the determination coefficient, R^2, corresponding to the percentage of the variance of the observed time-series explained by the model. In the model checking stage, the adequacy of the ARIMA model for the disturbance series in the DR model was examined using three diagnostic checks: (i) statistical significance of the parameters; (ii) checking of AR stationary parameters and the moving average (MA) invertibility parameters; and (iii) checking of residuals that effectively corresponded to white noise.

Results

Over the 5 year study period, there were 1381 MRSA cases identified out of a total of 177 709 admissions. Of the 1381 MRSA cases, 534 (38.7%) were classified as HA-MRSA and 847 (61.3%) were classified as colonized on admission. One hundred and eighty-seven (35%) HA-MRSA were isolated from clinical samples, whereas the remaining isolates resulted from patient screening. Among HA-MRSA cases, 275 (51.5%) were male patients, the mean age was 70.7 years ($n = 526$; range: 0.02–101.4 years) and the median duration of hospitalization was 17.84 days (range: 3–230 days). Two hundred and twenty-one (41.4%) patients with HA-MRSA were admitted from their own home, 99 (18.5%) from other hospitals and 96 (18%) from nursing homes. The source of admission could not be identified for 118 (22.1%) patients. The average observed monthly HA-MRSA incidence was 0.09/100 bed-days (range: 0.02–0.20). Analysis of the data on MRSA isolates that were obtained from the microbiology department showed that MRSA isolates were resistant to ciprofloxacin and erythromycin in 97.7% and 89.2% of the cases, respectively.

Trends in the use of each class of antibiotics are presented in Table 1. The use of most antibiotic classes remained constant during the study period. However, there were significant increasing trends in the use of combinations of penicillins with β-lactamase inhibitors (mostly amoxicillin/clavulanic acid), macrolides and fluoroquinolones, whereas other classes, e.g. penicillins with extended-spectrum and second-generation

Table 1. Characteristics of the monthly antimicrobial use in Antrim Area Hospital, January 2000–December 2004

Antimicrobial class (ATC group)	Average monthly use in DDD/100 bed-days (range)	Trend 2000–04	
		coefficient	*P* value
Tetracyclines (J01A)	0.7 (0.04–2.52)	0.220	0.092
Amphenicols (J01B)	0.02 (0–0.64)	−0.265	0.041
Penicillins with extended spectrum (J01CA)	3.26 (1.76–5.09)	−0.346	0.007
β-Lactamase-sensitive penicillins (J01CE)	1.25 (0.45–2.59)	−0.265	0.041
β-Lactamase-resistant penicillins (J01CF)	3.34 (1.38–5.81)	0.253	0.051
Combinations of penicillins including β-lactamase inhibitors (J01CR)	21.51 (12.02–42.6)	0.775	<0.0001
First-generation cephalosporins (J01DB)	0.47 (0.06–0.99)	0.362	0.005
Second-generation cephalosporins (J01DC)	3.51 (1.35–6.02)	−0.699	<0.0001
Third-generation cephalosporins (J01DD)	1.06 (0.48–2.64)	−0.212	0.104
Carbapenems (J01DH)	0.22 (0–1.11)	0.204	0.118
Trimethoprim and derivatives (J01EA)	2 (0.66–3.6)	−0.041	0.754
Combinations of sulphonamides and trimethoprim including derivatives (J01EE)	0.16 (0–1.31)	0.238	0.067
Macrolides (J01FA)	9.46 (4.25–20.21)	0.314	0.015
Lincosamides (J01FF)	0.39 (0–1.88)	0.141	0.283
Aminoglycosides (J01GB)	1.21 (0.41–4.05)	0.045	0.732
Fluoroquinolones (J01MA)	5.03 (1.65–11.73)	0.772	<0.0001
Glycopeptide (J01XA)[a]	1.01 (0.17–1.87)	0.616	<0.0001
Steroid antibacterials (J01XC)	0.52 (0–1.50)	0.64	<0.0001
Imidazole derivatives (J01XD)	3.83 (2.63–5.07)	0.277	0.032
Nitrofuran derivatives (J01XE)	0.18 (0–0.84)	0.153	0.244
Other antibacterials (J01XX)	0.12 (0–0.75)	0.353	0.006
Antibacterials for systemic use, total (J01)	59.76 (42.8–100.93)	0.719	<0.0001

[a]Mostly teicoplanin (J01XA02).

Table 2. Characteristics of the monthly infection control practices and related factors in Antrim Area Hospital, January 2000–December 2004

Variable (measurement unit)	Monthly average (range)	Trend 2000–04	
		coefficient	*P* value
Infection control practices			
alcohol-based handrub (L/100 bed-days)	0.17 (0–4.01)	0.189	0.149
alcohol-impregnated wipes (no./100 bed-days)	188.19 (72.56–362.2)	0.839	<0.0001
chlorhexidine (L/100 bed-days)	1.16 (0.82–1.58)	0.150	0.252
gloves (no. pairs/100 bed-days)	596.15 (301.05–1090.40)	0.896	<0.0001
mupirocin (g/100 bed-days)	1.69 (0.09–8.61)	−1.340	0.308
patients actively screened for MRSA (no./100 bed-days)	1.82 (0.85–3.89)	0.829	<0.0001
Other variable			
patients admitted with MRSA (no./100 bed-days)	0.14 (0.01–0.32)	0.253	0.051

cephalosporins, showed a significant decreasing trend in their use. Similarly, linear regression showed a significant positive trend for some infection control practices, i.e. the use of alcohol-impregnated wipes, the use of gloves and the number of patients actively screened for MRSA, whereas other practices remained fairly stable (Table 2).

Multivariate time-series analysis showed significant relationships between the incidence of HA-MRSA and a number of potential explanatory variables. Statistically significant positive relationships were observed for the use of fluoroquinolones, third-generation cephalosporins, macrolides and amoxicillin/clavulanic acid with various time lags (Table 3). The model showed that temporal variations in HA-MRSA incidence followed temporal variations in fluoroquinolone use with an average delay of 1 month. This means that, on average, an increase (or a decrease) in fluoroquinolone use by 1 DDD/100 bed-days resulted 1 month later in an increase (or a decrease) in the incidence of HA-MRSA by 0.005/100 bed-days. Effects of different size with a different delay were observed for third-generation cephalosporin use (average delay = 2 months, variation of HA-MRSA incidence = 0.03/100 bed-days), macrolide use (average delay = 4 months, variation of HA-MRSA incidence = 0.002/100 bed-days) and amoxicillin/clavulanic acid use (average delay = 1 month, variation of HA-MRSA incidence = 0.003/100 bed-days) (Table 3).

Temporal relationships were also observed between HA-MRSA incidence and infection control activities within the hospital. Increased infection control activity was associated with decreased HA-MRSA incidence and vice versa (Table 3). Significant relationships were observed for alcohol-based handrub use, alcohol-impregnated wipe use and the number of patients actively screened for MRSA with time lags varying from 2 to 4 months. As mentioned earlier, alcohol-based handrub was not used before February 2002; after that date, its use showed two marked peaks in October 2002 and April 2004. The model involved the analysis of the effect of these two peaks on HA-MRSA incidence and showed that bulk orders of alcohol handrub following hospitalwide promotion of hand hygiene resulted in a decrease in the incidence of HA-MRSA of 0.04/100 and 0.08/100 bed-days at an average delay of 3 and 4

Table 3. Estimated multivariate time-series analysis model for monthly HA-MRSA incidence ($R^2 = 0.784$)

Term	Time lag[a]	Coefficient (SE)[b]	*T* ratio	*P* value
Fluoroquinolone use (DDD/100 bed-days)	1	0.00481 (0.00098)	4.905	<0.0001
Third-generation cephalosporin use (DDD/100 bed-days)	2	0.0273 (0.00449)	6.080	<0.0001
Macrolide use (DDD/100 bed-days)	4	0.00212 (0.00099)	2.149	0.0376
Amoxicillin/clavulanic acid use (DDD/100 bed-days)	1	0.00349 (0.000651)	5.365	<0.0001
Alcohol-based handrub bulk orders	3	−0.0390 (0.0149)	−2.619	0.0123
	4	−0.0755 (0.0153)	−4.932	<0.0001
Alcohol-impregnated wipes (no./100 bed-days)	2	−0.000345 (0.0000496)	−6.956	<0.0001
Patients actively screened for MRSA (no./100 bed-days)	3	−0.00721 (0.00306)	−2.357	0.0233
Patients admitted with MRSA (no./100 bed-days)	2	0.223 (0.0312)	7.162	<0.0001
AR[c]	4	−0.552 (0.130)	−4.250	0.0001
MA[d]	2	−0.980 (0.000709)	−1382.67	<0.0001

[a]The delay necessary to observe the effect (in months).
[b]The size and the direction of the effect.
[c]AR, autoregressive term representing past incidence density of MRSA.
[d]MA, moving average term representing past disturbances in the incidence density of MRSA.

months, respectively. The model also showed that an increase in the use of alcohol-impregnated wipes by 1000 wipes/100 bed-days in a certain month led to a reduction of 0.3 HA-MRSA cases per 100 bed-days after an average of 2 months. No correlation was found between use of gloves and incidence of HA-MRSA. According to the model, each increase in MRSA screening intensity by one screened patient per 100 bed-days led to a decrease of 0.007 HA-MRSA cases per 100 bed-days with an average delay of 3 months.

The incidence of patients identified as MRSA-positive on admission to the hospital was also included in the multivariate model. Each increase in the incidence of admitted MRSA patients of one case per 100 bed-days resulted in an increase of 0.2 HA-MRSA cases per 100 bed-days with an average delay of 2 months (Table 3).

Two stochastic terms were introduced into the model, i.e. an AR term with a time lag of 4 months and an MA term with a time lag of 2 months (Table 3). Both terms reflected autocorrelation in the incidence of HA-MRSA, i.e. this incidence was related to the incidence observed in the previous months. The determination coefficient (R^2) of the final model was 0.784, i.e. 78.4% of the variations of the monthly incidence of HA-MRSA over the study period were explained by the factors included in the model.

Projections for Antrim Area Hospital on the items to use and the numbers of patients needed to be treated to cause or prevent one HA-MRSA case at the hospital are presented in Table 4.

Graphical representations of the relationships between the monthly use of amoxicillin/clavulanic acid, third-generation cephalosporins, macrolides and fluoroquinolones and the monthly incidence of HA-MRSA are presented in Figure 1. Similar graphical representations of the relationships between infection control-related factors and the monthly incidence of HA-MRSA are presented in Figure 2. In these figures, data were plotted 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 two previous months and the two following months. This transformation has no statistical value, but gives a better visual representation of the series.

Finally, a curve of the summed monthly use of all explanatory variables, taking into account their respective lags, was constructed and plotted on the same graph as the monthly incidence of HA-MRSA (data not shown). This showed the parallel nature of the relationship between these lagged explanatory variables and the incidence of HA-MRSA at the Antrim Area Hospital, and provided visual confirmation of the model.

Discussion

Our study, using time-series analysis, showed temporal relationships between the use of (i) certain antibiotic classes and (ii) infection control activities and related factors, and the incidence of HA-MRSA. Time-series analysis has previously been applied to study the association between antibiotic use and MRSA,[8,16] but this study is the first attempt to simultaneously quantify, in a multivariate model, the effect of both antibiotic use and several infection control practices on the HA-MRSA incidence.

The use of fluoroquinolones, third-generation cephalosporins, macrolides and amoxicillin/clavulanic acid was positively correlated with the incidence of HA-MRSA. The findings were consistent with the resistance patterns obtained from the Antrim Area Hospital microbiology department, which showed that MRSA isolates were almost always resistant to fluoroquinolones (ciprofloxacin) and macrolides (erythromycin), and that amoxicillin/clavulanic acid and third-generation cephalosporins were poorly active on MRSA. These results confirm what has been reported by others on the contribution of fluoroquinolone use,[7,8,17–20] third-generation cephalosporin use,[7,8,18] macrolide use,[7,8,17] and amoxicillin/clavulanic acid use[17,18,21] to patient

Table 4. Projections for Antrim Area Hospital on the required usage of items and on the number of patients needed to be treated to cause or prevent the occurrence of one HA-MRSA case

Variable	No. of items[a]	No. of patients[b]	Direction of effect[c]	Time lag[d]
Antimicrobials				
fluoroquinolone	208	30	positive	1
third-generation cephalosporin	37	5	positive	2
macrolide	472	67	positive	4
amoxicillin/clavulanic acid	287	41	positive	1
Infection control practices				
patients actively screened for MRSA	NA[e]	139	negative	3
alcohol-impregnated wipes	2899	NA	negative	2
Other				
patients admitted with MRSA	NA[e]	4	positive	2

[a]For antimicrobials, this represents the number of defined daily doses (DDDs) needed in a given month to contribute to the occurrence of one HA-MRSA case. For wipes, this is the number of wipes.
[b]For antimicrobials, this represents the number of patients needed to be treated in a given month to cause the occurrence of one HA-MRSA case. This number was based on the assumption of an average treatment course of 7 DDDs.
[c]A positive direction of effect means that an increase in the mentioned number of items and number of patients contributes to an increase in one HA-MRSA case and inversely. A negative direction of effect means that an increase in the mentioned number of items and number of patients contributes to a decrease in one HA-MRSA case and vice versa.
[d]The delay necessary to observe the effect (in months).
[e]NA, not applicable.

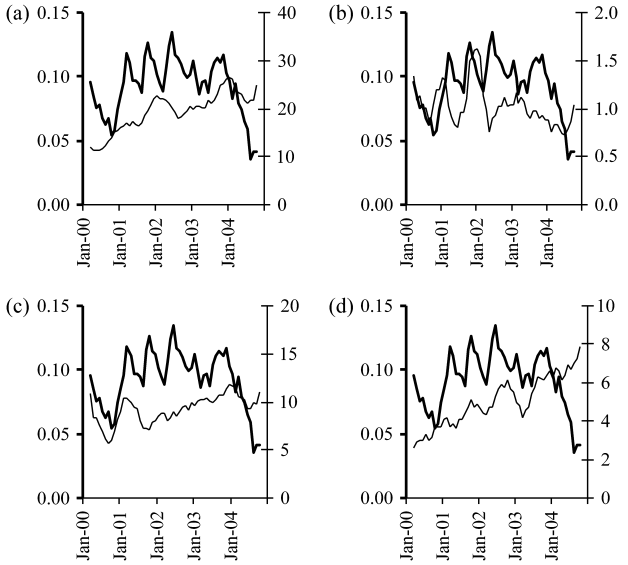

Figure 1. Monthly HA-MRSA incidence versus use of selected antibiotic classes, Antrim Area Hospital, January 2000–December 2004 (thick line, HA-MRSA, no. of cases/100 bed-days, 5 month MA, left-hand *y*-axis; thin line, antimicrobial use, DDD/100 bed-days, 5 month MA, right-hand *y*-axis). (a) Amoxicillin/clavulanic acid, (b) third-generation cephalosporins, (c) macrolides and (d) fluoroquinolones.

colonization and infection by MRSA or to high MRSA rates in healthcare settings, thus following the lines of evidence for a cause–effect relationship between antibiotic use and resistance proposed by McGowan.[22] It is plausible that increasing exposure to antimicrobials contributes to increasing the size of the reservoir of MRSA carriers. First, MRSA clones would be selected in antimicrobial-exposed patients, and then the size of this MRSA reservoir would gradually increase through the spread of these MRSA clones to other patients, hospital staff and the environment. This increase would only become evident after the MRSA reservoir has reached a certain size. It is unclear, however, why a longer delay is needed to observe an effect of variations in macrolide use compared with, e.g. fluoroquinolone or co-amoxiclav use. Further research is needed to clarify this point. Interestingly, the results of a recent systematic review have shown that the risk of acquiring MRSA was 1.8 times higher in patients who had taken antibiotics in the previous 126 days (~4 months).[23]

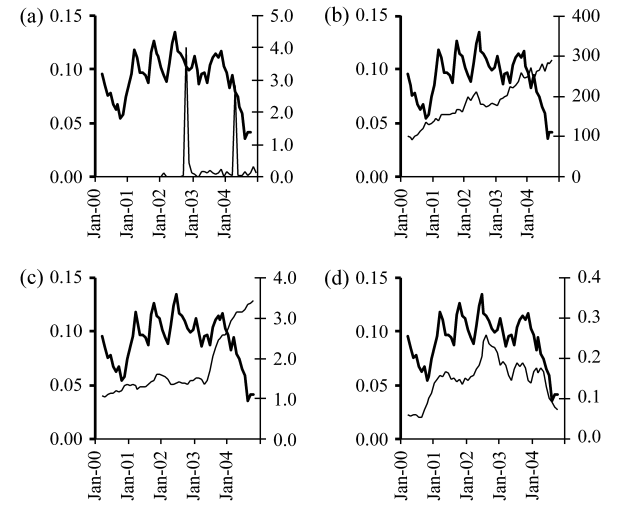

Figure 2. Monthly HA-MRSA incidence versus infection control practices and related factors, Antrim Area Hospital, January 2000–December 2004 (thick line, HA-MRSA, no. of cases/100 bed-days, 5 month MA, left-hand *y*-axis; thin line, infection control practice, right-hand *y*-axis). (a) Alcohol-based handrub (L/100 bed-days). (b) Alcohol-impregnated wipes (no. of cases/100 bed-days, 5 month MA). (c) Patients actively screened for MRSA (no. of cases/100 bed-days, 5 month MA). (d) Patients admitted with MRSA (no. of cases/100 bed-days, 5 month MA).

In addition to antibiotic use, the model included surrogate markers for the infection control practices and related factors in the hospital. As previously shown by others,[24,25] our results suggest that the admission of MRSA-colonized patients is an important contributor to high HA-MRSA incidence at Antrim Area Hospital. Once an MRSA carrier is admitted, they will serve as a reservoir for subsequent MRSA transmission to other patients, hospital staff and the environment. Thus, active screening for MRSA carriage is an essential strategy to limit further spread.[26,27]

Although it could be argued that the identified MRSA-positive patients were isolated and therefore could not contribute to spread, the standard clinical microbiological procedure at Antrim Area Hospital requires 2–3 days to identify MRSA following screening, thus allowing unidentified, non-isolated MRSA-positive patients to contaminate other patients, the personnel and the environment during that period. This highlights the need for implementing faster tests such as PCR techniques,[28] which have been shown to contribute to reducing MRSA transmission.[24]

The introduction of alcohol-based handrub has been shown to improve hand hygiene compliance and to reduce MRSA transmission rates in hospitals.[29–33] Our model showed that bulk orders of alcohol-based handrub, which occurred on two specific months during the study period as a result of hospitalwide promotion of hand hygiene, resulted in decreasing HA-MRSA incidence. Although it is likely that the ordered alcohol-based handrub was used by the wards in the months following delivery, it is impossible to determine when it was used. The time lag for observing the effect on HA-MRSA incidence must therefore be interpreted with caution.

The hospital environment is a reservoir for MRSA and participates in its spread.[34] Once equipment that is used for multiple patients becomes contaminated, it can serve as a potential vector for the transfer of MRSA to patients, either via direct contact or via contamination of healthcare workers' hands.[2] Recent studies have demonstrated that the use of alcohol-impregnated wipes to decontaminate the environment is associated with a reduction in hospital MRSA rates.[31,35] Our model showed that increasing use of alcohol-impregnated wipes contributed to decreasing HA-MRSA incidence. It should, however, be noted that disinfection (hand/equipment) practices may vary from institution to institution and that the model devised relates to activities within the Antrim Area Hospital and may not be directly generalizable.

The study involved all patients hospitalized during the study period, and data were collected as part of routine hospital practice and independently from the study. Selection and information bias are therefore unlikely. Because of the ecological observational study design, it was not possible to control for different

patient group characteristics and changes in patient population and case-mix, which may have affected the incidence of HA-MRSA. The study design also meant that data were collected for the whole hospital rather than for specific wards. However, policies were implemented in all clinical areas, and there was an ongoing programme of audit of clinical practices, decontamination of clinical equipment and environmental hygiene. Several outbreaks (gastroenteritis and MRSA) occurred throughout the study, but in particular in 2003 (five outbreaks including three involving MRSA) and 2004 (five outbreaks including one involving MRSA). These outbreaks undoubtedly led to an increase in infection control practices, in particular during the last year of the study, and may have contributed to the decrease in HA-MRSA incidence (Figure 2b and c). Finally, other parameters that can affect MRSA acquisition such as nursing staff levels[36] could not be obtained. Such parameters may be involved in the 21.6% remaining variability which was not explained by our model. In conclusion, our study showed that both antibiotic use and infection control practices, as well as the admission of MRSA-positive patients, contributed to the incidence of HA-MRSA during a 5 year period at the study-site hospital. Moreover, it provided a preliminary comparison of the effectiveness of these different activities in reducing HA-MRSA and suggested directions for future MRSA control activities at the hospital. Future research should aim at modifying one or several of the identified factors and following the effect of these interventions using a similar methodology.[16] Whereas there is little doubt that improving infection control interventions should decrease HA-MRSA incidence, the contribution that could be achieved via antibiotic use restriction is less certain. Restriction of selected antibiotic classes such as fluoroquinolones or third-generation cephalosporins seems to result in decreasing HA-MRSA.[20,37,38] How long such restrictions can be maintained is still unclear. Antibiotic cycling policies informed by a model such as that presented in this study could provide a solution; however, evidence to date suggests that cycling is not effective.[39] Future research should aim at identifying the single or combined interventions that are most likely to control HA-MRSA and thus help hospitals prioritize their MRSA control activities.

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References

1. Johnson AP, Pearson A, Duckworth G. Surveillance and epidemiology of MRSA bacteraemia in the UK. *J Antimicrob Chemother* 2005; **56**: 455–62.

2. Muto CA, Jernigan JA, Ostrowsky BE *et al*. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and enterococcus. *Infect Control Hosp Epidemiol* 2003; **24**: 362–86.

3. British Society for Antimicrobial Chemotherapy, Hospital Infection Society and the Infection Control Nurses Association. Revised guidelines for the control of methicillin-resistant *Staphylococcus aureus* infection in hospitals. *J Hosp Infect* 1998; **39**: 253–90.

4. Garner JS. Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. *Infect Control Hosp Epidemiol* 1996; **17**: 53–80.

5. Cooper BS, Stone SP, Kibbler CC *et al*. Isolation measures in the hospital management of methicillin resistant *Staphylococcus aureus* (MRSA): systematic review of the literature. *Br Med J* 2004; **329**: 533.

6. Centers for Disease Control Prevention. National nosocomial infection surveillance systems report, data summary from January 1992–June 2001, issued August 2001. *Am J Infect Control* 2002; **30**: 458–75.

7. Muller AA, Mauny F, Bertin M *et al*. Relationship between spread of methicillin-resistant *Staphylococcus aureus* and antimicrobial use in a French university hospital. *Clin Infect Dis* 2003; **36**: 971–8.

8. Monnet DL, Mackenzie FM, López-Lozano JM *et al*. Antimicrobial drug use and methicillin-resistant *Staphylococcus aureus*, Aberdeen, 1996–2000. *Emerg Infect Dis* 2004; **10**: 1432–41.

9. Aubert G, Carricago A, Vautrin CA *et al*. Impact of restricting fluoroquinolone prescription on bacterial resistance in an intensive care unit. *J Hosp Infect* 2005; **59**: 83–9.

10. Wilcox MH. Antibiotic prescribing as a risk factor for MRSA. *Hosp Med* 2005; **66**: 180–4.

11. Helfenstein U. Box–Jenkins modelling in medical research. *Stat Methods Med Res* 1996; **5**: 3–22.

12. López-Lozano JM, Monnet DL, Yague 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.

13. Cornaglia G, Hryniewicz W, Jarlier V *et al*. European recommendations for antimicrobial resistance surveillance. *Clin Microbiol Infect* 2005; **10**: 349–83.

14. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classifications and DDDs assignment. Oslo, Norway: WHO Collaborating Centre, 2002.

15. Pankratz A. *Forecasting with Dynamic Regression Models*. New York: Wiley, 1991.

16. Mahamat A, Mackenzie FM, Brooker K *et al*. Impact of infection control interventions and antibiotic use on hospital MRSA: a multivariate interrupted time-series analysis. *Int J Antimicrob Agents* 2007; **30**: 169–76.

17. Aldeyab M, Hughes CM, Scott MG *et al*. The role of antibiotics in the development of methicillin-resistant *Staphylococcus aureus* (MRSA). *Int J Pharm Pract* 2005; **13** Suppl: R92.

18. Crowcroft NS, Ronveaux O, Monnet DL *et al*. Methicillin-resistant *Staphylococcus aureus* and antimicrobial use in Belgian hospitals. *Infect Control Hosp Epidemiol* 1999; **20**: 31–6.

19. Weber SG, Gold HS, Hooper DC *et al*. Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized patients. *Emerg Infect Dis* 2003; **9**: 1415–22.

20. Charbonneau P, Parienti JJ, Thibon P *et al*. Fluoroquinolone use and methicillin-resistant *Staphylococcus aureus* isolation rates in hospitalized patients: a quasi experimental study. *Clin Infect Dis* 2006; **42**: 778–84.

21. Muller A, Mauny F, Talon D *et al*. Effect of individual- and group-level antibiotic exposure on MRSA isolation: a multilevel analysis. *J Antimicrob Chemother* 2006; **58**: 878–81.

22. McGowan JE, Jr. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Rev Infect Dis* 1983; **5**: 1033–48.

23. Tacconelli E, De Angelis G, Cataldo MA *et al*. Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *J Antimicrob Chemother* 2008; **61**: 26–38.

24. Cunningham R, Jenks P, Northwood J *et al*. Effect on MRSA transmission of rapid PCR testing of patients admitted to critical care. *J Hosp Infect* 2007; **65**: 24–8.

25. Lucet JC, Paoletti X, Lolom I *et al*. Successful long-term program for controlling methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intensive Care Med* 2005; **31**: 1051–7.

26. Rubinovitch B, Pittet D. Screening for methicillin-resistant *Staphylococcus aureus* in the endemic hospital: what have we learned? *J Hosp Infect* 2001; **47**: 9–18.

27. Farr BM, Jarvis WR. Would active surveillance cultures help control healthcare-related methicillin-resistant *Staphylococcus aureus* infections? *Infect Control Hosp Epidemiol* 2002; **23**: 65–8.

28. Francois P, Pittet D, Bento M *et al*. Rapid detection of methicillin-resistant *Staphylococcus aureus* directly from sterile or non-sterile clinical samples by a new molecular assay. *J Clin Microbiol* 2003; **41**: 254–60.

29. Widmer AF. Replace hand washing with use of a waterless alcohol hand rub? *Clin Infect Dis* 2000; **31**: 136–43.

30. Pittet D, Hugonnet S, Harbarth S *et al*. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene: infection control programme. *Lancet* 2000; **356**: 1307–12.

31. Johnson PD, Martin R, Burrell LJ *et al*. Efficacy of an alcohol/chlorhexidine hand hygiene program in a hospital with high rates of nosocomial methicillin-resistant *Staphylococcus aureu*s (MRSA) infection. *Med J Aust* 2005; **183**: 509–14.

32. Graham M, Nixon R, Burrell LJ *et al*. Low rates of cutaneous adverse reactions to alcohol-based hand hygiene solution during prolonged use in a large teaching hospital. *Antimicrob Agents Chemother* 2005; **49**: 4404–5.

33. Gordin FM, Schultz ME, Huber RA *et al*. Reduction in nosocomial transmission of drug-resistant bacteria after introduction of an alcohol-based handrub. *Infect Control Hosp Epidemiol* 2005; **26**: 650–3.

34. Sexton T, Clarke P, O'Neill E *et al*. Environmental reservoirs of methicillin-resistant *Staphylococcus aureus* in isolation rooms: correlation with patient isolates and implications for hospital hygiene. *J Hosp Infect* 2006; **62**: 187–94.

35. Hill C, King T, Day R. A strategy to reduce MRSA colonization of stethoscopes. *J Hosp Infect* 2005; **62**: 122–3.

36. Dancer SJ, Coyne M, Speekenbrink A *et al*. MRSA acquisition in an intensive care unit. *Am J Infect Control* 2006; **34**: 10–7.

37. Madaras-Kelly KJ, Remington RE, Lewis PG *et al*. Evaluation of an intervention designed to decrease the rate of nosocomial methicillin-resistant *Staphylococcus aureus* infection by encouraging decreased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2006; **27**: 155–69.

38. Apisarnthanarak A, Danchaivijitr S, Khawcharoenporn T *et al*. Effectiveness of education and an antibiotic-control program in a tertiary care hospital in Thailand. *Clin Infect Dis* 2006; **42**: 768–75.

39. Brown EM, Nathwani D. Antibiotic cycling or rotation: a systematic review of the evidence of efficacy. *J Antimicrob Chemother* 2005; **55**: 6–9.