

Use of Vital Pulp Therapies in Primary Teeth with Deep Caries Lesions

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Abstract

Purpose: This manuscript presents evidence-based guidance on the use of vital pulp therapies for treatment of deep caries lesions in children. A guideline panel convened by the American Academy of Pediatric Dentistry formulated evidence-based recommendations on three vital pulp therapies: indirect pulp treatment (IPT; also known as indirect pulp cap), direct pulp cap (DPC), and pulpotomy.

Methods: The basis of the guideline's recommendations was evidence from "Primary Tooth Vital Pulp Therapy: A Systematic Review and Meta-Analysis." (*Pediatr Dent* 2017;15;39[1]:16-23.) A systematic search was conducted in PubMed®/MEDLINE, Embase®, Cochrane Central Register of Controlled Trials, and trial databases to identify randomized controlled trials and systematic reviews addressing peripheral issues of vital pulp therapies such as patient preferences of treatment and impact of cost. Quality of the evidence was assessed through the Grading of Recommendations Assessment, Development, and Evaluation approach; the evidence-to-decision framework was used to formulate a recommendation.

Results: The panel was unable to make a recommendation on superiority of any particular type of vital pulp therapy owing to lack of studies directly comparing these interventions. The panel recommends use of mineral trioxide aggregate (MTA) and formocresol in pulpotomy treatments; these are recommendations based on moderate-quality evidence at 24 months. The panel made weak recommendations regarding choice of medicament in both IPT (moderate-quality evidence [24 months], low quality evidence [48 months]) and DPC (very-low quality evidence [24 months]). Success of both treatments was independent of type of medicament used. The panel also recommends use of ferric sulfate (low-quality evidence), lasers (low-quality evidence), sodium hypochlorite (very low-quality evidence), and tricalcium silicate (very low-quality evidence) in pulpotomies; these are weak recommendations based on low-quality evidence. The panel recommended against the use of calcium hydroxide as pulpotomy medicament in primary teeth with deep caries lesions.

Conclusions and practical implications: The guideline intends to inform the clinical practices with evidence-based recommendations on vital pulp therapies in primary teeth with deep caries lesions. These recommendations are based upon the best available evidence to-date.

KEYWORDS: PULPOTOMY, PULP THERAPY, VITAL PULP THERAPY, INDIRECT PULP TREATMENT, INDIRECT PULP CAP, DIRECT PULP CAP, FORMOCRESOL, MINERAL TRIOXIDE AGGREGATE, FERRIC SULFATE, SODIUM HYPOCHLORITE, CALCIUM HYDROXIDE, TRICALCIUM SILICATE

Scope and purpose

The American Academy of Pediatric Dentistry (AAPD) intends this guideline to aid clinicians in optimizing patient care when choosing vital pulp therapies to treat children with deep caries lesions[‡] in vital primary teeth. Carious primary teeth diagnosed with a normal pulp requiring pulp therapy or with reversible pulpitis should be treated with vital pulp procedures.²⁻⁶ Currently, there are three vital pulp therapy (VPT) options for treatment of deep dentin caries lesions approximating the pulp in vital primary teeth: (1) indirect pulp treatment (IPT), also known as indirect pulp cap;⁷ (2) direct pulp cap (DPC); and (3) pulpotomy.^{2,7}

‡ A caries lesion is a detectable change in the tooth structure that results from the biofilm-tooth interactions occurring due to the disease caries. It is the clinical manifestation (sign) of the caries process.

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For the purpose of this guideline, various interventions for vital pulp therapy were evaluated, including indirect pulp treatment using calcium hydroxide and alternates such as bonding agents/liners; direct pulp cap using calcium hydroxide and alternates such as bonding agents, mineral trioxide aggregate (MTA), or formocresol; and pulpotomies using formocresol, MTA, ferric sulfate (FS), sodium hypochlorite (NaOCl), lasers, calcium hydroxide, or tricalcium silicate. In addition to the reported adverse events, the evidence on outcome moderators such as type of final restorations and use of rubber dam was reviewed for this guideline.

ABBREVIATIONS

AAPD: American Academy of Pediatric Dentistry. **AGREE:** Appraisal of Guidelines Research and Evaluation. **CDC:** Centers for Disease Control. **DPC:** Direct pulp cap. **DQA:** Dental Quality Alliance. **GRADE:** Grading of Recommendations Assessment, Development and Evaluation. **FS:** Ferric sulfate. **IPT:** Indirect pulp therapy. **MTA:** Mineral trioxide aggregate. **NaOCl:** Sodium hypochlorite. **NGC:** National Guideline Clearinghouse. **NNT:** Number needed to treat. **PICO:** Population Intervention Control Outcome. **USDHHS:** U.S. Department of Health and Human Services. **VPT:** Vital pulp therapy.

The current recommendation supersedes the previous pulp therapy guideline² on the vital pulp therapies in primary teeth with deep caries lesions and does not cover non-vital pulp therapies, pulp therapy for immature permanent teeth, or pulp therapy for primary teeth with traumatic injuries. This clinical practice guideline adheres to the Appraisal of Guidelines Research and Evaluation (AGREE) reporting checklist.⁸

Clinical questions addressed. The panel members used the Population, Intervention, Control, and Outcome (PICO) formulation to develop the following clinical questions that will aid clinicians in the use of vital pulp therapies in primary teeth with deep caries lesions.

1. In vital primary teeth with deep caries lesions requiring pulp therapy, is one particular therapy (indirect pulp treatment, direct pulp cap, pulpotomy) more successful* than others?
2. In vital primary teeth treated with indirect pulp treatment due to deep caries lesions, does the choice of medicament affect success*?
3. In vital primary teeth with deep caries lesions treated with direct pulp cap due to pulp exposure (one mm or less) encountered during carious dentin removal, does the choice of medicament affect success*?
4. In vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during caries removal, does the choice of medicament or technique affect success*?

* Success was defined as overall success simultaneously observed both clinically and radiographically.

Methods

The AAPD previously published a guideline on pulp therapy entitled “Pulp Therapy for Primary and Immature Permanent Teeth”, last revised in 2014.² Evidence from “Primary Tooth Vital Pulp Therapy: A Systematic Review and Meta-Analysis”⁹ is the basis for the current guideline’s recommendations.

Search strategy and evidence inclusion criteria. Since it was decided a priori to use the aforementioned systematic review,⁹ multiple literature searches were conducted in PubMed®/MEDLINE, Embase®, Cochrane Central Register of Controlled Trials, and trial databases to identify randomized controlled

trials and systematic reviews addressing peripheral issues not covered by the review, such as patient preferences and impact of cost. The search strategy was updated by one of the authors (LG). Title and abstract and, when warranted, full-text of studies were reviewed in duplicate by workgroup members (VD, YC). Appendix for search strategy appears after References.

Assessment of the evidence. The main strength of this guideline is that it is based on a systematic review that adhered to the standards of the Cochrane Handbook for Systematic Reviews of Interventions¹⁰ and assessed the quality of the evidence using the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach.¹¹

Weakness of this guideline are inherent to the limitations found in the systematic review⁹ upon which this guideline is based. Limitations include failure to review non-English language studies other than those in Spanish or Portuguese, and that the recommendations are based on combined data from studies of differing risks of bias.

Formulation of the recommendations. The panel evaluated and voted on the level of certainty of the evidence using the GRADE approach.¹¹ The GRADE approach recognizes the evidence quality (Table 1)¹¹ and certainty as high, moderate, low, and very low, based on serious or very serious issues including risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias. To formulate the recommendations, the panel used an evidence-to-decision framework including domains such as priority of the problem, certainty in the evidence, balance between desirable and undesirable consequences, and patients’ values and preferences. The strength of a recommendation was assessed to be either strong or conditional, which presents different implications for patients, clinicians, and policy makers (Table 2).¹²

The guidelines were formulated via teleconferences and online forum discussion with members of the workgroup. The panel members discussed all recommendations and issues surrounding the topic under review, and all significant topics such as recommendations were voted upon anonymously.

Understanding the recommendations. These clinical practice guidelines provide recommendations for vital pulp therapies in primary teeth with deep caries lesions.

Table 1. QUALITY OF EVIDENCE GRADES†	
Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

† Quality of evidence is a continuum; any discrete categorization involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations.

Reprinted with permission. Quality of evidence and strength of recommendations. GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Update October 2013. Available at: “<http://gdt.guidelinedevelopment.org/app/handbook/handbook.html>”.

Table 2. IMPLICATIONS OF STRONG AND CONDITIONAL RECOMMENDATIONS FOR DIFFERENT USERS OF GUIDELINES

	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Reprinted with permission. GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Update October 2013. Available at: "<http://gdt.guidelinedevelopment.org/app/handbook/handbook.html>".

A strong recommendation implies in most situations that clinicians should follow the suggested intervention. A conditional recommendation indicates that while the clinician may want to follow the suggested intervention, the panel recognizes that different choices may be appropriate for individual patients.¹³ Table 3 shows a summary of the recommendations included in this guideline.

Recommendations*

Question 1. In vital primary teeth with deep caries lesions requiring pulp therapy, is one particular therapy (IPT, DPC, pulpotomy) more successful than others?

Recommendation: The panel was unable to make a recommendation on superiority of any particular type of vital pulp therapy owing to lack of studies directly comparing these interventions.

Summary of findings: The systematic review⁹ did not offer any direct comparison between IPT, DPC, and pulpotomy because of paucity of studies directly comparing these interventions. Out of the six studies on IPT^{3-6,14,15}, three studies^{3,5,14} with a follow up of 24 months, presented an overall success rate of 94.4 percent (95 percent confidence interval [95% CI]=84.9 to 98.0). For DPC, out of the four studies¹⁶⁻¹⁹ evaluated, the three studies^{16,18,19} with a follow up of 24 months, showed an overall success of 88.8 percent (95% CI=73.3 to 95.8). For pulpotomy, 12 studies²⁰⁻³¹ with a follow up of 24 months, showed an overall success of 82.6 percent (95% CI=75.8 to 87.8).⁹ Forty-eight-month outcome data were available only for IPT and showed that the overall success rate decreased to 83.4 percent (95% CI=72.9 to 90.4).⁹ The guideline panel was unable to determine superiority of any one type of vital pulp therapy over the others. The panel noted similar success rates

among the three therapies and suggests that the choice of pulp therapy in vital primary teeth with deep caries lesions should be based on a biological approach for caries-affected dentin removal, pulp exposures (if any), reported adverse effects (if any), clinical expertise, and patient preferences.

Research considerations: There is a dearth of research comparing types of vital pulp therapies (IPT vs. DPC vs. pulpotomy) in primary teeth. The panel urges researchers to conduct well-designed randomized clinical trials comparing the outcomes of IPT, DPC, and pulpotomies in primary teeth with deep caries lesions.

Question 2. In vital primary teeth treated with indirect pulp treatment due to deep caries lesions, does the choice of medicament affect success?

Recommendation: The panel found that the success of IPT in vital primary teeth with deep caries lesions was independent of the type of medicament used, and therefore recommends that clinicians choose the medicament based on individual preferences. (*Conditional recommendation, moderate-quality evidence [24 months], Low quality evidence [48 months]*)

Summary of findings: The systematic review⁹ of six studies^{3-6,14,15} compared IPT success using calcium hydroxide liners versus bonding agent liners. The meta-analysis showed that the liner had no effect on IPT success at 24 months ($P=0.88$) (relative risks [RR] 1.00, 95% CI=0.98 to 1.03 and 48 months follow-up [RR 1.10, 95% CI=0.92 to 1.32]) ($P=0.31$) (Table 5).⁹ The quality of the evidence for liners was best at 24 months, and was assessed as moderate due to small sample sizes. At 48-months, the quality of evidence was assessed as low due to the very small sample size issues. The summary of findings for IPT is included in Table 4.⁹

* For each of the following questions, success was defined as overall success simultaneously observed both clinically and radiographically.

Table 3. SUMMARY OF CLINICAL RECOMMENDATION ON VITAL PULP THERAPIES IN PRIMARY TEETH WITH DEEP CARIES

Question	Recommendation	Quality of evidence (follow-up duration)	Strength of recommendation
In vital primary teeth with deep caries lesions requiring pulp therapy, is one particular therapy (IPT, DPC, pulpotomy) more successful* than others?	The panel was unable to make a recommendation on superiority of any particular type of vital pulp therapy owing to lack of studies directly comparing these interventions. Panel noted the high success rates among IPT, DPC, and pulpotomy and recommends that the choice of pulp therapy in vital primary teeth with deep caries lesions should be based on a biologic approach. ^	----	----
In vital primary teeth treated with indirect pulp treatment (IPT) due to deep caries lesions, does the choice of medicament affect success*?	The panel found that the success of IPT in vital primary teeth with deep caries lesions is independent of the type of medicament used, and therefore conditionally recommends that clinicians choose the medicament based on individual preferences. †	Moderate [□] (24 mo.) Low [□] (48 mo.)	Conditional Conditional
In vital primary teeth with deep caries lesions treated with DPC due to pulp exposure (one mm or less) encountered during carious dentin removal, does the choice of medicament affect success*?	The panel found that in vital primary teeth with deep caries lesions treated with DPC due to pulp exposure (one mm or less) encountered during carious dentin removal, the success of DPC is independent of the type of medicament used, and therefore conditionally recommends that clinicians choose the medicament based on individual preferences. ‡	Very Low [□] (24 mo.)	Conditional
In vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during caries removal, does the choice of medicament or technique affect success*?	The panel strongly recommends the use of MTA in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal.	Moderate [□] (24 mo.)	Strong
	The panel strongly recommends the use of formocresol in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal.	Moderate [□] (24 mo.)	Strong
	The panel conditionally recommends the use of ferric sulfate in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal.	Low [□] (24 mo.)	Conditional
	The panel conditionally recommends <u>against</u> the use of calcium hydroxide in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal.	Low [□] (24 mo.)	Conditional
	The panel conditionally recommends the use of lasers in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal.	Low [□] (18 mo.)	Conditional
	The panel conditionally recommends the use of sodium hypochlorite in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal.	Very Low [□] (18 mo.)	Conditional
	The panel conditionally recommends the use of tricalcium silicate in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal.	Very Low [□] (12 mo.)	Conditional

IPT= Indirect pulp treatment; DPC= Direct pulp cap; MTA= Mineral trioxide aggregate.

* Success was defined as overall success simultaneously observed both clinically and radiographically.

^ The panel suggests clinicians take the most biological approach considering caries-affected dentin removal, pulp exposures (if any), reported adverse effects (if any), clinical expertise, and patient preferences.

† The medicaments evaluated were calcium hydroxide and alternates such as bonding agents/liners.

‡ The medicaments evaluated were calcium hydroxide and alternates such as dentin bonding agents, MTA, and formocresol.

□ Quality of evidence was downgraded by one level based on GRADE guidelines on handling indirect comparisons

Question 3. In vital primary teeth with deep caries lesions treated with direct pulp cap due to pulp exposure (one mm or less) encountered during carious dentin removal, does the choice of medicament affect success?

Recommendation: The panel found that in vital primary teeth with deep caries lesions treated with DPC due to pulp exposure (one mm or less) encountered during caries removal, the success of DPC was independent of the type of medicament (dentin bonding agents, MTA, and formocresol), and therefore recommends that clinicians choose the medicament based on individual preferences. (*Conditional recommendation, very-low quality evidence.*)

Summary of findings: The systematic review⁹ of three DPC studies compared calcium hydroxide versus alternative direct capping agents after 24-months (dentin bonding agents¹⁶, MTA¹⁸, and formocresol¹⁹). At 24-month follow-up, the meta-analysis showed the capping agent had no effect on success (RR 1.05, 95% CI=0.89 to 1.25) ($P=0.56$).⁹ The quality of the evidence for whether DPC capping agent affected success at 24 months was assessed as very low because of the high degree of heterogeneity in the studies ($I^2=83$ percent) and small sample size. All the three DPC studies involved immediate placement of the final restoration.⁹ The summary of findings for DPC is included in Table 5.

Question 4. In vital primary teeth with deep caries treated with pulpotomy due to pulp exposure during caries removal, does the choice of medicament or technique affect success?

Recommendations:

- The panel recommends the use of MTA in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal. (*Strong recommendation, moderate-quality evidence*)
- The panel recommends the use of formocresol in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal. (*Strong recommendation, moderate-quality evidence*)
- The panel recommends the use of FS in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal. (*Conditional recommendation, low-quality evidence*)
- The panel recommends the use of lasers in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal. (*Conditional recommendation, low-quality evidence*)
- The panel recommends the use of NaOCl in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal. (*Conditional recommendation, very low-quality evidence*)

Table 4. SUMMARY OF FINDINGS FOR IPT

Outcomes	Illustrative comparative risks (95% CI)	Relative effect (95% CI)	Number of participants	Quality of the evidence (GRADE)
Overall success at 24 mos.	CH IPT success= 91.6% (74.3 to 97.6) IPT without CH success= 96.8% (79.3 to 99.6)	RR 1.00 (0.98 to 1.03) $P=0.88$ All liners equally successful NNT= Not significant	3 studies with 319 teeth	Moderate
Overall success at 48 mos.	CH IPT success= 78.5% (61.2 to 89.5) IPT without CH success= 88.2% (74.5 to 95.0)	RR 1.10 (0.92 to 1.32) favors IPT without CH $P=0.31$ NNT= Not significant	3 studies with 81 teeth	Low
Comments: The 24 and 48 month studies used CH as one liner and the alternatives included Scotchbond ^{TM3,4} , Clearfill SE ^{TM14} , Vitremer ^{TM5} , Prime & Bond [®] , and Xeno ^{®13} .				

CH= Calcium hydroxide; IPT= Indirect pulp treatment; NNT= Number needed to treat; RR= Relative risks.

Table 5. SUMMARY OF FINDINGS FOR DPC

Outcomes	Illustrative comparative risks (95% CI)	Relative effect (95% CI)	Number of participants	Quality of the evidence (GRADE)
Overall success at 24 mos.	CH DPC success= 91.1% (41.7 to 99.3) Alternative DPC success= 88.5% (81.1 to 93.2)	RR 1.05 (0.89 to 1.25) favoring the alternative DPC $P=0.56$ NNT= Not significant	3 studies with 262 teeth	Very low
Comments: Distribution of teeth in the 24-month studies were: 100 teeth in the CH arms and 162 teeth in the alternative arms (60 FC teeth ¹⁸ , 80 NaOCl rinse followed by Prime & Bond [®] or Xeno ^{®15} , and 22 MTA ¹⁷ . All three 24-month DPC studies involved immediate placement of the final restoration (Aminabadi ¹⁸ 2010 had 120 teeth SSC's, Demir ¹⁵ 100 teeth amalgam or compomer surface sealed, Tuna ¹⁷ 42 teeth Kalzinol base and amalgam).				

CH= Calcium hydroxide; DPC= Direct pulp cap; NaOCl= Sodium hypochlorite; NNT= Number needed to treat; RR= Relative risks.

- The panel recommends the use of tricalcium silicate in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal. (*Conditional recommendation, very low-quality evidence*)
- The panel recommends against the use of calcium hydroxide in vital primary teeth with deep caries lesions treated with pulpotomy due to pulp exposure during carious dentin removal. (*Conditional recommendation, low-quality evidence*)

Summary of findings: The systematic review⁹ suggests that the overall success rate at 24 months for MTA, formocresol, FS, NaOCl, calcium hydroxide, and laser was 82.6 percent

(95% CI=75.8 to 87.8). MTA and formocresol success rates were the highest of all pulpotomy types in this time frame and were not significantly different ($P=0.15$). MTA's success rate was 89.6 percent (95% CI=82.5 to 94.0), and formocresol's was 85.0 percent (95% CI=76.3 to 91.0).⁹ MTA, formocresol, and FS success rates were all significantly better than calcium hydroxide at 24 months ($P<0.001$). Other studies showed NaOCl's success rate was significantly less than formocresol at 18 months ($P=0.01$), and other pulpotomy agents' success rates did not differ statistically (FS vs. laser; FS vs. NaOCl; and calcium hydroxide vs. laser). At 12 months, pulpotomy success rates for FS vs. laser and MTA vs. tricalcium silicate did not differ statistically. The summary of findings for pulpotomy interventions is included in Table 6.⁹

Table 6. SUMMARY OF FINDINGS FOR PULPOTOMY STUDIES

Outcome comparisons	Illustrative comparative risks (95% CI)	Relative effect (95% CI)	Number of participants	Quality of the evidence (GRADE)
1. FC vs. MTA overall success 24 mos.	FC success= 85.6% (76.9 to 91.4) MTA success= 89.6% (82.5 to 94.0)	RR 1.04 (0.98 to 1.10) favoring MTA $P=0.17$ NNT= Not significant	8 studies with 455 pulpotomies	High
FC vs. MTA Comments: At 24 months, the eight studies ^{19,20,22,23,24,25,26,27} involved 214 FC and 241 MTA pulpotomies. At the start of these multi-arm studies, there were 450 children with 810 teeth.				
2. FC vs. FS overall success 24 mos.	FC success= 87.1% (78.2 to 92.7) FS success= 84.8% (76.2 to 90.6)	RR 1.02 (0.93 to 1.13) favoring FC $P=0.65$ NNT= Not significant	4 studies with 216 teeth	Moderate
FC vs. FS Comments: At 24 months, the four studies ^{19,20,21,24} involved 112 FC and 104 FS pulpotomies. At the start of these multi-arm studies, there were 232 children with 508 teeth.				
3. FC vs. CH overall success 24 mos.	FC success= 79.0% (57.7 to 91.2) CH success= 41.4% (26.5 to 58.1)	RR 1.76 (1.40 to 2.23) favoring FC $P<0.001$ NNT (significant)= 3. On doing three pulpotomies, one failure would be prevented if FC was used instead of calcium hydroxide.	4 studies with 212 teeth	Moderate
FC vs. CH Comments: At 24 months, the four studies ^{19,20,21,24} involved 111 FC and 101 CH pulpotomies. At the start of these multi-arm studies, there were 165 children with 399 teeth.				
4. MTA vs. CH overall success 24 mos.	MTA success= 89.0% (59.6 to 97.8) CH success= 46.0% (35.0 to 57.3)	RR 1.96 (1.52 to 2.53) favoring MTA by 96% $P<0.001$ NNT (significant)= 3. On doing three pulpotomies, one failure would be prevented if MTA was used instead of calcium hydroxide.	3 studies with 190 teeth	Moderate
MTA vs. CH Comments: At 24 months, the three studies ^{22,24,28} involved 116 MTA and 74 CH pulpotomies. At the start of these multi-arm studies, there were 114 children with 264 teeth.				
5. FS vs. CH overall success 24 mos.	FS success= 82.1% (68.2 to 90.7) CH success= 52.8% (39.5 to 65.8)	RR 1.57 (1.19 to 2.06) favoring FS by 57% $P<0.001$ NNT (significant)= 4. On doing four pulpotomies, one failure would be prevented if FS was used instead of calcium hydroxide.	2 studies with 118 teeth	Low
FS vs. CH Comments: At 24 months, the two studies ^{17,68} involved 65 FS and 53 CH pulpotomies. At the start of these multi-arm studies, there were 118 children with 120 teeth.				

Table 6 continued on next page.

Table 6. CONTINUED

Outcome comparisons	Illustrative comparative risks (95% CI)	Relative effect (95% CI)	Number of participants	Quality of the evidence (GRADE)
6. MTA vs. FS overall success 24 mos.	MTA success= 92.2% (70.7 to 98.3) FS success= 79.3% (68.0 to 87.4)	RR 1.11 (0.99 to 1.26) favoring MTA $P=0.06$ NNT (significant)= 9. On doing nine pulpotomies, one failure would be if prevented MTA was used instead of calcium hydroxide.	4 studies with 207 teeth	Moderate
MTA vs. FS Comments: At 24 months, the four studies ^{19,20,24,29} involved 107 MTA and 10 FS pulpotomies. At the start of these multi-arm studies, there were 241 children with 578 teeth.				
7. FC vs. NaOCl overall success 18 mos.	FC success= 98.1% (97.6 to 99.7) NaOCl success= 82.9% (68.3 to 91.6)	RR 1.20 (1.04 to 1.40) favoring FC $P=0.01$ NNT (significant)= 6. On doing six pulpotomies, one failure would be prevented if FC was used instead of calcium hydroxide.	2 studies with 91 teeth	Low
FC vs. NaOCl Comments: At 18 months, the two studies ^{20,31} involved 50 FC and 41 NaOCl pulpotomies. At the start of these multi-arm studies, there were 181 children with 220 teeth.				
8. FC vs. Laser overall success 18 mos.	FC success= 94.4% (85.3 to 98.0) Laser success= 83.5% (63.0 to 93.8)	RR 1.14 (0.91 to 1.43) favoring FC $P=0.27$ NNT= 8 not significant	2 studies with 126 teeth	Moderate
FC vs. Laser Comments: At 18 months, the two studies ^{21,32} involved 64 FC and 62 laser pulpotomies. At the start of these multi-arm studies, there was an unknown number of children with 180 teeth.				
9. FS vs. NaOCl overall success 18 mos.	FS success= 89.2% (65.6 to 97.3) NaOCl success= 92.4% (79.0 to 97.5)	RR 0.99 (0.85 to 1.16) favoring neither pulpotomy $P=0.88$ NNT= Not significant	2 studies with 80 teeth	Low
FS vs. NaOCl Comments: At 18 months, the two studies ^{20,31} involved 40 FS and 40 NaOCl pulpotomies. At the start of these multi-arm studies, there were 181 children with 220 teeth.				
10. CH vs. Laser overall success 18 mos.	CH success= 74.0% (40.8 to 92.1) Laser success= 83.5% (63.0 to 93.8)	RR 1.07 (0.91 to 1.25) favoring laser $P=0.41$ NNT= Not Significant	2 studies with 116 teeth	Low
CH vs. Laser Comments: At 18 months, the two studies ^{21,32} involved 54 CH and 62 laser pulpotomies. At the start of these multi-arm studies, there were 184 children with 300 teeth.				
11. FS vs. Laser overall success 12 mos.	FS success= 81.9% (71.9 to 88.8) Laser success= 86.1% (56.8 to 96.7)	RR 1.06 (0.94 to 1.19) favoring laser $P=0.34$ NNT= Not Significant	2 studies with 177 teeth	Moderate
FS vs. Laser Comments: At 12 months the two studies ^{21,33} involved 90 FS and 87 laser pulpotomies. At the start of these multi-arm studies, there were 161 children with 320 teeth.				
12. MTA vs. Tricalcium silicate overall success 12 mos.	MTA success= 94.7% (84.8 to 98.3) Tricalcium silicate success= 95.2% (86.2 to 98.4)	RR 1.01 (0.94 to 1.09) favoring MTA $P=0.83$ NNT= Not Significant	2 studies with 116 teeth	Low
MTA vs. Tricalcium Silicate Comments: At 12 months the two studies ^{34,35} involved 62 MTA and 54 Tricalcium silicate pulpotomies. At the start of these multi-arm studies, there were 126 children with 144 teeth.				

CI=Confidence interval; CH= Calcium hydroxide; FC= Formocresol; FS= Ferric sulfate; MTA= Mineral trioxide aggregate; NaOCl= Sodium hypochlorite; NNT= Number needed to treat; RR= Relative risks.

Comparison 4.1. Formocresol vs. MTA pulpotomy (24-months). The systematic review⁹ evaluated eight studies^{20,21,23-28} comparing formocresol to MTA with a follow-up of 24 months, and the meta-analysis favored neither type of pulpotomy medicament (RR 1.04, 95% CI=0.98 to 1.11) ($P=0.15$). The quality of the evidence for this outcome at 24 months was assessed to be high.

Comparison 4.2. Formocresol vs. FS pulpotomy (24-months). The systematic review⁹ evaluated four studies^{20-22,25} comparing formocresol to FS with a follow-up of 24 months, and the meta-analysis favored neither type of pulpotomy medicament (RR .02, 95% CI=0.93 to 1.13) ($P=0.65$). The quality of the evidence for this outcome at 24 months was moderate due to small sample sizes.

Comparison 4.3. Formocresol vs. calcium hydroxide pulpotomy (24-months). The systematic review⁹ evaluated four studies^{22,23,25,31} comparing formocresol to calcium hydroxide with a follow-up of 24 months, and the meta-analysis indicated that formocresol was significantly better than calcium hydroxide (RR 1.76, 95% CI=1.40 to 2.23) ($P<0.001$). In terms of numbers needed to treat (NNT), on doing three pulpotomies, one failure would be prevented if formocresol was used instead of calcium hydroxide. The quality of the evidence for this outcome at 24 months was moderate due to small sample sizes.

Comparison 4.4. MTA vs. calcium hydroxide pulpotomy (24-months). The systematic review⁹ evaluated three studies^{23,25,29} comparing MTA to calcium hydroxide with a follow-up of 24 months, and the meta-analysis indicated that MTA was significantly better than calcium hydroxide (RR 1.96, 95% CI=1.52 to 2.53) ($P<0.0001$). In terms of NNT, on doing three pulpotomies, one failure could be prevented if MTA was used instead of calcium hydroxide. The quality of the evidence for this outcome at 24 months was moderate due to small sample sizes.

Comparison 4.5. FS vs. calcium hydroxide pulpotomy (24-months). The systematic review⁹ evaluated two studies^{22,25} comparing FS to CH with a follow-up of 24 months, and the meta-analysis indicated that FS was significantly better than calcium hydroxide. (RR 1.57, 95% CI=1.19 to 2.06) ($P<0.001$). In terms of NNT, on doing four pulpotomies, one failure could be prevented if FS was used instead of CH. The quality of the evidence for this outcome at 24 months was low due to very small sample sizes.

Comparison 4.6. MTA vs. FS pulpotomy (24-months). The systematic review⁹ evaluated four studies^{20,21,25,30} comparing MTA to FS with a follow-up of 24 months, with the meta-analysis nearing significance ($P=0.06$) favoring MTA (RR 1.13, 95% CI=1.00 to 1.29). In terms of NNT, on doing nine pulpotomies, one failure could be prevented if MTA was used instead of FS. The quality of the evidence for this outcome at 24 months was moderate due to small sample sizes.

Comparison 4.7. Formocresol vs. NaOCl pulpotomy (18-months). The systematic review⁹ evaluated two studies^{21,32} comparing formocresol to NaOCl with a maximum follow-up of 18 months, and the meta-analysis indicated that formocresol was significantly better than NaOCl (RR 1.20, 95% CI=1.04

to 1.40) ($P=0.01$). In terms of NNT, on doing six pulpotomies, one failure could be prevented if formocresol was used instead of NaOCl. The quality of the evidence for this outcome at 18 months was moderate due to small sample sizes.

Comparison 4.8. Formocresol vs. laser pulpotomy (18-months). The systematic review⁹ evaluated two studies^{22,33} comparing formocresol to laser, and the meta-analysis favored neither type of pulpotomy technique (RR 1.14, 95% CI=0.91 to 1.43) ($P=0.27$). The quality of the evidence for the outcomes of these agent comparisons at 18 months was low due to small sample sizes.

Comparison 4.9. FS vs. NaOCl pulpotomy (18-months). The systematic review⁹ evaluated two studies^{21,32} comparing FS to NaOCl, and the meta-analysis favored neither type of pulpotomy medicament (RR 0.99, 95% CI=0.85 to 1.16) ($P=0.88$). The quality of the evidence for the outcomes of these agent comparisons at 18 months was low due to small sample sizes.

Comparison 4.10. Calcium hydroxide vs. laser pulpotomy (18-months). The systematic review⁹ evaluated two studies^{22,33} comparing calcium hydroxide to laser, and the meta-analysis favored neither type of pulpotomy technique (RR 1.07, 95% CI=0.91 to 1.25) ($P=0.41$). The quality of the evidence for the outcomes of these agent comparisons at 18 months was low due to small sample sizes.

Comparison 4.11. FS vs. laser pulpotomy (12-months). The systematic review⁹ evaluated two studies^{22,34} comparing FS to laser, and the meta-analysis favored neither type of pulpotomy technique (RR 1.06, 95% CI=0.94 to 1.19) ($P=0.34$). The quality of the evidence for this outcome at 12 months was moderate due to small sample sizes.

Comparison 4.12. MTA vs. tricalcium silicate pulpotomy (12-months). The systematic review⁹ evaluated two studies^{35,36} comparing MTA to tricalcium silicate, and the meta-analysis favored neither type of pulpotomy medicament (RR 1.01, 95% CI=0.94 to 1.09) ($P=0.83$). The quality of the evidence for this outcome at 12 months was very low.

Remarks: The head-to-head analysis of all pulpotomy comparisons presented a challenge in assessing the evidence. The validity of the indirect comparison rests on similarity assumption that the study designs (Population, intervention, and outcomes) and the methodological quality are not sufficiently different to result in different effects.³⁷ As this assumption is always in some doubt, indirect comparisons always warrant rating down by one level in quality of evidence.³⁷ The panel recognized that the findings are of high clinical relevance and agreed that it will be of value to produce separate recommendation statements for various pulpotomy medicaments/techniques, even though the quality of evidence had to be downgraded. Therefore, for recommendations on pulpotomy medicaments and techniques, the panel decided to downgrade the quality of evidence by one level (from the highest level recorded for that intervention), owing to the indirect comparisons among various interventions.

The panel decided on a recommendation against the use of calcium hydroxide pulpotomy, because the data consistently showed inferior success for calcium hydroxide pulpotomy. The strength of evidence was conditional, since the quality of evidence was downgraded from moderate to low to account for indirect comparisons.

Research considerations. The panel recognized that to produce recommendations supported with higher quality evidence, there is a need for well-designed clinical trials with multiple arms allowing simultaneous comparisons of more than two medicaments or techniques.

Practice implications. The indications, objectives, and type of pulpal therapy depend on whether the pulp is vital or non-vital, which is based on the clinical diagnosis of normal pulp (symptom free and normally responsive to vitality testing), reversible pulpitis (pulp is capable of healing), symptomatic or asymptomatic irreversible pulpitis (vital inflamed pulp is incapable of healing), or necrotic pulp.² In order to replicate the recorded vital pulp therapy success rates, proper case selection, accurate diagnosis, and utilization of evidence-based technique are of key importance.

Indirect pulp treatment is a procedure that leaves the deepest caries adjacent to the pulp undisturbed in an effort to avoid a pulp exposure. This caries-affected dentin is covered with a biocompatible material to produce a biological seal.^{2,7}

Direct pulp cap is a technique in which the pulp is covered with a biocompatible material when caries excavation causes a pin-point pulp exposure.⁹ Past reports of DPC in primary teeth have shown limited success;^{16,38} therefore, DPC has had limited acceptance as a technique for management of carious pulp exposures in the primary dentition.

Pulpotomy is a procedure used when the excavation of carious dentin in primary teeth produces a pulp exposure. In this technique, the entire coronal pulp is removed, hemostasis of the radicular pulp is achieved, and the remaining radicular pulp is treated with one of several different medicaments.^{3,4,7} Published studies of this procedure have been reported since the early 1900's,³⁹ and pulpotomy currently is the most frequently used vital pulp therapy technique for deep dental caries lesions in primary teeth.⁴⁰

AAPD has published this current guideline on vital pulp therapy in primary teeth to provide evidence-based recommendations on vital pulp therapies in primary teeth with deep caries lesions. In view of the similar success of all three vital pulp therapies, the panel suggests clinicians take the most biological/conservative approach, which considers caries-affected dentin removal, pulp exposures (if any), reported adverse effects, and individual preferences. Based on the recommendations, IPT, DPC, and pulpotomy may all be viable options for treatment of primary teeth with deep caries lesions. Overall, the panel found moderate quality evidence supporting IPT, MTA pulpotomy, and formocresol pulpotomy. For all other interventions, the quality of evidence was low to very low. The success of IPT and DPC was found to be independent of the choice of medicament used. For pulpotomy, the panel found higher evidence supporting use of MTA and formocresol and evidence against the use of

calcium hydroxide. Treatment choices should be made based on the scientific evidence presented, clinical expertise, and patients' values and preferences. Clinicians should give greater care to consider individual patient factors where the guideline offers conditional recommendation.

The use of rubber dam is universally accepted as a gold standard for pulp therapies. Since it may be of ethical concern to design studies with a control group treated without using rubber dam isolation, there is limited research evaluating benefits of rubber dam use on primary teeth. However, the panel agreed that it is critical to use rubber dam in order to maintain the highest standard of care and to ensure patient safety.⁴¹

It is also important that clinicians select the best post-operative restoration using their clinical expertise and individual patient preferences. Either intra-coronal restoration or a stainless steel crown (SSC) may be adequate to achieve a good marginal seal for single surface (occlusal) restorations on a primary tooth with a life span of two years or less; whereas for multi-surface restorations, stainless steel crowns are the treatment of choice.^{2,42}

Potential adverse effects

Summary of findings: There have been concerns regarding toxicity related to formocresol and discoloration related to MTA, and more recently about the nontuberculosis mycobacterial infection linked to pulpotomy procedures.

Formocresol: The panel did not find any reports on toxicity related to use of formocresol for vital pulp therapies in children. Milnes⁴² reviewed the available evidence on formocresol and concluded that when used judiciously for pulpotomy procedure, it is unlikely to be genotoxic, immunotoxic, or carcinogenic in children. **The panel did not find sufficient evidence on adverse events that could influence the quality of evidence.**

MTA: The panel found reports of unintended grayish discoloration of teeth treated with MTA (gray and white) pulpotomy.⁴⁴⁻⁴⁸ One study reported that 94 percent of teeth that received white MTA pulpotomy and composite restoration turned gray, suggesting it was not an esthetic alternative to SSC.⁴⁵ The discoloration, however, had no influence on the success of vital pulp therapy. The panel, therefore, did not reduce the quality of evidence owing to the discoloration-related adverse effect of MTA. Clinicians should be aware of the possibility of coronal discoloration with MTA, especially while restoring a tooth with composite for esthetic considerations, and make decisions based on individual preferences. **The panel did not find sufficient evidence on adverse events that could influence the quality of evidence.**

Nontuberculosis mycobacterial infection: The U.S. Department of Health and Human Services (USDHHS)/Centers for Disease Control (CDC) and Prevention published a report on *Mycobacterium abscessus* (*M. abscessus*) infections among patients treated with pulpotomies.⁴⁹ The report identified the cause of outbreak to be the contaminated water used during pulpotomies, which introduced *M. abscessus* into the pulp chamber of the tooth. It was reported that out of 1,386 pulpotomies performed since January 2014, as of January 2016, a total of 20 patients were identified with confirmed or probable *M. abscessus*

infections, resulting in a prevalence rate of one percent. All patients (median age seven years) were severely ill and required at least one hospitalization (median hospital stay seven days; range: one-17 days); 17 patients required surgical excision, and 10 received outpatient intravenous antibiotics. As of April 5, 2016, no deaths had resulted from infection.⁴⁹ Since *M. abscessus* is ubiquitous in the environment, it poses a contamination risk. To prevent infections associated with waterlines, dental practices should monitor water quality, disinfect waterlines as per manufacturer's instructions, use point-of-use water filters, and eliminate dead ends in plumbing where stagnant water can enable biofilm formation.⁴⁹ **The panel did not find sufficient evidence on adverse events that could influence the quality of evidence.**

Remarks: The panel did not find sufficient evidence on adverse events related to medicaments used for IPT, DPC, and pulpotomy that could influence the quality of evidence. However, the panel recognizes that there may still be parental concerns regarding formocresol toxicity and discolorations associated with MTA and recommends that the clinicians should explain the evidence to parents and make decisions based on individual preferences. The panel encourages providers to closely monitor any updates from the CDC on *M. abscessus* infection related to pulpotomy procedures for its future implications and possible impact on the evidence.

Guideline implementation

This guideline, AAPD's first evidence-based guideline on pulp therapy, is published in both the journal, *Pediatric Dentistry*, and the AAPD's Reference Manual. By meeting the standards of the Institute of Medicine regarding the production of clinical practice guidelines, these recommendations will be submitted to the National Guidelines Clearinghouse (NGC), a database of evidence-based clinical practice guidelines and related documents maintained as a public resource by the Agency for Healthcare Research and Quality (AHRQ) of the USDHHS. Inclusion in the NGC guarantees the guidelines will be accessible and disseminated to private and public payors, policy makers, and the public. Additionally, AAPD members will be notified of the new guidelines via social media, newsletters, and presentations. The guidelines are available as an open access publication on the AAPD's website. Patient education materials are being developed and will be offered in the AAPD's online bookstore.

Practitioners seeking additional support implementing these guidelines are referred to the following resources:

- Treatment of Deep Caries, Vital Pulp Exposure, and Pulpless Teeth, Chapter 13, McDonald and Avery's Dentistry for the Child and Adolescent, 10th edition.⁵⁰
- Pulp Therapy for the Primary Dentition, Chapter 22, Pediatric Dentistry Infancy through Adolescence, 5th edition.⁵¹
- Pediatric Endodontics, Chapter 26, Cohen's Pathways of the Pulp, 11th edition.⁵²
- Endodontics: Colleagues for Excellence.⁵³ www.aae.org/colleagues.
- Preserving Pulp Vitality, Chapter 4, The Principles of Endodontics.⁵⁴
- Pediatric Endodontics: Current Concepts in Pulp Therapy for Primary and Young Permanent Teeth.⁵⁵

Cost-effectiveness of recommendation. Cost-effectiveness of a treatment is based on initial and possible retreatment costs.⁵⁶ Such a cost-analysis for therapies with proven health benefits and minimal adverse effects is an important consideration for clinicians, patients, and third-party payors.⁵⁶ This is especially important when different procedures with similar outcomes are available to treat a specific condition like in the case of vital pulp therapies. A research brief covering claims data for all children with private dental insurance lists vital pulpotomy, in primary or permanent teeth, as one of top 25 most common procedures performed in children with private dental benefits.⁵⁷ For ages one through six years, the spending is estimated to be \$257, ranging from \$160 for children in the lowest quartile of spending to \$996 among children in the highest quartile of spending.⁵⁷ Considering the number of pulp therapies performed on a population level, cost-effective treatment is a public health issue. However, very limited data exist on cost-effectiveness of various pulp therapies in the primary dentition. The most expensive pulp treatments and modalities with regards to initial costs are MTA and laser.^{56,58} Interestingly, a German study using the Markov model followed the first permanent molar with vital asymptomatic exposed pulp treated with DPC using MTA or calcium hydroxide over the lifetime of a 20 year old patient and reported that MTA was more cost-effective than calcium hydroxide despite higher initial treatment costs because expensive retreatments were avoided.⁵⁶

MTA is a suitable medicament for pulpotomy in primary teeth. The main reason for its underutilization has been its higher cost.^{58,59} The price of MTA is particularly elevated due to the recommendation to use each package for one patient only. However, new products marketed in a sealed desiccant-lined bottle quote a shelf life of three years, allowing use for multiple treatments. This has lowered the price to be competitive with other alternative materials.⁶⁰

Third-party reimbursement is another cost issue that may unintentionally increase utilization of a specific procedure over others. Pulpotomies are a widely performed procedure⁵⁷ and are reimbursed by both private and federally funded insurance companies. Alternatively, IPT with an overall success rate of 94.4 percent, is often bundled as part of the restoration and, therefore, not adequately reimbursed or not reimbursed at all. Reimbursement of more conservative, biological approaches of pulp therapy, such as IPT, will allow clinicians to make conservative choices based exclusively on efficacy and effectiveness of the specific procedures.⁶¹

Cost of pulp treatment may be contained by use of effective medicaments as determined by evidence-based research and detailed in this guideline, but the only way to reduce costs overall is to establish dental homes for every child and implement primary prevention by the child's parents or caregiver. Primary prevention must start early if treatment costs are to be reduced and oral health maintained.

Recommendation adherence criteria

Guidelines are used by insurers, patients, and health care practitioners to determine quality of care. Adherence to guideline

recommendations is measured, because it is believed following best practices reduces inappropriate care and improves outcomes.⁶² “Self-evaluation will ensure that dentistry as a profession can provide evidence to the community at large that its members are responsible stewards of oral health.”⁶³ While measurement of oral health care outcomes is in its nascent stage at both system and practice levels, the Dental Quality Alliance (DQA) of the American Dental Association in partnership with the AAPD and other dental organizations has developed system-level performance measures for some oral health areas. These measures further the goals of professional accountability, transparency, and oral health care quality through performance measurement. Under consideration by the DQA is a pediatric retreatment measure in relation to crowns and root canal therapies.⁶⁴

Workgroup and stakeholders. In December, 2016, the AAPD Board of Trustees approved a panel nominated by the Evidence-Based Dentistry Committee to develop a new evidence-based clinical practice guideline on vital pulp therapies in primary teeth with deep caries lesions. The panel consisted of pediatric dentists in public and private practice involved in research and education; the stakeholders consisted of authors of the systematic review in addition to representatives from general dentistry, governmental and non-governmental agencies, and international and specialty dental organizations.

External stakeholders. External and internal stakeholders reviewed the document periodically during the process of development of the guideline. Stakeholders also participated in anonymous surveys to determine the scope and outcomes of the guideline. All stakeholder comments were considered and addressed in the panel meetings. It is expected that the publication and dissemination of the guideline will generate additional dialogue, comments, and feedback from professional, academic, and community stakeholders.

Intended users. The target audiences for this guideline are dental team members in private, dental school, or public health care settings such as pediatric dentists, dental educators, general dentists, public health practitioners, policy makers, program managers, third-party insurers, and dental students/residents. The target populations include children and adolescents with deep caries lesions in vital primary teeth.

Review and feedback integration. This guideline was continuously reviewed by external and internal stakeholders from the beginning of the process until the formulation of the guidelines. Stakeholders were invited to take part in anonymous surveys to determine the scope and outcomes of the guideline. Comment was also sought on the draft guideline. All stakeholder comments were addressed and acted upon as appropriate per group deliberation.

Guideline updating process. The AAPD’s Evidence-Based Dentistry Committee will monitor the biomedical literature to identify new evidence that may impact the current recommendations. These recommendations will be updated five years from the time the last systematic search, unless the EBDC determines that an earlier revision or update is warranted.

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Appendix on next page.

Appendix

PubMed®/MEDLINE—date limit 01/2017

Search #1. 3607 results

(pulp therap* OR pulpotom* OR pulp cap* OR “Dental Pulp Capping”[MeSH terms] OR “Pulpotomy”[MeSH terms])

Search #2. 23275 results

(“Root Canal Therapy”[Mesh] OR “Root Canal Preparation”[Mesh] OR “Root Canal Obturation”[Mesh] OR “Root Canal Filling Materials”[Mesh] OR “Calcibiotic Root Canal Sealer”[Supplementary Concept] OR “Next root canal sealer”[Supplementary Concept] OR “calcium sulfate, zinc oxide, vinyl acetate, zinc phosphate root canal filling”[Supplementary Concept] OR “QMix root canal irrigant”[Supplementary Concept] OR “Root Canal Irrigants”[Mesh])

Search #3. 3570082 results

(Infant[MeSH] OR infant * OR infancy OR newborn * OR baby * OR babies OR neonat * OR preterm * OR premature * OR postmature * OR Child[MeSH] OR child * OR schoolchild * OR school age * OR preschool * OR Kid OR kids OR toddler * OR Adolescent[MeSH] OR adolesc * OR teen * OR Boy * OR girl * OR Minors[MeSH] OR minors * OR Puberty[MeSH] OR puberty * OR pubescent * OR prepubescent * OR Pediatrics[MeSH] OR paediatric * OR paediatric * OR paediatric * OR Schools [MeSH] OR nur-sery school * OR kinderman * OR primary school * OR secondary school * OR elementary school * OR high school * OR high school *)

Search #4. 144 results

(#1 OR #2) AND #3 AND PubMed systematic review filter applied

Search #5. 7589370 results

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization [tiab] OR randomisation[tiab] OR placebo [tiab] OR drug therapy[sh] OR randomly[tiab] OR trial [tiab] OR groups[tiab] OR clinical trial[pt] OR “clinical trial”[tw] OR “clinical trials” [tw] OR “evaluation studies” [publication type] OR “evaluation studies as topic” [MeSH terms] OR “evaluation study”[tw] OR evaluation studies [tw] OR “intervention studies”[MeSH terms] OR “intervention study”[tw] OR “intervention studies” [tw] OR “cohort studies”[MeSH terms] OR cohort[tw] OR “longitudinal studies”[MeSH terms] OR “longitudinal”[tw] OR longitudinally[tw] OR “prospective” [tw] OR prospectively [tw] OR “follow up”[tw] OR “comparative study”[publication type] OR “comparative study”[tw] OR systematic[subset] OR “meta-analysis” [publication type] OR “meta-analysis as topic” [MeSH terms] OR “meta-analysis”[tw] OR “meta-analyses”[tw])

Search #6. 1906 results

(#1 OR #2) AND #3 AND #5

Search #7. 890576 results

(“Economics”[Mesh] OR “Cost of Illness”[Mesh] OR “Cost Savings”[Mesh] OR “Cost Control”[Mesh] OR “Cost-Benefit Analysis”[Mesh] OR “Health Care Costs”[Mesh] OR “Direct Service Costs”[Mesh] OR “economics”[Sub-heading] OR cost)

Search #8. 78 results

(#1 OR #2) AND #3 AND #7