Sentinel

Use of Tree-Based Scan Statistics for Surveillance of Infant Outcomes Following Maternal Perinatal Medication Use: A Case Study

Presented at ICPE 2021 All Access

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August 25, 2021

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.
- This project was supported by Task Order HHSF22301012T under Master Agreement HHSF223201400030I from the US Food and Drug Administration (FDA).

TreeScan™ for Signal Identification in Pregnancy

- TreeScan is a statistical data mining tool that can be used for signal identification in administrative databases in pharmacovigilance/ pharmacoepidemiologic analyses
- Signal identification: systematic evaluation of potential adverse events related to the use of medical products without pre-specifying an outcome of interest
- TreeScan can supplement current practices (pregnancy exposure registries and administrative database studies) by using large administrative databases to simultaneously scan for new and unsuspected potential safety concerns that can be investigated in targeted studies
- TreeScan allows for scanning for all types of malformations individually and in clinically relevant groupings (e.g., atrial septal defect, any cardiac malformation)

http://www.treescan.org/

Kulldorff, et al. Drug safety data mining with a tree-based scan statistic. 2013. Pharmacoepidemiol Drug Saf.

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 observed 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

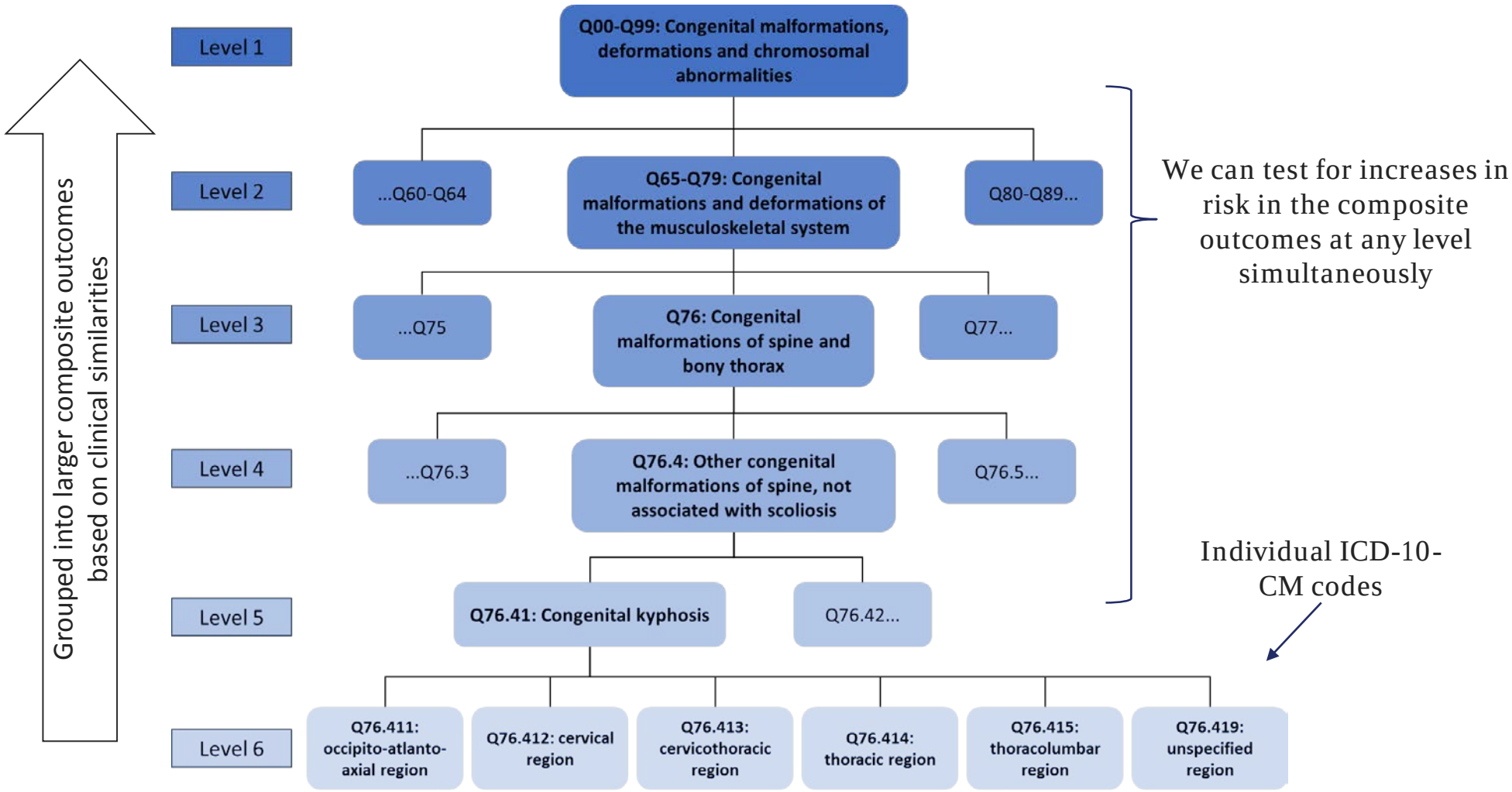
- Design an observational study for the specific exposure-outcome relationship of interest, including outcome validation and confounding control tailored to the studied association

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?
- Not designed to identify a new safety risk, therefore we chose drugs with known risk profiles and no known safety issues
  - Expected results: no alerts
- Selected case study: fluoroquinolone exposure in first trimester compared to cephalosporin exposure in first trimester
  - Antibiotics used to treat a variety of infections in pregnancy

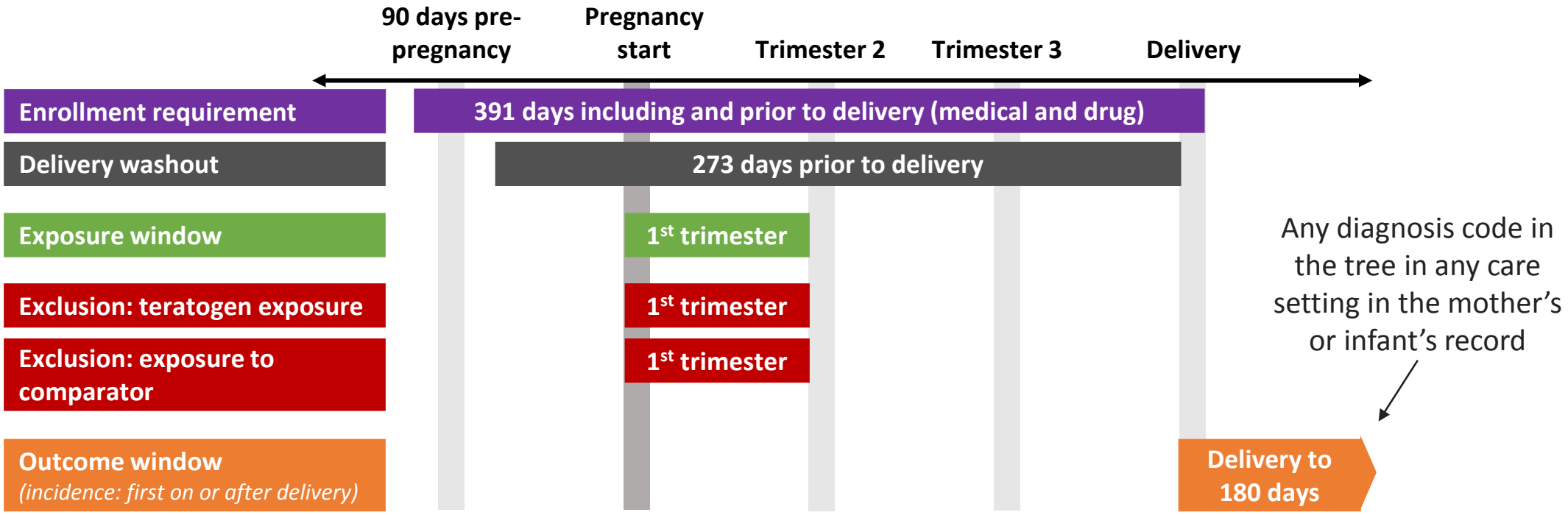
Methods

The Outcome Tree



Study Design

Data source	IBM MarketScan® Research Database
Eligible population	Women with live birth deliveries between October 1, 2015, and December 31, 2018, aged 10-54 years at delivery

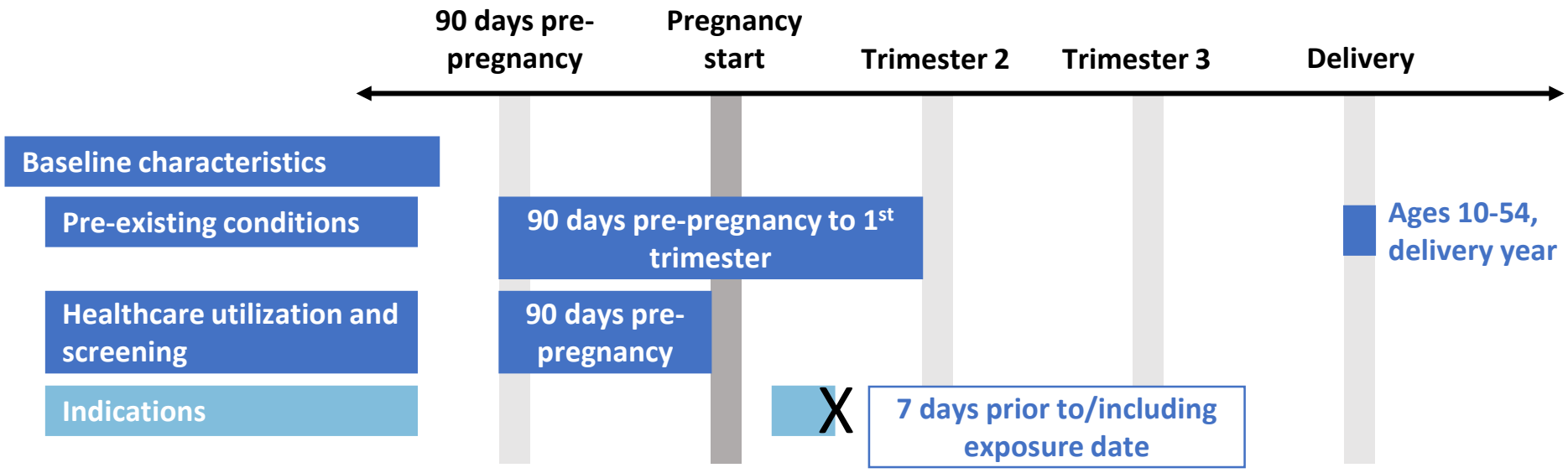


Propensity Score Models

1. **General model:** selected a general list of variables potentially related to increases in risk of adverse pregnancy outcomes that could be reused in future TreeScan evaluations
   - Similar to previous work to create a general propensity score model for the adult population (Wang, 2021)
   - Included: demographics, pre-existing conditions, screening behaviors, health care utilization metrics
2. **General model + indications:** added indications for fluoroquinolones and cephalosporins
   - Urinary tract and kidney infections, lower respiratory tract infections, ear, nose, and throat infections, gastrointestinal infections, and sexually transmitted infections
3. **High-dimensional propensity score:** used a data driven approach to select variables that are associated with the exposure

Wang SV, Maro JC, Gagne JJ, Patorno E, Kattinakere S, Stojanovic D, et al. A General Propensity Score for Signal Identification Using Tree-Based Scan Statistics. Am J Epidemiol [Internet]. 2021 Feb 22 [cited 2021 Jun 4]; Available from: https://doi.org/10.1093/aje/kwab034

Assessment of Potential Confounders



TreeScan Statistics and p-values for Alerting

- Simultaneously scans for increased risk across all outcomes in the tree
- Hypothesis testing:
  - Null: there is no increase in risk across any outcome in the tree in the exposed group
  - Alternative: there is an increase in risk for any outcome in the exposed group
- Formal adjustment for multiple testing to reduce false positives
- A statistical alert occurs when an outcome meets a pre-specified p-value threshold, e.g., <0.05
- Two probability models: Bernoulli and Poisson
  - These models use the referent population in different ways to calculate the expected outcome count in the exposed group
  - Both are compatible with different study designs with propensity scores that we will use to control for confounding:
    - Bernoulli: fixed ratio propensity score matching
    - Poisson: propensity score stratification or weighting

Select Analyses

	Matched analysis	Stratified analysis
TreeScan model	Bernoulli	Poisson
Propensity score models	3 models: general, general+indications, HDPS	3 models: general, general+indications, HDPS
Propensity score methods	Fix ratio matching, N:1 (ref:exposed) Main analysis: 1:1 matched Sensitivity analyses: 2:1, 3:1 matched	Stratification into deciles after trimming of non-overlapping regions of the PS distribution
Follow-up for outcomes	Follow-up time in the matched set is forced to be equal by truncating follow-up when one member loses enrollment within 180-day window	180 days of continuous enrollment required to ensure equal opportunity for outcome ascertainment
Calculation of expected exposed outcome counts	N/(N+1) x outcomes observed in the full matched population	Indirect standardization of outcome risk from referent group to exposed group by decile

Other sensitivity analyses that varied incidence criteria and outcome definitions will not be presented (results were consistent with main results)

Analyses were designed on Sentinel Query Request Package (QRP) version 9.6.0, with Propensity Score Analysis module, Signal Identification module, and ad hoc programming

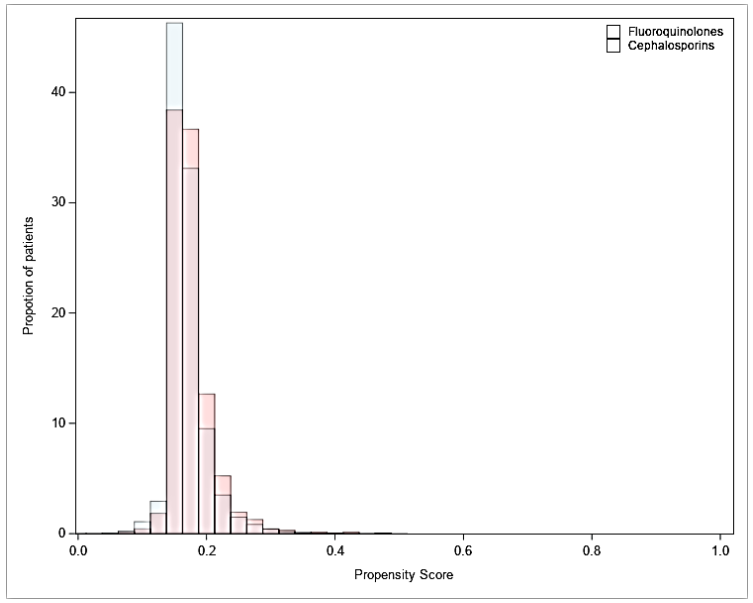
Results

Key Characteristics of the Cohort

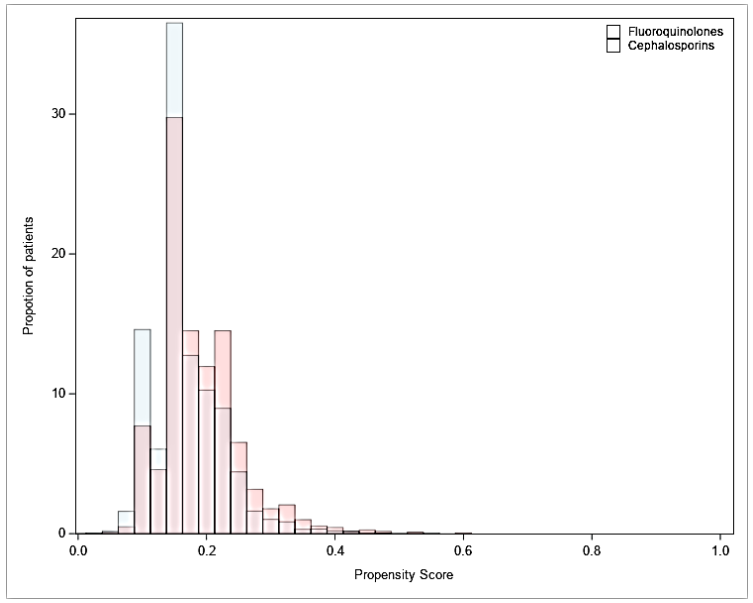
Characteristic	Fluoroquinolones exposed N/mean	Fluoroquinolones exposed %/SD	Cephalosporins exposed N/mean	Cephalosporins exposed %/SD	Standardized Difference
Number of live births exposed in first trimester	1,791		8,739		-
Mean maternal age at index date	31.9	4.7	31.3	4.7	0.12
Antibiotic indications					
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

Propensity Score Distributions

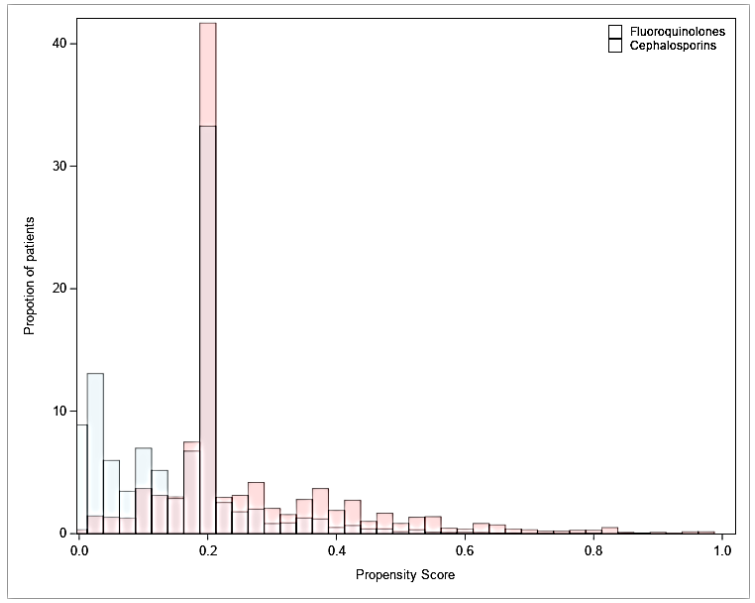
General model



General model + indications



HDPS



- Red = fluoroquinolones, Blue= cephalosporins
- Very good overlap in distributions between the groups in all models
- Adding indications and using HDPS differentiated groups more – potentially better confounding control

Results Using Propensity Score Matching and the Bernoulli Model

Analysis	Fluoroquinolone exposed N	Fluoroquinolone exposed N cases	Cephalosporin exposed N	Cephalosporin exposed N cases	TreeScan Results
TOTAL	1791		8739		
1:1 matched, general model	1791	504	1791	494	Q31grp (Congenital malformations of larynx) was significant ($p<0.05$)
1:1 matched, general + indications model	1790	506	1790	502	No significant alerts
1:1 matched, HDPS model	1732	494	1732	486	No significant alerts
2:1 matched, general + indications model	1787	510	3574	1028	No significant alerts
3:1 matched, general + indications model	1684	484	5052	1448	No significant alerts

Triaging the Observed Alert: Is it Worth Investigating?

Observed cases:

Code	Description	Fluoroquinolones	Cephalosporins
Q31	Total cases: Congenital malformations of larynx	27	7
Q31.5	Congenital laryngomalacia	25	7
Q31.8	Other congenital malformations of larynx	2	0

- 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

Results Using Propensity Score Stratification and the Poisson Model

	Fluoroquinolones		Cephalosporins		
Analysis	**N**	**N cases**	**N**	**N cases**	**TreeScan Results**
Full cohort	1,509		7,165		
Stratified Poisson, general model	1,508	426	7,160	2,030	Q513grp and Q513ngrp: bicornate uterus
Stratified Poisson, general + indications	1,507	426	7,155	2,028	Q513grp and Q513ngrp: bicornate uterus
Stratified Poisson, HDPS	1,500	423	7,089	2,008	Q513grp and Q513ngrp: bicornate uterus

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 of the Case Study

- 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

Thank You

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