A Self Controlled Case Series of Fluoroquinolone Exposure and the Risk of Aortic Aneurysm or Dissection

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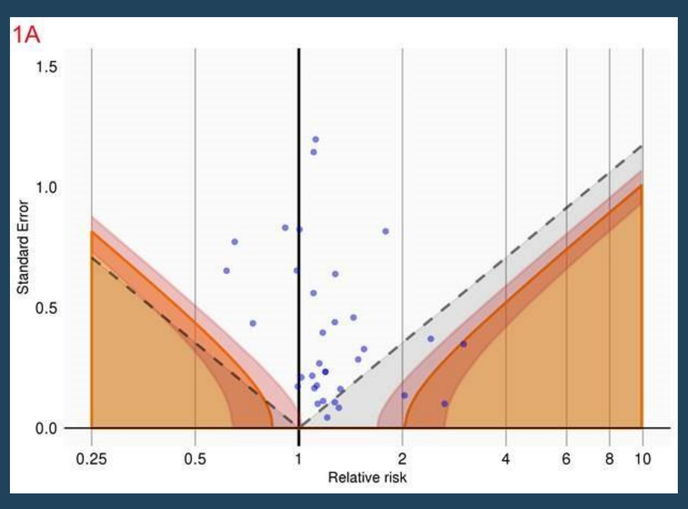
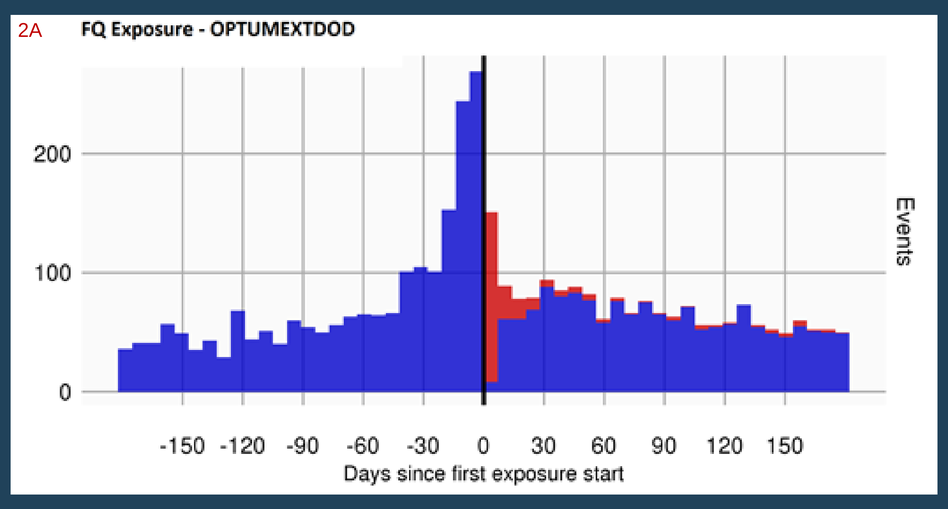
Reported associations between fluoroquinolones and aortic aneurysm or dissection do not adequately account for residual error and protopathic bias.





We observed positive residual bias and a surge in events prior to exposure, raising questions about the causal relationship between fluoroquinolones and aortic aneurysm or dissection.

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INTRO

- Recent observational studies report increased risk of aortic aneurysm and dissection (AAD) after exposure to fluoroquinolones (FQs)[1-4].
- We evaluated the risk of AAD following exposure to systemic FQs and other common antibiotics as well as untreated febrile illness

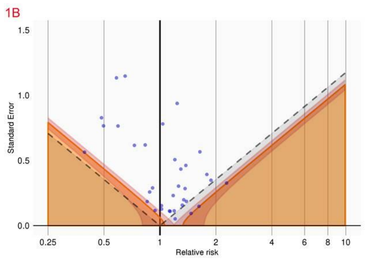
METHODS

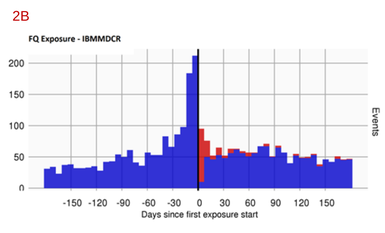
- Self controlled case series (SCCS) was used to minimize bias by controlling for within-patient, unobserved characteristics
- We conducted SCCS across 3 US administrative claims databases:
  - Optum© De-Identified Clinformatics® Data Mart Database (OPTUMEXTDOD), IBM MarketScan® Medicare Supplemental Database (IBMMDCR), and IBM MarketScan® Commercial Database (IBMCOM)
- AAD events must have occurred between April 1, 2012 and March 30, 2017, using patients of all ages.
- Risk windows were defined as drug exposure duration plus 30 days or febrile illness duration plus 30 days.

METHODS, continued

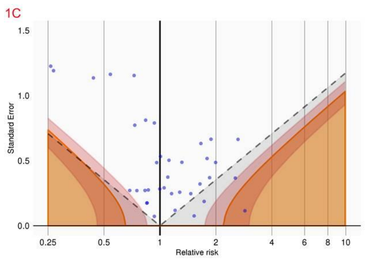
- We calibrated the analyses against 38 negative control exposures (i.e., exposures known *not* to affect AAD) to assess residual error and pre-exposure windows were used to evaluate timing of outcomes relative to exposures.
- P values were calibrated against the empirical null distribution, i.e. the distribution of incidence rate ratios (IRR) from the negative control exposures[5]
  - The empirical null distribution was visualized on calibration plots (1A: OPTUMEXTDOD, 1B: IBMMDCR, 1C: IBMCOM), where each dot represents the IRR and standard error from each negative control exposure. Estimates below the dashed line have uncalibrated p < 0.05. Estimates in the solid orange area have calibrated p < 0.05.
- We constructed pre-exposure windows to evaluate the timing of outcomes relative to exposures.
  - We report the IRR from pre-exposure windows and visualized event timing relative to first exposure. Exposure timeline plots (2A: OPTUMEXTOD, 2B: IBMMDCR, 2C: IBMCOM), show the frequency of AAD events (y-axis) over the 365-day period centered on the day of first exposure (x = 0). Red bars indicate that events occurred during the risk window.

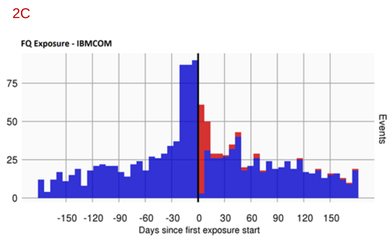
IBMMDCR: Empirical Calibration and Exposure Timeline Plots





IBMCOM: Empirical Calibration and Exposure Timeline Plots





RESULTS

- Across all 3 databases, negative control exposures produced effect estimates for AAD that were on average greater than the hypothetical null (i.e., incidence rate ratio [IRR] = 1) and indicative of residual bias, supporting the use of calibrated p values.
- In all databases, a peak in AAD events was observed during the 60 days before first exposure to FQ or trimethoprim with sulfamethoxazole, with IRRs increasing from the 60- to 30-day pre-exposure window to the 29- to 1-day pre-exposure window.
- The IRR for AAD in the 29 days preceding FQ exposure ranged from 2.38 (95% CI: 2.22-2.55) to 3.45 (95% CI: 3.09-3.85) across databases. The IRR following FQ exposure decreased to values ranging from 1.20 (95% CI: 1.12-1.30, calibrated p 0.82) to 1.85 (95% CI: 1.64-2.08, calibrated p 0.24).

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