Title: Analysis of cluster randomised trials as though individually randomised in meta-analyses

Authors:
Mark J Bolland, MBChB, PhD[1], m.bolland@auckland.ac.nz
Alison Avenell, MB BS MD[2], a.avenell@abdn.ac.uk
Andrew Grey, MD[1], a.grey@auckland.ac.nz

Author Affiliation:
[1]Department of Medicine, University of Auckland, Private Bag 92 019, Auckland 1142, New Zealand
[2]Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland

Word count: 393

Appendix: Not for publication, but to assist with the understanding of the letter, the appendix contains the results of the analyses referred to in the letter.

Address for correspondence:
Associate Professor Mark Bolland
Bone and Joint Research Group,
Department of Medicine,
University of Auckland
Private Bag 92 019,
Auckland 1142,
New Zealand
Email: m.bolland@auckland.ac.nz
Ph 64 9 373 7999
Fax 64 9 373 7677

Conflicts of interest:
The authors have no conflicts of interest to declare

The meta-analysis by Jolliffe and colleagues[1] includes two cluster randomised controlled trials (RCTs) that were analysed as though they were individually randomised. This approach will overestimate the precision of the effect size for cluster RCTs. This is illustrated by imagining a cluster RCT where the outcome event is highly contagious, such that if one person in a randomised cluster is infected, all other people in the cluster are likely to become infected. If everyone experiences the same outcome in the cluster, the effective sample size is the number of clusters not the number of participants. On the other hand, if there is no relationship between the cluster of a participant and the outcome (ie they are completely independent), the cluster provides no additional information and the sample size is effectively the number of participants. This relationship for the cluster and the outcome is measured by the intracluster correlation coefficient (ICC) which can lie between 0 and 1: 0 means the outcome is completely independent, and 1 that all participants have an identical outcome. For most cluster RCTs, the ICC is in the range of 0.01-0.10.

Incorporating cluster RCTs into a meta-analysis of individually randomised RCTs is not straightforward.[2] Three approaches could be undertaken.[2] If individual raw data are available, as for the cluster RCTs in the meta-analysis by Jolliffe, those data can be analysed using appropriate methods, (for these cluster RCTs, random-effects logistic regression would be one such approach), and the effect estimate for the study pooled with the data for the other RCTs. If individual patient data are not available, the effect size can be estimated by shrinking the sample size by the design factor which is calculated from the ICC and the average cluster size. Thus, the number of participants with the outcome and the total number of participants are divided by the design factor and the results analysed in standard fashion with the remaining RCTs. Finally, because the cluster RCTs have different study designs and

require different analytic methods, it would be sensible to perform a sensitivity analysis where the cluster RCTs are excluded.

For the current meta-analysis, when any of these three approaches are undertaken the results of the primary analysis change.[3,4] Therefore, it would be helpful for readers if the publication reported the results of analyses in which the cluster RCTs are not analysed as though individually randomised.

References

1. Jolliffe DA, Camargo CA, Jr., Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2021; **9**:276-92.
2. Higgins JPT, Eldridge S, Li T, (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane; 2021.
3. Bolland MJ, Avenell A, Grey A, Gamble GD. Vitamin D and acute respiratory infection: secondary analysis of a previous randomised controlled trial and updated meta-analyses. *medRxiv* 2022:https://www.medrxiv.org/content/10.1101/2022.02.03.22270409v1.
4. https://pubpeer.com/publications/7A8DA0A9B233618CB397F9DDF2A1A6

Appendix:

For review only (if required). Not intended for publication but to allow the verification that results of analyses do change when the cluster RCT is not analysed as individually randomised. Using all 3 methods, the pooled effect estimate is OR 0.94, 0.88-1.01.

Individual data are only publicly available for Camargo 2012. Data from ViDiFlu are not available for analyses.

Method 1:
Individual patient data from Camargo 2012 analysed using random effects logistic regression accounting for cluster design. Effect estimate is 0.43 (0.16-1.10) as described in https://www.medrxiv.org/content/10.1101/2022.02.03.22270409v1

Meta-analysis performed with Comprehensive Meta-analysis V2.

Figure 1: analysis replicating analysis by authors (pooled effect size OR 0.92, 0.86-0.99)

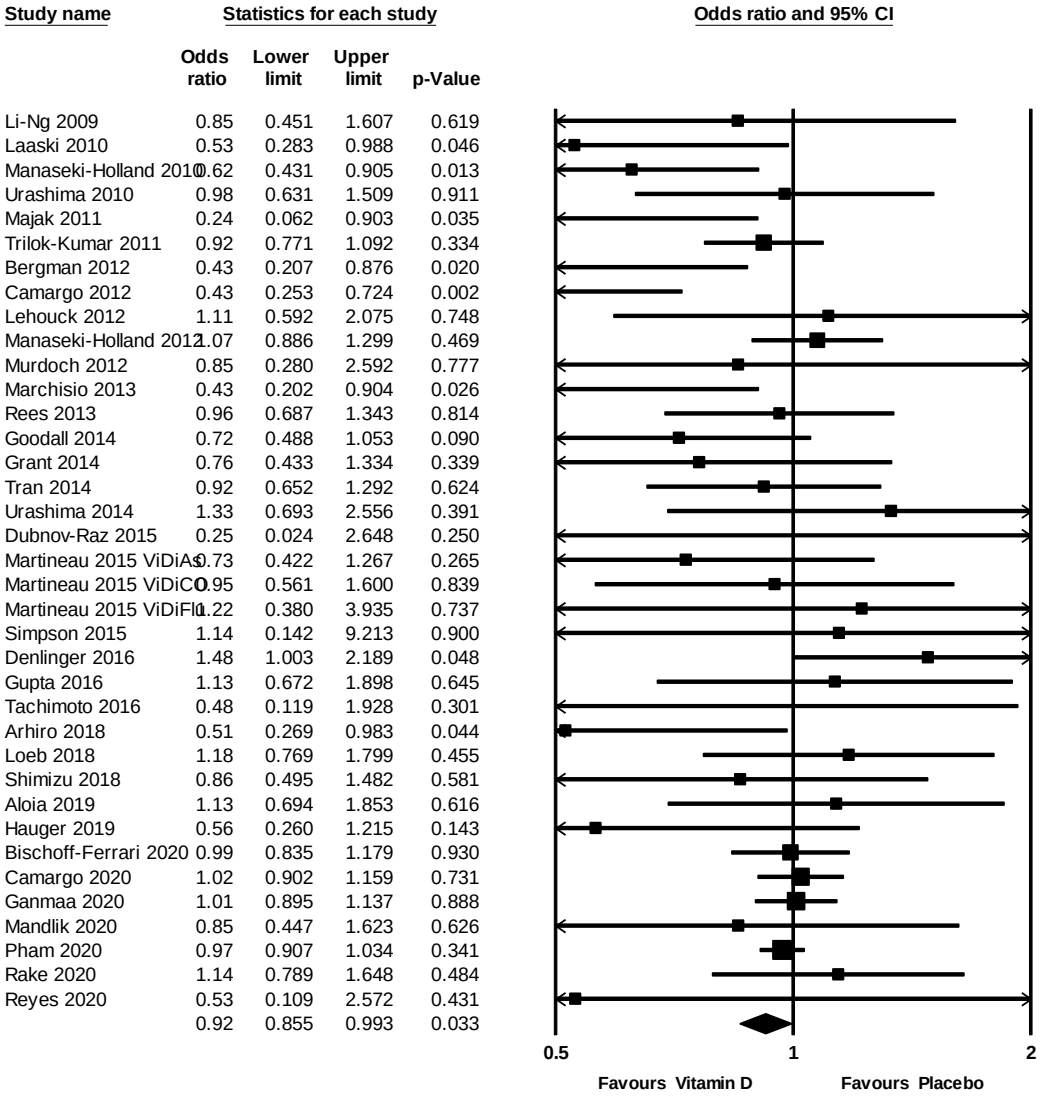
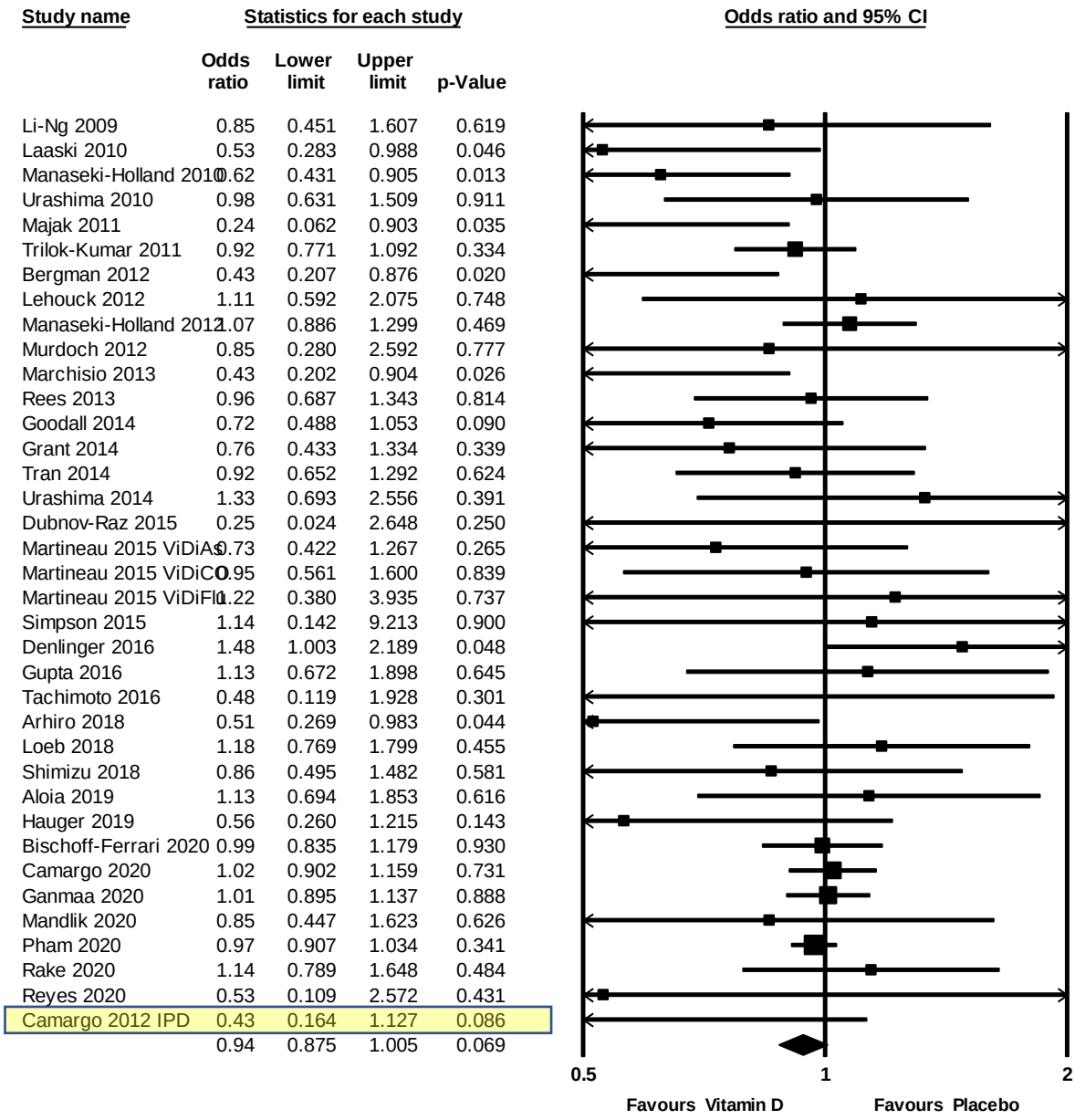


Figure 2: analysis uses effect estimate for Camargo 2012 from individual patient data (highlighted) (pooled effect size OR 0.94, 0.88-1.01)



Method 2:

Using ICC of 0.08 and design factor of 3.75 as calculated from individual patient data from entire trial, as described in
https://www.medrxiv.org/content/10.1101/2022.02.03.22270409v1

Thus, summary data for Camargo 2012 changes from 44/141, 53/103 to 11.7/37.6, 14.1/27.4

Meta-analyses performed using Meta package in R.

Figure 3: analysis replicating analysis by authors (pooled effect size OR 0.92, 0.86-0.99)

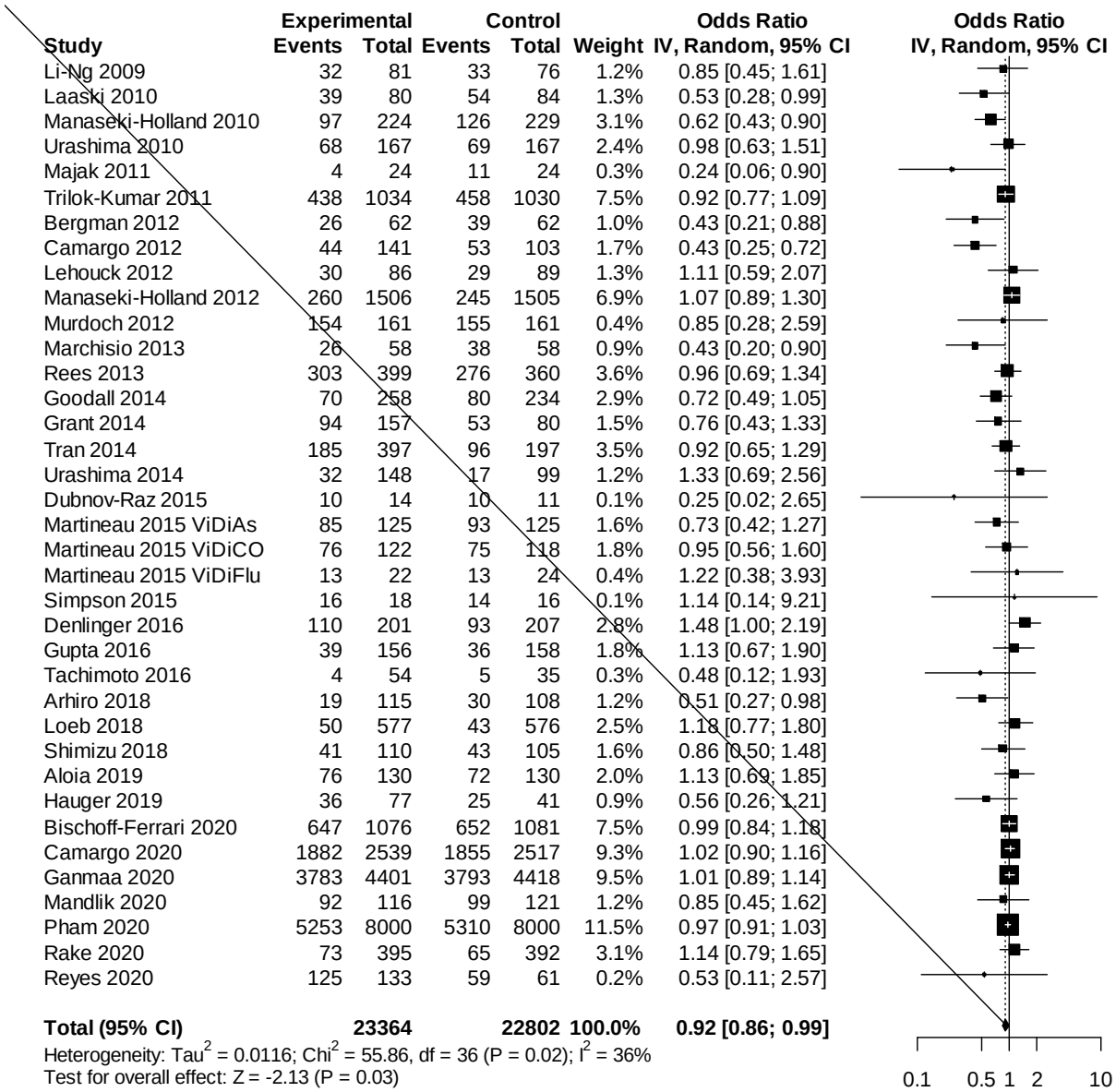
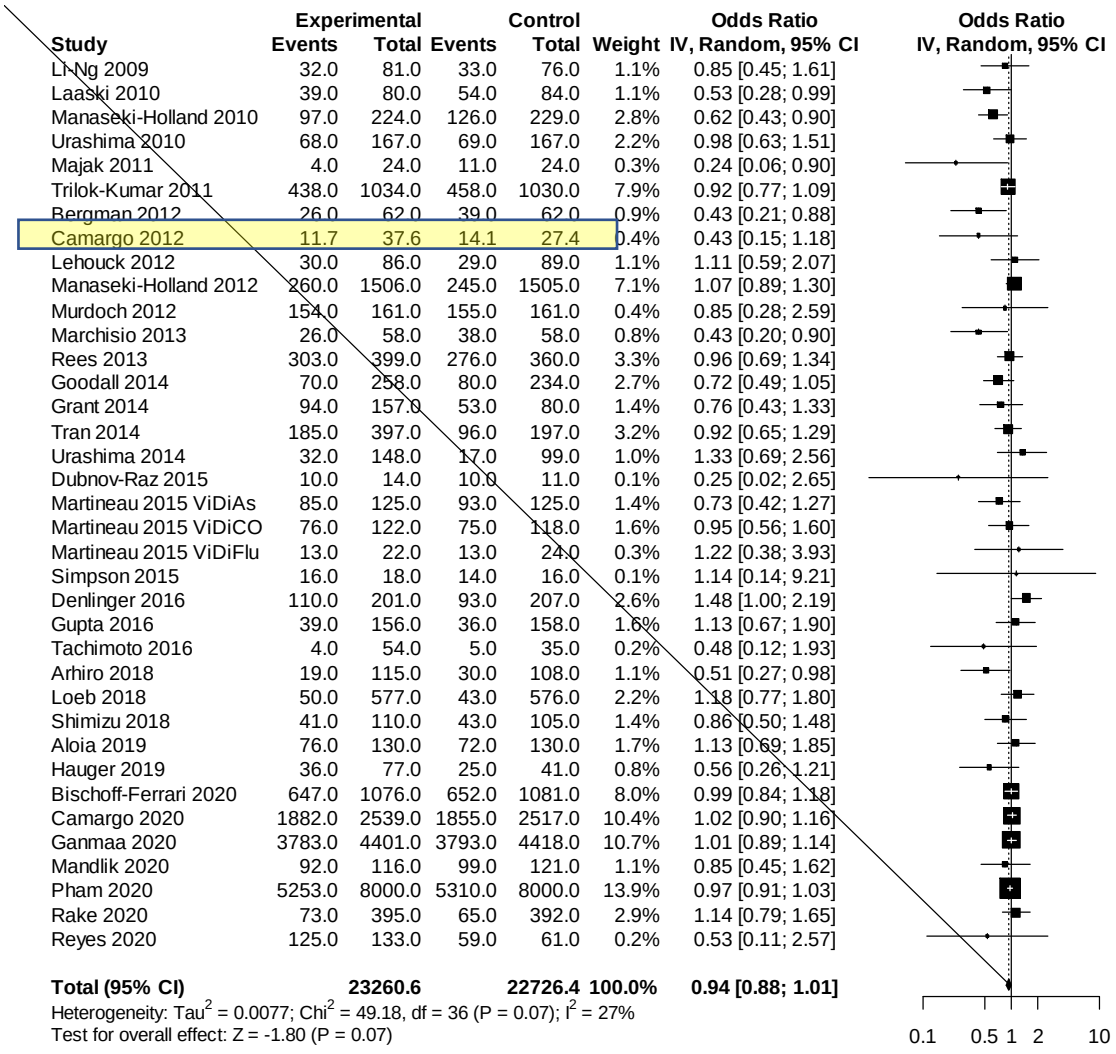


Figure 4: analysis uses effect estimate for Camargo 2012 from summary data adjusted for design factor (highlighted) (pooled effect size OR 0.94, 0.88-1.01)

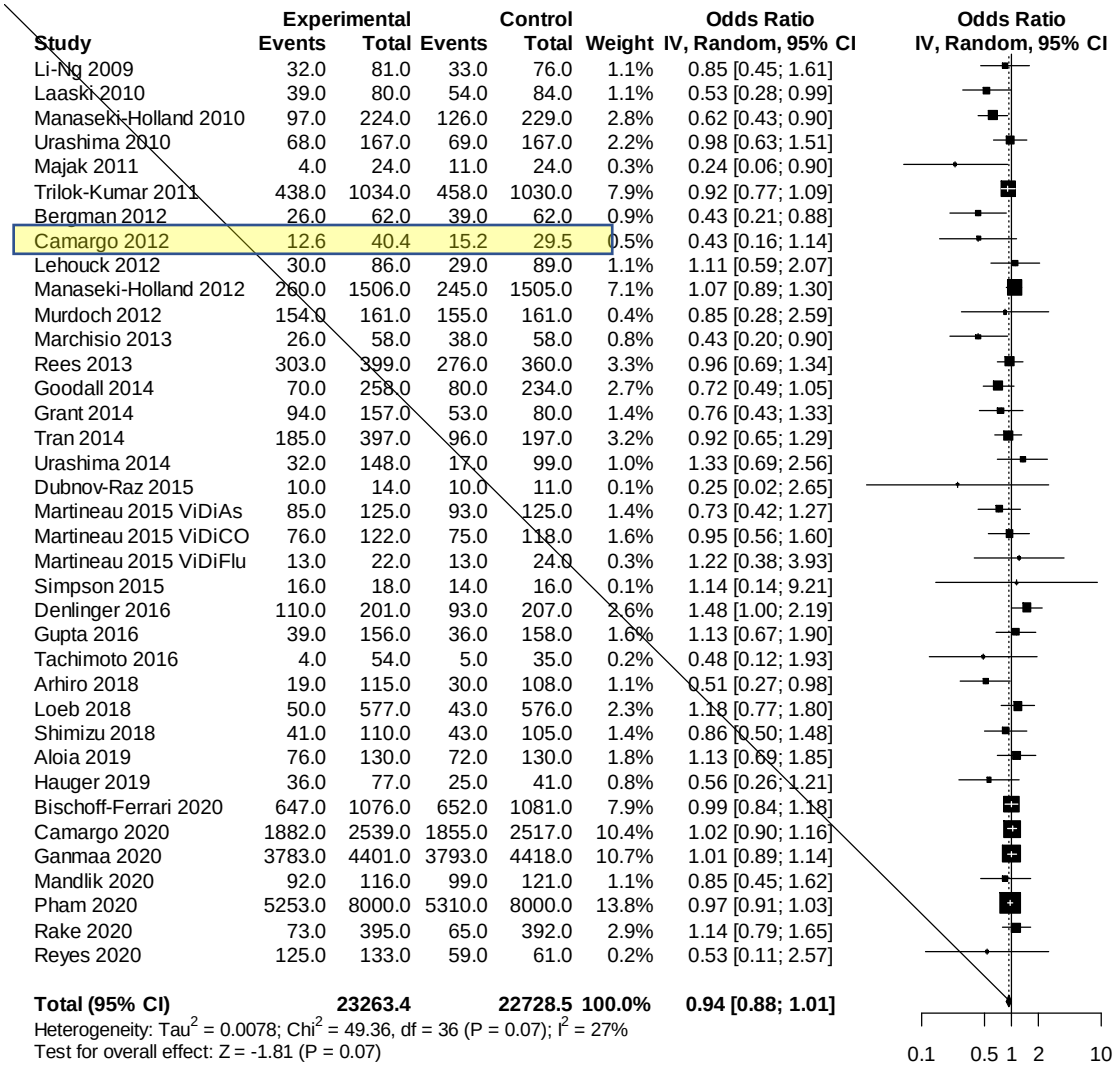


The ICC was calculated using the ICCbin package in R (anova method) and was 0.08. The authors responded https://pubpeer.com/publications/E6DBD1B0152D16244B71E72CEDA89D) that when only 2 arms of the Camargo 2012 are included, the ICC was 0.07 (no details of calculation provided), and therefore the design factor was 3.49.

Using the above methods and restricting the dataset to two arms of the trial, the ICC (anova method, ICCbin package) was unchanged at 0.08

Using a design factor of 3.49, as reported by the authors, summary data for Camargo 2012 changes from 44/141, 53/103 to 12.6/40.4, 15.2/29.5

Figure 5: analysis uses effect estimate for Camargo 2012 from summary data adjusted for design factor reported by authors (highlighted) (pooled effect size OR 0.94, 0.88-1.01)



Method 3:

Sensitivity analysis excluding both cluster randomised trials that were analysed as individually randomised. Note- pooled effect size is same whether Camargo 2012 alone or Camargo 2012 and ViDiFlu are excluded.

Figure 5: sensitivity analysis excluding Camargo 2012 and ViDiFlu (pooled effect size OR 0.94, 0.88-1.01)