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Examining an Impact of Peer Comparison Intervention on Vancomycin Utilization Using Interrupted Time Series Model, Negative Binomial Random Intercept Model, and Linear Mixed Model with AR(1) Covariance Structure

By

Young Moo Yoo

Master of Science in Public Health

Biostatistics and Bioinformatics

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B.A.

Emory University

2017

Thesis Committee Chair: Renee H. Moore, PhD

Thesis Committee Co-Chair: Robert Lyles, PhD

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Abstract

Examining an Impact of Peer Comparison Intervention on Vancomycin Utilization Using Interrupted Time Series Model, Negative Binomial Random Intercept Model, and Linear Mixed Model with AR(1) Covariance Structure

By Young Moo Yoo

Introduction: Irresponsible use of antibiotics has led to concern about antibiotic resistance. The Antibiotic Stewardship Program (ASP) was introduced nationally to control the antibiotic usage. At Grady Health System, an intervention was implemented by sending out an email to the internal medicine physicians with the report of their historical and current prescription of intravenous vancomycin. The objective of this quality improvement project was to evaluate whether the report card intervention was associated with the provider's vancomycin prescription behavior. This thesis examines various modeling strategies to assess this association.

Methods: As of December 1, 2016, the intervention was implemented by sending out the bi-weekly report on physicians' intravenous vancomycin use. In this analysis, the outcome measure is the days of therapy per 100 patient days, which is the vancomycin use rate. An Interrupted Time Series model, Negative Binomial repeated measures model with offset term, and linear mixed model with AR(1) covariance structure were fitted and compared to examine the impact of the intervention.

Results: A total of 64 physicians were included in this two-year period quality improvement project. The estimated baseline vancomycin prescription rate was 10.35 (95% confidence interval, 9.22 to 11.47). When physicians started to receive a report card, the vancomycin prescription rate declined by 2.33 (95% confidence interval, -3.79, to 0.87). Throughout the post-intervention year, the rate decreased by 0.13 (95% confidence interval, -0.24, -0.03) every two weeks.

Conclusion: During the historical year (pre-intervention period), no significant temporal trend of the vancomycin prescription rate was measured. However, once the intervention was introduced on December 1, 2016, there was an immediate drop of the vancomycin use rate. During the post-intervention period, constant decline of the vancomycin use rate was captured. These results were consistent over three modeling strategies that provides the audience options to choose based on their research questions.

Key Words: Antibiotic Stewardship Program, Longitudinal Intervention Data, Interrupted Time Series, Linear Mixed model, Negative Binomial random-intercept model.

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Young Moo (Daniel) Yoo

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1. Introduction

Antibiotics are truly a great discovery that saved us from manifold diseases and transformed healthcare industry but concerns around antibiotic therapy has been raised. Before prescribing antibiotics to patients, physicians now must take both benefits and toxic sequelae of antibiotics into account. Imprudent use of antibiotic may result in patients' developing a resistance to the therapy and can no longer take the advantage of this powerful medication.[1] As of March 2015, the White House issued the National Action Plan for Combating Antibiotic-Resistant Bacteria and it expressed the needs of nationally mandated program that control the antibiotic usage. Due to the possible side effect of antibiotics, the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Disease Society (PIDS) introduced an antibiotic stewardship program (ASP). By correctly measuring the appropriate use of antibiotic drugs, patient's outcome would be significantly improved, adverse effects caused by antibiotic drugs would be lessened, and health care industry would be able to reduce the cost effectively. The antibiotic stewardship program promotes the selection of optimal drug regime by controlling a dosage and duration of therapy.[2]

The antibiotic stewardship program proposed five strategies to efficiently control the antibiotic use: education/guidelines, formulary/restriction, review/feedback, computer assistance, and antimicrobial cycling.[3] The strongest recommendation made by the ASP is preauthorization or prospective audit and feedback which belong to formulary/restriction and review/feedback strategy, respectively. However, after the ASP was introduced to medical institutions, insufficient resources and limited research funding was available to determine the best possible strategies for the ASP in different settings. Few studies have been conducted to investigate the use of prescriber feedback on their own drug utilization compared to another prescriber.[2]

One of few studies was conducted by Meeker *et al.*, which studied the effect of behavior interventions among primary care practices. Meeker *et al.* investigated three different intervention strategies in the randomized clinical trial setting, which were suggested alternatives, accountable justification, and peer comparison. Results revealed that peer comparison and accountable justifications are the efficient strategies that led prescribers to reduce inappropriate antibiotic prescribing; peer comparison was performed by sending an email periodically and comparing the prescribers' performance and accountable justification was performed by prompting the prescriber to enter a justification for an inappropriate prescribed antibiotic.[4]

Staphylococcus aureus is a widespread pathogen that can cause varying damage from a skin infection to serious bone and joint infection. One of the popular and effective treatments of S. aureus was Penicillin. However, S. aureus strains soon became resistant to penicillin and even to methicillin. To treat methicillin-resistant strains of S. aureus (MRSA), many antibiotics were developed. Among those antibiotics, vancomycin has been the standard choice treat MRSA infections.[5] Clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, daptomycin, linezolid, and ceftaroline are the other possible treatments for MRSA infections. However, clindamycin, TMP-SMX, doxycycline, and linezolid usually are used for less severe indications such as mild skin infections. Also, daptomycin, linezolid, and ceftaroline are less prescribed to treat MRSA infections. In the clinical practice, physicians should only use vancomycin when a clinical suspicion for MRSA is evident or MRSA infection is diagnosed. Intravenous vancomycin and oral use of vancomycin are two ways to utilize drug but oral use cannot treat systematic illnesses as it is not absorbed. For these reasons, intravenous vancomycin use is the subject of interest in this study.

This study is an application of Meeker's findings that extends to the acute care inpatient hospitals. The aim of this study is to evaluate the impact of peer comparison on the utilization of intravenous (IV) vancomycin using data collected from an urban 650 bed tertiary academic medical center. Interrupted Time Series, Poisson random-effect, Negative Binomial random effect, and linear mixed model were considered to adequately analyze the change of the vancomycin prescription rate over the two year period (*e.g.,* pre-intervention period and post-intervention period).

2. Methods

2.1 Study Design and Intervention

A single-center observational pre-intervention and post-intervention quality improvement project was conducted at Grady Health System (GHS). The target population of interest was inpatient admitting internal medicine (IM) attending physicians at GHS. The study started on December 1, 2016 and ended on November 30, 2017. During this one-year period, internal medicine attending physicians at GHS were observed given report cards of their prescription use. No patient identifiers were used, and each physician received a random 4-digit number that was used to avoid personal identifiers. During the pre-intervention period, historical one-year baseline data from December 1, 2015 to November 30, 2016 were obtained from information warehouse.

Internal medicine physicians have their service time divided into approximately two-week time periods, which will be referred as blocks. Intervention was made by sending out emails with bi-weekly reports of antibiotic use for each physician in the block from the medical director of the antibiotics stewardship at the institution. The report was issued from 1st day of the

month to 15th or 16th day of the month, and the next report was issued from 15th or 16th day of the month to 30th and 31st day of the month. February was the only month that the report was issued from 1st day of the month to 14th day of the month, and the next report was issued from 15th day of the month to 28th or 29th day of the month. For the intervention, the director of Antimicrobial stewardship sent to each IM physician their historical individual block average and one-year cumulative individual average along with the entire IM group cumulative year average before doctor of medicine (MD) going on service. In addition, any subsequent physician time on service, historical information from the pre-intervention time period and up to two of their most recent block information, if available, was sent to each MD. All providers on the medical service were advised prior to the intervention to better understand the brief data description as well as the graphs included in the bi-weekly reports. As of December 1, 2016, the reports were sent to the physicians allowing for real-time peer comparison data. This period is called the post-intervention period.

2.2 Data Collection and Cleaning

Pre-intervention and post-intervention data were retrieved from the information warehouse. Collected data was kept on an encrypted drive and stored in a secure cloud-based location, to which both investigators and the Emory Biostatistics Collaboration Core group had access.

Because the study was focused on IV vancomycin drug use, all irrelevant drugs and drug diluents were excluded from the data set. Observations that did not have physician information or when the physician only contributed less than 3 days to each block were also excluded. One data set was used to calculate the days of vancomycin therapy. Each observation row in this data

set referred to one day of vancomycin therapy. The other data set was used to calculate the total patient-days physicians were in service. Each observation row in this data set referred to one patient day, which means that a patient admitted to IM team for at least one minute of a calendar day. The two data sets were merged together to calculate the days of therapy per number of patient days for each physician, which is the outcome measure that will be discussed in the following section. Because the report was distributed to the IM physicians bi-weekly, we formatted the data set by two-week block level (*e.g.*, December 1,2015 to December 16, 2015 refers to block 1).

2.3 Outcome of Interest

Days of therapy (DOT) is the number of days a patient was administered intravenous vancomycin, irrespective of number of administrations within a calendar day or dose (*i.e.*, if the patient was prescribed vancomycin twice on March 5, then DOT will be recorded as one). However, DOT alone is not an appropriate measurement because patient days (PD) would be higher for those physicians who see many patients, and those particular physicians tend to prescribe vancomycin drug more than others. Therefore, setting DOT as the outcome measure might overestimate or underestimate the result. DOT/PD was calculated by dividing DOT by the number of patient days and multiplying by 100, and this rate was used instead of DOT alone. If a physician prescribed vancomycin 33 times during block 1 period, the days of therapy for that specific physician in block 1 will be 33. If a physician gave a medical treatment to 247 patients for one day each during block 1 period, the number of patient days (PD) for that specific physician in block 1 will be 247. The outcome measure is $\frac{33}{247} \times 100 = 13.36$. This outcome measure will be referred to as vancomycin prescription rate throughout the paper.

2.4 Statistical Analysis

In this study, the physicians' prescription behavior change after the intervention was the focus of the study. To examine the effectiveness of the intervention, two scientific questions were addressed. The first sought to observe if there was an immediate impact when the intervention was implemented. The second sought to examine if the intervention effect was maintained over time. An interrupted time series model and different types of mixed-effect model were considered to navigate these study's objectives.

2.4.1 Interrupted Time Series

An Interrupted Time Series (ITS) model is a powerful statistical tool to evaluate healthcare intervention over regular time period after adjusting for secular trend. When data were collected from administrative data or medical records not for policy or intervention examining purposes, ITS can be ideally used to evaluate the intervention effect.[6] Segmented regression analysis is a modeling method for ITS, and this simple and easy to interpret model can deliver more formal conclusions of the impact of an intervention. In order to use segmented regression, data first need to be collected regularly over time with equally spaced time interval.[7] According to Rozario *et al*., at least six time points in each pre-intervention period and post intervention period are needed to achieve adequate power for ITS.[6] The outcome measure can be averages, proportions, and rates for time series studies.[7] Du *et al*. and Wagner A.K *et al*. suggested to use the unit of analysis as the monthly aggregated rate, rather than each physician's rate per month (*i.e.,* only one observation in one block).[7,8] Snap shot of data set that presents a difference between individual level data set and aggregated data set is shown in Table 1. Another important feature of an ITS using segmented regression is to include an autoregressive form. Since observations were collected over time, observations collected within short time period might

have stronger correlation than observation collected within long time period.[9] PROC AUTOREG in SAS 9.4 was used to detect autocorrelation in time series.[10] This function tests if the positive correlation or negative correlation exists, estimates significant autoregressive parameters, and estimates fixed effects after adjusting for significant autoregressive parameters.[9] The equation of the segmented autoregressive error model is expressed as follows:

$$Rate_t = B_0 + B_1 * Block_t + B_2 * intervention_t + B_3 * (Block_t - 24)_+ + e_t$$

$$where\ (Block_t - 24)_+ = \begin{cases} Block_t - 24, & if\ Block_t > 24 \\ 0, & otherwise \end{cases}$$

Let $Rate_t$ denote the vancomycin prescription rate at block t. In this model, B_0 estimates the baseline level of the outcome measure at the start point (*e.g.*, December 1, 2015). B_1 estimates the change of the vancomycin prescription rate over time before the intervention was implemented. B_2 estimates the immediate impact of the intervention on the vancomycin prescription rate. B_3 estimates the impact of the intervention on the vancomycin prescription rate over time during post-intervention period. The error term e_t has the appropriate autoregressive covariance matrix to account for the time variability.

Table 1. Snapshot of two different data sets used in ITS design

	Individual DOT/PD				Aggregated DOT/PD			
ID	block	prepost[1]	afterpost[2]	DOT/PD	block	prepost[1]	afterpost[2]	DOT/PD
7992	1	0	0	13.36	1	0	0	10.83
8564	1	0	0	3.4	2	0	0	10.08
4604	1	0	0	14.93	3	0	0	7.25
9016	1	0	0	12.29	4	0	0	11.22
6602	1	0	0	12.41	5	0	0	11.98
6387	1	0	0	14.58	6	0	0	10.39
3672	1	0	0	10.23	7	0	0	11.71
1098	1	0	0	9.46	8	0	0	10.79
2038	1	0	0	7.05	9	0	0	11.11
6258	1	0	0	15.87	10	0	0	13.18
8435	1	0	0	7.66	11	0	0	11.77
2652	1	0	0	8.11	12		0	10.86
		⋮				⋮		
5371	48	1	24	13.36	38	1	14	9.45
8564	48	1	24	3.39	39	1	15	8.88
9016	48	1	24	13.48	40	1	16	7.25
9897	48	1	24	6.62	41	1	17	8.35
5631	48	1	24	7.55	42	1	18	8.85
2331	48	1	24	4.48	43	1	19	6.62
9913	48	1	24	14.88	44	1	20	6.16
6562	48	1	24	6.37	45	1	21	7.26
6590	48	1	24	12.44	46	1	22	6.44
5932	48	1	24	6.39	47	1	23	6.89
6714	48	1	24	4.43	48	1	24	8.45

[1] 0 indicates pre-intervention period and 1 indicates post-intervention period
[2] number of block counts after the intervention

2.4.2 Nonlinear mixed model

Even though ITS can provide an audience a straight forward numerical presentation, the major limitation of ITS is that it cannot analyze by individual-level (*i.e.*, ITS model can consider time variability but cannot consider physician variability in this study). Using somewhat summarized data loses a flexibility compared to individual-level data. Poisson random-intercept regression with offset term was considered as an alternative modeling strategy to analyze individual-level data. The offset term was set as patient days (PD) that each physician

contributed. The days of therapy was assumed to follow the Poisson distribution. When analyzing longitudinal count data, an inherent correlation within subject is the major cause of over-dispersion. To relax this violation, the random intercept Poisson model was used to capture additional variability. Morris *et al.* argued that including random intercept to the Poisson regression adds between group variability in the baseline prescription level, while accounting for the correlation between repeated measurements on the same physician.[11]

PROC NLMIXED in SAS 9.4 was used to fit the Poisson regression models.[10] The equation of the Poisson random intercept model with offset term is expressed as follows:

$$DOT_{ij}|\theta_i \sim Poisson(\lambda_{ij})$$

$$\log(\lambda_{ij}) = \log(PD_{ij}/100) + B_0 + \theta_i + B_1 * Block_t + B_2 * intervention_t + B_3 * (Block_t - 24)_+$$

$$\theta_i \sim N(0, \tau^2)$$

$$where\ (Block_t - 24)_+ = \begin{cases} Block_t - 24, & if\ Block_t > 24 \\ 0, & otherwise \end{cases}$$

Let DOT_{ij} denote the vancomycin use at block j on the ith physician. In this model, B_0 estimates the log expected DOT at baseline averaged across physicians. e^{B_1} estimates relative rate of change of DOT over time before intervention. e^{B_2} estimates relative rate of immediate impact of the intervention on DOT. e^{B_3} estimates relative rate of change of DOT over time after intervention. τ^2 represents the heterogeneity variance, which explains the physician-specific deviation in baseline log expected DOT.

Morris et al. argued that the Poisson model with random effect assumes it to be equi-dispersion even after the longitudinal structure is absent.[11] The difference between the Poisson model and Negative Binomial model is that the Negative Binomial model allows over-dispersion. The Poisson distribution is the generalized negative binomial distribution, where the

mean parameter is the same as the variance parameter (*i.e.*, $E(X) = Var(X)$). However, for the Negative Binomial distribution, a mean parameter is different for all members of population and it follows gamma distribution. Because of this reason, a Negative Binomial model with random effect allows more flexibility into the model.[12] PROC NLMIXED in SAS 9.4 was used to fit the Negative Binomial regression model.[10] The Negative Binomial random intercept model with offset is expressed as follows:

$$DOT_{ij}|\theta_i \sim Negbin(\lambda_{ij}, k)$$

$$\log(\lambda_{ij}) = \log(PD_{ij}/100) + B_0 + \theta_i + B_1 * Block_t + B_2 * intervention_t + B_3 * (Block_t - 24)_+$$

$$\theta_i \sim N(0, \tau^2)$$

$$where\ (Block_t - 24)_+ = \begin{cases} Block_t - 24, & if\ Block_t > 24 \\ 0, & otherwise \end{cases}$$

Let DOT_{ij} denote the vancomycin use at block j on the i[th] physician. k is a dispersion parameter that detects if the over-dispersion is present. In this model, B_0 estimates the log expected DOT at baseline averaged across physicians. e^{B_1} estimates relative rate of change of DOT over time before intervention. e^{B_2} estimates relative rate of immediate impact of the intervention on DOT. e^{B_3} estimates relative rate of change of DOT over time after intervention. τ^2 represents the heterogeneity variance, which explains the physician-specific deviation in baseline log expected DOT.

2.4.3 Linear mixed model with AR(1) covariance structure

Considering repeated measures design, a mixed model method with special parametric structure on the covariance matrices was applied along with Poisson regression and Negative Binomial regression.[13] With this model, within-subject covariance can be manipulated so that the

model has more flexibility by choosing an appropriate covariance structure. Fitting an unstructured covariance matrix for within-subject errors was not adequate for highly unbalanced data. Instead, AR(1) covariance matrix was applied because it can handle unbalanced but equally spaced data.[14s] Also, an autoregressive form is reasonable covariance structure to be used for repeated measures because an observation is likely to be highly correlated to an observation measured within short-term interval than to an observation measured within long-term interval. However, there is no correlation between subjects but each physician is known to be independent. We call this covariance structure as AR(1)+RE.[13] To fit this model, an assumption was made that outcome measure is a continuous variable. PROC MIXED in SAS 9.4 was used to fit the mixed linear model.[10] The mixed linear model equation is expressed as follows:

$$Rate_{ij} = B_0 + \theta_i + B_1 * Block_{ij} + B_2 * intervention_{ij} + B_3 * \left(Block_{ij} - 24\right)_+ + e_{ij}$$

$$\theta_i \sim N(0, \tau^2)$$

$$where\ (Block_t - 24)_+ = \begin{cases} Block_t - 24, & if\ Block_t > 24 \\ 0, & otherwise \end{cases}$$

$$Var[\boldsymbol{e_i}] = \sigma^2 \begin{bmatrix} 1 & p & p^2 & \cdots & p^{j-1} \\ & 1 & p & \cdots & p^{j-2} \\ & & 1 & \cdots & \vdots \\ & & & \ddots & p \\ & & & & 1 \end{bmatrix}, if\ physician\ i\ has\ j\ observations$$

Let $Rate_{ij}$ denotes the vancomycin prescription rate at block j on the i[th] physician. In this model, B_0 estimates the baseline level of the outcome measure at the start point (*e.g.,* December 1, 2015). B_1 estimates the change of the vancomycin prescription rate over time before the intervention was implemented. B_2 estimates the immediate impact of the intervention on the vancomycin prescription rate. B_3 estimates the impact of the intervention on the vancomycin prescription rate over time during post-intervention period. τ^2 represents the heterogeneity variance, which is a between-group variability in the intercepts. σ^2 represents the residual

variance, which is a within-group variability in the residuals. p is a parameter that determines functional form of the correlation.

3. Result

The counterfactual refers to a hypothetical scenario where intervention was not enforced and pre-existing time trend stayed the same even after intervention. With the counterfactual scenario, we could visualize the impact of intervention if there was a change occurring in the post-intervention period.[15] A graphical display of the counterfactual scenario is shown in Figure 1. The continuous line shows the trend of the vancomycin prescription rate in the pre-intervention period. Assuming there was no intervention (*i.e.,* counterfactual scenario), the dashed line represents the pre-intervention trend of the vancomycin prescription rate. All of the points after intervention period (*e.g.,* grey zone) lie below the dashed line, which suggests a strong indication of intervention effect. With the graphical support, ITS model and random-effect models provided statistical evidence.

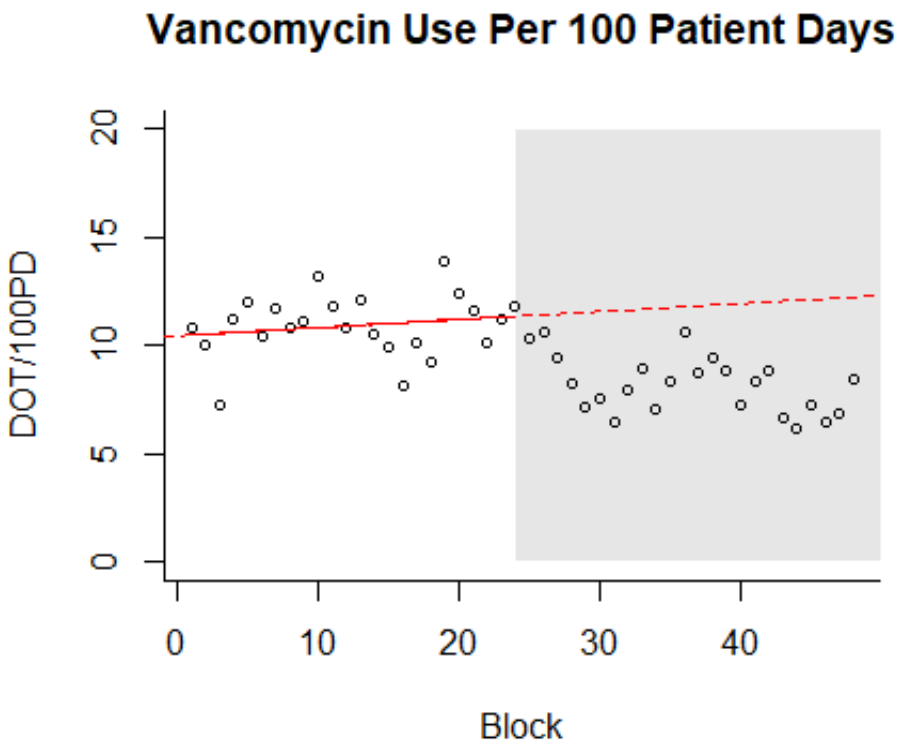

Figure 1. Scatter plot of DOT/PD over time.

The Durbin-Watson test was performed to examine the presence of autocorrelation. If the Durbin-Watson test statistic is close to 2.00, then that number suggests that there is no autocorrelation.[7] However, according to Table 2, the Durbin-Watson test statistic was 1.45 which indicates that the autocorrelation exists. The p-value for testing positive autocorrelation was 0.007, which suggests there is a positive autocorrelation. The p-value for testing negative autocorrelation was 0.99, which strongly suggests there is no negative autocorrelation.

The prescription of the antibiotic drugs is fluctuated with the influenza cases every year. Physicians tend to prescribe more antibiotic drugs to the patient during the flu season. Therefore, controlling for the flu season might reveal the true physicians' prescription behavior.[16] The flu season was set as September 1st – December 31st and January 1st – March 31st in this study. Since

a positive correlation exists and adjusting for flu effect might be critical, first-order autocorrelation and higher-order autocorrelation were tested. By performing backward elimination of first-order, second-order and higher-order autocorrelation, the most parsimonious model was fitted and the results are present in Table 2.

$\hat{B}_1$ refers to the coefficient that estimates the overall temporal trend. $\hat{B}_2$ refers to the coefficient that estimates immediate impact of the intervention. $\hat{B}_3$ refers to the coefficient that estimates the post-intervention trend on vancomycin prescription rate. These parameter's definitions will bes used throughout the paper. The baseline average expected vancomycin prescription rate was 10.79 (95% confidence interval, 10.05 to 11.53) for an ITS using aggregated data with appropriate AR parameters assumed given. Before the intervention, there was no statistical evidence that the vancomycin prescription rate changed over time. However, there was an immediate drop of the vancomycin prescription rate by 2.29 (95% confidence interval, -3.07 to -0.88) when the intervention was introduced, and this drop was statistically significant. The $\hat{B}_3$ parameter estimate suggests that the impact of intervention was not a one-time effect but the vancomycin prescription rate constantly decreased by 0.12 (95% confidence interval, -0.22 to -0.02) every two weeks after the intervention. The directions of the estimates using an ITS using individual-level data were the same as an ITS using aggregated data. Howevers, for individual-level data, the Durbin-Watson test statistic was close to 2.00, which suggests that no specific autocorrelation was captured. When individual-level data was used in PROC AUTOREG, each observation was treated as an independent observation, which ignored the fact that subjects were measured repeatedly. This might wash way the autocorrelation within the error terms. Therefore, individual-level data cannot be analyzed using PROC AUTOREG but

rather need alternative modeling strategies such as nonlinear random effect model or mixed linear model with AR(1) covariance structure.[10]

Table 2. Estimated parameters for ITS models

	Interrupted Time Series of Aggregated DOT/100 PD		Interrupted Time Series of Individual DOT/100 PD
	unadjusted	AR parameters assumed given	unadjusted
$\hat{B}_0$	10.464* (CI: 9.35, 11.56)	10.79* (CI: 10.05, 11.53)	10.48* (CI: 9.44, 11.52)
$\hat{B}_1$	0.037 (CI: -0.03, 0.11)	0.015 (CI: -0.03, 0.06)	0.041 (CI: -0.03, 0.11)
$\hat{B}_2$	-2.14* (CI: -3.66, -0.62)	-2.02* (CI: -3.13, -0.92)	-2.29* (CI: -3.71, -0.88)
$\hat{B}_3$	-0.12* (CI: -0.23, -0.01)	-0.09* (CI: -0.15, -0.02)	-0.12* (CI: -0.22, -0.02)
Durbin-Watson**	1.45	•	2.04

*Statistically significant, p-value < 0.05
**Durbin-Watson test statistics before AR parameters assumed given

For randomly chosen 15 physicians, the individual profiles for the vancomycin prescription rate are presented in Figure 2. In the spaghetti plot, the variability caused by different physicians is displayed. Each physician had a different starting point and a different prescription tendency over time. Using an ITS model might oversimplify this variability and may lead to inaccurate statistical inferences. To avoid this situation, between-subject variability should be added for individual-level data and thus other models were considered.

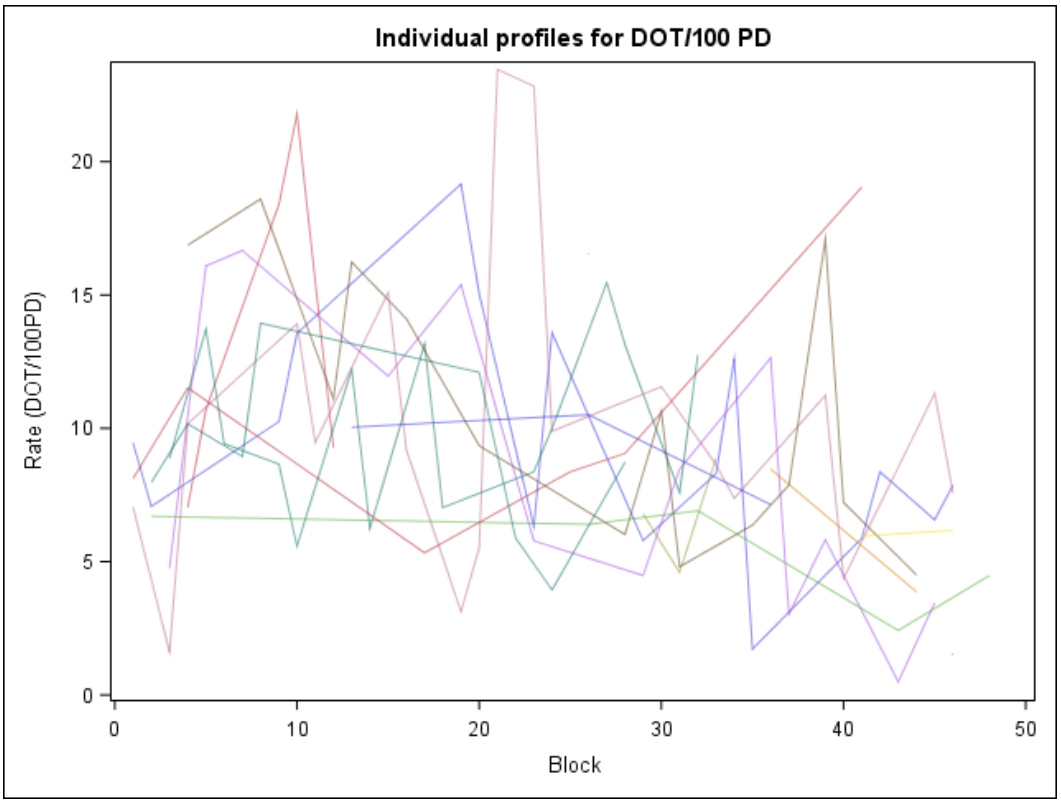

Figure 2. Individual profiles for DOT/PD in 15 randomly selected individuals

To fit Poisson random intercept model that allows to analyze individual-level data, a strong assumption should be made that random intercepts are uncorrelated with other exploratory variables in the model (*e.g.*, In this study, random intercept does not change across the two time periods, which are the pre-intervention and post-intervention). [17] Two separate Poisson random-intercept models were fitted to identify if there is a serious violation of this assumption; one for the pre-intervention only period and another for the post-intervention only period. Physicians who contributed more than 3 blocks both in pre-intervention and post-intervention were only included. Estimated random intercept values were extracted from those two models and plotted against each other. Through this exploratory analysis, we can examine if the random intercepts are correlated with the intervention variable.

An independence assumption between random intercept and exploratory variable was reviewed. To examine if the random intercepts are correlated with the covariate, the Poisson random intercept model from pre-intervention only data and the Poisson random intercept model from post-intervention data were fitted. The graphical display of the comparison between those two random intercepts are presented in Figure 3. If the dot is close to the diagonal line, then that indicates there was no abnormal physician behavior observed. However, if the dot is close to the y-axis, that individual physician during the post-intervention period prescribes more vancomycin to the patients than during the pre-intervention period. On the other hand, if the dot is close to the x-axis, that individual physician during the post-intervention period prescribes less vancomycin to the patients than during the pre-intervention period. As shown in Figure 3, no certain relationship between random intercepts and intervention variable was captured; plots were scattered without any pattern. On top of that, a simple linear regression was fitted for the estimated random intercepts from the pre-intervention and post-intervention period. The result came out that there was no statistically significant relationship captured between the random intercept and the intervention variable, which supports the finding from Figure 3. Since there was no serious violation, the Poisson random intercept model was fitted assuming the random intercepts were uncorrelated with other explanatory variables. Note that the same assumption was made for the Negative Binomial random intercept model.

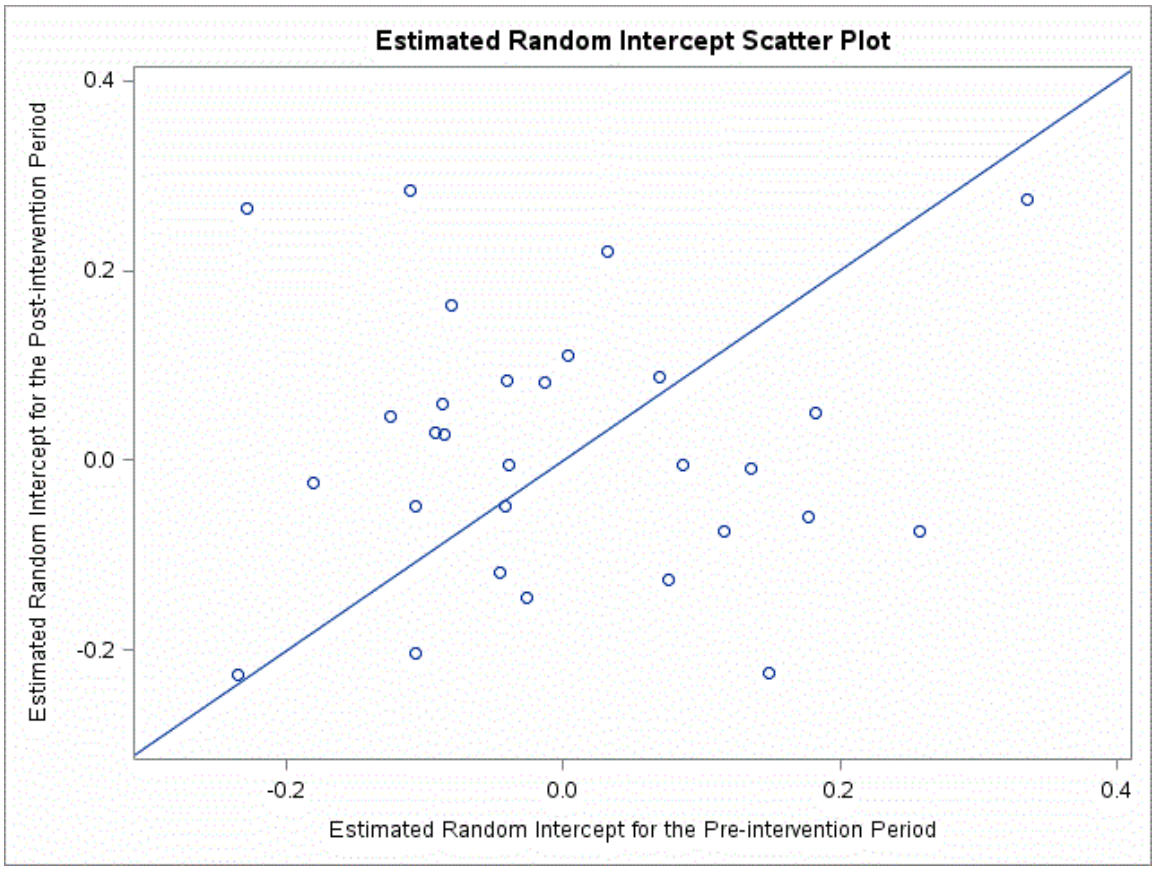

Figure 3. Scatter plot of estimated random intercepts

The estimates using Poisson random intercept and Negative Binomial random intercept models are presented in Table 3. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) are the measures used to examine improvement in model fitting. Smaller values represent better fitting model.[18] In this study, the Negative Binomial random-intercept model had smaller AIC and BIC than the Poisson random-intercept model. Even after adding a random effect to capture both between-subject and within-subject variability in Poisson regression model, $\hat{k}$ =0.15 suggests that additional over-dispersion is evident. For these reasons, the Negative Binomial random-intercept was more appropriate model for this data. As shown in Table 3, the baseline average expected vancomycin prescription rate was $e^{2.3437}$ =10.41 (95% confidence interval, 9.33 to 11.62). After controlling for within-physician correlation, the drop of the vancomycin prescription rate right after the intervention was statistically significant, and the

vancomycin prescription rate dropped by 18.23% ($1 - e^{-0.2086}$=0.1823, 95% confidence interval: 5.73% to 30.03%). The trend of vancomycin prescription rate was statistically significant for the post-intervention period. After seeing a peer-comparison report card, the vancomycin prescription rate continuously decreased by 1.4% ($1 - e^{-0.014}$=0.014 95% confidence interval: 0.3% to 2.5%) bi-weekly suggesting that there was a detectable impact in the long run. Between-physician variation in the days of therapy has a standard deviation of -2.66 on the log scale and the covariance parameter τ is statistically significant. Note that, block coefficient was statistically significant in Poisson random-intercept model setting, which disagreed with both ITS and Negative Binomial random-intercept models. Flu indicator variable (*e.g.*, $\hat{B}_4$) was included in the model to adjust for the flu effect. For both of the Poisson random effect model and Negative Binomial random effect model, there was no major change after the adjustment and flu coefficient was not statistically significant.

Table 3. Estimated parameters for Poisson and Negative Binomial random effect models

	Poisson Random Effect		NB Random Effect	
	Risk Ratio	Adjusted Risk Ratio	Risk Ratio	Adjusted Risk Ratio
$\hat{B}_0$	2.31* (95% CI: 2.25, 2.37)	2.31* (95% CI: 2.24, 2.38)	2.34* (95% CI: 2.23, 2.45)	2.36* (95% CI: 2.23, 2.48)
$\hat{B}_1$	0.004* (95% CI: 0.001, 0.008)	0.004* (95% CI: 0.001, 0.008)	0.003 (95% CI: -0.003, 0.011)	0.003 (95% CI: -0.004, 0.01)
$\hat{B}_2$	-0.21* (95% CI: -0.28, -0.13)	-0.21* (95% CI: -0.28, -0.12)	-0.21* (95% CI: -0.35, -0.05)	-0.19* (95% CI: -0.35, -0.04)
$\hat{B}_3$	-0.01* (95% CI: -0.02, -0.009)	-0.01* (95% CI: -0.02, -0.009)	-0.01* (95% CI: -0.02, -0.003)	-0.01* (95% CI: -0.02, -0.003)
$\hat{B}_4$	•	0.003 (95% CI: -0.04, 0.04)	•	-0.02 (95% CI: -0.11, 0.06)
k	•	•	0.15* (95% CI: 0.12, 0.17)	0.15* (95% CI: 0.12, 0.17)
τ	-1.93* (95% CI: -2.21, -1.65)	-1.93* (95% CI: -2.21, -1.65)	-2.66* (95% CI: -3.46, -1.87)	-2.68* (95% CI: -3.48, -1.87)
AIC	5130.9	5132.9	4284.2	4285.9
BIC	5141.7	5145.8	4297.2	4301.1

* Statistically significant, p-value < 0.05

For a mixed linear model, the normality assumption was made. The parameter estimates of linear random-intercept model with or without AR(1) components are present in Table 4. AR(1)+RE and RE models had similar fixed effects' estimates. According to Raftery, differences of 0-2 in BIC provide weak evidence favoring the more complex model and differences of 2-6 in BIC provide positive evidence favoring the more complex model.[18] For both unadjusted and adjusted model, the BIC difference was within 0-2 range so more complex model was favored (e.g., AR(1)+RE is more complex model). Moreover, the AR(1)+RE had slightly smaller AIC value than the RE model. For the unadjusted AR(1)+RE model, the baseline expected vancomycin prescription rate was 10.34 (95% confidence interval, 9.21 to 11.47). After controlling for within-physician correlation, the vancomycin prescription rate was dropped by

2.32 (95% confidence interval, -3.78 to -0.87) when the intervention was introduced. This decreasing trend continued until the end of the study (*e.g.*, the vancomycin prescription rate decreased by 0.13 bi-weekly). Pre-intervention vancomycin prescription trend and flu effect were not statistically significant. Note that the directions and values of the coefficients were similar to those of ITS and Negative Binomial random-intercept model.

Table 4. Estimated parameters for mixed linear model with different covariance matrix structure

	RE		AR(1)+RE	
	Unadjusted	Adjusted	Unadjusted	Adjusted
$\hat{B}_0$	10.41* (95% CI: 9.33, 11.48)	10.54* (95% CI: 9.30, 11.78)	10.34* (95% CI: 9.21, 11.47)	10.48* (95% CI: 9.18, 11.78)
$\hat{B}_1$	0.04 (95% CI: -0.02, 0.11)	0.042 (95% CI: -0.03, 0.11)	0.04 (95% CI: -0.02, 0.12)	0.04 (95% CI: -0.02, 0.12)
$\hat{B}_2$	-2.30* (95% CI: -3.7, -0.89)	-2.19* (95% CI: -3.67, -0.71)	-2.32* (95% CI: -3.78, -0.87)	-2.22* (95% CI: -3.75, -0.69)
$\hat{B}_3$	-0.12* (95% CI: -0.22, -0.02)	-0.13* (95% CI: -0.24, -0.02)	-0.13* (95% CI: -0.24, -0.025)	-0.14* (95% CI: -0.25, -0.02)
$\hat{B}_4$	•	-0.19 (95% CI: -1.08, 0.68)	•	-0.19 (95% CI: -1.10, 0.71)
τ^2	0.65** (SE: 0.41, P-value:0.056)	0.64** (SE: 0.41 P-value: 0.058)	0.43 (SE: 0.43 P-value: 0.15)	0.42 (SE: 0.42 P-value: 0.15)
p	•	•	0.09* (SE: 0.04 P-value: 0.03)	0.09* (SE: 0.04 P-value: 0.03)
σ^2	18.68* (SE: 1.11 P-value: <0.0001)	18.71* (SE: 1.12 P-value: <0.0001)	18.92* (SE: 1.15 P-value: <0.0001)	18.96* (SE: 1.16 P-value: <0.0001)
AIC	3499.2	3498.8	3497.0	3496.5
BIC	3503.5	3503.1	3503.4	3503.0

* Statistically significant, p-value < 0.05

**p-value slightly bigger than 0.05

For random-intercept only model, the within-group covariance is τ^2. However, for random intercept with AR(1) covariance matrix model, the within-group covariance is $\tau^2 + \sigma^2 p^{|j-j'|}$. The within-group covariance for random intercept only model was calculated as follows.

$$Var(\theta_i) = \tau^2, \quad Cov(\boldsymbol{\varepsilon_i}) = \begin{bmatrix} \sigma^2 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma^2 \end{bmatrix}$$

$$Cov\left(Rate_{ij}, Rate_{ij'}\right) = Cov\left(\boldsymbol{XB} + \theta_i + \varepsilon_{ij}, \boldsymbol{XB} + \theta_i + \varepsilon_{ij'}\right) = Cov(\theta_i, \theta_i) = \tau^2$$

The within-group covariance for random intercept with AR(1) covariance matrix model was calculated as follows.

$$Var(\theta_i) = \tau^2, \quad Cov(\boldsymbol{\varepsilon_i}) = \sigma^2 \begin{bmatrix} 1 & p & p^2 & \cdots & p^{k-1} \\ & 1 & p & \cdots & p^{k-2} \\ & & 1 & \cdots & \vdots \\ & & & \ddots & p \\ & & & & 1 \end{bmatrix}$$

$$Cov\left(Rate_{ij}, Rate_{ij'}\right) = Cov\left(\boldsymbol{XB} + \theta_i + \varepsilon_{ij}, \boldsymbol{XB} + \theta_i + \varepsilon_{ij'}\right) = Cov(\theta_i, \theta_i) + Cov\left(\varepsilon_{ij}, \varepsilon_{ij'}\right)$$

$$= \tau^2 + \sigma^2 p^{|j-j'|}$$

As shown in Table 4, τ^2 for both unadjusted and adjusted random intercept only model was mildly statistically significant. This confirmed that repeated measures taken from each physicians are not independent but correlated in this data. Furthermore, statistically significant p value from both unadjusted and adjusted AR(1)+RE model were even suggesting that the within-group covariance could be improved by adding AR(1) covariance matrix structure, which aligned well with AIC result. After adding AR(1) covariance structure, τ^2 became not significant. p may have played a role by partially absorbing the repeated measures correlation from τ^2. All the parameters were estimated after accounting for repeated measurement correlation.

To interpret the results in a direct way, the ratio of the predicted to the counterfactual value was used to express the intervention effect. Predicted the vancomycin prescription rate two weeks after the intervention was calculated as follows.

$$\hat{Y}_{25(with\ intervention)} = \hat{B}_0 + \hat{B}_1 \times 25 + \hat{B}_2 \times 1 + \hat{B}_3 \times 1$$

Predicted the vancomycin prescription rate at block 25 assuming there was no intervention was calculated as follows.

$$\hat{Y}_{25(without\ intervention)} = \hat{B}_0 + \hat{B}_1 \times 25$$

The difference between $\hat{Y}_{25(with\ intervention)}$ and $\hat{Y}_{25(without\ intervention)}$ represents the absolute intervention effect. $\frac{|\hat{Y}_{25(with\ intervention)} - \hat{Y}_{25(without\ intervention)}|}{\hat{Y}_{25(without\ intervention)}}$ represents the relative change in outcome associated with intervention.[7]

Predicted relative change in outcome was calculated for block 25 and 36. Block 25 is the time period right after the intervention and Block 36 is the mid-point of post-intervention period. Compared to the scenario when there was no intervention, the predicted vancomycin prescription rate per two weeks decreased by 21.46% in block 25. Compared to the scenario when there was no intervention, the predicted vancomycin prescription rate per two weeks decreased by 3.414% in block 36. As shown in Figure 1, these numbers well represent the counterfactual scenario result.

4. Discussion

The results of this study revealed that the intervention was effective on the reduction of the vancomycin prescription rate. The peer comparison intervention was implemented by sending out the report card to the IM physicians. This study supports that the peer comparison

intervention is an efficient strategy to manage antibiotics use in the acute care inpatient hospitals setting.

The use of statistical models to analyze longitudinal data has surged recently. From 2000 to 2012, 54.6% of studies in medical journals were declared to be longitudinal studies.[19] In public health, economics, and policy research settings, longitudinal intervention data are common to investigate the intervention effect. An interrupted time series analysis is a widely used quasi-experimental study design to estimate the impact of intervention that has been implemented at a clearly defined time point. The strength of using interrupted time series analysis is that segmented regression models can examine the change in response to an intervention while controlling the prior trend in the outcome. ITS also provides a straightforward visual presentation which makes possible to identify the intervention effects whether they are present or absent, one-time or persistent, and so on. Although ITS is an arguably strong model, limitations of ITS also exist. The segmented regression model assumes a linear trend in the outcome measure. In many practical situations, the linearity assumption might only hold for short time period. Instead, non-linear patterns may be observed within each time segment. These non-linear patterns will predict the future time trend better than linear patterns. As opposed to the prediction purpose, if the study purpose is just to examine the impact of the intervention, a linear trend assumption is adequate to be make. Moreover, aggregated individual-level data by evenly spaced time point are generally used in ITS model. Because data are somewhat summarized, an ITS model fails to control for individual-level characteristics, which restricts the scope of the study.[7] Even if one is fitting an ITS model with individual-level data, conventional ITS will not take individual variability into account, which will eventually lead to a biased conclusion about

the fixed effects. For this reason, ITS analysis is a good tool to study the population-based intervention data but not for the individual-based intervention data.

To capture within-subject variability for individual-level data (*e.g.,* time in the case of this study), the Negative Binomial random intercept model was considered. This model allows over dispersion, which loosens the Poisson equi-disperson assumption. On top of that, including random intercept into the model accounts for variability not only caused by each subject but also induced by the correlation of measurements within a subject.[11] The Negative Binomial random intercept model will fail if the assumption of independence between random intercept and predictors is not fulfilled. This model is adequate to analyze longitudinal count data when explanatory variables are uncorrelated with the random effects.[12, 20]

The random effect in a nonlinear model can take different covariance structures in theory. However, statistical packages restrict its use to particular cases because of controlling inferential processes and the complex computation.[20] Instead, the linear mixed model with special parametric structure on the covariance matrices was used to add more flexibility to the model. This model is an extension of ITS by adding a random-intercept and specifying the structure of the **R** covariance matrix to the segmented regression; the AR(1) structure was used in this study. Handling the between-subject and within-subject variability in a flexible way can provide richer output. However, the sample size should be bigger than 25 with at least 3 repeated measurement or else AR(1) correlation coefficients are not normally distributed and the variance of these coefficients are not constant.[21] Both strengths and limitations of three models are summarized in Table 5.

Table 5. Strengths and Limitations of three models

	Segmented Regression (Interrupted Time Series)	Nonlinear (Poisson, NB) random intercept model	Linear mixed model with AR(1) covariance structure
Outcome	▪ Continuous variable	▪ Discrete variable (count data)	▪ Continuous variable
Strength	▪ Simple and easy to interpret model ▪ Straightforward visual presentation ▪ Account for higher order autocorrelation ▪ Accounts for the prior trend in the outcome	▪ Can analyze individual-level data ▪ Able to adjust for individual characteristics ▪ Accounts for the prior trend in the outcome	▪ Add more flexibility to the within-subject covariance ▪ Can analyze individual-level data ▪ Able to adjust for individual characteristics ▪ Accounts for the prior trend in the outcome
Limitation	▪ Only for population-based data ▪ Not able to adjust for individual characteristics	▪ Cannot manipulate covariance structure ▪ Random effect should be independent to the covariates	▪ Need to have more than 25 samples with at least 3 repeated measurements for AR(1)

However, the reduction on the overall use of antibiotics still must be examined. After the intervention, the physicians might prescribe less intravenous (IV) vancomycin and prescribe other antibiotic drugs instead (*e.g.*, Doxycycline, TMP-SMX, Linezolid, Daptomycin, Clindamycin, Ceftaroline). Shifting to other antibiotic agents may retain or develop antibiotic-resistance patterns. This phenomenon is known as the balloon effect. When the balloon is squeezed, the air inside the balloon moves to the less restrictive area so that the air itself does not disappear. Increased use of other antibiotics would counteract the intervention effect. To observe whether the other antibiotic agents prescription rate deceased while there has been a decline for vancomycin prescription rate, stratified analysis can be considered for a possible modeling strategy. Investigating if the squeezing balloon effect presents might shed new light on studying the antibiotic resistance, and this can be a future research topic.

In conclusion, for an Interrupted Time Series, Negative Binomial random-intercept model, and mixed linear model, fixed effects were statistically significant except for the block

coefficient and their directions were the same. Negative Binomial random-intercept model and mixed linear model with AR(1) covariance structure can be alternative modeling strategies for Interrupted Time Series when analyzing individual-level data. Based on these results, we were able to answer this study's scientific questions. There was no statistically significant trend of vancomycin prescription rate in pre-intervention period. After the intervention was phased in on December 1, 2016, there was an immediate drop of the vancomycin prescription rate. This decreasing trend maintained until the end of the study. Therefore, peer-comparison intervention was effective on vancomycin utilization and it is evident that vancomycin usage has been dropped since the intervention.

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Appendix: SAS Programming Code

```
/**********************************
******Interrupted Time Series*******
**********************************/

proc autoreg data=its;
      model vanco_calc= block prepost afterpost/method=ml nlag=24 backstep
dwprob;
      test 24*block+prepost+12*afterpost=0;
run;


/**********************************
*********Poisson Regression**********
**********************************/

proc nlmixed data=poisson;
      parms logsig=-1.9376 beta0=2.3154 beta1=-0.2065 beta2=0.004894 beta3=-
0.01508;
      lambda=exp(offset+beta0+beta1*prepost+beta2*block+beta3*afterpost+u);
      model vanco_days ~ poisson(lambda);
      random u ~ normal(0,exp(2*logsig)) subject=physician;
      contrast 'pre vs post' beta1 + 24*beta2 + 12*beta3;
run;


/**********************************
*********Negative Binomial**********
**********************************/

proc nlmixed data=poisson;
      parms logsig=-2.6675 beta0=2.3437 beta1=-0.2086 beta2=0.003689 beta3=-
0.01420 k=0.1530;
      linp=beta0+beta1*prepost+beta2*block+beta3*afterpost+offset+u;
      mu=exp(linp);
      p=1/(1+mu*k);
      model vanco_days ~ negbin(1/k, p);
      random u ~ normal(0,exp(2*logsig)) subject=physician;
      contrast 'pre vs post' beta1 + 24*beta2 + 12*beta3;
run;
ods rtf close;


/**********************************
******Random Intercept/Slope********
**********************************/

proc mixed covtest data=mixed;
      class physician prepost(ref='0');
      model vanco_calc=prepost block afterpost / solution cl;
      random intercept / subject=physician;
      repeated / type=ar(1) subject=physician;
run;
```