Tackling Rare Events in Network Meta-Analysis: Comparative Performance of Methods for Sparse Safety Outcomes

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INTRODUCTION

- Network meta-analysis (NMA) is increasingly employed to compare multiple treatments simultaneously in healthcare research [1]
- **Synthesizing safety outcomes often involves sparse networks**, with limited direct evidence and/or few studies per comparison [2]
- These networks pose significant challenges in robustly estimating effects, particularly for rare event outcomes [2]

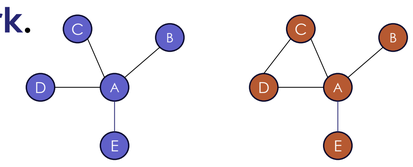
OBJECTIVES

- This study aimed to **identify and compare robust methodological approaches for analyzing binary rare event data**, to provide recommendations on model choice and implications in regulatory submissions.

METHODS

Simulations

- This **simulation study** followed the methodology outlined by Evrenoglou *et al.* [2] to generate data for **two distinct NMA structures: a star-shaped network and a network with a closed loop.** Only **two-arm studies** (each comparing a treatment against the reference) were constructed. The simulations were conducted under conditions of **no heterogeneity**, with **consistency maintained across treatment comparisons within the closed-loop network.**



- A total of **16 scenarios per network** were explored, varying baseline event risk, sample size per study arm, number of treatments in the network and number of studies per treatment comparison:

Table 1. *Overview of scenarios. For each scenario 100 datasets were generated.*

Scenario	Sample size (N)	Treatments	Studies per comparison	Mean Events Reference Arm	Mean Events Treatment Arms	% Studies with 0 events Reference Arm	% Studies with 0 events Treatment Arm
Baseline event risk (%): 1%-5%							
1	20-60	5	1	1.21	2.23	33.98%	18.28%
2	20-60	8	1	1.20	2.13	34.66%	19.01%
3	20-60	5	4	1.20	2.25	34.93%	17.66%
4	20-60	8	4	1.20	2.14	34.43%	19.08%
5	100-200	5	1	4.53	8.42	4.20%	0.93%
6	100-200	8	1	4.50	8.01	4.06%	1.30%
7	100-200	5	4	4.49	8.41	3.99%	1.02%
8	100-200	8	4	4.51	8.04	3.83%	1.10%
Baseline event risk (%): 0.5%-10%							
9	20-60	5	1	2.12	3.79	21.55%	11.03%
10	20-60	8	1	2.10	3.62	22.20%	12.10%
11	20-60	5	4	2.10	3.81	22.32%	11.26%
12	20-60	8	4	2.10	3.64	22.19%	12.06%
13	100-200	5	1	7.91	14.30	3.40%	1.15%
14	100-200	8	1	7.94	13.89	3.31%	1.26%
15	100-200	5	4	7.87	14.27	3.55%	1.09%
16	100-200	8	4	7.89	13.72	3.38%	1.33%

Evaluated models

Model **performance** was assessed by calculating **the mean difference between estimated and true log odds ratios averaged over 100 simulated datasets.**

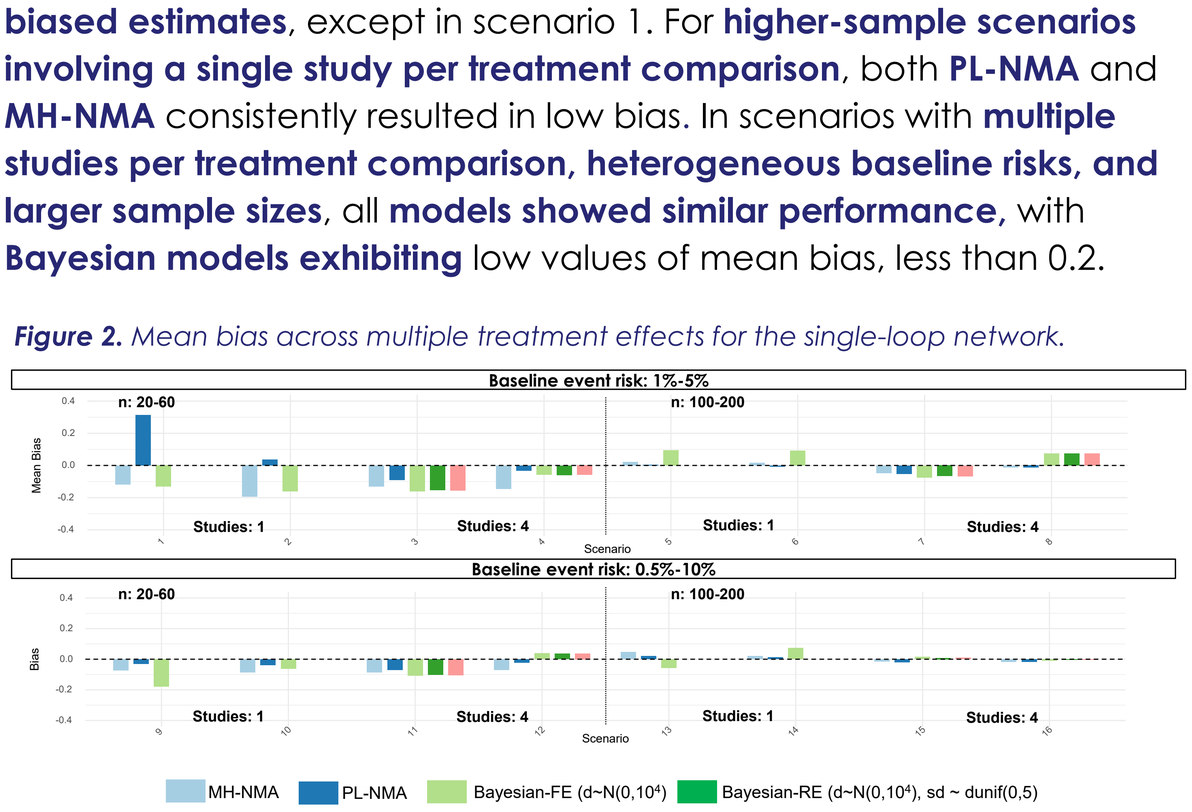
- Fixed-effect (FE) **Mantel-Haenszel (MH) NMA** with continuity correction for studies with zero event arms.[3]
- FE **Penalized Likelihood (PL) NMA** model.[2]
- **Fixed and random-effects (RE) Bayesian NMA with exact binomial likelihood with non-informative priors** and applying continuity correction for studies with zero event arms. [4]
- **RE Bayesian NMA with exact binomial likelihood model with a more informative prior** on the between study variance parameter and applying continuity correction for studies with zero event arms. [4]
- For Bayesian models, non-informative priors were used following NICE DSU TSD recommendations. [4] A half-normal (0,1) prior was chosen as the more informative prior for the between-study variance. **RE models were not run for networks with single-study treatment comparisons.** The Gelman-Rubin statistic was used to check model convergence.

RESULTS

Star-shaped network

Across **low-sample scenarios**, the **PL-NMA** model **generally provided the least biased estimates**, except in scenarios 1 and 9, where Bayesian FE models showed the lowest bias. For **higher-sample scenarios**, **PL-NMA consistently outperformed all other models.** In scenarios with **multiple studies per treatment comparison, heterogeneous baseline risks,** and **larger sample sizes**, **Bayesian models** also demonstrated robust performance with **least biased results.**

Figure 1. *Mean bias across multiple treatment effects for the star-shape network.*



Single-loop network

In **low-sample scenarios**, the **PL-NMA** model generally yielded the **least biased estimates**, except in scenario 1. For **higher-sample scenarios involving a single study per treatment comparison**, both **PL-NMA** and **MH-NMA** consistently resulted in low bias. In scenarios with **multiple studies per treatment comparison, heterogeneous baseline risks, and larger sample sizes**, all **models showed similar performance**, with **Bayesian models exhibiting** low values of mean bias, less than 0.2.

Figure 2. *Mean bias across multiple treatment effects for the single-loop network.*

CONCLUSIONS

- While some of the evaluated models offer reliable estimates, the **choice of approach for sparse NMAs is multi-faceted**.
- The utility of synthesising all-zero event studies need to be justified, and sensitivity analyses should always be conducted to ensure robustness of the results.

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DISCLOSURES

GF, AN, KP and AG are employees of Amaris Consulting. Authors declare no conflict of interest.

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