Synthesizing Evidence for Rare Events: a Novel Zero-Inflated Bivariate Model to Integrate Studies with Double-Zero Outcomes

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Background

When analyzing a relatively rare binary outcome, double-zero studies (DZS) — those with no events in both arms — present critical statistical challenges, leading to potential numerical instability and bias in estimating treatment effects [1, 2]. This studies are particularly prevalent in meta-analyses of observational health data in fields associated with rare events, such as surgical complications or adverse drug reactions [3, 4]. DZS are directly relevant to the OHDSI community as they could skew the conclusions drawn from observational health data, impacting the quality of research outputs and real-world decision-making in healthcare.

Strategies such as continuity correction [5, 1] or omission of DZS [1] in meta-analyses have been suggested. However, these approaches can lead to biased conclusions [6, 7, 8]. While continuity correction prevents computational errors, it typically biases study estimates towards null difference and inflates variance estimates. Excluding DZS, although straightforward, may not effectively leverage all available evidence and potentially result in bias if the omitted studies systematically differ from the included ones.

Generalized linear mixed models (GLMMs) offer a more flexible approach for modeling effect sizes and can incorporate information from DZS [9, 10]. Bivariate generalized linear mixed models (BGLMM) have been proposed to include random effects and potential correlation between treatment groups [11, 12, 13].

Despite their utility, all the models mentioned above fail to address one potential key cause of DZS, i.e., heterogeneity in the population. DZS may occur if the study involves sub-populations with a negligible or extremely low probability of experiencing the event of interest. For instance, healthy subjects less than 65 years old only have negligible risks of experiencing hospitalization or death due to severe symptoms from COVID-19, compared to immunocompromised, unhealthy or older subjects. This seems to support our argument of negligible risk: People with very young or old age are more likely to experience adverse drug reactions [14].

We propose a zero-inflated bivariate generalized linear mixed effects model (ZIBGLMM). Zero-inflated models have been commonly applied in other areas to model excess zero counts. Our work is the first one to apply zero-inflated models to meta-analyses. It assumes that a meta-analysis with many zero-event studies potentially contains two subpopulations: one with a near-zero risk and another with a higher risk. The ZIBGLMM can account for heterogeneity and correlation among studies and estimate the overall effect size as well as the proportion of the low-risk population in each study.

Methods

Let N_{ik} be the number of subjects, and p_{ik} be the probability of an event for the i^{th} study ($i = 1, 2, \ldots, m$) where $k = 1$ represents treatment (or exposure) group and $k = 0$ represents the control (or unexposed) group respectively. Let X_{ijk} denote a Bernoulli random variable with a value of 1 denoting an event and a value of 0 denoting a non-event for the j^{th} subject ($j = 1, 2, \ldots, N_{ik}$) of the i^{th} study in the kth treatment group. Let $Y_{ik} = \Sigma_{j=1}^{N_i} X_{ijk}$ be the total number of events in k^{th} group in the i^{th} study. The event counts follow a binomial distribution $Y_{ik} \sim Bin\left(N_{ik}, p_{ik}\right)$.

The bivariate generalized linear mixed effects model (BGLMM) directly models the event counts Y_{ik} with binomial likelihoods instead of estimating the effect sizes of individual studies and can be specified as follows: let $g(\cdot)$ denote the link function that transforms event probabilities into linear forms. We have

$$g\left(p_{i0}\right) = \mu_0 + \nu_{i0};$$
$$g\left(p_{i1}\right) = \mu_1 + \nu_{i1};$$
$$\left(\nu_{i0}\,, \nu_{i1}\right)^\top \sim N\left((0,0)^\top,\ \Sigma\right),\ \Sigma = \begin{pmatrix} \sigma_0^2 & r\sigma_0\sigma_1 \\ r\sigma_0\sigma_2 & \sigma_1^2 \end{pmatrix}.$$

To address population difference, we introduce the ZIBGLMM, which is a two-component finite mixture model. We denote π as the proportion of studies with healthy population representing individuals who have approximately zero risk for the event of interest.

The ZBGLMM combines two zero-generating processes for the number of events Y_{ik}. The first process generates double zeros for both arms from extremely low-risk sub-populations. The second process is governed by a binomial distribution that generates numbers of events, some of which may be zero due to chance. The mixture is described as follows:

$$P\left(Y_{i0} = 0, Y_{i1} = 0\right) = \pi + (1-\pi)\prod_{k=0}^{1}\left(1 - p_{ik}\right)^{N_{ik}};$$

$$P\left(Y_{i0} + Y_{i1} > 0\right) \times P\left(Y_{i0} = y_{ik},\ Y_{i1} = y_{ik} \mid Y_{i0} + Y_{i1} > 0\right) = (1-\pi)\prod_{k=0}^{1}\binom{N_{ik}}{y_{ik}}\left(p_{ik}\right)^{y_{ik}}\left(1 - p_{ik}\right)^{N_{ik}-y_{ik}};$$

$$g\left(p_{i0}\right) = \mu_0 + \nu_{i0}, g\left(p_{i1}\right) = \mu_1 + \nu_{i1}\ , \left(\nu_{i0}\,, \nu_{i1}\right)^\top \sim N\left((0,0)^\top,\ \Sigma\right),\ \Sigma = \begin{pmatrix} \sigma_0^2 & r\sigma_0\sigma_1 \\ r\sigma_0\sigma_2 & \sigma_1^2 \end{pmatrix}.$$

This formulation of ZIBGLMM is particularly advantageous because it incorporates a zero-risk subpopulation, accounting for sub-populations with a zero risk experiencing the studied outcome. Being an entirely data-driven approach, ZIBGLMM is capable of accurately capturing the excessive number of double zero studies, leading to improved model fitting and more reliable results in meta-analyses.

Results

We conducted extensive simulations to evaluate our methods. Detailed settings of the simulation studies can be found in Table 1.

Table 1: Specifications for the simulation studies.

Parameter	Value
Zero-inflation rate	25%, 50%
# studies (n)	10 (small), 25 (moderate), 50 (large)
Average event rates for the non-zero-inflated part	3% for the control group on average, generated from a BGLMM model
Marginal RR	1, 1.5, 2
Study sizes	50
# double zero studies	Binomial (# studies, Zero-inflation rate)

We compared the coverage properties of meta-analyses excluding DZS and both the frequentist and Bayesian versions of BGLMM and ZIBGLMM. The coverage probabilities, in addition to the mean lengths of confidence intervals, are depicted in Figure 1.

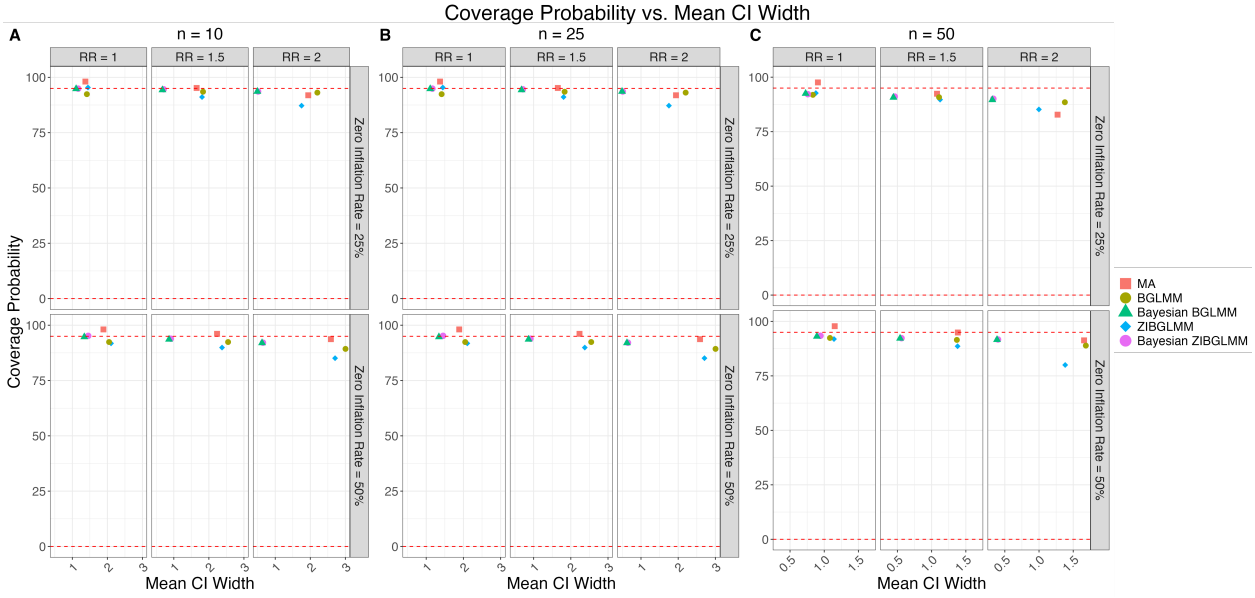

Figure 1: Coverage probability of the five methods: meta-analysis (MA), BGLMM, Bayesian BGLMM, ZIBGLMM, and Bayesian ZIBGLMM. The Bayesian BGLMM and Bayesian ZIBGLMM displayed comparable, consistently high coverage probabilities to meta-analysis, while maintaining the shortest mean confidence interval widths across all settings. The coverage probabilities for all methods decreased as the average marginal RR increased and as the size of studies increased.

Remarkably, the Bayesian BGLMM and Bayesian ZIBGLMM displayed comparable, consistently high coverage probabilities to meta-analysis, while maintaining the shortest mean confidence interval widths across all settings. The coverage probabilities for all methods decreased as marginal RR and size of studies increased.

Figure 2 portrays the bias in the estimation of relative risk by meta-analysis excluding DZS, alongside the BGLMM, ZIBGLMM, and the Bayesian versions of BGLMM and ZIBGLMM.

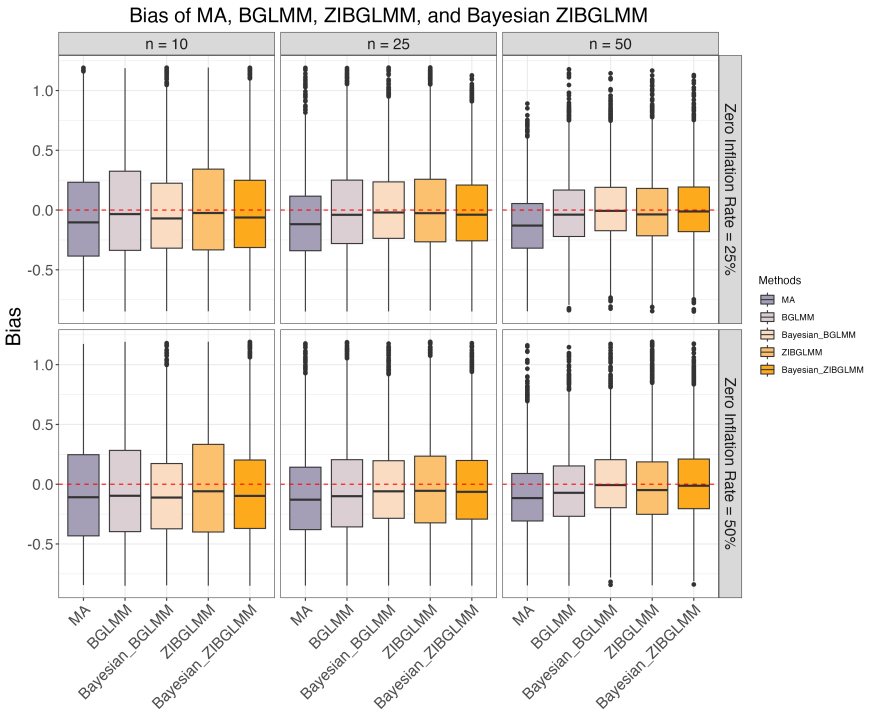

Figure 2: Bias in the estimation of relative risk procured from meta-analysis excluding DZS (MA), alongside the BGLMM, ZIBGLMM, and the Bayesian versions of BGLMM and ZIBGLMM based on all three simulated RRs (1, 1.5, and 2.0). For a small sample size of studies (10), the frequentist ZIBGLMM appears to exhibit the least bias in estimation. In a moderate sample size (25 studies), both Bayesian BGLMM and frequentist ZIBGLMM manifest the least bias. As the sample size expands to large (50 studies), the smallest bias is achieved by the Bayesian BGLMM and ZIBGLMM. Frequentist ZIBGLMM consistently demonstrates less bias than the frequentist BGLMM. For all settings, both frequentist and Bayesian BGLMM and ZIBGLMM consistently yield smaller biases compared to meta-analyses that exclude DZS.

Moreover, the frequentist ZIBGLMM consistently demonstrates less bias than the frequentist BGLMM. For all settings, both frequentist and Bayesian BGLMM and ZIBGLMM consistently yield smaller biases compared to meta-analyses that exclude DZS.

Conclusion

Our study illustrates the importance and potential of the ZIBGLMM as a new approach in handling double zero studies, thereby significantly contributing to the optimization of meta-analytic methods. The key advantage of ZIBGLMM lies in its superior ability to handle excess zero data and its robustness in estimating relative risk.

Evidence synthesis plays a central role in distributed research networks such as OHDSI. It is crucial to develop rigorous and data-adaptive methods to account for the intrinsic heterogeneity across populations within OHDSI network. Specifically, in pharmacoepidemiological studies focusing on adverse events where outcomes are rare, the integration of double-zero studies using suitable methods is necessary for generating reproducible and reliable clinical evidence. Our research aligns with the mission of OHDSI by advancing the frontier of methodology in clinical evidence generation and evidence synthesis.

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