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# Impact of common biases on simulated relative vaccine effectiveness estimates: implications for evidence synthesis, decision making, and real-world studies

***Pharmacoepidemiologic methods in real-world vaccine effectiveness research and policy***


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## BACKGROUND

- Health administrative data are being increasingly used to generate real-world vaccine effectiveness estimates
- Understanding the impact of biases and statistics errors on real-world vaccine estimates would be useful for generating better evidence, meta-analyzing the results of individual studies, and making recommendations

## OBJECTIVE

- To demonstrate the impact of low statistical power, uncontrolled confounding, and publication biases on meta-analyzed vaccine effectiveness estimates derived from randomized and observational studies using simulation

## METHODS

### Study design, key variables, and R code

**Study design:** We simulated 20 "randomized" (10 small and 10 large) and 20 "observational" (10 small and 10 large) studies

- *Small=6,000 to 10,000 observations*
- *Large=200,000 to 300,000 observations*

```
#Simulate a large study
  n <- round(runif(1, 200000, 300000))
```

**Exposure:** Binary variable representing an influenza vaccine treatment strategy

- *~1:1 allocation (vaccinated vs. unvaccinated)*

```
#Generate exposure
  vaccine <- sample(c(0,1), size = n, replace = TRUE)
```

**Confounders:** Continuous variable representing age and a binary variable representing "healthy vaccinee bias"

- *Confounders were only used to simulate observational studies, no confounding was assumed in the randomized studies*

```
#Generate confounders
  age <- round(runif(n, 65, 110)) + 4*vaccine
   age_center <- age-mean(age)
  healthy <- round(runif(n, 0, 100)) + 30*vaccine
   healthy <- as.numeric(healthy >= 95)
```

**Outcome:** Binary variable representing influenza/pneumonia hospitalization

- *Rare outcome (< 1.0%) in alignment with prior work[1]*
- ***Unbiased vaccine effectiveness was set to 20% (risk ratio=0.80)***

```
#Randomized study equation
  xb <- -4.5 + -0.22*vaccine
#Observational study equation with confounders
  xb <- -4.5 + -0.22*vaccine + 0.02*age_center + -2*healthy
#Generate logistic equation
  p <- 1/(1+exp(-xb))
  outcome <- rbinom(n = n, size = 1, prob = p)
```

### Statistical analysis

- Generalized linear models were run for each simulated study

```
#Estimate VE using regression
  mod_results<- glm(y~vaccine, family="binomial"(link="log"))
  CIs <- suppressMessages(confint(mod_results))
```

- Plotted individual study results and meta-analyzed study results by design, size, and statistical significance

```
#Meta-analyze small observational studies together
  meta.small.obs <- metagen(beta_a,se_beta_a, data=Data, sm="RR",
  backtransf = TRUE)
  forest(meta.small.rwe, prediction = TRUE)
```

## RESULTS

**Small observational studies**

- Mean RR=0.56
- Mean VE=44%
- Range RR=0.37-0.74
- 6/10 studies p<0.05
- Meta-analysis=0.54 [0.46-0.64]

**Small randomized studies**

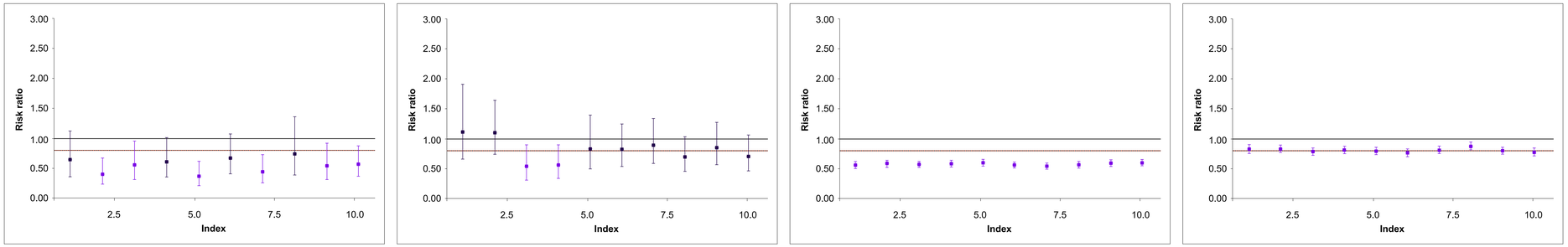
- Mean RR=0.81
- Mean VE=19%
- Range RR=0.54-1.12
- 2/10 studies p<0.05
- Meta-analysis=0.80 [0.67-0.95]

**Large observational studies**

- Mean RR=0.58
- Mean VE=42%
- Range RR=0.55-0.60
- 10/10 studies p<0.05
- Meta-analysis=0.58 [0.56-0.60]

**Large randomized studies**

- Mean RR=0.81
- Mean VE=19%
- Range RR=0.76-0.88
- 10/10 studies p<0.05
- Meta-analysis=0.80 [0.79-0.83]



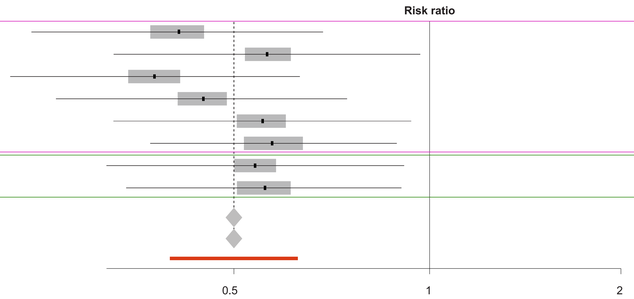

***Point estimates varied widely in small observational and randomized simulations, all estimates were imprecise, and observational studies overestimated the true effect size***

***Point estimates were consistent in large observational and randomized simulations, all estimates were precise, and observational studies overestimated the true effect size***

### Simulating publication BIAS

| Study | logRR | SE (logRR) | RR | 95%–CI | Weight (common) | Weight (random) |
|---|---|---|---|---|---|---|
| 1 | -0.8983 | 0.2635 | 0.41 | [0.24–0.68] | 12.0% | 12.0% |
| 2 | -0.5780 | 0.2784 | 0.56 | [0.33–0.97] | 10.7% | 10.7% |
| 3 | -0.9836 | 0.2623 | 0.37 | [0.22–0.63] | 12.1% | 12.1% |
| 4 | -0.8126 | 0.2618 | 0.44 | [0.27–0.74] | 12.1% | 12.1% |
| 5 | -0.6004 | 0.2698 | 0.55 | [0.32–0.93] | 11.4% | 11.4% |
| 6 | -0.5591 | 0.2222 | 0.57 | [0.37–0.88] | 16.9% | 16.9% |
| 7 | -0.6234 | 0.2708 | 0.54 | [0.32–0.91] | 11.4% | 11.4% |
| 8 | -0.5907 | 0.2494 | 0.55 | [0.34–0.90] | 13.4% | 13.4% |
| **Common effect model** | | | **0.50** | **[0.42–0.59]** | **100.0%** | – |
| **Random effects model** | | | **0.50** | **[0.42–0.59]** | – | **100.0%** |
| **Prediction interval** | | | | **[0.40–0.62]** | | – |

Heterogeneity: $I^2$ = 0%, $\tau^2$ = 0, $p$ = 0.89




***When restricting to small and statistically significant simulations, vaccine effectiveness was overestimated in the meta-analysis – showing larger VE than the true value***

## CONCLUSIONS

Low statistical power, uncontrolled confounding, and publication biases contributed to the overestimation of pooled VE

Decision-makers leveraging meta-analyses should be aware of these threats to validity, and study investigators should make concerted efforts to properly power studies, interrogate/address uncontrolled confounding, and pre-register observational study protocols

Additional guidance to identify and address these potential biases and errors in meta-analysis of vaccine effectiveness studies are needed


**REFERENCES**

**1.** Johansen ND, et al. *NEJM* Evid. 2023;2:EVIDoa2200206


**ABBREVIATIONS**

CI: confidence interval; RR: risk ratio; SE: standard error; VE: vaccine effectiveness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