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Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request: tspreg_mpl2p_wp003

Request ID: tspreg_mpl2p_wp003

Request Description: In this report, we performed signal identification for selected antibiotics by monitoring maternal outcomes among pregnant patients exposed to oral macrolides as compared to pregnant patients exposed to oral penicillins from twenty weeks of gestation.

Sentinel Routine Querying Module: Cohort Identification and Descriptive Analysis (CIDA) module, version 10.3.3, with Propensity Score Analysis and Signal Identification modules.

Data Source: We executed this query in the Merative™ MarketScan® Research Databases on May 17, 2022. The study period included data from October 1, 2015 through January 30, 2020 with the first valid live birth delivery of October 26, 2016 and the final valid live birth delivery date of December 31, 2019. Please see Appendix A for a list of dates of available data.

Study Design: We identified pregnant patients with use of oral macrolide or penicillin from 20 weeks gestation to before delivery. We excluded patients having preterm premature rupture of membrane diagnosis in the time from pregnancy start until index date or having used definite teratogenic drugs during any time of pregnancy. Patients using injectable macrolide/penicillins or having exposures to other antibiotics from pregnancy start until index were also removed. We used propensity score stratification and we monitored maternal pregnancy outcomes. This is a Type 4 analysis using the Propensity Score Analysis and Signal Identification modules in the Query Request Package (QRP) documentation.

Exposures of Interest: We identified users of macrolides and penicillins. Only the first qualifying treatment episode of the exposures of interest was evaluated. See [here](#) for a list of generic and brand names of medical products used to identify oral macrolides or penicillins, and [here](#) for a list of generic and brand names used to define injectable macrolides and penicillins for exclusion.

Cohort Eligibility Criteria: To be included in the cohorts, we required pregnant patients to be continuously enrolled in health plans with medical and drug coverage for at least 391 days prior to live birth delivery and 30 days post-partum during which gaps in coverage of up to 45 days were allowed. We only included qualifying members aged 10-54 with a single live birth outcome. A patient was defined as macrolide users 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 supply of penicillins from pregnancy start to 30 days after delivery. A similar definition was applied for penicillin users. We excluded pregnancies with any exposure of injectable macrolides or penicillins or any oral/injectable use of antibiotics other than macrolides and penicillins from pregnancy start to index date. We excluded deliveries with a preterm premature rupture of membrane-related diagnosis from pregnancy start to the date of antibiotic initiation. Any pregnancy episodes with any oral or injectable teratogenic drug from the pregnancy start date to index date are also excluded. See [here](#) for a list of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes to identify preexisting conditions and here for a 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.

Follow-up Time: We followed pregnant patients from the time of their first exposure to macrolides or penicillins following 20 weeks gestation and followed them through 30 days post-partum. We followed patients regardless of the days supply of the exposure medications in their pregnancy.

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Propensity Score Estimation: We assessed age on the day of live birth delivery, gestational age at the time of antibiotic initiation and antibiotic related indications (ear, nose, and throat infections, gastrointestinal infections, lower respiratory infections, sexually transmitted infections, pelvic inflammatory disease, skin and subcutaneous tissue, urinary track and kidney infections, and other indications) in the 14 days prior to 3 days after antibiotic initiation and included them in the propensity score model. We additionally assessed alcohol abuse, asthma, cardiac valvular disease, chronic congestive heart failure, chronic ischemic heart disease, chronic renal disease, congenital heart disease, cystic fibrosis, drug abuse, epilepsy/seizures, HIV, inflammatory bowel disease, leukemia/lymphoma, obesity, diabetes, hypertension, previous cesarean delivery, psychiatric disorders, pulmonary hypertension, rheumatoid arthritis, sickle cell disease, systemic lupus erythematosus, tobacco use, vaccine administration, screening examinations and disease management trial, PAP smear, HPV DNA test, fecal occult blood test, end stage liver disease in the 90 days before pregnancy start through the day prior to antibiotic indication and included these in the propensity score model. We assessed health service utilization intensity metrics from pregnancy start through the day prior to antibiotic initiation and included these in the propensity score model. The Propensity Score Analysis (PSA) module was used to calculate the propensity scores. Covariates were defined using ICD-10-CM, ICD-10-PCS, CPT-4, HCPCS, diagnosis and procedure codes as well as, NDC drug codes. For a list of codes used to defined covariates, please see [here](#).

Stratification: After trimming areas of non-overlap, pregnant patients were stratified into quartiles or deciles of the propensity score and gestational age at treatment initiation by the two approaches: two-variable stratification and two-step stratification. In the two-variable stratification approach, we divided the trimmed cohort into propensity score strata and then, within each propensity score stratum, we stratified based on gestational age groups at treatment initiation (2, 4, and 6 weeks). In the two-step approach, we first stratified the trimmed cohort into quartiles/deciles of the propensity score and then we only stratified based on gestational age at treatment initiation in a given propensity score stratum if we detected imbalanced distributions of that variable.

Outcome Assessment via Signal Identification: After trimming, we evaluated new health outcomes of interest (HOI). We used a hierarchical tree of ICD-10-CM diagnostic codes in the O00-O9A (Pregnancy, childbirth and the puerperium) chapter of the ICD-10 codebook.

In our analyses, we identified incident HOIs as the diagnosis to occur beginning 1 day after exposure initiation until the end of the 30 day post-partum period. For an outcome to be considered incident, there were required to be no outcomes with the same first 4 digits of the ICD-10-CM code from 90 days before pregnancy start date to the HOI date in any setting.

Tree-Based Scan Statistic: These data were evaluated via the TreeScan™ software (v.2.0) to determine whether there were imbalances in outcome occurrence between the two groups that rose to the level of statistical significance. TreeScan™ is a data-mining software that implements tree-based scan statistics. Under the null hypothesis, there is no position on the tree where outcomes are expected to occur in greater numbers than expected counts based on a referent rate. We used conditional Poisson tree-based scan statistic to calculate the log likelihood ratio for every node at level 3, 4 and 5 of the outcome tree. [See here](#) for list of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Codes Included in the Maternal Outcome Tree.

Sensitivity Analyses: We conducted several types of sensitivity analyses. First, we identified the HOIs in only inpatient and emergency department settings. All other identification rules remained unchanged. Second, we changed the incident level to require that the first three digits of the ICD-10-CM code were not the same in the 90 days before pregnancy start to the HOI date in any setting. Third, we allowed users of known teratogenic drugs into a larger cohort. Last, we restricted our cohort to patients with a respiratory tract infection to further eliminate residual confounding by indications.

Please see Appendix B for a design diagram for this request and Appendix C for the specifications of parameters used in this request.

Limitations: Algorithms to define exposures, outcomes, inclusion and exclusion criteria, and covariates are imperfect and may be misclassified. Therefore, data should be interpreted with this limitation in mind.

Notes: Please contact the Sentinel Operations Center (info@sentinelssystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's routine querying modules, please refer to the documentation (<https://dev.sentinelssystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse>).

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**Glossary of Terms for Analyses Using
Cohort Identification and Descriptive Analysis (CIDA) Module***

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency Department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). The Care Setting, along with the Principal Diagnosis Indicator (PDX), forms the Care Setting/PDX parameter.

Ambulatory Visit (AV) - includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.

Emergency Department (ED) - includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.

Inpatient Hospital Stay (IP) - includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.

Non-Acute Institutional Stay (IS) - includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.

Other Ambulatory Visit (OA) - includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email

Charlson/Elixhauser Combined Comorbidity Score - calculated based on comorbidities observed during a requester-defined window around the exposure episode start date (e.g., in the 183 days prior to index).

Code Days - the minimum number of times the diagnosis must be found during the evaluation period in order to fulfill the algorithm to identify the corresponding patient characteristic.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: 01: Cohort includes only the first valid treatment episode during the query period; 02: Cohort includes all valid treatment episodes during the query period; 03: Cohort includes all valid treatment episodes during the query period until an event occurs.

Computed Start Marketing Date - represents the first observed dispensing date among all valid users within a GROUP (scenario) within each Data Partner site.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled" sequence.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the episode gap.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the Modular Program (MP) algorithm: 0: Counts all occurrences of a health outcome of interest (HOI) during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions are added after any episode gaps have been bridged.

Lookback Period - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Member-Years - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Caresetting/PDX parameter.

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Switch Evaluation Step Value - value used to differentiate evaluation step. Each switch pattern can support up to 2 evaluation steps (0 = switch pattern evaluation start; 1 = first evaluation; 2 = second evaluation).

Switch Gap Inclusion Indicator - indicator for whether gaps in treatment episodes that are included in a switch episode will be counted as part of the switch episode duration.

Switch Pattern Cohort Inclusion Date - indicates which date to use for inclusion into the switch pattern cohort of interest as well as optionally as the index date of the treatment episode initiating the switch pattern. Valid options are the product approval date, product marketing date, other requester defined date, or computed start marketing date.

Switch Pattern Cohort Inclusion Strategy - indicates how the switch pattern cohort inclusion date will be used: 01: used only as a switch cohort entry date. First treatment episode dispensing date is used as index for computing time to first switch; 02: used as switch cohort entry date and as initial switch step index date for computing time to first

Treatment Episode Truncation Indicator - indicates whether the exposure episode will be truncated at the occurrence of a requester-specified code.

Washout Period (drug/exposure) - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

**Glossary of Terms for Analyses Using
Propensity Score Analysis (PSA) Module***

Covariate - requester defined binary variable to include in the propensity score estimation model (e.g., diabetes, heart failure, etc.) during requester-defined lookback period. Requester may also choose to add any of the following

1. Age (continuous)
2. Sex
3. Time period (i.e., monitoring period for sequential analyses)
4. Year of exposure
5. Comorbidity score
6. Medical utilization – number of inpatient stays
7. Medical utilization – number of institutional stays
8. Medical utilization – number of emergency department visits
9. Medical utilization – number of outpatient visits
10. Health care utilization – number of other ambulatory encounters (e.g., telemedicine, email consults)
11. Drug utilization – number of dispensings
12. Drug utilization – number of unique generics dispensed

Covariate Evaluation Window - specified number of days relative to index date to evaluate the occurrence of covariates of interest. Note: members are required to have continuous enrollment during the covariate evaluation window,

Individual Level Data Return - program may return individual-level, de-identified datasets to the Sentinel Operations Center (SOC). While the datasets contain a single row per patient for each specified analysis, patient identifiers such as a patient ID are not included in the output. Individual-level datasets are returned to the SOC, aggregated, and used to

Mahalanobis Distance - provides a measure of balance across all variables while accounting for their correlation.

Matching Caliper - maximum allowed difference in propensity scores between treatment and control patients. Requester may select any caliper (e.g., 0.01, 0.025, and 0.05).

Matching Ratio - patients in exposed and comparator groups are nearest neighbor matched by a 1:1 or 1:n (up to 10)

Matched Conditional and Unconditional Analysis - in a conditional matched analysis, a Cox model, stratified by Data Partner site and matched set, is run on the matched population. This can be done for both the both 1:1 and 1:n matched cohorts. In an unconditional analysis, a Cox model, stratified by Data Partner site only, is run on the matched population.

Propensity Score Stratification - option to stratify propensity scores based on requester-defined percentiles in the unmatched population. In a stratified analysis, a Cox model, stratified by Data Partner site, is run on the stratified

PSM Tool - performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts.

Propensity score estimation and matching are conducted within each Sentinel Data Partner site via distributed

Risk-set Level Data Return - alternative to the patient-level data return approach. In this approach, the PSM tool will produce de-identified, risk-set level datasets instead of or in addition to individual-level output. Whereas each observation in the patient-level datasets represents one patient in the cohort, each observation in the risk set dataset represents one event. Risk sets are created at the Data Partner site, returned to the SOC, aggregated, and used to calculate effect estimates via case-centered logistic regression.

Subgroup Analysis - may be conducted using any requester-defined covariates. Subgroup analyses may be performed in

Zero Cell Correction - indicator for whether to screen variables with a zero correction added to each cell in the confounder/outcome 2x2 table. Recommended when the number of exposed outcomes is fewer than 150.

*all terms may not be used in this report

Table 1a. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Unique patients	13,176	100.0%	18,503	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	30.9	5.2	0.160	0.031
Age						
10-54 years	13,176	100.0%	18,503	100.0%	0.000	N/A
Sex						
Female	13,176	100.0%	18,503	100.0%	0.000	N/A
Race ⁴						
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Hispanic origin						
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Year						
2016	770	5.8%	874	4.7%	1.120	0.050
2017	4,736	35.9%	5,985	32.3%	3.598	0.076
2018	3,957	30.0%	5,777	31.2%	-1.190	-0.026
2019	3,713	28.2%	5,867	31.7%	-3.528	-0.077
Pregnancy Characteristics						
Pre-Term (0-258 days)	807	6.1%	1,213	6.6%	-0.431	-0.018
Term (259-280 days)	8,638	65.6%	11,647	62.9%	2.612	0.055
Post-Term (281-301 days)	2,778	21.1%	4,233	22.9%	-1.794	-0.043
Unknown Term	953	7.2%	1,410	7.6%	-0.388	-0.015
Gestational age ⁵ at delivery	39.7	1.6	39.7	1.6	-0.008	-0.005
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.547	0.097
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A

Table 1a. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.032	-0.068
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.032	0.068
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,221	32.0%	6,522	35.2%	-3.213	-0.068
Exposed during third trimester	8,955	68.0%	11,981	64.8%	3.213	0.068
Health Characteristics						
Ear, Nose, and Throat Infections	4,585	34.8%	9,368	50.6%	-15.832	-0.324
Gastrointestinal Infections	32	0.2%	60	0.3%	-0.081	-0.015
Lower Respiratory Infections	1,302	9.9%	732	4.0%	5.925	0.235
Sexually Transmitted Infections	116	0.9%	31	0.2%	0.713	0.099
Other Indications	5	0.0%	95	0.5%	-0.475	-0.091
Pelvic Inflammatory Disease	105	0.8%	164	0.9%	-0.089	-0.010
Skin and Subcutaneous Tissue	31	0.2%	208	1.1%	-0.889	-0.108
Urinary Tract and Kidney Infections	114	0.9%	701	3.8%	-2.923	-0.195
Alcohol Abuse	32	0.2%	50	0.3%	-0.027	-0.005
Asthma	597	4.5%	749	4.0%	0.483	0.024
Cardiac Valvular Disease	79	0.6%	113	0.6%	-0.011	-0.001
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	9	0.1%	18	0.1%	-0.029	-0.010
Chronic Renal Disease	53	0.4%	67	0.4%	0.040	0.007
Congenital Heart Disease	40	0.3%	81	0.4%	-0.134	-0.022
Cystic Fibrosis	9	0.1%	22	0.1%	-0.051	-0.017
Drug Abuse	126	1.0%	156	0.8%	0.113	0.012
Epilepsy/Seizures	46	0.3%	68	0.4%	-0.018	-0.003

Table 1a. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
HIV	13	0.1%	17	0.1%	0.007	0.002
Inflammatory Bowel Disease	55	0.4%	81	0.4%	-0.020	-0.003
Leukemia/Lymphoma	3	0.0%	19	0.1%	-0.080	-0.032
Obesity	1,582	12.0%	2,386	12.9%	-0.889	-0.027
Preexisting Diabetes	219	1.7%	331	1.8%	-0.127	-0.010
Preexisting Hypertension	511	3.9%	674	3.6%	0.236	0.012
Previous Cesarean Delivery	409	3.1%	658	3.6%	-0.452	-0.025
Psychiatric Disorders	1,662	12.6%	2,438	13.2%	-0.562	-0.017
Pulmonary Hypertension	3	0.0%	3	0.0%	0.007	0.005
Rheumatoid Arthritis	31	0.2%	45	0.2%	-0.008	-0.002
Sickle Cell Disease	26	0.2%	48	0.3%	-0.062	-0.013
Systemic Lupus Erythematosus	44	0.3%	39	0.2%	0.123	0.024
Tobacco Use	223	1.7%	359	1.9%	-0.248	-0.019
Vaccine Administration	44	0.3%	65	0.4%	-0.017	-0.003
Screening Examinations and Disease Management Training	5	0.0%	6	0.0%	0.006	0.003
Pap Smear	1,564	11.9%	2,018	10.9%	0.964	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	20	0.2%	42	0.2%	-0.075	-0.017
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	2,886	21.9%	4,601	24.9%	-2.963	-0.070
Gestational Age 24-27 weeks	2,791	21.2%	4,039	21.8%	-0.646	-0.016
Gestational Age 28-31 weeks	2,657	20.2%	3,744	20.2%	-0.069	-0.002
Gestational Age 32-35 weeks	2,537	19.3%	3,508	19.0%	0.296	0.008
Gestational Age 36-42 weeks	2,305	17.5%	2,611	14.1%	3.383	0.093

Table 1a. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	-0.056	-0.012
Mean number of emergency room encounters	0.2	0.6	0.2	0.6	-0.013	-0.020
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.009
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	-0.050	-0.021
Mean number of filled prescriptions	2.6	3.6	2.5	3.5	0.187	0.053
Mean number of generics dispensed	1.5	1.8	1.4	1.7	0.111	0.064
Mean number of unique drug classes dispensed	1.5	1.7	1.4	1.6	0.103	0.062

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1b. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Unique patients	13,171	100.0%	18,467	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.129	0.025
Age						
10-54 years	13,171	100.0%	18,467	100.0%	0.000	N/A
Sex						
Female	13,171	100.0%	18,467	100.0%	0.000	N/A
Race ⁵						
Unknown	13,171	100.0%	18,467	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,171	100.0%	18,467	100.0%	0.000	N/A
Year						
2016	745	5.7%	886	4.8%	0.858	0.039
2017	4,727	35.9%	5,993	32.5%	3.436	0.072
2018	3,973	30.2%	5,775	31.3%	-1.109	-0.024
2019	3,726	28.3%	5,812	31.5%	-3.185	-0.070
Pregnancy Characteristics						
Pre-Term (0-258 days)	820	6.2%	1,202	6.5%	-0.281	-0.012
Term (259-280 days)	8,614	65.4%	11,620	62.9%	2.481	0.052
Post-Term (281-301 days)	2,792	21.2%	4,222	22.9%	-1.664	-0.040
Unknown Term	945	7.2%	1,423	7.7%	-0.535	-0.020
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	-0.014	-0.009

Table 1b. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.6	5.6	29.8	5.6	-0.150	-0.027
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	0.011	0.023
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	-0.011	-0.024
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,546	34.5%	6,169	33.4%	1.108	0.023
Exposed during third trimester	8,625	65.5%	12,298	66.6%	-1.108	-0.023
Health Characteristics						
Ear, Nose, and Throat Infections	5,881	44.7%	8,191	44.4%	0.298	0.006
Gastrointestinal Infections	41	0.3%	54	0.3%	0.017	0.003
Lower Respiratory Infections	981	7.5%	968	5.2%	2.208	0.091
Sexually Transmitted Infections	85	0.6%	40	0.2%	0.426	0.065
Other Indications	8	0.1%	52	0.3%	-0.225	-0.055
Pelvic Inflammatory Disease	117	0.9%	156	0.8%	0.043	0.005
Skin and Subcutaneous Tissue	47	0.4%	162	0.9%	-0.521	-0.066
Urinary Tract and Kidney Infections	171	1.3%	562	3.0%	-1.744	-0.120
Alcohol Abuse	34	0.3%	46	0.3%	0.009	0.002
Asthma	561	4.3%	783	4.2%	0.023	0.001
Cardiac Valvular Disease	79	0.6%	109	0.6%	0.011	0.001
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	15	0.1%	-0.001	-0.000
Chronic Renal Disease	49	0.4%	70	0.4%	-0.011	-0.002
Congenital Heart Disease	47	0.4%	68	0.4%	-0.014	-0.002
Cystic Fibrosis	11	0.1%	19	0.1%	-0.020	-0.006
Drug Abuse	115	0.9%	163	0.9%	-0.006	-0.001

Table 1b. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Epilepsy/Seizures	46	0.3%	62	0.3%	0.010	0.002
HIV	13	0.1%	18	0.1%	0.004	0.001
Inflammatory Bowel Disease	58	0.4%	79	0.4%	0.013	0.002
Leukemia/Lymphoma	5	0.0%	14	0.1%	-0.039	-0.017
Obesity	1,668	12.7%	2,291	12.4%	0.260	0.008
Preexisting Diabetes	233	1.8%	322	1.7%	0.031	0.002
Preexisting Hypertension	495	3.8%	697	3.8%	-0.015	-0.001
Previous Cesarean Delivery	456	3.5%	611	3.3%	0.156	0.009
Psychiatric Disorders	1,703	12.9%	2,392	13.0%	-0.019	-0.001
Pulmonary Hypertension	3	0.0%	3	0.0%	0.003	0.002
Rheumatoid Arthritis	35	0.3%	44	0.2%	0.023	0.005
Sickle Cell Disease	31	0.2%	42	0.2%	0.012	0.002
Systemic Lupus Erythematosus	38	0.3%	45	0.2%	0.044	0.009
Tobacco Use	250	1.9%	326	1.8%	0.135	0.010
Vaccine Administration	44	0.3%	66	0.4%	-0.023	-0.004
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.004	-0.003
Pap Smear	1,442	11.0%	2,119	11.5%	-0.522	-0.017
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	24	0.2%	37	0.2%	-0.016	-0.004
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	3,187	24.2%	4,275	23.1%	1.048	0.025
Gestational Age 24-27 weeks	2,844	21.6%	3,993	21.6%	-0.030	-0.001
Gestational Age 28-31 weeks	2,678	20.3%	3,735	20.2%	0.108	0.003
Gestational Age 32-35 weeks	2,466	18.7%	3,517	19.0%	-0.325	-0.008

Table 1b. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Gestational Age 36-42 weeks	1,996	15.2%	2,947	16.0%	-0.802	-0.022
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	0.007	0.001
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.005	0.007
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.000	-0.001
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.005	0.002
Mean number of filled prescriptions	2.5	3.5	2.6	3.6	-0.048	-0.013
Mean number of generics dispensed	1.5	1.7	1.5	1.7	-0.025	-0.014
Mean number of unique drug classes dispensed	1.4	1.6	1.5	1.7	-0.027	-0.016

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1c. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Unique patients	13,176	100.0%	18,503	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	30.9	5.2	0.160	0.031
Age						
10-54 years	13,176	100.0%	18,503	100.0%	0.000	N/A
Sex						
Female	13,176	100.0%	18,503	100.0%	0.000	N/A
Race ⁴						
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Year						
2016	770	5.8%	874	4.7%	1.120	0.050
2017	4,736	35.9%	5,985	32.3%	3.598	0.076
2018	3,957	30.0%	5,777	31.2%	-1.190	-0.026
2019	3,713	28.2%	5,867	31.7%	-3.528	-0.077
Pregnancy Characteristics						
Pre-Term (0-258 days)	807	6.1%	1,213	6.6%	-0.431	-0.018
Term (259-280 days)	8,638	65.6%	11,647	62.9%	2.612	0.055
Post-Term (281-301 days)	2,778	21.1%	4,233	22.9%	-1.794	-0.043
Unknown Term	953	7.2%	1,410	7.6%	-0.388	-0.015
Gestational age ⁵ at delivery	39.7	1.6	39.7	1.6	-0.008	-0.005

Table 1c. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.547	0.097
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second	0.3	0.5	0.4	0.5	-0.032	-0.068
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.032	0.068
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,221	32.0%	6,522	35.2%	-3.213	-0.068
Exposed during third trimester	8,955	68.0%	11,981	64.8%	3.213	0.068
Health Characteristics						
Ear, Nose, and Throat Infections	4,585	34.8%	9,368	50.6%	-15.832	-0.324
Gastrointestinal Infections	32	0.2%	60	0.3%	-0.081	-0.015
Lower Respiratory Infections	1,302	9.9%	732	4.0%	5.925	0.235
Sexually Transmitted Infections	116	0.9%	31	0.2%	0.713	0.099
Other Indications	5	0.0%	95	0.5%	-0.475	-0.091
Pelvic Inflammatory Disease	105	0.8%	164	0.9%	-0.089	-0.010
Skin and Subcutaneous Tissue	31	0.2%	208	1.1%	-0.889	-0.108
Urinary Tract and Kidney Infections	114	0.9%	701	3.8%	-2.923	-0.195
Alcohol Abuse	32	0.2%	50	0.3%	-0.027	-0.005
Asthma	597	4.5%	749	4.0%	0.483	0.024
Cardiac Valvular Disease	79	0.6%	113	0.6%	-0.011	-0.001
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	9	0.1%	18	0.1%	-0.029	-0.010
Chronic Renal Disease	53	0.4%	67	0.4%	0.040	0.007
Congenital Heart Disease	40	0.3%	81	0.4%	-0.134	-0.022
Cystic Fibrosis	9	0.1%	22	0.1%	-0.051	-0.017
Drug Abuse	126	1.0%	156	0.8%	0.113	0.012

Table 1c. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Epilepsy/Seizures	46	0.3%	68	0.4%	-0.018	-0.003
HIV	13	0.1%	17	0.1%	0.007	0.002
Inflammatory Bowel Disease	55	0.4%	81	0.4%	-0.020	-0.003
Leukemia/Lymphoma	3	0.0%	19	0.1%	-0.080	-0.032
Obesity	1,582	12.0%	2,386	12.9%	-0.889	-0.027
Preexisting Diabetes	219	1.7%	331	1.8%	-0.127	-0.010
Preexisting Hypertension	511	3.9%	674	3.6%	0.236	0.012
Previous Cesarean Delivery	409	3.1%	658	3.6%	-0.452	-0.025
Psychiatric Disorders	1,662	12.6%	2,438	13.2%	-0.562	-0.017
Pulmonary Hypertension	3	0.0%	3	0.0%	0.007	0.005
Rheumatoid Arthritis	31	0.2%	45	0.2%	-0.008	-0.002
Sickle Cell Disease	26	0.2%	48	0.3%	-0.062	-0.013
Systemic Lupus Erythematosus	44	0.3%	39	0.2%	0.123	0.024
Tobacco Use	223	1.7%	359	1.9%	-0.248	-0.019
Vaccine Administration	44	0.3%	65	0.4%	-0.017	-0.003
Screening Examinations and Disease Management Training	5	0.0%	6	0.0%	0.006	0.003
Pap Smear	1,564	11.9%	2,018	10.9%	0.964	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	20	0.2%	42	0.2%	-0.075	-0.017
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	2,886	21.9%	4,601	24.9%	-2.963	-0.070
Gestational Age 24-27 weeks	2,791	21.2%	4,039	21.8%	-0.646	-0.016
Gestational Age 28-31 weeks	2,657	20.2%	3,744	20.2%	-0.069	-0.002
Gestational Age 32-35 weeks	2,537	19.3%	3,508	19.0%	0.296	0.008

Table 1c. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Gestational Age 36-42 weeks	2,305	17.5%	2,611	14.1%	3.383	0.093
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	-0.056	-0.012
Mean number of emergency room encounters	0.2	0.6	0.2	0.6	-0.013	-0.020
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.009
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	-0.050	-0.021
Mean number of filled prescriptions	2.6	3.6	2.5	3.5	0.187	0.053
Mean number of generics dispensed	1.5	1.8	1.4	1.7	0.111	0.064
Mean number of unique drug classes dispensed	1.5	1.7	1.4	1.6	0.103	0.062

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1d. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Unique patients	13,169	100.0%	18,461	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.139	0.027
Age						
10-54 years	13,169	100.0%	18,461	100.0%	0.000	N/A
Sex						
Female	13,169	100.0%	18,461	100.0%	0.000	N/A
Race ⁵						
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Year						
2016	748	5.7%	884	4.8%	0.891	0.040
2017	4,708	35.7%	5,996	32.5%	3.266	0.069
2018	3,978	30.2%	5,767	31.2%	-1.034	-0.022
2019	3,735	28.4%	5,813	31.5%	-3.123	-0.068
Pregnancy Characteristics						
Pre-Term (0-258 days)	802	6.1%	1,225	6.6%	-0.541	-0.022
Term (259-280 days)	8,608	65.4%	11,622	63.0%	2.414	0.050
Post-Term (281-301 days)	2,808	21.3%	4,199	22.7%	-1.418	-0.034
Unknown Term	950	7.2%	1,416	7.7%	-0.455	-0.017
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	0.008	0.005

Table 1d. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.9	5.7	29.5	5.6	0.418	0.074
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	-0.024	-0.051
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	0.024	0.050
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,276	32.5%	6,435	34.9%	-2.392	-0.051
Exposed during third trimester	8,893	67.5%	12,026	65.1%	2.392	0.051
Health Characteristics						
Ear, Nose, and Throat Infections	5,892	44.7%	8,167	44.2%	0.501	0.010
Gastrointestinal Infections	41	0.3%	52	0.3%	0.026	0.005
Lower Respiratory Infections	995	7.6%	951	5.2%	2.401	0.099
Sexually Transmitted Infections	84	0.6%	39	0.2%	0.428	0.066
Other Indications	7	0.1%	48	0.3%	-0.202	-0.051
Pelvic Inflammatory Disease	124	0.9%	149	0.8%	0.136	0.015
Skin and Subcutaneous Tissue	46	0.4%	163	0.9%	-0.533	-0.068
Urinary Tract and Kidney Infections	169	1.3%	566	3.1%	-1.782	-0.122
Alcohol Abuse	35	0.3%	46	0.3%	0.017	0.003
Asthma	564	4.3%	781	4.2%	0.055	0.003
Cardiac Valvular Disease	80	0.6%	110	0.6%	0.008	0.001
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	15	0.1%	0.003	0.001
Chronic Renal Disease	48	0.4%	71	0.4%	-0.021	-0.003
Congenital Heart Disease	48	0.4%	68	0.4%	-0.003	-0.000
Cystic Fibrosis	11	0.1%	19	0.1%	-0.019	-0.006
Drug Abuse	116	0.9%	161	0.9%	0.007	0.001

Table 1d. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Epilepsy/Seizures	46	0.4%	63	0.3%	0.010	0.002
HIV	14	0.1%	17	0.1%	0.009	0.003
Inflammatory Bowel Disease	59	0.4%	77	0.4%	0.032	0.005
Leukemia/Lymphoma	4	0.0%	14	0.1%	-0.040	-0.017
Obesity	1,711	13.0%	2,251	12.2%	0.796	0.024
Preexisting Diabetes	238	1.8%	317	1.7%	0.088	0.007
Preexisting Hypertension	497	3.8%	695	3.8%	0.008	0.000
Previous Cesarean Delivery	480	3.6%	597	3.2%	0.411	0.023
Psychiatric Disorders	1,715	13.0%	2,381	12.9%	0.128	0.004
Pulmonary Hypertension	3	0.0%	3	0.0%	0.003	0.003
Rheumatoid Arthritis	35	0.3%	44	0.2%	0.031	0.006
Sickle Cell Disease	32	0.2%	41	0.2%	0.021	0.004
Systemic Lupus Erythematosus	39	0.3%	43	0.2%	0.062	0.012
Tobacco Use	256	1.9%	319	1.7%	0.218	0.016
Vaccine Administration	44	0.3%	67	0.4%	-0.029	-0.005
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.004	-0.002
Pap Smear	1,430	10.9%	2,138	11.6%	-0.719	-0.023
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	25	0.2%	36	0.2%	-0.006	-0.001
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	2,922	22.2%	4,537	24.6%	-2.385	-0.056
Gestational Age 24-27 weeks	2,837	21.5%	4,006	21.7%	-0.159	-0.004
Gestational Age 28-31 weeks	2,660	20.2%	3,760	20.4%	-0.164	-0.004
Gestational Age 32-35 weeks	2,489	18.9%	3,497	18.9%	-0.047	-0.001

Table 1d. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Gestational Age 36-42 weeks	2,261	17.2%	2,661	14.4%	2.755	0.076
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.0	4.5	5.9	4.5	0.026	0.006
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.008	0.013
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.000	0.002
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.013	0.006
Mean number of filled prescriptions	2.5	3.5	2.6	3.6	-0.060	-0.017
Mean number of generics dispensed	1.5	1.7	1.5	1.7	-0.034	-0.020
Mean number of unique drug classes dispensed	1.4	1.6	1.5	1.7	-0.036	-0.022

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1e. Unadjusted Characteristics of Step Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Database from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Unique patients	13,176	100.0%	18,503	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	30.9	5.2	0.160	0.031
Age						
10-54 years	13,176	100.0%	18,503	100.0%	0.000	N/A
Sex						
Female	13,176	100.0%	18,503	100.0%	0.000	N/A
Race ⁴						
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Year						
2016	770	5.8%	874	4.7%	1.120	0.050
2017	4,736	35.9%	5,985	32.3%	3.598	0.076
2018	3,957	30.0%	5,777	31.2%	-1.190	-0.026
2019	3,713	28.2%	5,867	31.7%	-3.528	-0.077
Pregnancy Characteristics						
Pre-Term (0-258 days)	807	6.1%	1,213	6.6%	-0.431	-0.018
Term (259-280 days)	8,638	65.6%	11,647	62.9%	2.612	0.055
Post-Term (281-301 days)	2,778	21.1%	4,233	22.9%	-1.794	-0.043
Unknown Term	953	7.2%	1,410	7.6%	-0.388	-0.015
Gestational age ⁵ at delivery	39.7	1.6	39.7	1.6	-0.008	-0.005

Table 1e. Unadjusted Characteristics of Step Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Database from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Mother Characteristics^{1,2}						
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.547	0.097
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.032	-0.068
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.032	0.068
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,221	32.0%	6,522	35.2%	-3.213	-0.068
Exposed during third trimester	8,955	68.0%	11,981	64.8%	3.213	0.068
Health Characteristics						
Ear, Nose, and Throat Infections	4,585	34.8%	9,368	50.6%	-15.832	-0.324
Gastrointestinal Infections	32	0.2%	60	0.3%	-0.081	-0.015
Lower Respiratory Infections	1,302	9.9%	732	4.0%	5.925	0.235
Sexually Transmitted Infections	116	0.9%	31	0.2%	0.713	0.099
Other Indications	5	0.0%	95	0.5%	-0.475	-0.091
Pelvic Inflammatory Disease	105	0.8%	164	0.9%	-0.089	-0.010
Skin and Subcutaneous Tissue	31	0.2%	208	1.1%	-0.889	-0.108
Urinary Tract and Kidney Infections	114	0.9%	701	3.8%	-2.923	-0.195
Alcohol Abuse	32	0.2%	50	0.3%	-0.027	-0.005
Asthma	597	4.5%	749	4.0%	0.483	0.024
Cardiac Valvular Disease	79	0.6%	113	0.6%	-0.011	-0.001
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	9	0.1%	18	0.1%	-0.029	-0.010
Chronic Renal Disease	53	0.4%	67	0.4%	0.040	0.007
Congenital Heart Disease	40	0.3%	81	0.4%	-0.134	-0.022
Cystic Fibrosis	9	0.1%	22	0.1%	-0.051	-0.017
Drug Abuse	126	1.0%	156	0.8%	0.113	0.012

Table 1e. Unadjusted Characteristics of Step Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Database from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Epilepsy/Seizures	46	0.3%	68	0.4%	-0.018	-0.003
HIV	13	0.1%	17	0.1%	0.007	0.002
Inflammatory Bowel Disease	55	0.4%	81	0.4%	-0.020	-0.003
Leukemia/Lymphoma	3	0.0%	19	0.1%	-0.080	-0.032
Obesity	1,582	12.0%	2,386	12.9%	-0.889	-0.027
Preexisting Diabetes	219	1.7%	331	1.8%	-0.127	-0.010
Preexisting Hypertension	511	3.9%	674	3.6%	0.236	0.012
Previous Cesarean Delivery	409	3.1%	658	3.6%	-0.452	-0.025
Psychiatric Disorders	1,662	12.6%	2,438	13.2%	-0.562	-0.017
Pulmonary Hypertension	3	0.0%	3	0.0%	0.007	0.005
Rheumatoid Arthritis	31	0.2%	45	0.2%	-0.008	-0.002
Sickle Cell Disease	26	0.2%	48	0.3%	-0.062	-0.013
Systemic Lupus Erythematosus	44	0.3%	39	0.2%	0.123	0.024
Tobacco Use	223	1.7%	359	1.9%	-0.248	-0.019
Vaccine Administration	44	0.3%	65	0.4%	-0.017	-0.003
Screening Examinations and Disease Management Training	5	0.0%	6	0.0%	0.006	0.003
Pap Smear	1,564	11.9%	2,018	10.9%	0.964	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	20	0.2%	42	0.2%	-0.075	-0.017
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-21 weeks	1,435	10.9%	2,360	12.8%	-1.864	-0.058
Gestational Age 22-23 weeks	1,451	11.0%	2,241	12.1%	-1.099	-0.034
Gestational Age 24-25 weeks	1,428	10.8%	2,068	11.2%	-0.339	-0.011
Gestational Age 26-27 weeks	1,363	10.3%	1,971	10.7%	-0.308	-0.010
Gestational Age 28-29 weeks	1,374	10.4%	1,940	10.5%	-0.057	-0.002

Table 1e. Unadjusted Characteristics of Step Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Database from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ³	Number/Mean	Percent/ Standard Deviation ³		
Gestational Age 30-31 weeks	1,283	9.7%	1,804	9.7%	-0.012	-0.000
Gestational Age 32-33 weeks	1,274	9.7%	1,741	9.4%	0.260	0.009
Gestational Age 34-35 weeks	1,263	9.6%	1,767	9.5%	0.036	0.001
Gestational Age 36-37 weeks	1,392	10.6%	1,572	8.5%	2.069	0.070
Gestational Age 38-42 weeks	913	6.9%	1,039	5.6%	1.314	0.054
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	-0.056	-0.012
Mean number of emergency room encounters	0.2	0.6	0.2	0.6	-0.013	-0.020
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.009
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	-0.050	-0.021
Mean number of filled prescriptions	2.6	3.6	2.5	3.5	0.187	0.053
Mean number of generics dispensed	1.5	1.8	1.4	1.7	0.111	0.064
Mean number of unique drug classes dispensed	1.5	1.7	1.4	1.6	0.103	0.062

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1f. Weighted Characteristics of Step Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Standard Deviation ⁴		
Unique patients	13,171	100.0%	18,472	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.127	0.024
Age						
10-54 years	13,171	100.0%	18,472	100.0%	0.000	N/A
Sex						
Female	13,171	100.0%	18,472	100.0%	0.000	N/A
Race ⁵						
Unknown	13,171	100.0%	18,472	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,171	100.0%	18,472	100.0%	0.000	N/A
Year						
2016	747	5.7%	886	4.8%	0.876	0.039
2017	4,726	35.9%	5,997	32.5%	3.414	0.072
2018	3,975	30.2%	5,778	31.3%	-1.100	-0.024
2019	3,723	28.3%	5,811	31.5%	-3.189	-0.070
Pregnancy Characteristics						
Pre-Term (0-258 days)	820	6.2%	1,202	6.5%	-0.287	-0.012
Term (259-280 days)	8,616	65.4%	11,620	62.9%	2.510	0.052
Post-Term (281-301 days)	2,791	21.2%	4,226	22.9%	-1.689	-0.041
Unknown Term	945	7.2%	1,424	7.7%	-0.534	-0.020
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	-0.014	-0.009

Table 1f. Weighted Characteristics of Step Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.6	5.6	29.8	5.6	-0.148	-0.026
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	0.010	0.020
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	-0.010	-0.021
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,533	34.4%	6,180	33.5%	0.962	0.020
Exposed during third trimester	8,638	65.6%	12,292	66.5%	-0.962	-0.020
Health Characteristics						
Ear, Nose, and Throat Infections	5,908	44.9%	8,168	44.2%	0.639	0.013
Gastrointestinal Infections	41	0.3%	53	0.3%	0.020	0.004
Lower Respiratory Infections	982	7.5%	968	5.2%	2.214	0.091
Sexually Transmitted Infections	85	0.6%	40	0.2%	0.426	0.065
Other Indications	8	0.1%	56	0.3%	-0.243	-0.058
Pelvic Inflammatory Disease	118	0.9%	156	0.8%	0.052	0.006
Skin and Subcutaneous Tissue	47	0.4%	163	0.9%	-0.525	-0.067
Urinary Tract and Kidney Infections	170	1.3%	564	3.1%	-1.763	-0.121
Alcohol Abuse	34	0.3%	46	0.3%	0.011	0.002
Asthma	565	4.3%	780	4.2%	0.068	0.003
Cardiac Valvular Disease	79	0.6%	109	0.6%	0.012	0.002
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	15	0.1%	-0.000	-0.000
Chronic Renal Disease	49	0.4%	71	0.4%	-0.008	-0.001
Congenital Heart Disease	47	0.4%	68	0.4%	-0.011	-0.002
Cystic Fibrosis	11	0.1%	19	0.1%	-0.019	-0.006
Drug Abuse	116	0.9%	163	0.9%	-0.000	-0.000

Table 1f. Weighted Characteristics of Step Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Standard Deviation ⁴		
Epilepsy/Seizures	46	0.3%	63	0.3%	0.008	0.001
HIV	13	0.1%	18	0.1%	0.004	0.001
Inflammatory Bowel Disease	58	0.4%	79	0.4%	0.013	0.002
Leukemia/Lymphoma	5	0.0%	14	0.1%	-0.044	-0.019
Obesity	1,671	12.7%	2,290	12.4%	0.292	0.009
Preexisting Diabetes	234	1.8%	321	1.7%	0.037	0.003
Preexisting Hypertension	498	3.8%	696	3.8%	0.016	0.001
Previous Cesarean Delivery	458	3.5%	610	3.3%	0.171	0.009
Psychiatric Disorders	1,708	13.0%	2,388	12.9%	0.038	0.001
Pulmonary Hypertension	3	0.0%	3	0.0%	0.004	0.003
Rheumatoid Arthritis	35	0.3%	44	0.2%	0.024	0.005
Sickle Cell Disease	32	0.2%	42	0.2%	0.014	0.003
Systemic Lupus Erythematosus	38	0.3%	45	0.2%	0.047	0.009
Tobacco Use	251	1.9%	325	1.8%	0.149	0.011
Vaccine Administration	44	0.3%	66	0.4%	-0.021	-0.004
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.002	-0.001
Pap Smear	1,451	11.0%	2,114	11.4%	-0.428	-0.014
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	24	0.2%	37	0.2%	-0.014	-0.003
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-21 weeks	1,624	12.3%	2,146	11.6%	0.713	0.022
Gestational Age 22-23 weeks	1,554	11.8%	2,132	11.5%	0.259	0.008
Gestational Age 24-25 weeks	1,448	11.0%	2,049	11.1%	-0.100	-0.003
Gestational Age 26-27 weeks	1,397	10.6%	1,949	10.5%	0.061	0.002
Gestational Age 28-29 weeks	1,392	10.6%	1,926	10.4%	0.137	0.004

Table 1f. Weighted Characteristics of Step Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Gestational Age 30-31 weeks	1,284	9.7%	1,812	9.8%	-0.064	-0.002
Gestational Age 32-33 weeks	1,232	9.4%	1,754	9.5%	-0.145	-0.005
Gestational Age 34-35 weeks	1,234	9.4%	1,765	9.6%	-0.183	-0.006
Gestational Age 36-37 weeks	1,219	9.3%	1,774	9.6%	-0.349	-0.012
Gestational Age 38-42 weeks	788	6.0%	1,165	6.3%	-0.326	-0.014
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	0.017	0.004
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.005	0.008
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.000	0.000
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.003	0.001
Mean number of filled prescriptions	2.5	3.5	2.6	3.6	-0.031	-0.009
Mean number of generics dispensed	1.5	1.7	1.5	1.7	-0.015	-0.009
Mean number of unique drug classes dispensed	1.4	1.6	1.4	1.7	-0.017	-0.010

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1g. Unadjusted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Unique patients	13,176	100.0%	18,503	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	30.9	5.2	0.160	0.031
Age						
10-54 years	13,176	100.0%	18,503	100.0%	0.000	N/A
Sex						
Female	13,176	100.0%	18,503	100.0%	0.000	N/A
Race ⁴						
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Year						
2016	770	5.8%	874	4.7%	1.120	0.050
2017	4,736	35.9%	5,985	32.3%	3.598	0.076
2018	3,957	30.0%	5,777	31.2%	-1.190	-0.026
2019	3,713	28.2%	5,867	31.7%	-3.528	-0.077
Pregnancy Characteristics						
Pre-Term (0-258 days)	807	6.1%	1,213	6.6%	-0.431	-0.018
Term (259-280 days)	8,638	65.6%	11,647	62.9%	2.612	0.055
Post-Term (281-301 days)	2,778	21.1%	4,233	22.9%	-1.794	-0.043
Unknown Term	953	7.2%	1,410	7.6%	-0.388	-0.015
Gestational age ⁵ at delivery	39.7	1.6	39.7	1.6	-0.008	-0.005

Table 1g. Unadjusted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.547	0.097
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.032	-0.068
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.032	0.068
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,221	32.0%	6,522	35.2%	-3.213	-0.068
Exposed during third trimester	8,955	68.0%	11,981	64.8%	3.213	0.068
Health Characteristics						
Ear, Nose, and Throat Infections	4,585	34.8%	9,368	50.6%	-15.832	-0.324
Gastrointestinal Infections	32	0.2%	60	0.3%	-0.081	-0.015
Lower Respiratory Infections	1,302	9.9%	732	4.0%	5.925	0.235
Sexually Transmitted Infections	116	0.9%	31	0.2%	0.713	0.099
Other Indications	5	0.0%	95	0.5%	-0.475	-0.091
Pelvic Inflammatory Disease	105	0.8%	164	0.9%	-0.089	-0.010
Skin and Subcutaneous Tissue	31	0.2%	208	1.1%	-0.889	-0.108
Urinary Tract and Kidney Infections	114	0.9%	701	3.8%	-2.923	-0.195
Alcohol Abuse	32	0.2%	50	0.3%	-0.027	-0.005
Asthma	597	4.5%	749	4.0%	0.483	0.024
Cardiac Valvular Disease	79	0.6%	113	0.6%	-0.011	-0.001
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	9	0.1%	18	0.1%	-0.029	-0.010
Chronic Renal Disease	53	0.4%	67	0.4%	0.040	0.007
Congenital Heart Disease	40	0.3%	81	0.4%	-0.134	-0.022
Cystic Fibrosis	9	0.1%	22	0.1%	-0.051	-0.017
Drug Abuse	126	1.0%	156	0.8%	0.113	0.012

Table 1g. Unadjusted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Epilepsy/Seizures	46	0.3%	68	0.4%	-0.018	-0.003
HIV	13	0.1%	17	0.1%	0.007	0.002
Inflammatory Bowel Disease	55	0.4%	81	0.4%	-0.020	-0.003
Leukemia/Lymphoma	3	0.0%	19	0.1%	-0.080	-0.032
Obesity	1,582	12.0%	2,386	12.9%	-0.889	-0.027
Preexisting Diabetes	219	1.7%	331	1.8%	-0.127	-0.010
Preexisting Hypertension	511	3.9%	674	3.6%	0.236	0.012
Previous Cesarean Delivery	409	3.1%	658	3.6%	-0.452	-0.025
Psychiatric Disorders	1,662	12.6%	2,438	13.2%	-0.562	-0.017
Pulmonary Hypertension	3	0.0%	3	0.0%	0.007	0.005
Rheumatoid Arthritis	31	0.2%	45	0.2%	-0.008	-0.002
Sickle Cell Disease	26	0.2%	48	0.3%	-0.062	-0.013
Systemic Lupus Erythematosus	44	0.3%	39	0.2%	0.123	0.024
Tobacco Use	223	1.7%	359	1.9%	-0.248	-0.019
Vaccine Administration	44	0.3%	65	0.4%	-0.017	-0.003
Screening Examinations and Disease Management Training	5	0.0%	6	0.0%	0.006	0.003
Pap Smear	1,564	11.9%	2,018	10.9%	0.964	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	20	0.2%	42	0.2%	-0.075	-0.017
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-21 weeks	1,435	10.9%	2,360	12.8%	-1.864	-0.058
Gestational Age 22-23 weeks	1,451	11.0%	2,241	12.1%	-1.099	-0.034
Gestational Age 24-25 weeks	1,428	10.8%	2,068	11.2%	-0.339	-0.011
Gestational Age 26-27 weeks	1,363	10.3%	1,971	10.7%	-0.308	-0.010
Gestational Age 28-29 weeks	1,374	10.4%	1,940	10.5%	-0.057	-0.002

Table 1g. Unadjusted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Gestational Age 30-31 weeks	1,283	9.7%	1,804	9.7%	-0.012	-0.000
Gestational Age 32-33 weeks	1,274	9.7%	1,741	9.4%	0.260	0.009
Gestational Age 34-35 weeks	1,263	9.6%	1,767	9.5%	0.036	0.001
Gestational Age 36-37 weeks	1,392	10.6%	1,572	8.5%	2.069	0.070
Gestational Age 38-42 weeks	913	6.9%	1,039	5.6%	1.314	0.054
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	-0.056	-0.012
Mean number of emergency room encounters	0.2	0.6	0.2	0.6	-0.013	-0.020
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.009
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	-0.050	-0.021
Mean number of filled prescriptions	2.6	3.6	2.5	3.5	0.187	0.053
Mean number of generics dispensed	1.5	1.8	1.4	1.7	0.111	0.064
Mean number of unique drug classes dispensed	1.5	1.7	1.4	1.6	0.103	0.062

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1h. Weighted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Unique patients	13,169	100.0%	18,461	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.139	0.027
Age						
10-54 years	13,169	100.0%	18,461	100.0%	0.000	N/A
Sex						
Female	13,169	100.0%	18,461	100.0%	0.000	N/A
Race ⁵						
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Year						
2016	748	5.7%	884	4.8%	0.891	0.040
2017	4,708	35.7%	5,996	32.5%	3.266	0.069
2018	3,978	30.2%	5,767	31.2%	-1.034	-0.022
2019	3,735	28.4%	5,813	31.5%	-3.123	-0.068
Pregnancy Characteristics						
Pre-Term (0-258 days)	802	6.1%	1,225	6.6%	-0.541	-0.022
Term (259-280 days)	8,608	65.4%	11,622	63.0%	2.414	0.050
Post-Term (281-301 days)	2,808	21.3%	4,199	22.7%	-1.418	-0.034
Unknown Term	950	7.2%	1,416	7.7%	-0.455	-0.017
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	0.008	0.005

Table 1h. Weighted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.9	5.7	29.5	5.6	0.418	0.074
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	-0.024	-0.051
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	0.024	0.050
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,276	32.5%	6,435	34.9%	-2.392	-0.051
Exposed during third trimester	8,893	67.5%	12,026	65.1%	2.392	0.051
Health Characteristics						
Ear, Nose, and Throat Infections	5,892	44.7%	8,167	44.2%	0.501	0.010
Gastrointestinal Infections	41	0.3%	52	0.3%	0.026	0.005
Lower Respiratory Infections	995	7.6%	951	5.2%	2.401	0.099
Sexually Transmitted Infections	84	0.6%	39	0.2%	0.428	0.066
Other Indications	7	0.1%	48	0.3%	-0.202	-0.051
Pelvic Inflammatory Disease	124	0.9%	149	0.8%	0.136	0.015
Skin and Subcutaneous Tissue	46	0.4%	163	0.9%	-0.533	-0.068
Urinary Tract and Kidney Infections	169	1.3%	566	3.1%	-1.782	-0.122
Alcohol Abuse	35	0.3%	46	0.3%	0.017	0.003
Asthma	564	4.3%	781	4.2%	0.055	0.003
Cardiac Valvular Disease	80	0.6%	110	0.6%	0.008	0.001
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	15	0.1%	0.003	0.001
Chronic Renal Disease	48	0.4%	71	0.4%	-0.021	-0.003
Congenital Heart Disease	48	0.4%	68	0.4%	-0.003	-0.000
Cystic Fibrosis	11	0.1%	19	0.1%	-0.019	-0.006
Drug Abuse	116	0.9%	161	0.9%	0.007	0.001

Table 1h. Weighted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Epilepsy/Seizures	46	0.4%	63	0.3%	0.010	0.002
HIV	14	0.1%	17	0.1%	0.009	0.003
Inflammatory Bowel Disease	59	0.4%	77	0.4%	0.032	0.005
Leukemia/Lymphoma	4	0.0%	14	0.1%	-0.040	-0.017
Obesity	1,711	13.0%	2,251	12.2%	0.796	0.024
Preexisting Diabetes	238	1.8%	317	1.7%	0.088	0.007
Preexisting Hypertension	497	3.8%	695	3.8%	0.008	0.000
Previous Cesarean Delivery	480	3.6%	597	3.2%	0.411	0.023
Psychiatric Disorders	1,715	13.0%	2,381	12.9%	0.128	0.004
Pulmonary Hypertension	3	0.0%	3	0.0%	0.003	0.003
Rheumatoid Arthritis	35	0.3%	44	0.2%	0.031	0.006
Sickle Cell Disease	32	0.2%	41	0.2%	0.021	0.004
Systemic Lupus Erythematosus	39	0.3%	43	0.2%	0.062	0.012
Tobacco Use	256	1.9%	319	1.7%	0.218	0.016
Vaccine Administration	44	0.3%	67	0.4%	-0.029	-0.005
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.004	-0.002
Pap Smear	1,430	10.9%	2,138	11.6%	-0.719	-0.023
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	25	0.2%	36	0.2%	-0.006	-0.001
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-21 weeks	1,446	11.0%	2,326	12.6%	-1.618	-0.050
Gestational Age 22-23 weeks	1,476	11.2%	2,211	12.0%	-0.767	-0.024
Gestational Age 24-25 weeks	1,447	11.0%	2,046	11.1%	-0.100	-0.003
Gestational Age 26-27 weeks	1,390	10.6%	1,960	10.6%	-0.059	-0.002
Gestational Age 28-29 weeks	1,374	10.4%	1,945	10.5%	-0.101	-0.003

Table 1h. Weighted Characteristics of Variable Approach with 2-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Gestational Age 30-31 weeks	1,286	9.8%	1,814	9.8%	-0.063	-0.002
Gestational Age 32-33 weeks	1,248	9.5%	1,743	9.4%	0.035	0.001
Gestational Age 34-35 weeks	1,241	9.4%	1,755	9.5%	-0.082	-0.003
Gestational Age 36-37 weeks	1,371	10.4%	1,607	8.7%	1.710	0.058
Gestational Age 38-42 weeks	889	6.8%	1,054	5.7%	1.045	0.043
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.0	4.5	5.9	4.5	0.026	0.006
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.008	0.013
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.000	0.002
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.013	0.006
Mean number of filled prescriptions	2.5	3.5	2.6	3.6	-0.060	-0.017
Mean number of generics dispensed	1.5	1.7	1.5	1.7	-0.034	-0.020
Mean number of unique drug classes dispensed	1.4	1.6	1.5	1.7	-0.036	-0.022

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1i. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Unique patients	13,176	100.0%	18,503	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	30.9	5.2	0.160	0.031
Age						
10-54 years	13,176	100.0%	18,503	100.0%	0.000	N/A
Sex						
Female	13,176	100.0%	18,503	100.0%	0.000	N/A
Race ⁴						
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Year						
2016	770	5.8%	874	4.7%	1.120	0.050
2017	4,736	35.9%	5,985	32.3%	3.598	0.076
2018	3,957	30.0%	5,777	31.2%	-1.190	-0.026
2019	3,713	28.2%	5,867	31.7%	-3.528	-0.077
Pregnancy Characteristics						
Pre-Term (0-258 days)	807	6.1%	1,213	6.6%	-0.431	-0.018
Term (259-280 days)	8,638	65.6%	11,647	62.9%	2.612	0.055
Post-Term (281-301 days)	2,778	21.1%	4,233	22.9%	-1.794	-0.043
Unknown Term	953	7.2%	1,410	7.6%	-0.388	-0.015
Gestational age ⁵ at delivery	39.7	1.6	39.7	1.6	-0.008	-0.005

Table 1i. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.547	0.097
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.032	-0.068
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.032	0.068
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,221	32.0%	6,522	35.2%	-3.213	-0.068
Exposed during third trimester	8,955	68.0%	11,981	64.8%	3.213	0.068
Health Characteristics						
Ear, Nose, and Throat Infections	4,585	34.8%	9,368	50.6%	-15.832	-0.324
Gastrointestinal Infections	32	0.2%	60	0.3%	-0.081	-0.015
Lower Respiratory Infections	1,302	9.9%	732	4.0%	5.925	0.235
Sexually Transmitted Infections	116	0.9%	31	0.2%	0.713	0.099
Other Indications	5	0.0%	95	0.5%	-0.475	-0.091
Pelvic Inflammatory Disease	105	0.8%	164	0.9%	-0.089	-0.010
Skin and Subcutaneous Tissue	31	0.2%	208	1.1%	-0.889	-0.108
Urinary Tract and Kidney Infections	114	0.9%	701	3.8%	-2.923	-0.195
Alcohol Abuse	32	0.2%	50	0.3%	-0.027	-0.005
Asthma	597	4.5%	749	4.0%	0.483	0.024
Cardiac Valvular Disease	79	0.6%	113	0.6%	-0.011	-0.001
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	9	0.1%	18	0.1%	-0.029	-0.010
Chronic Renal Disease	53	0.4%	67	0.4%	0.040	0.007
Congenital Heart Disease	40	0.3%	81	0.4%	-0.134	-0.022
Cystic Fibrosis	9	0.1%	22	0.1%	-0.051	-0.017
Drug Abuse	126	1.0%	156	0.8%	0.113	0.012

Table 1i. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Epilepsy/Seizures	46	0.3%	68	0.4%	-0.018	-0.003
HIV	13	0.1%	17	0.1%	0.007	0.002
Inflammatory Bowel Disease	55	0.4%	81	0.4%	-0.020	-0.003
Leukemia/Lymphoma	3	0.0%	19	0.1%	-0.080	-0.032
Obesity	1,582	12.0%	2,386	12.9%	-0.889	-0.027
Preexisting Diabetes	219	1.7%	331	1.8%	-0.127	-0.010
Preexisting Hypertension	511	3.9%	674	3.6%	0.236	0.012
Previous Cesarean Delivery	409	3.1%	658	3.6%	-0.452	-0.025
Psychiatric Disorders	1,662	12.6%	2,438	13.2%	-0.562	-0.017
Pulmonary Hypertension	3	0.0%	3	0.0%	0.007	0.005
Rheumatoid Arthritis	31	0.2%	45	0.2%	-0.008	-0.002
Sickle Cell Disease	26	0.2%	48	0.3%	-0.062	-0.013
Systemic Lupus Erythematosus	44	0.3%	39	0.2%	0.123	0.024
Tobacco Use	223	1.7%	359	1.9%	-0.248	-0.019
Vaccine Administration	44	0.3%	65	0.4%	-0.017	-0.003
Screening Examinations and Disease Management Training	5	0.0%	6	0.0%	0.006	0.003
Pap Smear	1,564	11.9%	2,018	10.9%	0.964	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	20	0.2%	42	0.2%	-0.075	-0.017
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-21 weeks	1,435	10.9%	2,360	12.8%	-1.864	-0.058
Gestational Age 22-23 weeks	1,451	11.0%	2,241	12.1%	-1.099	-0.034
Gestational Age 24-25 weeks	1,428	10.8%	2,068	11.2%	-0.339	-0.011
Gestational Age 26-27 weeks	1,363	10.3%	1,971	10.7%	-0.308	-0.010
Gestational Age 28-29 weeks	1,374	10.4%	1,940	10.5%	-0.057	-0.002

Table 1i. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Gestational Age 30-31 weeks	1,283	9.7%	1,804	9.7%	-0.012	-0.000
Gestational Age 32-33 weeks	1,274	9.7%	1,741	9.4%	0.260	0.009
Gestational Age 34-35 weeks	1,263	9.6%	1,767	9.5%	0.036	0.001
Gestational Age 36-37 weeks	1,392	10.6%	1,572	8.5%	2.069	0.070
Gestational Age 38-42 weeks	913	6.9%	1,039	5.6%	1.314	0.054
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	-0.056	-0.012
Mean number of emergency room encounters	0.2	0.6	0.2	0.6	-0.013	-0.020
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.009
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	-0.050	-0.021
Mean number of filled prescriptions	2.6	3.6	2.5	3.5	0.187	0.053
Mean number of generics dispensed	1.5	1.8	1.4	1.7	0.111	0.064
Mean number of unique drug classes dispensed	1.5	1.7	1.4	1.6	0.103	0.062

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1j. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Unique patients	13,171	100.0%	18,462	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.129	0.025
Age						
10-54 years	13,171	100.0%	18,462	100.0%	0.000	N/A
Sex						
Female	13,171	100.00%	18,462	100.0%	0.000	N/A
Race ⁵						
Unknown	13,171	100.0%	18,462	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,171	100.0%	18,462	100.0%	0.000	N/A
Year						
2016	744	5.7%	888	4.8%	0.842	0.038
2017	4,726	35.9%	5,995	32.5%	3.413	0.072
2018	3,975	30.2%	5,770	31.3%	-1.072	-0.023
2019	3,725	28.3%	5,809	31.5%	-3.184	-0.070
Pregnancy Characteristics						
Pre-Term (0-258 days)	815	6.2%	1,209	6.5%	-0.359	-0.015
Term (259-280 days)	8,618	65.4%	11,612	62.9%	2.534	0.053
Post-Term (281-301 days)	2,791	21.2%	4,221	22.9%	-1.676	-0.040
Unknown Term	946	7.2%	1,419	7.7%	-0.500	-0.019
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	-0.011	-0.007

Table 1j. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.6	5.6	29.8	5.6	-0.139	-0.025
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	0.013	0.028
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	-0.014	-0.029
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,563	34.6%	6,146	33.3%	1.356	0.029
Exposed during third trimester	8,608	65.4%	12,316	66.7%	-1.356	-0.029
Health Characteristics						
Ear, Nose, and Throat Infections	5,880	44.6%	8,187	44.3%	0.301	0.006
Gastrointestinal Infections	41	0.3%	53	0.3%	0.023	0.004
Lower Respiratory Infections	976	7.4%	976	5.3%	2.119	0.087
Sexually Transmitted Infections	84	0.6%	41	0.2%	0.420	0.064
Other Indications	8	0.1%	48	0.3%	-0.205	-0.051
Pelvic Inflammatory Disease	119	0.9%	154	0.8%	0.065	0.007
Skin and Subcutaneous Tissue	47	0.4%	163	0.9%	-0.530	-0.068
Urinary Tract and Kidney Infections	170	1.3%	565	3.1%	-1.766	-0.121
Alcohol Abuse	34	0.3%	46	0.2%	0.012	0.002
Asthma	564	4.3%	783	4.2%	0.042	0.002
Cardiac Valvular Disease	80	0.6%	109	0.6%	0.012	0.002
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	15	0.1%	0.000	0.000
Chronic Renal Disease	48	0.4%	70	0.4%	-0.016	-0.003
Congenital Heart Disease	48	0.4%	68	0.4%	-0.007	-0.001
Cystic Fibrosis	11	0.1%	19	0.1%	-0.019	-0.006
Drug Abuse	115	0.9%	162	0.9%	-0.003	-0.000

Table 1j. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Epilepsy/Seizures	46	0.4%	62	0.3%	0.016	0.003
HIV	14	0.1%	17	0.1%	0.013	0.004
Inflammatory Bowel Disease	59	0.4%	78	0.4%	0.020	0.003
Leukemia/Lymphoma	5	0.0%	14	0.1%	-0.040	-0.017
Obesity	1,684	12.8%	2,272	12.3%	0.479	0.014
Preexisting Diabetes	237	1.8%	318	1.7%	0.077	0.006
Preexisting Hypertension	499	3.8%	698	3.8%	0.008	0.000
Previous Cesarean Delivery	463	3.5%	608	3.3%	0.218	0.012
Psychiatric Disorders	1,710	13.0%	2,385	12.9%	0.059	0.002
Pulmonary Hypertension	3	0.0%	3	0.0%	0.003	0.002
Rheumatoid Arthritis	35	0.3%	44	0.2%	0.025	0.005
Sickle Cell Disease	32	0.2%	41	0.2%	0.017	0.003
Systemic Lupus Erythematosus	38	0.3%	44	0.2%	0.050	0.010
Tobacco Use	252	1.9%	323	1.7%	0.163	0.012
Vaccine Administration	44	0.3%	65	0.4%	-0.015	-0.003
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.005	-0.003
Pap Smear	1,444	11.0%	2,124	11.5%	-0.537	-0.017
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	25	0.2%	37	0.2%	-0.012	-0.003
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	4,664	35.4%	6,286	34.0%	1.365	0.029
Gestational Age 24-27 weeks	4,101	31.1%	5,669	30.7%	0.430	0.009
Gestational Age 28-31 weeks	3,621	27.5%	5,336	28.9%	-1.410	-0.031
Gestational Age 32-35 weeks	785	6.0%	1,171	6.3%	-0.384	-0.016
Gestational Age 36-42 weeks						

Table 1j. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.0	4.5	5.9	4.5	0.016	0.003
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.008	0.012
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.000	0.001
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.008	0.004
Mean number of filled prescriptions	2.5	3.5	2.6	3.6	-0.043	-0.012
Mean number of generics dispensed	1.5	1.7	1.5	1.7	-0.023	-0.013
Mean number of unique drug classes dispensed	1.4	1.6	1.5	1.7	-0.025	-0.015

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1k. Unadjusted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Unique patients	13,176	100.0%	18,503	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	30.9	5.2	0.160	0.031
Age						
10-54 years	13,176	100.0%	18,503	100.0%	0.000	N/A
Sex						
Female	13,176	100.0%	18,503	100.0%	0.000	N/A
Race ⁴						
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,176	100.0%	18,503	100.0%	0.000	N/A
Year						
2016	770	5.8%	874	4.7%	1.120	0.050
2017	4,736	35.9%	5,985	32.3%	3.598	0.076
2018	3,957	30.0%	5,777	31.2%	-1.190	-0.026
2019	3,713	28.2%	5,867	31.7%	-3.528	-0.077
Pregnancy Characteristics						
Pre-Term (0-258 days)	807	6.1%	1,213	6.6%	-0.431	-0.018
Term (259-280 days)	8,638	65.6%	11,647	62.9%	2.612	0.055
Post-Term (281-301 days)	2,778	21.1%	4,233	22.9%	-1.794	-0.043
Unknown Term	953	7.2%	1,410	7.6%	-0.388	-0.015
Gestational age ⁵ at delivery	39.7	1.6	39.7	1.6	-0.008	-0.005

Table 1k. Unadjusted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.547	0.097
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.032	-0.068
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.032	0.068
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,221	32.0%	6,522	35.2%	-3.213	-0.068
Exposed during third trimester	8,955	68.0%	11,981	64.8%	3.213	0.068
Health Characteristics						
Ear, Nose, and Throat Infections	4,585	34.8%	9,368	50.6%	-15.832	-0.324
Gastrointestinal Infections	32	0.2%	60	0.3%	-0.081	-0.015
Lower Respiratory Infections	1,302	9.9%	732	4.0%	5.925	0.235
Sexually Transmitted Infections	116	0.9%	31	0.2%	0.713	0.099
Other Indications	5	0.0%	95	0.5%	-0.475	-0.091
Pelvic Inflammatory Disease	105	0.8%	164	0.9%	-0.089	-0.010
Skin and Subcutaneous Tissue	31	0.2%	208	1.1%	-0.889	-0.108
Urinary Tract and Kidney Infections	114	0.9%	701	3.8%	-2.923	-0.195
Alcohol Abuse	32	0.2%	50	0.3%	-0.027	-0.005
Asthma	597	4.5%	749	4.0%	0.483	0.024
Cardiac Valvular Disease	79	0.6%	113	0.6%	-0.011	-0.001
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	9	0.1%	18	0.1%	-0.029	-0.010
Chronic Renal Disease	53	0.4%	67	0.4%	0.040	0.007
Congenital Heart Disease	40	0.3%	81	0.4%	-0.134	-0.022
Cystic Fibrosis	9	0.1%	22	0.1%	-0.051	-0.017
Drug Abuse	126	1.0%	156	0.8%	0.113	0.012

Table 1k. Unadjusted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Epilepsy/Seizures	46	0.3%	68	0.4%	-0.018	-0.003
HIV	13	0.1%	17	0.1%	0.007	0.002
Inflammatory Bowel Disease	55	0.4%	81	0.4%	-0.020	-0.003
Leukemia/Lymphoma	3	0.0%	19	0.1%	-0.080	-0.032
Obesity	1,582	12.0%	2,386	12.9%	-0.889	-0.027
Preexisting Diabetes	219	1.7%	331	1.8%	-0.127	-0.010
Preexisting Hypertension	511	3.9%	674	3.6%	0.236	0.012
Previous Cesarean Delivery	409	3.1%	658	3.6%	-0.452	-0.025
Psychiatric Disorders	1,662	12.6%	2,438	13.2%	-0.562	-0.017
Pulmonary Hypertension	3	0.0%	3	0.0%	0.007	0.005
Rheumatoid Arthritis	31	0.2%	45	0.2%	-0.008	-0.002
Sickle Cell Disease	26	0.2%	48	0.3%	-0.062	-0.013
Systemic Lupus Erythematosus	44	0.3%	39	0.2%	0.123	0.024
Tobacco Use	223	1.7%	359	1.9%	-0.248	-0.019
Vaccine Administration	44	0.3%	65	0.4%	-0.017	-0.003
Screening Examinations and Disease Management Training	5	0.0%	6	0.0%	0.006	0.003
Pap Smear	1,564	11.9%	2,018	10.9%	0.964	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	20	0.2%	42	0.2%	-0.075	-0.017
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-25 weeks	4,314	32.7%	6,669	36.0%	-3.301	-0.070
Gestational Age 26-31 weeks	4,020	30.5%	5,715	30.9%	-0.377	-0.008
Gestational Age 32-37 weeks	3,929	29.8%	5,080	27.5%	2.364	0.052
Gestational Age 38-42 weeks	913	6.9%	1,039	5.6%	1.314	0.054

Table 1k. Unadjusted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	5.9	4.5	5.9	4.5	-0.056	-0.012
Mean number of emergency room encounters	0.2	0.6	0.2	0.6	-0.013	-0.020
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.009
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	-0.050	-0.021
Mean number of filled prescriptions	2.6	3.6	2.5	3.5	0.187	0.053
Mean number of generics dispensed	1.5	1.8	1.4	1.7	0.111	0.064
Mean number of unique drug classes dispensed	1.5	1.7	1.4	1.6	0.103	0.062

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1I. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Unique patients	13,169	100.0%	18,461	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.139	0.027
Age						
10-54 years	13,169	100.0%	18,461	100.0%	0.000	N/A
Sex						
Female	13,169	100.0%	18,461	100.0%	0.000	N/A
Race ⁵						
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Year						
2016	748	5.7%	884	4.8%	0.891	0.040
2017	4,708	35.7%	5,996	32.5%	3.266	0.069
2018	3,978	30.2%	5,767	31.2%	-1.034	-0.022
2019	3,735	28.4%	5,813	31.5%	-3.123	-0.068
Pregnancy Characteristics						
Pre-Term (0-258 days)	802	6.1%	1,225	6.6%	-0.541	-0.022
Term (259-280 days)	8,608	65.4%	11,622	63.0%	2.414	0.050
Post-Term (281-301 days)	2,808	21.3%	4,199	22.7%	-1.418	-0.034
Unknown Term	950	7.2%	1,416	7.7%	-0.455	-0.017
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	0.008	0.005

Table 11. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.9	5.7	29.5	5.6	0.418	0.074
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	-0.024	-0.051
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	0.024	0.050
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,276	32.5%	6,435	34.9%	-2.392	-0.051
Exposed during third trimester	8,893	67.5%	12,026	65.1%	2.392	0.051
Health Characteristics						
Ear, Nose, and Throat Infections	5,892	44.7%	8,167	44.2%	0.501	0.010
Gastrointestinal Infections	41	0.3%	52	0.3%	0.026	0.005
Lower Respiratory Infections	995	7.6%	951	5.2%	2.401	0.099
Sexually Transmitted Infections	84	0.6%	39	0.2%	0.428	0.066
Other Indications	7	0.1%	48	0.3%	-0.202	-0.051
Pelvic Inflammatory Disease	124	0.9%	149	0.8%	0.136	0.015
Skin and Subcutaneous Tissue	46	0.4%	163	0.9%	-0.533	-0.068
Urinary Tract and Kidney Infections	169	1.3%	566	3.1%	-1.782	-0.122
Alcohol Abuse	35	0.3%	46	0.3%	0.017	0.003
Asthma	564	4.3%	781	4.2%	0.055	0.003
Cardiac Valvular Disease	80	0.6%	110	0.6%	0.008	0.001
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	15	0.1%	0.003	0.001
Chronic Renal Disease	48	0.4%	71	0.4%	-0.021	-0.003
Congenital Heart Disease	48	0.4%	68	0.4%	-0.003	-0.000
Cystic Fibrosis	11	0.1%	19	0.1%	-0.019	-0.006
Drug Abuse	116	0.9%	161	0.9%	0.007	0.001

Table 11. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Epilepsy/Seizures	46	0.4%	63	0.3%	0.010	0.002
HIV	14	0.1%	17	0.1%	0.009	0.003
Inflammatory Bowel Disease	59	0.4%	77	0.4%	0.032	0.005
Leukemia/Lymphoma	4	0.0%	14	0.1%	-0.040	-0.017
Obesity	1,711	13.0%	2,251	12.2%	0.796	0.024
Preexisting Diabetes	238	1.8%	317	1.7%	0.088	0.007
Preexisting Hypertension	497	3.8%	695	3.8%	0.008	0.000
Previous Cesarean Delivery	480	3.6%	597	3.2%	0.411	0.023
Psychiatric Disorders	1,715	13.0%	2,381	12.9%	0.128	0.004
Pulmonary Hypertension	3	0.0%	3	0.0%	0.003	0.003
Rheumatoid Arthritis	35	0.3%	44	0.2%	0.031	0.006
Sickle Cell Disease	32	0.2%	41	0.2%	0.021	0.004
Systemic Lupus Erythematosus	39	0.3%	43	0.2%	0.062	0.012
Tobacco Use	256	1.9%	319	1.7%	0.218	0.016
Vaccine Administration	44	0.3%	67	0.4%	-0.029	-0.005
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.004	-0.002
Pap Smear	1,430	10.9%	2,138	11.6%	-0.719	-0.023
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	25	0.2%	36	0.2%	-0.006	-0.001
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-25 weeks	4,369	33.2%	6,583	35.7%	-2.485	-0.052
Gestational Age 26-31 weeks	4,051	30.8%	5,720	31.0%	-0.223	-0.005
Gestational Age 32-37 weeks	3,860	29.3%	5,104	27.6%	1.663	0.037
Gestational Age 38-42 weeks	889	6.8%	1,054	5.7%	1.045	0.043

Table 1I. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.0	4.5	5.9	4.5	0.026	0.006
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.008	0.013
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.000	0.002
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.013	0.006
Mean number of filled prescriptions	2.5	3.5	2.6	3.6	-0.060	-0.017
Mean number of generics dispensed	1.5	1.7	1.5	1.7	-0.034	-0.020
Mean number of unique drug classes dispensed	1.4	1.6	1.5	1.7	-0.036	-0.022

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1m. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Unique patients	13,171	100.0%	18,462	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.116	0.022
Age						
10-54 years	13,171	100.0%	18,462	100.0%	0.000	N/A
Sex						
Female	13,171	100.0%	18,462	100.0%	0.000	N/A
Race ⁵						
Unknown	13,171	100.0%	18,462	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,171	100.0%	18,462	100.0%	0.000	N/A
Year						
2016	745	5.7%	884	4.8%	0.867	0.039
2017	4,726	35.9%	5,991	32.5%	3.433	0.072
2018	3,977	30.2%	5,772	31.3%	-1.068	-0.023
2019	3,723	28.3%	5,815	31.5%	-3.232	-0.071
Pregnancy Characteristics						
Pre-Term (0-258 days)	813	6.2%	1,207	6.5%	-0.365	-0.015
Term (259-280 days)	8,621	65.5%	11,618	62.9%	2.525	0.053
Post-Term (281-301 days)	2,790	21.2%	4,216	22.8%	-1.656	-0.040
Unknown Term	948	7.2%	1,421	7.7%	-0.504	-0.019
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	-0.011	-0.007

Table 1m. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.6	5.6	29.7	5.6	-0.099	-0.018
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	0.012	0.026
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	-0.013	-0.026
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,560	34.6%	6,165	33.4%	1.230	0.026
Exposed during third trimester	8,611	65.4%	12,297	66.6%	-1.230	-0.026
Health Characteristics						
Ear, Nose, and Throat Infections	5,921	45.0%	8,237	44.6%	0.337	0.007
Gastrointestinal Infections	43	0.3%	54	0.3%	0.038	0.007
Lower Respiratory Infections	892	6.8%	1,113	6.0%	0.745	0.030
Sexually Transmitted Infections	76	0.6%	48	0.3%	0.317	0.049
Other Indications	9	0.1%	45	0.2%	-0.175	-0.044
Pelvic Inflammatory Disease	117	0.9%	156	0.8%	0.049	0.005
Skin and Subcutaneous Tissue	57	0.4%	153	0.8%	-0.393	-0.050
Urinary Tract and Kidney Infections	203	1.5%	528	2.9%	-1.321	-0.090
Alcohol Abuse	34	0.3%	47	0.3%	0.003	0.001
Asthma	549	4.2%	804	4.4%	-0.186	-0.009
Cardiac Valvular Disease	77	0.6%	109	0.6%	-0.005	-0.001
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	15	0.1%	0.003	0.001
Chronic Renal Disease	47	0.4%	71	0.4%	-0.031	-0.005
Congenital Heart Disease	49	0.4%	68	0.4%	0.001	0.000
Cystic Fibrosis	11	0.1%	18	0.1%	-0.015	-0.005
Drug Abuse	114	0.9%	166	0.9%	-0.032	-0.003

Table 1m. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Epilepsy/Seizures	45	0.3%	63	0.3%	0.002	0.000
HIV	13	0.1%	17	0.1%	0.011	0.004
Inflammatory Bowel Disease	59	0.5%	78	0.4%	0.029	0.004
Leukemia/Lymphoma	6	0.0%	13	0.1%	-0.027	-0.012
Obesity	1,703	12.9%	2,281	12.4%	0.571	0.017
Preexisting Diabetes	240	1.8%	320	1.7%	0.090	0.007
Preexisting Hypertension	495	3.8%	703	3.8%	-0.046	-0.002
Previous Cesarean Delivery	469	3.6%	607	3.3%	0.268	0.015
Psychiatric Disorders	1,710	13.0%	2,403	13.0%	-0.037	-0.001
Pulmonary Hypertension	2	0.0%	3	0.0%	0.001	0.001
Rheumatoid Arthritis	36	0.3%	45	0.2%	0.033	0.006
Sickle Cell Disease	33	0.2%	42	0.2%	0.020	0.004
Systemic Lupus Erythematosus	36	0.3%	49	0.3%	0.008	0.002
Tobacco Use	258	2.0%	326	1.8%	0.196	0.014
Vaccine Administration	45	0.3%	66	0.4%	-0.015	-0.003
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.007	-0.004
Pap Smear	1,447	11.0%	2,133	11.6%	-0.561	-0.018
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	26	0.2%	36	0.2%	0.000	0.000
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-25 weeks	4,659	35.4%	6,306	34.2%	1.217	0.026
Gestational Age 26-31 weeks	4,052	30.8%	5,681	30.8%	-0.009	-0.000
Gestational Age 32-37 weeks	3,682	28.0%	5,285	28.6%	-0.668	-0.015
Gestational Age 38-42 weeks	778	5.9%	1,191	6.4%	-0.540	-0.022

Table 1m. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.0	4.5	5.9	4.5	0.005	0.001
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.008	0.012
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.000	-0.002
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.009	0.004
Mean number of filled prescriptions	2.5	3.5	2.6	3.6	-0.093	-0.026
Mean number of generics dispensed	1.5	1.7	1.5	1.8	-0.051	-0.029
Mean number of unique drug classes dispensed	1.4	1.6	1.5	1.7	-0.051	-0.031

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1n. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Unique patients	13,169	100.0%	18,461	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.130	0.025
Age						
10-54 years	13,169	100.0%	18,461	100.0%	0.000	N/A
Sex						
Female	13,169	100.0%	18,461	100.0%	0.000	N/A
Race ⁵						
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	13,169	100.0%	18,461	100.0%	0.000	N/A
Year						
2016	753	5.7%	882	4.8%	0.940	0.042
2017	4,713	35.8%	5,992	32.5%	3.333	0.070
2018	3,979	30.2%	5,773	31.3%	-1.057	-0.023
2019	3,724	28.3%	5,814	31.5%	-3.216	-0.070
Pregnancy Characteristics						
Pre-Term (0-258 days)	799	6.1%	1,225	6.6%	-0.567	-0.023
Term (259-280 days)	8,619	65.4%	11,620	62.9%	2.505	0.052
Post-Term (281-301 days)	2,805	21.3%	4,197	22.7%	-1.436	-0.035
Unknown Term	946	7.2%	1,419	7.7%	-0.502	-0.019
Gestational age ⁶ at delivery	39.7	1.6	39.7	1.6	0.007	0.005

Table 1n. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.9	5.7	29.5	5.6	0.428	0.076
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	-0.024	-0.051
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	0.024	0.051
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,274	32.5%	6,437	34.9%	-2.416	-0.051
Exposed during third trimester	8,895	67.5%	12,024	65.1%	2.416	0.051
Health Characteristics						
Ear, Nose, and Throat Infections	5,920	45.0%	8,232	44.6%	0.366	0.007
Gastrointestinal Infections	43	0.3%	54	0.3%	0.034	0.006
Lower Respiratory Infections	904	6.9%	1,097	5.9%	0.927	0.038
Sexually Transmitted Infections	76	0.6%	45	0.2%	0.333	0.052
Other Indications	9	0.1%	45	0.2%	-0.176	-0.045
Pelvic Inflammatory Disease	123	0.9%	151	0.8%	0.114	0.012
Skin and Subcutaneous Tissue	55	0.4%	154	0.8%	-0.415	-0.053
Urinary Tract and Kidney Infections	199	1.5%	533	2.9%	-1.378	-0.094
Alcohol Abuse	34	0.3%	47	0.3%	0.008	0.002
Asthma	546	4.1%	806	4.4%	-0.224	-0.011
Cardiac Valvular Disease	79	0.6%	110	0.6%	-0.000	-0.000
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	14	0.1%	0.003	0.001
Chronic Renal Disease	47	0.4%	71	0.4%	-0.029	-0.005
Congenital Heart Disease	49	0.4%	68	0.4%	0.003	0.000
Cystic Fibrosis	11	0.1%	19	0.1%	-0.019	-0.006
Drug Abuse	113	0.9%	166	0.9%	-0.043	-0.005

Table 1n. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Epilepsy/Seizures	46	0.3%	64	0.3%	0.003	0.001
HIV	14	0.1%	17	0.1%	0.016	0.005
Inflammatory Bowel Disease	60	0.5%	76	0.4%	0.043	0.006
Leukemia/Lymphoma	5	0.0%	13	0.1%	-0.030	-0.013
Obesity	1,744	13.2%	2,248	12.2%	1.064	0.032
Preexisting Diabetes	245	1.9%	317	1.7%	0.141	0.011
Preexisting Hypertension	498	3.8%	700	3.8%	-0.008	-0.000
Previous Cesarean Delivery	488	3.7%	596	3.2%	0.472	0.026
Psychiatric Disorders	1,725	13.1%	2,385	12.9%	0.177	0.005
Pulmonary Hypertension	2	0.0%	3	0.0%	0.002	0.001
Rheumatoid Arthritis	36	0.3%	45	0.2%	0.032	0.006
Sickle Cell Disease	32	0.2%	42	0.2%	0.017	0.004
Systemic Lupus Erythematosus	36	0.3%	47	0.3%	0.021	0.004
Tobacco Use	261	2.0%	320	1.7%	0.249	0.018
Vaccine Administration	44	0.3%	66	0.4%	-0.023	-0.004
Screening Examinations and Disease Management Training	4	0.0%	6	0.0%	-0.005	-0.003
Pap Smear	1,442	11.0%	2,140	11.6%	-0.640	-0.020
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	26	0.2%	36	0.2%	0.007	0.002
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-25 weeks	4,367	33.2%	6,584	35.7%	-2.506	-0.053
Gestational Age 26-31 weeks	4,046	30.7%	5,721	31.0%	-0.265	-0.006
Gestational Age 32-37 weeks	3,862	29.3%	5,102	27.6%	1.691	0.037
Gestational Age 38-42 weeks	894	6.8%	1,054	5.7%	1.080	0.045

Table 1n. Weighted Characteristics of Variable Approach with 6-Week Gestational Age Strata and Deciles for PS (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users		Pregnant Penicillin Users		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.0	4.5	5.9	4.5	0.015	0.003
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.013	0.020
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.000	0.001
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.010
Mean number of other ambulatory encounters	2.2	2.4	2.2	2.4	0.013	0.005
Mean number of filled prescriptions	2.5	3.4	2.6	3.6	-0.100	-0.028
Mean number of generics dispensed	1.5	1.7	1.5	1.8	-0.056	-0.032
Mean number of unique drug classes dispensed	1.4	1.6	1.5	1.7	-0.056	-0.034

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1o. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Unique patients	14,424	100.0%	20,338	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.138	0.026
Age						
10-54 years	14,424	100.0%	20,338	100.0%	0.000	N/A
Sex						
Female	14,424	100.0%	20,338	100.0%	0.000	N/A
Race ⁴						
Unknown	14,424	100.0%	20,338	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	14,424	100.0%	20,338	100.0%	0.000	N/A
Year						
2016	847	5.9%	967	4.8%	1.118	0.050
2017	5,181	35.9%	6,582	32.4%	3.556	0.075
2018	4,330	30.0%	6,313	31.0%	-1.021	-0.022
2019	4,066	28.2%	6,476	31.8%	-3.653	-0.080
Pregnancy Characteristics						
Pre-Term (0-258 days)	930	6.4%	1,415	7.0%	-0.510	-0.020
Term (259-280 days)	9,439	65.4%	12,780	62.8%	2.602	0.054
Post-Term (281-301 days)	3,013	20.9%	4,573	22.5%	-1.596	-0.039
Unknown Term	1,042	7.2%	1,570	7.7%	-0.495	-0.019
Gestational age ⁵ at delivery	39.6	1.6	39.6	1.7	-0.001	-0.001

Table 1o. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.550	0.098
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.032	-0.067
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.031	0.066
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,610	32.0%	7,141	35.1%	-3.151	-0.067
Exposed during third trimester	9,814	68.0%	13,197	64.9%	3.151	0.067
Health Characteristics						
Ear, Nose, and Throat Infections	5,019	34.8%	10,273	50.5%	-15.715	-0.322
Gastrointestinal Infections	32	0.2%	76	0.4%	-0.152	-0.028
Lower Respiratory Infections	1,422	9.9%	815	4.0%	5.851	0.232
Sexually Transmitted Infections	125	0.9%	31	0.2%	0.714	0.100
Other Indications	6	0.0%	106	0.5%	-0.480	-0.091
Pelvic Inflammatory Disease	120	0.8%	193	0.9%	-0.117	-0.012
Skin and Subcutaneous Tissue	32	0.2%	237	1.2%	-0.943	-0.114
Urinary Tract and Kidney Infections	128	0.9%	754	3.7%	-2.820	-0.189
Alcohol Abuse	33	0.2%	54	0.3%	-0.037	-0.007
Asthma	679	4.7%	844	4.1%	0.558	0.027
Cardiac Valvular Disease	87	0.6%	133	0.7%	-0.051	-0.006
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	17	0.1%	-0.007	-0.003
Chronic Renal Disease	67	0.5%	88	0.4%	0.032	0.005
Congenital Heart Disease	46	0.3%	93	0.5%	-0.138	-0.022
Cystic Fibrosis	11	0.1%	22	0.1%	-0.032	-0.011

Table 1o. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Drug Abuse	140	1.0%	177	0.9%	0.100	0.011
Epilepsy/Seizures	53	0.4%	80	0.4%	-0.026	-0.004
HIV	14	0.1%	19	0.1%	0.004	0.001
Inflammatory Bowel Disease	70	0.5%	102	0.5%	-0.016	-0.002
Leukemia/Lymphoma	4	0.0%	22	0.1%	-0.080	-0.031
Obesity	1,808	12.5%	2,726	13.4%	-0.869	-0.026
Preexisting Diabetes	264	1.8%	387	1.9%	-0.073	-0.005
Preexisting Hypertension	623	4.3%	833	4.1%	0.223	0.011
Previous Cesarean Delivery	447	3.1%	725	3.6%	-0.466	-0.026
Psychiatric Disorders	1,865	12.9%	2,781	13.7%	-0.744	-0.022
Pulmonary Hypertension	3	0.0%	5	0.0%	-0.004	-0.003
Rheumatoid Arthritis	37	0.3%	62	0.3%	-0.048	-0.009
Sickle Cell Disease	28	0.2%	55	0.3%	-0.076	-0.016
Systemic Lupus Erythematosus	53	0.4%	49	0.2%	0.127	0.023
Tobacco Use	250	1.7%	401	2.0%	-0.238	-0.018
Vaccine Administration	47	0.3%	70	0.3%	-0.018	-0.003
Screening Examinations and Disease Management Training	6	0.0%	7	0.0%	0.007	0.004
Pap Smear	1,727	12.0%	2,240	11.0%	0.959	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	24	0.2%	44	0.2%	-0.050	-0.011
Teratogenic Drugs	4	0.0%	2	0.0%	0.018	0.013
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	3,147	21.8%	5,030	24.7%	-2.914	-0.069
Gestational Age 24-27 weeks	3,051	21.2%	4,447	21.9%	-0.713	-0.017
Gestational Age 28-31 weeks	2,933	20.3%	4,139	20.4%	-0.017	-0.000

Table 1o. Unadjusted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Gestational Age 32-35 weeks	2,780	19.3%	3,882	19.1%	0.186	0.005
Gestational Age 36-42 weeks	2,513	17.4%	2,840	14.0%	3.458	0.095
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.1	4.7	6.2	4.7	-0.081	-0.017
Mean number of emergency room encounters	0.2	0.6	0.2	0.7	-0.014	-0.022
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.012
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.3	2.5	-0.059	-0.024
Mean number of filled prescriptions	2.9	3.8	2.7	3.8	0.161	0.042
Mean number of generics dispensed	1.7	1.9	1.6	1.9	0.095	0.051
Mean number of unique drug classes dispensed	1.6	1.8	1.5	1.8	0.090	0.050

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1p. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Unique patients	14,420	100.0%	20,252	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.104	0.020
Age						
10-54 years	14,420	100.0%	20,252	100.0%	0.000	N/A
Sex						
Female	14,420	100.0%	20,252	100.0%	0.000	N/A
Race ⁵						
Unknown	14,420	100.0%	20,252	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	14,420	100.0%	20,252	100.0%	0.000	N/A
Year						
2016	820	5.7%	974	4.8%	0.875	0.039
2017	5,168	35.8%	6,582	32.5%	3.339	0.070
2018	4,352	30.2%	6,287	31.0%	-0.862	-0.019
2019	4,080	28.3%	6,409	31.6%	-3.352	-0.073
Pregnancy Characteristics						
Pre-Term (0-258 days)	943	6.5%	1,398	6.9%	-0.360	-0.014
Term (259-280 days)	9,415	65.3%	12,720	62.8%	2.486	0.052
Post-Term (281-301 days)	3,027	21.0%	4,551	22.5%	-1.480	-0.036
Unknown Term	1,034	7.2%	1,583	7.8%	-0.645	-0.025
Gestational age ⁶ at delivery	39.6	1.6	39.6	1.7	-0.009	-0.005

Table 1p. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.6	5.6	29.8	5.6	-0.145	-0.026
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	0.012	0.026
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	-0.013	-0.027
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,971	34.5%	6,729	33.2%	1.250	0.026
Exposed during third trimester	9,449	65.5%	13,523	66.8%	-1.250	-0.026
Health Characteristics						
Ear, Nose, and Throat Infections	6,443	44.7%	8,969	44.3%	0.391	0.008
Gastrointestinal Infections	41	0.3%	66	0.3%	-0.037	-0.007
Lower Respiratory Infections	1,076	7.5%	1,069	5.3%	2.184	0.090
Sexually Transmitted Infections	93	0.6%	40	0.2%	0.445	0.069
Other Indications	9	0.1%	21	0.1%	-0.040	-0.014
Pelvic Inflammatory Disease	134	0.9%	179	0.9%	0.044	0.005
Skin and Subcutaneous Tissue	49	0.3%	186	0.9%	-0.580	-0.073
Urinary Tract and Kidney Infections	192	1.3%	605	3.0%	-1.658	-0.114
Alcohol Abuse	36	0.2%	49	0.2%	0.006	0.001
Asthma	634	4.4%	888	4.4%	0.014	0.001
Cardiac Valvular Disease	90	0.6%	124	0.6%	0.007	0.001
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	12	0.1%	16	0.1%	0.004	0.001
Chronic Renal Disease	62	0.4%	90	0.4%	-0.012	-0.002
Congenital Heart Disease	54	0.4%	80	0.4%	-0.015	-0.002
Cystic Fibrosis	13	0.1%	19	0.1%	-0.007	-0.002

Table 1p. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Drug Abuse	131	0.9%	180	0.9%	0.016	0.002
Epilepsy/Seizures	54	0.4%	75	0.4%	0.004	0.001
HIV	14	0.1%	19	0.1%	0.007	0.002
Inflammatory Bowel Disease	73	0.5%	100	0.5%	0.011	0.002
Leukemia/Lymphoma	6	0.0%	16	0.1%	-0.037	-0.015
Obesity	1,896	13.1%	2,620	12.9%	0.213	0.006
Preexisting Diabetes	271	1.9%	378	1.9%	0.010	0.001
Preexisting Hypertension	609	4.2%	857	4.2%	-0.007	-0.000
Previous Cesarean Delivery	501	3.5%	667	3.3%	0.178	0.010
Psychiatric Disorders	1,941	13.5%	2,705	13.4%	0.100	0.003
Pulmonary Hypertension	3	0.0%	4	0.0%	0.002	0.001
Rheumatoid Arthritis	45	0.3%	59	0.3%	0.017	0.003
Sickle Cell Disease	34	0.2%	48	0.2%	-0.001	-0.000
Systemic Lupus Erythematosus	47	0.3%	55	0.3%	0.057	0.010
Tobacco Use	280	1.9%	360	1.8%	0.169	0.012
Vaccine Administration	47	0.3%	71	0.4%	-0.024	-0.004
Screening Examinations and Disease Management Training	5	0.0%	7	0.0%	-0.004	-0.002
Pap Smear	1,590	11.0%	2,361	11.7%	-0.632	-0.020
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	28	0.2%	40	0.2%	-0.003	-0.001
Teratogenic Drugs	3	0.0%	2	0.0%	0.010	0.008
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	3,478	24.1%	4,665	23.0%	1.084	0.026
Gestational Age 24-27 weeks	3,127	21.7%	4,366	21.6%	0.130	0.003
Gestational Age 28-31 weeks	2,930	20.3%	4,151	20.5%	-0.173	-0.004

Table 1p. Weighted Characteristics of Step Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ⁴	Number/Mean	Percent/Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Gestational Age 32-35 weeks	2,700	18.7%	3,886	19.2%	-0.463	-0.012
Gestational Age 36-42 weeks	2,184	15.1%	3,185	15.7%	-0.578	-0.016
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.2	4.7	6.2	4.7	0.007	0.002
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.008	0.012
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.000	-0.000
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.009
Mean number of other ambulatory encounters	2.3	2.4	2.3	2.4	0.003	0.001
Mean number of filled prescriptions	2.7	3.8	2.8	3.9	-0.059	-0.015
Mean number of generics dispensed	1.6	1.8	1.7	1.9	-0.031	-0.017
Mean number of unique drug classes dispensed	1.6	1.8	1.6	1.8	-0.031	-0.017

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1q. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Unique patients	14,424	100.0%	20,338	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.138	0.026
Age						
10-54 years	14,424	100.0%	20,338	100.0%	0.000	N/A
Sex						
Female	14,424	100.0%	20,338	100.0%	0.000	N/A
Race ⁴						
Unknown	14,424	100.0%	20,338	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	14,424	100.0%	20,338	100.0%	0.000	N/A
Year						
2016	847	5.9%	967	4.8%	1.118	0.050
2017	5,181	35.9%	6,582	32.4%	3.556	0.075
2018	4,330	30.0%	6,313	31.0%	-1.021	-0.022
2019	4,066	28.2%	6,476	31.8%	-3.653	-0.080
Pregnancy Characteristics						
Pre-Term (0-258 days)	930	6.4%	1,415	7.0%	-0.510	-0.020
Term (259-280 days)	9,439	65.4%	12,780	62.8%	2.602	0.054
Post-Term (281-301 days)	3,013	20.9%	4,573	22.5%	-1.596	-0.039
Unknown Term	1,042	7.2%	1,570	7.7%	-0.495	-0.019
Gestational age ⁵ at delivery	39.6	1.6	39.6	1.7	-0.001	-0.001

Table 1q. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	30.0	5.7	29.5	5.6	0.550	0.098
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.032	-0.067
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.031	0.066
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,610	32.0%	7,141	35.1%	-3.151	-0.067
Exposed during third trimester	9,814	68.0%	13,197	64.9%	3.151	0.067
Health Characteristics						
Ear, Nose, and Throat Infections	5,019	34.8%	10,273	50.5%	-15.715	-0.322
Gastrointestinal Infections	32	0.2%	76	0.4%	-0.152	-0.028
Lower Respiratory Infections	1,422	9.9%	815	4.0%	5.851	0.232
Sexually Transmitted Infections	125	0.9%	31	0.2%	0.714	0.100
Other Indications	6	0.0%	106	0.5%	-0.480	-0.091
Pelvic Inflammatory Disease	120	0.8%	193	0.9%	-0.117	-0.012
Skin and Subcutaneous Tissue	32	0.2%	237	1.2%	-0.943	-0.114
Urinary Tract and Kidney Infections	128	0.9%	754	3.7%	-2.820	-0.189
Alcohol Abuse	33	0.2%	54	0.3%	-0.037	-0.007
Asthma	679	4.7%	844	4.1%	0.558	0.027
Cardiac Valvular Disease	87	0.6%	133	0.7%	-0.051	-0.006
Chronic Congestive Heart Failure	0	0.0%	3	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	11	0.1%	17	0.1%	-0.007	-0.003
Chronic Renal Disease	67	0.5%	88	0.4%	0.032	0.005
Congenital Heart Disease	46	0.3%	93	0.5%	-0.138	-0.022
Cystic Fibrosis	11	0.1%	22	0.1%	-0.032	-0.011

Table 1q. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Drug Abuse	140	1.0%	177	0.9%	0.100	0.011
Epilepsy/Seizures	53	0.4%	80	0.4%	-0.026	-0.004
HIV	14	0.1%	19	0.1%	0.004	0.001
Inflammatory Bowel Disease	70	0.5%	102	0.5%	-0.016	-0.002
Leukemia/Lymphoma	4	0.0%	22	0.1%	-0.080	-0.031
Obesity	1,808	12.5%	2,726	13.4%	-0.869	-0.026
Preexisting Diabetes	264	1.8%	387	1.9%	-0.073	-0.005
Preexisting Hypertension	623	4.3%	833	4.1%	0.223	0.011
Previous Cesarean Delivery	447	3.1%	725	3.6%	-0.466	-0.026
Psychiatric Disorders	1,865	12.9%	2,781	13.7%	-0.744	-0.022
Pulmonary Hypertension	3	0.0%	5	0.0%	-0.004	-0.003
Rheumatoid Arthritis	37	0.3%	62	0.3%	-0.048	-0.009
Sickle Cell Disease	28	0.2%	55	0.3%	-0.076	-0.016
Systemic Lupus Erythematosus	53	0.4%	49	0.2%	0.127	0.023
Tobacco Use	250	1.7%	401	2.0%	-0.238	-0.018
Vaccine Administration	47	0.3%	70	0.3%	-0.018	-0.003
Screening Examinations and Disease Management Training	6	0.0%	7	0.0%	0.007	0.004
Pap Smear	1,727	12.0%	2,240	11.0%	0.959	0.030
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	24	0.2%	44	0.2%	-0.050	-0.011
Teratogenic Drugs	4	0.0%	2	0.0%	0.018	0.013
End Stage Liver Disease	2	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	3,147	21.8%	5,030	24.7%	-2.914	-0.069
Gestational Age 24-27 weeks	3,051	21.2%	4,447	21.9%	-0.713	-0.017
Gestational Age 28-31 weeks	2,933	20.3%	4,139	20.4%	-0.017	-0.000

Table 1q. Unadjusted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Gestational Age 32-35 weeks	2,780	19.3%	3,882	19.1%	0.186	0.005
Gestational Age 36-42 weeks	2,513	17.4%	2,840	14.0%	3.458	0.095
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.1	4.7	6.2	4.7	-0.081	-0.017
Mean number of emergency room encounters	0.2	0.6	0.2	0.7	-0.014	-0.022
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.001	-0.012
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.2	2.4	2.3	2.5	-0.059	-0.024
Mean number of filled prescriptions	2.9	3.8	2.7	3.8	0.161	0.042
Mean number of generics dispensed	1.7	1.9	1.6	1.9	0.095	0.051
Mean number of unique drug classes dispensed	1.6	1.8	1.5	1.8	0.090	0.050

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1r. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Unique patients	14,415	100.0%	20,272	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.3	31.0	5.2	0.107	0.020
Age						
10-54 years	14,415	100.0%	20,272	100.0%	0.000	N/A
Sex						
Female	14,415	100.0%	20,272	100.0%	0.000	N/A
Race ⁵						
Unknown	14,415	100.0%	20,272	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	14,415	100.0%	20,272	100.0%	0.000	N/A
Year						
2016	823	5.7%	975	4.8%	0.898	0.040
2017	5,146	35.7%	6,592	32.5%	3.179	0.067
2018	4,352	30.2%	6,292	31.0%	-0.848	-0.018
2019	4,095	28.4%	6,413	31.6%	-3.230	-0.071
Pregnancy Characteristics						
Pre-Term (0-258 days)	926	6.4%	1,426	7.0%	-0.609	-0.024
Term (259-280 days)	9,408	65.3%	12,738	62.8%	2.426	0.051
Post-Term (281-301 days)	3,043	21.1%	4,528	22.3%	-1.227	-0.030
Unknown Term	1,038	7.2%	1,579	7.8%	-0.591	-0.022
Gestational age ⁶ at delivery	39.6	1.6	39.6	1.7	0.014	0.008

Table 1r. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.9	5.7	29.5	5.6	0.425	0.076
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.3	0.5	-0.023	-0.050
Mean number of dispensings in third trimester	0.7	0.5	0.7	0.5	0.023	0.049
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	4,670	32.4%	7,041	34.7%	-2.335	-0.049
Exposed during third trimester	9,745	67.6%	13,231	65.3%	2.335	0.049
Health Characteristics						
Ear, Nose, and Throat Infections	6,445	44.7%	8,957	44.2%	0.531	0.011
Gastrointestinal Infections	41	0.3%	66	0.3%	-0.043	-0.008
Lower Respiratory Infections	1,088	7.5%	1,053	5.2%	2.353	0.096
Sexually Transmitted Infections	90	0.6%	39	0.2%	0.431	0.067
Other Indications	9	0.1%	36	0.2%	-0.118	-0.034
Pelvic Inflammatory Disease	142	1.0%	173	0.9%	0.135	0.014
Skin and Subcutaneous Tissue	48	0.3%	187	0.9%	-0.591	-0.075
Urinary Tract and Kidney Infections	189	1.3%	610	3.0%	-1.700	-0.117
Alcohol Abuse	38	0.3%	49	0.2%	0.024	0.005
Asthma	637	4.4%	884	4.4%	0.058	0.003
Cardiac Valvular Disease	92	0.6%	123	0.6%	0.029	0.004
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	12	0.1%	16	0.1%	0.005	0.002
Chronic Renal Disease	62	0.4%	91	0.4%	-0.021	-0.003
Congenital Heart Disease	56	0.4%	79	0.4%	0.000	0.000
Cystic Fibrosis	13	0.1%	19	0.1%	0.000	0.000

Table 1r. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Drug Abuse	131	0.9%	181	0.9%	0.020	0.002
Epilepsy/Seizures	55	0.4%	73	0.4%	0.017	0.003
HIV	15	0.1%	18	0.1%	0.015	0.005
Inflammatory Bowel Disease	75	0.5%	100	0.5%	0.028	0.004
Leukemia/Lymphoma	6	0.0%	17	0.1%	-0.042	-0.017
Obesity	1,945	13.5%	2,577	12.7%	0.783	0.023
Preexisting Diabetes	277	1.9%	378	1.9%	0.059	0.004
Preexisting Hypertension	608	4.2%	856	4.2%	-0.003	-0.000
Previous Cesarean Delivery	529	3.7%	652	3.2%	0.457	0.025
Psychiatric Disorders	1,956	13.6%	2,692	13.3%	0.290	0.009
Pulmonary Hypertension	3	0.0%	4	0.0%	0.003	0.002
Rheumatoid Arthritis	46	0.3%	58	0.3%	0.031	0.006
Sickle Cell Disease	34	0.2%	47	0.2%	0.004	0.001
Systemic Lupus Erythematosus	48	0.3%	53	0.3%	0.067	0.012
Tobacco Use	288	2.0%	354	1.7%	0.252	0.019
Vaccine Administration	48	0.3%	72	0.4%	-0.025	-0.004
Screening Examinations and Disease Management Training	5	0.0%	7	0.0%	-0.003	-0.002
Pap Smear	1,577	10.9%	2,374	11.7%	-0.772	-0.024
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	29	0.2%	39	0.2%	0.007	0.002
Teratogenic Drugs	3	0.0%	2	0.0%	0.010	0.008
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-23 weeks	3,187	22.1%	4,956	24.4%	-2.337	-0.055
Gestational Age 24-27 weeks	3,101	21.5%	4,411	21.8%	-0.246	-0.006
Gestational Age 28-31 weeks	2,936	20.4%	4,155	20.5%	-0.132	-0.003

Table 1r. Weighted Characteristics of Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs (Propensity Score Stratified, Aggregated), Percentiles: 4, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users without Exclusion of Teratogenic Drugs		Pregnant Penicillin Users without Exclusion of Teratogenic Drugs		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Gestational Age 32-35 weeks	2,724	18.9%	3,864	19.1%	-0.160	-0.004
Gestational Age 36-42 weeks	2,467	17.1%	2,887	14.2%	2.874	0.079
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.2	4.8	6.1	4.7	0.020	0.004
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.012	0.018
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.000	0.003
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.009
Mean number of other ambulatory encounters	2.3	2.5	2.3	2.4	0.010	0.004
Mean number of filled prescriptions	2.7	3.8	2.8	3.9	-0.077	-0.020
Mean number of generics dispensed	1.6	1.9	1.7	1.9	-0.045	-0.024
Mean number of unique drug classes dispensed	1.6	1.8	1.6	1.8	-0.045	-0.025

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1s. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Unique patients	4,547	100.0%	9,443	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.2	5.2	31.0	5.1	0.260	0.050
Age						
10-54 years	4,547	100.0%	9,443	100.0%	0.000	N/A
Sex						
Female	4,547	100.0%	9,443	100.0%	0.000	N/A
Race ⁴						
Unknown	4,547	100.0%	9,443	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	4,547	100.0%	9,443	100.0%	0.000	N/A
Year						
2016	230	5.1%	408	4.3%	0.738	0.035
2017	1,599	35.2%	3,000	31.8%	3.396	0.072
2018	1,446	31.8%	2,915	30.9%	0.932	0.020
2019	1,272	28.0%	3,120	33.0%	-5.066	-0.110
Pregnancy Characteristics						
Pre-Term (0-258 days)	286	6.3%	600	6.4%	-0.064	-0.003
Term (259-280 days)	2,945	64.8%	6,035	63.9%	0.858	0.018
Post-Term (281-301 days)	977	21.5%	2,122	22.5%	-0.985	-0.024
Unknown Term	339	7.5%	686	7.3%	0.191	0.007
Gestational age ⁵ at delivery	39.7	1.5	39.7	1.6	0.010	0.006

Table 1s. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Exposure Characteristics						
Gestational age ⁵ of first exposure (weeks)	29.6	5.6	29.3	5.5	0.306	0.055
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	N/A	N/A
Mean number of dispensings in second trimester	0.3	0.5	0.4	0.5	-0.017	-0.037
Mean number of dispensings in third trimester	0.7	0.5	0.6	0.5	0.017	0.036
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	1,561	34.3%	3,405	36.1%	-1.728	-0.036
Exposed during third trimester	2,986	65.7%	6,038	63.9%	1.728	0.036
Health Characteristics						
Ear, Nose, and Throat Infections	2,994	65.8%	8,104	85.8%	-19.975	-0.480
Gastrointestinal Infections	10	0.2%	17	0.2%	0.040	0.009
Lower Respiratory Infections	1,283	28.2%	729	7.7%	20.496	0.554
Sexually Transmitted Infections	12	0.3%	18	0.2%	0.073	0.015
Other Indications	2	0.0%	14	0.1%	-0.104	-0.034
Pelvic Inflammatory Disease	29	0.6%	50	0.5%	0.108	0.014
Skin and Subcutaneous Tissue	7	0.2%	48	0.5%	-0.354	-0.062
Urinary Tract and Kidney Infections	46	1.0%	133	1.4%	-0.397	-0.036
Alcohol Abuse	16	0.4%	25	0.3%	0.087	0.016
Asthma	280	6.2%	422	4.5%	1.689	0.075
Cardiac Valvular Disease	35	0.8%	57	0.6%	0.166	0.020
Chronic Congestive Heart Failure	0	0.0%	1	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	5	0.1%	10	0.1%	0.004	0.001
Chronic Renal Disease	21	0.5%	33	0.3%	0.112	0.018
Congenital Heart Disease	18	0.4%	38	0.4%	-0.007	-0.001
Cystic Fibrosis	3	0.1%	10	0.1%	-0.040	-0.014

Table 1s. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Drug Abuse	54	1.2%	76	0.8%	0.383	0.039
Epilepsy/Seizures	16	0.4%	29	0.3%	0.045	0.008
HIV	4	0.1%	5	0.1%	0.035	0.013
Inflammatory Bowel Disease	24	0.5%	41	0.4%	0.094	0.014
Leukemia/Lymphoma	0	0.0%	12	0.1%	N/A	N/A
Obesity	627	13.8%	1,323	14.0%	-0.221	-0.006
Preexisting Diabetes	80	1.8%	173	1.8%	-0.073	-0.005
Preexisting Hypertension	192	4.2%	317	3.4%	0.866	0.045
Previous Cesarean Delivery	158	3.5%	351	3.7%	-0.242	-0.013
Psychiatric Disorders	661	14.5%	1,376	14.6%	-0.035	-0.001
Pulmonary Hypertension	2	0.0%	1	0.0%	0.033	0.020
Rheumatoid Arthritis	13	0.3%	25	0.3%	0.021	0.004
Sickle Cell Disease	9	0.2%	20	0.2%	-0.014	-0.003
Systemic Lupus Erythematosus	19	0.4%	21	0.2%	0.195	0.035
Tobacco Use	98	2.2%	171	1.8%	0.344	0.025
Vaccine Administration	18	0.4%	33	0.3%	0.046	0.008
Screening Examinations and Disease Management Training	2	0.0%	2	0.0%	0.023	0.013
Pap Smear	545	12.0%	1,048	11.1%	0.888	0.028
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	11	0.2%	25	0.3%	-0.023	-0.005
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-25 weeks	1,596	35.1%	3,480	36.9%	-1.753	-0.037
Gestational Age 26-31 weeks	1,419	31.2%	2,956	31.3%	-0.096	-0.002
Gestational Age 32-37 weeks	1,275	28.0%	2,510	26.6%	1.460	0.033

Table 1s. Unadjusted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Aggregated) in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/Standard Deviation ³	Number/Mean	Percent/Standard Deviation ³		
Mother Characteristics^{1,2}						
Gestational Age 38-42 weeks	257	5.7%	497	5.3%	0.389	0.017
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.5	4.7	6.3	4.7	0.251	0.054
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	0.027	0.040
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	0.001	0.008
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	N/A	N/A
Mean number of other ambulatory encounters	2.3	2.4	2.3	2.5	0.055	0.022
Mean number of filled prescriptions	2.9	3.9	2.6	3.6	0.359	0.096
Mean number of generics dispensed	1.7	1.9	1.5	1.8	0.206	0.113
Mean number of unique drug classes dispensed	1.7	1.8	1.5	1.7	0.199	0.114

¹Covariates in blue show a standardized difference greater than 0.1.

²Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

³Value represents standard deviation where no % follows the value.

⁴Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁵Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 1t. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Unique patients	4,535	100.0%	9,424	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	31.1	5.2	31.0	5.1	0.129	0.025
Age						
10-54 years	4,535	100.0%	9,424	100.0%	0.000	N/A
Sex						
Female	4,535	100.0%	9,424	100.0%	0.000	N/A
Race ⁵						
Unknown	4,535	100.0%	9,424	100.0%	0.000	N/A
Hispanic origin						
Yes	0	0.0%	0	0.0%	N/A	N/A
No	0	0.0%	0	0.0%	N/A	N/A
Unknown	4,535	100.0%	9,424	100.0%	0.000	N/A
Year						
2016	225	5.0%	408	4.3%	0.640	0.030
2017	1,604	35.4%	2,970	31.5%	3.859	0.082
2018	1,435	31.6%	2,934	31.1%	0.502	0.011
2019	1,270	28.0%	3,111	33.0%	-5.001	-0.109
Pregnancy Characteristics						
Pre-Term (0-258 days)	278	6.1%	606	6.4%	-0.312	-0.013
Term (259-280 days)	2,953	65.1%	6,033	64.0%	1.108	0.023
Post-Term (281-301 days)	995	21.9%	2,093	22.2%	-0.279	-0.007
Unknown Term	310	6.8%	692	7.3%	-0.516	-0.020
Gestational age ⁶ at delivery	39.7	1.5	39.7	1.6	0.035	0.023

Table 1t. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Exposure Characteristics						
Gestational age ⁶ of first exposure (weeks)	29.4	5.6	29.4	5.5	0.032	0.006
Mean number of dispensings in first trimester	0.0	N/A	0.0	N/A	0.000	N/A
Mean number of dispensings in second trimester	0.4	0.5	0.4	0.5	0.003	0.007
Mean number of dispensings in third trimester	0.6	0.5	0.6	0.5	-0.003	-0.007
Exposed during first trimester	0	0.0%	0	0.0%	N/A	N/A
Exposed during second trimester	1,618	35.7%	3,332	35.4%	0.335	0.007
Exposed during third trimester	2,917	64.3%	6,092	64.6%	-0.335	-0.007
Health Characteristics						
Ear, Nose, and Throat Infections	3,595	79.3%	7,548	80.1%	-0.835	-0.021
Gastrointestinal Infections	10	0.2%	19	0.2%	0.013	0.003
Lower Respiratory Infections	658	14.5%	1,331	14.1%	0.390	0.011
Sexually Transmitted Infections	9	0.2%	19	0.2%	-0.009	-0.002
Other Indications	2	0.0%	9	0.1%	-0.050	-0.019
Pelvic Inflammatory Disease	27	0.6%	57	0.6%	-0.005	-0.001
Skin and Subcutaneous Tissue	10	0.2%	39	0.4%	-0.188	-0.033
Urinary Tract and Kidney Infections	52	1.1%	125	1.3%	-0.187	-0.017
Alcohol Abuse	12	0.3%	28	0.3%	-0.023	-0.004
Asthma	219	4.8%	472	5.0%	-0.177	-0.008
Cardiac Valvular Disease	28	0.6%	62	0.7%	-0.037	-0.005
Chronic Congestive Heart Failure	0	0.0%	0	0.0%	N/A	N/A
Chronic Ischemic Heart Disease	5	0.1%	10	0.1%	0.002	0.001
Chronic Renal Disease	17	0.4%	37	0.4%	-0.012	-0.002
Congenital Heart Disease	17	0.4%	36	0.4%	0.000	0.000
Cystic Fibrosis	4	0.1%	9	0.1%	-0.013	-0.004

Table 1t. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Mother Characteristics ^{1,2,3}	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Drug Abuse	39	0.9%	85	0.9%	-0.043	-0.005
Epilepsy/Seizures	14	0.3%	29	0.3%	-0.010	-0.002
HIV	3	0.1%	6	0.1%	0.006	0.002
Inflammatory Bowel Disease	19	0.4%	44	0.5%	-0.036	-0.005
Leukemia/Lymphoma	0	0.0%	0	0.0%	N/A	N/A
Obesity	626	13.8%	1,307	13.9%	-0.061	-0.002
Preexisting Diabetes	87	1.9%	175	1.9%	0.051	0.004
Preexisting Hypertension	163	3.6%	349	3.7%	-0.120	-0.006
Previous Cesarean Delivery	169	3.7%	349	3.7%	0.036	0.002
Psychiatric Disorders	659	14.5%	1,373	14.6%	-0.048	-0.001
Pulmonary Hypertension	0	0.0%	1	0.0%	-0.004	-0.003
Rheumatoid Arthritis	14	0.3%	28	0.3%	0.015	0.003
Sickle Cell Disease	10	0.2%	20	0.2%	0.005	0.001
Systemic Lupus Erythematosus	13	0.3%	28	0.3%	-0.003	-0.001
Tobacco Use	86	1.9%	179	1.9%	0.003	0.000
Vaccine Administration	17	0.4%	35	0.4%	-0.006	-0.001
Screening Examinations and Disease Management Training	1	0.0%	3	0.0%	-0.009	-0.005
Pap Smear	507	11.2%	1,089	11.6%	-0.383	-0.012
HPV DNA Test	0	0.0%	0	0.0%	N/A	N/A
Fecal Occult Blood Test	11	0.3%	24	0.3%	-0.007	-0.001
Teratogenic Drugs	0	0.0%	0	0.0%	N/A	N/A
End Stage Liver Disease	0	0.0%	0	0.0%	N/A	N/A
Gestational Age 20-25 weeks	1,652	36.4%	3,405	36.1%	0.294	0.006
Gestational Age 26-31 weeks	1,419	31.3%	2,939	31.2%	0.096	0.002
Gestational Age 32-37 weeks	1,220	26.9%	2,551	27.1%	-0.172	-0.004

Table 1t. Weighted Characteristics of Step Approach with 6-Week Gestational Age Strata and Respiratory Infection Restriction (Propensity Score Stratified, Aggregated), Percentiles: 10, in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

	Medical Product				Covariate Balance	
	Pregnant Macrolide Users with Respiratory Infections		Pregnant Penicillin Users with Respiratory Infections		Absolute Difference	Standardized Difference
	Number/Mean	Percent/ Standard Deviation ⁴	Number/Mean	Percent/ Standard Deviation ⁴		
Mother Characteristics^{1,2,3}						
Gestational Age 38-42 weeks	245	5.4%	529	5.6%	-0.218	-0.010
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	6.3	4.5	6.4	4.8	-0.024	-0.005
Mean number of emergency room encounters	0.2	0.7	0.2	0.6	-0.005	-0.008
Mean number of inpatient hospital encounters	0.0	0.1	0.0	0.1	-0.000	-0.003
Mean number of non-acute institutional encounters	0.0	N/A	0.0	0.0	-0.000	-0.015
Mean number of other ambulatory encounters	2.3	2.2	2.3	2.6	-0.012	-0.005
Mean number of filled prescriptions	2.7	3.6	2.7	3.8	-0.036	-0.010
Mean number of generics dispensed	1.6	1.7	1.6	1.8	-0.023	-0.013
Mean number of unique drug classes dispensed	1.5	1.7	1.6	1.8	-0.018	-0.011

¹Covariates in blue show a standardized difference greater than 0.1.

²Weighted patient characteristics tables facilitate the assessment of covariate balance after propensity score (PS) stratification and should not be interpreted as a description of the unweighted population. Treated/control patients are weighted by the proportion of the total patient population included in their PS stratum divided by the proportion of the total treated/control patient population included in their PS stratum.

³Baseline period in reference to user defined index date (pregnancy start, exposure date, or delivery date).

⁴Value represents standard deviation where no % follows the value.

⁵Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

⁶Gestational age estimated using a claims-based algorithm, previously validated in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), to identify pregnancies ending in a live birth. ICD-10-CM diagnosis codes indicative of weeks of gestation, and ICD-9-CM and ICD-10-CM diagnosis codes for preterm and post-term deliveries, were used to calculate the length of the pregnancy episode. Codes had to occur within 7 days of a delivery date in the inpatient setting. In absence of pre-/post-term codes, pregnancy duration was set to 273 days.

Table 2a. Signal Identification Outcome Assessment via Conditional Poisson Tree Based Scan Statistic Among Penicillin Users Stratified by Propensity Score Deciles and Gestational Age at Treatment Initiation in Six Week Increments

Outcome Identifier	Outcome Description	Total Outcomes Among Penicillin Users	Expected Outcomes Among Penicillin Users	Relative Risk	Log Likelihood Ratio (Test Statistic)	P-value
O998grp	Other specified diseases and conditions complicating pregnancy, childbirth and the puerperium	4398	4073.0	1.08	13.35	0.00007
O9982grp	Streptococcus B carrier state complicating pregnancy, childbirth and the puerperium	2230	1802.1	1.24	48.41	0.00001
O99824grp	Streptococcus B carrier state complicating childbirth	1929	1549.0	1.25	44.16	0.00001
O2683grp	Pregnancy related renal disease	41	13.1	3.14	18.94	0.00001
O26833grp	Pregnancy related renal disease, third trimester	37	8.7	4.25	25.26	0.00001
O753grp	Other infection during labor	58	23.7	2.45	17.58	0.00001
O7023grp	Third degree perineal laceration during delivery, IIIc	11	0.9	12.1	17.33	0.00001
O234grp	Unspecified infection of urinary tract in pregnancy	326	234.1	1.39	16.11	0.00001
O8621grp	Infection of kidney following delivery	14	2.1	6.75	14.81	0.00003
O1410ngrp	Severe pre-eclampsia, unspecified trimester	137	84.4	1.62	13.79	0.00005
O9212grp	Cracked nipple associated with the puerperium	8	0.6	13.75	13.55	0.00006
O993grp	Mental disorders and diseases of the nervous system complicating pregnancy, childbirth and the puerperium	1507	1316.6	1.15	13.38	0.00007
O9934grp	Other mental disorders complicating pregnancy, childbirth, and the puerperium	1099	970.5	1.13	8.27	0.01579
O99345grp	Other mental disorders complicating the puerperium	84	50.1	1.68	9.54	0.00399
O99354grp	Diseases of the nervous system complicating childbirth	221	168.9	1.31	7.35	0.03974
O924grp	Hypogalactia	49	21.8	2.25	12.52	0.0002
O26819grp	Pregnancy related exhaustion and fatigue, unspecified trimester	9	1.1	8.1	10.93	0.0009
O26ngrp	Maternal care for other conditions predominantly related to pregnancy	11	1.8	6.2	10.85	0.00099
O480grp	Post-term pregnancy	2787	2556.7	1.09	10.43	0.00159
O9842grp	Viral hepatitis complicating childbirth	21	6.7	3.15	9.75	0.00324
O99119grp	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy, unspecified trimester	61	33.1	1.84	9.41	0.00471
O2340ngrp	Unspecified infection of urinary tract in pregnancy, unspecified trimester	63	34.9	1.81	9.11	0.00622
O2342ngrp	Unspecified infection of urinary tract in pregnancy, second trimester	55	29.8	1.85	8.50	0.01262
O218grp	Other vomiting complicating pregnancy	39	18.3	2.13	8.76	0.00932
O9121grp	Nonpurulent mastitis associated with pregnancy	11	2.5	4.49	7.96	0.02136
O2223ngrp	Superficial thrombophlebitis in pregnancy, third trimester	12	3.0	4.05	7.74	0.02627
O746grp	Other complications of spinal and epidural anesthesia during labor and delivery	10	2.1	4.76	7.70	0.02733
O860grp	Infection of obstetric surgical wound	116	79.0	1.47	7.55	0.03161
O861grp	Other infection of genital tract following delivery	104	69.4	1.5	7.49	0.03423
O36819grp	Decreased fetal movements, unspecified trimester	280	221.0	1.27	7.27	0.04299

Table 2b. Signal Identification Outcome Assessment via Conditional Poisson Tree Based Scan Statistic Among Penicillin Users Who Experienced a Respiratory Tract Infection and Were Stratified by Propensity Score Deciles and Gestational Age at Treatment Initiation in Six Week Increments

Outcome Identifier	Outcome Description	Total Outcomes Among Penicillin Users	Expected Outcomes Among Penicillin Users	Relative Risk	Log Likelihood Ratio (Test Statistic)	P-value
O4440ngrp	Low lying placenta NOS or without hemorrhage, unspecified trimester	20	3.9	5.14	16.63	0.00001
O993grp	Mental disorders and diseases of the nervous system complicating pregnancy, childbirth and the puerperium	831	693.5	1.2	13.06	0.0001
O9935grp	Diseases of the nervous system complicating pregnancy, childbirth, and the puerperium	193	130.9	1.48	12.90	0.00016
O99354grp	Diseases of the nervous system complicating childbirth	129	81.9	1.58	11.52	0.00042
O99345grp	Other mental disorders complicating the puerperium	46	23.1	2	8.83	0.00745
O2223ngrp	Superficial thrombophlebitis in pregnancy, third trimester	7	0.4	16.32	12.97	0.00015
O8621grp	Infection of kidney following delivery	6	0.4	13.98	10.26	0.00175
O41122grp	Chorioamnionitis, second trimester	6	0.4	13.98	10.26	0.00175
O99323grp	Drug use complicating pregnancy, third trimester	12	2.3	5.24	10.17	0.0019
O85ngrp	Puerperal sepsis	12	2.3	5.24	10.17	0.0019
O26891grp	Other specified pregnancy related conditions, first trimester	15	3.7	4.09	9.78	0.00264
O43103grp	Malformation of placenta, unspecified, third trimester	21	6.7	3.12	9.60	0.0031
O26833grp	Pregnancy related renal disease, third trimester	15	3.8	3.91	9.29	0.00432
O4690ngrp	Antepartum hemorrhage, unspecified, unspecified trimester	22	7.7	2.84	8.72	0.0082
O42912grp	Preterm premature rupture of membranes, unspecified as to length of time between rupture and onset of labor, second trimester	10	1.9	5.38	8.68	0.00888
O7022grp	Third degree perineal laceration during delivery, IIIb	9	1.5	6.01	8.64	0.00911
O2392ngrp	Unspecified genitourinary tract infection in pregnancy, second trimester	5	0.4	11.65	7.71	0.02502
O99824grp	Streptococcus B carrier state complicating childbirth	820	717.0	1.15	7.20	0.0397

Table 2c. Signal Identification Outcome Assessment via Conditional Poisson Tree Bases Scan Statistic Among Penicillin Users Who Experienced a Respiratory Tract Infection and Were Stratified by Propensity Score Deciles and Gestational Age at Treatment Initiation in Six Week Increments. Outcomes Assessed in the Inpatient and Emergency Department Settings.

Outcome Identifier	Outcome Description	Total Outcomes Among Penicillin Users	Expected Outcomes Among Penicillin Users	Relative Risk	Log Likelihood Ratio (Test Statistic)	P-value
O85ngrp	Puerperal sepsis	11	0.4	25.6	25.10	0.00001
O99210grp	Obesity complicating pregnancy, unspecified trimester	9	0.4	21.0	18.81	0.00001
O993grp	Mental disorders and diseases of the nervous system complicating pregnancy, childbirth and the	669	550.4	1.2	12.21	0.00015
O9935grp	Diseases of the nervous system complicating pregnancy, childbirth, and the puerperium	161	116.0	1.4	7.82	0.01585
O99354grp	Diseases of the nervous system complicating childbirth	127	82.0	1.6	10.58	0.0009
O43103grp	Malformation of placenta, unspecified, third trimester	11	1.9	5.9	10.40	0.00107
O24913grp	Unspecified diabetes mellitus in pregnancy, third trimester	11	1.9	5.9	10.40	0.00107
O41122grp	Chorioamnionitis, second trimester	6	0.4	14.0	10.25	0.00131
O42912grp	Preterm premature rupture of membranes, unspecified as to length of time between rupture and onset of labor, second trimester	10	1.9	5.4	8.67	0.00649
O99824grp	Streptococcus B carrier state complicating childbirth	794	684.0	1.2	8.63	0.00672
O7022grp	Third degree perineal laceration during delivery, IIIb	9	1.5	6.0	8.63	0.00677
O4100Xgrp	Oligohydramnios, unspecified trimester	32	14.2	2.3	8.18	0.01072
O36839grp	Maternal care for abnormalities of the fetal heart rate or rhythm, unspecified trimester	13	3.4	3.9	7.95	0.01408
O2223ngrp	Superficial thrombophlebitis in pregnancy, third trimester	5	0.4	11.6	7.70	0.02003
O8621grp	Infection of kidney following delivery	5	0.4	11.6	7.70	0.02003
O24425grp	Gestational diabetes mellitus in childbirth, controlled by oral hypoglycemic drugs	7	1.1	6.6	7.22	0.03257
O4690ngrp	Antepartum hemorrhage, unspecified, unspecified trimester	7	1.1	6.6	7.22	0.03257
O4310grp	Malformation of placenta, unspecified	13	3.7	3.5	6.97	0.04235
O358XXgrp	Maternal care for other (suspected) fetal abnormality and damage	39	20.1	1.9	6.93	0.0446

Table 2d. Signal Identification Outcome Assessment via Conditional Poisson Tree Based Scan Statistic Among Macrolide Users Stratified by Propensity Score Deciles and Gestational Age at Treatment Initiation in Six Week Increments

Outcome Identifier	Outcome Description	Total Outcomes Among Macrolide Users	Expected Outcomes Among Macrolide Users	Relative Risk	Log Likelihood Ratio (Test Statistic)	P-value
O267grp	Subluxation of symphysis (pubis) in pregnancy, childbirth and the puerperium	9	1.2	7.6	10.43	0.00151
O26713grp	Subluxation of symphysis (pubis) in pregnancy, third trimester	9	0.3	31.2	22.26	0.00001
O9831grp	Other infections with a predominantly sexual mode of transmission complicating pregnancy	82	39.9	2.1	16.96	0.00001
O98312grp	Other infections with a predominantly sexual mode of transmission complicating pregnancy, second trimester	13	1.1	11.6	19.93	0.00001
O333XXgrp	Maternal care for disproportion due to outlet contraction of pelvis	16	3.2	5.0	12.96	0.00014
O335XXgrp	Maternal care for disproportion due to unusually large fetus	63	34.4	1.8	9.57	0.00391
O600grp	Preterm labor without delivery	628	518.1	1.2	11.03	0.00078
O6003ngrp	Preterm labor without delivery, third trimester	482	389.4	1.2	10.31	0.00183
O13ngrp	Gestational [pregnancy-induced] hypertension without significant proteinuria	1159	1017.6	1.1	9.59	0.00382
O9962grp	Diseases of the digestive system complicating childbirth	404	326.0	1.2	8.72	0.00927
O332grp	Maternal care for disproportion due to inlet contraction of pelvis	7	0.9	8.1	8.50	0.01156
O996grp	Diseases of the digestive system complicating pregnancy, childbirth and the puerperium	611	517.4	1.2	8.09	0.01792
O36823grp	Fetal anemia and thrombocytopenia, third trimester	7	1.0	7.4	7.94	0.02114
O366grp	Maternal care for excessive fetal growth	1308	1174.4	1.1	7.50	0.03315

Table 2e. Signal Identification Outcome Assessment via Conditional Poisson Tree Based Scan Statistic Among Macrolide Users Who Experienced a Respiratory Tract Infection and Were Stratified by Propensity Score Deciles and Gestational Age at Treatment Initiation in Six Week Increments

Outcome Identifier	Outcome Description	Total Outcomes Among Macrolide Users	Expected Outcomes Among Macrolide Users	Relative Risk	Log Likelihood Ratio (Test Statistic)	P-value
O600grp	Preterm labor without delivery	253	186.9	1.4	10.63	0.0013
O6003ngrp	Preterm labor without delivery, third trimester	194	126.9	1.5	15.36	0.00002
O335XXgrp	Maternal care for disproportion due to unusually large fetus	27	10.0	2.7	9.91	0.00255
O26713grp	Subluxation of symphysis (pubis) in pregnancy, third trimester	4	0.3	14.7	7.02	0.04966

Table 2f. Signal Identification Outcome Assessment via Conditional Poisson Tree Based Scan Statistic Among Macrolide Users Who Experienced a Respiratory Tract Infection and Were Stratified by Propensity Score Deciles and Gestational Age at Treatment Initiation in Six Week Increments. Outcomes Assessed in the Inpatient and Emergency Department Settings.

Outcome Identifier	Outcome Description	Total Outcomes Among Macrolide Users	Expected Outcomes Among Macrolide Users	Relative Risk	Log Likelihood Ratio (Test Statistic)	P-value
O335XXgrp	Maternal care for disproportion due to unusually large fetus	20	7.0	2.9	8.10	0.01298

Figure 1a. Histograms Depicting Propensity Score Distributions Before Adjustment for Variable Approach with 4-Week Gestational Age Strata in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

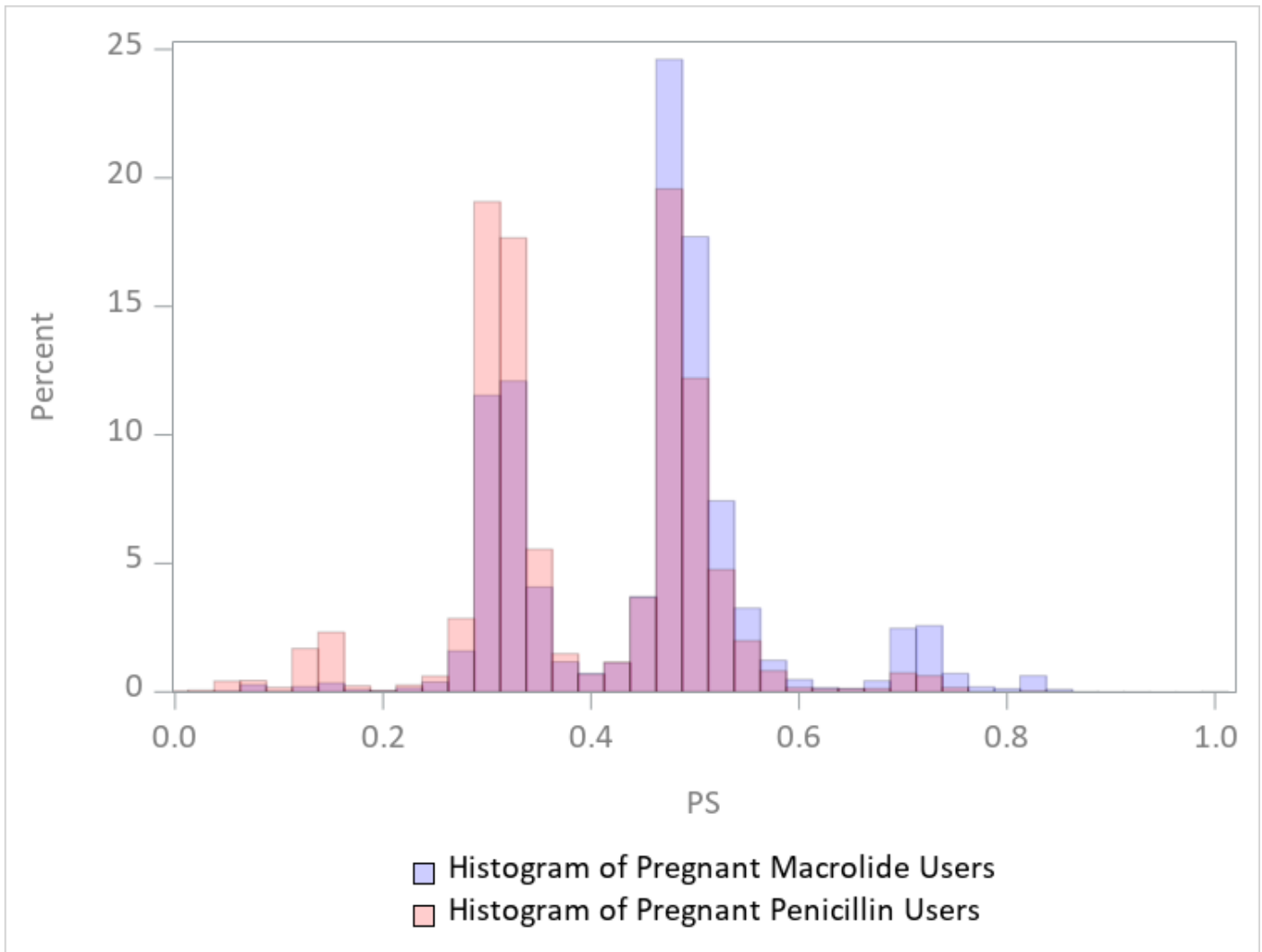


Figure 1b. Histograms Depicting Propensity Score Distributions Before Adjustment for Step Approach with 4-Week Gestational Age Strata in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

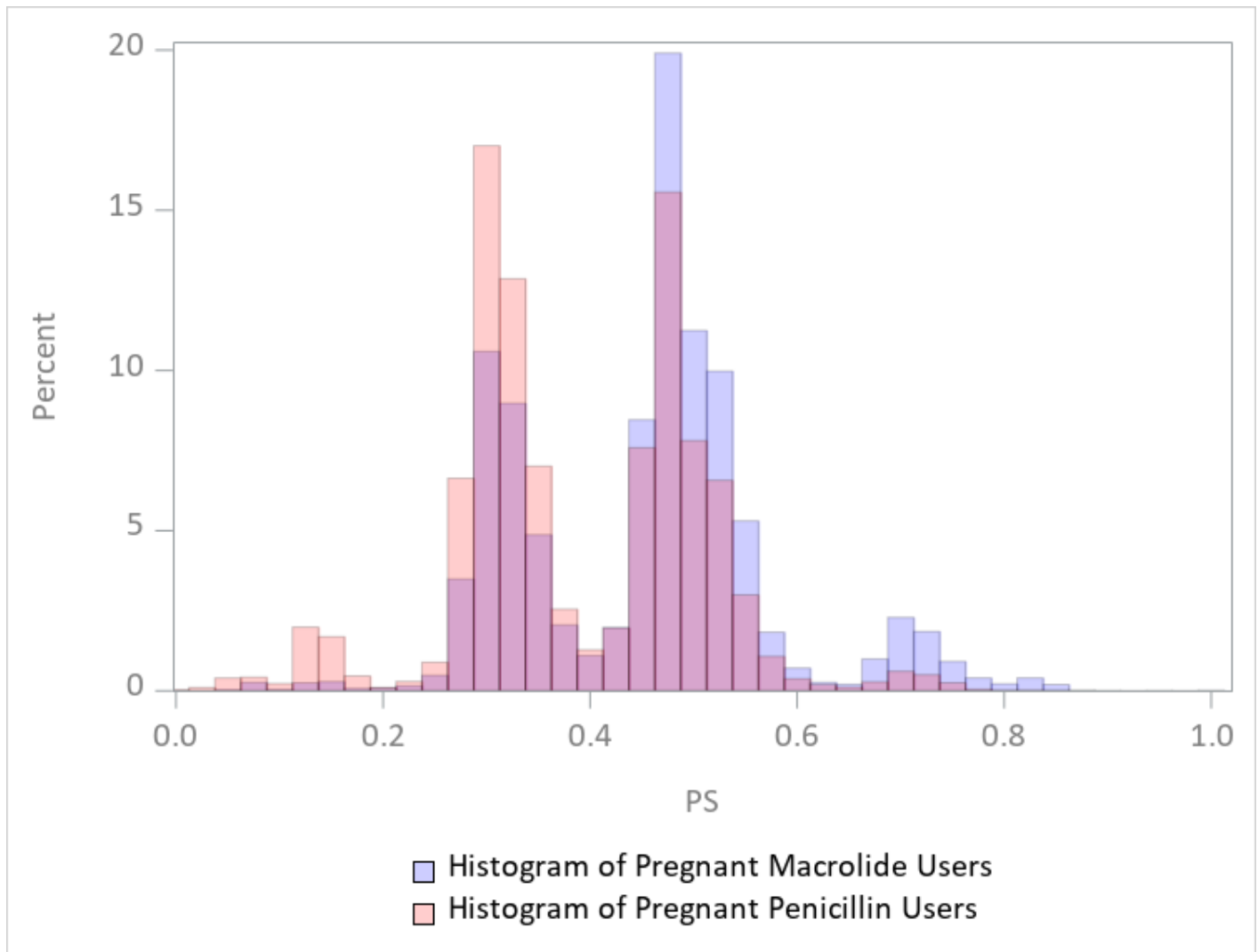


Figure 1c. Histograms Depicting Propensity Score Distributions Before Adjustment for Variable Approach with 2-Week Gestational Age Strata in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

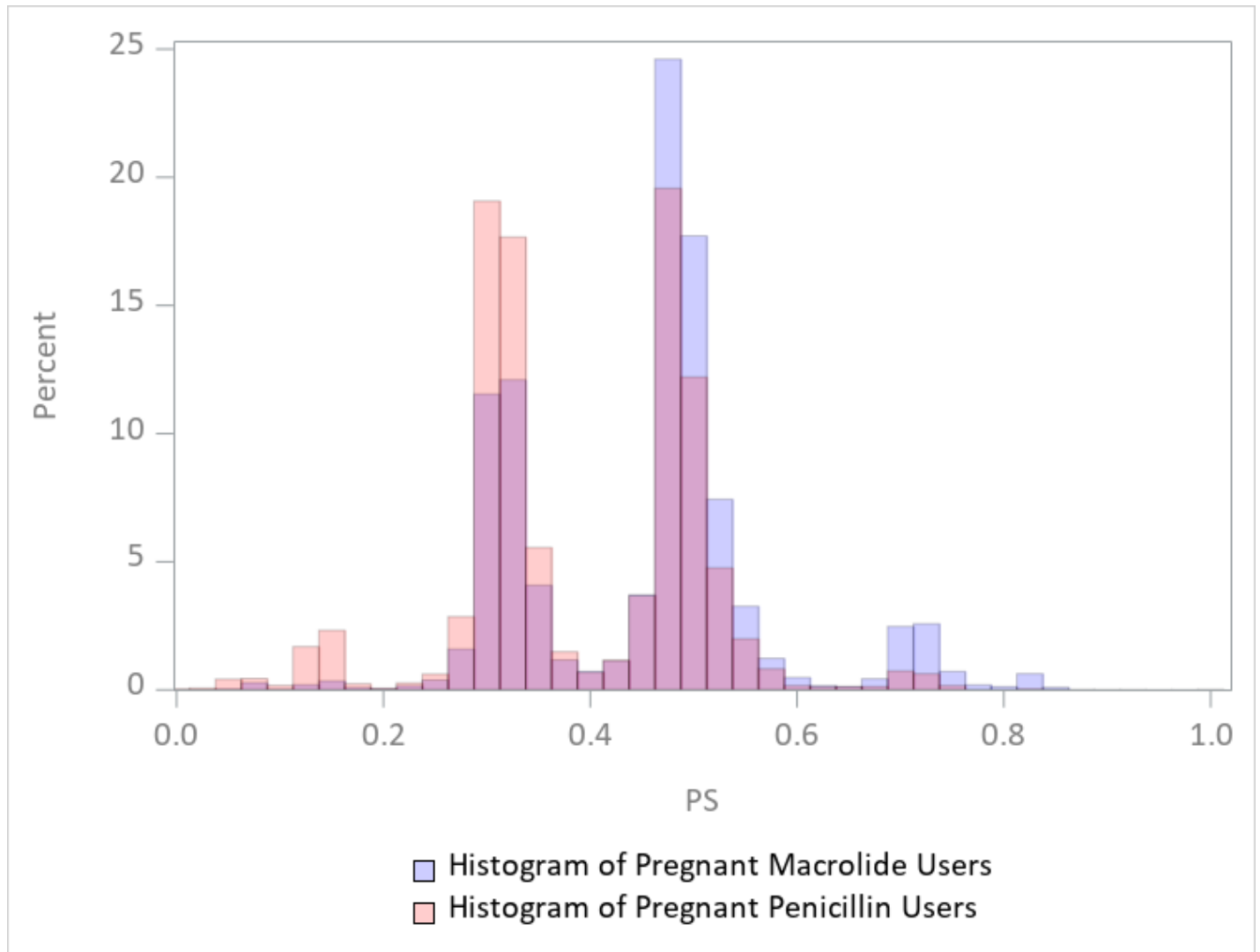


Figure 1d. Histograms Depicting Propensity Score Distributions Before Adjustment for Step Approach with 2-Week Gestational Age Strata in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

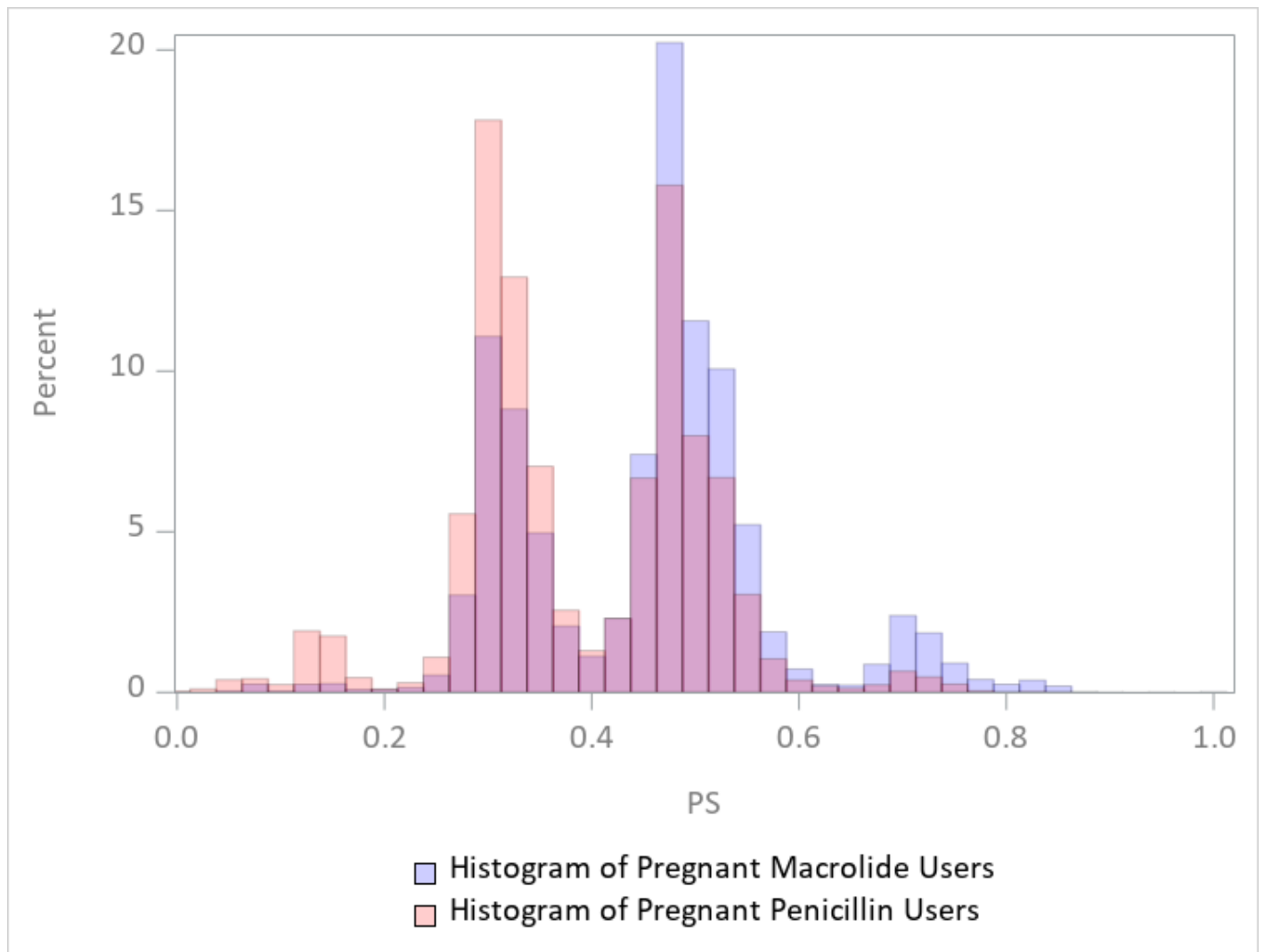


Figure 1e. Histograms Depicting Propensity Score Distributions Before Adjustment for Variable Approach with 6-Week Gestational Age Strata in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

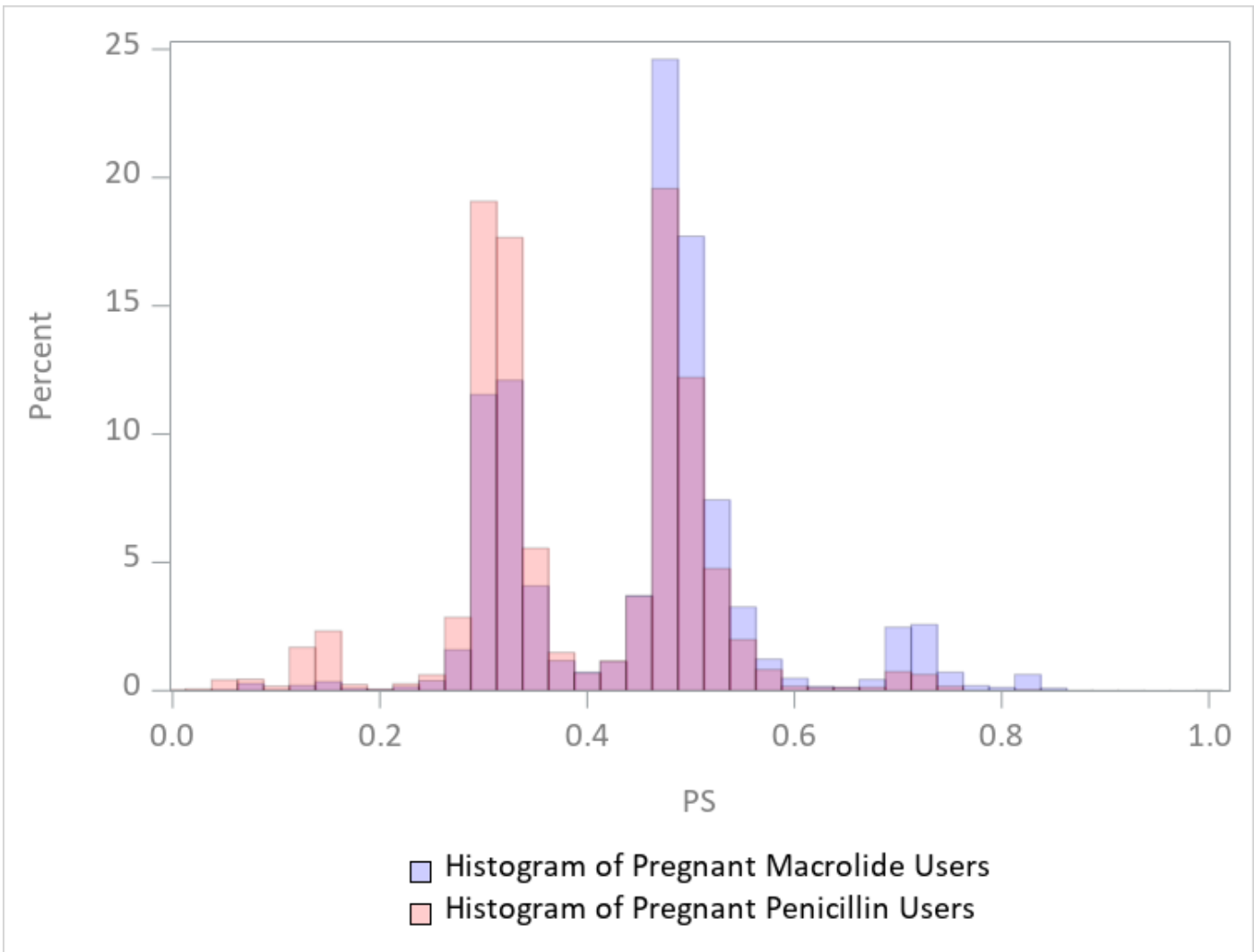


Figure 1f. Histograms Depicting Propensity Score Distributions Before Adjustment for Step Approach with 6-Week Gestational Age Strata in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

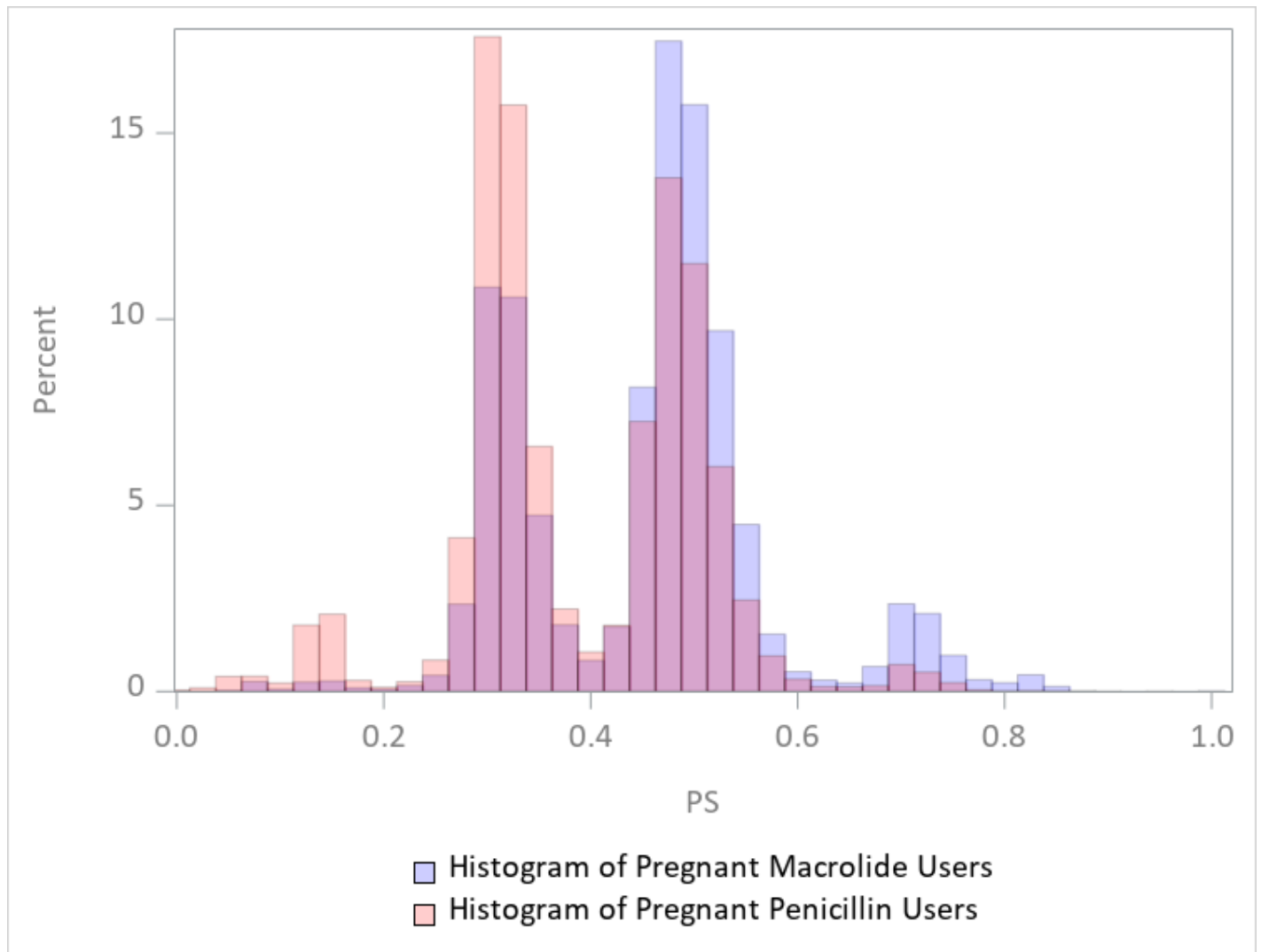


Figure 1g. Histograms Depicting Propensity Score Distributions Before Adjustment for Variable Approach with 6-Week Gestational Age Strata and Deciles for PS in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

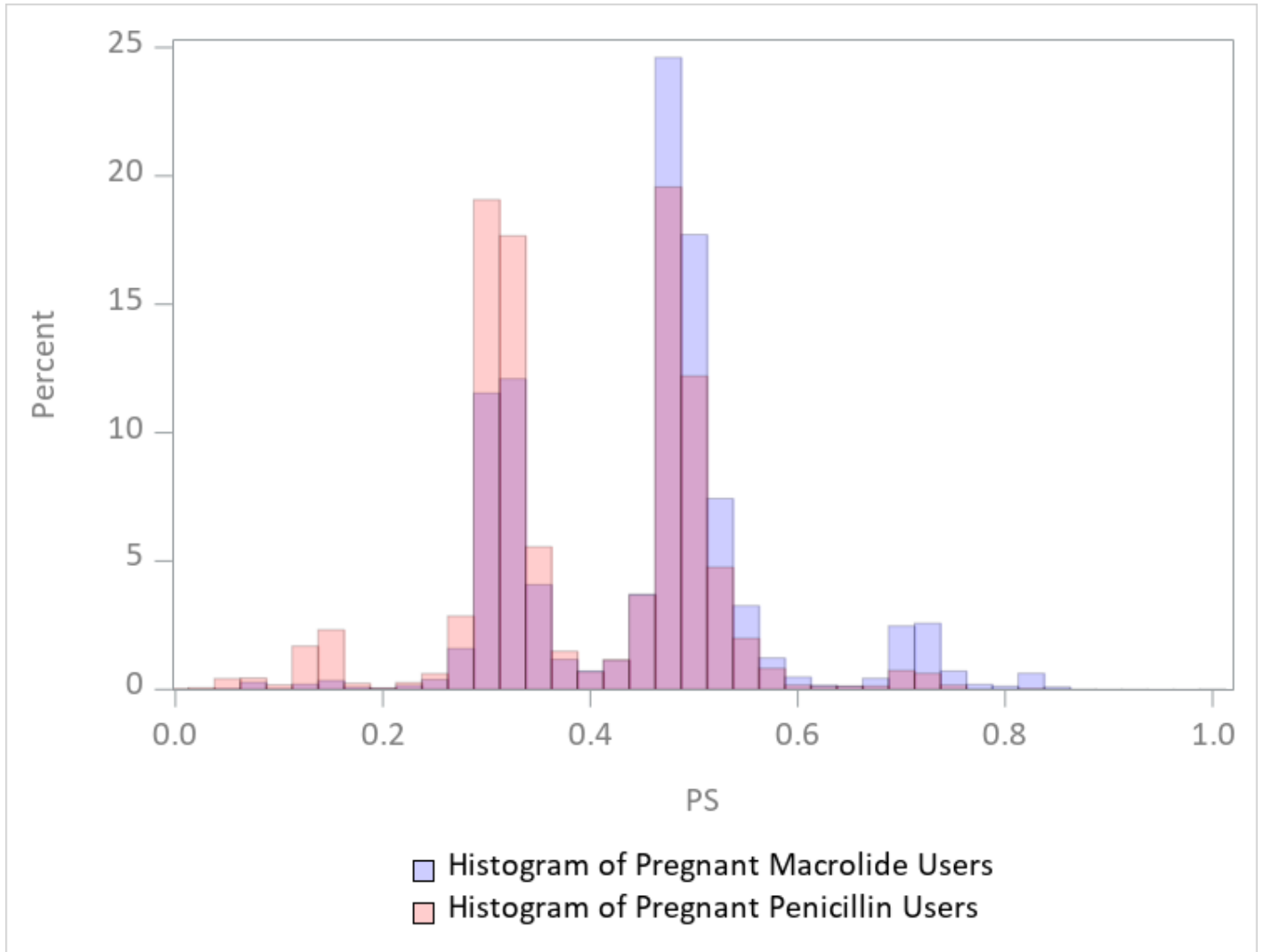


Figure 1h. Histograms Depicting Propensity Score Distributions Before Adjustment for Step Approach with 6-Week Gestational Age Strata and Deciles for PS in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

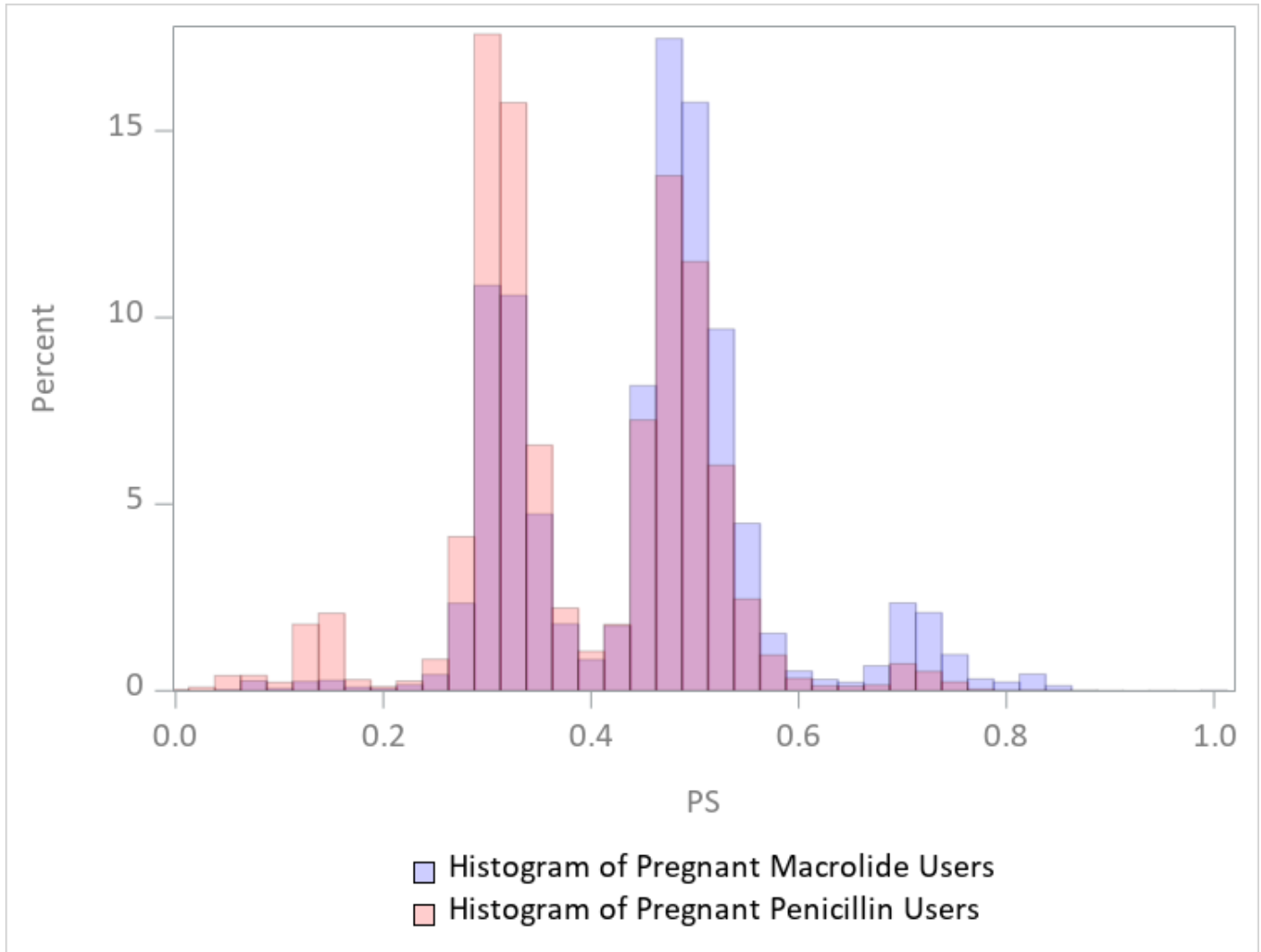


Figure 1i. Histograms Depicting Propensity Score Distributions Before Adjustment for Variable Approach with 4-Week Gestational Age Strata and no Exclusion of Teratogenic Drugs in the Merative MarketScan Research Databases from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

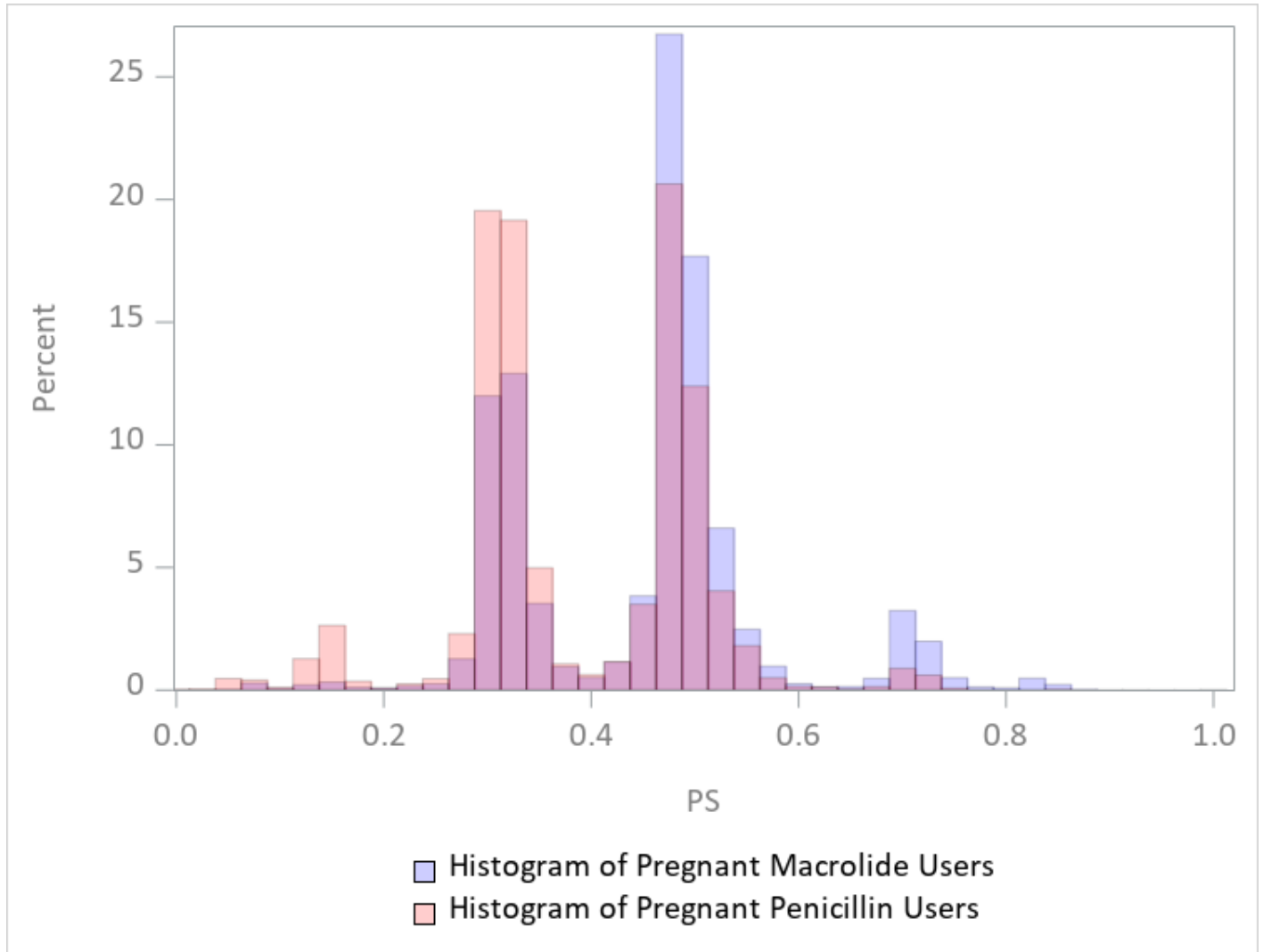


Figure 1j. Histograms Depicting Propensity Score Distributions Before Adjustment for Step Approach with 4-Week GA Strata and no Exclusion of Teratogenic Drugs in the Merative MarketScan Research Databases from October 26, 2016 to December 31,

Unadjusted Propensity Score Distribution 2019

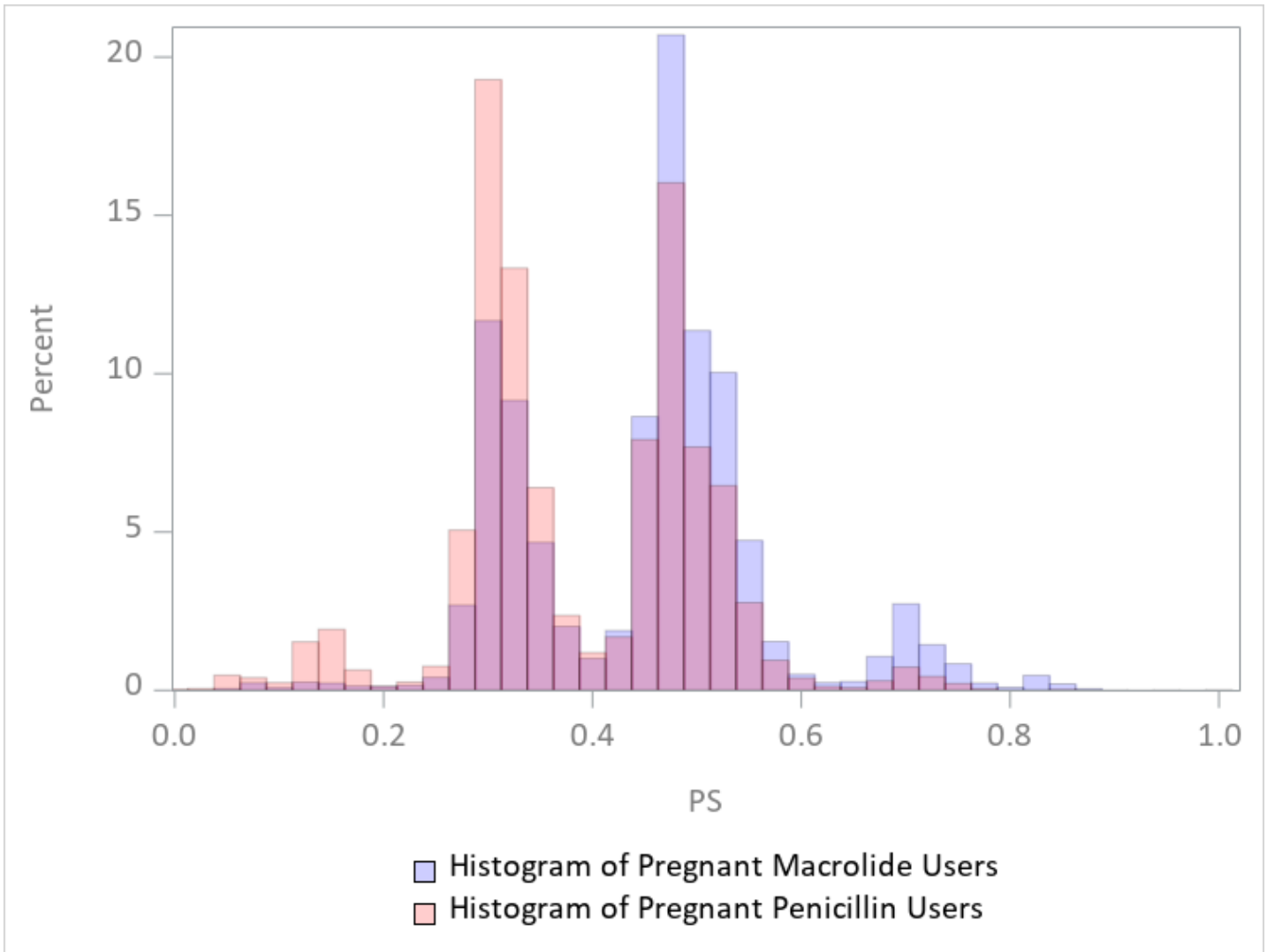


Figure 1k. Histograms Depicting Propensity Score Distributions Before Adjustment for Step Approach with 6-Week Gestational Age Strata and Inclusion of Respiratory Infections in the Merative MarketScan Research Database from October 26, 2016 to December 31, 2019

Unadjusted Propensity Score Distribution

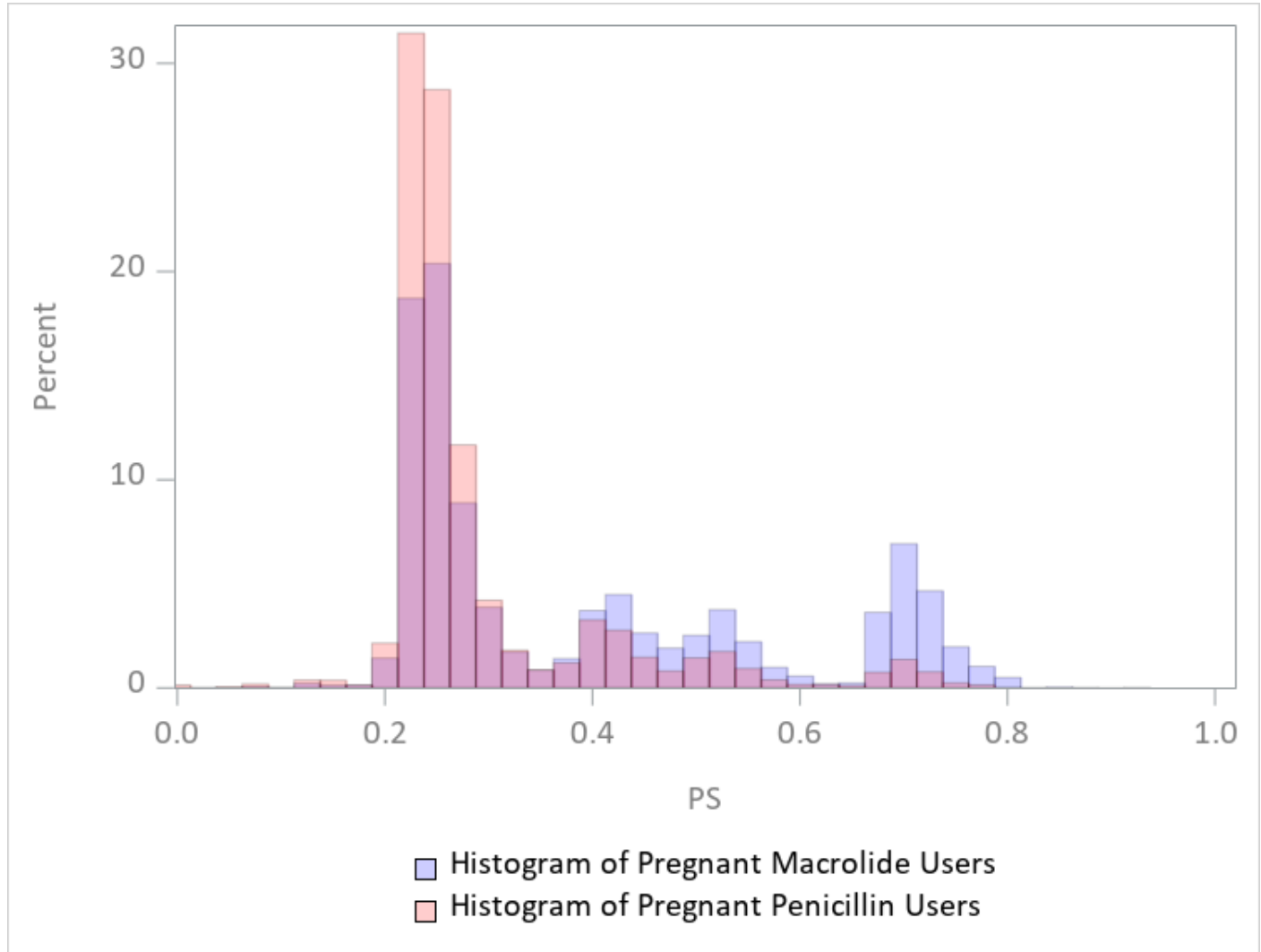
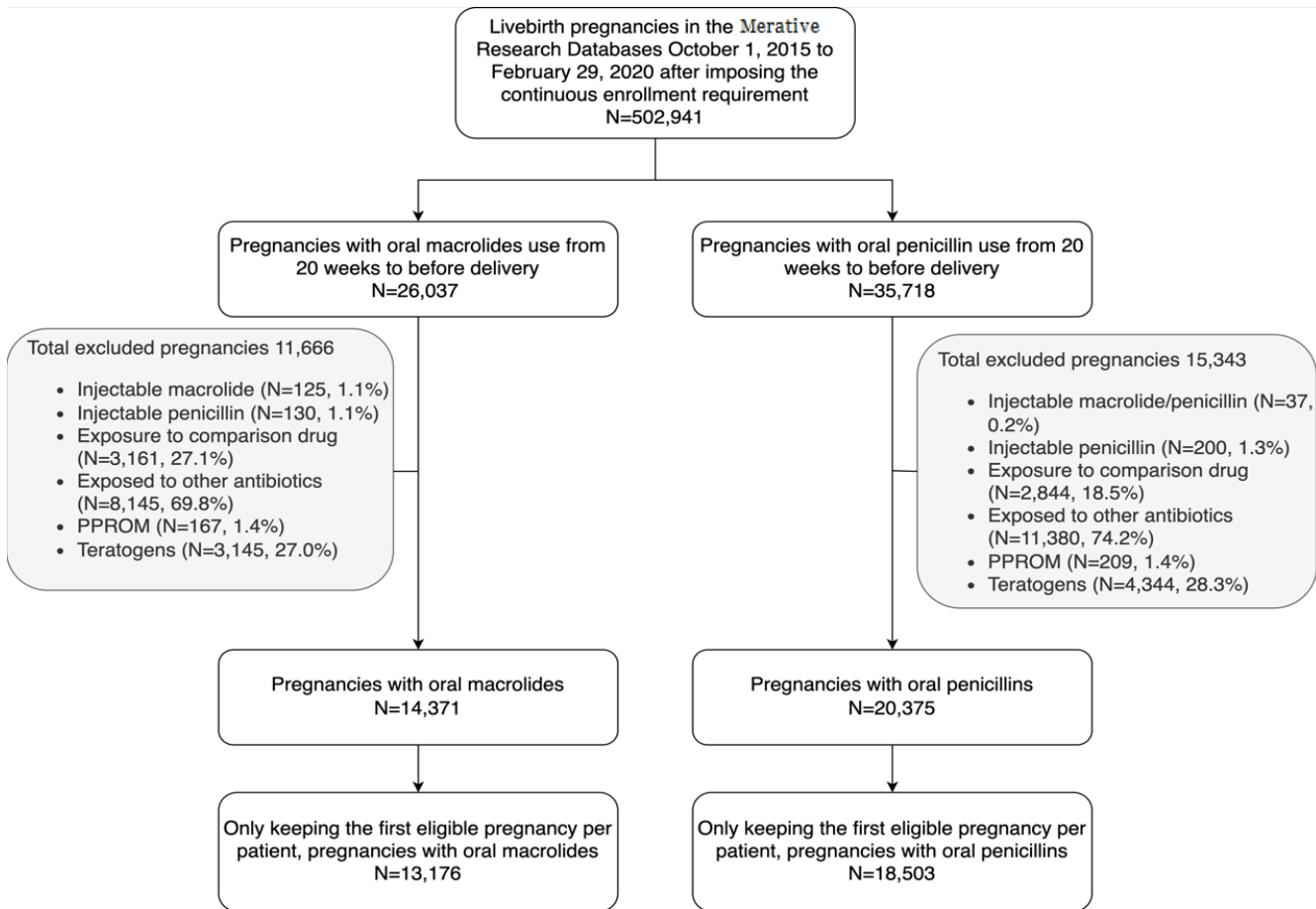


Figure 2. Attrition Table for the Macrolide and Penicillins Case Study



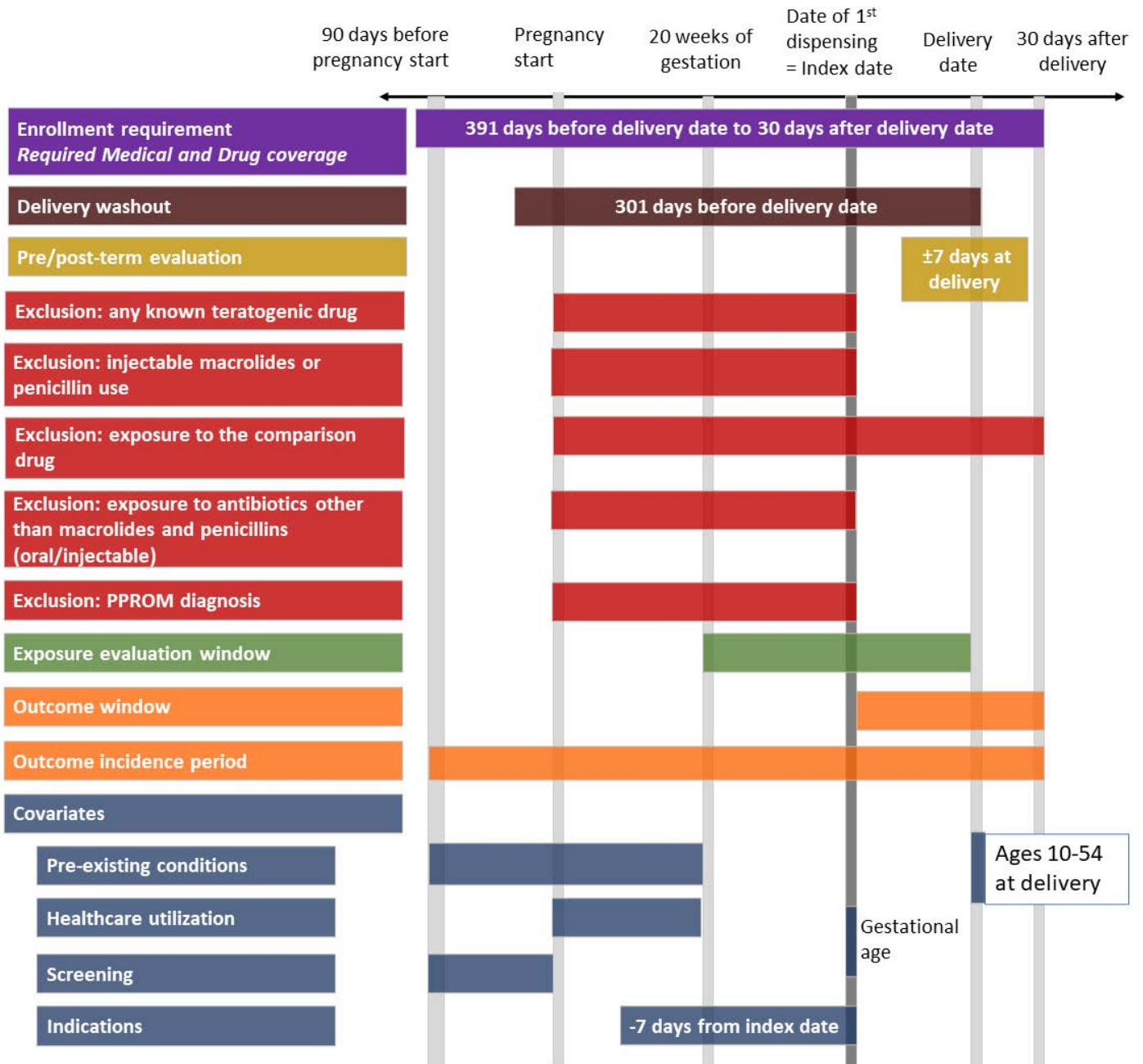
Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (11/15/2022)

Masked DP ID ¹	DP Start Date	DP End Date ²
DP01	10/01/2015	01/30/2020

¹Participating Data Partners include Merative MarketScan Research Databases

²End Date represents the earliest of: (1) query end date, or (2) most recent year-month of data for which all of a Data Partner's data tables (enrollment, dispensing, etc.) have at least 80% of the record count relative to the prior month.

Appendix B. Design Diagram for the Macrolides and Penicillins Case Study



Cohort: Singleton livebirth deliveries
Query period: October 1, 2015 – January 30, 2020
First valid livebirth delivery date: October 26, 2016
Last valid livebirth delivery date: December 31, 2019

Appendix C. Specifications for Type 4 Request: tspreg_mpl2p_wp003

Purpose: The execution of Cohort Identification and Descriptive Analysis (CIDA) Pregnancy tool [QRP 10.3.3] to create cohorts for analysis using the TreeScan software for comparison of macrolide and penicillin exposure.

Query period (*bound by the delivery date*): 10/26/2016 - 12/31/2019
Coverage requirement: Medical & Drug Coverage
Minimum enrollment requirement prior to delivery date: 391 Days (301 day delivery length + 90 day pre-pregnancy exposure assessment period)
Minimum enrollment requirement post delivery date: 30 days
Enrollment gap: 45 days
Pre-pregnancy period (*relative to pregnancy start date*): 90 days
Age groups (*calculated at delivery date*): 10-54 yrs
Sex: Female mothers
Stratifications: None
Output by gestational week: No
Restrictions: None
Envelope macro: Reclassify encounters during inpatient stay as inpatient
Freeze data: Yes

	Main Analysis	Sensitivity Analysis- Higher Tree Level
Pregnancy Cohort	preg	preg
Pregnancy Episode Creation	Use Pregnancy Algorithm Codes	Use Pregnancy Algorithm Codes
Delivery Definition	Cohort includes all valid pregnancy episodes during the query period	Cohort includes all valid pregnancy episodes during the query period
Pregnancy Cohort Definition		period
Delivery Caresetting	Inpatient	Inpatient
Create Baseline Table?	Yes	Yes
Delivery washout	301 days	301 days
Pregnancy Duration Definition (Pre/PostTerm Codes)	Use Pregnancy Algorithm Codes	Use Pregnancy Algorithm Codes
Pre/Post-Term Code Evaluation Window Relative to Delivery Date	7	7
Pregnancy Duration in Absence of Pre/Post-Term Codes	273	273
Mother-infant linkage requirement	None	None

Appendix C. Specifications for Type 4 Request: tspreg_mpl2p_wp003

Drug/Exposure	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>
Prevalent Exposure/Comparator	NA	NA	NA	NA
Incident w/ Respect to:	NA	NA	NA	NA
Incident exposure washout period	0 days	0 days	0 days	0 days
Exposure Episode Length (ITT)	1 day	1 day	1 day	1 day
Cohort Definition	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode
Build Episodes on Point Exposure?	Yes	Yes	Yes	Yes
Treatment episode gap	0 days	0 days	0 days	0 days
Blackout period relative to pregnancy start date	0 days	0 days	0 days	0 days
Remove MOI exposure on delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date
Care Setting/PDX	Any	Any	Any	Any
Exposure Unit	Weeks	Weeks	Weeks	Weeks
Evaluation window	(20, 42)	(20, 42)	(20, 42)	(20, 42)
Maximum Episode Duration	None	None	None	None
Stockpiling option	On	On	On	On
Forced supply to attach to code	NA	NA	NA	NA
Inclusion/Exclusion				
Inclusion/ Exclusion groups	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM
Criteria	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any
Evaluation Period Start Anchor	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date
Evaluation Period Start	0	0	0	0
Evaluation Period End Anchor	Exposure index date	Exposure index date	Exposure index date	Exposure index date
Evaluation Period End	0	0	0	0
Inclusion/ Exclusion group	Penicillins (oral)	Macrolides (oral)	Penicillins (oral)	Macrolides (oral)
Criteria	Exclusion	Exclusion	Exclusion	Exclusion

Appendix C. Specifications for Type 4 Request: tspreg_mpl2p_wp003				
Care Setting/PDX	Any	Any	Any	Any
Evaluation Period Start Anchor	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date
Evaluation Period Start	0	0	0	0
Evaluation Period End Anchor	Delivery date	Delivery date	Delivery date	Delivery date
Evaluation Period End	30	30	30	30
Inclusion/ Exclusion group	Penicillins (injectable)	Macrolides (injectable)	Penicillins (injectable)	Macrolides (injectable)
Criteria	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any
Evaluation Period Start Anchor	Exposure index date	Exposure index date	Exposure index date	Exposure index date
Evaluation Period Start	1	1	1	1
Evaluation Period End Anchor	Delivery date	Delivery date	Delivery date	Delivery date
Evaluation Period End	30	30	30	30
Inclusion/ Exclusion group				
Criteria				
Care Setting/PDX				
Evaluation Period Start Anchor				
Evaluation Period Start				
Evaluation Period End Anchor				
Evaluation Period End				
Exclude evidence of days supply if inclusion/exclusion evaluation period includes dispensings	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply
Number of instances the criteria should be found in evaluation period	1	1	1	1
Forced supply to attach to dispensings	NA	NA	NA	NA
Population to which inclusion/exclusion applies	Mother's claims	Mother's claims	Mother's claims	Mother's claims

Appendix C. Specifications for Type 4 Request: tspreg_mpl2p_wp003		
Event/Outcome	Maternal outcome ICD-10-CM tree	Maternal outcome ICD-10-CM tree
Index date to anchor for outcome assessment start	Exposure index date	Exposure index date
Outcome assessment start	1	1
Index date to anchor for outcome assessment end	Pregnancy Delivery Date	Pregnancy Delivery Date
Outcome assessment end	30	30
Care Setting/PDX	Any	Any
Claims to evaluate outcome	Mother's claims	Mother's claims
Incident w/ respect to:	Level 3 codes	Level 2 codes
Incident Care Setting	Any	Any
Washout (days)	Minimum of 230 days or time from delivery to outcome code date	Minimum of 230 days or time from delivery to outcome code
Blackout Period	NA	NA
Propensity Score Matching/stratification	Stratification	Stratification
Scenarios	2 scenarios: Variable model and Step model	2 scenarios: Variable model and Step model
Covariates	See Covariates tab	See Covariates tab
Covariate Evaluation Window	See Covariates tab	See Covariates tab
Index date for covariates and PS risk set	Pregnancy start date	Pregnancy start date
Matching Ratio / N strata	4	4
Trimming	Yes	Yes
Matching Caliper Settings	NA	NA
hdPS evaluation window	NA	NA
hdPS covariates considered/covariates selected	NA	NA
hdPS covariate selection method	NA	NA
hdPS exclusions	NA	NA
Zero cell correction	NA	NA
Code truncation	NA	NA

ICD-9, ICD-10, HCPCS, and CPT codes are provided by Optum360.

NDC codes are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

Appendix C.1. Specifications for Type 4 Request: tspreg_mpl2p_wp003						
Purpose: The execution of Cohort Identification and Descriptive Analysis (CIDA) Pregnancy tool [QRP 10.3.3] to create cohorts for analysis using the TreeScan software for comparison of macrolide and penicillin exposure.						
Pregnancy Cohort	Sensitivity Analysis- GA 2 week strata		Sensitivity Analysis- GA 6 week strata		Sensitivity Analysis- GA 6 week strata, deciles	
	preg		preg		preg	
Pregnancy Episode Creation	Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes	
Delivery Definition	Cohort includes all valid pregnancy episodes during the query period		Cohort includes all valid pregnancy episodes during the query period		Cohort includes all valid pregnancy episodes during the query period	
Pregnancy Cohort Definition	Any		Any		Any	
Delivery Caresetting	Yes		Yes		Yes	
Create Baseline Table?	301 days		301 days		301 days	
Delivery washout	Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes	
Pregnancy Duration Definition (Pre/PostTerm Codes)	7		7		7	
Pre/Post-Term Code Evaluation Window Relative to Delivery Date	273		273		273	
Pregnancy Duration in Absence of Pre/Post-Term Codes (ITT Days)	None		None		None	
Mother-infant linkage requirement						
Drug/Exposure						
Prevalent Exposure/Comparator Incident w/ Respect to:	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>
Incident exposure washout period	NA	NA	NA	NA	NA	NA
Exposure Episode Length (ITT)	0 days	0 days	0 days	0 days	0 days	0 days
Cohort Definition	1 day	1 day	1 day	1 day	1 day	1 day
Build Episodes on Point Exposure?	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode	Cohort includes all valid medical product exposure episodes during a pregnancy episode
Treatment episode gap	Yes	Yes	Yes	Yes	Yes	Yes
Blackout period relative to pregnancy start date	0 days	0 days	0 days	0 days	0 days	0 days

Appendix C.1. Specifications for Type 4 Request: tspreg_mpl2p_wp003

Remove MOI exposure on delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date
Care Setting/PDX	Any	Any	Any	Any	Any	Any
Exposure Unit	Weeks	Weeks	Weeks	Weeks	Weeks	Weeks
Evaluation window	(20, 42)	(20, 42)	(20, 42)	(20, 42)	(20, 42)	(20, 42)
Maximum Episode Duration	None	None	None	None	None	None
Stockpiling option	On	On	On	On	On	On
Forced supply to attach to code	NA	NA	NA	NA	NA	NA
Inclusion/Exclusion						
Inclusion/ Exclusion groups	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPROM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPROM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPROM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPROM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPROM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPROM
Criteria	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any	Any	Any
Evaluation Period Start Anchor	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date
Evaluation Period Start	0	0	0	0	0	0
Evaluation Period End Anchor	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date
Evaluation Period End	0	0	0	0	0	0
Inclusion/ Exclusion group	Penicillins (oral)	Macrolides (oral)	Penicillins (oral)	Macrolides (oral)	Penicillins (oral)	Macrolides (oral)
Criteria	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any	Any	Any
Evaluation Period Start Anchor	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date
Evaluation Period Start	0	0	0	0	0	0
Evaluation Period End Anchor	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date
Evaluation Period End	30	30	30	30	30	30
Inclusion/ Exclusion group	Penicillins (injectable)	Macrolides (injectable)	Penicillins (injectable)	Macrolides (injectable)	Penicillins (injectable)	Macrolides (injectable)
Criteria	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any	Any	Any

Appendix C.1. Specifications for Type 4 Request: tspreg_mpl2p_wp003						
Evaluation Period Start Anchor	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date
Evaluation Period Start	1	1	1	1	1	1
Evaluation Period End Anchor	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date
Evaluation Period End	30	30	30	30	30	30
Inclusion/ Exclusion group						
Criteria						
Care Setting/PDX						
Evaluation Period Start Anchor						
Evaluation Period Start						
Evaluation Period End Anchor						
Evaluation Period End						
Exclude evidence of days supply if inclusion/exclusion evaluation period includes dispensings	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply
Number of instances the criteria should be found in evaluation period	1	1	1	1	1	1
Forced supply to attach to dispensings	NA	NA	NA	NA	NA	NA
Population to which inclusion/exclusion applies	Mother's claims	Mother's claims	Mother's claims	Mother's claims	Mother's claims	Mother's claims
Event/Outcome	Maternal outcome ICD-10-CM tree		Maternal outcome ICD-10-CM tree		Maternal outcome ICD-10-CM tree	
Index date to anchor for outcome assessment start	Exposure index date		Exposure index date		Exposure index date	
Outcome assessment start	1		1		1	
Index date to anchor for outcome assessment end	Pregnancy Delivery Date		Pregnancy Delivery Date		Pregnancy Delivery Date	
Outcome assessment end	30		30		30	
Care Setting/PDX	Any		Any		Any	
Claims to evaluate outcome	Mother's claims		Mother's claims		Mother's claims	
Incident w/ respect to:	Level 3 codes		Level 3 codes		Level 3 codes	
Incident Care Setting	Any		Any		Any	
Washout (days)	Minimum of 230 days or time from delivery to outcome code date		Minimum of 230 days or time from delivery to outcome code date		Minimum of 230 days or time from delivery to outcome code date	
Blackout Period	NA		NA		NA	

Appendix C.1. Specifications for Type 4 Request: tspreg_mpl2p_wp003			
Propensity Score Matching/stratification	Stratification	Stratification	Stratification
Scenarios	2 scenarios: Variable model and Step model	2 scenarios: Variable model and Step model	2 scenarios: Variable model and Step model
Covariates	See Covariates tab	See Covariates tab	See Covariates tab
Covariate Evaluation Window	See Covariates tab	See Covariates tab	See Covariates tab
Index date for covariates and PS risk set	Pregnancy start date	Pregnancy start date	Pregnancy start date
Matching Ratio / N strata	4	4	10
Trimming	Yes	Yes	Yes
Matching Caliper Settings	NA	NA	NA
hdPS evaluation window	NA	NA	NA
hdPS covariates considered/covariates selected	NA	NA	NA
hdPS covariate selection method	NA	NA	NA
hdPS exclusions	NA	NA	NA
Zero cell correction	NA	NA	NA
Code truncation	NA	NA	NA

Appendix C.2. Specifications for Type 4 Request: tspreg_mpl2p_wp003						
Purpose: The execution of Cohort Identification and Descriptive Analysis (CIDA) Pregnancy tool [QRP 10.3.3] to create cohorts for analysis using the TreeScan software for comparison of macrolide and penicillin exposure.						
	Sensitivity Analysis- Remove Teratogenic drug exclusion		Sensitivity Analysis- Respiratory Infections Only		Sensitivity Analysis- Respiratory Infections and Inpatient and ED settings	
Pregnancy Cohort	preg_teratogen		preg_respir		preg_respir	
Pregnancy Episode Creation	Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes	
Delivery Definition	Cohort includes all valid pregnancy episodes during the query period		Cohort includes all valid pregnancy episodes during the query period		Cohort includes all valid pregnancy episodes during the query period	
Pregnancy Cohort Definition	Any		Any		Any	
Delivery Caresetting	Yes		Yes		Yes	
Create Baseline Table?	301 days		301 days		301 days	
Delivery washout	Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes		Use Pregnancy Algorithm Codes	
Pregnancy Duration Definition (Pre/PostTerm Codes)	7		7		7	
Pre/Post-Term Code Evaluation Window Relative to Delivery Date	273		273		273	
Pregnancy Duration in Absence of Pre/Post-Term Codes (ITT Days)	None		None		None	
Mother-infant linkage requirement						
Drug/Exposure	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>	<i>Macrolides (oral)</i>	<i>Penicillins (oral)</i>
Prevalent Exposure/Comparator	NA	NA	NA	NA	NA	NA
Incident w/ Respect to:	0 days	0 days	0 days	0 days	0 days	0 days
Incident exposure washout period	1 day	1 day	1 day	1 day	1 day	1 day
Exposure Episode Length (ITT)	Cohort includes all valid medical product exposure episodes during a pregnancy episode		Cohort includes all valid medical product exposure episodes during a pregnancy episode		Cohort includes all valid medical product exposure episodes during a pregnancy episode	
Cohort Definition	Cohort includes all valid medical product exposure episodes during a pregnancy episode		Cohort includes all valid medical product exposure episodes during a pregnancy episode		Cohort includes all valid medical product exposure episodes during a pregnancy episode	
Build Episodes on Point Exposure?	Yes		Yes		Yes	
Treatment episode gap	0 days	0 days	0 days	0 days	0 days	0 days
Blackout period relative to pregnancy start	0 days	0 days	0 days	0 days	0 days	0 days

Appendix C.2. Specifications for Type 4 Request: tspreg_mpl2p_wp003

Remove MOI exposure on delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date	Do not exclude MOIs with a date equivalent to pregnancy delivery date
Care Setting/PDX	Any	Any	Any	Any	Any	Any
Exposure Unit	Weeks	Weeks	Weeks	Weeks	Weeks	Weeks
Evaluation window	(20, 42)	(20, 42)	(20, 42)	(20, 42)	(20, 42)	(20, 42)
Maximum Episode Duration	None	None	None	None	None	None
Stockpiling option	On	On	On	On	On	On
Forced supply to attach to code	NA	NA	NA	NA	NA	NA
Inclusion/Exclusion						
Inclusion/ Exclusion groups	Penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM	Teratogenic drugs, penicillins (injectable), macrolides (injectable), other antibiotics, PPRM
Criteria	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any	Any	Any
Evaluation Period Start Anchor	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date
Evaluation Period Start	0	0	0	0	0	0
Evaluation Period End Anchor	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date
Evaluation Period End	0	0	0	0	0	0
Inclusion/ Exclusion group	Penicillins (oral)	Macrolides (oral)	Penicillins (oral)	Macrolides (oral)	Penicillins (oral)	Macrolides (oral)
Criteria	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any	Any	Any
Evaluation Period Start Anchor	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date	Pregnancy start date
Evaluation Period Start	0	0	0	0	0	0
Evaluation Period End Anchor	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date
Evaluation Period End	30	30	30	30	30	30

Appendix C.2. Specifications for Type 4 Request: tspreg_mpl2p_wp003

Inclusion/ Exclusion group	Penicillins (injectable)	Macrolides (injectable)	Penicillins (injectable)	Macrolides (injectable)	Penicillins (injectable)	Macrolides (injectable)
Criteria	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion	Exclusion
Care Setting/PDX	Any	Any	Any	Any	Any	Any
Evaluation Period Start Anchor	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date	Exposure index date
Evaluation Period Start	1	1	1	1	1	1
Evaluation Period End Anchor	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date	Delivery date
Evaluation Period End	30	30	30	30	30	30
Inclusion/ Exclusion group			Respiratory Tract Infections (COVAR 1,3)	Respiratory Tract Infections (COVAR 1,3)	Respiratory Tract Infections (COVAR 1,3)	Respiratory Tract Infections (COVAR 1,3)
Criteria			Inclusion	Inclusion	Inclusion	Inclusion
Care Setting/PDX			Any	Any	Any	Any
Evaluation Period Start Anchor			Exposure Index Date	Exposure Index Date	Exposure Index Date	Exposure Index Date
Evaluation Period Start			-7	-7	-7	-7
Evaluation Period End Anchor			Exposure Index Date	Exposure Index Date	Exposure Index Date	Exposure Index Date
Evaluation Period End			0	0	0	0
Exclude evidence of days supply if inclusion/exclusion evaluation period includes dispensings	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply	Evaluation period should search for evidence of days supply
Number of instances the criteria should be found in evaluation period	1	1	1	1	1	1
Forced supply to attach to dispensings	NA	NA	NA	NA	NA	NA
Population to which inclusion/exclusion applies	Mother's claims	Mother's claims	Mother's claims	Mother's claims	Mother's claims	Mother's claims
Event/Outcome	Maternal outcome ICD-10-CM tree		Maternal outcome ICD-10-CM tree		Maternal outcome ICD-10-CM tree	
Index date to anchor for outcome assessment start	Exposure index date		Exposure index date		Exposure index date	
Outcome assessment start	1		1		1	
Index date to anchor for outcome assessment	Pregnancy Delivery Date		Pregnancy Delivery Date		Pregnancy Delivery Date	
Outcome assessment end	30		30		30	
Care Setting/PDX	Any		Any		IP*, ED*	
Claims to evaluate outcome	Mother's claims		Mother's claims		Mother's claims	
Incident w/ respect to:	Level 3 codes		Level 3 codes		Level 3 codes	

Appendix C.2. Specifications for Type 4 Request: tspreg_mpl2p_wp003			
Incident Care Setting	Any	Any	Any
Washout (days)	Minimum of 230 days or time from delivery to outcome code date	Minimum of 230 days or time from delivery to outcome code date	Minimum of 230 days or time from delivery to outcome code date
Blackout Period	NA	NA	NA
Propensity Score Matching/stratification	Stratification	Stratification	Stratification
Scenarios	2 scenarios: Variable model and Step model	STEP MODEL ONLY	STEP MODEL ONLY
Covariates	See Covariates tab	See Covariates tab	See Covariates tab
Covariate Evaluation Window	See Covariates tab	See Covariates tab	See Covariates tab
Index date for covariates and PS risk set	Pregnancy start date	Pregnancy start date	Pregnancy start date
Matching Ratio / N strata	4	10	10
Trimming	Yes	Yes	Yes
Matching Caliper Settings	NA	NA	NA
hdPS evaluation window	NA	NA	NA
hdPS covariates considered/covariates selected	NA	NA	NA
hdPS covariate selection method	NA	NA	NA
hdPS exclusions	NA	NA	NA
Zero cell correction	NA	NA	NA
Code truncation	NA	NA	NA