Meta-Analysis of Incidence Rate Data in the Presence of Zero-Event and Single-Arm Studies

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Abstract: Unlike the classical two-stage DerSimonian and Laird meta-analysis method, the one-stage random-effects Poisson and Negative-binomial models have the great advantage of including the information contained in studies reporting zero event in one or both arms and in studies with one missing arm. Since the Negative-binomial distribution relaxes the assumption of equi-dispersion made by the Poisson, it should perform better when data exhibit over-dispersion. However, the superiority of the Negative-binomial model with rare events and single-arm studies is unclear and needs to be investigated. Moreover, to the best of our knowledge, this model has never been investigated in the context of a meta-analysis of incidence rate data with heterogeneous intervention effect. Therefore, we assessed the performance of the univariate and bivariate random-effects Poison and Negative-binomial models using simulations calibrated on a real dataset from a study on the surgical management of phyllodes tumors. Results suggested that the bivariate random-effects Negative-binomial model should be favored for the meta-analysis of incidence rate data exhibiting over-dispersion, even in the presence of zero-event and single-arm studies.

Keywords: Incidence rate, Meta-analysis, Negative-binomial model, Poisson model, Rare events, Random effects.

1. INTRODUCTION

Meta-analysis is considered as the gold standard of evidence-based medicine [1]. By combining the results of related but independent studies, it allows to evaluate the effect of a treatment (or an intervention; here-after we will use this latter terminology to emphasize the fact that we are in an observational framework) in situations where primary studies taken separately would not have sufficient power to detect a statistically significant effect [2]. Meta-analyses are thus particularly useful when studying rare events. For example, Nissen and Wolski studied the impact of a diabetes drug on the incidence of myocardial infarctions and cardiovascular deaths [3], whereas Niël-Weise, Stijnen, and van den Broek conducted a meta-analysis on the effect of anti-infective-treated central venous catheters on the incidence of catheter-related bloodstream infections [4].

When the data at hand are counts of events over time, the effect size (ES) of interest is often the incidence rate (IR) and different intervention arms can be contrasted using the incidence rate ratio or the incidence rate difference. In this setting, the most commonly-used approach, which can be applied in both fixed-effect (FE) and random-effects (RE) frameworks, consists in computing a weighted average of the primary study ESs with weights proportional to the inverse of each ES's variance [5] (the so-called "two-stage" approach [6]). Although this approach is very popular and enjoys good asymptotic properties, its use is problematic in small/finite samples, especially with rare events, when some studies report no event in one or both arms, and when some studies' arms are missing. Indeed, the ES and/or the weight computed in a single-zero (SZ), double-zero (DZ), or single-arm (SA) study are indefinite. To deal with SZ and DZ studies, researchers sometimes use a continuity correction factor [7]. However, this method is flawed and suffers from several criticisms [8-10]. In addition, SA studies are still excluded from the meta-analysis.

Under the assumption of a homogeneous intervention effect, Mantel-Haenszel (MH) is an alternative to the classical inverse variance method and has been shown to be very performant, even with very rare events [11]. Unlike the inverse variance method, the MH method can cope with SZ studies. However, DZ studies are simply discarded with that method and, therefore, do not contribute to the ES estimate. Similarly, the MH method fails to include the information contained in SA studies. Piaget-Rossel and Taffé have shown that only the exclusion of SA studies impacted the performance of this method (i.e. a loss of precision was observed in settings with a large proportion of SA studies) [12]. Another limitation of the MH method is that it is only valid under the assumption of a homogeneous intervention effect [13].

To improve these simple methods, one-stage or exact methods based on the likelihood principle have been developed. Such methods use the information contained in all the studies (i.e. including SZ, DZ, and SA studies) and allow for the inclusion of covariates. A natural way to model IR data is to use a Poisson likelihood [14]. This model can be adapted to the setting of a heterogeneous intervention effect by introducing random effects [15-16] and can be used to model the IR using either a univariate or a bivariate modelling approach [17]. One important limitation of the

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Poisson model is its reliance on the equi-dispersion assumption (i.e. the mean of the distribution is equal to its variance), which rarely holds with count data (because of unmeasured individual characteristics differing within studies for instance). A way to relax the equi-dispersion assumption is to replace the Poisson distribution by the Negative-binomial [18]. Although we found some applications of the Negative-binomial model for the meta-analysis of individual patient data in a two-stage approach or in the context of a homogeneous intervention effect [19-20], we are not aware of the use of the random-effects Negative-binomial (Re-NB) model for the meta-analysis of incidence rate data within a framework of a heterogeneous intervention effect, especially with rare events and SA studies.

Therefore, the goal of this paper was to assess the appropriateness of the Re-NB model for the meta-analysis of IR data in the presence of SZ, DZ, and even SA studies. Using simulations calibrated on a real clinical dataset, we compared this model with the random-effects Poisson (Re-Poi) model. We considered both univariate and bivariate versions of these two models. The data we used came from a recent systematic review on the impact of the width of the resection's margin on the rate of local recurrences in phyllodes tumors [21]. The use of a model allowing for over-dispersion seemed particularly adapted to this example where the exposure (i.e. the width of the resection's margin) had not been randomized and accounting for patient-level covariates affecting the incidence rate of recurrences at the analysis stage was difficult. We restricted our analyses to the framework of a heterogeneous intervention effect because the assumption of a homogeneous intervention effect was not plausible for the example considered.

In the remaining of this paper, we start by describing the illustrative example. Then, Section 3 presents the different models under investigation. In Section 4, we illustrate these models using data from the illustrative example and present results from a simulation study. Finally, Section 5 contains the discussion and some concluding remarks.

2. ILLUSTRATIVE EXAMPLE

The dataset used in this paper came from a systematic review on the surgical management of phyllodes tumors [21]. The author conducted a

Table 1: Data Extract from the Study on Surgical Management of Phyllodes Tumors

Study	Tumor's type	Control arm (i.e. margin < 10mm)			Intervention arm (i.e. margin ≥ 10mm)		
		n	t	Y	n	t	Y
1	Benign	14	1020.6	3	8	583.2	0
1	Borderline	4	291.6	2	11	801.9	4
1	Malignant	4	291.6	3	5	364.5	2
2	Benign	-	-	-	7	522.2	0
2	Malignant	-	-	-	3	98.1	0
3	Benign	104	10712	4	30	3090	1
3	Borderline	34	2856	2	23	1932	0
4	Benign	56	3976	7	44	3124	6
4	Borderline	1	71	0	3	213	0
4	Malignant	1	71	0	3	213	0
5	Malignant	10	1399	6	14	1958.6	4
6	Benign	126	9450	5	14	1050	0
6	Borderline	19	1121	4	13	767	1
6	Malignant	1	15	0	9	135	5
7	Benign	16	665.6	4	18	748.8	0
7	Borderline	1	57	0	2	114	0
7	Malignant	1	45	1	2	90	0
8	Malignant	6	726	0	30	3630	0
9	Benign	53	3074	0	5	290	0
9	Borderline	5	290	1	2	116	0
10	Benign	-	-	-	179	6748.3	12
10	Borderline	-	-	-	43	1406.1	3
10	Malignant	-	-	-	32	979.2	1

Note: n = sample size; t = person-months (number of patients × mean follow-up); Y = number of recurrences.

systematic review to assess the impact of the width of the resection's margin on the rate of tumor's recurrences (Table **1**).

The dataset entails 10 primary studies on tumors patients who underwent a surgical intervention to remove their tumor. Each tumor was classified as either benign, borderline, or malignant. Two arms were defined according to the margin of resection used during the surgery: intervention arm included patients with a margin above or equal to 10mm, and patients whose resection's margin was below 10mm belonged to the control arm. Study 2 and 10 corresponded to SA studies as they reported results only for margins above ten millimeters. One third of the control arms and more than half of the intervention arms reported zero event. Sample sizes and person-months varied widely across the studies.

3. MODELS TO COMBINE INCIDENCE RATES

3.1. The Random-Effects Poisson Model

3.1.1. Univariate Modelling

Let Y_{ijk} be the number of events occurring in study *i* ($i = 1, \dots, 10$), type of tumors *j* ($j \in$ {benign, borderline, malignant}) and arm *k* (*k* = *C* for control and *I* for intervention). Assume that the number of events is conditionally distributed as a Poisson variable with mean $\lambda_{ijk} = \mu_{ijk} * t_{ijk}$, where μ_{ijk} denotes the incidence rate and t_{ijk} the person-time. Consider the following univariate Re-Poi model:

$$Y_{ijk}|\lambda_{ijk} \sim Poisson(\lambda_{ijk})$$

$$\lambda_{ijk} = \mu_{ijk} * t_{ijk}$$

$$\log(\mu_{ijk}) = \beta_{0i} + \beta_{1i} * I_{ijk} + \gamma' * X_{ijk} + \theta' * Z_{ijk} * I_{ijk}$$

$$\begin{pmatrix}\beta_{0i}\\ \beta_{1i}\end{pmatrix} \sim N[\beta, \Omega], \beta = \begin{pmatrix}\beta_0\\ \beta_1\end{pmatrix}, \Omega = \begin{pmatrix}\sigma^2_{\beta_0} & 0\\ 0 & \sigma^2_{\beta_1}\end{pmatrix}$$

where I_{ijk} is an indicator variable taking the value *0.5* if *k* = *I* and *-0.5* if *k* = *C*, X_{ijk} is a vector of covariate affecting the baseline incidence rate, Z_{ijk} is a vector of covariates affecting the intervention effect. For the sake of clarity, we have separated the covariates affecting the baseline incidence rate from those affecting the intervention effect. Notice, however, that X_{ijk} and Z_{ijk} may contain the same covariates. In this model, one makes the assumption that the residual variance of the log(IR) is the same in the control and intervention groups [22]. Observe that $\beta_{0i} - \frac{1}{2}\beta_{1i}$ represents the residual log(IR) in the control group and $\beta_{0i} + \frac{1}{2}\beta_{1i}$ the residual log(IR) in the intervention group in study *i*. Therefore, β_{1i} is the residual log(IRR) in study *i* and β_1 the mean residual log(IRR) across the 10 studies. The vector of parameters γ measures the change in baseline log(IR) associated with a one-unit change of X_{ijk}, whereas θ allows one to account for a differential effect of the intervention according to the covariates contained in Z_{ijk}. Finally, $\sigma^2_{\beta_0}$ captures the residual baseline log(IR) heterogeneity, whereas $\sigma^2_{\beta_1}$ measures the residual heterogeneity of the intervention effect.

The likelihood function writes:

$$\prod_{i=1}^{10} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \left[\left(\prod_{j \in D} \prod_{k \in \{C,I\}} P(Y_{ijk}|\lambda_{ijk}, \beta_{0i}, \beta_{1i}) \right) \phi(\beta_{0i}, \beta_{1i}|\, \beta, \Omega) \right] d\beta_{0i} d\beta_{1i}$$

where *D* = {benign, borderline, malignant}, $P(Y_{ijk}|\lambda_{ijk}, \beta_{0i}, \beta_{1i})$ is the Poisson density with mean $\lambda_{ijk} = \mu_{ijk} * t_{ijk}$, and $\phi(\beta_{0i}, \beta_{1i}|\, \beta, \Omega)$ is the bivariate normal density with mean β and variance-covariance matrix Ω.

3.1.2. Bivariate Modelling

In the bivariate approach, the log incidence rates of events are modelled separately for the intervention and control arms and the variances of the residuals log(IR) for the control and intervention groups are allowed to be different. Therefore, the bivariate Re-Poi model is given by:

$$Y_{ijC}|\lambda_{ijC} \sim Poisson(\lambda_{ijC})$$

$$\lambda_{ijC} = \mu_{ijC} * t_{ijC}$$

$$\log(\mu_{ijC}) = \alpha_{iC} + \gamma' * X_{ijC} + \theta'_C * Z_{ijC}$$

$$Y_{ijI}|\lambda_{ijI} \sim Poisson(\lambda_{ijI})$$

$$\lambda_{ijI} = \mu_{ijI} * t_{ijI}$$

$$\log(\mu_{ijI}) = \alpha_{iI} + \gamma' * X_{ijI} + \theta'_I * Z_{ijI}$$

$$\begin{pmatrix}\alpha_{iC}\\ \alpha_{iI}\end{pmatrix} \sim N[\alpha, \Omega], \alpha = \begin{pmatrix}\alpha_C\\ \alpha_I\end{pmatrix}, \Omega = \begin{pmatrix}\sigma^2_C & \sigma_{CI}\\ \sigma_{CI} & \sigma^2_I\end{pmatrix}$$

where X_{ijI} and Z_{ijI} are defined as in the univariate Re-Poi model. Note that α_{iC} represents the residual log(IR) in the control group of study *i* and α_{iI} the residual log(IR) in the intervention group of study *i*. Therefore, $\alpha_{iI} - \alpha_{iC}$ is the residual log(IRR) in study *i* and $\alpha_I - \alpha_C$ the mean residual log(IRR) across the studies. Again, X_{ijk} contains the covariates affecting the baseline incidence, whereas Z_{ijk} contains those affecting the intervention effect. This bivariate model is more flexible than the univariate since it allows estimating two distinct variance parameters (σ^2_C, σ^2_I). Moreover, the covariance (σ_{CI}) links the two processes.

The likelihood is given by

$$\prod_{i=1}^{10} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \left[\left(\prod_{j \in D} \prod_{k \in \{C,I\}} P(Y_{ijk}|\lambda_{ijk}, \alpha_{iC}, \alpha_{iI}) \right) \phi(\alpha_{iC}, \alpha_{iI}|\, \alpha, \Omega) \right] d\alpha_{iC} d\alpha_{iI}$$

where $P(Y_{ijk}|\lambda_{ijk}, \alpha_{iC}, \alpha_{iI})$ is the Poisson density, $\phi(\alpha_{iC}, \alpha_{iI}|\, \alpha, \Omega)$ denotes the bivariate normal density with mean α and variance-covariance matrix Ω.

3.2. The Random-Effects Negative-Binomial Model

3.2.1. Univariate Modelling

To obtain a Negative-binomial model [18], one can introduce over-dispersion into the Re-Poi model by including a random multiplicative coefficient ν_i in the expression of the mean/variance parameter: $\lambda_{ijk} = \mu_{ijk} * t_{ijk} * \nu_i$, where $\nu_i \sim \text{Gamma}\left(\frac{1}{\eta}, \eta\right)$ (i.e. a one parameter Gamma distribution with unit mean and variance η, $\eta > 0$). With $Y_{ijk}|\lambda_{ijk} \sim Poisson(\lambda_{ijk})$, it can be shown that the marginal expectation $E(Y_{ijk}) = \lambda_{ijk}$ and marginal variance $Var(Y_{ijk}) = \lambda_{ijk}(1 + \eta\lambda_{ijk})$, thereby allowing the variance to differ from the mean. Consequently, the univariate Re-NB model is given by:

$$Y_{ijk}|\lambda_{ijk} \sim Poisson(\lambda_{ijk})$$

$$\lambda_{ijk} = \mu_{ijk} * t_{ijk} * \nu_i$$

$$\log(\mu_{ijk}) = \beta_{0i} + \beta_{1i} * I_{ijk} + \gamma' * X_{ijk} + \theta' * Z_{ijk} * I_{ijk}$$

$$\begin{pmatrix}\beta_{0i}\\ \beta_{1i}\end{pmatrix} \sim N[\beta, \Omega], \beta = \begin{pmatrix}\beta_0\\ \beta_1\end{pmatrix}, \Omega = \begin{pmatrix}\sigma^2_{\beta_0} & 0\\ 0 & \sigma^2_{\beta_1}\end{pmatrix}, \nu_i \sim \Gamma\left(\frac{1}{\eta}, \eta\right)$$

and the likelihood writes:

$$\prod_{i=1}^{10} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \left\{ \left[\prod_{j \in D} \prod_{k \in \{C,I\}} \int_{-\infty}^{+\infty} \left(P(Y_{ijk}|\lambda_{ijk}, \beta_{0i}, \beta_{1i}, \nu_i) \right. \right. \right.$$
$$\left. \left. \left. \Gamma(\nu_i|1/\eta, \eta) \right) d\nu_i \right] \phi(\beta_{0i}, \beta_{1i}|\beta, \Omega) \right\} d\beta_{0i} d\beta_{1i}$$

where $P(Y_{ijk}|\lambda_{ijk}, \beta_{0i}, \beta_{1i}, \nu_i)$ is the Poisson density, $\Gamma(\nu_i|1/\eta, \eta)$ is the Gamma density with mean 1 and variance η, $\phi(\beta_{0i}, \beta_{1i}|\beta, \Omega)$ is the bivariate Normal density with mean β and variance-covariance matrix Ω.

3.2.2. Bivariate Modelling

The bivariate Re-NB model is similar in structure to the bivariate Re-Poi model, except for the addition of the over-dispersion terms ν_{iC} and ν_{iI}:

$$Y_{ijC}|\lambda_{ijC} \sim Poisson(\lambda_{ijC})$$

$$\lambda_{ijC} = \mu_{ijC} * t_{ijC} * \nu_{iC}$$

$$\log(\mu_{ijC}) = \alpha_{iC} + \gamma' * X_{ijC} + \theta'_C * Z_{ijC}$$

$$Y_{ijI}|\lambda_{ijI} \sim Poisson(\lambda_{ijI})$$

$$\lambda_{ijT} = \mu_{ijI} * t_{ijI} * \nu_{iI}$$

$$\log(\mu_{ijI}) = \alpha_{iI} + \gamma' * X_{ijI} + \theta'_I * Z_{ijI}$$

$$\begin{pmatrix}\alpha_{iC}\\ \alpha_{iI}\end{pmatrix} \sim N[\alpha, \Omega], \alpha = \begin{pmatrix}\alpha_C\\ \alpha_I\end{pmatrix}, \Omega = \begin{pmatrix}\sigma^2_C & \sigma_{CI}\\ \sigma_{CI} & \sigma^2_I\end{pmatrix}$$

$$\nu_{iC} \sim \Gamma\left(\frac{1}{\eta_C}, \eta_C\right), \nu_{iI} \sim \Gamma\left(\frac{1}{\eta_I}, \eta_I\right)$$

The likelihood is given by:

$$\prod_{i=1}^{10} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \left\{ \left[\prod_{j \in D} \prod_{k \in \{C,I\}} \int_{-\infty}^{+\infty} \left(P(Y_{ijk}|\lambda_{ijk}, \alpha_{iC}, \alpha_{iT}, \nu_{ik}) \right. \right. \right.$$
$$\left. \left. \left. \Gamma(\nu_{ik}|1/\eta_k, \eta_k) \right) d\nu_{ik} \right] \phi(\alpha_{iC}, \alpha_{iI}|\alpha, \Omega) \right\} d\alpha_{iC} d\alpha_{iI}$$

where $P(Y_{ijk}|\lambda_{ijk}, \alpha_{iC}, \alpha_{iT}, \nu_{ik})$ is the Poisson density, $\Gamma(\nu_{ik}|1/\eta_k, \eta_k)$ is the Gamma density with mean 1 and variance η_k ($k = I, C$), $\phi(\alpha_{iC}, \alpha_{iI}|\alpha, \Omega)$ is the bivariate Normal density with mean α and variance-covariance matrix Ω. Close inspection of the likelihood function reveals that the bivariate Re-NB model allows not only two distinct variances to be estimated (i.e. one for each arm), but also two distinct over-dispersion parameters (η_C, η_I), which makes this model more flexible than the more commonly-used bivariate Re-Poi model.

4. NUMERICAL ANALYSES

All the numerical analyses were conducted using Stata/IC 15.1 [23]. We used the command mepoisson to fit both Re-Poi models, menbreg to fit the univariate Re-NB model, and gsem to fit the bivariate Re-NB model. To integrate the likelihood, we used the mean-variance adaptive Gauss-Hermite quadrature method with seven integration points (the default implementation in Stata). We set the maximum number of iterations at 1001.

4.1. Specifications of the Log Incidence Rate

For the univariate Re-Poi and the univariate Re-NB models, we considered the following log(IR) specification:

$$\log(\mu_{ijk}) = \beta_{0i} + \beta_{1i} * I_{ijk} + \beta_2 * M_{ijk} + \beta_3 * I_{ijk} * M_{ijk}$$

where M_{ijk} is an indicator for malignant tumors taking the value 1 for malignant and 0 otherwise and I_{ijk} is defined as in Section 3. The focus was on estimating the mean intervention effect for non-malignant tumors ($E(\beta_{1i}) \equiv \log IRR$), the residual heterogeneity of the intervention effect ($Var(\beta_{1i}) \equiv \sigma^2_{\log IRR}$), and the difference in the mean intervention effects between malignant and non-malignant tumors ($\beta_3 \equiv \Delta_{\log IRR}$).

For the bivariate models, we considered the following specifications for the log(IR):

$$\log(\mu_{ijC}) = \alpha_{iC} + \gamma_C * M_{ijC}$$

$$\log(\mu_{ijT}) = \alpha_{iT} + \gamma_T * M_{ijT}$$

Again, parameters of interest were the mean intervention effect for non-malignant tumors ($E(\alpha_{it} -$

$\alpha_{ic}) \equiv \log IRR$), the residual heterogeneity of the intervention effect ($Var(\alpha_{it} - \alpha_{ic}) \equiv \sigma^2_{\log IRR}$) and the difference in the mean intervention effect between malignant and non-malignant tumors ($\gamma_T - \gamma_C \equiv \Delta_{\log IRR}$).

4.2. Application to the Surgical Management of Phyllodes Tumors

Table **2** reports the results obtained by fitting the four models described in Section 3 to the data presented in Table **1**. Changing from the univariate to the bivariate framework had a smaller effect on the estimates obtained by the Re-Poi model than on those obtained by the Re-NB model.

For each model, the estimated effect of a margin of resection above 10mm was a reduction of the rate of local recurrence for non-malignant tumors (i.e. all estimates of $\log IRR$ were below zero). This reduction was larger for the Re-NB models, with the largest reduction estimated by the univariate model. Estimations of the residual heterogeneity of the intervention effect by both Re-Poi models were around 0.4, whereas the Re-NB models provided values close to zero for this parameter (the univariate Re-NB model even found an absence of residual heterogeneity).

With the two Re-Poi models, estimates of the impact of the margin was greater for malignant tumors (i.e. $\widehat{\Delta}_{\log IRR} < 0$), whereas with the Re-NB models the opposite result was obtained. While with the univariate Re-NB model it was still found that the margin above 10mm reduced the rate of local recurrences of malignant tumors, this was not the case anymore with the bivariate model (i.e. the estimated coefficients of $\log IRR$ and $\Delta_{\log IRR}$ cancelled each other out).

4.3. Simulations

To identify the best fitting model from Section 3, we conducted Monte-Carlo simulations that were calibrated in order to mimic the data from the studies selected in the systematic review on phyllodes tumors (Table **1**). The number of events were generated according to the bivariate Re-NB model described in Subsection 3.2.2. We set the parameters of this model in order to investigate four different scenarios (see Table **3** below). The first scenario used values closed to the estimates obtained when fitting the model on the example dataset. This was our baseline scenario, from which we derived the three others. Scenario 2 corresponded to a Poisson framework with no over-dispersion, scenario 3 was devised to study the impact of having a large amount of residual heterogeneity of the intervention effect, whereas the last scenario investigated the situation with no mean intervention effect.

For each scenario, we simulated $N = 1000$ datasets. Performance of each model was assessed by the median relative bias (i.e. relative difference between the median estimate and the true parameter's value), and coverage rate and median width of the 95% Wald confidence intervals (CIs) obtained for the three

Table 2: Estimation of the Three Parameters of Interest in the Illustrative Example Dataset

Model	$\log IRR$	$\sigma^2_{\log IRR}$	$\Delta_{\log IRR}$
Univariate Re-Poi	-0.27 (-1.15; 0.61)	0.40 (0.02 ; 7.35)	-0.33 (-1.58 ; 0.91)
Bivariate Re-Poi	-0.33 (-1.36 ; 0.70)	0.45 (0.02 ; 8.25)	-0.32 (-1.57 ; 0.92)
Univariate Re-NB	-0.58 (-1.66 ; 0.50)	0 (.)	0.24 (-1.70 ; 2.18)
Bivariate Re-NB	-0.48 (-1.61 ; 0.64)	0.02 (0.01 ; 0.03)	0.48 (-1.52 ; 2.48)

Note: 95% Wald confidence intervals are provided between parentheses. $\log IRR$ = mean intervention effect for the non-malignant tumors (i.e. impact of margin ≥ 10mm vs margin < 10mm); $\sigma^2_{\log IRR}$ = residual heterogeneity of the intervention effect; $\Delta_{\log IRR}$ = difference in the mean intervention effect between malignant and non-malignant tumors.

Table 3: Value of the Different Parameters under the Four Simulated Scenarios

Scenarios	η_C	η_I	α_C	α_I	γ_C	γ_I	σ^2_C	σ^2_I	σ_{CI}
1) Baseline	0.45	1.65	-6.5	-7	0.9	1.4	0.40	0.25	0.30
2) No over-dispersion	**0**	**0**	-6.5	-7	0.9	1.4	0.40	0.25	0.30
3) Large residual heterogeneity	0.45	1.65	-6.5	-7	0.9	1.4	**1.60**	**1.00**	0.30
4) No mean intervention effect	0.45	1.65	-6.5	**-6.5**	0.9	**0.9**	0.40	0.25	0.30

Note: η_k, α_k, γ_k, σ^2_k and σ_{CI}, for k = *C*, *I*, correspond to the parameters of the bivariate Re-NB model described in Subsection 3.2.2. Values in bold represent changes compared to the baseline scenario.

parameters of interest (i.e. the mean intervention effect for non-malignant tumors $\log IRR$, the residual heterogeneity of the intervention effect $\sigma^2_{\log IRR}$, and the difference in mean intervention effect between malignant vs non-malignant tumors $\Delta_{\log IRR}$). We decided to compute the median instead of the mean for the bias and CI's width to avoid the influence of exceedingly large or small values obtained in some simulations. Since the numerical algorithm used to estimate the different models sometimes failed to converge, we also reported the proportion of converged runs achieved by each model.

4.3.1. Scenario 1: Baseline

The baseline scenario corresponded to the situation with moderate mean intervention effect for non-malignant tumors ($\log IRR = -0.5$), moderate difference in mean intervention effect between malignant and non-malignant tumors ($\Delta_{\log IRR} = 0.5$) and small residual heterogeneity of the intervention effect ($\sigma^2_{\log IRR} = 0.05$). Results for this scenario are displayed in Table **4**. Overall, the univariate and bivariate versions of the Re-Poi model provided more similar results than the two versions of the Re-NB models. Moreover, these latter ran into more convergence issues.

The bivariate Re-NB models provided the best estimates for the mean intervention effect for non-malignant tumors; biases were lower and coverage rates closer to nominal (i.e. 95%). Regarding the estimation of the mean intervention effect between malignant and non-malignant tumors, all the models obtained small relative bias but only the bivariate Re-NB model's CIs provided acceptable coverage rates (91.14%). The model that performed the best for the estimation of the intervention's residual heterogeneity parameter was again the bivariate Re-NB model (although the relative bias was almost 300%). Coverage rates for this parameter were much too low whatever the model considered.

4.3.2. Scenario 2: No Over-dispersion

In the scenario without over-dispersion, all the models tended to encounter more numerical issues than under the scenario 1, especially the bivariate Re-NB model whose proportion of converged runs was below 10% (Table **5**). Again the bivariate Re-NB model provided the best estimate for the mean intervention effect for non-malignant tumors (relative bias < 5%). However, the CIs provided by this model for this parameter were too conservative. For the residual heterogeneity parameter, the bivariate Re-Poi model was the only one to obtain unbiased estimates but its CIs displayed the lowest coverage rates (15%). Compared to scenario 1, coverage rates obtained for parameter $\Delta_{\log IRR}$ was now satisfactory for all models.

4.3.3. Scenario 3: Large Residual Heterogeneity

With large residual heterogeneity ($\sigma^2_{\log IRR} = 2$; Table **6**), biases in the mean intervention effect for non-malignant tumors and difference in mean intervention effect estimates were more or less similar to those obtained in the baseline scenario (i.e. Scenario 1; Table **4**). However, coverage rates tended to be lower and confidence intervals wider. Regarding the estimate of the residual heterogeneity parameter, both Re-NB models underestimated this parameter (median relative bias = -63.77% for the univariate model and -30.90% for the bivariate one), whereas the

Table 4: Models Performances under Scenario 1

True para-meter value	Model	Estimate	Relative bias (in %)	Coverage rate (in %)	CI's width	Converged runs (in %)
$\log IRR = -0.5$	Uni Re-Poi	-0.68	-35.15	87.14	2.21	77.0
	Bi Re-Poi	-0.78	-55.24	84.21	2.24	85.4
	Uni Re-NB	-0.64	-27.90	91.91	2.20	59.2
	Bi Re-NB	-0.57	-13.77	94.76	2.49	55.3
$\sigma^2_{\log IRR} = 0.05$	Uni Re-Poi	1.02	1936.65	23.12	6.07	77.0
	Bi Re-Poi	1.02	1933.33	9.94	5.03	85.4
	Uni Re-NB	0.41	722.40	47.05	3.43	59.2
	Bi Re-NB	0.20	295.24	4.34	0.12*	55.3
$\Delta_{\log IRR} = 0.5$	Uni Re-Poi	0.46	-8.63	68.05	2.28	77.0
	Bi Re-Poi	0.49	-2.81	66.67	2.22	85.4
	Uni Re-NB	0.48	-3.46	89.54	3.22	59.2
	Bi Re-NB	0.48	-4.98	91.14	3.43	55.3

Note: Median values are provided for the estimate and CI's width. Confidence intervals were computed using the Wald method.
*Percentage value.

Table 5: Models Performances under Scenario 2

True para-meter value	Model	Estimate	Relative bias (in %)	Coverage rate (in %)	CI's width	Converged runs (in %)
$\log IRR = -0.5$	Uni Re-Poi	-0.54	-7.36	97.10	1.53	20.7
	Bi Re-Poi	-0.54	-7.12	95.40	1.36	54.4
	Uni Re-NB	-0.56	-12.06	94.68	1.29	79.0
	Bi Re-NB	-0.48	4.94	100	1.61	8.8
$\sigma^2_{\log IRR} = 0.05$	Uni Re-Poi	0.17	239.88	85.99	3.84	20.7
	Bi Re-Poi	0.05	6.04	15.07	0.04*	54.4
	Uni Re-NB	0.24	372.99	46.71	1.05	79.0
	Bi Re-NB	0.17	245.45	37.50	0.63	8.8
$\Delta_{\log IRR} = 0.5$	Uni Re-Poi	0.50	0.44	96.62	1.86	20.7
	Bi Re-Poi	0.50	-0.02	95.59	1.72	54.4
	Uni Re-NB	0.51	1.14	95.32	1.71	79.0
	Bi Re-NB	0.41	-18.26	97.73	1.98	8.8

Note: Median values are provided for the estimate and CI's width. Confidence intervals were computed using the Wald method.
*Percentage value.

Re-Poi models overestimated it (median relative bias around 30%). All CIs obtained for this parameter were wider than those obtained in the baseline scenario, which improved all models' coverage rates, especially for the univariate Re-Poi and Re-NB models, which obtained values close to nominal.

4.3.4. Scenario 4: No Mean Intervention Effect

The last scenario investigated was that of an intervention with a null average effect for both malignant and non-malignant tumors (i.e. $\log IRR = 0$ and $\Delta_{\log IRR} = 0$). Results obtained under this scenario are provided in Table **7**. They were virtually identical to those obtained under the scenario of efficient intervention for non-malignant tumors and non-efficient for malignant tumors (i.e. the baseline scenario; Table **4**). The bivariate Re-NB model again provided the most reliable results for estimating the mean intervention effect for non-malignant tumors and the difference in mean intervention effect between malignant and non-malignant tumors. However, it also encountered more numerical issues. As for the residual heterogeneity parameters, all models provided poor estimates.

5. DISCUSSION

In meta-analysis of IR data, the classical inverse-variance weighting method fails to provide valid estimates when the event rate is low. One possible solution is to use the MH method, but it is only valid

Table 6: Models Performances under Scenario 3

True para-meter value	Model	Estimate	Relative bias (in %)	Coverage rate (in %)	CI's width	Converged runs (in %)
$\log IRR = -0.5$	Uni Re-Poi	-0.86	-71.15	84.03	2.83	91.4
	Bi Re-Poi	-0.85	-69.42	83.97	2.99	94.8
	Uni Re-NB	-0.82	-64.96	84.74	2.84	67.5
	Bi Re-NB	-0.53	-6.98	89.03	2.98	69.3
$\sigma^2_{\log IRR} = 2$	Uni Re-Poi	2.57	28.49	93.44	9.68	91.4
	Bi Re-Poi	2.62	31.00	80.06	9.94	94.8
	Uni Re-NB	0.72	-63.77	96.30	4.49	67.5
	Bi Re-NB	1.38	-30.90	30.30	0.59*	69.3
$\Delta_{\log IRR} = 0.5$	Uni Re-Poi	0.48	-3.24	66.19	2.25	91.4
	Bi Re-Poi	0.51	1.85	64.45	2.24	94.8
	Uni Re-NB	0.51	1.69	89.19	3.69	67.5
	Bi Re-NB	0.57	14.09	90.19	3.71	69.3

Note: Median values are provided for the estimate and CI's width. Confidence intervals were computed using the Wald method.
*Percentage value.

Table 7: Models Performances under Scenario 4

True para-meter value	Model	Estimate	Relative bias (in %)	Coverage rate (in %)	CI's width	Converged runs (in %)
$\log IRR = 0$	Uni Re-Poi	-0.18	-	86.29	2.09	81.7
	Bi Re-Poi	-0.24	-	83.33	2.14	86.8
	Uni Re-NB	-0.15	-	91.09	2.14	60.6
	Bi Re-NB	-0.10	-	93.53	2.38	58.7
$\sigma^2_{\log IRR} = 0.05$	Uni Re-Poi	1.00	1905.72	20.44	5.81	81.7
	Bi Re-Poi	1.04	1970.04	11.15	4.81	86.8
	Uni Re-NB	0.41	710.59	46.70	3.36	60.6
	Bi Re-NB	0.21	312.32	4.60	0.1*	58.7
$\Delta_{\log IRR} = 0$	Uni Re-Poi	-0.06	-	65.73	2.13	81.7
	Bi Re-Poi	-0.10	-	64.02	2.06	86.8
	Uni Re-NB	-0.02	-	89.93	3.22	60.6
	Bi Re-NB	0.03	-	92.33	3.35	58.7

Note: Median values are provided for the estimate and CI's width. Confidence intervals were computed using the Wald method.
*Percentage value.

under the assumption of a homogeneous intervention effect and it fails to include the information contained in DZ and SA studies. In this paper, we investigated the use of the univariate and bivariate Re-NB models to conduct a meta-analysis of heterogeneous incidence rates, in the presence of rare events and SA studies. Through simulations calibrated to mimic a real clinical dataset, we compared the performance of these two models to that of the univariate and bivariate Re-Poi models, which are based on the restrictive assumption of equi-dispersion.

The use of the Re-Poi model for the meta-analysis of IR data is not new and has already been discussed in the literature. For example, Spittal, Pirkis, and Gurrin showed that the univariate Re-Poi model generally outperformed the DerSimonian and Laird method, notably when the number of SZ or DZ studies was high [16]. Stijnen, Hamza, and Özdemir investigated the bivariate Poisson modelling [17]. However, we did not find any published study investigating the use of either the univariate or bivariate Re-NB models for the meta-analysis of IR data in the context of a heterogeneous intervention effect with both rare events and SA studies.

We found larger discrepancies between the univariate and bivariate versions of the Re-NB model than between the univariate and bivariate Re-Poi models. This suggested that taking into account a difference of over-dispersions between the intervention and control arms (i.e. $\eta_T \neq \eta_C$) was more crucial than taking into account a difference between the residuals heterogeneity of the log(IR) (i.e. $\sigma_T^2 \neq \sigma_C^2$).

Overall, we found that except for the scenario of no over-dispersion where all models yielded similar results, the univariate and bivariate Re-NB models were more performant than the univariate and bivariate Re-Poi models. This result was by no means obvious, given the greater complexity of the Re-NB models, which comprise more parameters to be estimated than the Re-Poi models, and the particular settings considered of rare events with many SZ, DZ, and SA studies.

Regarding the estimation of the mean intervention effect for non-malignant tumors (i.e. $\log IRR$), the bivariate Re-NB model was the only model to provide acceptable bias (never larger than 14% of the true parameter's value) and coverage rates (most of the time above 90%) across all scenarios. Due to extreme scarcity of the data (i.e. very few events and studies), results obtained for the residual heterogeneity of the intervention effect (i.e. $\sigma^2_{\log IRR}$) were poor across all scenarios investigated and whatever the model considered. Finally, biases in the difference in mean intervention effect parameter (i.e. $\Delta_{\log IRR}$) were acceptable and approximately the same for the four models, across the four scenarios investigated. Nevertheless, both Re-NB models provided CIs for this parameter with better coverage rates than the Re-Poi models.

To sum up, in settings of rare events, intervention effect heterogeneity, and SA studies, we highly recommend the use of the Re-NB models for the meta-analysis of incidence rate data. Indeed, count data often exhibit over-dispersion (as groups of individuals considered are heterogeneous and there are many unmeasured risk factors) and we showed that these models performed better than the univariate and bivariate Re-Poi models. Under the simulated scenario of equi-dispersion, the Re-NB models

provided similar results as the Re-Poi models. We would furthermore recommend the bivariate Re-NB model, as it allows more flexibility in modelling the IRs than its univariate counterpart.

Nevertheless, there are two limitations worth mentioning. First, convergence might be more difficult to achieve with the bivariate Re-NB model (i.e. proportion of converged runs achieved by this model was often below 60%, whereas it was most of the time above 80% for both Re-Poi models). We believe that convergence rates can be improved by selecting better starting values, which could be provided by the estimation of a less complex model such as the bivariate Re-Poi. Another solution could be to choose a conjugate distribution for the random effects to obtain a closed-form likelihood, which would be easier to maximize [24].

Second, results obtained for the residual heterogeneity parameter were poor, whatever the scenario considered. Notice that our simulations were calibrated to mimic a real clinical dataset where not only events were rare, but also few studies were included in the meta-analysis. Gathering more studies might improve the situation. Nevertheless, even the most sophisticated statistical method cannot compensate for extreme scarcity of the data and absence of information. A Bayesian approach could be adopted, but it is well known that in the setting of rare events, the selection of priors matters and results are subjective [25-26]. Still another option could be to investigate the use of Zero-Inflated models [27]. Finally, to improve the CIs obtained for this parameter, one could consider using the profile likelihood method [28] instead of the Wald method

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CONFLICT OF INTEREST

None declared.

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