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

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Disclosure
The authors report no conflict of interest.

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Condensation

Merging comprehensive, complete and validated national registries, we found no excess risk of congenital malformations to be associated with 10 commonly prescribed antibiotics in pregnancy.

Short title

Antibiotics in pregnancy and risk of congenital malformations.

AJOG at a Glance

• 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.

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

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

Background: Antibiotics are commonly prescribed during pregnancy. While the safety of most penicillins are 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.

Study design: 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 population-wide Danish health-care and civic registries, we merged data on pregnancy, prescription drugs purchases during first trimester and congenital malformations. Using logistic regression, we calculated OR for congenital malformations (any), major congenital malformations and cardiac congenital malformations for the 10 most commonly prescribed antibiotics (excluding four penicillins that served as control). In the primary analysis the exposed cohort were compared to a cohort exposed to either of four penicillins considered safe during pregnancy (ampicillin, pivampicillin, benzylpenicillin ad phenoxymethylpenicillin). In sensitivity analysis, the exposed cohort were compared to an unexposed cohort. Covariate adjustments were made for maternal age at delivery, year of delivery, parity, pre-pregnancy BMI, smoking, educational status, employment status and annual personal income.

Results: We found no increased risk of congenital malformations 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 (OR 1.13; CI 1.06-1.19 and 1.15; CI 1.04-1.28, respectively), sulfamethizole (OR 1.15; CI 1.07-1.24 and 1.22; CI 1.07-1.39, respectively) and azithromycin (OR 1.19, CI 1.03-1.38 and 1.29, CI 0.99-1.67, respectively).

Conclusion: In this large population-wide 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.
Introduction

The use of drugs during pregnancy pose 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, is rarely solved by consulting by various decision support systems. A common recommendation is “should only be used if the benefits outweigh the potential risks to the unborn child”; a trivial statement rather than a clinically helpful advice. The 2014 revised FDA pregnancy categorization has yet to prove its value in everyday clinical decision support, but there are some reservations already.\(^1,2\)

Antibiotics are among the most commonly prescribed drugs during pregnancy, and the trend appears increasing worldwide.\(^3-5\) While many penicillins are generally considered safe during pregnancy, factual data remain a scarce commodity for several other commonly prescribed antibiotics.\(^6-10\) Such include beta-lactam antibiotics, macrolides, cephalosporins, nitrofurantoin, sulphonamides and tetracyclines. The amount of safety data on these drugs remain surprisingly scarce, except perhaps for erythromycin which is surrounded by some controversy pertaining to a possible increased risk of cardiac malformations.\(^11-16\)

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

Material and Methods

Source population

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

Data Sources and Data Linking

Data is obtained from four 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 (RMPS)

RMPS contains information about all prescription sales in Danish pharmacies, as well as the persons CPR-number and date of redemption.\(^18\) We used RMPS to identify the pregnant women’s prescription redemptions of antibiotics within the first trimester. RMPS does not include information about over-the-counter drugs or information on the underlying indication.
Danish Medicinal Birth Registry (DMBR)

DMBR contains information about deliveries in Denmark. We identified the relevant exposure window for each pregnancy, parity, pre-pregnancy BMI and smoking during pregnancy and pregnancy outcome. Malformation data from DMBR are merged with children records from the Danish National Patient Registry.

Danish National Patient Registry (DNPR)

DNPR carries comprehensive and complete populations-wide 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. 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).

Danish Civil Registration system (CRS)

CRS contains administrative information on all Danes that have lived in Denmark since April 1968. From CRS we confirmed residency in Denmark for least two years before delivery.

Study population

We restricted the study population to singleton pregnancies resulting in a livebirth of an infant without chromosomal abnormalities registered in the MBR were diagnosed within 12 months after delivery (ICD-10 codes Q90-99). To maximize data coverage, we restricted the study population to pregnancies among women residing in Denmark continuously for at least two years prior to their delivery. Multiple pregnancies were excluded to ensure only one event per exposure for the analysis. We excluded pregnancies with missing information on gestational age. We excluded women exposed to either of the following drugs and drug classes, for which there is evidence of teratogenic effects: retinoids, angiotensin-converting enzyme inhibitor, vitamin K antagonists, valproic acid, lithium, carbamazepine, oxcarbazepine, phenytoin, phenobarbital or methotrexate.

Exposure and study cohorts

We defined exposure to antibiotics in this study as a filling of a prescription of systemic anti-infective drugs at a Danish pharmacy within the exposure window (first trimester). Systemic anti-infective drugs were defined using the World Health Organizations’ Anatomical Therapeutic Chemical (ATC) Classification System code J01. First trimester of pregnancy was defined as the first 90 days from the first day of the last menstrual period, either calculated at the first trimester ultrasound scan offered to all 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 will be determined as 280 days after the first day of her last menstrual period.
All included pregnancies are split in three cohorts: exposed cohort, primary comparison cohort exposed to penicillins, and unexposed cohort. The exposed cohort includes all women who have filled a prescription for an antibiotic with ATC-code J01, except for the four penicillins comprising the primary comparison cohort.

The primary comparison cohort comprises women who have only filled a prescription for either of the following specific penicillins: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin) and J01CE02 (phenoxymethylpenicillin). These penicillins are considered 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 have any drug prescriptions filled during pregnancy.

**Malformation Outcomes**

We stratified congenital malformations into three groups: all malformations (without syndromes and generic abnormalities), major malformations and cardiovascular malformations. Stratification was made based on the European surveillance of congenital anomalies coding system (EUROCAT). Malformations were identified in DNPR and DMBR where malformations are coded based on EUROCAT guide 1.4.

**Covariates**

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

**Statistical analyses**

Descriptive analyses were made for all deliveries registered in the Danish medical birth registry. Using logistic regression models, we calculated the crude and adjusted odds ratios (OR and aOR) with 95% confidence intervals (95% CI) associating exposure to commonly prescribed systemic antibiotics to malformations. To address the issue of confounding by indication, our primary analysis compared the risk of congenital malformations among exposed to a cohort exposed to either of four penicillins (ampicillin, pivampicillin, benzylpenicillin and phenoxymethylpenicillin) that are considered safe during pregnancy. All analyses were repeated with pregnancies unexposed to systemic antibiotics as a referent 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 body mass index. We applied two different adjustment models: aOR_{partial} is only adjusted for the age at delivery and the year of delivery, while the fully adjusted aOR_{full} is 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 first trimester. The final cohorts yielded 82,318 women who filled a prescription for an J01 antibiotic outside the 4 control penicillins; 48,765 in the primary control cohort of women who filled a prescription for either of four penicillins in the first trimester, and an unexposed cohort of 801,648 women who did not fill a prescription for a J01 drug (Figure 1). 7531 (9.1%) were exposed to more than one J01 study drug during first trimester (data not shown).

Demographic and other socioeconomic characteristics are presented in Table 1. These characteristics appear comparable across the three cohorts. Concomitant medication characteristics are presented in Supplementary Table TS1. Overall, a tendency to have filled more prescriptions outside of the J01 ATC group is unsurprisingly apparent for the two 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 suffering from respiratory disease increases the risk of a bacterial upper airway infection requiring systemic antibiotic treatment.

The pattern of utilization of the 10 most commonly filled prescriptions for antibiotics outside the comparator group throughout the period is illustrated in Figure 2. Individually, the use of pivmecillinam has 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 generally stable throughout the period for the summarized groups.
Inferential analysis did not identify any association between exposure and either outcome compared to the primary control cohort or the unexposed cohort in the fully adjusted model. Compared to unexposed pregnancies, small increased risks for major malformations and cardiac malformations were apparent for pivmecillinam (OR 1.10; CI 1.05-1.15 and 1.17; CI 1.07-1.29, respectively), sulfamethizol (OR 1.11; CI 1.04-1.18 and 1.20; CI 1.06-1.36, respectively) and azithromycin (cardiac malformations only, OR 1.28, CI 1.00-1.64) as illustrated by forest plots in Figures 3 and 4, respectively. Forest plot for any malformations are illustrated in Supplementary Figure 3 and all inferential analysis are presented in Supplementary Tables TS2, TS3 and TS4.

Comment

Main findings

In this population wide 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. Our inferential point estimates come with a high degree of precision. This study contains the largest number reported of exposed pregnancies for several important antibiotics, notably dicloxacillin, ciprofloxacin, sulfamethizole, roxithromycin, azithromycin and doxycycline. Our data provide substantial and reassuring decision support for the treatment of pregnant women with infectious diseases in the first trimester. We document a change in the utilization pattern as filled prescriptions for pivmecillinam has increased sharply while filled prescriptions for sulfamethizole has declined substantially during the study period. This coincides with changes in National (and International) guidelines specifically with respect to treatment of urinary tract infections.22,23

Macrolides

Three macrolides, erythromycin, roxithromycin and azithromycin were among the most commonly filled prescriptions. Erythromycin has been surrounded with some controversy regarding the use during pregnancy, as some; especially earlier studies, suggested an increased risk of cardiac malformations.14,15,24,25 Other studies however failed to demonstrate such association and with our large dataset with more than 5500 first-trimester exposed live born we did not find any association to either cardiac malformations specifically or major malformations altogether. Current regulatory labelling in US 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”, respectively.  We believe our finding effectively closes this discussion and the overall amount of reassuring data calls for changing the labels. Our data for roxithromycin and azithromycin is by far the largest dataset yet reported. Neither drug was associated with increased risk of major- or cardiac malformations. We found no increased risk be associated with first trimester exposure to roxithromycin among 3027 first trimester exposed. Other data on roxithromycin are very scarce, as the previously largest study reported just 100 first trimester exposed. Azithromycin data for 5,037 exposed pregnancies - more than double the safety data previously reported - confirm previous findings that this drug is safe during first trimester pregnancy.

Broad spectrum penicillins

Our findings on broad-spectrum dicloxacillin, amoxicillin and pivmecillinam adds reassuring evidence pertaining to safety during pregnancy. Our findings on more than 6500 first trimester exposure to amoxicillin confirm the findings in a recent Canadian cohort and we believe amoxicillin should be considered safe during pregnancy. Pivmecillinam holds indications for urinary tract infections, and with this large cohort study with more than 36,000 first trimester exposed infants, we believe this drug can be used with confidence during pregnancy. The largest previous dataset reported was less than 600 first trimester exposed. For dicloxacillin, our dataset is 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 live born children exposed to ciprofloxacin in the first trimester. Our data does not suggest a clinically meaningful increased risk of congenital malformations though the precision of our estimates for cardiac malformations is moderate. Quinolones 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. Human epidemiological data do not substantiate this. Two recent reviews and meta-analyses agree that no increased risk is apparent, even if though the amount of drug-specific data is unimpressive. Specifically for ciprofloxacin a recent dataset reported no increased risk among 608 exposed to ciprofloxacin. An observational cohort reported a slight
increased risk of MCM (8 of 336 exposed) compared to women exposed to non-teratogenic drugs within a teratology information service setting.\textsuperscript{32}

\textit{Nitrofurantoin}

We found no increased risk of major congenital malformations among 3,076 first-trimester exposed newborn 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 suggesting different associations with some rare and specific malformations. One case-control study reported an increased risks 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).\textsuperscript{33} Compared to penicillin exposure, nitrofurantoin use was associated with oral clefts in the offspring (aOR 1.97; 95% CI 1.1-3.5).\textsuperscript{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.\textsuperscript{34} These case-control findings have all been disputed, and with clinical focus on overall risk of major malformations, the larger cohort data do not support a true association.\textsuperscript{4,35-37}

\textit{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 live born children. 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.\textsuperscript{38}

\textit{Doxycycline}

Our data comprising 1,101 exposed first trimester pregnancies do not suggest that in utero exposure doxycycline is associated with increased risk of major congenital malformations though 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 live-born children.\textsuperscript{39} A small dataset (N=164) published in 2017 support these observations as well.\textsuperscript{4}

\textit{Summary}
This comprehensive and updated analysis of nationwide data does not suggest first trimester exposure to 10 commonly prescribed systemic antibiotics is associated with an increased risk of congenital malformations. Data comply with EMA regulatory guidelines suggesting a labeling “comparable with use during pregnancy” if at least 1,000 first trimester exposed live born children do not suggest an increased risk of congenital malformations. Hence, we provide substantial and reassuring clinical decision support, and we suggest that drug labeling should be updated accordingly.

**Strengths**

We report updated nation-wide data from comprehensive, complete and validated registries on prescription drugs and pregnancy outcome, which eliminate recall bias. By using an active comparator group, exposed to penicillins, that are considered safe 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.

**Limitations**

We have adopted a ‘lumping’ approach i.e. pooling all specific malformations while only stratifying 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, i.e. assessing many [all] individual specific malformations, e.g. cleft palate, ventricular septal defect, unilateral clubfoot. Such approach may be mechanistically more “sound” but carries a substantial inherent risk of false positive and negative findings, both of which may have severe consequences to the pregnant women.

We use filled prescriptions as a proxy for exposure. While commonly accepted within pharmacoepidemiology, the assumption that filled prescription equals actual indigestion 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.
We cannot account for specific underlying diagnoses as such 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, with a high degree of precision, no increased risk of congenital malformations for 10 commonly prescribed antibiotics. 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 aspect of pregnancy outcome such as miscarriage, preterm birth, small for gestational age, and, for the individual antibiotic exposure, address specific malformations.

**Acknowledgement**

This study was partly funded by a grant from the Novo Nordisk Foundation; Grant #: NNF17OC0028866.
References


27. Erythromycin ethylsuccinate. HTTPS//drugbank/fda_labels/DB00199.


**Figure Legends**

**Figure 1**: Study cohort selection tree.

Legend:

1) Not resident in Denmark within two 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 (phenoxybenzylpenicillin)
4) J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin) and J01CE02 (phenoxybenzylpenicillin)

**Figure 2**: Utilization pattern of 10 commonly first trimester prescribed antibiotics from 2000-2015

Legend:
1) The 10 most commonly first trimester prescribed systemic antibiotics excluding comparator penicillins: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin) and J01CE02 (phenoxympenicillin)

**Figure 3:** Ten commonly first trimester prescribed antibiotics and risk of major congenital malformations

Legend

1) Any systemic J01 antibiotic not including comparator penicillins

2) Comparator penicillins: J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin) and J01CE02 (phenoxympenicillin)

**Figure 4:** Ten commonly first trimester prescribed antibiotics 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 (phenoxympenicillin)

**Supplementary figure 1:** Utilization pattern of antibiotics commonly prescribed antibiotics from 2000-2015

Legend

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 (phenoxympenicillin)

**Supplementary figure 2:** Utilization pattern of 4 comparator penicillins first trimester prescribed antibiotics from 2000-2015

**Supplementary figure 3:** Ten commonly first trimester prescribed antibiotics and of 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 (phenoxympenicillin)
Figure 1: Flowchart
Figure 2: Utilization pattern
Figure 3: Major malformations

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adjusted Odds Ratio</th>
<th>Penicillin² aOR (95% CI)</th>
<th>Unexposed aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic</td>
<td>1.00 (0.95-1.05)</td>
<td>1.02 (0.95-1.08)</td>
<td>1.12 (1.08-1.16)</td>
</tr>
<tr>
<td>J01AA02 Doxycyclin</td>
<td>0.95 (0.68-1.33)</td>
<td>0.95 (0.68-1.33)</td>
<td>1.06 (0.76-1.47)</td>
</tr>
<tr>
<td>J01CA04 Amoxicillin</td>
<td>0.99 (0.85-1.14)</td>
<td>0.99 (0.85-1.14)</td>
<td>1.09 (0.95-1.25)</td>
</tr>
<tr>
<td>J01CA08 Pivmecillinam</td>
<td>1.02 (0.94-1.10)</td>
<td>1.02 (0.94-1.10)</td>
<td>1.13 (1.06-1.19)</td>
</tr>
<tr>
<td>J01CF01 Dicloxacillin</td>
<td>0.95 (0.76-1.17)</td>
<td>0.95 (0.76-1.17)</td>
<td>1.04 (0.85-1.28)</td>
</tr>
<tr>
<td>J01EB02 Sulfamethizole</td>
<td>1.05 (0.96-1.15)</td>
<td>1.05 (0.96-1.15)</td>
<td>1.15 (1.07-1.24)</td>
</tr>
<tr>
<td>J01FA01 Erythromycin</td>
<td>0.94 (0.80-1.11)</td>
<td>0.94 (0.80-1.11)</td>
<td>1.02 (0.87-1.19)</td>
</tr>
<tr>
<td>J01FA06 Roxithromycin</td>
<td>0.90 (0.73-1.11)</td>
<td>0.90 (0.73-1.11)</td>
<td>1.00 (0.81-1.23)</td>
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<tr>
<td>J01FA10 Azithromycin</td>
<td>1.09 (0.93-1.27)</td>
<td>1.09 (0.93-1.27)</td>
<td>1.19 (1.03-1.38)</td>
</tr>
<tr>
<td>J01MA02 Ciprofloxacin</td>
<td>0.89 (0.64-1.25)</td>
<td>0.89 (0.64-1.25)</td>
<td>0.99 (0.72-1.38)</td>
</tr>
<tr>
<td>J01XE01 Nitrofurantoin</td>
<td>1.04 (0.85-1.27)</td>
<td>1.04 (0.85-1.27)</td>
<td>1.14 (0.94-1.39)</td>
</tr>
</tbody>
</table>
Figure 4: Cardiac malformations
### Table 1. Cohort characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exposed to study antibiotics¹ (n=82,318)</th>
<th>Exposed to reference penicillins² (n=48,765)</th>
<th>Unexposed (n=801,648)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>29.4 (5.2)</td>
<td>30.1 (4.9)</td>
<td>30.2 (4.9)</td>
</tr>
<tr>
<td><strong>Mothers’ education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: 7-10 yrs</td>
<td>8,387 (10%)</td>
<td>4,141 (8%)</td>
<td>49,045 (6%)</td>
</tr>
<tr>
<td>Medium: 11-12 yrs</td>
<td>16,024 (19%)</td>
<td>9,613 (20%)</td>
<td>163,897 (20%)</td>
</tr>
<tr>
<td>High: 13+ yrs</td>
<td>24,990 (30%)</td>
<td>16,329 (33%)</td>
<td>310,264 (39%)</td>
</tr>
<tr>
<td>Vocational training</td>
<td>22,781 (28%)</td>
<td>13,533 (28%)</td>
<td>184,201 (23%)</td>
</tr>
<tr>
<td>No information</td>
<td>10,136 (12%)</td>
<td>5,149 (11%)</td>
<td>94,241 (12%)</td>
</tr>
<tr>
<td><strong>Mothers’ employment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Un-employed</td>
<td>16,839 (20%)</td>
<td>8,968 (18%)</td>
<td>121,112 (15%)</td>
</tr>
<tr>
<td>Students</td>
<td>4,749 (6%)</td>
<td>1,999 (4%)</td>
<td>39,748 (5%)</td>
</tr>
<tr>
<td>Employed</td>
<td>52,789 (64%)</td>
<td>32,553 (67%)</td>
<td>549,843 (69%)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>1,287 (2%)</td>
<td>787 (2%)</td>
<td>14,593 (2%)</td>
</tr>
<tr>
<td>No information</td>
<td>6,654 (8%)</td>
<td>4,458 (9%)</td>
<td>76,352 (10%)</td>
</tr>
<tr>
<td><strong>Mothers’ annual income</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>15,556 (19%)</td>
<td>6,789 (14%)</td>
<td>128,194 (16%)</td>
</tr>
<tr>
<td>100,000-200,000</td>
<td>41,909 (51%)</td>
<td>26,395 (54%)</td>
<td>394,841 (49%)</td>
</tr>
<tr>
<td>200,000-400,000</td>
<td>17,689 (21%)</td>
<td>10,799 (22%)</td>
<td>196,246 (24%)</td>
</tr>
<tr>
<td>400,000+</td>
<td>510 (1%)</td>
<td>324 (1%)</td>
<td>6,015 (1%)</td>
</tr>
<tr>
<td>No information</td>
<td>6,654 (8%)</td>
<td>4,458 (9%)</td>
<td>76,352 (10%)</td>
</tr>
<tr>
<td><strong>Pre-pregnancy BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 Underweight</td>
<td>980 (1%)</td>
<td>487 (1%)</td>
<td>8,410 (1%)</td>
</tr>
<tr>
<td>18-24 Normal weight</td>
<td>34,686 (42%)</td>
<td>18,706 (38%)</td>
<td>350,204 (44%)</td>
</tr>
<tr>
<td>25-29 Overweight</td>
<td>14,759 (18%)</td>
<td>8,567 (18%)</td>
<td>133,036 (17%)</td>
</tr>
<tr>
<td>30-34 Obese class I</td>
<td>5,981 (7%)</td>
<td>3,657 (7%)</td>
<td>46,262 (6%)</td>
</tr>
<tr>
<td>35+ Obese class II&amp;III</td>
<td>4,107 (5%)</td>
<td>2,561 (5%)</td>
<td>27,505 (3%)</td>
</tr>
<tr>
<td>No information</td>
<td>21,805 (26%)</td>
<td>14,787 (30%)</td>
<td>236,231 (29%)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primipara</td>
<td>38,793 (47%)</td>
<td>15,804 (32%)</td>
<td>360,879 (45%)</td>
</tr>
<tr>
<td>Multipara</td>
<td>43,525 (53%)</td>
<td>32,961 (68%)</td>
<td>440,769 (55%)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>64,263 (78%)</td>
<td>37,847 (78%)</td>
<td>663,850 (83%)</td>
</tr>
<tr>
<td>Light smoker 1-10</td>
<td>11,665 (14%)</td>
<td>6,839 (14%)</td>
<td>87,742 (11%)</td>
</tr>
<tr>
<td>Heavy smoker 11+</td>
<td>4,236 (5%)</td>
<td>2,687 (6%)</td>
<td>27,454 (3%)</td>
</tr>
<tr>
<td>No information</td>
<td>2,154 (3%)</td>
<td>1,392 (3%)</td>
<td>22,602 (3%)</td>
</tr>
</tbody>
</table>

1) Any systemic J01 antibiotic but reference penicillins

4) J01CA01 (ampicillin), J01CA02 (pivampicillin), J01CE01 (benzylpenicillin) and J01CE02 (phenoxy methylpenicillin)