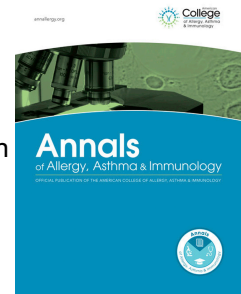


Accepted Manuscript

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PII: S1081-1206(19)30394-1

DOI: <https://doi.org/10.1016/j.anai.2019.05.018>

Reference: ANAI 2920

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 6 February 2019

Revised Date: 16 May 2019

Accepted Date: 23 May 2019

Please cite this article as: Fishman E, Crawford G, DeVries A, Hackell J, Haynes K, Helm M, Wall E, Agiro A, Association Between Early-Childhood Antibiotic Exposure and Subsequent Asthma in the US Medicaid Population, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.05.018>.

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**Association Between Early-Childhood Antibiotic Exposure and Subsequent Asthma in the
US Medicaid Population**

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Short title: Antibiotic Exposure and Asthma

Funding source: Funding for this study was provided by Anthem, Inc. Anthem, Inc. had no role
in the conduct of the study, manuscript preparation, or the decision to submit.

Financial disclosure: Ezra Fishman, Andrea DeVries, Kevin Haynes, and Abiy Agiro are
employees of HealthCore, Inc., a wholly owned subsidiary of Anthem, Inc. Geoffrey Crawford is
an employee of Anthem, Inc. The other authors have indicated they have no financial
relationships relevant to this article to disclose.

Conflict of interest: Ezra Fishman, Andrea DeVries, Kevin Haynes, and Abiy Agiro are
employees of HealthCore, Inc., a wholly owned subsidiary of Anthem, Inc. Geoffrey Crawford is
an employee of Anthem, Inc. The other authors have indicated they have no potential conflicts of
interest to disclose.

1 Introduction

2 The prevalence of physician-diagnosed asthma among US children was approximately 8% in
3 2016, but among poor children the prevalence was 12%.¹ Among people with asthma, those with
4 low income and those insured by Medicaid tend to have worse asthma control than those with
5 higher incomes.^{2,3} The socioeconomic disparities in asthma risk warrant particular attention to
6 modifiable risk factors for asthma in disadvantaged populations.⁴

7 Recent research has suggested that early-life exposure to antibiotics – a modifiable factor – may
8 raise a person's risk of developing asthma.⁵ The hypothesized mechanism includes antibiotic-
9 induced killing of commensal bacteria important for normal development of immune function,
10 which, in turn, raises a person's risk of developing allergic or immune conditions later in life.^{6,7}
11 Antibiotics taken early in life could be particularly consequential, because the gut microbiome
12 changes rapidly during the first two years of life.⁸

13 Nevertheless, it is difficult to determine the extent to which antibiotics themselves, as distinct
14 from the infections for which they were prescribed, play a role in the etiology of asthma.

15 Previous studies that have explored the relationship between antibiotics and asthma have shown
16 mixed results.⁹⁻¹⁷ The most rigorous studies of this topic addressed two potential biases:
17 confounding by indication, where respiratory infections that indicate antibiotics might raise the
18 risk of asthma; and reverse causality (protopathic bias), where symptoms of what is later
19 diagnosed as asthma are treated with antibiotics – a major concern given the difficulty of
20 diagnosing asthma in young children.^{12,14,18} Some of these studies have found a positive
21 relationship between antibiotics and asthma after addressing these biases,^{17,19,20} while others have
22 found a small or null association.^{9,13,16} A randomized clinical trial has demonstrated the

effectiveness of azithromycin in treating young children with recurrent lower respiratory tract infections,²¹ further complicating clinical decision making with regard to antibiotic prescribing.

Aside from showing mixed results, prior research on this topic is difficult to apply to clinical practice because the existing literature has reported associations only on *relative* scales, such as odds ratios and hazard ratios, and has not provided estimates of *absolute* risks of asthma, such as the probability of being diagnosed with asthma, at different levels of antibiotic exposure.

Estimates of absolute risks can help clinical decision makers quantify the risks and benefits of antibiotic prescribing.^{22,23}

Prior research on the association between antibiotics and asthma has focused mostly on European populations.⁹⁻¹⁷ The handful of studies of children elsewhere in the world have limited geographic scope,^{11,24} or have measured antibiotic exposure and asthma incidence using parental reporting.⁵ Additionally, because socioeconomic status can modify the effects of environmental exposures on asthma, US children with low socioeconomic status could face a different set of risks for asthma, compared to sampled children in other countries.^{25,26}

The current study aims to evaluate the association between antibiotic exposure in the first two years of life and incidence of asthma later in childhood among children with Medicaid insurance. These children are important to study because they are disproportionately of low socioeconomic status²⁷ and because Medicaid is a highly prevalent source of health insurance, covering 40% of US children in 2017.²⁸ This study contributes to the literature in several ways: (1) it diversifies the studied populations to include a relatively disadvantaged, geographically diverse US-based study population; and (2) it provides estimates of the absolute risk of asthma by antibiotic exposure.

Methods

This was an observational, longitudinal, retrospective cohort study utilizing administrative claims data. Data were obtained from medical and pharmacy claims and eligibility files from 13 Medicaid plans geographically dispersed across all regions of the United States.

The study period ran from July 1, 2012 to November 30, 2018. Data on mothers were queried from July 2012 onwards to ensure that children born in January 2013 could have at least 6 months of maternal history. All children included in the study cohort were required to have continuous coverage through Medicaid from birth to age 2.5 years. Children were allowed up to a 60-day gap in enrollment because Medicaid tends to have high enrollment volatility²⁹. The study entry date (index date) was set at the child's 2.5th birthday to allow a 6-month washout period between exposure and outcome assessment¹⁹; index dates spanned July 1, 2015 to November 30, 2018.

Children were excluded from the study cohort if they had evidence of complex chronic conditions (*International Classification of Diseases, Ninth Edition* and *Tenth Edition* diagnosis codes or Current Procedural Terminology (CPT) procedure codes in **Appendix A**) in the first 2.5 years of life, as these conditions complicate the management of early childhood infections.³⁰ Children with evidence of asthma in the first 2.5 years of life were excluded to limit the analysis to incident asthma in the follow-up period. The analyses further excluded children whose claims could not be linked to their mothers' claims. Children were linked to their mothers' data using relation codes and individual attributes within enrollment data to create mother-child pairs; the success rate of mother-child pairing was 76%.

The main exposure was the number of prescriptions filled for systemic antibiotics,³¹ identified by National Drug Codes in paid pharmacy claims that were converted to Generic Product Identifier (GPI) codes, and, much less frequently, by CPT codes in medical claims (**Appendix B**). The exposure assessment window was age 0 to 2 years,^{5,10} as this is a period of rapid change in the gut microbiome.⁸ The period from age 2.0 years to 2.5 years was a washout period, where antibiotics were not counted but where outcome events (i.e. new identifications of asthma) were still grounds for exclusion; the washout period serves to reduce the chance that measured antibiotic exposure results from latent asthma.¹⁹

In the main statistical models, the number of antibiotics was entered as a categorical variable with the following levels: 0 antibiotics (reference), 1 or 2 antibiotics, and 3 or more antibiotics. This specification arose from preliminary analysis of Kaplan-Meier curves stratified by number of antibiotics.

The primary outcome was new cases of asthma as evidenced in the claims data. Asthma was identified by at least 1 inpatient diagnosis (ICD-9 code beginning 493 or ICD-10 code beginning J45), at least 2 outpatient or emergency department diagnoses, or at least 2 prescription fills for asthma drugs (**Appendix C**); in a validation study, this identification algorithm had 67% sensitivity, 92% specificity, and 94% positive predictive value (PPV), the highest PPV of a number of algorithms assessed.³²

Other covariates were chosen based on theory and prior evidence of their relevance to the relationship between antibiotic exposure and asthma risk. Birth year was included to account for possible secular changes in antibiotic prescribing/filling and asthma incidence. Every child's exposure to antibiotics was measured over the same age window, so a separate covariate for

“age” was not included. We included indicators for female gender, rural residence (living outside a metropolitan statistical area), and geographic region of residence (South [reference], Midwest, West, Northeast), due to known differences in antibiotic prescribing patterns across US regions.³³ We included an indicator for the child being born in a state that had expanded Medicaid under the Affordable Care Act at the time of birth, and for the source of qualification for Medicaid: receipt of Temporary Assistance for Needy Families (TANF; reference), as a proxy for low-income status, versus all other sources. We also included covariates indicating the asthma status of the child's mother and whether the child was born via Caesarean section.^{13,24,34} Confounding by indication was addressed by including the number of bronchiolitis diagnoses and diagnoses for other respiratory conditions in the first 2 years of life as covariates.³⁵ Surveillance bias – the theory that patients seen more often in the health care system will be more likely to get treated with antibiotics and diagnosed with asthma, simply by virtue of being seen more often in the system – was addressed by including the number of outpatient visits in the first 2 years of life as a covariate. Pre-term birth was also included as a predictor of both antibiotic use and later-life asthma.²⁴

Given the difficulty of diagnosing asthma in young children, we considered the possibility that an apparent association between early-childhood antibiotics and asthma could be driven by early-life diagnoses of respiratory conditions that were later diagnosed as asthma.¹² Therefore, a sensitivity analysis excluded any child who had a diagnosis of bronchiolitis or another respiratory condition (see **Appendix D** for code list) in the first 2.5 years of life.^{9,16}

We assessed the sensitivity of the results to the choices of age cutoffs for exposure and outcome ascertainment. First, we fit our model using antibiotics in the first year of life only as the primary exposure, ignoring any antibiotics received in the second year of life. Then, we fit a model with

the number of antibiotics in the first year and the number in the second year entered as separate independent variables, and compared their coefficients with a Wald test. Finally, we adjusted the age cutoff for outcome ascertainment by estimating the association between antibiotics in the first year of life and asthma ascertained from age 18 months and onward, with age 12 to 18 months as the washout period.

Statistical analysis was conducted using Cox proportional hazard models with SAS Enterprise Guide software, Version 7.1 (SAS Institute 2014, Cary, NC, USA). The event was a new diagnosis of asthma, and the time at risk was the number of days from the age 2.5 years until the first date of asthma identification, exit from insurance plan enrollment, or the end of the study period, whichever occurred first. The association between antibiotic exposure and asthma was presented as hazard ratios (HR) with 95% confidence intervals (CI). Covariate-adjusted absolute risk of developing asthma by age 4.0 years, by number of antibiotics, was estimated using a simulation method developed by Austin.³⁶ Confidence intervals for the estimates of covariate-adjusted absolute risk were obtained by bootstrapping from the original study cohort. The proportional hazards assumption was assessed with an interaction term of continuous time with the number of antibiotics.

Effect modification was explored with Cox models that included interaction terms, i.e. the product of the antibiotic exposure variable with the potential effect modifier. The potential effect modifiers tested were the number of bronchiolitis diagnoses (a count variable), mode of birth (Caesarean section vs. vaginal (reference)) and maternal asthma status. We estimated HRs with CIs at key values of the potential effect modifiers.

This study was conducted in full compliance with relevant provisions of the Health Insurance Portability and Accountability Act. Researchers had access only to a limited data set, and no patients were contacted directly. Institutional review board approval was not necessary because the study was an analysis of the managed care organization's membership data for the purposes of health plan treatment, planning, and operations.

Results

There were 160,373 children born 01/01/2013 or later with continuous enrollment from birth to at least age 2.5 years. After excluding those with complex chronic conditions,³⁰ 143,873 remained. After excluding those with evidence of asthma in the first 2.5 years of life, 104,192 children remained. The analytic sample consisted of the 79,582 children whose claims were linked to their mothers' claims.

In the follow-up period, 2,381 new asthma cases were observed in 89,545 person-years of follow-up, for a crude asthma incidence rate of 2.7 new asthma cases per 100 person-years at risk. Children were followed, on average, until age 3.6 years and maximally until age 5.9 years.

Differences in the distribution of sex, birth year, geographic region, and rural status across different levels of antibiotic exposure were small in magnitude and did not show a clear gradient across increasing levels of antibiotic exposure (**Table 1**). The differences across levels of antibiotic exposure were larger when considering baseline health characteristics. For example, a smaller share of children who received no antibiotics had a bronchiolitis episode (18%), compared with children who got 1 or 2 antibiotics (25%) or 3 or more antibiotics (37%).

Before adjusting for covariates, the hazard ratio for asthma associated with 1 to 2 antibiotics (versus 0) was 1.38 (CI 1.25, 1.53) and with 3 or more antibiotics (versus 0) was 1.91 (CI 1.73, 2.12).

After adjustment for covariates, all shown in Table 2, receipt of 1 or 2 antibiotics was associated with increased risk of developing asthma, relative to 0 antibiotics (HR 1.34, CI 1.21-1.49), and receipt of 3 or more antibiotics was associated with greater increased risk relative to 0 antibiotics (HR 1.71, CI 1.54-1.90). Receiving 3 or more antibiotics was also associated with greater risk of asthma when compared with receiving 1 or 2 antibiotics (HR 1.27, CI 1.15-1.41).

Those with early-childhood respiratory diagnoses other than asthma were slightly less likely to be diagnosed with asthma in the follow-up period than those without other childhood respiratory diagnoses (bronchiolitis HR 0.86, CI 0.81-0.92; other diagnoses HR 0.98, CI 0.86-1.12; **Table 2**). Children born via Caesarean section (HR 1.11, CI 1.02-1.21) or whose mothers had asthma (HR 1.68 CI 1.48-1.91) were more likely to develop asthma themselves. Controlling for the number of antibiotic exposures and baseline respiratory diagnoses, females developed asthma at a 15% lower rate than males (HR 0.85, CI 0.78 – 0.92), and children the Northeast developed asthma at much higher rates than those from the South (HR 1.30, CI 1.15-1.47). The HR of 0.73 for birth year implies a considerable downward trend in asthma incidence across cohorts.

The estimated covariate-adjusted absolute risk of developing asthma between the index age 2.5 y and age 4.0 y increased from 2.7% (CI 2.0%-3.4%) for children who received 0 antibiotics in the first 2 years of life to 3.6% (CI 2.8%-4.3%) for children who received 1 or 2 antibiotics, to 4.5% (CI 3.6% - 5.6%) for children who received 3 or more antibiotics. Thus, the estimated absolute risk difference associated with 1 or 2 antibiotics (vs 0) was 0.9% (CI 0.1% - 1.8%), and the

absolute risk difference associated with 3 or more antibiotics (vs 0) was 1.8% (CI 0.7%-3.0%).

These absolute-risk estimates are summarized in **Figure 1**.

The sensitivity analysis excluding children who had at least 1 pre-index diagnosis of any respiratory condition, including bronchiolitis, were largely consistent with the main results. The estimated HR for 1 or 2 antibiotics 1.41 (CI 1.25-1.58) (compared with 1.34 in the full sample) and HR for 3 or more antibiotics 1.88 (CI 1.66-2.11) (compared with 1.71 in the full sample). These results indicate that pre-index respiratory diagnoses were not the main source of the positive association between antibiotics and later risk of asthma (**Table 3**).

Assessing the sensitivity of the results to the age cutoffs for the quantification of antibiotic exposure, we found that children who had 1-2 antibiotics in the first year of life developed asthma after age 2.5 at a 19% higher rate than those with no antibiotics (HR 1.19, CI 1.09-1.30, **Table 4-A**), and children who had 3+ antibiotics in the first year of life developed asthma at a 29% higher rate (HR 1.29, CI 1.13-1.47). When counting antibiotics in the first year separately from those in the second year, each antibiotic dispensed in the second year was associated with asthma risk increase of 11% (HR 1.11, CI 1.08-1.13; **Table 4-B**), while antibiotics in the first year were not associated with asthma (HR 0.99, CI 0.96-1.01; p-value for difference in coefficients <0.001).

Assessing the sensitivity of the results to the age cutoffs for outcome ascertainment, we found that children who had 1-2 antibiotics in the first year of life developed asthma after age 1.5 years at an 18% higher rate than children with 0 antibiotics in the first year of life (HR 1.18, CI 1.09-1.28; **Table 4-C**). The increased risk was similar for children with 3+ antibiotics compared to those with none (HR 1.19, CI 1.06-1.35). These HRs indicated that the association between

antibiotics in the first year of life and later asthma was similar whether asthma was ascertained from age 1.5 years or age 2.5 years.

The relation between the number of early-life antibiotics and the risk of asthma did not differ significantly between children who were born via Caesarean Section and children born vaginally or between children whose mothers had asthma and children whose mothers did not (**eTable 1**). However, the relation between antibiotics and asthma did differ by early-life bronchiolitis diagnosis. Specifically, the HRs for asthma declined as the number of early-life bronchiolitis diagnoses increased. Early-life antibiotics were not associated with increased risk of asthma among children who had more than 1 early-life bronchiolitis diagnosis (**Table 5**).

Discussion

The results of this analysis demonstrate a positive relationship between early-childhood antibiotic exposure and subsequent asthma risk among children insured through Medicaid. This relationship was robust to attempts to avoid reverse causality by using a 6-month washout period and, in a sensitivity analysis, excluding children with any respiratory diagnosis in the exposure period. After controlling for observed confounders, filling 1 or 2 prescriptions for antibiotics in the first 2 years of life was associated with an approximately 34% increase in the risk of developing asthma later in childhood. In absolute terms, among children who were asthma-free at age 2.5 y, the estimated risk of developing asthma by age 4.0 y increased from 2.7% among children who received 0 antibiotics in their first 2 years of life to 3.6% among children who received 1 or 2, and finally to 4.5% among children who received 3 or more antibiotics.

The positive relationship between early-childhood antibiotic exposure and subsequent asthma risk remained after controlling for potential sources of confounding and reverse causality,

contrasting with several other studies on this topic that have attempted to address these potential biases.³⁷ Those studies found the association between antibiotics and asthma disappeared after addressing confounding by indication and protopathic bias;^{9,10,13,16} however, contrasting studies have found that the association was maintained even after extensive controls were included.^{15,17,20,24} Discrepancies across studies could reflect differences in the underlying epidemiologic environment, or differences across populations in the composition of the microbiome.^{38,39} Another explanation for the differences in study findings is that a number of the studies finding a null association limited the antibiotic exposure window to the first year of life only;¹⁶ in contrast, our study included the first two years of life. Counting antibiotics in only the first year of life has potential advantages in avoiding reverse causality; however, it potentially underestimates the effect of antibiotics by treating children who receive antibiotics in their second year of life as part of the "unexposed" group. Our sensitivity analyses showed that the association between early-life antibiotics and asthma was actually stronger for antibiotics in the second year of life than in the first. Moreover, changing the age cutoff for ascertainment of asthma (from age 2.5 to age 1.5 years or later) did not alter the study results. Counterintuitively, early-childhood respiratory diagnoses of bronchiolitis was correlated with lower incidence of asthma. This result could have arisen from variation in diagnosing preferences across providers, or from the exclusion of pre-index asthma cases from the sample.

We are aware of only one prior study that used administrative records (rather than parental reports) to assess the relationship between early-childhood antibiotics and asthma in the US.²¹ It found that the odds of developing asthma increased by 21% for each additional course of antibiotics.²¹ It is difficult to compare our results quantitatively to these results, given that the prior study reported odds ratios while our study uses hazard ratios. Nevertheless, our findings are

qualitatively similar, showing that the risk of asthma increases with the number of early-life antibiotics in a dose-response fashion. We build on the prior study's results in several ways. First, we extend the geographic and socioeconomic diversity of the populations under study by including Medicaid members from 13 states, covering all regions of the US (though disproportionately the South). Second, we report estimates of the association among children who had no baseline respiratory diagnoses, which reduces the possibility that reverse causality drives the results. Third, we include the second year of life as part of the exposure window, showing that antibiotics in the second year of life are positively associated with later asthma, independent of antibiotics received in the first year of life. Finally, our estimates of absolute risk of asthma at different levels of antibiotic exposure are novel in the literature and may instruct clinicians in quantifying the risks of prescribing antibiotics at the individual patient level.²³

This study has several important limitations. Antibiotic exposure levels could not be randomized; therefore, unmeasured genetic, perinatal, or environmental factors that increase the need for antibiotics and raise the risk of asthma could explain the results.^{16,19} Further, without randomization, it is difficult to distinguish between asthma resulting from the antibiotics and asthma resulting from the infections that indicated antibiotic use, or from viral infections predominant among children susceptible to asthma. We attempted to address this limitation by statistically controlling for the number and type of respiratory conditions observed in the baseline period. We were not able to observe maternal smoking or the number of siblings in the household, two possible confounders.^{16,24} We could not explore confounding or effect modification by race, as it is not well-reported in claims data.

Using prescriptions filled as the measure of exposure may have overestimated actual consumption of antibiotics. Although studies relying on parent-reported antibiotic use are subject

to significant measurement error and recall bias, not all prescriptions that are filled are consumed as prescribed. Additionally, relative to the number of post-index date cases, a large number of asthma cases were identified in the first 2.5 years of life and thus excluded from the study cohort. These cases reflect the difficulty of diagnosing asthma accurately in young children.¹⁸ Both the high number of pre-index cases and the young age at follow-up events suggest there is measurement error in the dependent variable. However, the measurement error issues raised here likely bias our results toward finding no association.⁴⁰ Furthermore, sensitivity analyses adjusting the age of asthma ascertainment – and reducing the number of exclusions from pre-index asthma – suggest that our results are not sensitive to the choice of age cutoffs for asthma ascertainment.

Although our study could not investigate possible biological mechanisms underlying the association between antibiotics and asthma, other research has shown that antibiotics can destroy or alter T cells in the gut microbiome that are necessary for proper immune system development.⁸ A reduction in the level of biodiversity in the gut microbiome may also contribute to immune-system pathophysiology.⁸

Growing concern about antibiotic resistance has led to increased focus on the overuse of antibiotics in clinical practice.⁴¹ The most recent estimate of the antibiotic prescription rate was 1,141 antibiotics per 1,000 children aged 0-2 per year.^{32,42} Although antibiotic prescription fill rates among children have declined 13% since 2011,⁴³ about 29% of pediatric antibiotic prescriptions are still written for unnecessary indications.⁴² There is evidence that the parents of children on Medicaid have a greater tendency than the parents of commercially insured children to express a preference for possibly unnecessary antibiotics over watchful waiting.⁴⁴ As a consequence, it is possible that providers prescribe an excess of unnecessary antibiotics to

287 Medicaid-insured children versus commercially-insured children.⁴⁵ At the same time, children
288 with low socioeconomic status, who are overrepresented in the Medicaid population, are more
289 likely to develop asthma than children of higher socioeconomic status.¹

290 Findings of this analysis indicate that antibiotic dispensing in the first 2 years of life is associated
291 with an increased risk of asthma in later years among children insured through Medicaid, even
292 after controlling for observed sources of confounding and reverse causality. Providers should
293 consider this risk as a potential factor in the decision to prescribe antibiotics to young children.

Acknowledgments

Alan Rosenberg, formerly of Anthem Inc., Katherine Fleming-Dutra of the CDC, and Joseph Perez of the U.S. Coast Guard provided comments on earlier versions of the draft manuscript. Dianna Hayden, Zhengzheng Jiang, and Nianya Liu from HealthCore provided programming support. Cheryl Jones from HealthCore provided writing and editorial support. None were compensated for their work beyond salaries.

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Figure legend

Figure 1. Estimates of covariate-adjusted absolute risk of developing asthma by age 4, by level of antibiotic exposure in the first 2 years of life. (Population asthma-free at age 2.5.)

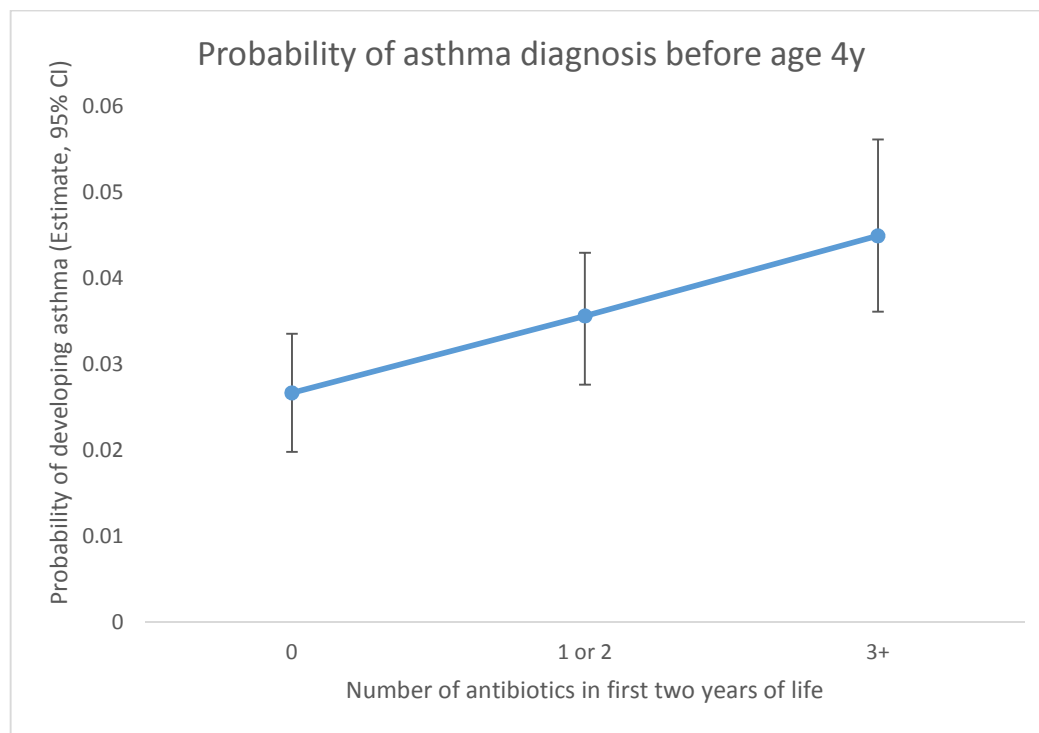


Table 1. Descriptive Statistics

	Number of Antibiotic prescription fills in first 2 years of life					
	0 Antibiotics		1-2 Antibiotics		3 or more Antibiotics	
On index date unless otherwise noted	N or Mean	% or SD	N or Mean	% or SD	N or Mean	% or SD
Sample size, N (row %)	29,931	37.6%	27,403	34.4%	22,248	28.0%
Age in months at 1st antibiotic exposure, mean SD	-	-	12.7	5.7	7.9	4.1
Female, n %	15,813	53%	14,342	52%	11,269	51%
Birth year, n %						
2013	7,501	25%	6,423	23%	5,026	23%
2014	8,622	29%	7,335	27%	6,094	27%
2015	9,884	33%	9,532	35%	7,765	35%
2016	3,924	13%	4,113	15%	3,363	15%
Geographic region (Census Bureau), n %						
Northeast	4,441	15%	4,161	15%	2,201	10%
South	20,971	70%	18,780	69%	16,916	76%
Midwest	1,763	6%	2,054	7%	1,940	9%
West	2,756	9%	2,408	9%	1,191	5%
Medicaid eligibility based on low income (TANF)	27,548	92%	24,657	90%	20,391	92%
Medicaid expansion	7,198	24%	6,634	24%	3,599	16%
Urban-Rural residence, n %						
Urban or suburban	25,071	84%	23,576	86%	17,879	81%
Rural	4,966	17%	3,799	14%	4,404	20%
% of adults in patient's zip w/o HS degree, mean SD	16.9	6.0	16.9	6.0	17.3	6.2

No antibiotics in first year of life, n %	29,931	100%	13,954	51%	3,376	15%
Any episode of bronchiolitis in 1st 2y of life, n %	5,478	18%	6,922	25%	8,317	37%
Episodes of bronchiolitis among those w/ any, mean SD	1.39	0.93	1.25	0.62	1.42	0.78
Any diagnosis of pneumonia in 1st 2y of life, n %	736	2%	1,451	5%	2,089	9%
Any diagnosis of bronchospasm in 1st 2y of life, n %	186	1%	255	1%	286	1%
Any diagnosis of chronic bronchitis in 1st 2y of life, n %	29	0%	28	0%	71	0%
Any diagnosis of non-specific bronchitis in 1st 2y of life, n %	414	1%	657	2%	1,135	5%
Pre-term birth, n %	1,752	6%	1,547	6%	1,123	5%
Inpatient stay in first 2 years of life, n %	1,539	5%	1,820	7%	2,159	10%
ED visit w/o inpatient stay in first 2 years of life, n %	16,579	55%	19,320	71%	17,561	79%
Number of outpatient visits in first 2 years of life, mean SD	13	7.6	15	7.1	21	9.7
Number of well-child visits in first 2 years of life, mean SD	3.8	3.2	3.7	3.2	3.9	3.2
Characteristics of mothers of study subjects						
Mothers w/ evidence of asthma, n %	1,969	7%	2,104	8%	1,800	8%
Mothers w/ any antibiotics in last 7d prior to giving birth, n %	612	2%	925	3%	745	3%
C-Section, n %	9,440	32%	8,636	32%	7,110	32%

Table 2. Main Regression Results^a

Independent variable	Hazard ratio	Lower Confidence Limit	Upper Confidence Limit	p-Value
1 or 2 antibiotics dispensed in first 2 years of life (vs. none)	1.34	1.21	1.49	<0.001
3 or more antibiotics (vs. none)	1.71	1.54	1.90	<0.001
Female	0.85	0.78	0.92	<0.001
Birth year (2013=0, 2014=1, etc.)	0.73	0.69	0.77	<0.001
Region of residence				
Northeast (vs. South)	1.30	1.15	1.47	<0.001
Midwest (vs. South)	0.87	0.74	1.03	0.109
West (vs. South)	0.71	0.56	0.88	0.002
Rural (vs. urban/suburban)	0.90	0.80	1.02	0.095
Not TANF (vs. TANF)	1.02	0.86	1.21	0.812
Medicaid expansion state	1.15	1.00	1.32	0.042
Born pre-term	1.15	0.98	1.35	0.089
Number of pre-index diagnoses of bronchiolitis	0.86	0.81	0.92	<0.001
Number of pre-index diagnoses of other respiratory conditions	0.98	0.86	1.12	0.775
Pre-index autoimmune condition	1.12	0.28	4.48	0.874
Number of pre-index outpatient visits	1.02	1.02	1.03	<0.001
Born via C-Section (vs. vaginal)	1.11	1.02	1.21	0.015
Mother had asthma	1.68	1.48	1.91	<0.001

Summary statistics for asthma incidence

Number of subjects	79,582
Number of events (new asthma cases)	2,381
Person-years at risk	89,545
Crude rate of asthma (new cases per person-year at risk)	0.027
Mean age (in years) at event or censoring	3.62

^a Dependent variable = hazard of new asthma case

Table 3. Sensitivity Analysis Excluding Children With Any Baseline Respiratory Condition

Independent variable	Hazard ratio	Lower Confidence Limit	Upper Confidence Limit	p-Value
1 or 2 antibiotics in first 2 years of life (vs. none)	1.41	1.25	1.58	<0.001
3 or more antibiotics (vs. none)	1.88	1.66	2.11	<0.001
Female	0.83	0.76	0.91	<0.001
Birth year (2013=0, 2014=1, etc.)	0.74	0.69	0.79	<0.001
Region of residence				
Northeast (vs. South)	1.31	1.15	1.49	<0.001
Midwest (vs. South)	0.82	0.67	1.00	0.045
West (vs. South)	0.67	0.53	0.86	0.002
Rural (vs. urban)	0.88	0.76	1.02	0.082
No TANF (vs. TANF)	1.09	0.90	1.31	0.391
Born in Medicaid expansion state	1.14	0.98	1.33	0.083
Born pre-term	1.20	1.00	1.44	0.047
Pre-index autoimmune condition	1.61	0.40	6.45	0.501
Number of pre-index outpatient visits	1.02	1.02	1.03	<0.001
Born via C-Section (vs. vaginal)	1.11	1.01	1.22	0.038
Mother had asthma	1.68	1.45	1.94	<0.001
Summary statistics for asthma incidence				
Number of subjects	58,865			
Number of events (new asthma cases)	1,858			
Person-years at risk	66,684			
Crude rate of asthma (new cases per person-year at risk)	0.028			
Mean age (in years) at event or censoring	3.63			

Table 4. Sensitivity analysis of age cutoffs for exposure and outcome ascertainment

A) Exposure = Antibiotics in 1st year of life; Outcome = asthma from age 2.5 y

Number of antibiotics in 1st yr of life	HR	CI
1-2 (vs 0)	1.19	1.09-1.30
3+ (vs 0)	1.29	1.13-1.47
3+ (vs 1-2)	1.08	0.95-1.24

B) Exposure = Antibiotics in 1st year of life and antibiotics in 2nd year of life, entered separately as continuous variables; Outcome = asthma from age 2.5 y

Continuous exposure variable	HR	CI
Number of antibiotics in 1st yr of life	0.98	0.96-1.01
Number of antibiotics in 2nd yr of life	1.11	1.08-1.13

P-value for difference between above HRs (from Wald test) <0.001

C) Exposure = Antibiotics in 1st year of life; Outcome = asthma from age 1.5 y

Number of antibiotics in 1st yr of life	HR	CI
1-2 (vs 0)	1.18	1.09-1.28
3+ (vs 0)	1.19	1.06-1.35

Note: All models adjusted for the same covariates as in Table 3 above. For (C), patients were excluded if they had evidence of asthma prior to their 1.5th birthday.

Table 5. Bronchiolitis modifying the association between antibiotics and asthma

Number of bronchiolitis diagnoses	Number of antibiotics	HR for asthma	CI
0	1-2 vs 0	1.41	(1.27, 1.58)
0	3+ vs 0	1.87	(1.66, 2.10)
1	1-2 vs 0	1.16	(1.00, 1.36)
1	3+ vs 0	1.42	(1.24, 1.63)
2	1-2 vs 0	0.95	(0.71, 1.28)
2	3+ vs 0	1.08	(0.84, 1.39)

P-value for coefficient on product of "1-2 antibiotics" with bronchiolitis: 0.015.

P-value for coefficient on product of "3+ antibiotics" with bronchiolitis: <0.001.

Note: Models adjusted for the same covariates as in Table 3 above, and added an interaction term between the number of bronchiolitis diagnoses (count variable) and the number of antibiotics (0 (reference), 1-2, or 3+).

eTable 1: Exploration of effect modification by mode of birth and maternal asthma

A) Effect modifier tested: Mode of birth (C-section vs. vaginal)

Mode of birth	Number of antibiotics	HR for asthma	CI
Vaginal	1-2 vs 0	1.31	(1.15, 1.49)
Vaginal	3+ vs 0	1.70	(1.49, 1.93)
C-Section	1-2 vs 0	1.41	(1.19, 1.68)
C-Section	3+ vs 0	1.74	(1.46, 2.07)

P-value for coefficient on product of "3+ antibiotics" with c-section indicator: 0.48

P-value for coefficient on product of "1-2 antibiotics" with c-section indicator: 0.82

B) Effect modifier tested: Maternal asthma

Maternal asthma	Number of antibiotics	HR for asthma	CI
No	1-2 vs 0	1.36	(1.22, 1.51)
No	3+ vs 0	1.74	(1.56, 1.95)
Yes	1-2 vs 0	1.24	(0.91, 1.69)
Yes	3+ vs 0	1.48	(1.09, 2.01)

P-value for coefficient on product of "1-2 antibiotics" with maternal asthma: 0.61

P-value for coefficient on product of "3+ antibiotics" with maternal asthma: 0.32

Notes: Models were the same as that shown in Table 2 in the main text, with the addition of interaction terms (product of the proposed effect modifier with the levels of antibiotic exposure). Dependent variable was the hazard of a new asthma case.

Lists of codes and generic drug names used

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Appendix A:

Complex Chronic Conditions, Type 1 Diabetes, Inflammatory Bowel Disease, Celiac Disease

Categories	Subcategories	ICD-9	ICD-10
Neurologic and Neuromuscular	Brain and spinal cord malformations	740.0-742.9	Q00-Q07, G90.1
	Mental retardation	318.0-318.2	F71-F73
	CNS degeneration and diseases	330.0-330.9, 334, 335.0-335.9, 331.1, 331.11, 331.19, 331.4, 331.8, 331.89, 331.9, 333.2, 336.1, 336.8, 337.9, 759.5	E75.0, E75.1, E75.2, E75.4, F84.2, G11.1-G11.4, G11.8, G11.9, G12.0-G12.2, G12.8, G12.9, G31.01, G31.09, G31.8, G31.89, G32.89, G93.8, G93.9, G94, G91.1, G31.9, G25.3, G95.19, G95.89, G90.9, Q85.1
	Infantile cerebral palsy	343.0-343.9	G80
	Epilepsy	345.01, 345.11, 345.3, 345.41, 345.61, 345.71, 345.81, 345.91	G40.311, G40.301, G40.211, G40.219, G40.411, G40.419, G40.111, G40.119, G40.804, G40.911, G40.919
	Other disorders of CNS	341.8, 342.90, 344.0, 344.81, 344.9, 348.1, 348.4, 780.03, 01.52, 01.53	G37.1, G37.2, G37.8, G81.90, G82.90, G82.50-G82.54, G83.5, G83.9, G93.1, G93.5, R40.3, 0016070, 0016071, 0016072, 0016073, 0016074, 0016075, 0016076, 0016077, 0016078, 001607B, 0016370, 0016371, 0016372, 0016373, 0016374, 0016375, 0016376, 0016377, 0016378, 001637B, 001U074, 001U076, 001U077, 001U079, 001U374, 001U376, 001U377, 001U379, 00B70ZZ, 00B73ZZ, 00B74ZZ, 00T70ZZ, 00T73ZZ, 00T74ZZ
	Occlusion of cerebral arteries	434.01, 434.91	I63.30, I63.50
	Muscular dystrophies and myopathies	359.0-359.3	G71, G72
	Movement diseases	332.0, 332.1, 333.0, 333.2, 333.4, 333.5, 333.7, 333.9	G10, G20, G21.0, G21.11, G21.19, G21.8, G23.0-G23.2, G23.8, G24.02, G24.8, G25.3-G25.5, G25.81-G25.83,

			G25.89, G25.9, G80.3
	Devices	996.2, 996.63, V45.2, V53.01, V53.02, 02.2, 02.21, 02.22, 02.3, 02.31, 02.32, 02.33, 02.34, 02.35, 02.39, 02.4, 02.41, 02.42, 02.93, 03.7, 03.71, 03.72, 03.79, 03.93, 03.97, 04.92	T85.09XA, T85.190A, T85.192A, T85.199A, T85.79XA, Z98.2, Z45.41, Z45.42, 00160J0, 00160J1, 00160J2, 00160J3, 00160J4, 00160J5, 00160J6, 00160J7, 00160J8, 00160JB, 00160K0, 00160K1, 00160K2, 00160K3, 00160K4, 00160K5, 00160K6, 00160K7, 00160K8, 00160KB, 00163J0, 00163J1, 00163J2, 00163J3, 00163J4, 00163J5, 00163J6, 00163J7, 00163J8, 00163JB, 00163K0, 00163K1, 00163K2, 00163K3, 00163K4, 00163K5, 00163K6, 00163K7, 00163K8, 00163KB, 001U0J4, 001U0J6, 001U0J7, 001U0J9, 001U0K4, 001U0K6, 001U0K7, 001U0K9, 001U3J4, 001U3J6, 001U3J7, 001U3J9, 001U3K4, 001U3K6, 001U3K7, 001U3K9, 009600Z, 009630Z, 009640Z, 00H00MZ, 00H03MZ, 00H04MZ, 00H60MZ, 00H63MZ, 00H64MZ, 00HE0MZ, 00HE3MZ, 00HE4MZ, 00HU0MZ, 00HU3MZ, 00HU4MZ, 00HV0MZ, 00HV3MZ, 00HV4MZ, 00W60JZ, 00W63JZ, 00W64JZ, 00WU0JZ, 00WU3JZ, 00WU4JZ, 01HY0MZ, 01HY3MZ, 01HY4MZ, 0DH60MZ, 0DH63MZ, 0DH64MZ, 0W110J9, 0W110JB, 0W110JG, 0W110JJ, 3E1Q38X, 3E1Q38Z
	Transplantation	N/A	N/A
Cardiovascular	Heart and great vessel malformations	745.0-745.3, 745.60-745.69, 746, 747.1-747.49, 747.81, 747.89, 35.8, 35.81, 35.82, 35.83, 35.84	Q20, Q21.2-Q24, Q25.1-Q26, Q28.2, Q28.3, Q28.9, 02170ZP, 02170ZQ, 02170ZR, 02BK0ZZ, 02LR0ZT, 02LS0ZZ, 02LT0ZZ, 02NH0ZZ, 02RK0JZ, 02RL0JZ, 02RM0JZ, 02RP0JZ, 02RQ07Z, 02RQ0JZ, 02RR07Z, 02RR0JZ, 02SP0ZZ, 02SW0ZZ, 02U70JZ, 02UA0JZ, 02UA3JZ, 02UA4JZ, 02VR0ZT, 02WA0JZ
	Endocardium diseases	424.0, 424.2, 424.3	I34.0, I34.8, I36.0, I36.8, I37.0, I37.8
	Cardiomyopathies	425.0-425.4, 425.8, 429.1	I42, I43, I51.5
	Conduction disorder	426.0-427.4	I44, I45, I47, I48, I49.0

Dysrhythmias	427.6-427.9	I49.1-I49.5, I49.8, I49.9, R00.1
Other	416.1, 416.8, 416.9, 428.0, 429.3, 428.83, 433.11, V45.81	I27.0, I27.1, I27.2, I27.81, I27.89, I27.9, I50.9, I51.7, I51.81, I63.139, I63.239, Z95.1
Devices	996.0, 996.1, 996.61, 996.62, V43.3, V45.0, V53.31, V53.32, V53.39, 00.50, 00.51, 00.53, 00.54, 00.55, 00.57, 17.51, 17.52, 37.41, 37.52, 37.53, 37.54, 37.55, 37.6, 37.60, 37.61, 37.63, 37.65, 37.66, 37.67, 37.68, 37.7, 37.71, 37.72, 37.74, 37.76, 37.79, 37.8, 37.80, 37.81, 37.82, 37.83, 37.85, 37.86, 37.87, 37.89, 37.94, 37.95, 37.96, 37.97, 37.98, 39.81, 39.82, 39.83, 39.84, 39.85, 89.46, 89.47, 89.48, 89.49	T82.519A, T82.529A, T82.539A, T82.599A, T82.110A, T82.111A, T82.120A, T82.121A, T82.190A, T82.191A, T82.01XA, T82.02XA, T82.03XA, T82.09XA, T82.211A, T82.212A, T82.213A, T82.218A, T82.221A, T82.222A, T82.223A, T82.228A, T82.518A, T82.528A, T82.538A, T82.598A, T82.6XXA, T82.7XXA, Z95.0, Z95.2, Z95.3, Z95.810-Z95.812, Z95.818, Z45.010, Z45.018, Z45.02, Z45.09, Z95.9, 02H40JZ, 02H40KZ, 02H43JZ, 02H44JZ, 02H44KZ, 02H60JZ, 02H60KZ, 02H63JZ, 02H63KZ, 02H63MZ, 02H64JZ, 02H64KZ, 02H70KZ, 02H73JZ, 02H73KZ, 02H73MZ, 02H74KZ, 02HA0QZ, 02HA0RS, 02HA0RZ, 02HA3QZ, 02HA3RS, 02HA4QZ, 02HA4RS, 02HK0JZ, 02HK0KZ, 02HK3JZ, 02HK3KZ, 02HK3MZ, 02HK4JZ, 02HK4KZ, 02HL0JZ, 02HL0KZ, 02HL0MZ, 02HL3JZ, 02HL3KZ, 02HL3MZ, 02HL4JZ, 02HL4KZ, 02HL4MZ, 02HN0JZ, 02HN0KZ, 02HN0MZ, 02HN3JZ, 02HN3KZ, 02HN3MZ, 02HN4JZ, 02HN4KZ, 02HN4MZ, 02WA0QZ, 02WA0RZ, 02WA3QZ, 02WA3RZ, 02WA4QZ, 02WA4RZ, 03HK0MZ, 03HK3MZ, 03HK4MZ, 03HLOMZ, 03HL3MZ, 03HL4MZ, 03WY0MZ, 03WY3MZ, 03WY4MZ, 0JH600Z, 0JH605Z, 0JH606Z, 0JH607Z, 0JH608Z, 0JH609Z, 0JH60AZ, 0JH60MZ, 0JH60PZ, 0JH630Z, 0JH635Z, 0JH636Z, 0JH637Z, 0JH638Z, 0JH639Z, 0JH63AZ, 0JH63MZ, 0JH63PZ, 0JH70MZ, 0JH73MZ, 0JH800Z, 0JH805Z, 0JH806Z, 0JH807Z, 0JH808Z, 0JH809Z, 0JH80AZ, 0JH80MZ, 0JH80PZ, 0JH830Z, 0JH835Z, 0JH836Z, 0JH837Z, 0JH838Z, 0JH839Z, 0JH83AZ, 0JH83MZ, 0JH83PZ, 0JWT0MZ, 0JWT0PZ, 0JWT3MZ,

			0JW3PZ, 0JW3MZ, 4B02XSZ, 4B02XTZ, 5A02110, 5A02116, 5A0211D, 5A02210, 5A02216, 5A0221D
	Transplantation	996.83,V42.1, V42.2, V43.2, 37.5, 37.51	T86.20-T86.22, Z94.1, 02YA0Z0, 02YA0Z1, 02YA0Z2
Respiratory	Respiratory malformations	748.0-748.9	Q30-Q34, P280
	Chronic respiratory diseases	327.25, 416.2, 516.3, 516.31, 518.84, 770.4, V45.76	G47.35, I27.82, I43, J84.112, J96.20, Z90.2
	Cystic fibrosis	277	E84
	Other	30.3, 30.4, 32.4, 32.41, 32.49, 32.5, 32.50, 32.59	0B110Z4, 0B113Z4, 0B114Z4, 0BTC0ZZ, 0BTC4ZZ, 0BTD0ZZ, 0BTD4ZZ, 0BTF0ZZ, 0BTF4ZZ, 0BTG0ZZ, 0BTG4ZZ, 0BTJ0ZZ, 0BTJ4ZZ, 0BTK0ZZ, 0BTK4ZZ, 0BTL0ZZ, 0BTL4ZZ, 0BTM0ZZ, 0BTM4ZZ, 0CTS0ZZ, 0CTS4ZZ, 0CTS7ZZ, 0CTS8ZZ

	Devices	519.0, V44.0, V55.0, V46.0, V46.1, 31.2, 31.21, 31.29, 31.41, 31.74, 33.21, 34.85, 96.55, 97.23	J95.00-J95.04, J95.09, Z43.0, Z93.0, Z99.0, J95.850, Z99.11, Z99.12, 0B110F4, 0B113F4, 0B114F4, 0B21XFZ, 0BHR0MZ, 0BHR3MZ, 0BHR4MZ, 0BHS0MZ, 0BHS3MZ, 0BHS4MZ, 0BW10FZ, 0BW13FZ, 0BW14FZ, 0JH604Z, 0JH634Z, 0JH804Z, 0JH834Z, 0WQ6XZ2, 3E1F78Z
	Transplantation	996.84, V42.6, 33.5, 33.50, 33.51, 33.52, 33.6	T86.810, T86.811, T86.819, Z94.2, 0BYC0Z0, 0BYC0Z1, 0BYC0Z2, 0BYD0Z0, 0BYD0Z1, 0BYD0Z2, 0BYF0Z0, 0BYF0Z1, 0BYF0Z2, 0BYG0Z0, 0BYG0Z1, 0BYG0Z2, 0BYH0Z0, 0BYH0Z1, 0BYH0Z2, 0BYJ0Z0, 0BYJ0Z1, 0BYJ0Z2, 0BYK0Z0, 0BYK0Z1, 0BYK0Z2, 0BYL0Z0, 0BYL0Z1, 0BYL0Z2, 0BYM0Z0, 0BYM0Z1, 0BYM0Z2
Renal and Urologic	Congenital anomalies	753.0-753.9	Q60-Q64
	Chronic renal failure	585	N18
	Other	V45.73, V45.74, 55.5, 55.51, 55.52, 55.53, 55.54, 56.4, 56.41, 56.42, 56.7, 56.71, 56.79, 57.7, 57.71, 57.79	Z90.5, Z90.6, 0T160Z8, 0T160ZA, 0T164Z8, 0T164ZA, 0T170Z8, 0T170ZA, 0T174Z8, 0T174ZA, 0T180Z8, 0T180ZA, 0T184Z8, 0T184ZA, 0TB60ZZ, 0TB63ZZ, 0TB64ZZ, 0TB67ZZ, 0TB68ZZ, 0TB70ZZ, 0TB73ZZ, 0TB74ZZ, 0TB77ZZ, 0TB78ZZ, 0TT00ZZ, 0TT04ZZ, 0TT10ZZ, 0TT14ZZ, 0TT20ZZ, 0TT24ZZ, 0TT60ZZ, 0TT64ZZ, 0TT67ZZ, 0TT68ZZ, 0TT70ZZ, 0TT74ZZ, 0TT77ZZ, 0TT78ZZ, 0TTB0ZZ, 0TTB4ZZ, 0TTB7ZZ, 0TTB8ZZ, 0TTD0ZZ, 0TTD4ZZ, 0TTD7ZZ, 0TTD8ZZ
	Chronic bladder diseases	344.61, 596.4, 596.53, 596.54	G83.4, N31.2, N31.9

		T85.71XA, Z93.50-Z93.52, Z93.59, Z93.6, Z91.15, Z99.2, Z43.5, Z43.6, Z46.6, 031209D, 031209F, 03120AD, 03120AF, 03120JD, 03120JF, 03120KD, 03120KF, 03120ZD, 03120ZF, 031309D, 031309F, 03130AD, 03130AF, 03130JD, 03130JF, 03130KD, 03130KF, 03130ZD, 03130ZF, 031409D, 031409F, 03140AD, 03140AF, 03140JD, 03140JF, 03140KD, 03140KF, 03140ZD, 03140ZF, 031509D, 031509F, 03150AD, 03150AF, 03150JD, 03150JF, 03150KD, 03150KF, 03150ZD, 03150ZF, 031609D, 031609F, 03160AD, 03160AF, 03160JD, 03160JF, 03160KD, 03160KF, 03160ZD, 03160ZF, 031709D, 031709F, 03170AD, 03170AF, 03170JD, 03170JF, 03170KD, 03170KF, 03170ZD, 03170ZF, 031809D, 031809F, 03180AD, 03180AF, 03180JD, 03180JF, 03180KD, 03180KF, 03180ZD, 03180ZF, 031909F, 03190AF, 03190JF, 03190KF, 03190ZF, 031A09F, 031A0AF, 031A0JF, 031A0KF, 031A0ZF, 031B09F, 031B0AF, 031B0JF, 031B0KF, 031B0ZF, 031C09F, 031C0AF, 031C0JF, 031C0KF, 031C0ZF, 03WY0JZ, 03WY3JZ, 03WY4JZ, 03WYXJZ, 05HY33Z, 06HY33Z, 0JH60WZ, 0JH60XZ, 0JH63WZ, 0JH63XZ, 0JH80WZ, 0JH80XZ, 0JH83WZ, 0JH83XZ, 0JHD0WZ, 0JHD0XZ, 0JHD3WZ, 0JHD3XZ, 0JHF0WZ, 0JHF0XZ, 0JHF3WZ, 0JHF3XZ, 0JHL0WZ, 0JHL0XZ, 0JHL3WZ, 0JHL3XZ, 0JHM0WZ, 0JHM0XZ, 0JHM3WZ, 0JHM3XZ, 0T130ZB, 0T134ZB, 0T140ZB, 0T144ZB, 0T16079, 0T1607C, 0T1607D, 0T160J9, 0T160JC, 0T160JD, 0T160K9, 0T160KC, 0T160KD, 0T160Z9, 0T160ZC, 0T160ZD, 0T163JD, 0T16479, 0T1647C, 0T1647D, 0T164J9, 0T164JC, 0T164JD, 0T164K9, 0T164KC, 0T164KD, 0T164Z9, 0T164ZC, 0T164ZD, 0T17079, 0T1707C, 0T1707D, 0T170J9, 0T170JC, 0T170JD, 0T170K9, 0T170KC, 0T170KD, 0T170Z9, 0T170ZC, 0T170ZD, 0T173JD, 0T17479, 0T1747C, 0T1747D, 0T174J9, 0T174JC, 0T174JD, 0T174K9, 0T174KC, 0T174KD, 0T174Z9, 0T174ZC, 0T174ZD, 0T18079, 0T1807C, 0T1807D, 0T180J9, 0T180JC, 0T180JD,
Devices	996.68, V44.5, V44.6, V45.1, V53.6, V55.5, V55.6, 38.95, 39.27, 39.42, 39.93, 39.94, 39.95, 54.98, 55.02, 55.03, 55.04, 55.12, 55.93, 55.94, 55.97, 56.5, 56.51, 56.52, 56.6, 56.61, 56.62, 56.72, 56.73, 56.74, 56.75, 57.2, 57.21, 57.22, 59.93, 59.94, 86.07, 96.45, 96.46, 96.47	

			0T180K9, 0T180KC, 0T180KD, 0T180Z9, 0T180ZC, 0T180ZD, 0T183JD, 0T18479, 0T1847C, 0T1847D, 0T184J9, 0T184JC, 0T184JD, 0T184K9, 0T184KC, 0T184KD, 0T184Z9, 0T184ZC, 0T184ZD, 0T1B0ZD, 0T1B4ZD, 0T25X0Z, 0T29X0Z, 0T29XYZ, 0T2BX0Z, 0T9000Z, 0T9030Z, 0T9040Z, 0T9070Z, 0T9080Z, 0T9100Z, 0T9130Z, 0T9140Z, 0T9170Z, 0T9180Z, 0T9370Z, 0T9380Z, 0T9470Z, 0T9480Z, 0TQ67ZZ, 0TQ77ZZ, 3E1K38Z, 3E1M39Z, 5A1D60Z
	Transplantation	996.81, V42.0, 55.6, 55.61, 55.69	T86.10-T86.12, Z94.0, 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, 0TY10Z2
Gastrointestinal	Congenital anomalies	750.3, 751.1-751.9	Q39.0-Q39.4, Q41-Q45
	Chronic liver disease and cirrhosis	571.4-571.9	K73, K74, K75.4, K760-K763, K765, K768
	Inflammatory bowel diseases	555.0-556.9	K50, K51
	Other	453.0, 557.1, 560.2, 564.7, V45.3, V45.72, V45.75, 25.3, 25.4, 42.42, 43.9, 43.91, 43.99, 45.63, 45.8, 45.81, 45.82, 45.83, 50.4, 52.6, 52.7, 54.71	I82.0, K55.1, K56.2, K59.3, Z98.0, Z90.3, Z90.49, 0CT70ZZ, 0CT7XZZ, 0D13079, 0D1307A, 0D1307B, 0D1607A, 0D160ZA, 0DT50ZZ, 0DT54ZZ, 0DT57ZZ, 0DT58ZZ, 0DT60ZZ, 0DT64ZZ, 0DT67ZZ, 0DT68ZZ, 0DT80ZZ, 0DT84ZZ, 0DT87ZZ, 0DT88ZZ, 0DT90ZZ, 0DT94ZZ, 0DT97ZZ, 0DT98ZZ, 0DTE0ZZ, 0DTE4ZZ, 0DTE7ZZ, 0DTE8ZZ, 0FT00ZZ, 0FT04ZZ, 0FTG0ZZ, 0FTG4ZZ

	Devices	536.4, V44.1-V44.4, V53.50, V53.51, V53.59, V55.1-V55.4, 42.1, 42.10, 42.11, 42.81, 43.1, 43.11, 43.19, 44.12, 44.3, 44.32, 44.38, 44.39, 46.1, 46.13, 46.2, 46.22, 46.23, 46.3, 46.32, 46.4, 46.40, 46.41, 46.43, 96.24, 96.36, 97.02	K94.20, K94.22, K94.23, K94.29, Z93.1-Z93.4, Z43.1-Z43.4, Z46.51, Z46.59, 0D11074, 0D110J4, 0D110K4, 0D110Z4, 0D113J4, 0D11474, 0D114J4, 0D114K4, 0D114Z4, 0D15074, 0D150J4, 0D150K4, 0D150Z4, 0D153J4, 0D15474, 0D154J4, 0D154K4, 0D154Z4, 0D16074, 0D160J4, 0D160J9, 0D160JA, 0D160K4, 0D160K9, 0D160KA, 0D160Z4, 0D163J4, 0D16474, 0D164J4, 0D164J9, 0D164JA, 0D164K4, 0D164K9, 0D164KA, 0D164Z4, 0D16874, 0D168J4, 0D168J9, 0D168JA, 0D168K4, 0D168K9, 0D168KA, 0D168Z4, 0D1B0Z4, 0D1B4Z4, 0D1B8Z4, 0D1H0Z4, 0D1H4Z4, 0D1H8Z4, 0D1K0Z4, 0D1K4Z4, 0D1K8Z4, 0D1L0Z4, 0D1L4Z4, 0D1L8Z4, 0D1N0Z4, 0D1N4Z4, 0D1N8Z4, 0D20X0Z, 0D20XUZ, 0D20XYZ, 0D787ZZ, 0D7E7ZZ, 0DBB7ZZ, 0DH50DZ, 0DH50UZ, 0DH53DZ, 0DH53UZ, 0DH54DZ, 0DH54UZ, 0DH57DZ, 0DH57UZ, 0DH58DZ, 0DH58UZ, 0DH63UZ, 0DH64UZ, 0DHA3UZ, 0DHA4UZ, 0DHA8UZ, 0DN87ZZ, 0DNE7ZZ, 0DW04UZ, 0DW08UZ, 0WQFXZ2, 3E1G78Z, 3E1H78Z
	Transplantation	996.82, 996.86, 996.87, V42.7, V42.83, V42.84, 46.97, 50.5, 50.51, 50.59, 52.8, 52.80, 52.82, 52.83, 52.84, 52.85, 52.86	T86.40-T86.42, T86.890, T86.891, T86.899, T86.850, T86.851, T86.859, Z94.4, Z94.82, Z94.83, 0DY80Z0, 0DY80Z1, 0DY80Z2, 0DYE0Z0, 0DYE0Z1, 0DYE0Z2, 0FY00Z0, 0FY00Z1, 0FY00Z2, 0FYG0Z0, 0FYG0Z1, 0FYG0Z2, 3E030U0, 3E030U1, 3E033U0, 3E033U1, 3E0J3U0, 3E0J3U1, 3E0J7U0, 3E0J7U1, 3E0J8U0, 3E0J8U1
Hematologic or immunologic	Hereditary anemias	282.0-282.6	D55-D58
	Aplastic anemias	284	D60-D61, D71
	Hereditary immunodeficiency	279.0-279.9, 288.1, 288.2, 446.1	D80-D89, D72.0, M30.3, M35.9
	Coagulation/hemorrhagic	286.0, 286.3, 287.32, 287.33, 287.39	D66, D68.2, D69.41, D69.42, D69.49
	Leukopenia	288.01, 288.02	D70.0, D70.4
	Hemophagocytic Syndromes	288.4	D76.1-D76.3
	Sarcoidosis	135	D86.9
	Acquired immunodeficiency	042-044	B20-B24

	Polyarteritis nodosa and related conditions	446.0, 446.21, 446.4-446.7	M30.0, M31.0, M31.1, M31.30, M31.4, M31.6
	Diffuse diseases of connective tissue	710.0, 710.1, 710.3	M32.10, M33.90, M34.0, M34.1, M34.9
	Other	41.5	07TP0ZZ, 07TP4ZZ
	Devices	N/A	N/A
	Transplantation	41.00, 41.01, 41.02, 41.03, 41.04, 41.05, 41.06, 41.07, 41.08, 41.09, 41.94	07YP0Z0, 07YP0Z1, 07YP0Z2, 30230AZ, 30230G0, 30230G1, 30230X0, 30230X1, 30230Y0, 30230Y1, 30233AZ, 30233G0, 30233G1, 30233X0, 30233X1, 30233Y0, 30233Y1, 30240AZ, 30240G0, 30240G1, 30240X0, 30240X1, 30240Y0, 30240Y1, 30243AZ, 30243G0, 30243G1, 30243X0, 30243X1, 30243Y0, 30243Y1, 30250G0, 30250G1, 30250X0, 30250X1, 30250Y0, 30250Y1, 30253G0, 30253G1, 30253X0, 30253X1, 30253Y0, 30253Y1, 30260G0, 30260G1, 30260X0, 30260X1, 30260Y0, 30260Y1, 30263G0, 30263G1, 30263X0, 30263X1, 30263Y0, 30263Y1
Metabolic	Amino acid metabolism	270.0-270.9	E70.0, E70.2, E70.3, E70.4, E70.8, E71.0-E71.5, E72.0-E72.4, E72.8, E72.9
	Carbohydrate metabolism	271.0-271.9	E74.0-E74.4, E74.8, E74.9
	Lipid metabolism	272.0-272.9	E75, E77.0, E77.1, E78.0-E78.4, E78.5-E78.9, E88.1, E88.8
	Storage disorder	277.3, 277.5	E76.0-E76.3, E85
	Other metabolic disorders	275.0-275.3, 277.2, 277.6, 277.8-277.9	277.4, E79.1, E79.8, E80.4-E80.7, E83.0, E83.1, E83.3, E83.4, D84.1, E88, H49.8

	Endocrine disorders	243, 253.2, 253.5, 253.6, 235.9, 255.0, 255.13, 255.2, 06.4, 06.52, 06.81, 07.3, 07.64, 07.65, 07.68, 07.69, 62.4, 62.41, 64.5, 65.5, 65.51, 65.53, 65.6, 65.61, 65.63, 68.4, 68.41, 68.49, 68.5, 68.51, 68.59, 68.6, 68.61, 68.69, 68.7, 68.71, 68.79	E00.9, E23.0, E23.2, E22.2, E23.3, E23.7, E24.0, E24.2, E24.3, E24.8, E24.9, E26.81, E25.0, E25.8, E25.9, 0GT00ZZ, 0GT04ZZ, 0GT40ZZ, 0GT44ZZ, 0GTK0ZZ, 0GTK4ZZ, 0GTR0ZZ, 0GTR4ZZ, 0UT20ZZ, 0UT24ZZ, 0UT27ZZ, 0UT28ZZ, 0UT2FZZ, 0UT40ZZ, 0UT44ZZ, 0UT47ZZ, 0UT48ZZ, 0UT70ZZ, 0UT74ZZ, 0UT90ZZ, 0UT94ZZ, 0UT97ZZ, 0UT98ZZ, 0UT9FZZ, 0UTC0ZZ, 0UTC7ZZ, 0UTC8ZZ, 0VTC0ZZ, 0VTC4ZZ, 0W4M070, 0W4M0J0, 0W4M0K0, 0W4M0Z0, 0W4N071, 0W4N0J1, 0W4N0K1, 0W4N0Z1
	Devices	V45.85, V53.91, 86.06	Z46.81, Z96.41, 0JH60VZ, 0JH63VZ, 0JH70VZ, 0JH73VZ, 0JH80VZ, 0JH83VZ, 0JHD0VZ, 0JHD3VZ, 0JHF0VZ, 0JHF3VZ, 0JHG0VZ, 0JHG3VZ, 0JHH0VZ, 0JHH3VZ, 0JHL0VZ, 0JHL3VZ, 0JHM0VZ, 0JHM3VZ, 0JHN0VZ, 0JHN3VZ, 0JHP0VZ, 0JHP3VZ, 0JHT0VZ, 0JHT3VZ
	Transplantation	N/A	N/A
Other Congenital or Genetic Defect	Chromosomal anomalies	758.0-758.9	Q90.9, Q91.3, Q91.4, Q91.7, Q92.8, Q93, Q95.0, Q96.9, Q97, Q98, Q99.8, Q99.9
	Bone and join anomalies	259.4, 737.3, 756.0-756.5	E34.3, M41.0, M41.2, M41.30, M41.8, M41.9, M43.30, M96.5, Q72.2, Q75.0, Q75.2, Q75.9, Q76.0-Q76.2, Q76.4-Q76.7, Q77, Q78.0-Q78.4, Q78.8, Q78.9
	Diaphragm and abdominal wall	553.3, 756.6, 756.7	K44.9, Q79.0-Q79.5, Q79.9, Q79.59
	Other congenital anomalies	757.39, 759.7-759.9	Q81, Q87.1-Q87.3, Q87.40, Q87.81, Q87.89, Q89.7, Q89.9, Q99.2
Malignancy	Neoplasms	140-209, 230-239, 00.10, 99.25	C00-C96, D01-D09, D3A.0, D37-D49, Q85.0, 3E00X05, 3E01305, 3E02305, 3E03005, 3E03305, 3E04005, 3E04305, 3E05005, 3E05305, 3E06005, 3E06305, 3E0A305, 3E0F305, 3E0F705, 3E0F805, 3E0G305, 3E0G705, 3E0G805, 3E0H305, 3E0H705, 3E0H805, 3E0J305, 3E0J705, 3E0J805, 3E0K305, 3E0K705, 3E0K805, 3E0L305, 3E0L705, 3E0M305, 3E0M705, 3E0N305, 3E0N705, 3E0N805, 3E0P305, 3E0P705, 3E0P805, 3E0Q305, 3E0Q705, 3E0R305, 3E0S305, 3E0V305, 3E0W305, 3E0Y305, 3E0Y705
	Devices	N/A	N/A

	Transplantation	996.85, V42.81, V42.82	T86.00-T86.02, T86.09, Z94.81, Z94.84
Premature and Neonatal	Fetal malnutrition	764.01, 764.02, 764.11, 764.12, 764.21, 764.22, 764.91, 764.92	P05.01, P05.11, P05.02, P05.12, P05.2, P05.9
	Extreme immaturity	765.01, 765.02, 765.11, 765.12, 765.21-765.23	P07.01, P07.02, P07.21-P07.25
	Cerebral hemorrhage at birth	767	P10.0, P10.1, P10.4, P52.4, P52.8
	Spinal cord injury at birth	767.4	P11.5
	Birth asphyxia	768.5, 768.9	P21.0, P21.9, P84
	Respiratory diseases	770.2, 770.7	P25.0-P25.3, P25.8, P27.0, P27.1, P27.8
	Hypoxic-ischemic encephalopathy	768.7	P91.6
	Other	771.0, 771.1, 772.13, 772.14, 773.3, 773.4, 774.7, 776.5, 777.53, 778.0, 779.7	P35.0, P35.1, P25.21, P25.22, P56.0, P57.0, P57.8, P61.3, P61.4, P77.3, P83.2, P91.2

Miscellaneous, Not Elsewhere Classified	Devices	996.4, 996.66, 996.67, 996.9, V46.2 81.00, 81.01, 81.02, 81.03, 81.04, 81.05, 81.06, 81.07, 81.08, 81.09, 81.30, 81.31, 81.32, 81.33, 81.34, 81.35, 81.36, 81.37, 81.38, 81.39, 84.51	T84.019A, T84.029A, T84.039A, T84.049A, T84.059A, T84.069A, T84.099A, T84.498A, T84.119A, T84.129A, T84.199A, T84.498A, T84.50XA, T84.60XA, , T84.7XXA, T86.90-T86.92, T86.99, T86.10-T86.12, T86.40-T86.42, T86.20-T86.22, T86.810, T86.811, T86.819, T86.00-T86.02, T86.09, T86.890, T86.891, T86.899, T86.850, T86.851, T86.859, T86.5, T86.890, T86.891, T86.899, T87.0X9, T87.1X9, T87.2, Y83.1, Y83.3, Z99.81, ORG00J0, ORG00J1, ORG00JJ, ORG00K0, ORG00K1, ORG00KJ, ORG00Z0, ORG00Z1, ORG00ZJ, ORG03J0, ORG03J1, ORG03JJ, ORG03K0, ORG03K1, ORG03KJ, ORG03Z0, ORG03Z1, ORG03ZJ, ORG04J0, ORG04J1, ORG04JJ, ORG04K0, ORG04K1, ORG04KJ, ORG04Z0, ORG04Z1, ORG04ZJ, ORG10J0, ORG10J1, ORG10JJ, ORG10K0, ORG10K1, ORG10KJ, ORG10Z0, ORG10Z1, ORG10ZJ, ORG13J0, ORG13J1, ORG13JJ, ORG13K0, ORG13K1, ORG13KJ, ORG13Z0, ORG13Z1, ORG13ZJ, ORG14J0, ORG14J1, ORG14JJ, ORG14K0, ORG14K1, ORG14KJ, ORG14Z0, ORG14Z1, ORG14ZJ, ORG40J0, ORG40J1, ORG40JJ, ORG40K0, ORG40K1, ORG40KJ, ORG40Z0, ORG40Z1, ORG40ZJ, ORG43J0, ORG43J1, ORG43JJ, ORG43K0, ORG43K1, ORG43KJ, ORG43Z0, ORG43Z1, ORG43ZJ, ORG44J0, ORG44J1, ORG44JJ, ORG44K0, ORG44K1, ORG44KJ, ORG44Z0, ORG44Z1, ORG44ZJ, ORG60J0, ORG60J1, ORG60JJ, ORG60K0, ORG60K1, ORG60KJ, ORG60Z0, ORG60Z1, ORG60ZJ, ORG63J0, ORG63J1, ORG63JJ, ORG63K0, ORG63K1, ORG63KJ, ORG63Z0, ORG63Z1, ORG63ZJ, ORG64J0, ORG64J1, ORG64JJ, ORG64K0, ORG64K1, ORG64KJ, ORG64Z0, ORG64Z1, ORG64ZJ, ORGA0J0, ORGA0J1, ORGA0JJ, ORGA0K0, ORGA0K1, ORGA0KJ, ORGA0Z0, ORGA0Z1, ORGA0ZJ, ORGA3J0, ORGA3J1, ORGA3JJ, ORGA3K0, ORGA3K1, ORGA3KJ, ORGA3Z0, ORGA3Z1, ORGA3ZJ, ORGA4J0, ORGA4J1, ORGA4JJ, ORGA4K0, ORGA4K1, ORGA4KJ, ORGA4Z0, ORGA4Z1, ORGA4ZJ, OSG00J0, OSG00J1, OSG00JJ, OSG00K0, OSG00K1, OSG00KJ, OSG00Z0, OSG00Z1, OSG00ZJ, OSG03J0, OSG03J1, OSG03JJ, OSG03K0,
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			0SG03K1, 0SG03KJ, 0SG03Z0, 0SG03Z1, 0SG03ZJ, 0SG04J0, 0SG04J1, 0SG04JJ, 0SG04K0, 0SG04K1, 0SG04KJ, 0SG04Z0, 0SG04Z1, 0SG04ZJ
	Transplantation	996.80, 6.88, 996.89, 00.91, 00.92, 00.93	T86.5, T86.90-T86.92, T86.99, T86.890, T86.891, T86.899

Additional excluding conditions:

Description	ICD-9 Diagnosis code	ICD-10 Diagnosis code
Inflammatory Bowel Disease (IBD)	555x or 556x	K50% or K51%
Celiac Disease	579.0x	K90.0%
Type 1 Diabetes Mellitus (T1DM)	250.x1, 250.x3	E10%

Appendix B: Antibiotics

Antibiotics identified in pharmacy claims:

Generic Name	Drug Class
Penicillin G Potassium	Natural Penicillins
Penicillin G Pot in Dextrose	Natural Penicillins
Penicillin G Sodium	Natural Penicillins
Penicillin G Benzathine	Natural Penicillins
Penicillin G Procaine	Natural Penicillins
Penicillin V	Natural Penicillins
Penicillin V Potassium	Natural Penicillins
Amoxicillin	Aminopenicillins
Ampicillin	Aminopenicillins
Ampicillin Sodium	Aminopenicillins
Bacampicillin HCl	Aminopenicillins
Cloxacillin Sodium	Penicillinase-Resistant Penicillins
Dicloxacillin Sodium	Penicillinase-Resistant Penicillins
Nafcillin Sodium	Penicillinase-Resistant Penicillins
Nafcillin Sodium in Dextrose	Penicillinase-Resistant Penicillins
Oxacillin Sodium	Penicillinase-Resistant Penicillins
Oxacillin Sodium in Dextrose	Penicillinase-Resistant Penicillins
Carbenicillin Indanyl Sodium	Extended-Spectrum Penicillins
Mezlocillin Sodium	Extended-Spectrum Penicillins
Piperacillin Sodium	Extended-Spectrum Penicillins
Piperacillin Sodium-D5W	Extended-Spectrum Penicillins
Ticarcillin Disodium	Extended-Spectrum Penicillins
Ticarcillin Disodium-D5W	Extended-Spectrum Penicillins
Penicillin G Benzathine & Procaine	Penicillin Combinations
Amoxicillin & Pot Clavulanate	Penicillin Combinations
Ampicillin & Sulbactam Sodium	Penicillin Combinations
Ticarcillin & Pot Clavulanate	Penicillin Combinations
Piperacillin Sodium-Tazobactam Sodium	Penicillin Combinations
Piperacillin Sodium-Tazobactam Sodium in Dextrose	Penicillin Combinations
Cefadroxil	Cephalosporins - 1st Generation
Cefazolin Sodium	Cephalosporins - 1st Generation
Cefazolin in D5W	Cephalosporins - 1st Generation
Cefazolin Sodium in Sodium Chloride	Cephalosporins - 1st Generation
Cefazolin Sodium and Dextrose	Cephalosporins - 1st Generation
Cephalexin	Cephalosporins - 1st Generation
Cephalexin HCl	Cephalosporins - 1st Generation
Cephalothin in D5W	Cephalosporins - 1st Generation

Cephapirin Sodium	Cephalosporins - 1st Generation
Cephradine	Cephalosporins - 1st Generation
Cefaclor	Cephalosporins - 2nd Generation
Cefaclor Monohydrate	Cephalosporins - 2nd Generation
Cefamandole Nafate	Cephalosporins - 2nd Generation
Cefamandole Nafate in D5W	Cephalosporins - 2nd Generation
Cefonicid Sodium	Cephalosporins - 2nd Generation
Cefotetan Disodium	Cephalosporins - 2nd Generation
Cefotetan Disodium in Dextrose	Cephalosporins - 2nd Generation
Cefotetan Disodium and Dextrose	Cephalosporins - 2nd Generation
Cefoxitin Sodium	Cephalosporins - 2nd Generation
Cefoxitin Sodium in Dextrose	Cephalosporins - 2nd Generation
Cefoxitin Sodium and Dextrose	Cephalosporins - 2nd Generation
Cefprozil	Cephalosporins - 2nd Generation
Cefuroxime Axetil	Cephalosporins - 2nd Generation
Cefuroxime Sodium	Cephalosporins - 2nd Generation
Cefuroxime Sodium in D5W	Cephalosporins - 2nd Generation
Cefuroxime in Sterile Water	Cephalosporins - 2nd Generation
Cefuroxime Sodium and Dextrose	Cephalosporins - 2nd Generation
Cefdinir	Cephalosporins - 3rd Generation
Cefditoren Pivoxil	Cephalosporins - 3rd Generation
Cefixime	Cephalosporins - 3rd Generation
Cefpodoxime Proxetil	Cephalosporins - 3rd Generation
Cefoperazone Sodium	Cephalosporins - 3rd Generation
Cefoperazone Sod in Dextrose	Cephalosporins - 3rd Generation
Cefotaxime Sodium	Cephalosporins - 3rd Generation
Cefotaxime Sodium in D5W	Cephalosporins - 3rd Generation
Cefotetan Disodium	Cephalosporins - 3rd Generation
Ceftazidime	Cephalosporins - 3rd Generation
Ceftazidime Sodium in D5W	Cephalosporins - 3rd Generation
Ceftazidime Sodium in Dextrose	Cephalosporins - 3rd Generation
Ceftazidime and Dextrose	Cephalosporins - 3rd Generation
Ceftibuten	Cephalosporins - 3rd Generation
Ceftizoxime Sodium	Cephalosporins - 3rd Generation
Ceftizoxime in D5W	Cephalosporins - 3rd Generation
Ceftriaxone Sodium	Cephalosporins - 3rd Generation
Ceftriaxone Sodium in Dextrose	Cephalosporins - 3rd Generation
Ceftriaxone Sodium w/ Lidocaine	Cephalosporins - 3rd Generation
Ceftriaxone Sodium and Dextrose	Cephalosporins - 3rd Generation
Cefepime HCl	Cephalosporins - 4th Generation
Cefepime HCl and Dextrose	Cephalosporins - 4th Generation

Ceftaroline Fosamil	Cephalosporins - 5th Generation
Ceftazidime-Avibactam Sodium	Cephalosporin Combinations
Ceftolozane Sulfate-Tazobactam Sodium	Cephalosporin Combinations
Erythromycin Base	Erythromycins
Erythromycin Base (Coated)	Erythromycins
Erythromycin Stearate	Erythromycins
Erythromycin Estolate	Erythromycins
Erythromycin Ethylsuccinate	Erythromycins
Erythromycin Lactobionate	Erythromycins
Troleandomycin	Troleandomycin
Lincomycin HCl	Lincomycins
Clindamycin HCl	Lincomycins
Clindamycin Phosphate	Lincomycins
Clindamycin Phosphate in D5W	Lincomycins
Azithromycin	Azithromycin
Azithromycin Hydrogencitrate	Azithromycin
Clarithromycin	Clarithromycin
Dirithromycin	Dirithromycin
Fidaxomicin	Fidaxomicin
Chlortetracycline HCl	Tetracyclines
Demeclocycline HCl	Tetracyclines
Doxycycline (Monohydrate)	Tetracyclines
Doxycycline Hyclate	Tetracyclines
Doxycycline Calcium	Tetracyclines
Doxycycline Hyclate w/ Cleanser	Tetracyclines
Doxycycline Hyclate w/ Eyelid Cleansers	Tetracyclines
Doxycycline Hyclate w/ Eyelid Cleanser & Spray	Tetracyclines
Doxycycline Monohydrate w/ Cleanser	Tetracyclines
Doxycycline Monohydrate w/ Omega 3-Vit E	Tetracyclines
Minocycline HCl	Tetracyclines
Minocycline HCl w/ Acne Care Products	Tetracyclines
Minocycline HCl w/ Eyelid Cleanser	Tetracyclines
Oxytetracycline HCl	Tetracyclines
Oxytetracycline w/ Lidocaine	Tetracyclines
Tetracycline HCl	Tetracyclines
Doxycycline Monohydrate-Benzoyl Peroxide	Tetracycline Combinations

Doxycycline Monohydrate-Multiple Vitamins w/ Minerals	Tetracycline Combinations
Doxycycline w/ Sunscreen & Salicylic Acid	Tetracycline Combinations
Alatrofloxacin Mesylate	Fluoroquinolones
Ciprofloxacin	Fluoroquinolones
Ciprofloxacin-Ciprofloxacin HCl	Fluoroquinolones
Ciprofloxacin HCl	Fluoroquinolones
Ciprofloxacin in D5W	Fluoroquinolones
Enoxacin	Fluoroquinolones
Levofloxacin	Fluoroquinolones
Levofloxacin in D5W	Fluoroquinolones
Lomefloxacin HCl	Fluoroquinolones
Moxifloxacin HCl	Fluoroquinolones
Moxifloxacin HCl in Sodium Chloride	Fluoroquinolones
Norfloxacin	Fluoroquinolones
Ofloxacin	Fluoroquinolones
Ofloxacin in D5W	Fluoroquinolones
Sparfloxacin	Fluoroquinolones
Trovafloxacin Mesylate	Fluoroquinolones
Gatifloxacin	Fluoroquinolones
Gatifloxacin-D5W	Fluoroquinolones
Gemifloxacin Mesylate	Fluoroquinolones
Amikacin Sulfate	Aminoglycosides
Gentamicin Sulfate	Aminoglycosides
Gentamicin in Saline	Aminoglycosides
Kanamycin Sulfate	Aminoglycosides
Neomycin Sulfate	Aminoglycosides
Netilmicin Sulfate	Aminoglycosides
Paromomycin Sulfate	Aminoglycosides
Streptomycin Sulfate	Aminoglycosides
Tobramycin	Aminoglycosides
Tobramycin Sulfate	Aminoglycosides
Tobramycin Sulfate in Saline	Aminoglycosides
Sulfadiazine	Sulfonamides
Sulfadiazine Sodium	Sulfonamides
Sulfamethoxazole	Sulfonamides
Sulfapyridine	Sulfonamides
Sulfisoxazole	Sulfonamides
Sulfisoxazole Acetyl	Sulfonamides
Sulfathiazole	Sulfonamides
Aztreonam	Anti-infective Agents - Misc.

Aztreonam in Dextrose	Anti-infective Agents - Misc.
Aztreonam Lysine	Anti-infective Agents - Misc.
Bacitracin	Anti-infective Agents - Misc.
Colistimethate Sodium	Anti-infective Agents - Misc.
Dalbavancin HCl	Anti-infective Agents - Misc.
Metronidazole	Anti-infective Agents - Misc.
Metronidazole Benzoate	Anti-infective Agents - Misc.
Metronidazole HCl	Anti-infective Agents - Misc.
Metronidazole in NaCl	Anti-infective Agents - Misc.
Oritavancin Diphosphate	Anti-infective Agents - Misc.
Rifaximin	Anti-infective Agents - Misc.
Spectinomycin HCl	Anti-infective Agents - Misc.
Telavancin HCl	Anti-infective Agents - Misc.
Tinidazole	Anti-infective Agents - Misc.
Trimethoprim	Anti-infective Agents - Misc.
Trimethoprim HCl	Anti-infective Agents - Misc.
Vancomycin HCl	Anti-infective Agents - Misc.
Vancomycin HCl in Dextrose	Anti-infective Agents - Misc.
Vancomycin HCl in Sodium Chloride	Anti-infective Agents - Misc.
Polymyxin B Sulfate	Polymyxins
Doripenem	Carbapenems
Ertapenem Sodium	Carbapenems
Meropenem	Carbapenems
Meropenem % Sodium Chloride	Carbapenems
Imipenem-Cilastatin	Carbapenems
Chloramphenicol	Chloramphenicols
Chloramphenicol Sodium Succinate	Chloramphenicols
Telithromycin	Ketolides
Lincomycin HCl	Lincosamides
Clindamycin HCl	Lincosamides
Clindamycin Palmitate Hydrochloride	Lincosamides
Clindamycin Phosphate	Lincosamides
Clindamycin Phosphate in D5W	Lincosamides
Lincomycin HCl-Lidocaine HCl	Lincosamides
Clindamycin-Lidocaine-Epinephrine-Sodium Bicarbonate	Lincosamides
Linezolid	Oxazolidinones
Linezolid in Sodium Chloride	Oxazolidinones
Tedizolid Phosphate	Oxazolidinones
Quinupristin-Dalfopristin	Streptogramins
Daptomycin	Cyclic Lipopeptides
Tigecycline	Glycylcyclines

Erythromycin-Sulfisoxazole	Anti-infective Misc. - Combinations
Cilastatin & Imipenem	Anti-infective Misc. - Combinations
Sulfamethoxazole-Trimethoprim	Anti-infective Misc. - Combinations
Urinary anti-infective	Urinary anti-infective

Antibiotics identified with CPT code in medical claims:

CPTCode	CodeShortDescr
J0278	Amikacin sulfate injection
J0290	Ampicillin 500 mg inj
J0295	Ampicillin sodium per 1.5 gm
J0456	Azithromycin
S0073	aztreonam injection
J0690	Cefazolin sodium injection
J0692	Cefepime hcl for injection
S0021	cefoperazone sodium
J0698	Cefotaxime sodium injection
S0074	cefotetan injection
J0694	Cefoxitin sodium injection
C9282	ceftaroline fosamil
J0712	Ceftaroline fosamil inj
J0714	Ceftazidime and avibactam
J0713	ceftazidime per 500 mg
J0715	Ceftizoxime sodium / 500 mg
J0695	ceftolozane tazobactam
C9452	ceftolozane/tazobactam
J0696	Ceftriaxone sodium injection
J1890	Cephalothin sodium injection
J0720	Chloramphenicol sodium injec
J0743	Cilastatin sodium injection
J0744	Ciprofloxacin iv
S0077	clindamycin injection
J0770	Colistimethate sodium inj
C9443	dalbavancin
J0875	dalbavancin
C9124	daptomycin
J0878	Daptomycin injection
J1267	Doripenem injection
J1335	Ertapenem injection
J1364	Erythro lactobionate /500 mg
J1580	Garamycin gentamicin inj
J1590	Gatifloxacin injection

J1840	Kanamycin sulfate 500 mg inj
J1850	Kanamycin sulfate 75 mg inj
J2010	Lincomycin injection
J2020	Linezolid injection
J2185	Meropenem
S0030	metronidazole injection
J2265	Minocycline hydrochloride
J2280	moxifloxacin 100 mg
S0032	nafcillin sodium injection
S0034	ofloxacin injection
C9444	oritavancin
J2407	oritavancin
J2700	Oxacillin sodium injecton
J0558	Penicillin g benzathine/procaine inj
J0559	Penicillin g benzathine/procaine inj
J0530	Penicillin g benzathine inj
J0540	Penicillin g benzathine inj
J0550	Penicillin g benzathine inj
J0560	Penicillin g benzathine inj
J0561	Penicillin g benzathine inj
J0580	Penicillin g benzathine inj
J2540	Penicillin g potassium inj
J2510	Penicillin g procaine inj
S0081	piperacillin injection
J2543	Piperacillin/tazobactam
J2770	Quinupristin/dalfopristin
J3320	Spectinomycin di-hcl inj
J3000	Streptomycin injection
S0039	sulfamethoxazole and trimethoprim injection
J3090	tedizolid phosphate
C9446	tedizolid phosphate
C9258	Telavancin injection
J3095	Telavancin injection
J0120	Tetracycline injection
S0040	ticarcillin disodium and clavulanate potassium injection
C9228	tigecycline
J3243	Tigecycline injection
J7685	Tobramycin comp unit
J7682	Tobramycin non-comp unit
J3260	Tobramycin sulfate injection
J3370	Vancomycin hcl injection

Appendix C: Asthma

Diagnosis codes:

Description	ICD-9 diagnosis codes	ICD-10 diagnosis codes
Asthma (exact codes)	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92	J45.20, J45.21, J45.22, J45.30, J45.31, J45.32, J45.40, J45.41, J45.42, J45.50, J45.51, J45.52, J45.901, J45.902, J45.909, J45.990, J45.991, J45.998

Asthma medications:

Short Acting Beta-2 Agonists (SABA):

- Albuterol
- Bitolterol
- Isoetharine
- Isoproterenol
- Levalbuterol
- Metaproterenol
- Pirbuterol
- Terbutaline

Inhaled corticosteroids (ICS):

- Beclomethasone
- Budesonide
- Ciclesonide
- Dexamethasone
- Flunisolide
- Fluticasone
- Mometasone
- Triamcinolone

Ipratropium

Leukotriene receptor antagonist (LTRA):

- Zileuton
- Montelukast
- Zafirlukast

Appendix D: Other diagnoses

Condition	ICD 9 -CM diag	ICD 10-diag	Use in this study
Pre-term birth	76510, 76520, 76511, 76521, 76512, 76522, 76513, 76523, 76514, 76524, 76515, 76525, 76516, 76526, 76517, 76527, 76518, 76528, 76519	P07.2, P07.3	Covariate in statistical models
Wheeze	786.07	R06.2%	Bronchiolitis
Bronchitis (acute)	466.0x	J20.%	Bronchiolitis
Bronchiolitis (acute)	466.1x	J21.%	Bronchiolitis
Bronchospasm	519.11	J98.01	Other respiratory diagnosis
Reactive airway (ICD-10 only)	N/A	J68.3%	Other respiratory diagnosis
Bronchitis (chronic)	491.xx	J41.%	Other respiratory diagnosis
Bronchitis unspec.	490.xx	J40.%	Other respiratory diagnosis
Pneumonia	481.xx-486.xx	J12 through J18.%	Other respiratory diagnosis

Note: For ICD-9 CM, 'x' indicates a wildcard character. For ICD-10, the '%' sign indicates a wildcard character.