The Potential Effects of Implementing an Antibiotic Stewardship Program by Integrating It with Medication Therapy Service in a Low-Income Serving Clinic - A Single-Center Experience

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Abstract

Background: *Bacterial antimicrobial resistance (AMR) is a leading cause of mortality worldwide. Although AMR is common in low-income communities, there is limited evidence of the effect of antibiotic stewardship programs in low-income communities in the United States.* ***Objectives:*** *Our goal is to assess the effects of implementing pharmacist-led ASP by integrating it with medication therapy management service (MTM) in a low-income serving clinic. We evaluated the following 1) antibiotic prescriptions per 1000 patients, 2) the frequency of clinic (office) visits 30-day post-index clinic visits for recurring infections.* ***Methods:*** *To achieve our goal, we conducted a pre-post, quasi-experimental intervention study using an interrupted time-series analysis to assess the following: 1) antibiotic prescriptions per 1000 patients and the 2) frequency of office visits (including telehealth) within 30-day post-index clinic visits associated with recurrent infection.* ***Results:*** *Our findings revealed that the long-term effect of our antibiotic stewardship program intervention was associated with 63.69% reduction in antibiotic prescriptions per 1000 patients (change in slope = -0.173, [95% CI: (-0.30, -0.05)], P < 0.007) and a reduction in the frequency of office visits within 30-day post-index clinic visits by 67.27% (change in slope = -2.043, [95% CI: (-3.84, -0.24)], P < 0.028).* ***Conclusion:*** *Implementing antibiotic stewardship programs is feasible for clinics serving low-income populations. It was associated with a reduction in antibiotic prescriptions and preventable clinic (office) visits within 30 days due to infection recurrence.*

Keywords: antibiotics, low-income populations, pharmacist-led Antibiotic Stewardship Programs, medication adherence

Introduction

Bacterial antimicrobial resistance (AMR) is a leading cause of mortality worldwide.[1] In the United States (U.S.) alone, 2.8 million cases of AMR occur annually, causing over 35,000 deaths.[1] With such significant negative consequences associated with AMR, there is a keen interest among policymakers to curb the rise of AMR in our community.

It is well recognized that inappropriate antibiotic prescribing is a significant contributor to AMR, especially in outpatient settings.[2,3] It is estimated that more than 50% of antibiotics prescribed in outpatient settings are inappropriate.[4] Unfortunately, such inappropriate antibiotic prescribing is particularly common in rural or low-income communities.[5] Hence, decreasing the overuse of antibiotics and improving antibiotic adherence are core elements for reducing AMR among rural or low-income populations.[6,7]

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The clinical benefits of pharmacist-led antibiotic stewardship programs (ASP) are well-recognized by healthcare and governmental organizations.[8,9] The implementation of pharmacist-led ASP reportedly reduces unnecessary antibiotic prescribing and healthcare resource utilization.[10-12] However, most of the robust findings are mostly limited to inpatient care.[13]

Published data on the effect of pharmacist-led ASPs in outpatient settings (in the U.S) are mainly limited to the emergency department and urgent care setting.[14] Currently, there are only three published studies describing the impact of ASP on the primary care (PC) center (in the U.S.). These studies are retrospective and limited to a particular disease state – Urinary Tract Infection or Upper Respiratory Disease.[15-17] To the best of our knowledge, no study has examined the effect of pharmacist-led ASP among PC centers serving low-income populations (including homeless patients).

Based on the findings of the aforementioned studies, we hypothesized that the implementation of ASP would positively influence healthcare providers' antibiotic prescribing practice, reducing the unnecessary frequency of clinic visits associated with the suboptimal treatment of infections.

To test our hypothesis, we proposed to integrate ASP into our medication therapy management (MTM) services provided to patients. With this strategy, we hope to effectively integrate

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the four core elements of the antibiotic stewardship program as recommended by the Centers for Disease Prevention and Control (CDC) – "Commitment, Action, Reporting and Tracking and Reporting, Education." [18, 19]

Our overarching goal is to assess the potential effects of implementing pharmacist-led ASP integrated with medication therapy management service (MTM) in a low-income serving clinic. Our approach is unique as most studies report implementing ASP services as a standalone program, which may require additional pharmacist resources – which is one of the significant barriers to implementing ASP in outpatient services. We envision that our unique approach minimizes the need for additional resources to implement ASP services.

Therefore, this study aimed to assess the effects of implementing pharmacist-led ASP by integrating it with medication therapy management service (MTM) in a low-income serving clinic by evaluating the number of antibiotic prescriptions per 1000 patients and the frequency of clinic (office) visits within 30-day post-index clinic visit for recurring infections.

Methods

Overview of Study design: We conducted a non-randomized, pre-post (quasi-experimental) study. The pre-intervention period was from February 2017 to October 2019, whereas the intervention (i.e., ASP implementation) spanned from November 2019 to June 2021. Following the end of the intervention phase, data on patients' visits were extracted from the electronic health record (EHR) database. Only patients that met our inclusion criteria as determined using the International Classification of Disease – 10th revision (ICD-10) [see predetermined inclusion and exclusion criteria below] in both the pre-and post-intervention periods were analyzed. Patient sets with no similarity to the corresponding ICD-10 in both the pre-intervention and intervention period were excluded from further analyses.

Setting: The study was conducted at Bond Community Health Center (BCHC), Tallahassee, a Federally Qualified Health Center (FQHC). BCHC being an FQHC, provides PC services to low-income and homeless populations. There are 17 providers in the adult PC clinic. There is also an in-house pharmacy participating in a 340B drug pricing program, allowing the patients to purchase medications at a low or no "out-of-pocket" cost. The study was approved by the Florida A&M University Institutional Review Board (IRB).

Study population/inclusion and exclusion criteria

The populations involved in this study were adult patients (at least 18 years old) with symptoms associated with infection as defined by the provider. Patients were excluded if they had the following: infections that necessitate a long course of antimicrobial therapy (e.g., endocarditis, neutropenic patients), cognitively impaired, and unable to follow instructions, and patients prescribed antibiotics for preventive measures only. Because the clinic already has an established treatment protocol for patients with sexually transmitted disease (STD) or HIV, we excluded patients taking STD or HIV medications.

Description of services

Pre-intervention period: Before November 2019, there was no ASP. Healthcare providers' antibiotic prescriptions were automatically sent to the in-house pharmacy or drug chain pharmacies for dispensing. Pharmacists (with the affiliated pharmacy) are often asked to manage warfarin dosing, HIV medications (sometimes other medications for the management of sexually transmitted diseases), and cardiovascular disease risk factors such as diabetes, hyperlipidemia, and hypertension. However, no routine comprehensive medication therapy management (MTM) services were offered, nor was there an ASP service.

Intervention period: Initiated in November 2019, a pharmacist with an infectious disease (ID) background provided educational training to all physicians, nurses, and other clinical staff; focusing on the importance of an ASP, the clinical benefits of ASPs, and our overall implementation process. A reminder flyer on the new antibiotic stewardship services was also posted in the clinic. With clinic leadership buy-in (which includes the Chief Medical Officer and Chief Executive Officer), we integrated pharmacist-led ASP services. Pharmacist-led ASP services consist of three components (see Supplementary Table 1 for details of pharmacist services): 1. Pharmacists provide MTM and reconciliation services to assess antibiotic-drug interactions and disease-antibiotic interactions. 2. Pharmacists review antibiotics/culture results/point of care antimicrobial test results and other laboratory results in collaboration with the provider/prescriber. 3. Provision of patient education at the conclusion of the visit. Additionally, during a follow-up visit, pharmacists may prescribe over-the-counter (OTC) medicine for certain infections when indicated.

Antibiotic stewardship program (ASP) implementation process

The goal of our ASP was to ensure that the prescribed antibiotic is in concordance with the International Society of Infectious Disease (IDSA) and CDC guidelines. We assessed for the following: antibiotic-drug interactions, antibiotic-disease interactions, potential antibiotic-related adverse outcomes/side effects, renal function (for possible renal adjustment), and patient knowledge regarding antibiotic use/education. For additional details of implementation steps, see Supplemental Table 1. For this service, we dedicated a pharmacist, a Board-Certified Pharmacotherapy Specialist, to provide the service – hereafter referred to as the ASP pharmacist. We recognized that due to the involvement of only one pharmacist providing this care, it might be impossible to extend this service to all the patients who present at the clinic. Nevertheless, we anticipate that the healthcare providers' knowledge and awareness of the pharmacist-led ASP (or

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learning from the pharmacist intervention) would positively influence their antibiotic prescribing behavior.

Before the COVID-19 pandemic, the ASP pharmacist worked collaboratively with healthcare providers to offer ASP services. However, after the beginning of the unprecedented COVID-19 pandemic in March 2020, a change in plan was set in motion where patients were contacted telephonically after being examined by a healthcare provider. During this period, all ASP services were provided telephonically, and the preplanned goal was to reach patients within 24 hours after concluding their virtual visit with a healthcare provider. This 24-hour period was chosen because some patients (from our experience) who decided to pick up their medication outside the in-house pharmacy wait till the next day before presenting to the pharmacy to receive their prescription. This allows us time to provide the necessary clinical intervention before the patient visits the pharmacy or prescriptions are electronically transmitted to the outside pharmacy.

Research coordinators prospectively identified eligible patients by continuously reviewing the electronic health record (EHR). We ensured that we followed the patients within 24-36 hours after their index clinic visits.

Outcome measures and definitions

We measured the following two primary outcomes. 1) the number of antibiotic prescriptions per 1000 patients before and after the intervention - calculated based on the "prescription order dates" as entered on the EHR; 2) the number of patient visits 30-day post-index clinic visits associated with recurring ID – measured using the "encounter dates" for the specified ID following the ICD-10 codes.

Statistical analysis

Baseline patient socio-demographic and clinical characteristics were summarized using descriptive statistics. Baseline cohort characteristics were calculated using proportions, means, and standard deviations, as appropriate and were compared between groups with ANOVA or t-test for continuous variables where appropriate; Chi-square tests were used to test for relationships between categorical and binary variables.
Inferential statistical analyses were conducted using an interrupted times series (ITS) model following the Cochrane Effective Practice and Organization of Care recommendations (EPOC).[20] ITS is one of the well-recognized robust approaches for assessing an intervention effect when a randomized controlled study is unfeasible.[21,22] The ITS included pre-intervention and intervention phases. The period is a continuous variable indicating the time in "weeks" from the start of the study period. The variable "intervention" is an indicator variable where a value of 0 indicates the time points in the study before the intervention (pre-intervention phase), and a value of 1 indicates the time points in the study during the intervention phase. Study period, intervention, and time after the intervention were included as fixed effects. A random residual with an autoregressive variance structure was used to account for the correlation of measurements over time and overdispersion. We estimated regression coefficients corresponding to the magnitude of the effect of changes in level and trends pre-and post-intervention periods. The intervention variable was assessed to estimate both the immediate intervention effect (within a week) and the long-term intervention effect (sustained effect over months). To assess the immediate intervention effect on antibiotic prescribing rates and on the frequency of office (clinic) visits, we calculated the difference between the observed frequency in the week immediately following the ASP intervention and the level of frequency predicted by the pre-intervention trend. To assess the long-term effect of the ASP intervention, we calculated the long-term effect as the change in slope, that is, the difference between the pre-and post-intervention slopes; thus indicating whether the intervention effect persisted after the immediate intervention effect into the post-intervention period.[23,24] To account for the impact of COVID-19, we included a binary variable indicating the presence (1) or absence (0) of the pandemic during the study. The ITS model was adjusted for autocorrelation and seasonality according to the CDC, which defined the peak of Winter respiratory virus season,[25] assessed using Durbin–Watson statistic and Dickey-Fuller tests, respectively.[26,27] All statistical tests performed were 2-sided, and *P* values of < 0.05 were considered statistically significant. All analyses were performed with SAS 9.4 version (SAS Institute Inc., Cary, NC, U.S.).

Results

Descriptive analysis

There were 1,306 patients in the pre-intervention period and 475 patients in the post-intervention period. Table 1 presents the demographic characteristics of patients included in the analysis during the pre-and post-intervention periods. Supplemental Table 2 presents the top ten antibiotics, where the total number of antibiotic prescriptions throughout the post-intervention period was 1,845 (21%) and during the pre-intervention period was 6,912 (78.9%). The most commonly diagnosed IDs were candidiasis and upper and lower respiratory infectious (see Supplemental Table 3). Supplemental Table 3 provides information on the total number of clinic visits within 30 days of index visits associated with signs and symptoms of infections based on the ICD-10 codes. The information regarding the total number of clinic visits (including their demographics), the mean antibiotic prescribing rate, and clinic visits within the 30 days of index visit are also presented in Supplemental Tables 4 and 5.

ITS Analysis

In this section, we present the results of our ITS analysis on all two outcomes in the following subsections:

Antibiotic prescriptions per 1000 patients: The estimated immediate effect (within a week of ASP implementation) revealed a 65.22% increase in antibiotics prescription per 1000 patients, with 95% confidence interval (CI) [95% CI: (2.85,

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23.72)] (change in level = 13.284; $P < 0.014$). In contrast, the long-term effect of our ASP intervention was associated with 63.69% reduction in antibiotics prescription per 1000 patients (change in slope = -0.173, [95% CI: (-0.30, -0.05)], $P < 0.007$) (see Table 2). A graphical depiction of the change in levels and slope is shown in Figure 1.

Frequency of 30-day clinic visits: The estimated immediate effect of the ASP intervention revealed a 45.33% increase in the frequency of 30-day clinic visits (change in level = 147.2, [95% CI: (-4.91, 299.32)], $P < 0.060$). The long-term effect of our ASP intervention showed a reduction in the frequency of 30-day clinic visits by 67.27% (Change in slope = -2.043, [95% CI: (-3.84, -0.24)], $P < 0.028$) (see Table 3). A graphical depiction of the change in levels and slope is shown in Figure 2.

Discussion

As previously discussed, our overarching goal is to assess the potential effects of implementing ASP by integrating it with MTM among low-income patients.

We report that pharmacist-led ASP in our center was associated with reduced number of antibiotic prescriptions per 1000 patients sustained throughout the post-intervention phase during the COVID-19 pandemic. The observation suggests that implementing ASP (with MTM services) can help improve the appropriateness of antibiotic prescriptions in a PC setting by ensuring that patients can receive antibiotics only when clinically needed and the right antibiotics are selected. A similar positive effect of improving antibiotic prescribing behavior in PC was demonstrated by Fernández-Urrusuno et al. (2020).[28] Notably, our study is the first to examine the effects of implementing ASP among patients receiving treatment in a low-income serving clinic.

Also, we observed a reduction in the frequency of clinic visits associated with the ASP service. During ASP implementation, there were follow-up calls made by the ASP pharmacist for improved symptoms and to address other concerns of the patients. During follow-up calls, the ASP pharmacist also recommended other OTC medications to the patient to treat any other underlying symptoms. Two examples of such recommendations included using OTC creams to treat a rash or fungal candidiasis and antihistamines or nasal steroids to treat allergic rhinitis when it became evident that it was not a bacterial infection. These and other telephonic follow-up patient encounters made by the ASP pharmacist may have contributed to the reduced frequency of clinic (office) visits within 30 days post index visit associated with infection.

Our result did show an increase in "change in levels," indicating an immediate effect of ASP within a week of intervention. We speculate that this is related to the impact of COVID-19 and our transition from in-person provision of ASP services to telephonic services. For example, nationally, there was an initial increase in antibiotic prescriptions which was believed to treat COVID. Such sudden disruption may have contributed to the observation. Despite the increase, the long-term effect did point us in the right direction of improving antibiotic prescribing behavior. Additional study is needed to confirm our observation. Also, our future study will focus on antibiotic days of therapy (DOT), which is another metric recommended by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America as a preferred metric for antibiotic use.[29]

As shown, our observations revealed significant favorable healthcare policy and public health implications as follows: First, with AMR being a major challenge in outpatient settings, the Joint Commission (JC) mandated implementing an antibiotic stewardship program (ASP) in all outpatient settings.[30] Thus, clinics planning to implement ASP can learn from our clinical experience. Second, recent studies have proposed the framework of effective implementation of ASP through telehealth services. [31,32] Therefore, health care policyholders can advance policies, funding, and telehealth communications to enhance the provision of antibiotic stewardship services in low-income serving clinics or underserved areas.

The strength of our study relies on using strong analytical methods to evaluate our outcomes, increasing the internal validity of our study. This is important as ITS adjusted for any changes in the number of antibiotic prescriptions or office visits associated with either COVID or seasonality with time.

Limitations

Common to single-center clinic practice-based research, the ability to extend our findings to other settings is limited. Furthermore, because our goal was only to assess the potential effects of ASP implementation through its integration with MTM services and the unprecedented disruption caused by COVID-19, we did not have a mechanism to track the number of accepted or rejected pharmacist recommendations. As we systematically implement ASP in our clinic, we are working on developing a strategy to track the number of patients seen and the recommendations provided. From our experience, we believe that more studies are needed to show if a similar impact can be observed in other low-income serving clinics. This is especially true with all quasi experimental study design; because the extent of establishing a casual relationship is limited.[33] Therefore; more clinical data, driven by randomized clinical design, is needed to understand how to bridge the gap in curbing AMR in low-income communities.

It is possible that other FQHC or FQHC-like institutions may have a different setup than ours. Our practice-based research underscores three important innovations that can be adapted irrespective of the structure of the clinic. 1) Our ASP was not a standalone program, but rather integrated as part of the MTM service. 2) Our framework leveraged partnerships with pharmacists with pharmacies affiliated with the clinic (FQHC)

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and 3.) ASP was provided through telehealth service. Therefore, institutions planning to implement ASP should consider initially conducting a strengths-weaknesses-opportunities-threats (SWOT) analysis to identify gaps and potential interventions.[34] Additionally, we observed that pharmacist involvement with ASP puts them in a position to screen for non-medical or social needs that will impact patient compliance with the recommended antibiotic regimen. Hence, our plan is to adapt the WellRx screening tool developed by Page-Reeves et al. (2016)[35]. Our choice for WellRx is because of its ease of implementation in a clinic.

As with any practice-based research, we faced two unique challenges during the implementation process. First, during the in-person provision of ASP (with MTM service), contacting the healthcare providers for needed antibiotic modification before patient discharge was convenient. However, with the emergence of COVID and the obligatory transition to telehealth, it was challenging to communicate on time with healthcare providers. Therefore, several antibiotic modifications occurred after discharge. Secondly, we expectedly missed several patients during the telehealth transition. Nonetheless, a research coordinator who assisted with patients' enrollment helped minimize these two inconveniences.

Conclusion

Integrating ASP with MTM services can improve health outcomes and patients' perceived confidence in medication-taking among underserved populations. Similar positive outcomes with ASP can also be accomplished through telehealth services. Our opinion is that ASP should be mandated as a quality measure in PC settings. Patients, health care policyholders, and managed care organizations can equally benefit from implementing a pharmacist-led ASP (integrated with MTM services).

The opinions expressed in this paper are those of the authors.

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Author Contributions: ANO designed and directed the project and retrieved funding; MT was involved in enrolling patients and obtaining informed consent forms; CB and VS conducted the statistical analysis; US conducted the in-house service for all providers and SGB independently reviewed statistical analysis conducted. All authors discussed the results and commented on the manuscript.
Data availability: Additional data will be made available upon reasonable request.

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Table 1: Sample characteristics

Patient Demographic Characteristics	Overall Patients Population		Antibiotic Stewardship Program (ASP)				p-values
			Pre-ASP		Post-ASP		
	N =1781	%	N =1306	%	N= 475	%	
Gender							0.7288
Female	1265	71	930	71.2	335	70.5	
Male	503	28.2	366	28	137	28.8	
Choose not to disclose	13	0.7	10	0.8	3	0.6	
Age groups							0.0378
18 - 44	778	43.7	539	41.3	239	50.3	
45 - 64	744	41.8	564	43.2	180	37.9	
65 - 74	212	11.9	168	12.9	44	9.3	
74 <	47	2.6	35	2.7	12	2.5	
Race							0.0192
American Indian or Alaska Native	3	0.2	3	0.2	0	0	
Asian	11	0.6	10	0.8	1	0.2	
Black or African American	1181	66.3	864	66.2	317	66.7	
White	461	25.9	340	26	121	25.5	
Native Hawaiian or Pacific Islander	11	0.6	9	0.7	2	0.4	
Other Race	64	3.6	38	2.9	26	5.5	
Patient Declined	50	2.7	42	3.2	8	1.3	
Ethnicity							<.0001
Hispanic or Latino/Spanish or Latin American/Latin, Latino	150	8.4	103	7.9	47	9.9	
Not Hispanic or Latino	1373	77.1	974	74.6	399	84	
Patient Declined	258	14.5	229	17.5	29	6.1	
Education Level							<.0001
less than 8th grade	23	1.3	14	1.1	9	1.9	
8th grade	245	13.8	241	18.5	4	0.8	
9th grade	27	1.5	25	1.9	2	0.4	
10th grade	52	2.9	42	3.2	10	2.1	
11th grade	78	4.4	61	4.7	17	3.6	
12th grade	428	24	304	23.3	124	26.1	
2 years college	181	10.2	140	10.7	41	8.6	
4 years college	54	3	37	2.8	17	3.6	
Post-graduate	12	0.7	5	0.4	7	1.5	
Others	681	38.2	437	33.5	244	51.4	
Tobacco Use							0.0631
Currently Every Day	369	20.7	268	20.5	101	21.3	
Currently Some Days	89	5	61	4.7	28	5.9	

Formerly	295	16.6	203	15.5	92	19.4	
Never	865	48.6	647	49.5	218	45.9	
Unknown	163	9.1	127	9.6	36	7.6	
Insurance Type							0.2539
Personal Payment (Cash – No Insurance)	832	46.7	603	46.2	229	48.2	
Commercial	146	8.2	108	8.3	38	8	
Group Policy	81	4.5	55	4.2	26	5.5	
Health Maintenance Organization (HMO)	5	0.3	3	0.2	2	0.4	
Medicaid	535	30	403	30.9	132	27.8	
Medicare Part B	125	7	90	6.9	35	7.4	
Supplemental Policy	4	0.2	2	0.2	2	0.4	
Others	53	3	42	3.2	11	2.3	
Provider Type							<.0001
Medical Doctor (MD)	288	16.2	172	13.2	116	24.4	
Nurse Practitioner, Supervising (NP, S) or Advanced Practice Registered Nurse	1486	83.4	1134	86.8	352	74.1	
Others	7	0.4	0	0	7	1.5	

Table 2: Antibiotic Prescriptions per 1000 Patients	**Baseline Level**	**Baseline Slope**	**Change in Level**	**P-value**	**Change in Slope**	**P-value**
Before Antibiotic Stewardship Program	2.796	-0.038	-	-	-	-
After Antibiotic Stewardship Program	-	-	13.284	0.014	-0.173	0.007
Covid19	-	-	-15.283	0.006	-	-
interaction asp treat., postime, and covid19	-	-	-	-	0.169	0.009
seasonality	-	-	0.2928	0.002	-	-

Figure legends

Figure 1: Rate of antibiotic prescriptions per 1000 patients. Graphical representation of the immediate effect (change in levels) and the long-term effects (change in slope) associated with the implementation of the Antibiotic Stewardship Program (ASP). The vertical line (observation) represents the time when pharmacist-led ASP was initiated.

Figure 2: The 30-day frequency of clinic visits. Graphical representation of the immediate effect (change in levels) and the long-term effects (change in slope) associated with the implementation of the Antibiotic Stewardship Program (ASP). The vertical line (observation) represents the time when pharmacist-led ASP was initiated.

Figure 1

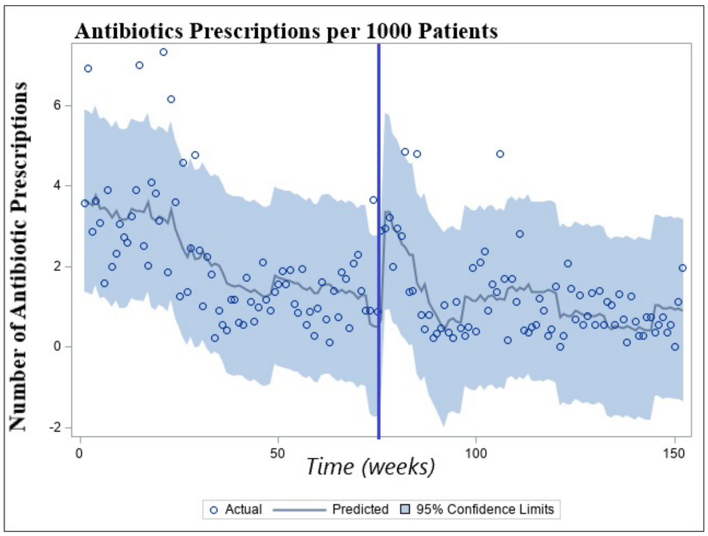

Figure 2

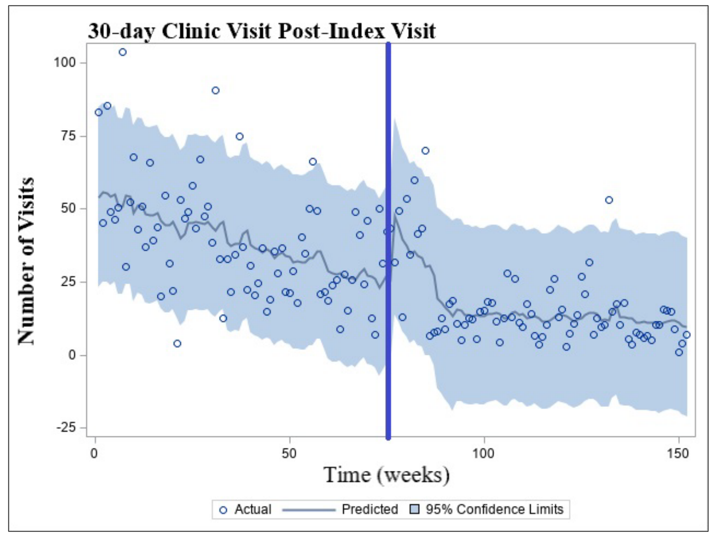

Table 3: Clinic visits within 30 days post index visit associated with recurring infectious disease	Baseline Level	Baseline Slope	Change in Level	P-value	Change in Slope	P-value
Before Antibiotic Stewardship Program	55.38	-0.4	-	-	-	-
After Antibiotic Stewardship Program	-	-	147.204	0.06	-2.043	0.028
Covid19	-	-	-181.757	0.024	-	-
Interaction asp treat., postime, and covid19	-	-	-	-	1.985	0.034
Seasonality	-	-	-0.364	0.794	-	-

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