Associations between macrolide antibiotics prescribed during pregnancy and adverse child outcomes

Study Protocol

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1. Background

Macrolide antibiotics are the third most frequently prescribed antibacterial class during pregnancy in western countries and are generally considered safe.(1-4) Over the last 20 years, concerns have been raised about some rare but serious adverse outcomes associated with macrolide use during pregnancy.(5-8) The strongest evidence comes from a large factorial randomised controlled trial (RCT, OCSII) of women with spontaneous preterm labour (SPL). The investigators reported an increased risk of cerebral palsy in children whose mothers received any erythromycin (i.e. erythromycin only or erythromycin and co-amoxiclav, 3.3%) compared with those who received no erythromycin (i.e. co-amoxiclav or placebo, 1.7%) (odds ratio (OR) 1·93, 95% Confidence Interval (CI): 1·21-3·09).(8) The increased risk of cerebral palsy (CP) or epilepsy was also observed in a large cohort study of 195,909 unselected pregnant women, where erythromycin was compared with penicillins.(7) Additionally, increased risks of stillbirth, miscarriage, major malformations, cardiovascular malformation and pyloric stenosis have been reported by some observational studies,(5, 9-12) but not in others.(13-15) Currently, there is no consensus about how to respond to this evidence. In Sweden in 2005, national policy advised against the use of erythromycin during early pregnancy.(11) In April 2015, the UK Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the evidence reported by Meeraus et al. and decided there was insufficient evidence to warn against the use of macrolides in pregnancy.(7, 16)

Prompt and adequate treatment for infection during pregnancy is vital given the well-established association between maternal infection during pregnancy and adverse birth outcomes, including miscarriage and stillbirth.(17) More evidence is needed on whether there is a causal association between maternal macrolide antibiotics treatment during pregnancy and adverse child outcomes.

2. Objectives

We will conduct a population-based cohort study to evaluate the association between the macrolide antibiotics prescription in pregnancy and adverse child outcomes (neurodevelopmental disorders and major malformation (overall and system-specific)) (**primary analysis**), and to examine this association by macrolides subtypes and length of prescriptions (**subgroup analysis**).

3. Data source

We will use the Clinical Practice Research Datalink (CPRD), a UK-representative database which captures prospective, anonymised data on prescriptions, diagnoses, and symptoms records in primary care.(18) A Mother-baby link was built within CPRD using family ID, practice ID, and date of birth/delivery, with details reported elsewhere.(19, 20) For each mother-baby pair, a delivery date was estimated (Appendix).

4. Methods

4.1 Study design

Retrospective cohort study with prospectively collected data.

4.2 Study Population

The Mother-baby link includes 1,071,379 children born from Jan 1st 1990 to June 30th 2016.

Inclusion Criteria:
-   Children whose mother was prescribed an only monotherapy of macrolide or penicillin during pregnancy (between 5 Gestational Week [GW] and delivery)
-   Children who registered with the general practice (GP) within 6 months of birth
-   Children whose mother was aged 14 to 50 years at delivery and had been registered with GP from at least 50 weeks before estimated conception date to delivery

Exclusion Criteria:

Children with known chromosomal abnormalities or with fetal exposure to known teratogenic medications (warfarin, angiotensin-converting enzyme (ACE) inhibitors, antineoplastic agents, isotretinoin, misoprostol, and thalidomide).

Children will be followed from birth to death, end of follow-up (June 30th, 2016), or age 14, whichever came first.

4.3 Study Variables

4.3.1 Exposure

The exposure group will include children whose mother were prescribed an only monotherapy of macrolide antibiotics from 5 GW to delivery (hereafter, "during pregnancy"). A monotherapy is defined as one or more consecutive prescriptions for a single antibiotic (i.e. same drug substance) separated by no more than 30 days and uninterrupted by prescriptions for other antibiotic drug substances. The macrolides prescription is identified using a drug code list based on chapter 5.1.5 of the British National Formulary. The date of first prescription is used as the index date. The reference group includes children whose mothers were exposed to an only monotherapy of penicillins during pregnancy. Preliminary analysis shows that 81% of all antibiotic prescriptions were monotherapies. We further divide the time window into 1) 5GW to 13GW (29 Gestational Day [GD] to 91GD, hereafter, "1st trimester"), the critical period for most major malformation, and 2) 14GW to delivery (hereafter, "2nd–3rd trimester").(21) The negative control cohort (see "4.4.2 Sensitivity analyses [1]) includes children of mothers prescribed an only monotherapy of macrolides or penicillins during 10-50 weeks prior to conception and are not included in the study cohort.

4.3.2 Outcome

Based on previous evidence from experimental and epidemiological studies, we hypothesized that short-term fetal hypoxia induced by fetal arrhythmia could possibly be the underlying mechanism of observed adverse effects of macrolides.(22) We therefore include outcomes which could potentially result from short-term fetal hypoxia, i.e. neurodevelopmental disorders (CP, epilepsy, attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)) and major congenital malformation (malformation overall and system-specific malformations).

Neurodevelopmental disorders (CP, epilepsy, ADHD and ASD) are defined as the time to the first Read code or prescription indicating the outcomes by 14 years old. We have identified CP cases from informative prescription or Read codes using the Random Forest approach and were validated by a paediatric-neurologist blinded to the prenatal antibiotics exposure.(23) Other neurodevelopmental disorders (epilepsy, ADHD and ASD) will be identified with previously validated criteria using diagnostic codes and/or prescriptions (table 1). (24-26)

Major malformations will be identified from the European Surveillance of Congenital Anomalies (EUROCAT).(27) We will exclude musculoskeletal malformations (e.g. Club foot, knock-knee and hip dislocation) because they are not reliably recorded in GP records.(28) We also exclude children with known chromosomal abnormalities and children whose mother were exposed to known teratogenic medications (warfarin, angiotensin converting enzyme (ACE) inhibitors, antineoplastic agents, isotretinoin, misoprostol, and thalidomide). Any of the remaining 11 system-specific malformations are defined as major malformation overall, identified from child GP records up to 3 years old using Read codes which are mapped to the tenth edition of the International Classification of Diseases (ICD–10) code lists in EUROCAT (Table 1).(27) Five system-specific malformations (nervous, cardiovascular, digestive, genital tract, and urinary tract) were included which met the power criterion using the EUROCAT prevalence table.(29) (see "4.5 Power analysis")

Table 1. Outcome identification.

Outcome	Case identification criteria
Cerebral palsy	Method based on predictor selection and prediction (23)
Epilepsy	2 prescriptions of antiepileptic drug (AED, identified based on British National Formula Chapter 4.8) within 4 months or >= 1 diagnosis
Attention deficit hyperactivity disorder (ADHD)	>= 2 occurrence of prescriptions for ADHD (identified based on British National Formula Chapter 4.4) or diagnoses (attention deficit hyperactivity disorder, hyperkinetic disorders, hyperkinetic syndrome, hyperkinetic reaction of childhood or adolescence, overactive child syndrome and disturbance of activity and attention)
Autism spectrum disorder (ASD)	At least 1 diagnostic code ((infantile or childhood) autism, Asperger's syndrome, Rett's syndrome, Heller's syndrome, Autistic spectrum disorder, disintegrative disorder, and other pervasive developmental disorders)
Major congenital malformation	Any major system specific malformation according to the EUROCAT classification. We use Read code list mapped to ICD 10 codes Chapter Q. Exclude: 1) minor anomalies post-2005; 2) musculoskeletal malformations; 3) malformations caused by known chromosomal abnormalities and teratogens (i.e. Teratogenic syndromes with malformations, Fetal alcohol syndrome, Valproate syndrome, Maternal infections resulting in malformations, Genetic syndromes + microdeletions, Chromosomal malformations)
Cardiovascular malformation	1 Read code mapped from ICD 10 (Q20-Q26, exclude Q2111, Q250 if GA <37 weeks, Q2541, Q256 if GA<37 weeks, Q261)

Gastrointestinal malformation	Read code mapped from ICD 10 (Q38-Q45, Q790, exclude Q381, Q382, Q3850, Q400, Q401, Q4021, Q430, Q4320, Q4381, Q4382)
Nervous system malformation	Read code mapped from ICD 10 (Q00-Q07, exclude Q0461, Q0782)
Genital tract malformation	Read code mapped from ICD 10 (Q50-Q52, Q54-Q56, exclude Q523, Q525, Q527, Q5520, Q5521)
Urinary tract malformation	Read code mapped from ICD 10 (Q60-Q64, Q794, exclude Q610, Q627, Q633)

4.3.3 Covariates

We will control the covariates which are potential risk factors for adverse child outcomes. These include: 1) maternal characteristics at baseline (i.e. age at child birth, problematic alcohol use, illicit drug use, recent tobacco use, and obesity); 2) pregnancy related variables (i.e. birth year, parity, multiple birth, hypertension, diabetes, epilepsy, depression, anxiety, maternal chronic medical conditions during pregnancy, potentially fetal-damaging maternal infection during pregnancy, and baby gender) (details given below). Gestational age at delivery and Apgar score after birth are considered mediators on the pathway for the association between prenatal antibiotics exposure and adverse child outcomes and therefore not adjusted.

1. ***Maternal variables***

   1) **Maternal age (at birth)**

      By 5 year categories.

   2) **Maternal life style:**

      a. <u>Problematic alcohol use</u>:

      Most recent record between 10 years prior to and during pregnancy:

      - a Read code indicating alcohol misuse; or

      - a prescription for disulfarim or acamprosate; or

      - self-reported average weekly alcohol intakes of between 14-500 units of alcohol a week.

      b. <u>Illicit drug use</u>:

      Most recent record between 10 years prior to and during pregnancy:

      - a read code for drug use, addiction, and overdose; or

      - a prescription for methadone treatment

      c. <u>Recent smoking/tobacco use</u>:

      Most recent record between 3 years prior to and during pregnancy:

- self-reported daily cigarette consumption of 1-100 cigarettes per day unless there was evidence of smoking cessation; or

- a read code indicating tobacco consumption; or

- a prescription to assist smoking cessation

d. Obesity

Most recent record from 3 years prior to the end of 1st trimester:

A read code for obesity (or a BMI of $\geq$30 kg/m^2 - either directly entered or calculated from the most recent height measurement and median pre-pregnancy weight after outliers, i.e. height outside the range 1-2m and weight outside the range 35-300kg, were removed).

2. *Pregnancy related variables*

3) Baby birth year

Grouped into categories of 5 calendar years.

4) Parity

Categorised as "0", and ">= 1".

5) Multiple births

Categorize the baby as "singleton", or "(one of the) twin, triplets, or quadruplets".

6) Hypertension

Measurement from 50 weeks prior to delivery:

- systolic and diastolic blood pressure was above 140mmHg and 90mmHg, respectively, or

- a Read codes for hypertension and associated diagnoses (including pre-eclampsia, eclampsia and HELLP syndrome), or

- a prescription for hypertension drugs from sections 2.2 and 2.5 of the BNF. This variable identified mothers with both treated and untreated hypertension in pregnancy.

7) Diabetes

Measurement from 50 weeks prior to delivery:

- a Read code for type I, type II, or gestational diabetes;

- two or more prescriptions for anti-diabetic medication; or

- laboratory tests indicative of diabetes (defined as $\geq$2 abnormal glucose tests, fasting glucose >7.0 millimoles per litre [mmol/L] or >126 milligrams per decilitre

[mg/dL], plasma glucose after glucose tolerance test >11.1 mmol/L or 200mg/dL, glycated haemoglobin >=6.5%, or with diabetes annual review).

8) **Epilepsy**

Measurement from 50 weeks prior to delivery: 2 prescriptions of antiepileptic drugs (AEDs) within 4 months or >= 1 diagnosis

9) **Depression**

Measurement from 50 weeks prior to delivery: >= 2 occurrences of diagnostic code, treatment code or symptom

10) **Anxiety**

Measurement from 50 weeks prior to delivery: >= 2 occurrences of diagnostic code, treatment code or symptom

11) **Treatment of chronic medical conditions during pregnancy**

Measurement during pregnancy: two or more prescriptions (on separate days during pregnancy and not more than four months apart) for drugs from the same BNF section or paragraph. Drugs used to treat common conditions in pregnancy such as reflux (BNF section 1.2), nausea and vomiting (BNF section 4.6), and constipation (BNF section 1.3) were not included.

12) **Potentially fetal-damaging infections during pregnancy.**

Mothers are classified as having a potentially fetal-damaging infection in pregnancy if they had recorded at any time during their pregnancy, a Read code for a diagnosis or a laboratory test confirming any of the following infection: genitourinary infection, "TORCH" (Toxoplasmosis, Other agents such as HIV, Rubella, Cytomegalovirus and Herpes simplex) and sexually transmitted infections (STIs). "TORCH" and STIs have long been known as important risk factors to adverse pregnancy outcomes and teratogenic pathogens. (22, 23) Intrauterine infection has been recognised as an important mechanism of disease in preterm labor. (24) Hyelonephritis and bacteriuria have also been linked with preterm labor and low birthweight. (25)

3. *Neonatal variables*

13) **Baby gender**

4.4 Analyses

4.4.1 Statistical methods

Standardized differences will be used to assess covariate balance between the macrolides group and the penicillins group; meaningful imbalances are defined by an absolute standardized difference of more than 0.1.(30) For neurodevelopmental disorders, absolute rates of outcomes and unadjusted hazard ratios with 95% confidence intervals will be calculated. For malformations, absolute risks of outcomes and unadjusted risk ratios with 95% confidence intervals, will be calculated. Exposure propensity scores will be estimated as the predicted probability of receiving the macrolides prescription (vs. penicillins), conditional on the covariates described above, with the use of logistic-regression models. For each estimated propensity score, the population in the nonoverlapping areas of the propensity-score distributions will be trimmed, and 50 strata will be created on the basis of the distribution of the treated women.(31) Weights for the reference group will be calculated according to the distribution of the treated women among propensity-score strata. We then use the weight to estimate adjusted baseline characteristics, and adjusted hazard ratios (in Cox proportional hazard models with weight statement for neurodevelopmental disorders) or risk ratios (in log-binomial model with weight statement for malformations) as well as their 95% confidence intervals. To account for the clustering of siblings and multiple births within mother, robust standard errors will be estimated. The analyses will be conducted using RStudio version 3.5.1.. No adjustment will be made for multiple comparisons, and results for comparisons of exposure timing and subgroup analysis should be interpreted as exploratory.

4.4.2 Primary, subgroup and sensitivity analyses

Primary analysis

1. Association between adverse child outcomes and macrolide (versus penicillins) prescription during pregnancy (from 5 GW to delivery).

2. Association between adverse child outcomes and macrolide (versus penicillins) prescription during 1st trimester (from 5 to 13 GW).

3. Association between adverse child outcomes and macrolide (versus penicillins) prescription during 2st to 3rd trimester (from 14 GW to delivery).

Subgroup analyses

1. Association between adverse child outcomes and macrolide (versus penicillins) prescription during pregnancy, by macrolide subtype (erythromycin, clarithromycin and azithromycin).

2. Association between adverse child outcomes and macrolide (versus penicillins) prescription during pregnancy, by duration of antibiotics prescription (<7days and >=7days).

Sensitivity analyses

1. To evaluate the effect of potential confounding due to maternal baseline characteristics: association between adverse child outcomes and macrolide (versus penicillins) prescription 10-50 weeks prior to pregnancy (negative control analysis).

2. To evaluate the effect of potential bias due to infection: association between adverse child outcomes and macrolides (versus penicillins) prescription during pregnancy, restricted to children of mother whose antibiotics were prescribed for respiratory tract infection (RTI).

3. To evaluate the potential effect of outcome misclassification for CP and malformations: define CP cases with diagnostic codes only, and identify malformation cases as only those with repeated (>=2) child diagnoses, or with diagnoses in both the maternal (18GW to 6 months postpartum) and child records (before age 3).

4. To evaluate the potential effect of live-birth bias: Evaluate the direction and quantity of the potential live-birth bias by simulating proportions of fetal deaths among women exposed to macrolides versus those exposed to penicillins.

4.5 Power analysis

Initially interested outcomes include: cerebral palsy, epilepsy, ADHD, ASD, major malformation overall, and system-specific malformations according to the classification of EUROCAT.

To avoid spurious associations by chance we will restrict our analyses to outcomes which have >= 80% statistical power to detect a 2-fold relative risk increase at a 5% level of significance. Baseline risks of CP, epilepsy, ADHD, and ASD were calculated based on literature review and preliminary analyses, while the prevalence of major malformations (overall and system-specific) were based on the EUROCAT estimates.(29) The needed sample size of macrolides group was calculated for each outcome, based on a cohort of about 100,000 pregnancies exposed to penicillins (data from preliminary analyses). Preliminary analysis shows there are about 10,000 pregnancies in the macrolides group, therefore outcomes which requires more than 10,000 samples in macrolides group were excluded and will not be evaluated in this study (i.e. eye malformation, ear and face malformation, orofacial cleft, respiratory malformation, abdominal wall malformation and other malformation). Power calculations were performed using R package "pwr". (Figure 1 and Table 2)

Figure 1. Sample size estimation for macrolides group, n (penicillins) =100000, Sig=0.05, power=80%, risk ratio=2.

Sample Size Estimation for Macrolides group, n(penicillins)=100000, power= 80%, Sig=0.05, Risk ratio=2
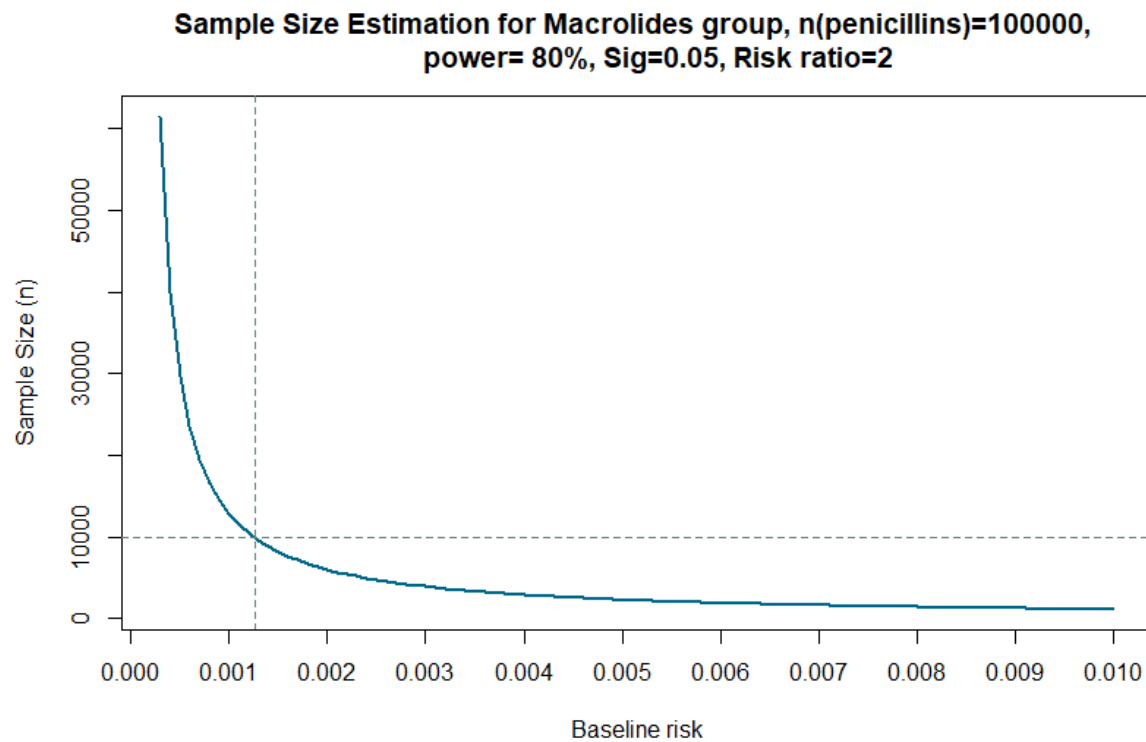
Table 2. Baseline risks and inclusion result for each outcome.

Outcome	Baseline Risk	Included
Cerebral palsy	0.002	Yes
Epilepsy	0.006	Yes
ADHD	0.006	Yes
ASD	0.008	Yes
Any major malformation	0.02	Yes
Cardiac malformation	0.007	Yes
Genital tract malformation	0.002	Yes
Urinary tract malformation	0.003	Yes
Gastrointestinal malformation	0.002	Yes
Nervous system malformation	0.002	Yes
Eye malformation	0.0003	No
Ear and face malformation	0.0001	No
Orofacial cleft	0.001	No
Respiratory system malformation	0.0004	No
Abdominal wall malformation	0.0005	No
Other malformation	<0.001	No

Appendix

A hierarchy of available pregnancy markers was chosen that reflects their potential accuracy to estimate start of the pregnancy episode. Pregnancy markers that directly provide gestational age such as gestational age in weeks, prenatal examination, and fertility procedures (IVF) were on the top of the hierarchy. Next hierarchy of markers include ranges of gestational week indicators (e.g. premature 24-26 weeks) and outcome-specific estimates (e.g. premature labour, imputed as 36 weeks, because around 60% live premature births born at 36 gestational weeks). Gestational weeks imputed from birthweight was on the 3rd hierarchy, based on the intrauterine growth curves published by Irene E. Olsen et al.(32) For pregnancies with no information available for the above three hierarchies of markers, full term births were assumed and gestational week 40 were used to calculate pregnancy start dates. Codes used in each hierarchy is referenced from Matcho, A. et al. (33)

For babies in the Mother-baby link, gestational age were measured from each hierarchy with the following proportion: 27.8% from the first hierarchy (from codes for gestational age), 14.3% from the second hierarchy (from codes for gestational week range), 8.2% from the third hierarchy (imputed based on birthweight), 49.6% (imputed as full term, 40 gestational weeks). The proportion of preterm birth was 6.2% preterm births in general populations, which is marginally lower than reported by the Office for National Statistics (7.1%).(34) The potentially underestimated proportion of preterm births would over-record antibiotic exposure during the early pregnancy, which would bias the association towards null.

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