ADA CE Program **ARTICLE 3**

A practical approach to evidence-based dentistry: VI

How to use a systematic review

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SIXTH IN A SERIES

In the previous articles in this series, we introduced the process of evidence-based dentistry (EBD),[1] how to search for evidence to inform clinical practice,[2] and how to use articles about therapy,[3] harm,[4] and diagnosis.[5] In this article, we will explain how to use a systematic review to answer a clinical question, introduce and describe the basic concepts for understanding the

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design of a systematic review, and explain how to use these concepts to critically appraise such studies. In addition, readers will learn how to interpret and use the results presented in the systematic review to inform clinical decisions. In a subsequent article, we will describe how to use evidence-based clinical practice guidelines.

ABSTRACT

Background and Overview. Dental practitioners face new clinical challenges on a daily basis. New treatment options and diagnostic tools are disseminated quickly, and the volume of articles and new evidence is overwhelming. Systematic reviews summarize and synthesize the available evidence related to diagnosis, therapy, prognosis, and harm for clinicians, patients, and decision makers. Such reviews represent one of the most powerful tools to translate knowledge into action.

Practical Implications. The critical appraisal of this type of study involves assessing the risk of bias, results, and applicability of such study. The authors provide guidance for clinicians to critically appraise systematic reviews and apply the findings in clinical practice.

Key Words. Systematic reviews; evidence-based dentistry; critical appraisal; meta-analysis.
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Clinical scenario.

While working at a clinic in a remote rural location, you meet with a 55-year-old woman who has been referred to you for treatment of open caries on tooth #20, which the referring clinician has diagnosed as having irreversible pulpitis. After conducting a clinical examination, you recommend that the tooth be extracted. The patient asks if she will need to attend many follow-up appointments, because traveling from her home to your clinic is a burden. Among other measures, you decide to minimize your patient's risk of having alveolar osteitis (dry socket) as a postoperative complication. You have been in the habit of prescribing chlorhexidine in cases such as this one; however, you wonder if this medication is actually of any use in decreasing the patient's risk of experiencing dry socket. You consult the Cochrane Library and find a recently published systematic review that addresses this issue.[6]

KNOWLEDGE SYNTHESIS AND TRANSLATION

Keeping updated in knowledge related to any clinical discipline is challenging. According to the Medline (PubMed) Trend Database,[7] more than 30,000 randomized controlled trials (RCTs) were published in 2012. Of these, approximately 1,500 were dental trials. This overwhelming amount of information can be impossible to manage for any health care provider, including dentists. Systematic reviews represent an efficient way to learn about the available evidence for an intervention or exposure.

According to the Cochrane Collaboration,[8] a systematic review is defined as "… a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review." Like primary observational studies and randomized controlled trials, systematic reviews represent a type of study that requires implementation in a manner that minimizes the risk of bias. If these bias-reducing strategies (that is, the systematic review process) are in place, then readers can trust that the appropriate analysis will provide the best available estimate of the effect of an intervention or exposure.[8]

WHAT IS THE DIFFERENCE BETWEEN NARRATIVE AND SYSTEMATIC REVIEWS?

Authors of many articles published in the dental literature refer to their work as "reviews"; only a small number of these articles, however, are systematic reviews. For this reason, clinicians interested in using review articles must be able to distinguish between narrative and systematic reviews. In narrative reviews, authors discuss one or more aspects related to a particular condition or disease (that is, etiology, diagnosis, prognosis, or therapy and management). Although this type of review may be useful for dental students (and sometimes dentists) who are interested in background information, the failure of authors to systematically collect and process the data makes the conclusions that arise from such articles potentially misleading.[9,10] In contrast, authors of

trustworthy reviews use systematic, transparent, and comprehensive methods to retrieve, select, critically appraise, and summarize all the available evidence regarding the effectiveness of an intervention, prognosis, and diagnosis questions. Although it is possible to have systematic reviews that focus on prognosis, diagnosis (and harm) issues, in this article, we will focus on therapy (and harm) issues. Table 1[11] presents additional details regarding the difference between narrative and systematic reviews.

One of the key limitations of systematic reviews and meta-analyses is that the summary estimates produced are only as trustworthy as the results of the primary studies that inform the review.[12] Thus, the authors of rigorously conducted systematic reviews still may report low-quality evidence that warrants only weak inferences.

WHY ARE SYSTEMATIC REVIEWS CONSIDERED TO BE A STUDY DESIGN?

Systematic reviews and evidence-based clinical practice guidelines represent the most valuable documents that can inform clinical decision making.[12] Review authors start by defining a clear and focused research clinical question in a way that is similar to that described in a previous article in this series that addressed the framing of a question using the Population, Intervention, Comparison, Outcomes (PICO) approach.[2] The components of this PICO question correspond with the eligibility criteria outlined by the authors of the studies that are included in the review. For example, if the author specifies the population of interest as patients after tooth extraction, eligible studies must enroll such patients, and only such patients. Authors of systematic reviews should present clearly the population or type of patients, clinical intervention or exposure of interest, the comparator for such an intervention, and the selection of patient-important outcomes.

After specifying all these criteria, review authors should describe their methods in a protocol that, ideally, should be published or made available to users. Many reasons support the authors' explicit and transparent declaration of selection criteria and methods in systematic reviews. Investigators have described important discrepancies between the selection of outcomes and methods when comparing before the review starts with after the final manuscript is published.[13] Ideally, reviewers will describe the comprehensive search for all the available (published and unpublished) evidence they

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ABBREVIATION KEY. EBD: Evidence-based dentistry. **FC:** Formocresol. **GRADE:** Grading of Recommendations Assessment, Development, and Evaluation. **MTA:** Mineral trioxide aggregate. **PICO:** Population, Intervention, Comparison, Outcomes. **RCT:** Randomized controlled trial.

have conducted. As a result of this process, researchers should screen a set of references at the level of title and abstract first, and complete study reports later, to establish finally whether the articles retrieved meet the selection criteria (Figure 1[11]). Having identified all the relevant studies, reviewers abstract data that are related to the studies' characteristics, risk of bias assessment, and results. Finally, they summarize the evidence and assess the quality of the body of evidence[14] (Figure 1[11]).

BOX 2

The study you found.

You consult the Cochrane Library and find a recently published systematic review whose authors aimed to assess the effects of local interventions on the prevention and treatment of alveolar osteitis (dry socket) after tooth extraction.[6] Reviewers identified 21 trials, and among these, the authors of 18 trials, which included more than 2,370 participants, reported results related to the prevention of dry socket. Although the authors of the systematic review reported more than 10 intrasocket interventions, they found limited evidence for each of these interventions.

CRITICALLY APPRAISING SYSTEMATIC REVIEWS TO INFORM CLINICAL DECISIONS

As described in articles previously published in this series, the process of using an article from the dental literature involves assessing the risk of bias, assessing the results, and assessing the applicability of the results.[14]

1. How serious is the risk of bias? The probability that the results of a systematic review are correct depends on whether reviewers identified, retrieved, selected, critically appraised, and summarized all the relevant studies.[15] Table 2[16-21] presents examples of the aspects to consider when assessing the risk of bias of a systematic review.

1a. Did the review present explicit and appropriate eligibility criteria? Consider a systematic review whose author intended to pool the effects of all antibiotics for treating all types of maxillofacial infections. Now, consider a review whose author intended to pool the results of the effects of fluoride varnishes for reducing the incidence of carious lesions in children and adolescents. Clearly, the first review would be excessively broad in its scope; equally clearly, the second review would be satisfactorily narrow.

What makes a systematic review question too broad? There are pathophysiological and microbiological aspects of maxillofacial infections and of the mechanism of the action of antibiotics that suggest that treatment effects vary across different types of patients (different types of infections) and interventions (different types of antibiotics).[11] A single pooled estimate summarizing all these data would not be applicable to any specific group of patient or any specific antibiotic, and therefore, it would be of no use to the clinician. On the other hand, results from the more focused question are likely to be similar for children and adolescents, for the available fluoride

TABLE 1

Differences between narrative and systematic reviews.*

| CHARACTERISTIC	NARRATIVE REVIEWS	SYSTEMATIC REVIEWS
Clinical Question of the Review	Seldom reported, or addressed several broad questions	Focused question specifying population, intervention or exposure, and outcome
Search for Primary Studies	Seldom reported; if reported, not comprehensive	Comprehensive search of databases of evidence resources
Selection of Primary Studies	Seldom reported; if reported, often biased sample of studies	Explicit selection criteria for primary studies
Assessment of the Risk of Bias of Primary Studies	Seldom reported; if reported, not usually systematic	Risk of bias of primary studies assessed
Methods to Summarize the Included Studies' Results	Usually qualitative nonsystematic summary	Synthesis is systematic (qualitative or quantitative)

* Reprinted with permission of JAMA and The JAMA Network from Guyatt and colleagues.[11]

varnishes, and for the available approaches to identifying carious lesions. This similarity of effect across patients, interventions, and outcomes is what legitimizes the single pooled estimate of effect.[22]

1b. Was the search for relevant studies exhaustive? Secure estimates of treatment effect require a comprehensive search for eligible studies. Unfortunately, even a search that includes all the relevant electronic databases may be insufficient. If the authors of a primary study selectively report and publish research results according to the effect (that is, studies favoring the intervention get published; studies that are negative do not), then the results will be a systematic overestimate of effect (that is, publication bias).[23,24] One way to mitigate this issue is to search and include "gray literature," which includes documents such as dissertations, conference abstracts, personal correspondence, records of studies' methods and results found in investigators' file drawers or on their hard drives, and policy documents.[25,26]

When assessing whether the search strategy was comprehensive, users should focus on which databases the authors consulted, and whether the systematic reviewers restricted their search to resources published in one particular language or to only published reports.[19] To learn more about specific databases and their characteristics, please refer to a previously published article in this series, entitled "A Practical Approach to Evidence-Based Dentistry: How to Search for Evidence to Inform Clinical Decisions."[2]

1c. Did the primary studies have a low risk of bias? The credibility of the results of a systematic review is as only as great as the credibility of the primary
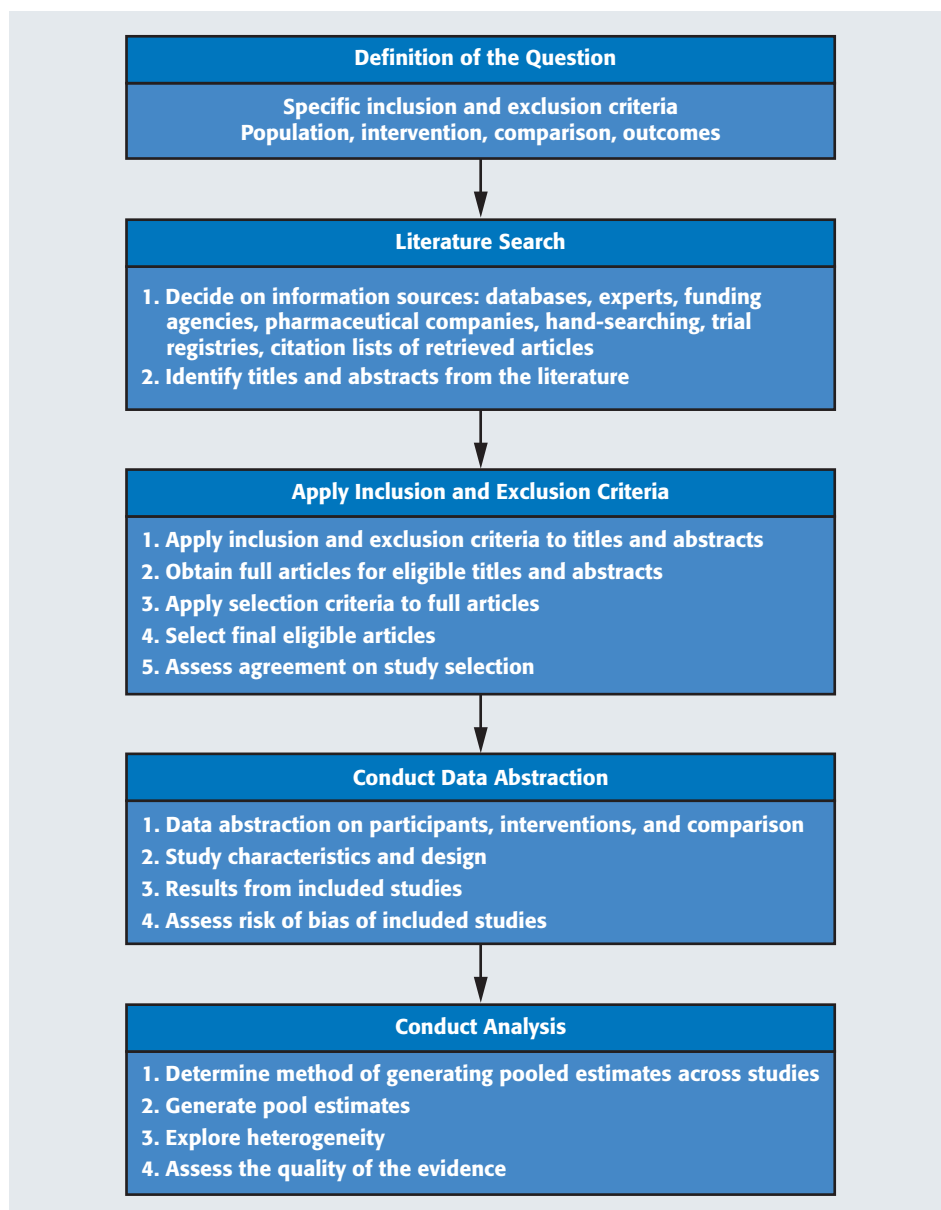
Figure 1. Process of conducting a systematic review. *Adapted with permission of JAMA and The JAMA Network from Guyatt and colleagues.*[11]

considerations include concealment of randomization, blinding, and minimizing loss to follow-up.[5,28]

1d. Were the selection and assessment of primary studies reproducible? All of the steps that investigators perform when conducting a systematic review (Figure 1[11]) are susceptible to error.[29] For example, including and excluding studies from the review requires making judgments. Likewise, errors may occur during data abstraction: for example, investigators found that 20 of 34 reviews conducted by the Cochrane Cystic Fibrosis and Genetic Disorders Group included errors such as miscalculations and misinterpretation of data from the primary studies.[30] Independent, duplicate eligibility review and data extraction with resolution of discrepancies can minimize such errors and other unintentional or subconscious bias.[31] Hence, users of systematic reviews should check whether reviewers conducted screening and data extraction in duplicate.

studies included. Assessing credibility requires addressing the risk of bias associated with the primary studies that are included in a systematic review. Studies assessed as having a high risk of bias may overestimate treatment effects by up to 150%.[27] Thus, when the risk of bias across the included studies is low, credibility increases.[11] Different primary study designs are associated with specific sets of potential biases and, consequently, require reviewers to follow specific checklists to assess the risk of bias. For issues of therapy addressed in RCTs, key

BOX 3

Your assessment of the risk of bias of the systematic review you identified.

The authors of the systematic review[6] defined a sufficiently narrow range of patients, interventions, comparisons, and outcomes, and they conducted a comprehensive search that included reviewing several databases and making an effort to retrieve unpublished data. The reporting by authors of the included primary studies was poor, and the result was that risks of bias ratings were often assessed as unclear risk of bias. Finally, the authors of the systematic review reported that they selected the studies in duplicate and independently. Thus, you determine that this systematic review has a low to moderate risk of bias, and you proceed to read and interpret the results.

TABLE 2

Examples illustrating critical appraisal of the risk of bias of a systematic review.

ASPECT	EXAMPLE	EXPLANATION
How Serious Is the Risk of Bias?		
Did the review include explicit and appropriate eligibility criteria?	"Population: orthodontics patients of either gender, any age and any type of malocclusion (Class I, II, or III) and crowding treated with fixed multibrackets on both arches with first molars included over the course of at least 12 months. Intervention: only in vivo studies on human participants involving different oral health motivation strategies, and oral and dental hygiene techniques and procedures. Comparison: no treatment or usual care (the gold standard), or inactive control. Outcome: as a primary outcome, the following data were evaluated: plaque index (PI) and gingival index (GI). The secondary outcomes considered were carious lesions and the presence/absence of white spot."[16]	The reviewers aimed to answer the question "whether it is clinically possible to avoid plaque increase and prevent permanent teeth lesions in orthodontics patients, and in particular, whether prophylactic procedures performed by the dental hygienist are efficacious in reducing the risk of demineralization in orthodontics patients fitted with multibrackets appliances."[16] The authors described in detail the different components of the research question. These components represented the selection criteria (inclusion and exclusion criteria). The criteria described here reflect a sensitive and focused question. The outcomes defined in the review were classified as patient-important.
Was the search for relevant studies detailed and exhaustive?	"Relevant articles were identified in any language by searching MEDLINE (from 1950 to September 2011), the entire Cochrane Library (from 1990 to September 2011), CINAHL Nursing database (from 1980 to September 2011), and the University of Michigan School of Dentistry 'Dentistry and Oral Sciences' database (EBSCO host) (from 1990 to September 2011). The final search update was performed on September 19, 2011. To locate potentially relevant studies in MEDLINE, exploded MeSH terms and key words were used to generate sets for the following themes: 1) periodontitis; 2) preterm birth; and 3) scaling treatment. We then found the intersection of these terms using the Boolean term 'AND.' This basic approach was modified as necessary to search each electronic database (see Supplementary Appendix 3 in the online Journal of Periodontology). No limitations in the search were used."[17] "To locate unpublished trials, ClinicalTrials.gov and abstracts of scientific conferences were searched (National Academy for State Health Policy's 20th Annual State Health Policy Conference, Denver, Colorado, October 15, 2007; 34th National Conference of Indian Society of Periodontology, Dharwad, India, December 3-5, 2009)."[17]	Study authors described every electronic database consulted during the review searching process along with the time frame searched. They also reported the complete search strategy in an online supplementary appendix. Additionally, they searched for "gray literature" in clinical trials registries and conference abstracts. One potential limitation in this review is that the authors did not include EMBASE among the included databases for searching. Some reports show that systematic reviews including one or a few databases have a higher risk of missing relevant studies compared with reviews including all of the most important databases.[18] The Cochrane Handbook suggests that at least MEDLINE, EMBASE, and CENTRAL should be consulted in every systematic review search.[19] The possibility that this review missed some relevant primary studies cannot be discarded.
Were the primary studies of high methodological quality?	"We performed the risk-of-bias assessment for the included trials by using the Cochrane Collaboration's risk-of-bias assessment tool, which incorporated six domains: random sequence generation, allocation concealment, masking, completeness of outcome data, risk of selective outcome reporting and risk of other bias."[20] "Using the predetermined six domains for risk-of-bias assessment, we determined three of the five RCTs* to have a high risk of bias, whereas we judged two to have an unclear risk of bias and none to have a low risk of bias."[20]	The authors presented a table with a detailed description of the risk of bias for each of the included studies. This analysis showed that most of the studies were judged as having a high risk of bias. The rest of the studies were classified as unclear risk of bias, which raises concerns about the review results.
Were assessments of studies reproducible?	"Two review authors (Anneli Ahovuo-Saloranta [AAS] and Helenab Forss [HF]) independently carried out the selection of papers on the basis of the title, keywords and abstract, and the decisions about eligibility. The full text of every study considered for inclusion was obtained. If the information relevant to the inclusion criteria was not available in the abstract or if the title was relevant but the abstract was not available, the full text of the report was obtained."[21] "Data were extracted independently and in duplicate by two review authors (AAS, HF) using a previously prepared data extraction form. The extraction form was pilot-tested independently by two review authors in the previous review version (AAS, Anne Hiiri [AH]) with a sample of studies to be included."[21]	Authors provided an exhaustive explanation about all the methodological steps involved to minimize the risk of mistakes and arbitrary judgments during the review process. Critical steps were conducted independently and in duplicate.

* RCT: Randomized controlled trial.

2. What are the results? After assessing the magnitude of the risk of bias, clinicians must consider the results—in particular, the magnitude and the precision of the treatment effects—and the implications for patient care. Industry-supported reviews of drugs tend to rank eligible studies at low risk of bias, and although showing similar treatment effects, provide more positive and favorable conclusions when compared with Cochrane systematic reviews on the same clinical question. Ideally, clinicians should look for reviews that are not funded by industry, and if none of these are available, clinicians should exercise skepticism about authors' inferences.[32]

Evaluating the results of a systematic review requires clinicians to consider whether effects are similar across studies, as well as to assess the magnitude and the precision of the effects. Table 3[20,21] presents examples of assessments of the results of systematic reviews in dentistry.

2a. Were the results similar from study to study? Systematic reviewers collect data on characteristics of the eligible studies, particularly related to patients, interventions, exposures, comparisons, and outcomes measures. The results of primary studies may differ, and variation in these characteristics may be responsible for the differences. When results differ and remain unexplained, the reader's confidence in the pooled estimated should decrease. The following list offers 4 ways to assess whether the results of primary studies are sufficiently similar to maintain confidence in the pooled summary estimate[11]:

▬ The point estimates (that is, the estimates of treatment effect): these estimates should be similar among trials; the more they differ, the greater the concern regarding inconsistency.

▬ The overlapping of the confidence intervals (CIs): the more overlap across CIs, the less the concern regarding inconsistency.

▬ The statistical test for heterogeneity (χ^2): this test assesses whether the point estimates of the individual study results are the same (relative risk [RR] study 1 = RR study 2 = RR study 3). The lower the P value, the more the concern regarding inconsistency (increasing concern as the P value decreases below .1, .05, .01, or .001).

▬ The I^2 statistic: this estimate represents the percentage of heterogeneity in effect estimates across trials owing to real variability between them.[33] As a rule of thumb, I^2 values higher than 50% may represent large heterogeneity.

The greater the heterogeneity identified, the more compelling the need for reviewers to explore possible explanations for between-study variability. Ideally, reviewers will, before looking at the data, have generated a priori possible explanations of heterogeneity in the as-yet unknown study results. If heterogeneity remains unexplained, the confidence in the estimates of effect (quality of the evidence) decreases[34] (Figure 2[35-38]).

2b. What are the overall results of the review? Sometimes systematic reviewers are not able to conduct a meta-analysis to obtain a single estimate of the effect across all the included studies. Reasons include incomplete outcome reporting, as well as substantial differences across patients, interventions, and outcomes. In situations in which it is not possible or appropriate to conduct a meta-analysis, reviewers present results of individual studies in tables.

Often, however, reviewers are able to conduct a meta-analysis and present a pooled estimate that represents the weighted average effect of the intervention under study. Pooled estimates (that is, the meta-analysis result) are usually expressed in the same way as the results from primary studies. For dichotomous outcomes (such as the presence of any carious lesion or the occurrence of an infection event), clinicians will find RR, RR reduction, risk difference, or odds ratios (OR). For continuous outcomes, like probing depth, quality of life, and the amount of trismus, reviewers may use mean difference or standardized mean difference.[5]

Each trial's results contribute a particular "weight" of data to the final pooled estimate. The results of trials whose investigators described a small number of events have less weight compared with the results of trials whose investigators described a large number of events. If the authors of studies report the same outcome of interest but using different units, the results still can be pooled and presented in standard deviation (SD) units (for example, a standardized mean difference of 0.5 means that the treatment intervention effect in comparison with the control is 0.5 SD).

To learn where to find the primary studies' point estimates and the pooled (summary) estimate in a meta-analysis, readers should refer to Figure 2.[35-38]

ANATOMY OF A META-ANALYSIS

In general, a forest plot (that is, the figure reporting a standard meta-analysis) has the following components:
▬ study identifier, which can be the name of the study author, as well as the year of publication or the name of the study;
▬ vertical line of no effect (in other words, when there is no difference between the two groups under comparison, the point estimate lies on this line);
▬ point estimate and 95% CI for each primary study;
▬ pooled (summary) estimate, which corresponds with the vertical component of the diamond, and its 95% CI, which corresponds to the horizontal component of the diamond;

TABLE 3

Examples illustrating critical appraisal of the results of a systematic review.

EXAMPLE	HOW LARGE WAS THE TREATMENT EFFECT?	HOW PRECISE WAS THE ESTIMATE OF TREATMENT EFFECT?
"Additionally, we noted no significant difference in the likelihood of clinical success between primary molars treated with MTA* and primary molars treated with FC† (RR‡ = 1.01; 95 percent confidence interval [CI], 0.98-1.05) during the observational period, as shown in Figure 2."[20]	The RR for having clinical success when treating a primary molar with MTA compared with FC is 1.01. This represents a 1% increase in the probability of experiencing clinical success using MTA compared with FC. The point estimate in this case is suggesting that there may be no difference between using MTA compared with FC to have clinical success when treating primary molars.	The 95% CI§ (0.98-1.05) suggested in the lower limit a 2% reduction on clinical success when using MTA compared with FC. On the other hand, the upper limit shows that there may be a 5% increase in clinical success when using MTA compared with FC. Since it is likely that both extremes of the CI would lead to a similar clinical action (because both an RR reduction of 2% and 5% can be considered clinically irrelevant to prefer MTA over FC), this CI could be considered to be precise or narrow enough.
"Resin-based sealant compared with no sealant: Compared to control without sealant, second or third or fourth generation resin based sealants prevented caries in first permanent molars in children aged 5 to 10 years (at 2 years of follow-up odds ratio (OR) 0.12, 95% confidence interval (CI) 0.07 to 0.19."[21] "If we were to assume that 40% of the control tooth surfaces were decayed during 2 years of follow-up (400 carious teeth per 1,000), then applying a resin-based sealant will reduce the proportion of the carious surfaces to 6.25% (95% CI 3.84% to 9.63%); similarly if we were to assume that 70% of the control tooth surfaces were decayed (700 carious teeth per 1,000), then applying a resin-based sealant will reduce the proportion of the carious surfaces to 18.92% (95% CI 12.28% to 27.18%)."[21]	Authors presented relative and absolute estimates. In relative terms, resin-based sealants compared with no sealant reduce the proportion of carious surfaces by 88%. Although this seems to be a large treatment effect, this should be expressed in absolute terms to appreciate the complete benefit of sealants. When expressing the results in absolute terms using as reference 2 hypothetical populations, one with 40% (moderate baseline risk) of tooth surfaces decayed and another one with 70% (high baseline risk), use of resin-based sealants reduces this proportion to 6.25% and 18.92%, respectively. In both populations, the effect seems to be large and clinically relevant.	Authors presented CIs for both relative and absolute estimates. In relative terms, using resin-based sealants compared with no sealant shows an impressive 93% reduction in the proportion of carious surfaces in its lower limit. The upper limit still suggests a large treatment effect of 81% reduction in the outcome. Since both extremes are showing clinically relevant and large treatment effects, the CI is precise or narrow enough. In absolute terms, for the moderate risk population, the CI shows a reduction from a baseline risk of 40% to 3.8% in the lower limit and 9.6% in the upper limit. This large reduction in absolute terms in both extremes of the CI suggests that these results are precise. For the high-risk population, the lower limit of the CI shows a reduction from a 70% baseline risk to 12.3% in the lower limit and 27.2% in the upper limit. Both extremes suggest a large treatment effect. This CI also can be considered precise enough.

* MTA: Mineral trioxide aggregate.
† FC: Formocresol.
‡ RR: Relative risk.
§ CI: Confidence interval.

━ measure of association used and exact point estimates and CIs of each primary study, in numbers;

━ weight of each included study, expressed as a percentage;

━ statistical test and I^2 statistic of heterogeneity.

Figure 2[35-38] illustrates these elements in a meta-analysis.

Consider the following clinical question: To avoid fluorosis, should children initiate brushing with fluoride toothpaste before or after age 2 years? A recently published systematic review included a meta-analysis of 3 primary studies that showed a 34% reduction in the development of fluorosis when brushing after age 2 (OR = 0.66; 95% CI, 0.48-0.90).[38] Figure 2[35-38] shows a forest plot presenting the review results.

2c. How precise were the results? Every meta-analysis should provide a point estimate and a CI. A CI can be defined as a plausible range of values within which the true effect actually lies.[39] Thus, the CI expresses the degree of uncertainty around the point estimate. Narrow CIs represent precise results (that is, a large number of participants or events), whereas wide CIs represent imprecise results (that is, a small number of participants or events).

To determine whether the CI is too wide, clinicians should focus on both boundaries of the CI and judge what these boundaries are suggesting, either including or excluding any important benefit or harm.[39] For example, a systematic review that summarized the role of antibiotic prophylaxis for preventing inflammatory complications after tooth extraction showed that the use of this intervention both preoperatively and postoperatively slightly increases the risk of complications by 9% (RR = 1.09; 95% CI, 0.40-2.94).[40] However, the lower boundary of the CI suggests a 60% reduction in complications, whereas the upper limit shows an increase in the risk of having complications of 194%. Because CI boundaries include appreciable benefit and important harm, the evidence leaves clinicians with uncertainty regarding the effect of the intervention: the evidence is consistent with major benefit, has no effect at all, or has appreciable harm. Therefore, this CI is imprecise (that is, too wide).
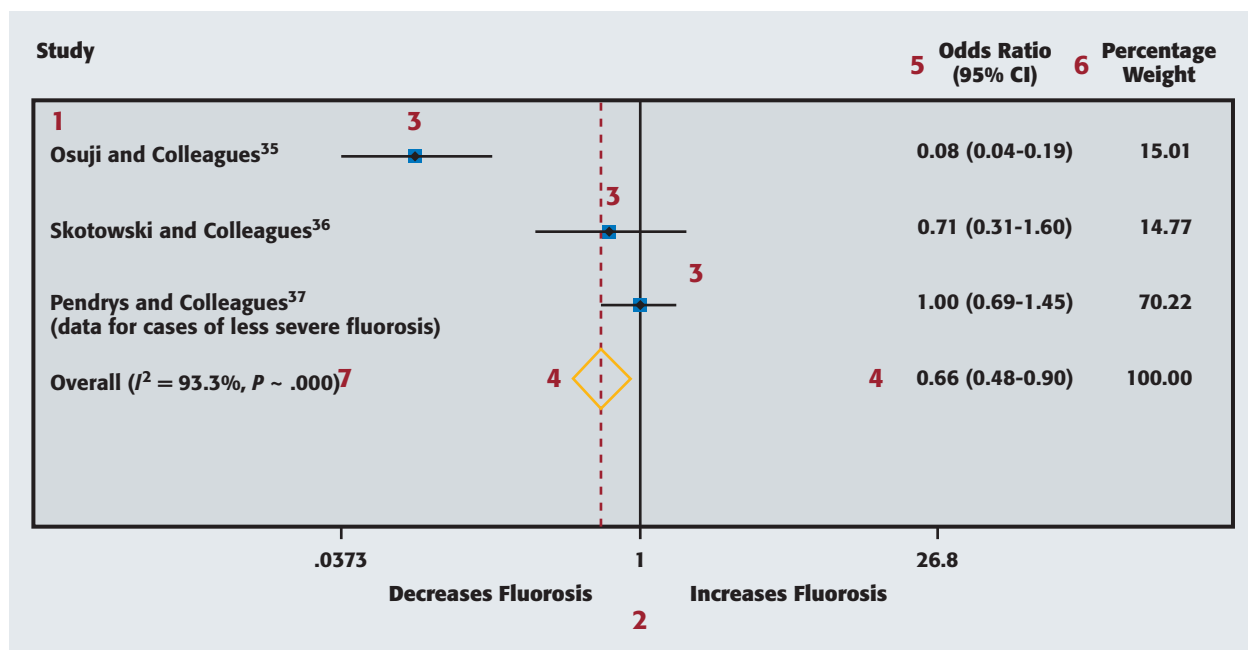
Figure 2. Meta-analysis on the effect of initiating brushing with fluoride toothpaste after age of 2 years versus before age of 2 years on the development of fluorosis. **1.** Primary study author.[35] **2.** Line of no effect. **3.** Study point estimate and 95% confidence interval.[35-37] **4.** Pooled (summary) estimate. **5.** Exact point estimate and confidence intervals (CI). **6.** Weight of each included study. **7.** Statistical test and estimates to assess heterogeneity. *Adapted with permission of The Journal of the American Dental Association from Wright and colleagues.*[38]

Consider another example from the same review assessing the effect of preoperative antibiotic prophylaxis on the outcome "local sign of infection." The meta-analysis that included 7 studies showed a 71% reduction in this outcome (RR = 0.29; 95% CI, 0.15-0.54). The CI indicates what can be considered an appreciable benefit in both limits. The boundary consistent with the largest plausible treatment effect suggests a reduction of 85% (1.00-0.15) and the upper limit shows a 46% reduction in local signs of infection (1.00-0.54). At either extreme of the CI, the intervention seems to be highly effective. Hence, this CI is sufficiently precise.[40] To learn where to find in the forest plot of a meta-analysis the primary studies' and pooled (summary) estimates' 95% CI, see Figure 2.[35-38]

2d. What is the overall quality of the evidence (also known as confidence in the estimate of effect)? The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group is an international collaboration created in the year 2000 with the purpose of developing a common, sensible, and transparent approach to rating quality of evidence and grading strength of recommendations (www.gradeworkinggroup.org). GRADE defines quality of the evidence in the context of a systematic review as "the extent of confidence that an estimate of effect is correct."[41] Clinicians need to learn not only about the best estimates of an intervention's benefits and

harmful consequences but also what is the quality or certainty of these estimates. In the GRADE approach, evidence from RCTs starts as high-quality evidence. However, the following 5 factors can decrease the certainty in the estimates from high to moderate, low, or very low[42]:

- risk of bias of the included studies,[43]
- inconsistency of the results across studies,[34]
- indirectness of the identified evidence compared with the review's research question components,[44]
- imprecision of the results of the primary studies,[45]
- suspicion of publication bias.[46]

Review authors should explore each of these factors and present their findings in the results, discussion, and conclusion sections of the manuscript (Table 4). For example, the quality of the evidence can be moderate for the outcome "alveolar osteitis," which means that the investigators are moderately confident that the estimates of effect calculated are close to the truth. On the other hand, for the same intervention, a single or a group of investigators can have low-quality evidence for the outcome "adverse effect," which means that the investigators are extremely uncertain about the estimate for this outcome. Clinicians may proceed differently when the reviewers assess all included patient-important outcomes as high or at least moderate quality evidence, as compared with when the quality is low or very low. Examples of systematic reviews in

dentistry that have used the GRADE approach are published by the Cochrane Oral Health Group and others.[47-49]

3. How can I apply the results to patient care? In these final steps, clinicians should determine to what extent the results of the review are applicable to their particular context. Factors to consider when applying the results are whether the investigators considered all of the patient-important outcomes, what is the overall quality of the evidence (also known as the certainty of the estimates of effect), and whether the benefits are worth the costs and potential risks.

3a. Were all patient-important outcomes considered? A patient-important outcome means that if the patient were informed that only this outcome would change after implementing an intervention, the patient still would consider receiving the intervention even if it is associated with adverse effects, additional burdens, or costs.[54,55] Frequently, authors of systematic reviews do not report the negative aspects (that is, adverse effects) of the intervention under study.[56,57] Users should avoid making clinical decisions without considering all patient-important outcomes. The costs and burdens of the intervention also can be considered patient-important outcomes. Other examples of patient-important outcomes in dentistry are tooth loss, pain, swelling, and tooth discoloration.

3b. Are the likely treatment benefits worth the potential harms and costs? Finally, when considering whether to administer a treatment to patients, the clinicians should consider the balance in benefits and harms, costs,[11] and treatment burdens.[58] Patients' values and preferences (that is, "the collection of goals, expectations, predispositions, and beliefs that people have for certain decisions and their potential outcomes"[59]) and the context of the health system are required for conducting this balancing exercise.

TABLE 4

Grading of Recommendations Assessment, Development, and Evaluation approach to assess the quality of the evidence in systematic reviews of randomized controlled trials.

ISSUE	CRITERIA
Randomized Trials Start High but Move Down Because of Serious Issues Related to:	
Risk of bias[43]	Randomization Allocation concealment Blinding Lost to follow-up Selective outcome reporting
Imprecision[45]	Confidence intervals are too wide Small number of participants and events
Indirectness[44]	Included studies showing differences from the clinical review question regarding the population, intervention, comparison, and outcomes included
Inconsistency[34]	Presence of heterogeneity among the included studies identified analyzing the similarities between point estimates, overlap of confidence intervals, and statistical methods to detect heterogeneity (χ^2 test and I^2 estimate)
Publication bias[46]	Asymmetry of the funnel plot No comprehensive searching methods Small sample size trials All trials industry funded All included studies showing positive and "hard to believe" treatment effects

CONCLUSION

The amount of scientific information available for clinical decision making is overwhelming. Clinicians interested in informing their decisions with the best available evidence need high-quality and comprehensive summaries. When conducted and reported appropriately, systematic reviews provide crucial information for informing clinical decisions. However, the results of systematic reviews are susceptible to bias. Clinicians need to critically appraise systematic reviews to inform their decisions adequately. The critical appraisal of a systematic review focuses on aspects of risk of bias, results, and applicability. Clinicians should apply these guidelines to achieve the best possible results for their own practices. ■

Study or Subgroup	Chlorhexidine Rinse n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Delilbasi and Colleagues,[50] 2002	13/62	14/59		18.5%	0.88 (0.45-1.72)
Hermesch and Colleagues,[51] 1998	25/136	40/135		40.0%	0.62 (0.40-0.96)
Larsen,[52] 1991	12/144	28/134		20.3%	0.40 (0.21-0.75)
Ragno and Szkutnik,[53] 1991	10/40	20/40		21.2%	0.50 (0.27-0.93)
Total (95% CI)	**382**	**368**		**100.0%**	**0.58 (0.43-0.78)**

Total events: 60 (chlorhexidine rinse), 102 (placebo)

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 3.20$, *df* = 3, *P* = .36; $I^2 = 6\%$

Test for overall effect: *z* = 3.66 (*P* = .00026)

Test for subgroup differences: Not applicable

0.5 0.7 1 1.5 2

Favors Chlorhexidine Rinse   **Favors Placebo**

Figure 3. Meta-analysis on the effect of chlorhexidine rinse versus placebo for preventing dry socket (alveolar osteitis).[50-53] CI: Confidence interval. M-H: Mantel Haenszel. *Reproduced with permission of John Wiley and Sons from Daly and colleagues.*[6]

BOX 6

What you say to your patient.

After having a discussion with your patient, you prescribe the use of a chlorhexidine rinse and plan to check the patient's progress at the follow-up appointment. A week after you extracted the tooth, you determine that the patient has no signs of developing alveolar osteitis, and that the surgical wound is healing well. The eTable[6] (available online at the end of this article) presents a detailed description of the critical appraisal conducted in this review.

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.adaj.2015.01.025.

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eTABLE

Example of critically appraising a systematic review.*

1. How serious is the risk of bias?	
1a. Did the review include explicit and appropriate eligibility criteria?	Yes. The authors described in detail the type of participants, interventions, comparisons, outcome measures, and characteristics of the types of studies to include in the review. (See criteria for considering studies for this review section.)
1b. Was the search for relevant studies detailed and exhaustive?	Yes. Review authors searched MEDLINE, EMBASE, CENTRAL, and the Cochrane Oral Health Group registry. There was no restriction by language of publication, and they also searched for unpublished data by means of contacting investigators, experts, and other organizations. These searches were complemented by screening the reference lists of the identified studies. Finally, a complete description of the search strategy and search terms was provided in the article.
1c. Were the primary studies of high methodological quality?	Probably not. Using the Cochrane risk of bias tool, authors reported that only 30% of the included RCTs[†] appropriately concealed the allocation sequence. In addition, only 25% of the studies implemented appropriate strategies for blinding participants, personnel, and outcome assessors.
1d. Were the selection and assessments of studies reproducible?	Yes. Both screening of title and abstract and full text were conducted independently and in duplicate. The data extraction process was conducted in the same way. A flowchart describing the number of references at every stage of the study also was provided.
2. What are the results?	
2a. Were the results similar from study to study?	Regarding the heterogeneity of the included studies, the point estimates seemed to align relatively close to each other, and the confidence intervals showed large overlapping. The P value of the χ^2 test for heterogeneity (yes-no test) was .36, which did not allow rejecting the hypothesis that the estimates of the primary studies were the same. The I^2 estimate was only 6%, which was consistent with the previous findings of the analysis of heterogeneity. In summary, heterogeneity seemed negligible across included studies.
2b. What are the overall results of the review?	The meta-analysis including 4 RCTs showed that the use of chlorhexidine rinse reduced the risk of having alveolar osteitis (dry socket) in 42% (relative risk = 58%). This represents a large treatment effect on reducing the incidence of the outcome.
2c. How precise were the results?	The 95% confidence interval suggests an appreciable benefit at both the lower and upper limit (95% confidence interval, 0.43-0.78) with a 57% reduction in the lower limit and a 22% reduction on the outcome in the upper limit. Because both extremes show that the intervention provides important benefits, the results are precise.
2d. What is the overall quality of the evidence? (Also known as certainty on the estimates of effect)	The quality of the evidence for the outcome presence of alveolar osteitis (dry socket) was moderate owing to serious issues of risk of bias that were described in the section on risk of bias of this critical appraisal. For the outcome adverse events, the quality of the evidence was low owing to serious issues of risk of bias and inconsistency.
3. How can I apply the results to my patient care?	
3a. Were all patient-important outcomes considered?	Probably yes. For the prevention of alveolar osteitis (dry socket), reviewers considered the proportion of participants presenting with dry socket within 1 week post-treatment as the main outcome for effectiveness. In addition, authors collected data on any reported adverse event in the included studies.
3b. Are the benefits worth the costs and potential risks?	Yes. The benefit is clinically relevant measured in patient-important outcomes. Although some adverse events were reported—taste disturbance and stained tooth—these are reversible and considered by many patients as tolerable to prevent the occurrence of alveolar osteitis. Chlorhexidine rinse is an inexpensive medication.
Conclusion: The results of the systematic review are likely to be correct, although there is some concern about the risk of bias of the included studies. The magnitude of effect shows a large reduction in the incidence of alveolar osteitis (dry socket) when using chlorhexidine rinse in a preventive way. The applicability assessment shows that this intervention can be implemented with a minimum burden to patients at a reasonable cost and with no severe adverse effects.	

* Source: Daly and colleagues.[6]
† RCT: Randomized controlled trial.