An EUMAEUS investigation: how much can be gained in vaccine safety surveillance by including second dose data?

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INTRO
- The EUMAEUS (Evaluating Use of Methods for Adverse Event Under Surveillance) study for vaccines compared differing approaches to vaccine safety surveillance in observational real-world data.1, 2
- There is no standard approach to vaccine safety surveillance for multiple dose vaccines.
- Does the addition of second dose exposure periods to the first dose exposure periods improve time to sufficient statistical power?

DATA
- Zoster and HPV multi-dose vaccines.
- CCAE and OptumEhr observational health databases (2018).
- Negative controls used to establish Type I error.
- Positive controls (synthetically derived) with hazard ratios of 1.5, 2 and 4 used to establish time-course of Type II error.

ANALYSIS
- Self-controlled case series (SCCS), age & season adjusted excluding pre-vaccination window.
- Significance assessed using maximized sequential probability ratio test (maxSPRT).
- Empirical calibration3 and uncalibrated results were considered.

RESULTS

- **Empirical calibration** is required to control Type I error.
- The time to detect vaccine-outcome associations (small Type II error) might be reduced with sufficient second dose data.

CONCLUSIONS
- Empirical calibration reduces Type I error close to nominal (0.05) levels.
- However, controlling Type I error with empirical calibration does increase Type II error (reduces power) marginally.
- Despite the trade-off, Type II error below 50% is reached prior to 12-months follow-up in all databases for true effects (hazard ratios) of 2 and 4.
- Zoster second dose data from the CCAE database (the only database with >30% second dose uptake) improved the time to 50% Type II error for a true effect of 1.5 when compared to first dose follow-up only.

REFERENCES

Ty Stanford, Nicole Pratt, on behalf of the EUMAEUS task force;
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Figure 1. Dose accumulation of the zoster and HPV vaccines in the two databases over 12-month follow-up.

Figure 2. A comparison of Type I and type II error over follow-up when using single dose (top row) and both dose data (bottom row) for uncalibrated maxSPRT.

Figure 3. A comparison of Type I and type II error over follow-up when using single dose (top row) and both dose data (bottom row) for empirically calibrated maxSPRT.