

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

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Background

When new vaccines are introduced to market it is important that robust systems are in place to ensure that any unexpected events, not detected in clinical trials, are identified early. Adverse events are not always identified in clinical trials due to their smaller sample sizes and strict implementation regimens, particularly for those vaccines that require multiple doses. In practice, not all patients return to receive second doses and the timing between doses is not always strictly adhered to. One of the goals of vaccine safety surveillance is to identify rare adverse events in the shortest possible time. However, it is critical that methods used to measure harm in practice are not only sensitive, that is they can identify true signals, but are also specific, that is they do not identify false positives from the larger pool of non-signals. The EUMAEUS study (Evaluating Use of Methods for Adverse Event Under Surveillance for vaccines) aimed to compare differing approaches to vaccine safety surveillance in observational real-world data by evaluating bias, precision and 'timeliness' of vaccine safety signal identification.^{1, 2} EUMAEUS examined six existing vaccines including H1N1, seasonal flu, zoster, and HPV vaccinations. Both the zoster and HPV vaccines are multiple dose vaccines in which two doses are required after a fixed interval. For multiple dose vaccines, there is no standard approach to vaccine safety surveillance and multiple doses are treated either by ignoring the second dose, considering the first and second dose separately, or combining first and second dose as one period of exposure. The aim of our study was to determine whether the addition of second dose exposure periods to the analysis of first dose exposure periods would improve time to achieving sufficient statistical power compared to using first dose only.

Methods

We conducted an empirical retrospective experiment of multi-dose vaccines, zoster and HPV vaccines, to determine the impact of design choices on study bias, precision and timeliness using the EUMAEUS study. Here we present the results for zoster and HPV vaccines from two observational health databases (CCAIE and OptumEhr) for the 2018 calendar year. Negative control outcomes (outcomes in which the vaccine is not associated) were used to synthetically derive positive control outcomes with hazard ratios (HRs) of 1.5, 2 and 4. Empirical type I error (false positives) and type II error (false negatives) were calculated as the proportion of statistically significant negative controls and the proportion of non-significant positive controls, respectively. Four observational study designs were assessed: case-control, cohort method, historical comparator, and the self-controlled case series/self-controlled risk interval (SCCS/SCRI). Statistical significance of vaccine-outcome associations were calculated using maxSPRT (maximized sequential probability ratio test) with and without empirical calibration to present results representative of real-world analysis scenarios.^{3, 4}

Vaccine dose data were analysed in two ways: considering first dose only, or the combination of first and second dose. To quantify whether time to sufficient power was improved with the addition of second dose data, we compared the minimum number of months required to achieve 50% power ($\beta=0.5$) with $\alpha=0.05$ using first dose only compared to the combination of first and second doses.

Results

At least 100,000 first doses were accumulated over the study period for both the zoster and HPV vaccines in both data sources (Figure 1). The largest cohort was for the HPC vaccine in the CCAIE database with 376,341 first doses and 49,283 second doses. HPV vaccination second doses occur between three and six months after the initial

dose and zoster vaccination second doses occur from two months onwards. This reflects the dosing regimens for each vaccine course. The zoster vaccine had a greater percentage of first doses having received a second dose by end of follow-up with 48.6% and 28.9% for the CCAE and OptumEhr databases, respectively. However, less than 15% of first doses received a second dose in both databases for the HPV vaccination.

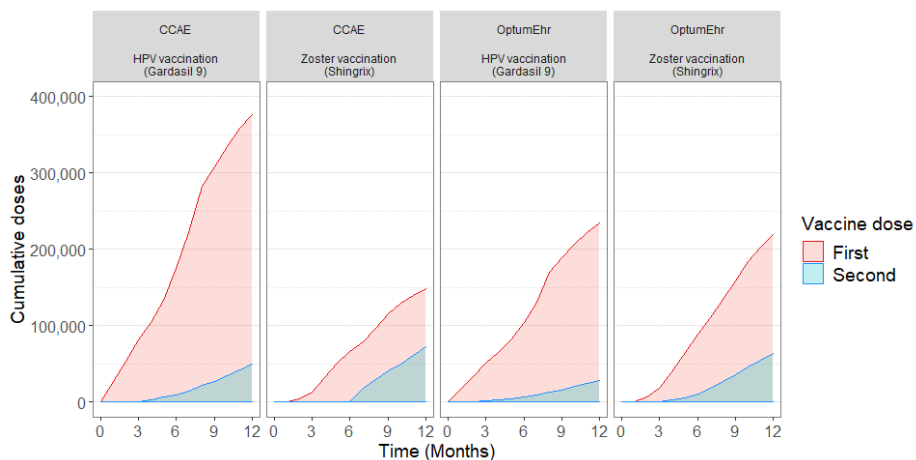


Figure 1. Dose accumulation of the zoster and HPV vaccines in the CCAE and OptumEhr databases over the 12-month follow-up.

For each of the study designs implemented, Figure 2A shows the study design variant that achieved earliest time to 50% power (type II error of 0.5) for nominal (or smallest when not achieved) type I error in uncalibrated analyses. Figure 2B shows the corresponding power and type I error in *calibrated* analyses. These plots show that calibration achieves close to nominal type I error for most designs however there was a corresponding loss of statistical power. Positive controls with the largest signal (HR=4) were able to achieve 50% power prior to the end of the 12-month follow-up in calibrated analyses for many of the designs (Figure 2B).

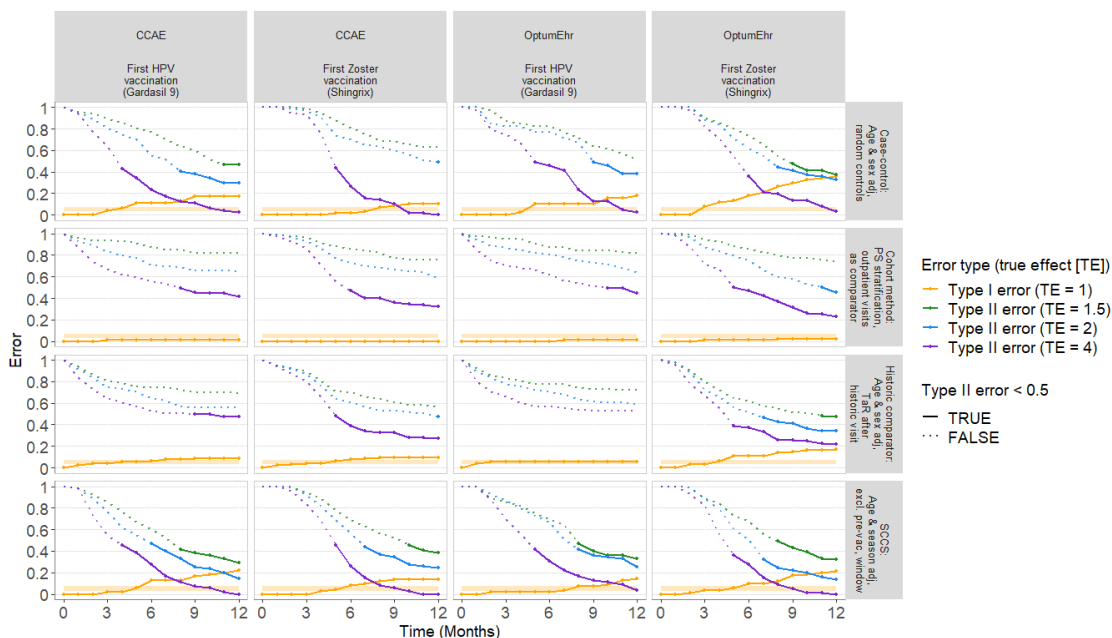


Figure 2A: Best performing study design variation before empirical calibration.

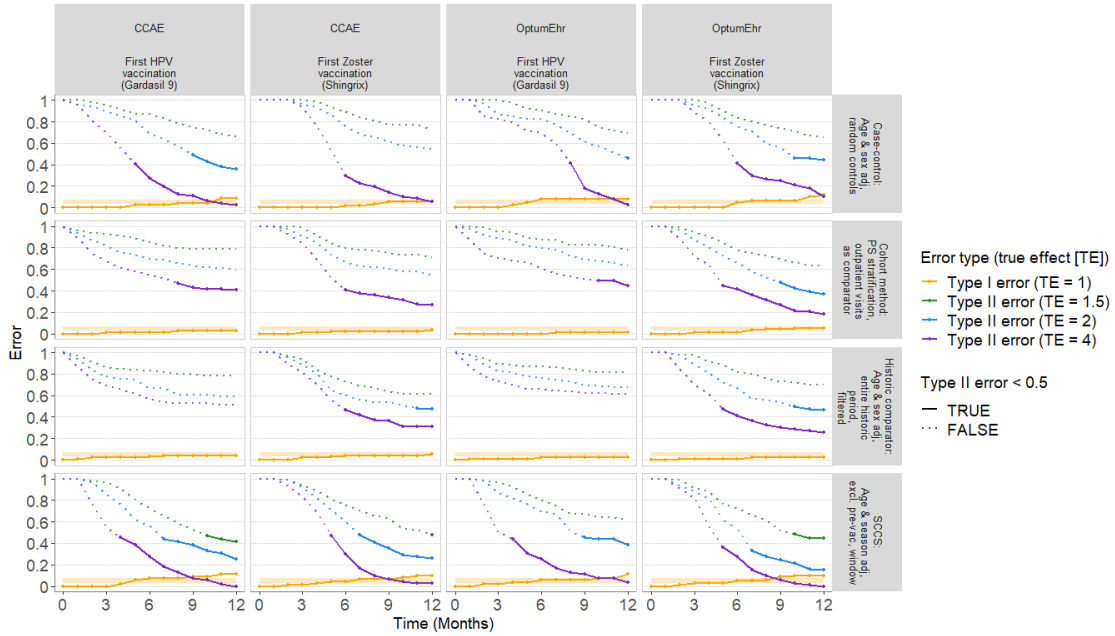


Figure 2B: Best performing study design variation after empirical calibration.

For the best performing calibrated study design variation, SCCS with age & season adjustment excluding pre-vaccination window, the time to 50% power for the zoster vaccine in the CCAIE database (the only vaccine with >30% second dose uptake in a specific database) was improved when including both first and second dose compared to first dose only (Figure 3).

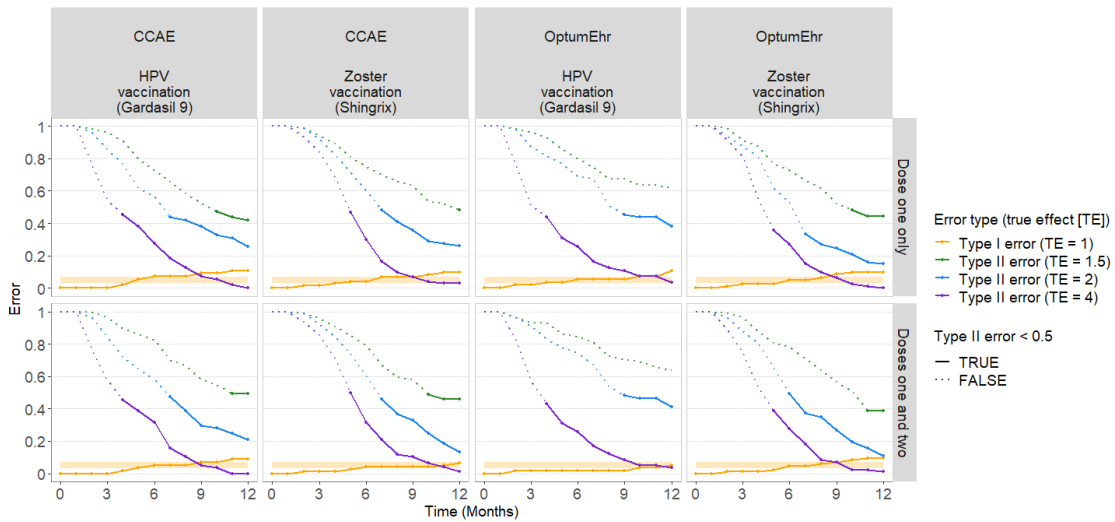


Figure 3. A comparison of type I and type II error over follow-up when using single dose (top row) and both dose data (bottom row) for calibrated maxSPRT in the SCCS with age & season adjustment excluding pre-vaccination window .

Conclusion

Identifying true safety signals is important in the real world to maintain confidence in vaccination regimens, however, there is an inherent trade off in surveillance methods between statistical power (detecting true positives) and type I error (detecting false positives). In this study we identified that restoring nominal or near-nominal type I error, via empirical calibration, can come at the cost of statistical power. Including second dose data in the analysis, does improve time to sufficient power in some scenarios but is likely underestimated given the small proportion of second doses observed in the data included in this study. In the EUMAEUS experiment true positive controls were simulated under the assumption of equal risk across doses, however in practice it may be that different doses have different risk profiles. Future research could investigate the impact of varied risk profiles between doses.

References/Citations

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