A REVIEW

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Systematic reviews and Meta-analysis: The best evidence by combining data from several studies

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The practice of evidence based medicine is the integration of individual clinical expertise with the best available external clinical evidence from systematic research and patient's values and expectations. We need evidence for both clinical practice and for public health decision making. The evidence come from good reviews which is a state-of-the-art synthesis of current evidence on a given research question. Given the explosion of medical literature, and the fact that time is always scarce, review articles play a vital role in decision-making in evidence based medical practice. Given that most clinicians and public health professionals do not have the time to track down all the original articles, critically read them, and obtain the evidence they need for their questions, therefore, systematic reviews and clinical practice guidelines may be their best source of evidence. Hence, the objective of this article is to introduce readers to the concept of systematic reviews and meta-analysis, outlining why they are important, describing their methods and terminologies used and thereby helping readers with the skills to recognize and understand a reliable review.

Key words : Evidence based medicine, Systematic review, Meta-analysis

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INTRODUCTION

Evidence-based healthcare is the integration of best research evidence with clinical expertise and patient values (Sackett *et al*., 1996). Using evidence from reliable research, to inform healthcare decisions, has the potential to ensure best practice and reduce variations in healthcare delivery. However, incorporating research into practice is time consuming, and so we need methods of facilitating easy access to evidence for busy clinicians. Systematic reviews aim to inform and facilitate this process through research synthesis of multiple studies, enabling increased and efficient access to evidence (Green, 2005). Objectives of this article are to introduce readers to the two approaches to evaluating all the available evidence on an issue *i.e.* systematic reviews and meta-analysis, to discuss the steps in doing a systematic review , to introduce the terms used in systematic reviews and meta-analysis, to interpret results of a meta-analysis and the advantage and flaws of systematic review and meta analysis.

What is the effect of anti viral treatment in dengue fever?

To find out the solutions or answers to a clinical question like this, one has either to refer textbooks, ask a colleague or search electronic data-base for reports of clinical trials. Doctors need reliable information on such problems and on the effectiveness of large number of therapeutic interventions – but the information sources are too many: nearly 20,000 journals – 2 million articles per year with unclear or confusing results. Because no study, regardless of its type, should be interpreted in isolation, a systematic review is generally the best form of evidence (Glasziou *et al.,* 2004). So the preferred method is a good summary of research reports *i.e.* systematic reviews and meta-analysis.

There are two fundamental categories of research: primary research and secondary research. Primary research is collecting data directly from patients or population while the secondary research is the analysis of data already collected through primary research.

A review is an article that summarizes a number of

primary studies and may draw conclusions on the topic of interest which can be traditional (unsystematic) or systematic.

Systematic review:

A systematic review is a summary of the medical literature that uses explicit and reproducible methods to systematically search, critically appraise and synthesize on a specific issue. It synthesizes the results of multiple primary studies related to each other by using strategies that reduce biases and random errors (Cook *et al.,* 1997). To this end, systematic reviews may or may not include a statistical synthesis called meta-analysis, depending on whether the studies are similar enough so that combining their results is meaningful (Clarke, 2007). Systematic reviews are often called overviews. The evidence-based practitioner, (Sackett *et al*., 1996) defines,

– Review: the general term for all attempts to synthesize the results and conclusions of two or more publications on a given topic.

– Overview: when a review strives to comprehensively identify and track down all the literature on a given topic (also called "systematic literature review").

– Meta-analysis: a specific statistical strategy for assembling the results of several studies into a single estimate (Green, 2005).

Cochrane reviews:

Cochrane reviews are systematic reviews undertaken by members of the Cochrane Collaboration which is an international organization that aims to help people to make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions.

Meta analysis:

A meta-analysis is the combination of data from several independent primary studies that address the same question to produce a single estimate like the effect of treatment or risk factor. It is the statistical analysis of a large collection of analysis and results from individual studies for the purpose of integrating the findings (Glass, 1979). The term Meta-analysis has been used to denote the full range of quantitative methods for research reviews (Goldman *et al.*, 1979). Meta-analyses are studies of studies.(Kassirer, 1992) Meta-analysis provides a logical framework to a research review where similar measures from comparable studies are listed systematically and the available effect measures are combined wherever possible (Kavale *et al.*, 1998).

The fundamental rationale of meta-analysis is that it reduces the quantity of data and helps to plan research as well as to frame guidelines. It also helps to make efficient use of existing data, ensuring generalizability, helping to check consistency of relationships, explaining data inconsistency and quantifies the data. It helps to improve the precision in estimating the risk by using explicit methods.

Therefore 'systematic review' will refer to the entire process of collecting, reviewing and presenting all available evidence, while the term 'meta-analysis' will refer to the statistical technique involved in extracting and combining data to produce a summary result (Anonymous, 2002).

Steps in doing Systematic Reviews / Meta-Analysis:

There are 6 steps in doing Systematic reviews / Meta-analysis (Higgins and Green, 2009).

Define the question:

This is the most important part of Systematic reviews / Meta-Analysis. The research question for the systematic reviews may be related to a major public health problem or a controversial clinical situation which requires acceptable intervention as a possible solution to the present healthcare need of the community. This step is most important since the remaining steps will be based on this.

Reviewing the literature:

This can be done by going through the electronic database, controlled clinical trials registers, other biomedical databases, non-english literatures, "grey literatures" (thesis, internal reports, non-peer reviewed journals, pharmaceutical industry files), references listed in primary sources, raw data from published trials and other unpublished sources known to experts in the field etc.

Shift the studies to select relevant ones:

To select the relevant studies from the searches, we need to sift through the studies thus identified. The first sift is 'pre-screening' , it is to decide which studies to retrieve in full and the second sift is 'selection' which is to look again at these studies and decide which are to be included in the review. The next step is selecting the eligible studies based on similar study designs, year of publication, language, choice among multiple articles, sample size or follow up issues, similarity of exposure

and or treatment and completeness of information.

It is necessary to ensure that the sifting includes all relevant studies like the unpublished studies (desk drawer problem), studies which came with negative conclusions or published in non-English journals and studies with small sample size.

Assess the quality of studies:

The steps undertaken in evaluating the study quality are early definition of study quality and criteria, setting up a good scoring system, developing a standard form for assessment, calculating quality for each study and finally using this for sensitivity analysis.

For example the quality of a randomized controlled trial can be assessed by finding out the answers to the following questions:

– Was the 'assignment' to the treatment groups really 'random'?

– Was the 'treatment allocation concealed'?

– Were the 'groups similar at baseline' in terms of prognostic factors?

– Were the 'eligibility criteria specified'?

– Were the 'assessors, the care provider', and the 'patient blinded'?

– Were the 'point estimates and measure of variability' presented for the primary outcome measure?

– Did the analyses include 'intention-to- treat analysis'?

Calculate the outcome measures of each study and combining them:

We need a standard measure of outcome which can be applied to each study on the basis of its effect size. Based on their type of outcome following are their measures of outcome such as studies with binary outcomes (cured/not cured) have odds ratio, risk ratio, studies with continuous outcomes (blood pressure) have means, difference in means, standardized difference in means (effect sizes) and survival or time to event data have hazard ratios.

Combining studies:

Homogeneity of different studies can be estimated at a glance from a Forest plot (explained below). For example if the lower confidence Interval of every trial is below the upper of all the others *i.e.* the lines all overlap to some extent then the trials are homogeneous. If some lines do not overlap at all, these trials may be said to be heterogeneous.

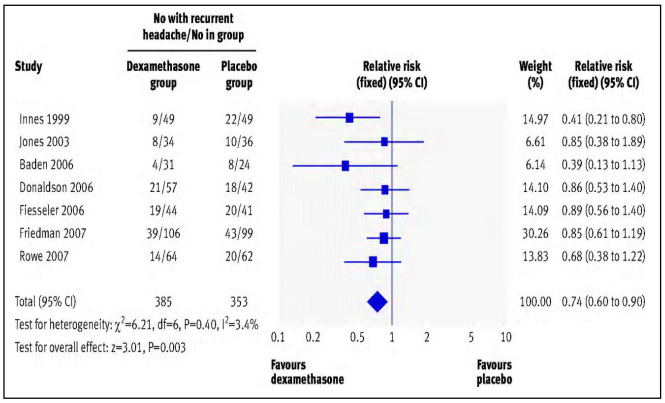
The definitive test for assessing the heterogeneity of studies is a variant of chi-square test (Mantel-Haenszel test). The final step is calculating the common estimate and its confidence interval with the original data or with the summary statistics from all the studies. The best estimate of treatment effect can be derived from the weighted summary statistics of all studies which will be based on weighting to sample size, standard errors etc. Log Scale is used to combine the data to estimate the weighting.

Interpret results: Forest plot

The results of a meta-analysis are usually presented as a graph called Forest plot because the typical forest plots appear as forest of lines. It provides a simple visual presentation of individual studies that went into the meta-analysis at a glance. They show the variation between the studies and an estimate of the overall result of all the studies together.

In the Forest plot, the horizontal lines represent individual studies. Length of line is the Confidence Interval (usually 95%), squares on the line represent effect size (risk ratio) for the study, area of the square being the study size (proportional to weight given) and position as point estimate (Relative Risk) of the study (Cook *et al.,* 1997).

For example the forest plot of the effectiveness of dexamethasone compared with placebo in preventing the recurrence of acute severe migraine headache in adults is shown below (Sedgwick, 2011)



The overall effect is shown as diamond where the position towards the centre represents pooled point estimate, the width represent estimated 95% Confidence Interval for all studies and the black plain line vertically in the middle of plot is the "line of no effect" (*e.g.* Relative Risk = 1).

Therefore, when examining the results of a systematic reviews / meta-analysis, the following questions should be kept in mind:

– Were apples combined with oranges?
- Heterogeneity among studies may make any pooled estimate meaningless.

– Were all of the apples rotten?
- The quality of a meta-analysis cannot be any better than the quality of the studies it is summarizing.

– Were some apples left on the tree?
- An incomplete search of the literature can bias the findings of a meta-analysis.

– Did the pile of apples amount to more than just a hill of beans?
- Make sure that the meta-analysis quantifies the size of the effect in units that you can understand

Subgroup analysis and sensitivity analysis:

Subgroup analysis looks at the results of different subgroups of trials, *e.g.* by considering trials on adults and children separately. This should be planned at the protocol stage itself which is based on good scientific reasoning and is to be kept to a minimum.

Sensitivity analysis is used to determine how results of a systematic reviews / meta-analysis change by fiddling with data, for example "what if" changed exclusion criteria or excluded unpublished studies or weightings assigned differently etc. Thus after the analysis if changing makes little or no difference to the overall results, the reviewer's conclusions are robust. If the key findings disappear, then the conclusions need to be expressed more cautiously.

Advantages of systematic reviews (Greenhalgh, 1997):

Systematic reviews have specific advantages because of using explicit methods which limits bias, draw reliable and accurate conclusions, easily delivers required information to healthcare providers, researchers and policymakers, helps to reduce the time delay in the research discoveries to implementation, improves the generalizability and consistency of results, generation of new hypotheses about subgroups of the study population and overall it increases precision of the results.

Flaws in systematic reviews/Meta-analysis:

Even though systematic review and meta analysis are considered best evidence for getting a definitive answer to a research question, there are certain inherent flaws associated with it, such as the location and selection of studies, heterogeneity, loss of information on important outcomes, inappropriate subgroup analyses, conflict with new experimental data and duplication of publication.

Publication bias:

Publication bias results in it being easier to find studies with a 'positive' result (Anonymous, 2002). This occurs particularly due to inappropriate sifting of the studies where there is always a tendency towards the studies with positive (significant) outcomes. This effect occurs more commonly in systematic reviews / meta-analysis which need to be eliminated.

Summary points:

A systematic review is an overview of primary studies which contains an explicit statement of objectives, materials has been conducted according to explicit and reproducible methodology. A meta-analysis is a mathematical synthesis of the results of two or more primary studies that addressed the same hypothesis in the same way. Although meta-analysis can increase the precision of a result, it is important to ensure that the methods used for the reviews were valid and reliable Chalmers and Altman, 1995).

High–quality systematic reviews and meta-analysis take great care to find all relevant studies, critically assess each study, synthesis the findings from individual studies in an unbiased manner and present balanced important summary of findings with due consideration of any flaws in the evidence. Thus, systematic reviews and meta analysis is a way of summarizing research evidence, which is generally the best form of evidence, and hence positioned at the top of the hierarchy of evidence.

LITERATURE CITED

Anonymous (2002). *An introduction to meta-analysis*, Cochrane Collaboration open learning material for reviewers, Version 1.1, November 2002, available at: http://www.cochrane-net.org/openlearning/html/mod3-2.htm

Anonymous (2002). Publication Bias, Cochrane Collaboration open learning material for reviewers, Version 1.1, November 2002. Available at : http://www.cochrane-net.org/openlearning/html/mod15-2.htm

Chalmers, I. and Altman, D.G. (1995). *Systematic reviews*. London: BMJ Publishing Group, 1995.

Clarke, M. (2007). The Cochrane Collaboration and systematic reviews. *British J. Surgery*, **94**: 391–392. doi: 10.1002/bjs.5812

Cook, D.J., Mulrow, C.D. and Haynes, R.B. (1997). Systematic reviews: synthesis of best evidence for clinical decisions. *Ann. Internat. Med.,* **126**(5):376-380.

Glass, G. V. (1976). Primary, secondary, and meta-analysis of research. *Edu. Researcher,* **5**: 3-8.

Glasziou, P., Vanderbroucke, J. and Chalmers, I. (2004). Assessing the quality of research. BMJ., **328**:39-41.

Green, S. (2005). Systematic review and meta analysis, *Singapore Med. J.,* **46**(6): 270.

Greenhalgh T. (1997). Papers that summarise other papers (systematic reviews and meta-analyses). *BMJ*. **315**(7109):672-675.

Goldman, L. and Feinstein, AR. (1979). Anticoagulants and myocardial infarction. The problems of pooling, drowning, and floating. *Ann. Internat. Med.,* **90**(1): 92-94.

Higgins, J.P.T. and Green, S. (editors). (2009). *Cochrane Handbook for systematic reviews of interventions* Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

Kassirer, J.P. (1992). Clinical trials and meta-analysis. What do they do for us? *N England J. Med.,* **327**(4):273-274.

Kavale, K.A. and Glass, G.V. (1998). Meta-analysis and the integration of research in special education. *J. Learn Disabil.,* **14**(9):531-538.

Sackett, D., Rosenberg, W.M., Gray, J.A., Haynes, R.B. and Richardson, W.S. (1996). Evidence based medicine: what it is and what it isn't. BMJ, **312**:71-72.

Sedgwick, P. (2011). Meta-analyses I. BMJ, 342:345.

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