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The Effect of Entry of Generic Antibiotics on Prescriptions of the Antibiotic: The Case of Sulfamethoxazole-Trimethoprim

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Abstract

The nonrenewable nature of antibiotic therapy has led many medical professionals, policy makers, and researchers to questions regarding the optimal use of antibiotics. To build out a more robust understanding of antibiotic usage and its contributing factors, careful attention must be paid to the study of antibiotic demand and its characteristics. The purpose of this paper is to estimate the effect of generic entry on antibiotic demand through changes in the probability of prescription using sulfamethoxazole-trimethoprim as a case study. The data used are visits where sulfamethoxazole-trimethoprim could have been prescribed pooled from the National Ambulatory Medical Care Surveys over the years 2006-2016. The probabilities of prescription of sulfamethoxazole-trimethoprim for various patient groups who could have been prescribed the drug both before and after entry of an off brand version are estimated. If a patient has at least one diagnosis of a medical condition for which the Food and Drug Administration (FDA) of the United States has approved the use of sulfamethoxazole-trimethoprim to treat, the probability the patient is prescribed the antibiotic initially increases an estimated 1.87 percentage points in the first months the generic is on sale. This increase in probability of prescription is greater for non-white patients and patients on either Medicare or Medicaid. Visits where patients were not diagnosed with an FDA approved reason for prescription of the antibiotic saw no significant change in the probability of being prescribed the antibiotic after entry of the generic.

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Chapter 1

Introduction

An antibiotic's effectiveness is an exhaustible resource. Efficient use of antibiotics would eventually render them ineffective due to bacterial resistance. Additionally, privately optimal levels of antibiotic usage increases the rate in which these drugs lose their effectiveness. In the United States alone, over 2.8 million Americans per year are sickened by antibiotic resistant bacteria leading to at least 35,000 deaths [Centers for Disease Control and Prevention (U.S.), 2019]. Over usage and over medication of antibiotics amplify these adverse effects [Gerber, 2019].

The entry of manufacturers of generic versions of an antibiotic increases the amount of treatment options available to a patient and their doctor. Furthermore, the entry of generic manufacturers shifts the supply curve to the right which lowers the price of consumption of an antibiotic. This price decrease would lead to an increase in the equilibrium quantity of prescriptions demanded. As consumption increases along with prescriptions, an acceleration in the evolution of resistance may develop.

This paper aims to test the first part this hypothesis that entry of generic antibiotic manufacturers leads to an increase in the demand of prescriptions for said antibiotic. To do so, prescription trends of sulfamethoxazole-trimethoprim before and after entry of its generic counterpart in July of 2012 are compared. Data from the National Ambulatory Medical Care Survey, a nationally representative survey of medical visits, are used track prescriptions of sulfamethoxazole-trimethoprim from January of 2006 to December of 2016. Differences in sets of linear probability models are then used to determine the effect of entry of generics on the probability a given patient will be prescribed the antibiotic assuming that an increase in this probability indicates an increase in aggregate consump-

tion. Specific attention is given to patients with Food and Drug Administration (FDA) approved reasons for prescription, also known as on-label indications, of sulfamethoxazole-trimethoprim.

I find that, despite negative trends in probability of prescription over time, a small but significant (90% CI) increase is present in the probability of prescription of sulfamethoxazole-trimethoprim for individuals diagnosed with FDA approved indications. This trend becomes larger and more significant for patients on Medicare or Medicaid and patients who are a race other than white. These changes were not present in individuals diagnosed solely with non-FDA approved indications of sulfamethoxazole-trimethoprim although these visits made up a majority of the drug's prescriptions.

The market for generic medications as it is known in the United States now did not exist until 1984. Prior to then, FDA rules required generic drug companies to repeat clinical trials which had already been undertaken by their on brand predecessors. Hence, even after a formula had proven to be safe and effective, generic companies would have to subject a similar formula to the same level of scrutiny as it had already overcome. This costly redundancy served as a barrier to entry preventing generic drug companies from competing with larger brands [Eban, 2019].

Senators Orrin Hatch and Henry Waxman authored the Drug Price Competition and Patent Term Restoration Act (known now as the Hatch-Waxman Act) which served to lower the cost and expedite the process for FDA approval of generic drugs. The Hatch-Waxman Act, passed in 1984, removed the requirements that a generic medication needed to undergo all of the clinical trials and safety procedures first undertaken by the original product. Instead, generics simply need to prove bioequivalence to the brand name and demonstrate both drugs exhibit a similar behavior inside of the body. Proving bioequivalence requires determining that, in addition to having the same active ingredient, the rate and extent at which the active ingredient becomes available to the body is not significantly different between the branded drug and the generic version being tested [Raines]. This new standard greatly lowered the fixed cost of bringing a generic to market and built the foundation for the modern generic drug industry in the United States.

In the case of antibiotics, evidence shows that markets behave consistently with economic theory regarding entrance of a close or perfect substitute. Demand for an antibiotic's active ingredient persists beyond patent expiration and entry of generics. In the 15 to 30 years after initial patent expiration, between 64% and 99% demand remains [Mansley et al., 2008]. The price of the antibiotic is negatively correlated, with the number of suppliers [Alpern et al., 2017]. Also, the

average price decreases significantly upon entry of generic medications [Frank and Salkever, 1997, Grabowski and Vernon, 1992]. One study found this price decrease to be between 6.6% and 66% of the original market price [Vondeling et al., 2018].

Empirical evidence has found treatment outcomes using generic medications to be comparable or equivalent to therapies with brand name medications [Lin et al., 2017, Desai et al., 2019] In spite of the evidence, patients still do hold some negative views about generics. A 2015 meta analysis of generic medicine usage found patients have strong opinions that cheaper drugs are of lower quality although doctors do not share such views[Dunne and Dunne, 2015]. The meta analysis goes on to show, however, that more educated patients are significantly more likely to accept generic treatment and overall trust of generics has improved over time. Finally, a patient's trust in their doctor's judgment also tends to overrule biases that a patient has about cheaper generics.

Chapter 2

Economic Framework

2.1 Theoretical Model

To elucidate how entry of generics may lead to an increase in demand for antibiotics, I first posit the following model. The model assumes that, with assistance from their physician, an individual patient seeks to maximize their utility from the treatment of their specific medical condition. To do so, a patient considers both the cost of a treatment option and how effective this treatment will be. Weighing these two characteristics, a patient will choose treatment with a given antibiotic if it is the utility maximizing treatment option. A patient may be willing to trade a higher probability of treatment success (effectiveness) for a less expensive treatment. Conversely, a patient may be willing to pay more for treatment if it shortens convalescence or has a higher probability of effectiveness. I assume, holding effectiveness constant, a patient will choose the lower priced treatment option. Entry of generic manufacturers shifts the supply curve to right and lowers the price of an antibiotic. Following the model laid out above, this price reduction would increase demand for treatments in which the active ingredient of said antibiotic is used.

Formally, a patient's utility (U) decreases with the cost of the treatment (C) and increases with the treatment's efficacy (E). Hence, a patient's utility can be expressed as $U(C, E)$ where $U_C < 0$ and $U_E > 0$. In the case of antibiotic therapy, C represents the sum of the costs of the antibiotic as well as the cost of associated services. Effectiveness can also be broken down further to be a reflection of both the probability an ailment will be cured and the convalescence of a treatment.

Simply put, the patient can either demand a treatment that leverages the active ingredient

in antibiotic α or not. The case of choosing a treatment which does not use α will be denoted by the ω superscript and serves as the utility maximize treatment choice which does not use the antibiotic. The patient will demand a treatment for medical condition m that uses the active ingredient of antibiotic α if the expected utility of a treatment with antibiotic α, $\mathbb{E}[U(C_m^\alpha, E_m^\alpha)]$, is greater than the expected value of the utility maximizing treatment for the patient's condition that does not include the active ingredient of antibiotic α, $(\mathbb{E}[U(C_m^\omega, E_m^\omega)])$.

Extending this notation, define the patient's decision, y, to be $y = 1$ if the patient demands a treatment that uses the active ingredient in antibiotic α and $y = 0$ otherwise. Hence, the entire decision can be described symbolically as

$$y = \begin{cases} 1, & \text{if } \mathbb{E}[U(C_m^\alpha, E_m^\alpha)] > (\mathbb{E}[U(C_m^\omega, E_m^\omega)]) \\ 0, & \text{if } (\mathbb{E}[U(C_m^\omega, E_m^\omega)]) > \mathbb{E}[U(C_m^\alpha, E_m^\alpha)] \end{cases} \tag{2.1}$$

Theory says that the entry of generic antibiotic manufacturers would increase the supply of antibiotic α. This increase in supply will lower the price of treatments using its active ingredient. Holding efficacy constant, one can anticipate expected utility of treatment to increase in response to a decrease in prices caused by entry of the generic. At the margin, this increase in expected utility causes consumers to substitute treatments that do not use the active ingredient of antibiotic α with treatments that do, raising the number of total prescriptions of antibiotic α.

2.2 Econometric Model and Estimation Procedures

It is important to distinguish that, although these expected utilities are known to the patient, they cannot be observed by a researcher. Instead, the binary decision must be transformed into a probabilistic one [Train, 2009, Templeton et al., 2008]. To do so, define the transformed expected utility of a given treatment, $\mathbb{E}[U(C_m^s, E_m^s)]$ where $s = \{\alpha, \omega\}$ into two parts

$$\mathbb{E}[U(C_m^s, E_m^s)] = \bar{U}_m^s + \nu_m^s \tag{2.2}$$

where $\bar{U}_m^s$ is the observable portion of the expectation of the patient's expected utility from treatment choice s for medical condition a and ν_m^s is the unobservable portion. $\bar{U}_m^s$ is a function of characteristics of the treatment, the visit, and the patient. The variable ν_m^s is an independently

and identically distributed random variable. This makes the decision to demand a treatment with antibiotic α for medical condition m to be

$$\begin{aligned} \Pr(y=1)_m &= \Pr(\bar{U}_m^\alpha + \nu_m^\alpha > \bar{U}_m^\omega + \nu_m^\omega)) \\ &= \Pr(\nu_m^\alpha - \nu_m^\omega > \bar{U}_m^\omega - \bar{U}_m^\alpha)) \end{aligned} \tag{2.3}$$

which is the probability a patient i chooses a treatment that utilizes antibiotic α.

$\bar{U}_m^s$ can be broken down further to reflect theory and data as

$$\begin{aligned} \mathbb{E}[U_m^s] &= \bar{U}_m^s + \nu_m^s \\ &= \beta_m^s + \gamma C_m^s + \delta_m^s t + \zeta_m^s K + \nu_m^s \end{aligned} \tag{2.4}$$

For this equation, β_m^s is the treatment choice specific constant representing the mean effect of omitted variables for medical condition a with treatment s. γ is the effect on expected utility from C_m^s which is the cost of treatment s for medical condition a. δ_m^s is marginal effect of time since entry of a generic form of α, t, specific to the medical condition and treatment. ζ_m^s are marginal effects of the vector of patient characteristics K specific to the treatment and medical condition. Lastly, ν_m^s serves as an error term which is assumed to be uncorrelated with the other variables and have an expected value of zero.

The final step is to derive the differences in expected utility due to treatment-specific values. Define $\bar{U}_m \equiv \bar{U}_m^\alpha - \bar{U}_m^\omega$ which implies

$$\begin{aligned} \mathbb{E}[U_m] &= (\beta_m^\alpha - \beta_m^\omega) + \gamma(C_m^\alpha - C_m^\omega) + (\delta_m^\alpha - \delta_m^\omega)t \\ &\quad + (\zeta_m^\alpha - \zeta_m^\omega)K + (\nu_m^\alpha - \nu_m^\omega) \\ &= \beta_m + \gamma C_m + \delta_m t + \zeta_m K + \nu_m \end{aligned} \tag{2.5}$$

This yields an equation whose coefficients represent the marginal effect differences in the treatment options on a patient's expected utility. Assuming $\mathbb{E}[U_m] \in [0, 1]$, equations 2.3 and 2.5 can be combined to give the following linear probability model

$$\Pr(y=1)_m = \beta_m + \gamma C_m + \delta_m t + \zeta_m K + \nu_m \tag{2.6}$$

This equation is estimated once before entry of the generic and again after in order to see how these equations change between the two time periods.

For the patient characteristics, I consider the age (**Age**) of the patient, the squared age of the patient (**AgeSQ**), whether the patient is on Medicare or Medicaid (**GovInsurance**=1), and whether or not the patient is white (**NonWhite**=1). Additionally I consider whether the patient has any diagnoses whose treatment is associated with FDA approved uses for using sulfamethozaxole-trimethoprim (**OffLabel**=1). The time in months since entry of the generic antibiotic is indicated by **TimeSinceGeneric** Interactions between the off-label distinction and the time since entry of the generic as well as interaction between the age and age squared variables with time since entry of the generic are also included. To test the significance of the differences among coefficients for the two possible treatment times, I use a cross model hypothesis test which rejects the null hypothesis that $\beta_i^{before} = \beta_i^{after}$ if

$$\Pr\left(\frac{\hat{\beta}_i^{\text{before}} - \hat{\beta}_i^{\text{after}}}{[\hat{\sigma}^2\{\hat{\beta}_i^{\text{before}}\} + \hat{\sigma}^2\{\hat{\beta}_i^{\text{after}}\}]^{\frac{1}{2}}}\right) \tag{2.7}$$

exceeds the chi squared threshold.

Chapter 3

Data and Variables

3.1 Sulfamethoxazole-Trimethoprim

I focus my analysis on prescriptions of sulfamethoxazole-trimethoprim. This decision was made because of the antibiotic's generic counterpart entering the market in the middle of the observational period and a sufficient number of prescriptions occurring in the data. Sulfamethoxazole-trimethoprim is a combination antibiotic from the class antimetabolite/sulfonamide and was first introduced in 1968. The brand versions of the drug include Bactrim, Bactrim DS, Septra, and Septra DS and the generic form entered the American market in July of 2012. The antibiotic was popular even before entry of the generic due its high familiarity among physicians and low cost [drugbank.ca, 2020, Ho and Juurlink, 2011].

The drug has FDA approval to fight urinary tract infections, ear infections (acute otitis media), acute exacerbations of chronic bronchitis in adults, Shigellosis, treatment and prophylaxis of *Pneumocystis jirovecii* pneumonia, and Traveler's diarrhea in adults. The antibiotic is also approved for use against infections due to *Listeria, Nocardia, Salmonella, Brucella, Paracoccidioides,* melioidosis, *Burkholderia, Stenotrophomonas,* cyclospora, isospora, Whipple's disease, and alternative therapy for toxoplasmosis and community-acquired MRSA skin infections [Schlossberg and Samuel, 2017].

3.2 National Ambulatory Medical Care Survey

Data used are from the National Ambulatory Medical Care Survey (NAMCS) which is a nationally representative survey of outpatient medical visits. Included in the scope of the survey are freestanding clinics/urgicenters, community health centers, mental health centers, health maintenance organizations, non-federal government clinics, family practice plans, and private solo or group practices. Not included are hospital emergency or outpatient departments, ambulatory surgicenters, institutional settings such as schools or prisons, industrial outpatient facilities, clinics operated by the federal government, and laser vision surgery centers [Hing et al.]. The surveys include information about the patient, the visit, and the provider seen. Weights are provided in order to create national estimates.

I pool observations from the years 2006 to 2016 and drop variables which are not consistently tracked across this time or have more than 30% missing values as instructed in the survey documentation [Myrick]. For the specific cases of diagnoses and prescriptions, the maximum amount of available entries increased during the study period. The 2006 NAMCS survey provided three slots to record diagnoses and eight slots to record prescriptions. This set up means that even if more than three diagnoses were made during a medical visit, only three of them would be recorded as there was no option in the survey to add additional diagnoses. The same restriction applies in the case where more than eight medications were prescribed. In 2012, the maximum number of medications recorded was raised to twelve and rose again in 2014 to thirty. The maximum number of diagnoses recorded was raised from 3 to 5 in 2014 as well. In order to accurately measure trends across the study period, I only use the first three diagnoses and the first eight prescriptions as instructed in the survey documentation [Schappert and Rechtsteiner].

In order to restrict observations to only those which may have led to a prescription of sulfamethoxazole-trimethoprim, I track all diagnoses which occurred during visits where the antibiotic was prescribed. It must be noted that, while sulfamethoxazole and trimethoprim can be each prescribed on their own, the combination sulfamethoxazole-trimethoprim is distinct enough to be considered its own entity. Hence, when considering visits where sulfamethoxazole-trimethoprim was prescribed, I only consider visits where the distinct combination is prescribed and not when each element of the combination is prescribed seperately. For the sake of analysis, these diagnoses which occurred during visits where sulfamethoxazole-trimethoprim was prescribed are considered relevant

diagnoses. Then, all visits where one of these relevant diagnoses are made are then marked as relevant visits. This characterization indicates that at least one of the diagnoses made during this visit could have led to the prescription of sulfamethoxazole-trimethoprim based on the behavior of other prescribing physicians. Hence, this visit is considered relevant because it could have led to a prescription of sulfamethoxazole-trimethoprim.

Visits where no diagnosis made ever leads to a prescription of the antibiotic are dropped from the sample. For years 2006-2015 diagnoses are labeled using ICD-9-CM codes and ICD-10-CM codes are used for the year 2016. To allow for comparability across all years of the study, each ICD-10-CM code was recoded as its exact or closest ICD-9-CM counterpart. Because all relevant diagnoses are given equal importance regardless of whether it was the specific one which led to the prescription, it is possible that this strategy does not fully rid the sample of all non relevant visits which would negatively bias estimates.

To further control for nonrelevant visits, I create an indicator for visits where at least one diagnosis is associated with an FDA approved use of sulfamethoxazole-trimethoprim. The reasons for prescribing antibiotics can be categorized as on-label and off-label. On-label uses of the antibiotic are the FDA approved reasons for prescribing sulfamethoxazole-trimethoprim mentioned previously while off-label indications are non FDA approved uses. Each on-label indication is mapped to one or more ICD-9-CM codes shown in the appendix. Figure 3.1 shows the 12-month moving average probability of prescription for on-label and off-label uses of sulfamethoxazole-trimethoprim.

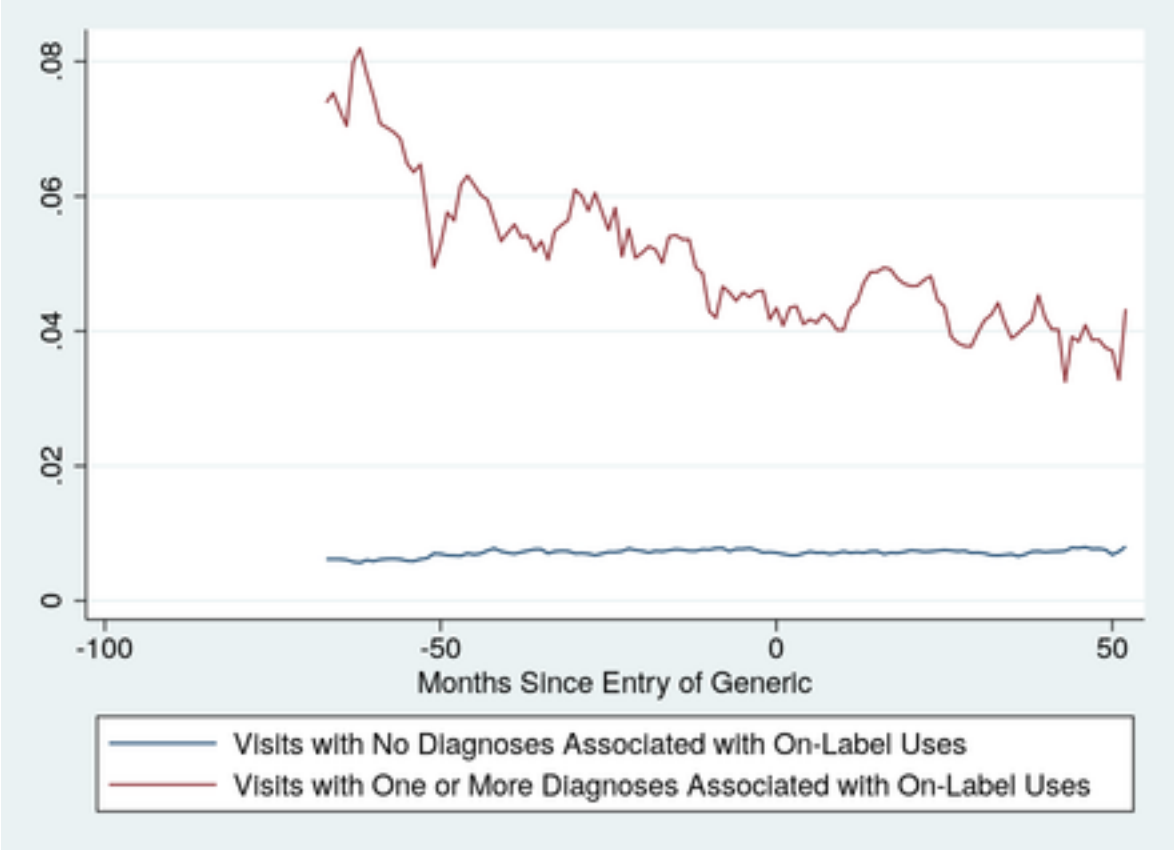

Figure 3.1: 12-Month Moving-Average Probabilities of Prescription of Sulfamethoxazole-Trimethoprim by Type of Diagnosis

3.3 Variables

The independent variables considered in the analysis are as follows. **TimeSinceGeneric** is a continuous variable from -79 to 52 and indicates the number months since the first full month in which the generic version of sulfamethoxazole-trimethoprim was in the market the market, August of 2012. Defining the timeline this way means that the months before August of 2012 take negative values. For example, June of 2012 (2 months before generic entry) would be coded as **TimeSinceGeneric**$= -2$. I include **Age** and **AgeSQ** which are the ages and squared ages of the patient at the time of the visit. **OffLabel** indicates that none of the diagnoses which resulted from the visit were associated with an FDA approved usage of sulfamethoxazole-trimethoprim. **GovInsurance** and **NonWhite** indicate whether a patient was on Medicare or Medicaid and if the patient was of an ethnicity other than white. Controlling for Medicare and Medicaid help to control for differences in the choice set faced by consumers due to insurance and **NonWhite** is used as a proxy for lower income patients.

Table 3.1 is a statistical summary of the continuous variables **TimeSinceGeneric** and **age**. I present the variables in the context of the entire study followed by summaries for before and after entry of the generic. The study goes across 131 months from January of 2006 (**TimeSinceGeneric**$= -82$) to December of 2016 (**TimeSinceGeneric**$= 49$) with **TimeSinceGeneric**$= 0$ indicating August of 2012 which was the first full month the generic sulfamethoxazole-trimethoprim had been in the market. It is important to note that **TimeSinceGeneric**$= 0$ is included in "After Entry of Generic". The final item of note from the table is the average age of the patient during the study period increased in the time after entry of the generic from 45.2 years old to 47.1 years old.

Table 3.1: Statistical Descriptions of Continuous Variables

Variable	Time Frame	Weighted Mean	Weighted Median	Standard Deviation	Min	Max
TimeSinceGeneric	2006-2026	-15.316	-17	37.167	-79	52
(Time in months since	Before Entry of Generic	-39.703	-40	22.497	-79	-1
entry of generic)	After Entry of Generic	25.013	25	14.792	0	52
Age	2006-2026	45.917	50	25.09	0	100
(Age of patient in years)	Before Entry of Generic	45.221	49	25.207	0	100
	After Entry of Generic	47.069	51	24.853	0	92
Sample Size for Years 2006-2016 = 399245						
Sample Size before Entry of Generic = 230182						
Sample Size after Entry of Generic = 169063						

All observations after August 2012 are considered to be after entry of generic.

Table 3.2 is a statistical summary of the categorical variables **offLabel**, **govInsurance**, and **NonWhite**. The vast majority of visits in the sample did not have a diagnosis associated with an on-label use of sulfamethoxazole-trimethoprim. These visits accounted for over 96% of the weighted sample across each time period. Patients on government insurance (Medicare or Medicaid) made up over a quarter of visits over the entire study and their weighted share of the sample increased from 24.8% before entry of the generic to 28% during the time after the generic was introduced. Non-white patients make up less of the sample with a weighted average of 16.4% over the entire study. Similar to the government insurance group, this category saw an increase in their weighted proportion of the sample after the generic came on from 16% to 17.1%.

Table 3.2: Statistical Descriptions of Categorical Variables

Variable	Time Frame	Total	Weighted Share of Sample
OffLabel	Entire Study	387264	.967
(=1 if no diagnoses made were	Before Entry of Generic	223267	.966
FDA approved indications of	After Entry of Generic	163997	.968
sulfamethoxazole-trimethoprim)			
GovInsurance	Entire Study	105273	.26
(=1 if patient is on either)	Before Entry of Generic	30480	.248
Medicare or Medicaid)	After Entry of Generic	44793	.28
NonWhite	Entire Study	61442	.164
(=1 if patient is a race	Before Entry of Generic	37733	.16
other than white)	After Entry of Generic	23709	.171
Sample Size for Years 2006-2016 = 399245			
Sample Size before Entry of Generic = 230182			
Sample Size after Entry of Generic = 169063			

All observations after August 2012 are considered to be after entry of generic.

Table 3.3 provides the weighted proportion of patients of each type who were prescribed sulfamethoxazole-trimethoprim. Overall, .861% of visits lead to a prescription of sulfamethoxazole-trimethoprim over the study period with an increase of .014 percentage points post entry of the generic. Looking only at visits that did not have a diagnosis associated with an on-label use of sulfamethoxazole-trimethoprim, the numbers do not change a great deal. The weighted proportion prescribed the drug was .718% across the study and increased from .7% to .749% between the time before the generic entered and after. The story does change for the compliment of the off-label category, however. Visits that resulted in at least one diagnosis associated with an on-label use of sulfamethoxazole-trimethoprim led to a prescription of the antibiotic 5.07% of the time. However,

this proportion decreased from 5.35% to 4.78% between the two time periods.

The other categories share a similar trend with the entire sample. Patients on government insurance were prescribed sulfamethoxazole-trimethoprim for .871% of their total visits and saw an increase from .803% to .97%. The proportion of patients not on any form of government insurance who were prescribed the antibiotic fell slightly from .873% to .831%. For non-white patients, the weighted proportion of visits leading to a prescription of the drug was .933% with an increase from .857% to 1.05% between between before entry of the generic and after. The proportion of white patients prescribed the antibiotic decreased from .856% to .832%.

Table 3.3: Proportions of Patients Prescribed Sulfamethoxazole-Trimethoprim by Patient Characteristics

Variable	Time Frame	Total Prescriptions	Weighted Proportion
Total Sample	Years 2006-2016	3340	.00861
	Before Entry of Generic	1931	.00856
	After Entry of Generic	1409	.0087
OffLabel	Years 2006-2016	2736	.00718
(=1 if no diagnoses made were FDA approved	Before Entry of Generic	1548	.007
indications of Sulfamethoxazole-Trimethoprim)	After Entry of Generic	1188	.00749
(=0 if at least one diagnosis made during	Years 2006-2016	604	.0507
visit is an FDA approved indication of	Before Entry of Generic	383	.0535
Sulfamethoxazole-Trimethoprim)	After Entry of Generic	221	.0478
GovInsurance	Years 2006-2016	869	.00871
(=1 if patient is on either	Before Entry of Generic	488	.00803
Medicare of Medicaid)	After Entry of Generic	381	.0097
(=0 if patient is on neither	Years 2006-2016	2471	.00858
Medicare nor Medicaid)	Before Entry of Generic	383	.00873
	After Entry of Generic	1028	.00831
NonWhite	Years 2006-2016	534	.00933
(=1 if patient is race other than white)	Before Entry of Generic	336	.00857
	After Entry of Generic	198	.0105
(=0 if patient is white)	Years 2006-2016	2806	.00847
	Before Entry of Generic	1595	.00856
	After Entry of Generic	1211	.00832
Sample Size for Years 2006-2016 = 399245			
Sample Size before Entry of Generic = 230182			
Sample Size after Entry of Generic = 169063			

All observations after August 2012 are considered to be after entry of generic.

Chapter 4

Empirical Analysis and Results

Table 1 shows the results of the two binary linear probability models. In both cases, the probability of a white patient with an ailment whose treatment is associated with an on-label use of sulfamethozaxole-trimethoprim who is not on government insurance has a statistically nonzero probability of demanding treatment with the antibiotic. The change in this probability of prescription after entry of the generic is 2.03 percentage points and significant at the 90% confidence level. The probability of being prescribed sulfamethozaxole-trimethoprim was decreasing over time before and after the generic entered. The positive coefficients for the interactions between **TimeSinceGeneric** and **OffLabel** are greater than the negative coefficient attached to **TimeSinceGeneric** in absolute value indiacting the probability of prescription for off-label visits was increasing with time. Significant positive coefficents on **Age** and significant negative coefficients on **AgeSQ** indicate that a patient's probability of prescription is increasing with age but this effect decreases as the patient gets older. The interactions between **Age** and **TimeSinceGeneric** as well as **AgeSQ** and **TimeSinceGeneric** show how this age effect changes over the course of time. During the period of time before the generic had entered, there was a small but significant decrease in the probability of prescription for older patients over time. This effect decreased further as a patient increased in age. This effect loses significance once the generic enters the market.

Both patients on Medicare or Medicaid and patients of a race other than white did not have a probability of being prescribed the antibiotic which was significantly different from a white patient not on government insurance before entry of the generic. After entry of the generic, however, patients on government insurance became .185 percentage points more likely to be prescribed

sulfamethozaxole-trimethoprim than those not on Medicare or Medicaid. Similarly, patients of a race other than white became .219 percentage points more likely to be prescribed sulfamethozaxole-trimethoprim than their white counterparts. Both of these estimates are significant at the 99% confidence level.

Table 4.1: Estimated Effects on Probability of Prescription Before and After Generic Entry

Variable	Before Entry of Generic	After Entry of Generic	Difference
Constant	0.0383***	0.0586***	0.0203*
	(16.83)	(21.83)	[0.0403]
OffLabel	-0.0326***	-0.0513***	-.0188
(=1 if no diagnoses made were FDA approved indications of Sulfamethoxazole-Trimethoprim)	(-14.65)	(-20.05)	[0.0676]
TimeSinceGeneric	-0.00032***	-0.000592***	-.000272
(Time in months since generic entry of Sulfamethoxazole-Trimethoprim)	(-6.51)	(-6.72)	[0.368]
OffLabel×TimeSinceGeneric	0.000372***	0.00047***	.0000984
	(7.7)	(5.64)	[0.757]
GovInsurance	0.000176	0.00185**	0.00168
(=1 if patient is on either Medicare or Medicaid)	(0.38)	(3.54)	[0.161]
Nonwhite	-0.00000675	0.00219***	0.00222
(=1 if patient is race other than white)	(-0.01)	(3.65)	[0.164]
Age	0.000172*	0.0000696*	-.000103
(Age of patient in years)	(3.08)	(1.06)	[0.378]
AgeSQ	-0.00000215**	-0.00000128*	0.000000863
(Age of patient in years squared)	(-3.36)	(-1.74)	[0.495]
Age×TimeSinceGeneric	-0.00000229**	0.00000419	0.000000648
	(-1.88)	(1.88)	[0.107]
AgeSQ×TimeSinceGeneric	.0000000274**	-0.000000031	-0.000000059
	(1.98)	(-1.23)	[0.184]
r2	0.009	0.0058	
N	230182	169063	

t statistics in parentheses, $\Pr(\frac{\hat{\beta}_i^{\text{before}} - \hat{\beta}_i^{\text{after}}}{[\hat{\sigma}^2\{\hat{\beta}_i^{\text{before}}\} + \hat{\sigma}^2\{\hat{\beta}_i^{\text{after}}\}]^{\frac{1}{2}}} > X^2)$ in brackets

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

To find the expected changes in probability for patient's before and after entry of the generic, I use the expected value of the categorical variables and their coefficients. I calculate the mean effects of the variables to hold them constant while fixing **TimeSinceGeneric** = 0. The resulting estimates can be interpreted as the expected probability an individual is prescribed sulfamethozaxole-

trimethoprim immediately before and after the antibiotic entered the market. The results are shown in Table 4.2 along with the results of the same hypothesis test used previously.

Patient's with at least one diagnosis associated with an on-label use of sulfamethozaxole-trimethoprim are estimated to be 1.87 percentage points more likely to demand a prescription of the antibiotic immediately after entry of the generic. This increase is significant at the 90% confidence level. Patients without a diagnosis associated with an on-label use of the antibiotic are estimated to have a much smaller and insignificant increase in the probability of being prescribed the antibiotic. Visits associated with on-label uses with patients who were on Medicare or Medicaid are estimated to be 1.99 percentage points more likely to result in a prescription of the antibiotic after entry of the generic. The same visits but with non-white patients are estimated to be 2.05 percentage points more likely to result in a prescription of sulfamethozaxole-trimethoprim.

Table 4.2: Estimated Probability of Prescription of Sulfamethoxazole-Trimethoprim Immediately Before and After Generic Entry

Patient Group	Before Entry of Generic	After Entry of Generic	Difference
OnLabel (=1 if at least one diagnosis made during visit is associated with FDA approved use of sulfamethoxazole-trimethoprim)	0.0404*** [0.000]	0.0591*** [0.000]	.0187 [0.0675]
OffLabel (=1 if no diagnoses made were associated with FDA approved uses of sulfamethoxazole-trimethoprim)	0.00783*** [0.000]	.00778*** [.000]	-.0000418 [0.955]
GovInsurance×OnLabel (Patient on Medicare or Medicaid and **OnLabel**=1)	0.0405*** [0.000]	0.0604*** [0.000]	0.0199 [0.0526]
Nonwhite×OnLabel (Patient race other than white and **OnLabel**=1)	0.0403*** [0.000]	0.0609*** [0.000]	0.0205* [0.0466]
N	230182	169063	

$\Pr(\frac{\hat{\beta}_i^{\text{before}} - \hat{\beta}_i^{\text{after}}}{[\hat{\sigma}^2\{\hat{\beta}_i^{\text{before}}\} + \hat{\sigma}^2\{\hat{\beta}_i^{\text{after}}\}]^{\frac{1}{2}}} > X^2)$ in brackets

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Chapter 5

Discussion

Patients with diagnoses whose treatments are associated with on-label uses of sulfamethoxazole-trimethoprim were 1.87 percentage points (90% CI) more likely to demand treatments which used the antibiotic. This increase in demand can be seen as a result of the entry of generic manufacturers creating a cheaper, close substitute for the sulfamethoxazole-trimethoprim products already in the market. This increases the number of patients who can afford these prescriptions causing patients to substitute other prescriptions or treatments with prescriptions of the antibiotic. This is consistent with what is known about demand for antibiotics already. As stated earlier, the price of an antibiotic is negatively correlated with the number of manufacturers [Alpern et al., 2017]. Additionally, significant negative own and cross price elasticities have been observed for antibiotics [Kaier, 2013], [Kianmehr et al., 2020] which further reinforces the underlying theory behind the hypothesis.

Patients on Medicare or Medicaid and non-white patients were no more or less likely to demand treatment with the antibiotic before entry of the generic than other patient groups. After the entry of the generic, both patient groups became more likely to be prescribed the antibiotic than their compliments. For patients on Medicare or Medicaid, this increase may be able to be attributed to incentives of the patient or prescriber. The reimbursement structure of Medicare and Medicaid may require some patients be prescribed generics meaning they would be more likely to adopt usage of a generic when it enters the market. The increase in probability of prescription for non-white patients is in line with the assumptions made when first discussing inclusion of the indicator in the model. Because the average non-white patient is assumed to have a lower income than the average white patient, this shift in the supply curve benefits the non-white patients more as they make up

a greater percentage of the lower end of the demand curve.

Probability of prescription of the antibiotic was decreasing before the generic began being sold. After an initial increase in the probability of prescription, patients still became less inclined to demand the antibiotic over time. It is possible this trend may be attributed to the rise in sulfamethoxazole-trimethoprim resistant bacteria. Studies have found evidence of sulfamethoxazole-trimethoprim resistant bacteria as early as 1997 [Gales et al., 2002] and resistance has continued to develop through the 2000s and the 2010s [Hu et al., 2016], [Khamash et al., 2019].

Chapter 6

Conclusions

While not uniform across all patient groups, I find a small but significant increase in the probability of prescription of sulfamethoxazole-trimethoprim due to entry of the generic for patients with diagnoses associated with FDA approved indications of the antibiotic. The expected probability of a patient demanding treatment which used the antibiotic increased by 1.87 percentage points (90% CI) for patients with diagnoses associated with on-label uses of the antibiotic immediately after entry of the generic. Members of this patient group who were on Medicare or Medicaid or who were non-white saw increases in expected probability of prescription of 1.99 percentage points (90% CI) and 2.05 percentage points (95% CI) respectively. I attribute these changes to a decrease in price caused by entry of the generic. Patients with no diagnoses associated with FDA approved indications of sulfamethoxazole-trimethoprim did not see significant changes to their probability of prescription. This finding is important because these cases made up more the majority of all prescriptions of sulfamethoxazole-trimethoprim.

6.1 Limitations of the Study

These results of this study may be limited by the specific setting from which they come. Because emergency departments are not included in the analysis, populations more likely to leverage those services as well as diagnoses which are more likely to occur in that setting are underrepresented. Second, sulfamethoxazole-trimethoprim is only one antibiotic which had already seen resistance forming before entry of the generic. Because of this, consumers may have been more reluctant

to demand the drug as time progressed. Entry of the generic of antibiotics with less reported resistance may have a higher proportion of patients adopting generic treatment. This study is additionally limited by its selection of variables. Considerations of a patient's gender, region of visit, and characteristics of the physician may reveal some omitted variable bias albeit at the cost of increased complexity within the model. Finally, a more refined process could be implemented in order to determine what visits can be considered relevant in the study of a given antibiotic. Including all diagnoses which lead to the prescription of sulfamethoxazole-trimethoprim may lead to inclusion of irrelevant visits. One possible example would be and individual who is diagnosed with a diagnosis associated with an on-label use of the drug as well one not associated such as hypertension. The method employed in this study would go on to count all visits where a diagnosis of hypertension was made to be relevant visits even though sulfamethoxazole-trimethoprim would not be prescribed for that condition. This occurrence could could negatively bias empirical results. Another possible shortcoming of the method used to select observations is only prescriptions of the distinct entity sulfamethoxazole-trimethoprim were counted as prescriptions. There is the possiblity that some prescriptions could have been recorded as seperate prescriptions of the components sulfamethoxazole and trimethoprim.

6.2 Recommendations for Future Research

The limitations mentioned above serve as directions for future research. First, expanding the scope of the study to include emergency department and non ambulatory care would help provide a more complete understanding of sulfamethoxazole-trimethoprim before and after entry of the generic. Second, subjecting different drugs to a similar methodology is needed to determine if results from this study are products of specific characteristics of sulfamethoxazole-trimethoprim. Third, inclusion of additional variables about the patient and physician may help lead to additional findings not seen in this study. Fourth, development of a more sophisticated method to control for relevant diagnoses could further ensure unbiased results. Finally, controlling for prescription trends of close substitutes would provide the researcher with an idea of what the opportunity cost of adoption of generics may specifically be.

Appendices

Appendix A On-Label Diagnosis Codes

The table below shows the ICD-9-CM diagnosis codes associated with FDA approved uses of sulfamethoxazole-trimethoprim. If no diagnosis made during a visit correspond to the codes below, **OffLabel=1**. The first column of the table is the FDA indication, the second column is the corresponding code, and the third column is the specific description used for by the ICD-9-CM coding system.

Table 1: On Label Indications

Indication	ICD-9-CM Code	ICD-9-CM Description
Travelers Diarrhea	78791	Diarrhea
Urinary Tract Infection	5990	Urinary tract infection, site unspecified
Ear Infection	382	Otitis media
Chronic Bronchitis	491	Chronic Bronchitis
Shigellosis	004	Shigellosis
Pneumonia	480-488	Pneumonia of Various Classifications
Brucella	023	Brucellosis
Nocardia	039	Actinomycotic infections
Salmonella	003	Other Salmonella Infections
Paracoccidioides	1161	Paracoccidiodomycosis
Melioidoisis	025	Melioidosis
Burkholderia	2002	Burckett's Tumors of Lymphatic Tissue
Stenotrophomonas	n.a.	n.a.
Cyclospora	0075	Cyclosporiasis
Isospora	0072	Coccidiosis
Whipple's Disease	0402	Whipple's Disease
Toxoplasmosis	130	Toxoplasmosis
MRSA Related Skin Infection	0412	Pneumococcus infection

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