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The Impact of Patent Expiration on Overall Utilization of Azithromycin

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2015

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Health Policy and Health Services Research
2017

Abstract

The Impact of Patent Expiration on Overall Utilization of Azithromycin

By Dongzhe Hong

Objectives

Antibiotics have been widely used to treat patients with bacterial infections. Overuse of antibiotics is one of the most pressing public health problems worldwide because of its association with the increase in antibiotic resistance. Azithromycin is a widely used antibiotic and commonly prescribed for Upper Respiratory Tract Infections (URIs) and Urinary Tract Infections (UTIs). In 2005, azithromycin went off patent. The average price of both branded and generic azithromycin decreased, and the copayment of generic azithromycin was much lower than branded azithromycin. This study examined the impact of patent expiration on overall utilization of both branded and generic azithromycin.

Methods

The National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 2002 – 2009 were used as the data source. The sample included patient visits with URIs and/or UTIs. Five multivariate logistic regression models determined the association between patent expiration and the probability that azithromycin was prescribed in a particular visit among all patients with URIs and/or UTIs, including privately insured patients and patients covered by Medicaid.

Results

The likelihood of receiving azithromycin for URIs and/or UTIs increased from 10.8% to 14.0% after patent expiration. The increase in the likelihood of patients receiving azithromycin was larger among privately-insured patients than patients covered by Medicaid, 6.3% and 2.9%, respectively. There was a statistically significant 0.03 percentage point increase, or a 27.8% increase, in azithromycin utilization after patent expiration.

Conclusion

There was an increase in azithromycin utilization for patients with URIs and/or UTIs after patent expiration. The larger increase among privately insured patients is expected since private insurance programs try harder than Medicaid to reduce pharmaceutical use. This study also shows that generic entry leads to increased drug use. Consumers bear negative consumption externalities since generic entry may increase antibiotic resistance and harm the whole society. One approach for reducing antibiotic resistance is to grant longer patents to antibiotics, thereby delaying generic entry and increased use. Other price-based interventions, including changes in demand side cost sharing by patients, and the use of physician bonuses for antibiotic rational use, may also reduce antibiotic use in outpatient settings.

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List of Abbreviations

URIs	Upper Respiratory Tract Infections
UTIs	Urinary Tract Infections
NAMCS	National Ambulatory Medical Care Survey
NHAMCS	National Hospital Ambulatory Medical Care Survey
CDC	the Centers for Disease Control and Prevention
FDA	the U.S. Food and Drug Administration
R&D	Research and Development
AMA	American Medical Association
AOA	American Osteopathic Association
PSUs	Primary Sampling Units
HMO	Health Maintenance Organization

INTRODUCTION

Antibiotics have been widely used to treat patients who have infectious diseases, saving millions of people, as an essential public health tool since the 1940s.[1,2] However, overuse of antibiotics has made the drugs less effective.[3] The Centers for Disease Control and Prevention (CDC) estimates that direct health care costs of antibiotic resistant infections per year is $20–35 billion in the United States.[4] Horowitz et al.'s (2004) study methodologically shows that antibiotic resistance tends to increase after patent expiration.[5] More of the antibiotic is produced and the average price falls because other companies can now sell the antibiotic. In addition, insurance coverage reduces the copayment of the generic antibiotic so that patients pay less and are likely to use more antibiotics. Linked with the increase in antibiotic use and hence the increase in selective pressure that is specific for the antibiotic and the bacterial species, antibiotic resistance may develop more rapidly after patent expiration.[5,6] Interest in understanding the impact of patent expiration on antibiotic utilization is derived from the perception that antibiotic use is the main factor in the development of resistance.[1]

Azithromycin is used to treat a wide range of infections.[7] Azithromycin is a broad-spectrum drug, which means that it acts against a wide range of disease-causing bacteria. While the effect of patent expiration on the market position of drugs has been well studied, no empirical studies have examined the overall utilization changes of both generic and brand name azithromycin after its patent expiration.[8] This is a significant gap in the literature, given the relationship between antibiotic overutilization and resistance, and the importance of understanding azithromycin utilization changes. Thus, the purpose

of this study is to estimate the association between patent expiration and overall utilization of azithromycin in the United States.

LITERATURE REVIEW

Overuse of antibiotics is one of the most pressing public health problems worldwide because of its association with the increase in antibiotic resistance.[3] Antibiotic utilization and resistance are considerably concerning because scientists fear that the rate of innovation cannot keep up with the resistance. Though bacteria may develop resistance to on-patent antibiotics as well, antibiotic resistance may be exacerbated by patent expiration.[9,10] Additionally, overuse of antibiotics may have dangerous side effects, including the destruction of beneficial bacteria within our bodies.[1,3,11] In the United States, more than two million people are diagnosed with infections per year caused by antibiotic resistant bacteria, and at least 23,000 of them die because of these infections.[12] Patients with resistant infections are often prescribed antibiotics that may be more toxic and more expensive. Even when patients survive, they have significantly longer hospital stays and delayed recoveries and long-term disabilities such as neurological damage in children with meningitis that is caused by a pneumococcus not recognized as resistant. Despite warnings regarding antibiotic overuse and its consequences, antibiotics continue to be overprescribed worldwide.[13]

Azithromycin

Azithromycin is a widely used antibiotic that belongs to the family of macrolides.[14] Azithromycin is active against a broad spectrum of both aerobic and anaerobic Gram-positive as well as Gram-negative bacteria, and it is useful for the treatment of a wide range of mild to moderate infections.[7] Additionally, azithromycin is particularly recommended for the following conditions that are listed on azithromycin's

label: acute bacterial exacerbations of chronic obstructive pulmonary disease, community acquired pneumonia of mild severity, streptococcal pharyngitis/tonsillitis, and uncomplicated skin-to-skin structure infections.[7,14] Azithromycin is also commonly prescribed by physicians for upper respiratory tract infections (URIs). A meta-analysis study shows that short courses of azithromycin are convenient and as effective as other macrolides, such as erythromycin, clarithromycin, roxithromycin and dirithromycin, with fewer side effects.[15]

The first generic azithromycin was produced by PLIVA and SANDOZ, and entered the U.S. market on November 14, 2005.[16] According to the Orange Book from the FDA, there are eight companies producing generic azithromycin oral tablets in the U.S. that are produced by Teva Pharmaceuticals USA Inc, Sandoz Inc, PLIVA Inc, Wockhardt Ltd, and other pharmaceutical companies.[16] The single-dose oral therapy of azithromycin – once a day for five days a week – could increase the number of patients treated and reduce future infections, which makes it a popular option with patients.[17]

Azithromycin Utilization and Resistance

The total prescription number of antibiotics was 262.5 million (842 prescriptions per 1000 persons), of which the prescription number of azithromycin was 54.1 million (174 prescriptions per 1000 persons) in 2011.[18] Analyzing the impact of patent expiration on azithromycin utilization is critical since antibiotic resistance tends to increase faster after antibiotics' patent expiration. In addition, studies showed that the development of azithromycin resistance may be faster than the innovation rate of azithromycin substitutes.[9,10] For example, a growing amount of literature has reported that a strain of

gonorrhea is highly resistant to azithromycin in many different countries, such as Argentina, the United States, and China.[19-26] Likewise, several studies found that azithromycin resistance may be the consequence of extensive use for chlamydial infections.[21,25,27]

Drug Prices

The prices of brand name drugs, which are on-patent, usually exceed their costs due to the firm's monopoly power, although some pharmaceutical manufacturers argue that prices are based on research and development (R&D) costs.[28,29] The price of generics is typically much lower than the pre-generic entry price of the brand name drug because of the competition. Grabowski's study found that the average retail price of generics is only 65% of the average price of the brand name drugs one year after patent expiration.[30] Even if the price of branded azithromycin increased after patent expiration (which is actually not that unusual), consumers had the option of shifting to generic azithromycin, which is much cheaper. [31,32]

The price of branded azithromycin (ZITHROMAX®) increased slightly after patent expiration. Though it is difficult to find the price before 2005, a cost-effectiveness study shows that the public-sector pricing of brand name azithromycin was $11.5 per tablet in 2003, which could be a reference for the price at that time.[17] Additionally, the price of branded azithromycin increased to $14.9 per tablet in 2017.[33] The price per tablet of generic azithromycin today is much lower than the pre-/post-patent expiration branded azithromycin (ZITHROMAX®),which were $2.8 vs $11.5, and $2.8 vs $14.9, respectively.[33,34] The post-expiration average price reflects the use and relative prices of

branded versus generic azithromycin. If the case of azithromycin was similar to other instances where branded drugs went off-patent, generics would have gained market share rapidly.

Demand for Antibiotics

Demand for antibiotics is determined by three decision makers: the patient, who is the actual consumer; the physician, who prescribes medications; and insurers, who pay most of the cost of the drug prescribed.[29]

Patient demand for antibiotics is generally determined by the patient's cost-sharing for antibiotic consumptions and patient preferences.[35] The RAND study claimed that consumers with a cost-sharing requirement for insurance would use fewer antibiotics than consumers whose health care expense were all covered due to less patient visits.[36] In terms of patient preferences, Filippini's study on characteristics of demand for antibiotics in primary care suggested that the patient preferences for specific antibiotics may not be essential factors influencing the demand since antibiotics are generally prescribed by doctors based on their pharmacological characteristics.[37] In contrast, Coenen's study of antibiotic prescribing for acute cough found that perceived patient demand for any antibiotic versus no antibiotic significantly and clinically increased antibiotic prescriptions (odds ratio [OR] = 4.64, 95% confidence interval [CI] = 2.96 to 7.26).[38]

Patient preferences and expectations usually contribute to inappropriate antibiotic prescribing and antibiotic resistance since most people lack the knowledge to differentiate viral and bacterial infections.[35,39] For example, one third of the people in the

United Kingdom still believe that antibiotics can be used for the treatment of coughs and colds.[40] Therefore, cost sharing seems a useful tool to reduce antibiotic use.

Conversely, the drug formularies may be expanded to extend physicians' prescribing options after brand name drugs go off patent. The patients' copayments for brand name azithromycin did not change or become even higher than the pre-patent expiration copayments. Additionally, the copayments for generic azithromycin were much lower than the copayments of brand name azithromycin. For instance, after patent expiration, the branded azithromycin (ZITHROMAX®) is in tier 3 of a prescription drug plan with original Medicare, whose cost-sharing is $25 per month (6 tablets). Meanwhile, generic azithromycin is preferred as a tier 1 drug, the cost-sharing of which is $0 per month (6 tablets) in the same prescription drug plan.[41] Thus, the average co-payments of both brand name and generic drugs may be reduced because the generic drugs enter the market with a more affordable price than brand name drugs.[31,42]

Antibiotic Regulations

The regulations on antibiotic treatments also affect utilization.[32] For example, the FDA warned the public that azithromycin might lead to a potentially fatal irregular heart rhythm in May 2012, which might narrow the target population of azithromycin and might change physician prescribing preferences. Thus, there might be a decrease in utilization of azithromycin among patients after the FDA's warning.[43] Furthermore, the FDA is cooperating with the CDC to promote public awareness of antibiotic resistance, and is regulating labeling to address proper use of both on-patent and off-patent

antibiotics, which may decrease utilization.[44] Therefore, the establishment of antibiotic regulations may decrease the utilization of antibiotics.

Patent Expiration and Utilization

Generally, the changes of the overall utilization likely increase with the decreased price.[28,45] In addition, the demand for drugs depends not only on patient preferences, but also on the physicians' behaviors regarding prescriptions. It is unclear if patent expiration will increase use of azithromycin after patent expiration. Physicians may ignore price differences when deciding between brand name drugs and their generic substitutes and prescribe drugs based on their habits and previous prescribing experiences.[42] However, patients may pressure physicians to prescribe low cost drugs. There may be a larger increase in azithromycin utilization among privately-insured patients than patients covered by Medicaid because private insurers may charge higher copayments than Medicaid does for azithromycin, and because there are no copayments or copayments are too small to vary between drug types.[46,47] Lack of empirical study on overall utilization of azithromycin before and after patent expiration is the gap in current literature. Filling this gap will allow policy makers to make future policies to reduce the utilization of azithromycin and other antibiotics based on evidence. According to the theories and design of previous studies, it is hypothesized that there will be an increase in azithromycin utilization, furthering the problem of antibiotic resistance.

METHODS

Conceptual Model

This study developed a conceptual model that is based on the economic theory of demand for health services, to examine the focal relationship between azithromycin's patent expiration and its overall utilization.[48] Figure 1 emphasizes that the demand for a particular health good, in this case, both brand name and generic azithromycin, is a function of its price, a patient's characteristics and state of health, insurance co-payment, and both patient and physician preferences. This model draws on other evidence from medical literature to inform the hypothesized relationships between these factors, including physician patient relationship and practice ownership. In the model, unmeasured factors are shown in dotted boxes.

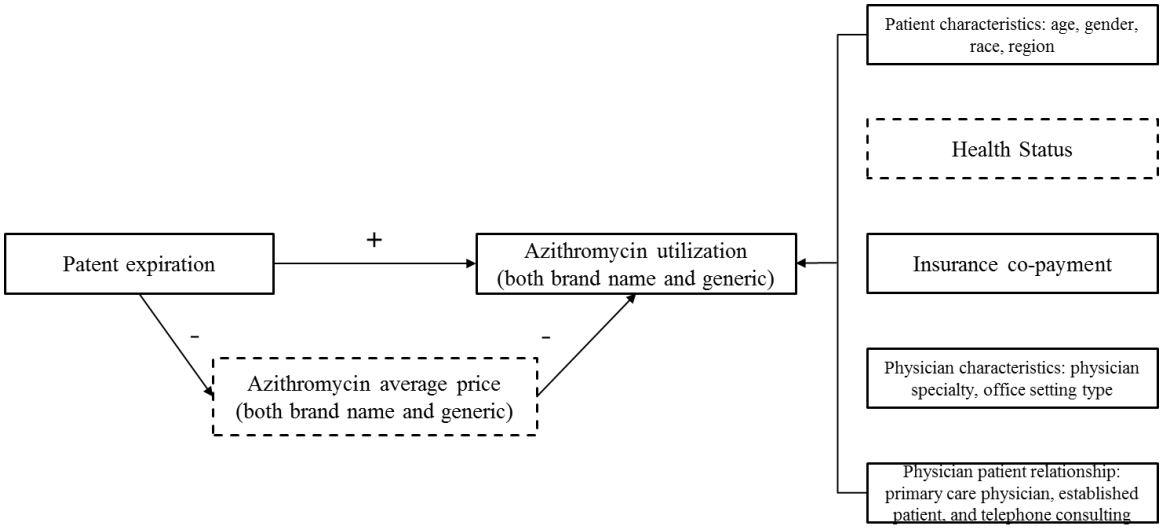

Figure 1. Conceptual Framework

Study Sample Identification

Institutional Review Board: Emory University

An exemption was received on 2/21/2017 since this study uses secondary data that are unidentified.

Data Source

This study used multiple years of data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 2002 to 2009, to analyze individual-level data on prescription drug utilization for URIs and/or UTIs.[49,50]

Background

The NAMCS/NHAMCS are national probability sample surveys conducted by the National Center for Health Statistics for the Centers for Disease Control and Prevention (CDC). The NAMCS includes office-based visits to non-federally funded, community, and office-based physicians based in federally qualified health centers and non-federal government clinics, and provides information about the provision and use of ambulatory medical care services in the U.S. Physicians are classified by the American Medical Association (AMA) or the American Osteopathic Association (AOA). Anesthesiologists, pathologists, and radiologists are excluded from the survey. The NAMCS includes data on patient characteristics, diagnoses and medications, and physician patient relationships.

The NAMCS uses a multistage probability design. The first stage sample includes primary sampling units (PSUs) that are geographic segments. The second stage is comprised of a probability sample of practicing physicians within PSUs. All physicians were classified into fifteen groups. The third stage consists of the selection of patient

visits within the sample of practicing physicians. Each year of cross-sectional data can be used to estimate prescribed drug utilization for each calendar year.

The NHAMCS measures utilization and provision of ambulatory care services at outpatient department and emergency department of US hospitals. The NHAMCS includes a nationally representative sample of visits to hospital outpatient, departments and emergency departments based in nonfederal, general and short-stay hospitals. The NHAMCS also uses a multistage probability design. This first stage sample includes PSUs that are geographically defined areas, and the second stage includes hospitals within primary sampling units. The third stage includes emergency departments and outpatient departments within hospitals. The fourth stage includes patient visits within emergency departments and outpatient departments. During the study period, NAMCS sample sizes range from 25,286 (2004) to 32,778 (2007), and overall response rates are more than 59% (2006). NHAMCS sample sizes range from 29,975 (2005) to 35,586 (2002), and overall response rates are more than 68% (2007). Missing data on patients' age, sex, and race were imputed.

Study Sample Identification

Previous studies suggested that azithromycin is broadly used in the treatment of Upper Respiratory Tract Infections (URIs) and Urinary Tract Infections (UTIs).[15,51,52] Using the NAMCS and the outpatient files of NHAMCS data, all patient visits with URIs and/or UTIs were identified in the study sample. Figure 2 documents the inclusion criterion used to create the study sample. To examine the azithromycin utilization for URIs and/or UTIs before and after patent expiration, we examined all visits with the primary diagnoses of acute URI of unspecified site (using International Classification of

Diseases, Ninth Revision, Clinical Modification [*ICD-9-CM*] code 465), strep throat (*ICD-9-CM* code 034), acute pharyngitis (*ICD-9-CM* code 462), suppurative otitis (*ICD-9-CM* code 382), acute nasopharyngitis (*ICD-9-CM* code 382), acute pharyngitis (*ICD-9-CM* code 462), acute tonsillitis (*ICD-9-CM* code 463), chronic sinusitis (*ICD-9-CM* code 473), pneumonia (*ICD-9-CM* code 486), acute sinusitis (*ICD-9-CM* code 461), acute bronchitis (*ICD-9-CM* code 466), bronchitis not otherwise specified (NOS) (*ICD-9-CM* code 490), and UTIs (*ICD-9-CM* code 466).

This study identified azithromycin prescription for each visit using both brand name and generic antibiotic assigned by NAMCS/NHAMCS to each medication prescribed. The NAMCS/NHAMCS do not distinguish between brand name and generic azithromycin. Thus, the azithromycin prescription in NAMCS/NHAMCS only included brand name azithromycin before patent expiration, and included both brand name and generic azithromycin after patent expiration. Azithromycin prescriptions for each visit were identified through use of the National Drug Code Directory codes for "antimicrobial agents" assigned by NAMCS/NHAMCS from 2002-2005. Drugs are coded in terms of their generic components and therapeutic classifications using Lexicon Plus® of Cerner Multum, Inc. To minimize the likelihood that an antibiotic prescription was unrelated to the principal diagnosis, this study counted only those prescriptions entered as the "primary" medication on the patient record form.

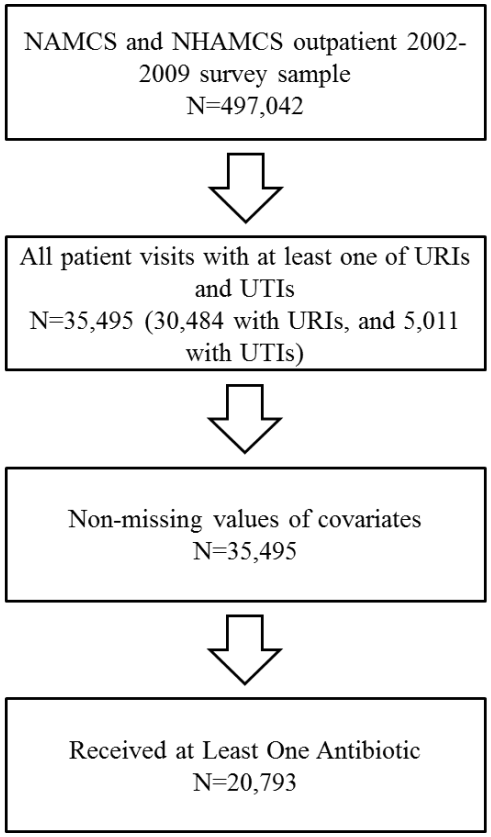

Figure 2. Algorithm for Identification of Study Sample: URIs and/or UTIs

Focal Relationship & Mediator

The focal relationship of the conceptual framework is azithromycin's patent expiration and its effect on overall utilization. Patent expiration is defined as a loss of the marketing right when generic copies of brand name drugs may be marketed.[53] Drug utilization is defined as the "marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences."[54] The economic theory of demand suggests that demand of a certain good will increase due to its average price decrease.[48] Following the patent expiration of

azithromycin, generic substitutes entered the market, which is hypothesized to have decreased the average price of this prescription drug and increased the overall utilization.

Azithromycin's average price is the mediator to the focal relationship. Azithromycin's patent expiration may affect its overall utilization by lowering azithromycin's average price due to market competition after the entry of generic medications. Previous studies examined the relationship between patent expiration and utilization of specialty drugs and several antibiotics and found that different drugs' utilization, prices, and market shares would change differently after patent expiration.[28,31,32,42,45,54,55] Aronsson et al.'s study of the impact of generic drug competition on the brand name drug market shares demonstrates that generic drugs have a lower price with a greater market share than their brand name equivalents.[56] Although there is conflicting evidence from Caves et al.'s (1991) and Frank et al.'s (1997) studies about whether the price of brand name drugs decreases or increases after the entry of generic drugs into the market, both studies repeated that the market share of the brand name drugs decline.[28,42] Overall, the availability of generic azithromycin in the market introduces lower-priced products to consumers, and the replacement of higher-priced brand name azithromycin should lead to a decrease in the average price of azithromycin. More patients are able to fill their prescriptions given a more affordable option provided by generic drugs. Thus, the overall utilization of azithromycin will likely increase with the decreased average price. Based on economic theory and studies examining patent expirations of other medications, this paper hypothesizes that there should be a positive relationship between the patent expiration and overall utilization of azithromycin.

Covariates

Physician characteristics

Physician specialty and the type of office setting may directly influence a physician's prescribing behavior and affect drug utilization pre- and post- patent expiration. Prescribing regulations regarding antibiotic drugs for physicians working in physician offices may be less strict than for those who work at academic hospitals. As a result, hospital-based physicians may be more likely to prescribe antibiotics than office-based physicians.[57,58] In addition, physicians in different specialties also have different prescribing preferences. More specifically, pediatricians may prescribe antibiotics more often than cardiologists because they may encounter more infections.[58] Thus, physician specialty should be considered pre- and post- patent expiration. Lastly, each physician has a prescribing preference, which is unmeasured and could be based on knowledge about antibiotics or influenced by drug advertisements.[31] Since drug advertising and promotion of the brand name drug may decline after patent expiration, physician prescribing preference of antibiotics might change after patent expiration.[31,42]

Patient characteristics

Differences in patient characteristics, including age, gender, race, and region, may be correlated with patients' infections pre- and post- patent expiration. Infants, young children, and elderly people may be likely to be infected because they have lower immunity to bacterial infections than do younger people. There are also differences in infections between males and females, as well as among the racial/ethnic groups, because of differences in biological and social factors.[59] Demographic factors may also be correlated with utilization of azithromycin.[60] Individuals who have health insurance plans

with lower cost-sharing are more likely to use antibiotics than those who have higher cost-sharing plans.[36]

An individual's health status refers to one's mental, social and physical well-being.[61] One's perceived health status is associated with his/her possibility of seeking health care services. In addition, one's diagnosed health status is associated with a physician's prescriptions and overall drug utilization. For example, patients with lower health status use significantly more antibiotics than those with higher health status.[36]

Variables

Independent Variable

The independent variable is the patent expiration. The patent expiration was assessed using a time frame. Since the patent protection for azithromycin in the U.S. market expired in November 2005, the NAMCS/NHAMCS data from 2002-2005 were used to analyze overall utilization of azithromycin pre-patent expiration, and the data from 2006-2009 were used for analyzing overall utilization of azithromycin post-patent expiration.[62] A dichotomous variable was created for each visit that categorizes the time frame in which the visit occurred as pre-patent expiration (i.e. the years from 2002-2005) or post-patent expiration (i.e. the years from 2006-2009).

Dependent Variables

The dependent variable is the overall utilization of azithromycin from 2002 to 2009. Overall utilization of azithromycin was measured by physicians' prescriptions for both brand name azithromycin (Zithromax) and generic azithromycin. Physicians' prescriptions were abstracted from the medical record for each visit. A dichotomous

variable was created that categorizes visits as those in which azithromycin was prescribed (either brand name, generic azithromycin, or both) versus those in which no azithromycin was prescribed.

Covariates

Physician characteristics

Physician's specialty was abstracted from the medical record according to the 15 specialty groups outlined by the American Medical Association (AMA). Those groups were then organized into two categories: (1) general and family practice, internal medicine, and pediatrics, and (2) other specialties. Type of office setting was also abstracted from the medical record. Each visit was classified into two location categories: "physician's office" and "hospital outpatient department".

Patient characteristics

Age was measured as a continuous variable using reported age. Gender was measured with a dichotomous indicator (i.e. male, female) using reported sex. Patients then identified their race as either White, Black, or other. Insurance status was assessed using a proxy measure of expected primary source of payment. Expected primary source of payment for the patient visit was abstracted from the medical record, including Medicare, Medicaid, worker's compensation, self-pay, no charge, and other. Only one type of insurance could be chosen. Insurance status was classified into four categories: "only Medicare", "only Medicaid", "only private insurance", and "other".

Physician patient relationship

Primary care physician was classified into two categories: "patient's primary care physician" and "not patient's primary care physician". Established patients were

classified into two categories: “established patient” and “new patient”. Consulting was classified into two categories: “received telephone consulting before the visit” and “not received telephone consulting before the visit”. Practice ownership was classified into two groups: “physician group owns” and “hospital, HMO, and others own”.

Unmeasured constructs

Two constructs cannot be measured: health status, and azithromycin’s price.

Table 1. Variables, Measures, and Hypothesized Relationships to the Dependent Variable

Construct	**Measure**	**Hypothesized relationship to the dependent variable**
Overall utilization of azithromycin	***Generic code for medications***. Generic code for medications was categorized into two groups: • Dichotomous variable: - Azithromycin prescribed - No azithromycin prescribed	Overall utilization of azithromycin was the dependent variable
Patent expiration	***Time frame***. The time frame was categorized into two groups: • Dichotomous variable: - Pre-patent expiration: the year of 2002-2005 - Post-patent expiration: the year of 2006-2009	Overall utilization of azithromycin will increase after patent expiration.
Azithromycin’s price	Unmeasured	Overall utilization of azithromycin will increase as the average price decrease.

Age	***Age.*** Age was classified into eight categories: • ≤5 • 6-13 • 14-17 • 18-24 • 25-34 • 35-49 • 50-64 • ≥64	Different age group has different probabilities receiving azithromycin. To be assessed.
Sex	***Sex.*** Sex was measured with a dichotomous indicator: • Male • Female	Female may use azithromycin more than males.
Race	***Race.*** Race was classified into three groups: • White • Black • Other	
Region	***Region.*** Region was measured in two ways: Census region: • Northeast • Midwest • South • West Metropolitan: • Metropolitan • Non-Metropolitan	
Health Status	Unmeasured	Patient with better health will less likely to use azithromycin.
Insurance type	***The expected primary source of payment.*** The expected primary sources of payment for the visit were classified into four categories: • Only private insurance • Only Medicare • Only Medicaid • Other	Patient's insurance with high copayment will decrease the utilization of azithromycin.

Physician's specialty	***Physician's specialty.*** Physicians were classified into two categories: • General and family practice, internal medicine, and Pediatrics • Other	The physicians in general and family practice, internal medicine, and pediatrics are more likely to prescribe antibiotics than any other physicians.
Type of office setting	***Type of office setting.*** Type of setting of physicians was classified into three categories: • Physician office • Hospital outpatient department	Hospital outpatient is more likely to use azithromycin.
Primary care physician	Primary care physician was classified into two categories: • Patient's primary care physician • Not patient's primary care physician	To be assessed.
Established patient	Established patient was classified into two categories: • Established patient • New patient	To be assessed.
Consulting	Telephone Consulting was classified into two categories: • Received telephone consulting before the visit • Not received telephone consulting before the visit	Patient received telephone consulting is less likely to use azithromycin.
Practice ownership	Practice ownership • Physician group owns Physician office • Hospital, HMO, and others own	Patient visit that physician group owns is less likely to use azithromycin.

Research Questions

Q_1: Will patent expiration have an impact on the overall utilization of azithromycin for upper respiratory tract infections and urinary tract infections in physician clinics and hospital outpatient departments in the United States?

Q_2: Is there a difference in azithromycin utilization between privately-insured patients and patients covered by Medicaid after patent expiration?

Testable Hypotheses

H_1: There is a positive association between patent expiration and overall utilization of azithromycin for upper respiratory tract infections and urinary tract infections in physician clinics and hospital outpatient departments, after controlling for the covariates.

H_2: There is a larger increase in azithromycin utilization among privately-insured patients than patients covered by Medicaid after patent expiration.

Research Design

Using NAMCS/NHAMCS data from 2002 to 2009, this study measured the relationship between patent expiration and azithromycin utilization using the economic theory of demand for health services.

Analytic strategy

The analytic sample includes all patient visits with URIs and/or UTIs that were abstracted from medical records. To test the hypothesis, the analysis uses interrupted time

series modeling (**model 1-5**) and multivariate logistic regression to determine the association between patent expiration and the probability that azithromycin was prescribed in a particular visit.

Model 1:

$$\ln\left(\frac{p(receiving\ azithromycin)}{1-p(receiving\ azithromycin)}\right) = \beta_0 + \beta_1 * patent\ expiration + \beta_2 * age + \beta_3 * gender + \beta_4 * race + \beta_5 * primary\ source\ of\ payment + \beta_6 * census\ region + \beta_7 * metropolitan\ + \beta_8 * GP, IM, and\ Pediatrics + \beta_9 * primary\ care\ physician + \beta_{10} * established\ patient + \beta_{11} * setting\ type + \beta_{12} * consulting + \beta_{13} * practice\ ownership + \varepsilon\ ,\ (1)$$

Model 2:

$$\ln\left(\frac{p(receiving\ azithromycin\ among\ patient\ visits\ covered\ by\ private\ insurance)}{1-p(receiving\ azithromycin\ among\ patient\ visits\ covered\ by\ private\ insurance)}\right) = \beta_0 + \beta_1 * patent\ expiration + \beta_2 * age + \beta_3 * gender + \beta_4 * race + \beta_5 * census\ region + \beta_6 * metropolitan\ + \beta_7 * GP, IM, and\ Pediatrics + \beta_8 * primary\ care\ physician + \beta_9 * established\ patient + \beta_{10} * setting\ type + \beta_{11} * consulting + \beta_{12} * practice\ ownership + \varepsilon,\ (2)$$

Model 3:

$$\ln\left(\frac{p(receiving\ azithromycin\ among\ patient\ visits\ covered\ by\ Medicaid)}{1-p(receiving\ azithromycin\ among\ patient\ visits\ covered\ by\ Medicaid)}\right) = \beta_0 + \beta_1 * patent\ expiration + \beta_2 * age + \beta_3 * gender + \beta_4 * race + \beta_5 * census\ region + \beta_6 * metropolitan\ + \beta_7 * GP, IM, and\ Pediatrics + \beta_8 * primary\ care\ physician + \beta_9 * established\ patient + \beta_{10} * setting\ type + \beta_{11} * consulting + \beta_{12} * practice\ ownership + \varepsilon,\ (3)$$

Model 4:

$$\ln\left(\frac{p(\textit{receiving azithromycin among patient visits who received at least one antibiotic and covered by private insurance})}{1-p(\textit{receiving azithromycina mong patient visits who received at least one antibiotic and covered by private insuranc})}\right) =$$

$$\beta_0 + \beta_1 * \textit{patent expiration} + \beta_2 * \textit{age} + \beta_3 * \textit{gender} + \beta_4 * \textit{race} + \beta_5 * \textit{census region} +$$

$$\beta_6 * \textit{metropolitan} + \beta_7 * \textit{GP, IM, and Pediatrics} + \beta_8 * \textit{primary care physician} + \beta_9 *$$

$$\textit{established patient} + \beta_{10} * \textit{setting type} + \beta_{11} * \textit{consulting} + \beta_{12} *$$

$$\textit{practice ownership} + \varepsilon \text{ , } (4)$$

Model 5:

$$\ln\left(\frac{p(\textit{receiving azithromycina mong patient visits who received at least one antibiotic and covered by Medicaid})}{1-p(\textit{receiving azithromycina mong patient visits who received at least one antibiotic and covered by Medicaid})}\right) =$$

$$\beta_0 + \beta_1 * \textit{patent expiration} + \beta_2 * \textit{age} + \beta_3 * \textit{gender} + \beta_4 * \textit{race} + \beta_5 * \textit{census region} +$$

$$\beta_6 * \textit{metropolitan} + \beta_7 * \textit{GP, IM, and Pediatrics} + \beta_8 * \textit{primary care physician} + \beta_9 *$$

$$\textit{established patient} + \beta_{10} * \textit{setting type} + \beta_{11} * \textit{consulting} + \beta_{12} *$$

$$\textit{practice ownership} + \varepsilon \text{ , } (5)$$

RESULTS

Descriptive Statistics

There were 35,495 patient visits for URIs and UTIs during the study period from 2002 to 2009. Table 2 describes the characteristics of patient visits in physician clinics and hospital outpatient department for URIs and/or UTIs before and after Azithromycin's patent expiration. The percentage of patient visits covered by private insurance as the primary source decreased from 65.1% to 60.0% after patent expiration. The percentage of patient visits covered by Medicaid as the primary source, meanwhile, increased from 15.1% to 20.0%. However, the percentage of patient visits covered by Medicare or other sources did not change over time.

The difference in the method of using telephone consulting before going to the physician visit was also statistically significant between the two groups ($p<0.001$). The percentage of patient visits before which the patient called his/her physician was 56.3% before the patent expiration, and decreased to 47.1% after patent expiration. In addition, the difference in patient race was statistically significant ($p<0.05$). The proportion of patient visits of whites decreased from 86.1% to 83.3% after patent expiration. The proportion of patient visits of blacks increased from 9.2% to 11.1%, and the proportion of patient visits of other races increased from 4.7% to 5.7%.

The majority of the study sample was children aged 0-5 years. Around 58% of the study population were female. The majority of the study sample resided in the South, around 39%, and in metropolitan areas, at 84.6%. 90.4% of the patient visits were in

physician clinics during the study period. Most physicians in the study were general/family practice, internal medicine, and pediatrics, at 80.4% in average.

Table 2. Weighted Characteristics of Patient Visits for Upper Respiratory Tract Infections and Urinary Tract Infections, by Percentage: United States, 2002-2009

	Before patent expiration, 2002-2005	After patent expiration, 2006-2009	p-value	Overall
	N=17,858	N=17,637		N=35,495 (783,110,912)
Patient age, y				
<=5	26.2	26.4	0.36	26.3
6-13	15.0	15.5		15.3
14-17	6.7	6.9		6.8
18-24	4.5	4.2		4.4
25-34	8.4	8.3		8.4
35-49	17.0	15.0		16.0
50-64	12.2	12.8		12.5
>=65	10.1	10.9		10.5
Patient gender				
Male	42.4	41.0	0.11	41.7
Female	57.6	59.0		58.3
Patient race				
White	86.1	83.3	0.04*	84.7
Black	9.2	11.1		10.1
Others	4.7	5.7		5.2
Primary source of payment				
Private	65.1	60.0	0.00*	62.6
Medicare	10.0	10.4		10.2
Medicaid	15.1	20.0		17.5
Other	9.8	9.6		9.7
Region				
Northeast	18.6	16.8	0.50	17.7
Midwest	25.5	23.7		24.6
South	38.7	40.3		39.5
West	17.2	19.2		18.2

Metropolitan	83.5	85.8	0.29	84.6
Non-metropolitan	16.5	14.2		15.4
Physician patient relationship				
Primary care physician	73.1	72.8	0.83	73.0
Non-primary care physician	26.9	27.2		27.0
Established patient	90.7	89.8	0.37	90.3
New patient	9.3	10.2		9.7
Telephone consulting	56.3	47.1	0.00***	51.7
Non consulting	43.7	52.9		48.3
Physician Specialty				
General/family practice, Internal medicine, and Pediatrics	79.8	80.9	0.37	80.4
Other	20.2	19.1		19.6
Setting type				
Physician office	90.3	90.4	0.97	90.4
Hospital outpatient department	9.7	9.6		9.7
Practice characteristics				
Physician group owns	75.4	72.3	0.09	73.9
Hospital, HMO, and others own	24.6	27.8		26.2

Note: *p<0.05 ** p<0.01*** p<0.001

Table 3 describes the use of antibiotic and azithromycin for URIs and/or UTIs by year, from 2002-2009. The share of patient visits receiving an antibiotic did not change over time. (**Figure 3**) Meanwhile, the average percentage of patient visits using azithromycin for URIs and/or UTIs increased, from 10.8% to 14.0%. (**Figure 4**) The proportion of patient visits receiving azithromycin for URIs and/or UTIs out of patient visits who received at least one antibiotic increased from 17.5% to 22.9% after patent expiration. (**Figure 4**)

The increase in the share of patients receiving azithromycin was larger among privately-insured patients than among patients with Medicaid. For patient visits covered by private insurance, the percentage of patient visits receiving azithromycin out of patient visits who received at least one antibiotic increased by 6.3%, from 17.8% to 24.1%. For patient visits covered by Medicaid, the percentage of patient visits receiving azithromycin out of patient visits who received at least one antibiotic increased by 2.9%, from 16.4% to 19.3%. (**Figure 5**)

Table 3. The Percentage of Patient Visits Receiving Antibiotic/Azithromycin for Upper Respiratory Tract Infections and Urinary Tract Infections, by Percentage: United States, 2002-2009

Annual utilization frequencies of antibiotic/azithromycin (%)	**Year**							
	2002 n=5,092	**2003** n=4,655	**2004** n=3,838	**2005** n=4,273	**2006** n=4,602	**2007** n=4,135	**2008** n=4,340	**2009** n=4,560
Patient visits receiving an antibiotic	64.3	63.2	61.5	57.4	60.2	60.6	64.0	57.4
Patient visits receiving azithromycin out of all patient visits	10.3	11.4	11.5	9.9	12.8	13.2	15.6	14.6
Private Insurance	9.8	12.1	11.5	11.3	13.3	14.1	17.2	16.3
Medicaid	10.1	10.8	11.8	6.9	10.0	10.5	12.5	10.4
Patient visits receiving azithromycin out of patient visits that received at least one antibiotic	16.1	18.0	18.6	17.3	20.9	21.6	24.2	25.0
Private Insurance	15.2	18.2	18.7	19.7	21.6	23.0	25.9	25.8
Medicaid	15.3	19.2	18.3	12.6	17.1	17.8	21.1	21.3

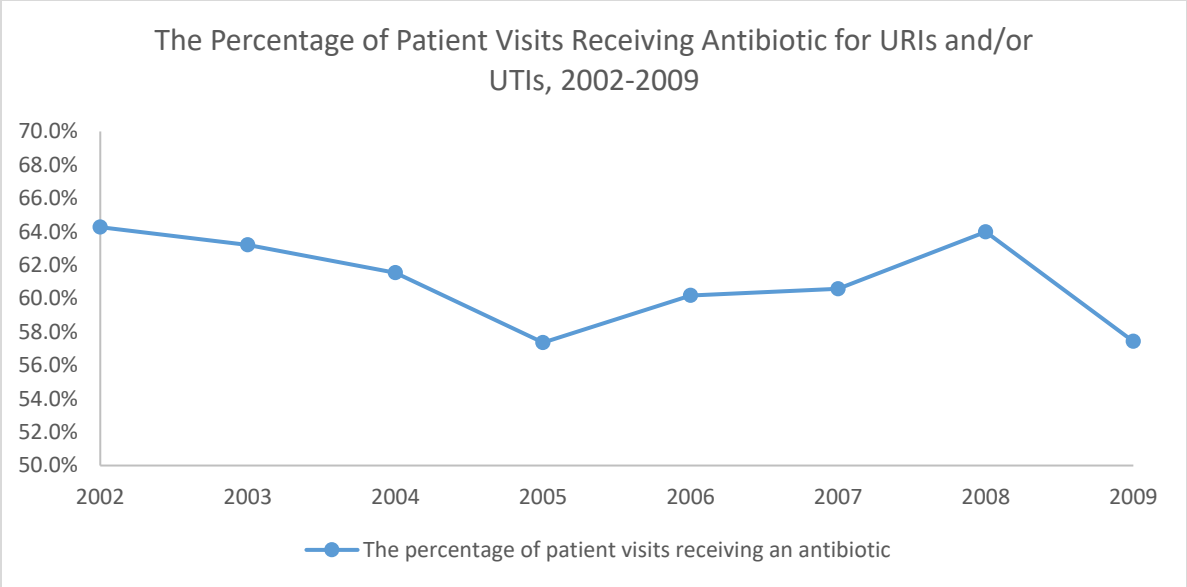

Figure 3. The Percentage of Patient Visits Receiving Antibiotic for URIs and/or UTIs, 2002-2009

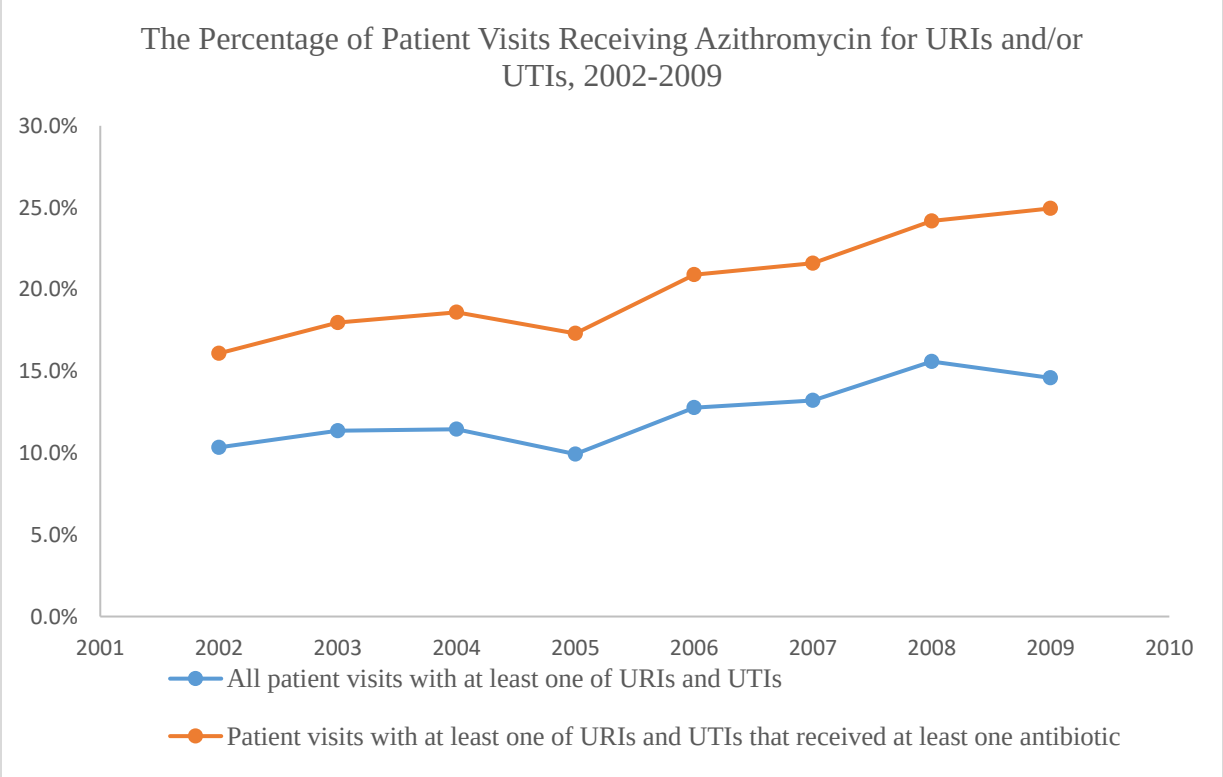

Figure 4. The Percentage of Patient Visits Receiving Azithromycin for URIs and/or UTIs, 2002-2009

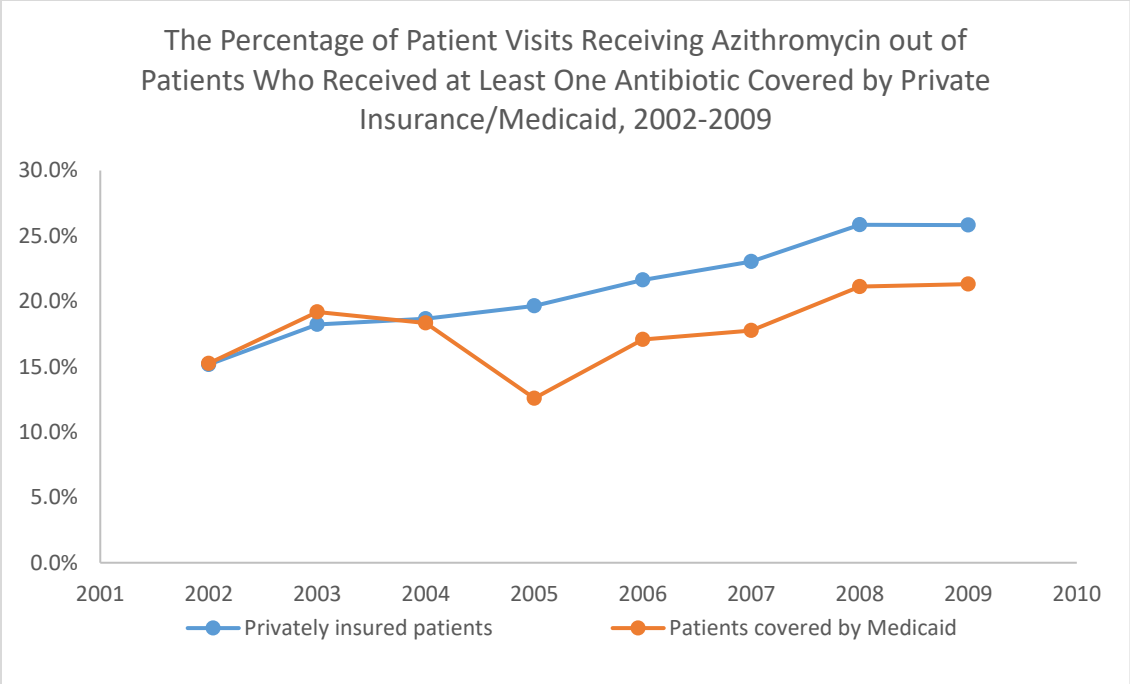

Figure 5. The Percentage of Patient Visits Receiving Azithromycin out of Patients Who Received at Least One Antibiotic Covered by Private Insurance/Medicaid, 2002-2009

Regression Results

Table 4 presents the marginal effects of the association between the patient visits receiving azithromycin and the patent expiration of azithromycin in Model 1. There was a statistically significant 0.03 percentage point increase, or a 27.8% increase, in azithromycin utilization after patent expiration (Marginal Effect (ME)=0.03 percentage points; Standard Error (SE)=0.01).

The visits of patients aged 14-64 years were statistically significantly different from the visits of patients aged 0-5 years. Compared to patient visits covered by private insurance as the primary source of payment, the patient visits covered by Medicaid as the primary source of payment were less likely to receive azithromycin (ME=-0.02; SE=0.01).

Patient visits in metropolitan areas (versus non-metropolitan areas) was negatively associated with the azithromycin utilization. Established patient visits were more likely to receive azithromycin than new patient visits (ME=0.02; SE=0.01). Patient visits in hospital outpatient departments (versus physician clinics) and whose physician's specialty is in general/family practice, internal medicine, and pediatrics (versus other specialty) were more likely to receive azithromycin than in physician clinics after patent expiration ($p<0.001$).

In Table 5, Model 2 and Model 3 present the marginal effects of the association between the patient visits receiving azithromycin and the patent expiration of azithromycin among patient visits for UTIs and URIs who covered by private insurance or Medicaid as primary source of payment. For patient visits for UTIs and URIs, there was a statistically significant increase in azithromycin utilization after patent expiration among patient visits covered by private insurance (ME=0.04; SE=0.01). However, the slight increase in azithromycin utilization after patent expiration among patient visits covered by Medicaid was not statistically significant.

Model 4 and Model 5 present the marginal effects of the association between the patient visits receiving azithromycin and the patent expiration of azithromycin among patient visits who received at least one antibiotic for UTIs and URIs and covered by private insurance or Medicaid as primary source of payment. The findings remained statistically significant after restricting the patient visits who received at least one antibiotic and were covered by private insurance as primary source of payment (ME=0.06; SE=0.01). However, the increase in azithromycin utilization for patient visits

who received at least one antibiotic and were covered by Medicaid was not statistically significant.

Table 4. Weighted Logistic Regression Model of Azithromycin Utilization for Upper Respiratory Tract Infections and Urinary Tract Infections, 2002-2009

	Marginal Effects	SE	p-value	95% Confidential Interval	
Patent Expiration	0.03	0.01	0.00***	0.02	0.05
Patient age, y [a]					
6-13	0.01	0.01	0.23	-0.01	0.02
14-17	0.07	0.01	0.00***	0.04	0.09
18-24	0.06	0.02	0.00***	0.03	0.09
25-34	0.05	0.01	0.00***	0.03	0.08
35-49	0.05	0.01	0.00***	0.03	0.08
50-64	0.04	0.01	0.00***	0.02	0.06
>=65	0.01	0.01	0.38	-0.02	0.04
Patient gender					
Male	0.00	0.01	0.73	-0.01	0.01
Patient race/ethnicity [b]					
Black	-0.01	0.01	0.18	-0.03	0.01
Other	0.00	0.01	0.84	-0.03	0.02
Primary source of payment [c]					
Medicare	-0.01	0.01	0.56	-0.03	0.02
Medicaid	-0.02	0.01	0.00***	-0.04	-0.01
Others	-0.01	0.01	0.63	-0.03	0.02
Region [d]					
Midwest	0.00	0.01	0.66	-0.02	0.03
South	0.02	0.01	0.20	-0.01	0.04
West	0.00	0.01	0.96	-0.03	0.03
Metropolitan areas	-0.02	0.01	0.04*	-0.05	0.00
Physician Specialty					
General/family practice, Internal medicine, and Pediatrics	0.08	0.02	0.00***	0.05	0.11
Physician patient relationship					
Primary care physician	-0.01	0.01	0.24	-0.03	0.01
Established patient	0.02	0.01	0.03*	0.00	0.04
Telephone consulting	-0.01	0.01	0.49	-0.02	0.01
Setting type					
Hospital outpatient department	0.07	0.02	0.00***	0.03	0.11
Practice characteristics					
Physician group owns	-0.02	0.01	0.09	-0.04	0.00

Note: a. age group 0-5 years is omitted; b. White race is omitted.
c. Private insurance as primary source of payment is omitted; d. Northeast region is omitted.
*p<0.05 ** p<0.01*** p<0.001

Table 5. Weighted Logistic Regression Model of Azithromycin Utilization Covered by Private Insurance for Upper Respiratory Tract Infections and Urinary Tract Infections, 2002-2009

	Marginal Effects			
	Model 2	Model 3	Model 4	Model 5
Patent Expiration	0.04***	0.01	0.06***	0.03
Patient age, y [a]				
6-13	0.01	0.03*	0.01	0.05*
14-17	0.05***	0.13***	0.08***	0.18***
18-24	0.06***	0.07	0.07***	0.09
25-34	0.06***	0.08**	0.06***	0.11*
35-49	0.06***	0.03	0.07***	0.04
50-64	0.04***	0.05	0.06***	0.06
>=65	0.03	0.01	0.07*	0.04
Patient gender				
Male	0.01	-0.01	0.01	-0.02
Patient race/ethnicity [b]				
Black	0.00	-0.01	0.02	-0.03
Other	0.00	0.03	0.02	0.09
Region [c]				
Midwest	0.01	0.01	-0.01	-0.01
South	0.02	0.03	0.01	0.00
West	0.01	-0.03	0.01	-0.07
Metropolitan areas	-0.03*	-0.03	-0.03	-0.02
Physician Specialty				
General/family practice, Internal medicine, and Pediatrics	0.08***	0.06*	0.03	0.05
Physician patient relationship				
Primary care physician	-0.01	-0.02	0.00	-0.01
Established patient	0.02	0.05	0.03	0.09
Telephone consulting	-0.01	-0.01	-0.01	0.01
Setting type				
Hospital outpatient department	0.07***	0.06	0.02	0.03
Practice characteristics				
Physician group owns	-0.02	-0.01	-0.02	0.02

Note: N (Model2) = 11,745, N (Model3) = 4,912, N (Model 4) = 18,894, N (Model 5) = 8,969

a. age group 0-5 years is omitted.

b. White race is omitted.

c. Northeast region is omitted.

*p<0.05 ** p<0.01*** p<0.001

DISCUSSION

Conclusion

There was an increase in azithromycin utilization for patients with URIs and/or UTIs after patent expiration. The patent expiration of azithromycin was associated with an approximately 28% increase in azithromycin prescriptions during visits for URIs and/or UTIs from 2002 to 2009. This study also found significant differences in azithromycin utilization between privately insured patients and patients covered by Medicaid.

The larger increase among privately insured patients is expected since private insurance tries harder than Medicaid to reduce pharmaceutical use or steer patients to less-expensive drugs via sophisticated tiered formularies.[63] Prior to patent expiration, private insurers might have charged higher copayments for branded azithromycin (Zithromax®), compared to alternative antibiotics, most of which were already generic.[17] Medicaid patients also face copayments, but the copayments for Medicaid enrollees are too small to encourage patients to use less expensive drugs or vary between brand name and generic drugs. For example, though states have the option to charge premiums and to establish out of pocket spending (cost sharing) requirements for Medicaid enrollees, copayments are limited to nominal amounts that are very small.[64]

This study also found a significant difference in azithromycin prescribing habits between clinic-based physicians and hospital-based physicians. This may indicate that hospital-based physicians may see more patients in the same or less time than office-

based physicians, which is associated with an increase in antibiotic prescribing, and referrals of a new patient to a specialist.[65]

Limitations

This study does face limitations. Patients may not fill prescriptions after visits. The measurement of utilization might bias the actual azithromycin consumption since NAMCS/NHAMCS collect prescribing information for each patient visit. Before patent expiration, patients may wait to see if the infectious condition would resolve on its own. Once the drug became cheaper, they may have just filled the prescription. This study will understate the impact of patent expiration on azithromycin utilization if patients may have been more likely to fill a prescription after the generic versions became available.

In addition, the substitutions between azithromycin and other alternative antibiotics was not addressed in the study. Maxipime® (cefepime) and Zosyn® (piperacillin plus tazobactam) also lost their U.S. patent during the study period, thereby the average price decreased and use increased. This study will underestimate the impact of patent expiration on azithromycin utilization if there are substitutions between azithromycin and other generic alternative antibiotics. There is a growing attention to the problem of antibiotic resistance.[2,66,67] As a result, physicians may substitute away from older antibiotics to newer antibiotics like azithromycin, and this study will overestimate the impact of patent expiration.

Another limitation is the pre-existing growth trend of azithromycin utilization. The use of azithromycin was already increasing prior to 2005 for privately insured patients. The increase after 2005 was due to patent expiration since the study result was

statistically significant. However, a portion of the increase might be just a continuation of past trends, which will overestimate the impact of patent expiration. In addition, the growing awareness of antibiotic resistance may have put downward pressure on azithromycin utilization during the study period, which will underestimate the impact of patent expiration. This study also lacks enough observations for no insurance or the self-pay group, which will confirm the influence of price differences less than if the study had enough observations for this group.

Despite these limitations, this study still contributes to the literature. First, it allows for an estimation of the rates of azithromycin prescriptions issued during outpatient visits using a large and nationally representative dataset. Additionally, this study is the first to examine the overall utilization of both brand name and generic azithromycin pre- and post- patent expiration. Finally, NAMCS/NHAMCS collects information of physician and patient characteristics, which enables the analysis to control for a number of important confounders.

Recommendations for Future Studies

Future studies would benefit from the use of data that contain more information on categories of generic and branded medications, which would be helpful for understanding the substitute influence on azithromycin. Additional studies examining the filled prescriptions are also recommended, which would help reveal the magnitude of patent expiration on azithromycin utilization more precisely. Future studies that use difference in differences methods to investigate the causal relationship between patent expiration and azithromycin would also be informative. Finally, future studies should

examine the effects of comorbidity and severity of illness, especially other coexisting illnesses, immunosuppression, long durations of symptoms, and other clinical conditions that might influence antibiotic use, on the relationship between patent expiration and azithromycin utilization.

Policy Implications

Policymakers have promoted generic entry to reduce drug costs. This study shows that the premise behind this policy–that generic entry leads to increased drug use–is correct. Antibiotics are different from other drugs. Consumers bear negative consumption externalities because generic entry may increase antibiotic resistance and harm society. People fear that the rate of antibiotic innovation cannot keep up with the resistance. Part of the reason is that research and development of antibiotics takes a long time, and even those antibiotics that have successfully developed also face various obstacles in making profits in the market. One approach for reducing resistance is to grant longer patents to antibiotics, thereby delaying generic entry and increased use. Other price-based interventions, including changes in demand side cost sharing by patients, and the use of physician bonuses for antibiotic rational use, may also reduce antibiotic use in outpatient settings.[66]

The CDC has made national efforts to address antibiotic overuse through education of healthcare providers, and support of developing and evaluating antibiotic stewardship.[68] This study finds that overall antibiotic prescribing rates for URIs and/or UTIs did not change over time, meanwhile, the utilization of azithromycin, a broad-spectrum antibiotic, increased after patent expiration. This may indicate that educational

programs for broad-spectrum antibiotics are needed after patent expiration, which may help reduce antibiotic use. Patients should also be educated about the difference between bacterial and viral infections, and why antibiotics will be ineffective for a viral illness.

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