Abstract

Behavioural Model for Community-Based Antimicrobial Resistance, Vellore, India

Abegunde, Dele Olawale (1); Holloway, Kathleen (1); Mathai, Elizabeth (1); Gray, Andy (2); Ondari, Clive (1); Chandry, Sujith (3)

abegunded@who.int

1: World Health Organization, Switzerland; 2: Nelson Mandela School of Medicine, University of KwaZulu-Natal, South Africa; 3: Christian Medical College Hospital, Vellore, India

Problem statement: Resistance to antimicrobial agents compounds the burden of diseases worldwide. Difficulties to estimating the impact of AMR on individuals and the community or the impact of AM use on resistance in resource-constrained settings is compounded by the paucity of community-based data. Robust surveillance data collection methodologies are lacking in such settings. More explorations and improved analytical methods are needed to fully understand trends and impact of AMR on cost of illness and to inform AMR surveillance.

Objectives: To determine the behavioural trends—seasonality (periodicity) and the temporal associations—between community-based AMR and AM use; to forecast the short-run pattern in AMR through the behaviour of AMR and the predictors (indicators) of AMR; and to compare the temporal correlation of the trends in DDD and the proportion of patients prescribed antibiotics, with community based AMR

Design: Longitudinal, non-comparison time-series

S**ettings:** A multi-centre WHO study in India and South Africa. We use AMR surveillance data obtained from Vellore (urban area) and Kuppam (rural area) with a combined population of 500,000 within Vellore District, Tamil Nadu State of southern India.

Study population: Study isolated commensal E. coli (*N=2,026*) from pregnant women attending antenatal clinics. Monthly AM-use data were obtained from exit interviews from hospitals or PHC clinics (including not-for-profit and for-profit hospitals in the urban area and public sector PHC clinics and a not-for-profit hospital in the rural areas); private sector pharmacies; and private sector general medical practitioners' practices. Prescriptions containing antibiotics totaling 21,600 were obtained from 52,788 prescriptions. Data were collected in two time periods, from August 2003 to July 2004 and from January to December 2005.

Outcome measure(s): Monthly proportion of isolated E. coli resistant to co-trimoxazole, extended spectrum penicillin, and quinolones; monthly antibiotic use in DDD and proportion of patients prescribed antibiotics

Results: Both AMR and AM use demonstrated lagged trends and seasonality. AMR lags vary between 3 and 5 months of AM use. Impulse-response could last as much as 15 to 45 months. AM use demonstrated significant Granger-causality with AMR in addition to circularity. Both monthly DDD per patient and proportion of patients on specific antibiotics show similar effects on AMR, but DDD per patient appear to demonstrate more reactive effect on AMR.

Conclusions: Community AM use can predict AMR. Our results provide additional evidence for estimating the economic impact of AMR and could inform the design of community-based antimicrobial surveillance and interventions in low-resource settings.

Funding source(s): WHO

Background

Resistance to antimicrobial agents compounds the burden of diseases worldwide.

Difficulties to estimating the impact of AMR on individuals and the community or the impact of AM use on resistance in resource-constrained settings is compounded by the paucity of community-based data.

Robust surveillance data collection methodologies are lacking in such settings.

More explorations and improved analytical methods are needed to fully understand trends and impact of AMR on cost of illness and to inform AMR surveillance.

Objectives

To determine the behavioural trends—seasonality (periodicity) and the temporal associations—between community-based AMR and AM use;

To forecast the short-run pattern in AMR through the behaviour of AMR and the predictors (indicators) of AMR; and

To compare the temporal correlation of the trends in DDD and the proportion of patients prescribed antibiotics, with community based AMR

Methods

Data

- AMR surveillance data from Vellore (urban area) and KV Kuppam, situated between Chennai and Bangalore with a combined population of 500, 000 in a 3.5million Vellore district in the state of Tamil Nadu, Southern India.
- AMR surveillance data consist of commensal *E. coli* isolated from urine/perinea (swab) samples obtained from asymptomatic pregnant women attending antenatal clinics.
- Monthly AM-use data were those obtained from exit interviews conducted by pharmacists from urban and rural facilities: (1) hospitals or primary care clinics (including not-for-profit and for-profit hospitals in the rural and urban areas); (2) private sector pharmacies; and (3) private sector general medical practitioners' practices.
- All data were collected in two-time period, from August 2003 to July 2004 and from January to December 2005.

Variables.

- AMR data was converted into proportion of the total *E coli* isolates, which were resistant to a specific antibiotics class:

  co-trimoxazole,
  extended spectrum penicillin (ESP) and
  quinolones (nalidixic acid and fluoroquinolones).

- The AM-use data was standardized to (1) DDD of the respective antimicrobials and (2) the proportion of prescriptions containing specific antimicrobial groups within the total prescriptions for the month.

Methods: Analysis Models:

$$AM\,\mathrm{Re}sis\tan ce_t = f(AMUuse_{t-p})$$

Autoregressive Integrated Moving Average **(ARIMA) Univariate**

Assumes causal links

$$Y_t = X_t\beta + \mu_t$$

$$\mu_t = \rho\mu_{t-1} + \theta\varepsilon_{t-1} + \varepsilon_t$$

- X_t = M x 1 Vector of exogenous variables – antimicrobial use in monthly total of DDD or Proportion receiving antibiotics, and β is a K x M matrix of coefficients,
- P = first order autocorrelation parameter
- θ = first order moving average parameter
- ε_t = white noise ~ i.i.d. N(0, δ^2)

Vector Autoregressive Analysis **(VAR)**

Multivariate

Allows for examination of causality

$$Y_t = \delta + \eta_1 Y_{t-1} + \ldots + \eta_p Y_{t-p} + \beta X_t + \mu_t \qquad t \in \{-\infty, \infty\}$$

- **Y_t** = Proportion of AMR in month *t*, (Y_{1t} ..... Y_{kt}) is a K x 1 random vector of lags and the *ηi* are fixed K x K matrices of parameters,
- **δ** = Constant – K x 1 vector of fixed parameters,
- **μ_t** = The disturbance term assumed to be the white noise,
- **P** = lags of Y_t, and
- **t** = month.

Holts-Winters seasonal smoothening technique for trends

Results

Both AMR and AM-use demonstrated lagged trends and seasonality. (tables 2 &3, and figures 1 & 2)

Parameter estimates from the VAR (table 3) are more efficient compared to those form ARIMA (table 2).

Seasonality spurs of resistance appear to synchronise with cold (catarrh) seasons when the antibiotics are freely and routinely used.

AMR lags vary between 3-5 months of AM-use. This also synchronizes with the cold periods.

AMR trend is sustained even though antibiotic use trends downward.

Coefficients more efficient with VAR models compared to ARIMA models.

VAR Modes showed the presence of endogeneity between Antibiotic resistance and Antibiotic use

Impulse-response could last as much as 15 to 45 months. Indicating that AMR resistance generated by a bout of inappropriate use can last in the communities for up to 15 -45 months (Figure 3).

AM-use demonstrated significant Granger causality with AMR in addition to circularity.

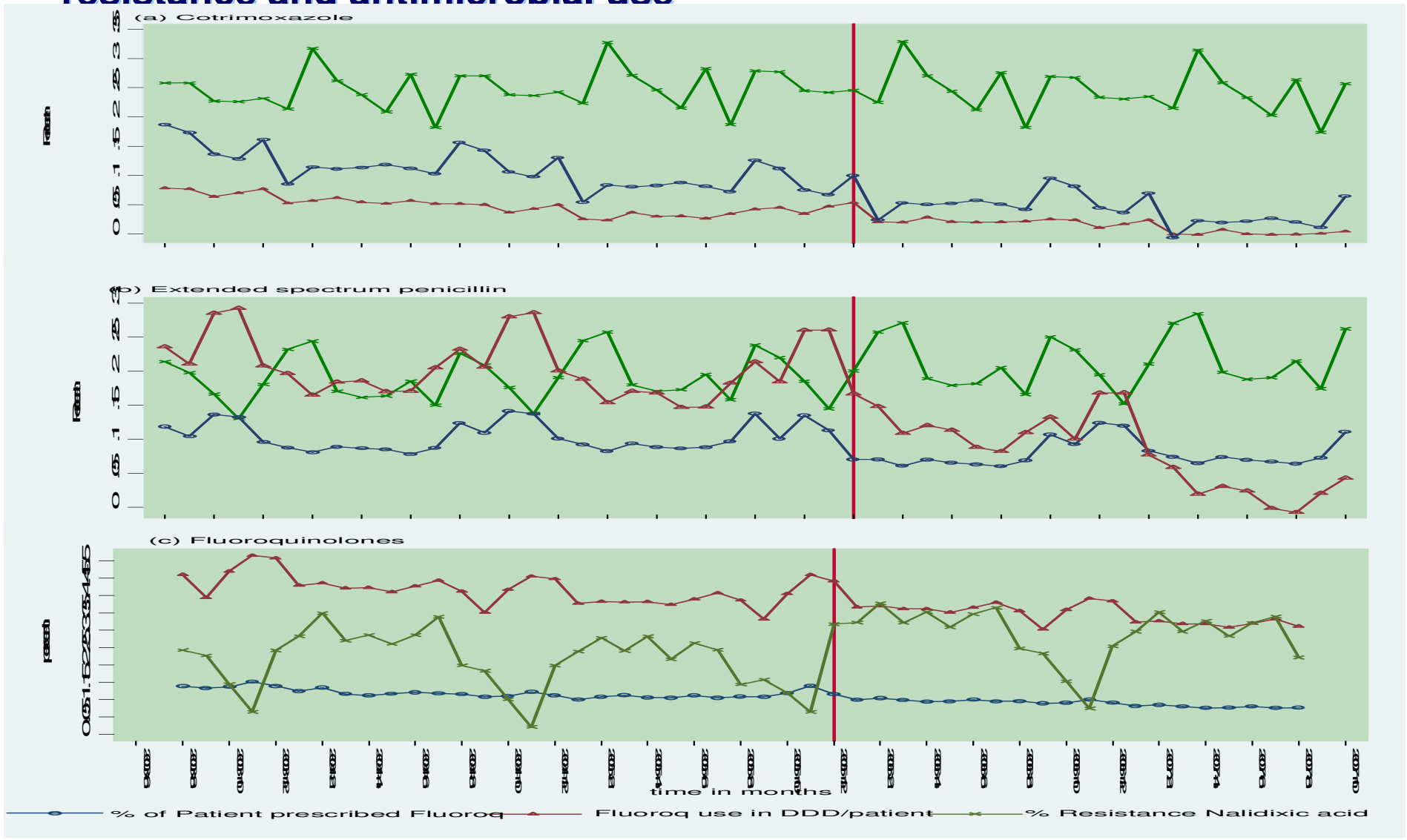
Both monthly DDD per patient and proportion of patients on specific antibiotics show similar effects on AMR, but DDD per patient appear to demonstrate more reactive effect on AMR (figure 2).

Results

Table 1 : Granger causality tests

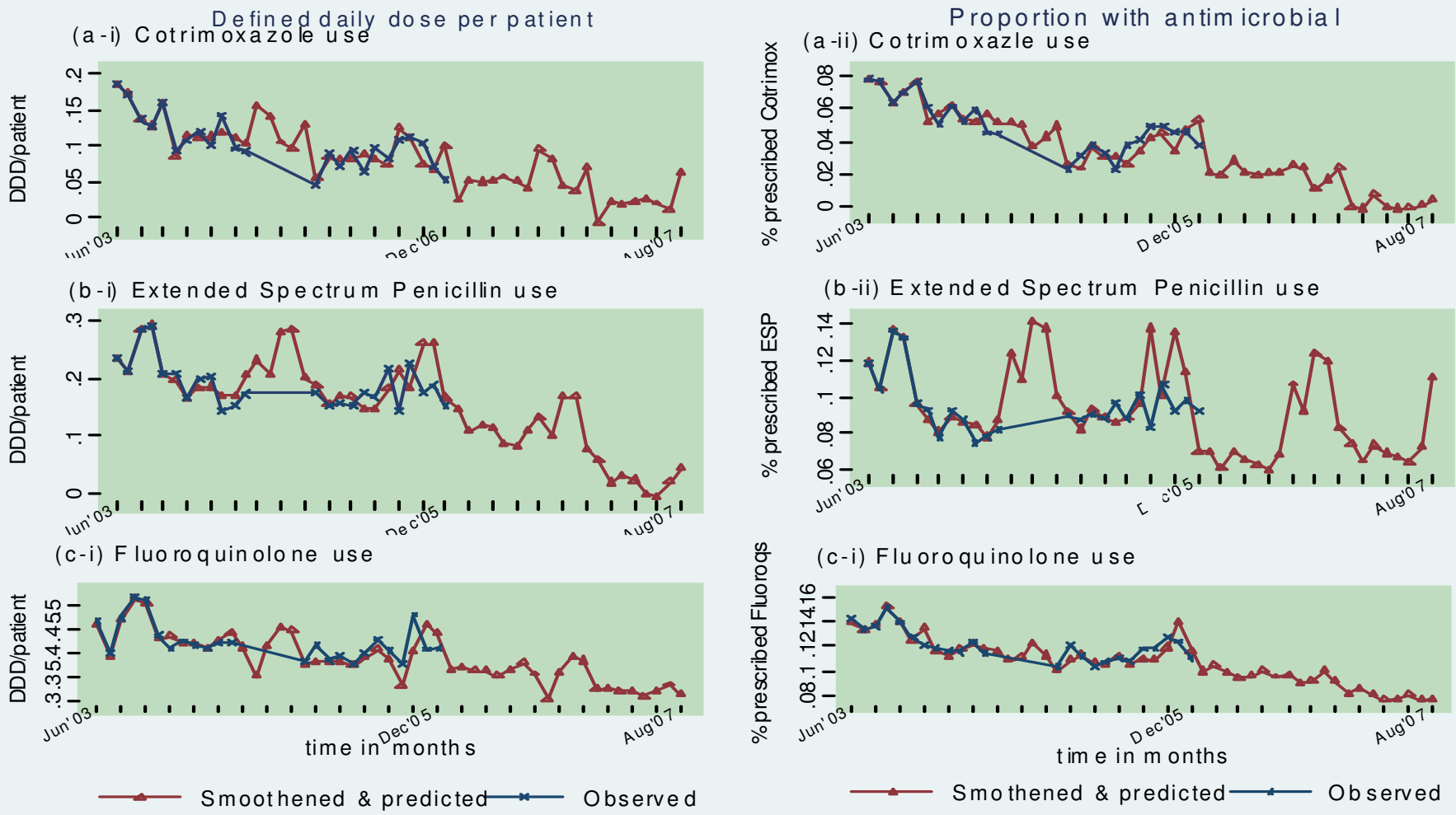
		Granger Causality test: Ho = estimated coefficients (AMR & AM-use) are jointly zero.		
Antimicrobial use indicators		Antibiotics		
Antimicrobial resistance (AMR)	**Anti microbial use (AM-use)**	**Co-trimoxazole**	**Extended Spectrum Penicillin**	**Quinolone**
Resistance	DDD/patient	Negative	Positive	Positive
Resistance	Monthly proportion on antibiotic:	Negative	Negative	Positive
Resistance	Both variables jointly	Negative	Positive	Positive

Figure 1: Predicted trend in community-base antimicrobial resistance and antimicrobial use



World Health Organization

Figure 2: Trends in antibiotic use variables compared.



World Health Organization

Figure 3: Impulse response function

Summary

Both AMR and AM-use demonstrated lagged trends and seasonality.

Parameter estimates from the VAR (table 3) are more efficient compared to those form ARIMA (table 2).

Seasonality spurs of resistance appear to synchronise with cold (catarrh) seasons when the antibiotics are freely and routinely used.

AMR lags vary between 3-5 months of AM-use. This also synchronizes with the cold periods (table 3)

AMR trend is sustained even though antibiotic use trends downward.

Impulse-response could last as much as 15 to 45 months (figure3). Indicating that AMR resistance generated by a bout of inappropriate use can last in the communities for up to 15 -45 months.

AM-use demonstrated significant Granger causality with AMR in addition to circularity. Both monthly DDD per patient and proportion of patients on specific antibiotics show similar effects on AMR, but DDD per patient appear to demonstrate more reactive effect on AMR.

Summary of findings

- Refined models provide clearer knowledge of the dynamic and systematic relationships between antibiotic use and antimicrobial resistance in respective communities.
- Community AM use can predict AMR.
- Linearised models are scientifically and empirically intuitive, and are useful tools for forecasting, monitoring and evaluating future deviating observations
- Results provide additional evidence for estimating the economic impact of AMR and could inform the design of community-based antimicrobial surveillance and interventions in low-resource settings.
- Results provide evidence to support the of utility of cheaper-to-measure antibiotic-use variable

Table 1: Autoregressive Integrated Moving Average Regression (ARIMA) results

Dependent variable: %resistant isolates			
	Cotrimoxazole	**Extended Spectrum Penecillin**	**Fluoroquinolones**
No. of observations	Aug 2003 - Dec 2005, Number of observation = 24		
Independent variables	**Coefficients (SE)**	**Coefficients (SE)**	**Coefficients (SE)**
% prescribed	**1.14*** (0.47)	0.30 (1.70)	-0.44 (0.36)
Cotrimoxazole			
Monthly per patient DDD	**-1.97*** *(0.98)*	-1.34 (4.40)	-1.20 (1.11)
_cons	0.22* (0.01)	**0.26*** (0.09)	**0.57*** (0.18)
ARMA			
Autoregressoion			
Lag1	0.29 (0.86)	**-0.88*** *(0.40)*	
Lag2.	-0.08 (0.35)		
Lag3.	-0.31 (0.85)		**0.53*** (0.14)
Moving average			
Lag1.	**-1.26*** *(0.61)*	**1.40*** (0.49)	0.25 (0.16)
Lag2.	0.29 (0.85)	0.77 (0.44)	0.32 (0.24)
Lag3.	0.31 (0.58)		-0.1065
Lag4.	**-1.27*** *(0.24)*		
Lag5.	0.98 (1.08)		
Lag6.	0.01 (0.85)		
Sigma	**0.03*** (0.00)	**0.04*** (0.01)	**0.05*** (0.01)
Log pseudolikelihood	44.08	38.8	36.33
Wald chi2(9)	4.27E+08	82.2	6.33E+09
Prob > chi2	0.00	0	0.00
Interpolated Dickey-Fuller (MacKinnon)	0.88	0.98	
Unit root test: (MacKinnon)	0.00	0.00	0.00

Table 2: Vector Autoregression (VAR) results

	Co-trimoxazole		Extended Spectrum Penicillin		Fluoroquinolones	
	Coeff	*(SE)*	Coeff	*(SE)*	Coeff	*(SE)*
Dependent variable: Percent resistant isolate						
Percent resistant						
L1. (month 1)	**-0.53***	*(0.25)*	**-0.56***	*(0.18)*	-0.18	*(0.21)*
L2. (month 2)	-0.21	*(0.21)*	-0.13	*(0.14)*	**0.84***	*(0.21)*
L3. (month 3)	-0.21	*(0.24)*	**-0.35***	*(0.12)*	**0.69***	*(0.23)*
Defined daily dose per patient						
L1. (month 1)	-0.12	*(0.70)*	**-1.94***	*(0.54)*	**2.48***	*(0.57)*
L2. (month 2)	-1.31	*(0.72)*	0.73	*(0.67)*	**3.11***	*(0.58)*
L3. (month 3)	-0.49	*(0.66*	**1.99***	*(0.69)*	**1.63***	*(0.60)*
Monthly proportion on antimicrobial						
L1. (month 1)	0.80	*(1.75)*	**4.19***	*(1.48)*	**-5.08***	*(2.07)*
L2. (month 2)	1.39	*(1.95)*	-1.31	*(1.87)*	-4.07	*(2.12)*
L3. (month 3)	1.12	*(1.50)*	**-4.58***	*(1.73)*	**-6.41***	*(1.93)*
Constant	**0.51***	*(0.16)*	**0.37***	*(0.08)*	**-1.28***	*(0.30)*
Dependent variable: Defined daily dose per patient						
Percent resistant						
L1. (month 1)	0.09	*(0.14)*	0.13	*(0.19)*	-0.13	*(0.10)*
L2. (month 2)	-0.02	*(0.12)*	0.04	*(0.14)*	**-0.23***	*(0.10)*
L3. (month 3)	-0.19	*(0.14)*	-0.19	*(0.12)*	0.09	*(0.11)*
Defined daily dose per patient						
L1. (month 1)	-0.22	*(0.40)*	**-1.17***	*(0.54)*	**-0.71***	*(0.26)*
L2. (month 2)	0.02	*(0.41)*	1.12	*(0.68)*	**-0.70***	*(0.27)*
L3. (month 3)	0.47	*(0.38)*	-0.15	*(0.70)*	0.24	*(0.28)*
Monthly proportion on antimicrobial						
L1. (month 1)	0.59	*(1.00)*	**4.19***	*(1.49)*	**3.72***	*(0.95)*
L2. (month 2)	0.00	*(1.11)*	-2.37	*(1.88)*	1.25	*(0.98)*
L3. (month 3)	-0.37	*(0.86)*	0.43	*(1.74)*	-0.04	*(0.89)*
Constant	0.09	*(0.09*	0.02	*(0.08)*	**0.39***	*(0.14)*
Dependent variable: Monthly proportion on antimicrobial agent						
Percent resistant						
L1. (month 1)	-0.02	*(0.04)*	0.07	*(0.06)*	-0.03	*(0.03)*
L2. (month 2)	-0.03	*(0.03)*	0.00	*(0.04)*	-0.04	*(0.03)*
L3. (month 3)	**-0.11***	*(0.04)*	-0.02	*(0.04)*	-0.01	*(0.04)*
Defined daily dose per patient						
L1. (month 1)	-0.08	*(0.12)*	**-0.54***	*(0.16)*	-0.04	*(0.09)*
L2. (month 2)	0.03	*(0.12)*	**0.44***	*(0.21)*	-0.15	*(0.09)*
L3. (month 3)	**0.27***	*(0.11)*	-0.25	*(0.21)*	0.08	*(0.09)*
Monthly proportion on antimicrobial						
L1. (month 1)	0.38	*(0.29)*	**1.84***	*(0.45)*	**0.82***	*(0.31)*
L2. (month 2)	-0.04	*(0.33)*	-1.03	*(0.57)*	-0.09	*(0.32)*
L3. (month 3)	-0.14	*(0.25)*	0.59	*(0.53)*	0.14	*(0.29)*
Constant	**0.05***	*(0.03)*	0.02	*(0.02)*	0.08	*(0.05)*
Stability						
Lagrange-multiplier test for autocorrelation	-ve		**-ve**		**-ve**	
Jarque-Bera test for normality in disturbance	+ve		+ve		+ve	