Quantifying replicability in systematic reviews: the \( r \)-value

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Abstract

In order to assess the effect of a health care intervention, it is useful to look at an ensemble of relevant studies. The Cochrane Collaboration’s admirable goal is to provide systematic reviews of all relevant clinical studies, in order to establish whether or not there is a conclusive evidence about a specific intervention. This is done mainly by conducting a meta-analysis: a statistical synthesis of results from a series of systematically collected studies. Health practitioners often interpret a significant meta-analysis summary effect as a statement that the treatment effect is consistent across a series of studies. However, the meta-analysis significance may be driven by an effect in only one of the studies. Indeed, in an analysis of two domains of Cochrane reviews we show that in a non-negligible fraction of reviews, the removal of a single study from the meta-analysis of primary endpoints makes the conclusion non-significant. Therefore, reporting the evidence towards replicability of the effect across studies in addition to the significant meta-analysis summary effect will provide credibility to the interpretation that the effect was replicated across studies. We suggest an objective, easily computed quantity, we term the \( r \)-value, that quantifies the extent of this reliance on single studies. We suggest adding the \( r \)-values to the main results and to the forest plots of systematic reviews.
1 Introduction

In systematic reviews, several studies that examine the same questions are analyzed together. Viewing all the information is extremely valuable for practitioners in the health sciences. A notable example is the Cochrane systematic reviews on the effects of healthcare interventions. The process of preparing and maintaining Cochrane systematic reviews is described in detail in their manual [Higgins et al., 2011]. The reviews attempt to assemble all the evidence that is relevant to a specific healthcare intervention.

Deriving conclusions about the overall health benefits or harms from an ensemble of studies can be difficult, since the studies are never exactly the same and there is danger that these differences affect the inference. For example, factors that are particular to the study, such as the specific cohorts in the study that are from specific populations exposed to specific environments, the specific experimental protocol used in the study, the specific care givers in the study, etc., may have an impact on the treatment effect.

A desired property of a systematic review is that the effect has been observed in more than one study, i.e., the overall conclusion is not entirely driven by a single study. If a significant meta-analysis finding becomes non-significant by leaving out one of the studies, this is worrisome for two reasons: first, the finding may be too particular to the single study (e.g., the specific age group in the study); second, there is greater danger that the significant meta-analysis finding is due to bias in the single study (e.g., due to improper randomization or blindness). We view this problem as a replicability problem: the conclusion about the significance of the effect is completely driven by a single study, and thus we cannot rule out the possibility that the effect is particular to the single study, i.e., that the effect was not replicated across studies.

A replicability claim is not merely a vague description. A precise computation of the extent of replicability is possible. An objective way to quantify the evidence that the meta-analytic findings do not rely on single studies is as follows. For a meta-analysis of several studies (N studies), the minimal replicability claim is that results have been replicated in at least two studies. This claim can be asserted if the meta-analysis results remains significant after dropping (leaving-out) any single study. We suggest accompanying the review with a quantity we term the $r$-value, which quantifies the evidence towards replicability of the effects across studies. The $r$-value is the largest of the $N$ meta-analysis $p$-values. Like a $p$-value, which quantifies the evidence against the null hypothesis of no effect, the $r$-value quantifies the evidence against no replicability of effects. The smaller the $r$-value, the greater the evidence that the conclusion about a primary outcome is not driven by a single study.

The report of the $r$-value is valuable for meta-analyses of narrow scope as well as of broad scope. In Section 5.6 of the manual [Higgins et al., 2011] the scope of the review question is addressed. If the scope is broad, then a review that produced a single meta-
analytic conclusion may be criticized for ‘mixing apples and oranges’, particularly when good biologic or sociological evidence suggests that various formulations of an intervention behave very differently or that various definitions of the condition of interest are associated with markedly different effects of the intervention. The advantage of a broad scope is that it can give a comprehensive summary of evidence. The narrow scope is more manageable, but the evidence may be sparse, and findings may not be generalizable to other settings or populations. If the $r$-value is large (say above 0.05) for a meta-analyses with a narrow scope, this is worrisome since the scope has already been selected, and the large $r$-value indicates that an even stricter selection that removes one single additional study can change the significant conclusion. If the $r$-value is large for a meta-analyses with a broad scope, this is worrisome since the reason for the significant finding may be the single “orange” among the several (null) “apples”.

We examined the extent of the replicability problem in systematic reviews. We found that there may be lack of replicability in a large proportion of studies. In Section 2 we show that out of the 21 reviews with a significant meta-analysis result on the most important outcomes of interest published on breast cancer, 13 reviews were sensitive to leaving one study out of the meta-analysis. The problem was less pronounced in the reviews published on influenza, where 2 reviews were sensitive to leaving one study out of the meta-analysis, out of 6 updated reviews with significant primary outcomes.

[Anzures-Carbera and Higgins, 2010] write that a useful sensitivity analysis is one in which the meta-analysis is repeated, each time omitting one of the studies. A plot of the results of these meta-analysis, called an ‘exclusion sensitivity plot’ by [Bax et al, 2006], will reveal any studies that have a particularly large influence on the results of the meta-analysis. In this work, we concur with this view, but recommend the most relevant single number of summary information of such a sensitivity analysis be added to the report of the main results, and to the forest plot, of the meta-analysis. The code for the computation of the $r$-values and sensitivity intervals is available from the first author upon request.

2 The lack of replicability in systematic reviews

We took all the updated reviews in two domains: breast cancer and influenza. Our eligibility criteria were as follows: (a) the review included forest plots; (b) at least one primary outcome was significant at the .05 level, which is the default significant level used in Cochrane Reviews; (c) the meta-analysis of at least one of the primary outcomes was based on at least three studies and (d) there was no reporting in the review of unreliable/biased primary outcomes or poor quality of available evidence. We consider as primary outcomes the outcomes that were defined as primary by the review authors, and if none were defined we selected the most important findings
from the review summaries and treated the outcomes for these findings as primary. We limit ourselves to meta-analyses that include at least three studies, since this is the minimum number of studies for which even if the single studies are not significant the meta-analysis may still be non-sensitive (i.e., that a meta analysis based on every subset of two studies can have a significant finding).

In Cochrane reviews, the meta-analyses are of two types: fixed effect and random effects. Under the fixed effect model all studies in the meta-analysis are assumed to share a common (unknown) effect $\theta$. Since all studies share the same effect, it follows that the observed effect varies from one study to the next only because of the random error inherent in each study. The summary effect is the estimate of this common effect $\theta$. Under the random effects model, the effects in the studies $\theta_i$, $i = 1, 2, ..., N$ are assumed to have been sampled from a distribution with mean $\bar{\theta}$. Therefore, there are two sources of variance: the within-study error in estimating the effect in each study and the variance in the true effects across studies. The summary effect is the estimate of the effects distribution mean $\bar{\theta}$. For details on estimation of these effects and their confidence intervals, see [Higgins et al., 2011].

In the breast cancer domain 48 updated reviews were published by the Cochrane Breast Cancer Group in the Cochrane library, out of which we analyzed 21 updated reviews that met our eligibility criteria (14, 8 , 4 and 1 reviews was excluded due reasons a, b, c and d respectively). Out of the 21 eligible reviews, 13 reviews were sensitive to leaving one study out in at least one primary outcome. Moreover, in 8 out of 13 reviews all the significant primary outcomes were sensitive. The prevalence of sensitive meta-analyses was similar among the fixed effect and random effect meta-analyses, see Table 1. Among the 15 fixed effect meta-analyses, 6 reviews where sensitive in all their primary outcomes, 2 reviews were sensitive in 66% of the primary outcomes, 1 review was sensitive in 50% of the primary outcomes, and 6 reviews were not sensitive in any of their primary outcomes. Among the 7 Random effect meta-analyses, 3 reviews were sensitive in all their primary outcomes, 2 review were sensitive in 50% of their primary outcomes, and 2 reviews were not sensitive in any of their primary outcomes.

In the influenza domain 25 reviews were published by different groups (e.g., Cochrane Acute Respiratory Infections Group, Cochrane Childhood Cancer Group etc.) in the Cochrane library, out of which we analyzed 6 updated reviews that met our eligibility criteria (9, 2 , 7 and 1 review was excluded due reasons a, b, c and d respectively). Out of the 6 eligible reviews, 2 reviews were sensitive to leaving 1 study out. Among the two fixed effect meta-analyses reviews, one review was sensitive in all primary outcomes and one review was not sensitive in all primary outcomes. Among the five reviews with random effect meta-analyses, 1 review was sensitive in 40% of the primary outcomes, and four reviews were not sensitive in any of their outcomes.

The influenza domain has a much smaller number of reviews with significant primary results than the breast cancer domain. In the influenza domain, most of the reviews
Table 1: Table of results for the breast cancer domain. The review name (column 2); the type of meta-analysis (column 3); the number of significant primary outcomes (column 4); the number of outcomes with \( r \)-values at most (0.01,0.05,0.1) (columns 5,6,7); the actual \( r \)-values of the primary outcomes, arranged in increasing order (column 8). The smaller the \( r \)-value, the stronger the evidence towards replicability. The rows are arranged by order of increasing sensitivity; the last 8 rows are sensitive in all primary outcomes.

| Review   | Random/Fixed | number of significant outcomes | number of outcomes non-sensitive at level 0.01 | 0.05 | 0.1 | \( r \)-values |
|----------|--------------|-------------------------------|-----------------------------------------------|------|-----|----------------|
| 1 CD004421 Fixed | 2 | 2 2 2 2 | (1.300e-10, 1.405e-07) |
| 2 CD003372 Fixed | 2 | 2 2 2 2 | (4.000e-14, 5.368e-05) |
| 3 CD002943 Fixed | 2 | 2 2 2 2 | (9.853e-09, 0.0012) |
| 4 CD006242 Random | 2 | 2 2 2 2 | (2.580e-09, 0.03549) |
| 5 CD000563 Fixed | 1 | 1 1 1 | 1.28e-11 |
| 6 CD008941 Fixed | 1 | 1 1 1 | 1.025e-04 |
| 7 CD005001 Random | 1 | 0 1 1 | 0.0335 |
| 8 CD003370 Fixed | 1 | 0 1 1 | 0.0341 |
| 9 CD003367 Fixed | 2 | 1 1 1 | (7.440e-07, 0.18) |
| 10 CD005211 Random | 4 | 1 2 2 | (0.0017, 0.0167, 0.1231, 0.178) |
| 11 CD003474 Random | 2 | 1 1 1 | (0.0463, 0.253) |
| 12 CD003366 Fixed | 3 | 1 1 1 | (3.200e-05, 0.21, 0.38) |
| 13 CD003139 Fixed | 3 | 1 1 1 | (0.1053, 0.1852, 0.002) |
| 14 CD008623 Random | 1 | 0 0 0 0 | 0.08 |
| 15 CD004253 Random | 1 | 0 0 0 0 | 0.1028 |
| 16 CD005002 Fixed | 1 | 0 0 0 0 | 0.15 |
| 17 CD008792 Fixed | 1 | 0 0 0 0 | 0.24 |
| 28 CD007077 Fixed | 1 | 0 0 0 0 | 0.3 |
| 19 CD002747 Fixed | 1 | 0 0 0 0 | 0.9641 |
| 20 CD007913 (Random,Fixed) | 2 | 0 0 0 0 | (0.0712,0.0756) |
| 21 CD003142 Fixed | 2 | 0 0 0 0 | (0.1243,0.1827) |

have non-significant endpoints or low quality of evidence.

3 Calculating and reporting the \( r \)-value: examples

In this section we shall give examples of sensitive and non-sensitive (fixed and random effect) meta-analyses in the breast cancer domain. For examples in the influenza domain, see Appendix A. For each example, we shall compute the \( r \)-value, which is based on the \( N \) leave-one out meta-analysis \( p \)-values, as well as the sensitivity interval, which is the union of these \( N \) meta-analysis confidence intervals. The detailed computations are given in Appendix B. We shall show how to incorporate these new quantities in the Cochrane reviews’ abstract and forest plots.

Our first example is based on a meta-analysis in review CD006242, analyzed by the authors as a random effect meta-analysis, which is non-sensitive and thus has a small \( r \)-value. The objective of review CD006242 was to assess the efficacy of therapy with Trastuzumab in women with HER2-positive metastatic breast cancer. Only one of the studies was (barely) significant, and the remaining four studies had non-significant effects at the .05 significance level. However, when combined in a meta-analysis the
Table 2: Table of results for the influenza domain. The review name (column 2); the type of meta-analysis (column 3); the number of significant primary outcomes (column 4); the number of outcomes with r-values at most (0.01,0.05,0.1) (columns 5,6,7); the actual r-values of the primary outcomes, arranged in increasing order (column 8). The smaller the r-value, the stronger the evidence towards replicability. The rows are arranged by order of increasing sensitivity. The value 0.0001∗ indicates that the r-value was smaller than 0.0001.

| Review   | Random/Fixed | number of significant outcomes | number of outcomes non-sensitive at level | r-values        |
|----------|--------------|--------------------------------|----------------------------------------|----------------|
| CD001269 | (Fixed,Random) 4 4 4 4 | (0.0001*, 0.0001*, 0.0014, 0.0188) |
| CD001169 | Random        4 4 4 4 | (0.0001*, 0.0014, 0.0016, 0.0025) |
| CD004879 | Random        4 4 4 4 | (0.0001*, 0.0001*, 0.0007, 0.006) |
| CD002744 | Random        1 1 1 1 | 0.0009                             |
| CD008965 | Random        5 1 3 3 | (0.0001*, 0.0108, 0.0471, 0.118, 0.1206) |
| CD005050 | Fixed         1 0 0 0 | 0.9888                             |

The evidence was highly significant, and the review conclusion was that Trastuzumab improved overall survival in HER2-positive women with metastatic breast cancer, see the left panel of Figure 1. This is a nice example that shows how a meta-analysis can increase power. Even after removing the single significant study (study number 5) there was still a significant effect in the meta-analysis at the 0.05 level; see the right panel of Figure 1. The r-value is 0.03549.

We suggest accompanying the original forest plot with this r-value, see Figure 2. The significant meta-analytic conclusion can therefore be accompanied by a statement that the replicability claim is established at the .05 level of significance. This is a stronger scientific claim than that of the meta-analysis, and it is supported by the data in this example. In the main results of Review CD006242 the authors write "The combined HRs for overall survival and progression-free survival favoured the trastuzumab-containing regimens (HR 0.82, 95% confidence interval (CI) 0.71 to 0.94, P = 0.004; moderate-quality evidence)". To this, we suggest adding the following information “This result was replicated in more than one study (r-value = 0.03549)".

Our second example, also from the breast cancer domain, is based on a meta-analysis in review CD008792, that was analyzed by the authors as a fixed effect meta-analysis. In this example the fixed effect meta-analysis was sensitive. The objective of Review CD008792 was to assess the effect of combination chemotherapy compared to the same drugs given sequentially in women with metastatic breast cancer. In the meta-analysis a significant finding was discovered, see the left panel of Figure 3. However, note that the different studies seem to have different effects. Nevertheless, the review conclusion was that the combination arm had a higher risk of progression than the sequential arm. After removing study number 7, there was no longer a significant effect in the meta-analysis, see the right panel of Figure 3. The r-value was 0.24. The replicability claim was not established at the .05 level of significance. This lack of replicability, quantified by the r-value, cautions practitioners that the significant
meta-analysis finding may depend critically on a single study.

We suggest accompanying the original forest plot with this $r$-value, see Figure 4. In the main results of Review CD008792 the authors write "The combination arm had a higher risk of progression than the sequential arm (HR 1.16; 95% CI 1.03 to 1.31; $P = 0.01$) with no significant heterogeneity". To this, we suggest adding the following information "We cannot rule out the possibility that this result is based on a single study (r-value = 0.24)".

In the right panels of Figures 1 and 3, the meta-analysis confidence intervals that would have been computed had we considered only this specific subset of studies is shown. The sensitivity intervals has an additional tail in the direction favoured by the data.

4 Methodological extensions

4.1 A lower bound on the extent of replicability

A review is less sensitive than another review if a larger fraction of studies are excluded without reversing the significant conclusions. We can calculate the meta-analysis significance not only after dropping each single study, but also after dropping all pairs of studies, triplets of studies etc. Each time we calculate the maximum $p$-value and stop at the first time it exceeded $\alpha$. The bigger the number of studies that can
Figure 2: The forest plot in the original Review CD006242 including the $r$-value, which was 0.03549. The asterisks indicate which study was excluded for the $r$-value computation.

be dropped, the stronger the replicability claim.

For example, the objective of Review CD004421 was to assess the efficacy of therapy taxane containing chemotherapy regimens as adjuvant treatment of pre- or post-menopausal women with early breast cancer. The review included 11 studies, out of which only three studies were significant, and the remaining eight studies had non-significant effects. When combined in a meta-analysis, the evidence was highly significant, and the review conclusion was that the use of taxane containing adjuvant chemotherapy regimens improved the overall survival of women with early breast cancer, see Figure 5.

In order to reverse the significant conclusion, we need to leave out 6 studies: for $u = 6$, the $r$-value was 0.0281, but for $u = 7$, the $r$-value was 0.0628, see Table 3. Therefore, with 95% confidence, the true number of studies with an effect (in the same direction) is at least 6. More generally, testing in order at significance level $\alpha$, results in a $1-\alpha$ confidence lower bound on the number of studies with an effect in a fixed-effect meta-analysis (see [Heller, 2011] for proof). Note that although we have a lower bound on the number of studies that show an effect, we cannot point
Figure 3: The forest plot in Review CD008792 (Left) and excluding study 7 (Right). The $r$-value was 0.24. The sensitivity interval, $[0.94, 1.356]$, is the confidence interval excluding study 7 (the black diamond in the right panel) with an additional (small) right tail. The axis is on the logarithmic scale.

out to which studies these are. This is so since the pooling of evidence in the same direction in several studies increases the lower bound, even though each study on its own maybe non-significant.

Table 3: The $r$-value excluding $u − 1$ studies, for $u = 2, \ldots, 7$, in Review CD004421. This exclusion is in worst-case order, i.e in order of the study that will show the highest lower bound.

| $u$ | $r$-value | lower bound | excluded study   |
|-----|-----------|-------------|------------------|
| 1   | 2.91e-06  | 0.89        | BCIRG 001        |
| 2   | 1.64e-04  | 0.91        | BIG 2-98         |
| 3   | 2.29e-03  | 0.94        | Taxit 216        |
| 4   | 8.32e-03  | 0.96        | NSABP B-28       |
| 5   | 2.81e-02  | 0.99        | HeCOG            |
| 6   | 6.28e-02  | 1.01        | PACS 01          |

4.2 Accounting for multiplicity

When more than one primary endpoint is examined, the $r$-value needs to be smaller in order to establish replicability. This is exactly the same logic as with $p$-values, for which we need to lower the significance threshold when faced with multiplicity of endpoints. Family-wise error rate (FWER) or false discovery rate (FDR) controlling procedures can be applied to the individual $r$-values in order to account for the
Figure 4: The forest plot in the original Review CD008792 including the $r$-value, which was 0.24. The asterisks indicate which study was excluded for the $r$-value computation.

For multiple primary endpoints, see [Benjamini et al., 2009] for details.

For example, in Review CD005211 four endpoints were examined, with the following $r$-values: (1) 0.1231; (2) 0.0017; (3) 0.0167; (4) 0.1776. For FWER control over replicability claims at the 0.05 level, the Bonferroni-adjusted $r$-values are the number of endpoints multiplied by the original $r$-values. Only endpoint (2) is reported as replicated using Bonferroni at the 0.05 level, since it is the only Bonferroni-adjusted $r$-value below 0.05, $4 \times 0.0017 < 0.05$.

For FDR control over replicability claims, we can use the Benjamini-Hochberg (BH) procedure ([Benjamini and Hochberg, 1995]) on the reported $r$-values. The BH-adjusted $r$-values for a sorted list of $M$ $r$-values, $r(1) \leq \ldots \leq r(M)$, are $\min_{i \geq j} \frac{M r(j)}{i}$, $j = 1, \ldots, M$. In Review CD005211, the sorted list is $(0.0017, 0.0167, 0.1231, 0.1776)$ and the adjusted $r$-values are $(0.0068, 0.0334, 0.1641, 0.1776)$. Therefore, endpoints (2) and (3), the two endpoints with the smallest $p$-values in the sorted list, are reported as replicated using FDR at the 0.05 level, since for both endpoints the BH-adjusted $r$-values are below 0.05.
Figure 5: The forest plot in the original Review CD004421 including the \( r \)-value, which was 2.91e-06. The asterisks indicate which study was excluded for the \( r \)-value computation.

5 Discussion

In this work we suggested enhancing the systematic reviews meta-analyses with a measure that quantifies the strength of replicability, i.e., the \( r \)-value. In the reporting, if the \( r \)-value is small we have evidence that the conclusion is based on more than one study, i.e., that the effect was replicated across studies. We suggest adding a cautionary note if the \( r \)-value is greater than the significance level (say = 0.05), that states that the conclusion depends critically on a single study. This does not mean that the conclusion is necessarily reversed, but the large \( r \)-value warrants another examination of the studies in the meta-analysis, and if the single study upon which the review relies was very well conducted the conclusion may still be justified despite it being only a single study.

In our two domains there were typically 1-4 primary endpoints per review. We briefly discussed ways to account for the multiplicity of primary endpoints in assessing replicability in Section 4.2. We regard this as an extension since the emphasis, and the new contribution, of this paper is the introduction of the \( r \)-value into the meta-analysis.
conclusions.

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A Examples for the influenza domain

Our first example is based on a meta-analysis in review CD001269, analyzed by the authors as a random effect meta-analysis, which is non-sensitive and thus has a small $r$-value. The objective of Review CD001269 was to assess the effects of
vaccines against influenza in healthy adults. Four studies were significant (all favoured treatment), and the remaining twelve studies had non-significant effects at the .05 significance level (seven favoured the treatment, five favoured the control). When combined in a meta-analysis the evidence was significant, and the review conclusion was that the placebo arm had a higher risk of Influenza-like illness than the vaccine arm, see the left panel of Figure 6. Even after removing each significant study (in particular the most influential: study number 9) there was still a significant effect in the meta-analysis at the 0.05 level, see the right panel of Figure 6. The \( r \)-value is 0.0014. The significant meta-analytic conclusion can therefore be accompanied by a statement that the replicability claim is established at the .05 level of significance. This is a stronger scientific claim than that of the meta-analysis, and it is supported by the data in this example.

We suggest accompanying the original forest plot with this \( r \)-value, see Figure 7. Note that although the referred meta-analysis is significant and the replicability claim is established at the .05 level of significance, in the main results of Review CD001269 the authors write: “The overall effectiveness of parenteral inactivated vaccine against influenza-like illness (ILI) is limited, corresponding to a number needed to vaccinate (NNV) of 40 (95% confidence interval (CI) 26 to 128).” To this, we suggest adding the following information: “This result was replicated in more than one study (\( r \)-value = 0.0014).” The replicability claim is relevant even in the presence of a limited effect size: at least two studies showed that there is a (possibly limited) effect of parenteral inactivated vaccine against influenza-like illness (ILI) is limited.

![Figure 6](image)

Figure 6: The forest plot in Review CD001269 (Left) and excluding study 9 (Right). The \( r \)-value was 0.0014. The sensitivity interval, [0.75,0.96], is the confidence interval excluding study 9 (the black diamond in the right panel) with an additional (very small) left tail. The axis is on the logarithmic scale.

Our second example, also from the influenza domain, is based on a meta-analysis in review CD001269, analyzed by the authors as a random effects meta-analysis.
Figure 7: The forest plot in the original Review CD001269 including the \( r \)-value, which was 0.0014. The asterisks indicate which study was excluded for the \( r \)-value computation.

In this example the random effect meta-analysis was sensitive. The objective of Review CD008965 was to describe the potential benefits and harms of Neuraminidase inhibitors for influenza in all age groups. In the meta-analysis a significant finding was discovered, see the left panel of Figure 8. Note that only one study was significant and the remaining seven studies were not significant (with large confidence intervals). After removing study number 1, there was no longer a significant effect in the meta-analysis, see the right panel of Figure 8. The \( r \)-value was 0.1206. The replicability claim was not established at the .05 level of significance. This lack of replicability, quantified by the \( r \)-value, cautions practitioners that the significant meta-analysis finding may depend critically on a single study.

We suggest accompanying the original forest plot with this \( r \)-value, see Figure 9. In the main results of Review CD008965 the authors write "In adults treatment tri-
als, Oseltamivir significantly reduced self reported, investigator-mediated, unverified pneumonia (RR 0.55, 95% CI 0.33 to 0.9)”; To this, we suggest adding the following information: “We cannot rule out the possibility that this result is based on a single study (r-value = 0.1206)”. Note that the conclusion was not that complication were reduced, but this was due to lack of diagnostic definitions. The authors conclusion in this review was that "treatment trials with oseltamivir do not settle the question of whether the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions”.

Figure 8: The forest plot in Review CD008965 (Left) and excluding study 1 (Right). The r-value was 0.1206. The sensitivity interval, [0.24, 1.13], is the confidence interval excluding study 1 (the black diamond in the right panel) with an additional (small) right tail. The axis is on the logarithmic scale.

B Sensitivity analysis computation details

Let \( p_{L_{i_1,\ldots,i_k}} \) and \( p_{R_{i_1,\ldots,i_k}} \) be, respectively, the left- and right- p-values from a meta-analysis on the subset \( (i_1,\ldots,i_k) \subset \{1,\ldots,N\} \) of the \( N \) studies in the full meta-analysis, \( k < N \). Let \( \Pi(k) \) denote the set of all possible subsets of size \( k \).

B.1 The r-value computation

For a meta-analysis based on \( N \) studies, a replicability claim is a claim that the conclusion remains significant (e.g., rejection of the null hypothesis of no treatment effect) using a meta-analysis of each of the \( \binom{N}{u-1} \) subsets of \( N - u + 1 \) studies, where \( u = 2,\ldots,N \) is a parameter chosen by the investigator. Specifically, for \( u = 2 \), a replicability claim is a claim that the conclusion remains significant using a meta-analysis of each of the \( N \) subsets of \( N - 1 \) studies.
Figure 9: The forest plot in the original Review CD008965 including the \( r \)-value, which was 0.1206. The asterisks indicate which study was excluded for the \( r \)-value computation.

The \( r \)-value for replicability analysis, where we claim replicability if the conclusion remains significant using a meta-analysis of each of the \( \binom{N}{u-1} \) subsets of \( N - u + 1 \) studies is computed as follows. For left- sided alternative, the \( r \)-value is

\[
r^L = \max_{(i_1, \ldots, i_{N-u+1}) \in \Pi(N-u+1)} p^L_{i_1, \ldots, i_{N-u+1}}.
\]

For right- sided alternative, the \( r \)-value is

\[
r^R = \max_{(i_1, \ldots, i_{N-u+1}) \in \Pi(N-u+1)} p^R_{i_1, \ldots, i_{N-u+1}}.
\]

For two-sided alternatives, the \( r \)-value is

\[
r = 2 \min(r^L, r^R).
\]

### B.2 Sensitivity analysis for confidence intervals

The sensitivity interval is the union of all the meta-analysis confidence intervals using the \( \binom{N}{u-1} \) subsets of \( N - u + 1 \) studies. The upper limit of the \( (1 - \alpha) \) sensitivity
interval is the upper limit of the \((1 - \alpha)\) confidence interval from the meta-analysis on \((i^L_1, \ldots, i^L_{N-u+1})\), where \((i^L_1, \ldots, i^L_{N-u+1})\) is the subset that achieves the maximum \(p\)-value for the left-sided \(r\)-value computation. Similarly, the lower limit of the \((1 - \alpha)\) sensitivity interval is the lower limit of the \((1 - \alpha)\) confidence interval from the meta-analysis on \((i^R_1, \ldots, i^R_{N-u+1})\), where \((i^R_1, \ldots, i^R_{N-u+1})\) is the subset that achieves the maximum \(p\)-value for the right-sided \(r\)-value computation.

The meta-analysis is non-sensitive (at the desired value of \(u\)) if and only if the sensitivity interval does not contain the null hypothesis value. This follows from the following argument. To see this, note that \(r \leq \alpha\), if and only if \(r^L \leq \alpha/2\) or \(r^R \leq \alpha/2\). Since \(r^L \leq \alpha/2\) if and only if the upper limit of all the meta-analysis \(1 - \alpha\) confidence intervals of subsets of size \(N - u + 1\) is below the null value, and \(r^R \leq \alpha/2\) if and only if the lower limit of all the meta-analysis \(1 - \alpha\) confidence intervals of subsets of size \(N - u + 1\) is above the null value, the result follows.

**B.3 Leave-one-out sensitivity procedure**

For meta-analysis with \(N\) studies and significant effect size \(\theta < \theta_0\), where \(\theta_0\) is the null effect, e.g., \(1\) for HR (two-sided alternative):
1) Compute meta-analysis of each of the \(\binom{N}{u-1}\) subsets of \(N - u + 1\) studies.
2) Choose the \(N - u + 1\) subset of studies that achieves the maximum \(p\)-value for the left-sided \(r\)-value computation: \((i^L_1, \ldots, i^L_{N-u+1})\).
3) Compute the two-sided \(r\)-value:
\[
r = 2 \min(r^L, r^R).
\]
4) If the \(r\)-value \(\leq 0.05\), the replicability is established in at least \(u\) studies. Otherwise, the replicability is established in at most \(u - 1\) studies (for \(u=2\), \(r\)-value \(> 0.05\) means that the finding is not replicable).

For meta-analysis with \(N\) studies and significant effect size \(\theta > \theta_0\), where \(\theta_0\) is the null effect, e.g., \(1\) for HR (two-sided alternative):
1) Compute meta-analysis of each of the \(\binom{N}{u-1}\) subsets of \(N - u + 1\) studies.
2) Choose the \(N - u + 1\) subset of studies that achieves the maximum \(p\)-value for the right-sided \(r\)-value computation: \((i^R_1, \ldots, i^R_{N-u+1})\).
3) Compute the two-sided \(r\)-value:
\[
r = 2 \min(r^L, r^R).
\]
4) If the \(r\)-value \(\leq 0.05\), the replicability is established in at least \(u\) studies. Otherwise, the replicability is established in at most \(u - 1\) studies (for \(u=2\), \(r\)-value \(> 0.05\) means that the finding is not replicable).