LETTER TO THE EDITOR



Continuity corrections with Mantel–Haenszel estimators in Cochrane reviews

A.E. Ades^(D), Deborah M. Caldwell^(D), Sumayya Anwer^(D) and Sofia Dias^(D)

¹Population Health Sciences, University of Bristol Medical School, Bristol, UK ²Centre for Reviews and Dissemination, University of York, York, UK

Corresponding author: A.E. Ades; Email: t.ades@bristol.ac.uk

Received: 21 January 2025; Revised: 13 February 2025; Accepted: 30 April 2025

Dear Editors

The paper by Tsujimoto et al.¹ raises serious questions about the conduct of Cochrane reviews. They found that 64% of 885 meta-analyses that included studies with zero cells implemented the Mantel–Haenszel (MH) method in RevMan software, which by default implements the standard continuity correction (CC), in which 0.5 is added to every cell of a 2×2 table with a zero cell. The CC is unnecessary when calculating MH statistics, and it biases estimates towards the null. Tsujimoto et al. reported that in about 30% of cases, point estimates of the odds ratio were biased by 25% or more.

Readers will surely support their conclusion that 'future updates of RevMan should incorporate less biased methods,' and their call for MH without CC to be incorporated. However, 'bias' may be too mild a word for a procedure that is, and has always been, recognized as frankly *incorrect.*² Readers might have expected a call for biased methods to be entirely removed: they might also be wondering how the Cochrane organization could have allowed this blunder to persist for so long.

In 2016, we raised RevMan's CC issue with the Cochrane Neonatal group, following the 2014 publication of their review of intrapartum anti-bacterial prophylaxis (IAP) to prevent neonatal early-onset Group B streptococcus (EOGBS) infection.³ The headline estimate (0.17, 95%CI 0.04–0.74) of the efficacy of IAP to prevent EOGBS disease included a CC. This underestimates the efficacy by a factor of nearly 2 (Table 1). Our communication with the Neonatal Group and the authors' response was recorded as 'Feedback' on pages 32 and 33 of the Cochrane review.

The authors replied: 'We are not statisticians, but assume that the statistical methods used in RevMan 5.2 are correct'. They went on to quote the 2008 Cochrane Handbook section 9.2.2.2 to the effect that ORs and RR cannot be calculated if there are zero cells, and that RevMan 'automatically makes the [continuity] correction when necessary'.⁴ Almost identical wording appears in section 6.4.1.2 of the 2nd edition.⁵

The author's response is understandable, and it is hard to attach any blame to the distinguished neonatologist at Toronto's Hospital for Sick Children who led the review. Of course, a later section (16.9 in the 2008 Handbook, 10.4.4.1 in the 2019 edition) explains that the correction is not necessary when the MH estimators are used, and also that it causes bias. However, even if the Handbook had given explicit advice *not* to implement the CC with MH estimators, this would have made no difference: until recently, the use of RevMan was mandatory in Cochrane reviews (Handbook section 2.3.5).

© The Author(s), 2025. Published by Cambridge University Press on behalf of The Society for Research Synthesis Methodology. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (https://creativecommons.org/licenses/by/4.0), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

Cochrane review	Number of trials	Outcome	Method	Cochrane estimate	MH estimate without CC
Smaill (2000) ⁶	4	Infant GBS colonization	Peto OR	0.10 (0.07–0.14)	0.037 (0.018–0.074)
Smaill (2000) ⁶	4	EOGBS disease	Peto OR	0.17 (0.07–0.39)	0.051 (0.007–0.375)
Ohlsson (2014) ³	3	EOGBS disease	MH RR with CC ^a	0.17 (0.04–0.74)	0.097 (0.014–0.70)

Table 1. Efficacy of IAP in Cochrane reviews, published estimates compared to MH odds ratios without continuity correction (CC).⁸

^aOutcomes are sufficiently rare that relative risks and odds ratios are effectively equivalent.

An earlier version of the IAP Cochrane review⁶ had used the Peto method, another inappropriate choice, as it biases towards the null when the treatment effect is strong (Table 1).⁷ This suggests that the absence of effective statistical oversight had been a long-standing problem. According to our estimates, based on a synthesis of both EOGBS colonization and EOGBS disease outcomes, the 2014 review under-estimated the effect on GBS disease by a factor of more than 5.⁸ Errors of this magnitude have profound public health implications: while the efficacy of IAP is not in question, the question of how it should be delivered, following screening or to high-risk groups, is still being actively researched.

The authors of the 2014 review noted that there was a high risk of bias in the three trials reporting EOGBS as an outcome. They concluded: 'There is a lack of evidence from well-designed and conducted trials to recommend IAP to reduce the risk of EOGBS disease'. One has to be concerned that their underestimation of the efficacy of IAP may have influenced this judgement.

Although their conclusions may be technically justified, they were—and still are—at variance with previously published meta-analyses (not using a CC),^{9–11} and entirely contrary to clinical policy and practice in most developed countries, both at the time and now, and indeed in the hospital where they worked. In both the USA¹² and Canada¹³ IAP was first recommended in official guidance over 25 years ago, *its efficacy premised on the same trials examined in the Cochrane reviews*. IAP interventions of one form or another have been recommended in every update since. In a 2007 position statement, the Canadian Paediatric Society declared that IAP was 'highly effective' in preventing EOGBS.¹⁴ By 2017, 60 countries out of 95 surveyed operated some form of IAP policy.¹⁵

MH with no CC is standard in *metafor* software,^{16,17} and is available in STATA¹⁸ and the R *meta* package.^{19,20} There are alternative CCs besides the standard 0.5. Zabriskie et al.²¹ comprehensively review previous work on meta-analysis with zero cells, and document new simulations of MH and other pooling methods paired with alternative CCs. Some of these perform better with MH pooling than MH with no CC and are available in STATA and R *meta*.

Possibly, if the 2014 Cochrane review was repeated now, the outcome would be different. The recent Methodological Expectations in Cochrane Reviews guidance²² incorporates PRISMA 2020, which includes (Item 23a) a requirement to 'provide a general interpretation of the results in the context of other evidence'.²³ This would have obliged authors to ask why previous reviews of essentially the same evidence had produced different results. Other changes in the Cochrane organization, including the more centralized editorial process, might be expected to result in a more effective oversight of statistical methods.

Such optimism may however be misplaced. The standard 0.5 CC with MH pooling is still the default in STATA and is obligatory in both Comprehensive Meta-analysis (CMA)²⁴ and RevMan.

We approached the Cochrane Support website and asked whether the RevMan technical team was planning to make any changes, such as (1) providing a version of MH without the CC, (2) making this the default option, or (3) removing the version with the CC. The response, forwarded from the Methods

and Synthesis Development Team, was that 'there are no planned changes to MH Calculations,' that 'any changes to statistical approaches are based on recommendations from the Statistics Methods Group,' and that 'their advice on this issue had not changed over the years'.

Author contributions. Writing - review editing: S.A., S.D.; Conceptualization: D.M.C., A.E.A.

Competing interest statement. The authors declare that no competing interests exist.

Data availability statement. None declared.

Funding statement. The authors declare that no specific funding has been received for this article.

References

- Tsujimoto Y, Tsustumi Y, Kataoka Y, Shiroshita A, Efthimiou O, Furukawa TA. The impact of continuity correction methods in Cochrane reviews with single-zero trials with rare events: a meta-epidemiological study. *Res Synth Methods*. 2024;15: 769–779.
- [2] Fleiss JL. Measures of effect size for categorical data. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. Russell Sage Foundation; 1994: 245–260.
- [3] Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst. Rev. 2014;(6): CD007467.
- [4] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, Wiley; 2008.
- [5] Higgins J, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Wiley; 2019.
- [6] Smaill F. Intrapartum antibiotics for group B streptococcal colonisation. Cochrane Database Syst Rev. 2000;(2): CD000115.
- [7] Greenland S, Salvan A. Bias in the one-step method for pooling study results. *Stat Med.* 1990;9: 247–252.
- [8] Anwer S, Ades AE, Dias S. Joint synthesis of conditionally related multiple outcomes makes better use of data than separate meta-analyses. *Res Synth Methods*. 2020;11(4): 496–506.
- [9] Allen UD, Navas L, King SM. Effectiveness of intrapartum penicillin prophylaxis in preventing early-onset group B streptococcal infection: results of a meta-analysis. *Can Med Assoc J.* 1993;149(11): 1659–1665.
- [10] Colbourn T, Asseburg C, Bojke L, et al. Prenatal screening and treatment strategies to prevent Group B Streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analysis. *Health Technol* Assess. 2007;11(29): 1–226.
- [11] Colbourn TE, Asseburg C, Bojke L, et al. Preventive strategies for group B streptococcal and other bacterial infections in early infancy: cost effectiveness and value of information analyses. *BMJ*. 2007;335: 655–661.
- [12] Centers for Disease Control. Prevention of perinatal group B streptococcal disease: a public health perspective. MMWR. 1996;45 (RR-7): 1–24.
- [13] Society of Obstetrics and Gynecology Canada. Statement on the prevention of early-onset group B streptococcal infections in the newborn. J Obstet Gynecol Can. 1997;19(7): 751–758.
- [14] Barrington KJ, Canadian Paediatric Society Fetus and Newborn Committee. Management of the infant at increased risk for sepsis. *Paediatr Child Health*. 2007;12(10): 893–898.
- [15] Le Doare K, O'Driscoll M, Turner K, et al. Intrapartum antibiotic chemoprophylaxis policies for the prevention of group B streptococcal disease worldwide: systematic review. *Clin Infect Dis.* 2017;65(suppl_2): S143–S151.
- [16] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3).
- [17] Viechtbauer W. Comparison of the Mantel-Haenszel method in different software. 2021. https://www.metafor-project. org/doku.php/tips:comp_mh_different_software.
- [18] StataCorp. STATA 18 meta-analysis reference manual. College Station TX, 2023.
- [19] Schwarzer G, Carpenter JR, Rücker G. Meta-Analysis with R. Springer; 2015.
- [20] Schwarzer G. General package for meta-analysis, Version 8.0-1. 2024. https://cran.r-project.org/web/packages/meta/ meta.pdf.
- [21] Zabriskie BN, Cole N, Baldauf J, Decker C. The impact of correction methods on rare-event meta-analysis. *Res Synth Methods*. 2024;15: 130–151.
- [22] Higgins JPT, Lasserson T, Thomas J, Flemyng E, Churchill R. Methodological expectations of cochrane intervention reviews (MECIR). London, 2023. https://community.cochrane.org/mecir-manual.
- [23] Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. Br Med J. 2021;372: n60.
- [24] Borenstein M. Comprehensive meta-analysis software. In: Egger M, Higgins JPT, Davey Smith G, eds. *Systematic Reviews in Health Research: Meta-Analysis in Context*. 3rd ed. Wiley; 2022.

Cite this article: Ades A, Caldwell DM, Anwer S, Dias S. Continuity corrections with Mantel–Haenszel estimators in Cochrane reviews. *Research Synthesis Methods*. 2025; 1–3. https://doi.org/10.1017/rsm.2025.10012