Test file: Methodological Comparison of Case-Control and Cohort Designs in Vaccine Safety Studies: A Systematic Replication Analysis

Authors: Xiantao Zeng[1], Mohammad Tarique[2], Shengli Wu[3]*

Affiliations:

[1] Zhongnan Hospital of Wuhan University, Wuhan 430071, China

[2] University of Missouri, Columbia 65211, USA

[3] LifeCenter Northwest, Seattle 98101, USA

Corresponding Author:

*Shengli Wu, Email: victorywu2000@163.com

Abstract

This methodological replication study compared effect estimates from case-control and cohort designs applied to the same vaccine safety datasets. Analyzing six vaccine-adverse event pairs across three databases, we found high concordance between designs when confounding control and outcome definitions were standardized. Discrepancies arose primarily from differential misclassification and selection biases. The findings support the utility of both designs in vaccine safety assessment when rigorously implemented.

Keywords: Vaccine Safety; Case-Control; Cohort; Methodology; Comparative Design; Bias; Pharmacoepidemiology

1. Introduction

Vaccine safety evidence relies heavily on observational studies due to ethical and practical limitations of randomized trials for rare adverse events. Both case-control and cohort designs are widely used, yet their comparative validity remains debated. Case-control studies are efficient for rare outcomes but susceptible to recall and selection biases. Cohort designs minimize temporal ambiguity but may be inefficient for rare events. While theoretical comparisons abound, empirical comparisons using identical populations and outcome definitions are limited. Such methodological studies are crucial for interpreting vaccine safety evidence and guiding design choices. This systematic replication analysis applied both designs to the same vaccine exposure and outcome data to quantify concordance and identify sources of discrepancy.

2. Methods

2.1 Data Sources and Study Pairs

We utilized three large healthcare databases: two from integrated health systems and one national claims database. Six vaccine-safety pairs were selected based on public health importance and prior evidence: 1) MMR and febrile seizures; 2) Influenza vaccine and Guillain-Barré syndrome; 3) HPV vaccine and autonomic dysfunction; 4) Rotavirus vaccine and intussusception; 5) Meningococcal vaccine and anaphylaxis; 6) COVID-19 vaccine and myocarditis. For each pair, we implemented both a case-control and cohort analysis using identical source populations, exposure definitions, and covariate data.

2.2 Design Implementation

For cohort designs, we defined exposed cohorts as vaccine recipients and unexposed as matched individuals during the same period without vaccination. For case-control designs, we nested these within the cohort framework, selecting all cases and sampling controls from the risk sets.

Exposure ascertainment used identical procedures across designs. We applied standardized confounding control using propensity score weighting and high-dimensional propensity scores. Primary analysis compared hazard ratios from cohort designs with odds ratios from case-control designs using the ratio of estimates with 95% confidence intervals.

3. Results

3.1 Overall Concordance

Across the six vaccine-safety pairs, we observed high concordance between designs when methodological parameters were standardized. The median ratio of case-control to cohort estimates was 0.98. For four pairs, confidence intervals overlapped substantially. The strongest concordance was observed for acute outcomes with clear temporal relationships and validated ascertainment algorithms.

3.2 Sources of Discordance

Discordance emerged in settings with differential outcome misclassification or complex exposure timing. For Guillain-Barré syndrome, the case-control design yielded higher estimates, potentially due to more complete outcome capture through multiple ascertainment methods. For autonomic dysfunction following HPV vaccination, the cohort design showed stronger associations, possibly due to more accurate exposure timing. Differences were magnified when varying confounder control approaches, highlighting the primacy of confounding control over design selection.

4. Discussion

This empirical comparison demonstrates that both case-control and cohort designs can generate similar vaccine safety estimates when rigorously implemented. The findings challenge dogmatic preferences for either design and emphasize the importance of bias minimization strategies. The results support the use of case-control designs for rare outcomes when nested within well-defined cohorts and with careful attention to selection procedures. Similarly, cohort designs require sufficient outcome ascertainment and confounder measurement to ensure validity. These findings should reassure stakeholders that well-conducted studies of either design can contribute valid evidence to vaccine safety assessment.

5. Conclusion

The choice between case-control and cohort designs for vaccine safety studies should be guided by practical considerations including outcome frequency, data structure, and available confounder information rather than presumed superiority of either design. Methodological standardization and bias minimization are more critical than design selection per se. These findings support the use of multiple designs in vaccine safety signal evaluation and emphasize the value of methodological transparency in evidence synthesis.

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