THE JOURNAL OF INDUSTRIAL ECONOMICS 0022-1821
Volume LXIII June 2015 No. 2

HEALTH CARE COMPETITION AND ANTIBIOTIC USE IN TAIWAN*

Daniel Bennett†
Che-Lun Hung‡
Tsai-Ling Lauderdale§

Antibiotic resistance, a negative externality of antibiotic use, is a growing threat to public health. Health care competition may encourage antibiotic use because receiving an antibiotic is a form of 'quality' for many patients. This paper examines the effect of market concentration on antibiotic use in a large, nationally-representative data set from Taiwan. Moving from the 75th percentile to the 25th percentile of market concentration is associated with 6.6 per cent greater antibiotic use. We control for leading market-level confounds, including population density and community health. We also show that the correlation is robust using fixed effects for patients, physicians and diagnoses. We document the correlation between antibiotic use and patient retention, which suggests a mechanism for this result. Finally, we show that strict regulation of antibiotics reduces but does not eliminate the effect of competition on antibiotic use.

I. INTRODUCTION

Fee-for-service is a common model of health care provision throughout the world (Docteur and Oxley [2003]). Under this system, the government

*We thank Nathaniel Baum-Snow, Kerwin Charles, Kenneth Chay, Likwang Chen, Nelly Chen, Shou-Hsia Cheng, Chun-Fang Chiang, Andrew Foster, Susan Foster, Douglas Gollin, Jeffrey Grogger, Vernon Henderson, Monto Ho, Jill Huang, Peter Iliev, Calvin Kunin, Shuen-Zen Liu, Rachel Lu, Bruce Meyer, Kaivan Munshi, Ying Pan, Dimitra Politi, James Romeis, Mao-Ting Sheen, Svetla Vitanova, Nicholas Wilson and seminar participants at the University of Chicago and National Taiwan University for many helpful suggestions. This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

†Authors' affiliations: Harris School of Public Policy Studies, University of Chicago, 1155 East 60th Street, Chicago, Illinois 60637, U.S.A.
e-mail: dmbennett@uchicago.edu
‡Department of Computer Science and Communication Engineering, Providence University, 200 Chung Chi Road, Taichung 43301, Taiwan.
e-mail: clhung@pu.edu.tw
§National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, 35 Keyan Road, Zhunan, Miaoli County 350, Taiwan.
e-mail: lauderdale@nhri.org.tw

or private insurers set prices at which they reimburse providers for medical services. By restricting price competition, fee-for-service encourages firms to attract patients through quality or other attributes. Competition among firms may accentuate this incentive by giving patients additional provider choices and thereby increasing the quality elasticity of demand. The health economics literature has investigated quality competition in terms of the so-called medical arms race, in which hospitals compete for patients through investments in costly medical equipment (Robinson and Luft [1985], Dranove and Satterthwaite [2000], Propper *et al.* [2004] Section 4.2). In addition to driving up costs, quality competition may have unintended consequences if quality (as patients perceive it) has negative externalities.

This paper considers the effect of competition on antibiotic use in Taiwan. Taiwan's government sets reimbursement rates to private providers through its universal fee-for-service health care system. Because of low copayments, patients often seek care for mild conditions such as sore throats and colds. Antibiotic prescription is a quality dimension of these visits because many patients expect to receive an antibiotic. Although the medical best practice is to confirm that an infection is bacterial before prescribing antibiotics, doctors often feel pressure to prescribe antibiotics immediately just in case (Brody [2005]). A physician in Butler *et al.*'s [1998] focus group remarks, 'You can't just say "It's viral, you don't need antibiotics, go away," because [patients] feel they're being fobbed off. They feel that their illness is not being taken seriously.'

Antibiotic use has a negative externality because it contributes to global antibiotic resistance. Antibiotics encourage bacteria to become resistant through mutation and make it easier for resistant bacteria to compete for nutrients. People share resistant bacteria within communities through everyday interactions. Through years of intensive use, resistance to erythromycin (a common and important antibiotic) is now 28.3 per cent in the United States, 33.3 per cent in Mexico, 71.5 per cent in Japan, and 72.4 per cent in Hong Kong (McGeer and Low [2003]). Resistant infections are more costly and difficult to treat. Providers may need to switch to stronger antibiotics and consider alternatives such as surgery.[1]

This paper shows a robust correlation between market concentration and antibiotic use in a large, nationally representative panel of outpatient claims. Using census and mortality records, we control directly for population density and the disease environment, which are the two most likely confounds. We further examine the robustness of this result through

[1] The U.S. spends \$4–7 billion per year to treat resistant infections (ASM [1995], Lautenbach *et al.* [2001]). Mortality from methicillin-resistant *S. aureus* (MRSA) now exceeds mortality due to HIV, Parkinson's Disease, emphysema, and homicide in the U.S. (Klevens *et al.* [2007]). Drug resistance also necessitates the development of new antibiotics to replace drugs with high resistance (Spellberg *et al.* [2004]).

visit-level regression that controls for patient, physician, and diagnosis fixed effects, which exploit distinct sources of variation. Next we provide evidence of the underlying mechanism by showing a robust correlation between antibiotic use and patient retention.[2] Finally, we assess the role of policy by comparing the effect of competition on antibiotic prescription under lax and strict regulatory regimes, which existed before and after a 2001 reform. Strict regulation reduces but does not eliminate the effect of competition on antibiotic use.

Any analysis of the effects of competition relies on assumptions about the definition of firms and markets. Our baseline analysis uses township boundaries to define markets. However we also show that results are similar if county boundaries are used instead. We justify the use of the HHI as a market concentration index by showing that antibiotic use rises as the number of firms increases and as firms become more homogeneous.

This paper contributes to the literature on competition and health care quality. Papers in this area mainly focus on the interactions of hospitals in the United States and Europe. We provide the first analysis to our knowledge of quality competition through prescription. Antibiotic prescription is a novel and tangible quality dimension, which our data allow us to measure precisely. This paper also contributes to a small literature on the economics of drug resistance (Laxminarayan and Brown [2001], Mechoulan [2007], Herrmann and Laxminarayan [2010]). Perhaps because of the lack of data (and with the notable exception of Currie *et al*. [2011]), this literature has remained primarily theoretical.

We proceed in Section II to motivate our approach theoretically. In Section III, we describe the context, the data, and our market and firm definitions. Section IV describes our identification strategy and shows regressions of antibiotic use on market concentration. Here we also provide suggestive evidence of the patient retention mechanism and show the effect of strict regulation on competitive prescription. We conclude in Section V by discussing the impact of this phenomenon on antibiotic resistance.

II. THEORETICAL MOTIVATION

This section discusses the theoretical reasons why competition may affect antibiotic use. Therapeutic benefits aside, an antibiotic prescription is often an important quality attribute for ambulatory patients in Taiwan and elsewhere. In Taiwan, a plurality of patients arrive with mild conditions such as the common cold, ear aches, and sore throats. Although most of these illnesses are viral infections, it is often difficult to reach a definitive

[2] Competition may also affect the selection of patients and physicians in the market and directly encourage drug sales.

diagnosis without additional tests (Fitch [2002]). An antibiotic prescription gives the patient the option to treat with antibiotics, which usually have no side effects.[3] An antibiotic prescription may also help to resolve an information asymmetry between patients and providers. Patients have limited information about whether a doctor has exerted effort on their behalf. By prescribing an antibiotic in cases where it may or may not be necessary, the doctor signals that he is proactive about the patient's treatment in other unobservable dimensions.

Antibiotic use has an ethical and regulatory cost for the physician. Doctors are taught that excessive and inappropriate use of antibiotics fosters drug resistance. Medical best practices discourage prescription unless the physician reasonably suspects a bacterial infection (Snow *et al.* [2001a], Snow *et al.* [2001b], Snow *et al.* [2001c]). According to Reese and Betts, eds. [1996, p. 1060], 'The otherwise healthy patient with mild illness and no focal findings does not require [antibiotic] treatment until a diagnosis has been reached.' Physicians who cave in to patient demands for antibiotics too easily may face social sanctions from their physician peers. Depending on the policy environment, doctors who prescribe antibiotics too often may face greater regulatory scrutiny, as we explore below.

If an antibiotic prescription is a quality attribute of outpatient care, antibiotic use may be sensitive to market forces. A literature in Industrial Organization considers the theoretical effect of competition on product quality. In general, the direction of this relationship is ambiguous because firms may either adjust price or quality in response to competition. Which response is optimal depends loosely on the relative magnitudes of the price and quality elasticities of demand (Dorfman and Steiner [1954]), as well as the cost of improving quality. A firm facing price-responsive consumers may optimally respond to competition by reducing price (and possibly also quality). A firm with quality-responsive consumers may instead opt to improve quality. A fee-for-service health care system encourages quality competition by ruling out price competition (Dranove and Satterthwaite [2000]). As long as the elasticity of firm profits with respect to antibiotic use is greater than the elasticity with respect to other quality dimensions, competition is likely to encourage antibiotic use.[4]

[3] In this discussion, we set aside the possibility that some patients would rather not receive antibiotics. This simplification is reasonable because many patients specifically seek care to obtain medicine (Brody [2005], Bauchner *et al.* [1999], Butler *et al.* [1998]). For patients who do not want antibiotics, the effect of competition on antibiotic use may work in the other direction, particularly if physicians can distinguish these patient types.

[4] The effect of competition on quality remains ambiguous if consumers have heterogeneous quality preferences. Spence [1975] shows that competition may affect quality by changing the identity of the marginal consumer, whose preferences dictate the firm's optimal quality choice. Firms facing heterogeneous consumers may also respond to competition by differentiating vertically in an effort to occupy a less competitive quality niche (Shaked and Sutton [1982]).

III. CONTEXT

III(i). *Health Care Setting*

Taiwan is a small, densely populated island with a population of 22.8 million and per capita GDP of around U.S. $30,000. The infant mortality rate of 5.4 and the median age of 37.6 are similar to the United States. In 2005, life expectancy at birth in Taiwan was 71.8 years for men and 77.7 years for women. Taiwan is made up of 25 cities and counties, which are subdivided into 366 urban districts and townships. Throughout the paper, we refer to these units as 'counties' and 'townships', respectively. County boundaries did not change from 1997 to 2005 but townships merged or split in two instances.

In 1995, Taiwan established a public single-payer health insurance system. The program, which serves 96 per cent of the population, reimburses private providers for health care according to a fixed fee schedule. The system is financed through payroll taxes and copayments, which are less than U.S. $5 for outpatient visits and prescriptions. Because only 57 per cent of the population had insurance before the reform, universal health care dramatically increased health care demand in the late 1990's (Chiang [1997], Cheng and Chiang [1997]).

Physicians who provide outpatient care are organized into either hospital outpatient departments or clinics. All hospitals operate outpatient departments, which employ a median of 25 physicians. These departments contribute to the profits of the hospital but usually function independently of other departments. Hospitals offer less personalized but more technologically-advanced care. Hospitals utilize a 'staff model HMO' compensation structure, in which physicians receive salaries according to seniority and rank. Many hospitals incentivize physicians based on patient volume. Chu *et al*. [2003] describe a typical scheme, in which physicians receive bonuses that are 70 per cent weighted by their individual contributions to revenue and 30 per cent weighted by their teams' contributions to cost reduction.

Patients can receive both 'prescription' and 'over the counter' drugs through a doctor's prescription. The health insurance system's generous drug subsidy incentivizes patients to see a doctor for mild conditions to obtain discounted drugs (Ho [2005]). Patients in Taiwan seek outpatient care a median of 10 times per year, roughly double the frequency of outpatient care in the U.S. Twenty per cent of these visits are for upper respiratory infections (URI's), including sore throats and the common cold. Although URI's are rarely bacterial, patients with these conditions often request antibiotics. Many outpatient visits last only five minutes because the patient's main objective is to obtain medicine. Ho ([2005], p. 246) argues that the intensive use of antibiotics also reflects cultural norms: 'The patient's primary purpose in seeing a doctor is to get a prescription. In the Chinese conception, every illness requires some sort of medicine. The idea that some diseases do not require medicine is unacceptable.'[5]

Children are the heaviest users of antibiotics. During the sample period, children under ten received antibiotics in 28 per cent of visits, compared to 19 per cent for patients aged 10–59 and 11 per cent for patients aged 60 and over. Because elderly patients visit more frequently overall, they receive more total antibiotic prescriptions than non-elderly adults. One reason that young and elderly patients receive more antibiotics is that they are more susceptible to bacterial infections. Age may also be a clinical factor that affects the need to prescribe. Because young and elderly patients tend to be more frail, physicians have less discretion to withhold antibiotics from these patients, conditional on the diagnosis.[6]

In response to research showing alarming rates of antibiotic resistance (Lauderdale *et al*. [2004], McDonald *et al*. [2004]), public health officials implemented a novel regulation of antibiotics in February of 2001. Conventionally, antibiotic control policies have focused on dosage management and sequestration of infected patients. Instead, regulators in Taiwan began requiring additional evidence of a bacterial infection from doctors prescribing antibiotics for URI's. The Bureau of National Health Insurance (BNHI) enforced this rule by auditing doctors who prescribed antibiotics frequently, incentivizing doctors to curtail unnecessary prescription to avoid the audits. Figure 1 plots the intensity of antibiotic use by quarter from 1997 to 2005. The rate of antibiotic prescription climbed to a peak in the first quarter of 2000, when over 30 per cent of all outpatient visits included an antibiotic prescription. Public health officials considered and debated the policy from February, 2000 to February, 2001, as indicated in the figure. The policy debate may have affected behavior by changing social norms around antibiotics or by fostering the perception that regulators were already monitoring physicians. After the reform, antibiotic use fell by 16 per cent in 2002 and by another 4 per cent by 2005. The figure also shows a parallel pattern for the antibiotic share of prescribed drugs, indicating that the decline in consumption was specific to antibiotics.

[5] All hospitals and 60–70 per cent of clinics operate on-site pharmacies (Chou *et al*. [2003]). These shops must employ licensed pharmacists, but firms receive the residual profit from drug sales. Income from antibiotic sales provides another channel through which competition affects prescription. However in practice, prescription drugs account for less than 20 per cent of outpatient revenue.

[6] In a regression of antibiotic use on dummies for the age categories above, the age dummies have a jointly significant effect ($p = 0.009$). Including diagnosis fixed effects in the regression reduces the significance of the dummies, so that $p = 0.17$. This comparison suggests that age affects antibiotic use both directly and through the patient's health status.

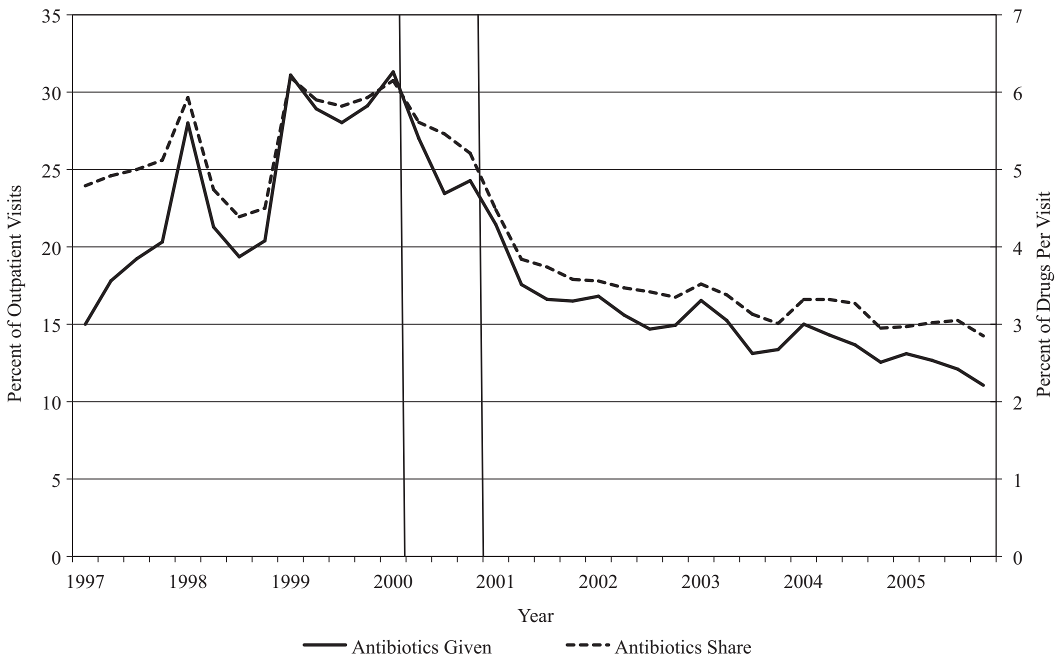

Figure 1
Quarterly Antibiotic Use, 1997–2005

III(ii). *Health Care Markets*

Any empirical analysis of competition relies on an assumption about the definition of markets. In health economics, markets are typically defined geographically according to administrative boundaries or endogenous catchment areas. We cannot compute catchment areas because our data do not include the residential locations of patients. Instead we proceed by using townships to proxy for markets. Townships are plausible proxies because convenience is an important factor for many ambulatory patients. Only 24 per cent of patients visit providers in multiple townships within a quarter. According to Kessler and McClellan [2000], the key threat to identification under this approach is classical measurement error, which creates attenuation bias.[7] Counties are the only alternative administrative proxies for markets. Appendix Table III shows that a county level analysis yields similar results.

Our analysis treats hospitals and clinics, rather than doctors, as competitors. Physicians are organized and compensated through these firms. These compensation arrangements affect physician incentives to attract and retain patients. Although physicians have authority to offer or withhold antibiotics in individual cases, firms can encourage or discourage antibiotic use in general (Chu *et al*. [2003]).

[7] Administratively defined markets may incorporate non-classical measurement error if market structure is systematically different near the boundaries. Administrative boundaries in Taiwan rarely bisect town centers, where most providers are located.

We rely on outpatient claims data from 1997 to 2005 for a panel of 200,000 patients who were selected to be nationally representative of the 2000 population. The data set includes the details of each ambulatory visit, including the ICD9 diagnosis code and the drugs prescribed. The BNHI provides a directory of health care providers and personnel, which allows us to calculate the HHI. We also use census data and mortality records to calculate the annual population density of each township and age-specific mortality rates.

We measure market concentration using the HHI with market shares calculated according to patient volume. The HHI is a sensible market concentration index if the elasticity of demand is sensitive to both the number of firms in the market and their homogeneity. Figure 2 plots the HHI distribution in our data. Markets around the median of 0.14 contain an average of 0.8 hospitals and 31 clinics. Eight per cent of markets have an HHI of 1 because one provider (usually a clinic) has a monopoly. Moving from the 75th percentile to the 25th percentile of the HHI is associated with the addition of two hospitals and 49 clinics.

In Panels A and B of Table I, we compare the characteristics of markets above and below the median HHI (0.14). The large sample size ensures that every difference in means is statistically significant. Although characteristics are not generally balanced by HHI, the regressions below control for the most serious possible confounds. Patients in low-concentration town-

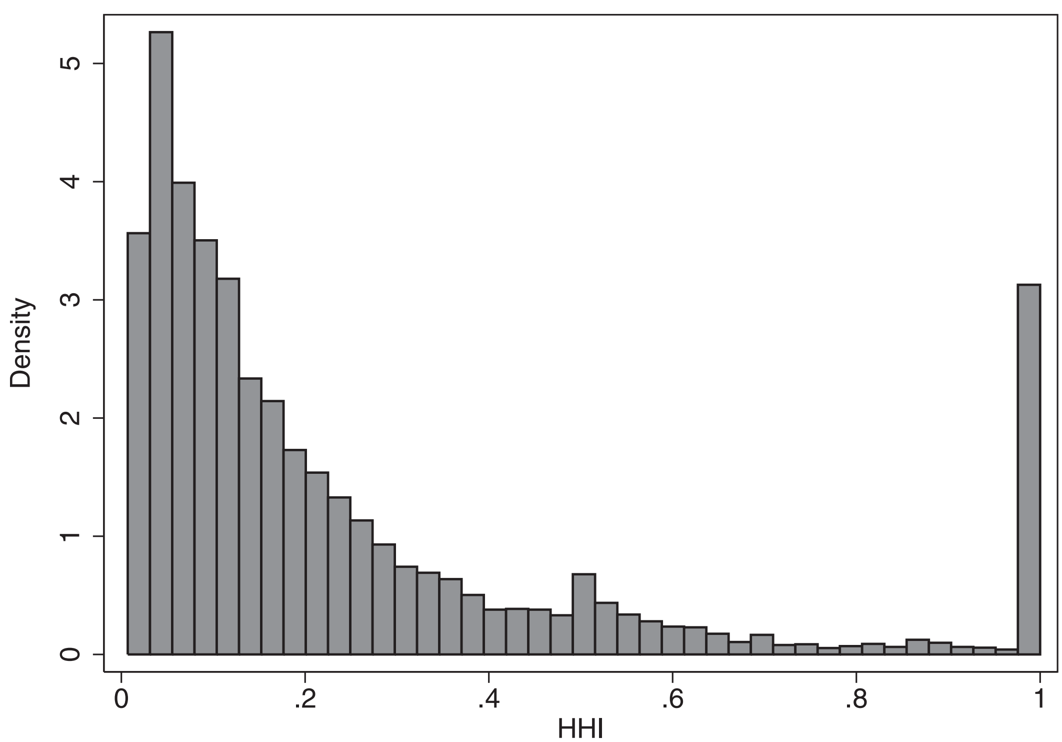

Figure 2
The HHI Distribution

TABLE I
PATIENT AND MARKET CHARACTERISTICS

HHI:	Below Median (1)	Above Median (2)
Panel A: Patient Characteristics		
Age < 10	0.18	0.13
Age 10–59	0.62	0.57
Age ≥ 60	0.20	0.30
Male	0.44	0.46
Sample size (millions)	*17.7*	*3.8*
Panel B: Market Characteristics		
Population density	4695	966
Hospitals	2.7	0.4
Clinics	66.4	10.5
Hospital-based physicians	48.8	22.9
Clinic-based physicians	94.0	14.6
Mortality rate × 1000: age < 10	0.20	0.32
Mortality rate × 1000: age 10–59	0.54	0.84
Mortality rate × 1000: age ≥ 60	8.45	9.54
Sample size	*6315*	*6648*
Panel C: Antibiotic Prescription		
Patient receive a drug	0.94	0.94
Number of drugs if > 0	4.56	4.61
Patient receives an antibiotic	0.20	0.15
Number of antibiotics if > 0	1.13	1.13
Sample size (millions)	*4.34*	*0.94*

Notes: The median value of the HHI is 0.14. All differences are statistically significant.

ships are younger but have a similar gender distribution. Population density is five times greater in low-concentration townships. This pattern is not surprising because dense townships are able to support many health care providers. The mortality rate is lower in low-concentration markets in all age categories, which minimizes the concern about health heterogeneity as a confound.

Panel C of Table I compares prescription patterns of unconcentrated and concentrated townships. Patients receive four to five prescriptions per visit, regardless of market concentration. This rate of prescription is consistent with Ho's [2005] view that many patients seek care to obtain medicine. In contrast, concentrated and unconcentrated markets have different rates of antibiotic use. Patients in unconcentrated markets are five percentage points more likely to receive an antibiotic. These figures indicate that whether or not an antibiotic is given is the relevant margin, rather than the number of antibiotics or total drugs.

IV. ESTIMATION

IV(i). *Market-Level Analysis*

In this subsection, we use market level regressions to illustrate the correlation between market concentration and antibiotic use. This approach allows us to control directly for key market level confounding factors, including population density, the age distribution of patients, and township health characteristics. It also weights the data in a useful way, as we describe below. In the specification below, j indexes the market and t indexes the year × quarter.

$$(1) \qquad a_{kt} = \beta_0 + \beta_1 H_{kt} + X_{kt} + \delta_t + \varepsilon_{kt}$$

In these regressions, a_{kt} is the per cent of ambulatory visits that lead to an antibiotic, H_{kt} is the HHI, which is calculated by township and year × quarter as described above, and X_{kt} is a vector of controls. Standard errors are clustered by township.

Table II shows estimates based on this approach. The parsimonious specification in Column 1, which only controls for time fixed effects, shows a significant correlation between market concentration and antibiotic use. According to this estimate, moving from the 75th percentile of the HHI to the 25th percentile increases antibiotic prescription by 1.2 percentage points (6.6 per cent). With township × time observations, this approach weights townships equally. In contrast, Column 2 weights townships by patient volume to obtain a nationally representative estimate, which is comparable to visit level estimates below. Column 2 is much larger than

Table II
Market Concentration and Antibiotic Use

	Antibiotic use (market average)				
Dependent variable:	(1)	(2)	(3)	(4)	(5)
HHI	–0.048***	–0.16***	–0.047***	–0.040***	–0.049**
	(0.014)	(0.014)	(0.014)	(0.014)	(0.023)
Population density			0.14	–0.060	–5.96
			(0.32)	(0.39)	(4.69)
Population share: age < 10				0.36*	1.02**
				(0.20)	(0.45)
Population share: age 10–59				–0.061	–0.20*
				(0.052)	(0.10)
Population share: age ≥ 60				–0.36***	–0.39
				(0.078)	(0.49)
Mortality rate: age < 10				1.02	–2.21
				(3.44)	(3.05)
Mortality rate: age 10–59				11.6*	5.07
				(6.62)	(4.57)
Mortality rate: age ≥ 60				0.35	0.93
				(0.78)	(0.63)
P-value of controls	—	—	—	< 0.001	0.18
Year × quarter fixed effects	Yes	Yes	Yes	Yes	Yes
Market fixed effects	—	—	—	—	Yes
Weights	—	Traffic	—	—	—
Observations	12,958	12,958	12,958	12,958	12,958
R^2	0.32	0.65	0.32	0.35	0.55

Notes: Standard errors appear in parentheses. Standard errors are clustered by township. The population density coefficient is multiplied by 1,000,000. The mortality rate coefficients are multiplied by 10,000. *$p < 0.1$, **$p < 0.05$, ***$p < 0.01$.

TABLE III
THE NUMBER AND HETEROGENEITY OF FIRMS

	Antibiotic use (market average)			
Dependent variable:	(1)	(2)	(3)	(4)
Log number of firms	0.0074***	0.020**	0.0095***	0.021**
	(0.0029)	(0.0099)	(0.0029)	(0.011)
Standard deviation of firm size			–0.0015***	–0.0013**
			(0.00021)	(0.00052)
Demo and health controls	Yes	Yes	Yes	Yes
Time fixed effects	Yes	Yes	Yes	Yes
Market fixed effects	—	Yes	—	Yes
Observations	12,958	12,958	11,982	11,982
R^2	0.35	0.55	0.44	0.64

Notes: Standard errors appear in parentheses. Standard errors are clustered by township. Firm size is measured by patient volume. $*p < 0.1$, $**p < 0.05$, $***p < 0.01$.

Column 1 because the effect of market concentration is stronger in low-concentration markets, which contribute a disproportionate number of visits.[8] This heterogeneous treatment effect lacks an economic interpretation because the HHI is not a cardinal index.

The rest of the table shows that leading confounders do not explain the result. Population density is a possible confounding factor because it is correlated with both market concentration and disease transmission. However Column 3 shows that the effect of market concentration on antibiotic use is insensitive to controlling for population density. The age and health status of patients may confound estimates because these factors influence the demand for outpatient care and the demand for antibiotics. Column 4 shows that the effect of market concentration declines only slightly if we control for the age distribution of patients and age specific mortality rates. The preceding specifications are identified in part through cross-sectional variation. Column 5 also controls for township fixed effects, which absorb arbitrary time-constant market characteristics. This specification is identified through the correlation between trend deviations in the HHI and antibiotic use, rather than cross-sectional variation. The HHI coefficient estimate is very similar in this specification.

The HHI is a function of the number of firms and the level of size homogeneity among firms. In Table III, we examine the contributions of these elements by regressing antibiotic use on the log number of firms and the intra-township standard deviation in firm size. These regressions, which include demographic and health controls, are analogous to Columns 4 and 5 of Table II. Columns 1 and 2 show that antibiotic use is strongly

[8] While Column 2 and the visit level estimates in Section IV(ii) are nationally representative, they do not address the thought experiment in which the HHI varies but the volume of care remains constant. The HHI coefficient from a market level (or market weighted) regression provides the effect of moving from one point in the HHI distribution to another.

correlated with the number of firms in specifications with and without township fixed effects. Columns 3 and 4 show that the antibiotic use declines as firms become more heterogeneous. These results illustrate intuitively why the HHI is correlated with antibiotic use.

IV(ii). *Visit-Level Analysis*

The preceding market level analysis may mask individual-level heterogeneity that confounds the effect of competition on antibiotic use. This subsection uses the panel of visits from 200,000 nationally representative patients to estimate the relationship between the HHI and per-visit antibiotic use. In the following specification, each observation is an outpatient visit for patient i with physician j in township k and year × quarter t.

$$a_{ijkt} = \beta_0 + \beta_1 H_{kt} + X_{kt} + \delta_t + \varepsilon_{ijkt} \quad (2)$$

The dependent variable, a_{ijkt}, indicates that the patient received at least one antibiotic. We cluster standard errors by township, which allows for an arbitrary correlation between observations within a township.

Visit level data allow us to test the robustness of the correlation between market concentration and antibiotic use while controlling for restrictive fixed effects. Patients and doctors may be heterogeneous in their attitudes toward antibiotics. Patient × time and physician × time fixed effects control for arbitrary, time-varying sources of patient and physician heterogeneity. Patients may also arrive with heterogeneous levels of illness. Diagnosis × time fixed effects address patient health heterogeneity.

Fixed effects specifications rely on the subset of observations for which there is intra-group variation. This aspect does not undermine the internal validity of the fixed effects estimates but may affect the comparison to non-fixed effect estimates. Within a quarter, 24 per cent of patients, 3 per cent of physicians and 76 per cent of diagnoses appear in multiple townships. Appendix Table I compares patients who visit one township and many townships within a quarter. Multi-township patients have greater health care utilization but similar demographic and antibiotic use profiles to single-township patients. Appendix Table II compares physicians who practice in one township and multiple townships within a quarter. Multi-township doctors see more patients but prescribe antibiotics at a similar rate to single-township doctors.

Table IV reports the HHI coefficient from visit level regressions that exclude and include market demographic and health controls. Column 1, which only controls for time fixed effects, yields the same estimate as the volume weighted regression in Column 2 of Table II. In Column 2, estimates do not change if we control for patient × time fixed effects, which absorb any patient heterogeneity that varies by quarter. Column 3 controls for

TABLE IV
THE COEFFICIENT ON HHI IN VISIT-LEVEL REGRESSIONS

	Antibiotics given			
Dependent variable:	(1)	(2)	(3)	(4)
Regressions without controls	–0.16***	–0.15***	–0.070***	–0.028***
	(0.014)	(0.013)	(0.015)	(0.0074)
Regressions with controls	–0.16***	–0.16***	–0.072***	–0.024***
	(0.012)	(0.013)	(0.017)	(0.0060)
Fixed effects:	Time	Pat × time	Doc × time	Diag. × time
Observations (millions)	21.5	21.5	21.5	14.2

Notes: Standard errors appear in parentheses. Standard errors are clustered by township. Regressions in the second row control for market demographic and health variables, as described in the text. Column 4 uses data from 2000–2005, when diagnosis data are available. *$p < 0.1$, **$p < 0.05$, ***$p < 0.01$.

physician × time fixed effects. These estimates are 66 per cent smaller than the Column 1 estimates but remain statistically significant. These estimates may differ because multi-township physicians are a selected sample or because a portion of the treatment effect of market concentration works through the location choices of physicians. The continued significance of the estimate suggests that these factors are not solely responsible for the correlation between the HHI and antibiotic use. Finally, Column 4 controls for diagnosis × time fixed effects. These regressions use data from 2000–2005 because diagnosis data only become available in 2000. The result is highly attenuated but remains statistically significant. Because some physicians choose diagnoses that support their intention to prescribe antibiotics, conditioning on the diagnosis limits the available variation in the data.

IV(iii). *Patient Retention*

This subsection examines the correlation between antibiotic use and patient retention. Competition may increase antibiotic use because providers fear that withholding antibiotics encourages patients to go elsewhere (Chen *et al*. [2006]). A robust, positive relationship between antibiotic use and patient retention suggests a mechanism through which competition encourages antibiotic use. This relationship should be particularly strong for physicians who treat many respiratory patients since many of these patients expect antibiotics. However, a regression of patient retention on antibiotic use is difficult to interpret because several other factors may cause these variables to be correlated.[9]

Visit level regressions of patient retention on antibiotic use allow us to address these confounding factors using fixed effects. In the specification

[9] A patient's loyalty to a physician may be correlated with the patient's demand for antibiotics. Physicians who offer antibiotics may also take other steps to retain patients. People may avoid changing doctors during an illness, when they also require antibiotics.

below, we regress an indicator that the patient returns to the same doctor during visit $l+1$ on an indicator that the patient received an antibiotic during visit l.

$$s_{ijklt} = \beta_0 + \beta_1 a_{ijklt} + X_{kt} + \delta_t + \varepsilon_{ijklt} \tag{3}$$

In this expression, a_{ijklt} indicates that the patient received an antibiotic during visit l. We construct two versions of the patient retention outcome, s_{ijklt}. The first version indicates whether the patient returns to the same physician she saw for visit l during visit $l+1$. The second version indicates whether the patient returns to the physician she saw for visit l during any of visits $l+1$ to $l+5$. The second construction measures more reliably whether the patient has abandoned the physician. Thirty-nine per cent of patients see the same doctor on the subsequent visit and 62 per cent see the same doctor within five subsequent visits. X_{kt} includes the market demographic and health controls used previously.

The incentive to retain patients with antibiotics may be particularly strong for doctors who specialize in respiratory infections. We categorize doctors by the frequency of upper respiratory infection diagnosis. One specification below distinguishes between the effect of a_{ijklt} for respiratory doctors (RD's) and non-respiratory doctors (ND's). We define respiratory doctors as doctors for whom at least 10 per cent of patients have upper respiratory infections, which is the 75th percentile of the distribution.[10]

Patient retention estimates appear in Table V. Column 1 shows a positive and significant correlation between antibiotic use and patient retention. Patients who receive an antibiotic are 4.3 percentage points more likely to return to the same doctor for their next visit and 2.0 percentage points more likely to return to the same doctor for any of the five subsequent visits. Column 2 shows a differentially large effect for respiratory doctors: antibiotic prescription increases the probability of a return visit by 14 percentage points for respiratory doctors in Panel A. The correlation is negative for non-respiratory doctors. The bulk of inappropriate antibiotic use occurs among respiratory conditions. Non-respiratory patients who receive antibiotics may be sicker and more subject to referrals. Column 3 shows that demographic and health controls do not effect these estimates. Columns 4 and 5 control for patient $\times$ time and physician $\times$ time fixed effects. These fixed effects do not attenuate the correlation between antibiotic use and patient retention, suggesting that patient and doctor heterogeneity do not lead to this correlation spuriously. Column 6 controls for

[10] Results do not depend on the specific cut point. We obtain a similar result by interacting a_{ijklt} with a continuous measure of the physician's respiratory percentage.

TABLE V
ANTIBIOTIC USE AND PATIENT RETENTION

	Patient Retention					
Dependent variable:	(1)	(2)	(3)	(4)	(5)	(6)
Panel A: One-Visit Horizon						
Antibiotics given	0.043***		0.043***	0.041***	0.041***	0.025***
	(0.0020)		(0.0020)	(0.0024)	(0.0024)	(0.0020)
Antibiotics given × RD		0.144***				
		(0.0037)				
Antibiotics given × ND		–0.021***				
		(0.0027)				
Panel B: Five-Visit Horizon						
Antibiotics given	0.020***		0.021***	0.039***	0.025***	0.015***
	(0.0017)		(0.0017)	(0.0020)	(0.0019)	(0.0015)
Antibiotics given × RD		0.092***				
		(0.0026)				
Antibiotics given × ND		–0.021***				
		(0.0019)				
Market demo and health controls	—	—	Yes	Yes	Yes	Yes
Fixed effects	Time	Time	Time	Pat × time	Doc × time	Diag × time
Observations (millions)	21.3	21.3	21.3	21.3	21.3	14.1

Notes: Standard errors appear in parentheses. Standard errors are clustered by township. Panel A examines whether the patient returns to the same doctor for his or her subsequent visit. Panel B examines whether the patient returns to the same doctor for any of his or her five subsequent visits. In Column 2, we define respiratory doctors (RD's) as doctors who diagnose upper respiratory infections in more than 10 per cent of visits and non-respiratory doctors (ND's) as all others. Column 6 uses data from 2000–2005, when diagnosis data are available. *$p < 0.1$, **$p < 0.05$, ***$p < 0.01$

diagnosis × time fixed effects. The correlation is attenuated but remains highly significant, which minimizes the concern that patient health heterogeneity leads to this correlation.

IV(iv). *The Policy Environment*

In this subsection, we consider how the policy environment mediates the effect of competition on antibiotic use. As we describe in Section II, providers have an incentive to attract patients through the quality dimension with the greatest marginal impact on profit. The February, 2001, reform in Taiwan increased the cost for physicians of prescribing antibiotics to patients with respiratory infections. This policy dramatically reduced antibiotic use, as Figure 1 illustrates. In theory, the reform should cause physicians to rely less on antibiotics to attract patients and reduce the correlation between competition and antibiotic use.

To estimate the impact of the policy environment, we modify equations (2) and (3) by interacting the explanatory variable with pre-reform and post-reform dummies. Regulators implemented the reform in a uniform fashion, so all policy variation is temporal. For each specification, we

Table VI
The Impact of Regulation

	Antibiotics given		Patient retention	
Dependent variable:	(1)	(2)	(3)	(4)
HHI × light regulation	–0.20***	–0.21***		
	(0.020)	(0.019)		
HHI × heavy regulation	–0.11***	–0.12***		
	(0.012)	(0.0098)		
ABX given previously × light regulation			0.048***	0.048***
			(0.002)	(0.002)
ABX given previously × heavy regulation			0.035***	0.036***
			(0.002)	(0.002)
P-value (coefficients are equivalent)	0.00	0.00	0.00	0.00
Demographic and health controls	—	Yes	—	Yes
Observations (millions)	21.5	21.5	21.3	21.3
R^2	0.028	0.028	0.005	0.006

Notes: Standard errors appear in parentheses. Standard errors are clustered by township. 'Light Regulation' refers to the period before the first quarter of 2001. 'Heavy regulation' refers to the period afterward. $*p < 0.1$, $**p < 0.05$, $***p < 0.01$.

report results that exclude and include demographic and health controls. We also report the p value from the test for the equivalence of the pre-reform and post-reform coefficients.

Estimates of the impact of the policy environment appear in Table VI. In Columns 1 and 2, the pre-reform coefficient on the HHI is 75–82 per cent larger than the post-reform coefficient, regardless of demographic and health controls. In Columns 3 and 4, the correlation between antibiotic use and patient retention is 33–37 per cent larger in the pre-reform period. We obtain similar results, which are available from the authors, using more restrictive fixed effects. These findings suggest that strict regulation made it less profitable for physicians to attract patients by prescribing antibiotics liberally. The continued significance of the HHI after the policy reform indicates that the policy did not completely eliminate competition as a determinant of antibiotic use.[11]

To analyze these patterns further, we interact the explanatory variables in equations (2) and (3) with a full set of time dummies. Figures 3 and 4 plot these coefficients and confidence intervals. The figures include two vertical bars, which connote the beginning of the reform debate and the implementation of the reform. The figures confirm that pre/post differences in Table VI coincide with the discussion and implementation of the policy change. The effect of competition on prescription peaks immediately before the proposal of tighter regulation in the second quarter of 2000. The policy discussion may have influenced antibiotic use by changing social norms

[11] The level of antibiotic use is lower under strict regulation, which may mechanically reduce the coefficient estimates during this period. However the results are robust if we examine elasticities rather than coefficients.

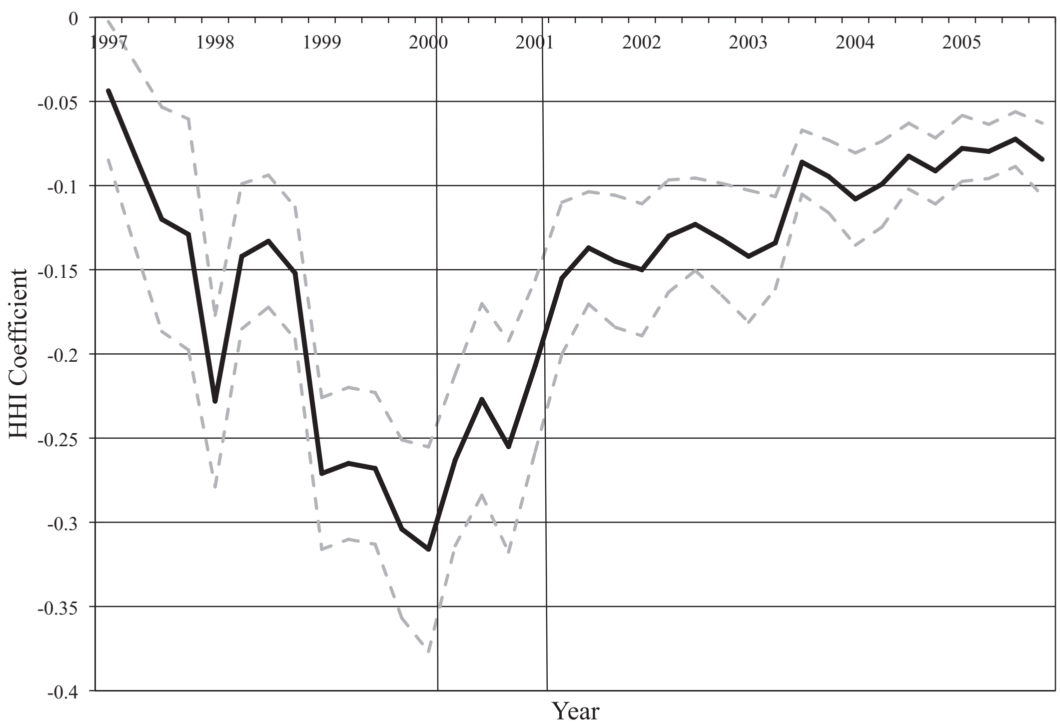

Figure 3
The Effect of Market Concentration on Antibiotic Use, 1997–2005

among physicians. Doctors may also have feared that regulators were monitoring their antibiotic use. A juxtaposition of these figures with Figure 1 shows that these series track closely with the level of antibiotic use. This similarity suggests that competitive prescription contributed to the high rates of antibiotic use prior to the reform.

V. CONCLUSION: THE IMPACT ON DRUG RESISTANCE?

In this paper, we show a robust and statistically significant correlation between market concentration and antibiotic use. We show that population density, the age distribution of patients, and age-specific mortality rates do not cause this pattern spuriously. In visit-level regressions, we show that estimates are robust under restrictive patient, physician and diagnosis fixed effects, which control for arbitrary sources of heterogeneity from these sources. The correlation between antibiotic use and patient retention suggests a mechanism behind this pattern.

We find that the effect of competition on quality depends upon the policy environment. A novel reform to strictly regulate antibiotic use reduces but does not eliminate the correlation between competition and prescription. This finding suggests that competition through antibiotic use may exist in other settings where incentives to prescribe antibiotics are less stark. For instance, more research is needed on the market determinants of antibiotic use in settings without fee-for-service health care.

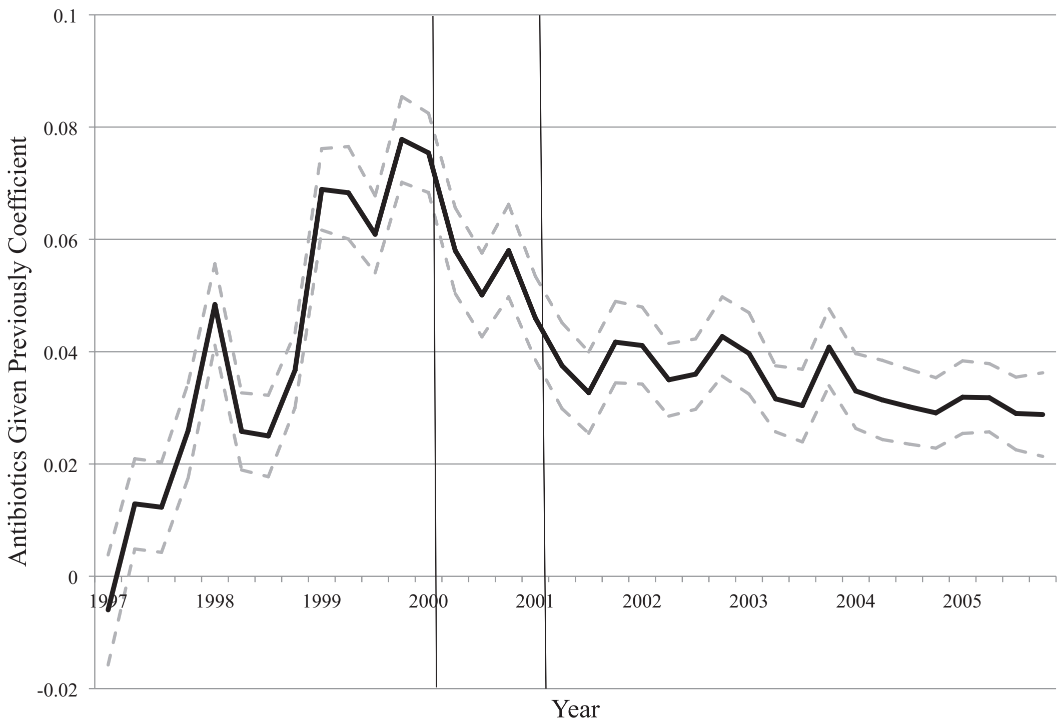

Figure 4
The Effect of Antibiotic Use on Patient Retention, 1997–2005

Unlike other forms of health care quality, antibiotic use incorporates the externality of antibiotic resistance. It is difficult to estimate the effect of health care competition on antibiotic resistance because the link between antibiotic use and resistance is biologically complex and features an uncertain lag. Another challenge is that exogenous variation in sustained antibiotic use is difficult to find. Existing studies, which show a positive cross-sectional correlation between antibiotic use and antibiotic resistance (Bronzwaer *et al*. [2002], Seppala *et al*. [1997]), do not address these challenges.

We obtain a rough idea of the effect of competition on antibiotic resistance by estimating the relationship between drug age and antibiotic resistance. Figure 5 plots the age and resistance rate for 24 drugs in the Taiwan Surveillance of Antibiotic Resistance (TSAR). We estimate a logit model, which generates a sigmoidal growth path that is consistent with epidemiological models of drug resistance (Austin *et al*. [1997], Stewart *et al*. [1998]). In the figure, the solid line shows the predicted growth path of antibiotic resistance under several strong assumptions.[12] To estimate the role of competition, we consider the impact of a move from the 75th percentile to the 25th percentile of the HHI, which increases antibiotic use by 6.7 per cent in Section IV(i). Under an assumption of a unitary elasticity of antibiotic

[12] For this exercise, we assume that resistance evolves in a homogeneous way across drugs. We also ignore physician substitution toward antibiotics with low-resistance.

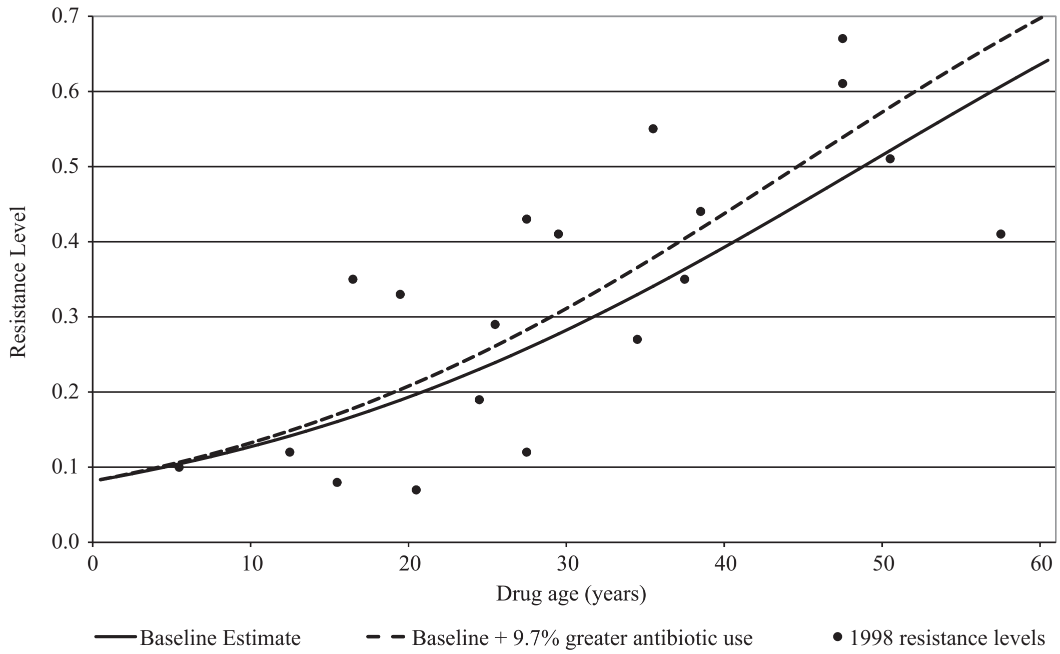

Figure 5
Drug Age and Antibiotic Resistance

resistance with respect to antibiotic use, this change shifts the antibiotic resistance growth path to the left, as the dashed line indicates in the figure. The difference between these growth paths is significant from a public health standpoint. For instance, after 30 years, resistance is around five percentage points higher because of elevated antibiotic use.

APPENDIX

Appendix Table I
Patients Who Visit Multiple Townships

Townships per quarter:	One (1)	Multiple (2)
Visits per quarter	3.34	6.94
Age < 10	0.15	0.15
Age 10–59	0.72	0.66
Age ≥ 60	0.12	0.18
Male	0.49	0.42
Patient receives a drug	0.70	0.70
Number of drugs if > 0	3.85	3.78
Patient receives an antibiotic	0.20	0.19
Number of antibiotics if > 0	1.10	1.12
Sample size (millions)	*2.8*	*1.7*

Notes: The table is based on patient × time observations and excludes patients with zero visits. All differences are statistically significant.

APPENDIX TABLE II
PHYSICIANS WHO PRACTICE IN MULTIPLE TOWNSHIPS

	One	Multiple
Townships per quarter:	(1)	(2)
Visits per day	24.3	27.9
Age	43.1	42.5
Male	0.88	0.88
Patient receives a drug	0.57	0.69
Number of drugs if > 0	3.53	3.58
Patient receives an antibiotic	0.14	0.13
Number of antibiotics if > 0	1.11	1.12
Sample size	*1,084,085*	*29,641*

Notes: The table is based on physician × time observations. All differences are statistically significant.

APPENDIX TABLE III
VISIT-LEVEL REGRESSIONS WITH COUNTY MARKETS

	Antibiotics given			
Dependent variable:	(1)	(2)	(3)	(4)
Regressions without controls	–0.43	–1.13**	–0.93***	–0.27
	(0.35)	(0.44)	(0.28)	(0.24)
Regressions with controls	–0.27	–0.77**	–0.85**	–0.067
	(0.23)	(0.30)	(0.34)	(0.10)
Fixed effects:	Time	Pat × time	Doc × time	Diag × time
Observations (millions)	21.5	21.5	21.5	14.15

Notes: Standard errors appear in parentheses. Standard errors are clustered by county. Regressions in the second row control for market demographic and health variables, as described in the text. Column 4 uses data from 2000–2005, when diagnosis data are available. *$p < 0.1$, **$p < 0.05$, ***$p < 0.01$.

APPENDIX TABLE IV
THE IMPACT OF REGULATION (ELASTICITIES)

	Antibiotics given		Patient retention	
Dependent variable:	(1)	(2)	(3)	(4)
HHI × light regulation	–0.047***	–0.048***		
	(0.0048)	(0.0045)		
HHI × heavy regulation	–0.029***	–0.029***		
	(0.0029)	(0.0024)		
ABX given previously × light regulation			0.014***	0.014***
			(0.0007)	(0.0007)
ABX given previously × heavy regulation			0.0067***	0.0068***
			(0.0004)	(0.0004)
P value (coefficients are equivalent)	0.00	0.00	0.00	0.00
Demo and health controls	—	Yes	—	Yes

Notes: The table reports elasticities. Standard errors appear in parentheses. Standard errors are clustered by township. 'Light Regulation' refers to the period before the first quarter of 2001. 'Heavy regulation' refers to the period afterward. *$p < 0.1$, **$p < 0.05$, ***$p < 0.01$.

REFERENCES

American Society for Microbiology, 1995, 'Report of the ASM Task Force on Antibiotic Resistance,' *Antimicrobial Agents and Chemotherapy*, 39, pp. S1–S23.

Austin, D. J.; Kakehashi, M. and Anderson, R. M., 1997, 'The Transition Dynamics of Antibiotic Resistant Bacteria: The Relationship between Resistance in Commensal Organisms and Antibiotic Consumption,' *Proceedings of the Royal Society of London (Biological Sciences)*, 264, pp. 1629–1638.

Bauchner, H.; Pelton, S. I. and Klein, J. O., 1999, 'Parents, Physicians and Antibiotic Use,' *Pediatrics*, 103(2), pp. 395–401.

Brody, H., 2005, 'Patient Ethics and Evidence-Based Medicine: The Good Healthcare Citizen,' *Cambridge Quarterly of Healthcare Ethics*, 14, pp. 141–146.

Bronzwaer, S. L.; Cars, O.; Buchholz, U.; Molstad, S.; Goettsch, W.; Veldhuijzen, I. K.; Sprenger, M. J.; Degener, J. E. and the European Antimicrobial Resistance Surveillance System, 2002, 'A European Study on the Relationship between Antimicrobial Use and Antimicrobial Resistance,' *Emerging Infectious Diseases*, 8(3), pp. 278–282.

Butler, C. C.; Rollnick, S.; Pill, R.; Maggs-Rappaport, F. and Slott, N., 1998, 'Understanding the Culture of Prescribing: Qualitative Study of General Practitioners' and Patients' Perceptions of Antibiotics for Sore Throats,' *BMJ*, 317(7159), pp. 637–642.

Chen, T.-J.; Chou, L.-F. and Hwang, S.-J., 2006, 'Patterns of Ambulatory Care Utilization in Taiwan,' *BMC Health Services Research*, 6(54) (online only).

Cheng, S.-H. and Chiang, T.-L., 1997, 'The Effect of Universal Health Insurance on Health Care Utilization in Taiwan: Results from a Natural Experiment,' *Journal of the American Medical Association*, 278(2), pp. 89–93.

Chiang, T.-L., 1997, 'Taiwan's 1995 Health Care Reform,' *Health Policy*, 39(3), pp. 225–239.

Chou, Y. J.; Yip, W. C.; Lee, C. H.; Huang, N.; Sun, Y. P. and Chang, H. J., 2003, 'Impact of Separating Drug Prescribing and Dispensing on Provider Behaviour: Taiwan's Experience,' *Health Policy and Planning*, 18(3), pp. 316–329.

Chu, H.-L.; Liu, S.-Z.; Romeis, J. C. and Yaung, C.-L., 2003, 'The Initial Effects of Physician Compensation Programs in Taiwan Hospitals: Implications for Staff Model HMO's,' *Health Care Management Science*, 6, pp. 17–26.

Currie, J.; Lin, W. and Zhang, W., 2011, 'Patient Knowledge and Antibiotic Abuse: Evidence from an Audit Study in China,' *Journal of Health Economics*, 30, pp. 933–949.

Docteur, E. and Oxley, H., 2003, 'Health-Care Systems: Lessons from the Reform Experience,' OECD Health working paper 9 (*OECDilibrary.org*).

Dorfman, A. and Steiner, P. O., 1954, 'Optimal Advertising and Optimal Quality,' *American Economic Review*, 44(5), pp. 826–836.

Dranove, D. and Satterthwaite, M. A., 2000, 'The Industrial Organization of Health Care Markets,' in Culyer, A. J. and Newhouse, J. P. (eds.), *Handbook of Health Economics*, Volume 1, pp. 1093–1139 (North Holland Press, Amsterdam, The Netherlands).

Fitch, R., 2002, 'Bacterial Resistance: The Clinical Challenge,' *Clinical Microbiology and Infection*, 8, pp. 21–32.

Herrmann, M. and Laxminarayan, R., 2010, 'Antibiotic Effectiveness: New Challenges in Natural Resource Management,' *Annual Review of Resource Economics*, 2, pp. 125–138.

Ho, M., 2005, *Several Worlds: Reminiscences and Reflections of a Chinese-American Physician* (World Scientific Publishing Company, Singapore).

Kessler, D. and McClellan, M., 2000, 'Is Hospital Competition Socially Wasteful?' *Quarterly Journal of Economics*, 115(2), pp. 488–506.

Klevens, R. M.; Morrison, M. A.; Nadle, J.; Petit, S.; Gershman, K.; Ray, S.; Harrison, L. H.; Lynfield, R.; Dumyati, G.; Townes, J. M.; Craig, A. S.; Zell, E. R.; Fosheim, G. E.; McDougal, L. K.; Carey, R. B.; Fridkin, S. K. and ABCs MSRA Investigators, 2007, 'Invasive Methicillin-Resistant *staphylococcus aureus* Infections in the United States,' *Journal of the American Medical Association*, 298(15), pp. 1763–1771.

Lauderdale, T.-L.; McDonald, L. C.; Shiau, Y.-R.; Chen, P.-C.; Wang, H.-Y.; Lai, J.-F.; Ho, M. and TSAR Participating Hospitals, 2004, 'The Status of Antimicrobial Resistance in Taiwan among Gram-Negative Pathogens: The Taiwan Surveillance of Antimicrobial Resistance (TSAR) Program, 2000,' *Diagnostic Microbiology and Infectious Disease*, 48, pp. 211–219.

Lautenbach, E.; Patel, J. B.; Bilker, W. B.; Edelstein, P. H. and Fishman, N. O., 2001, 'Extended-Spectrum β-Lactamase-Producing *Escherichia Coli* and *Klebsiella Pneumoniae*: Risk Factors for Infection and Impact of Resistance on Outcomes,' *Clinical Infectious Diseases*, 32(8), pp. 1162–1171.

Laxminarayan, R. and Brown, G. M., 2001, 'Economics of Antibiotic Resistance: A Theory of Optimal Use,' *Journal of Environmental Economics and Management*, 42(2), pp. 183–206.

McDonald, L. C.; Lauderdale, T.-L.; Shiau, Y.-R.; Chen, P.-C.; Lai, J.-F.; Wang, H.-Y.; Ho, M. and TSAR Participating Hospitals, 2004, 'The Status of Antimicrobial Resistance in Taiwan among Gram-Positive Pathogens: The Taiwan Surveillance of Antibiotic Resistance (TSAR) Programme, 2000,' *International Journal of Antimicrobial Agents*, 23, pp. 362–370.

McGeer, A. and Low, D., 2003, 'Is Resistance Futile?' *Nature Medicine*, 9(4), pp. 390–392.

Mechoulan, S., 2007, 'Market Structure and Communicable Diseases,' *Canadian Journal of Economics*, 40(2), pp. 468–492.

Propper, C.; Burgess, S. and Green, K., 2004, 'Does Competition among Hospitals Improve the Quality of Care? Hospital Death Rates and the NHS Internal Market,' *Journal of Public Economics*, 88, pp. 1247–1272.

Reese, R. E. and Betts, R. F. (eds.), 1996, *A Practical Approach to Infectious Diseases* (Little, Brown and Company, New York, New York, U.S.A.).

Robinson, J. C. and Luft, H. S., 1985, 'The Impact of Hospital Market Structure on Patient Volume, Average Length of Stay and the Cost of Care,' *Journal of Health Economics*, 4(4), pp. 333–356.

Seppala, H.; Klaukka, T.; Vuopio-Varkila, J.; Muotiala, A.; Helenius, H.; Lager, K. and Huovinen, P., 1997, 'The Effect of Changes in the Consumption of Macrolide Antibiotics on Erythromycin Resistance in Group a Streptococci in Finland,' *New England Journal of Medicine*, 337(7), pp. 441–446.

Shaked, A. and Sutton, J., 1982, 'Relaxing Price Competition through Product Differentiation,' *Review of Economic Studies*, 49(1), pp. 3–13.

Snow, V.; Mottur-Pilson, C. and Hickner, J., 2001a, 'Principles of Appropriate Antibiotic Use for Acute Sinusitis in Adults,' *Annals of Internal Medicine*, 134, pp. 495–497.

Snow, V.; Mottur-Pilson, C. and Gonzales, R., 2001b, 'Principles of Appropriate Antibiotic Use for Treatment of Nonspecific Upper Respiratory Tract Infections in Adults,' *Annals of Internal Medicine*, 134, pp. 487–489.

Snow, V.; Mottur-Pilson, C.; Cooper, R. and Hoffman, J., 2001c, 'Principles of Appropriate Antibiotic Use for Acute Pharyngitis in Adults,' *Annals of Internal Medicine*, 134, pp. 506–508.

Spellberg, B.; Powers, J. H.; Brass, E. P.; Miller, L. G. and Edwards, J. E., 2004, 'Trends in Antimicrobial Drug Development: Implications for the Future,' *Clinical Infectious Diseases*, 38, pp. 1279–1286.

Spence, A. M., 1975, 'Monopoly, Quality and Regulation,' *Bell Journal of Economics*, 6(2), pp. 417–429.

Stewart, F. M.; Antia, R.; Levin, B. R.; Lipsitch, M. and Mittler, J. E., 1998, 'The Population Genetics of Antibiotic Resistance II: Analytic Theory for Sustained Populations of Bacteria in a Community of Hosts,' *Theoretical Population Biology*, 53, pp. 152–165.