Understanding and Appraising Systematic Reviews and Meta-Analysis

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Systematic reviews and meta-analysis seek to answer a pre-framed research question to lead to a valid answer through a systematic, explicit and reproducible method of locating; identifying, including and appraising appropriate trials. The results are synthesized considering the methodological rigor of included trials. While the meta-analysis quantitatively pools the results from individual included studies, the systematic review summarizes the findings as qualitative conclusions. These reviews are crux of evidence based dentistry for various stake-holders, i.e., clinicians, researchers and policy-makers. Although the meticulous methodology of systematic review and meta-analysis minimizes the elements of bias, yet the validity and reliability of their findings should be explored prior to translating their conclusions to practice. The goal of this paper is to familiarize readers with rationale, conduct and appraisal of systematic review and meta-analysis. Further, guidance is provided on tracing potential elements of bias in the review to enable readers to judge the quality of evidence generated from the review.

Key words: *AMSTAR, Evidence based dentistry, Meta-analysis, Systematic review.*

INTRODUCTION

Owing to the avalanche of studies being published in the recent years, looking for the best evidence has become like *'looking for a needle in a giant heap of sawdust'*. The 'PubMed' comprises more than 24 million citations for biomedical literature from MEDLINE, life science journals and online books.[1] Sorting out the best evidence from this vast pool of available literature is an off-putting task if one tries to look at the individual studies and attempts to fit the findings of these multiple studies to a particular clinical situation.[2,3] Moreover, it becomes even tougher when individual studies report disparate results of the same research question In such a scenario, systematic review and meta-analysis come to rescue and facilitate path to conclusive overview of the vast literature (Box 1). Cleanly stating systematic reviews provide a comprehensive qualitative overview of literature and meta-analysis provide a collective quantitative summary of the available literature to answer a specific pre-framed research question or a clinical situation.[2] These are considered to be the best available evidence and occupy top place in the hierarchy of the evidence.[3]

Box 1: Utility of systematic review and meta-analysis[2,3]

1. Provide conclusive evidence from pre-appraised literature.
2. Pool the results from individual studies and overcome the limitation of small sample size; thereby, increases the power as well as precision of effect estimates
3. Resolve conflict arising from disparate findings across multiple studies
4. Serve as a basis of evidence based practice, formulation of clinical guidelines and directing future research

The following text in the present paper has been framed to enable readers understand the current standing, conduct, appraisal and application of these. With the help of this paper we seek to provide guidance on framing the research question, locating systematic review and understanding as well as appraising systematic review and meta-analysis.

Current standing of systematic reviews and meta-analysis

Systematic reviews and meta-analysis are becoming increasingly popular scientific documents in the bio-medical literature. Their popularity is rising swiftly in dentistry and this is clearly visible by observed trends of publication of systematic review and meta-analysis in the dental journals (Figure 1). Our search through PubMed with filters activated for article types (systematic review and meta-analysis), language (English), journal categories (dental

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journals) and publication dates revealed that from 1996-2015 a total of 3175 systematic reviews and meta-analysis were published (Figure 1).

Although most prevalent review types, it is interesting to note that systematic reviews and meta-analysis are one of the 14 types of reviews prevalent in biomedical literature[4] (Box 2; for avoiding confusion only relevant ones are described here). These various types of reviews have been classified on the basis of search methodology, appraisal of collected literature (qualitative or quantitative) and synthesis of evidence (Table 1). All identified review types are not mutually exclusive of each other (Box 2) e.g. a meta-analysis is often preceded by a systematic review. Nevertheless, the comprehensive, explicit and reproducible methodology of systematic review and meta-analysis with a provision for pooling the results from included studies makes them stand apart from other types of reviews (Box 2, Table 1). Although most of the systematic reviews and meta-analysis focus on interventions, i.e., therapy or prevention the province of these reviews are diverse, i.e., adverse effects, etiology, risk, prevalence, prognosis, disease markers, diagnostic tests and economic evaluations, etc.

Figure 1a: Gradual rise in number of published systematic reviews and meta-analysis (on the basis of PubMed search)

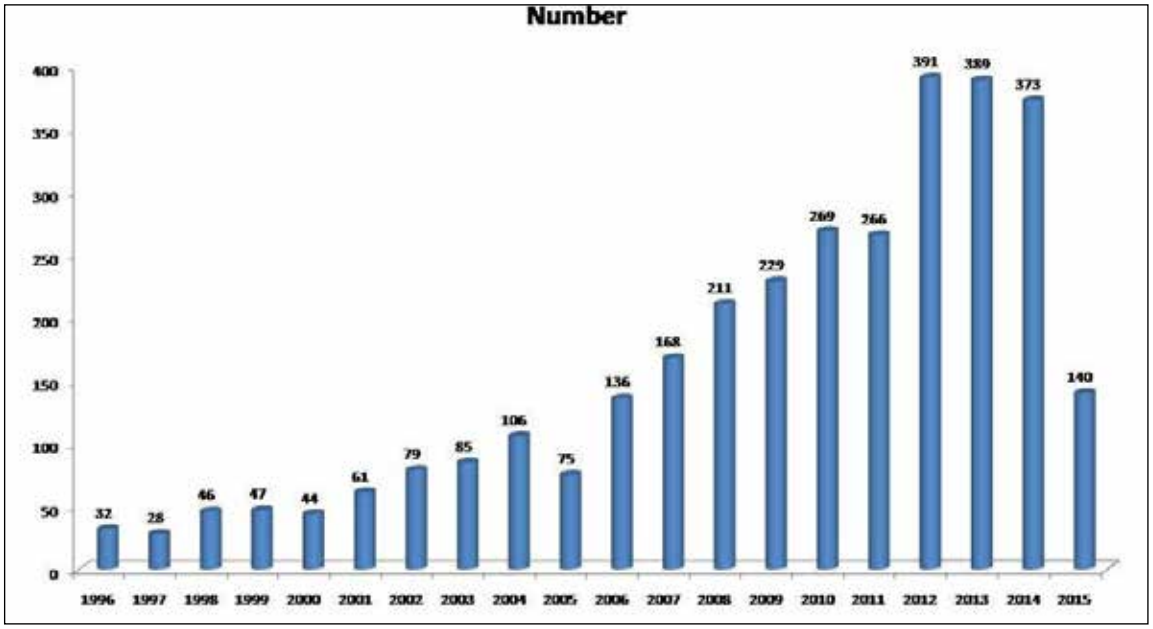


Figure 1b: Distribution of published systematic review and meta-analysis (in percentage)

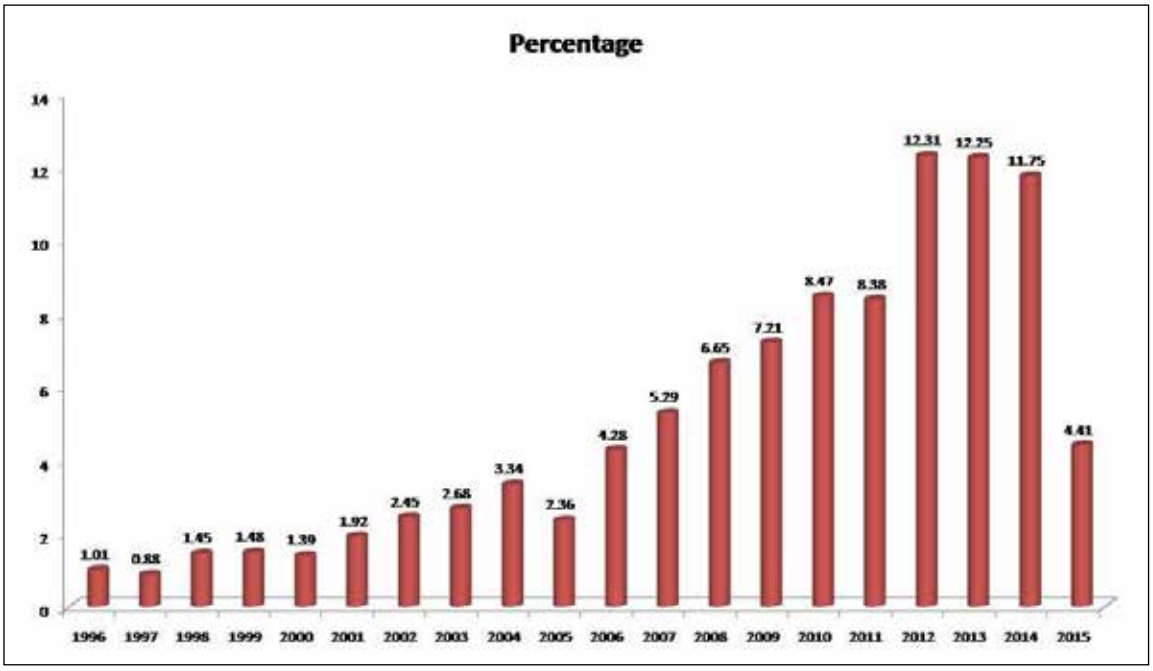


Table 1: A comparative insight into various types of reviews in biomedical literature[4]

Type of review	Search strategy	Appraisal of literature	Evidence synthesis	Strength	Weakness
Critical review	Comprehensive Non-systematic	Conceptual Analytical Subjective Informal	Qualitative Subjective	Gives a conceptual analytic overview of the published literature	Dependent on authors' inclinations and experience. Has an inherent component of subjectivity and bias
Systematic review[5]	Comprehensive Systematic Predefined	Developed a priori Pragmatic Explicit Reproducible	Qualitative Objective	Summarizes the best available evidence	Only gives an insight into effectiveness/in-effectiveness of a particular intervention and misses on why any intervention was particularly effective
Meta-analysis[5]	Comprehensive Systematic Predefined	Developed a priori Pragmatic Explicit Reproducible Statistical approach	Quantitative Objective	Mathematical synthesis of best available evidence to give objective quantitative overview	May give misleading results in presence of heterogeneity
Overview	Comprehensive Non-systematic	Random Subjective	Qualitative Subjective	Provides a broad overview	Discriminate component for quality of primary studies is not included
Umbrella review	Inclusion of reviews (usually systematic and meta-analysis) No attempt to include primary studies	Focused on reviews May appraise primary studies as component of included reviews	Qualitative Objective	Gives the overall picture of a broad topic by combining multiple existing reviews into one	Depends on pre-existence of quality reviews, i.e., systematic reviews and meta-analysis
State of the art review	Comprehensive Temporal Systematic Predefined	Informal	Qualitative Subjective	Gives an insight into current standing on any existing topic	Ignorant of past evidence

Locating systematic reviews

The most popular and user friendly databases to locate systematic review are PubMed systematic review search page[6] and Cochrane Library.[7] Latter is a freely accessible database of an international non-profit organization Cochrane, promoting conduction and dissemination of systematic reviews pertaining to healthcare interventions.[8] 'Dentistry and Oral Health' stem of Cochrane library contains 212 titles (158 completed reviews and 54 protocols) covering systematic reviews of preventive and therapeutic interventions.[8] The unique advantage of Cochrane reviews is that the reviews are updated timely and as such these are prospective reviews. The reviews are freely accessible as summary or full PDF.

In addition to Cochrane library, the summaries of reviews can be located at Journal of Evidence based dental Practice,[9] Databases of Abstracts of Reviews of Effectiveness (DARE)[10] and Evidence based dentistry Journal.[11]

Appraisal of systematic review

The methodology of systematic reviews and meta-analysis has to be rigorous to lead to valid and reliable conclusions. As a result, appraising systematic review and meta-analysis must be an integral part of evidence based dentistry to ensure translating valid findings to practice.[2,3]

For this purpose, multiple tools and checklists have been developed for appraising systematic review and meta-analysis (Box 3); the most popular tool is AMSTAR tool (The assessment of multiple systematic reviews).[15-17] AMSTAR is a simple user friendly tool to assess the quality of systematic reviews and meta-analysis and has been developed in line with Cochrane oral health group. There are a total of 11 domains to assess potential sources of bias in systematic review and the responses are recorded as yes/no/can't answer/not applicable (Box 4).

Box 3: Tools/checklist for appraisal of systematic review and meta-analysis

1. SQAC (Sack's quality assessment checklist)[12]
2. OQAQ (Overview quality assessment questionnaire)[13-14]
3. AMSTAR (The assessment of multiple systematic reviews)[15-17]
4. CASP (Critical appraisal skills programme) checklist[18]
5. NICE (National institute of clinical excellence) checklist[19]
6. JBI (Joanna Briggs Institute) module[20]

The 'a priori' research design and research question

It is mandatory that the research question, outcomes of interest and methodology of the systematic review and meta-analysis should be established beforehand. It is imperative to formulate a focused research question to lead to a valid and applicable conclusion.[2,3] However, one must bear in mind that narrow research question may yield fewer results while searching databases.[21-23] On the other hand, looking for broad clinical queries may lead to inconclusive and/

Box 4: Domains for assessment of systematic review as per AMSTAR checklist[15]

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest included?

or misleading evidence. The PICO/PECO approach is a consensus based widely followed methodology to formulate an appropriate research question.[21-23] The four blocks of PICO/PECO approach are P = patient/population; I/E = intervention/exposition; C = comparator/control; O = outcome.

Example A.=

1. Patient/population = children ≤ 6 years living in non-fluoridated areas
2. Intervention = low fluoride 500 ppm toothpastes
3. Comparator/control = non-fluoridated toothpastes
4. Outcome = reducing new carious lesions in primary dentition

"In children ≤ 6years of age and living in non-fluoridated area, whether 500 ppm low fluoride toothpastes are effective in reducing new carious lesions in primary dentition compared to non-fluoridated toothpastes?."

The right literature for systematic review (i.e., appropriate search strategy)

The suitable eligibility criteria for inclusion of studies in a systematic review

The pre-defined unambiguous eligibility criteria for inclusion of studies based on research question as formulated by PICO/PECO strategy should be established to ensure explicit and reproducible search strategy. The target study population and outcomes of interests in included reports are recognized by documenting research question using the PICO approach[21-23] as explained in the preceding text. In most of the reviews for studying interventions, randomized controlled trials (RCTs) are preferred study designs for inclusion.[24] However, high quality observational studies and non-randomized controlled studies may also be included.[24] Furthermore, additional design specifications like level of blinding, length of follow-up and cross-over versus parallel comparison group may also form criteria for inclusion or exclusion of studies in a review.[23,24] It is to be noted that the chosen study design specifications should be supported by sound scientific rationale. For instance, in a recently updated systematic review on efficacy of sedative agents in pediatric dentistry, cross-over study designs were excluded as cross-over study designs are not appropriate for interventions with long term residual effects.[25]

The study selection and data extraction from individual studies should be done by at least two independent reviewers.[24] Any disagreement among those should be addressed by third reviewer and a consensus based strategy should be adopted for resolving any doubts regarding inclusion or exclusion of study in the review.[23,24]

The efficient search strategy for locating desired individual studies

The comprehensive search strategy with appropriate search terms and targeting adequate sources should be adopted. The AMSTAR group[15] recommends that there should be at least two electronic sources which should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. Cochrane methodological standards[24,26] for conduct of review require that CENTRAL, MedLine (via PubMed) and Embase should be searched and this should be supplemented by multiple sources including grey literature (Box 5). Relying on single database would result in 'database bias' as no database is complete regardless of it being exhaustive or comprehensive.[27-9] In fact, it has been reported that only 30-80% of reports were retrievable through MedLine depending upon the targeted topic.[30]

Another commonly reported bias in systematic review is 'temporal bias.'[31] In most of the reviews, there is time gap between publication of review and date when the last search was conducted and at the time of publication, the review may have become outdated. To avoid this, there should be a provision for re-running the searches to appraise the new reports in the review. In fact, Cochrane methodological standards[24,26] require that published reviews should be updated timely to avoid temporal bias.

The search strategy and the conduct (by whom and how) should be well recorded so that entire search is explicit and reproducible.

Box 5: Supplementary sources for literature search[15,23,24]

1. Appropriate national, regional and subject specific databases
2. Trial registries for searching ongoing/unpublished researches (e.g. Clinicaltrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) portal[32]
3. Grey literature sources such as reports/dissertations/ theses databases and databases of conference abstracts.
4. Previous reviews on the same topic
5. Reference lists in included studies and any relevant systematic reviews identified.
6. Communicating with experts in the field and organisations for information about unpublished or ongoing studies

The unpublished work should not be ignored, lest there may be chances of introduction of 'publication bias' (file-drawer bias).[32-4] There is a misconception that unpublished work is often of poor quality, while it has been reported that it has more to do with the findings of the study rather than its quality.[31] In fact, the positive findings are more likely to be published compared to negative or statistically insignificant findings.[36-8] So, relying only on findings of published work with no or insufficient attempts to locate and include unpublished work may result in over-estimation of effect size.[39-40]

The publication bias is assessed and represented using graphical display, i.e., inverted funnel plot, which plots the effect size against the sample size of individual studies (Figure 4).[41-3] An asymmetric inverted funnel plots suggests the likelihood of publication bias.[43]

Assessing the quality of individual studies

The quality of included studies is assessed by exploring internal validity (i.e. methodological rigor) and external validity (i.e., study population, interventions and outcomes of interest). The methodological rigor of included studies contributes quantitatively to the weight of the evidence generated in a review. Thus, the assessment strategy for appraisal of the quality of the individual reports in systematic review and meta-analysis is the crux of the review and should be established 'a priori'. A plethora of tools based on, checklist/summary scores, scales and domain/component based scoring are available for appraisal of quality of individual trials included in a systematic review.[44-6] However, as per recent consensus based approach, the most appropriate tools are domain/component based tools as summary scores and scales may have an inherent component of error/bias.[47] A summary score uses an overall score to rate the quality of individual trials. The problem with this approach is that serious defects can be masked by an overall high score achieved by scoring high in some of the items on checklist. On the other hand, scales use grading criteria, i.e., good, fair or poor, etc. The element of bias in these grading criteria is the arbitrariness and lack of evidence to support gradation from good to fair or fair to poor and so on. While, in a domain base tool, each domain of tool is compared across all individual trials in a review.

The most popular and widely accepted domain based tool is Cochrane collaboration tool for assessing risk of bias in randomized controlled trials. This tool has five pre-decided domains and one customizable domain, i.e., 'other sources of bias'.[47] The first five domains are based on appraising key methodological features of randomized controlled trials which have an evidence supported potential to introduce risk of bias in trial. The customizable domain judges the unique sources of risk of bias in trial peculiar to a study design or a study topic and it is to be designed a priori. The risk of bias is graded as low, unclear or high risk of bias for each individual domain. The summary judgment for any trial is low/unclear/high based on risk of bias from individual domains (table 3).

Reading the findings of review

The findings of review are presented as aggregate data from included studies in form of tables as well as graphs. Tabulated data from individual studies are extracted for study participants (e.g. sample size, age, sex, socio-economic status, etc.), interventions (type as well as duration of intervention) and outcomes (e.g. effect size, risk ratio).[23,24,26] The end outcome of meta-analysis is pooled effect size from included studies (Figure 5). The pooling of outcomes across all eligible studies in a meta-analysis involves a trade-off between bias and precision. The impact of risk of bias is to be explored judiciously before inclusion or exclusion of a study based on risk of bias. The overall results are best presented graphically as 'forest plots.' Latter is graphical representation of intervention effect estimates stratified according to risk of bias (Figure 5).

Although, combining results from multiple studies increases the precision of effect estimates; it may be erroneous if combined studies suffer from considerable heterogeneity; i.e., diversity.[49-51] The heterogeneity may be methodological (e.g., different measures of outcome assessment) or clinical (e.g. dosages, length of follow-up) diversity amongst the studies. If it is considerable then combining

Figure 4: The Funnel Plot; Effect size is plotted on X-axis and sample size is plotted on Y-axis. Each circle represents an individual trial. (a). Symmetrical distribution of circles in the graph represents absence of publication bias. (b) Selective absence of circles on right side of graph (insignificant/negative findings) with cumulating circles at the top (studies with larger sample size and large effect) are suggestive of publication bias. This is owing to higher chances of publication of studies with larger effect size.

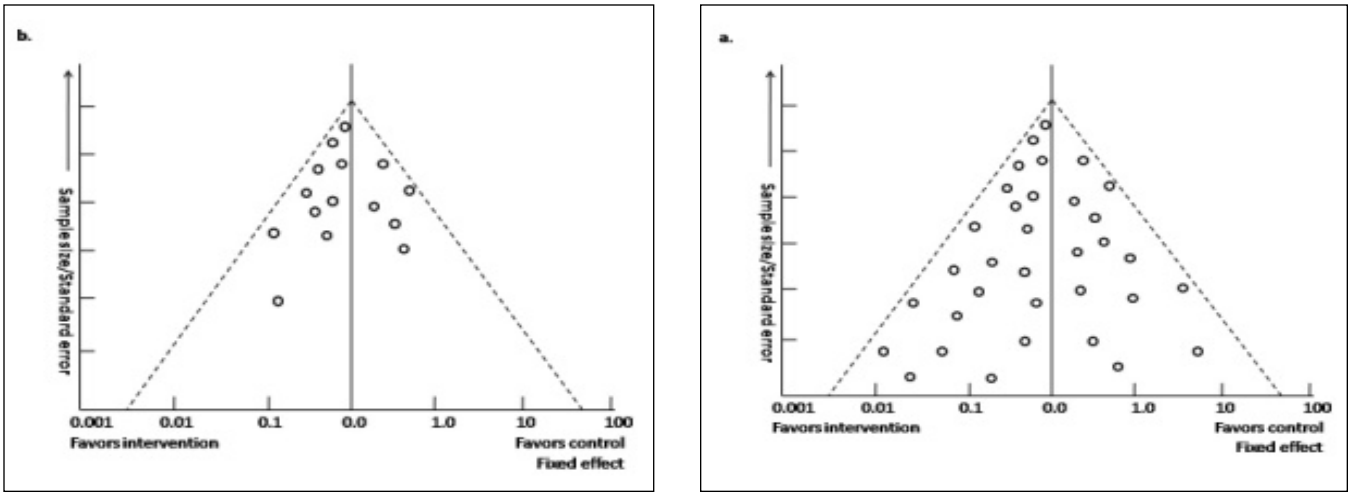
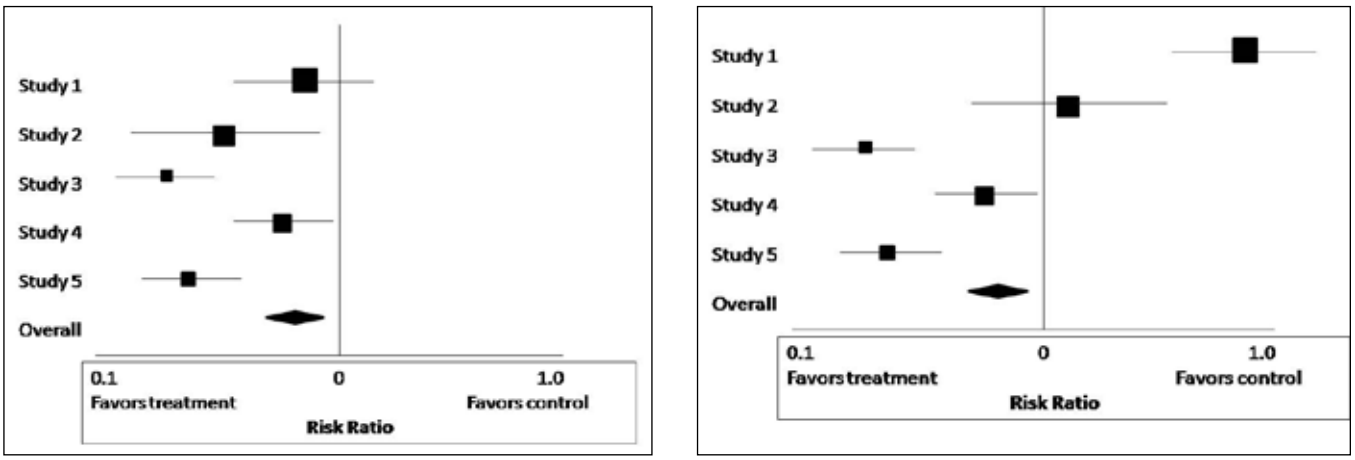


Table 2: Cochrane collaboration risk of bias tool[47]

Bias domain/ component	Key methodological traits of RCT to appraise look for detecting bias	Rationale for assigning low/unclear or high risk of bias
Selection bias	Random sequence generation Allocation concealment	Look for methods of randomization, i.e., whether true random, partial random or selective allocation to intervention groups was done. Failure to ensure randomization affects baseline equivalence of subjects and this may increase or decrease the observed effect size of an intervention. The allocation of interventions is to be kept concealed from interventionists as well as outcome assessors. In fact allocation concealment has more potential to introduce bias than random sequence generation.
Performance bias	Blinding of participants and researchers	Failure to blind either of the participants or researchers interferes with provision of equal care to intervention and control group. This may increase as well as decrease the observed effect size of an intervention as a whole or only some of the outcomes.
Detection bias	Blinding of outcome assessment	The potential conflict of interests or a tendency to report positive effect size owing to investigator's own interests is a known source of detection bias. This can be avoided by blinding of outcome assessor and data analyst.
Attrition bias	Loss of participants/data during follow up	This bias usually arises when baseline equivalence established at the time of random allocation is disturbed by loss of participants during follow up. Such a loss introduces systematic difference between the study groups.
Reporting bias	Selective reporting	Poor reporting has been identified as one of the most common attributes of scientific reports contributing to generation of poor/insufficient evidence. It is recommended that all outcomes planned to be evaluated in a study protocol should be reported accordingly.
Other sources of bias	Dependent on design peculiarities and scope of individual study	There may be other sources of bias not covered by above mentioned domains. For example, in a recent systematic review by Mittal et al. (2015)[48] on methods of intra-canal reinforcement in grossly decayed primary anterior teeth; three separate sources of bias were identified to evaluate risk of bias from individual reports. These were elaboration of clinical assessment methods and parameters, elaboration of radiographic assessment methods and parameters, adequate follow-up period.

Figure 5: The Forest Plot: The squares represent the individual trial. Size of square is proportional to weight contributed by trial while the position on X-axis represents effect size. The whiskers, i.e., horizontal lines depict confidence intervals. The diamond at the bottom of Y-axis represents overall effect size of the intervention obtained by pooling results from individual trials. In the upper graph, the confidence intervals (as depicted by span of whiskers across X-axis) overlap, so, it is appropriate to pool the data (low heterogeneity). In lower graph, the confidence intervals do not overlap and this is suggestive of heterogeneity. Thus, it is not appropriate to pool the results from these trials.



the studies may mean combining 'apples with oranges and the result is a mango'. Thus, every meta-analysis should quantify the heterogeneity statistically to assess whether the observed variation in studies is indisputable or just a random observation.

The heterogeneity does not disprove a meta-analysis. But, it must be identified, quantified and explained. Two commonly applied statistical measures for quantifying heterogeneity are Cochran's Q statistics (Chi-square test for heterogeneity) and I^2 statistics.[50] A significant value of Q implies that the observed variation in effect sizes across included studies is real. On the other hand, a non-significant value means that the observed variation is mostly spurious. However, a non-significant value may also appear in case of studies with poor precision. I^2 is a ratio and is expressed in percentage which represents the proportion of true variation due to heterogeneity to total observed variation. The increasing magnitude of I^2 implies increasing heterogeneity (I^2 >60% = severe heterogeneity). Fortunately, there exist measures to handle heterogeneity, i.e., by selecting suitable model (fixed-effect or random-effect model) to compute summary estimates.[50] The fixed-effect model assumes that observed variation amongst included studies are by chance only and this model is applied when there is mild heterogeneity, i.e., I^2 <30%.[50] On the other hand, the random effect model takes into account the observed variation across included studies and it incorporated two sources of variability, i.e., within study and across studies (i.e., heterogeneity). If I^2 is large, the reasons for the observed heterogeneity should be explored. This can be achieved by sub-group analysis and meta-regression.

Analyzing the conclusions of review

The methodological rigor of included studies should be borne in mind while formulating conclusions and stating future recommendations.[23] 'The garbage in and garbage out approach' states that the evidence generated from review cannot be superior to primary trials. The Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) has developed a system (GRADE approach) for grading the quality of evidence and strength of recommendations.[54-8] The principles of GRADE approach have been incorporated into Cochrane methods of systematic reviews of intervention.[24,26] For a systematic review, the quality of evidence translates into the confidence which can be placed in effect estimates of the studied intervention. This approach specifies four levels of quality (Table 3) and its uniqueness lies in its flexibility to upgrade and downgrade evidence based on explicit, transparent and pre-set criteria (Figure 5). Latter has been identified as five factors which can upgrade the quality of evidence and three factors which can downgrade evidence (figure 5). The quality of evidence generated from the systematic review is translated into strength of recommendations (weak or strong). Application of GRADE is in fact mandatory while formulating clinical guidelines to ensure clarity of the confidence in clinical recommendation or guidance. High quality evidence (i.e., from high quality systematic review, meta-analysis or randomized controlled trials) favoring any intervention will translate into strong recommendations to support the intervention. On the other hand, if the evidence is of low quality (i.e, derived from poorly controlled randomized trials or observational research) the result will be weak recommendation.

CONCLUSION

Although systematic review and meta-analysis provide filtered overview of existing evidence to ease practice of evidencebased medicine; their findings should be interpreted with caution. The qualities of primary studies as well as the methodology of conduct of review affect the evidence synthesis in systematic review and meta-analysis. Thus, quality appraisal of systematic review and meta-analysis should a pre-requisite for extrapolating the findings into practice

Figure 5: Factors which can upgrade and downgrade the evidence

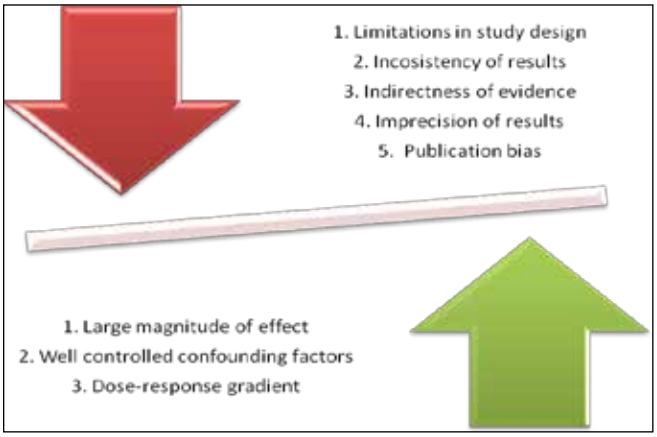


Table 3: GRADE approach for rating quality of evidence

Quality of evidence	Interpretation	Study Characteristics
High	There are poor chances that future research will affect the effect estimate generated by present source of evidence	High quality randomized trials (with no serious limitations in design) and well performed observation studies (often with clear cut large effect estimates)
Moderate	There are chances that future research may change effect estimates	Randomized trials (with serious limitations in design) and well performed observation studies (often with clear cut large effect estimates)
Low	There are high chances that future research may change effect estimates	Randomized trials (with serious limitations in design) and observational studies (poorly controlled and low/unclear effect estimates)
Very low	It is difficult to have any level of confidence in effect estimates as there is lot of uncertainty	Randomized trials (with serious limitations in design), observational studies (poorly controlled and low/unclear effect estimates) and most of the evidence is from case series/case reports

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