Summer 2010

Evaluating Risks from Antibacterial Medication Therapy

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A version of Chapter 3 has been published: Meropol SB, Chen Z, Metlay JP. Reduced antibiotic use for acute respiratory infections in adults and children. Br J Gen Prac. Oct. 2009; 59(567)3321-328.DOI:10.3399/bjgp09X472610. E321-328 PMID: 19843412

Evaluating Risks from Antibacterial Medication Therapy

Abstract

ABSTRACT EVALUATING RISKS FROM ANTIBACTERIAL MEDICATION THERAPY USING AN OBSERVATIONAL PRIMARY CARE DATABASE Sharon B. Meropol Joshua P. Metlay Virtually everyone in the U.S. is exposed to antibacterial drugs at some point in their lives. It is important to understand the benefits and risks related to these medications with nearly universal public exposure. Most information on antibacterial drug-associated adverse events comes from spontaneous reports. Without an unexposed control group, it is impossible to know the real risks for treated vs. untreated patients. We used an electronic medical record database to select a cohort of office visits for non-bacterial acute respiratory tract infections (excluding patients with pneumonia, sinusitis, or acute exacerbations of chronic bronchitis), and compared outcomes of antibacterial drug-exposed vs. -unexposed patients. By limiting our assessment to visits with acute nonspecific respiratory infections, we promoted comparability between exposed and unexposed patients. To further control for confounding by indication and practice, we explored methods to promote further comparability between exposure groups. Our rare outcome presented an additional analytic challenge. Antibacterial drug prescribing for acute nonspecific respiratory infections decreased over the study period, but, in contrast to the U.S., broad spectrum antibacterial prescribing remained low. Conditional fixed effects linear regression provided stable estimates of exposure effects on rare outcomes; results were similar to those using more traditional methods for binary outcomes. Patients with acute nonspecific respiratory infections treated with antibacterial drugs were not at increased risk of severe adverse events compared to untreated patients. Patients with acute nonspecific respiratory infections exposed to antibacterials had a small decreased risk of pneumonia hospitalizations vs. unexposed patients. This very small measurable benefit of antibacterial drug therapy for acute nonspecific respiratory infections at the patient level must be weighed against the public health risk of emerging antibacterial resistance. Our data provide valuable point estimates of risks and benefits that can be used to inform future decision analysis and guideline recommendations for patients with acute nonspecific respiratory infections. Ultimately, improved point-of-care diagnostic testing may help direct antibacterial drugs to the subset of patients most likely to derive benefit.

Degree Type

Dissertation

Degree Name

Doctor of Philosophy (PhD)

Graduate Group

Epidemiology & Biostatistics

First Advisor

Joshua P. Metlay, MD, PhD

Keywords

anti-infective agents, databases, health services research, prescriptions, respiratory tract infections, drug toxicity

Subject Categories

Therapeutics

Comments

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EVALUATING RISKS FROM ANTIBACTERIAL MEDICATION THERAPY

USING AN OBSERVATIONAL PRIMARY CARE DATABASE

Sharon B. Meropol

A DISSERTATION

in

Epidemiology

Presented to the Faculties of the University of Pennsylvania

in

Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

2010

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EVALUATING RISKS FROM ANTIBACTERIAL MEDICATION THERAPY

USING AN OBSERVATIONAL PRIMARY CARE DATABASE©

2010

Sharon B. Meropol

Dedication

For Neal, Dan and Hannah

Acknowledgement

I thank the faculties of the University of Pennsylvania Department of Biostatistics and Epidemiology and the Center for Clinical Epidemiology and Biostatistics for their mentorship and consistently open doors and minds. I'm particularly grateful to Brian Strom for providing me the opportunity to be part of this exceptional community, to Josh Metlay for his scholarship, lucidity, patience, and endless optimism, and to the members of my Committee for giving me the gifts of their time, support, intellect, and inspiration. Special thanks go to Neal, Dan, and Hannah for their continual support and love.

Zhen Chen provided statistical support for the early part of this work, especially Chapter 3. All authors have no competing interests to disclose

This work was supported in part by a Ruth L. Kirschstein National Research Service Award (grant number F32-AI-073015-01A1) from the National Institute for Allergy and Infectious Diseases, an Agency for Healthcare Research and Quality (AHRQ) Centers for Education and Research on Therapeutics cooperative agreement (grant number U18-HS-016946) from the Agency for Healthcare Research and Quality, by an NIH Clinical and Translational Science Award (grant UL1-RR02-4134) and by a grant from CDC EPIC, London, U.K.. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

This work was presented, in part, at the Pediatric Academic Societies Annual Meeting, May 4, 2008, Honolulu, HA, and the 4th Annual International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 20, 2008, Copenhagen, Denmark.

The limited dataset used in this study is covered by a data use agreement between the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania and EPIC Database Research Company. EPIC is a licence holder of an historical part of the GPRD dataset. GPRD is owned by the Secretary of State for Health and is managed on his behalf by the GPRD Group at the MHRA. The name GPRD is a trade mark of the GPRD group.

This study was granted exempt status by the University of Pennsylvania Institutional Review Board, and approval by both the University of Pennsylvania THIN User Committee and EPIC Database Research Company in the U.K.

ABSTRACT

EVALUATING RISKS FROM ANTIBACTERIAL MEDICATION THERAPY

USING AN OBSERVATIONAL PRIMARY CARE DATABASE

Sharon B. Meropol

Joshua P. Metlay

Virtually everyone in the U.S. is exposed to antibacterial drugs at some point in their lives. It is important to understand the benefits and risks related to these medications with nearly universal public exposure. Most information on antibacterial drug-associated adverse events comes from spontaneous reports. Without an unexposed control group, it is impossible to know the real risks for treated vs. untreated patients. We used an electronic medical record database to select a cohort of office visits for non-bacterial acute respiratory tract infections (excluding patients with pneumonia, sinusitis, or acute exacerbations of chronic bronchitis), and compared outcomes of antibacterial drug-exposed vs. -unexposed patients. By limiting our assessment to visits with acute nonspecific respiratory infections, we promoted comparability between exposed and unexposed patients. To further control for confounding by indication and practice, we explored methods to promote further comparability between exposure groups. Our rare outcome presented an additional analytic challenge. Antibacterial drug prescribing for acute nonspecific respiratory infections decreased over the study period, but, in contrast to the U.S., broad spectrum antibacterial prescribing remained low. Conditional fixed effects linear regression provided stable estimates of exposure effects on rare outcomes; results were similar to those using more traditional methods for binary outcomes. Patients with acute nonspecific respiratory infections treated with antibacterial drugs were not at increased risk of severe adverse events compared to untreated patients. Patients with acute nonspecific respiratory infections exposed to antibacterials had a small decreased risk of pneumonia hospitalizations vs. unexposed patients. This very small measurable benefit of antibacterial drug therapy for acute nonspecific respiratory infections at the patient level must be weighed against the public health risk of emerging antibacterial resistance. Our data provide valuable point estimates of risks and benefits that can be used to inform future decision analysis and guideline recommendations for patients with acute

nonspecific respiratory infections. Ultimately, improved point-of-care diagnostic testing may help direct antibacterial drugs to the subset of patients most likely to derive benefit.

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A. ANTIBIOTIC USE IN THE UNITED STATES

Virtually everyone in the U.S. will be exposed to at least one course of antibacterial medications during his/her lifetime. In the year 2000, persons ≥age 15 received a total of 68,481,645 antibacterial prescriptions, averaging 0.31 prescriptions per person per year.[1-4] It is doubtful that the U.S. population has such an extraordinarily high exposure to any other class of medications.

Antibacterials are often prescribed for acute nonspecific respiratory tract infections, despite the fact that they are unlikely to be of benefit; adults at approximately half of U.S. office visits for acute nonspecific respiratory infections receive antibacterial prescriptions.[5, 6] At the level of the physician-patient encounter, each decision to prescribe an antibacterial medication weighs the potential benefits from the medication vs. the potential risks. For example, the risk of a mild, severe, and fatal adverse drug event from amoxicillin is estimated to be approximately .056-0.07, 0.0057, and 0.000006 respectively. [7-12] For acute nonspecific respiratory infections, the risk of an adverse drug event from a single extra antibacterial drug prescription must often be perceived as low, at least lower than the perceived benefit. Although the perceived risk of an adverse event related to antibacterial use may be low, with such a high level of prescribing, the population-attributable risk of serious adverse drug events due to this medication class could be quite high.

There are several reasons why this is a particularly timely issue.

B. Trends in Antibacterial Drug Risk Exposure

1. *Rising antibacterial drug resistance*: Antimicrobial resistance is growing. Up to 30% of U.S. *Streptococcus pneumoniae* isolates are penicillin resistant, pneumococcal resistance to penicillin is associated with multi-drug resistance,[13-15] pneumococcal macrolide and fluoroquinolone resistance are spreading,[14, 16] and resistance is associated with worse clinical outcomes.[17-19] Most U.S. *Staphylococcus aureus* is now penicillin resistant, and methicillin and vancomycin resistance are increasing.[15]

For most pathogens, the spread of antibacterial drug resistance is influenced by selective forces related to the volume and types of community antibacterial drug use.[20, 21] Outpatient antibacterial drug use is the most important driver of this escalating resistance, [22]. Our ability to treat patients' bacterial infections continues to erode as the development of new effective antibacterial medications has not kept pace with this pattern of increasing antibacterial resistance; our options for treating antibacterial infections are shrinking over time.[23-25] There is increasing urgency for new antibacterial drugs to combat this resistance,[23-25] Concomitantly, improved methods are needed for utilizing population-based data to detect relatively rare adverse event risks in any new medications after drug approval when the volume and complexity of exposure to the new drug rapidly increases, discussed further below.[26]

2. *Antibacterial drug overuse*: Antibacterial drugs, increasingly broad-spectrum antibacterials, are often used to treat conditions for which they would be unlikely to be of benefit, such as viral acute respiratory illnesses.[5, 6] Programs targeting providers, patients, and the public can significantly decrease unnecessary antibacterial prescribing.[27] Interventions in Finland[28] and Iceland[29] during the 1980's and1990's, led to decreases in both macrolide-resistant streptococcus in Finland, and carriage of resistant pneumococcus in daycare children in Iceland and demonstrated that it is possible to reverse the trend toward increasing antibacterial resistance.

Studies in the U. S. have also demonstrated that multifaceted programs can significantly decrease antibacterial drug prescribing, and recent efforts in this country to curtail unnecessary antibacterial use have met with some success.[30-36] During the 1990's, adult antibacterial drug use fell by 23% for upper respiratory infections in the U.S., but broad spectrum antibacterial use doubled. By 2001-2002, 49% of adult outpatient visits for conditions for which an antibacterial drug is rarely indicated still

received an antibacterial prescription, and 77% of these were for a broad spectrum antibacterial drug, an increase of 87% over six years.[6] More recent data show that while antibacterial drug use for acute nonspecific respiratory infections continued to fall, by the 2005-2006, about half of U.S. patients over 5 years of age, diagnosed with a nonspecific respiratory infection received an antibacterial drug prescription, and broad spectrum antibacterial use for acute nonspecific respiratory infections continues to rapidly increase.[37]

3. *Antibacterial drugs to treat infections in the elderly*: As the U.S. population ages, there will be increasing incidence of conditions that are more common in the older age groups; this may influence antibacterial drug use and associated adverse events in this particularly vulnerable population.[38] Takahashi et.al. found that when urinary tract infections were treated in the elderly, nursing home residents were more likely than nonresidents to experience antibacterial drug-related adverse drug events.[39] Juurlink et.al. showed that elderly patients hospitalized for drug toxicity were more than six times as likely to have been treated with trimethoprim sulfamethosazole, and those admitted with digoxin toxicity were about twelve times more likely to have been treated with clarithromycin.[40] Gurwitz found that antibacterials was the second most frequent class of drugs associated with adverse drug events in elderly persons treated in the ambulatory setting, [38] and Budnitz et.al. found that trimethoprim-sulfamethoxazole was among the most common medications implicated in adverse drug events among elderly patients treated in U.S. emergency departments.[41]

C. Adverse Events Related to Antibacterial Drug Use

After U.S. FDA approval, drugs are used for many more patients, for a wider variety of indications, and for a more heterogeneous patient population than in pre-approval trials. The importance of post-marketing drug safely surveillance is increasingly recognized.[42]

In the U.S., we have virtually universal exposure to antibacterial medications; on average, each adult receives 0.3 antibacterial prescriptions per year. Antibacterials are also among the most common drugs implicated in adverse events.[41, 43, 44] Many adverse events have been reported following antibacterial drug use. Certain antibacterial classes are believed to be associated with certain types of adverse events. For example, antibacterial drugs account for 55% of reported cutaneous drug eruptions; penicillins and trimethoprim-sulfamethoxazole have been most frequently implicated.[45, 46] The tetracyclines, amoxicillin-clavulanic acid, erythromycin, clindamycin, sulfonamides, and trimethoprim sulfamethoxazole are most commonly associated with liver injury.[47] Several cephalosporins and most of the penems are considered nephrotoxic. Clostridia difficile colitis has been associated with cephalosporins, clindamycin, and during a recent Canadian epidemic, with flouroquinolones.[48] The most common agents associated with photosensitivity are the tetracyclines and sulfonamides.[49] Beta-lactams, imipenum and quinolones have been associated with seizures,[50] and erythromycin and clarithromycin with digoxin toxicity, prolonged QT syndrome and Torsades de Pointes.[51-55]

Of particular recent interest are drugs that are suspected of increasing the risk of cardiac arrhythmia by prolonging the QT_c interval and/or directly causing Torsades de Pointes; macrolides and some fluoroquinolones are frequently implicated in adverse events through this mechanism.[56] Also of recent interest are drugs with suspected adverse events related to their relationship with the hepatic CYP3A4 pathway. For example, macrolides are metabolized by the CP3A4 pathway and both macrolides and fluoroquinolones are inhibitors of the CYP3A4 pathway and thus their interaction with other drugs could heighten the risk of associated adverse events.[57, 58]

It is notable that most of these associations have been described with case reports and cases series; they almost never include a control group measuring adverse events in unexposed patients and thus the true absolute and relative risks of adverse events associated with these agents remain unknown.

Antibacterials are often prescribed for acute nonspecific respiratory tract infections, despite the fact that they are unlikely to be of benefit; adults at about half of U.S. office visits for acute nonspecific respiratory tract infections receive antibacterial prescriptions.[5, 37] As a result, using observational data, we can compare adverse event rates between patients treated vs. not treated with antibacterial medications for similar conditions.

D. Data Sources For Estimating Adverse Drug Event Risks

There are limited premarketing data regarding population-based antibacterial drug ADE risks. Most premarketing studies include only ~3000 subjects, and are not designed to reveal risks <1/1,000 exposed individuals.[26, 59] There are many examples of antibacterial drug-associated adverse event risks that became apparent, usually with population-based post-marketing studies, when more and increasingly medically complex patients experienced drug exposure. For example, erythromycin was shown to be associated with sudden death[60]and infantile pyloric stenosis,[61, 62] amoxicillin-clavulanic acid and telithromycin with severe hepatotoxicity,[47, 63, 64] and gatifloxacin with dysglycemia.[65] However, after drug approval, there are limited systematic reviews of antibacterial drug risks. The U.S. Food and Drug Administration's Adverse Event Reporting System database and the U.K's Drug Safety Research Unit's Prescription-Event Monitoring contain spontaneous reports of adverse drug reactions.[66, 67] Without an unexposed control group, it is not possible to distinguish what portion of these reported adverse events[68-72] is due to antibacterial drug exposure vs. other risk factors. In 2005, Brennan made this critique of his own iatrogenic death estimates in the 1991 Harvard Medical Practice Study: "Researchers questioned the real effect on mortality…given the absence of control groups to test the counterfactual situation."[73, 74] Ecologic data, such as from large prescription databases,[75] can examine associations between medication use and other parameters, but cannot define individual-level factors related to outcomes from antibacterial drug use, or address confounding by health status and other important covariates.[26, 76]

The growing availability and comprehensiveness of vast ambulatory electronic medical records such as the General Practice Research Database (GPRD), and its newer cousin, The

Health Improvement Network (THIN), (CDC EPIC, London U.K.),[77-80] linked inpatient/outpatient electronic medical records such as those provided by the U.S. EPIC Systems Corporation and Eclipsys Corporation, and linked administrative datasets[31, 81, 82] (Kaiser, Medicare), are adding breadth and depth to our ability to explore treatment-outcome relationships at the individual level with improved ability to adjust for confounders.[26, 83, 84] Currently, approximately 17% of U.S. ambulatory care practices have adopted electronic medical records,[85, 86] and the availability of electronic medical record data is likely to increase rapidly over the near future. The American Recovery and Reinvestment Act of 2009 and recent Medicare and Medicaid legislation provides over $20 billion in funding and incentives for development and adoption of health information technology by health care providers,[87] some hospitals are offering further large incentives for practices to computerize and share data,[86] while physician practices may forfeit up to 3% of their Medicare reimbursements if they have not adopted an electronic medical record by the year 2014.[88] Concurrently, the importance of enhanced post-marketing drug safety surveillance, is increasingly recognized.[42]

E. Advantages and challenges of using observational data

A randomized clinical trial is considered the best way to control confounding, by ensuring balance of both measured and unmeasured confounding variables between exposed and unexposed subjects,[89] however opportunities and resources to perform large prospective randomized trials are limited. Randomized trials to investigate subtle, rare, or complex effects would need to be quite large, would be infeasible to perform for every important research question, and are not always ethical.[83] Observational data, available from a growing number of clinical databases, can be used to help ascertain risks of antibacterial medication exposure. Longitudinal observational data with individual-level links have the potential to help shed light on the outcomes of antibacterial drug use. However, while observational data can helpfully address many of these issues, they do present certain other challenges. Efficient and resourceful ways of

addressing some of these issues would help us use observational data to yield helpful information.

1. Adjustment for confounding

Ideally, to estimate the causal effect of antibacterial drug treatment we would want to compare the effect of treatment and non-treatment on the same set of subjects at the same time; but we cannot.[67, 90] Randomization balances on unobserved as well as observed covariates and thus attempts to select a control group that is the same as the treated (exchangeable). In non-experimental studies, we still seek to find an exchangeable control group but with much difficulty because exposures are not randomly assigned.[91]

Our goal is to estimate the effects of antibacterial drug treatment by comparing treated and untreated patients.[67, 92] In a randomized study, the treatment groups are considered comparable prior to treatment. In non-experimental observational studies, since exposures are not randomly assigned patients with different exposures are likely to have other underlying differences, measured or unmeasured, Systematic differences between antibacterial drug-users and the comparison group, especially confounding by indication, can limit the conclusions.[26, 92, 93] With observational data, any apparent temporal relationship between an episode of antibacterial drug use and an adverse event may be confounded by patients' demographic, clinical, and prescribing physician characteristics. Schneeweiss suggested that longitudinal observational studies can provide information regarding causal inferences between exposure and effect, but potential biases due to differences between subgroups must be explored.[94]

a) Adjustment for measured confounding

Visible, recorded pretreatment differences (also called *overt bias),* can be removed by adjustment, exclusion, stratification, matching, and by using propensity scores, most commonly by utilizing combinations of some or all of these methods.[91] For example, comorbidity adjustment has been used in the past to help address confounding by indication, most commonly to study chronic diseases, [95] and less commonly in the study of acute conditions.[96] Hunter noted that databases with clinical data regarding patients' co-existing illnesses can be used to

address confounding using multivariate techniques and propensity scores.[83] Chan and Shaw[89] advised that evidence from observational data is stronger if any risk persists after adjustment for subject demographic characteristics, baseline health status, co-morbid conditions, the tendency to be exposed to medical care, and other medication use. There are many possible ways to attempt to adjust for co-morbidity and other patient-related factors; for studies of rare outcomes, power becomes problematic when we start adding additional variables. Using a propensity score is a way of efficiently modeling rare outcomes and common treatments. Outcomes for treated and untreated patients are compared within strata of patients with a similar propensity to have received treatment, or propensity score matching is performed; this maximizes the balance of measured covariates between treatment and control groups.[97-99]

b) Adjustment for unmeasured confounding

While adjustment for a history of known, measured, and recorded comorbidities can be useful, of course it does not adjust for unmeasured confounders.[100] Unobserved, or unmeasured, pretreatment differences (also called *hidden bias)* must be estimated using other methods.[67, 92] There are several ways to address unmeasured confounding that have been used in the past, but experience is limited with their use in GPRD or THIN.

Studies vary in their degree of sensitivity to unmeasured factors.[90, 92] A sensitivity analysis asks how hidden biases of various magnitudes might alter conclusions, [92] in other words, how sensitive are the results are to unmeasured factors? [101, 102] Models for sensitivity analysis can be expressed in terms of assignment probabilities: how large in magnitude would differences in the probability of receiving treatment depending on hidden biases need to be to alter the quantitative conclusions of a study? Alternatively, models for sensitivity analysis can be expressed in terms of unobserved covariates: how large in magnitude would confounding due to unobserved covariates need to be to alter the quantitative conclusions of a study? Mathematically, these two types of models are equivalent.[90]

ii. Known Effects

A sensitivity analysis shows how biases of different magnitudes might change conclusions, but it does not determine if biases are present, and their possible extent.[90] An additional method to address hidden bias involves measuring an additional outcome for which there is no logical causal relationship with the studied treatment, or exposure.[90] If a systematic difference in this outcome is detected between treated and untreated subjects, this cannot be an effect of the treatment and must be evidence of a hidden bias. The use of multiple control groups in a case-control study is a related method.

iii. Instrumental variables

Instrumental variables, observable factors related to treatment choice but unrelated to characteristics of patients or to outcomes, can help adjust for unmeasured confounders.[101, 102] A major potential limitation of the instrumental approach is that it is often difficult to find a suitable instrument.

iv. Case-crossover studies

Case-crossover and crossover-cohort studies can also help minimize inter-individual differences in indication for receiving antibacterials.[103, 104] In this analysis, only data from patients experiencing adverse events are used. A window of case exposure time is defined related to the adverse event occurrence, and exposure during this case-time is compared with exposure during either all control time (crossover-cohort studies) or exposure during a portion of the subjects' control time (case crossover studies). In sensitivity analysis, we can determine how much unmeasured confounding would be needed to change the odds ratio for serious adverse events for antibacterial drug-exposed vs. unexposed patients.[97]

Utilizing these analytic methods with THIN data will support these research projects regarding antibacterial drug use as well as inform future THIN research projects and other studies using observational data where randomized clinical trials are not immediately feasible.

c) Measurement error/misclassification

Electronic medical record data tend to have rich longitudinal clinical information at the individual patient level. Most pharmacoepidemiology techniques for utilizing observational data have come from studies of long-term drug use to treat chronic diseases and may not be as appropriate for studying more short-term drug exposures for acute conditions, for example acute infectious illnesses. For acute conditions, even modest errors in measuring the onset or duration of acute conditions and/or exposures could bias the results. We need to develop or adapt, and validate techniques developed using observational data to study chronic treatments and outcomes of chronic diseases to study acute conditions and/or exposures

i. Misclassified outcome

Hospitalization outcomes in electronic medical record data.

Manually-entered outcomes may be particularly subject to error; for example hospitalizations, which are important markers of severe adverse events. If hospitalization dates are incorrectly recorded outside of a specified exposure window that is overly-narrow, we may systematically miss important outcomes; using an unnecessarily long window risks introducing noise, thus errors in either direction can reduce our power to reveal true relationships between drugs and adverse events.

Data regarding hospitalizations often are not directly linked to the outpatient record but instead need to be entered manually. THIN hospitalization data are entered manually by patients' general practitioners after they review patients' hospital discharge summaries.

There are four main areas of uncertainty to be addressed if electronic medical record hospitalization data are to be useful for drug safety surveillance. First, when hospitalization codes indicate a patient was hospitalized, did the patient truly have an overnight hospitalization, or, what is the positive predictive value of the electronic medical record hospitalization codes for identifying a hospitalization? Second, if the patient was indeed hospitalized, is the discharge diagnosis recorded the true primary discharge diagnosis from the hospitalization? Third, and important for studying acute exposures, what is the relationship between the recorded hospital admission date and the true hospital admission date? If a hospitalization is recorded after receipt

of the discharge summary, it may be recorded with a later date than the true admission date. Even if the hospitalization date falls within the exposure window of interest, if the recorded date erroneously falls outside the window, the adverse hospitalization event might be missed. Fourth, what is the sensitivity of the electronic medical record for detecting adverse event hospitalizations? The first three of these areas of uncertainty will be addressed with the current projects within the U.K. electronic medical record The Health Improvement Network (THIN); the fourth is beyond the scope of presently-available resources.

ii. Misclassified covariates/exposure

Electronic medical record prescription data are generally considered to be highly valid, as data entry usually generates the prescription of interest, and prescriptions are usually linked to their corresponding diagnostic indications.[105, 106] Prescriptions in THIN are generated with data entry this way, and linked to a diagnosis at the time of entry; studies have supported good concordance with other prescribing measures, for example, THIN prescribing rates for asthma medication were similar to UK asthma prescribing rates using other national measures.[105] However, there remain several routes of potential exposure misclassification. First, medications not associated with a medical record entry may be missed, such as medications from emergency department visits, administered in the hospital, or administered over the telephone without written record. Second, these data describe what was prescribed, but not necessarily what medication was obtained and/or ingested by the patient of interest; data on which prescriptions were filled are not available in THIN. Previous studies have shown that approximately 2% of prescriptions remain unfilled, and approximately 70% of these are for new prescriptions.[107] Medications may be prescribed but not obtained, obtained but not ingested as directed, or, alternatively, medications may be ingested by patients that are unrecorded in the medical record, for example, given by medical provider as samples but not recorded, obtained from family members or friends, or purchased over-the-counter or otherwise without a prescription. Third, exposure status will depend on the definitions used for that study, for example, how encounters are included and/or grouped, and how exposures are otherwise defined for that particular study. Medication

adherence rates are typically higher in patients with acute vs. chronic conditions,[108, 109] and, unlike for many U.S. patients,[110] payment for medications should not be a barrier in THIN as antibiotic prescriptions should be covered by the U.K.'s National Health Service. In this study, we used a dichotomous exposure, exposed vs. unexposed. THIN does have medication dose and days supplied fields, but due to the extra potential for misclassification with these further variables described above, a dichotomous exposure was considered more useful for this study. In addition, as the severe adverse events we were studying would mostly be considered Type B, or idiosyncratic adverse drug events, less likely dose related than the more common Type A adverse drug events,[111] the dose would not necessarily be as clinically relevant for this study.

F. Preliminary Data

1. *Adverse events related to antibacterial drug use in the GPRD:* In a preliminary study, a 50% sample of 2½ years of the GPRD was used to compare the incidence of adverse events for patients on short term (≤28 days) vs. prolonged (>28 days) therapy with one of the seven oral antibacterial drugs: amoxicillin, amoxicillin-clavulanate, clarithromycin, azithromycin, ciprofloxacin, levofloxacin, and doxycycline.[112] Serious adverse events resulting in hospitalization were identified including: nephrotoxicity, hepatotoxicity, anaphylaxis, infectious colitis, phototoxicity, seizures, and ventricular arrhythmias. No analysis of unexposed patients was performed, and there was no adjustment for potential confounders. Overall, 24% of patients were exposed to an antibacterial drugs of interest, including 542,817 person-years of observation. Overall adverse event rates were highest for ciprofloxacin (24 events per 100,000 person days exposure) amoxicillin-clavulanate (15 events per 100,000 person days exposure) and amoxicillin (6 events per 100,000 person days exposure). For most events, the incidence rate ratio, comparing >28 vs. 0-28 person-days of antibacterial drug exposure was <1, showing limited evidence for cumulative dose-related adverse events from long-term exposure. Limitations of this preliminary study include its relatively smaller sample size than this current study, no control group of patients not exposed to antibacterials, and no adjustment for potential confounders

2. *The Health Improvement Network (THIN):* THIN is a large longitudinal observational database of anonymized computerized primary care medical records. The GPRD was originally established by EPIC, London, U.K. in 1987 for research purposes; participating general practitioners received practice computers and Vision clinical practice management software in return for undertaking data quality training and submitting anonymized patient data. Beginning in 2002, a more formal collaboration of CDC EPIC with InPS, supplier of the Vision software, paved the way for the introduction of THIN. THIN collects anonymised patient data records from general practices throughout the UK using the Vision software to create a medical research database. Within the UK, approximately 98% of the population is registered with general practitioner physician who is responsible for almost the entirety of the patient's medical care. THIN contains primary care records including demographics, provider information, medical diagnoses that are part of routine care or result from hospitalization, visits for acute conditions and diagnoses, consultations, hospital referrals, new and repeat prescriptions with indications for all new prescriptions (cross-referenced to medical events on the same date) and events leading to withdrawal of a drug or treatment, preventive care, hospital admissions, mortality and cause of death, lifestyle factors, and free text.[113] The most current THIN data used in this study include information on 32.6 million person-years regarding 4.85 million patients from 326 practices. These data are completely de-identified; there is no way for investigators to link THIN records with any individual patient. Diagnoses are recorded with Read diagnostic codes, using a comprehensive hierarchical nosologic system to group and define specific illnesses. Prescriptions are recorded using codes issued by the Prescription Pricing Authority (PPA) of the National Health Service in the UK. Practitioners are trained in data entry and their data are reviewed on an ongoing basis for quality and completeness.[114, 115] THIN helps GPs improve their data quality by offering training and analysis of the practice's anonymised patient information, and reports back to practices on a regular basis. Studies have confirmed very good validity of general practitioners' documented diagnoses,[105] prescription information,[105] and capture of information from specialists.[116] THIN also offers the option of obtaining additional

data from GPs if needed, while maintaining complete anonymization of data; this can be especially helpful for data validation. All studies using THIN data must be approved by the local University of Pennsylvania THIN user committee, the local institution's Institutional Review Board, and EPIC in the UK, to ensure scientific and ethical standards for THIN data utilization.

G. Summary of background and relation to objectives of proposed study

Every individual in the U.S. is prescribed a short-term course of systemic antibacterial drugs once every three years to almost twice per year, on average, resulting from a visit to an ambulatory health care provider.[3, 4, 6, 37, 117, 118] This extraordinarily high exposure to antibacterial medicines should command careful vigilance to the consequences. Much U.S. antibacterial use is unnecessary, and contributes to rising antibacterial resistance. Yet the factors that inform patient and provider expectations and decisions regarding antibacterial drug prescribing at the individual encounter level are influenced less by societal issues and more by prescriber and patient perceptions of patient-level attributes regarding individual benefit and risk.[119] It is important to have a comprehensive understanding of the risk of adverse events related to this class of medication to which the U.S. public has virtually universal exposure.

Several recent trends that are likely to influence antibacterial drug use make it even more important to accurately assess risk. As we face increasingly resistant organisms, and our antibacterial drug stewardship becomes ever more vital, providers are being urged to further decrease the rate of unnecessary antibacterial drug use. However, an increasing prevalence of relatively frail and medically complex elderly members of the U.S. population works against our ability to use fewer antibacterial drugs. Advances in personalized medicine and more complex decision modeling[120] require more precise information available regarding risk, adjusted for individual characteristics.

Many adverse events associated with antibacterial drug use have been documented in the past, those related to cardiac arrhythmia and CYP3A4 metabolism are of particular recent interest, however the causal relationship between antibacterial drug exposure and the adverse

event is not always evident, and risk models do not always address complex confounding issues, especially confounding by indication.

More information about individual patient outcomes of antibacterial drug use might help us learn how to better address antibacterial use and overuse at the individual level. While large prospective randomized studies would be ideal to explore antibacterial drug outcomes, they are not immediately feasible for every research question.

THIN offers unique access to individual patients' longitudinal demographic, clinical, pharmaceutical, and outcome data, and the opportunity for data validation. Although these observational cohort data are more accessible than are the resources for performing a very large randomized clinical trial, great care needs to be taken to assure that the antibacterial drug -exposed and -unexposed groups are as comparable as possible. Methods to control confounding, especially confounding by indication, and confounding by practice in observational studies can be used to enhance THIN studies regarding outcomes of medication use.

These studies expand on the preliminary study in that we use a subset of the entire THIN cohort with an office visit for acute nonspecific respiratory infection, and compare adverse event rates of antibacterial drug-exposed and antibacterial drug-unexposed patients. By limiting the comparison to patients with visits for acute nonspecific respiratory infection, we promote comparability between exposed and unexposed patients in the cohort. In addition, we explore a set of secondary adverse event endpoints of less serious events resulting in outpatient office visits. We also comprehensively address confounding issues by utilizing different ways to adjust for practice-level confounding as well as patient-related covariates such as demographic variables, underlying health status and intensity of exposure to the medical care system. The rarity of our outcome presents an additional analytic challenge. To further assess our methods, and put our results in perspective, we also consider other outcomes, both benefits and adverse outcomes.

With its wealth of longitudinal clinical information, THIN is the most logical database choice for this project, giving the best chance of teasing out antibacterial drug-related adverse

events from the confounding factors. We also validate THIN hospitalization dates, which is pertinent for this study as well as for future studies of acute drug exposures using THIN data.

This study provides the opportunity to learn about important antibacterial drug risks, as well as gain experience with methodologies that can be applied to future THIN studies to address issues inherent in using observational data. As The Health Improvement Network (THIN) as well as other electronic medical record databases continue to grow in number and size, experience with effective and efficient methodologies will help us to exploit their potential.

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Chapter 2. Specific Aims

The increasing availability of observational data from large electronic medical record databases provides opportunities to enhance our understanding regarding drug safety. Most pharmacoepidemiology techniques for utilizing these data have come from studies of long-term drug use to treat chronic diseases and may not be as appropriate for studying more short-term drug exposures for acute conditions. For example, there are limited data validating correct time windows for ascertaining acute medication exposures and the outcomes of cute conditions.

The first study will describe patterns of antibacterial drug use associated with outpatient visits for acute nonspecific respiratory tract infections in the THIN database. The second study is a validation study addressing the accuracy of hospitalization dates in The Health Improvement Network (THIN), an electronic medical record database. First, we will measure the positive predictive value of hospitalization codes in the database. Next, for validated hospitalizations, we will explore the relationship between the recorded and true hospitalization dates. Evidence either for or against the null hypothesis that the recorded dates are true dates, and resulting insight regarding a useful antibiotic exposure window will be essential for the subsequent studies assessing hospitalizations related to acute exposures.

Most adverse event reports regarding antibacterial drugs do not contain a control group of unexposed patients. The third study in this thesis will use the knowledge acquired from the validation project regarding THIN hospitalization dates and appropriate drug exposure windows to study risks and benefits related to antibacterial drug use for acute nonspecific respiratory tract infections. Antibacterial drugs are often prescribed for acute nonspecific respiratory infections, although they are unlikely to provide clinical benefit. This scenario provides the opportunity to compare outcomes for exposed vs. for unexposed patients with similar conditions. We will take advantage of THIN's rich clinical data by applying several techniques to control for confounding by indication.

The goals of this dissertation are to address the unique methodological challenges of applying pharmacoepidemiologic techniques developed to study drug use for chronic diseases to

study more acute conditions, exposures, and outcomes, and specifically to validate hospitalization dates in THIN and to assess the relationship between acute antibacterial drug use and adverse events.

Specific Aims:

1. Describing antibacterial drug use for nonspecific acute respiratory illnesses in the U.K.

The objective of this study was to describe antibacterial drug use associated with a primary care visit for nonspecific acute respiratory illnesses in the U.K.'s The Health Improvement Network primary care database. Specific aims were to:

Primary aim:

1. Describe overall antibacterial drug use for acute nonspecific respiratory tract infections in the U.K.
2. Describe broad spectrum antibacterial drug use for acute nonspecific respiratory infections in the U.K.

Hypothesis 1: Overall antibacterial drug prescribing for acute nonspecific respiratory infections is decreasing, similar to U.S. trends.

Hypothesis 2: Broad spectrum antibacterial drug prescribing for acute nonspecific respiratory infections is rapidly increasing, also similar to U.S. trends.

2. Assessing misclassification and validation of hospitalization dates and diagnoses in The Health Improvement Network (THIN) database

The objective of this study was to validate hospitalizations for community acquired pneumonia in the THIN database. Specific aims were to:

Primary aims:

1. Assess the positive predictive value (PPV) of a hospitalization for pneumonia identified using THIN hospitalization codes

2. Assess the relationship between THIN hospital admission date and true hospital admission date.

Hypothesis: 100% of THIN hospitalizations are recorded as occurring within a 14-day window of the true hospitalization date.

Hypothesis 1: : The PPV of a pneumonia hospitalization is 100%.

Hypothesis 2: 100% of THIN hospitalizations are recorded as occurring within a 14-day window of the true hospitalization date

3. Assessing methods for controlling bias and confounding while using observational clustered data to study rare outcomes.

The objective of this study was to compare various potential methods to control bias and confounding while using a primary care observational database to study rare acute outcomes.

Primary aim:

1. Compare methods for controlling bias and confounding caused by measured variables.

Secondary aim:

1. Compare methods to evaluate the impact of unmeasured variables, including instrumental variable analysis and sensitivity analysis

4. Potential Risks of Antibacterial Drug Use: Adverse Events Associated with Adult Antibacterial Treatment

The objective of this study was to compare the risk of a serious adverse event between patients prescribed antibacterial medications vs. the risk for those not prescribed antibacterials, conditional on a primary care visit for acute nonspecific respiratory tract infection. Specific aims were:

Primary Aim:

1. To compare the risk of hospitalization with a severe adverse event between patients prescribed antibacterial medications vs. the risk for patients unexposed to antibacterials, conditional on a primary care visit for an acute nonspecific respiratory infection.

Hypothesis:

Patients with visits for acute nonspecific respiratory infections with exposure to antibacterial medications have an increased risk of adverse event hospitalizations compared with antibacterial-unexposed patients with visits for acute nonspecific respiratory infections.

5. Potential Benefits of Antibacterial Drug Use: Pneumonia hospitalization outcomes after acute nonspecific respiratory infection; assessing the influence of antibacterial treatment

The objective of this study was to compare the risk of a hospital admission for community acquired pneumonia between patients prescribed antibacterial medications vs. the risk for those not prescribed antibacterials, conditional on a primary care visit for acute nonspecific respiratory infection.

Primary aim:

1. To compare the risk of hospital admission with community acquired pneumonia between patients prescribed antibacterial medications vs. the risk for patients unexposed to antibacterials, conditional on a primary care visit for an acute nonspecific respiratory infection.

Hypothesis:

Patients with visits for acute nonspecific respiratory infections with exposure to antibacterial medications have a decreased risk of pneumonia hospitalizations compared with antibacterial-unexposed patients with acute nonspecific respiratory infections.

Chapter 3. Describing antibacterial drug use for nonspecific acute respiratory illnesses in the U.K.

Meropol SB, Chen Z, Metlay JP. Reduced antibiotic prescribing for acute respiratory infections for adults and children. Br J Gen Pract. 2009;59(56):e321-328. DOI: 10.3399/bjgp09X472610

Resistance to antibacterial medications among community-acquired pathogens is a growing public health threat.[1-5] Key drivers are the volume and type of antibacterials used in ambulatory settings.[6-8] Antibacterials are often prescribed for acute nonspecific respiratory infections which they are unlikely to benefit..[9, 10] Reducing such use can slow, or even reverse resistance rates.[11, 12] U.S. and U.K campaigns have discouraged unnecessary antibacterial use.[2, 13-16] Recent U.S. data have demonstrated decreased unnecessary adult and child use, but U.S. broad spectrum antibacterial use for adult and child acute nonspecific respiratory infections more than doubled during the 1990s, and have continued to rapidly increase through 2006. [17-23] U.K. studies have similarly shown decreased diagnoses of acute nonspecific respiratory tract infection and related and overall antibacterial use for all ages, [24-28], but they provided limited information regarding trends in adult and child antibacterial and broad-spectrum antibacterial use for this diagnosis.

The objective of this study was to assess recent U.K. trends in overall and broad spectrum antibacterial drug use for adult and child acute nonspecific respiratory tract infections. We hypothesized that overall use declined, that this decline varied by age and, like recent U.S. patterns, that there was a concomitant increase in broad spectrum drug utilization.

Methods

Study Design: This retrospective cohort study utilized de-identified data from a large U.K. primary care electronic medical record database, The Health Improvement Network (THIN).[29] Data collection commenced in 1985 through the General Practice Research Database (GPRD); THIN, introduced in 2002, includes data from many original GPRD practices and continues to enroll additional practices with ongoing data collection.

THIN includes demographics, visits, diagnoses, and prescriptions. Prescriptions are generated by data entry, and general practitioners are responsible for most prescribing, with virtually 100% capture of prescription data. Data quality is reviewed on an ongoing basis.[29] Studies have confirmed good validity regarding documented diagnoses,[30, 31] prescriptions,[31] and specialists' information.[32]

Study Population: The population of interest included permanently registered members of computerized THIN practices, utilizing THIN data as of September, 2007 describing 4.85 million patients from 326 practices, including >32 million person-years. We used valid available data from January 1, 1990 or the date of practice computerization, if later, through December 31, 2004 or the latest date of data collection for that practice.

THIN records birth year for all patients and birth month for children <15 years of age. We defined adults as individuals >=18 years of age on the day of the acute nonspecific respiratory tract infection visit and children as being <18 years of age, according to THIN recorded birthdates.

We selected a cohort of visits from January 1, 1990 through December 31, 2004 using Read diagnostic codes for acute non-specific respiratory infections, chosen to represent conditions that are typically viral in origin and unlikely to respond to antibacterials (Table 1). We excluded conditions for which some guidelines recommend antibacterials, such as otitis media and sinusitis. Because data from multiple visits within the same illness episode may be highly correlated, we grouped adjacent visits within a two-week window for our primary analysis; sensitivity analysis explored the impact of considering adjacent visits independently. As results of the sensitivity analysis were identical to the primary analysis, we only present results of the grouped approach.

Table 1. Acute Nonspecific Respiratory Tract Infection Diagnostic Codes

THIN Read Code Description
Other acute upper respiratory infections
Acute upper respiratory tract infection
Upper respiratory infection NOS
Upper respiratory tract infection NOS
Acute nasopharyngitis
Acute pharyngitis
Throat infection – pharyngitis
Acute pharyngitis NOS
Sore throat NOS
Acute bronchitis
Bronchitis unspecified

Outcome Classification: The outcome of interest was receiving any antibacterial medication prescription within one day of an acute nonspecific respiratory tract infection visit. Drugs of interest included oral antibacterials typically used for respiratory infections. We excluded topical, vaginal, ophthalmologic, otic, and parenteral antibacterials, and those typically used for tuberculosis, fungal and parasitic infections. We classified amoxicillin/clavulanate, azithromycin, clarithromycin, fosfomycin, second- and third-generation cephalosporins and quinolones as broad spectrum, and all others as narrow-spectrum medications.[22]

Exposure Classification: The main exposure was visit year, considered individually for all analyses.

Covariates: For children, age was stratified as 0-<5 and >=5 years of age. For adults, age was stratified as 18-<65 and >=65 years. These age categories are clinically relevant (i.e. pre-school vs. school-aged), are in line with those used by the U.S. National Center for Health Statistics,[33] and can facilitate comparisons with U.S. Medicare data for adults >=age 65. Other covariates included sex, the number of comorbidities by the day of the ARI visit, and the number of different classes of prescribed medications and the number of visits within the year before the visit.[34-36] As changes in drug use could vary by age, we also tested for an interaction between year and age category.

Analysis: We first described trends in visit rates and antimicrobial prescribing rates for acute nonspecific respiratory tract infections over the study period using Cuzick's nonparametric test for trend across ordered groups by individual visit year. Person time was calculated using each patient's THIN birthdate, practice enrollment date, date of transfer out of practice, and/or date of death, and each practice's computerization and/or last data collection date, as appropriate.

Next, we used generalized linear models to model the probability of an antibacterial prescription, conditional on a visit for acute nonspecific respiratory tract infection. To predict probabilities, we used a Poisson distribution and logarithm link function in the generalized linear models, with robust variance estimates [37]. Separate adult and pediatric models adjusted for clustering by patient and practice using Generalized Estimating Equations,[38, 39]. We modeled the probability that an antibacterial was prescribed, first using models adjusted only for year. We report probabilities of antibacterial use for each year, and report trend across year using Cusik's test. We then modeled the probability of antibacterial prescribing using fully-adjusted models, with year as a linear term, including all covariates described above, to report adjusted trend across year, described as an incidence rate ratio (IRR) for each successive year. We also explored the age-year interaction using the fully adjusted model including the interaction between age category and categorical year and tested whether interaction terms were significant using the deviance difference test.[40] If interaction terms were statistically significant, we report IRRs for each successive year stratified by age category.

We performed a parallel set of analyses for broad spectrum antibacterial drugs, including trends in prescribing rates and the probability of antibiotic prescriptions conditional on a visit for acute nonspecific respiratory tract infection.

Analyses were performed using Stata version 9, StataCorp LP.

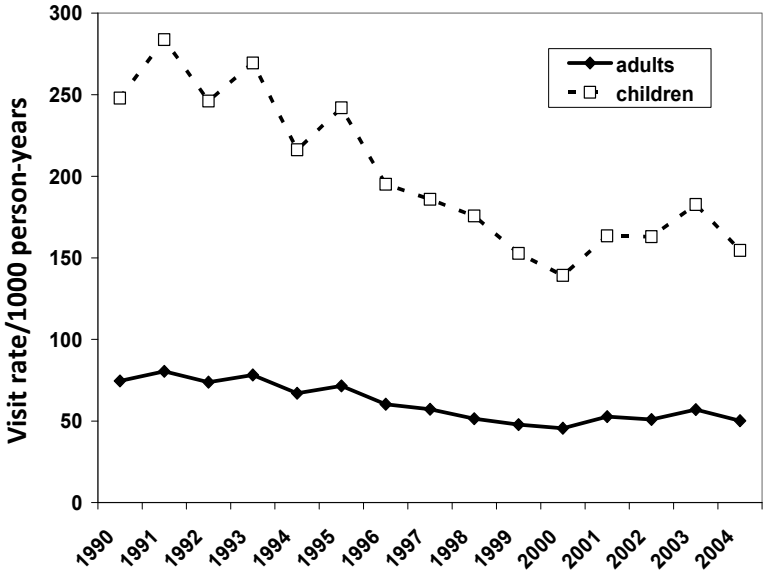
This study was granted exempt status by the University of Pennsylvania Institutional Review Board, and approval by the University of Pennsylvania THIN User Committee and the U.K.EPIC Database Research Company.

Results

ARI visit rate

We identified 1,342,365 visits for acute nonspecific respiratory tract infection diagnoses in 745,044 adults followed for 22,741,927 person-years and 1,117,596 visits for acute nonspecific respiratory tract infection diagnoses in 453,584 children followed for 5,831,438 person-years. For adults, the visit rate during 1990 was 74.5 visits per 1000 person-years and by 2004 was 50.2 visits per 1000 person-years (Figure 1). For children, the visit rate during 1990 was 247.9 per 1000 person-years and by 2004 was 154.5 per 1000 person-years (Figure 1). Visit rates decreased over the study period for adults and children (both p for trend=0.001).

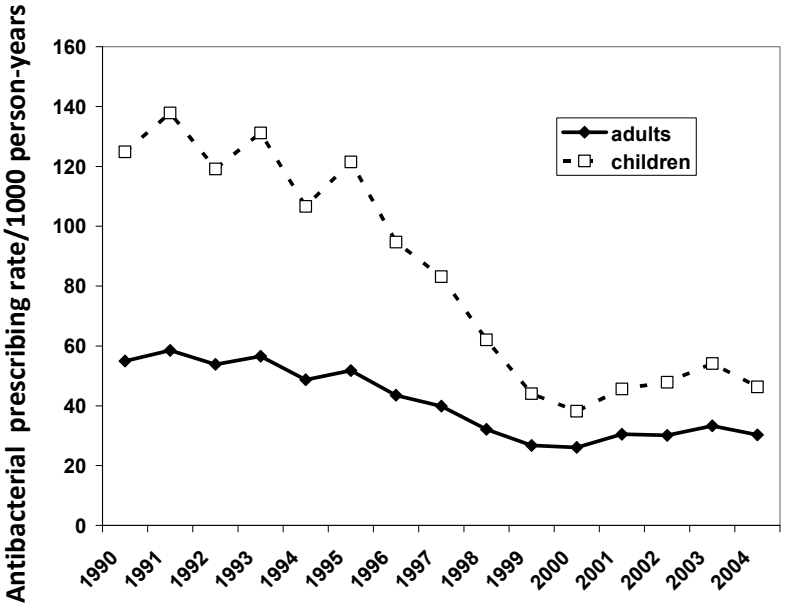
Figure 1, Adult and Child Visit Rates for Acute Nonspecific Respiratory Tract Infections per 1000 Person-years



Acute Nonspecific Respiratory Tract Infection antibacterial prescription rate

For adults, in 1990, the antibacterial prescription rate for acute nonspecific respiratory tract infection visits was 55.0 per 1000 person-years, and by 2004 it was 30.3 per 1000 person-years (p=0.001 for trend) (Figure 2). For children, in 1990, the antibacterial prescription rate was 124.8 per 1000 person-years, and by 2004 it was 46.3 per 1000 person-years (p=0.001 for trend).

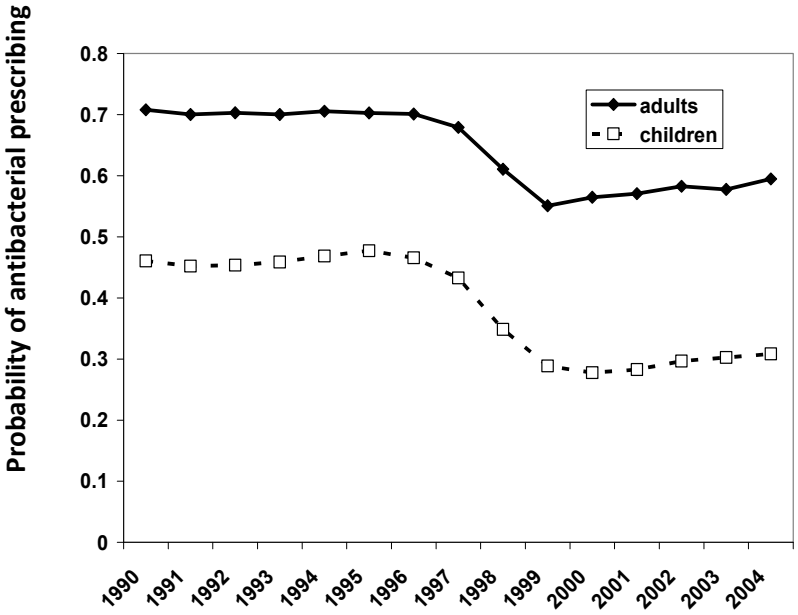
Figure 2, Adult and Child Antibacterial Drug Prescribing Rates for Acute Nonspecific Respiratory Tract Infections per 1000 Person-years



Probability of antibacterial drug prescribing conditional on visit for acute nonspecific respiratory tract infection

For adults, during 1990, 71% of visits were associated with an antibacterial prescription, and by 2004, 59% of visits were associated with antibacterials (p=0.003 for trend) (Figure 3).

Figure 3, Probability of Antibacterial Drug Prescribing after Acute Nonspecific Respiratory Tract Infection Visit.



Using the fully-adjusted model for adults, adjusting for sex, age category, year, comorbidities, number of medications and number of visits, there was a significant decrease in the probability of antibacterial prescribing for each successive year, with an IRR of 0.979 (95% c.i. 0.979-0.980, p<0.001).

Using the fully-adjusted model for adults, and including the year-age category interaction, older adults were initially less likely to receive antibacterials (p<0.001 comparing older and younger adults in every year) until 1998; when older and younger adults were equally likely to receive antibacterials (p=0.93 older vs. younger adults); after 1998, older adults were more likely to receive antibacterials (p<0.001 comparing older and younger adults in every year after 1998). Both age categories experienced significant declines in the probability of antibacterial prescribing over the study period; the IRR for year for ages 18-<65 years was 0.977 (95% c.i. 0.977-0.978) and for >=65 years was 0.988 (0.987-0.988). The age-year interaction was significant (p<0.001) indicating that over time, antibacterial prescribing declined more steeply for younger than for older adults.

For children, during 1990, 46% of acute nonspecific respiratory tract infection visits were associated with antibacterial prescriptions, and by 2004, 31% of visits were associated with antibacterials (p=0.007 for trend) (Figure 3).

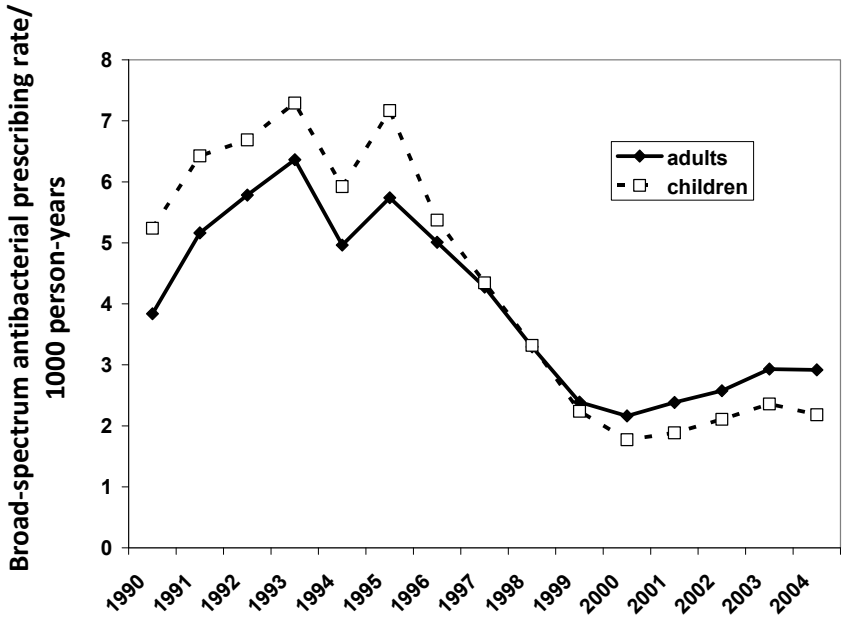
Using the fully-adjusted model for children, there was a significant decrease in the probability of antibacterial prescribing for each successive year, with an IRR of 0.959 (95% c.i. 0.959-0.960, p<0.001).

Using the fully adjusted model for children, and including the year-age category interaction, older children were 30%-40% more likely than younger children to receive antibacterial prescriptions in every study year (p <0.001 comparing older vs. younger children in each study year). Both age categories experienced significant declines in antibacterial drug prescribing over the study period; the IRR for year for ages 0-<5 years was 0.959 (95% c.i. 0.958-0.959) and for >=5 years was 0.962 (0.961-0.963) indicating the rate of decline was similar in both age groups. While the age-year interaction term was statistically significant, the effect of year, and thus its public health relevance, was essentially the same in both age groups.

Broad spectrum antibacterial prescribing rate for acute nonspecific respiratory tract infections

For adults, the broad spectrum antibacterial drug prescription rate during 1990 was 3.8 prescriptions per 1000 person-years, and by 2004, was 2.9 prescriptions per 1000 person-years (p=0.005 for trend) (Figure 4). For children, the broad spectrum antibacterial prescription rate during 1990 was 5.2 prescriptions per 1000 person-years, and by 2004 was 2.2 prescriptions per 1000 person-years (p=0.003 for trend) (Figure 4).

Figure 4. Broad Spectrum Antibacterial Drugs .for Acute Nonspecific Respiratory Tract Infections per 1000 Person-years, Adults and Children



Probability of broad spectrum antibacterial prescribing conditional on visit for acute nonspecific respiratory tract infection

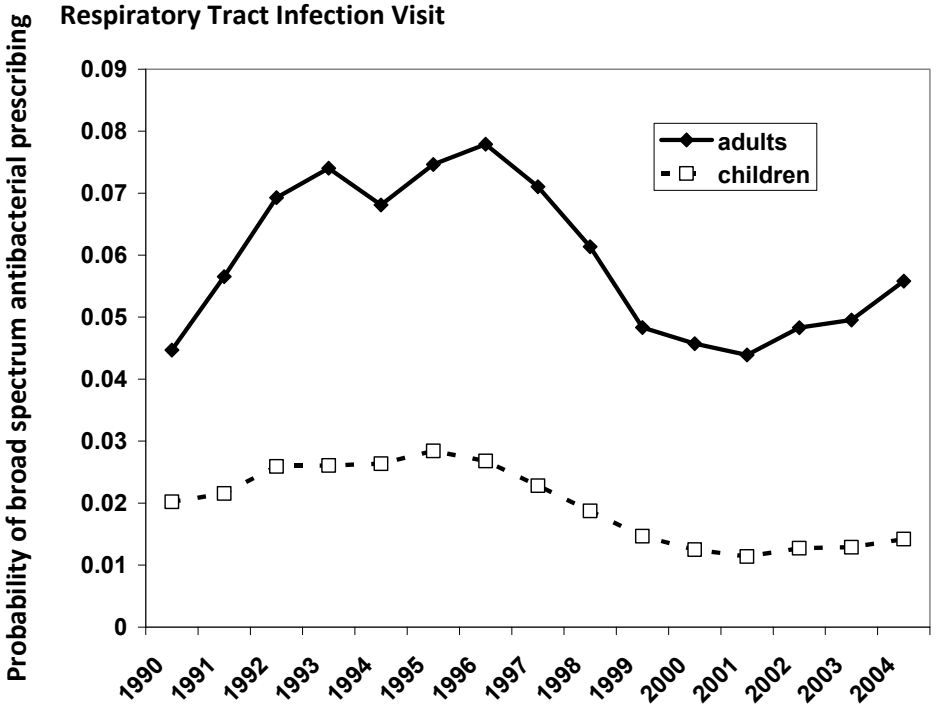
For adults, during 1990, 4.4% of visits for acute nonspecific respiratory tract infection were associated with broad spectrum antibacterials, this portion peaked at 7.8% by 1996 and then decreased to 5.6% by 2004 (p=0.16 for linear trend over study period) (Figure 5).

Using the fully adjusted model for adults, there was a small decline in the probability of broad spectrum antibacterial prescribing for each successive year, with an IRR of 0.96 (95% c.i. 0.96-0.97, p<0.001).

For children, during 1990, 2.0% of visits were associated with broad spectrum antibacterial prescriptions, (Figure 5); this percentage peaked at 2.8% in 1995 and then decreased to 1.4% by 2004 (p=0.01 for trend).

Using the fully adjusted model for children, there was a small decline in the probability of broad spectrum antibacterial prescribing for each successive year, with an IRR of 0.95 (95% c.i. 0.94-0.95, p<0.001).

Figure 5. Probability of Broad Spectrum Antibacterial Drug Prescribing after Acute Nonspecific Respiratory Tract Infection Visit



Discussion

Summary of main findings

Our study demonstrated that antibacterial drug prescribing for acute nonspecific respiratory tract infections decreased in the U.K. for adults and children from 1990-2004. The decline in antibacterial use was faster for both older and younger children than for adults, although use in younger adult declined faster than for older adults. Possible reasons for these differences include the influence of the pneumococcal conjugate vaccine on the perceived risk of child bacterial illness,[41-43] and on parents' health through herd effects,[43, 44] a potentially initially wider pool of unneeded antibacterial use in younger individuals, and a possible differential effect of public educational efforts regarding antibacterial use for young adults, influencing their own use and that of their children. The relative contributions of each of these or other factors to our results are unknown.

Despite decreasing antibacterial use for acute nonspecific respiratory tract infections, we did not observe a concomitant increase in broad spectrum antibacterial prescribing. In fact, we found encouraging evidence for low and recently decreasing broad spectrum antibacterial use associated with this diagnosis for U.K. adults and children.

Strengths and limitations of the study

Strengths of this study relate to the use of THIN data. Advantages of THIN vs. claims data are THIN's direct links to longitudinal clinical data and that THIN does not depend on billing or insurance status. Advantages of THIN vs. survey data are that THIN is a 100% sample of practice patients and that the medical record itself *is* the data collection form.

Potential limitations of this study include that some antibacterials may have been missed, for example, telephoned prescriptions without an associated visit. Second, we have no data regarding whether prescribed drugs were ingested. Third, visit grouping may have misclassified some unexposed visits as exposed and falsely inflated our antibacterial use estimates, however our sensitivity analysis considering ungrouped visits showed similar results. Next, our observational study does not allow us to address which policies or clinical trends caused the observed changes. Finally, our study did not address outcomes of antibacterial use and could not directly assess prescriptions' appropriateness.

Comparisons with existing literature

The population rates of visits for acute nonspecific respiratory tract infections we observed are similar to those previously reported for U.S.adults and children.[19, 21, 45]

The trends in overall antibacterial use we observed are comparable to U.S. trends. Using National Ambulatory Medical Care Survey (NAMCS) data, Roumie et al, reported that antibacterial prescribing for adult acute nonspecific respiratory respiratory tract infections declined from 60% in 1995-1997 to 43% in 1999-2000.[19] Steinman et al. also used NAMCS data to report decreased antibacterial prescribing for adult acute nonspecific respiratory tract infections from 56% in 1991 to 43% in 1999.[20] Similarly, Steinman et.al. reported declining antibacterial use for child acute nonspecific respiratory tract infections, from 41% in 1991 to 21% in 1999.[20]

Grijalva and colleagues used NAMCS data to show that U.S. use of antibacterials to treat adult and child acute nonspecific respiratory tract infections continued to decrease during the early 2000s, and that broad spectrum antibacterial drug use for this diagnosis continued to increase in adults and children.[23]

Our demonstrated decline in U.K. antibacterial drug prescribing for adult acute nonspecific respiratory tract infections, from 71% in 1990 to 59% in 2004, is similar to these U.S. reports. In our cohort, child antibacterial use for acute nonspecific respiratory tract infections decreased from 46% in 1990 to 31% in 2004.

Our low and recently decreasing use of broad spectrum antibacterials for adults and children in the U.K. are quite different from U.S. trends, evidence that recent U.K. campaigns to enhance judicious antibacterial use may be paying off.[14-16]

Implications for further research or clinical practice

Reasons for the large discrepancies in trends in broad spectrum antibacterial use between the U.K. and U.S. are unknown, but could relate, at least in part, to differences in health care delivery. U.S. health care is managed by a mix of privately- and publicly-financed mechanisms, emphasizing a competitive business model. Prescribing is influenced by separate formularies for each of thousands of individual health plans, and pharmaceutical industry promotion to physicians and the public. The U.S. CDC's "Get Smart" campaign targeted parents with the message that using antibacterials for acute nonspecific respiratory tract infections put their children at greater risk of a future resistant infection. U.K. health care is managed by a government-financed national system which sets explicit priorities to enhance public health through specific incentives. Medications are managed through national formularies with performance monitoring of antibacterial drug prescribing. The U.K.'s campaign, "Antibiotics: Don't Wear Me Out," targeted the general public with the message that controlling antibacterial drug resistance benefits everyone.

Successful strategies to further reduce antibacterial drug overuse are likely to have strong central leadership, with explicit priorities emphasizing societal benefit, and be supported by

robust financial and regulatory incentives. Professional and public education, while necessary, are usually not sufficient to change behavior; successful strategies for improving antibacterial use are usually multifaceted. More data are needed regarding outcomes of strategies to reduce antibacterial use and whether decreasing use may be affecting trends in antimicrobial resistance.

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Chapter 4. Methods I: Misclassification and validation of pneumonia hospitalizations in a primary care electronic medical record database

To take advantage of the increasingly available observational electronic medical record data to support post-marketing drug effectiveness and drug safety surveillance, it is important to validate the outcomes that will be used in such studies. In particular, hospitalization diagnoses are important markers of adverse event severity. To be able to identify adverse events within a specified exposure time window, it is also important to able to ascertain the precision of hospitalization dates. Validation of The Health Improvement Network (THIN) adverse events and hospitalization dates in this study can thus inform many important future observational THIN studies of the outcomes of medication use, for antibacterial drugs as well as for other types of medications. The hypothesis is that hospitalization diagnoses and dates will be valid within clinically important limits.

After U.S. FDA approval, drugs are used for many more patients, for a wider variety of indications, and for a more heterogeneous patient population than in pre-approval trials. The importance of post-marketing drug safely surveillance is increasingly recognized. Observational studies can take advantage of accumulating electronic medical record data to enhance post-marketing outcome studies. Electronic data come in two basic flavors, with some overlap. Because they are used for billing, administrative data tend to have information on drugs dispensed, and relatively precise hospital admission dates and discharge diagnoses. Electronic medical records on the other hand tend to have rich longitudinal clinical data at the individual patient level, however inpatient data regarding hospitalizations often are not directly linked to the outpatient record and instead need to be entered manually.

The projects in this dissertation used data from The Health Improvement Network (THIN). THIN is an electronic medical record database containing longitudinal primary care data from patients in the United Kingdom including demographics, visits, diagnoses, prescription medications, laboratory testing, mortality, cause of death, and hospital admissions. However, as indicated above, the software used for THIN was developed as an ambulatory medical record

system; inpatient and ambulatory medical records are not yet integrated in the U.K., and hospitalization data are entered manually by patients' general practitioners after they review patients' hospital discharge summaries.

There are three main areas of uncertainties to be addressed if THIN hospitalization data are to be useful for drug outcome research. First, when THIN hospital admission codes indicate a patient was hospitalized, did the patient truly have an admission to a hospital, or what is the positive predictive value of the THIN hospitalization coded for identifying a hospitalization? Second, if the patient was indeed hospitalized, is the primary discharge diagnosis recorded in THIN the true primary discharge diagnosis from the hospitalization? Third, what is the relationship between the recorded hospital admission date and the true hospital admission date? If the hospitalization is recorded after receipt of the discharge summary, it may be recorded with a later date than the true admission date. Even if the true hospitalization date falls within the exposure window of interest, if the recorded date erroneously falls outside the exposure window of interest, the hospitalization event might be missed.

The objective of this study is to validate hospitalizations in the THIN database. The specific aims were to:

1. Assess the positive predictive value (PPV) of a hospital admission for community acquired pneumonia identified using THIN hospitalization codes. Our hypothesis was that the PPV of a pneumonia hospitalization is 100%.
2. Assess the relationship between THIN hospital admission date and true hospital admission date. Our hypothesis was that 100% of THIN hospitalizations will be recorded as occurring within a 14-day window of the true hospitalization date.

Methods

This study design was a retrospective cohort study. Adults with ambulatory primary care visits for acute nonspecific respiratory tract infections in the THIN database from June, 1985

through August, 2006 were identified using Read diagnostic codes. (Table 1) These visits are hereafter referred to as our cohort of ARI visits.

Study Outcome

Adults with overnight hospital admissions for community acquired pneumonia within 30 days of an ambulatory encounter for acute respiratory tract infection in the THIN database were identified using Read diagnostic codes for pneumonia and THIN hospitalization codes. Of these adults with hospital admissions for pneumonia, sixty were randomly selected for validation. Validation of 60 hospital admissions for pneumonia was feasible given available resources, and would give us the power to test both of our hypotheses within clinically significant limits (see below).

We focused on hospitalizations for community acquired pneumonia for this aim for several reasons. First, hospital admission for community acquired pneumonia is a relatively common event following ARI, giving us a robust sample of reasonably similar outcomes to be able to correctly estimate the measurement error. Additionally, we had a separate clinical research interest in whether risk of hospitalization for community acquired pneumonia is elevated after an ARI visit, and whether antibiotic treatment reduces this risk. We pursued this related question in Chapter 7 of this dissertation.

Gold Standard Outcome

Each subject's de-identified THIN patient and practice identification codes, and a date window including 90 days before and following the ARI visit were forwarded to the subject's general practitioner (GP) through EPIC Database Research Company. The GPs identified records from their patients' charts that are supplementary to the electronic THIN data. For the specified patients, GPs returned de-identified photocopies of all hospitalization discharge summaries, consultants' letters, and any additional material related to any overnight hospitalizations within the specified date window.

EPIC checked the data to ensure complete anonymization prior to forwarding them to investigators. We then examined patient records for the following information:

a) Did the subject have an overnight hospitalization within the window?

b) What was the hospital admission date?

c) What were the primary and additional discharge diagnoses?

This study was approved by the University of Pennsylvania Institutional Review Board and the Medical Research Ethics Committee, National Research Ethics Service of the U.K. National Health Service.

Analysis

For our first aim, the PPV of a THIN hospital admission for community acquired pneumonia during the 30 days following the ARI visit was calculated as the number of patients with GP-validated hospital admissions divided by the total number of THIN hospitalizations, with exact binomial confidence intervals. The PPV of the *specific pneumonia* THIN adverse event hospitalization diagnosis was calculated as the number of patients with confirmed GP-validated *pneumonia* diagnoses divided by the total number of confirmed hospitalizations, with exact 95% binomial confidence intervals. Two-sided two-sample t-tests were used to compare means of characteristics between admitted and nonadmitted patients, assuming unequal variances between groups.

For our second aim, analysis included data only for those patients with confirmed overnight hospital admissions. The mean and median absolute difference in dates between the THIN and the actual hospital admission date were defined. Stata, versions 9.2 and 10.0, were used for all analyses (StataCorp College Station TX, 29-Jan 2007 and 1 Oct 2009).

Power

PPV of a hospital admission for community acquired pneumonia

We included 60 patients in this validation study. Lewis and colleagues, using the General Practice Research Database, a precursor to THIN, found the PPV for identifying inflammatory bowel disease hospitalizations was only near 50%.[1] With a 2-sided α=0.05, and N=60, examples of confidence intervals predicted for a widely representative range of PPVs are shown in Table 2.

Table 2. Positive Predictive Value (PPV) of a THIN-coded Hospital Admission for Community Acquired Pneumonia after a Ambulatory THIN ARI Visit

PPV	95% confidence interval	
	N=30	N=60
0.50	0.31-0.69	0.37-0.63
0.75	0.57-0.90	0.62-0.85
0.80	0.61-0.92	0.68-0.89
0.85	0.69-0.96	0.73-0.93
0.90	0.73-0.98	0.79-0.96
0.95	0.78-0.99	0.86-0.99

The better the PPV (closer to 100%) the narrower the 95% confidence limits. As shown above, with 60 patients, even with a low PPV, we should have the power to estimate the PPV of a THIN pneumonia hospitalization within clinically significant limits.

Difference, THIN hospitalization date vs. true hospitalization date

Our power to detect a difference in days between the THIN hospitalization date and the true hospitalization date is most dependent on the PPV and the standard deviation of the distribution of differences. Lewis and colleagues compared the first mention of inflammatory bowel disease diagnoses with the diagnosis dates confirmed by GP survey; these date differences showed a highly skewed distribution with an estimated standard deviation approximately twice the mean days difference.[1] For our patients with documented hospitalizations within the date window, the differences between the true and documented hospitalization dates are constrained by our date window 30 days following the ARI visit and thus are unlikely to be as skewed. McPhee and colleagues validated mammogram and PAP smear recall dates and analyzed mean date differences.[2] They found standard deviations (SDs) equal to the mean days difference.

Using a 2-sided α=0.05, with N=60, with our estimated standard deviation equal to the mean days difference, even with a PPV as low as 50%, we would have 99% power to detect an

absolute difference as small as 1-2 days. As differences smaller than this would not be clinically significant, and time of hospitalization is not recorded in THIN, the analysis does not need to be sensitive down to the level of hours, or fraction of a day. With a PPV of 75%, even if our standard deviation is twice the mean days difference, we would still have 92% power to detect a clinically important difference in days. In Table 3, we present power estimates based on a targeted collection of 60 hospitalization records and a conservative collection of 30 hospitalization records, based on PPV for hospitalization, missing records or physician non-participation.

Table 3. Power, Difference, THIN Hospitalization Date vs. True Hospitalization Date, α, 2-sided = 0.05,

Days	SD (days)	PPV	Power	
			N=30	N=60
30	60	0.50	0.78	0.49
30	30	0.50	0.99	0.97
30	60	0.75	0.92	0.65
30	30	0.75	0.99	0.99
14	28	0.50	0.78	0.49
14	28	0.75	0.92	0.65
14	14	0.50	0.99	0.97
7	14	0.50	0.78	0.49
7	14	0.75	0.92	0.65
7	7	0.50	0.99	0.97
2	4	0.50	0.78	0.49
2	4	0.75	0.92	0.65
2	2	0.50	0.99	0.97

Chapter 4
Results

Predictive value of a THIN pneumonia hospitalization

Out of 60 patients with THIN pneumonia hospitalizations randomly selected and sent to EPIC for validation, 59 chart records were received from GPs (one GP did not respond to the inquiry). Fifty two of these 59 patients were admitted to the hospital for an overnight stay within the 90-day window on each side of the ARI index visit date, giving a PPV of a THIN hospital admission of 88% (95% confidence interval 77% to 95%). There was no difference in gender or age between the admitted vs. the unadmitted patients. Twenty-three of 53 (43%) admitted patients and 3 of 7 (43%) unadmitted patients were male, Fisher's exact test p=0.99. The mean age of admitted patients was 52 years vs. 44 years for unadmitted patients, (p=0.33). One of these admissions did not have a discharge diagnosis of pneumonia according to the GPs chart records, giving a PPV for THIN pneumonia admission of 51/59 or 86% (95% c.i. 75% to 94%);. All of these admissions had pneumonia as the primary admission diagnosis.

Difference between THIN hospitalization date and true hospital admission date

Of the 52 patients with valid THIN hospitalizations, 50 were actually admitted within 14 days of the date recorded in THIN, with a range of -2 to +18 days. The absolute median difference between the THIN and validated admission dates was 1 day and the absolute mean difference was 3.1 days.

In 16 of the 52 admitted patients, the THIN admission date was the discharge date listed on the GP hospital discharge notes.

Discussion

Electronic medical records are a potentially enormous and rich source of data to examine, evaluate, and compare clinical outcomes. Such large datasets can provide impressive results, however, size is of little value here if the data are of poor quality, and proceeding to analysis without validating important study parameters can corrupt the value of any results and

lead us to erroneous conclusions. To take advantage of the increasingly available observational electronic medical record data to support post-marketing drug safety surveillance, it is important to validate the outcomes that will be used in such studies.[1, 3] Hospitalization diagnoses are particularly important markers of adverse event severity. To be able to identify acute events within a specified time window related to acute exposure, it is also important to able to ascertain the precision and accuracy of hospitalization dates. This study had the power to validate THIN hospitalization dates within clinically important limits.

Our PPV for THIN pneumonia hospitalization was as good or better than the PPV for acute care date estimation methods described in other studies.[1, 2, 4-7] There were no obvious differences between the patient admissions that were validated and those that were not. Our finding that 16 of the 52 admitted patients had the true hospital discharge date as the recorded THIN admission date implies that the accuracy of admission dates might be better for conditions that are associated with shorter vs. longer hospitalizations,.

Virtually all (50/52 or 96.1%) of the recorded hospital admission dates were accurate within a 14-day window, providing support for our ability to identify adverse events resulting in hospitalizations related to acute drug exposures within THIN.

Limitations

Bias: Limitations of this study include that we were limited by the validity of our presumed gold standard data from the GP charts. The GPs were highly unlikely to find discharge summaries when a hospitalization did not actually take place, however, if the charts were missing discharge summaries from true hospitalizations, or if the GPs were unable to find them, then we may have misclassified some hospitalization diagnoses as false positives. This information bias would tend to bias us away from the null hypothesis of 100% specificity. This project is strengthened by the fact that THIN GPs are not just recruited for this study, but have a longitudinal relationship with EPIC Database Research Company. Responding to research

queries is part of this relationship and they are financially compensated for their time and effort. EPIC thus has a track record of successful validation efforts similar to this study.[1, 8-10]

Generalizability: PPV and date differences may vary with patient age. PPV and date differences may vary with diagnosis type; one potential source of this variation is the association of discharge date with THIN recorded admission date found in our study. We had limited power to detect differences in PPV and date differences between hospitalization diagnoses included in this study, and did not address outcomes in addition to the included pneumonia hospitalization diagnoses in adults. The validity of other outcomes, for example, death, was not addressed, nor were adverse events for children; our results are not necessarily generalizable to patients with different ages and different hospitalization diagnoses than included in this study. We had more power to validate the PPV of any hospitalization than we did to validate diagnosis-specific hospitalization. The validity of medication exposure was not addressed. The validity of THIN for identifying prescriptions is usually considered good, as the electronic medical record entry actually generates the patient's prescription. There are data from early adoption of the computer system that support this validity. [9, 10]

Pharmacoepidemiologic studies using electronic medical record data regarding outcomes related to acute outpatient exposures depend on the ability to accurately and precisely identify the timing of valid outcomes. THIN hospitalization codes performed well in identifying the timing of hospitalization events of interest. This study supports observational THIN studies regarding additional medication use outcomes, especially outcomes related to acute conditions and acute exposures to antibiotics as well as other medications. Future studies should also pursue validating additional THIN outcomes, including those for children, further increasing the generalizability of our findings.

It is likely that electronic medical records will become increasing complex, potentially integrating patients' ambulatory and inpatient data. While this may improve the precision of admission diagnoses and dates, it could also introduce additional misclassification. We will need

to continue to consider the precision of these clinical measures as we look forward to using these increasingly available data to help improve health outcomes,.

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Chapter 5

Chapter 5. Methods II: Using observational clustered data to study rare outcomes, controlling bias and confounding

Drug benefits are established in pre-marketing clinical trials. These randomized clinical trials are designed to be conservative in demonstrating drug efficacy and liberal in measuring drug safety;they assess whether the drug produces benefit when users are perfectly compliant under otherwise ideal circumstances, and are typically evaluated using intention to treat (ITT) analyses.[1] However this type of trial, may not be the best way to study risks under conditions of less-than-complete adherence in real-world practice settings where it's not always straightforward to determine who is taking the drug in question. In addition, small pre-marketing clinical trials are usually too small to evaluate even moderately common drug risks.[2, 3] Large prospective randomized trials are not feasible for many research questions regarding moderate to small drug risks. Most warnings of drug-related adverse event risks come from case reports, which, usually lacking an exposed denominator, and subject to under- and biased reporting, do not establish the true relative risk of adverse event risks related to drug exposure vs. non-exposure.[3] Studies of exposures and outcomes using large administrative datasets without clinical data often do not address complex confounding issues, especially confounding by indication.[4] For these reasons, studies utilizing large databases are often better-suited to help us understand drugs' effectiveness and risks in the real-world practice setting.

The growing availability of electronic medical records can provide databases containing large scale observational data. The U.K.'s The Health Improvement Network (THIN) electronic medical record database offers access to individual patients' longitudinal demographic, clinical, pharmaceutical, and outcome data. These data are often more accessible than are the resources for performing very large randomized clinical trials, however if observational data are used to assess drug use outcomes, great care needs to be taken to assure that the drug -exposed and -unexposed groups are as comparable as possible.[5].

We used a subset of the entire THIN cohort with an office visit for acute nonspecific respiratory infection (ARI), and compared adverse event rates of antibacterial drug-exposed vs.

antibacterial-unexposed patients. By limiting the comparison to patients with ARI visits, we promoted comparability between exposed and unexposed patients in this cohort of otherwise similar patients.

We sought an unbiased estimate for the association between antibacterial drug exposure for ARIs and our adverse event outcome. Ideally, we would want to know, for the same patient with the same ARI visit, what is the relative risk of an adverse event if he/she receives a prescription for antibiotics at that ARI visit vs. if he/she doesn't receive antibacterial drugs at that visit, or the 'counterfactual' estimate.[6] Of course, there is no way to compare outcomes of antibacterial drug treatment vs. non-treatment for the same patient at the same visit. A randomized clinical trial is the best way to approximate this counterfactual approach; successful randomization would ensure that exposures are balanced in terms of covariates at all levels. As discussed above, randomized trials to explore the risks of potential rare events are not always feasible for every clinical question. Using observational data, we aimed to estimate this counterfactual effect by obtaining the relative risk (or odds ratio or risk difference) of similar patients exposed vs. unexposed to antibacterial drugs. To the extent that antibacterial prescribing was random among patients with ARI visits, and that all exposed and unexposed patients were otherwise at equal risk of an adverse event outcome, this estimate would provide an unbiased estimate of this counterfactual effect.

However, our research problem presented three major challenges to obtaining this unbiased estimate of adverse event risks related to antibacterial drug use. First, preliminary data showed that there was likely to be significant clustering by practice; exposure, outcomes, and covariates within practices will likely be much more similar than exposure, outcomes and covariates across (or between) practices. As a result, an additional subject within a cluster adds less information than would an additional subject from a different cluster. This effect on the variance, and resultant loss of power by the use of cluster sampling instead of simple random sampling is termed the design effect, and needed to be accounted for in the analysis.

Second, antibacterial drug prescribing *and* baseline adverse event risk may both vary

widely between (across) practices, and this may result in a large degree of confounding by practice. Some practices may be more likely than others to prescribe antibacterials as they might have sicker or more demanding patients and/or physicians with higher tendency to use antibacterials, thus there may be different ratios of untreated vs. treated patient visits between practices. Preliminary data showed that antibacterial drug exposure is indeed highly variable and highly related to practice. Even within practice, treatment allocation may not be random but instead may be associated with many measured and unmeasured practice- and patient-level covariates. Practices may also vary in their patients' baseline risk of adverse events; some practices may be more likely than others to experience severe adverse events due to observed and unobserved factors; for example, they may include more medically fragile patients. Because of this potentially intense clustering and confounding by practice, involving both exposure and outcome, we needed to stratify our analysis by practice. We sought the counterfactual effect of antibacterial drug exposure, specifically the relative risk of adverse event for a patient in a particular practice at a particular time *exposed* to antibacterials vs. that same patient in that same practice at that same time *unexposed* to antibacterials. To minimize, as much as possible, the confounding by practice, our analysis needed to decompose overall antibiotic effects into the between- practice effects and the within-practice effects, because we were really interested in only these within-practice estimates of antibacterial drug risks.

Our third major analytic challenge was that our outcome was exceedingly rare. As we stratified on practice to consider these within-practice estimates, there woud be many practices expected to have zero outcomes. In this situation, conventional methods of regression conditional on practice may not have been successful because of sparse data; we would lose all information from the practices with zero outcomes. These zero-event practice sites added to the denominator of total exposure to antibacterial drugs. There is reason to believe that adverse events would not be distributed randomly across practices, but instead that practices with zero outcomes may be different, in both measured and unmeasured ways, than practices with adverse event outcomes. To maximize the knowledge we could gain from this study, we wanted our

analytic methods to allow us to make use of the information from practices with zero outcomes. We explored this problem using methods to adjust for confounding with different types of multivariable regression techniques. These different multivariable methods utilized different assumptions, and may provide different, complementary, estimates, giving us a multifaceted picture of the relationship between exposure and outcome. .We needed to consider analytic methods suitable for trials of very rare outcomes; in some ways, this problem was similar to performing meta-analyses of studies of rare events.[7]

The objective of this study was to compare various potential methods to control bias and confounding while using a primary care observational database to study rare acute outcomes. The primary aim was to compare methods for controlling bias and confounding caused by measured variables. Our secondary aim was to compare methods to evaluate the impact of unmeasured variables, including instrumental variable analysis. We hypothesized that standard methods for controlling bias and confounding by measured and unmeasured variables can be adapted for observational studies of clustered rare outcomes.

Methods

A. *Description of the cohort*

The data source for this retrospective cohort study was the September 2007 dataset from The Health Improvement Network (THIN). A cohort of adult THIN primary care visits for nonspecific ARIs between January 1, 1985 and December 31, 2006 was selected from for THIN continuously-enrolled valid patients ≥18 years of age in THIN practices with valid data using the Read diagnostic codes for nonspecific respiratory infections listed in Chapter 3, Table 1. Codes for respiratory infections were excluded if some guidelines recommend antibacterial treatment, such as *streptococcal* pharyngitis, otitis media and sinusitis. Because data from multiple visits within the same ARI episode may tend to be highly correlated, visits were grouped if they occurred within a two-week period. The outcome of interest for this study was severe adverse event, defined as hospitalization within 14 days following the index ARI visit with, cardiac arrhythmia, diarrhea, hepatic toxicity, hypersensitivity, photo-toxicity, renal toxicity, or seizure.

Exposure of interest was antibiotic prescription within one day of the index ARI visit; antibacterial drugs of interest included oral antibacterials typically used for respiratory infections. We excluded topical, vaginal, ophthalmologic, otic, and parenteral antibacterials, and those typically used for tuberculosis, fungal and parasitic infections. Covariates included patient age at time of visit, sex, visit year, Townsend score (a measure of neighborhood material deprivation), neighborhood racial mix, and patient comorbidity history, with comorbiditites grouped into the categories shown in Table 4 (Lewis, J.D., unpublished data). Considering what clinical data might be relevant from a clinical aspect to help predict indication for antibacterial treatment of ARIs, we also included alternative summary measures of the intensity of medical care use, including the number of THIN recorded comorbidities,[8] and the number of different classes of medications[8, 9] and number of visits within the year prior to the index ARI visit.

Table 4. Comorbidity Categories

Comorbidity Categories	
Congestive heart failure	**Malignancy**
Lung disease	**Metastatic malignancy**
Rheumatologic disease	**Mild liver disease**
Cerebrovascular disease	**Moderate/severe liver disease**
Dementia	**Myocardial infarction**
Diabetes	**Peptic ulcer disease**
Weakness	**Peripheral vascular disease**
HIV	**Kidney disease**

B. Methods to model conditional rare outcomes

We compared several different multivariable methods to model hospitalization within 14 days of the ARI visit for any severe adverse event, Table 5. As described above, we are really interested in the counterfactual difference in risk of an extremely rare adverse event for an ARI patient in a particular practice exposed to an antibacterial drug vs. the risk for that same patient visiting the same practice for that same ARI at the same time, *not* exposed to an antibacterial. To estimate the counterfactual *within-practice* outcome of interest, we explored several ways to decompose

within- vs. among-practice effects of antibacterial ldrug exposure, thus minimizing confounding by practice, in the setting of our extraordinarily rare outcomes and extreme imbalance of exposure and, potentially, outcomes across groups. We also sought methods that could minimize the bias in the estimates for our very rare outcome by using data from practices with no adverse events

1. *Marginal Models (GEE method):* We first considered implementing Generalized Estimating Equations (GEE), using Stata's xtgee command. GEE, a marginal model, can be used to adjust for clustering[10] and is typically not difficult to implement with a relatively large number of cluster groups (such as the number of patients and practices in this study). GEE could potentially help us decompose the within- and between-practice effects to focus on the within-practice association between antibacterial drugs and adverse events, our contrast of interest. However there are several reasons why GEE might not be an ideal method for this study. First, using GEE requires us to specify a correlation structure, although GEE is relatively robust to misspecification in this regard. Second, it may be difficult to address multiple levels of clustering in GEE. Third, GEE derives population-averaged outcomes. With normally-distributed outcomes and a linear model, the marginal effects derived from GEE, or the average differences for subject strata defined for different covariate values, can be expected to be the same as the subject-specific effects, or expected difference for individual subjects with different covariate values. However, this may not hold true for dichotomous outcome measures where the link function between predictors and the probability of an outcome is nonlinear.[11] Fourth, since GEE is not based upon maximum likelihood theory, we could not utilize standard methods used with maximum likelihood-based regression to test model fit and compare models.[12]

2. *Subject-specific methods*

a. *Random effects methods:* Logistic regression models would be the most conventional approach for studying our dichotomous yes/no outcome. We used Stata's logistic function to model adverse event risk on antibacterial drug use. , We decomposed antibacterial drug exposure into between practice and within practice exposures; and we used robust variance estimators to adjust standard errors for clustering by practice.

A potential limitation of these methods is that logistic models cannot make use of data from practices with zero outcomes. If the risk of an adverse event without antibacterial drug exposure is zero, the odds of an adverse event without antibacterial exposure is also zero. No matter what the odds of an adverse event *with* antibacterial exposure, the denominator of the odds ratio will be zero, and thus there will be no odds ratio result for this practice. This will also be a problem with some practices with non-zero outcomes if the outcomes are all in the exposed group, giving a non-zero odds in the numerator, but the odds for the unexposed would still be zero. We would thus lose all information from these practices with zero odds in the unexposed. As discussed above, there is reason to believe that practices with zero odds in the unexposed may be different from practices with more adverse event outcomes, and, this method could provide biased estimates of our true conditional within-practice effect of interest.

b. *Mixed effects methods: Mixed effects conditional regression models* could provide estimates of both fixed and random effects. This could be accomplished with Stata's xtmelogit, or Stata's xtlogit and xtreg, using the mle option. However, we were not necessarily interested in modeling the random effect of practice in the association of the antibacterial drug and adverse events, we were interested in the within-practice effects, as explained above. In addition, random effects models can be very slow and cumbersome and would not be the most efficient for our research problem.

c. *Fixed effects (stratified) methods:* Fixed effects logistic or linear models can allow random intercepts for the individual practices, allowing us to estimate within-practice effects of interest.

i. *Conditional fixed effects logistic regression models*: Conditional fixed effects logistic models could decompose within- and among- practice associations between antibacterial drug use and adverse events. Using Stata's clogit and xtlogit functions, we modeled adverse event risk on antibacterial drug use, conditioning on practice. As discussed above, a potential limitation of these logistic methods is that logistic models cannot make use of data from practices with zero outcomes.

ii. *Conditional fixed-effects linear regression models:* Similar to conditional logistic regression models, linear conditional models could provide fixed effects estimates, conditioning on practice. This model would be inappropriate with a non-rare dichotomous outcome. However, our outcome was sufficiently rare that all estimated outcomes would be <1. As our anticipated effect size (risk) is small, there should not be an important difference using an additive instead of a multiplicative model. Using linear regression we could operate on the risk-difference scale; this allowed us to make use of information from practices with zero outcomes, similar to what can be done with meta-analysis of very rare outcomes.[13, 14] Conditional linear regression, using Stata's xtreg, can fit fixed effects longitudinal models with linear outcomes.Using Stata's xtreg, we again decomposed within- and among-practice effects, This result should be similar to using area average as an instrumental variable in helping to control for confounding by cluster.[14]

As these methods are based upon maximum likelihood theory, we used standard methods to test model fit and compare models, including the likelihood ratio test and Akaike's Information Criterion (AIC).

C. Methods to adjust for confounding

1. Confounding by measured variables

a. *Propensity Score analysis:*

Propensity scores can be useful for modeling rare outcomes with common treatments.[5, 15-17] They have been used in observational studies to assure that potential confounders are balanced within the treatment and control groups being compared. In propensity score analysis, the risk of outcome is estimated for treated vs. untreated patients within strata of patients with the same propensity for being treated, based on their other measured covariates. However, standard propensity score analysis is far from ideal for this study. We are concerned with two different levels of confounding: within-practice confounders and between practice confounders. If, as expected, antibiotic exposure is heavily related to practice, we could need a separate propensity

score model within each practice. This need might arise if, for example, for a given patient indication, clinicians at two different practices might prescribe antibacterial medications at different rates. A propensity score developed with patient-level factors but across all practices might balance poorly within practices. Thus, to achieve covariate balance might require inclusion of different important variables and their interactions in different practices, as well as variable-by-practice interaction terms, which could be quite cumbersome, if not impossible. Then, we would also need to adjust further for between-practice confounders. As we don't have adequate physician-level data here, we were missing that dimension, and our models' performance were be handicapped by this limitation.

We determined the probability of antibacterial drug exposure within each practice, defined as the propensity score for each practice, using the same covariates for each propensity score. We performed multivariable analysis, considering several options for utilizing the propensity score: Additional covariates could be added to models in addition to the propensity score as needed.

1. *Matching by propensity score* [18-20]: This was not a good option for our study as exposure is extremely unbalanced between practices; matching would be difficult, and many visits would likely be unmatched, and thus not included in the analysis.

2. *Stratifying by propensity score*: We stratified the propensity score for each practice into quantiles and then compared outcomes for treated vs. untreated visits within each propensity score stratum. [15, 20]

3. *Using the propensity score directly in the model as a covariate*[20]. This should result in estimates similar to those using xtlogit above, decomposing estimates into within- and among- practice effects.

4. *Using a weighted propensity score with inverse probability of treatment weighting*,[21] assigning a [pw=weight] for each ARI visit equal to 1/propensity score for that practice if an antibacterial drug was received, and equal to 1/(1-propensity score) if an antibacterial drug was not received. We explored using this propensity score method within our

conditional fixed effects model.

The purpose of pursuing these methods was to allow us to simultaneously control for patient-level and practice-level factors, to have strata that reflected groups of practices with similar propensity to prescribe antibiotics, and to have sufficient numbers of adverse events within strata to avoid zero-cell problems.

2. Confounding by unmeasured variables

a. *Instrumental variable analysis::*

The analyses described above could help control for measured confounders but would not address confounders that are unmeasured.[5] An instrumental variable (IV) is an observable factor related to treatment choice but that is not related to study outcomes either directly or indirectly through pathways through unmeasured variables, except through its effect on treatment. Thus, an IV can be considered a variable that induces, or simulates, random variation in the study treatment assignment.[22] If a suitable instrument can be found, it can help adjust for unmeasured confounders.[23-25] An IV relies on the following assumptions: First, an IV should affect treatment, or be associated with the treatment through their mutual association with a common cause. Second, an IV should be unrelated (or randomly associated with) patient characteristics. An third, an IV should be related to the outcome only through its association with the treatment. If an adequate instrumental variable (IV) can be identified, an IV technique can help control for unmeasured confounding.

Visit provider prescribing history was likely to be associated with the probability of exposure and unlikely to be associated with adverse event outcome, except through the exposure of interest, antibacterial medications; provider prescribing history was thus a candidate for instrumental variable. Ideally, we could perform an instrumental variable analysis, using the past prescribing history of the visit provider as the instrument, including the other covariates. We could consider that provider's most recent previous ARI treatment as an instrument (antibacterial treatment vs. none)[23, 24], that clinician's antibacterial prescribing rate,[14] and/or whether that clinician is a high vs. low antibacterial prescriber.[18] However, unfortunately, prescriber is not a

reliable field in THIN (Bhuller, H, personal communication, October 6, 2008). Alternatively, practice could be used as an instrument; as we expect that practice may be highly correlated with exposure. We explored whether IV methods can provide estimates of fixed effects results, conditional on practice.

b. *Randomization-test based inference*

In randomization inference, each subject has two potential responses, the response observed if the subject was assigned to treatment, and the alternative response observed if that same subject were assigned to control, or no treatment. The treatment effect tau is defined as the difference in outcome between a treated individual and the alternative potential outcome if that same individual was untreated. If we assume no hidden bias, and an additive treatment effect, there is a constant treatment effect tau such that every subject would have the same tau if treated with antibacterial drugs vs. if that subject was untreated. Control responses might vary from subject to subject, but treatment should change the outcome by the same amount. Our null hypothesis was that, adjusted for covariates, if there was no hidden bias, treatment status was distributed randomly with respect to outcome. The alternative hypothesis is that there was a significant relationship between outcome and treatment status.[5, 26]

The potential benefit of randomization-test-based methods is that they are assumption free, i.e., they do not rely on the assumptions behind any model. Nor do they rely on large sample theory as a basis for variance estimates [27, 28] But these methods are not without challenges.

First, in the application of interest, the outcomes across multiple clinical practices, randomization-test-based methods must consider the possibility of confounding by practice. We would need to consider the choice of a test statistic with this potential for confounding in mind. Second, the outcomes in this study were rare. Care must be taken that the method chosen does not unintentionally drop practices because no events occur. Third, although randomization-test-based methods control for Type I error, the study of adverse events demands special attention to power (or Type II error).

Several alternative methods for implementing randomization-test-based methods could be compared with model-based methods. An initial issue is whether the effect of exposure is to be expressed on a multiplicative score (as with an odds ratio) or on an additive scale (as with a risk difference). A key exposition on the use of randomization-test-based methods for multicenter data with binary outcomes,[27] assumes that the effect should be measured on an additive scale. But the methods should not be confined to additive estimates.

Stratified rank based methods as described by Rosenbaum [26] (section 7) and Small, [29] rely less on statistical models to obtain a test statistic, while they allow use of regression methods to adjust for covariates. However, these methods would not be straightforward to implement for this study as they rely on grid searches and inverting test-statistics[30] (section 9.2) to obtain point estimates and confidence bounds, would have had to be adapted for binary outcomes, and would need to address confounding by practice. Thus, we do not include these methods in our analysis but plan to address this topic in a future project.

We compared our results obtained using the methods described above.

c. *Simulations:*

When we use simulated data, in contrast to when we use real data, we know the underlying true parameter values and have complete control over the data structure. A simulated dataset is relatively easy to construct, and, while simplistic, can be structured to reflect almost any type of underlying data values and distribution. We can examine the effect of varying one parameter at a time, or multiple parameters in combination, holding everything else constant. Simulations can help us explore what happens to our expected bias and power as we vary our data structure and model assumptions throughout an endless variety of possible variations, and how robust our coverage and power are to our model assumptions.. We generated simulated datasets using known distributions for patient-level parameters of interest to reflect conditions similar to our data: large (~2 million visits relevant to the study of antibacterial drug use) highly hierarchical (200 practices), extremely unbalanced exposure across clusters (practices), and rare outcomes with lots of zero-outcome cells. We compared the performance of the different types of

models described above in describing the stipulated values in terms of bias and power with very rare events and highly clustered data. We also used these simulations to explore the effect of different levels of data clustering, the influence of parameter variability between clusters, and how robust our results were to confounding due to unmeasured variables.

Each practice was stipulated to have a different baseline rate of antibacterial drug use, with a mean risk of antibacterial drug exposure of 0.60 (60%), and a standard deviation of 0.2 (20%) across practices. Each practice was stipulated to have a different baseline risk of an adverse event, with a mean of 0.0000866 and a standard deviation of ± 0.00005 on the additive scale. Based upon preliminary data (Chapter 6), the parameter for the difference in rare severe adverse event risk for those exposed to antibacterial drugs vs. for those not exposed was stipulated at -0.0000411 (a protective effect of 4.11 per 100,000 exposures). Each practice was stipulated to have a different baseline risk of the continuous covariate (for example, centered weight, with a mean of 0 and a standard deviation of 15 kg.). This covariate was modeled both as a true confounder, associated with both exposure and outcome (beta=25 and beta = 0.0000045871, respectively), and a noise covariate, not associated with exposure but included in the model for the outcome (same beta = 0.0000045871).

Using the simulated datasets, we implemented Stata's xtreg to develop a conditional fixed effects linear model, modeling the risk of severe adverse event on antibacterial drug exposure using 200 simulations and an alpha of 0.05. For each run, we report the mean of the regression slopes from the simulation model, which is the risk difference for adverse event comparing antibacterial exposed vs. unexposed visits, to compare with the stipulated slope used to generate the data. We also report the number of zero-event practices, and the estimated power of the model to show a difference in adverse event risks between antibacterial-treated and untreated visits.

Our primary analysis used 200 practices (clusters) with 10,000 patient visits each, variable antibacterial drug exposure and adverse event risk between practices, and no unmeasured covariates. For subsequent analyses, we varied the number of practices from 50

practices with 40,000 visits per practice up to 400,000 practices with 5 visits per practice, holding the total number of visits constant at 2,000,000. We also explored the effect on the parameter estimate and power of eliminating the variability in exposure and/or outcome risk, and using a multiplicative conditional fixed effects logit model (Stata's xtlogit) for simulation estimates instead of an additive model (Stata's xtreg).

Table 5 Summary of Methods

Summary of Methods		
Method	Potential Advantages	Potential Disadvantages
Methods to model conditional rare outcomes		
1. Marginal models (GEE)	Adjusts for clustering Tolerates high numbers of groups	Requires correlation structure specificiation Difficult to address multiple cluster levels Population-averaged result Not based on maximum likelihood theory
2. Subject-specific methods		
a. Random-effects methods	Can decompose within- and between practice effects	Does not use data from clusters with zero outcomes
b. Mixed-effects methods	Can provide estimates of both fixed and random effects	Random effects not of interest Slow, cumbersome
c. Fixed-effects (stratified) methods		
i. Conditional fixed effects logistic regression		Does not use data from clusters with zero outcomes
ii. Conditional fixed effects linear regression	Can estimate fixed-effects, or within practice effects Can use data from practices with zero outcomes Based on maximum likelihood theory	Cannot be used with a non-rare dichotomous outcome
Methods to adjust for confounding		

1. Confounding by measured variables		
a. Propensity score analysis	Useful with common exposure and rare outcome	With varying exposure by cluster, need a separate propensity score for each cluster Hard to fit a propensity score with highly unbalanced exposure
2. Confounding by unmeasured variables		
a. Instrumental variable analysis	Simulates random treatment assignment	Difficult to find a suitable instrument
b. Randomization test based inference	Assumption-free	May be difficult to adjust for confounding by practice May not be able to use practices with zero outcomes May not have sufficient power Complex to implement Would need to be adpted for binary outcomes
c. Simulations	Can easily vary parameters and assumptions Can test sensitivity of results to unmeasured variables	Complexity more limited than real data Relies on model assumptions

Results

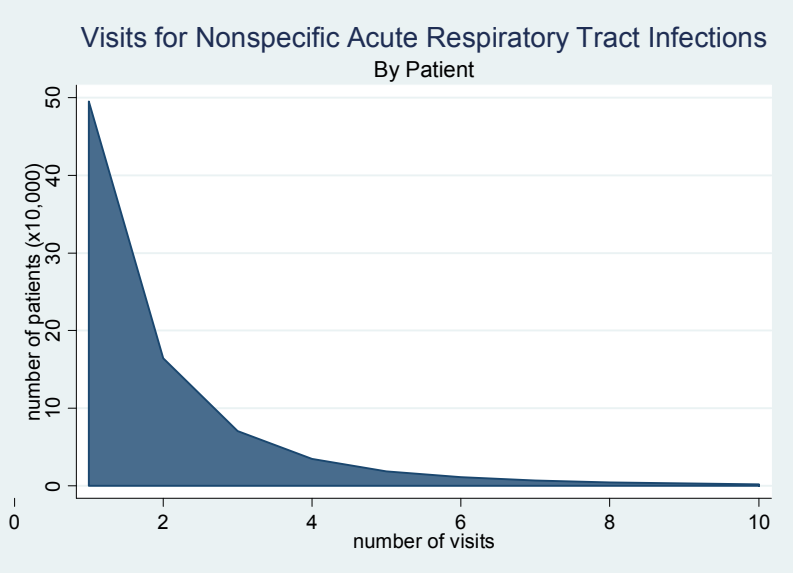
A. Description of the cohort

Our cohort contained 1,646,229 total visits and 1,531,019 grouped visits by 814,283 patients. The mean number of grouped visits per patient was 1.9 (median 1, range 1 to 88 visits). There were 495,129, 164,447, 70,145, 34,373, 18,466 and 748,479 patients with 1,2,3,4,5, and >5 visits, respectively (Table 6, Figure 6).

Table 6 Visits for Acute Nonspecific Respiratory Infections, By Patient

Visits Per Subject	Frequency
1	495129
2	164447
3	70145
4	34373
5	18466
6	10919
7	6713
8	4171
9	2849
10	1914
11	1316
12	919
13	632
14	510
15	362
16	293
17	197
18	163
19	145
20	93
>20	620
TOTAL	**814,283**

Figure 6. Visits for Acute Nonspecific Respiratory Infections, by Patient

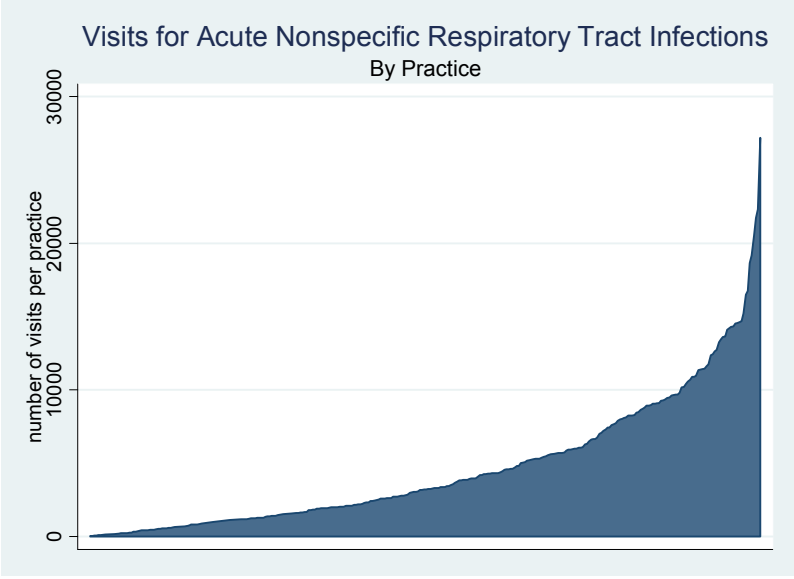


There were 326 practices included in the cohort. The mean number of grouped visits per practice was 4696.4 (median 3232.5, range 24 to 27,190, Table 7 and Figure 7)

Table 7. Visits for Acute Nonspecific Respiratory Infections per Practice

Visits for Acute Nonspecific Respiratory Infections, per Practice	
Visit category	**Number of practices**
0<1000 visits	59
1000-<2000 visits	59
2000-<3000 visits	38
3000-<4000 visits	32
4000-<5000 visits	22
5000-<6000 visits	27
6000-<7000 visits	10
7000-<8000 visits	11
8000-<9000 visits	15
9000-<10,000 visits	14
10,000-<11,000 visits	8
11,000-<30,000 visits	31
TOTAL	**326**

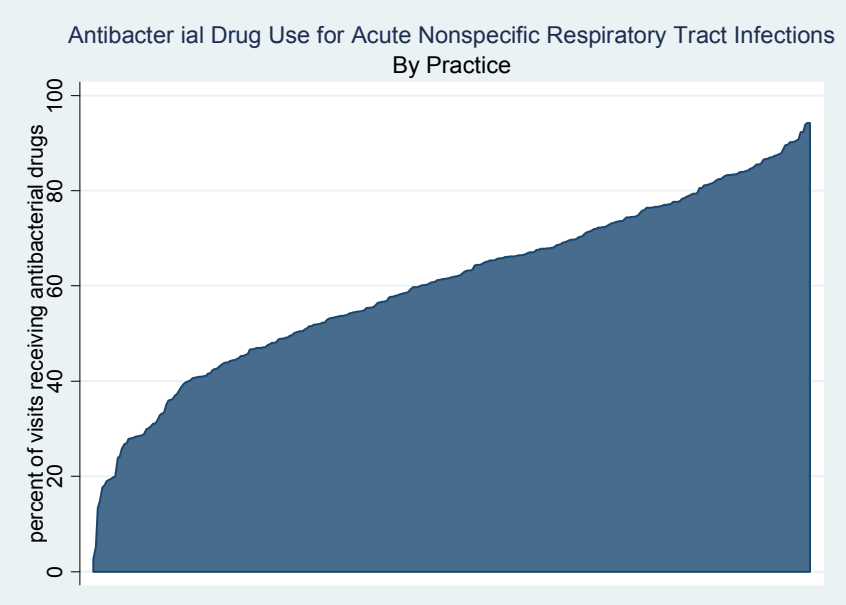
Figure 7. Visits for Acute Nonspecific Respiratory Infections, by Practice



Chapter 5
Antibacterial Drugs

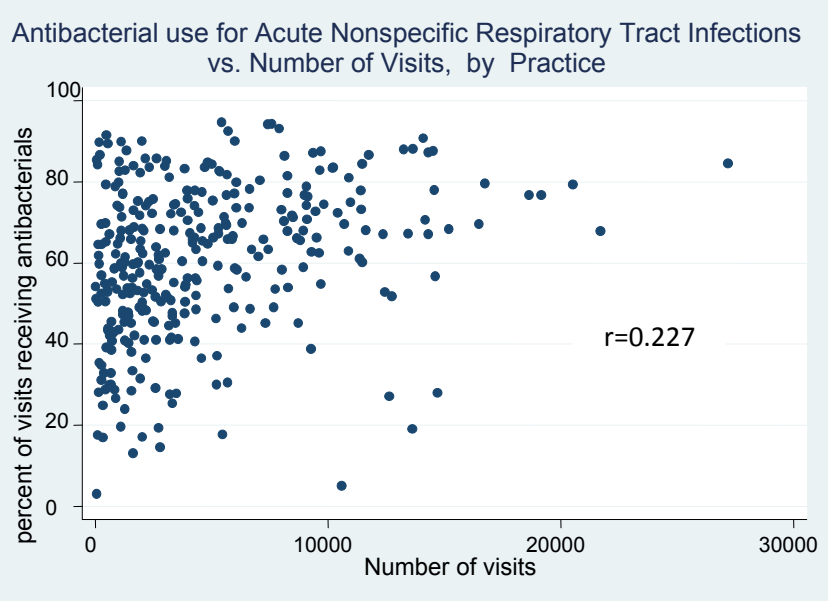
Overall, patients at 65.4% of ARI visits received antibacterial drug prescriptions. As expected, antibacterial prescribing varied widely between practices, from a low of 3.1% to a high of 94.7% of grouped visits receiving antibacterial drug prescriptions (Figure 8).

Figure 8. Antibacterial Drugs for Acute Nonspecific Respiratory Infections, by Practice



This extreme imbalance of antibacterial drug prescribing across practices provided strong evidence that we needed to address any clustering and confounding by practice. There was not a strong association between the number of visits and antibacterial drug use by practice (r=0.227, Figure 9).

Figure 9. Antibacterial Drug Use for Acute Nonspecific Respiratory Tract Infections vs. Number of Visits, by Practice



The outcome was extremely rare with a mean incidence rate of 7.71 per 100,000 grouped visits (8.87 ungrouped, Figure 10). There were 244 practices with zero severe adverse event outcomes within 14 days of grouped visits and 58, 16, 5, 2, and 1 practices with 1, 2, 3, 4, and 5 severe adverse event outcomes, respectively, Table 8.

Figure 10. Severe Adverse Events after Acute Nonspecific Respiratory Infections, by Practice

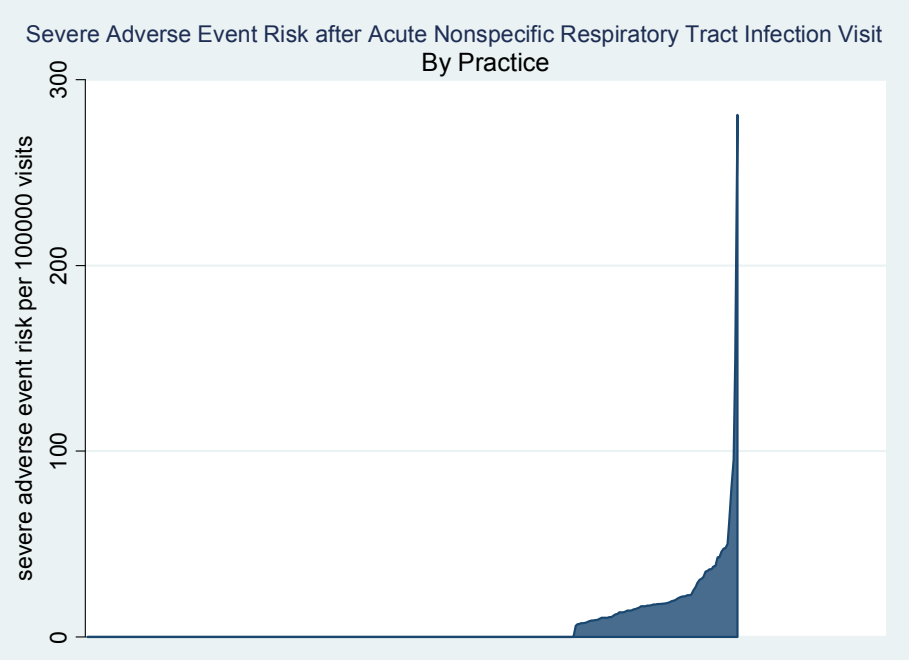


Figure 11. Severe Adverse Events after Acute Nonspecific Respiratory Infections, by Practice, excluding zero-event practices

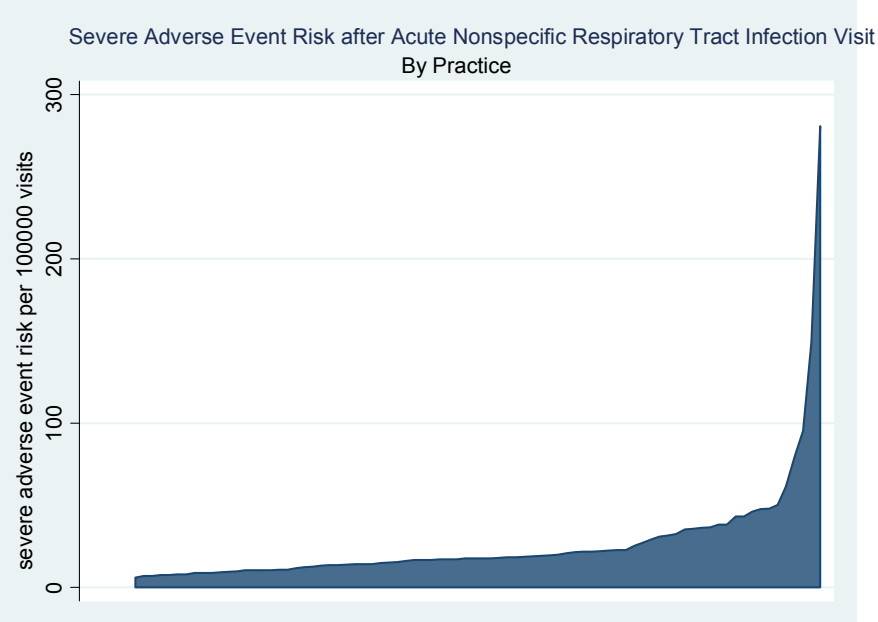


Table 8. Severe Adverse Events within 14 Days of Visit for Acute Nonspecific Respiratory Tract Infection, Grouped Visits

Severe Adverse Events within 14 Days of Acute Nonspecific Respiratory Tract Infection Visit, Grouped Visits	
Severe adverse events	**Number of practices**
0	244
1	58
2	16
3	5
4	2
5	1
TOTAL **118**	**326**

This extreme imbalance of outcome by practice, particularly with many practices (74.8%) experiencing zero outcomes, provided support that we were most likely to achieve unbiased results if we could include information from practices with zero outcomes in the analysis.

B. Methods to model conditional rare outcomes

1. Marginal Models

Generalized estimating equations

Using GEE, with the panel variable specified as patient, the time variable specified as patient's visit number during the cohort, and an exchangeable correlation structure, the unadjusted odds ratio of a severe adverse event within 14 days of the index visit was 1.07 (95% confidence interval 0.73 to 1.57, p=0.73), Table 9, for patients prescribed vs. for those not prescribed antibacterial drugs; as described above, this is a marginal, or population-averaged result and does not adjust for confounding by practice. Adjusted for year, the number of comorbidities, the number of different classes of drugs within the previous year, Townsend

score, and neighborhood racial mix, the covariates, aside from practice, found to be confounders in this model, the OR was 0.82 (95% c.i. 0.55 to 1.23, p=0.34), Table 9 . Substituting an independent correlation structure, the OR was unchanged. However, we found that GEE required too large a memory size to allow us to specify practice as the panel variable. An alternative approach would be to adjust for practice as a categorical variable, however this model would not converge with our data, even without any additional covariates. GEE apparently did not allow us to adjust for confounding by practice, and thus cannot be relied upon to provide an unbiased estimate of the true relationship between antibacterial drug use and adverse events. However, despite this limitation, for our problem, GEE provided similar results to the potentially more robust methods described below.

2. *Subject-specific methods*

Random effects methods:

Logistic regression: Using logistic regression we began to decompose the effects of within-practice vs. across- (or among) practice antibacterial drug exposure. We modeled adverse event risk on antibacterial drug use, using robust variance estimators to adjust for clustering by practice, and decomposing antibacterial exposure into between-practice and within-practice exposure. The unadjusted odds ratio of a severe adverse event within 14 days of the index visit for visits exposed vs. those not exposed to antibacterial drugs was 1.07 (95% c.i. 0.72 to 1.58, p=0.74), Table 9. Adjusted for centered year, the number of different classes of drugs used in the preceding year, the number of visits during the preceding year, and neighborhood racial mix, the conditional within-practice odds ratio of a severe adverse event within 14 days of the index visit for visits exposed vs. those not exposed to antibacterial drugs was 0.79 (95% c.i. 0.51 to 1.22, p=0.29), Table 9.

Fixed effects (stratified) methods: conditional regression

Conditional logistic regression: Implementing conditional logistic regression using Stata's clogit command, with practice as the group variable, the unadjusted odds ratio of a severe adverse event within 14 days of the index visit for visits exposed vs. those not exposed to antibacterial drugs was 0.92 (95% c.i. 0.61 to 1.38, p=0.67), Table 9. Adjusted for the number of different classes of drugs used in the preceding year, the odds ratio was 0.81 (95% confidence interval 0.54 to 1.22, p=0.32). However, data from 244 zero-outcome practices out of 326 total practices, including 842,712 out of 1,531,019 total visits were dropped. There is strong reason to suspect that practices with zero outcomes may differ in important ways from practices without zero outcomes; to the extent that these differences were unmeasured, we cannot adjust for them, and thus these very limited results, only including data from practices with positive outcomes, are at risk of being significantly biased. Thus, in our effort to estimate the within-practice effect of antibiotic exposure, here we are inherently constrained to use only those practices with both events and with some variation at the patient level in the use of anbiotics.

We next used Stata's xtlogit to fit multiplicative logit conditional fixed effects models, decomposing antibacterial drug exposure to examine within- rather than between-practice effects. The unadjusted OR for a severe adverse event for patients exposed vs. unexposed to an antibacterial drugs was 0.92 (95% c.i. 0.61 to 1.38, p=0.67, identical to the results using the clogit command, above). Adjusted for the number of different drug classes prescribed during the past year and Townsend score, the OR was 0.77 (0.50 to 1.17, p=0.22), Table 9. Similar to conditional logistic regression using clogit, a limitation of this method is that xtlogit could not make use of data from practices with zero outcomes (giving an odds of zero for severe adverse events without antibacterial drugs, and a zero denominator for the odds ratio), and thus lost all information from 780,333 visits (55% of the visits!) from these 238 practices with this method; again, the data from the practices with zero events are likely to be different in many respects from data from practices with non-zero events; to the extent that these events are not distributed randomly across practices, losing this information in the analysis risks obtaining biased results..

Chapter 5

Conditional linear regression

Stata's xtreg was used to fit additive linear conditional fixed effects models. As xtreg is estimating risk differences, unlike estimating odds ratios using xtlogit's multiplicative model where zero-event practices drop out because of unusable zero denominators, information from zero-event practices is used in the xtreg estimates' additive model. Thus, with xtreg, we could take a more comprehensive look at the influence of potential clustering and confounding by practice using all of the data. First using subject as the panel variable, and using the mle option, our random effects estimate for the unadjusted risk difference for a severe adverse event for patients exposed vs. those unexposed to antibiotics was 0.511 per 100,000 visits (95% c.i. -2.41 to +3.44, p=0.73), Table 9, note that the point estimate was positive. Using the fe option, again decomposing antibacterial drug exposure to examine within-patient vs. between-patient exposure effects , our unadjusted conditional (on patient) fixed effects estimate for the risk difference for a severe adverse event for patient visits exposed vs. unexposed to antibacterials was -0.145 per 100,000 visits (-5.03 to +4.74, p=0.954), note the point estimate, conditioning on patient, was negative.

Using practice as the panel variable, with the mle option, our random effects estimate for the unadjusted risk difference for a severe adverse event for patients exposed vs. those unexposed to antibacterial drugs was the same, of course, as with patient as the panel variable: 0.511 per 100,000 visits (95% c.i. -2.41 to +3.44, p=0.73), Table 9. Using the fe option, the unadjusted conditional (on practice) fixed effects estimate of the risk difference for a severe adverse event for patients exposed vs. those unexposed to antibacterials, was -0.6777 per 100,000 visits (95% c.i. -3.83 to +2.47, p=0.67). Thus, using the mle random effects model, ignoring potential confounding by patient or practice, antibacterials appeared to increase the point estimate for the risk of adverse events, while, using the model conditional on practice or patient, antibacterials appeared protective! This is evidence that confounding by patient and practice is very important here!

This confounding may not have been a serious problem at the patient level, as we had many potential measured patient-level covariates to include in the model. However, at the practice level, there were fewer options for covariate adjustment. Unfortunately, prescriber is not a reliable field in THIN (Bhuller, H, personal communication, October 6, 2008). The practice-level variables available in THIN, such as the Townsend score (missing for 8.2% of our visits), and the racial/ethnic mix of the population served (missing for 4.4% of our visits), are somewhat inconsistently available, and less directly related to the encounter between the patient and physician during the visit than individual characteristics of the specific patient and physician involved. With prescribing extremely unbalanced across practices, as discussed above and shown in Figure 6, confounding by practice appeared to be of extreme importance and our models needed to adjust for this to obtain unbiased estimates for our outcome of interest.

Using xtreg with the fe option, and practice as the panel variable, adjusted for age, year, the number of different classes of drugs and the number of office visits within the year prior to the visit, and the Townsend score, the conditional fixed effects estimate for the risk difference for severe adverse event for patients exposed vs. those unexposed to antibacterial drugs was -1.42 per 100,000 (95% c.i. -4.75 to +1.91, p=0.40) Table 9. We found an interaction between antibacterial exposure and the number of different classes of medications used in the previous year, expressed as quintiles. Adjusted for age, year, the number of different classes of drugs and the number of office visits within the year prior to the visit, and the Townsend score, the risk difference for severe adverse event for patients exposed vs. those unexposed to antibacterials was significant only for the highest quintile of drug use during the previous year: -29.14 per 100,000 visits (95% c.i. -44.98 to -13.29, p<0.001).

C. Methods to adjust for confounding

Propensity score analysis

Using a propensity score presents a particularly interesting challenge for this problem. If we generated a propensity score in the typical fashion, we would have used a common

propensity score model across each of our 326 practices. However, this type of model would have been wildly inappropriate here, as we know that the propensity for antibacterial exposure varies so extremely between practices (Figure 8). In order to develop a propensity score that is actually helpful in modeling the propensity for antibacterial drug exposure, we needed, as noted previously, to model a separate propensity score for each practice. A separate propensity score for antibacterial drug exposure for each practice was modeled using Stata's pscore command with the following covariates: sex, age, visit year, the number of comorbidities at the time of the visit, the number of different classes of medications prescribed and the number of office visits during the year prior to the index visit, and patient smoking history. In order to get the propensity score models to successfully converge, we needed to dichotomize our continuous covariates, and we were still not able to generate propensisty scores for eleven of the 326 practices (including 90,885 of 1,531,019 visits). In theory, it might have been difficult to generate pscores for practices with very low use of antibacterial medications, however that did not seem to fully explain the problem here. Mean use of antibacterials among omitted practices was 68.2% (range 50.6% to 83.1%) compared with 65.4% for all practices, using grouped visits.

Because our propensity score analysis was limited to visits from practices with propensity scores, for comparison, we fitted the xtreg model adjusted for age, year, number of drugs and number of visits during the past year, and Townsend score, as above, but only included visits from practices with fitted propensity scores, eliminating those 90,885 visits without propensity scores. The adjusted conditional fixed effects estimate for severe adverse event for patients exposed vs. those unexposed to antibacterial drugs was again significant only for the highest quintile of drug use during the previous year, when antibacterial use was again protective with a risk difference for those exposed vs. unexposed of -30.56 per 100,000 visits (-47.17 to 113.96, $p<0.001$) (this estimate was slightly farther away from the null than the point estimate of -29.14 per 100,000 visits, using data from all of the practices described above), Table 9.

Using the propensity score as a continuous variable, the risk difference for adverse event for exposed vs. for unexposed patients was again significant only in the highest

drug use quintile, with a risk difference of -32.62 per 100,000 visits (95% c.i. -49.21 to -16.03, p<0.001), very similar to the comparison point estimate, above, without the propensity score of --30.56 per 100,000 visits. However, this model assumed a linear relationship between our severe adverse event outcome and our propensity score. A model stratified by propensity score will make fewer assumptions in this regard.

Dividing our propensity score across quintiles, we used the propensity score quintile as a categorical variable, essentially stratifying (subclassifying) by propensity score, comparing the risk of an adverse event for exposed vs. for unexposed patients within quintiles of the propensity to have been prescribed an antibacterial drug, and conditional on practice. Using xtreg, the fixed effects estimate of the risk difference for severe adverse event for exposed vs. unexposed patients, conditional on practice, and adjusting for Townsend score was again significant only for the stratum of patients who are in the highest quintile of medication use, and antibacterials were again protective with an estimated risk difference of -32.62 per 100,000 visits (95% c.i. -49.22 to -16.03, p<0.001), very close to our estimate of -30.56 obtained without the propensity score, Table 9.

Because our panel variable was practice, we were unable to utilize the propensity score with an inverse probability of treatment weighting approach, as our treatment weights could not be constant within practice. This was a limitation of this method for our type of analytic problem.

Instrumental variable analysis

As discussed above, if a strong instrumental variable can be identified, an instrumental variable technique can help control for unmeasured confounding. However, unfortunately, our best candidate for a strong instrumental variable, visit provider prescribing history, is not reliable field in THIN, as discussed above. Alternatively, practice could be used as an instrument; as we have shown that practice is highly correlated with exposure.

Using Stata's ivregress function, we performed 2-stage least squares regression, modeling practice on Townsend score, racial/ethnic mix, and visit year, and then using practice as

an instrument in a linear regression modeling severe adverse event on antibacterial drug exposure, adjusting for age, visit year, number of different classes of medications used in the past year, and number of office visits in the past year. Again, the risk difference for antibiotic exposed vs. for unexposed visits was significant only in the highest quintile of medication use, and was again protective here in the IV model, with a point estimate of -28.11 per 100,000 visits (98% ci. -43.93 to -12.29, p<0.1001), Table 9. This is similar to the type of result Stukel et. al. obtained, using instrumental variable regression, with Stata's ivregress to examine the effects of invasive cardiac management on survival after acute myocardial infarction.[14] They used regional cardiac catheterization rate as an instrumental variable, as it is thought to be highly correlated with treatment but not to effect the outcome independently of the exposure of interest. Their result estimates the treatment effect on the marginal subjects, or those who would receive treatment in high-prescribing but not low-prescribing regions. Thus, their result describes between- region, and not within-region risks. The counterfactual contrast of interest would be what would be the effect of catheterizing vs. not catherizing on the same patient at the same time, in the same region, or the within-region contrast.

Our fixed effects model using xtreg conditional on practice should provide less biased estimates compared with this instrumental variable method, by helping to control for confounding by practice.[14] That model's risk difference estimates were similar to the methods obtained using IV methods.

Table 9. Regression Results Summary

Regression Results Summary						
	Unadjusted			Adjusted		
Method	**Point estimate**	**95% c.i.**	**P Value**	**Point estimate**	**95% c.i.**	**P value**
GEE						
Patient = group	1.07	0.73 to 1.57	0.73	0.82	0.55 to 1.23	0.34
Practice=group	X	X	X	X	X	X
Logistic regression	1.07	0.72 to 1.58	0.74	0.79	0.51 to 1.22	0.29
Clogit	0.92	0.61 to 1.38	0.67	0.81	0.54 to 1.22	0.32
Xtlogit	0.92	0.61 to 1.38	0.67	0.77	0.50 to 1.17	0.22
Xtreg						
Panel = subject						
Not conditional on subject	0.511 per 100,000 visits	. -2.41 to +3.44	0.73			
Conditional on subject	-0.145 per 100,000 visits	-5.03 to +4.74	p=0.954			
Panel = practice **Not conditional on practice**	: 0.511 per 100,000 visits	-2.41 to +3.44,	0.73			
Conditional on practice (no interaction)	-0.6777 per 100,000 visits	-3.83 to +2.47	0.67	-1.42 per 100,000 visits	-4.75 to +1.91	0.40
Conditional on practice, interaction				For highest quintile of drugs within past year		
				-29.14 per 100,000 visits	. -44.98 to -13.29	p<0.001
Conditional on practice but only visits with propensity scores	-1.45	-4.96 to +2.06	0.419	For highest quintile of drugs within past year		
				-30.56 per	-47.17 to	<0.001

				100,000 visits	113.96	
Propensity score as continuous variable for visits with propensity scores				For highest quintile of drugs within past year		
				-32.62 per 100,000 visits	. 49.22 to -16.03	<0.001
Propensity score as quintiles for visits with propensity scores	-2.53	-6.09 to +1.03	0.163	For highest quintile of drugs within past year		
				-32.62 per 100,000 visits	-.0004922 to -.0001603	P<0.001
Instrumental variable	-0.290	-3.54 to +2.96	0.861	-28.11 per 100,000 visits	-43.93 to -12.29	<0.001

Chapter 5

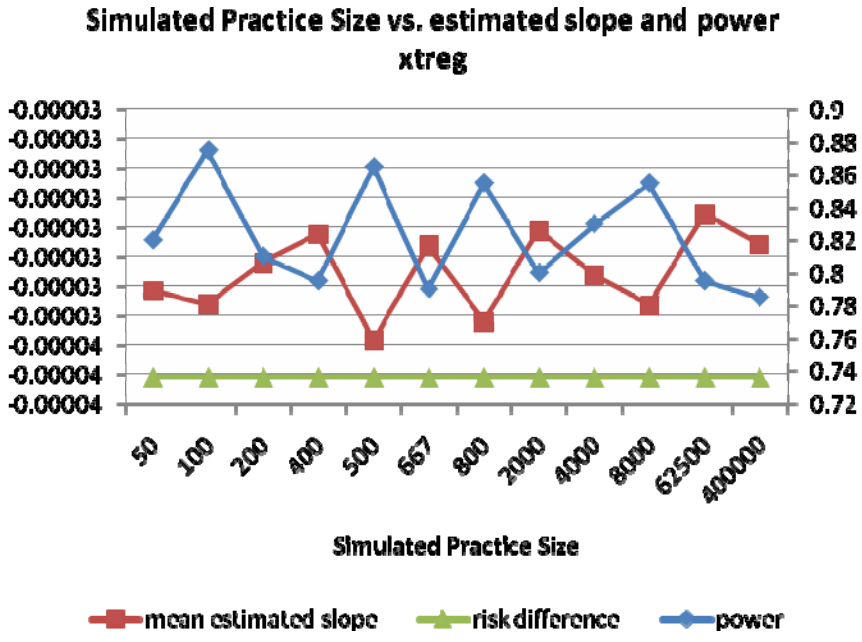
Simulations

As described above, our dataset was large (1,646,229 visits) highly hierarchical (326 practices) with a relatively common and variable exposure across practices (patients at 65.4% of visits received antibacterial drugs, ranging from 3.1% to 94.7% depending on practice), and a very rare and variable outcome across practices (severe adverse event risk of 7.71 per 100,000 visits, ranging from 0 to 280.9 depending on practice). We compared the performance of our conditional fixed effects linear model (using xtreg) under varying conditions and assumptions, and compared these results with those using a conditional fixed effects logistic model (using xtlogit) conditional fixed effects logit model, using simulated datasets, generated to reflect conditions similar to our data: large (2 million visits), highly hierarchical (ranging from 50 to 400,000 practices with 5 to 40,000 visits per practice), a relatively common and variable exposure across practices, and a rare outcome (specified to be 8.66 per 100,000 visits, with a risk difference of -0.0000411 (-4.11 per 100,000 visits) for the protective effect for exposed vs. unexposed visits); many practices thus included zero outcomes. We explored the effect of increasing the number of practices on expected power, holding the total sample size constant; with an extremely rare outcome, as the number of practices increases we would expect an increase in power due to the design effect, but may see a decrease due to an increased number of zero-event practices. We also used these simulations to explore how robust our results and our power were to ignoring or mis-specifying the variability in the models' estimated parameters, and confounding due to unmeasured variables.

For a baseline analysis, with our primary seed, using 200 practice with 10,000 visits per practice, the mean regression slope from the simulated data was -3.72 per 100,000 visits, compared with the true value of -4.11 used to generate the data, or a 9.5% bias toward the null value of the slope =0, Table 10. The power to find this difference in slope using this model was estimated at .81, and there were 112.93 practices with zero adverse events (zero-event practices). Using a different seed, this same model yielded an estimated mean regression slope of -3.817 per 100,000 visits, or a 7.1% bias toward the null, with a power of 0.885, with 87.68 zero-event practices.

Decreasing the number of practices from 200 to 100, we found an estimated mean regression slope of -3.86 per 100,000 visits, or a 6.1% bias toward the null, with a power of .875. Decreasing the number of practices still further to 50, the estimated mean regression slope was -3.814 per 100,000 visits, a 7.2% bias toward the null, with a power of 0.82 (Figure 12 and Table 10). Power and bias estimations using additional practice sizes are shown in Table 10 and Figure 12. As shown, we did not see the increase in power to detect our very small risk difference that we would expect from the design effect with increasing numbers of practices, in fact, power stayed about the same despite large increases in the number of practices in the model. The power suffered from the progressively increasing numbers of zero-event practices seen, as the number of visits per practice decreased with increasing practice size, holding total visits constant, demonstrated in Table 10. With increasing numbers of zero-event practices, it gets progressively more difficult to show significant differences between antibacterial-exposed and –unexposed visits within each practice.

Figure 12. Simulated Practice Size vs. Estimated Slope and Power using xtreg



When we eliminated the baseline variability of antibiotic prescribing between practices, the mean estimated slope was -3.741 per 100,000 visits with a bias of 9.0% toward the null, and a power of 0.875 (Table 10). When we eliminated the baseline variability of adverse event risk between practices, the mean estimated slope was -4.063 per 100,000 visits, with a bias of 1.1% toward the null and a power of 0.92. When we eliminated *both* the baseline variability of antibacterial drug prescribing and the baseline variability of adverse event risk between practices, the mean estimated slope was -4.089 per 100,000 visits with a bias of only 0.5% toward the null and a power of 0.935. This implies that, if baseline variability between cluster groups is ignored for power estimation, we risk potentially grossly overestimating our power to detect a difference between groups, especially when we ignore potential variability in rare outcome risk between clusters. This effect also makes us vulnerable to quite biased results from errors in measurement of exposure or outcome.

When we consider the impact of unmeasured covariates, adding a confounder as described above, and ignoring this (unmeasured) confounder in the analysis, resulted in an estimated mean slope of +4.741 per 100,000 visits, an over 200% bias and a point estimate for the risk difference in the opposite direction, indicating a *risk* from antibacterial drug exposure rather than the stipulated true protective effect, with a power of 0.71. (Table 10) If the same unmeasured covariate is not a confounder but merely a noise variable, associated with the outcome but not with the exposure, the estimated mean slope was -3.998 per 100,000 visits, a 2.7% bias toward the null, and a power of .72 (Table 10). Thus, an unmeasured covariate will obviously effect power; if the covariate is a noise variable, our point estimate will be relatively unbiased, but we would have less power to show a difference, but if the unmeasured covariate is a confounder, there is a risk of obtaining an extremely biased result!

Finally, given the stipulated simulated data, our stipulated risk difference for severe adverse event of -4.11 per 100,000 visits in antibacterial drug exposed vs. unexposed visits

should correspond to an odds ratio of 0.5357. Using xtreg instead of xtlogit, we found an odds ratio of 0.574, biased 7.1% toward the null, similar to our xtreg results, with a power of 0.80.

Table 10. Simulation Results

Simulation Results 200 reps, 2,000,000 total patient visits, α = 0.05, Risk difference specified at -0.0000411 or -4.11 per 100,000 visits with antibacterial drug exposure					
Comments	**Number of Practices**	**Visits per practice**	**Mean regression slope from simulated data, per 100,000 visits**	**Power**	**Number of zero-event practices**
Linear regression, conditional on practice					
Variable antibacterial drug exposure and adverse event risk between practices					
No unmeasured covariates	50	40,000	-3.814	0.82	
↓	100	20,000	-3.86	0.875	
↓	200	10,000	-3.72	0.81	112.93
↓	400	5000	-3.623	0.795	293.26
↓	500	4000	-3.983	0.865	387.29
↓	667	3000	-3.661	0.79	550.74
↓	800	2500	-3.92	0.855	679.72
↓	2000	1000	-3.612	0.8	1871.18
↓	4000	500	-3.761	0.83	3869.355
↓	8000	250	-3.864	0.855	7866.1899
↓	62500	32	-3.555	.795	62364.578
↓	400000	5	-3.658	0.785	399858.28
Unmeasured confounder	200	10,000	+4.741	0.71	51.73
Unmeasured noise covariate	200	10,000	-3.998	.72	86.25
Variable antibiotic exposure but NOT variable adverse event risk between					

practices					
No unmeasured covariates	200	10,000	-4.063	.92	
Variable adverse event risk but NOT variable antibacterial drug exposure between practices					
No unmeasured covariates	200	10,000	-3.741	.875	
NOT variable antibacterial drug exposure or adverse event risk between practices					
No unmeasured covariates	200	10,000	-4.089	.935	
Logistic regression, conditional on practice Risk difference = -0.0000411 or 4.11 per 100,000 visits, odds ratio = 0.535					
Variable antibacterial drug exposure and adverse event risk between practices					
No unmeasured covariates	200	10,000	Odds ratio = 0.574	0.80	112.93

Discussion

Our data presented at least three major analytic challenges. First, exposure, outcomes, and covariates were extremely clustered by practice. Second, antibacterial drug prescribing and outcomes were extremely unbalanced among practices. Third, our outcome was exceedingly rare, resulting in many practices with zero outcomes. Overall, despite the method used, as long as we decomposed within- from between-practice results, we obtained similar results for our outcome of interest, the within-practice estimates.

GEE had a large memory requirement which made it cumbersome to perform complex analysis, even without additional covariates.

Conventional and conditional logistic regression did not allow us to make use of groups with zero events; given our many practices and extremely rare outcomes, we would end up losing information from most of our data with logistic regression analysis, and to the extent that adverse outcomes were not distributed randomly across practices, risk obtaining biased outcomes. On the other hand, logistic regression would appear the right choice based on theory; a multiplicative

model could be a more reasonable choice for our dichotomous outcome rather than an additive model.

Conditional fixed effects linear regression models converged easily, and were able to make use of all of our data, even data from practices with zero outcomes. As discussed above, this problem is similar to using meta-analysis to study data regarding rare events. [13] Results using this method for our rare binary outcome appeared relatively unbiased and stable using simulated datasets with known parameter estimates.

Our results from the random effects conventional and conditional logistic regression models were quite similar to those from the linear regression models; as long as we focused on within-practice estimates; the bias and power of the logistic and linear models were virtually identical. Somewhat counter-intuitively, although logistic regression was not able to make use of data from practices with zero outcomes, our power was essentially no different with linear regression as with logistic regression. Thus, for the research question addressed in this study, the conditional logistic regression results were robust to losing data from zero-event practices. It is unknown whether this is specific to our particular question, or generalizable to other very large datasets with common exposures and rare outcomes. Other investigators have shown with simulations that conditional logistic regression does not always give the best results, in terms of bias, coverage,and power, under conditions of rare dichotomous events.[7]

The propensity score analysis was quite cumbersome; as propensity for antibacterial drug prescribing was so unbalanced between practices, we needed to model a separate propensity score for each practice. Covariates for some practices were too unbalanced for the propensity score models to converge, and thus we were not able to use data from those practices in the propensity score analysis. We were not able to utilize inverse probability of treatment weighting in Stata with our data clustered by practice. However we used the propensity score, our point estimates for the effect of antibacterial drug exposure were similar to our estimates obtained using our other models. Although the estimates using the propensity score models are close, they do not seem to provide much advantage to the non propensity score models, and do

not fully utilize all available information (for example, we had to dichotomize continuous variables and omit data).

Unfortunately, we were not able to use provider prescribing history as an instrumental variable; practice seemed to be the strongest available potential instrument, and our results using other methods seem to adequately adjust for practice; IV methods did not seem to add any advantage to our other more straightforward methods yielding similar results. IV methods may suffer from some of the same limitations of propensity score analysis, in that some variables may be extremely unbalanced across the dataset, in a nonrandom manner. Additionally, care must be taken when using IV methods that the analysis can decompose the effects to provide the contrast of interest; plugging data into an IV program may miss important effects, for example those due to clustering and confounding by site. This is similar to the problem experienced by Stukel et. al, when they used Stata's previous generation instrumental variable command to model mortality rates on cardiac catheterization, using regional cardiac catheterization rates as an instrumental variable.[20] We obtain the between-practice (or between-region) rather than the within-practice estimates of interest using these instrumental variable methods.

When planning a trial with clustered data. other parameters being equal, it should always improve our power to show a difference if we can include more patients in the study. Adding more practices should further increase the power due to the design effect. However, sometimes trade-offs need to be made between the number of practices included in the study, and the number of patients per practice. We showed that, with our rare outcome, comparing many smaller practices with fewer larger practices, the usual advantage of having many practices for increasing power due to the design effect is at least partially outweighed by the increased number of practices with zero events, giving less power to make within-practice estimates. In planning a study of rare outcomes, the advantages of using many practices with fewer patients each to maximize the design effect has to be weighed against the advantages of more patients, and thus more events, per practice using fewer practices with more patients each.

For reliable power calculations, we need good data on baseline risks, and good estimates of baseline variability between clusters, or practices, especially variability in rare outcomes between practices. With baseline variability in exposure and outcome risk between practices, we need more data to show an effect, even if we are already adjusting for confounding by practice. We showed that ignoring baseline variability in exposure or outcome in power calculations can lead to extremely biased power estimates. We also showed that omitting consideration of the effects of confounding variables from power calculations can have drastic consequences, resulting in loss of power and potential biased results.

In summary, we showed that conditional fixed effects linear regression provided stable and relatively estimates of common exposure treatment effects on rare outcomes. Although they were able to utilize all available information, even from groups with zero events, results using these models were quite similar to results obtained using more traditional methods for binary outcomes,. It is unclear that there is an obvious 'best' method for modeling rare events such as those modeled here, although it is reassuring that the different methods used yielded such similar results. Comparing the risk of very rare events between very unbalanced groups presents real challenges to power, even with very large datasets. Additionally, if power estimations for observational studies of rare events ignore potential baseline variability between groups, and potential confounding covariates, results could be quite biased and power estimates may be grossly inflated.

As The Health Improvement Network (THIN) as well as other electronic medical record databases continue to grow in number and size, experience and insights with effective and efficient methodologies for using observational data to explore rare outcomes will help us to exploit their potential.

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Chapter 5

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Chapter 6.Outcomes I, Potential Risks of Antibacterial Drug Use: Adverse events associated with adult antibacterial drug use

In the U.S., we have virtually universal exposure to antibacterial medications; in the year 2000, persons ≥age 15 received a total of 68,481,645 antibacterial drug prescriptions. Every individual in the U.S. is prescribed a short-term course of systemic antibacterials once every three years to almost twice per year, on average, resulting from a visit to an ambulatory health care provider.[1-6] Virtually everyone will be exposed to at least one course of antibacterial drugs during his/her lifetime. It is doubtful that the U.S. population has such a high exposure to any other class of medications. This extraordinarily high exposure to antibacterials should command careful vigilance to the consequences. Although the perceived risk of an adverse event related to antibacterial drug use may be low, with such a high level of prescribing, the population-attributable risk of serious adverse drug events due to this medication class could be quite high.

Antibacterial drugs are also among the most common drugs implicated in adverse events.[7-9]. Of particular recent interest are drugs that are suspected of increasing the risk of cardiac arrhythmia by prolonging the QT_c interval and/or directly causing Torsades de Pointes; macrolides and fluorquinolones are frequently implicated in adverse events through this mechanism.[10] Also of recent interest are drugs with suspected adverse events related to their relationship with the hepatic CYP3A4 pathway. For example, macrolides are metabolized by the CP3A4 pathway and both macrolides and fluoroquinolones are inhibitors of the CYP3A4 pathway; this could heighten the risk of associated adverse events.[11, 12]

Most of these associations have been described with case reports and cases series; they almost never include a control group measuring adverse events in unexposed patients and thus the true absolute and relative risks of adverse events associated with these agents remain unknown. A randomized clinical trial is considered the gold standard to best ensure comparability of measured and unmeasured confounding variables between exposed and unexposed subjects,[13] however opportunities and resources to perform large prospective randomized trials are limited. Randomized trials to investigate subtle, rare, or complex effects would need to be

quite large, would be infeasible to perform for every important research question, and are not always ethical.[14] Longitudinal observational data with individual-level links have the potential to help shed light on the outcomes of antibacterial drug use.

Antibacterial drugs are often prescribed for acute nonspecific respiratory infections, despite the fact that they are unlikely to be of benefit; adults at about half of U.S. office visits for acute nonspecific respiratory infections receive antibacterial drug prescriptions.[3, 4, 15] The UK's The Health Improvement Network (THIN) primary care electronic medical record database contains large amounts of linked longitudinal clinical prescription and outcome data. The objective of this study is to use a subset of the entire THIN cohort with an office visit for acute nonspecific respiratory infections to compare adverse event rates of antibacterial drug-exposed vs. antibacterial-unexposed patients. By limiting the comparison to patients with acute nonspecific respiratory infection visits, we promote comparability between exposed and unexposed patients in the cohort. However, in these analyses, we need to address three key methodological issues. First, our outcome is extraordinarily rare. Second, our exposure, while common, is not randomized, and thus is likely to be confounded by many patient- and practice-related covariates, especially confounding by practice and by indication. Third, exposure and outcome will both likely be clustered by patient and practice. We use different methods to address these methodological challenges. To the extent that our results from these various methods agree, this supports our results; to the extent that they disagree, they can give us further insights into the relationship between antibacterial drug exposure and adverse events.

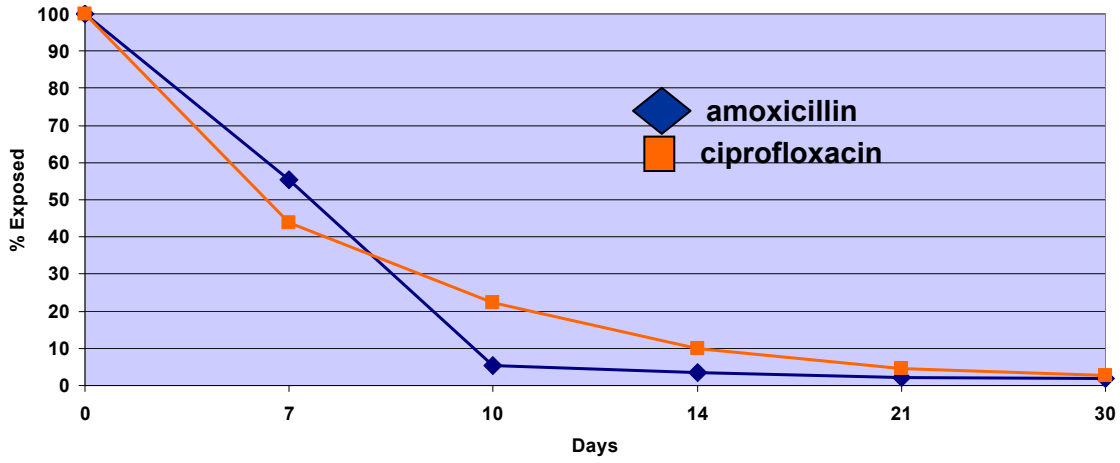
Methods

We conducted a retrospective cohort study using data accessed from THIN in September 2007. Data were restricted to practices meeting acceptable standards set by EPIC for research data collection. We identified all adult primary care visits for acute nonspecific respiratory infections between January 1, 1985 and December 31, 2006 among all continuously-enrolled patients ≥18 years of age. Visits were identified based on Read diagnostic codes for acute

nonspecific respiratory infections. (Chapter 3, Table 1). We excluded codes for diagnoses often attributed to a focus of bacterial origin for which guidelines recommend antibacterial therapy such as *streptococcal* pharyngitis, otitis media, sinusitis, and pneumonia. Because data from multiple visits within the same illness episode may tend to be highly correlated, visits were grouped if they occurred within a two-week period; grouped visits are defined as acute nonspecific respiratory infection encounters. For sensitivity analysis, we eliminated the visit grouping.

Exposure: Exposure of interest was antibacterial drug prescription within one day of the index acute nonspecific respiratory infection visit; antibacterial drugs of interest included oral antibacterials typically used for respiratory infections. We excluded topical, vaginal, ophthalmologic, otic, and parenteral antibacterials, and those typically used for tuberculosis, fungal and parasitic infections. The primary exposure window was within 14 days of the index visit. Fourteen days was chosen as the primary exposure of interest as we have demonstrated that for most antibacterials commonly used for acute nonspecific respiratory infections, most exposure is completed within 14 days, as shown for the two examples in Figure 13.[16]

Figure 13. Antibacterial Exposure after Visit for Acute Nonspecific Respiratory Infection [16]



Outcome: The primary outcome for this study was a severe adverse event within a 14 day window following the index acute nonspecific respiratory infection encounter, defined as overnight hospital admission with one of the following acute diagnoses: cardiac arrhythmia,

diarrhea, hepatic toxicity, hypersensitivity, photo-toxicity, renal toxicity, or seizure (Appendix). Hospitalizations were identified using the THIN Source codes suggested by EPIC to detect an overnight hospital admission. (Bhullar, H, personal communication March 1, 2007). We previously showed that these same THIN hospitalization codes had a good positive predictive value for identifying valid overnight hospital admissions for community acquired pneumonia, another acute diagnosis (Chapter 4), and that, of the identified hospitalizations, almost all (>96%) were identified within a 14-day window after the acute nonspecific respiratory infection index visit. However, if an adverse event occurred within the 14 day window but was recorded late, after the 14 day window, we would miss the outcome of interest. For this reason, our sensitivity analysis extended the window out to 30-days exposures to address how robust our results are to misclassification of hospitalization dates. Additional sensitivity analyses include eliminating the visit grouping, and utilizing propensity score analysis, described in more detail below. We explore our ability to control for unmeasured variables by performing instrumental variable analysis and a case-cohort study, also decribed further below.

By confining our primary outcome to the more severe adverse events, defined as overnight hospital admissions, we minimized misclassification bias due to misidentification of outcome. It is less likely that an adverse event was not recorded in THIN, and thus missed, if it resulted in a hospital admission and thus generated at least a hospital discharge report and perhaps an office and/or emergency department visit. It is likely that if a hospitalization was recorded, an adverse event actually took place; this assumption was confirmed with our validation project. Thus, using hospitalizations as our primary outcome, we may have missed some exposure-associated adverse events, but the adverse events we identified will likely be valid.

Secondary outcomes included less serious adverse events, events resulting in a primary care encounter but not resulting in hospital admission. We chose to make these secondary outcomes, first because of concern that the less severe events might not be recorded in the medical record and second, we were focusing our primary analysis on more clinically severe, and thus perhaps more clinically relevant, adverse events. We also included automobile crash

hospital admissions as an additional secondary outcome, as a control outcome. This explored the possibility that our antibacterial drug exposure measure was a marker for certain patient characteristics which made it more likely a patient would be hospitalized, rather than a marker of a causal relationship between our antibacterial drug exposure and the hospitalization outcome.

Exploratory analyses included modeling each individual adverse event category as a separate outcome , and modeling severe adverse event hospital admissions on antibacterial drug class specific exposure, focusing on beta-lactams, macrolides, and flouroquinolones, first as class-specific antibacterial drug vs. no antibacterial exposure, and second as class-specific antibacterial drug vs other antibacterial exposure. Although we had less power to detect this outcome than our primary outcomes, the risk of certain adverse events may vary with exposure to specific antibacterial drug class, for example, beta-lactam antibacterials may increase the risk of seizures,[17] and macrolides and fluoroquinolones may increase the risk of cardiac arrhythmias.[18] As it is possible that some severe adverse events could result in death without recording an overnight hospitalization; to explore the possibility that severe adverse events might be missed in this way, we also modeled death as an exploratory outcome.

Covariates: Covariates included patient age at visit, sex, visit year, and patient co-morbidity history, with co-morbiditites grouped into the categories shown in Chapter 5, Table 4 (Lewis, JD,unpublished data). Considering what clinical data might be relevant from a clinical aspect to help predict indication for antibacterial treatment of acute nonspecific respiratory infections, we also included alternative summary measures of the intensity of medical care use, including the number of THIN recorded co-morbidities,[8] and the number of different classes of medications that the patient was prescribed[8, 19] and the number of THIN visits recorded for that patient within the year prior to the patient's index acute nonspecific respiratory infection visit. Although it would have been ideal to include them in the analysis, THIN does not include direct measures of patients' socioeconomic, racial and ethnic characteristics. THIN does include other variables based on the patient's post code that were used as proxies of these characteristics; these variables include the Townsend score, a five-quintile measure of neighborhood deprivation,

and a five-quintile variable describing the proportion of the patient's neighborhood who define themselves as "Black" or "Black British."

Analysis: We first summarized acute nonspecific respiratory infection encounters and antibacterial drug exposure, overall and by specific antibacterial class defined by British National Formulary (BNF) class, [20] and we summarized the frequency and type of adverse events outcomes.

As described in Chapter 5, antibacterial drug prescribing was profoundly unbalanced between practices, and there was enormous confounding by practice in the relationship between severe adverse events and antibacterial drug exposure. For multivariable analysis, we performed fixed effects conditional linear regression using Stata's xtreg command, described in further detail in Chapter 5. We modeled hospitalization for any severe adverse event, using practice as the grouping variable. The primary independent variable was antibacterial drug exposure modeled as: any antibacterial exposure vs. no antibacterial exposure. Covariates included those listed above. Model covariates were included using a two-step process. First, we initially included all covariates that were associated with the outcome, conditional on the exposure of interest. Then, we retained each covariate in the final model if removing it caused a change of >=10% in the risk difference for antibacterial drug use. Akaike's Information Criterion (AIC) was used to help assess model fit, and Cuzick's nonparametric test for trend across ordered groups was used to test for trend (Stata's nptrend).

For sensitivity analysis, we eliminated the visit grouping, and examined results at 30 days, as described above. In addition, we explored the impact of using a propensity score in the regression models. Because our analysis was conditional on practice, and because we expected extremely unbalanced antibacterial drug prescribing by practice (propensity for antibacterial drug exposure based on other covariates varied widely between practice), a propensity score was calculated separately for each practice, using the same covariates in each practice's model, as described in Chapter 5. Within each practice, propensity scores were divided into quintiles, and

then these quintiles of the propensity score for each practice, across all practices were used in the conditional linear regression, replacing their included covariates.

We also considered less severe adverse events, not resulting in hospital admission. We used the same THIN adverse event diagnosis codes for this analysis, but excluded those cases associated with THIN hospital admission codes.

As mentioned above, we modeled a control outcome, overnight hospital admission for automobile crash within 15 days of the acute nonspecific respiratory infection visit, which should not be related to antibacterial exposure; if a systematic difference is shown in the risk of hospitalization for automobile crashes between antibacterial drug-exposed and –unexposed patients, this would not plausibly be an effect of exposure and would be evidence of a hidden bias due to unmeasured confounding.[21]

Because of the concern that some severe adverse events may present with death without hospitalization, we also modeled death as exploratory outcomes.

Additionally, to further explore the influence of unmeasured variables on inter-individual confounding by indication, we performed a crossover cohort study.[22] A crossover cohort study eliminates inter-individual differences in indication for receiving antibacterials.[22, 23] In this analysis, patients with adverse event hospitalizations and >1 visit for acute nonspecific respiratory infection were included in the study population. Case time was defined as the 14 days following a severe adverse event index acute nonspecific respiratory infection grouped visit. A history of severe adverse event after antibacterial drug use would have been a contraindication for future use of this antibacterial drug. To minimize bias from confounding due to depletion by susceptibles, control time was defined as the 14 days following the previous[22] non-index visit; control time after the index acute nonspecific respiratory infection visit was not included. Chi-square testing was used to calculate the odds ratio comparing adverse event for antibacterial drug-exposed vs. unexposed visits for each patient.

Power

Primary analysis: Power calculations were performed conservatively, using PS Power and

Sample Size Calculations, Version 2.1.30, 2003.[24] THIN covers 32.6 million person-years,[25] and using the 2001-2002 U.S. outpatient visit rate of 1985.7 visits per 1000 adults,[3] predicts an estimated 64,733,820 THIN outpatient visits, assuming the U.K. outpatient visit rate is similar to that of the U.S. Approximately 11% of adult outpatient visits are for acute respiratory infections other than pneumonia;[3, 26, 27] assuming a similar rate for the U.K., we estimated a total of 7,120,720 outpatient acute nonspecific respiratory infection visits covered in THIN. In the U.S., 61.8% of adults diagnosed with acute nonspecific respiratory infection in the outpatient setting are prescribed antibacterial medications,[3] and our power calculations conservatively assumed that the U.K. antibacterial prescribing rate could be only ½ of the U.S., or 30.9% of acute nonspecific respiratory infection visits. The preliminary study found an adverse event rate of 0.207 serious adverse events per 1000 antibacterial drug-prescribing visits.[28]

With these assumptions, assuming data are independent, using the U.S. antibacterial drug prescribing rate of 61.8%, even if our sample size is half that estimated above, or 3,500,000, we would have 95% power to detect a relative risk of 1.20 for a serious adverse event for a patient exposed to antibacterials compared with an unexposed patient, or a 20% increased risk from antibacterial exposure. The clustered nature of our data means that data within practices are likely to be more similar than data across, or between practices; this imparts variance inflation. With visits clustered by practice, assuming a mean of 10,700 visits per practice, with an intracluster correlation coefficient as high as 0.2, we would still have over 95% power to detect this difference with this expected sample size. [29] f the U.K. antibacterial drug prescribing rate was only 30.9% of acute nonspecific respiratory infection visits, we would have 90% power to detect this same difference (Table 11). These results indicate that we would have the power to detect a clinically significant increased risk of a serious adverse event associated with antibacterial drug exposure. While these relative increases in risks are large, the associated absolute increases in risk are small but clinically meaningful, particularly given the limited clinical efficacy of the treatment under consideration.

Table 11. Power, Relative Risk of Severe Adverse Event, Exposed vs. Unexposed Visits

Power, Relative Risk of Severe Adverse Event Exposed vs. Unexposed Visits		
Power	**Acute Nonspsecific Respiratory Infection Antibacterial Prescription Rate**	**Detectable Relative Risk exposed/unexposed**
.95	0.618 (U.S. rate)	1.20
.90	0.309	1.20

Crossover cohort study

For the crossover-cohort study, preliminary data show that 136 adults had a severe adverse event after >1st acute nonspecific respiratory infection visit. Using the methods of Julious et. al., we should have at least 80% power to detect an OR of ~2.5 for antibacterial-exposed vs.–unexposed patients.[23]

Results

Description of the cohort

Visits

Our cohort contained 1,646,229 total visits and 1,531,019 grouped encounters by 814,283 patients. The mean number of grouped encounters per patient was 1.9 (median 1, range 1 to 88 visits, Chapter 5, Figure 6). There were 495,129, 164,447, 70,145, 34,373, 18,466 and 748,479 patients with 1,2,3,4,5, and >5 visits, respectively (Chapter 5, Table 6, Figure 6). There were 326 practices included in the cohort. The mean number of grouped visits per practice was 4696.4 (median 3232.5, range 24 to 27,190, Chapter 5, Table 7 and Figure 7)

Antibacterial drugs

Overall, patients at 65.4% of acute nonspecific respiratory infection visits received antibacterial drug prescriptions. As expected, antibacterial drug prescribing varied widely between practices, from a low of 3.1% to a high of 94.7% of grouped visits receiving antibacterial prescriptions (Chapter 5, Figure 8). As described in more detail in Chapter 5, this extreme

unbalance of antibacterial drug prescribing across practices provided strong evidence that we needed to address any clustering and confounding by practice.

The most frequent antibacterial drug prescribed was amoxicillin followed by penicillin and then erythromycin for 51.2%, 17.0%, and 12.7%, respectively of encounters prescribed antibacterial drugs (Table 12).

Table 12. Antibacterial Drugs Prescribed

Antibacterial Drugs Prescribed		
BNF Code	**Generic Name**	**Grouped encounters**
05.01.01.03	Amoxicillin Co-amoxiclav Amoxicillin S/F Flocloxacillin and Ampicillin Amoxicillin/Clavulanic Acid	512,934
05.01.01.01	Penicillin V Phenoxymethylpenicillin Benzathine penicillin Benzylpenicillin Penicillin	170,440
05.01.05.00	Erythromycin Erythromycin ethylsuccinate Erythromycin ethylsuccinate S/F Erythromycin ethylsuccinate coated Erythromycin sachet S/F Clarithromycin Azithromycin Erythromycin stearate Erythromycin sprinkle	126,934
05.01.02.00	Cefalexin Cefalexinpaed Cefaclor Cefaclor M/R Cefadroxyl Cefuroximeaxetil Cefpodoxime Cefalexinpaed Cefixime Cefradine Cephradine Ceftibuten Cephalexin	71,646

05.01.03.00	Tetracycline+chlortet+demeclocyc Oxytetracycline Tetracycline Minocycline Doxycycline (as hyclate) Chlortetracycline Demeclocycline Doxycycline Doxycycline HC Doxycycline monohydrate Lymecycline Minocycline Tetracycline+amphoteracin Tetracycline+nystatin Tetracycline + pancreatic enzymes Tetracycline+chortet&democlocyc	70,554
05.01.08.00	Trimethoprim & Co-trimoxazole Co-trimoxazolepaed Co-trifamole (sulphamoxole/trimethoprim) Co- trimazine/sulphadiazine&trimethop rim Co- trimoxazole(sulphameth/trimeth160 Co- trimoxazole(sulphamethox/trimeth) paed Co- trimoxazole/trimethoprim&sulpham ethaz Co- trimoxazole/trimethoprim&sulpham ethox Co-trimoxazoleadult Cotrimoxazolepaed	34,629
05.01.12.00	Ciprofloxacin Levofloxacin Moxifloxacin Nalidixic acid Nalidixic acid + sodium citrate Norfloxacin Ofloxacin Temafloxacin	12,203
05.01.01.02	Flucloxacillin Ampicillin + cloxacillin Cloxacillin Flucloxacillin	1,891
05.01.11.00	Metronidazole	609
05.01.13.00	Methenamine hippurate	119

	Nitrofurantoin Fosfomycin	
01.03.05.00	Amox/clarithro/lansop Clarithromycin + lansop and amox	55
05.01.06.00	Clindamycin hydrochloride	25
05.01.07.00	Colistimethatesodium Colistinsulphate Chloramphenicol palmitate Chloramphenicol Sodium fusidate	11
		1,002,050 grouped encounters with antibacterials

Covariates

In general, subjects with visits where antibacterial drugs were prescribed had more pre-existing health conditions, for most of our co-morbidity measures for example they were older (mean age for those receiving antibacterials vs. for those not receiving antibacterials was 47.9 vs. 44.0 years), had a more frequent history of any co-morbidities (34.9% vs. 30.6%), more different types of co-morbidities (mean 0.48 v. 0.41), and more classes of drugs (mean 6.0 v. 4.3) within the year prior to the acute nonspecific respiratory infection visit, although the number of primary care visits within the previous year was similar between the two exposure groups (Table 13).

Table 13. Characteristics of Patients with Antibacterial Drug-exposed vs.Antibacterial-unexposed Encounters

Characteristics of Patients with Antibacterial-exposed vs. Antibacterial-unexposed Encounters		
Adults 1,531,019 encounters	**With Antibacterials** 1,002,050 encounters (65.4%)	**Without antibacterials** 528,969 encounters
Age, years Median Mean	 46 47.91	 40 43.98
Male (%)	385,712 (38.5)	184,720 (35)
Congestive heart failure	26,692 (2.66%)	10,352 (1.96%)
Lung disease	195,831 (19.54%)	90,894 (17.18%)
Rheumatologic disease	29,607 (2.95%)	14,251 (2.69%)

Cerebrovascular disease	35,224 (3.52%)	16,073 (3.04%)
Dementia	3,216 (0.32%)	2,425 (0.46%)
Diabetes	43,785 (4.37%)	18,682 (3.53%)
Weakness	6,436 (0.64%)	2,849 (0.54%)
Human Immunodeficiency virus infection	296 (0.03%)	178 (0.03%)
Malignancy	43,816 (4.37%)	18,723 (3.54%)
Metastatic malignancy	1,345 (0.13%)	565 (0.11%)
Mild liver disease	6,777 (0.68%)	3,052 (0.58%)
Moderate-severe liver disease	708 (0.07%)	341 (0.06%)
Myocardial infarction	26,192 (2.61%)	9,959 (1.88%)
Peptic ulcer disease	35,105 (3.50%)	14,385 (2.72%)
Peripheral vascular disease	21,982 (2.19%)	8,963 (1.69%)
Renal disease	6,571 (0.66%)	2,982 (0.56%)
Any comorbidity	350,078 (34.94%)	161,607 (30.55%)
Number of comorbidities Mean Median	 0.48 0	 0.41 0
Number of different classes of drugs used in previous year Mean Median	 5.98 5	 4.25 3
Number of visits made in previous year Mean Median	 8.94 6	 8.87 6

Adverse Events

Severe adverse event hospitalizations

The incidence rate of severe adverse events within 14 days of encounters was 0.0000771 events per encounter, or 7.71 events per 100,000 encounters, shown in Figures 10 and 11 and Table 14. The unadjusted incidence rate was 7.88 per 100,000 encounters with antibacterial drug exposure, and 7.37 per 100,000 encounters without antibacterial exposure.

Table 14. Severe Adverse Events

Adverse Events			
1,531,019 encounters	**With antibacterial drugs** 1,002,050 encounters	**Without antibacterial drugs** 528,969 encounters	**TOTAL**
Severe ADE 14 day	79 7.88/100,000 visits 32 hypersensitivity 10 diarrhea 6 liver toxicity 13 renal toxicity 6 arrythmia 12 seizure	39 7.37/100,000 visits 11 hypersensitivity 7 diarrhea 5 liver toxicity 6 renal toxicity 0 arrhythmia 9 seizure	118
Severe ADE 30 day	148 14.77/100,000 visits 54 hypersensitivity 13 diarrhea 20 liver toxicity 25 renal toxicity 8 arrythmia 28 seizure	80 15.12/100,000 visits 25 hypersensitivity 12 diarrhea 8 liver toxicity 14 renal toxicity 3 arrythmia 18 seizure	228

Multivariable Analysis

Primary outcome

Any antibacterial drug exposure vs. no antibacterial drug exposure

Severe adverse event hospitalization

Using practice as the cluster variable, the unadjusted conditional fixed-effects within-practice estimate for the risk difference for severe adverse event for patients exposed vs. those unexposed to antibacterial drugs was -0.00000677 (95% c.i. -0.0000383 to +0.0000247); this crude result implies that antibacterial drugs decrease the risk of severe adverse events with a risk of -0.677 per 100,000 visits.

The variables found to be confounders when considered individually (age as a four-knot spline, number of comorbidities, number of different classes of drugs used and the number of recorded visits in the previous year, Townsend score, and racial distribution) and centered year were used for the initial multivariable model. Variables were eliminated individually, and remained out of the model if their elimination resulted in a <10% in the coefficient of interest, the risk of severe adverse event. Ultimately, the final model included age, year, the number of drugs,

number of visits, and the Townsend score, with a risk difference of -1.42 per 100,000 visits (95% c.i. -4.75 to +1.91, p=0.40) comparing antibacterial drug-exposed vs. unexposed visits, Table 15.

Sensitivity analysis

Eliminating visit grouping: Eliminating visit grouping, results were the same, with a risk difference of -1.42 (95% c.i. -4.75 to +1.91, p=0.403) comparing exposed vs. unexposed visits. Results for 30 days demonstrated even greater risk reduction for antibacterial drug exposure vs. unexposed patients, although still not statistally significant, with a point estimate for the risk difference of -3.79 (95% c.i. -8.38 to +0.802, p=0.106) .

Propensity score analysis: In order to get the propensity score models to successfully converge, we needed to dichotomize our continuous predictors of exposure, and we were still not able to generate pscores for eleven of the 326 practices (including 90,885 of 1,531,019 visits in the cohort) (Chapter 5). Including encounters from only the 311 practices with propensity scores, the risk difference for severe adverse event was .-1.45 (95% c.i. -4.96 to +2.06, p=0.419) comparing exposed vs. unexposed encounters, similar to the risk difference estimate using all of the data (Table 15). We then fitted the same model, substituting categorical propensity score for the included covariates. Risk difference for severe adverse event, stratified by propensity score category, was -1.87 (-5.43 to +1.68, p=0.301), comparing antibacterial drug-exposed vs. unexposed visits, with the point estimate slightly farther from the null, but with overlapping confidence intervals compared with the estimate using the model without the propensity score (Table 16). We also examined what happened to the risk difference estimate when the model was used for only one propensity score category at a time; there did not appear to be a trend in these risk difference estimates over propensity score categories (Table 15).

Table 15. Adverse Event Outcomes

Adverse Event Outcomes			
	Per 100,00 encounters		
All antibacterial drugs, at 14 days, grouped encounters	**Risk difference for antibacterial use**		
	Point Estimate	**95% c.i.**	**p-value**
SEVERE ADVERSE EVENTS			
Model without propensity score			
Including all encounters	-1.42	-4.75 to +1.91	0.403
Including only encounters with a propensity score	-1.45	-4.96 to +2.06	0.419
Model with propensity score			
All propensity score quintiles	-1.87	-5.43 to +1.68	0.301
1st propensity score quintile	+3.07	3.58 to +9.72	0.365
2nd propensity score quintile	-4.93	-12.41 to +2.56	0.197
3rd propensity score quintile	-4.55	-12.42 to +3.32	0.257
4th propensity score quintile	-0.366	-9.88 to +9.14	0.940
5th propensity score quintile	-2.56	-11.72 to +6.60	0.584
Crossover cohort analysis	-0.99	-4.15 to +5.61	.66
LESS SEVERE ADVERSE EVENTS	+55.58	+28.00 to +83.18	<0.001
HOSPITALIZATION FOR MOTOR VEHICLE CRASHES	-0.78	-1.70 to +0.13	0.093

Less severe adverse events

For less adverse events that did not result in hospitalization, the risk difference for mild adverse event for antibacterial drug-exposed vs. antibacterial-unexposed visits was +55.58 per 100,000 visits (95% c.i. +28 to +83.18, p<0.001), Table 19, implying a significant increased risk for adverse events, rather than the null effect seen for the more severe adverse events (Table 15).

Control outcome: Hospitalization for motor vehicle crashes

We modeled a *control outcome,* hospitalization for motor vehicle crash, which should not be related to antibacterial exposure. Using the multivariable model, the risk difference for hospitalization for antibacterial drug-exposed vs. unexposed visits was -0.783 per 100,000 visits (95% c.i. -1.7 to +0.131, p=0.093), Table 15.

Crossover cohort study

Sixty-one case visits were matched with 173 control visits by the case patients. All control visits occurred prior to the case visit for each patient. Odds ratio for antibacterial drug-exposed vs. unexposed visits was 0.87 (95% c.i. 0.44 to 1.76, p=0.66), Table 15. Using the value for risk of severe adverse event for patients with baseline covariates from the conditional linear regression results above, this implies a risk difference of - 0.9927, compared with -1.42 from the conditional linear regression results. The crossover cohort results were thus closer to the null result of no risk difference than the point estimate of the risk difference from the conditional linear regression results.

Exploratory Analyses

Individual adverse event category:

Individual adverse event category and all antibacterial drugs

Considering individual adverse event categories, risk difference point estimates ranged from -1.42 per 100,000 visits up to +0.556 per 100,000 visits but only one, for diarrhea, was statistically significant, an unremarkable result considering the multiple comparisons. (Table 16).

Table 16. Regression Results for Individual Adverse Event Types

Regression Results for Individual Adverse Event Types			
	Per 100,00 visits		
	Risk difference for antibacterial drug use		
All antibacterial drugs, at 14 days, grouped encounters	**Point estimate**	**95% c.i.**	**p-value**
Severe adverse events	-1.42	-4.75 to +1.91	0.403
Hypersensitivity	+0.464	-1.58 to +2.51	0.656
Diarrhea	-1.25	-2.46 to -.0407	0.043
Hepatic toxicity	-0.518	-1.49 to +0.452	0.295
Renal toxicity	+0.820	-0.588 to +2.33	0.254
Arrhythmia	+0.556	-0.166 to +1.28	0.131
Seizure	-1,18	-2,55 to +0.189	0.091

Class-specific antibacterial drug exposure

Class-specific antibacterial drug exposure vs. no antibacterial exposure

When assessing class-specific antibacterial drug exposure vs. no exposure, we were faced with sparse data and multiple comparisons (Table 17). Point estimates of the risk difference for severe adverse events for beta lactams and macrolides were negative, and for flouroquinolone was positive, but none of these differences were statistically significant.

Class-specific antibacterial exposure vs. other-antibacterial exposure

When assessing class-specific antibacterial drug exposure vs. other antibacterial exposure, point estimates of the risk difference for severe adverse events for beta lactams was negative, and for macrolides and flouroquinolones was positive, but again, none of these estimates were statistically significant (Table 17).

Table 17. Regression Results by Antibacterial Drug Class: Severe Adverse Events

	Severe Adverse Events Per 100,00 visits		
Grouped encounters	**Risk difference for antibacterial drug use**		
	Point estimate	**95% c.i.**	**p-value**
All antibacterial drugs			
Antibacterial drug use vs. none	-1.42	-4.75 to +1.91	0.403
Ungrouped	-1.42	-4.75 to +1.91	0.403
Specific antibacterial class vs. none			
Beta-lactams	-1.70	-5.15 to +1.76	0.335
Macrolides	-0.10	-6.29 to +6.09	0.975
Flouroquinolones	+1.43	-16.21 to +19.06	0.874
Specific antibacterial class vs. other antibacterial class			
Beta lactams	-1.35	-5.59 to +2.88	0.531
Macrolides	+2.10	-3.34 to +7.53	0.450
Flouroquinolones	+10.39	-6.15 to +26.92	0.218

Deaths

Deaths within 14 days of encounters were rare, with a mean incidence rate of 87.9 per 100,000 encounters. The unadjusted rate was 70.66 per 100,000 encounters with antibacterial drug exposure and 120.61 deaths per 100,000 acute nonspecific respiratory infection encounters without antibacterial exposure. There were 102 practices with zero death outcomes within 14 days of grouped visits, and 46, 32, 29, 19, 18, and 80 practices with 1,2,3,4,5, and >5 death outcomes, respectively.

Using practice as the panel variable, the unadjusted conditional fixed-effects within-practice estimate for the risk difference for death for patients exposed vs. those unexposed to antibacterial drug was -0.0006239 (95% c.i. -0.0007302 to -0.0005175, p<0.001); this unadjusted result implies that antibacterial drugs decrease the risk of death by 62.39 per 100,000 visits.

The variables found to be confounders when considered individually analysis (age as a five-knot spline, number of co-morbidities, and the number of different classes of drugs used) and centered year were retained for consideration in the multivariable model. Adjusting for age and the number of comorbidies and different types of drugs used in the previous year, the risk difference was -84.26 (95% c.i. -95.00 to -73.53, p<0.001, comparing antibacterial exposed vs. unexposed visits (Table 16,18). Eliminating visit grouping, results were the same, an estimated risk difference of -84.26 per 100,000 visits (95% c.i. 95.0 to -73.53, p<0.001). Results at 30 days, similar to adverse event results, were away from the null at -99.70 per 100,000 visits (95% c.i. -113.93 to -85.47, p<0.001). In propensity score analysis, *r*isk difference for death, stratified by propensity score category, was -92.52 (-104.01 to -81.03, p<0.001), comparing antibacterial exposed vs. unexposed visits.

Discussion

Antibacterial drug use is very common, and patients sometimes experience severe adverse events that are temporally related to taking these medications. Certain adverse events, particularly the conditions included in this study, are often believed to have a causal relationship with patients' antibacterial drug use; most of these associations have been established using case reports, but case reports of adverse events do not include an unexposed comparison group, and are thus ill-suited for establishing a causal association.

Approximately half of patients with primary care visits for acute nonspecific respiratory tract infections receive treatment with antibacterial drugs. In this study, we compared the risk of a severe adverse event or death for antibacterial exposed vs. unexposed patients who were similar otherwise in that they experienced a primary care visit for nonspecific respiratory tract infection.

Methods outlined in Chapter 5 were used to model our extremely rare outcome, and help control for clustering and confounding by practice and confounding by indication. In addition, sensitivity analyses explored how robust our results were to our primary model assumptions. We also explored some secondary and exploratory outcomes of interest.

Patients with acute nonspecific respiratory infections treated with antibacterial drugs were not at increased risk of severe adverse events, with a point estimate for the risk difference of -1.42 per 100,000 visits with a confidence interval that included zero.

The results were robust to eliminating the visit grouping. Extending the exposure window from 14 to 30 days after the index visit moved both the adverse event and death estimates somewhat away from the null, most likely from including more events less related to the index visit, and more related to patients' underlying condition, but did not alter the general conclusions.

Results using a propensity score analysis were slightly farther from the null, in the direction of protection against adverse events, although still did not reach statistical significance. In theory, the propensity score is well suited to increase our power to show a risk difference, with our rare outcome and common exposure, However, many practices had to be dropped from the our propensity score analysis because the propensity score models would not converge, due to covariate imbalance. There is reason to believe that practices with missing propensity scores may be different in systematic ways from practices with more covariate balance between exposure groups. Further information was lost when some continuous variables needed to be dichotomized to reach propensity score convergence. For these reasons, the model without the propensity score most likely provided less biased estimates than the propensity score model.

Antibacterial drug class-specific analyses were limited by sparse data and multiple comparisons. When compared to no antibacterial drug use, none of the antibacterial classes seemed to definitively increase the risk of an adverse event. As we were underpowered to assess these subgroup effects, while our composite result provides overall reassurance about

the safety of these drugs in this setting, it does not eliminate very small increased risk for specific outcomes due to specific drug classes.

Considering less severe adverse events, those resulting in a subsequent primary care visit within the 14-day exposure window, but not resulting in hospitalization, there was an apparent increased risk of less severe events with antibacterial drug exposure of +55.58 per 100,000 visits. Given that this effect was not seen with the severe events, it is possible that this result is secondary to misclassification, in that minor adverse events after antibacterial exposure might be more likely to be reported and recorded than similar events without antibacterial exposure, while hospitalizations are more likely to be reported and recorded whether or not the patient is on antibacterial drug treatment. This is the reason we chose the much rarer but more specific severe event category for our primary outcome, and our results seem to support this choice. Alternative possibilities are that antibacterial drugs increase the risk of minor but not severe adverse events, and/or that our hospital admission outcomes suffer from additional misclassification and/or bias compared with the outpatient outcomes.

If a systematic difference was shown in the risk of a known, control outcome, such as hospitalization for automobile crashes, between antibacterial drug-exposed and –unexposed patients, this would not plausibly be an effect of exposure and would be evidence of a hidden bias due to unmeasured confounding.[21] In this study, patients with antibacterial drug exposure were not more likely than unexposed patients to be hospitalized with a diagnosis of motor vehicle crash; this result is expected and reassuring that our methods yielded these expected results. The two types of outcomes may not be directly comparable however. Our study did not address the issue of disparities in health care access, which might differentially affect different outcomes, for example automobile crash outcomes may be more or less likely to be related to patient characteristics that could be correlated with access to health care. This is less likely to be an issue in the U.K., with their National Health Service, than in the U.S.

The instrumental variable analysis seemed to look somewhat different from results from the other models, closer to the null. However, as described in Chapter 5, the IV results really

describe between-practice estimates of the risk difference, when our estimate of interest was the within-practice risk differences.

Results from the crossover cohort study further support the null results of the primary analysis, in that results are even closer to the null when antibacterial drug-exposed time is compared to antibacterial-unexposed time within the same patient; this may reflect a true control of some inter- patient confounding by indication. However crossover cohort methods are less suitable for some outcomes, like deaths, where it's difficult to find suitable control time. Crossover cohort methods in this study are somewhat limited by the difficulty of using control time sampled after the adverse event, Patient's comorbidities change with time, (usually they tend to get sicker with time), and thus their indication for treatment tends to change with time in a positive fashion. Because many studies, like this one, have difficulty making use of control time after the case event (most phyisicns would be less likely to prescribe an antibacterial drug if the patient has previously had a severe adverse event associated with one. thus, we still have to deal with the possibility of within patient confounding by indication; despite having some temporal information in our visit date variable, we were probably not completely able to deal with the fact that our patients have different indications at different times.

Limitations:

Misclassification: Limitations of this study include that we were limited by the potential inaccuracy of THIN data. For example, there may have been exposure misclassification (antibacterial use with acute nonspecific respiratory infections). Drug prescriptions are generated by data entry into the electronic medical record, and primary care general practitioners are responsible for most medication prescribing, so capture of drug prescription information in THIN is virtually 100%.[30, 31] However, some antibacterial drugs used to treat patients may be missed, for example, telephoned prescriptions not associated with an coded visit, and some more recent urgent care visits, would not be included in our data. Also, we have no data regarding whether the prescriptions were filled or ingested. Our visit grouping classified the encounter as

antibacterial drug-exposed if any of the visits within the included two-week window included an antibacterial prescription , and thus may have misclassified in favor of antibacterial use, however our results were virtually identical with ungrouped analysis.

We also need to consider outcome misclassification (adverse events after the visit). As the outcome is entered after exposure, it is possible that there will be differential ascertainment of outcome based on antibacterial drug exposure, for example, patients exposed to antibacterial drugs who experience an adverse event may be more likely to come to medical attention than unexposed patients. Differential ascertainment of outcome may be less likely for our primary outcome of severe adverse events resulting in hospitalization than for less severe events, however it is possible that adverse events may be more likely to be identified and diagnosed as such for patients who are hospitalized. People who get admitted to the hospital for any reason may be more likely than people who do not get admitted to receive an adverse event diagnosis. If people who do not receive antibacterial drugs are more likely to be admitted to the hospital, they may be more likely to receive a severe adverse event diagnosis; this would have biased our results toward the null.

We addressed the specificity of our hospitalization diagnosis with the validation study described in Chapter 4, which supported the validity of our hospitalization outcome, however we did not address diagnosis sensitivity; some of our outcome diagnoses may have been missed, however there is no reason to suspect that hospitalization diagnoses would be more or less likely to be recorded in antibacterial drug-exposed vs. unexposed patients, as discussed above.

Confounding: Confounding, especially confounding by indication is another potential limitation of this study. We addressed measured confounders using the methods described above; a strong instrumental variable would have been helpful to address unmeasured confounders; future studies including validated data on prescriber within practice may be able to further address this issue.

. *Generalizability:* THIN data come from the U.K., however there is no reason to think that individuals in the U.K. have different risks related to antibacterial drug exposure than individuals

living elsewhere. Results from this study are not necessarily be generalizable to patients with illnesses other than acute nonspecific respiratory infections, other types of hospitalization outcomes than those specifically measured here, or in other very different populations, for example, for children.

In conclusion, case reports of adverse events temporally associated with antibacterial drug use have traditionally been used as evidence of a causal relationship between use of that drug and the adverse event. This anecdotal evidence does not provide strong support for a causal association, in particular because such analyses lack a control group and do not control for confounding by indication, the fact that patients who are more likely to be at baseline risk of adverse event are also more likely to be prescribed the medication in question. This very large study included a control group of similar patients without antibacterial drug exposure, and took advantage of linked clinical and demographic data to minimize confounding by indication, and analytic techniques to minimize confounding by practice. Patients with acute nonspecific respiratory tract infection treated with antibacterial drugs were not at increased risk of severe adverse event or death within 14 days of exposure compared with antibacterial-unexposed patients. Adverse event reporting without data on unexposed patients may not reflect a true causal relationship between the drug and the adverse event. While there are other compelling reasons to not treat patients with acute nonspecific respiratory infections with antibacterial drugs (e.g., drug costs, contribution to emerging drug resistance), the use of antibacterial drugs in these settings is not associated with increased risk of serious adverse drug events.

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Chapter 7. Outcomes II: Potential Benefits of Antibacterial Drug Use: Pneumonia hospitalization outcomes after acute nonspecific respiratory infection; assessing the influence of antibacterial drug treatment

Every individual in the U.S. is prescribed a short-term course of systemic antibacterial drugs once every three years to almost twice per year, on average, resulting from a visit to an ambulatory health care provider.[1-6] Acute respiratory tract infections account for approximately 10% of the 6.2 billion annual U.S. outpatient visits.[4] Approximately half of these diagnoses are for acute nonspecific respiratory tract infections. Unlike conditions with a defined presumed bacterial focus, such as pneumonia, bacterial sinusitis, and acute exacerbations of chronic bronchitis, for which antibacterial drugs have demonstrated benefit, multiple randomized clinical trials have failed to demonstrate a clear benefit from the use of antibacterial drugs to treat acute nonspecific respiratory infections, such as nasopharyngitis, acute bronchitis, and acute rhinitis, usually of viral etiology.[4, 7]

In Chapter 6, we showed that serious risks related to antibacterial drug use for acute nonspecific respiratory infections are very low; in this chapter, we explore potential benefits of antibacterial drug use. Numerous practice guidelines[8-12] recommend against antibacterial drug treatment of acute nonspecific respiratory infections, but antibacterials are often prescribed; adults at about half of U.S. office visits for acute nonspecific respiratory infections receive antibacterial prescriptions.[3, 4, 13] Many of the randomized clinical trials that failed to measure a significant benefit to antibacterial drugs for acute nonspecific respiratory infections were relatively small and potentially underpowered to detect small but clinically significant benefits. [7, 9, 14, 15] These benefits could include faster disease resolution or prevention of progression to more serious bacterial infections. Given the large number of acute nonspecific respiratory infections per year, even a small relative benefit might translate into a large public health effect.

The objective of this study is to compare the risk of a hospitalization for pneumonia between THIN patients prescribed antibacterial drugs vs. the risk for those not prescribed antibacterial drugs, conditional on a primary care visit for acute nonspecific respiratory infection.

Our hypothesis is that patients with acute nonspecific respiratory infections with exposure to antibacterial drugs have a decreased risk of pneumonia hospitalizations compared with antibacterial-unexposed patients with acute nonspecific respiratory infection. We used methods discussed in Chapters 5 and 6 to address analytic issues related to rare outcomes, clustering and confounding by practice, and confounding by indication.

Methods

The data source for this retrospective cohort study was again the September 2007 dataset from The Health Improvement Network (THIN). We used the same cohort of adult THIN primary care visits for acute nonspecific respiratory infection used for the study of adverse events described in Chapter 6. Because data from multiple visits within the same illness episode may tend to be highly correlated, visits were again grouped if they occurred within a two-week period; grouped visits were defined as encounters. For sensitivity analysis, we eliminated the visit grouping.

Exposure: Exposure of interest was antibacterial drug prescription within one day of the index visit for acute nonspecific respiratory infection; antibacterials of interest included oral antibacterials typically used for respiratory infections. We excluded topical, vaginal, ophthalmologic, otic, and parenteral antibacterials, and those typically used for tuberculosis, fungal and parasitic infections. Primary exposure window was within 14 days of the index encounter as most antibacterial exposure associated with treatment of acute nonspecific respiratory infection is completed within 15 days (Figure 13).[16]

Outcome: The primary outcome for this study was hospitalization for pneumonia within a 0-15 day window following the index encounter for acute nonspecific respiratory infection, defined using Read diagnostic codes for pneumonia (Table 21) and THIN hospitalization Source codes (Bhullar, H, personal communication March 1, 2007). We previously showed that these same THIN pneumonia and hospitalization codes had a good positive predictive value for identifying valid hospitalizations for pneumonia, (Chapter 4), and that, of the identified

hospitalizations, almost all (>96%) were identified within two weeks after the acute index visit. In sensitivity analysis , we extended the window out to 30-days exposures to address how robust our results are to misclassification of hospitalization dates. We also modeled admission between 2 and 15 days after the index encounter, to see how robust our results were to eliminating relatively immediate hospitalizations occurring within one day of the visit for acute nonspecific respiratory infection, which may be more related to the patient's original condition than to the physician's antibacterial drug treatment decision. Also, for comparison, we modeled hospital admissions in general for all diagnoses other than the severe adverse event diagnoses considered in Chapter 6.

Table 18. Pneumonia Diagnostic Codes

THIN Read Code Description
Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr
Klebsiella pneumoniae/cause/disease classifd/oth chapters
[X]Mycoplasma pneumoniae [PPLO]cause/dis classifd/oth chaptr
Acute bronchitis due to mycoplasma pneumonia
Pneumonia and influenza
Viral pneumonia
Pneumonia due to adenovirus
Pneumonia due to respiratory syncytial virus
Pneumonia due to parainfluenza virus
Viral pneumonia NEC
Viral pneumonia NOS
Lobar (pneumococcal) pneumonia
Other bacterial pneumonia
Pneumonia due to haemophilus influenza
Pneumonia due to haemophilus influenza
Pneumonia due to streptococcus
Pneumonia due to streptococcus, group B
Pneumonia due to staphylococcus
Pneumonia due to other specified bacteria
Pneumonia due to other aerobic gram-negative bacteria

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Pneumonia due to bacteria NOS
Bacterial pneumonia NOS
Pneumonia due to other specified organisms
Pneumonia due to mycoplasma pneumonia
Pneumonia due to pleuropneumonia like organisms
Chlamydial pneumonia
Pneumonia due to specified organism NOS
Pneumonia with infectious diseases EC
Pneumonia with whooping cough
Pneumonia with pertussis
Pneumonia with other infectious diseases EC
Pneumonia with varicella
Pneumonia with other infectious diseases EC NOS
Pneumonia with infectious diseases EC NOS
Bronchopneumonia due to unspecified organism
Pneumonia due to unspecified organism
Lobar pneumonia due to unspecified organism
Basal pneumonia due to unspecified organism
Postoperative pneumonia
Influenza with pneumonia
Influenza with bronchopneumonia
Influenza with pneumonia, influenza virus identified
Influenza with pneumonia NOS
Atypical pneumonia
Other specified pneumonia or influenza
Pneumonia or influenza NOS
Aspiration pneumonia due to vomit
Abscess of lung with pneumonia
Bronchiolitis obliterans organising pneumonia
Interstitial pneumonia
Other viral pneumonia
Pneumonia due to other aerobic gram-negative bacteria
Other bacterial pneumonia
Pneumonia due to other specified infectious organisms
Pneumonia in bacterial diseases classified elsewhere
Pneumonia in viral diseases classified elsewhere

Pneumonia in other diseases classified elsewhere
Other pneumonia, organism unspecified
Other aspiration pneumonia as a complication of care

Covariates: Covariates included patient age at visit, sex, and visit year. Although it would have been ideal to include them in the analysis, THIN does not include direct measures of patients' socioeconomic, racial and ethnic characteristics. THIN does include other variables based on the patient's post code that were used as proxies of these characteristics; these variables include the Townsend score, a five-quintile measure of neighborhood deprivation, and a five-quintile variable describing the proportion of the patient's neighborhood who define themselves as "Black" or "Black British.". As above for the severe adverse event outcome (Chapter 6) .considering what clinical data might be relevant from a clinical aspect to help predict indication for antibacterial treatment of acute nonspecific respiratory infections, we also included alternative summary measures of the intensity of medical care use, including including the number of THIN recorded co-morbidities, with co-morbiditites grouped into the categories shown in Chapter 5, Table 4 (Lewis, JD,unpublished data),[17] and the number of different classes of medications that the patient was prescribed[17, 18] and the number of THIN visits recorded for that patient within the year prior to the patient's index encounter.

Analysis: We calculated descriptive statistics for exposures and outcomes separately. For the primary multivariable analysis our previous studies, above, showed that antibacterial drug prescribing was profoundly unbalanced between practices, and that there was enormous confounding by practice in the relationship between our rare outcome and antibacterial exposure, that practice level covariable data were limited, and covariable adjustment was unlikely to be able to adjust for this confounding by practice. Thus, to obtain unbiased estimates for our outcome of interest, hospitalization for any pneumonia diagnosis, our models needed to condition on practice, and our models used practice as the grouping variable; Confounding by patient was more likely to be well-controlled using available patient-level covariates. For consistency and comparison with the other studies described above, and to control for clustering and confounding by practice, and

to provide within-practice risk difference estimates, we performed fixed effects conditional linear regression using Stata's xtreg function, described in further detail in Chapter 5.

Model covariates were included using the two-step process described in Chapter 6. First, we initially included all covariates that were associated with the outcome, conditional on the exposure of interest. Then, we retained each covariate in the final model if removing it caused a change of >=10% in the risk difference for antibacterial drug use.

For sensitivity analysis, we eliminated the visit grouping, and examined results at 30 days, as described above. As described above, we also modeled admission between 2 and 15 days after the index encounter for acute nonspecific respiratory infection, to see how robust our results were to eliminating relatively early hospitalizations within one day of the encounter.

We also explore the possibility that bronchitis encounters might behave differently than acute nonspecific respiratory infections with comparatively more upper respiratory symptoms, modeling pneumonia hospitalization outcomes in two additional ways, first eliminating encounters with a bronchitis acute nonspecific respiratory infection diagnosis, and second, including only encounters with a bronchitis diagnosis.

Power

Power calculations were performed conservatively, using Stata version 10.1, StataCorp LP. As in Chapter 6, we estimated a cohort of 3.5 million ARI visits In the U.S., 61.8% of adults diagnosed with acute nonspecific respiratory infection in the outpatient setting are prescribed antibacterial drugs,[3] and our power calculations conservatively assumed that the U.K. antibacterial prescribing rate could be only ½ of the U.S., or 30.9% of index encounters.

With these assumptions, with visits clustered by practice, assuming a mean of 10,700 visits per practice, with an intracluster correlation coefficient (ICC) of 0.15, using the U.S. antibacterial drug prescribing rate, a conservative alpha of 0.025, allowing for covariate adjustment, and a baseline pneumonia rate without antibacterials of 0.017, or 17 in 1000 visits, we would have 90% power to detect a risk difference of 0.0017, or a relative risk of 0.90 comparing antibacterial drug exposed vs. exposed visits, and we would have 80% power to

detect this risk difference with a ICC as high as 0.2. With only half the U.S. antibacterial drug prescribing rate for ARIs, or 30.9%, we would have 90% power to detect this risk difference with an ICC of 0.15, and 80% power to detect this risk difference with an ICC as high as 0.20. A study by Petersen et.al. showed that the risk of an outpatient consultation for 'chest infection' during the month after an outpatient consultation for upper respiratory infection was 17 per 1000 in those not treated with antibacterial drugs and 11 per 1000 in those treated with antibacterials, giving a risk difference of 6 in 1000 visits, or a 35% decrease in risk.[19] These results indicate that we would have the power to detect any expected, and certainly any clinically significant change in pneumonia risk associated with antibacterial drug exposure.

Results

Description of the cohort

Visits

The cohort was described in greater detail in Chapter 6; it contained 1,646,229 total visits and 1,531,019 grouped acute nonspecific respiratory infection encounters by 814283 patients in 326 practices. 361,553 of these encounters were for bronchitis diagnoses.

Antibacterial drugs

Overall, patients at 65.4% of encounters for acute nonspecific respiratory infections received antibacterial drug prescriptions. As expected, antibacterial drug prescribing varied widely between practices, from a low of 3.1% to a high of 94.7% of grouped visits receiving antibacterial prescriptions (Chapter 5, Figure 8). As described in more detail in Chapters 5 and 6, this extreme unbalance of antibacterial drug prescribing across practices provided strong evidence that analytic methods needed to adjust for clustering and confounding by practice.

For the 361,553 encounters with bronchitis acute nonspecific respiratory infection diagnoses from all 326 practices, 303,631 (84.0%) received antibacterial drugs.

Covariates

In general, as described in Chapter 6, subjects with encounters where antibacterial drugs were prescribed generally had more pre-existing health conditions (Table 12).

Pneumonia Outcomes

There were 296 pneumonia hospitalizations within 15 days of encounters for acute nonspecific respiratory infections, 180 in patients who received antibacterial drugs and 116 in patients without antibacterial exposure. The unadjusted mean incidence rate of pneumonia hospitalization was 0.0001933, or 19.33 per 100,000 encounters; 21.93 in patients without antibacterial drug exposure, and 17.96 in patients with antibacterial exposure, giving a crude risk difference of 3.97 per 100,000 encounters and relative risk of 0.82. There were 211 practices with zero pneumonia hospitalizations within 15 days of index encounters for acute nonspecific respiratory infections.

Using conditional fixed effects linear regression, with practice as the grouping variable, the unadjusted within-practice risk difference was a protective effect of antibacterial drug use of -4.53 per 100,000 encounters for antibacterial exposed vs. unexposed encounters. The final model adjusted for age, year, the number of comorbidities and, and the number of different classes of drugs used by the patient within the year prior to the index ARI encounter; there was a risk difference of -8.16 per 100,000 encounters (-13.24 to -3.08, p=0.002), comparing antibacterial-exposed to antibacterial unexposed encounters.

Results from ungrouped analysis were unchanged. There were 396 pneumonia hospitalizations at 30 days after the index encounter for acute nonspecific respiratory infection, 248 after receiving antibacterial drugs and 148 without antibacterials. Using the conditional fixed effects linear regression model, adjusted for the same covariates, age, year, number of comorbidities and number of drugs used in the previous year, the protective effect of antibacterial drug use was 14.6% farther from the null, with a risk difference of -9.35 per 100,000 encounters for antibacterial exposed vs. unexposed encounters (95% c.i. -15.22 to -3.47, p=0.002).

Results with the 2-15 day window yielded a risk difference of -4.38 pneumonia hospitalizations per 100,000 visits (-9.08 to +0.331, p=0.068), comparing antibiotic exposed vs. unexposed encounters

Eliminating the 361,553 patients with bronchitis, the risk difference for antibacterial drug-exposed vs. unexposed encounters was farther away from the null, at -9.01 per 100,000 encounters (-13.43 to -4.58, p<0.001). Considering only the 361,553 bronchitis encounters, the within-practice risk difference for pneumonia admission at 15 days was -37.26 per 100,000 encounters (-59.71 to -14.81 per 100,000 encounters, p=0.001).

Hospitalization for other diagnoses:

We also modeled hospitalizations in general for all diagnoses, to consider outcomes not thought to be related to antibacterial drugs. The risk difference for hospitalization with any diagnosis other than the previously-described severe adverse events (hypersensitivity, diarrhea, hepatic toxicity, renal toxicity, arrhythmia, or seizure), describing antibacterial-exposed vs. – unexposed encounters, was -202 per 100,000 visits (-227 to -176, p<0.001)

Discussion

Antibacterial drugs are often prescribed for acute nonspecific respiratory infections, over half of patients at U.S. visits for acute nonspecific respiratory infections receive antibacterial drug prescriptions,[3] despite numerous practice guidelines[9-12] and public health campaigns[20-22] urging otherwise. Individual decisions regarding antibacterial prescribing are made, not at the public policy level, but at the level of each individual physician-patient relationship, where patient-level risk/benefit considerations are likely to take precedence over societal considerations.[23]

By limiting our comparison of pneumonia hospitalizations to patients with acute nonspecific respiratory infection visits, we simulated a randomized clinical trial by promoting comparability between exposed and unexposed patients. We addressed remaining confounding by practice, and confounding by indication with the analytic techniques explored in Chapter 6.

We found that the crude risk of pneumonia hospitalization after a visit for acute nonspecific respiratory infection was small, at 19.33 per 100,000 visits. The adjusted within-

practice risk difference, comparing antibacterial exposed vs. unexposed visits of -4.53 per 100,000 visits was of larger magnitude than that for avoiding severe adverse events(-1.42 per 100,000 visits, p=0.40). This corresponds to a number needed to treat of 22,075 to prevent one hospital admission for community acquired pneumonia Results were robust to eliminating our visit grouping and to extending the window of exposure. The risk difference was attenuated toward the null when not considering pneumonia hospitalizations during the first day after the acute nonspecific respiratory infection encounter. This could potentially reflect that antibacterial drugs would have their greatest effect on the acute exacerbation of a rapidly evolving bacterial illness.

Although practice guidelines recommend that antibacterial drugs not be prescribed for both acute nonspecific upper respiratory infections,[7, 9, 10, 24, 25] and bronchitis illnesses,[26] some clinicians may treat patients with predominantly upper respiratory symptoms differently than patients with predominant cough symptoms. The similar findings when bronchitis visits were eliminated was reassuring. The protective effect of antibacterial drugs for patients with bronchitis diagnoses was further from the null; this deserves further study.

Patients given antibacterial drugs were at significantly lower risk of being hospitalized with any other diagnosis. Speculating on the reasons for this unexpected result, confounding by indication does not adequately explain it, unless patients given antibacterials were likely to be healthier such that antibacterials were selectively given to healthier patients and selectively withheld from patients with more baseline health problems, which doesn't make clinical sense. It is possible that there is an underlying reason for this result other than bias; for example antibacterial drugs could be protective due to their anti-inflammatory effect, or their effect on bacterial colonization. Further studies are needed to explore the reasons behind this outcome.

Ecologic studies from the U.S. and the U.K. have examined the relationship between antibacterial drug use and hospital admissions. Majeed et. al. used U.K. National Health Service primary care prescribing data and hospital admission data to show that, between 1996 and 2002, the overall antibacterial drug prescribing rate decreased by 23%, while hospital admissions for

respiratory tract infections increased by 15%.[27] Mainous et. al. used U.S. population-based survey data to conclude that trends in decreasing antibacterial drug prescribing for acute bronchitis and cough illnesses between 1996 and 2003 were associated with increasing hospitalizations for respiratory infections during that same time period.[28] Petersen et.al.,performed a cohort study more similar to ours, using another U.K. primary care electronic medical record database, the General Practice Research Database (GPRD) to look at hospitalization for pneumonia within one month of outpatient treatment for "upper respiratory tract infection" and "chest infection."[19] They found an odds ratiofor "chest infection" in the month after a visit for upper respiratory infection of 0.64 for patients treated vs. those untreated with antibacterial drugs. They found that the risk of pneumonia within one month of chest infection was high, and substantially reduced by initial antibacterial drug treatment, with odds ratios comparing treated to untreated visits ranging from 0.22 to 0.35, depending on patient age. However, bronchitis codes were included among the codes used to identify "chest infections", and "bronchopneumonia" codes were included among codes used to identify pneumonia outcomes, and hospitalization status was not specified, so it is difficult to directly compare their results to those of our study. A key issue relates to misclassification of diagnosis at the initial visit; if early bacterial pneumonia is misclassified as chest infection or bronchitis, the absence of antibacterial drug treatment is more likely to be associated with failure to improve and an increased risk of hospitalization for pneumonia.

Limitations:

Misclassification: Limitations of this study are similar to those in Chapter 6, and include that we were limited by the potential inaccuracy of THIN data. For example, there may have been exposure misclassification (antibacterial use with acute nonspecific respiratory infections). Drug prescriptions are generated by data entry into the electronic medical record, and primary care general practitioners are responsible for most medication prescribing, so capture of drug prescription information in THIN is virtually 100%.[29, 30] However, some antibacterial drugs used to treat patients may be missed, for example, telephoned prescriptions not associated with

an coded visit, and some more recent urgent care visits, would not be included in our data. Also, we have no data regarding whether the prescriptions were filled or ingested. As with the previous study, our visit grouping classified the encounter as antibacterial drug-exposed if any of the visits within the included two-week window included an antibacterial prescription; this may have misclassified in favor of antibacterial use, and thus may have caused differential misclassification of exposure, however our results were virtually identical with ungrouped analysis. We also need to consider outcome misclassification (adverse events after the visit), however we demonstrated in Chapter 4 that pneumonia and hospitalization codes had good specificity for identifying pneumonia hospitalizations in THIN. Even so, there could have been differential ascertainment of outcome such that pneumonias may have been more likely to be identified and diagnosed as such for patients who are hospitalized; and our finding that patients have increased risk of admission for any diagnosis after antibacterial use for acute nonspecific respiratory infections is pertinent here, however this should not have been related to antibacterial drug exposure and would have tended to bias our results toward the null. However, if the decisison to admit for pneumonia treatment was more likely if the patient had not been previously prescribed antibiotics, this could have biased our results away from the null. From a clinical standpoint, it might be just as likely that a history of previously not receiving antibiotics would have instead triggered an outpatient antibiotic prescription instead of a hospital admission.

Another relevant area of potential misclassification is that of visit diagnosis misclassification. It is unclear why physicians code for nonspecific respiratory illnesses despite their decision to treat with antibacterial drugs. Physicians seem to persistently prescribe antibacterials while coding for nonspecific acute respiratory infection diagnoses (nasopharyngitis, acute bronchitis, acute rhinitis), supporting the apparent purposeful classification of these illnesses as nonspecific vs. coding instead for diagnoses implying a focal bacterial source, such as acute sinusitis, pneumonia, etc. which would better support their decision for antibacterial drug treatment.. However, perhaps some of the THIN coded acute nonspecific respiratory tract infections were really illnesses with an apparent bacterial focus. To the extent that this

misclassification was non-differential, it would have biased our results toward the null. If misclassification was differential, if conditions coded as acute nonspecific bacterial infections with bacterial focus were more likely to be prescribed antibacterial drugs than similarly-coded illnesses without a bacterial focus, this would have biased our results toward the null, in that patients given antibacterial drugs may have been more likely, and certainly not less likely, to end up hospitalized with bacterial illness. It would be less plausible that patients with an apparent bacterial focus would be less likely to be prescribed antibacterial drugs than patients without a bacterial focus.

Confounding: Similar to Chapter 6, confounding, especially confounding by indication is another potential limitation of this study. We addressed measured confounders using the methods described above.; If patients prescribed antibacterial drugs were sicker, as indicated by unmeasured counfounders not included in this study but considered by treating physicians, the sicker patients receiving antibacterial drugs would have been more likely to experience subsequent pneumonia hospitalizations, the opposite result to that found in our study..A strong instrumental variable would have been helpful to address unmeasured confounders; future studies including validated data on prescriber within practice may be able to further address this issue.

. *Generalizability:* THIN data come from the U.K., however there is no reason to think that individuals in the U.K. have different risks related to antibacterial drug exposure than individuals living elsewhere. Results from this study are not necessarily be generalizable to patients with illnesses other than acute nonspecific respiratory infections, other types of hospitalization outcomes than those specifically measured here, or in other very different populations, for example, for children.

In conclusion, patients with acute nonspecific respiratory infections with exposure to antibacterial drugs do seem to have a small decreased risk of pneumonia hospitalizations compared with antibacterial-unexposed patients with acute nonspecific respiratory infections. At the societal level, we are very interested in eliminating unnecessary antibacterial drug prescribing to help slow the spread of antibacterial resistance, and the need to treat 22,000 patients with

antibiotics to avoid one hospital admission might seem excessive. At the level of the physician-patient encounter, we are most interested in providing the treatment that will best balance benefits and risks for that particular patient; the apparent best decision at the patient level is not always the ideal decision at the societal level. Even with a very small likelihood of patient benefit from antibacterial drug use, given how common acute nonspecific respiratory infections and antibacterial drug treatment are in our society, this dilemma creates an enormous challenge. One solution is to create more practice guidelines, and continue to educate physicians and the public regarding more responsible antibacterial drug use, from a societal perspective. Another solution, not mutually exclusive, is to continue to develop win-win solutions, so the interests of the individual patient and society can be served together.[31] For example, improvement of point of service rapid diagnostic techniques and biochemical markers of disease severity[32] can help us target antibacterial drugs to those patients most likely to benefit These services are quite costly, however scaling up their use would decrease marginal costs considerably, and, from a societal standpoint, this investment in decreasing antibacterial drug use may be considered cost effective. Expanding the use of influenza vaccine would also be helpful in this regard.

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Chapter 8. Conclusions/ Future Directions

To help slow the development of resistance to antibacterial drug, physicians are urged to decrease unnecessary antibacterial use, but their patients are increasingly elderly and vulnerable, making treatment decisions seem more complex than addressed by current treatment guidelines. Antibacterial drug prescribing decisions are made within the context of the physician-patient encounter, where the perceived benefit/risk ratio for that patient's present condition is likely to take top priority over other competing interests. It is important to have a comprehensive understanding of the pertinent patient-specific benefits and risks related to this class of medication to which the U.S. public has virtually universal exposure. The move toward increasingly more personalized medicine calls for a more sophisticated understanding of how to use patient- and environmental characteristics to help target antibacterial drug treatment to those most likely to benefit.

Most information on adverse events associated with antibacterial drug use come from spontaneous reports, which suffer from under- and to a lesser extent, over-reporting of events. . Without an unexposed control group, it is impossible to know the real risks for treated relative to untreated patients, however large prospective randomized studies are not feasible for every research question. Large observational electronic medical record databases contain longitudinal data regarding drug utilization from a real-world setting, linked to covariates and outcomes. Improving methods to utilize these rich but complex data might help us learn how to better address antibacterial drug misuse and overuse at the individual level.

We used a subset of the entire THIN cohort with an office visit for acute nonspecific respiratory infection, to consider antibacterial drug prescribing for acute nonspecific respiratory infections and compare outcomes of antibacterial-exposed and antibacterial-unexposed patients.

We found that antibacterial drug prescribing for acute nonspecific respiratory infections decreased over the study period in the U.K., but, in contrast to antibacterial drug use in the U.S., broad spectrum antibacterial prescribing remained quite low, and even most recently, appeared

to be decreasing. More data are needed regarding whether decreasing use may be affecting patient outcomes and trends in antimicrobial resistance.

We found that THIN hospitalization codes performed well in identifying the timing of hospitalization events of interest. This work supports observational THIN studies regarding additional medication use outcomes, especially outcomes related to acute conditions and acute exposures to antibacterial drugs as well as other medications.

By limiting our comparison of outcomes to antibacterial drug exposed vs. unexposed patients with visits for acute nonspecific respiratory infections, we promoted comparability between exposed and unexposed patients in the cohort. To further control for confounding by indication and confounding by practice, we explored methods to assure that the antibacterial -exposed and -unexposed groups were as comparable as possible. The rarity of our outcome presented an additional analytic challenge.

We showed that conditional fixed effects linear regression provided stable estimates of common exposure treatment effects on rare outcomes. Results using these models were quite similar to results obtained using more traditional methods for binary outcomes, but could utilize all available information, even from groups with zero events. However, comparing the risk of very rare events between quite unbalanced groups presents real challenges to power, even with very large datasets. Additionally, if power estimations for observational studies of rare events ignore potential baseline variability between groups, and potential confounding covariates, results could be quite biased and power estimates may be grossly inflated.

In our cohort, patients with acute nonspecific respiratory tract infections treated with antibacterial drug were not at increased risk of severe adverse events compared to antibacterial-untreated patients. It is clear that adverse event reporting without data on unexposed patients may not reflect a true causal relationship between the drug and the adverse event.

Patients with acute nonspecific respiratory infectionswith exposure to antibacterials had a small decreased risk of pneumonia hospitalizations compared with antibacterial drug-unexposed patients with acute nonspecific respiratory infections. At the societal level, we are very interested

in eliminating unnecessary antibacterial drug prescribing to help slow the spread of antibacterial resistance. At the level of the physician-patient encounter, we are most interested in providing the treatment that will best balance benefits and risks for that particular patient; the apparent best decision at the patient level is not always the ideal decision at the societal level. Even with a very small likelihood of patient benefit from antibacterial drug use, given how common acute nonspecific respiratory infections and antibacterial drug treatment are in our society, balancing very small potential risks of benefit from antibacterial drug treatment of acute nonspecific respiratory infections vs. societal benefits of reducing overall antibacterial drug use creates persistent tension. Win-win solutions include expanding the use of influenza vaccination, and improving point of service rapid diagnostic testing and biochemical markers of disease severity[1] to help us target antibacterial drugs to those patients most likely to benefit.

Our work supports future observational studies regarding additional medication use outcomes, especially rare outcomes related to acute conditions and acute exposures to antibacterial drugs as well as other medications. Improving methods for utilizing observational data will help us learn how to use the rich and growing electronic medical record data to their full potential.

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Appendix

Adverse Event Read Codes

THIN Read Code Description
Hypersensitivity
Dermatitis allergic
Skin allergic reaction
Dermatitis nummular
Erythema multiforme exudativum
Syndrome Stevens-Johnson
Toxic epidermal necrolysis
Acne cachecticorum (Hebra)
Oedema angioneurotic
Urticaria giant
Syndrome scalded skin
Allergy penicillin
Chloromycetin allergy
Allergy cephalosporin
Suphonamides allergy
Septrin allergy
Drug allergy
Reaction anaphylactic drug
Erythema due medicine ingested
Adverse reaction drug ingested
Allergy drug by mouth
Shock reaction anaphylactic
Medical care adverse effects
Antibodies anaphylactic present
Lyell?s disease
Epidermal necrolysis
Diarrhea
Diarrhoea
Diarrheoea cause not determined
Bloody diarrhoea
Hepatic toxicity
Hepatic function abnormal
Liver enzymes abnormal

Appendix

Liver function test abnormal
Necrosis massive hepatic acute
Acute hepatitis
Subacute massive hepatic necrosis
Hepatic coma
Hepatic failure
Liver disease
Hepatitis
Toxic hepatitis due drug sensitivity
Jaudice cholestatic
Jaundice drug induced
Serum jaundice
Renal toxicity
Nephritis acute
Membranous glomerulonephritis
Nephrosis
Nephritis
Glomerulonephitis antiglomerular basement membrane
Nephritis glomerulonephritis
Nephritis interstitial diffuse
Glomerulonephritis acute
Glomerulonephritis subacute
Mesangiocapillary glomerulonephritis
Glomerulonephritis membranous
Membranoproliferative glomerulonephritis
Proliferative glomerulonephritis
Rapidly progressive glomerulonephritis
Necrosis kidney acute tubular
Renal failure
Renal medullary necrosis
Renal papillary necrosis
Necrosis renal cortical bilateral
Uraemia
Cardiac arrhythmia
Cardiac arrest
Rhythm ventricular conduction aberrant

Tachycardia paroxysmal
Arrhythmia ectopic
Ventricular fibrillation
Heartbeats ectopic
Ventricular ectopic beats
Heartbeat extrasystoles
Cardiac arrhythmia
Fibrillation/flutter
Ventricular flutter
Ventricular tachycardia paroxysmal
Premature heartbeats
Premature contractions heart
Premature beats junctional
Supraventricular ectopic beats
Seizure
Epilepsy nonconvulsive generalized
Petit mal
Grand mal epilepsy
Epilepsy convulsions
Idiopathic epilepsy
Convulsion
Seizure
Convulsion nonepileptic
Infantile spasm
Photodermatotosis
Dermatitis sunlight
Photosensitivity
Patient died
ENT drug side effect
Rep.presc. drug side effect
Dr stopped drugs - side effect
Drug declined by patient - side effects
Drug side effect - acceptable to patient
Adverse drug reaction notif
Yellow card drug react notif
Anaphylactoid purpura

Appendix

Phacoanaphylactic endophthalmitis
Upper respiratory tract hypersensitivity reaction NOS
Drug-induced interstitial lung disorders
Acute drug-induced interstitial lung disorders
Anaphylactoid glomerulonephritis
Ingestion dermatitis due to drugs
Generalized skin eruption due to drugs and medicaments
Localized skin eruption due to drugs and medicaments
Drug-induced erythroderma
Drug-induced pemphigus
Lichenoid drug reaction
Drug-induced androgenic alopecia
Drug induced urticaria
Drug-induced systemic lupus erythematosus
Systemic sclerosis induced by drugs and chemicals
Arthropathy due to hypersensitivity reaction
Newborn drug reaction and intoxication
Newborn drug reaction or intoxication NOS
Late effect of poison drug/medicament/biological substance
Drug poisoning
Overdose of drug
Poisoning by drug and biological substances
ENT drug poisoning
Ear nose and throat drug poisoning NEC
Other and unspecified drug and medicament poisoning
Other drug and medicament poisoning OS
Other drug and medicament poisoning NOS
Drug and medicament poisoning NOS
Drug medicament or biological substance poisoning NOS
Adverse drug reaction NOS
Drug idiosyncrasy NOS
Allergic reaction
Unspecified adverse effect of drug or medicament
Accidental poisoning by drugs medicines and biologicals
Accidental poisoning by other drugs
Accidental poisoning by other drugs OS

Appendix

Accidental poisoning by other drugs NOS
Accidental poisoning by unspecified drugs
Accidental poisoning by drugs NOS
Adverse reaction to antibiotics
Adverse reaction to natural penicillins
Adverse reaction to cloxacillin
Adverse reaction to flucloxacillin
Adverse reaction to amoxycillin
Adverse reaction to amoxicillin
Adverse reaction to ampicillin
Adverse reaction to bacampicillin
Adverse reaction to ciclacillin
Adverse reaction to mezlocillin
Adverse reaction to pivampicillin
Adverse reaction to talampicillin
Adverse reaction to azlocillin
Adverse reaction to carbenicillin
Adverse reaction to carfecillin sodium
Adverse reaction to piperacillin
Adverse reaction to ticarcillin
Adverse reaction to mecillinam
Adverse reaction to pivmecillinam
Adverse reaction to penicillin NOS
Adverse reaction to chloramphenicol group
Adverse reaction to thiamphenicol
Adverse reaction to chloramphenicol group NOS
Adverse reaction to erythromycin and other macrolides
Adverse reaction to erythromycin
Adverse reaction to oleandomycin
Adverse reaction to spiramycin
Adverse reaction to macrolide NOS
Adverse reaction to tetracycline group
Adverse reaction to tetracycline
Adverse reaction to chlortetracycline hydrochloride
Adverse reaction to clomocycline sodium
Adverse reaction to demeclocycline hydrochloride

Appendix

Adverse reaction to doxycycline
Adverse reaction to lymecycline
Adverse reaction to minocycline
Adverse reaction to oxytetracycline
Adverse reaction to tetracycline NOS
Adverse reaction to cefaclor
Adverse reaction to cefadroxil
Adverse reaction to cefotaxime
Adverse reaction to cefoxitin
Adverse reaction to cefsulodin sodium
Adverse reaction to ceftazidime
Adverse reaction to ceftizoxime
Adverse reaction to cephalexin
Adverse reaction to cefalexin
Adverse reaction to cephalothin
Adverse reaction to cephamandole
Adverse reaction to cephazolin
Adverse reaction to cefazolin
Adverse reaction to cephradine
Adverse reaction to cefradine
Adverse reaction to cephalosporin NOS
Adverse reaction to other antibiotics
Adverse reaction to clindamycin
Adverse reaction to lincomycin
Adverse reaction to colistin
Adverse reaction to sodium fusidate
Adverse reaction to polymyxin B sulphate
Adverse reaction to vancomycin
Adverse reaction to trimethoprim
Adverse reaction to other antibiotics NOS
Adverse reaction to antibiotic NOS
Adverse reaction to other anti-infectives
Adverse reaction to sulphadiazine
Adverse reaction to sulfadiazine
Adverse reaction to sulphadimidine
Adverse reaction to sulfadimidine

Appendix

Adverse reaction to sulphaguanidine
Adverse reaction to sulphamethoxazole
Adverse reaction to sulfamethoxazole
Adverse reaction to sulphafurazole
Adverse reaction to sulphaurea
Adverse reaction to sulphonamide NOS
Adverse reaction to ciprofloxacin
Adverse reaction to anti-infective NOS
Adverse reaction to primarily systemic agents
Adverse reaction to systemic agent NOS
Adverse reaction to anti-common cold drugs
Adverse reaction to other respiratory system drugs
Adverse reaction smooth/skeletal+respiratory system drug NOS
Adverse reaction to skin mucous membrane eye ENT dental drug
Adverse reaction to anti-infectives and other ENT drugs
Adverse reaction to other skin eye ENT and dental drugs
Adverse reaction to skin eye ENT and dental drugs NOS
Adverse reaction to other drugs and medicines
Adverse reaction to other drugs and medicines
Adverse reaction to other drug or medicine NOS
Adverse reaction to drug or medicinal substance NOS
Adverse reaction to drug NOS
Injury ?accidental poisoning by other spec drug/medicament
Injury ?accidental poisoning by drug or medicament NOS
Drug induced gastrointestinal disturbance
Pseudomembranous colitis
Pseudomembranous colitis
Pseudomembranous colitis
Acute hepatic failure
Subacute hepatic failure
Encephalopathy - hepatic
Hepatic failure NOS
Hepatitis unspecified NOS
Hepatic infarction
Toxic liver disease with hepatic necrosis
Toxic liver disease with acute hepatitis

Appendix

Acute hepatic failure due to drugs
Nonspecific reactive hepatitis
Hepatic failure as a complication of care
Haemorrhagic nephrosonephritis
Henoch-Schonlein nephritis
Acute proliferative glomerulonephritis
Acute nephritis with lesions of necrotising glomerulitis
Other acute glomerulonephritis
Acute glomerulonephritis in diseases EC
Acute exudative nephritis
Acute focal nephritis
Acute diffuse nephritis
Other acute glomerulonephritis NOS
Acute glomerulonephritis NOS
Nephrotic syndrome with proliferative glomerulonephritis
Nephrotic syndrome+membranoproliferative glomerulonephritis
Nephrotic syndrome with minimal change glomerulonephritis
Lipoid nephrosis
Steroid sensitive nephrotic syndrome
Nephrotic syndrome minor glomerular abnormality
Nephrotic syndrome focal and segmental glomerular lesions
Nephrotic syndrome diffuse membranous glomerulonephritis
Nephrotic syn difus mesangial prolifertiv glomerulonephritis
Nephrotic syn difus endocapilary proliftv glomerulonephritis
Nephrotic syn diffuse mesangiocapillary glomerulonephritis
Nephrotic syndrome dense deposit disease
Nephrotic syndrome diffuse crescentic glomerulonephritis
Nephrotic syndrome in diseases EC
Nephrotic syndrome in diseases EC NOS
Nephrotic syndrome with other pathological kidney lesions
Nephrotic syndrome NOS
Nephritis and nephropathy unspecified
Nephropathy unspecified
Focal membranoproliferative glomerulonephritis
Anaphylactoid glomerulonephritis
Nephritis unsp+OS membranoprolif glomerulonephritis lesion

Appendix

Lobular glomerulonephritis NEC
Mesangioproliferative glomerulonephritis NEC
Mixed membranous and proliferative glomerulonephritis NEC
Nephritis unsp+membranoprolif glomerulonephritis lesion NOS
Tubulo-interstit nephritis not specif as acute or chron
Unspecif nephr synd diff concentric glomerulonephritis
Unspecified nephritic syndrome dense deposit disease
Unsp nephrit synd diff endocap prolif glomerulonephritis
Unsp nephrit synd diff mesang prolif glomerulonephritis
Other nephritis and nephrosis unspecified
Other nephritis and nephrosis in diseases EC
Other exudative nephritis
Other nephritis and nephrosis NOS
Acute renal failure
Acute drug-induced renal failure
Other acute renal failure
Acute renal failure NOS
End stage renal failure
End stage renal failure
Renal impairment
Impaired renal function
Impaired renal function disorder
Other impaired renal function disorder
Acute interstitial nephritis
Other impaired renal function disorder NOS
Impaired renal function disorder NOS
Acute nephritic syndrome
Acute nephritic syndrome minor glomerular abnormality
Acute nephritic syndrome focal+segmental glomerular lesions
Acute nephritic syn diffuse membranous glomerulonephritis
Acut neph syn diffuse mesangial prolifrative glomnephritis
Ac neph syn difus endocaplry prolifrative glomerulonephritis
Acute neph syn diffuse mesangiocapillary glomerulonephritis
Acute nephritic syndrome dense deposit disease
Acute nephrotic syndrm diffuse crescentic glomerulonephritis
Acute nephrotic syndrm diffuse crescentic glomerulonephritis

Appendix

Rapidly progressive nephritic syndrome
Rapid progres nephritic syn focal+segmental glomerulr lesion
Rapid progres neph syn diffuse membranous glomerulonephritis
Rpd prog neph syn df mesangial prolifratv glomerulonephritis
Rapid progres neph syn df endocapilary prolifv glomnephritis
Rapid prog neph syn df mesangiocapillary glomerulonephritis
Rapid progressive nephritic syndrome dense deposit disease
Rapid progres nephritic syn df crescentic glomerulonephritis
Recur+persist haematuria difus membranous glomerulonephritis
Recur+persist haemuria df mesangial prolif glomerulnephritis
Recur+persist hmuria df mesangiocapilary glomerulonephritis
Recur+persist haematuria difus crescentic glomerulonephritis
Renal tubulo-interstitial disorders in diseases EC
Balkan nephropathy
Drug/heavy-metal-induced tubulo-interstitial and tub conditn
Analgesic nephropathy
Nephropathy induced by other drugs meds and biologl substncs
Nephropathy induced by unspec drug medicament or biol subs
Toxic nephropathy not elsewhere classified
End-stage renal disease
Other specified nephritis nephrosis or nephrotic syndrome
Nephritis nephrosis and nephrotic syndrome NOS
Nephropathy NOS in pregnancy without hypertension
Acute renal failure following labour and delivery
Post-delivery acute renal failure unspecified
Post-delivery acute renal failure - delivered with p/n prob
Post-delivery acute renal failure with postnatal problem
Post-delivery acute renal failure NOS
Renal failure as a complication of care
ECG: ventricular ectopics
ECG: no ventricular arrhythmia
ECG: ventricular tachycardia
ECG: ventricular fibrillation
ECG: supraventricular arrhythmia
ECG: ventricular arrhythmia
ECG: ventricular arrhythmia NOS

Appendix

Cardiac arrhythmias
Ventricular tachycardia
Ventricular fibrillation and flutter
Cardiac arrest-ventricular fibrillation
Ventricular fibrillation and flutter NOS
Cardio-respiratory arrest
Cardiac arrest with successful resuscitation
Sudden cardiac death so described
Cardiac arrest unspecified
Ventricular premature depolarization
Sinus arrhythmia
Other cardiac dysrhythmias
Re-entry ventricular arrhythmia
Other cardiac dysrhythmia NOS
Cardiac rhythm drug poisoning
Cardiac rhythm drug poisoning NOS
Cardiac complications of care
Cardiac arrest as a complication of care
Cardiac complication of care NOS
Had a fit
Fit - had one symptom
Had a convulsion
Convulsion - symptom
Myoclonic seizure
Epileptic seizures - atonic
Epileptic seizures - akinetic
Other specified generalised nonconvulsive epilepsy
Generalised nonconvulsive epilepsy NOS
Generalised convulsive epilepsy
Epileptic seizures - clonic
Epileptic seizures - myoclonic
Epileptic seizures - tonic
Grand mal seizure
Other specified generalised convulsive epilepsy
Generalised convulsive epilepsy NOS
Complex partial epileptic seizure

Appendix

Drug-induced epilepsy
Fit (in known epileptic) NOS
Convulsions in newborn
Fits in newborn
Seizures in newborn
Accidental poisoning by other drugs acting on nervous system
Accid. poisoning by other drugs acting on nervous system OS
Accidental poisoning by drugs acting on nervous system NOS
Sunburn
Sunburn of first degree
Sunburn of second degree
Sunburn of third degree
Photocontact dermatitis [berloque dermatitis]
Drug phototoxic response
Drug photoallergic response

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