

Use Of The Tree-Based Scan Statistic For Surveillance Of Maternal Outcomes Following Medication Use During Gestation

Sentinel Methods

Thuy N Thai¹, Almut G Winterstein^{1,2,3}, Elizabeth A Suarez⁴, Michael Nguyen⁵, Danijela Stojanovic⁵, Jane Liedtka⁶, Abby Anderson⁷, Di Zhang⁸, Yueqin Zhao⁸, Monica Munoz⁹, Wei Liu¹⁰, Inna Dashevsky⁴, David Cole⁴, Talia Menzin⁴, Elizabeth Messenger-Jones⁴, Elizabeth Siranosian⁴, Judith C Maro⁴

1. Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL; 2. Center for Drug Evaluation and Safety, University of Florida, Gainesville, FL; 3. Department of Epidemiology, College of Medicine and College of Public Health and Health Professions, University of Florida, Gainesville, FL; 4. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 5. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; 6. Division of Pediatric and Maternal Health, Center for Drug and Evaluation Research, US Food and Drug Administration, Silver Spring, MD; 7. Division of Urology, Obstetrics and Gynecology, Center for Drug and Evaluation Research, US Food and Drug Administration, Silver Spring, MD; 8. Office of Biostatistics, Center for Drug Evaluation and Research, FDA, Silver Spring, MD; 9. Division of Pharmacovigilance, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 10. Division of Epidemiology, Center for Drug and Evaluation Research, US Food and Drug Administration, Silver Spring, MD

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History of Modifications

Version	Date	Modification	Author
1.0	06/01/2021	Original Version	Sentinel Operations Center
2.0	08/17/2022	Added a sensitivity analysis for Aim 1 Updated the maternal tree for Aim 1 Added post hoc analyses for Aim 1 Added Aim 2 – A non-user design Added Aim 3 – A simulation study	Sentinel Operations Center

1 Introduction

Medication use during pregnancy is common. In the United States, about 70% of pregnant women use at least one prescription medication during pregnancy and four medications on average.¹ Using medications during pregnancy imposes potential risk on pregnancy outcomes, including teratogenic risk for fetal development as well as risk for adverse maternal outcomes such as gestational diabetes. Almost 98% of medications approved from 2000 to 2010 have an undetermined teratogenic risk.² For pregnant women with acute or chronic diseases unrelated to pregnancy, there is also a risk if treatment is avoided due to unknown teratogenic effects.³ More evidence is needed to evaluate these competing risks and guide women and clinicians in making decisions.

Historically, pregnant women have been excluded from enrollment in clinical trials, so there is limited human data on medication safety during pregnancy at the time of product approval. Consequently, there is an important need for post-marketing pregnancy safety studies (e.g., pregnancy registries, pregnancy surveillance programs, or epidemiologic studies using data collected from routine clinical care).⁴ The advantages of registry data include the prospective nature of the data collection, which provides detailed patient information.⁵ However, registry data have a limited sample size due to the longer time it takes to enroll patients, and lose generalizability due to self-selection into the registry.^{6,7,8}

Real-world data from routine clinical care can provide retrospective data before registry studies can be completed and can be a useful complement to pregnancy registry data.⁶ Administrative claims data capture routinely reimbursed healthcare utilization and do not require active recruitment of patients, allowing for larger and more heterogeneous cohorts for analysis. Incidence rates and risk estimates associated with drug exposure during pregnancy can be calculated with these data and be compared with women exposed to an active comparator drug or unexposed women from the same source population. Generally, database studies are retrospective in nature, and particularly in pregnancy studies, evidence of gestational age in pregnancy is typically indicated by livebirth delivery.^{9,10} Gestational age (and thus start of pregnancy) are more challenging to be determined for pregnancies that do not result in livebirth, although there is active research in this area.^{11,12}

TreeScan™ (<http://www.treescan.org>) is a signal identification method that evaluates thousands of outcomes simultaneously to identify potential adverse events after adjusting for multiple testing.¹³ TreeScan can screen for maternal complications during pregnancy and identify unusually elevated frequencies of these complications that may require further evaluation. Moreover, because potential maternal complications are classified into a hierarchical tree structure, TreeScan can screen for specific potential adverse events (e.g., mild to moderate pre-eclampsia) as well as composite clinical outcomes (e.g., any form of pre-eclampsia). TreeScan is also compatible with multiple study designs and can be used with appropriate methods to control potential confounding in observational studies.¹⁴ TreeScan has been tested in the general adult and adolescent population^{14,15,16,17,18,19} and has been used to assess birth outcomes,^{20,21} but has not been used to assess maternal complications in the pregnant population. Simulation studies have shown a consistent ability to maintain overall Type 1 error over multiple hypothesis tests and conditions that are favorable to minimize Type II error.^{16,17,22} The FDA initiated this project to develop new methods to conduct surveillance using real-world data for maternal and obstetric outcomes following medication use during pregnancy.

2 Specific Aims

In Aim 1, we will assess the performance of the TreeScan method to identify signals for maternal and obstetric adverse outcomes occurring from 20 weeks of gestation to 30 days after delivery among women with livebirths exposed to oral macrolides compared to oral penicillins.

In Aim 2, we will assess the performance of the TreeScan method to identify signals for maternal and obstetric adverse outcomes occurring from 20 weeks of gestation to delivery among mothers with livebirths exposed to oral macrolides, penicillins, or cephalosporins compared to mothers without any antibiotic use.

In Aim 3, we will conduct a simulation study to evaluate the effect of statistical uncertainty of the background rate in the performance of TreeScan in identifying signals for maternal and obstetric adverse outcomes.

3 Case Study: Use of Macrolides and Penicillins

The purpose of this methods project is to evaluate the performance of TreeScan rather than find potential unexpected maternal complications. Therefore, we selected a case study of drug exposure that is expected to yield a large enough sample size to detect outcomes with smaller baseline prevalence or smaller increased risk. We also considered the availability of an appropriate active comparator to limit the need to control for potential confounders. Finally, we prioritized exposure and control drugs with known safety profiles so that the TreeScan results could be interpreted in the context of a robust body of existing safety data.

Antibiotics are among the most common medications used during pregnancy.^{1,23} The percentage of women enrolled in Medicaid insurance having livebirths with \geq one dispensing of macrolides or penicillins during pregnancy was 17% and 18%, respectively.²³ Macrolides and penicillins share similar indications, such as upper and lower respiratory tract infections, gastrointestinal infections, and sexually transmitted infections. Both macrolides and penicillins are generally considered safe antibiotics during pregnancy, with limited safety concerns regarding maternal outcomes.

Although not the focus of our analysis, there is a more complicated safety profile for fetal and neonatal outcomes following maternal exposures than maternal outcomes. Some studies have suggested that women with macrolide exposure would have a small increased risk of miscarriage and fetus with congenital malformation, cerebral palsy, or epilepsy.^{24,25,26} Penicillins were not associated with congenital malformations in most studies;^{27,28,29,30,31,32} however, some studies have reported a small increased risk of oral clefts with exposure during the first trimester and a higher risk of necrotizing enterocolitis with exposure to amoxicillin and clavulanic acid during the third trimester.^{33,34,35,36} These well-documented safety profiles make macrolides and penicillins ideal candidates for our exposure and control drugs for this case study.

4 Aim 1 Methods: Empirical Study

4.1 Data and Study Period

We will use the Merative™ MarketScan® Research Database, one of the largest samples of employer-sponsored health insurance enrollees in the U.S. It provides longitudinal detail for patient-level healthcare utilization. Our study period is from October 1, 2015 to February 29, 2020, which confines disease codes to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes and excludes healthcare utilization after the start of the COVID-19 pandemic. Based on our study parameters, the first valid livebirth delivery date is October 26, 2016, and the final valid livebirth delivery date is January 30, 2020.

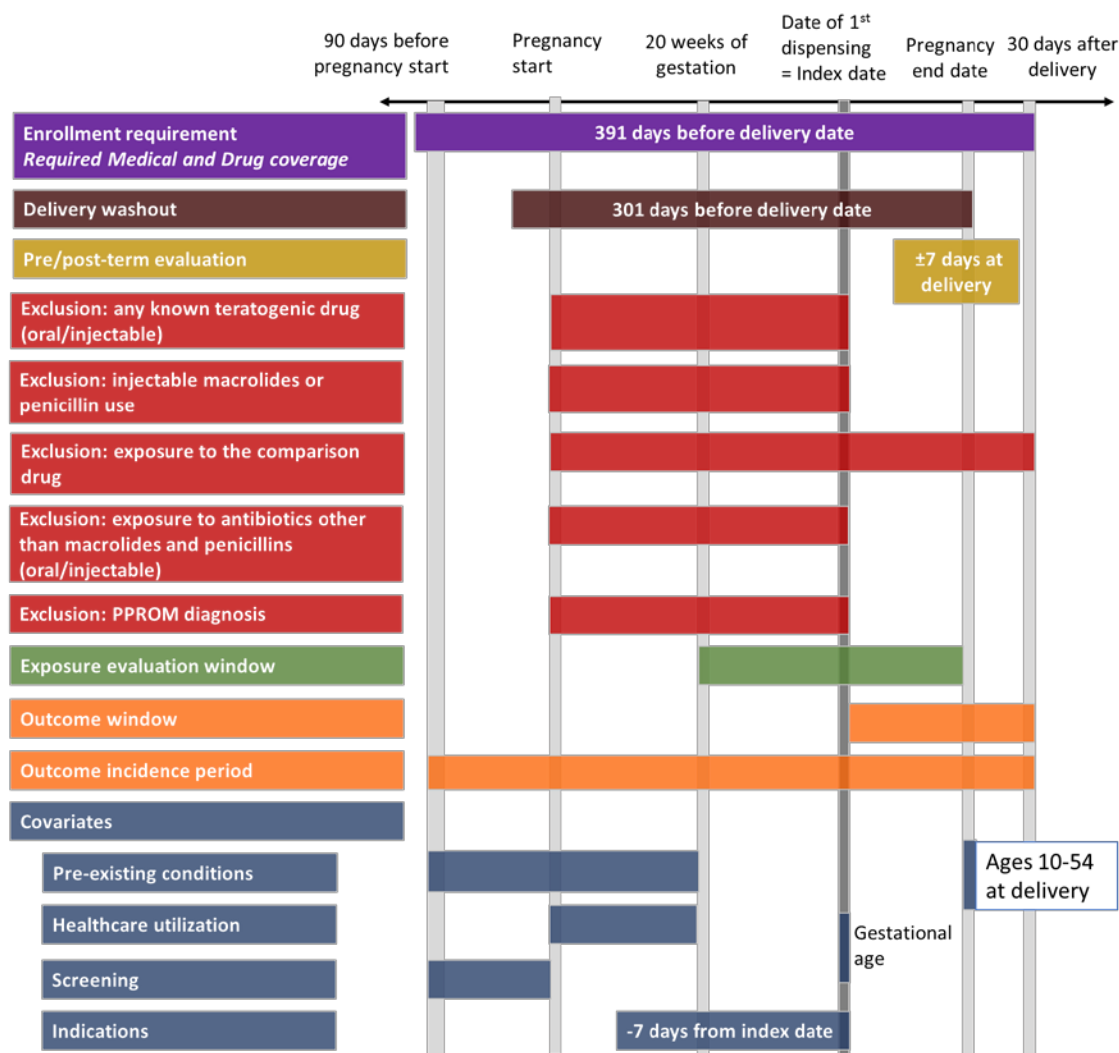
4.2 Defining Livebirth Pregnancy Episodes and Exclusion Criteria

We will include single livebirth deliveries using a previously validated code set of ICD-10-CM diagnosis, ICD-10 procedure Coding System (ICD-10-PCS), and Current Procedural Terminology, Fourth Edition (CPT-4) codes recorded and without any restriction in code position.³⁷ Pregnant women aged 10 to 54 years with livebirth delivery are required to have continuous medical and drug coverage (with a 45-day gap allowance) for at least 391 days before to 30 days after the delivery date. The pregnancy start date is calculated from the estimated gestational age at delivery using a validated algorithm from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) data that has been extended to ICD-10-CM.^{9,37} We will exclude livebirth pregnancy episodes that also had at least one livebirth delivery code within 301 days before the defined delivery date.

We will exclude multiple livebirths or pregnancies with both livebirth and stillbirth outcomes. Both macrolides and penicillins are used as prophylaxis for pregnant women with preterm premature rupture of membranes (PPROM). Therefore, maternal complications after PPRM diagnosis may be related to PPRM and not antibiotic exposure. Therefore, we will exclude deliveries with a PPRM-related diagnosis (ICD-10-CM codes O42.*) from pregnancy start to the date of antibiotic initiation. Any pregnancy episodes with at least one dispensing or one outpatient procedure related to any oral or injectable teratogenic drug from the pregnancy start date to index date are also excluded. Exposure to these drugs may complicate a pregnancy including manifestation of maternal complications.

Figure 1 shows the study design diagram including related in- and exclusion criteria. Code lists to describe the concepts demonstrated in the design diagram and this protocol are located in the Appendix organized as described in Table 1. Appendix A includes the list of generic and brand names to identify teratogenic drugs through the National Drug Codes (NDC). Appendix B lists Healthcare Common Procedure Coding System (HCPCS) codes of teratogenic drugs administered during clinical encounters.

Figure 1. Design Diagram for the Macrolides and Penicillins Case Study



Cohort: Singleton livebirth deliveries
Query period: October 1, 2015 – February 29, 2020
First valid livebirth delivery date: October 26, 2016
Last valid livebirth delivery date: January 30, 2020

Table 1. Summary of Appendix Tables and Their Content

Appendix	Appendix name	Description	Role
A	Generic and Brand Names of Medical Products to Identify Teratogenic Drugs with Oral and Injectable Routes for Exclusion	List of teratogenic drugs	Exclusion criterion
B	List of Healthcare Common Procedure Coding System (HCPCS) Codes to Identify	HCPCS codes of teratogenic drugs	Exclusion criterion

Teratogenic Drugs with Oral and Injectable Routes for Exclusion			
C	Generic and Brand Names of Medical Products to Identify Oral Macrolides or Penicillins	List of oral macrolides and penicillin	Study drug exposure definition and exclusion criterion
D	Generic and Brand Names of Medical Products to Identify Injectable Macrolides and Penicillins for Exclusion	List of injectable macrolides and penicillin	Exclusion criterion
E	List of Healthcare Common Procedure Coding System (HCPCS) Codes to Identify Injectable Macrolides and Penicillins for Exclusion	HCPCS codes of injectable macrolides and penicillin	Exclusion criterion
F	Generic and Brand Names of Medical Products to Identify Other Antibiotics with Oral and Injectable Routes for Exclusion	List of other antibiotics with both oral and injectable routes	Exclusion criterion
G	List of Healthcare Common Procedure Coding System (HCPCS) Codes to Identify Other Antibiotics with Oral and Injectable Routes for Exclusion	HCPCS codes of other antibiotics with both oral and injectable routes	Exclusion criterion
H	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes to Identify Preexisting Conditions	List of preexisting conditions	Covariates in propensity score
I	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT-4) Diagnosis and Procedure Codes to Identify Screening	List of screening tests	Covariates in propensity score
J	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes to Identify Exposure Indications	List of indications	Covariates in propensity score
K	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes Included in the Maternal Outcome Tree	List of maternal outcome tree	Outcome definition
L	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes of Maternal Outcomes That are Related to Indications	List of maternal outcomes related to infections	Alert classification
M	Generic and Brand Names of Medical Products to Identify Other Antibiotics with Oral and Injectable Routes for Exclusion in the Non-user Design	List of other antibiotics with both oral and injectable routes	Exclusion criterion

N	List of Healthcare Common Procedure Coding System (HCPCS) Codes to Identify Other Antibiotics with Oral and Injectable Routes for Exclusion in the non-user design	HCPCS codes of other antibiotics with both oral and injectable routes	Exclusion criterion
O	List of Healthcare Common Procedure Coding System (HCPCS) Codes to Identify Injectable Macrolides, Penicillins, and Cephalosporins for Exclusion	HCPCS codes of injectable macrolides, penicillin, and cephalosporins	Exclusion criterion
P	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes to Identify Indications for Exclusion in the Non-user Design	List of Other Indications	Exclusion criterion
Q	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes to Identify Mild to Moderate Respiratory Tract Infections	List of Respiratory Tract Infections	Inclusion criteria and covariates
R	Generic and Brand Names of Medical Products to Identify Oral Macrolides, Penicillins, or Cephalosporins	List of oral macrolides, penicillin, or cephalosporin	Study drug exposure definition and exclusion criterion
S	List of Healthcare Common Procedure Coding System (HCPCS) Codes to Identify Oral Macrolides	List of oral macrolides	Study drug exposure definition and exclusion criterion
T	List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes Included in the Maternal Outcome Tree without post-partum conditions	List of maternal outcome tree without post-partum conditions	Outcome definition

4.3 Defining Exposure

We will use NDC codes to identify pregnant women with oral macrolide or penicillin exposure. The list of generic and brand name medical products used to identify oral macrolide and penicillin exposure is in Appendix C. We will focus on exposures after 20 weeks gestation as our study focuses on maternal outcomes rather than infant outcomes. A pregnant woman will be defined as a macrolide user if she had at least one dispensing for an oral macrolide from 20 weeks of gestation to the day before the delivery date and without any days of supply of penicillins (oral or parenteral) from pregnancy start to 30 days after the delivery date. Similarly, a pregnant woman will be defined as a penicillin user if she had at least one dispensing of oral penicillin from 20 weeks of gestation to the day before the delivery date without any days of supply of macrolides (oral or parenteral) from pregnancy start to 30 days after the delivery date. The index date is the earliest date of the macrolides or penicillins dispensing during the assessed window. We exclude women with injectable macrolide or penicillin use (Appendix D: Generic and Brand Names of Medical Products to Identify Injectable Macrolides and Penicillins and Appendix E: List of HCPCS codes of Injectable Macrolides and Penicillin) from pregnancy start to index date. Women with any exposure to other antibiotics from pregnancy start date to index

date are also excluded (Appendix F: Generic and Brand Names of Medical Products to Identify Other Antibiotics for Exclusion and Appendix G: List of HCPCS Codes of Other Antibiotics).

4.4 Confounding Control

In pregnancy studies focusing on maternal complications, one of the primary confounders is gestational age at the time of treatment initiation. With a wide exposure assessment window (i.e., from 20 weeks gestation to 30 days post-partum), it is necessary to balance cohorts on this confounder specifically. For more general confounding control in observational studies, propensity score methods are typically used to condense multiple confounders into a single index value. Patients with propensity scores in non-overlapping regions are typically removed. Percentiles of the propensity score will be used to define strata for the outcome evaluation (see Section 4.5.6).

We will try two approaches to balance gestational age at treatment initiation. One approach stratifies by both a) gestational age at treatment initiation and b) a propensity score that does not include this variable (two-variable stratification approach). The second approach includes gestational age at treatment initiation in the propensity score and then stratifies on the propensity score alone. If the balance is not achieved, then further stratification on the gestational age at treatment initiation will be performed (two-step stratification approach). More detail is described in Section 4.5.6. Stratification analysis.

In signal identification, we are evaluating thousands of outcomes which makes it challenging to identify confounders in the traditional sense of being required to be associated independently with both the outcome and exposure. Therefore, the propensity score model includes covariates that have been commonly found to be associated with a variety of adverse pregnancy outcomes.

A previous Sentinel project developed a general set of covariates for a propensity score specifically for the pregnant population, including maternal demographics, pre-existing conditions, prenatal screening, and measures of previous healthcare utilization (Appendix H: List of ICD-10-CM to identify preexisting conditions and Appendix I: List of ICD-10-CM, HCPCS, and CPT-4 Diagnosis and Procedure Codes to Identify Screening), which we will also employ for this study.²⁰

Additionally, we will include the specific indications for macrolides and penicillins to control for confounding by indication. The code list was selected based on a previous study evaluating the appropriateness of antibiotic use and is based on diseases categories from the Clinical Classification Software developed by the Agency for Healthcare Research and Quality (Appendix J: List of ICD-10-CM to identify Indications).^{38,39}

4.5 TreeScan and Analysis Methods

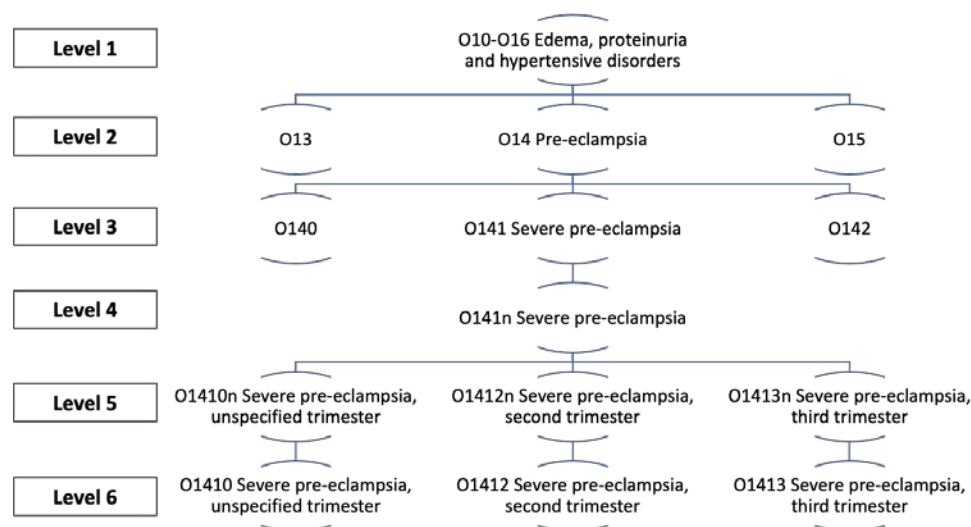
4.5.1 Maternal outcome selection

This study focuses on pregnancy-related maternal health complications contained in ICD-10-CM Chapter 15 (Pregnancy, childbirth, and the puerperium, O00-O9A).⁴⁰ This chapter contains important outcomes of interest such as pre-term labor, gestational diabetes, oligo- and polyhydramnios, pre/eclampsia, and chorioamnionitis. We curated this chapter into the outcome tree used by TreeScan by excluding codes that could not have been reasonably associated with exposure (e.g., multiple gestation) or that are impossible given our cohort definition of livebirth deliveries (e.g., stillbirth). The final code list in the maternal outcome tree is in Appendix K.

4.5.2 Defining the hierarchical tree structure for maternal outcomes

We use the hierarchical structure inherent in the ICD-10-CM coding system to determine the maternal outcomes tree with six levels based on the curated outcome list as described above. An example of the maternal outcome tree is shown in Figure 2.

Figure 2. An Example of the ICD-10-CM Hierarchical Tree for Maternal Outcomes. Each circle represents either a specific or composite clinical outcome on the tree and is the unit of analysis in the scanning procedure for TreeScan.



4.5.3 Defining incident outcomes

In TreeScan, an incident outcome criterion is needed to identify new-onset conditions emerging after drug exposure and to prevent repeat counting of the same condition that is being followed by a clinician. Incident outcomes will be identified from one day after the index date to 30 days after delivery. Incident outcomes will be defined as the first code under that level 3 clinical grouping in any care setting without any codes in the same grouping from 90 days before pregnancy start date to the outcome date. See Figure 2 to show an example of a level 3 clinical grouping (e.g., severe pre-eclampsia). A pregnant woman is allowed to have multiple incident outcomes as long as these outcomes meet the incident outcome criteria.

4.5.4 Calculating expected outcome counts in TreeScan

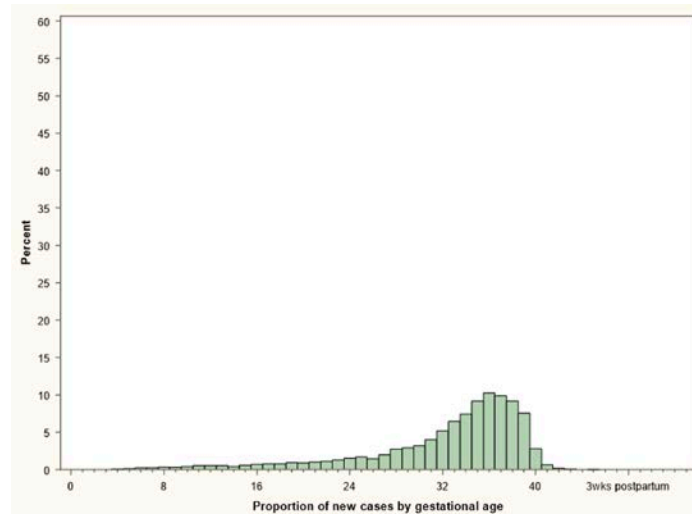
For each outcome in the tree, TreeScan compares the observed and expected number of events among the exposed group to evaluate for a potential elevated frequency. TreeScan supports two probability models to calculate the expected number of events: Bernoulli and Poisson. The Bernoulli model maximizes bias control at the cost of precision through a fixed ratio matching technique.^{17,20} Matched sets are required to be of uniform size throughout the analysis. This requirement is hard to maintain with varying gestational lengths. Thus, a proper Bernoulli analysis would need to match on both gestational age at treatment initiation and gestational age at delivery in addition to other propensity score criteria. Sample size loss in these circumstances is expected to be considerable.

For the Poisson model, background rates for each outcome are based on a control group. These rates are used to calculate the expected event count in the exposed group using indirect standardization after stratification on a propensity score.^{16,20} We chose the Poisson model rather than the Bernoulli model to evaluate maternal complications because it maximizes sample size while maintaining good confounding control. The Poisson model does not require matching or the same follow-up time.

In the Poisson model, the null hypothesis is that maternal complications are expected to occur in proportion to the expected count.¹⁶ To meet the assumptions of the Poisson distribution, the background rate should be constant over the unit time being measured. However, maternal outcome manifestation often depends on gestational age. In brief, the risk of specific maternal complications tends to have a skewed distribution (e.g.,

Figure 3) or is confined to only a specific time period, such as at delivery or post-partum. Therefore, the required assumption of constant risk over follow-up time is unlikely to be satisfied for many maternal outcomes if we look at outcome rates in units of weeks or months of pregnancy.

Figure 3. The proportion of Women with Newly Diagnosed Pre-eclampsia by Gestational Age



Instead of looking at rates per unit time, one can also use total pregnant women as the denominator in the Poisson model (i.e., rate of gestational diabetes per pregnant women evaluated). Pregnancy duration is still variable in our study because we *only* balance pregnant women on gestational age at treatment initiation rather than gestational age at treatment initiation *and* gestational age at delivery. Given the interchangeability of the two antibiotic classes and no documented effect on preterm deliveries, we do not expect different distributions of gestational age at delivery; therefore, using total persons as the denominator in the Poisson model will be most appropriate for calculating the observed and expected outcome counts.

4.5.5 The Poisson TreeScan statistic

Tree-based scan statistics can be unconditional or conditional on the total number of observed outcomes in the dataset.¹⁶ The conditional statistic controls for increases in general healthcare utilization believed to be unrelated to the exposure of interest.¹⁶ Because there is increased healthcare utilization around delivery that is unlikely to be related to antibiotic exposure, the conditional Poisson version is more appropriate. The conditional log likelihood ratio (LLR) based test statistic T can be calculated for the Poisson model as follows:

$$LLR(G) = \left[c_G \ln \left(\frac{c_G}{n_G} \right) + (C - c_G) \ln \left(\frac{C - c_G}{N - n_G} \right) \right] I \left(\frac{c_G}{n_G} > \frac{C - c_G}{N - n_G} \right)$$

$$T = \max_G LLR(G)$$

Where: T = conditional Poisson tree scan statistic

c_G = observed cases in the treatment group for a given maternal outcome
 n_G = expected cases in the treatment group for a given maternal outcome
 C = total number of maternal outcomes in the risk window summed over the tree
 N = total number of expected maternal outcomes summed over the tree
 G = maternal outcome of interest

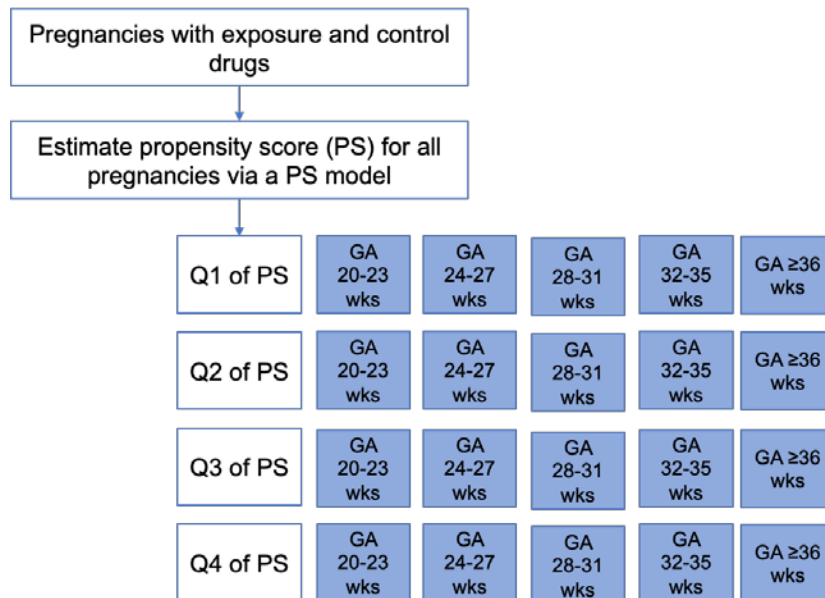
Random datasets are generated under the null hypothesis, and the test statistic T is calculated for each random dataset. The Monte Carlo based p-value is the rank of the test statistic in the real dataset divided by the number of replicated random datasets plus 1. If the statistical significance is set as $\alpha=0.05$, an outcome alert occurs if that outcome's test statistic in the real dataset ranks in the top 5% of all test statistics among the real and replicated datasets.

4.5.6 Stratification analysis

After trimming non-overlapping regions of the propensity score, the cohort will be stratified based on propensity score quartiles and gestational age at treatment initiation by the two approaches described earlier: two-variable stratification and two-step stratification.

In the two-variable stratification approach, we divide the trimmed cohort into quartiles of the propensity score. Then, within each propensity score stratum, we stratify based on 4-week gestational age groups at treatment initiation: at 20-23, 24-27, 28-31, 32-35, and ≥ 36 weeks. As a result, we have a total of 20 strata, as depicted in *Figure 4*.

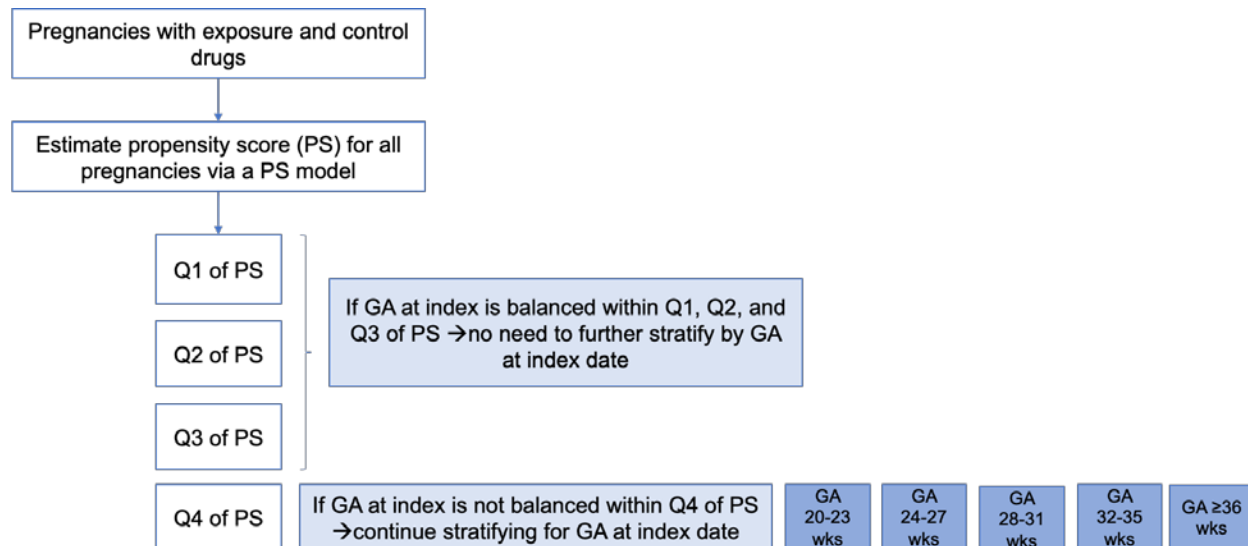
Figure 4. Two-Variable Stratification Approach



Note: GA – gestational age; PS: propensity score; Q1-Q4 – 1st, 2nd, 3rd, and 4th quartile

In the two-step approach, we add gestational age at treatment initiation as a categorical covariate in the propensity score model (note: gestational age at treatment initiation is not included in the propensity score model for the two-variable approach). We first stratify the trimmed cohort into quartiles of the propensity score and then examine gestational age distribution in each stratum. We only stratify based on gestational age at treatment initiation in a given propensity score stratum if we detect imbalanced distributions of that variable (Figure 5).

Figure 5. Two-step Stratification Approach



Note: GA – gestational age; PS: propensity score; Q1-Q4 – 1st, 2nd, 3rd, and 4th quartile

Outcome risk varies by gestational age, so these strata create a more similar follow up time within each stratum. For example, women that initiate treatment at 20-23 weeks are grouped separately from women that initiate treatment at 36 weeks. More granular strata of gestational age at treatment initiation ensure more similarity in the time available to experience certain maternal complications and theoretically better control of confounding. However, too many strata may result in small sample sizes in each stratum and a zero count of maternal outcomes in a non-informative stratum.

The two-variable approach increases accuracy in estimating the expected count but naturally creates more strata which have the disadvantage of smaller sample sizes per stratum. The two-step approach, in turn, aims to prevent the issue of a low count of outcomes while still addressing confounding by gestational age at treatment initiation as needed and might offer some efficiencies. Both stratification approaches have advantages and disadvantages, so we aim to explore both methods.

4.5.7 Identifying alerts using TreeScan

In the main analysis, we will conduct the hypothesis testing at levels 3 to 5. The threshold for an alert will be $p \leq 0.05$. Because the hypothesis testing in TreeScan is one-sided, we will conduct two analyses to capture potential alerts fully: one compares macrolides vs. penicillins and one compares penicillins vs. macrolides. Because no previous studies have raised concerns about maternal outcomes associated with macrolide or penicillin use, alerts will be triaged to be “expected” (i.e., alerts representing labeled conditions or those related to the underlying drug indications) or unclassified. Appendix L shows a list of ICD-10-CM codes of maternal infection outcomes related to antibiotic indications.

4.6 Sensitivity Analyses

We will conduct several sensitivity analyses to evaluate TreeScan performance.

First, we will conduct hypothesis testing at level 2 nodes, which have a broader outcome definition, and the incident outcome criterion is redefined at level 2.

Second, an increased specificity in outcome measurement will help to decrease outcome misclassification, resulting in enhancing risk estimate accuracy. We will therefore restrict outcomes to those captured from inpatient or emergency department visits while still requiring no related outcomes in any setting prior to outcome occurrence.

Third, we will vary the number of strata of gestational age at treatment initiation and the propensity score for both stratification approaches. We expect a larger number of strata will increase the ability to control for bias but will also result in a loss of precision.

Fourth, we expect that excluding women with any known teratogenic drug exposure before the index date will enable better confounding control. This is mainly a concern when studying infant outcomes and is less of a priority when studying maternal obstetric outcomes. To increase the sample size in this analysis, we will include women exposed to any known teratogenic drugs and adjust for those drugs' exposure in the propensity score.

Table 2 summarizes all analyses in this protocol.

Table 2. Summary Analysis Scenarios

#	Analysis scenarios	Stratification approach	Cut-off of gestation age at index	Cut-off of propensity score	Incident outcome	Incident outcome criteria
Main analyses						
1	Vary stratification approach	Two-variable approach	Every four weeks	Quartiles	Levels 3 to 5 at any care setting	At level 3 in any care setting
2		Two-step approach	Every four weeks	Quartiles	Levels 3 to 5 at any care setting	At level 3 in any care setting
Sensitivity analyses						
3	Add level 2 for hypothesis testing	Two-variable approach	Every four weeks	Quartiles	Levels 2 to 5 at any care setting	At level 2 in any care setting
4		Two-step approach	Every four weeks	Quartiles	Levels 2 to 5 at any care setting	At level 2 in any care setting
5	Restrict to inpatient or emergency department visit	Two-variable approach	Every four weeks	Quartiles	Levels 3 to 5 at inpatient or emergency department visits	At level 3 in any care setting
6		Two-step approach	Every four weeks	Quartiles	Levels 3 to 5 at inpatient or emergency department visits	At level 3 in any care setting
7	Vary cut-off of gestational age at treatment initiation	Two-variable approach	Every two weeks	Quartiles	Levels 3 to 5 at any care setting	At level 3 in any care setting
8		Two-step approach	Every two weeks	Quartiles	Levels 3 to 5 at any care setting	At level 3 in any care setting
9		Two-variable approach	Every six weeks	Quartiles	Levels 3 to 5 at any care setting	At level 3 in any care setting
10		Two-step approach	Every six weeks	Quartiles	Level 3 to 5 at any care setting	At level 3 in any care setting
11	Vary cut-off of GA	Two-variable approach	Every six weeks	Deciles	Levels 3 to 5 at any care setting	At level 3 in any care setting

#	Analysis scenarios	Stratification approach	Cut-off of gestation age at index	Cut-off of propensity score	Incident outcome	Incident outcome criteria
12	propensity score	Two-step approach	Every six weeks	Deciles	Levels 3 to 5 at any care setting	At level 3 in any care setting
13	Lift known teratogenic drug	Two-variable approach	Every four weeks	Quartiles	Levels 3 to 5 at any care setting	At level 3 in any care setting
14	exclusion criterion	Two-step approach	Every four weeks	Quartiles	Levels 3 to 5 at any care setting	At level 3 in any care setting

4.7 Post Hoc Analyses Following Initial Exploration of Aim 1 Data

After conducting all the above analyses, we observed alerts for both macrolide and penicillin users that indicated potential data concerns, specifically misclassification of gestational age. We also did not identify as many indications for the study drug antibiotics as we expected to identify. In response, we made the following post hoc adjustments.

First, we observed two unique alerts belonging to the first trimester among penicillin users, although our outcome evaluation window was from 20 weeks of gestation. After reviewing claims profiles among patients with those alerts, we recognized that delivery dates among those patients were misclassified, leading to an inaccurate estimation of the pregnancy start date. We observed this pattern among pregnant patients with delivery diagnoses in outpatient settings. Therefore, we limited our cohort to deliveries based on inpatient claims only and re-ran some selected analyses as in Table 2.

Second, we did not find any indication for 67% of macrolide users and 48% of penicillin users. After reviewing claims profiles, we observed that about 15% of macrolide and 9% of penicillin users had other respiratory tract infections for which antibiotics are not the recommended course of therapy and were not included in our indication list.³⁸ However, our aim in this project was to balance the indications between macrolide and penicillin users instead of evaluating the appropriateness of antibiotic use, so we updated the indication code list by adding missing respiratory tract infection diagnoses (e.g., common cold). Additionally, we added a post hoc sensitivity analysis by limiting our cohort to those with a respiratory tract infection diagnosis to further examine an indicated cohort.

5 Aim 2 – Non-User Design

5.1 Introduction

Using an active comparator design is typically preferred in a pharmacoepidemiology study because patients in the exposure and control groups are more comparable, resulting in an improved ability to control confounding by design. In pregnancy, women may be channeled to a specific treatment due to a lack of safety data on other treatment options or provider preferences, limiting the ability to use an active comparator. Pregnant women may also be confronted with the choice of treatment or no treatment (i.e., watchful waiting) for certain conditions. Non-user designs become a clinically valuable option for those situations, but they bring two major challenges. First, there is no natural index date for the non-user group. Second, there is potential for exaggerated confounding issues such as indication bias or confounding by

disease severity. Still, it is important to assess how TreeScan can improve signal detection with a non-user design in a pregnant population.

Objective: We assess the performance of the TreeScan method to identify signals for maternal and obstetric adverse outcomes occurring from 20 weeks of gestation to delivery among women with livebirths and documented ear, nose, throat, or respiratory tract infections who are exposed to oral macrolides, penicillins or cephalosporins or did not receive any antibiotic treatment.

5.2 Data, Study Period, and Pregnancy cohort

We will use the Merative™ MarketScan® Research Database with the same study period and algorithm to identify single livebirth pregnancies as Aim 1. We will limit to pregnancies with deliveries in the inpatient setting to enhance the accuracy of gestational age and pregnancy start date estimates.⁹

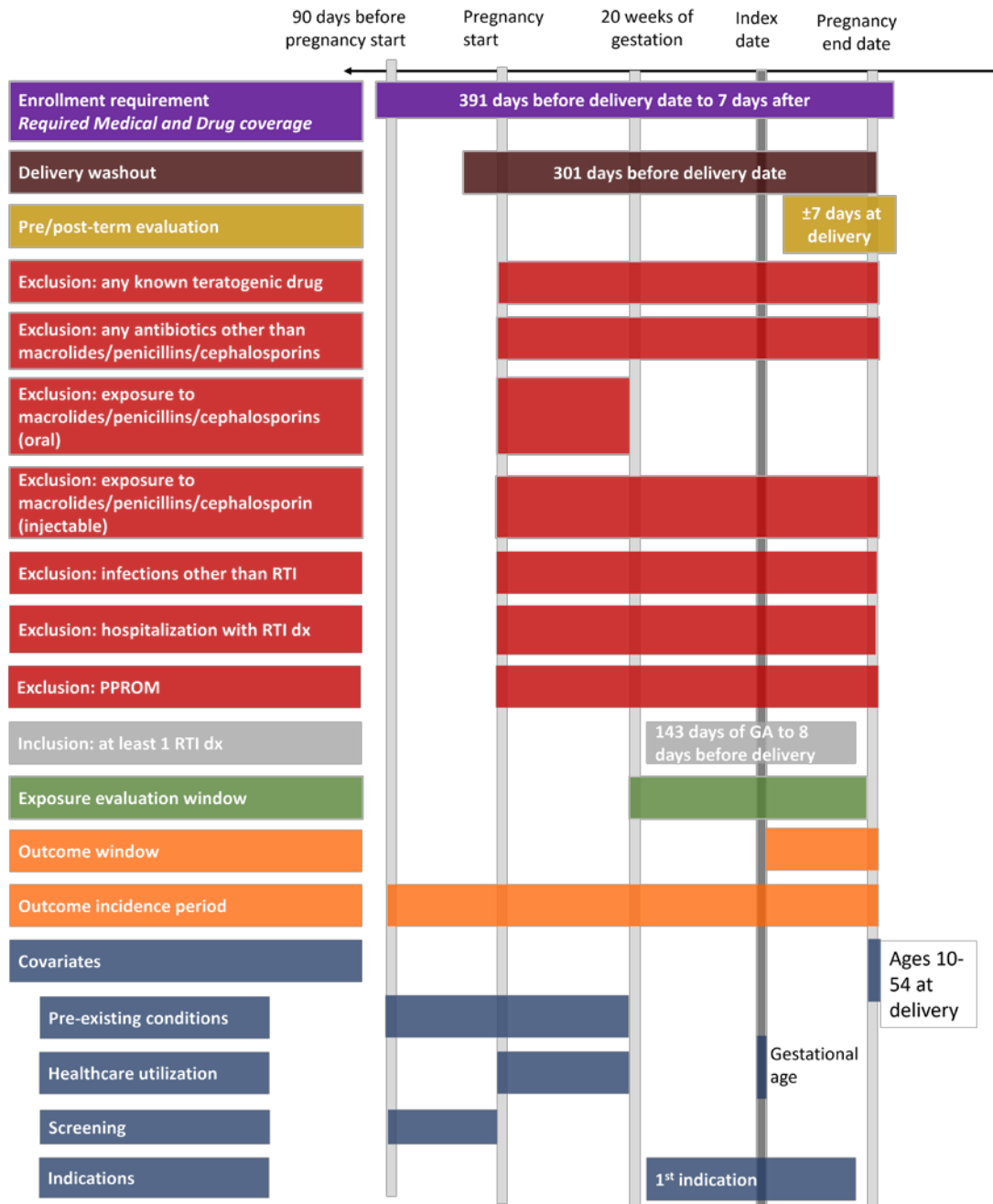
5.3 Inclusion and Exclusion Criteria

We will exclude multiple livebirths or mixed birth pregnancies. Pregnant women using any known teratogenic drug (Appendices A and B) are removed. To only include patients with mild or moderate infectious conditions, we apply the following exclusion criteria with the assessment window from pregnancy start to delivery date: 1) having any antibiotic other than the study drugs (e.g., fluoroquinolones, aminoglycosides, etc.) (Appendices M and N); 2) having any injectable macrolide, penicillin, or cephalosporin (Appendix O); 3) having any infection other than ear, nose, throat or respiratory tract infection diagnosis (we reference as RTIs from herein) (Appendix P); 4) or being hospitalized with any RTI diagnosis (Appendix Q). We also remove pregnant women using oral macrolides, penicillins, and cephalosporins from pregnancy start to before 20 weeks of gestation so that antibiotic history before 20 weeks is comparable between the exposure and control groups (Appendices R and S).

Furthermore, to balance disease severity and indications, we require women to have at least one RTI diagnosis (Appendix Q) within seven days before to three days after the antibiotic fill date (for the exposure group) or the randomly assigned index (for non-user group). The antibiotic exposure assessment window is from gestational age of 140 days to one day before delivery date; thus, the RTI evaluation window is from 143 days after pregnancy start to eight days before delivery date. The RTI diagnosis occurring within the RTI evaluation window is considered the indication date. We group the RTI diagnosis codes into sub-indications. If the percentage of a particular sub-indication in the antibiotic exposure group appears very imbalanced compared to the non-user group, we will remove all pregnant women with this sub-indication rather than attempting to balance it in the propensity score stratification step. We also exclude all pregnancies with any PPRM-related diagnosis (ICD-10-CM codes O42.*) at any time during the gestation period.

Figure 6 describes a design diagram for the non-user design.

Figure 6. Design Diagram for the Non-User Design



Cohort: Singleton livebirth deliveries

Query period: October 1, 2015 – February 29, 2020

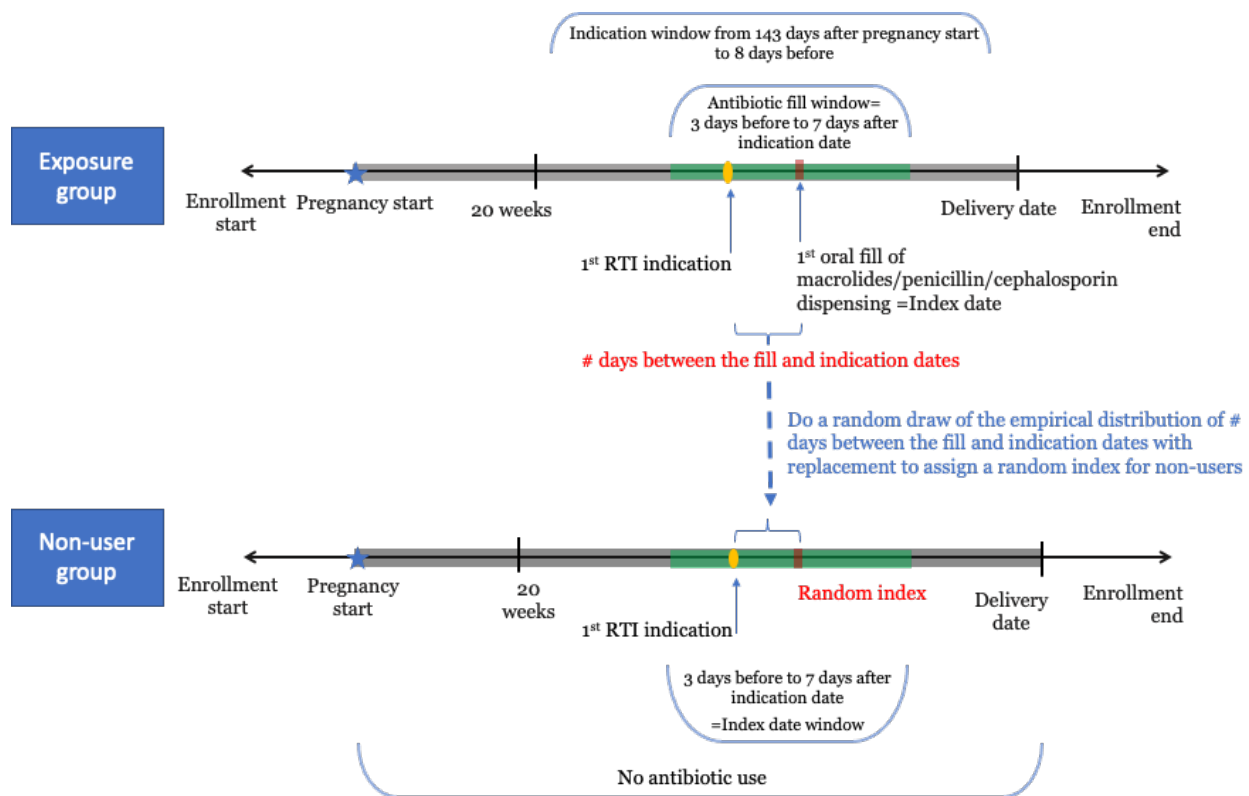
First valid livebirth delivery date: October 26, 2016

Last valid livebirth delivery date: January 30, 2020

5.4 Defining Exposure Groups

We will use NDC and HCPCS codes to identify oral macrolide, penicillin, or cephalosporin exposure (Appendices R and S). A pregnant woman will be classified as exposed if she has a dispensing/code for an oral macrolide, penicillin, or cephalosporin within three days before to seven days after the indication date and no previous dispensings/codes for any of these drugs during pregnancy. The index date is defined as the date of the first qualifying antibiotic dispensing/code. Pregnant women with antibiotic exposure that does not fall within three days before or seven days after the indication date will be excluded from the analysis because their antibiotic exposure may be for a different indication. A pregnant woman will be classified as a non-user if she has no dispensings/codes for an oral macrolide, penicillin, or cephalosporin during the entire pregnancy period. The index date among the non-user patients will be randomly assigned based on a random draw of the empirical distribution of the number of days between the fill and indication dates in the exposed group. A diagram illustrating how to assign the index date for the exposed and control groups is in Figure 7.

Figure 7. A Diagram to Assign Index Date for the Exposure and Control Groups.



5.5 Confounding Control

We use the same covariate list as in Aim 1 to control potential confounders. Of note, the only difference is that we restrict to women with an RTI related diagnosis within the indication evaluation window. We use the two-step approach with a decile PS stratification to balance gestational age at index date (which is included in the PS model) and other covariates.

5.6 TreeScan and Analysis Methods

5.6.1 Maternal outcome selection

We expect that many women might receive antibiotics in the peri-delivery period and post-partum based on complications resulting from labor. One limitation of the administrative claims data is that drug exposure typically is not measured in the inpatient setting, resulting in a potential misclassification of women with antibiotic use during hospitalization as non-users. With an active comparator design in Aim 1, we require antibiotic exposure in both exposure and control groups before delivery, so the exposure misclassification is less likely to be impacted by antibiotic use during delivery, and if there is any antibiotic use after index date, we assume that the antibiotic use would occur equally in both groups. Thus, in the active comparator design, we allow measuring outcomes occurring after the delivery date, while we limit the outcome assessment window from one day after the index date to the delivery date and exclude post-partum conditions in the non-user design. A curated tree that excludes all post-partum conditions is listed in Appendix T.

5.6.2 TreeScan statistics

We use the step stratification approach with Poisson statistics for the TreeScan analysis. Maternal outcomes are measured in the inpatient setting or during emergency department visits and are incident at level 3 within any care setting. We conduct hypothesis testing at levels 3 to 5, and the alert threshold is set at $\alpha=0.05$.

5.6.3 Sensitivity analyses

We conduct two sensitivity analyses by enhancing the ability of confounding control. One analysis is with 20 strata in the propensity score stratification. Another one uses the high dimension propensity score in addition to the empirical-specified covariates in the propensity score model.

Table 3. Summary Analysis Scenarios in Aim 2

#	Stratification approach	Cut-off of gestation age at index	Number of strata	Incident outcome	Incident outcome criteria
1	Two-step approach	Every 6 weeks	10	Levels 3 to 5 at inpatient or emergency department visits	At level 3 in any care setting
Sensitivity analyses					
2	Two-step approach	Every 6 weeks	20	Levels 3 to 5 at inpatient or emergency	At level 3 in any care setting

#	Stratification approach	Cut-off of gestation age at index	Number of strata	Incident outcome	Incident outcome criteria
3	Two-step approach and adding HdPS	Every 6 weeks	10	department visits Levels 3 to 5 at inpatient or emergency department visits	At level 3 in any care setting

5.7 Future Consideration Defining Exposure

There are several limitations to consider for future studies. First, the follow-up time to evaluate maternal outcomes depends on gestational age at delivery. If the exposure drug increases the risk for preterm births, the risk period of having maternal outcomes is no longer the same between the exposure and control drugs, and the analysis becomes a competing risk problem. An appropriate method using survival analysis and accounting for this competing risk issue will need to be investigated in the future so that TreeScan can be used for drugs with or without impact on preterm risk. Second, the current project only focuses on maternal outcomes among mothers with livebirths because pregnancy identification algorithms for non-livebirth pregnancies have not been fully developed. Evaluating maternal outcomes among mothers with livebirth and non-livebirth outcomes will provide a more complete picture of adverse drug effects during pregnancy. Third, in claims data, we use the delivery date to determine the pregnancy start date, which is common practice for pregnancy and birth outcomes studies. Thus, women whose pregnancies do not result in livebirth (e.g., non-livebirth outcomes or maternal demise) are excluded. If a drug increases risk of maternal death, this exclusion may create a bias that attenuates the drug's adverse effect. Using other data sources or alternative algorithms to identify the start of pregnancy can address this limitation.

6 Aim 3: Simulation Study

6.1 Introduction

The TreeScan method compares observed counts of outcomes among exposure groups. TreeScan considers an outcome a potential alert if that outcome in the exposure group has more observed counts than expected above a pre-specified threshold. Expected outcome counts are calculated using indirect standardization from the background rates of a comparable reference group. The Poisson model assumes that the expected events (and therefore the reference group background rate) are known without error. However, if the reference group event rates are based on a small sample size, the observed background rate may be unrepresentative of the true background rate. The unaccounted-for variation in the observed background rate increases the presence of random error for the expected event counts, which can, in turn, result in erroneous conclusions.⁴¹

This problem is compounded if expected events are calculated within strata to control for confounding. Many strata (e.g., deciles of the propensity score) may ensure exchangeability within each stratum, but a smaller sample size is more likely to generate an imperfect background rate. This is a classic bias-variance tradeoff that is confronted throughout pharmacoepidemiology. Although the Poisson model has been commonly employed in TreeScan,^{16,20,21} there is little knowledge of how imperfect background rates may affect TreeScan's ability to detect potential signals. In aim 2, we aim to evaluate the effect of statistical

uncertainty of the background rate in the performance of TreeScan in identifying signals for maternal and obstetric adverse outcomes by performing a simulation study with a known investigator-injected increased risk.

6.2 Methods

We will create different observed background rates by varying two parameters: the true background rate and sample size of the reference group per stratum, which is determined by the sample size of the control group and the number of strata. For simplicity, we assume the number of strata is given by n-tiles of the propensity score distribution in the entire population after trimming and all covariates (including gestational age at index) are appropriately balanced with the propensity score alone. We assume that there is no effect modification by propensity score strata. With an active comparator design, we also assume high overlap in the propensity score distribution between the exposure and control group results in an approximately equal representation of the comparison group within each stratum.

We evaluate the impact of those background rates on TreeScan’s performance to detect different magnitudes of the investigator-injected relative risks. Table 4 shows sample parameters that we will vary in the simulated datasets.

Table 4. Scenarios to be Assessed in the Simulation Study

Specified outcome prevalence	Sample size per stratum in the control group (N in the control and N of PS strata)	Relative risk
Approximate 20 per 1000	50 (N=2500, 50 strata)	1.0
Approximate 10 per 1000	100 (N=5000, 50 strata)	1.5
Approximate 5 per 1000	250 (N=2500, 10 PS strata)	2.0
	500 (N=5000, 10 PS strata)	4.0
	1000 (N=10,000, 10 PS strata)	
	2500 (N=2500, 1 PS stratum)	
	5000 (N=5,000, 1 PS stratum)	
	10,000 (N=10,000, 1 PS stratum)	

We will use the empirical data in Aim 1 to select three maternal outcomes with the prevalences as specified in Table 4. We assume these prevalences are true background rates, i.e., known without error. Using the total size of the comparator group in combination with the number of strata, we create an observed set of background rates based on those stratum sizes. For example, suppose we have an outcome that occurs at 20 events per 1000 pregnancies, and we are testing a scenario where we have 2500 reference group pregnancies and ten strata. In that case, we will have 250 pregnancies in each stratum. Therefore, we will sample the true background rates from samples of 250 pregnancies and generate an observed background rate per stratum (which is more likely to have a greater distance from the true background rate when based on smaller numbers of individuals). We will use these observed background rates to construct our analytical dataset and report the power for each simulated scenario with the varied parameters in Table 4 and the fixed parameter of the sample size of the exposure group.

The sample size of the exposure group is fixed for all simulated scenarios to evaluate the impact of the sample size in the control group on power for the different outcome prevalences and relative risks. In an active comparator design, we expect the exposure and control group’s sample sizes to be similar. Therefore, we set the number of exposed pregnancies to 5000 so that the sample sizes of the exposed and control groups are equal to or smaller than a 2-fold difference. Based on the true background rate in the empirical dataset, we inject node-specific

risk for the exposed group to reflect the selected increased risk. Therefore, the observed number of events in the exposure is a product of three parameters: the specified relative risk, true background rate, and total sample size of 5000. The estimated expected number of events in the exposure group per stratum is a product of the observed background rate in a particular stratum and the number of exposed pregnancies in that stratum. Then we aggregate all the expected numbers to obtain total events per outcome in the cohort. Last, the power is calculated using the Trees can software with the statistical significance of $\alpha=0.05$.

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