Antibiotic Use in Cold and Flu Season and Prescribing Quality

A Retrospective Cohort Study

Marcella Alsan, MD, MPH, PhD,† Nancy E. Morden, MD, MPH,‡§ Joshua D. Gottlieb, PhD,†‖ Weiping Zhou, MS,‡ and Jonathan Skinner, PhD†‡§¶*

Background: Excessive antibiotic use in cold and flu season is costly and contributes to antibiotic resistance. The study objective was to develop an index of excessive antibiotic use in cold and flu season and determine its correlation with other indicators of prescribing quality.

Methods and Findings: We included Medicare beneficiaries in the 40% random sample denominator file continuously enrolled in fee-for-service benefits for 2010 or 2011 (7,961,201 person-years) and extracted data on prescription fills for oral antibiotics that treat respiratory pathogens. We collapsed the data to the state level so they could be merged with monthly flu activity data from the Centers for Disease Control and Prevention. Linear regression, adjusted for state-specific mean antibiotic use and demographic characteristics, was used to estimate how antibiotic prescribing responded to state-specific flu activity. Flu-activity associated antibiotic use varied substantially across states—lowest in Vermont and Connecticut, highest in Mississippi and Florida. There was a robust positive correlation between flu-activity associated prescribing and use of medications that often cause adverse events in the elderly (0.755; $P < 0.001$), whereas there was a strong negative correlation with beta-blocker use after a myocardial infarction (-0.413; $P = 0.003$).

Conclusions: Adjusted flu-activity associated antibiotic use was positively correlated with prescribing high-risk medications to the elderly and negatively correlated with beta-blocker use after myocardial infarction. These findings suggest that excessive antibiotic use reflects low-quality prescribing. They imply that practice and policy solutions should go beyond narrow, antibiotic specific, approaches to encourage evidence-based prescribing for the elderly Medicare population.

Key Words: antibiotic use, antibiotic resistance, influenza, evidence-based prescribing

(*Med Care* 2015;53: 1066–1071)

An estimated 2 million people are infected with drug-resistant organisms annually in the United States, resulting in 23,000 deaths and over $20 billion in excess costs.[1,2] The use of antibiotics for viral-associated upper respiratory infections contributes to the spread of antibiotic resistance.[3] Although seasonal and influenza-related trends in antibiotic prescribing have been described,[4–8] few studies to date assess excessive antibiotic use at the population level.[5,9–11] Those that do use methods vulnerable to the critique that risk-adjusted geographic variation does not necessarily discern appropriate from inappropriate use.[12] Furthermore, excessive antibiotic use could reflect a tendency by providers to prescribe all types of medications—including those that are clinically indicated—and therefore would not be synonymous with poor prescribing quality.

To better understand patterns of antibiotic overuse and whether such patterns reflect prescribing quality, we developed a novel measure that isolates antibiotic prescribing in response to local influenza activity. We focus on the elderly as nationally representative data on antibiotic use are readily available and because polypharmacy and drug interactions are particularly important for this population. We extracted data on prescription fills for oral antibiotics commonly used to treat respiratory pathogens and collapsed the data to the state level so that they could be merged with monthly flu activity data from the Centers for Disease Control and Prevention (CDC). We model antibiotic prescribing as depending on the calendar month (thus capturing seasonal patterns of antibiotic use), the state (reflecting permanent differences in state-level antibiotic prescriptions), monthly state-level CDC influenza activity, and state-level demographics. Our index of state-level excessive antibiotic

From the *Center for Health Policy and the Center for Primary Care and Outcomes Research, Stanford University, Stanford, CA; †National Bureau of Economic Research, Cambridge, MA; ‡Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH; §Department of Community and Family Medicine, Geisel School of Medicine at Dartmouth, Hanover, NH; ‖Vancouver School of Economics, University of British Columbia, Vancouver, BC, Canada; and ¶Department of Economics, Dartmouth College, Hanover, NH.

Supported by the National Institutes of Aging (P01-AG019783). Additional funding from the National Institutes of Health Common Fund (U01-AG046830).

J.S. is an investor in Dorsata Inc., a startup clinical pathway software company. The remaining authors declare no conflict of interest.

Reprints: Marcella Alsan, MD, MPH, PhD, Stanford University School of Medicine, 117 Encina Commons, Stanford, CA 94305. E-mail: malsan@stanford.edu.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website, www.lww-medicalcare.com.

ISSN: 0025-7079/15/5312-1066

prescribing is defined as the regression coefficient on the CDC influenza activity, which varies by state, times a common level of flu activity. In other words, if every state had an identical (moderate) flu outbreak, this index predicts by how much we would expect per-enrollee antibiotic use to rise in each state.

To determine whether excessive antibiotic use reflects low prescribing quality to the elderly more broadly, we correlate our index with 2 quality measures: prescribing frequency of medications that often cause adverse events in the elderly, and clinically indicated prescriptions such as beta-blocker use after a myocardial infarction (MI). If overuse of antibiotics is positively correlated with both of these indicators, this would imply that physicians in some places are simply prescribing more frequently. If, on the other hand, inappropriate use of 1 medication is correlated with failure to use a different medication when indicated, this would suggest that antibiotic overuse is symptomatic of low prescribing quality.

METHODS

Study Cohorts and Data Sources

We use Medicare Administrative data for a 40% random sample denominator file and corresponding inpatient, outpatient, and prescription claims records. We identified 9,335,698 person-years representing individuals over age 65 who were enrolled for at least a full calendar year. From this sample, we studied beneficiaries enrolled in fee-for-service Medicare plans to ensure full drug use and morbidity status ascertainment. To exclude those who might justifiably have unique antibiotic use patterns or medication fills not apparent in Part D claims, we removed 1,282,862 with a cancer diagnosis (other than nonmelanoma skin cancer patients); 79,294 enrolled in hospice and 12,341 with end-stage renal disease as the original eligibility for Medicare enrollment. Our final cohort therefore included 7,961,201 person-years.

Respiratory Antibiotic Data

The Medicare Prescription Drug Event data files include national drug codes, prescription fill date, and type of antibiotic filled. We defined antibiotics used for respiratory infections as cephalosporins, macrolides, tetracyclines, penicillins, and quinolones. We limited our analysis to oral antibiotics. We excluded sulfonamides, nitrofurantoin, fosfomycin, methenamine, and trimethoprim that are often used to treat urinary tract infections. We used residential ZIP codes to assign each beneficiary to a state. To calculate the number of respiratory antibiotics prescriptions filled by state and month over the 2-year period of the analysis, we summed the total number of respiratory antibiotic fills by month for each state. We counted the number of unique individuals receiving antibiotics and so did not count multiple prescriptions. This measure was used to construct the number of respiratory antibiotics per 100 Medicare Part D beneficiaries for the 2010–2011 period.

Influenza Activity Data

The US Outpatient Influenza-like Illness Program Surveillance Network (ILINet) coordinated by the CDC, and consisting of >2900 outpatient providers, measures influenza activity across US states. Each week, these providers report to the CDC the total number of patients and the number of those patients with ILI,[13] defined as a fever (temperature of 100°F or greater), cough, and/or sore throat without a known cause other than influenza. The CDC determines influenza activity by comparing the ILI prevalence in a given week with a region-specific baseline. This procedure yields 10 activity levels ranging from minimal (level 1–3), low (levels 4–5), moderate (levels 6–7), to high (levels 8–10) activity. An activity level of 1 corresponds to values that are below the mean and values of 2–10 correspond to activity levels above the mean. Further details of the CDC methodology can be found on their website.[13] We used the ILINet data to construct state-level monthly measures of influenza, which was the finest temporal level we could use without encountering problems of censorship for low frequency antibiotic cell values, and accounted for the nonlinearity of the activity levels scale by using its natural logarithm in the analysis.

High-risk and Beta-blocker Prescribing Data

The Dartmouth Atlas of Health Care provides measures of the proportion of the elderly Medicare population filling at least 1 prescription for a high-risk medication by state.[14] This measure is constructed with drug use rates from a 40% Medicare random sample for the year 2010. The numerator is the number of beneficiaries filling 1 or more prescriptions that have been classified as high risk for individuals over 65 years of age by the Healthcare Effectiveness Data and Information Set (HEDIS),[15,16] whereas the denominator is the number of eligible people in the sample. The HEDIS list includes prescription drugs that often result in adverse drug events that contribute to hospitalization, increased duration of illness, nursing home placement, falls, and fractures. A similar measure of effective prescription use is constructed for the proportion of the Medicare population appropriately receiving a beta-blocker within 6 months of an MI hospital admission.

Demographic Data From Medicare

We used Medicare data to calculate the percent of beneficiaries who are: minority (black or Hispanic), male, old (age 65–69 y), medium old (70–79 y), and very old (80 y or older), receiving a Part D benefits low-income subsidy, and have a diagnosis of chronic pulmonary disease or tobacco use. The pulmonary/tobacco category included individuals with ICD-9 diagnostic codes 415 (acute cor pulmonale), 416.8 (chronic pulmonary heart disease), 416.9 (chronic pulmonary heart disease, unspecified), 491 (chronic bronchitis), 492 (emphysema), 494 (bronchiectasis), 496 (chronic airway obstruction), 305.1 (tobacco use disorder), V15.82 (history of tobacco use), and 989.84 (tobacco use). These variables were used as time-varying, state-level controls in the analysis. This means that the regression model adjusts for systematic differences across states, and over time, in rates of chronic pulmonary disease or tobacco use.

Analysis

We constructed a longitudinal state by month dataset of respiratory antibiotic prescriptions and flu activity (approximately 24 observations per state for a total of 1188 observations; 12 observations were dropped due to missing flu observations). A linear regression on these data estimated how the number of respiratory antibiotic prescription fills per 100 Medicare Part D beneficiaries responded to changes in state-specific flu activity. In the regression, the sensitivity of antibiotic prescribing to changes in flu activity was allowed to vary across each state by interacting the flu variable with a state-specific indicator variable.[17] By also including indicator variables for each state and month, the regression explicitly controls for state-level average effects (ie, antibiotic use in Mississippi may be different from its use in Vermont because of higher underlying disease burdens) and for monthly average effects (all states may experience higher rates of bronchitis in January). In addition, we adjust for demographic factors also believed to influence prescribing behavior, such as patient age, chronic pulmonary disease, tobacco use, minority share, and the share of the beneficiary population receiving a Part D benefits low-income subsidy (to measure poverty in this population).

To calculate flu-activity associated respiratory antibiotic prescriptions, we take the product of the state-specific interaction coefficient and a constant moderate flu activity (levels 6–7). The state-specific response for New Hampshire could not be calculated as the flu activity data did not vary over the analysis period within the state. A negative coefficient suggests certain states are responding to the heightened flu activity by prescribing a substitute (such as an antiviral) or symptomatic relief, whereas a positive sign reflects increased antibiotic prescribing within a state in response to upward deviations in flu activity. The exact equations used to estimate the relationship between flu and antibiotic use, and to calculate the predicted values, are available in the technical Appendix (Supplemental Digital Content 1, http://links.lww.com/MLR/B43). Analyses were conducted using STATA version 13.0 (StataCorp, College Station, TX). Standard errors were clustered at the state level.

Ethical Approval

The analysis, which required the creation of deidentified aggregate Medicare Data, was approved by the Dartmouth Institutional Review Board (IRB). The Stanford University and University of British Colombia researchers, who only had access to the deidentified aggregate data, were exempt from IRB approval.

RESULTS

There is considerable heterogeneity in our measure of excessive antibiotic use across the United States. Mississippi and Florida had the greatest prescribing response to flu activity, with increases in antibiotic prescriptions per 100 Medicare Part D beneficiaries of 2.58 and 1.91, respectively (see Appendix Table 1, Supplemental Digital Content 1, http://links.lww.com/MLR/B43 for all values). Other states, particularly those in the Northeast, responded to heightened flu activity by decreasing their use of antibiotic prescriptions, perhaps reflecting greater patient and/or provider awareness of the likelihood of a viral versus bacterial etiology for respiratory tract symptoms. Figure 1 shows these results on a map of the predicted, adjusted flu-activity associated antibiotic use per 100 Medicare Part D beneficiaries. Red tones indicate heightened antibiotic prescribing responsiveness to flu activity and green tones indicate less responsiveness. The specific tones represent deciles of the adjusted flu-activity associated antibiotic use index.

Excessive antibiotic use seems to reflect poor prescribing quality. Figure 2 shows the relationship between the adjusted flu-activity associated respiratory antibiotic fills per 100 Medicare Part D beneficiaries and an independent measure of poor quality prescribing: the fraction of the eligible Medicare population receiving 1 or more high-risk nonantibiotic drugs. The correlation coefficient is positive and significant (0.755; $P<0.001$). Figure 3 shows that the adjusted flu-activity associated antibiotic use per 100 Medicare Part D beneficiaries correlates negatively with the fraction of the elderly Medicare population receiving beta-blockers within 6 months of an MI (correlation coefficient of -0.413; $P=0.003$). To ensure that these relationships are not driven by states with the most extreme antibiotic use index, we also measured these correlations excluding Vermont, Connecticut, Rhode Island, and Mississippi. This exclusion does not appreciably change the correlation between predicted, adjusted flu-activity associated antibiotic use per 100 Medicare beneficiaries and high-risk medications or effective beta-blocker use (Appendix Fig. 1, Supplemental Digital Content 1, http://links.lww.com/MLR/B43).

DISCUSSION

Our study makes 2 contributions. First, we develop a novel method of estimating excessive antibiotic use. We found wide geographic variation in this index measure across the United States. Our findings concur with those of Zhang and colleagues who demonstrated considerable variation in antibiotic use across regions of the United States, with highest use in the South. Our study differs from Zhang and colleagues by focusing on state rather than census region, and by using an independent CDC measure of monthly flu activity to exclusively capture variation in the responsiveness of antibiotic prescribing to viral etiologies.

Our second contribution is to correlate our index measure of excessive antibiotic use with prescribing for other medications. We find adjusted flu-activity associated antibiotic prescriptions tightly positively associated with distinct geographic practices of high-risk prescribing in the elderly and negatively associated with use of beta-blockers after an MI (high prescribing quality). These findings support the hypothesis that excessive antibiotic use is symptomatic of low-quality prescribing more broadly.

Our findings are subject to several limitations. First, the index we develop is at the state level. The same index could be developed at a more granular level of analysis if finer data on influenza were publicly available. Second, some geographic differences in antibiotic prescribing are warranted and may reflect changes in the incidence of bacterial pneumonia or

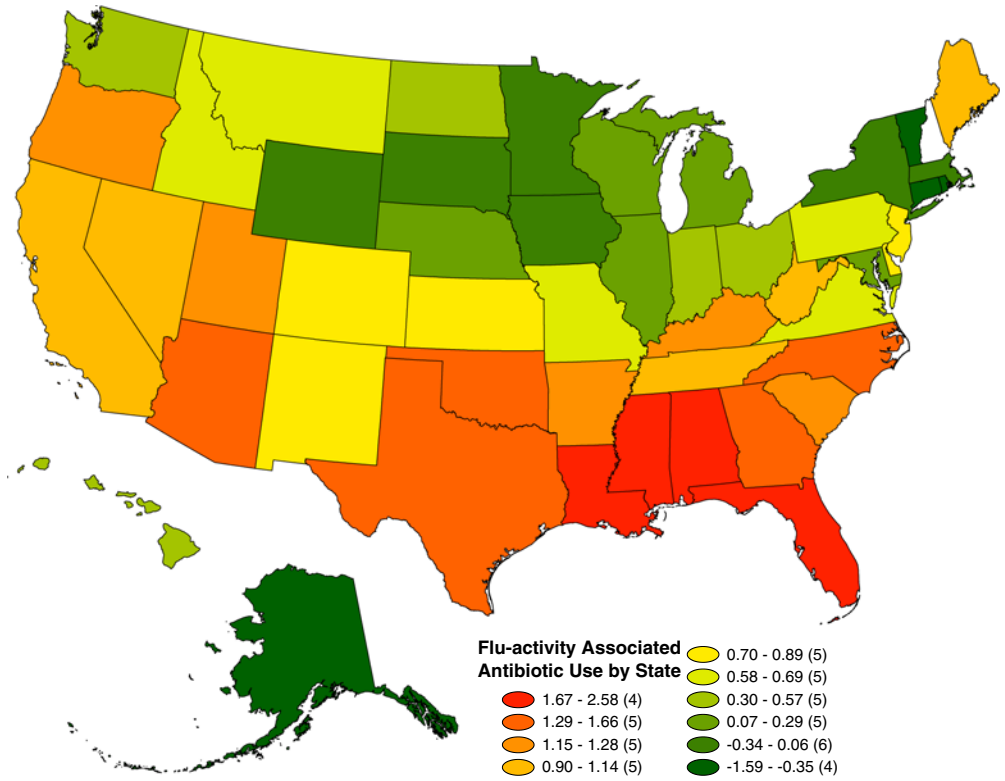

FIGURE 1. Geographic variation in adjusted flu-activity associated antibiotic use per 100 Medicare Part D beneficiaries. Deciles of predicted, adjusted flu-activity associated antibiotic use per 100 Medicare beneficiaries are represented with varying colors. Predicted values are obtained using linear regression that controls for mean antibiotic use by state (using state-fixed effects) and time-varying demographic characteristics including the percent of beneficiaries that are in certain age categories, percent on a low-income subsidy, percent male, percent minority, and percent with chronic pulmonary disease/tobacco use. The red tones indicate states with greater antibiotic prescribing responsiveness to flu activity and the green tones indicate states with less responsiveness. The value for each state is provided in the Appendix Table 1 (Supplemental Digital Content 1, http://links.lww.com/MLR/B43).

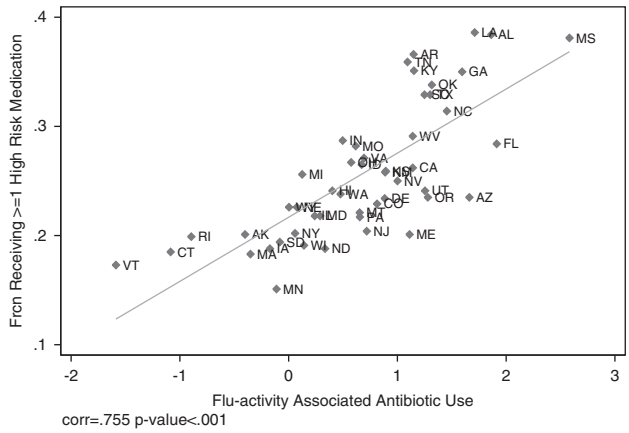

FIGURE 2. High-risk medications and flu-activity associated antibiotic use. The adjusted flu-activity associated antibiotic use index of respiratory antibiotic is positively correlated with an independent measure of inappropriate prescribing: the fraction of the eligible Medicare population receiving 1 or more high-risk drugs as defined by the HEDIS high-risk drug list.[14]

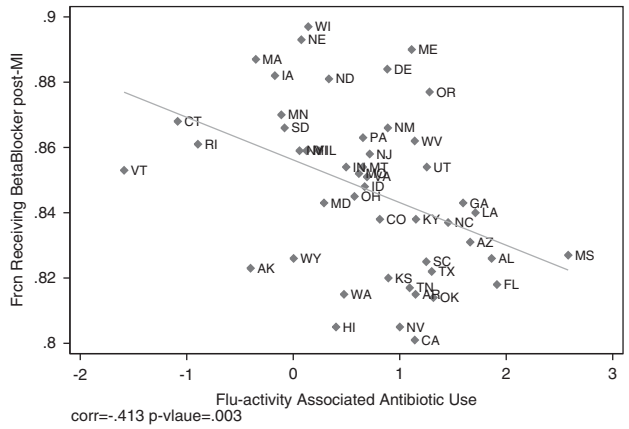

FIGURE 3. Beta-blocker and flu-activity associated responsive antibiotic use. The adjusted flu-activity associated antibiotic use index of respiratory antibiotic is negatively correlated with an independent measure of appropriate prescribing: the fraction of the eligible Medicare population receiving a beta-blocker within 6 months of a myocardial infarction.[14]

chronic obstructive pulmonary disease. However, our empirical strategy is designed specifically to measure only respiratory antibiotic fills associated with differences in flu activity within states controlling for demographic characteristics. An alternative approach to capturing pneumonia-based differences in prescribing would be to include physician billing codes for bacterial infections in office visits as an additional control in the analysis. We did not follow this approach because it raises a concern about potential reverse causation as physicians prescribing antibiotics may be more likely to code for bacterial infection. Using hospitalizations for pneumonia instead of outpatient visits is also problematic given secular changes in diagnostic coding.[18]

Third, part of the state-level variation in antibiotic overuse may be the consequence of patient demand.[19–21] Disentangling the extent to which geographic variation reflects patient demand versus provider supply side factors is an active area of research.[22–24] Although patient demand for inappropriate antibiotic prescriptions may require public education campaigns, ultimately the physician, as health care provider, must authorize the prescription. Fourth, beta-blocker and high-risk medication measures are based on a single year (2010) of the Part D data, whereas our study uses a 2-year (2010–2011) panel. Fifth, we acknowledge the possibility that some of the antibiotic use we attribute to flu patients could be used to treat other diseases such as urinary tract infections and soft tissue disease. For this bias to occur, however, the incidence of these other diseases would have to be strongly correlated with the month-to-month movements in influenza activity within states (and more strongly associated in Mississippi than in Minnesota). We are not aware of evidence pointing to such a correlation.

Finally, there may be concern about extrapolating these results to other populations. There were roughly 23 million fee-for-service Part D enrollees in 2013, and they were slightly sicker, older, and poorer than the elderly Medicare beneficiaries in general.[25] More worrisome is that physicians might follow different prescription patterns for managed care or under-65 populations, although evidence suggests that physician practice patterns are largely similar across patients with different types of insurance coverage.[26]

Antibiotic use associated with influenza-like illness serves as a valuable index of excessive antibiotic use. Overuse of antibiotics has prompted calls for new policies designed to address potential public health threats and excess costs this practice generates.[2,27–29] However, this study suggests monitoring and addressing antibiotic overuse should not be done in isolation but rather part of a broader agenda of improving safe, evidence-based prescribing to the elderly.[30–34]

REFERENCES

1. Centers for Disease Control and Prevention. CDC principles of appropriate antibiotic use. 2012. Available at: http://www.cdc.gov/getsmart/campaign-materials/info-sheets/adult-approp-summary.html. Accessed June 14, 2015..
2. Centers for Disease Control and Prevention. *World health day media fact sheet: antimicrobial resistance no action today no cure tomorrow*. 2011. Available at: http://www.cdc.gov/media/releases/2011/f0407_antimicrobialresistance.html. Accessed June 14, 2015.
3. Centers for Disease Control and Prevention. Cold and flu season: no reason for antibiotics. 2009. Available at: http://www.cdc.gov/getsmart/campaign-materials/press_kit/Cold-Flu_Season-508.pdf.Accessed June 14, 2015.
4. Suda KJ, Hicks LA, Roberts RM, et al. Trends and seasonal variation in outpatient antibiotic prescription rates in the United States, 2006 to 2010. *Antimicrob Agents Chemother*. 2014;58:2763–2766.
5. Zhang Y, Steinman MA, Kaplan CM. Geographic variation in outpatient antibiotic prescribing among older adults. *Arch Intern Med*. 2012;172:1465–1471.
6. Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. *Clin Infect Dis*. 2012;55:687–694.
7. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA*. 1997;278:901–904.
8. Ciesla G, Leader S, Stoddard J. Antibiotic prescribing rates in the US ambulatory care setting for patients diagnosed with influenza, 1997-2001. *Respir Med*. 2004;98:1093–1101.
9. Barnett ML, Linder JA. Antibiotic prescribing for adults with acute bronchitis in the United States, 1996-2010. *JAMA*. 2014;311:2020–2022.
10. Linder J, Bates D, Lee G, et al. Antibiotic treatment of children with sore throat. *J Am Med Assoc*. 2005;294:2315–2322.
11. Linder J, Stafford R. Antibiotic treatment of adults with sore throat by community primary care physicians. *J Am Med Assoc*. 2001;286:1181–1186.
12. McWilliams JM, Dalton JB, Landrum MB, et al. Geographic variation in cancer-related imaging: Veterans Affairs Health Care System Versus Medicare. *Ann Intern Med*. 2014;161:794–802. doi:10.7326/M14-0650.
13. Centers for Disease Control and Prevention. Overview of influenza surveillance in the United States|Seasonal Influenza (Flu)|CDC. 2014. Available at: http://www.cdc.gov/flu/weekly/overview.htm. Accessed October 14, 2014.
14. Dartmouth College. The Dartmouth Atlas. 2013. Available at: http://www.dartmouthatlas.org/. Accessed June 14, 2015.
15. NCQA. HEDIS 2014 Final NDC Lists. 2014. Available at: http://www.ncqa.org/HEDISQualityMeasurement/HEDISMeasures/HEDIS2014/HEDIS2014FinalNDCLists.aspx. Accessed June 14, 2015.
16. Munson JC, Morden NE, Goodman DC, et al. The Dartmouth Atlas of Medicare Prescription Drug Use. The Dartmouth Atlas Project; 2013. Available at http://www.dartmouthatlas.org/downloads/reports/Prescription_Drug_Atlas_101513.pdf. Accessed June 14, 2015.
17. US Census Bureau. Census Regions and Divisions of the United States. Available at: http://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf. Accessed June 14, 2015.
18. Lindenauer PK, Lagu T, Shieh MS, et al. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003-2009. *J Am Med Assoc*. 2012;307:1405–1413.
19. Macfarlane J, Holmes W, Macfarlane R, et al. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *BMJ*. 1997;315:1211–1214.
20. Cals JWL, Boumans D, Lardinois RJM, et al. Public beliefs on antibiotics and respiratory tract infections: an internet-based questionnaire study. *Br J Gen Pract*. 2007;57:942–947.
21. Coenen S, Michiels B, Renard D, et al. Antibiotic prescribing for acute cough: the effect of perceived patient demand. *Br J Gen Pract*. 2006;56:183–190.
22. Cutler D, Stern A, Skinner J, et al. Physician beliefs and patient preferences: a new look at regional variation in health care spending. NBER Working Paper No 19320. 2013.
23. Finkelstein A, Gentzkow M, Williams H. Sources of geographic variation in health care: evidence from patient migrationWork Pap. 2014.
24. Clemens J, Gottlieb J. Do physician's financial incentives affect medical treatment and patient health? *Am Econ Rev*. 2014;104:1320–1349.
25. Riley GF, Levy JM, Montgomery MA. Adverse selection in the medicare prescription drug program. *Health Aff*. 2009;28:1826–1837.
26. Glied S, Zivin JG. How do doctors behave when some (but not all) of their patients are in managed care? *J Health Econ*. 2002;21:337–353.
27. Laxminarayan R, Duse A, Wattal C, et al. The Lancet infectious diseases commission antibiotic resistance—the need for global solutions. *Lancet Infect Dis*. 2013;3099:1–42.

28. House TW. Executive order—combatting antibiotic-resistant bacteria. 2014. Available at: http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria. Accessed June 14, 2015.
29. Gonzales R, Corbett KK, Wong S, et al. "Get Smart Colorado": impact of a mass media campaign to improve community antibiotic use. *Med Care*. 2008;46:597–605.
30. Liu GG, Christensen DB. The continuing challenge of inappropriate prescribing in the elderly: an update of the evidence. *J Am Pharm Assoc (Wash)*. 2002;42:847–857.
31. Barry PJ, O'Keefe N, O'Connor KA, et al. Inappropriate prescribing in the elderly: a comparison of the Beers criteria and the improved prescribing in the elderly tool (IPET) in acutely ill elderly hospitalized patients. *J Clin Pharm Ther*. 2006;31:617–626.
32. Curtis LH, Østbye T, Sendersky V, et al. Inappropriate prescribing for elderly Americans in a large outpatient population. *Arch Intern Med*. 2004;164:1621–1625.
33. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. *J Clin Pharm Ther*. 2007;32:113–121.
34. Lai H-Y, Hwang S-J, Chen Y-C, et al. Prevalence of the prescribing of potentially inappropriate medications at ambulatory care visits by elderly patients covered by the Taiwanese National Health Insurance program. *Clin Ther*. 2009;31:1859–1870.