Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Safety of macrolide antibiotics in pregnancy: a review of the epidemiological evidence

MHRA Public Assessment Report

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Contents

1. Plain language summary

Key message

The Commission on Human Medicines (CHM) has reviewed the available safety data for the use of the macrolide antibiotics erythromycin, clarithromycin and azithromycin during pregnancy.

The available evidence is insufficient to confirm with certainty whether there is a small increased risk of malformations (birth defects) or miscarriage when macrolides are taken in early pregnancy.

There remains a need for high-quality research into the effect of erythromycin, clarithromycin or azithromycin in pregnancy. Further data are needed to draw firm conclusions.

Certain infections in pregnancy can cause serious harm to both to the mother and baby if not treated. In such cases, pregnant women should receive treatment with an appropriate antibiotic. Decisions by the prescriber of which antibiotic to use should be based on the benefits and risk to mother and baby. If a prescriber views that the potential benefits of treatment will outweigh the risks and that no suitable and safe alternative is available, for example in true penicillin allergy, a macrolide can be used during pregnancy.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK and ensuring their safety, quality and effectiveness. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates.

The CHM advises government ministers and the MHRA on the safety, efficacy and quality of medicines. The MHRA safety public assessment reports aim to discuss evidence-based reviews of safety issues linked with a particular medicine or group of medicines.

This report presents our review of the safety of macrolide antibiotics erythromycin, clarithromycin and azithromycin during early pregnancy. The review evaluated the quality of the safety evidence in relation to three outcomes: major malformations of the baby in the womb, heart or blood vessel malformations, and miscarriage.

About macrolides

The macrolide drug group are antibiotics used to treat acute and chronic infections. These medicines are effective treatments for a range of infections similar to penicillin, another antibiotic, and so macrolides are often used in patients allergic to penicillin.

The three main macrolide antibiotics used in the UK are azithromycin, clarithromycin and erythromycin:

- Azithromycin is used in infections of the respiratory tract, ear, skin and soft tissue infections, infections of the urethra and sexually transmitted infections including chlamydia and gonorrhoea.
- Clarithromycin is used to treat infections of the respiratory tract, ear, skin and soft tissue infections and also treating stomach ulcers caused by the bacteria Helicobacter pylori
- Erythromycin is used in infections of the respiratory tract, ear, eyes or mouth, skin and soft tissue infections, infections of the stomach and intestines, infections of the urethra and sexually transmitted infections including syphilis, chlamydia and gonorrhoea

A previous review of the respective Summaries of Product Characteristics (SmPCs) for macrolides marketed in the UK indicated varying levels of information and advice regarding use in pregnancy. There is therefore inconsistent and conflicting information in the various SmPCs regarding the safety and risk-benefit balance of macrolides in pregnancy.

Reason for the review

This review was initiated following the publication of a large cohort study in the UK (Fan and others, 2020), which reported a small increased risk of the baby being born with major malformation associated with use of macrolide antibiotics during pregnancy. Specifically, the study reported increased risks of malformations relating to the heart or blood vessels in babies born to mothers who were prescribed macrolide antibiotics in the first trimester of pregnancy.

The CHM recommended that the MHRA should undertake a review on whether the available data raise any new safety concerns or change current understanding about the safety of macrolide antibiotics during pregnancy.

Conclusions of the review

A range of studies were evaluated in this systematic review of the evidence. The overall quality of observational data on the safety of erythromycin, clarithromycin and azithromycin by mothers was low. Most studies included in the review were judged to have a serious risk of bias, according to a bias evaluating tool (ROBINS-I). There is also a lack of a known biological mechanism for malformations in the womb associated with macrolide antibiotics.

The overarching findings of the review are that the available evidence is insufficient to confirm with certainty the presence or absence of a small increased risk of malformations or miscarriage when macrolides are taken in early pregnancy.

The data were insufficient to confirm:

- small increased risk of major congenital malformations or cardiac malformations following exposure to erythromycin
- increased risk of miscarriage following exposure to clarithromycin or azithromycin

The data were also insufficient to establish:

- the absence of small increased risk of major congenital malformations or cardiovascular malformations following azithromycin or clarithromycin exposure
- the absence of small increased risks of miscarriage following exposure to erythromycin

There remains a need for high-quality research into the effect of erythromycin, clarithromycin or azithromycin prescription in pregnancy.

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The aim of MHRA safety public assessment reports is to discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

A glossary is provided for an explanation of the terms used in this report.

The following report discusses our review of the relating to the safety of medicines containing macrolide antibiotics during pregnancy.

The information and analyses contained in this report reflect evidence that was available at the time of the review in 2020. They are not intended to provide clinical advice. The MHRA will continue to monitor the safety of all medicines. The information in this report will not be actively updated with new data or studies unless major new safety information is available that results in critical changes.

Reason for this review

In 2020, a large UK cohort study reported a significant association between maternal use of macrolide antibiotics in early pregnancy and major congenital malformations, specifically cardiovascular malformations (Fan and others, 2020).

Following publication of this study, the Commission on Human Medicines (CHM) recommended that the MHRA review all available epidemiological evidence to understand reasons why the findings conflicted with that of other studies and to determine whether an updated meta-analysis of evidence may be a feasible option.

Macrolide antibiotics

The 3 main macrolide antibiotics authorised and used in the UK are azithromycin, clarithromycin and erythromycin.

These macrolides have a similar antibacterial spectrum to penicillin and are frequently used as an alternative to penicillin, for example in patients allergic to penicillin:

- Azithromycin is indicated for respiratory tract infections (RTIs), otitis media, skin and soft tissue infections, chlamydia, gonorrhoea and urethritis

- Clarithromycin is indicated for RTIs, otitis media, skin and soft tissue infections and Helicobacter pylori eradication
- Erythromycin is indicated for RTIs, ear, eye and oral infections, skin and soft tissue infections, gastrointestinal infections and various other infections such as chlamydia, gonorrhoea and urethritis

Clinical guidelines on use of macrolides in pregnancy

The NHS website states that erythromycin is the only macrolide which can be taken during pregnancy.

National Institute for Health and Care Excellence (NICE) antimicrobial prescribing guidelines for managing common infections includes macrolides within their recommended antibiotic choices. Examples include treatment of acute sore throat, acute sinusitis, acute otitis media, community-acquired pneumonia, cellulitis, erysipelas, diabetic foot infection and leg ulcer infection. Erythromycin is recommended as the preferred choice for pregnant women where a macrolide is deemed suitable, if, for example, true penicillin allergy is present.

NICE guidelines for use of these medicines in pregnancy are informed by recommendations from the UK Teratology Information Service (UKTIS). The UKTIS monograph on the use of macrolides in pregnancy was updated in April 2020 to reflect the findings of Fan and others (2020) and to highlight that macrolides should only be used in pregnancy when clinically necessary and if the benefit of treatment is expected to outweigh any small increased risks which may exist.

Pregnancy warnings in macrolide product information

A previous review of the respective Summaries of Product Characteristics (SmPCs) for macrolides marketed in the UK indicated varying levels of information and advice regarding use in pregnancy.

All the azithromycin and clarithromycin SmPCs include a risk-benefit statement regarding use during pregnancy, stating that the prescriber should consider whether the benefits to use outweigh the risks and there is a clinical need. However, information on use in pregnancy appears to be more variable in the SmPCs for erythromycin products, with some stating that there is ‘no evidence of hazard from erythromycin in human pregnancy’ and some mentioning the increased risk of cardiovascular malformations, which is likely to have been prompted by findings of Källén and others (2005, 2014)

There is therefore inconsistent and conflicting information in the various SmPCs regarding the safety and risk-benefit balance of macrolides in pregnancy.

3. Epidemiological studies on macrolide safety in pregnancy

Recent studies presenting conflicting findings on macrolide safety in pregnancy

Findings by Fan and others: a population-based cohort study

In February 2020, a large cohort study conducted in the UK Clinical Practice Research Datalink (CPRD) and published in the BMJ (Fan and others, 2020) reported an increased risk of major congenital malformations in infants whose mothers received a prescription for a macrolide antibiotic during early pregnancy compared to those who received a prescription for penicillin (adjusted risk ratio (aRR) 1.55, 95% confidence interval (CI) 1.19 to 2.03).

Increased risks were also reported for cardiovascular defects with macrolide prescribing in the first trimester (aRR 1.62, 1.05 to 2.51), and for major congenital malformations with erythromycin prescribing in the first trimester (aRR 1.50, 1.13 to 1.99).

This contrasted with several studies performed in other countries that did not find a statistically significant increased risk of these outcomes with macrolides as a class or for erythromycin specifically (Damkier and others, 2019; Muanda and others, 2017b; Lin and others, 2013; Bahat Dinur and others, 2013; Romoren and others, 2012; Bar-Oz and others, 2012; Crider and others, 2009; Cooper and others, 2009; Bar Oz and others, 2008, and Czeizel and others, 1999).

The study by Fan included a retrospective cohort of women who received one prescription for either a macrolide or a penicillin antibiotic during pregnancy in routine clinical practice between 1990 and 2016.

Fan's cohort study recorded a range of adverse outcomes in the children such as major malformations, cerebral palsy, epilepsy, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder. The selection of outcomes of interest was based on the authors' theory that the proarrhythmic effects of macrolides induce fetal hypoxia, which may in turn lead to these events.

Findings by Damkier and others: a population-based study (2019)

When considering the findings of the Fan study (2020), the findings of another recently published cohort study were noted (Damkier and others, 2019).

In contrast to the UK study, this large Danish cohort study investigated associations between in-utero exposure to various antibiotics and the risk of congenital malformations.

Damkier did not report increased risks for major congenital malformations or cardiovascular malformations in infants exposed to erythromycin or azithromycin in the first trimester when compared to infants exposed to penicillin (adjusted odds ratio (aOR) for major congenital malformations 0.94, 95% CI 0.80 to 1.11 (erythromycin) and 1.09, 0.93 to 1.27 (azithromycin); aOR for cardiovascular malformations: 0.94, 0.69 to 1.28; and 1.14, 0.86 to 1.51, respectively).

Further analysis of study findings

The MHRA conducted further analysis of these studies to try and understand the reasons for the different findings (see table at Annex 1).

In summary, both studies presented an appropriate approach to a collection of population-based data from national databases and their analysis. However, with the difference in the selection of outcomes and grouping of exposures (as in Fan and others, 2020), and potentially due to fundamental differences in the distribution of exposures between the 2 populations (as discussed below), the comparison of findings of the 2 studies is difficult. Neither study presented rates of outcomes of interest in the general population, which would provide a context and a reference.

Both studies were considered to have used an appropriate statistical method. The analytical approach taken by Fan is appropriate, and Cox regression is generally the stronger modelling approach, since it utilises more information, while logistic regression (used in Damkier's study) estimates are prone to bias and reduced precision with increasing follow-up time.

The use of propensity scores (used by Fan's study) to match exposed and unexposed individuals can help to control heterogeneity of characteristics between patients, but the effect of variables on the outcome of interest that were matched on cannot be estimated.

Propensity score matching was used by Fan to adjust for covariates by applying weighting of the sample of units in each treatment group to match covariate distribution of a target population. The propensity scores derived from the macrolide-exposed group were used to weight children from the penicillin-exposed group.

Although this non-parametric balancing strategy is a recognised approach, application of this method commonly excludes unmatched units or units with extremely large weights. The remaining sample may only represent a subpopulation of the original targeted population, which can vary from study to study. This is referred to as 'trimming'.

Fan's study does not report on the number of observations that were trimmed during the matching and discrepancies between treatment groups were not discussed. However, given the large sample size, it might be assumed that this might not have had a significant effect on the estimates.

Fan's study evaluated macrolides as a class and presented analyses restricted to erythromycin, whereas Damkier studied only the effects of individual macrolides azithromycin and erythromycin within their study. Damkier also only presented limited data on the prevalence of outcomes by exposures in descriptive statistics.

Logistic regression analysis (used by Damkier) is an appropriate method; the estimates from this analysis approximate those from Cox regression for rare outcomes. However, as previously highlighted the Cox model would usually be preferred.

Data on outcomes were collected by Damkier within 1 year after birth, while Fan had 14 years of follow-up, which allowed inclusion of developmental disorders that can manifest or be diagnosed in later life. Damkier considered a smaller number of potential confounders compared to the study by Fan.

No adjustment for previous or chronic maternal infection status was considered by Damkier. As such, confounding by indication cannot be ruled out, although this might be expected to bias the analyses away from the null and produce increased risk estimates for the outcomes, which was not the case in Damkier's study

The difference in proportions of penicillin prescriptions between the studies cannot be overlooked. The difference in prescribing practice regarding antibiotic choice may influence the respective findings. In Damkier's study, 37% of all prescriptions were penicillin, while in Fan's study prescriptions of penicillin constituted over 64% of antibiotic prescriptions in pregnant study participants requiring antibiotics.

If the choice of macrolide is associated with the severity or type of infection, then this could show systematic differences between groups of pregnant women prescribed macrolides or penicillin.

Although Fan tried to adjust their analysis for infections (for example sexually transmitted or genito-urinary), these variables might not have captured the whole variation in types of infection. Additionally, while Fan attempted to adjust for severity of infection by excluding pregnancies exposed to more than one course of macrolides, this would not fully eliminate confounding related to infection severity.

If the rationale for the choice of macrolide is non-differential across different indications, then confounding by severity or type of infection may not be present. Thus, the absence of difference in the effect of macrolides to those of penicillin could be true for the study population.

However, if penicillin is prescribed for specific types or severity of infection associated with adverse fetal outcomes and analysis failed to adjust for the effect of infection, this would increase the rate in penicillin group and bias any effect of macrolides toward the null.

Given the apparent higher use of macrolides in the Damkier study, it is not clear whether

they were used predominantly in women with a reported penicillin allergy, as seems to be mainly the case in the Fan study.

Furthermore, the rate of any malformations in infants exposed to erythromycin (283 in 5563) was 50.87 per 1000 (calculated from data in supplementary tables) in the study by Damkier. This was much higher than the rate reported by Fan of 27.6 per 1000, albeit this rate was calculated using data on prescriptions in the first trimester only, which might have under-represented the rate by not capturing the whole duration of pregnancy.

However, the rates of malformation in control groups (exposed to penicillin and non-exposed) might have been relatively high to render non-significant results when compared to the rate of malformations in macrolide-exposed groups in the study by Damkier (the data were not presented to enable the calculation). This raises questions about the level of outcome misclassification.

While external estimates of the rate of congenital malformations vary, and these estimates are within the normal range, limitations to the data in both studies (which rely on the secondary use of data) may have led to different levels in the capture of relevant outcomes.

Finally, there were key differences in the classification of first trimester exposure, with Fan restricting to 4 to 13 weeks' gestation, thereby eliminating the first few weeks of pregnancy, prior to organogenesis.

Like several other studies that did not report associations between macrolide exposure during pregnancy and fetal harm, Damkier and others classed pregnancies as exposed if a macrolide prescription was recorded between 0 and 14 weeks' gestation, which may have resulted in a dilution of any risk. This is further discussed in the overall discussion section below.

Meta-analyses on the safety of macrolides during pregnancy

Two meta-analyses have been conducted to evaluate the body of evidence on macrolides and adverse child or pregnancy outcomes (Fan and others, 2019; Mallah and others, 2019). However, the authors considered different outcomes and applied slightly different study inclusion criteria. A comparison of the studies can be found in Annex 1.

Based on the hypothesis that short-term fetal hypoxia induced by fetal arrhythmia could possibly be the underlying mechanism of observed adverse effects of macrolides, Fan's 2019 meta-analysis included outcomes that could potentially result from short-term fetal hypoxia.

These outcomes included fetal and neonatal death, congenital malformations, and conditions resulting from central nervous system damage such as epilepsy, cerebral palsy, ADHD and autism.

Mallah and others commented that Fan's 2019 meta-analysis only assessed 'general adverse child outcomes' and only included a limited number of original studies, therefore their review included any congenital malformation as an outcome.

Both meta-analyses demonstrated a systematic approach to search, selection, evaluation and analysis of studies. The objectives of both analyses were to consolidate evidence on the effects of the use of macrolides in pregnancy on paediatric and fetal outcomes.

Although both were methodologically appropriate, each of the studies demonstrated their individual approach to the conduct of systematic review and meta-analysis. This was primarily due to subjectivity inherent in the selection of search terms, databases, selection and application of inclusions, and inclusion criteria to primary research studies.

The meta-analyses were composed of 2 separate sets of studies. There was partial overlap between the studies in the two metanalyses (6 of the 16 total studies). Despite this, there was mild agreement that there was either no association, or a very weak association between first-trimester exposures to macrolides and congenital malformations.

Fan's 2019 meta-analysis reported a pooled OR for major malformations of 1.13 (95% CI 0.99 to 1.29) compared to alternative antibiotics, based on 3 studies: Einarson and others, 1998; Romoren and others, 2012; and Muanda and others 2017b (pooled OR 1.03, 95% CI 0.86 to 1.22 based on 4 studies for all malformations).

Mallah and others reported an OR for all malformations of 1.06 (1.00 to 1.12) compared to the group exposed to non-macrolide anti-bacterials and other non-teratogenic drugs, based on 9 unspecified studies.

Use of mixed study designs (randomised control studies and observational studies) might not be appropriate but they were handled separately in the review by Fan and others. In contrast, Mallah and others only included observational studies.

Outcomes used by Fan were more inclusive and included central nervous system damage and miscarriage, while Mallah only considered outcomes in live births by different anatomic locations.

Ultimately, given the heterogeneity of conduct and findings of the 2 meta-analyses it is difficult to compare the findings presented in the 2 publications.

A systematic appraisal of their corresponding primary research studies was considered be a more appropriate approach for consolidation of available evidence on macrolide safety in pregnancy.

In order to facilitate this approach, a previously developed tool for assessing the quality of evidence was used, the ROBINS-I tool.

4. Systematic review of the evidence on the safety of macrolide use in early pregnancy

The objective of this systematic review by the MHRA was to evaluate the available epidemiological evidence on the effects of exposure to macrolides in early pregnancy.

The quality of studies was assessed using the ROBINS-I tool for non-randomised studies of interventions. The review was conducted to ascertain the effects of individual macrolides (erythromycin, azithromycin, and clarithromycin) on miscarriage, major congenital malformations, and cardiovascular malformations.

Full details of the systematic quality review are available upon request.

Materials and methods

Studies previously included in 2 meta-analyses on the effects of macrolide antibiotics (Mallah and others, 2020; Fan and others, 2019), along with the 2 most recent primary research publications (Damkier and others, 2019; Fan and others, 2020) were included. This resulted in a total of 38 studies for initial review to determine whether they qualified according to the agreed criteria in terms of the review questions.

This review evaluated the evidence under 3 separate objectives for each of the 3 reviewed macrolide antibiotics, developed using the Population Intervention Control Outcome criteria (PICO) (Higgins and others, 2019).

Studies with penicillin as a comparator were initially prioritised over the studies with comparator groups unexposed to antibiotics. This decision was made with the objective to review research with a reduced presence of confounding by indication.

The presence of this type of confounding can compromise the quality of observational studies on the effects of medication. However, on closer review of the studies, only a small number used penicillin as a comparator group (Fan, 2020; Damkier, 2019; Muanda, 2017a; Muanda, 2017b). Therefore, studies with unexposed pregnancies were also included in the review.

The objectives were to:

- evaluate the effect of erythromycin, azithromycin and clarithromycin use in the first trimester of pregnancy on the risk of major congenital malformations compared to penicillin exposure or pregnancies not exposed to antibiotics

- evaluate the effect of erythromycin, azithromycin and clarithromycin use in the first trimester of pregnancy on the risk of congenital cardiovascular malformations compared to penicillin exposure or pregnancies not exposed to antibiotics

- evaluate the effect of erythromycin, azithromycin and clarithromycin use in the first trimester of pregnancy on the risk of miscarriage compared to penicillin exposure or pregnancies not exposed to antibiotics

The studies that addressed these objectives qualified for further review and assessment of the risk of bias using the ROBINS-I tool for non-randomised studies of interventions (Sterne and others, 2016).

Data on study design, study period, location, participants characteristics (age, health, pregnancy characteristics, and so on), and intervention characteristics (erythromycin, penicillin or control) were extracted and recorded on a pre-defined form.

The quality of the studies was independently evaluated by 2 MHRA reviewers using the ROBINS-I tool (Sterne and others, 2016). The ROBINS-I approach is based on the evaluation of bias in relation to a target trial, which is designed to allow an unbiased unconfounded study of the association without concern over feasibility or ethical considerations.

Each study was assessed across 7 bias domains from the ROBINS-I tool, adapted below from Sterne and others (2016).

Bias Domain	Related terms	Explanation
Pre-intervention		
D1 Confounding	Selection bias, allocation bias, channelling bias	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline. ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline
D2 Participant selection	Selection bias, inception bias, immortal time bias	When exclusion of some eligible participants, or the initial follow up time of some participants, or some outcome events, is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical. This form of selection bias is distinct from confounding.
At intervention		
D3 Intervention classification	Misclassification bias, information bias, recall bias, observer bias	Introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome and is likely to lead to bias.
Post-intervention		
D4 Deviation from intended interventions	Time-varying confounding	Arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s). Depends on the type of effect of interest (assignment to intervention or adherence to intervention
D5 Missing data	Attrition bias, selection bias	Arises when later follow-up is missing for individuals initially included and followed (for example differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.
D6 Measurement of outcomes	Recall bias, information bias, misclassification bias, observer bias, measurement bias.	Introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.
D7 Selection of reported result	Outcome reporting bias; Analysis reporting bias	Selective reporting of results in a way that depends on the findings.

The judgement on the risk of bias was recorded as low, moderate, serious, critical or no information for each of the bias domains:

1. Low risk of bias: the study is comparable to a well-performed randomised trial
2. Moderate risk of bias: the study is sound for a non-randomised study but cannot be considered comparable to a well-performed randomised trial
3. Serious risk of bias: the study has some important problems
4. Critical risk of bias: the study is too problematic to provide any useful evidence on the effects of intervention; and
5. No information on which to base a judgement about risk of bias for this domain.

The overall risk of bias was determined by combining the outcomes from 7 domains with priority given to the most serious risk of bias. The final decision on the risk of bias was reached through discussion between the reviewers, with discrepancies in judgement being resolved by reciprocal consultation between the reviewers.

Results

Of the 38 observational studies selected for review, 12 were considered to satisfy the criteria of the research question. See Annex 2 for a list of the 38 studies including the rationale for exclusion.

The judgments on the risk of bias are presented for each of the 7 domains and overall using a rating system of low, medium, or high. It is suggested these are considered alongside the forest plots available in the full PDF of this public assessment report.

Absolute rates were not available for most of the studies, and no information on risk in a comparator group was available for about 30% of the studies to enable the calculation (see table at Annex 3).

Erythromycin

A total of 11 studies investigated the effect of erythromycin exposure in the first trimester of over 24,000 pregnancies on 1 or more outcomes, jointly covering a period between 1980 and 2019 in 8 countries. Several studies evaluated more than 1 outcome of interest.

Major congenital malformations

Of 7 studies that investigated the effect of erythromycin on major congenital malformations:

- 5 were judged to be at serious risk of bias (due to selection bias introduced by inclusion of live births only)
- 2 at moderate risk of bias (Romoren 2012 and Czeizel 1999) as these studies included stillbirths and induced abortions in their analysis
- only 1 study reported a statistically significant association (Table 1) however this study was judged to be at serious risk of bias overall (Fan and others, 2020)

While most studies are not suggestive of an increased risk of major congenital malformations with erythromycin exposure, the association or the absence of association remains uncertain and may require further investigation using a more robust study design.

*Table 1. Forest plot for studies on erythromycin and major congenital malformations (MCM). Note: number of cases from case-control study design exposed marked with * and presented, where available over the total number of exposed, while for cohort study design the number of cases is given for the exposed cohort.*

Study	Design	Setting	Comparator	Erythromycin, n/N	Effect Estimate
Fan et al 2020	cohort	UK, 1990–2016	Penicillin	53/7,987	1.5
Damkier et al 2019	cohort	Denmark, 2000–2015	Penicillin	283/5,563	0.94
Muanda et al June 2017	cohort	Quebec, 1998–2009	Penicillin	64/697	1.02
Romoren et al 2012	cohort	Norway, 2004–2007	Unexposed	90/1,785	1.02
Cooper et al 2009	cohort	US, Tennessee, 1985–2000	Unexposed	55/2,128	0.86
Kallen et al 2014	cohort	Sweden, 1996–2011	Unexposed	99/2,531	1.18
Czeizel et al 1999	case–control	Hungary, 1980–1996	Unexposed	113*	1.1

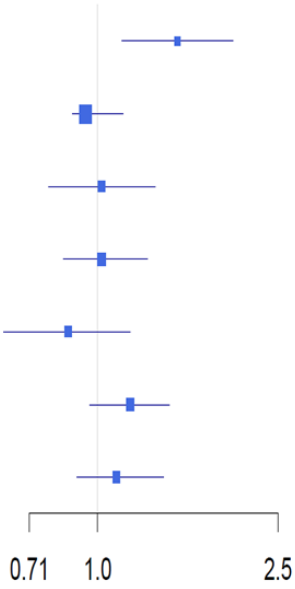

Table 2. Risk of bias assessment for studies on erythromycin and major congenital malformations, Bias domains adapted from Sterne and others, 2016

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Fan 2020	low	serious	low	low	-	moderate	low	serious
Damkier 2019	serious	serious	moderate	low	low	moderate	moderate	serious
Muanda 2017b	low	serious	moderate	low	low	moderate	low	serious
Romoren 2012	moderate	moderate	moderate	low	moderate	low	low	moderate
Cooper 2009	serious	serious	low	low	moderate	moderate	moderate	serious
Kallen 2014	serious	serious	low	low	low	moderate	low	serious
Czeizel 1999	moderate	moderate	moderate	low	serious	low	moderate	serious

Key: D1 bias due to confounding; D2 bias due to selection of participants; D3 bias in classification of interventions; D4 bias due to deviations from intended interventions; D5 bias due to missing data; D6 bias in measurement of outcomes; D7 bias in selection of the reported result.
- indicates not where bias was not assessable

Cardiovascular malformations

Of the 9 studies that investigated congenital heart defects in relation to erythromycin exposure Table 4 shows that 8 of the studies were judged to be at serious risk of bias and one at moderate risk (Romoren and others, 2012).

Of the 2 Swedish studies by Källén and others, the 2005 study reported an increased risk of cardiovascular malformations (OR 1.84, 1.29 to 2.62). In the 2014 study based on data from 2004 to 2011 (n=9), after a change in Swedish guidelines advising on using erythromycin in pregnancy, the risk of cardiovascular malformations was non-significant due to the small number of cases (n=9) (RR 1.71, 0.78 to 3.25).

The change in significance was attributed by Källén (2014) to a decline in prescription numbers. However, the risk estimate based on the period covering both studies (1996–2011) remained significant: (OR 1.70, 1.26 to 2.29).

Based on the reviewed evidence, which is generally of low quality, it is not possible to rule out a small increase in the risk of cardiovascular malformations in association with maternal use of erythromycin during the first trimester.

*Table 3. Forest plots for studies on erythromycin and cardiovascular malformations (CVM). Note: number of exposed cases from case-control study design marked with * and presented, where available over the total number of cases, while for cohort study design the number of cases is given for the exposed cohort.*

Study	Design	Setting	Comparator	Erythromycin, n/N	Effect Estimate
Fan et al 2020	cohort	UK, 1990–2016	Penicillin	19/1935	1.48
Damkier et al 2019	cohort	Denmark, 2000–2015	Penicillin	46/5563	0.94
Muanda et al June 2017	cohort	Quebec, 1998–2009	Penicillin	15/697	1.09
Kallen et al 2005	cohort	Sweden, 1996–2003	Unexposed	34/1844	1.84
Kallen et al 2014	cohort	Sweden, 2004–2011	Unexposed	43/2531	1.7
Romoren et al 2012	cohort	Norway, 2004–2007	Unexposed	21/1785	1.16
Crider et al 2009	case–control	US, 1997–2003	Unexposed	81*	1
Lin et al 2013	case–control	US, Canada, 1994–2008	Unexposed	18/4132*	1.3
Cooper et al 2009	cohort	US, Tennessee, 1985–2000	Unexposed	9/2128	0.93

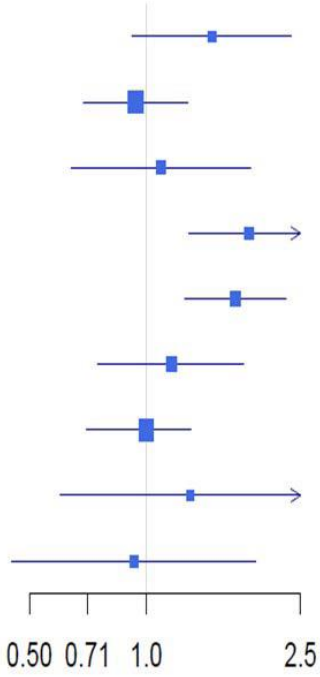

Table 4. Risk of bias assessment for studies on erythromycin and cardiovascular malformations. Bias domains adapted from Sterne and others, 2016.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Fan 2020	low	serious	low	low	-	moderate	low	serious
Damkier 2019	moderate	serious	moderate	low	low	moderate	moderate	serious
Muanda 2017b	low	serious	moderate	low	low	moderate	low	serious
Kallen 2005	serious	serious	serious	low	low	moderate	low	serious
Kallen 2014	serious	serious	moderate	low	low	moderate	low	serious
Romoren 2012	moderate	moderate	moderate	low	moderate	low	low	moderate
Crider 2009	moderate	serious	serious	low	moderate	low	moderate	serious
Lin 2013	moderate	serious	serious	low	moderate	low	moderate	serious
Cooper 2009	serious	serious	low	low	moderate	moderate	moderate	serious

Key: D1 bias due to confounding; D2 bias due to selection of participants; D3 bias in classification of interventions; D4 bias due to deviations from intended interventions; D5 bias due to missing data; D6 bias in measurement of outcomes; D7 bias in selection of the reported result.
- indicates not where bias was not assessable

Miscarriage

A total of 2 studies evaluated the effect of erythromycin prescription on miscarriage (Muanda and others, 2017a; Andersen and others, 2013). Neither study reported an association (table 5). Muanda's study was judged to be at moderate risk of bias and Andersen's at serious risk of bias.

There was an agreement of no association between erythromycin and the risk of miscarriage in 2 studies available for review. However, it was not possible to conclude an absence of risk due to the small number of publications and their poor quality.

*Table 5. Forest plots for studies on erythromycin and miscarriage. Note: number of exposed cases from case-control study design marked with * and presented, where available over the total number of cases, while for cohort study design the number of cases is given for the exposed cohort*

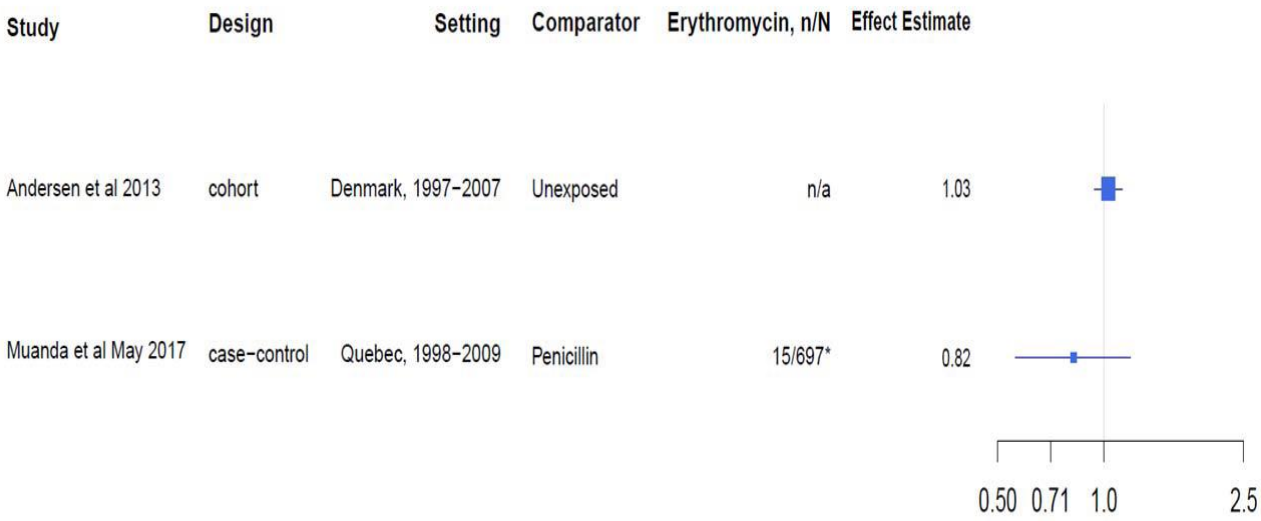

Table 6. Risk of bias assessment for studies on erythromycin and miscarriage. Bias domains adapted from Sterne and others, 2016.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Andersen 2013	serious	moderate	moderate	low	moderate	low	moderate	serious
Muanda 2017a	low	low	low	low	low	low	moderate	moderate

Key: D1 bias due to confounding; D2 bias due to selection of participants; D3 bias in classification of interventions; D4 bias due to deviations from intended interventions; D5 bias due to missing data; D6 bias in measurement of outcomes; D7 bias in selection of the reported result.

Clarithromycin

For clarithromycin, 4 studies investigated the effect of clarithromycin exposure in the first trimester of over 1,400 pregnancies on one or more outcomes, jointly covering a period between 1990 and 2016 in 3 countries. 3 studies evaluated more than one outcome of interest.

Major congenital malformations

No association was detected between first-trimester exposure to clarithromycin and major congenital malformations in the 3 studies in 3 different countries reporting on this outcome.

The studies were assessed to be of low-quality evidence by the overall serious risk of bias. The study by Andersen and others (2013) lacked control for confounding, and the studies by Muanda and others (2017b) and Fan and others (2020) suffered from selection bias (Table 8).

Therefore, although there was a trend of an absence of association, it was concluded that these 3 studies did not provide robust evidence for the absence of a small risk of major congenital malformations following exposure to clarithromycin.

Cardiovascular malformations

A single study reported on cardiovascular malformations following first trimester exposure to clarithromycin, concluding an absence of association (Muanda and others, 2017b) (Table 7). However, this study was judged to be at serious risk of bias, due to selection bias, as, like many of the reviewed studies, only live births were included. This may bias effect estimates towards the null.

Given the lack of publications on the effect of clarithromycin on cardiovascular outcome in pregnancy, and the presence of selection bias in the studies that qualified for this review, it was not possible to conclude or refute the absence of an association.

Miscarriage

Both studies evaluating the effect of clarithromycin exposure during pregnancy on miscarriage reported an increased risk. These were 1.6-fold compared to unexposed pregnancies (Andersen and others, 2013) and 2.73 times compared to penicillin (Muanda and others, 2017a).

Table 8 shows that the Andersen study was judged to be at serious risk of bias mainly due to a lack of control for confounding, which could result in a false positive association. The Muanda (2017a) study was assessed as being at a moderate risk of bias because many comparisons were made, but not all were fully presented (bias in selection of the reported result).

The available evidence indicates an increased risk of miscarriage following the prescription of clarithromycin. However, the observed risk is associated with a degree of uncertainty owing to the small number of studies, while the poor quality of the studies prevents concluding with certainty the strength of the reported association between clarithromycin and miscarriage**.**

*Table 7. Effect estimates for studies on clarithromycin and major congenital malformations (MCM), miscarriage and cardiovascular malformations (CVM) outcomes. Note: number of exposed cases from case-control study design marked with * and presented, where available over the total number of cases, while for cohort study design the number of cases is given for the exposed cohort.*

Table 8. Risk of bias assessment for studies on clarithromycin and major congenital malformations (MCM), miscarriage and cardiovascular (CVM) outcomes. Bias domains adapted from Sterne and others, 2016.

Study	Outcome	D1	D2	D3	D4	D5	D6	D7	Overall
Fan 2020	MCM	low	serious	low	low	-	moderate	low	serious
Andersen 2013	MCM, Miscarriage	serious	moderate	moderate	low	moderate	low	moderate	serious
Muanda 2017b	Miscarriage	low	low	low	low	low	low	moderate	moderate
Muanda 2017a	MCM, CVM	low	serious	moderate	low	low	moderate	low	serious

Key: D1 bias due to confounding; D2 bias due to selection of participants; D3 bias in classification of interventions; D4 bias due to deviations from intended interventions; D5 bias due to missing data; D6 bias in measurement of outcomes; D7 bias in selection of the reported result.
- indicates not where bias was not assessable

Azithromycin

Of the studies considered, 4 studies investigated the effect of azithromycin on one or more outcomes, based on exposure in the first trimester of over 7,300 pregnancies, jointly covering a period between 1985 and 2015 in 3 countries. 3 studies evaluated more than one outcome of interest. 3 studies were judged to be at serious risk of bias overall, and one at moderate risk.

Major congenital malformations

3 studies investigated the effect of first-trimester azithromycin on major congenital malformations (table 9). 2 studies were not suggestive of an association between azithromycin and major congenital malformations and the third, a large Canadian cohort study, reported a borderline association between azithromycin and major congenital malformations compared to penicillin prescription (OR 1.25, 95% CI 1.01 to 1.53). All 3 studies were judged overall to be at serious risk of bias, due to selection bias related to inclusion of outcomes from live births only. As discussed, this may result in regression of effect to the null.

Although there was a trend of an absence of association, it was concluded that these 3 studies did not provide robust evidence for the absence of a small risk of major congenital malformations following exposure to azithromycin.

Cardiovascular malformations

None of the 3 studies investigating the effect of exposure to azithromycin during the first trimester on cardiovascular malformations reported an association. However, as discussed above, all 3 studies were judged to be at serious risk of bias in the selection of participants domain. Therefore, the risk estimates could be biased towards the null.

While the evidence reviewed does not suggest a trend for an increased risk of cardiovascular malformations with maternal exposure to azithromycin, due to the serious risks of bias affecting the studies, the evidence cannot be considered robust enough to exclude the absence of a risk.

Miscarriage

The only study that investigated the effect of azithromycin exposure in early pregnancy on miscarriage (Muanda and others, 2017a) found a statistically significant association versus penicillin (aOR 1.91, 95% CI 1.53 to 2.39) (Table 9). This study was judged to be at moderate risk of bias due to a concern over selective reporting of results, as many comparisons were made, but not all were presented in the article.

The available evidence indicates an increased risk of miscarriage following the prescription of azithromycin. However, the observed risk is based on one study considered to be at moderate risk of bias, which prevents concluding with certainty the strength of the reported association between azithromycin and miscarriage.

*Table 9. Effect estimates for studies on azithromycin and Major congenital malformations (MCM), cardiovascular malformations (CVM) and miscarriage. Note: number of exposed cases from case-control study design marked with * and presented, where available over the total number of cases, while for cohort study design the number of cases is given for the exposed cohort*

Study	Outcome	Setting	Comparator	Azythromycin, n/N	Effect Estimate
Damkier et al 2019	MCM	Denmark, 2000–2015	Penicillin	182/5,037	1.09
Muanda et al June 2017	MCM	Quebec, 1998–2009	Penicillin	118/883	1.25
Cooper et al 2009	MCM	US, Tennessee, 1985–2000	Unexposed	23/559	1.37
Muanda et al May 2017	Miscarriage	Quebec, 1998–2009	Penicillin	110/na*	1.91
Damkier et al 2019	Cardiovascular	Denmark, 2000–2015	Penicillin	57/5,037	1.14
Muanda et al June 2017	Cardiovascular	Quebec, 1998–2009	Penicillin	19/883	0.92
Cooper et al 2009	Cardiovascular	US, Tennessee, 1985–2000	Unexposed	7/559	1.13

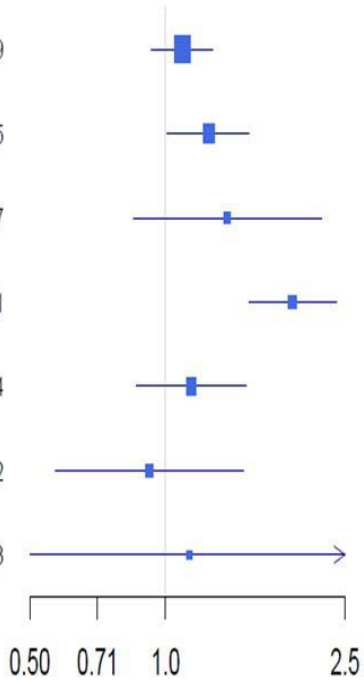

Table 10. Risk of bias assessment for studies on azithromycin and Major Congenital Malformations (MCM), cardiovascular malformations (CVM) and miscarriage. Bias domains adapted from Sterne and others, 2016.

Study	Outcome	D1	D2	D3	D4	D5	D6	D7	Overall
Damkier, 2019	MCM	moderate	serious	moderate	low	low	moderate	moderate	serious
Muanda, 2017b	MCM	low	serious	moderate	low	low	moderate	low	serious
Cooper, 2009	MCM	serious	serious	low	low	moderate	moderate	moderate	serious
Muanda, 2017a	Miscarriage	low	low	low	low	low	low	moderate	moderate
Damkier, 2019	CVM	moderate	serious	moderate	low	low	moderate	moderate	serious
Muanda, 2017b	CVM	low	serious	moderate	low	low	moderate	low	serious
Cooper, 2009	CVM	serious	serious	low	low	moderate	moderate	moderate	serious

Key: D1 bias due to confounding; D2 bias due to selection of participants; D3 bias in classification of interventions; D4 bias due to deviations from intended interventions; D5 bias due to missing data; D6 bias in measurement of outcomes; D7 bias in selection of the reported result.

Discussion on use of the ROBINS-I framework to evaluate bias.

The characteristics of the 'target trial' against which the studies evaluated were described as:

> *'… a large trial that achieved concealment of randomised allocation; maintained blinding patients, health care professionals and outcome assessors to the intervention received throughout follow up; ascertained outcomes in all randomised participants; and reported intervention effects for all measured outcomes'* (Sterne and others, 2016),

Thus, it became apparent that certain bias domains (confounding (D1), selection bias (D2) and presentation of findings (D7)) were most challenging in assigning an overall risk of bias for each study. The reviewers found the most inter-study inconsistency within these domains.

The ROBINS-I framework that was used for the evaluation of the presence of bias had some limitations. There was no provision made for the assessment of multiplicity, which was present in nearly all reviewed studies reporting on multiple outcomes. Multiplicity is a

concern when multiple outcomes are investigated, the observed association may be a result of chance alone and must be adjusted for in the analysis.

Furthermore, with the timing of exposure and exposure ascertainment being a concern for pregnancy medication use, the ROBINS-I tool evaluated these characteristics of the study under one question (specifically 3.1: risk of bias in classification of interventions – where the intervention groups definition is assessed). This did not provide an opportunity to differentiate between the studies with more pronounced issues of one or the other type, which were judged simultaneously and therefore might not be systematically evaluated under ROBINS-I framework.

It was decided that the 2 MHRA reviewers were to take this lack of detail into consideration in the overall judgement of the studies; however, this might not have been carried out in a systematic manner and introduced subjectivity.

Evaluation of confounding might have also suffered from subjectivity. Although confounding was considered under the 2 separate sections of the ROBINS-I protocol, the multitude of possible underlying factors presented a challenge for consistent evaluation.

A range of potential confounders was reported in various combinations between the studies, whereas some studies focused on indication for prescription and others on pregnancy characteristics. Therefore, it was decided that studies with the indication for prescription and penicillin used as a comparator made an adequate provision for confounding evaluation if some additional pregnancy risk factors were also considered (including co-morbidity, BMI, age, smoking or alcohol consumption).

This approach has potentially lowered the requirement for the studies' quality control regarding confounding. Given the overall lack of consideration of the whole range of factors available for review in the studies, this approach was selected to systematise the review, albeit some of important confounders might have been overlooked.

5. Discussion

In an attempt to provide clinically helpful information on the safety of macrolides, a systematic review of epidemiological data was conducted for each of the 3 macrolides (erythromycin, clarithromycin and azithromycin).

For each of the macrolides, 3 adverse outcomes were considered based on conflicting findings reported from different studies (major congenital malformations, cardiovascular malformations, and miscarriage).

The exposure period of interest was restricted to the first trimester of pregnancy when organogenesis occurs and exposure to potential teratogens may have adverse effects, resulting in one of the outcomes of interest.

Initially this review focused on studies comparing macrolides to penicillins to minimise confounding by infection. However, due to a small number of studies, these criteria were expanded to include unexposed studies as comparators.

Although at first it appeared that there were many relevant studies (n=38), further appraisal according to the review objectives excluded most studies (n=26). Of the 12 remaining studies, 11 reported data on erythromycin, and 4 reported on azithromycin and clarithromycin (table 11).

The quality of studies was assessed using the ROBINS-I tool for non-randomised studies of interventions (Sterne and others, 2016).

Most studies were assessed to have a serious risk of bias, mainly due to confounding or bias in selection of participants. This excludes the Canadian case-control study that evaluated the risk of miscarriage with macrolides (Muanda and others, 2017a), and the Norwegian cohort study which evaluated major malformations and cardiovascular malformations (Romoren and others, 2012).

Table 11. Summary of reviewed studies for the outcomes of major congenital malformations (MCM), cardiovascular malformations (CVM) and miscarriage.

Study	Setting	Outcome	Overall risk of bias	Number of first trimester exposures from published studies: erythromycin	Number of first trimester exposures from published studies: clarithromycin	Number of first trimester exposures from published studies: azithromycin
Fan (2020) cohort	UK 1990-2016	MCM, CVM	Serious	1935	162	73
Damkier (2019) cohort	Denmark 2000-2015	MCM, CVM	Serious	5563	0	5037
Muanda (2017b) cohort	Canada, Quebec 1998-2009	MCM, CVM	Serious	697	658	883
Muanda (2017a)* Case-control	Canada, Quebec 1998-2009	Miscarriage	Moderate	15	111	110
Källén (2005 and 2014) cohort	Sweden 1996-2011	CVM	Serious	2531	0	0
Lin (2013) case-control	Canada 1994-2008	CVM	Serious	4132	0	0
Anderson (2013) cohort	Denmark 1997-2007	MCM, Miscarriage	Serious	6492	253	0
Romoren (2012) cohort	Norway 2004-2007	MCM, CVM	Moderate	1786	229	643
Cooper (2009) cohort	US, Tennessee 1985-2000	MCM, CVM	Serious	903	0	559
Crider (2009)* case-control	US, 1997-2003	CVM	Serious	81	0	0
Czeizel (1999) case-control	Hungary, 1980-1996	MCM	Serious	34	0	0
Total first trimester exposures	Time period: 1985 - 2016			24169 (>24,000)	1413 (>1,400)	7305 (>7,300)

**number of exposed cases - actual exposure will be higher but figure unknown*

Strength of evidence

Erythromycin

Of 11 studies reviewed, consisting of over 24,000 first-trimester exposures, only 2 studies reported an increased risk of either major congenital malformations or cardiovascular defects (Fan and others (2019); Källén and others (2005, 2014)). The rest of the studies reported no association between prescription of erythromycin and any of the 3 studied outcomes.

The strength of association and the validity of the statistical association can provide strong evidence of causal relationships between the exposure and outcome. The magnitude of the association expressed as a large risk ratio combined with a high probability of the observed effect (small p-value) is a benchmark for judgement on causality.

There was an increase in the risk of 1.5 (major congenital malformations) and 1.8 times (cardiovascular malformations) compared to the reference category in studies by Fan and Källén respectively (Fan and others, 2020; Källén and others, 2005 and 2014). However, the validity of both studies was uncertain due to the presence of bias in the study design. In addition, the rest of the studies that reported no association were judged to be at risk of bias.

Despite Fan‘s attempts to account for various types of bias, selection bias was still considered to be a problem. It can be hypothesised that when severe malformation is developing in a fetus, it might present a risk to the pregnancy. Thus, the most severe outcomes could result in pregnancy termination, limiting the number of malformations in live-born children. A failure to account for selection bias will, therefore, bias the results toward no effect.

In the study by Fan where the selection bias was the main caveat to its quality, the detected increase in risk could be therefore concerning as it an unlikely result of live-birth selection bias. However, it is also likely that confounding by severity of underlying infection, and other unmeasured confounding factors are likely to be influencing the finding of an increased risk of major congenital malformations for erythromycin in the study by Fan and others.

Combined with the less robust epidemiological evidence contributed by the other studies and the lack of association reported in them, it is not possible to conclude on a presence of risk associated with erythromycin use in the first trimester of pregnancy.

Clarithromycin

Data on the safety of clarithromycin in early pregnancy is the most limited of the 3 macrolides, with around 1,400 first-trimester exposures included in the four studies reviewed. None of the 3 studies evaluating a risk of major congenital malformations, or the study evaluating cardiovascular malformations reported an association.

An association between clarithromycin prescription and miscarriage was reported at a statistically significant level from 2 studies with an increase of 1.6 and 2.7 times compared to the reference category (Andersen and others, 2013; Muanda and others, 2017a). While the adequate size of the studies added confidence in the reported results, the certainty in the reported association was undermined by the uncertainty around the validity of the studies, judged as being at moderate (Muanda and others, 2017a) and serious (Andersen and others, 2013) risk of bias.

Although there was a trend for an absence of association between clarithromycin exposure in early pregnancy and either major malformations or cardiovascular malformations, based on the small number of studies at a serious risk of bias, it is not possible to conclude on the absence of a risk.

The evidence regarding clarithromycin and miscarriage indicates an increased risk, although due to the small number of studies (n=2) this is associated with a degree of uncertainty. Moreover, the poor quality of the studies prevents a conclusion on the strength of the association.

Azithromycin

There is a moderate amount of epidemiological evidence on the risk of adverse pregnancy outcomes associated with maternal use of azithromycin (more than 7,300 first-trimester exposures).

Regarding major congenital malformations, only 1 of the 3 studies evaluated presented a small increased risk of borderline significance (OR 1.25, 95% CI 1.01 to 1.53; Muanda and others, 2017b). However, this study was judged to be at serious risk of bias, which raises uncertainty over the validity of the findings.

There was no evidence of an increased risk of cardiovascular defects with azithromycin exposure during pregnancy in the 3 studies evaluated. However, all 3 studies were judged as being at serious risk of bias.

There was limited evidence to support an association between azithromycin and miscarriage, with the only study meeting the inclusion criteria for review presenting an almost 2-fold increased risk, compared to exposure to penicillin (OR 1.91, 95% CI 1.53 to 2.39; Muanda and others, 2017a). However, as discussed, there were many comparisons made in this study, not all of which were presented in the article.

In addition, concern was raised over the extent to which confounding was controlled for and overall the study was judged to be at moderate risk of bias and provides insufficient evidence to confirm that the use of azithromycin in early pregnancy may cause an increased risk of miscarriage.

Biological plausibility of macrolide-induced fetal harm

Major congenital malformations

The analysis focused on studies evaluating the risk of major congenital malformations, cardiac malformations, and miscarriage.

There is no established mechanism by which macrolides could induce major birth defects. The product information for erythromycin states that there are no teratogenicity data. No teratogenic effects were observed in animal studies with azithromycin. Studies with clarithromycin (at high doses) reported variable results with some reporting an increase in cardiovascular malformations and cleft palate in rats and mice, and embryonic loss in monkeys, but only at doses toxic to the mother animals (included in the clarithromycin product information).

As major congenital malformations comprise a wide variety of organ systems that develop at different times during gestation and that are susceptible to disruption via specific mechanisms, it is difficult to comment on the biological plausibility of macrolide-induced birth defects in general.

Additionally, the causes of congenital malformations can be complex and multifactorial. Non-genetic risk factors include alcohol use, folic acid intake, obesity, uncontrolled maternal diabetes, and some maternal infections. Moreover, the studies reviewed do not suggest a pattern in terms of the types of defects observed in infants exposed to macrolides in early pregnancy.

Cardiac defects

Cardiovascular defects are among the most common congenital anomalies. The NHS website states that congenital heart disease (CHD) affects up to 8 of every 1,000 babies born in the UK.

Factors suggested to be associated with an increased risk of CHD include maternal smoking or alcohol consumption (both of which are difficult to control for in observational studies) and poorly controlled maternal diabetes.

Septal defects are some of the most common cardiac defects and range in terms of severity. Of note, ventricular septal defects were the most frequently reported cardiac defect in the Fan 2020 study, followed by patent ductus arteriosus.

However, publications reporting increased risks of cardiovascular malformations (Fan and others 2020; Källén and others 2005, 2014) speculate over the possibility that macrolides, which are known to influence cardiac repolarisation, could induce fetal arrhythmia, which may in turn lead to short-term fetal hypoxia.

This hypothesis is based on publications by Danielson and others (2007) and Nilsson (2014). Danielson and others discuss that drugs which block the rapid delayed rectifier (IKr) channel may exert teratogenicity through cardiac arrhythmia and the development of reactive oxygen species (ROS).

Nilsson and colleagues (2014) discuss that the proposed teratogenic mechanism for macrolides is blockade of the human ether-a-go-go-related (hERG)/IKr current in the embryonic heart causing bradycardia and arrhythmia, resulting in altered cardiac blood flow or embryonic hypoxia but only at levels above those expected from normal use of macrolides during pregnancy.

Källén (2014) discusses that in animal studies, several drugs known to prolong QT interval have been shown to be teratogenic because of embryonic cardiac arrhythmia leading to fetal hypoxia and subsequently cardiac and vessel damage (such as clomipramine, lithium, paroxetine).

However, the duration of fetal exposure to erythromycin, which is typically prescribed for a relatively short period of time (5 to 7 days), is likely to be considerably less than for many other hERG-blocking agents, which are generally taken for longer periods of time.

It is also important to consider the timing of macrolide exposure in relation to the critical period of organogenesis (between 3 and 8 weeks).

Given that macrolides are generally prescribed for short periods of time (for example, up to 5 or 10 days depending on the macrolide and infection being treated) exposure to a macrolide during the first 2 weeks of pregnancy might seem unlikely to cause structural defects in the developing fetus. This may be especially true to erythromycin, which has a short half-life of 1.5 to 2 hours. Therefore, any effect of erythromycin may be difficult to detect.

Table 12 shows that half the studies that evaluated the risk of birth defects with first-trimester exposure classified infants as exposed if a macrolide prescription was issued sometime between the last menstrual period (week 0) and the end of the first trimester, which could be a period of 12 to 14 weeks.

Most of the risk estimates from these studies were non-significant except for a borderline association for azithromycin and major congenital malformations reported by Muanda and others ((2017b): OR 1.25, 95% CI 1.01 to 1.53).

Lin and others (2013) and Romoren and others (2012) considered an exposure period of interest from conception (week 2). However, these studies also did not find any associations with the outcomes of interest.

3 studies (Fan and others (2020); Czeizel and others (1999) and Romoren and others (2013)) excluded infants exposed during the first 4 weeks of gestation and in the 2 Swedish cohort studies that report an association between erythromycin and cardiovascular

malformations, it is not clear during what period pregnancies were considered to be exposed (Källén and others, 2005 and 2014).

Studies by Fan and Källén discuss a potential ‘dilution’ of any effect in studies that included cases exposed outside the critical period of organogenesis.

Fan and others (2020) state that 36% of first-trimester macrolide prescriptions were issued before 4 gestational weeks and so were excluded from the analyses.

It is noted that while Romoren and others (2013) did not find a statistically significant association between first trimester erythromycin use (2 to 13 weeks) and cardiac malformations (aOR 1.2, 95% CI 0.8 to 1.8).

When the exposure period was restricted to the most critical period in terms of heart formation (4 to 8 weeks), the adjusted risk estimate increased, although remained non-significant (aOR 1.6, 0.9 to 3.0).

While these data do not provide strong evidence to explain the reason for the conflicting findings between some of the studies, this aspect of timing of exposure should be a consideration in any future studies.

Table 12. Distribution of exposure periods considered in the reviewed studies

			Risk estimate for erythromycin		
Exposure period (weeks)	**Study**	**Comparator**	**MCM**	**CVM**	**Miscarriage**
4 to 13 weeks	Fan (2020)	penicillin	1.5* (1.13-1.99)	1.48 (0.92-2.37)	-
4 to 8 weeks (sensitivity analysis)	Romoren (2012)	unexposed	-	*1.62 (0.86-3.02)*	-
4 to 8 weeks	Czeizel (1999)	unexposed	0.8 (0.5-1.4)	-	-
2 to 14 weeks	Lin (2013)	unexposed	-	1.3 (0.6-2.6)	-
2 to 13 weeks	Romoren (2012)	unexposed	1.02 (0.77-1.35)	1.16 (0.75-1.78)	-
Not known to 13 weeks*	Källén (2014)	unexposed	1.18 (0.96-1.44)	1.7* (1.26-2.29)	-
0 to 14 weeks	Damkier (2019)	penicillin	0.94 (0.8-1.11)	0.94 (0.69-1.28)	-
0 to 13 weeks	Muanda (2017b)	penicillin	1.02 (0.78-1.34)	1.09 (0.64-1.86)	-
0 to 16 weeks	Cooper (2009)	unexposed	0.86 (0.62-1.18)	0.93 (0.45-1.91)	-
minus 2 to 12 weeks	Crider (2009)	unexposed	-	1.0 (0.7-1.3)	-
0 to 13 weeks	Andersen (2013)	unexposed	-	-	1.03 (0.94-1.13)
0 to 20 weeks	Muanda (2017a)	penicillin	-	-	0.82 (0.56-1.19)

** Källén and others (2005 & 2014) do not state the start of first trimester exposure, article states that women were asked about medication taken since the start of pregnancy.*
- indicates where risk estimates were not measured

Miscarriage

Miscarriage is relatively common during the first trimester of pregnancy and is estimated by the NHS to affect up to 1 in 8 pregnancies in the UK.

Miscarriage may be associated by a range of factors including chromosomal defects, advanced maternal age, obesity, smoking, and alcohol use. Miscarriage in the second trimester may be linked to underlying health conditions such as diabetes, severe

hypertension or maternal infections including some sexually transmitted infections for which macrolides are indicated.

Of the studies reviewed, 2 studies reported an increased risk of miscarriage with clarithromycin use (Andersen and others (2013): OR 1.66, 95% CI 1.22 to 2.26 and Muanda and others, (2017a): aOR 2.73, 2.16 to 3.44). Muanda and others (2017a) also reported an increased risk of miscarriage for azithromycin (adjusted OR 1.91, 1.53 to 2.39).

None of the studies discussed possible biological mechanisms for macrolide-induced miscarriage.

However, Andersen and others discuss that placental transfer of clarithromycin has been shown to be twice that of erythromycin, referencing the work of Heikkinen and colleagues (2000) who stated that placental transfer rates of erythromycin and azithromycin were reported to be 3.0% and 2.6%. Witt and colleagues found the mean rate of transfer for clarithromycin to be 6.1% (Witt and others, 2003).

Andersen and others propose this as a possible explanation for the apparent increased risk of miscarriage for clarithromycin but not erythromycin. However, this would not explain the increased risk of miscarriage with azithromycin presented by Muanda and colleagues (2017a).

Magnitude of absolute effects

Since the reviewed studies were performed in several different countries where background rates of the outcomes differ, it is difficult to translate relative risks into absolute and excess risks.

In addition, several studies, including Muanda and others (2017a) that reported a statistically significant increased risk of miscarriage with exposure to clarithromycin and azithromycin were case-control studies and did not provide total numbers of exposed women. Moreover, most studies did not report statistically significant risk estimates.

The only UK data was from the recent cohort study by Fan and others (2020), which was the only study to report a statistically significant increased risk of major congenital malformations with first-trimester erythromycin exposure.

Using data provided from the reviewed studies, rates per 1000 first-trimester exposures to each macrolide were compared to rates per 1000 exposed to comparator or unexposed (see Annex 3).

Based on data from Fan and others (2020), the rate of major malformations following first-trimester use of erythromycin is 27.39 per 1000 exposed and 17.65 per 1000 for penicillin-exposed (rate difference 9.74).

To put this into context, the prevalence of congenital anomalies reported in the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) statistics from 2018 is stated as 213.3 per 10,000 (or 21.3 per 1000).

Therefore, assuming the association between erythromycin prescription in the first trimester and major congenital malformations reported by Fan and others (2020) is true, the attributable risk would be relatively small.

Implications for national treatment guidelines on the use of macrolides in pregnancy

As discussed at the start of this report, erythromycin is recommended for treating many common infections such as respiratory tract infections, as an alternative for pregnant patients who are allergic to penicillin.

In the UK, the British Association for Sexual Health and HIV (BASHH) recommend azithromycin as a first-line option for treatment of chlamydia in pregnant women, and as an option for the treatment for gonorrhoea if no adequate alternatives are available. Both infections are associated with adverse pregnancy or fetal outcomes if left untreated.

The recently updated UKTIS monograph on macrolides states that

> *'although the majority of the available data do not provide evidence that macrolide use in pregnancy increases the risk of adverse pregnancy outcome, a limited number of studies have described small increased risks of malformation and miscarriage. Macrolide use in pregnancy should therefore be reserved for compelling indications where there are no suitable alternatives with adequate pregnancy safety data, and should only be used if the benefit of treatment is expected to outweigh any small increased risks which may exist.'*

The findings of the current review of available evidence on macrolide use during pregnancy and the risk of adverse fetal outcomes would appear to support this position.

Considering the uncertainty over the validity of epidemiological evidence on the risk of major congenital malformations, cardiovascular malformations and miscarriage, the data reviewed appear to be consistent with current clinical guidelines on the use of the respective macrolides during pregnancy.

Options for further review

Previously, it was intended to use data from recent studies (Fan and others, 2020; Damkier and others, 2019) to conduct a further updated meta-analysis of the data on macrolide safety in pregnancy.

However, following review of these studies together with the previous studies included in the meta-analyses conducted by Fan and others (2019) and Mallah and others (2020) it was concluded that the evidence on the effects of macrolides use in pregnancy is heterogeneous and of low quality.

Therefore, conducting another meta-analysis by macrolide, using studies with a high degree of bias, would contradict the requirement for good-quality data from the primary studies.

6. Conclusions

Of the 3 macrolides included in this review, the most experience of use in pregnancy is seen for erythromycin (>24,000 first trimester exposures) and only 2 of the 11 studies suggested an increased risk of major congenital or cardiovascular malformations. The number of first trimester exposures to azithromycin and clarithromycin are more moderate (>7,300 and >1,400, respectively)

Overall, the quality of observational data on the safety of maternal use of erythromycin, clarithromycin and azithromycin during early pregnancy is low. Furthermore, a biological mechanism for teratogenic effects has not been established. Therefore, it is considered that the available evidence is insufficient to confirm the presence of small increased risks of major congenital malformations or cardiovascular malformations following first-trimester exposure to erythromycin, or an increased risk of miscarriage following exposure to clarithromycin or azithromycin in early pregnancy.

The evidence is also insufficient to confirm the absence of small increased risks of major congenital malformations or cardiovascular malformations following first trimester exposure to azithromycin or clarithromycin, or miscarriage following exposure to erythromycin.

A previous review of SmPC warnings about use in pregnancy for the three macrolides revealed inconsistency in the level of detail and presence of statements about considerations of the benefits and risks.

To ensure consistency across macrolide product information, the experience from observational studies evaluating the safety of use in early pregnancy will be reflected along with an appropriate statement reflecting that the product should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any possible risk.

Due to the low quality of the available studies, it is not considered advisable to conduct an updated meta-analysis. This would be unlikely to produce reliable estimates of whether macrolide use in early pregnancy is associated with fetal harm.

There remains a need for high-quality research into the effect of erythromycin, clarithromycin or azithromycin prescription in pregnancy.

Certain infections in pregnancy can cause serious harm to both to the mother and baby if not treated. In such cases, pregnant women should receive treatment with an appropriate antibiotic. Decisions by the prescriber of which antibiotic to use should be based on the benefits and risk to mother and baby. If a prescriber views that the potential benefits of treatment will outweigh the risks and that no suitable and safe alternative is available, for example in true penicillin allergy, a macrolide can be used during pregnancy.

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Sterne JAC and others. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions]. BMJ 2016: volume 355, i4919

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8. Glossary of Terms

Clinical data or clinical studies
Data on the effects of medicines that come from studies of people taking the medicines. This includes data from clinical trials and epidemiological studies.

Clinical trial
A research study that tests the effectiveness and safety of medicines in humans.

Cohort study
In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Confidence interval
A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between two groups, and usually accompany ratio values such as odds ratios, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded
Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Congenital
A medical condition that is acquired by the fetus during pregnancy and is present at birth.

Congenital Malformations
A physical defect present in a baby at birth that can involve many different parts of the body, including the brain, heart, lungs, liver, bones, and intestinal tract.

Defect
A fault or imperfection in the body.

Epidemiological studies
Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

Fetus
An unborn baby developing in the mother's womb

Gestational age
Gestational age is the common term used during pregnancy to describe how far along the pregnancy is. It is measured in weeks, from the first day of the woman's last menstrual cycle (period) to the current date. A normal pregnancy can range from 38 to 42 weeks.

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

In utero
The time that the fetus is in the uterus of the pregnant female.

Major congenital malformations
Physical defects present in a baby at birth that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention.

Meta-analysis
A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Odds ratio
A measure of risk for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than one suggests a decreased risk.

Null Hypothesis / Null
The theory or hypothesis that an observed difference is due to chance alone and not due to a systematic cause.

Prevalence
The proportion of individuals in a defined population that have a disease or other health outcomes of interest at either a specified point in time (known as point prevalence) or during a specified period of time (period prevalence).

Randomised controlled clinical trial
A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention.

Regression analysis
Regression is a statistical method that attempts to determine the strength and character of the relationship between one dependent variable and a series of other variables.

Retrospective study
A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). A retrospective study looks backwards and examines the medical and lifestyle histories of the people in each group to learn what factors may be associated with a disease or condition that is established at the start of the study.

Risk factor
A substance or activity that increases the likelihood of someone developing an illness or medical condition.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Systematic review
A review of the published scientific literature that aims to find as much as possible of the research relevant to a particular research question and based on appraisal of the research summarises the main findings (qualitative or quantitative).

Teratogen/ teratogenic
A teratogen is an agent that can disrupt the anatomical development of the embryo resulting in a birth defect.

Trimester
One of the three 3-month periods into which a human 9-month pregnancy can be divided.

9. Annexes

List of Annexes:

Annex 1: Comparison table of Fan and Damkier studies
Annex 2: Studies reviewed for inclusion in the review
Annex 3: Rate differences for outcomes presented in the macrolide studies

Annex 1: Comparison table of Fan and Damkier studies

Table 1: A comparison of the studies by Fan and others (2020) and Mallah and others (2019)

	Associations between use of macrolide antibiotics during pregnancy and adverse child outcomes: A systematic review and meta-analysis (Fan et al. 2019) *Focused on studies with comparison groups exposed to similar antibiotics (mostly penicillins and cephasporins)*	**Prenatal Exposure to Macrolides and Risk of Congenital Malformations: A Meta-Analysis. (Mallah et al. 2019)** *Three comparison groups:* *Group 1: infants unexposed to any medicine in utero* *Group 2: infants exposed to non-macrolide antibiotics or non-teratogens in utero* *Group 3: mixed population of Groups 1 and 2*
Findings	• Fan and colleagues conducted a review of **10 observational studies** and 11 RCTs assessing fetal and child outcomes in 228,556 study participants. • The analysis suggested that prescription of macrolides in pregnancy was associated with an **increased risk of miscarriage (pooled OR 1.82, 95% CI 1.57–2.11, three studies, I^2 = 0%),** cerebral palsy and/or epilepsy (OR 1.78, 1.18–2.69; one study), epilepsy alone (OR 2.02, 1.30–3.14, one study; OR 1.03, 0.79–1.35, two studies), and **gastrointestinal malformations (OR 1.56, 1.05–2.32, two studies)** compared with alternative antibiotics (1st trimester). • no difference in risk was identified for **major malformations (pooled OR 1.13, 0.99-1.29, three studies**) or **cardiovascular malformations (pooled OR 1.14, 0.8-1.62, four studies),** all with 1st trimester exposure. • No association found for musculoskeletal malformations (pooled OR 1.18, 0.95-1.47, 2 studies)	• Mallah and colleagues conducted a review of **21 observational studies** conducted between 1990-2019 assessing effects on macrolides antibiotics on congenital malformations in live births. • The analysis suggested a **weak association between exposure to macrolides and any type of congenital malformation (OR 1.06, 95% CI 1.01–1.10) when compared to a mixed population (group 3).** • This association for **any congenital malformation** was also observed for fetal exposure limited to the first trimester **(ORgroup3 1.06, 95% CI 1.01–1.11, 21 studies) and when restricted to evidence from 17 cohort studies (OR 1.07, 95% CI 1.02–1.13).** • **Digestive system malformations were found to be weakly associated with prenatal exposure to macrolides (ORgroup3 1.14 [95% CI 1.02–1.26] based on 9 studies).** • The musculoskeletal system was also found to be potentially affected (ORgroup2 1.21 [95% CI 1.08–1.35], 4 studies and (ORgroup3 1.15 [95% CI 1.05–1.26] 6 studies). • No association was found for cardiovascular malformations: ORgroup2 0.87, 0.81-0.95, 7 studies)
Research question	To determine the effects of macrolide treatment during pregnancy on fetal and	To assess the relation between prenatal exposure to macrolides and occurrence of

	child outcomes.	congenital malformations.
Literature search, study selection, and quality analysis	The search strategy involved the use of PubMed, Embase, Cochrane Library, Conference Proceeding Citation Index-Science and ClinicalTrials.govto find included studies. Various search terms specific to the research question and the requirements of the database were applied to identify primary research articles. **Bias was assessed using Cochrane Collaboration's tool for assessing the risk of bias in randomised trials and ROBINS-I for observational studies**. The selection criteria for all included and excluded studies are outlined and described. Furthermore, the quality of 10% of the studies was methodologically and independently assessed by two reviewers, achieving 81% of an inter-observer agreement.	The studies were searched in MEDLINE, Embase, five regional bibliographic databases of the World Health Organization, the Open Access Thesis and Dissertations, and Conference Proceeding Citation Index. Various search terms specific to the research question and the requirements of the database were applied to identify primary research articles. **The quality of studies was assessed using Newcastle–Ottawa scale. No additional framework was reported for assessment of bias for observational studies**. The selection criteria for all included and excluded studies are outlined and described. Furthermore, data extraction and analysis were independently performed by two epidemiologists.
Outcome measures and combination of studies:	All fetal and/or childhood outcomes were considered. Randomised controlled trials (n=9) and observational studies(cohort=12) were included in the review according to different eligibility criteria indicated and analysed separately. Data were pooled to estimate pooled ORs for each adverse outcome using a random-effects meta-analysis, considering the heterogeneity among studies.	Congenital malformations in live births only were considered. Case-control studies (n=4) and observational studies(cohort=17) were included in the review and their data were analyzed together using pooled ORs by weighting the log RRs and log ORs for cohort and case-control studies, respectively.
Main results and tests of significance	Maternal exposure to macrolide antibiotics was associated with an increased risk of miscarriage, while evidence of its association with cerebral palsy and epilepsy was inconsistent.	Prenatal use of macrolides in early pregnancy was weakly associated with congenital malformations and was primarily limited to musculoskeletal and digestive systems.
Comments	• Focused on studies with comparison groups exposed to other antibiotics (mostly penicillins and cephalosporins) • Did indicate which study contributed to each pooled estimate • Finding for miscarriage based on three studies but dominated by Muanda and others (2017a)	• Included studies with mixed/unexposed comparison groups. • Did not restrict to first trimester exposure • Included studies solely investigating risk of pyloric stenosis which likely explains the association seen for digestive system malformations, • Included the most recent study using same population (such as Källén 2014, not Källén 2005). • Did not indicate which studies were included in pooled estimates (just numbers of studies).

Annex 2: Studies reviewed for inclusion in the review

Table 1: Studies published since Mallah and Fan reviews (n=2)

Study	Includes erythromycin, azithromycin or clarithromycin	Includes outcome of interest (MCM, CVM or miscarriage)	Comparator	Included or excluded	Reason for exclusion
Damkier P, Brønniche LM, Korch-Frandsen JF, Broe A. In utero exposure to antibiotics and risk of congenital malformations: a population-based study. American journal of obstetrics and gynecology. 2019 Dec 1;221(6):648-e1	yes (erythromycin, azithromycin)	MCM, CVM	women exposed to penicillin	included	N/A
Fan H, Gilbert R, O'Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. bmj. 2020 Feb 19;368.	yes (erythromycin, clarithromycin, azithromycin)	MCM, CVM	women exposed to penicillin	included	N/A

Table 2: Studies included in Mallah et al. (2019)

Study	Includes erythromycin, azithromycin or clarithromycin	Includes outcome of interest (MCM, CVM or miscarriage)	Comparator	Included or excluded	Reason for exclusion
Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. A Population based case–control teratologic study of oral erythromycin treatment during pregnancy. Reprod Toxicol. 1999;13(6):531–6.	yes (erythromycin)	any congenital malformation	NA (case-control)	Included	NA
Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ. Antibacterial medication use during pregnancy and risk of birth defects: national birth defects prevention study. Arch Pediatr Adolesc Med. 2009;163(11):978–85. https://doi.org/10.1001/archpediatrics.2009.188.	yes (erythromycin)	MCM	NA (case-control)	Included	NA
Andersen JT, Petersen M, Jimenez-Solem E, Broedbaek K, Andersen NL, Torp-Pedersen C, et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. PLoS One. 2013;8(1):e53327. https://doi.org/10.1371/journal.pone.0053327.	yes (clarithromycin)	MCM, miscarriage (spontaneous abortion)	unexposed women	included	NA
Lin KJ, Mitchell AA, Yau WP, Louik C, Hernandez-Diaz S. Safety of macrolides during pregnancy. Am J Obstet Gynecol. 2013;208(3):221. https://doi.org/10.1016/j.ajog.2012.12.023.	yes (erythromycin)	CVM	NA (case-control)	included	NA
Kallen B, Danielsson BR. Fetal safety of erythromycin. An update of Swedish data. Eur J Clin	yes (erythromycin)	CVM	unexposed women	included	NA

Pharmacol. 2014;70(3):355–60. https://doi.org/10.1007/s00228-013-1624-3.					
Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. Br J Obstet Gynaecol. 1998;105(8):882–9.	yes (azithromycin)	stillbirths, abortions (missed, spontaneous, therapeutic), intaruterine death, ectopic pregnancy, congenital malformations	NA	excluded	no outcomes of interest reported for azithromycin
Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. A case–control teratological study of spiramycin, roxithromycin, oleandomycin and josamycin. Acta Obstet Gynecol Scand. 2000;79(3):234–7.	no	MCM	NA	excluded	did not study macrolide of interest
Mahon BE, Rosenman MB, Kleiman MB. Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. J Pediatr. 2001;139(3):380–4. https//doi.org/10.1067/mpd.2001.11757 7.	yes (all 3 macrolides)	no (pyloric stenosis)	unexposed women	excluded	did not study outcome of interest
Cooper WO, Griffin MR, Arbogast P, Hickson GB, Gautam S, Ray WA. Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. Arch Pediatr Adolesc Med. 2002;156(7):647–50. https ://doi.org/10.1001/archpedi.156.7.647.	yes (erythromycin)	no (pyloric stenosis)	other antibiotics	excluded	did not study outcome of interest
Louik C, Werler MM, Mitchell AA. Erythromycin use during pregnancy in relation to pyloric stenosis. Am J Obstet Gynecol. 2002;186(2):288–90. https ://doi.org/10.1067/mob.2002.11971 8.	yes (erythromycin)	no (pyloric stenosis)	NA (case-control)	excluded	did not study outcome of interest
Wolfgang P, Schloemp S, Sterzik K, Stoz F, editors. Does roxithromycin affect embryo development? 33rd Annual	no	all congenital malformations, miscarriage	unexposed women	excluded	did not study macrolide of

Conference of the European Teratology Society; 3–7 Sep, 2005; Haarlem, The Netherlands: Reproductive Toxicology.					interest
Chun JY, Han JY, Ahn HK, Choi JS, Koong MK, Nava-Ocampo AA, et al. Fetal outcome following roxithromycin exposure in early pregnancy. J Matern Fetal Neonatal Med. 2006;19(3):189–92. https ://doi.org/10.1080/14767 05050 04396 57.	no	congenital malformations	unexposed women	excluded	did not study macrolide of interest
Bar-Oz B, Diav-Citrin O, Shechtman S, Tellem R, Arnon J, Francetic I, et al. Pregnancy outcome after gestational exposure to the new macrolides: a prospective multi-center observational study. Eur J Obstet Gynecol Reprod Biol. 2008;141(1):31–4. https ://doi.org/10.1016/j.ejogr b.2008.07.008.	yes (azithromycin, clarithromycin)	MCMs, spontaneous abortions	women exposed to other antibiotics or other non teratogenic drug	excluded	mixed comparator groups
Sarkar M, Woodland C, Koren G, Einarson AR. Pregnancy outcome following gestational exposure to azithromycin. BMC Pregnancy Childbirth. 2006;6:18. https ://doi.org/10.1186/1471-2393-6-18.	yes (azithromycin)	MCM, spontaneous abortion	women exposed to nonteratogenic antibiotics for similar indications or nonteratogens	excluded	mixed comparator groups, only event rates presented
Bar-Oz B, Weber-Schoendorfer C, Berlin M, Clementi M, Di Gianantonio E, de Vries L, et al. The outcomes of pregnancy in women exposed to the new macrolides in the first trimester:a prospective, multicentre, observational study. Drug Saf. 2012;35(7):589–98. https ://doi.org/10.2165/11630 920-000000000-00000	yes (azithromycin, clarithromycin)	congenital malformations	women exposed to nonteratogens	excluded	mixed comparator group
Dinur AB, Koren G, Matok I, Wiznitzer A, Uziel E, Gorodischer R, et al. Fetal safety of macrolides. Antimicrob Agents Chemother. 2013;57(7):3307–11. https://doi.org/10.1128/AAC.01691-12.	yes (erythromycin, azithromycin and clarithromycin)	MCM	unexposed women	excluded	no individual analysis per macrolide

Table 3: Studies common between Mallah (2019) and Fan (2019)

Study	Includes erythromycin, azithromycin or clarithromycin	Includes outcome of interest (MCM, CVM or miscarriage)	Comparator	Included or excluded	Reason for exclusion
Muanda FT, Sheehy O, Berard A. Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study. Br J Clin Pharmacol. 2017;83(11):2557–71. https://doi.org/10.1111/bcp.13364	yes (erythromycin, azithromycin and clarithromycin)	MCM, CVM	unexposed women (main analysis), women exposed to penicillin (sens analysis)	included	NA
Romoren M, Lindbaek M, Nordeng H. Pregnancy outcome after gestational exposure to erythromycin—a population-based register study from Norway. Br J Clin Pharmacol. 2012;74(6):1053–62. https ://doi.org/10.1111/j.1365-2125.2012.04286 .x.	yes (erythromycin, azithromycin and clarithromycin)	MCM, CVM	unexposed	included	NA
Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer SM, Gideon PS, et al. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol. 2008;23(1):18–28. https ://doi.org/10.1111/j.1365-3016.2008.00978 .x.	yes (azithromycin, erythromycin)	MCM	unexposed	included	NA
Lund M, Pasternak B, Davidsen RB, Feenstra B, Krogh C, Diaz LJ, et al. Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study. BMJ. 2014;348:g1908. https://doi.org/10.1136/bmj.g1908	any macrolide	no (pyloric stenosis)	NA (casecontrol)	excluded	did not study outcome of interest
Lê Nguyên T, Araujo M, Hurault-Delarue C, Lacroix I, Damase-Michel	any macrolide	congenital malformation	unexposed women and women	excluded	no individual analysis

C, Sommet A. Teratogenic risk of macrolides during the first trimester of pregnancy: a study with two complementary approaches within the EFEMERIS database. Clin Ther. 2017;39(8):e11–2.		s	exposed to penicillin		per macrolide (also could only find an abstract so limited detail)
Einarson A, Phillips E, Mawji F, D'Alimonte D, Schick B, Addis A, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. Am J Perinatol. 1998;15(9):523–5. https ://doi.org/10.1055/s-2007-994053.	yes (clarithromycin)	MCM, miscarriage (spontaneous abortion)	women exposed to a nonteratogen with a similar indication to clarithromycin	excluded	mixed comparator group, only event rates presented

Table 4: Studies only included in Fan (2019)

Study	Includes erythromycin, azithromycin or clarithromycin	Includes outcome of interest (MCM, CVM or miscarriage)	Comparator	Included or excluded	Reason for exclusion
Andersen JT, Petersen M, Jimenez-Solem E, Broedbaek K, Andersen NL, Torp-Pedersen C, et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. PLoS One. 2013; 8(1):e53327. Epub 2013/01/10. https://doi.org/10.1371/journal.pone. 0053327 PMID: 23301061; PubMed Central PMCID: PMCPmc3534696.	Yes (clarithromycin, erythromycin)	MCM, miscarriage (spontaneous abortion)	unexposed women	included	NA
Kallen BA, Otterblad Olausson P, Danielsson BR. Is erythromycin therapy teratogenic in humans?Reproductive toxicology (Elmsford, NY). 2005; 20(2):209–14. Epub 2005/05/24. https://doi.org/10.1016/j.reprotox.2005.01.010 PMID: 15907655.	yes (erythromycin)	CVM	all live born infants	included	NA
Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. ORACLE Collaborative Group. Lancet. 2001; 357(9261):989–94. Epub 2001/04/11. PMID: 11293641.	yes (erythomycin)	No (composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital)	placebo	excluded	did not study 1st trimester use or outcome of interest
Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of	yes (erythomycin)	No (composite of neonatal death,	placebo	excluded	did not study 1st trimester

fetal membranes: the ORACLE I randomised trial. ORACLE Collaborative Group. Lancet. 2001; 357 (9261):979–88. Epub 2001/04/11. PMID: 11293640.		chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital)			use or outcome of interest
Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet. 2008; 372(9646):1319–27. Epub 2008/09/23. https://doi.org/10.1016/S0140-6736(08)61203-9 PMID: 18804276.	yes (erythomycin)	No (long-term developmental outcomes)	placebo	excluded	did not study 1st trimester use or outcome of interest
Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, et al. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. Lancet. 2008; 372(9646):1310–8. Epub 2008/09/23. https://doi.org/10.1016/S0140-6736(08)61202-7 PMID: 18804274.	yes (erythomycin)	No (functional impairment)	placebo	excluded	did not study 1st trimester use or outcome of interest
Eschenbach DA, Nugent RP, Rao AV, Cotch MF, Gibbs RS, Lipscomb KA, et al. A randomized placebo-controlled trial of erythromycin for the treatment of Ureaplasma urealyticum to prevent premature delivery. The Vaginal Infections and Prematurity Study Group. Am J Obstet Gynecol. 1991; 164(3):734–42. Epub	yes (erythomycin)	No (premature delivery)	placebo	excluded	did not study 1st trimester use or outcome of interest

1991/03/01. PMID: 2003533.					
Kwak HM, Shin MY, Cha HH, Choi SJ, Lee JH, Kim JS, et al. The efficacy of cefazolin plus macrolide (erythromycin or clarithromycin) versus cefazolin alone in neonatal morbidity and placental inflammation for women with preterm premature rupture of membranes. Placenta. 2013; 34(4):346–52. Epub 2013/03/08. https://doi.org/10.1016/j.placenta.2013.01.016 PMID: 23465535.	yes (erythromycin, clarithromycin)	No (composite of neonatal morbidity)	women randomly assigned to cefazolin, cefazolin plus erythromycin, or cefazolin plus clarithromycin	excluded	did not study 1st trimester use or outcome of interest
Martin DH, Eschenbach DA, Cotch MF, Nugent RP, Rao AV, Klebanoff MA, et al. Double-Blind Placebo Controlled Treatment Trial of Chlamydia trachomatis Endocervical Infections in Pregnant Women. Infectious diseases in obstetrics and gynecology. 1997; 5(1):10–7. Epub 1997/01/01. https://doi.org/10.1155/S1064744997000057 PMID: 18476128; PubMed Central PMCID: PMCPmc2364533.	yes (erythromycin)	No (preterm delivery, low birth weight)	unexposed	excluded	did not study 1st trimester use or outcome of interest
McGregor JA, French JI, Seo K. Antimicrobial therapy in preterm premature rupture of membranes: results of a prospective, doubleblind, placebo-controlled trial of erythromycin. Am J Obstet Gynecol. 1991; 165(3):632–40. Epub 1991/09/01. PMID: 1892190.	yes (erythromycin)	No (prolongation of pregnancy in women with PRoM)	placebo	excluded	did not study 1st trimester use or outcome of interest
Mercer BM, Moretti ML, Prevost RR, Sibai BM. Erythromycin therapy in preterm premature rupture of the membranes: a prospective, randomized trial of 220 patients. Am J Obstet Gynecol. 1992; 166 (3):794–802. Epub 1992/03/01. PMID: 1550145.	yes (erythromycin)	No (prolongation of latency and reduction of infectious morbidity after preterm PRoM)	placebo	excluded	did not study 1st trimester use or outcome of interest
Tita AT, Szychowski JM, Boggess K, Saade G, Longo S, Clark E, et al.	yes (azithromycin)	No (maternal outcomes and a	placebo	excluded	did not study 1st

Adjunctive Azithromycin Prophylaxis for Cesarean Delivery. New England journal of medicine [Internet]. 2016; 375(13):[1231–41 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/880/CN-01260880/frame.html.		composite neonatal outcome including death and sepsis)			trimester use or outcome of interest
Ye Y, Tu S, Li H. Clinic intervention study on urogenital mycoplasma infection of pregnant women. [Chinese].Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2001; 22(4):293–5. PMID: 11718071.	yes (erythromycin)	No ('adverse perinatal outcomes')	placebo	excluded	did not study 1st trimester use or outcome of interest
Meeraus WH, Petersen I, Gilbert R. Association between antibiotic prescribing in pregnancy and cerebral palsy or epilepsy in children born at term: a cohort study using the health improvement network. PLoS One. 2015; 10(3):e0122034. Epub 2015/03/26. https://doi.org/10.1371/journal.pone.0122034 PMID: 25807115; PubMed Central PMCID: PMCPmc4373729.	yes (erythromycin, clarithromycin, azithromycin)	No (cerebral palsy, epilepsy)	women exposed to penicillin	excluded	did not include outcomes of interest, analysis was grouped for macrolides)

Annex 3: Rate differences for outcomes presented in the macrolide studies

Table 1: Erythromycin

Setting	Study Design	Comparator	Erythromycin, n*/N	Comparator	Outcome	Study	Risk Estimate (95% CI)	Rate per 1000 exposed to macrolide	Rate per 1000 exposed to comparator	Rate difference	Overall Bias
UK, 1990-2016	Cohort	Penicillin	53/1,935	398/22,544	MCM	Fan et al, 2020	1.5* (1.13-1.99)	27.39	17.65	9.74	serious
Denmark, 2000-2015	Cohort	Penicillin	283/5,563	n/a /48,765	MCM	Damkier et al 2019	1.01 (0.88-1.14)	n/a	n/a	n/a	serious
Quebec, 1998-2009	Cohort	Penicillin	64/697	894/9,106	MCM	Muanda et al 2017b	1.02 (0.78-1.34)	91.82	98.18	-6.35	serious
Norway, 2004-2007	Cohort	unexposed	90/1,786	8,073/163,653	MCM	Romoren et al 2012	1.04 (0.84-1.29)	50.39	49.33	1.06	moderate
US, Tennessee, 1985-2000	Cohort	unexposed	23/903	102/3,400	MCM	Cooper et al 2009	0.86 (0.62-1.18)	25.47	30.00	-4.53	serious
Sweden, 1996-2011	Cohort	unexposed	99/2,531	48,499/1,575,847	MCM	Kallen et al 2014	1.18 (0.96-1.44)	39.11	30.78	8.34	serious
Hungary, 1980-1996	casecontrol	unexposed	20/43	n/a	MCM	Czeizel et al 1999	0.8 (0.9-1.6)	n/a	n/a	n/a	serious
UK, 1990-2016	cohort	Penicillin	19/1,935	149/22,544	CVM	Fan et al 2020	1.48 (0.92-	9.82	6.61	3.21	serious

							2.37)				
Denmark, 2000-2015	cohort	penicillin	46/5,563	n/a	CVM	Damkier et al 2019	0.94 (0.69-1.28)	n/a	n/a	n/a	serious
Quebec, 1998-2009	cohort	penicillin	15/697	192/9106	CVM	Muanda et al, 2017b	1.09 (0.64-1.86)	21.52	21.08	0.44	serious
Sweden, 1996-2003	cohort	unexposed	34/1,844	n/a	CVM	Kallen et al 2005	1.84* (1.29-2.62)	n/a	n/a	n/a	serious
Sweden, 1996-2011	cohort	unexposed	43/2,531	16,153/1,575,847	CVM	Kallen et al 2014	1.7* (1.26-2.29)	16.99	10.25	6.74	serious
Norway, 2004-2007	cohort	unexposed	21/1,786	1,653/163653	CVM	Romoren et al 2012	1.16 (0.75-1.78)	11.76	10.10	1.66	moderate
US, 1997-2003	Case-control	unexposed	81*	n/a	CVM	Crider et al 2009	1.0 (0.7-1.3)	n/a	n/a	n/a	serious
US, Canada, 1994-2008	Case-control	unexposed	18/4,132	28/6,952	CVM	Lin et al 2013	1.3 (0.6-2.6)	n/a	n/a	n/a	serious
US, Tennessee, 1985-2000	cohort	unexposed	9/903	37/3,400	CVM	Cooper et al 2009	0.93 (0.45-1.91)	9.97	10.88	-0.92	serious
Denmark, 1997-2007	cohort	unexposed	n/a	n/a	Miscarriage	Andersen et al 2013	1.03 (0.94-1.13)	n/a	n/a	n/a	serious
Quebec, 1998-2009	Case-control	penicillin	15/697(2.15 %)	25/854	Miscarriage	Muanda et al May 2017	0.82 (0.56-1.19)	n/a	n/a	n/a	serious

Table 2: Clarithromycin

Setting	Study Design	Comparator	Erythromycin, n*/N	Comparator, n*/N	Outcome	Study	Risk Estimate (95% Cl)	Rate per 1000 exposed to macrolide	Rate per 1000 exposed to comparator	Rate difference	Overall Bias
UK, 1990-2016	Cohort	Penicillin	6/162	398/22,544	MCM	Fan et al, 2020	1.83(0.83-4.04)	36.81	17.65	19.16	serious
Denmark, 1997-2007	Cohort	unexposed	9/253 (3.6%)	24/808	MCM	Andersen et al 2013	1.01 (0.52-1.97)	35.57	29.70	5.87	serious
Quebec, 1998-2009	Cohort	Penicillin	77/658 (11.7%)	894/9,106	MCM	Muanda (2017b)	1.15 (0.90-1.48)	117.02	98.18	18.84	serious
Denmark, 1997-2007	Cohort	unexposed	40/401	77,513/931,103	Miscarriage	Andersen et al 2013	1.66* (1.22–2.26).	99.75	83.25	16.50	serious
Quebec, 1998-2009	Case-control	Penicillin	111/8,702*	5,573/87,020	Miscarriage	Muanda 2017a	2.73* (2.16-3.44)	n/a	n/a	n/a	Moderate
Quebec, 1998-2009	Cohort	Penicillin	12/658	192/9,106	CVM	Muana, 2017b	0.82 (0.46-1.48)	18.24	18.24	-2.85	serious

Table 3: Azithromycin

Setting	Study Design	Comparator	Erythromycin, n*/N	Comparator, n*/N	Outcome	Study	Risk Estimate (95% CI)	Rate per 1000 exposed to macrolide	Rate per 1000 exposed to comparator	Rate difference	Overall Bias
Denmark, 2000-2015	Cohort	Penicillin	182/5,037	na /48,765	MCM	Damkier et al 2019	1.09 (0.93-1.27)	n/a	n/a	n/a	serious
Quebec, 1998-2009	Cohort	Penicillin	118/883	894/9,106	MCM	Muanda et al 2017b	OR 1.25*(1.01-1.53)	133.64	98.18	35.46	serious
US, Tennessee, 1985-2000	Cohort	unexposed	23/559	102/3,400	MCM	Cooper (2009)	RR 1.37 (0.85-2.22)	41.14	30.00	11.14	serious
Quebec, 1998-2009	Case-control	Penicillin	110/n/a	500/6,073	Miscarriage	Muanda 2017a	aOR 1.91 (1.53–2.39)	n/a	n/a	n/a	moderate
Denmark, 2000-2015	Cohort	Penicillin	57/5,037	n/a	CVM	Damkier 2019	aOR 1.14 (0.86-1.51)	n/a	n/a	n/a	serious
Quebec, 1998-2009	Cohort	Penicillin	19/883	192/9,106(2.11)	CVM	Muanda 2017b	OR 0.92 (0.57-1.49)	21.52	21.08	0.43	serious
US, Tennessee, 1985-2000	Cohort	unexposed	7/559	37/3,400	CVM	Cooper et al 2009	RR 1.13 (0.5-2.55)	12.52	10.88	1.64	serious

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