ANNALS OF FAMILY MEDICINE

Online Supplementary Material

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Supplemental Appendix. Additional Analyses

Methods

Our visit grouping for the principal analysis classified encounters as antibiotic-exposed if any visits within the 2-week window included an antibiotic prescription. To address the possibility that this may have misclassified in favor of antibiotic use, we performed additional analyses using ungrouped visits, analyzing visits independently.

Because we anticipated that the propensity for prescribing antibiotics, and thus antibiotic exposure could vary widely between practices, we calculated separate propensity scores for each practice using the same covariates in each practice's model. The propensity score quintile was used in the principal regression model, replacing the included covariates. We also considered results stratified by propensity score quintile, looking for a potential dose effect; this compares risk for adverse events among patients with similar propensities to be prescribed antibiotics. Additionally, we modeled the odds of a severe adverse event using a more conventional multiplicative model, with conditional fixed- effects *logistic* regression.

The risk of certain adverse events may vary with exposure to specific antibiotic class, for example, β-lactams may increase the risk of seizures,[1] and macrolides and fluoroquinolones may increase the risk of cardiac arrhythmias.[2] Accordingly, we also modeled specific antibiotic drug class exposure, focusing on β-lactams, macrolides, and fluoroquinolones, as class-specific antibiotic vs no antibiotic exposure, and as class-specific antibiotic vs other antibiotic exposure. We did not have adequate power to model each individual adverse event category as a separate outcome.

If antibiotic exposure was a marker for certain unmeasured patient characteristics which make it more likely a patient would be admitted to the hospital, this could bias our results, making us more likely to find hospital admissions in antibiotic-exposed individuals because of residual confounding by these factors. To address this possibility, we included a control outcome, hospital admissions due to motor vehicle accidents. These admissions should have no plausible causal relationship with previous antibiotic exposure; if an association was found it would be evidence of residual confounding.[1]

We performed a crossover-cohort study for patients with severe adverse events and multiple visits within the cohort. Case time was defined as the 14 days following each acute nonspecific respiratory infection index visit associated with a severe adverse event. Control time was defined as the 14 days following all of that patient's previous[3] non-index visits. χ^2 Testing was used to calculate the odds ratio comparing adverse events for antibiotic-exposed vs unexposed visits for each patient. We were unable to include visits after the severe adverse event episode, because we wanted to avoid potential selection bias due to "depletion of susceptibles"; physicians may have been less likely to prescribe an antibiotic to a patient who had previously experienced an antibiotic-associated severe adverse event. Thus, although this method helps adjust for unmeasured inter-individual confounders and intra-individual time-invariate confounders, it does not adjust for unmeasured intra-individual confounders that vary with time.

We performed simulations to explore whether our results were robust to our assumptions, using a linear fixed-effects model for our very rare dichotomas outcome. One potential limitation of using a more conventional conditional logistic regression to model a rare outcome is that data from practices with zero outcomes in the comparator (no antibiotic) group would provide a zero in the odds ratio denominators for those practices, and information from those practices would not be included in the analysis. 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. We compared the performance of our conditional fixed-effects linear model (using Stata's xtreg command) under varying conditions and assumptions, and compared these results with those using a fixed-effects logistic model, conditional on practice, using Stata's xtlogit command. We generated simulated datasets to reflect conditions similar to our data: large (2 million visits), highly hierarchical (200 practices with 10,000 patient visits each), a relatively common and variable exposure across practices, and a rare outcome, variable across practices (specified to be 0.0000866, with a mean risk difference of –0.0000411 for the protective effect for exposed vs unexposed visits); many practices thus included zero outcomes.

Results

Our cohort contained 1,646,229 total and 1,531,019 grouped visits. Using ungrouped visits, our results were virtually identical to those of the primary analysis, a risk difference of 1.07 fewer severe adverse events per 100,000 patient visits (95% CI, –4.52 to 2.38; $P = .54$) comparing antibiotic-exposed vs unexposed patients. In the propensity-adjusted model, results were similar to those of the principal analysis; the risk difference for severe adverse events was 1.60 fewer events per 100,000 patient visits (95% CI, –5.29 to 2.09; $P = .39$), comparing antibiotic-exposed with unexposed patients. Stratifying the analysis by propensity score category, comparing patients with similar propensities to be prescribed antibiotics, and thus relatively similar underlying conditions, there remained no association of adverse events with antibiotic exposure, and there did not appear to be a clear trend over propensity score categories, (Table A4) further evidence against residual confounding by indication.

Using fixed-effects logistic regression, conditional on practice (Stata's xtlogit), adjusted for the number of different drug classes prescribed during the past year and Townsend score, the odds ratio for a severe adverse event for patients exposed compared with unexposed to an antibiotic was 0.81 (95% CI, 0.53 to 1.22l; $P = .31$); data from 770,601 visits (50% of the visits) from the 237 practices with zero adverse events were dropped from this analysis.

We obtained the expected null result of no association between antibiotic exposure and hospital admission for motor vehicle accident, with an adjusted risk difference for antibiotic-exposed vs unexposed visits of 0.78 fewer per 100,000 visits (95% CI, –1.70 to 0.13; $P = .09$).

The crossover-cohort study compared 61 case visits matched with 173 previous control visits by the case patients, and yielded an odds ratio for antibiotic-exposed vs unexposed visits of 0.87 per 100,000 visits (95% CI, 0.44 to 1.76; $P = .66$), results qualitatively similar to our primary analysis.

When assessing class-specific antibiotic exposure vs other antibiotic exposure, while point estimates varied, none were statistically significant (Table A5).

The mean regression slope from the simulated data was -0.0000372, using the conditional fixed-effects additive model (xtreg), compared with the true value of –0.0000411 used to generate the data, or a 9.5% bias toward the null value of the slope = 0. The power to find this difference in slope using this model was estimated at 0.81. This result was robust to varying the number of practices. Despite the design effect, which should give us increased power with more practices, keeping the number of visits constant, the power diminishes with the progressively increasing numbers of zero-event practices seen, as the number of visits per practice decreases with increasing practice size. With increasing numbers of zero-event practices, it gets progressively more difficult to show significant differences between antibiotic-exposed and -unexposed visits within each practice. Given the stipulated simulated data, our stipulated risk difference for severe adverse event of –0.0000411 in antibiotic exposed vs unexposed visits should correspond to an odds ratio of 0.5357. Using the same

simulated data, with a conditional fixed-effects logistic model (xtlogit), we found an odds ratio of 0.574, biased 7.1% toward the null, similar to our conditional linear regression xtreg results, with a power of 0.80.

Thus, using simulations, we confirmed that conditional fixed-effects linear regression provided reliable estimates of common exposure treatment effects on rare outcome risks, compared with fixed-effects conditional logistic regression. Results using these models were quite similar to results obtained using more traditional methods for binary outcomes, but were able to utilize all available information, even from groups with zero events.

References

1. Meropol SB, Chen Z, Metlay JP. Reduced antibiotic prescribing for acute respiratory infections in adults and children. *Br J Gen Pract.* 2009;59(567):e321-e328.
2. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg.* 2007;137(3)(Suppl):S1-S31.
3. Bucher HC, Tschudi P, Young J, et al.; BASINUS (Basel Sinusitis Study) Investigators. Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis: a placebo-controlled, double-blind, randomized trial in general practice. *Arch Intern Med.* 2003;163(15):1793-1798.

Table A1. Acute Respiratory Infection Diagnostic Codes

THIN Read Code Description	Read Code
Other acute upper respiratory infections	H05..00
Acute upper respiratory tract infection	H051.00
Upper respiratory infection NOS	H05z.00
Upper respiratory tract infection NOS	H05z.11
Acute nasopharyngitis	H00..00
Acute pharyngitis	H02..00
Throat infection – pharyngitis	H02..13
Acute pharyngitis NOS	H02z.00
Sore throat NOS	H02..11
Acute bronchitis	H060.00
Bronchitis unspecified	H30..00

NOS = not otherwise specified; THIN = The Health Improvement Network (CSD Medical Research, UK).

Table A2. Adverse Event Diagnostic Codes

Category	THIN Read Code Description	Read Code
Cardiac arrhythmia	Cardiac arrest	G575.00
	Rhythm ventricular conduction aberrant	G56y.00
	Tachycardia paroxysmal	G572z00
	Arrhythmia ectopic	G576.00
	Ventricular fibrillation	G574000
	Heartbeats ectopic	G576000
	Ventricular ectopic beats	G576200
	Heartbeat extrasystoles	G576011
	Cardiac arrhythmia	G57z.00
	Fibrillation/flutter	G57..00
	Ventricular flutter	G574100
	Ventricular tachycardia paroxysmal	G571.00
	Premature heartbeats	G576.11
	Premature contractions heart	G576000
	Premature beats junctional	G576400
	Supraventricular ectopic beats	G576100
Diarrhea	Diarrhoea	19F..11
	Diarrheoea cause not determined	19F2.00
	Bloody diarrhoea	19E6.00
Liver toxicity	Hepatic function abnormal	44D2.00
	Liver enzymes abnormal	44G2.00
	Liver function test abnormal	L3260AB
	Necrosis massive hepatic acute	J600.00
	Acute hepatitis	J600100
	Subacute massive hepatic necrosis	J601.00
	Hepatic coma	J622.00
	Hepatic failure	J62y.13
	Liver disease	J63..00
	Hepatitis	J633.00
	Toxic hepatitis due drug sensitivity	J633000
	Jaundice cholestatic	J66y600
	Jaundice drug induced	R024.00
	Serum jaundice	A703.00
Hypersensitivity	Dermatitis allergic	M128.00
	Skin allergic reaction	M12zz00
	Dermatitis nummular	M1y0.00
	Erythema multiforme exudativum	M151.00

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Table A2. Adverse Event Diagnostic Codes, *continued*

Category	THIN Read Code Description	Read Code
	Syndrome Stevens-Johnson	M151700
	Toxic epidermal necrolysis	M151800
	Acne cachecticorum (Hebra)	M261X00
	Oedema angioneurotic	SN51.00
	Urticaria giant	M28..00
	Syndrome scalded skin	M15y000
	Allergy penicillin	TJ00.00
	Chloromycetin allergy	TJ02000
	Allergy cephalosporin	TJ05.00
	Suphonamides allergy	TJ10.00
	Septrin allergy	TJ0yD00
	Drug allergy	SN52.12
	Reaction anaphylactic drug	SN50100
	Erythema due medicine ingested	M130.11
	Adverse reaction drug ingested	TJ...00
	Allergy drug by mouth	SN52.00
	Shock reaction anaphylactic	SN50.00
	Medical care adverse effects	SP...00
	Antibodies anaphylactic present	R15z000
	Lyell's disease	M151.11
	Epidermal necrolysis	M151.12
Phototoxicity	Photodermatosis	M127300
	Dermatitis sunlight	M127000
	Photosensitivity	M127400
Renal toxicity	Nephritis acute	K00..11
	Membranous glomerulonephritis	K011.00
	Nephrosis	K01..00
	Nephritis	K0...00
	Glomerulonephritis antiglomerular basement membrane	K03..00
	Nephritis glomerulonephritis	K03z.00
	Nephritis interstitial diffuse	K03y200
	Glomerulonephritis acute	K00..00
	Glomerulonephritis subacute	583 GB
	Mesangiocapillary glomerulonephritis	K032y14
	Glomerulonephritis membranous	K031.00
	Membranoproliferative glomerulonephritis	K032.00
	Proliferative glomerulonephritis	K030.00
	Rapidly progressive glomerulonephritis	K033.00
	Necrosis kidney acute tubular	K040.00

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Table A2. Adverse Event Diagnostic Codes, *continued*

Category	THIN Read Code Description	Read Code
	Renal failure	K06..00
	Renal medullary necrosis	K042.00
	Renal papillary necrosis	K042.11
	Necrosis renal cortical bilateral	K041.00
	Uraemia	K06..11
Seizure	Epilepsy nonconvulsive generalized	F250.00
	Petit mal	F250000
	Grand mal epilepsy	F251000
	Epilepsy convulsions	F25z.00
	Idiopathic epilepsy	F25..00
	Convulsion	R003.00
	Seizure	R003z11
	Convulsion nonepileptic	R003z00
	Infantile spasm	F256.00

THIN = The Health Improvement Network (CSD Medical Research UK).

Table A3. Community-Acquired Pneumonia Diagnostic Codes

THIN Read Code Description	Read Code
Mycoplasma pneumonia	A3BXA00
Mycoplasma pneumonia	AyuK900
Klebsiella pneumoniae	A3BXB00
Acute bronchitis due to mycoplasma pneumonia	H060A00
Pneumonia and influenza	H2...00
Viral pneumonia	H20..00
Pneumonia due to adenovirus	H200.00
Pneumonia due to respiratory syncytial virus	H201.00
Pneumonia due to parainfluenza virus	H202.00
Viral pneumonia NEC	H20y.00
Viral pneumonia NOS	H20z.00
Lobar (pneumococcal) pneumonia	H21..00
Other bacterial pneumonia	H22..00
Pneumonia due to haemophilus influenza	H222.00
Pneumonia due to haemophilus influenza	H222.11
Pneumonia due to streptococcus	H223.00
Pneumonia due to streptococcus, group B	H223000
Pneumonia due to staphylococcus	H224.00
Pneumonia due to other specified bacteria	H22y.00
Pneumonia due to other aerobic gram-negative bacteria	H22yX00
Pneumonia due to bacteria NOS	H22yz00
Bacterial pneumonia NOS	H22z.00
Pneumonia due to other specified organisms	H23..00
Pneumonia due to mycoplasma pneumonia	H231.00
Pneumonia due to pleuropneumonia like organisms	H232.00
Chlamydial pneumonia	H233.00
Pneumonia due to specified organism NOS	H23z.00
Pneumonia with infectious diseases EC	H24..00
Pneumonia with whooping cough	H243.00
Pneumonia with pertussis	H243.11
Pneumonia with other infectious diseases EC	H24y.00
Pneumonia with varicella	H24y700
Pneumonia with other infectious diseases EC NOS	H24yz00
Pneumonia with infectious diseases EC NOS	H24z.00
Bronchopneumonia due to unspecified organism	H25..00
Pneumonia due to unspecified organism	H26..00
Lobar pneumonia due to unspecified organism	H260.00
Basal pneumonia due to unspecified organism	H261.00

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Table A3. Community-Acquired Pneumonia Diagnostic Codes, *continued*

THIN Read Code Description	Read Code
Postoperative pneumonia	H262.00
Influenza with pneumonia	H270.00
Influenza with bronchopneumonia	H270000
Influenza with pneumonia, influenza virus identified	H270100
Influenza with pneumonia NOS	H270z00
Atypical pneumonia	H28..00
Other specified pneumonia or influenza	H2y..00
Pneumonia or influenza NOS	H2z..00
Aspiration pneumonia due to vomit	H470312
Abscess of lung with pneumonia	H530300
Bronchiolitis obliterans organising pneumonia	H564.00
Interstitial pneumonia	H56y100
Other viral pneumonia	Hyu0800
Pneumonia due to other aerobic gram-negative bacteria	Hyu0900
Other bacterial pneumonia	Hyu0A00
Pneumonia due to other specified infectious organisms	Hyu0B00
Pneumonia in bacterial diseases classified elsewhere	Hyu0C00
Pneumonia in viral diseases classified elsewhere	Hyu0D00
Pneumonia in other diseases classified elsewhere	Hyu0G00
Other pneumonia, organism unspecified	Hyu0H00
Other aspiration pneumonia as a complication of care	SP13100

EC = elsewhere classified; NEC = not elsewhere classified; NOS = not otherwise specified; THIN = The Health Improvement Network (CSD Medical Research UK).

Table A4. Severe Adverse Events Per 100,000 Visits by Propensity Score Quintile

Propensity Score Quintile	Risk Difference for Antibiotic Use			
	No.	Point Estimate	95% CI	*P* Value
All	1,316,340	−1.60	−5.29 to 2.09	.39
1st	270,655	−1.62	−5.31 to 2.07	.39
2nd	267,012	1.73	−3.20 to 6.66	.49
3rd	263,496	1.27	−3.71 to 6.25	.62
4th	260,914	4.50	−5.31 to 9.53	.08
5th	254.263	2.87	−2.25 to 7.99	.27

Table A5. Severe Adverse Events Per 100,00 Visits: Specific vs Other Antibiotic Class

	Risk Difference for Antibiotic Use		
Antibiotic	**Point Estimate**	**95% CI**	***P* Value**
Any antibiotic vs none	−1.07	−4.52 to 2.38	.54
Specific antibiotic class vs other antibiotic classes			
β-Lactams	−2.41	−6.52 to 1.70	.25
Macrolides	2.40	−3.26 to 8.07	.40
Fluoroquinolones	9.00	−8.24 to 26.24	.31