



Efthimiou, O., Rücker, G., Schwarzer, G., Higgins, J., Egger, M., & Salanti, G. (2019). Network meta-analysis of rare events using the Mantel-Haenszel method. *Statistics in Medicine*, 38(16), 2992-3012. <https://doi.org/10.1002/sim.8158>

Peer reviewed version

Link to published version (if available):
[10.1002/sim.8158](https://doi.org/10.1002/sim.8158)

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Network meta-analysis of rare events using the Mantel-Haenszel method

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Abstract

The Mantel-Haenszel method has been used for decades to synthesize data obtained from studies that compare two interventions with respect to a binary outcome. It has been shown to perform better than the inverse-variance method or Peto's odds ratio when data is sparse. Network meta-analysis (NMA) is increasingly used to compare the safety of medical interventions, synthesising for example data on mortality or serious adverse events. In this setting, sparse data occur often and yet there is to-date no extension of the Mantel-Haenszel method for the case of NMA. In this paper we fill this gap by presenting a Mantel-Haenszel NMA method for odds ratios. Similarly to the pairwise Mantel-Haenszel method, we assume common treatment effects. We implement our approach in R, and we provide freely available, easy-to-use routines. We illustrate our approach using data from two previously published networks. We compare our results to those obtained from three other approaches to NMA: NMA with non-central hypergeometric likelihood, an inverse-variance NMA and a Bayesian NMA with a binomial likelihood. We also perform simulations to assess the performance of our method and compare it with alternative methods. We conclude that our Mantel-Haenszel NMA method offers a reliable approach to the network meta-analysis of binary outcomes, especially in the case of sparse data, and when the assumption of methodological and clinical homogeneity is justifiable.

1 Introduction

Meta-analysing studies with rare binary outcomes can be methodologically challenging, especially when some of the studies report zero events in one or both treatment arms. The inverse-variance method, assuming a common-effects (“fixed-effects”) or random-effects¹, is the most widely used approach to pairwise meta-analysis². The method requires estimates of a relative treatment effect from each study along with a standard error. For the case of binary outcomes the approach employs approximations that do not perform well when event rates are low and/or the sample sizes of the included studies are small. If studies report zero events in one of their arms, the basic formulae cannot be used to estimate odds ratios, risk ratios and their standard errors because the calculations involve division by zero. A simple way to overcome this problem is to add a fixed number (e.g. 0.5) to the number of events and non-events of all treatment arms in studies that report zero events in one of their arms; studies with zero events in both arms are usually excluded from the analysis. This so-called ‘continuity correction’ bypasses the problem of zero events, and allows the use of the inverse variance method. However, it has been shown that this approach leads to bias in estimated effects³. Sweeting et al. suggested a flexible approach, where the continuity correction is adapted to each study, and showed that such corrections performed better than fixed ones⁴. However, the use of any type of continuity correction has been criticized because data are imputed and because the – essentially arbitrary – choice of the correction may bias results^{5,6}.

Another approach to address this problem is to use the risk difference instead of odds or risk ratios. The risk difference can readily be estimated in the presence of zero events. Unfortunately, as shown in simulations by Bradburn et al.³ *“all risk difference methods yield very conservative confidence interval coverage when events are rare, and have associated poor statistical power, which make them unsuitable for meta-analysis of rare events”*. Alternative methods have been proposed, including the use of the arcsine difference⁷, an exact method combining confidence intervals⁸, beta-binomial models⁶ etc; for a short review see a recent paper by Efthimiou⁹.

The Mantel-Haenszel (MH) method is a popular approach to meta-analysing binary outcomes¹⁰. It has been formulated for the case of odds ratios, risk ratios and risk differences. Estimating MH odds-ratios does not require a continuity correction for the case of studies with zero events in one of their arms, unless all studies in the dataset have zero events for the same treatment. Meta-analysis using the MH odds-ratio has been shown to outperform the inverse variance method when events are rare³. Note that using the MH method we exclude studies with zero events in all treatment arms. This has been criticised, because such studies may carry information through their sample size⁶. Another popular approach to meta-analysing rare binary outcomes is Peto’s odds ratio¹¹. This method has been shown to work well when specific conditions are met (event rates are less than 1%, treatment groups are balanced and relative effects are not very large)^{3,4}.

Network meta-analysis (NMA) is an extension of pairwise meta-analysis for the case when studies compare multiple treatments¹²⁻¹⁶. The frequentist approaches that are usually employed for

fitting a NMA follow the inverse-variance method. Thus, they are expected to perform poorly when event rates are low. Bayesian approaches to NMA that utilize the exact binomial likelihood of the data¹⁷ are also widely used¹⁸. However, when data are sparse, the choice of prior distributions for a Bayesian NMA becomes very important, and distributions that are thought to be “uninformative” or “vague” may strongly influence results¹⁹. This problem may be even more pronounced for the case of priors for heterogeneity in a random-effects meta-analysis²⁰. Including informative priors in the analysis may help overcoming such issues. Stijnen et al. proposed an alternative approach to NMA of sparse data, based on a non-central hypergeometric function¹⁹. Higgins and Whitehead proposed an extension of Peto’s method for NMA²¹. This method, however, will have the same limitations as Peto’s pairwise meta-analysis.

In this paper we introduce a MH-NMA method for odds ratios, which can be of particular value when event rates are low. We implement our method in the **netmeta** package in R. In order to illustrate our approach we re-analyze data from two previously published NMAs. We also perform simulations to assess the performance of our method in comparison with alternative NMA methods.

2 Illustrative data from published networks

In this section we briefly describe two datasets that we use to illustrate the methods we present in this paper.

2.1 Inhaled medications for patients with chronic obstructive pulmonary disease

The first dataset comes from a review that compared the safety of inhaled medications in patients with chronic obstructive pulmonary disease²². The outcome we focus on is mortality. The available data included 41 randomized trials, with a total of 52462 patients. Mortality was low, with 2408 deaths (4.6%) reported across all studies. There were nine studies that reported zero events in at least one of the treatment arms and three additional studies had zero events in all treatment arms (‘all-zero studies’). The network is depicted in the left panel of Figure 1. The data is given in Section 1 of the Appendix.

2.2 Methods to decrease blood loss and blood transfusion requirements for patients with liver transplantation

The second dataset comes from a review that compared methods for decreasing blood loss and blood transfusion requirements during liver transplantation²³. The outcome we analyse is mortality at 60 days post-transplantation. The network compared seven alternative methods. Fourteen studies reported mortality at 60 days, in 1002 patients. Forty-five deaths were reported across all studies (4.5%). Six studies observed deaths in all treatment arms while three studies did not observe any deaths. The network is depicted in the right panel of Figure 1. Note that one of the treatments in the original dataset (solvent detergent plasma) was only included in one study with zero events in all treatment arms (‘all-zero study’). This treatment was excluded from the network graph.

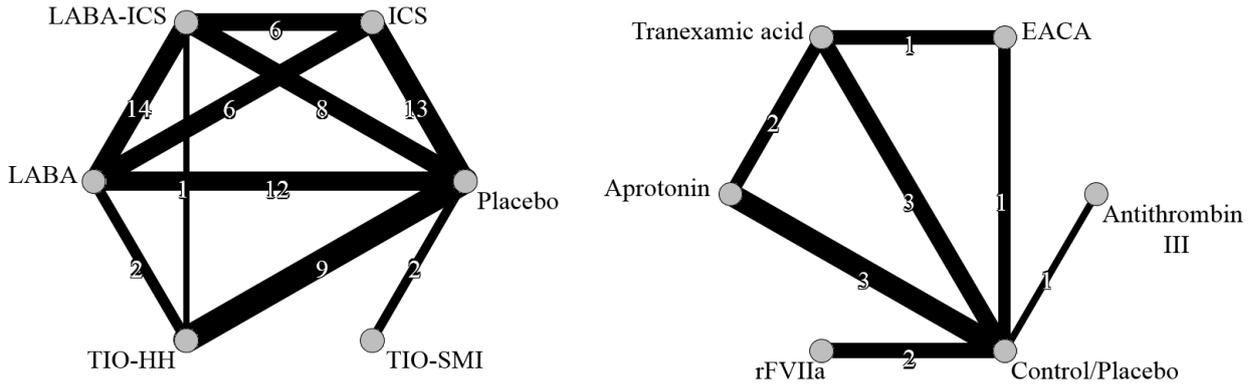


Figure 1. a) inhaled medications in patients with chronic obstructive pulmonary disease. LABA: long-acting $\beta 2$ agonists. ICS: inhaled corticosteroids. TIO-HH: tiotropium dry powder; TIO-SMI: tiotropium solution. b) Methods to prevent blood loss in liver transfusion. EACA: Epsilon amino caproic acid; rFVIIa: recombinant factor VIIa.

The thickness of the lines connecting the treatments is proportional to the inverse standard error of the corresponding treatment effects, based on a Mantel-Haenszel NMA. The numbers on the edges show the number of studies per comparison.

3 Methods

3.1 Mantel-Haenszel network meta-analysis method (MH-NMA)

In this section we describe our method for network meta-analysis using MH odds ratios. The analysis is performed in three stages.

Stage 1: setting up the data

In the first stage we bring the data in an appropriate format for MH-NMA in five steps.

- i. We remove all-zero studies from the dataset. These studies contribute no information to the calculation of MH odds ratios.
- ii. We group studies by design. Here the word “design” is used to denote the treatments being compared in each study²⁴. E.g. a study comparing treatments X and Y is of an XY design, a study comparing X, Y and Z is of an XYZ design, etc.
- iii. Within each design, we search for treatments for which all studies in the design reported zero events, and remove the treatments from the design. For example, if in all XYZW studies there were no events observed in arm Y, we remove the Y arms from these studies. These studies now include information only on X, Z and W. This is required because MH odds-ratios cannot be estimated; however, the design will still be labelled as XYZW. We follow this approach aiming to be consistent with the original idea about how study design may interact with treatment effects²⁴. Quoting from that paper, “...we implicitly assume that different designs (i.e. different sets of included treatments) may serve as a proxy for one or more important effect modifiers”. Note that all these relate to the way we later assess

inconsistency, see Section 3.2 below. Also note that instead of removing these treatment arms, we could use a continuity correction, but as discussed above, this strategy has important limitations. In our software implementation we allow both choices (see section 4.1).

- iv. If designs are left with only one treatment arm after step (iii), we completely remove these designs from the data.
- v. We check the network connectivity. After steps (iii) and (iv) above, there is the chance that the network becomes disconnected (or completely disappear, if all designs are affected). In such cases a NMA cannot be performed in the whole dataset, but only in connected subnetworks.

At the end of this first stage we have a new dataset, typically a subset of the original data, in which all studies are grouped by design

Stage 2: Direct MH meta-analyses per design

At the second stage we synthesise data within each design using the MH meta-analysis method. Note that a total of $T_d(T_d - 1)/2$ different log-odds ratios can be estimated from each design d , where T_d is the number of treatments in this design. For the NMA, however, we only need $T_d - 1$ parameters to be estimated per design²⁵. These parameters can be chosen to be the log-odds ratios of all treatments versus an arbitrary treatment in this design. Thus, at the end of this stage, for each design d we need to obtain a vector $\hat{\boldsymbol{\theta}}_{(d)}$ of MH summary log-odds ratios with dimensions $1 \times (T_d - 1)$ and the corresponding variance-covariance matrix $\mathbf{V}_{(d)}$. $\mathbf{V}_{(d)}$ is a symmetric matrix, with dimensionality $(T_d - 1) \times (T_d - 1)$. Following Lu et al.²⁵, the summary information of this first stage of the analysis can be then written compactly as a vector $\boldsymbol{\theta} = (\hat{\boldsymbol{\theta}}_{(1)}, \hat{\boldsymbol{\theta}}_{(2)}, \dots, \hat{\boldsymbol{\theta}}_{(N_d)})$ and a matrix $\mathbf{V} = \text{diag}(\mathbf{V}_{(1)}, \mathbf{V}_{(2)}, \dots, \mathbf{V}_{(N_d)})$, where N_d is the number of different designs in the network. Thus, the dimensions of $\boldsymbol{\theta}$ are $1 \times \sum_d (T_d - 1)$ and the dimensions of \mathbf{V} are $\sum_d (T_d - 1) \times \sum_d (T_d - 1)$. Estimation of $\hat{\boldsymbol{\theta}}_{(d)}$ and $\mathbf{V}_{(d)}$ is standard when the design has only two arms ($T_d = 2$) and can be performed using already available software (e.g. **metan**²⁶ in Stata or **meta**²⁷ in R). For designs with more than two arms ($T_d > 2$) we employ a generalized MH estimator, as proposed by Greenland²⁸. The details of this estimator are presented below.

Let us assume that in design d there are S_d studies comparing T_d different treatments. Assume that study i provides data in the form of a $(T_d \times 2)$ table, as shown in Table 1. Following Greenland's notation, we define $c_{XYi} = a_{Xi}b_{Yi}/t_{+i}$ and $C_{XY} = \sum_{i=1}^{S_d} c_{XYi}$. In this notation, C_{XY}/C_{YX} corresponds to the usual MH estimator for the comparison X vs. Y, when $T_d = 2$. Mickey and Elashoff suggested that this expression can also be used to estimate odds ratios for $T_d > 2$ ²⁹. Greenland provided an alternative estimator which he showed to have an efficiency advantage²⁸, and this is what we will use here.

Study arm	Events	Non-events	Total
Treatment X	a_{Xi}	b_{Xi}	t_{Xi}
Treatment Y	a_{Yi}	b_{Yi}	t_{Yi}
Treatment Z	a_{Zi}	b_{Zi}	t_{Zi}
...
Total	a_{+i}	b_{+i}	t_{+i}

Table 1. Data available from study i , comparing treatments X, Y, Z, ...

For simplicity, and without loss of generality, let us consider treatment X to be the reference treatment for this design. Then, our goal is to estimate the $T_d - 1$ summary MH log-odds ratios $\hat{\theta}_{(d)} = (\hat{\theta}_{d,XY}, \hat{\theta}_{d,XZ}, \dots)$ and their variance-covariance matrix $\mathbf{V}_{(d)}$. Let us define $L_{XY} = \ln(C_{XY}/C_{YX})$, and $w_{XYi} = (a_{Xi} + b_{Yi})/t_{+i}$. Greenland's estimator is defined as:

$$\hat{\theta}_{d,XY} = \frac{L_{X+} - L_{Y+}}{T_d} \quad (1)$$

where $L_{X+} = \sum_{j=1}^{T_d} L_{Xj}$. This estimator incorporates all data from each $(T_d \times 2)$ table. As an example, for the case of three treatments XYZ, $\hat{\theta}_{d,XY} = (2L_{XY} + (L_{XZ} - L_{YZ}))/3$.

The variance of L_{XY} is $\text{var}(L_{XY}) = U_{XY}$, where

$$U_{XY} = \frac{\sum_{i=1}^{S_d} c_{XYi} w_{XYi}}{2C_{XY}^2} + \frac{\sum_{i=1}^{S_d} c_{XYi} w_{YXi} + c_{YXi} w_{XYi}}{2C_{XY}C_{YX}} + \frac{\sum_{i=1}^{S_d} c_{YXi} w_{YXi}}{2C_{YX}^2} \quad (2)$$

Note that $U_{XY} = U_{YX}$, and thus $\text{var}(L_{XY}) = \text{var}(L_{YX})$. The covariance of L_{XY} and L_{XZ} , when $X \neq Y \neq Z \neq X$ is given by

$$U_{XYZ} = \frac{\sum_{i=1}^{S_d} a_{Xi} b_{Yi} b_{Zi} / t_{+i}^2}{3C_{XY}C_{XZ}} + \frac{\sum_{i=1}^{S_d} t_{Xi} b_{Yi} a_{Zi} / t_{+i}^2}{3C_{XY}C_{ZX}} + \frac{\sum_{i=1}^{S_d} t_{Xi} a_{Yi} b_{Zi} / t_{+i}^2}{3C_{YX}C_{XZ}} + \frac{\sum_{i=1}^{S_d} b_{Xi} a_{Yi} a_{Zi} / t_{+i}^2}{3C_{YX}C_{ZX}} \quad (3)$$

All elements of U_{XYZ} for which $X = Y$ or $X = Z$ are set to zero. Following Greenland's notation, let us also define $U_{XX}^+ = U_{X++} = \sum_{Y,Z} U_{XYZ}$ and $U_{XY}^+ = \sum_J (U_{JXY} - U_{XYJ} - U_{YXJ}) + U_{XY}$, $X \neq Y$. Using these two definitions, the variance of $\hat{\theta}_{d,XY}$ is:

$$\text{var}(\hat{\theta}_{d,XY}) = \frac{U_{X++} - 2U_{XY}^+ + U_{Y++}}{T_d^2} \quad (4)$$

The covariance between two estimates $\hat{\theta}_{d,XY}, \hat{\theta}_{d,XZ}$ is

$$\text{cov}(\hat{\theta}_{d,XY}, \hat{\theta}_{d,XZ}) = \frac{U_{XX}^+ - U_{XZ}^+ - U_{YX}^+ + U_{YZ}^+}{T_d^2} \quad (5)$$

More generally, the covariance between $\hat{\theta}_{d,XY}$ and $\hat{\theta}_{d,WZ}$ is

$$\text{cov}(\hat{\theta}_{d,XY}, \hat{\theta}_{d,WZ}) = \frac{U_{XW}^+ - U_{XZ}^+ - U_{YW}^+ + U_{YZ}^+}{T_d^2} \quad (6)$$

Equations (1), (4) and (5) can be used to estimate $\hat{\theta}_d$ and $\mathbf{V}_{(d)}$, and consequently θ and \mathbf{V} .

Stage 3: synthesis of direct MH odds-ratios across designs assuming consistency

In this stage we start by arbitrarily defining a reference treatment for the network. All treatment contrasts versus this reference treatment are the *basic parameters* of the NMA model. Without loss in generality let us define X to be the reference treatment in the network. Then the relative effects δ_{XY} , δ_{XZ} , ... are the basic parameters of the model. All other relative effects, the *functional parameters*, can be calculated as linear combinations of the basic parameters, e.g. $\delta_{YZ} = \delta_{XZ} - \delta_{XY}$. If the dataset includes a total of T treatments, then there are $T(T - 1)/2$ different treatment contrasts, which can be grouped in a vector $\boldsymbol{\delta}$. From these contrasts, $T - 1$ are the basic parameters ($\boldsymbol{\delta}_{basic}$) and the rest are functional. Following Lu et al.²⁵ we can write $\boldsymbol{\delta} = \mathbf{H}\boldsymbol{\delta}_{basic}$. Matrix \mathbf{H} has elements 1, 0 and -1 and maps the basic parameters into all possible treatment comparisons in the network. \mathbf{H} has dimensions $\frac{T(T-1)}{2} \times (T - 1)$.

Next, we need to define the design matrix \mathbf{X} . This is a matrix with dimensions $\sum_d (T_d - 1) \times (T - 1)$, which describes which treatments are being compared in each design and maps the corresponding comparison into the basic parameters. For additional details on how to setup \mathbf{X} we refer our readers to Lu et al., Section 3.2.1²⁵.

The weighted least squares NMA estimates for the basic parameters are given by $\widehat{\boldsymbol{\delta}}_{basic} = (\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{V}^{-1} \boldsymbol{\theta}$ ³⁰. The corresponding variance-covariance matrix is given by $Cov(\boldsymbol{\delta}_{basic}) = (\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1}$. Finally, the NMA estimates for all treatment effects is given by²⁵:

$$\widehat{\boldsymbol{\delta}} = \mathbf{H}(\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{V}^{-1} \boldsymbol{\theta} \quad (7)$$

with a variance-covariance matrix equal to

$$Cov(\widehat{\boldsymbol{\delta}}) = \mathbf{H}(\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{H}^T \quad (8)$$

3.2 Statistical evaluation of the consistency assumption in MH-NMA

Consistency refers to the (statistical) agreement between the various sources of information in NMA^{24,31}. We employ two approaches for assessing consistency: the first is a global approach (in the whole network), and the second is local (corresponding to each design).

The global method is based on a generalized Cochran's Q statistic, calculated for the whole network as $Q_{inc} = (\boldsymbol{\theta} - \mathbf{X} \widehat{\boldsymbol{\delta}}_{basic})' \mathbf{V}^{-1} (\boldsymbol{\theta} - \mathbf{X} \widehat{\boldsymbol{\delta}}_{basic})$ ³². Under the null hypothesis of consistency, the Q_{inc} statistic follows a chi-squared distribution with $\sum_d (T_d - 1) - T + 1$ degrees of freedom, where T corresponds to the total number of treatments in the network. This statistic can be used to assess inconsistency in the whole network.

In order to identify local inconsistency in the network, we propose a new approach, which shares similarities with the so-called "separate indirect from direct evidence" (SIDE) or "node-splitting" approach³³. In the SIDE approach the focus is on one pairwise comparison at a time, e.g. XY. Following this approach, if there are only two-arm (and no multi-arm) studies comparing X and Y we remove them from the network, and we use them to perform a pairwise meta-analysis. This provides a direct estimate

of the relative treatment effects of X vs. Y. We then perform a NMA on the remaining studies, which provides an indirect estimate for X vs Y. The indirect and direct relative treatments effects are subsequently compared. If there are multi-arm studies in the network that compare X and Y, this approach splits only the corresponding direct estimate. E.g. if there is a three-arm study XYZ, this approach uses the XY estimate in the pairwise meta-analysis of direct effects, and the XZ and YZ estimates in the NMA that estimates the indirect effects.

Although this method works well when all studies are two-arm, it runs into problems for the case when there are multi-arm studies in the network. In the example, the removed XY direct estimate from the multi-arm study will always agree with the indirect estimate obtained from the XZ and ZY estimates of the same study. This might dilute the evidence of inconsistency from the rest of the network. In addition, different choices of the baseline treatment in each study may lead to different estimates regarding the difference between direct and indirect evidence and some practical approaches have been suggested, e.g. see the documentation in the **network**³⁴ command in Stata.

An adaptation that can overcome this problem is to “Separate Indirect from Direct Design Evidence” (SIDDE). Focusing again on XY, we remove all studies that compare these two treatments, both two-arm and multi-arm. Thus, all XY, XYZ, XYZW etc. studies are excluded from the network. The rest of the estimating procedure is the same as in the standard SIDE approach, i.e. we use the excluded studies to estimate the XY effects directly, and the rest of the network to estimate them indirectly. Note that the SIDDE approach shares some similarities with the net heat plot for detecting inconsistency, proposed by Krahn et al.³² Also note that using this approach we can only estimate inconsistency for treatment comparisons for which there is both direct and indirect evidence.

3.3 Software for fitting MH-NMA

We developed a function, `netmetabin`, which is included in the **netmeta** package³⁵ in R³⁶. This function can be used to fit the MH-NMA method presented above. It can also fit NMA with a non-central hypergeometric likelihood using the Breslow approximation, as proposed by Stijnen et al.¹⁹. This approximation is valid when the total number of events is small relative to the group sizes. In that case the non-central hypergeometric distribution can be approximated by a binomial distribution³⁷. We will refer to this approach as NCH-NMA. We have also implemented the SIDDE approach to inconsistency in the (existing) `netsplit` function of R package **netmeta**.

On a technical note, following section 3.1, and more specifically the discussion in step (iii) of Stage 1, the default of `netmetabin` when fitting MH-NMA does not perform any continuity correction when there are designs in which some of the treatment arms had no events. Instead, the arms are excluded from the network. However, the user can override this default by setting argument `cc.pooled` to TRUE and specify a fixed value for the continuity correction (argument `incr`). Note that NCH-NMA can be used in these scenarios without having to remove treatment arms or to use continuity corrections, as long as there are events for all the treatments in the network, irrespective of design.

4 Clinical examples

4.1 Fitting details

We compared the results from our MH-NMA method to three alternative approaches. First, we fitted NCH-NMA, using the R function `netmetabin`. Second, we fitted a common-effects NMA with the usual, inverse-variance approach³⁸, also using `netmetabin`. We will term this method IV-NMA. In order to use this approach we employed a 0.5 continuity correction in studies with zero events in one or more treatment arms. All-zero studies were removed from the dataset. Third, we fitted a common-effect Bayesian NMA model with a binomial likelihood. The Bayesian model was fitted in OpenBUGS³⁹. For all model parameters, i.e. the baseline risk in each study and the true log-odds ratio, we used ‘vague’ prior distributions, $N(0, \sigma^2 = 100)$. We ran 2 chains in parallel, performed 100,000 iterations, and discarded the first 20,000 samples of each chain. We checked convergence using the Brooks-Gelman-Rubin criterion⁴⁰. The code we used for fitting all methods is provided in the Appendix.

4.2 Inhaled medications for patients with chronic obstructive pulmonary disease

Results are shown in the upper part of Table 2. We also fitted random-effects IV-NMA, but between-study variance (τ^2) was estimated to be zero and thus results were identical to the common-effects IV-NMA.

It is clear that all methods give almost identical results. This is due to the fact that even though the event was relatively rare, there were many large studies in the network: the average sample size in the studies was 1280 patients. This resulted in many of the studies having enough events to adequately allow all methods to estimate relative treatment effects between the treatments in the network.

Regarding inconsistency, the Q_{inc} statistic was found to be 8.35 (9 degrees of freedom), corresponding to a p-value of 0.50, thus showing no evidence of global network inconsistency. The SIDDE approach to local inconsistency identified three treatment comparisons that showed some disagreement between direct and indirect estimates; LABA vs. LABA-ICS, LABA vs. TIO-HH and LABA-ICS vs. TIO-HH (p-values 0.02, 0.06 and 0.08 respectively). This in turn might call for a closer examination of the studies that contribute to these particular comparisons, to check for breaches in the transitivity assumption or the appropriateness of the assumption of homogeneity. More specifically, there are two studies comparing LABA vs. TIO-HH, which also contribute to the indirect evidence for LABA vs. LABA-ICS and LABA vs. TIO-HH. These studies may warrant further investigation.

	Treatment	MH-NMA	NCH-NMA	IV-NMA	Bayesian NMA binomial likelihood
Inhaled medications for patients with chronic obstructive pulmonary disease (COPD) ²² <i>Mortality odds ratios compared to placebo [95% Confidence / Credible Intervals]</i>	ICS	1.03 [0.88; 1.21]	1.02 [0.88; 1.19]	1.02 [0.86; 1.19]	1.03 [0.88, 1.21]
	LABA	0.93 [0.79; 1.08]	0.94 [0.81; 1.09]	0.93 [0.79; 1.08]	0.93 [0.79; 1.09]
	LABA-ICS	0.79 [0.67; 0.94]	0.81 [0.69, 0.95]	0.78 [0.66; 0.93]	0.80 [0.67, 0.95]
	TIO-HH	0.92 [0.81; 1.05]	0.93 [0.82; 1.05]	0.92 [0.81; 1.04]	0.92 [0.81; 1.04]
	TIO-SMI	1.52 [1.05; 2.19]	1.50 [1.05; 2.14]	1.50 [1.04; 2.17]	1.52 [1.06; 2.19]
Methods to decrease blood loss and blood transfusion requirements for patients with liver transplantation ²³ <i>Mortality odds ratios compared to control/placebo [95% Confidence / Credible Intervals]</i>	Aprotonin	0.36 [0.13; 0.99]	0.36 [0.14; 0.96]	0.40 [0.15; 1.08]	0.32 [0.11; 0.87]
	EACA	0.74 [0.14; 3.89]	0.77 [0.16; 3.77]	0.81 [0.16; 4.26]	0.71 [0.12; 3.92]
	rFVIIa	1.54 [0.31; 7.53]	1.51 [0.32; 7.17]	1.54 [0.31; 7.53]	1.58 [0.37; 10.42]
	Tranexamic acid	0.77 [0.23; 2.61]	0.81 [0.27; 2.43]	0.90 [0.28; 2.96]	0.76 [0.24; 2.54]
	Antithrombin III	-	-	0.21 [0.01; 4.89]	0.0003 [0.00; 0.72]

Table 2. Comparison of four common-effects methods to estimate summary odds ratios in two previously published networks^{22,23}. Treatment abbreviations as given in Figure 1. MH-NMA: Mantel-Haenszel network meta-analysis. IV-NMA: inverse-variance network meta-analysis. NCH-NMA: non-central hypergeometric network meta-analysis. An odds ratio larger than 1 favours placebo in the COPD network, and control/placebo in the liver transplantation network

4.3 Methods to decrease blood loss and blood transfusion requirements for patients with liver transplantation

Results are shown in the lower part of Table 2. As in the previous example, we also fitted a random-effects IV-NMA, but heterogeneity (τ^2) was estimated to be zero. Thus, results from this method were identical to the common-effects IV-NMA shown in Table 2.

In contrast to the first example, there are differences between the approaches. The data that we imputed using the continuity correction accounted for almost 20% of the total events included in the IV-NMA. Thus, results will be strongly influenced by the imputed data, and the method cannot be trusted to give reliable results³. The Bayesian model might also be problematic, because the prior distributions used for the models' parameters, although chosen to be "uninformative" or "vague", might have a strong effect on results²⁰. In this example, if we switch the prior distributions for the model parameters to $U(-5,5)$, we get quite different estimates. E.g. for rFVIIa vs. placebo the point estimate [95% Credible Interval, CrI] changes from 1.58 [0.37; 10.42] to 1.11 [0.32; 3.75]. Thus, in this example, given that

there is no available external information to feed in the Bayesian models in the form of informative priors, our MH-NMA or the NCH-NMA might be the best option for analysis.

Note that Antithrombin III does not feature in the results of MH-NMA and NCH-NMA in Table 2. This is because this treatment was only included in one two-arm study with zero events in one of each arms, and such designs are removed from these two methods (unless a continuity correction is used). This highlights one of the potential disadvantages of the frequentist approaches, as opposed to the Bayesian ones. Based on the findings of the Bayesian model with the binomial likelihood presented in Table 2, one might argue that there is enough evidence that Antithrombin III is safer than control/placebo (estimated odds ratio 0.0003, with a 95% CrI 0.00 to 0.72). However, as discussed above, such results are heavily dependent on the prior. Using a $U(-5,5)$ prior, the odds ratio estimate is 0.02 [0.0002; 1.36], shedding doubts about the effectiveness of this intervention.

No evidence of global inconsistency was found for this network. Q_{inc} was 1.88 (2 degrees of freedom, for a p-value of 0.39). The SIDDE approach did not provide any evidence for inconsistency either. Results are shown in Table 3.

5 Simulations

In this section we describe a simulation study to compare our MH-NMA method with other methods for NMA. Our aim was to assess the performance of the competing approaches under different scenarios, by varying factors regarding data availability, heterogeneity, network structure, event rates etc. Our simulation study follows the structure proposed by Morris et al. ⁴¹.

5.1 Data generating mechanisms

We explored a total of 20 scenarios. In all scenarios we generated only fully connected networks, with at least two studies for every treatment comparison, in order to avoid having simulated datasets that result in disconnected networks when the assumed event rate is very low. For each scenario we independently generated 1000 datasets. The simulated a number of studies varied across scenarios (see details below). In all studies we assumed equal number of patients per treatment arm. The number of patients per treatment arm was generated separately for each study.

Inhaled medications for patients with chronic obstructive pulmonary disease			
	Q	df	p-value
Global inconsistency in the network	8.35	9	0.50
Inconsistency estimated using the SIDDE approach	Ratio of odd ratios (direct over indirect odds ratios)		p-value
ICS:LABA	1.29 [0.77; 2.17]		0.34
ICS: LABA-ICS	1.03 [0.58; 1.85]		0.92
LABA : LABA-ICS	0.47 [0.24; 0.89]		0.02
LABA : Placebo	0.88 [0.60; 1.29]		0.52
LABA:TIO-HH	1.45 [0.98; 2.16]		0.06
LABA-ICS:Placebo	1.10 [0.69; 1.75]		0.78
LABA-ICS:TIO-HH	0.59 [0.33; 1.06]		0.08
Placebo:TIO-HH	1.05 [0.74; 1.50]		0.79
Methods to decrease blood loss and blood transfusion requirements for patients with liver transplantation			
	Q	df	p-value
Global inconsistency in the network	1.88	2	0.39
Inconsistency estimated using the SIDDE approach	Ratio of odd ratios (direct over indirect odds ratios)		p-value
Aprotonin:Control/Placebo	5.97 [0.36; 98.99]		0.21
Aprotonin:Tranexamic acid	0.17 [0.01; 2.78]		0.21
Control/Placebo:Tranexamic acid	0.16 [0.01; 2.62]		0.20

Table 3: Results from the assessment of inconsistency in the two clinical examples

In scenarios 1-16 we generated only two-arm studies. The number of patients per treatment arm was simulated by drawing from a uniform distribution $U(30,60)$, and then rounding to a whole number. For each study we generated a study baseline risk; that is the risk of event of patients receiving a reference treatment (treatment 1) irrespective of whether this was evaluated in the study. The study baseline risk was generated from a uniform distribution with parameters that varied by scenario (details below). The underlying true log-odds ratios (logORs) of each treatment vs. treatment 1 were fixed at equal intervals between 0 and 1. For example in a scenario with 5 treatments, the true logORs for treatments 2, 3, 4 and 5 vs. treatment 1 were set to 0.25, 0.50, 0.75 and 1.00 respectively. For scenarios assuming homogeneity, we used these logORs together with the simulated, study-specific baseline risk, to calculate the probability of an event in each study treatment arm. The number of events in a study arm was generated from a Binomial distribution, using the (study- and treatment-specific) probability of an event, as well as the study-specific number of patients per treatment arm. For scenarios that assume heterogeneity, we set a common standard deviation of the random effects (τ) for all treatment comparisons in the network. For these scenarios, we simulated study-specific logORs, accounting for τ , i.e. by drawing from a normal distribution with a mean determined by the comparison, and standard deviation equal to τ ; otherwise the procedure was unchanged. In scenarios 1-16 we explored the following settings:

- number of treatments in the network: 5 or 8.
- number per studies per treatment comparison: 2 or 4.

- standard deviation of random effects: $\tau = 0$ (homogeneous treatment effects) and $\tau = 0.1$ (heterogeneous treatment effects).
- baseline event rate in each study: generated after drawing from $U(0.03,0.05)$ or $U(0.05,0.10)$

In scenarios 17-20 we considered more complicated situations that included multi-arm studies, large sample sizes and event rates, or very small event rates. More specifically:

- In Scenario 17 we assumed 3 treatments in the network populated by 3-arm studies and no heterogeneity.
- In Scenario 18 we assumed more patients per treatment arm ($U(100,200)$) and large event rates (baseline risk $U(0.30,0.50)$), only two-arm studies and no heterogeneity.
- Scenario 19 was equivalent with Scenario 18 but with heterogeneity $\tau = 0.1$.
- In Scenario 20 we assumed three 3 treatments in the network, and very low baseline event rates from $U(0.01,0.02)$). We assumed only two-arm studies and no heterogeneity.

Table 4 provides an overview of the data generating mechanism in each scenario.

#	Treatments in the network	Patients per treatment arm	Number or studies per comparison	Heterogeneity standard deviation (τ)	Baseline risk
1	5	30 to 60	2	0	3-5%
2	5	30 to 60	2	0.1	3-5%
3	5	30 to 60	2	0	5-10%
4	5	30 to 60	2	0.1	5-10%
5	5	30 to 60	4	0	3-5%
6	5	30 to 60	4	0.1	3-5%
7	5	30 to 60	4	0	5-10%
8	5	30 to 60	4	0.1	5-10%
9	8	30 to 60	2	0	3-5%
10	8	30 to 60	2	0.1	3-5%
11	8	30 to 60	2	0	5-10%
12	8	30 to 60	2	0.1	5-10%
13	8	30 to 60	4	0	3-5%
14	8	30 to 60	4	0.1	3-5%
15	8	30 to 60	4	0	5-10%
16	8	30 to 60	4	0.1	5-10%
17	3	30 to 60	8	0	1-10%
18	5	100 to 200	2	0	30-50%
19	5	100 to 200	2	0.1	30-50%
20	3	30 to 60	8	0	1-2%

Table 4: Overview of the scenarios we explored in our simulations. For each scenario we generated 1000 independent datasets. Rows shaded grey correspond to scenarios where we assumed heterogeneity.

5.2 Methods compared, estimands and measures of performance

Each of the 1000 datasets of each scenario was analysed using four different approaches: (i) common-effects IV-NMA with 0.5 continuity correction; (ii) random effects IV-NMA with 0.5 continuity correction; (iii) MH-NMA without continuity correction; and (iv) NHC-NMA without continuity correction. We did not consider Bayesian models, as for rare outcomes the performance of a Bayesian model might heavily depend on the prior distributions used (see Section 4.3 for an illustration).

The target estimands of our analyses were the logORs between treatments versus treatment 1 (i.e. the basic parameters). The performance of each method was assessed by comparing the estimated logORs with their corresponding true values. We calculated the mean bias, defined as the mean difference between the estimated and the true logORs, the mean absolute bias, and the mean coverage in each scenario, as the percent of 95% confidence intervals that included the corresponding true logOR. All analyses were performed in R using the **netmeta** package. The codes used for our simulations can be found in https://github.com/esm-ispm-unibe-ch-REPRODUCIBLE/MH_NMA.

5.3 Results from simulations

We present the results of the simulation study in Table 5.

IV-FE and IV-RE gave almost identical results for all scenarios. This is because when event rates are low, it is difficult to estimate τ , and the method of moments estimates $\hat{\tau} = 0$. In scenarios 1 to 16, MH-NMA always provided the least biased estimates, followed closely by NCH, which had identical mean bias in 4 of 16 scenarios. In most of these scenarios, NCH had a coverage slightly closer to the nominal level (95%) than MH. The IV method had the worst performance both in terms of bias and coverage, although in some cases differences were trivial. Also, simulating heterogeneity led to only a marginal increase of bias in the estimates of MH and NCH.

In scenario 17, with multi-arm studies only, MH gave again the least biased results, with similar coverage with NCH. Scenarios 18 and 19 assumed higher frequencies of events and NCH performed very poorly due to using the Breslow approximation, which is only valid for rare events (see Section 3.3). In Scenario 20, with very low event rates, the IV method showed large biases, while MH and NCH were practically unbiased. NCH again provided a slightly better coverage, i.e. slightly closer to the nominal level.

Note that in Table 5 we show the values of mean bias, absolute bias and coverage of all estimated logORs, i.e. we average over all basic parameters of each scenario. Thus, the values presented in Table 5 could be further split, for each basic parameter in each scenario. For example, in Scenario 1, where we assumed 5 treatments (4 basic parameters), the true values of the logORs were (0.25, 0.50, 0.75, 1.00). The corresponding mean biases across the four basic parameters were (-0.04, -0.07, -0.09, -0.11), while the mean bias for the common-effects IV-NMA across all basic parameters was -0.08 (as shown in Table 5). Similarly, for MH the mean bias across all basic parameters was -0.05, and the biases of the basic parameter were (-0.04, -0.05, -0.05, -0.06) respectively.

Overall, we conclude that IV-NMA with a continuity correction is a suboptimal choice, when events are rare. MH-NMA and NCH-NMA with the Breslow approximation performed comparably in most scenarios. Due to the fact that this approximation is inadequate for large event rates or when there is a mixture of low and high event rates across the studies, we recommend the use of MH-NMA. For the case when all studies show low event rates, NCH-NMA might offer a slight advantage over MH-NMA in terms of coverage. Readers should keep in mind, however, that in our simulations we did not explore the performance of the full NCH-NMA method (i.e. including random effects, without the Breslow approximation). See also the Discussion section, regarding possible areas of future research.

Scenario	IV - FIXED			IV - RANDOM			MH-NMA			NCH-NMA		
	Mean bias	Mean absolute bias	Coverage	Mean bias	Mean absolute bias	Coverage	Mean bias	Mean absolute bias	Coverage	Mean bias	Mean absolute bias	Coverage
1	-0.08	0.30	97.8%	-0.07	0.30	97.9%	-0.05	0.31	97.4%	-0.05	0.31	96.4%
2	-0.07	0.31	97.6%	-0.07	0.31	97.6%	-0.05	0.32	96.8%	-0.05	0.32	96.0%
3	-0.04	0.24	97.6%	-0.04	0.23	97.8%	-0.01	0.24	96.8%	-0.06	0.23	95.8%
4	-0.04	0.24	96.7%	-0.03	0.24	97.2%	-0.01	0.25	95.7%	-0.06	0.24	95.2%
5	-0.08	0.22	97.2%	-0.08	0.22	97.2%	0.00	0.23	96.0%	-0.02	0.22	95.1%
6	-0.09	0.22	97.4%	-0.08	0.22	97.4%	-0.01	0.23	96.2%	-0.03	0.22	95.5%
7	-0.04	0.17	96.5%	-0.04	0.17	96.8%	0.00	0.17	95.6%	-0.06	0.17	94.0%
8	-0.05	0.17	96.6%	-0.05	0.17	96.9%	-0.01	0.18	95.3%	-0.07	0.17	94.2%
9	-0.07	0.24	97.3%	-0.07	0.24	97.3%	-0.05	0.26	96.8%	-0.05	0.25	95.8%
10	-0.08	0.24	97.5%	-0.07	0.24	97.5%	-0.05	0.25	96.6%	-0.05	0.25	95.8%
11	-0.04	0.19	96.5%	-0.04	0.19	96.7%	-0.02	0.19	95.9%	-0.06	0.19	95.0%
12	-0.04	0.19	96.7%	-0.04	0.19	96.9%	-0.02	0.20	95.9%	-0.06	0.19	94.8%
13	-0.07	0.18	96.8%	-0.07	0.18	96.9%	0.00	0.18	96.1%	-0.02	0.18	95.3%
14	-0.08	0.18	97.1%	-0.08	0.18	97.1%	-0.02	0.18	95.8%	-0.04	0.18	95.0%
15	-0.04	0.14	96.5%	-0.04	0.14	96.6%	0.00	0.14	95.6%	-0.05	0.14	94.2%
16	-0.05	0.14	96.2%	-0.05	0.14	96.3%	-0.01	0.14	95.4%	-0.07	0.14	93.3%
17	-0.06	0.23	96.2%	-0.06	0.23	96.6%	0.03	0.25	94.3%	-0.05	0.23	94.5%
18	0.00	0.08	95.7%	0.00	0.08	96.6%	0.00	0.08	95.7%	-0.31	0.31	21.0%
19	0.00	0.09	92.5%	0.00	0.09	94.6%	0.00	0.09	92.4%	-0.31	0.31	21.0%
20	-0.18	0.26	97.1%	-0.18	0.26	97.1%	0.01	0.29	96.2%	0.00	0.29	95.5%

Table 5: Overview of simulation results. Methods' abbreviations as per Table 2. Rows shaded grey correspond to scenarios where we assumed heterogeneity.

6 Discussion

We presented a method for NMA of binary outcomes, using a generalized version of the Mantel-Haenszel approach to pairwise meta-analysis. The method synthesises odds ratios and it does not rely on the normal approximation to estimate study variances. It allows the inclusion of information from studies with zero events in some, but not all, treatment arms, without a continuity correction.

One limitation of our method is that it is limited to odds-ratios. An extension to risk ratios might be interesting to pursue in future work. However, for the case of sparse data, the difference between odds and risks becomes negligible, and thus odds ratios can be interpreted as risk ratios for practical purposes. Another limitation of our method is that it can only be used to perform a common-effects network meta-analysis. However, when the event rate is low, the estimation of heterogeneity in a frequentist setting can be difficult⁴². In both clinical applications we presented in this paper the heterogeneity standard deviation was estimated to be zero using the method of moments⁴³, and the IV-NMA analyses were performed under a common-effect assumption. A similar picture was seen in our simulation study: when events were rare, the random-effects IV-NMA gave on average almost identical results to the fixed-effects IV-NMA. Thus, although our MH-NMA method's inability to include random effects is in theory a disadvantage, for the case of rare events the IV-NMA method might in practice be also limited to the common-effects approach. Note that the Cochrane Handbook suggests that incorporation of heterogeneity should be a secondary consideration when attempting to estimate treatment effects from sparse data⁴⁴.

The fact that the MH-NMA method does not account for heterogeneity suggests that the results from the global test or the SIDDE method to assess inconsistency should be interpreted with caution. If heterogeneity is present in the form of within-design variability, then ignoring it when estimating the variance of the direct summary odds-ratios might contribute to inconsistency. Hence, important inconsistency in the data should challenge the assumption of the homogeneity that underlines the model. Researchers should also keep in mind that tests for inconsistency have in general low power⁴⁵. Consequently, lack of evidence for inconsistency should not be interpreted as evidence for consistency. Careful consideration of the study inclusion criteria and evaluation of their similarity with respect to effect modifiers should always take place to ensure that the network has low risk of intransitivity¹⁶.

The majority of published NMA are fitted within a Bayesian framework^{18,46}. In this case, the exact binomial likelihood for the data can be employed without requiring any 'correction' for zero events in study arms. However, similar to other Bayesian analyses, the sparser the data, the bigger the influence of the prior distributions on the posterior estimates of the model. Different "uninformative" or "vague" prior distributions may lead to different estimated effects sizes. The impact is generally larger for scale parameters (e.g. the variance of random effects) than location parameters (e.g. the true underlying effect size)²⁰. The problem can be mitigated with the use of informative priors for at least some of the model parameters, and in particular for heterogeneity⁴⁷. As illustrated in the liver transplant example in Section

4.3, the choice of priors for the location parameters can have a strong impact on some of the estimated effect sizes in a NMA. Thus, unless meta-analysts have at their disposal high-quality external information for all model parameters, results from applying Bayesian methods may not be robust.

As illustrated in the chronic obstructive pulmonary disease example, the IV-NMA method might be a reasonable frequentist alternative when there are several studies with relatively large numbers of events in the dataset. Conversely, in cases where the IV-NMA method requires the imputation of a large amount of data (as in the liver transplant example), MH-NMA might be a better option for a frequentist analysis. Stijnen et al. proposed an alternative frequentist approach to NMA, that can be used when the outcome is rare¹⁹. This uses an exact conditional likelihood, i.e. it models the likelihood of events in each study arm given the total number of events in the study using the non-central hypergeometric distribution. For both examples presented in this paper MH-NMA and the common-effect non-central hypergeometric method gave similar results. However, the two methods make different distributional assumptions about the observed data (i.e. the approach by Stijnen et al. implements a non-central hypergeometric distribution) and might provide different estimates in other cases, especially if the random effects version of that approach is used (but we have not yet implemented this option in **netmeta**).

In our simulation study we compared the performance of MH-NMA with the IV-NMA method (both fixed- and random-effects IV-NMA, using a 0.5 continuity correction) and also with the fixed effects method proposed by Stijnen et al. (NCH-NMA), employing an approximation only valid for small event rates. We found that our method performed similarly to NCH-NMA in most scenarios, when events are rare; both methods performed better than IV-NMA. Consequently, we recommend that researchers perform sensitivity analyses using these two methods alongside Bayesian NMAs, to evaluate the robustness of conclusions^{5,9}. The use of IV-NMA for binary outcomes should be restricted to the case when events are not rare.

In order to provide recommendations regarding the optimal approach in more variable scenarios, future work could focus on comparing in simulations our MH-NMA model with the random-effects method by Stijnen et al. (without approximation) and also Bayesian NMA models with different priors. The different approaches could also be empirically compared in large collections of meta-analyses, to see if, and in which cases, there are important differences in the estimates of the different methods in practice. Additional simulation studies would also be needed to assess the performance of the available methods for assessing inconsistency. One other area of future research could be to explore different approaches to MH-NMA. For example, one could perform a ‘data-augmentation’ to all studies⁴⁸, i.e. artificially impute treatment arms with zero events and zero non-events for the missing treatments of all studies. This would lead to all studies having the same design (comparing all treatments), and would render Stage 3 of Section 3.1 obsolete. However, there might be no way to check for inconsistency with this approach. Finally, other models currently available only for pairwise meta-analysis could also be

extended for the case of NMA, such as beta-binomial models^{6,49}, the simple average estimator⁴² and others.

In summary, our extension of the Mantel-Haenszel method to network meta-analysis offers a useful new approach for the synthesis of binary outcomes, especially when the events are rare, and/or the sample sizes of the included studies are small. Moreover, using the **netmeta** command in R, the application of our methods is straightforward in practice.

Funding

This project was supported by project grant No. 166656 from the Swiss National Science Foundation (SNSF). ME was supported by special project funding (No. 174281) from the SNSF.

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