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 calibration[3] and uncalibrated results were considered

RESULTS

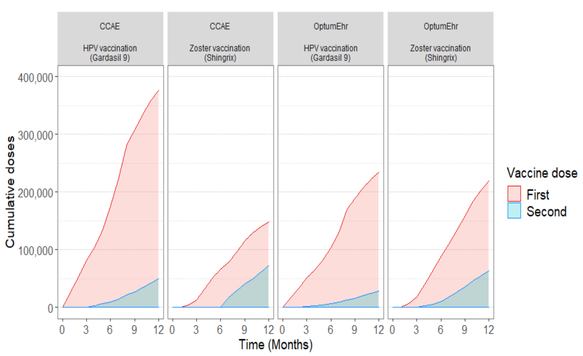

Figure 1. Dose accumulation of the zoster and HPV vaccines in the two databases over 12-month follow-up.

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- **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

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REFERENCES

1. EU PAS Register: EUPAS40259. http://www.encepp.eu/encepp/viewResource.htm?id=40341.
2. Schuemie MJ et al. Evaluating Use of Methods for Adverse Event Under Surveillance (for vaccines) [Internet]. https://github.com/ohdsi-studies/Eumaeus.
3. Schuemie MJ, Hripcsak G, Ryan PB, Madigan D, Suchard MA (2018). "Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data." Proc. Natl. Acad. Sci., 115(11): 2571-2577. https://doi.org/10.1073/pnas.1708282114.

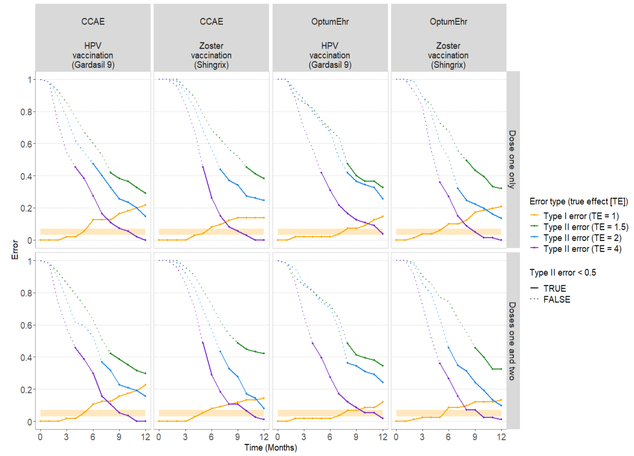

Figure 2. A comparison of Type I and type II error over follow-up when using single dose (top row) and both dose data (bottom row) for ***uncalibrated*** maxSPRT

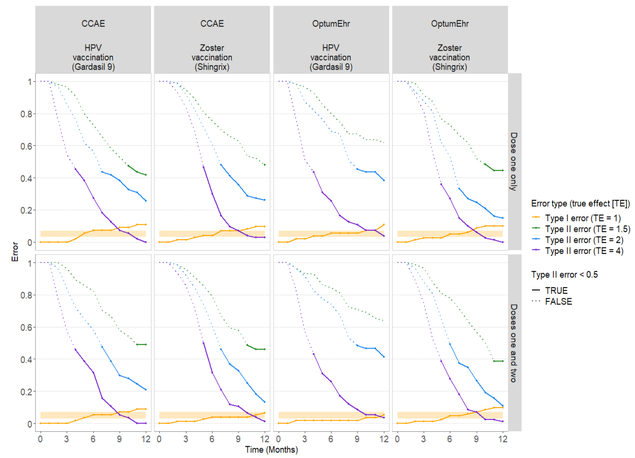

Figure 3. A comparison of Type I and type II error over follow-up when using single dose (top row) and both dose data (bottom row) for ***empirically calibrated*** maxSPRT

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

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