OBSTETRICS

In utero exposure to antibiotics and risk of congenital malformations: a population-based study

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BACKGROUND: Antibiotics are commonly prescribed during pregnancy. Although the safety of most penicillins is well established, some controversy and uncertainty are associated with the use of other commonly prescribed antibiotics.

OBJECTIVE: To determine the risk of congenital malformations following first-trimester in utero exposure to 10 commonly prescribed antibiotics in Denmark.

MATERIALS AND METHODS: This was a cohort study comprising all singleton liveborn children in Denmark between 2000 and 2015. Data on malformations were collected through 2016. Merging validated and comprehensive populationwide Danish healthcare and civic registries, we merged data on pregnancy, prescription drugs purchases during first trimester and congenital malformations. Using logistic regression, we calculated the odds ratio for congenital malformations (any), major congenital malformations, and cardiac congenital malformations for the 10 most commonly prescribed antibiotics (excluding 4 penicillins that served as control). In the primary analysis, the exposed cohort was compared to a cohort exposed to any of 4 penicillins considered safe during pregnancy (ampicillin, pivampicillin, benzylpenicillin, and phenoxymethylpenicillin). In sensitivity analysis, the exposed cohort was compared to an unexposed cohort. Covariate adjustments were made for maternal age at delivery, year of delivery, parity, pre-pregnancy body mass index, smoking, educational status, employment status, and annual personal income.

RESULTS: We found no increased risk of congenital malformations to be related to first-trimester in utero exposure to the 10 most commonly prescribed antibiotics in Denmark compared to a cohort of pregnant women exposed to penicillins that are considered safe during pregnancy. Compared to unexposed pregnancies, small increased risks for major malformations and cardiac malformations were apparent for pivmecillinam (odds ratio, 1.13; confidence interval, 1.06—1.19; and odds ratio, 1.15; confidence interval, 1.04—1.28, respectively), sulfamethizole (odds ratio, 1.15; confidence interval, 1.07—1.24; and odds ratio, 1.22; confidence interval, 1.07—1.39, respectively), and azithromycin (odds ratio, 1.19, confidence interval, 1.03—1.38; and odds ratio, 1.29, confidence interval, 0.99—1.67, respectively).

CONCLUSION: In this large populationwide cohort study, we found, with a high degree of precision, no increased risk of congenital malformations following first-trimester exposure to 10 commonly prescribed systemic antibiotics.

Key words: antibiotics, congenital malformations, pregnancy

The use of drugs during pregnancy poses unique challenges to the treating physicians and their patients. Concerns of possible adverse effects to the unborn child, notably the risk of congenital malformations and miscarriage, are rarely resolved by consulting various decision support systems. A common recommendation is "*should only be used if the benefits of [drug name] outweigh the potential risks to the unborn child.*" This is a trivial statement rather than clinically helpful advice. The 2014 revised US Food and Drug Administration (FDA) pregnancy categorization has yet to prove its value in everyday clinical decision support, but there are some reservations already. Based on responses to a survey using clinical vignettes, physicians appeared less likely to prescribe category "B" and "C" drugs upon removal of the FDA pregnancy categories A, B, C, and D.[1,2]

Antibiotics are among the drugs most commonly prescribed during pregnancy, and the trend appears to be increasing worldwide.[3–5] Although many penicillins are generally considered safe during pregnancy, data on potential risk of congenital malformations for other commonly prescribed antibiotics require further study.[6–10] Erythromycin is surrounded by some controversy pertaining to a possible increased risk of cardiac malformations.[11–16] The amount of safety data on pivmecillinam, some macrolides, and cephalosporins remain insufficient to support clinical decisions.

To quantify the risk of congenital malformations related to first-trimester in utero exposure to commonly prescribed antibiotics, we performed a populationwide pharmacoepidemiological cohort study using the comprehensive and validated Danish healthcare registries.

Material and Methods

Source population

We included all liveborn singleton deliveries in Denmark between January 1, 2000, and December 31, 2015.

Data sources and data linking

Data are obtained from 4 different Danish national registers linked at an individual level through the Danish unique personal 10-digit identification number, which enables linkage across registers.[17]

Registry of Medicinal Product Statistics

The Registry of Medicinal Product Statistics (RMPS) contains information about all prescription sales in Danish pharmacies, as well as the person's CPR

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AJOG at a Glance

Why was this study conducted?

The safety of several commonly prescribed antibiotics in pregnancy is insufficiently studied, and for some antibiotics, results are conflicting. The ensuing decision support to patients and prescribers is unsatisfactory.

Key findings

In a national cohort study from 2000 to 2015 covering 932,731 live-born children, we found no increased risk of congenital malformations for 10 commonly prescribed antibiotics during first-trimester pregnancy in our primary analysis. We compared exposure to controls exposed to penicillins regarded as safe during pregnancy (primary analysis) and to unexposed controls (secondary analysis). Confounder adjustments were made for maternal age, year of delivery, body mass index, parity, smoking, and socioeconomic status.

What does this add to what is known?

With these findings, we provide substantial and reassuring decision support to patients and prescribers for use of several antibiotics in pregnancy. We present, by far, the largest amount of pregnancy safety data on dicloxacillin, ciprofloxacin, sulfamethizole, roxithromycin, azithromycin, and doxycycline.

number and date of redemption.[18] We used the RMPS to identify the pregnant women's prescription redemptions of antibiotics within the first trimester. The RMPS does not include information about over-the-counter drugs or information on the underlying indication.

Danish Medicinal Birth Registry

The Danish Medicinal Birth Registry (DMBR) contains information about deliveries in Denmark.[19] We identified the relevant exposure window for each pregnancy, parity, pre-pregnancy body mass index (BMI), smoking during pregnancy, and pregnancy outcome. Malformation data from the DMBR are merged with children's records from the Danish National Patient Registry.

Danish National Patient Registry

The Danish National Patient Registry (DNPR) carries comprehensive and complete populationwide information on hospital-assigned medical diagnoses (10th version of the International Statistical Classification of Diseases and Related Health Problems [ICD-10]) and treatments of all Danish citizens.[20] We identified the congenital malformations in offspring within the first year of life according to the classification system of European Surveillance of Congenital Anomalies (EUROCAT).[21]

Danish Civil Registration system

The Danish Civil Registration system (CRS) contains administrative information on all Danes who have lived in Denmark since April 1968.[17] From the CRS, we confirmed residency in Denmark for least 2 years before delivery.

Study population

We restricted the study population to singleton pregnancies resulting in a live birth of an infant without chromosomal abnormalities registered in the MBR within 12 months after delivery (ICD-10 [International Classification of Diseases 10th Revision] codes Q90-99 [Chromosomal abnormalities, not elsewhere classified]). We restricted the study population to pregnancies among women residing in Denmark continuously for at least 2 years prior to their delivery. Multiple pregnancies were excluded to ensure only 1 event per exposure for the analysis. We excluded pregnancies with missing information on gestational age. We also excluded women exposed to any of the following drugs and drug classes, for which there is evidence of teratogenic effects: retinoids, angiotensin-converting enzyme inhibitors, vitamin K antagonists, valproic acid, lithium, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, or methotrexate.

Exposure and study cohorts

We defined exposure to antibiotics as the filling of a prescription for a systemic anti-infective drug at a Danish pharmacy within the first trimester. Systemic anti-infective drugs were defined using the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System code J01.[22] The first trimester of pregnancy was defined as the first 90 days from the first day of the last menstrual period, calculated either at the first trimester ultrasound scan offered to all women as part of the Danish antenatal program, or by actual date known to the mother. If the woman did not participate in the ultrasound screening, the delivery date was determined as 280 days after the first day of her last menstrual period. All included pregnancies were split in 3 cohorts: (1) an exposed cohort, (2) a primary comparison cohort exposed to penicillins, and (3) an unexposed cohort. The exposed cohort, which comprised the primary comparison cohort, included all women who had filled a prescription for an antibiotic with the ATC code J01, except for the 4 penicillins (ampicillin, pivampicillin, benzylpenicillinm and phenoxymethylpenicillin).

The primary comparison cohort comprised women who had filled a prescription only for any of the following specific penicillins: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin). These penicillins are considered to be safe with respect to congenital malformations, and this comparison cohort was constructed to minimize an underlying effect of disease. A secondary comparison group consisted of women who did not fill any drug prescriptions during pregnancy.

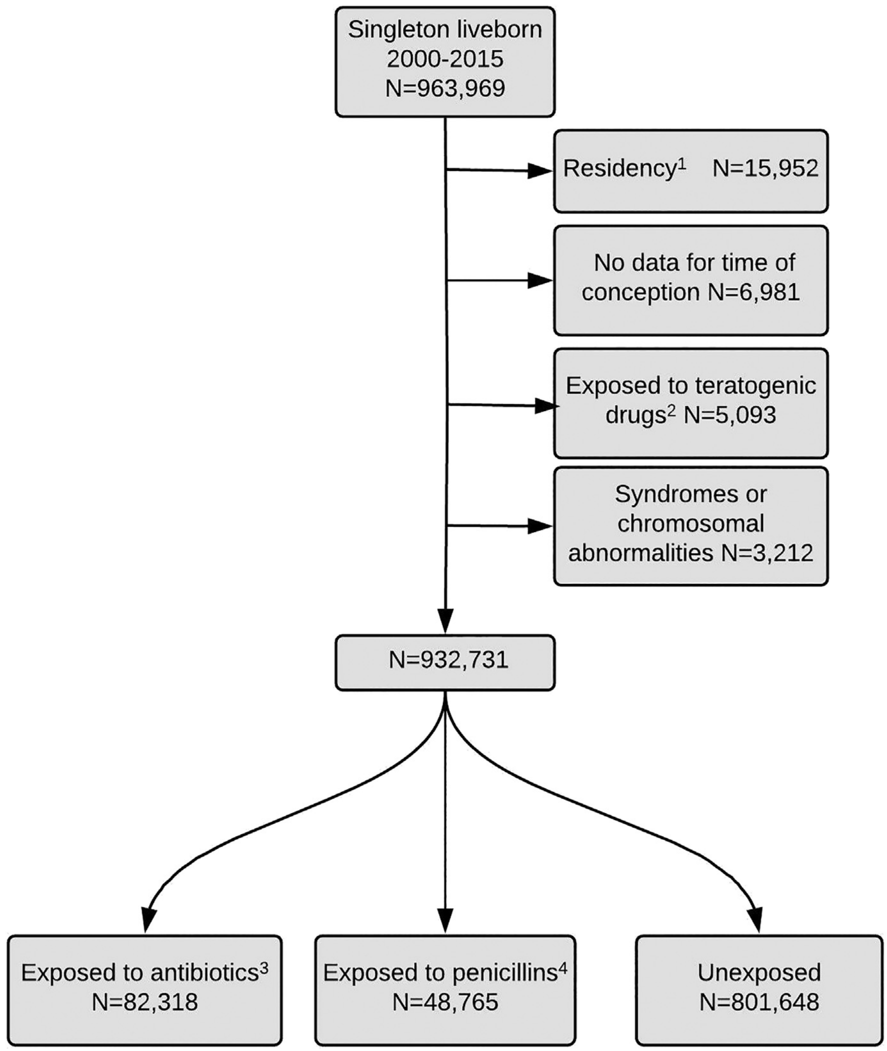
Malformation outcomes

We stratified congenital malformations into 3 groups: (1) all malformations (without syndromes and generic abnormalities), (2) major congenital malformations (MCM), and (3) cardiovascular malformations. Stratification was made based on the European Surveillance of Congenital Anomalies coding system (EUROCAT). Malformations were identified in the DNPR and DMBR where malformations are coded based on the EUROCAT guide 1.4.[21]

Covariates

Covariates included were age at conception (<20, 21–24, 25–29, 30–34, 35–39, and 40+ years), calendar year of conception, parity, smoking status (nonsmoker, light smoker, heavy smoker), prepregnancy BMI measured at the first antenatal visit (<18, 18–24, 25–29, 30–34, 35+), level of mother's education at delivery (7–10 years, 11–12 years, 13+ years, vocational training), employment status (unemployed, student, employed, self-employed), and annual income (<100,000 (∼$15,000), 100,000–200,000 (∼$30,000), 200,000–400,000 (∼$60,000), and 400,000+ Danish Kroner).

FIGURE 1
Study cohort selection tree



[1]Not resident in Denmark within 2 years prior to delivery. [2]Retinoids, angiotensin-converting enzyme inhibitor, vitamin K antagonists, valproic acid, lithium, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, or methotrexate. [3]Any systemic J01 antibiotic excluding J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin. [4]J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin.

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Statistical analyses

Descriptive analyses were performed for all deliveries registered in the DMBR. Using logistic regression models, we calculated the crude odds ratio (OR) and adjusted odds ratio (aOR), with 95% confidence intervals (95% CI) associating exposure to commonly prescribed systemic antibiotics with malformations. To address the issue of confounding by indication, our primary analysis compared the risk of congenital malformations among the exposed pregnancies to a cohort exposed to any of 4 penicillins (ampicillin, pivampicillin, benzylpenicillin, and phenoxymethylpenicillin) that are considered to be safe for use during pregnancy. All analyses were repeated with pregnancies unexposed to systemic antibiotics as a reference group. In the adjusted analyses, we adjusted for year of delivery, mother's age at delivery, income, employment status, level of education, parity, smoking, and BMI. We applied 2 different adjustment models: $aOR_{partial}$, adjusted only for the age at delivery and the year of delivery, and fully adjusted aOR_{full}, adjusted for all covariates above.

Ethics

According to Danish law, ethical approval is not required for studies based on anonymized register data.

Results

We identified a total of 963,969 singleton deliveries from January 2000 through December 2015. We excluded 31,238 due to residence criteria, missing gestational data, deliveries resulting in a diagnosed syndrome, or exposure to known teratogenic drugs during the first trimester. The final cohorts yielded 82,318 women who filled a prescription for a J01 antibiotic outside the 4 control penicillins: 48,765 in the primary control cohort of women who filled a prescription for any of 4 penicillins in the first

TABLE 1
Cohort characteristics

	Exposed to study antibiotics[a] (n = 82,318)	Exposed to reference penicillins[b] (n = 48,765)	Unexposed (n = 801,648)
Age, mean (SD)	29.4 (5.2)	30.1 (4.9)	30.2 (4.9)
Mother's education			
Low: 7–10 y	8387 (10%)	4141 (8%)	49,045 (6%)
Medium: 11–12 y	16,024 (19%)	9613 (20%)	163,897 (20%)
High: 13+ y	24,990 (30%)	16,329 (33%)	310,264 (39%)
Vocational training	22,781 (28%)	13,533 (28%)	184,201 (23%)
No information	10,136 (12%)	5149 (11%)	94,241 (12%)
Mother's employment			
Unemployed	16,839 (20%)	8968 (18%)	121,112 (15%)
Student	4749 (6%)	1999 (4%)	39,748 (5%)
Employed	52,789 (64%)	32,553 (67%)	549,843 (69%)
Self-employed	1287 (2%)	787 (2%)	14,593 (2%)
No information	6654 (8%)	4458 (9%)	76,352 (10%)
Mother's annual income in Danish Kroner			
<100,000	15,556 (19%)	6789 (14%)	128,194 (16%)
100,000–200,000	41,909 (51%)	26,395 (54%)	394,841 (49%)
200,000–400,000	17,689 (21%)	10,799 (22%)	196,246 (24%)
400,000+	510 (1%)	324 (1%)	6015 (1%)
No information	6654 (8%)	4458 (9%)	76,352 (10%)
Pre-pregnancy BMI			
<18 Underweight	980 (1%)	487 (1%)	8,410 (1%)
18–24 Normal weight	34,686 (42%)	18,706 (38%)	350,204 (44%)
25–29 Overweight	14,759 (18%)	8567 (18%)	133,036 (17%)
30–34 Obese class I	5981 (7%)	3657 (7%)	46,262 (6%)
35+ Obese class II and III	4107 (5%)	2561 (5%)	27,505 (3%)
No information	21,805 (26%)	14,787 (30%)	236,231 (29%)
Parity			
Primipara	38,793 (47%)	15,804 (32%)	360,879 (45%)
Multipara	43,525 (53%)	32,961 (68%)	440,769 (55%)
Smoking status			
Nonsmoker	64,263 (78%)	37,847 (78%)	663,850 (83%)
Light smoker, 1–10	11,665 (14%)	6839 (14%)	87,742 (11%)
Heavy smoker, 11+	4236 (5%)	2687 (6%)	27,454 (3%)
No information	2154 (3%)	1392 (3%)	22,602 (3%)

BMI, body mass index.

[a] Any systemic J01 antibiotic except reference penicillins; [b] J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin).

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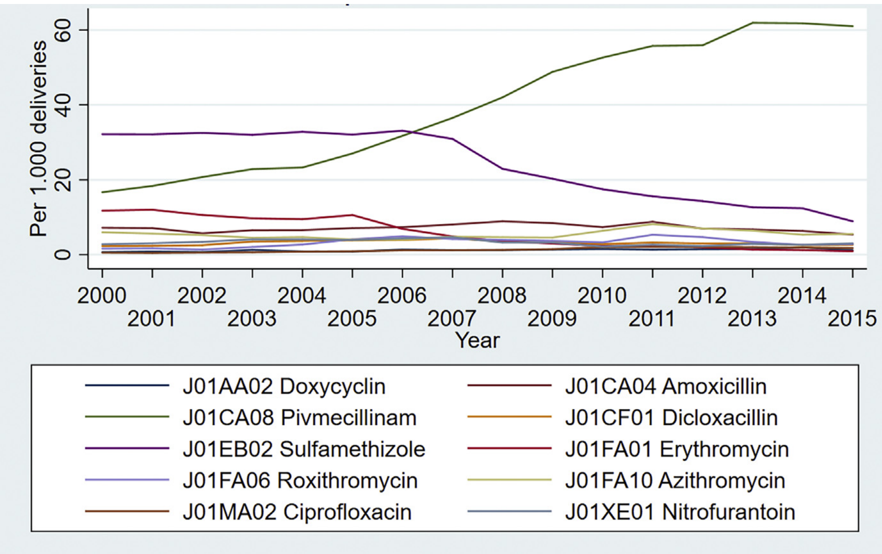
FIGURE 2
Use pattern of 10 antibiotics commonly prescribed in the first trimester from 2000 to 2015



The 4 systemic antibiotics most commonly prescribed in the first trimester, excluding comparator penicillins, are J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin).

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trimester, and an unexposed cohort of 801,648 women who did not fill a prescription for a J01 drug (Figure 1). In all, 7531 (9.1%) were exposed to more than one J01 study drug during the first trimester (data not shown). These patients were included in our analysis.

Demographic and other socioeconomic characteristics are presented in Table 1. These characteristics appear to be comparable across the 3 cohorts. Concomitant medication characteristics are presented in Supplementary Table 1. Overall, a tendency to have filled more prescriptions outside of the J01 ATC group is, not surprisingly, apparent for the 2 cohorts comprising the exposure cohort and the primary control cohort. The most obvious difference lies within the respiratory drug group (ATC group R), which makes sense, as having respiratory disease increases the risk of a bacterial upper-airway infection requiring systemic antibiotic treatment.

The pattern of use of the 10 most commonly filled prescriptions for antibiotics (doxycycline, amoxicillin, pivmecillinam, dicloxacillin, sulfamethizole, erythromycin, roxithromycin, azithromycin, ciprofloxacin, and nitrofurantoin) outside the comparator group throughout the period is illustrated in Figure 2. Individually, the use of pivmecillinam increased substantially from about 2004, coinciding with a marked decrease in filled prescriptions for sulfamethizole from about 2006. Period patterns of filled prescriptions for grouped antibiotics and the individual comparator penicillins are illustrated in Supplementary Figure 1 and 2, respectively. Filled prescriptions per 1000 deliveries appear to be generally stable throughout the period for the summarized groups.

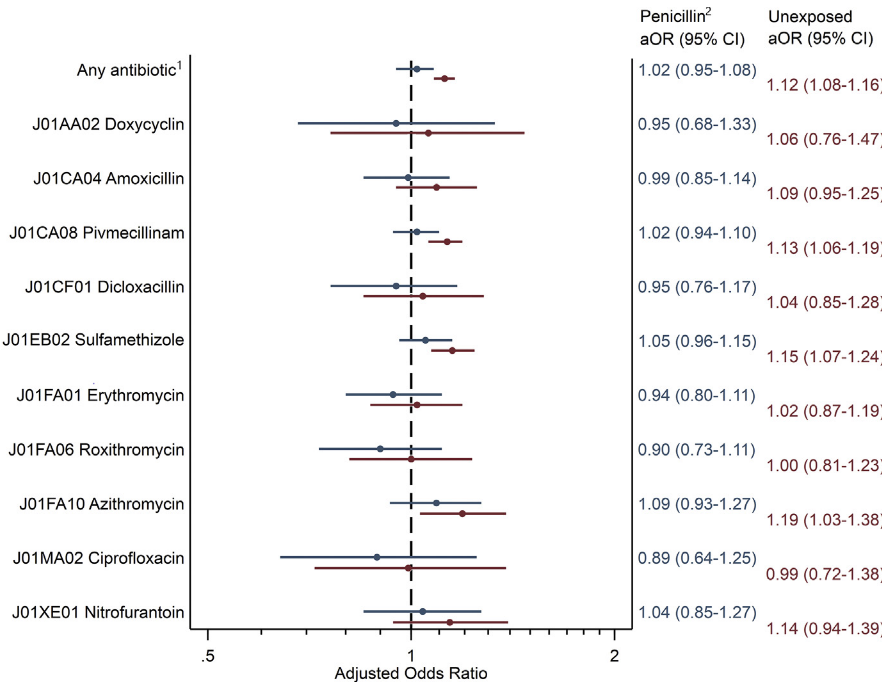
Inferential analysis did not identify any association between exposure and any of the 3 outcomes (major congenital malformations [MCM], cardiac malformation, and any malformation), compared to the primary control cohort (penicillin group) in the fully adjusted model. Compared to unexposed pregnancies, small increased risks for major malformations and cardiac malformations were apparent for pivmecillinam (odds ratio [OR], 1.13; confidence interval [CI], 1.06–1.19; and OR, 1.15; CI, 1.04–1.28, respectively); sulfamethizole (OR, 1.15; CI, 1.07–1.24; and OR, 1.22; CI, 1.07–1.39, respectively); and azithromycin (OR, 1.19; CI, 1.03–1.38; and OR, 1.29; CI, 0.99–1.67, respectively), as illustrated by forest plots in Figure 3 and 4, respectively. A forest plot for any malformations is provided in Supplementary Figure 3, and all inferential analyses are summarized in Supplementary Tables 2, 3, and 4.

Comment

Main findings

In this populationwide cohort study, we did not find any clinically relevant associations between first trimester exposure to 10 commonly prescribed antibiotics and the risk of congenital malformations in our primary analysis when comparing with exposure to penicillins considered safe in pregnancy. In our secondary analysis, comparing to a control group not exposed to antibiotics, results were similar, with some small increased risk for pivmecillinam, sulfamethizole, and azithromycin. Our inferential point estimates generally come with narrow confidence intervals. This study contains the largest number reported of exposed pregnancies for several important antibiotics, notably dicloxacillin, ciprofloxacin, sulfamethizole, roxithromycin, azithromycin, and doxycycline. We believe that our data provide a substantial and reassuring contribution to support decisions for the treatment of pregnant women with infectious diseases in the first trimester. We document a change in the use pattern, as filled prescriptions for pivmecillinam have increased sharply, whereas filled prescriptions for sulfamethizole have declined substantially during the study period. This coincides with changes in national (and international) guidelines, specifically with respect to treatment of urinary tract infections.[23,24]

FIGURE 3
Ten antibiotics commonly prescribed in the first trimester, and risk of major congenital malformations



[1]Any systemic J01 antibiotic not including comparator penicillins. [2]Comparator penicillins: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin).

aOR, adjusted odds ratio; *CI*, confidence interval.

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Macrolides

Three macrolides, namely erythromycin, roxithromycin, and azithromycin, were among the most commonly filled prescriptions. Erythromycin has been surrounded with some controversy regarding use during pregnancy, as some earlier studies suggested an increased risk of cardiac malformations.[14,15,25,26] Other studies have failed to demonstrate such an association. In our study, with more than 5500 first-trimester exposed pregnancies, we did not find any association with cardiac malformations specifically or major malformations altogether. Current regulatory labeling in United States and Europe (EMA) states, "*There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed*" and "*There are no adequate and well-controlled studies in pregnant women. However, observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.*"[27,28] Our findings provide further substantiation of the overall reassuring data, and we believe that the regulatory authorities should consider a change to labeling accordingly. Our data for roxithromycin and azithromycin are by far the largest dataset yet reported. Neither drug was associated with an increased risk of major or cardiac malformations. We found no increased risk to be associated with first-trimester exposure to roxithromycin among 3027 first-trimester exposed pregnancies. Other data on roxithromycin are very scarce, as the previously largest study reported just 100 first-trimester exposed pregnancies.[16,29] Azithromycin data for 5037 exposed pregnancies, which are more than twice the safety data previously reported, confirm previous findings that this drug is safe or confers only minimal risk during first-trimester pregnancy.[14,16,30] Although we found a small excess risk of cardiac malformations when comparing exposed against nonexposed controls, this signal was not present in our primary analysis against an active comparator group. This suggest that the apparent signal detected when comparing against the nonexposed cohort is due to confounding.

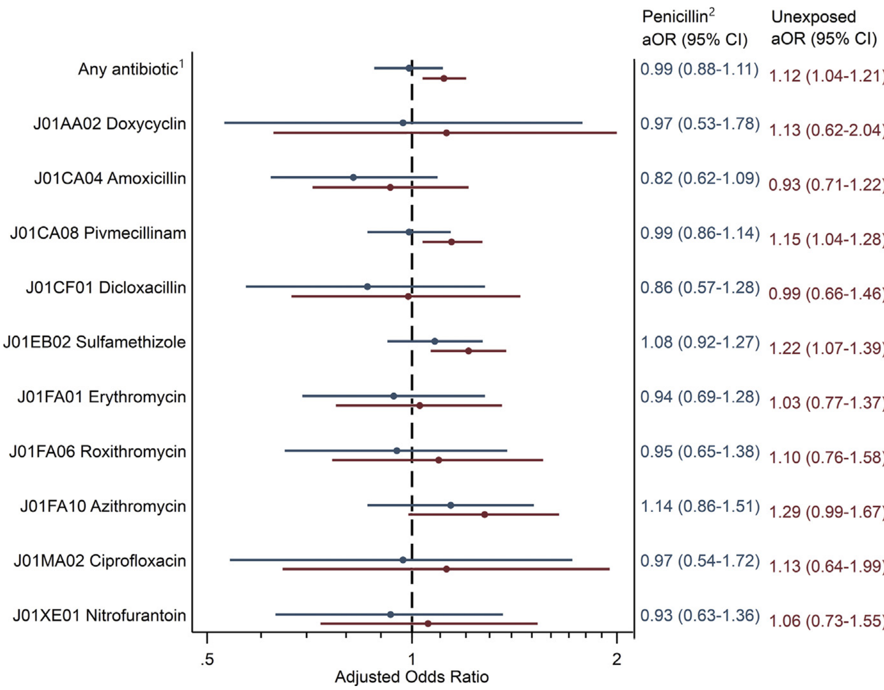
Broad-spectrum penicillins

Our findings on broad-spectrum dicloxacillin, amoxicillin, and pivmecillinam add reassuring evidence pertaining to safety during pregnancy. Our findings on more than 6500 first-trimester exposures to amoxicillin confirm the findings in a recent Canadian cohort, and we believe that amoxicillin should be considered safe during pregnancy.[4] Pivmecillinam holds indications for urinary tract infections, and with this large cohort study with more than 36,000 first-trimester—exposed infants, we believe that this drug can be used with confidence during pregnancy. No excess risk was apparent in our primary analysis against the active control group, but we did find a small increased risk of MCM and cardiac malformations in our secondary analysis against nonexposed controls. We believe that our study design substantiates that the latter finding is likely due to confounding by indication. The largest previous dataset reported was less than 600 first-trimester—exposed pregnancies.[31] For dicloxacillin, our dataset comprises the only pharmacoepidemiological data reported, and suggests that this drug can be used during first-trimester pregnancy as well.

Ciprofloxacin

We present the largest yet set of data comprising more than 1100 liveborn children exposed to ciprofloxacin in the first trimester. Our data do not suggest a clinically meaningful increased risk of congenital malformations, although the precision of our estimates for cardiac malformations is moderate. Quinolones

FIGURE 4
Ten antibiotics commonly prescribed in the first trimester, and risk of cardiac congenital malformations



[1]Any systemic J01 antibiotic not including comparator penicillins. [2]Comparator penicillins: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin).

aOR, adjusted odds ratio; *CI*, confidence interval.

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have a high affinity for connective tissues, including bone and cartilage, and there have been concerns with respect to musculoskeletal effects if exposed in utero.[12,32] Human epidemiological data do not substantiate this. Two recent reviews and meta-analyses agree that no increased risk is apparent, even if they agree that the amount of drug-specific data are insufficient to draw firm conclusions.[12,32] Specifically for ciprofloxacin, a recent dataset showed no increased risk among 608 pregnancies exposed to ciprofloxacin.[4] An observational cohort reported a slight increased risk of MCM (8 of 336 exposed) compared to that in women exposed to nonteratogenic drugs within a teratology information service setting.[33]

Nitrofurantoin

We found no increased risk of MCM among 3076 first-trimester—exposed newborns in the largest single dataset yet reported. The issue of nitrofurantoin and fetal risks has been subject to some controversy and discordant data. Some case-control studies suggest different associations with some rare and specific malformations. One case-control study reported an increased risk of anophthalmia or microphthalmia (aOR, 3.7; 95% CI, 1.1—12), hypoplastic left heart syndrome (aOR, 4.2; 95% CI, 1.9—9.1), atrial septal defects (aOR, 1.9; 95% CI, 1.1—3.4), and cleft lip with cleft palate (aOR, 2.1; 95% CI, 1.2—3.9).[34] Compared to penicillin exposure, nitrofurantoin use was associated with oral clefts in the offspring (aOR, 1.97; 95% CI, 1.1—3.5).[11] A case-control study from 2003 found associations between maternal drug use and infant cardiovascular defect, but this was probably due to confounding from underlying disease.[35] These case-control findings have all been disputed, and with clinical focus on overall risk of major malformations, and the larger cohort data do not support a true association.[4,36—38]

Sulfamethizole

We present by far the largest dataset on early pregnancy exposure to sulfamethizole available. No increased risk of major malformations was observed among 22,684 exposed liveborn children in our primary analysis against the control group exposed to penicillins that carry no risk of MCM. In our secondary analysis against nonexposed children, small increased risks were apparent for MCM and cardiac malformations. Again, our study design and analysis plan suggest that this is due to confounding. We confirm and substantiate previous findings. A large 2016 study based on US health-plan data reported that first-trimester trimethoprim—sulfamethizole exposure was not associated with a higher risk of several specific (including cardiac) congenital anomalies, compared with either exposure to penicillins and/or cephalosporins or no exposure to antibacterial drugs. Overall risk of malformations was not reported.[39]

Doxycycline

Our data comprising 1101 first-trimester—exposed pregnancies do not suggest that in utero exposure to doxycycline is associated with increased risk of MCM, although the precision of our estimate for cardiac malformations is moderate. This is in line with a 2016 review summarizing the evidence on about 2000 exposed liveborn children.[40] A small dataset (N = 164) published in 2017 supports these observations as well.[4]

Summary

This comprehensive and updated analysis of nationwide data does not suggest that first-trimester exposure to 10 commonly prescribed systemic antibiotics is associated with an increased risk of congenital malformations when compared to a control group exposed to penicillins that are considered not to carry any risk of MCM. In a secondary analysis, we found small increased risks of MCM (pivmecillinam and sulfamethizole) and cardiac malformations (pivmecillinam, sulfamethizole, and azithromycin) in exposed compared to nonexposed pregnancies. We believe that it is justifiable, based on our study design and analysis plan, that the latter findings are most likely due to confounding. Data comply with EMA regulatory guidelines suggesting a labeling "comparable with use during pregnancy" if at least 1000 first-trimester−exposed liveborn children do not suggest an increased risk of congenital malformations.[41] Hence, we provide substantial and reassuring clinical decision support, and we suggest that drug labeling be updated accordingly.

Study strengths

We report updated nationwide data from comprehensive, complete, and validated registries on prescription drugs and pregnancy outcome, which eliminate recall bias. By using an active comparator group, namely, one exposed to penicillins that are considered safe to use during pregnancy, we have addressed confounding by indication to a substantial extent. The available information allows for the most important covariate adjustments such as age, parity, BMI, smoking, and socioeconomic status.

Study limitations

We have adopted a "lumping" approach, that is, pooling all specific malformations while stratifying only by major, all, and cardiac malformations. We clearly believe this to be the most informative knowledge in clinical decision support for the treating physician as well as for the pregnant woman. Lumping allows for a better overall and clinically relevant picture with high precision estimates while sacrificing proportions of the underlying biological rationale. There are valid arguments to be made for a "splitting" approach, that is, assessing many or all individual specific malformations, for example, cleft palate, ventricular septal defect, and unilateral clubfoot. Such an approach may be mechanistically more sound but carries a substantial inherent risk of false-positive and false-negative findings, both of which may have severe consequences to the pregnant women.[42−45]

We use filled prescriptions as a proxy for exposure. Although commonly accepted within pharmacoepidemiology, the assumption that filled prescription equals actual ingestion of the drug by the pregnant woman is not well substantiated. Our data are based on prescriptions that are filled and bought by the patient at the pharmacy, which indicates a certain level of motivation for adherence. For systemic antibiotics, both a high (prospective patient reporting, New Mexico) and an unimpressive (retrospective patient reporting, Norway) concordance between register-based and patient-based information on drug exposure have been reported.[46,47]

We cannot account for specific underlying diagnoses, as these are not available from general practitioners' prescriptions in the Danish registries. This means that while using an active comparator group exposed to safe penicillins, women prescribed other antibiotics may suffer from more severe infections. Consequently, there may be residual confounding by indication that elude our analysis. Some of the important covariates in our dataset are not complete, notably pre-pregnancy BMI, which has missing values for about 26−30%.

Implications

Our findings are reassuring, as we found no increased risk of MCM for 10 antibiotics commonly prescribed compared to that in a control group exposed to penicillins carrying no risk of MCM. Our findings offer strong and immediate clinical decision support for the use of these antibiotics during first-trimester pregnancy to treating physicians and patients.

Future research

Future research should focus on other aspects of pregnancy outcomes, such as miscarriage, preterm birth, small for gestational age, and, for the individual antibiotic exposure, should address specific malformations. ■

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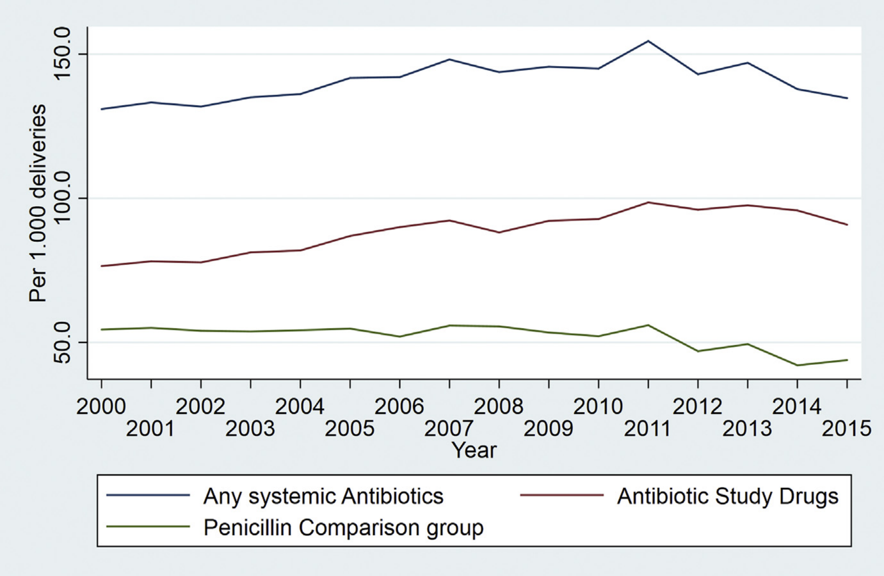
SUPPLEMENTARY FIGURE 1

Use pattern of antibiotics commonly prescribed from 2000 to 2015



[1]Any systemic antibiotic: ATC code J01. [2]Antibiotic study drugs: J01 antibiotics excluding penicillin comparison. [3]Penicillin comparison group: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin).

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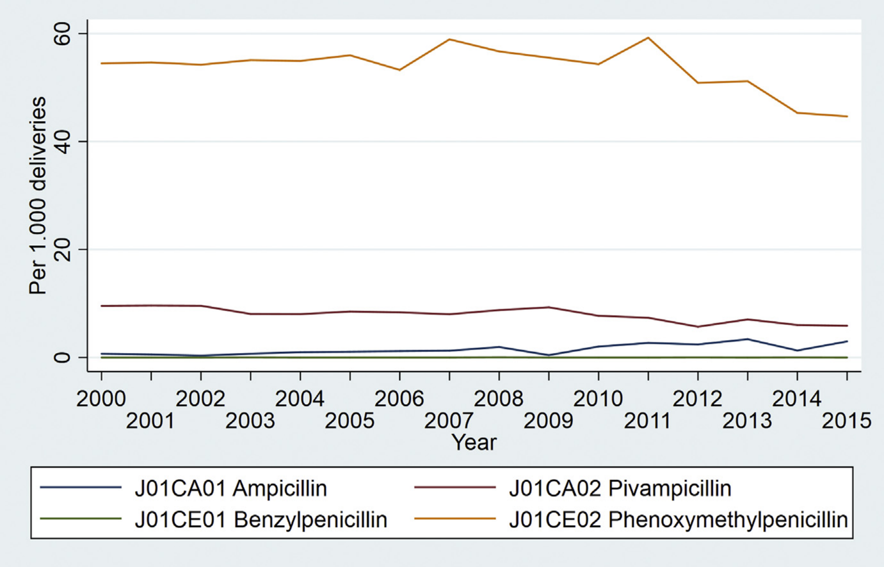
SUPPLEMENTARY FIGURE 2

Use pattern of 4 comparator penicillins prescribed in the first trimester from 2000 to 2015



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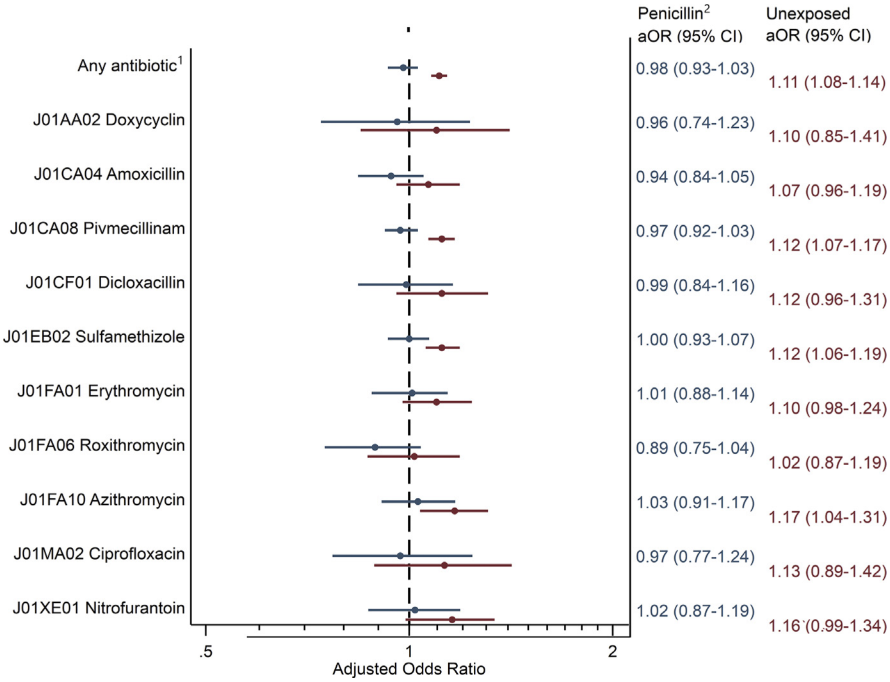
SUPPLEMENTARY FIGURE 3

Ten antibiotics commonly prescribed in the first trimester, and overall risk of congenital malformations



[1]Any systemic J01 antibiotic not including comparator penicillins. [2]Comparator penicillins: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin), and J01CE02 (phenoxymethylpenicillin).

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SUPPLEMENTARY TABLE 1
Concomitant drug exposure by ATC codes

	Exposed to study antibiotics[a] (n = 82,318)	Exposed to reference penicillins[b] (n = 48,765)	Unexposed (n = 801,648)
Any drug (other than J01)	45,820 (56%)	27,535 (56%)	340,129 (42%)
ATC group A	9705 (12%)	4829 (10%)	56,056 (7%)
ATC group B	1795 (2%)	1016 (2%)	13,493 (2%)
ATC group C	2102 (3%)	1230 (3%)	14,636 (2%)
ATC group D	12,460 (15%)	6579 (13%)	78,164 (10%)
ATC group G	16,448 (20%)	9269 (19%)	132,782 (17%)
ATC group H	2764 (3%)	1588 (3%)	24,573 (3%)
ATC group J (not J01)	2680 (3%)	1408 (3%)	13,442 (2%)
ATC group L	566 (1%)	455 (1%)	5723 (1%)
ATC group M	3939 (5%)	3194 (7%)	20,067 (3%)
ATC group N	6388 (8%)	3680 (8%)	37,413 (5%)
ATC group P	1824 (2%)	1040 (2%)	5456 (1%)
ATC group R	8,184 (10%)	6148 (13%)	48,123 (6%)
ATC group S	5439 (7%)	3953 (8%)	40,621 (5%)
ATC group V	119 (0%)	68 (0%)	972 (0%)

[a] Any systemic J01 antibiotic but reference penicillins; [b] J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin) and J01CE02 (phenoxymethylpenicillin).

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SUPPLEMENTARY TABLE 2
Inferential statistical analysis for any malformation

		Comparator: penicillin[a] exposed (n = 48,765)			Comparator: unexposed (n = 801,648)		
Antibiotic	n (Malformations)	OR_{crude}	$aOR_{partial}$[b]	aOR_{full}[c]	OR_{crude}	$aOR_{partial}$[b]	aOR_{full}[c]
Doxycyclin	1101 (66)	1.05 (0.81—1.34)	0.98 (0.76—1.26)	0.96 (0.74—1.23)	1.15 (0.89—1.47)	1.10 (0.86—1.41)	1.10 (0.85—1.41)
Amoxicillin	6679 (366)	0.95 (0.85—1.06)	0.94 (0.84—1.05)	0.94 (0.84—1.05)	1.04 (0.94—1.16)	1.04 (0.94—1.16)	1.07 (0.96—1.19)
Pivmecillinam	36,423 (2,291)	1.10 (1.04—1.16)	0.99 (0.93—1.05)	0.97 (0.92—1.03)	1.21 (1.16—1.26)	1.12 (1.07—1.17)	1.12 (1.07—1.17)
Dicloxacillin	2946 (170)	1.00 (0.86—1.18)	0.99 (0.85—1.17)	0.99 (0.84—1.16)	1.10 (0.94—1.29)	1.10 (0.94—1.29)	1.12 (0.96—1.31)
Sulfamethizole	22,684 (1246)	0.95 (0.89—1.02)	1.02 (0.95—1.09)	1.00 (0.93—1.07)	1.05 (0.99—1.11)	1.11 (1.05—1.18)	1.12 (1.06—1.19)
Erythromycin	5563 (283)	0.88 (0.77—1.00)	1.02 (0.89—1.15)	1.01 (0.88—1.14)	0.96 (0.86—1.09)	1.09 (0.97—1.23)	1.10 (0.98—1.24)
Roxithromycin	3027 (163)	0.93 (0.79—1.10)	0.89 (0.75—1.04)	0.89 (0.75—1.04)	1.02 (0.87—1.20)	0.99 (0.85—1.16)	1.02 (0.87—1.19)
Azithromycin	5037 (311)	1.08 (0.96—1.22)	1.04 (0.92—1.18)	1.03 (0.91—1.17)	1.18 (1.06—1.33)	1.16 (1.03—1.30)	1.17 (1.04—1.31)
Ciprofloxacin	1180 (75)	1.11 (0.88—1.41)	1.00 (0.79—1.27)	0.97 (0.77—1.24)	1.22 (0.97—1.54)	1.13 (0.89—1.43)	1.13 (0.89—1.42)
Nitrofurantoin	3076 (182)	1.03 (0.88—1.20)	1.04 (0.89—1.21)	1.02 (0.87—1.19)	1.13 (0.97—1.32)	1.15 (0.99—1.34)	1.16 (0.99—1.34)

Note: A patient can be exposed to more groups, and can even be exposed to study antibiotics not listed in the tabulation. The number of patients exposed to more than one J01 study group was 7531 (9.1%). Of these, 6966 (8.5%) were exposed to 2 study drugs, and 565 (.7%) were exposed to 3 or more study drugs.

aOR, adjusted odds ratio; *OR,* odds ratio.

[a] Exposed to ampicillin, pivampicillin, benzylpenicillin, or phenoxymethylpenicillin; [b] Adjusted for maternal age at delivery and year of delivery; [c] Adjusted for maternal age at delivery, year of delivery, parity, pre-pregnancy body mass index, smoking, educational status, employment status, and income.

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SUPPLEMENTARY TABLE 3

Inferential statistical analysis for major malformations

Antibiotic	n (Malformations)	Comparator: penicillin[a] exposed (n = 48,765)			Comparator: unexposed (n = 801,648)		
		OR_{crude}	$aOR_{partial}$[b]	aOR_{full}[c]	OR_{crude}	$aOR_{partial}$[b]	aOR_{full}[c]
Doxycyclin	1101 (36)	0.99 (0.71—1.39)	0.96 (0.69—1.35)	0.95 (0.68—1.33)	1.08 (0.77—1.50)	1.06 (0.76—1.47)	1.06 (0.76—1.47)
Amoxicillin	6679 (218)	0.99 (0.86—1.15)	0.99 (0.86—1.14)	0.99 (0.85—1.14)	1.08 (0.94—1.23)	1.08 (0.94—1.23)	1.09 (0.95—1.25)
Pivmecillinam	36,423 (1,286)	1.08 (1.00—1.16)	1.02 (0.95—1.10)	1.02 (0.94—1.10)	1.17 (1.10—1.24)	1.12 (1.06—1.19)	1.13 (1.06—1.19)
Dicloxacillin	2946 (92)	0.95 (0.77—1.17)	0.94 (0.76—1.17)	0.95 (0.76—1.17)	1.03 (0.84—1.27)	1.03 (0.84—1.27)	1.04 (0.85—1.28)
Sulfamethizole	22,684 (763)	1.02 (0.94—1.12)	1.06 (0.97—1.16)	1.05 (0.96—1.15)	1.11 (1.03—1.20)	1.15 (1.06—1.23)	1.15 (1.07—1.24)
Erythromycin	5563 (161)	0.88 (0.74—1.03)	0.94 (0.80—1.11)	0.94 (0.80—1.11)	0.95 (0.81—1.11)	1.01 (0.86—1.18)	1.02 (0.87—1.19)
Roxithromycin	3027 (92)	0.92 (0.75—1.14)	0.90 (0.72—1.11)	0.90 (0.73—1.11)	1.00 (0.81—1.23)	0.98 (0.80—1.21)	1.00 (0.81—1.23)
Azithromycin	5037 (182)	1.10 (0.94—1.29)	1.09 (0.93—1.27)	1.09 (0.93—1.27)	1.20 (1.03—1.39)	1.19 (1.02—1.38)	1.19 (1.03—1.38)
Ciprofloxacin	1180 (37)	0.95 (0.68—1.33)	0.90 (0.65—1.26)	0.89 (0.64—1.25)	1.03 (0.74—1.43)	0.99 (0.72—1.38)	0.99 (0.72—1.38)
Nitrofurantoin	3076 (105)	1.04 (0.85—1.27)	1.04 (0.85—1.28)	1.04 (0.85—1.27)	1.13 (0.93—1.37)	1.14 (0.94—1.38)	1.14 (0.94—1.39)

aOR, adjusted odds ratio; *OR,* odds ratio.

[a] Exposed to either ampicillin, pivampicillin, benzylpenicillin, or phenoxymethylpenicillin; [b] Adjusted for maternal age at delivery and year of delivery; [c] Adjusted for maternal age at delivery, year of delivery, parity, pre-pregnancy body mass index, smoking, educational status, employment status, and income.

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SUPPLEMENTARY TABLE 4
Inferential statistical analysis for cardiac malformations

Antibiotic	n (Malformations)	Comparator: penicillin[a] exposed (n = 48,765)			Comparator: unexposed (n = 801,648)		
		OR_{crude}	$aOR_{partial}$[b]	aOR_{full}[c]	OR_{crude}	$aOR_{partial}$[b]	aOR_{full}[c]
Doxycyclin	1101 (11)	1.02 (0.56—1.87)	0.98 (0.54—1.79)	0.97 (0.53—1.78)	1.16 (0.64—2.10)	1.13 (0.62—2.05)	1.13 (0.62—2.04)
Amoxicillin	6679 (54)	0.83 (0.62—1.10)	0.82 (0.62—1.09)	0.82 (0.62—1.09)	0.94 (0.72—1.23)	0.94 (0.71—1.22)	0.93 (0.71—1.22)
Pivmecillinam	36,423 (380)	1.07 (0.93—1.22)	1.00 (0.87—1.15)	0.99 (0.86—1.14)	1.21 (1.09—1.35)	1.15 (1.04—1.28)	1.15 (1.04—1.28)
Dicloxacillin	2946 (25)	0.87 (0.58—1.30)	0.86 (0.58—1.30)	0.86 (0.57—1.28)	0.98 (0.66—1.46)	0.98 (0.66—1.46)	0.99 (0.66—1.46)
Sulfamethizole	22,684 (231)	1.04 (0.89—1.22)	1.09 (0.93—1.28)	1.08 (0.92—1.27)	1.18 (1.04—1.35)	1.22 (1.07—1.39)	1.22 (1.07—1.39)
Erythromycin	5563 (46)	0.85 (0.62—1.15)	0.94 (0.69—1.28)	0.94 (0.69—1.28)	0.96 (0.72—1.28)	1.02 (0.77—1.37)	1.03 (0.77—1.37)
Roxithromycin	3027 (29)	0.98 (0.67—1.43)	0.95 (0.65—1.38)	0.95 (0.65—1.38)	1.11 (0.77—1.61)	1.09 (0.76—1.57)	1.10 (0.76—1.58)
Azithromycin	5037 (57)	1.16 (0.88—1.53)	1.14 (0.86—1.51)	1.14 (0.86—1.51)	1.32 (1.01—1.71)	1.29 (0.99—1.68)	1.29 (0.99—1.67)
Ciprofloxacin	1180 (12)	1.04 (0.59—1.85)	0.98 (0.55—1.74)	0.97 (0.54—1.72)	1.18 (0.67—2.09)	1.13 (0.64—1.99)	1.13 (0.64—1.99)
Nitrofurantoin	3076 (28)	0.93 (0.64—1.37)	0.94 (0.64—1.38)	0.93 (0.63—1.36)	1.06 (0.73—1.53)	1.06 (0.73—1.54)	1.06 (0.73—1.55)

aOR, adjusted odds ratio; *OR,* odds ratio.

[a] Exposed to either ampicillin, pivampicillin, benzylpenicillin, or phenoxymethylpenicillin; [b] Adjusted for maternal age at delivery and year of delivery; [c] Adjusted for maternal age at delivery, year of delivery, parity, pre-pregnancy body mass index, smoking, educational status, employment status and income.

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