Novel Methods for Pregnancy Drug Safety Surveillance in the FDA Sentinel System

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Disclosures

- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.
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Monitoring of pregnancy exposures

- Pregnant individuals are rarely included in clinical trials during drug development, therefore data on teratogenicity and other potential adverse effects are collected post-market
- Pregnancy Exposure Registries are a primary source of post-market data, however:
  - Registries often miss enrollment targets
  - Registries are often underpowered for individual malformations
- Healthcare utilization data can be used for complementary studies

Gelperin K, Hammad H, Leishear K, et al. A systematic review of pregnancy exposure registries: examination of protocol-specified pregnancy outcomes, target sample size, and comparator selection. Pharmacoepidemiol Drug Saf. 2017;26(2):208–14

Signal identification analyses can supplement current practices for monitoring

- Signal identification = systematic evaluation of potential adverse events related to the use of medical products without prespecifying an outcome of interest
  - Allows for detection of new and unsuspected potential safety concerns
- Signal identification can identify potential adverse events to prioritize for targeted study when there are not known specific safety concerns
- Utilize the large sample sizes available in administrative data

How did this project come about?

- Sentinel Initiative: lead by the US FDA to develop new ways to assess the safety of approved medical products including drugs, vaccines, and medical devices
- Sentinel System: system to answer questions on approved medications using standardized analysis programs and a common data model for electronic healthcare data
- Development and adaption of signal identification methods is a priority
- We were tasked with the application of a signal identification method to pregnancy medication exposure monitoring

Signal Identification Process

Alert: meets a pre-specified threshold indicating lack of compatibility with the null hypothesis of no increase in risk

Signal: an alert that has been deemed a potential safety issue, for further evaluation

Alert detection

- Use data mining tools (e.g., TreeScan) to assess a large number of outcomes simultaneously for a single exposure comparison

Alert triage

- Review labeled conditions and published assessments to determine if alerts are expected
- Review patient episodes from claims data to inform whether other likely causes are evident, and to inform potential targeted studies
- Determine if deemed a “signal”

Targeted follow-up

- Design an observational study for the specific exposure-outcome relationship of interest, including outcome validation and confounding control tailored to the studied association

TreeScan™

- TreeScan is a program that implements a tree-based scanning statistic analysis: a statistical data mining tool that can be used for signal identification in pharmacovigilance/pharmacoepidemiologic analyses
  - Simultaneously scans for increased risk across multiple outcomes and allows for testing of very specific outcomes (e.g., atrial septal defect) or in groupings of concepts (e.g., congenital malformations of the circulatory system)
  - Formally adjust for multiple scenarios
  - Compatible with multiple epidemiologic study designs and confounding control methods

http://www.treescan.org/

Purpose of This Case Study

- **Demonstrate the use of TreeScan in real-world data, to inform future implementations of TreeScan for pregnancy exposure monitoring in the FDA Sentinel system**
  - How do results look in real data?
  - How do results compare when we use different propensity score methods/TreeScan models?

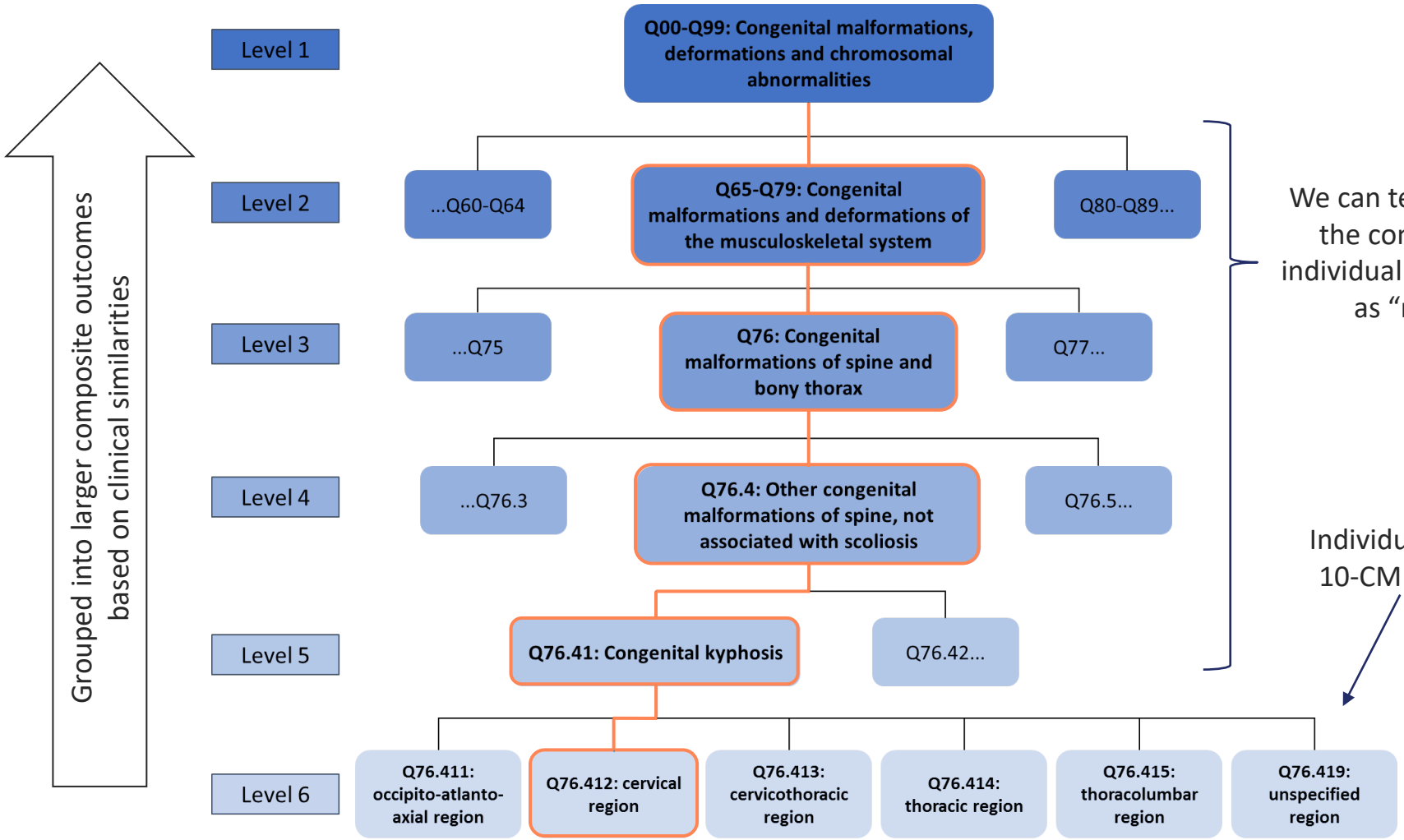
Methods

Tree-based scan statistics

- The “**tree**” allows for testing at individual outcomes or related groupings
- The “**scan**” statistic allows for adjustment of multiple testing across the tree

The tree

In the tree: Major congenital malformations, conditions related to gestational length and birth weight



TreeScan™ - a tree-based scan statistic

Single null hypothesis: there is no increase in risk across any node in the tree

1. Log likelihood ratios (LLR) are calculated based on the observed and expected counts for every node in the tree
2. The test statistic *T* is the maximum LLR across all nodes
3. Monte Carlo hypothesis testing is used to calculate p-values by generating random datasets (e.g. 99,999) under the null hypothesis
   a. *T* is calculated for every random dataset
   b. *R* = the rank of the real *T* among all randomly generated *T*
   c. *P* = *R*/(99,999+1)
   d. Choose our alerting threshold: $p \leq 0.05$

Study design and confounding control

- Self-controlled designs or cohort designs
  - We're using a cohort design – comparing an exposed to a referent group
  - Need to control for confounding – use propensity score methods
- The LLR can be derived from either a binomial-based or Poisson-based maximum likelihood estimator
  - Bernoulli: assumes all outcomes occur uniformly in a population with a fixed probability of belonging to the exposed group
    - Works well with fixed ratio propensity score matching
  - Poisson: assumes outcomes in the exposed group follow a Poisson distribution based on the outcome rate in the referent group
    - Works well with propensity score stratification

Wang SV, Maro JC, Baro E, Izem R, Dashevsky I, Rogers JR, et al. Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic. Epidemiology. 2018;29(6):895–903

Overview of the case study

Selected case study: fluoroquinolones compared to cephalosporins in the first trimester
Both drugs considered safe, no alerts expected – therefore assessing potential false positives

Bernoulli TreeScan model with propensity score matching (1:1, 2:1, 3:1) **or** Poisson TreeScan model with propensity score stratification (10 strata)

with one of the following propensity score models

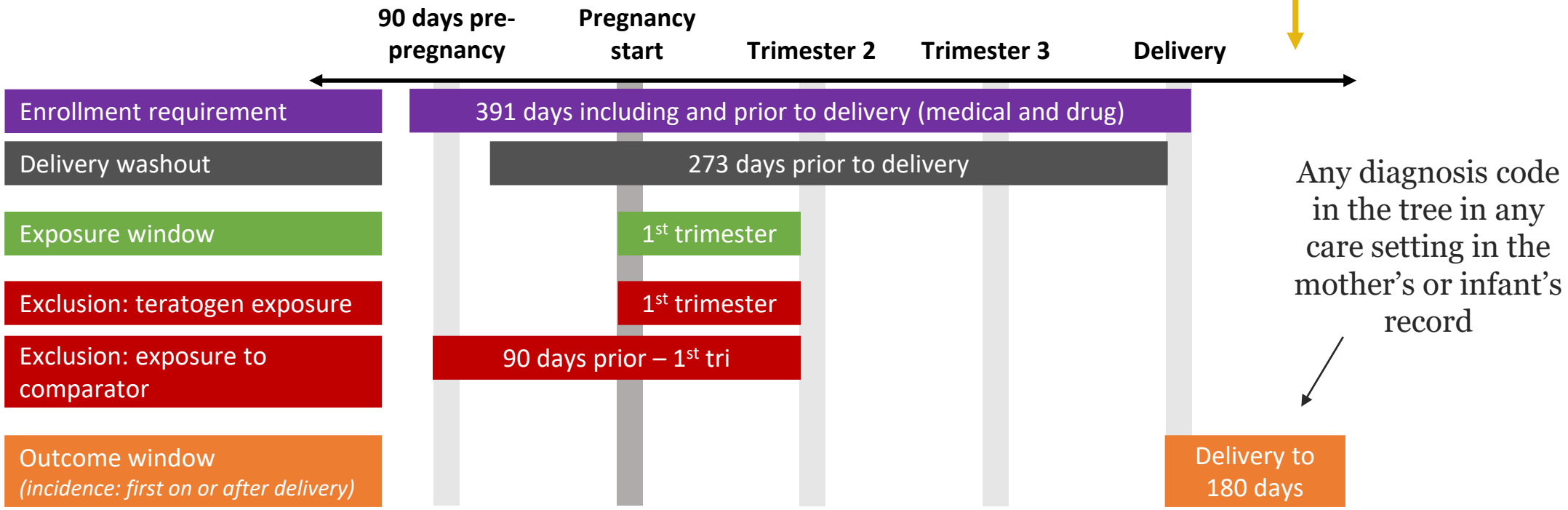
General model: Demographics, pre-existing conditions, screening behaviors, health care utilization metrics **or** **Tailored model:** general model + indications (common infections) **or** **High-dimensional model**: empirically selected based on exposure association

Data source: Merative MarketScan® Research Database
Eligible population: live birth deliveries linked to infants between October 1, 2015, and December 31, 2018, aged 10-55 years at delivery, with ≥1 fill of a fluoroquinolone or cephalosporin in the first trimester

Wang SV, Maro JC, Gagne JJ, et al. A general propensity score for signal identification using tree-based scan statistics. Am J Epidemiol. 2021;22:1424-1433.
Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology. 2009;20(4):512-522

Study design

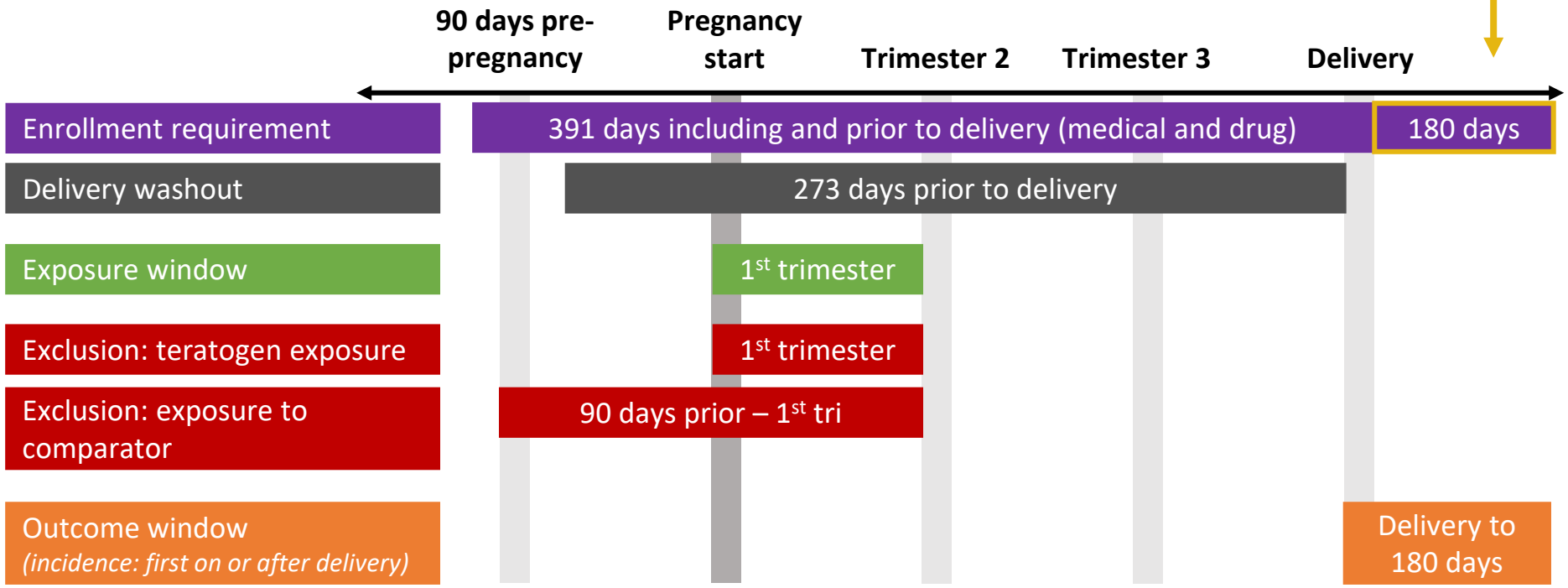
Bernoulli analysis: no requirement of maternal and infant enrollment because we censor matched pairs at first end of enrollment



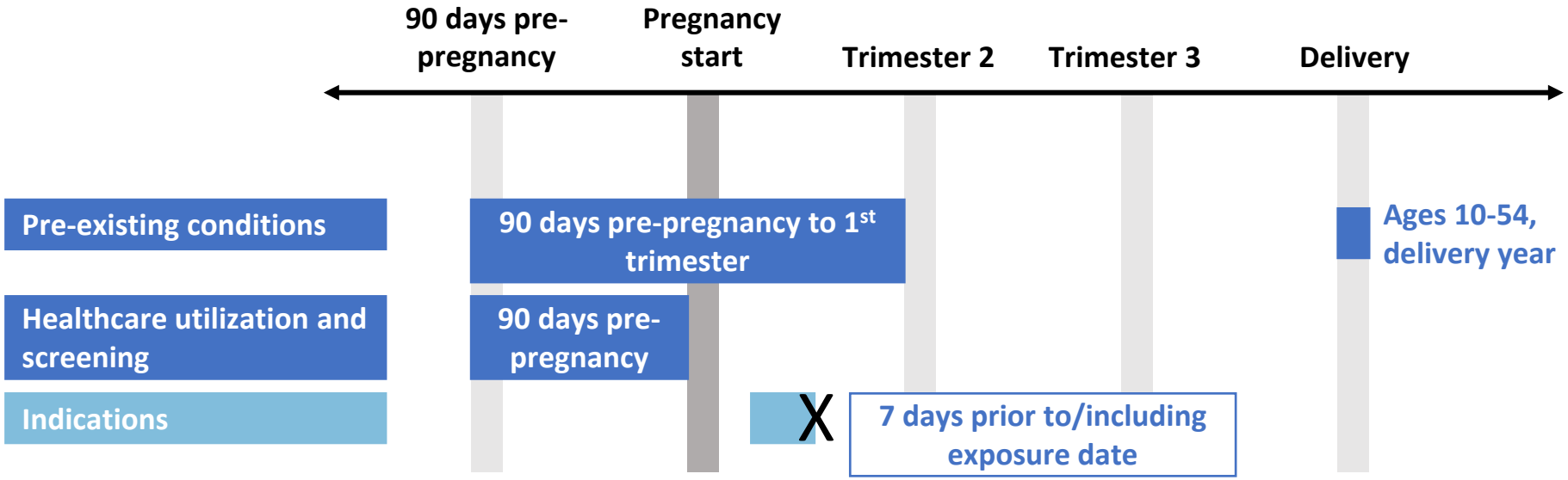
Any diagnosis code in the tree in any care setting in the mother's or infant's record

Study design

Poisson analysis: requirement of maternal and infant enrollment to ensure we are following the exposed and referent patients for the same duration



Confounder assessment



Results

Key Characteristics of the Cohort

Characteristic	Fluoroquinolones exposed N/mean	Fluoroquinolones exposed %/SD	Cephalosporins exposed N/mean	Cephalosporins exposed %/SD	Standardized Difference
Number of live births exposed in first trimester	1,791		8,739		-
Mean maternal age at index date	31.9	4.7	31.3	4.7	0.12
Antibiotic indications					
Ear, nose, and throat infections	219	12.2%	1,764	20.2%	-0.22
Gastrointestinal infections	36	2.0%	68	0.8%	0.11
Lower respiratory infections	42	2.3%	90	1.0%	0.10
Sexually transmitted infections	5	0.3%	60	0.7%	-0.06
Urinary tract infections	533	29.8%	1,777	20.3%	0.22

Bernoulli

Comparing these columns

"Alert" at p≤0.05

1:1 matched, general model

Node ID	Node description	Tree level	Total cases[a]	Observed exposed cases	Expected exposed cases[b]	Ratio: observed/ expected	LLR	*P*-value
General propensity score, 1:1 matching (N = 1791 in each group)								
Q31grp	Congenital malformations of larynx	3	34	27	17	1.59	6.280	0.014
Q315grp	Congenital laryngomalacia	4	32	25	16	1.56	5.370	0.077
Q248grp	Other specified congenital malformations of heart	4	6	6	3	2	4.159	0.283
Q03grp	Congenital hydrocephalus	3	4	4	2	2	2.773	0.824
P0716grp	Other low birth weight newborn, 1500–1749 g	4	8	7	4	1.75	2.531	0.881

Bernoulli

Comparing these columns

"Alert" at p≤0.05

Node ID	Node description	Tree level	Total cases[a]	Observed exposed cases	Expected exposed cases[b]	Ratio: observed/ expected	LLR	*P*-value
General + indications propensity score, 1:1 matching (N = 1790 in each group)								
Q600grp	Renal agenesis, unilateral	4	3	3	1.5	2	2.079	0.994
Q60grp	Renal agenesis and other reduction defects of kidney	3	3	3	1.5	2	2.079	0.994
Q100grp	Congenital ptosis	4	3	3	1.5	2	2.079	0.994
Q248grp	Other specified congenital malformations of heart	4	7	6	3.5	1.71	1.981	0.996
Q69grp	Polydactyly	3	10	8	5	1.6	1.927	0.997

1:1 matched, general + indications model

Bernoulli

Comparing these columns

"Alert" at p≤0.05

Node ID	Node description	Tree level	Total cases[a]	Observed exposed cases	Expected exposed cases[b]	Ratio: observed/ expected	LLR	*P*-value
HDPS, 1:1 matching (N = 1732 in each group)								
Q048grp	Other specified congenital malformations of brain	4	4	4	2	2	2.773	0.835
Q31grp	Congenital malformations of larynx	3	45	30	22.5	1.33	2.548	0.847
Q120grp	Congenital cataract	4	3	3	1.5	2	2.079	0.990
Q100grp	Congenital ptosis	4	3	3	1.5	2	2.079	0.990
Q12grp	Congenital lens malformations	3	3	3	1.5	2	2.079	0.990

1:1 matched, HDPS model

Bernoulli: sensitivity analyses

Node ID	Node Description	Tree Level	Total Cases[1]	Observed Exposed Cases	Expected Exposed Cases[2]	Observed/ expected	LLR	P-value
General + indications propensity score, 1:2 matching (N=1,787 fluoroquinolone exposed, N=3,574 cephalosporin exposed)								
Q513grp	Bicornate uterus	4	8	6	2.67	2.25	2.904	0.896
Q318grp	Other congenital malformations of larynx	4	2	2	0.67	3	2.197	1.000
Q692grp	Accessory toe(s)	4	2	2	0.67	3	2.197	1.000
Q796grp	Ehlers-Danlos syndromes	4	2	2	0.67	3	2.197	1.000
Q78grp	Other osteochondrodysplasias	3	2	2	0.67	3	2.197	1.000
General + indications propensity score, 1:3 matching (N=1,684 fluoroquinolone exposed, N=5,052 cephalosporin exposed)								
Q318grp	Other congenital malformations of larynx	4	2	2	0.5	4	2.773	0.990
Q692grp	Accessory toe(s)	4	2	2	0.5	4	2.773	0.990
Q78grp	Other osteochondrodysplasias	3	2	2	0.5	4	2.773	0.990
Q513grp	Bicornate uterus	4	10	6	2.5	2.4	2.738	0.991
Q31grp	Congenital malformations of larynx	3	67	25	16.75	1.49	2.480	0.994

Triaging the Observed Alert: Is it Worth Investigating?

- We provided claims profiles – a list of all maternal and infant claims around the time of pregnancy and delivery – for all cases for review by FDA workgroup members
- Congenital malformations of the larynx are generally not considered serious and often do not require intervention
- The observed alert was likely due to uncontrolled confounding, given that we did not observe it in analyses with theoretically better confounding control
- **Conclusion: no need for additional follow-up**

Poisson

Comparing these columns

"Alert" at p≤0.05

General model

Node ID	Node description	Tree level	Observed exposed cases	Expected exposed cases[a]	Ratio: observed/ expected	LLR	*P*-value
General propensity score							
Q513grp	Bicornate uterus	4	6	0.92	6.51	6.163	0.051
P0731grp	Preterm newborn, gestational age 28 completed weeks	4	6	1.11	5.4	5.230	0.137
P0508grp	Newborn light for gestational age, 2000–2499 grams	4	3	0.41	7.32	3.383	0.653
Q318grp	Other congenital malformations of larynx	4	2	0.23	8.89	2.594	0.951
Q412grp	Congenital absence, atresia and stenosis of ileum	4	2	0.25	7.9	2.387	0.978

Poisson

Comparing these columns

"Alert" at p≤0.05

General + indications model

Node ID	Node description	Tree level	Observed exposed cases	Expected exposed cases[a]	Ratio: observed/ expected	LLR	*P*-value
General + indications propensity score							
Q513grp	Bicornate uterus	4	6	0.83	7.26	6.721	0.026
P0731grp	Preterm newborn, gestational age 28 completed weeks	4	6	1.08	5.57	5.378	0.117
P0508grp	Newborn light for gestational age, 2000–2499 grams	4	3	0.31	9.57	4.089	0.383
Q318grp	Other congenital malformations of larynx	4	2	0.15	13.15	3.305	0.735
Q412grp	Congenital absence, atresia and stenosis of ileum	4	2	0.22	9.21	2.658	0.932

Poisson

Comparing these columns

"Alert" at p≤0.05

Node ID	Node description	Tree level	Observed exposed cases	Expected exposed cases[a]	Ratio: observed/ expected	LLR	*P*-value
HDPS							
Q513grp	Bicornate uterus	4	6	0.86	6.99	6.526	0.044
Q318grp	Other congenital malformations of larynx	4	2	0.079	25.4	4.548	0.287
P0731grp	Preterm newborn, gestational age 28 completed weeks	4	6	1.33	4.5	4.357	0.324
P0718grp	Other low birth weight newborn, 2000–2499 g	4	32	19.37	1.65	3.434	0.579
Q60grp	Renal agenesis and other reduction defects of kidney	3	3	0.56	5.36	2.597	0.883

HDPS

Triaging the Observed Alert: Is it Worth Investigating?

- Q51.3: Bicornate uterus
  - A rare malformation that is not diagnosed in infants
- We observed 6 cases in the exposed group and expected <1 case, leading to a large relative risk
- This is very likely associated with the mother's record
  - We include outcomes recorded in the mother's record and the infant's record after delivery because the infant may have a 30-60-day gap between delivery and insurance enrollment
  - This may result in false alerts like we observe here, but they are easily explained, and individual maternal and infant records can be reviewed to confirm

Summary

- We did not observe evidence that fluoroquinolone use in first trimester increases the risk of adverse infant outcomes when compared to cephalosporin use in first trimester
- Two alerts were observed that can be explained without targeted follow-up studies
- Why were results different by method?
  - The Poisson model has greater power than the Bernoulli model, therefore alerts observed with Poisson may not be able to be observed using Bernoulli
  - Different propensity score methods result in slight changes to the referent population, resulting in different expected counts
- At 1791 fluoroquinolone exposed, we are underpowered to see smaller increases in risk
- Use of propensity score stratification did not result in many spurious alerts
  - In this active comparator setting, a slight decrease in confounding control is likely worth the increase in power attained by using Poisson vs Bernoulli

Related studies

Suarez EA, Nguyen M, Zhang D, et al. Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs. Epidemiology 2023;34(1):90–8.

- Simulation study comparing power between Bernoulli and Poisson approaches

Thai T, Winterstein A, Suarez EA, et al. Design Considerations for Using the Tree-based Scan Statistic in Surveillance of Maternal Outcomes Following Medication Use During Pregnancy. Presented at ICPE 2022.

Thai T, Winterstein A, Suarez EA, et al. Triple Challenges – Small Sample Sizes in Both Exposure and Control Groups When Scanning Rare Maternal Outcomes in Signal Identification: A Simulation Study. Presented at ICPE 2023.

- From our workgroup: TreeScan for maternal outcomes following medication use in pregnancy

Huybrechts KF, Kulldorff M, Hernández-Díaz S, et al. Active Surveillance of the Safety of Medications Used During Pregnancy. Am J Epidemiol 2021;190(6):1159–68.

- Another case study, focusing on drugs with known harms

Thank You

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