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ANTIBIOTICS POTENTIALLY USED IN RESPONSE TO BIOTERRORISM AND THE RISK OF MAJOR CONGENITAL MALFORMATIONS

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SUMMARY

This study was designed to assess the association between pregnancy-related exposures to antibiotics recommended for use in the event of a bioterrorism attack and major congenital malformations. A retrospective cohort study included 30,049 infants from Tennessee Medicaid born between 1985–2000 identified from computerized state databases. Infants with fetal exposures to ciprofloxacin, azithromycin, doxycycline, and amoxicillin (antibiotics recommended for potential bioterrorism attacks) and erythromycin (included as a positive control) were compared to infants with no fetal exposure to any antibiotics. Major congenital malformations identified from computerized records were confirmed through medical record review. Overall, 869 (2.9%) of infants in the cohort had a confirmed major congenital malformation, with major malformations ranging from 2.5%–3.0% among the antibiotic-specific exposure groups. No increased risk was present in multivariable analyses for any malformations and for malformations of specific organ systems. In conclusion, these data suggest that ciprofloxacin, azithromycin, doxycycline, or amoxicillin use by pregnant women should not result in a greater incidence of overall major congenital malformations in infants whose mothers take these medications, though a large increase in risk cannot be ruled out.

INTRODUCTION

Recent events have shown that bioterrorism is a potential threat to the public health.^{1–4} In the event of a bioterrorist attack, it is likely that large populations of individuals would require antibiotic prophylaxis or treatment, including many pregnant women.⁵ Unfortunately, little is known about the safety of fetal exposure to these drugs.^{6–9} Data from animal studies suggest that some of the agents might plausibly be associated with congenital malformations including fluoroquinolones, which have been associated with degeneration of cartilage tissue in mice,¹⁰ and doxycycline, which has been shown to result in placental anomalies in mice, possibly due to doxycycline's inhibitory effect on cytokines and matrix metalloproteinases.¹¹ In addition, a previous study by our group suggested an association between pregnancy exposures to non-erythromycin macrolides and pyloric stenosis.¹² Much

of the current information on antibiotic use during pregnancies in humans comes from voluntary reporting mechanisms, unpublished data, case reports of exposure, and relatively small controlled studies.^{6, 9, 13} Given the limitations of these methodologies, better data on the fetal effects of antibiotics are needed.⁹

We thus used a large Medicaid database, linked with birth and fetal death certificates, to conduct an epidemiologic study assessing the association between exposure to antibiotics recommended for use in the event of an anthrax, plague, or tularemia attack (ciprofloxacin, doxycycline, amoxicillin, and azithromycin) and an antibiotic selected as a positive control (erythromycin) and major congenital malformations.^{1, 3–5, 14} The risk for fetal exposure to these antibiotics was compared with that of infants with no fetal exposure to any antibiotics.

METHODS

The study was performed using the Tennessee Medicaid database, in which filled prescriptions provide a good record of maternal medication use and links to birth certificates and medical records permit identification of pregnant women, estimated conception dates, and potential congenital malformations.^{12, 15–18} Linkage of maternal records with birth certificates has been shown to result in linkage of 90–92% of pregnancies using Tennessee data.¹⁹ All study data were obtained from computerized Tennessee vital records (birth, death, and fetal death certificates) linked with Tennessee Medicaid (including TennCare) files^{19, 20} and U.S. census data.²¹ Vital records, Medicaid enrollment, and census files provided information on maternal and infant factors (age, race, education, prior pregnancies, last menstrual period [LMP], county of residence, block group income, late entry into prenatal care,²² smoking, and county of residence, birth year, multiple births). Maternal use of prescribed medications was identified from Medicaid pharmacy files. Drug exposure began on the date that the prescription was filled and extended through the end of the days of supply. Diagnoses (ICD-9-CM) from Medicaid inpatient, emergency department, and physician visit records were used to identify both potential congenital malformations and chronic maternal illnesses.

The study cohort was selected from all births in Tennessee between 1985 and 2000 (n=1,260,807) with maternal enrollment in Medicaid on the date of delivery (n=509,202) (Figure 1). To ensure complete ascertainment of exposures and outcomes, the cohort was restricted to 164,808 pregnancies in which the mother was enrolled throughout pregnancy (90 days preceding the LMP through delivery/fetal death with no gaps >30 days), there was complete information on the birth certificate for key variables, and the infant was enrolled for the first 90 days of life or through the date of death. From this group, 33,456 infants were selected who: 1) had exposure to one of the antibiotics of interest (including any use of ciprofloxacin, azithromycin, or doxycycline, and a random sample of 50% of women with use of amoxicillin), 2) were included in a random sample women who took erythromycin during pregnancy (a positive control), selected at a ratio of 5:1 to ciprofloxacin users based on year of birth, or 3) were included in a random sample from 52,474 women who did not take any antibiotics during pregnancy, selected at a ratio of 5:1 to ciprofloxacin users based on year of birth. Births with evidence of maternal diabetes (defined as maternal filling of at least one prescription for insulin or an oral hypoglycemic, a single hospitalization with a diabetes diagnosis, or two outpatient encounters with a diabetes diagnosis) (n=1,002) or filling of other medications thought to be teratogenic (leuprolide, danazol, angiotensin converting enzyme inhibitors, coumadin, carbamazepine, phenytoin, valproic acid, lithium, streptomycin, kanamycin, fluconazole, quinine, tetracycline, diethylstilbestrol, estradiol, misoprostol, thalidomide, iodine, methimazole, arbmiazole, etretinate, acitretin, isotretinoin, statins, ribavirin, aminopterin)^{6, 23} (n=2,405) were excluded, leaving 30,049 in the final cohort.

The study outcome was the presence of a major congenital malformation not related to a chromosomal defect. Possible malformations were identified from multiple sources, including the birth certificate checkbox for congenital malformations (from 1989 on) and hospital discharge diagnoses indicating possible malformations for the birth or subsequent infant hospitalizations (first 365 days of life), fetal death (fetal deaths occurring after 20 weeks gestation) or death certificates (deaths occurring before the 1st birthday), and the maternal delivery hospitalization or that associated with the fetal death. For multiple births in which the computer files identified one child with a possible malformation, the associated twin or triplets also were considered to have possible malformations.

For each possible congenital malformation, trained study nurses unaware of maternal drug exposure reviewed the pertinent medical records to complete a structured abstract form. The reviewers confirmed demographic information, recorded any congenital malformations included in the face sheet, discharge summary, birth record, admission history and physical, surgical reports, radiology reports, or autopsy records.²³ Reviewers also identified any transfer hospitalizations and obtained and reviewed records for these. Quality control procedures included reabstraction of a random sample of nurse charts, where agreement between the presence or absence of a selected malformation was found in 100% of the charts. In addition, a 10% random sample of a charts in which the physician reviewers had made a final diagnosis were readjudicated without knowledge of the original decision (n=191). In this sample, there were no cases reclassified as to case status or organ system involvement.

Confirmed malformations were those meeting the definitions of the Metropolitan Atlanta Congenital Defects Program.²⁴ These utilized data from the medical records, including physical examination, imaging studies and surgical procedures, appropriate for each individual malformation. For example, confirmation of a diagnosis of transposition of the great vessels required an echocardiograph, cardiac catheterization, surgical note, or autopsy that included this diagnosis. The study definitions from the Metropolitan Atlanta Congenital Defects Program also consider gestational age; for example, infants classified as having patent ductus arteriosus had to have a gestational age of greater than 36 weeks.²⁴ The study principal investigator used the structured abstract form to assign a final diagnosis using the code book index from the Metropolitan Atlanta Congenital Defects Program.²⁴ In ambiguous cases, the diagnosis was adjudicated in consultation with a second investigator. Possible cases in which the medical record mentioned the diagnosis, but the necessary supporting data were absent were not considered confirmed malformations. Unconfirmed cases were excluded from the analysis.

All births in the study group were classified according to maternal antibiotic use during pregnancy. Mutually exclusive categories of fetal exposure were created based on the frequency of recommendations for use of each antibiotic in a bioterrorism attack (e.g. ciprofloxacin was the most commonly recommended antibiotic) and the relative frequency of exposures (with priority given to antibiotics with fewer exposures to ensure adequate power). A hierarchical exposure variable based on these groups included: any ciprofloxacin exposure, any azithromycin in the absence of ciprofloxacin, only doxycycline, only amoxicillin, only erythromycin, exposure to more than one antibiotic (i.e. doxycycline, amoxicillin, or erythromycin), and a group of infants with no fetal antimicrobial exposure. The analyses considered both the first four lunar months of pregnancy (LMP through the subsequent 112 days), which is considered to be the period of greatest risk for congenital malformations, as well as the entire pregnancy.

Proportions of congenital malformations for each exposure category were calculated by dividing the number of infants with congenital malformations by the corresponding number

of births. Univariate risk-ratios were calculated with no antimicrobials as the reference category. Infants with multiple congenital malformations were included in the analyses for each of the individual malformations. The risk-ratios were adjusted for potential confounders using a modified Poisson regression.^{25, 26} The final model included maternal year of delivery, age, race, residence outside of a standard metropolitan statistical area, quartile of neighborhood income, chronic maternal illness (hypertension, epilepsy, sickle cell disease, asthma, renal disease, neoplastic disease, cardiovascular disease other than hypertension or diabetes, HIV infection, cystic fibrosis, autoimmune diseases, chronic mental illness, obesity, migraine headaches, Crohn's disease, ulcerative colitis, organ transplant), and delivery in a hospital with a level III neonatal intensive care unit. Delivery in a hospital with a level III neonatal intensive care unit was included because of the possibility of ascertainment bias if infants with maternal antibiotic exposure were more likely to be delivered in hospitals with more sophisticated diagnostic equipment. Inclusion of other potential confounders did not materially affect study findings.

To account for the possible correlation induced by multiple pregnancies during the study period and multiple gestations, models were fit using generalized estimating equations.²⁷ In multiple gestation pregnancies (identified by linking each women with a unique study identification number throughout the study years),¹⁹ we included all infants from the pregnancy and controlled statistically for non-independence of the outcomes. For some congenital malformations, small numbers of malformations, pregnancies, or multiple gestations precluded controlling for possible correlations; we assumed independence. For malformations in which we could account for such correlations, the regression results were not materially different from results using models in which we assumed independence. In some analyses, proportions were estimated adjusting for potential confounders using the method of marginal prediction,^{28, 29} with bootstrapping³⁰ to calculate p-values and 95% confidence intervals. For the primary outcome of having any major malformation, detectable risk ratios ranged from 1.4 for amoxicillin to 1.9 for ciprofloxacin, assuming $\alpha=.05$, $\beta=.8$.

Permission to perform the study was obtained from the Vanderbilt University Institutional Review Board, the State of Tennessee Health Department, the TennCare Bureau, and the hospitals where medical records were reviewed. The study was considered exempt by the Vanderbilt University Institutional Review Board.

RESULTS

The 30,049 study births included 26,649 infants who had fetal exposure to antimicrobials. Mean and median days of exposure and daily dose and other maternal characteristics for each antibiotic category are shown in Table 1. When compared to the 3,400 infants without such exposure, the former had mothers that were more likely to have one or more chronic illnesses. The maternal characteristics for infants exposed to antimicrobials were generally similar, although the ciprofloxacin-exposed infants had mothers that were slightly older, more likely to live in a rural county, and to have a chronic illness. Azithromycin-exposed infants had mothers who were more likely to be black and live in urban settings. Reported maternal smoking was increased in the ciprofloxacin, amoxicillin, and erythromycin groups, consistent with the frequent use of these antibiotics for smoking-related respiratory infections.

There were 869 (2.9 percent) study infants with major congenital malformations; 203 had more than one malformation. The 869 infants with major malformations included 304 infants with cardiovascular malformations (including 141 atrial septal defects, 121 persistent ductus arteriosus, 76 ventricular septal defects, 27 pulmonic stenosis), 207 with musculoskeletal malformations (147 polydactyly, 21 upper limb defects, 10 craniofacial

anomalies), 166 with genitourinary anomalies (89 genital anomalies, 82 urologic anomalies, 27 renal anomalies), 121 with gastrointestinal malformations (64 pyloric stenosis, 19 intestinal atresias), 82 with central nervous system malformations (25 hydrocephalus, 17 microcephaly, 8 spina bifida, 2 encephalocele), and 55 infants with orofacial malformations.

The adjusted proportions of infants with major congenital malformations did not vary materially according to maternal antibiotic use (Figure 2) with risks ranging between 2.5 percent and 3.0 percent. The multivariable analysis provided no evidence that infants with fetal exposure to study antibiotics during the first four lunar months of pregnancy had greater risk of malformations than did infants with no fetal antibiotic exposure (Table 2). Similar findings were present in analyses for cardiovascular, genitourinary, central nervous system, gastrointestinal, musculoskeletal, and orofacial defects. Of note, with the exception of oral clefts, none of the point estimates for exposures during the first four lunar months of pregnancy indicated a greater than 2-fold increase in risk.

We assessed the risk of major congenital malformations for infants with fetal exposure to antimicrobials at any time during pregnancy (Table 3). There was no significantly increased risk of congenital malformations associated with fetal exposure to any of the study antimicrobials during the entire pregnancy.

DISCUSSION

In this study of a cohort of more than 30,000 infants, we found no evidence that the risk of overall major congenital malformations in infants with fetal exposure to antibiotics likely to be used in the event of a bioterrorism attack during the first four lunar months of pregnancy was greater than that of comparable infants with no fetal antibiotic exposure.¹² We also found no increased risk for fetal exposure for exposures occurring at any time during pregnancy. For many of the drugs of interest, this study was the largest to date analyzing pregnancy-related exposures. For example, the most exposures to ciprofloxacin previously described in a single study was 105;³¹ our study identified 588 exposures. Nevertheless, there was insufficient power to rule out large increases in risk.

Although the primary purpose of our study was to evaluate the fetal effects of antibiotics indicated for exposure to the organisms most likely to be used in a bioterrorism attack, the findings also provide important safety data for the use of these antibiotics in clinical practice. Women receive the study antibiotics for a variety of indications, and previous data suggest that use is relatively common during pregnancy.^{9, 32, 33} All of the study antibiotics cross the placenta and are expressed in human breast milk.^{6, 9} Thus, pregnancy-related exposures would result in fetal exposure to the antibiotics, highlighting the importance of understanding the potential teratogenic effects of these medications.⁹

Prior studies have used several methods to identify exposures and cases of birth defects.^{7, 13} Most have relied on voluntary reporting by mothers or health care providers to identify exposures, which may introduce recall or other information bias. This limitation may be more pronounced for case-control studies that relied on unconfirmed maternal recall of pregnancy-related antibiotic exposures. Some studies have identified birth defects from computerized records of health care encounters, with no further verification. We identified medication exposure from pharmacy records of filled prescriptions, which should not be subject to recall bias. We also confirmed potential birth through medical record review. Finally, we included several previously described predictors of birth defects in multivariable analyses. Our data thus provide good evidence that exposure to the study antibiotics is not associated to a material degree with common birth defects.

Our study also included large numbers of racial minorities and low-income persons, populations of women and infants that have been understudied previously and are particularly less likely to participate in voluntary reporting studies.^{34–36} Thus, these populations have not been included in many previous studies of pregnancy-related medication exposures and birth defects.

Our study had some limitations. First, while the prescription data used in this study have been previously validated and shown to provide unbiased estimates of medication use in several populations,^{20, 37–39} we do not know whether or not the women in our study actually took the medications that were prescribed. In a previous study of pregnancy-related prescribing, many women filled repeated prescriptions for various medications throughout pregnancy, suggesting that filling is a reasonable indicator of taking the medication.¹⁸ In addition, it is possible that our birth defect algorithms failed to identify all birth defects occurring in infants whose mother took the medications of interest. For example, there may be a very small number of malformations that would become evident only after the first year of life. Extending the continuous enrollment requirement to capture all of these outcomes would potentially lead to a significant loss of power, however. In addition, failure to identify all birth defects would not be expected to be differential among the exposure groups in our study. While power to detect differences in malformations was adequate to detect a 2-fold increase in risk of any major congenital malformation, power for specific organ systems and specific malformations was somewhat lower. In addition, our grouping of defects by organ system using study definitions from the Metropolitan Atlanta Congenital Defects Program could potentially mask associations for specific malformations.²⁴ Study power was not sufficient to allow comparisons for each malformation.

The study Medicaid population could introduce concerns about generalizability of study findings to the entire US population. However, in this study, which only involves medication use and possible birth defects, generalizability is less of an issue due to the fact that detection of birth defects should not be different among the Medicaid population than the US population in general. In addition, currently the Medicaid program covers 50% of births in Tennessee, and nationwide covers 30% of children.⁴⁰ Thus, the large numbers of women and their infants in our study represent an important proportion of the overall US population. Finally, the data sources used for this study do not include pregnancy losses occurring before 20 weeks post-conception. The inclusion of a cohort of women and infants with complete enrollment records reduced the size of our potential cohort, but at the same time facilitated complete ascertainment of exposures and outcomes.

In conclusion, these data suggest that the use of ciprofloxacin, azithromycin, doxycycline, or amoxicillin in the event of a bioterrorism attack in large populations of women, including pregnant women, should not result in a greater overall incidence of birth defects in infants whose mothers take these medications. However, because this study cannot rule out large increases in risk for the many types of specific birth defects, further study of specific congenital malformations is warranted.

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* Any use of Ciprofloxacin, Azithromycin or Doxycycline and a random sample of 50% of 44,836 women who took Amoxicillin during pregnancy, a random sample of 31,428 women who took Erythromycin during pregnancy, at a ratio of 5:1 to Ciprofloxacin users, and a random sample of 52,474 women who did not take any antibiotics during pregnancy, at a ratio of 5:1 to Ciprofloxacin users

FIGURE 1.
Cohort assembly.

FIGURE 2.

Adjusted proportions of infants with major congenital malformations, according to fetal exposure to antibiotics among infants born to mothers enrolled in the Tennessee Medicaid program, 1985–2000. Proportions are adjusted for potential confounders, including maternal age, race, presence of a chronic health condition in the mother, rural residence, income quartile, delivery in a hospital with a level III neonatal intensive care unit, and birth year. Estimation accounts for clustering due to multiple pregnancies and twins/triplets.

Distribution of maternal characteristics for study infants according to fetal exposure to antibiotics among infants born to mothers enrolled in the Tennessee Medicaid program, 1985–2000.

TABLE 1

	Any Ciprofloxacin	Any Azithromycin ^a	Doxycycline only ^b	Amoxicillin only ^b	Erythromycin only ^b	Multiple antibiotics	No antibiotics
N of infants	588	1459	1843	14534	2128	6097	3400
Maternal age at delivery, mean	23.2	21.6	22.6	22.6	22.0	22.2	23.1
Days of exposure during pregnancy, mean/median	8.4/7	3.5/2	9.6/10	11.9/10	11.1/10	--	--
Daily dose of study drug, mg, mean/median	952.2/1000	718.7/1000	194.5/200	1320.2/1500	1470.8/1500	--	--
Black race, %	46.3	68.1	63.2	41.4	54.5	50.6	56.4
Education 12 years, %	49.5	53.4	52.8	50.5	46.9	48.7	53.5
Prima gravida, %	19.0	27.0	18.4	24.8	24.3	23.7	22.9
Rural residence, % ^c	35.4	15.6	22.0	34.7	26.9	30.2	24.0
Lowest income quartile, %	22.9	30.2	33.2	22.0	29.9	27.9	28.6
Chronic illness, % ^d	25.5	19.8	19.3	20.9	20.2	23.3	15.3
Cardiovascular, %	2.4	1.3	1.7	1.7	1.4	1.8	1.1
Mental illness, %	7.8	4.7	5.0	5.6	4.7	6.2	2.8
Asthma, %	2.9	3.7	2.4	2.9	3.1	4.0	0.9
Late prenatal care, %	14.1	12.8	14.5	11.1	15.5	11.0	16.9
Smoking, %	35.2	17.8	25.1	30.4	29.7	30.5	25.6
Delivered in a hospital with level 3 neonatal intensive care, %	41.3	44.0	51.1	34.2	45.8	43.5	45.8

^aIn the absence of ciprofloxacin.

^bIn the absence of any other antibiotics

^cDefined as residence outside of Standard Metropolitan Statistical Area

^dThese include hypertension, epilepsy, sickle cell disease, asthma, renal disease, neoplastic disease, cardiovascular disease, HIV infection, cystic fibrosis, autoimmune diseases, cerebrovascular disease, chronic mental illness, diagnosed obesity, migraine headaches, Crohn's disease, ulcerative colitis, and organ transplant.

Risk^a of major congenital malformations among study infants, according to fetal antibiotic exposure during the first 4 lunar months among infants born to mothers enrolled in the Tennessee Medicaid program, 1985–2000.

TABLE 2

		Ciprofloxacin in first four lunar months	Azithromycin in first four lunar months, no ciprofloxacin	Doxycycline in first four lunar months and no other antibiotics	Amoxicillin in first four lunar months and no other antibiotics	Erythromycin in first four lunar months and no other antibiotics	Multiple antibiotics in first four lunar months	No antibiotics in first four lunar months
N infants		439	559	1691	7216	903	1988	3400
Any malformation	N	8	23	42	232	23	75	102
	RR ^a	0.64	1.37	0.85	1.09	0.86	1.29	1
	95% CI	[0.31, 1.30]	[0.85, 2.22]	[0.59, 1.23]	[0.86, 1.37]	[0.55, 1.34]	[0.96, 1.73]	reference
Cardiac^b	N	3	7	15	89	9	14	37
	RR	0.70	1.13	0.86	1.15	0.93	0.67	1
	95% CI	[0.22, 2.26]	[0.50, 2.55]	[0.47, 1.57]	[0.79, 1.68]	[0.45, 1.91]	[0.37, 1.24]	reference
Musculoskeletal	N	0	8	12	52	5	20	26
	RR	--	1.58	0.94	1.05	0.79	1.45	1
	95% CI	--	[0.61, 4.10]	[0.47, 1.88]	[0.66, 1.69]	[0.30, 2.06]	[0.81, 2.60]	reference
Genitourinary	N	2	4	4	52	7	16	17
	RR	0.80	1.34	0.45	1.38	1.42	1.47	1
	95% CI	[0.19, 3.40]	[0.44, 4.03]	[0.15, 1.34]	[0.78, 2.43]	[0.58, 3.44]	[0.74, 2.94]	reference
Gastrointestinal	N	2	4	3	26	0	14	18
	RR	0.78	1.57	0.35	0.63	--	1.29	1
	95% CI	[0.18, 3.48]	[0.52, 4.75]	[0.10, 1.20]	[0.35, 1.16]	--	[0.61, 2.71]	reference
Central nervous system^c	N	0	1	4	23	1	9	10
	RR	--	0.81	0.87	1.08	0.37	1.62	1
	95% CI	--	[0.10, 6.27]	[0.27, 2.78]	[0.50, 2.32]	[0.05, 2.94]	[0.65, 4.07]	reference
Orofacial	N	1	2	5	15	0	6	4
	RR	1.72	4.85	2.96	1.67	--	2.92	1
	95% CI	[0.18, 16.55]	[0.88, 26.60]	[0.75, 11.67]	[0.56, 5.04]	--	[0.86, 9.93]	reference

^aExpressed as risk ratios and 95% confidence intervals adjusted for potential confounders. Models include: maternal age, race, presence of a chronic health condition in the mother, rural residence, income quartile, and birth year. Estimation accounts for clustering due to multiple pregnancies and twins/triplets.

^bInfants with multiple congenital malformations were included in the analyses for each of the individual malformations.

^cDid not account for clustering from multiple pregnancies and twins/triplets.

Risk^a of major congenital malformations among study infants, according to fetal exposure to antibiotics at any time during pregnancy among infants born to mothers enrolled in the Tennessee Medicaid program, 1985–2000.

TABLE 3

		Any Ciprofloxacin	Any Azithromycin ^b	Doxycycline only ^c	Amoxicillin only ^c	Erythromycin only ^c	Multiple antibiotics	No antibiotics
N of infants		588	1459	1843	14534	2128	6097	3400
Any malformation	N	16	46	46	426	55	178	102
	RR ^a	0.97	1.00	0.84	0.99	0.86	0.98	1
	95% CI	[0.58, 1.63]	[0.71, 1.42]	[0.59, 1.19]	[0.80, 1.23]	[0.62, 1.18]	[0.77, 1.24]	reference
Cardiac^d	N	6	13	17	168	23	40	37
	RR	1.04	0.77	0.87	1.06	0.99	0.60	1
	95% CI	[0.44, 2.43]	[0.41, 1.44]	[0.49, 1.53]	[0.74, 1.51]	[0.59, 1.65]	[0.39, 0.94]	reference
Musculoskeletal	N	2	14	13	90	12	50	26
	RR	0.54	0.86	0.89	0.84	0.73	1.08	1
	95% CI	[0.13, 2.27]	[0.43, 1.75]	[0.45, 1.75]	[0.55, 1.31]	[0.37, 1.45]	[0.67, 1.75]	reference
Genitourinary	N	3	10	4	87	11	34	17
	RR	0.99	1.29	0.42	1.18	1.02	1.07	1
	95% CI	[2.29, 3.35]	[0.59, 2.84]	[0.14, 1.26]	[0.70, 2.00]	[0.48, 2.19]	[0.60, 1.93]	reference
Gastrointestinal	N	4	7	3	58	4	27	18
	RR	1.22	1.02	0.34	0.71	0.36	0.76	1
	95% CI	[0.41, 3.65]	[0.42, 2.45]	[0.10, 1.15]	[0.4, 1.20]	[0.12, 1.07]	[0.41, 1.41]	reference
Central nervous system^d	N	0	4	4	38	5	21	10
	RR	--	1.11	0.80	0.88	0.77	1.15	1
	95% CI	--	[0.34, 3.58]	[0.25, 2.88]	[0.43, 1.77]	[0.26, 2.26]	[0.54, 2.46]	reference
Orofacial	N	1	3	6	25	1	13	4
	RR	1.44	2.19	2.79	1.39	0.41	1.92	1
	95% CI	[0.16, 13.37]	[0.49, 9.67]	[0.77, 10.19]	[0.48, 4.01]	[0.05, 3.65]	[0.64, 5.82]	reference

^aExpressed as risk ratios (RR) and 95% confidence intervals (CI) adjusted for potential confounders. Models include: maternal age, race, presence of a chronic health condition in the mother, rural residence, income quartile, filling of prescriptions for other known teratogens, and birth year. Estimation accounts for clustering due to multiple pregnancies and twins/triplets.

^bIn the absence of ciprofloxacin;

^cIn the absence of any other antibiotics

^dInfants with multiple congenital malformations were included in the analyses for each of the individual malformations.

^eDid not account for clustering from multiple pregnancies and twins/triplets.