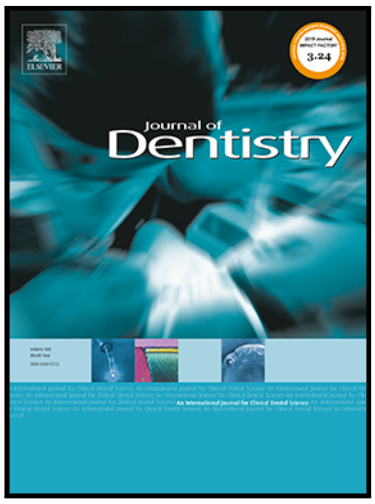

Deep Dentine Caries Management of Immature Permanent Posterior Teeth with Vital Pulp: A Systematic Review and Meta-analysis

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Title page

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Deep Dentine Caries Management of Immature Permanent Posterior Teeth with Vital Pulp: A Systematic Review and Meta-analysis.

Abstract

Title: Deep Dentine Caries Management of Immature Permanent Posterior Teeth with Vital Pulp: A Systematic Review and Meta-analysis.

• **Objectives:** Preservation of pulpal vitality in immature permanent teeth with deep carious lesions is essential to enable further root development and apical closure. This systematic review aimed to evaluate the evidence regarding the efficacy, presented clinical and radiographic success, and bacteriological outcomes of techniques and materials used for deep caries management in vital immature permanent teeth.

• **Data:** Randomised controlled trials evaluating Vital Pulp Therapy (VPT) for deep caries in immature permanent posterior teeth without history of irreversible pulpitis, and a follow up period of ≥12 months were included. Study characteristics and outcomes of all included studies were summarized. Cochrane's Risk-of-bias tool 2.0 was used to assess the quality of eligible studies. Meta-analyses using a random effects model was performed.

• **Sources:** Electronic databases PubMed, Medline, Embase, LILACS, CENTRAL and Cochrane Library were searched, followed by a manual search.

• **Study Selection:** Twelve papers were included into the review. Overall success rates were 98%, 93.5%, 93.6% for direct pulp cap (DPC), indirect pulp cap (IPC) and pulpotomy (PP) respectively. Regardless of VPT technique, there were no significant differences between

clinical and radiographic success rates. Completion of root development was achieved in more than 83% of the cases in all VPT techniques.

• **Conclusions**: All treatment modalities for PP were equally efficient with high overall success rates. Biodentine showed high success rates regardless of technique. No significant differences were found in the clinical and radiographic success rates between various follow-up intervals. There are no clear conclusions regarding superiority of either VPT technique on apical closure.

Clinical significance: This manuscript systematically evaluates the evidence and summarises all available data on each vital pulp therapy technique and materials used in treatment of deep caries in immature permanent teeth with vital pulps. The limitations in the current scientific literature and recommendations for future research are also highlighted.

Keywords: Immature permanent teeth, deep dentin caries, vital pulp therapy, systematic review

1. Introduction

Carious lesions in young permanent teeth with incompletely developed apices pose the greatest challenge in terms of maintaining pulp vitality and allowing further root development and apical closure. Preservation of pulp vitality is paramount as vital and functional pulp tissues can initiate self-reparative mechanisms and protect the tooth from bacterial invasion [1], while irreversible damage can cause necrosis and arrest root development [2].

Traditionally, non-selective removal of carious tissue has been advocated for management of deep caries lesions, where demineralized dentine was completely removed to reach hard tissue in translucent or hypermineralized dentine [3]. Not only do the destructive nature of conventional methods pose the risk of accidental pulpal exposure, but studies have also shown that 25-50% of bacteria still remain in the cavity even after complete removal of carious tissue [4, 5].

Contemporary views and current research points towards the fact that dental caries should not be treated by complete removal of existing bacteria, but instead as a disease that can be controlled by judicious management of the quantity and quality of the bacterial biofilm [6]. Emerging evidence suggests that risk of pulp exposure associated with complete caries removal can potentially be avoided by adopting more conservative caries removal approaches [6]. A biological approach is therefore advocated, which includes either no removal or selective removal (SR) of carious tissue, and sealing of the cavitated lesion with various materials, or the use of remineralization techniques with different agents [7]. This is based on the concept of minimal intervention and aims at maintaining a high amount of healthy tooth structure and therefore keeping teeth functional [8]. It is a less invasive technique as only infected tissue from the cavity walls is removed, allowing remineralization of affected dentine in the pulpal wall, while decreasing potential exposure of the pulp and preserving pulp vitality [4, 9].

Currently, there is no consensus on the most appropriate approach to the management of deep carious lesions in immature vital teeth, with much of the existing data being focused mainly on pulp related techniques or survival rates of materials in permanent teeth with complete root development. Data on the effect of treatment on continuation and completion of root development in immature permanent teeth with deep carious lesions remain sparse [10, 11], and does not reflect the impact of the disease on the long-term survival of the teeth and effects on stability of the developing occlusion. Therefore, the aim of this systematic review was to evaluate the evidence regarding the efficacy, presented clinical and radiographic success, and bacteriological outcomes of techniques and materials used for the management of deep caries in immature permanent teeth (with incompletely developed apices).

2. Methods

2.1 Study registration

The review protocol was registered in the PROSPERO international prospective register of systematic reviews hosted by the National Institute for Health Research (NIHR), University of York, UK, Center for Reviews and Dissemination (identification number: CRD42020181499).

2.2 Definitions of procedures evaluated [12]

Indirect pulp capping: Application of a biomaterial onto a thin dentine barrier in a one-stage carious-tissue removal technique generally to hard dentine. Considered more aggressive than selective carious-tissue removal in one-stage and stepwise excavation. Leaves neither soft nor firm carious dentine behind.

Selective carious-tissue removal in one-stage: Application of a biomaterial onto a dentine barrier in an indirect one-stage selective carious-tissue removal technique. Removal to soft or firm dentine. Immediate placement of a permanent restoration.

Stepwise excavation: Application of a biomaterial in an indirect two-stage selective carious-tissue removal technique. Temporary restoration placement between visits and re-entry after 6–12 months. First stage involves selective carious removal to soft dentine, to an extent that facilitates proper placement of a temporary restoration, and second stage removal to firm dentine. Final placement of a permanent restoration.

Direct pulp capping: Following the preservation of an aseptic working field, application of a biomaterial directly onto the exposed pulp, prior to immediate placement of a permanent restoration.

Partial pulpotomy: Removal of a small portion of coronal pulp tissue after exposure, followed by application of a biomaterial directly onto the remaining pulp tissue prior to placement of a permanent restoration.

Full pulpotomy: Complete removal of the coronal pulp and application of a biomaterial directly onto the pulp tissue at the level of the root canal orifice(s), prior to placement of a permanent restoration.

2.3 Reporting format

This review was planned, conducted, and reported in adherence to PRISMA standards of quality for reporting systematic reviews and meta-analyses [13]. The PICO methodology was utilized to formulate the research question (Table 1). The research question was: "What are the outcomes of clinical trials in humans on dentine caries management of immature permanent posterior teeth with vital pulp?"

2.4 Inclusion and Exclusion Criteria

A study was deemed eligible for inclusion if it fulfilled the following criteria:

- Studies reporting on any vital pulp treatment (VPT) technique (direct pulp capping, indirect pulp capping, selective caries removal in one stage, stepwise excavation, partial and full pulpotomy) and/or any technique or medicament used for the treatment of deep caries.
- Immature permanent posterior teeth (i.e. open root apices) with deep caries into dentine (ICDAS 4-6 [14] and /or radiographic lesions extending to $\geq 2/3^{rd}$ thickness of dentine).
- Clinically asymptomatic teeth or teeth with signs of reversible pulpitis.
- Randomised clinical trials (RCTs) and Controlled Clinical Trials (CCT).
- Minimum of 10 cases in each intervention/comparative arm.
- Follow-up period of at least 12 months.

Non-randomised prospective and retrospective studies, cross-sectional studies, case reports, editorials and review articles were excluded. Studies reporting on treatment of primary teeth, teeth with superficial caries (no radiolucency or radiolucency in outer $1/3^{rd}$ of dentine), teeth with closed apices, teeth with signs of irreversible pulpitis, single cohorts or studies with a follow-up period of < 12 months, and

those with < 10 case per intervention/comparative arm were excluded. The PICO criteria for the included studies are listed in **Table 1**.

2.5 Search Strategy

Detailed search strategies were developed and appropriately revised for each database, considering the differences in controlled vocabulary and syntax rules. The search strategy used can be found in Appendices 1 and 2.

2.5.1 Electronic search

The initial search of electronic databases was conducted on 26th February 2020 and updated on 1st July, 2021. A subsequent specific keyword search was conducted on 6th Dec 2021. No language or publication date restrictions were applied. The following electronic databases were searched to find reports of relevant published studies:

• The Cochrane Central Register of Controlled Trials (CENTRAL) (up to 6 Dec 2021);

• MEDLINE (PubMed) (1946 to 6 Dec 2021);

• Ovid MEDLINE (In-Process & Other Non-Indexed Citations, 6 Dec 2021);

• Ovid EMBASE (1974 to 6th Dec 2021)

• LILACS (1982 to 6th Dec 2021)

2.5.2 Unpublished literature search

In order to further identify potential articles for inclusion, grey literature was searched in the register of clinical studies hosted by the US National Institutes of Health (www.clinicaltrials.gov), the multidisciplinary European database (www.opengrey.eu), the National Research Register, and Pro-Quest Dissertation Abstracts and Thesis databases (https://about.proquest.com).

2.5.3 Manual search

The reference lists of all identified eligible studies and other published systematic reviews were hand-searched in order to identify further eligible studies. Again, no publication date or language restrictions were applied.

2.6 Inter-rater Reliability

A full calibration procedure was carried out prior to the beginning of the study collection. The two examiners (ES & HJT) who performed the screening of the studies and data extraction were calibrated until they reached inter-examiner reliability of k> 0.8. The same procedure was followed by the two other authors (KS & SG) who performed the risk of bias (k> 0.8).

2.7 Study selection

Study selection was performed independently and in duplicate by the 2 authors of the review (ES and HJT) who were not blinded to the identity of the authors of the studies, their institutions, or the results of their research. Study selection procedure comprised of title-reading, abstract-reading and full-text-reading stages. After exclusion of non-eligible studies, the full report of publications considered by either author as eligible for inclusion was obtained and assessed independently. In studies reporting on the same patient sample, only the publication with the longest follow-up was considered. Disagreements were resolved by discussion and consultation with the third author of the review (KS). A record of all decisions on study identification was kept.

2.7.1 Data collection

Two authors (ES and HJT) performed data extraction independently and in duplicate. Disagreements were resolved by discussion with a third author (KS). Specifically designed data collection forms were used to record the desired information. The following data were collected: author/title/year of study, study affiliation data, design of the study, number/age/gender of participants in intervention and control groups, intervention applied, and outcome assessed with all relevant clinical and radiographic variables.

If stated, the sources of funding, trial registration, and publishing of the trial's protocol was recorded. This information was used to aid assessment of heterogeneity and the external validity of included studies. In case of missing data, attempts were made to contact the authors.

2.7.2 Quality Assessment

The Risk of Bias 2.0. tool was used [15] to assess the quality of included studies. Risk of bias assessment was performed independently and in duplicate by two authors (KS and SG) for the primary outcomes. Any concern was resolved by discussion with the third author (DK).

2.7.3 Outcome measures

A narrative synthesis of the findings from the included studies, structured around the type of intervention, the target population characteristics, and the type interventions was collated and tabulated. Mean values and range of success rates of the technique or the medicament used were calculated from the values reported in all included studies. Mean percentage rate (presented as reported cases) of continuation of root development and apical closure was also reported for each technique and medicament. Cases where partial or complete root development was not determined or where the word apexification was used to determine root development, continuation of development without apical closure was assumed. Pathological clinical and radiographic symptoms were also reported to support aetiology of failed cases. The outcome measures recorded for bacteriological studies were colour, consistency and humidity of dentine and colony forming units (CFU) for both *lactobacilli* and *s.mutans* organisms.

2.7.4 Heterogeneity

Clinical and methodological heterogeneity were assessed by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes as specified in the inclusion criteria for considering studies for this review. Heterogeneity was assessed using a Chi^2

test and the I^2 statistic, where I^2 values over 50% indicated substantial heterogeneity. Significant heterogeneity was present when the p-value was less than 0.1.

2.7.5 Unit of analysis issues

It was anticipated that some of the included studies presented data from repeated or paired observations on participants, which could lead to unit-of-analysis errors. In such cases, advice provided in section 9.3.4 of the Cochrane Handbook for Systematic Reviews of Interventions [16] was followed.

2.8 Data synthesis or quantitative synthesis

Meta-analysis was carried out for studies with similar comparisons reporting the same outcomes at the same follow-up time-points. For dichotomous data, number of participants with events and total number of participants in experimental and control groups were analysed. Regarding meta-analysis for dichotomous data, risk ratios (RRs) and their 95% confidence intervals (Cls) were calculated. Inverse variance statistical method with a Random Effects analysis (DerSimonian and Laird) method was applied in RevMan (Review Manager, Version 5.4, The Cochrane Collaboration, 2020). Assessment of statistical heterogeneity was also undertaken.

3.0 Results

3.1 Search results

A total of 858 articles were initially identified, to which 143 studies were added after repeated electronic searches at different time points (**Appendix 1**) and another 15 papers after hand search. A second search with more specific key words was run/performed that identified another 439 papers (**Appendix 2**). After duplicates removal, a total of 1273 articles underwent title and abstract screening, of which 1163 were excluded. A total of 110 articles were retrieved for full text appraisal. From these, 98 articles were excluded with reasons **(Table 2)**. Upon further evaluation, 2 manuscripts [17, 18] were found to be related to one cohort population but as they reported on different outcome measures, they were analysed as 2 separate papers. Therefore, a total of 12 manuscripts from 11 study cohorts were finally included. The search and screening process results are presented in detail in the PRISMA flowchart **(Figure 1)**.

For studies reporting mixed population of primary and permanent teeth (**Table 2**), attempts were made to contact authors to request for raw data in order to evaluate data solely for immature teeth within their sample. Some authors were uncontactable, while others informed that no data was collected on root development status, or that no distinction was made between open versus closed apex teeth during the analysis. For studies where, raw data was available and patient age was provided, the team attempted to calculate root immaturity (open apex) based on the cut off age of 10 years. This was based on the estimation that 3 years duration is required for complete apex formation of a 1st permanent molars which erupts at age 7. However, despite application of this criteria, some did not meet the minimum sample size of 10 teeth per intervention arm. As such, they were omitted and hence the risk of selective reporting cannot be excluded.

3.2 Study characteristics

The characteristics of the included studies are summarized in **Table 3**. From the 12 manuscripts included into the analysis, all were RCTs, of which 5 [17-21] had split mouth designs, and 7 were parallel group designs [1, 22-27]. No CCTs fitting the inclusion criteria were found. The sample size ranged from 13 to 90 children, with the corresponding number of teeth ranging between 26 and 162 teeth, yielding a total of 791 teeth in 614 patients. The age of the participants ranged between 6-15 years. All studies were conducted in either a University or Dental College setting. Seven studies had single operators for treatment [19-22, 24, 25, 27], 1 had 2 operators [23], and 3 studies did not report on the number of operators[1, 17, 18, 26]. Four studies were funded by University grants [19, 22, 25, 26], 4 studies received no funding [19, 22, 25, 26], 2 studies did not report funding sources [23], and 1 study had the MTA funded by a material company [20].

Regarding interventions, the majority of the papers evaluated pulpotomy (PP) (n=7) [1, 19, 21, 22, 24-26], 1 evaluated indirect pulp capping (IPC) [27], 7 direct pulp capping (DPC) [20, 23], and 2 stepwise excavation papers belonging to the same study cohort [17, 18]. The dental material appraised the most

among studies was Mineral Trioxide Aggregate (MTA) (n=10), used as a pulpotomy or a direct pulp capping medicament. In the 2 DPC studies, MTA was evaluated against Biodentine (BioD) [20] or calcium hydroxide (CH)[23]. For studies on pulpotomy, 2 studies compared MTA to CH (n=3) [19, 25]. Other pulpotomy medicaments less frequently evaluated included BioD (n=1), abscess remedy (n=1) [1], platelet-rich fibrin (n=1) [24], calcium-enriched mixture cement (n=1) [22] and Er:CrYSGG laser (n=1) [26]. In all IPC studies, CH was evaluated against BioD and Theracal (n=1) [27].

Materials used for final restoration of the teeth after vital pulp therapy varied across studies, with composite resin (CR) being the most commonly used, either alone (n=4) [17, 20, 21, 25] or in combination with other restorative materials such as GIC or resin-modified GIC (n=2) [26, 27]. Other restorative materials used were amalgam (n=3) [19, 23, 24] and preformed metal crowns (n=2) [1, 24].

The majority of included studies (n=10) evaluated treatment success rates based on clinical and radiographic findings, with the main clinical parameters reported being pain, swelling, mobility, and tenderness to percussion. Only 3 studies additionally ascertained pulpal status using sensibility testing prior to study commencement, out of which only 2 studies continued to evaluate this during recall visits. Radiographic parameters included continuation/completion of root formation, presence/absence of periapical or furcation radiolucency, root resorption (internal and external), widening of periodontal ligament space or loss of lamina dura. The majority of the studies (n=5) reported on progression of root development up to apical closure, 3 studies [19, 23, 25] reported only on continuation of root development and another 3 studies [17, 20, 27] did not evaluate it at all. One study [21] reported scoring the radiographs at baseline using the Demerjian teeth maturity score [28], and subsequently utilising the Nosrat radiographic criteria for assessment of root development [22]. Another study quantified increases in root lengths using a software that transformed and standardized dimensional changes between pre and post-operative radiographs prior to analysis [26].

Two manuscripts from Safwat et al. reported on bacteriological and dentine characteristics for stepwise excavation procedure [17, 18]. The outcome measures recorded included colour, consistency and

humidity of dentine. Dentine colour and consistency were assessed according to the criteria by Bjørndal et al. [3], and colour classification was done by comparing the clinical observation with photographs illustrating the 5 typical dentine colour classes. Collection of carious dentine sample was done for microbiological assessments and quantifications of colony forming units (CFU) for both *lactobacilli* and *s.mutans* organisms.

Timings for outcome evaluation varied widely among the studies, and range from 3 months to 45 months post-treatment. Six studies reported reviews up to 24 months duration [1, 23-27], 1 study for up to 18 months [21], and another 4 studies reported results for up to 12 months.

3.3 Quality assessment

Figures 2 and 3 present the summary findings of the quality assessment for potential risk of bias in all included studies. Overall, 4 studies were considered as being at low risk [23-25, 27], another 6 at unclear risk [17-19, 21, 22, 26] and 2 at high risk of bias [1, 20].

Regarding sample size, 7 studies reported on the exact methods and supported the evidence for their calculations, with 4 [17, 24, 26, 27] using power analysis, 1 based upon high success rates of MTA pulpotomy [21] and 1 using mean of ordinal data presuming that the sample displays normal distribution [20]. Clear randomisation for treatment allocation was reported in all but 1 study [1], where neither information about sample selection or treatment allocation was provided.

Most studies were rated as being at low risk for attrition bias since either there were no drop-outs reported or drop-out rate had been compensated for and incorporated in the initial sample calculation or had been calculated below the statistically accepted non-respondent rate [29]. Correspondingly, the study by Katge and Patil (2017) was rated as being as high risk of bias due to the high dropout rate. Almost all studies were rated as being at low of reporting bias as there was sufficient information regarding methods of outcome assessment and their standardization, apart from 1 which was at high risk due to limited description of standardized outcome measures [1].

Regarding performance bias, the majority of studies were rated as being at unclear risk of bias, with only 4 studies [23-25, 27] reporting blinding of both participants and personnel. Finally, regarding detection bias more than ¾ of the studies were rated as being at low risk as there was clear information regarding blinding of outcome assessment. Two studies [1, 20] were rated as being at unclear risk due to insufficient information necessary for a clear judgment to be made.

3.4 Qualitative synthesis: Analysis of VPT protocols and outcomes

Overall, success rates exceeded 75% in majority of studies, irrespective of procedure and medicament used, with clinical and radiographic success being similar in almost all cases. The most common clinical symptom reported was pain and tenderness to percussion, with the most common radiographic being periapical radiolucency followed by widening of PDL. **Table 4a** presents success rates and frequency of specific clinical and radiographic findings reported in included studies. Cumulative results are presented as there were no statistically significant differences recorded in the success rates between various follow-up intervals in all studies.

3.4.1 Direct Pulp Capping (DPC)

Direct pulp capping was evaluated in 2 papers (Chailertvanitkul *et al.* 2014, Katge & Patil 2017, where the cavity was cleaned with disinfected round burs and bleeding was controlled with pressure application using cotton pellets moistened with either 2% NaOCl [23] or saline [20]. Calculated overall success rate was equal to 98%, regardless of the medicament used. Clinical and radiographic success was 100% at 12 months and 96% at 24 months. The highest value for both clinical and radiographic success was recorded for BioD (100% for both), which was marginally higher than that of MTA (97.5%) and CH (97% for both). None of the specific clinical or radiographic characteristics were reported in any of the studies.

Continuation of root development was evaluated in only 1 paper [23] with the mean percentage reported as being 96% at 24 months. In this study, CH performed marginally better than MTA (97.1% and 95.1% respectively).

3.4.2 Indirect Pulp Capping (IPC)

Efficacy of IPC was evaluated in 1 paper [27], in which, caries were removed up to the point where dentine showed increased resistance and the cavity was also irrigated every 3 minutes with a solution of 1% NaOCl in order for debris to be removed.

Overall success rate was 93.5%, with radiographic success being slightly higher than clinical success. Regarding efficacy of different medicaments, Theracal demonstrated excellent results, reaching 100% for both clinical and radiographic success at 24 months. BioD showed similar results (94% clinical and 100% radiographic), which were higher than CH (78% and 89% respectively). Completion of root development was not evaluated.

3.4.3 Pulpotomy

Pulpotomy was evaluated in 7 papers, all of which evaluated efficacy of various PP medicaments. In most studies [1, 19, 21, 22, 24] haemostasis was achieved by application of light pressure using a cotton pellet soaked in saline solution, with the application time varying between 2 to 10 minutes. In the study by Tozar et al. (2020) bleeding was ceased within 5 minutes after the application of a solution of 5.25% NaOCl and in the study by Özgür et al. (2017), after the application of either one of the above haemostatic solutions (sterile saline or NaOCl).

Overall success was 93.6 %, regardless of medicament used and with clinical and radiographic success rate being almost equal among the studies and ranging between 71% and 100%. Mean values at 12 months were 95.8 % for clinical and 86.5 % for radiographic success, and 88.9% and 83.4% respectively at 18 months. At 24 months mean value for clinical success was 94.5% and 90.9%, for radiographic success while corresponding values for >24 months were 85.4% for both.

The medicament with the highest success rate was MTA, with a mean value of 97.4 % (range: 89%-100%) for clinical and 92.3 % (range: 71%-100%) for radiographic success respectively. This was

followed by CH, with a mean value for both clinical and radiographic success equal to 92.3%. Corresponding values for BioD were 89% for clinical success and 82% for radiographic success. Success rates of other medicaments less frequently used were equally high ranging from 80% for abscess remedy and calcium-enriched mixture cement to 100% for MTA, triple antibiotic and platelet-rich fibrin. The most commonly reported clinical failure was pain followed by abscess formation and tenderness to percussion. Periapical radiolucency was the most common reason for radiographic failure.

Overall rate for continued root development was 90.9% at 12 months and 97.3% at 24 months, with values ranging from 81.8% up to 100%. MTA performed better than CH at 12 months (100 % and 81.8% respectively) but at 24 months both medicaments showed similar performance (97.5% and 97.2% respectively). Regarding apical closure, corresponding overall mean rate was 74.5% regardless of the medicament used, with values ranging from 64.3% at 12 months to 89.2% at 24 months. Among the most commonly used pulpotomy medicaments, MTA showed slightly higher percentages of apical closure at 12 months compared to BioD (66.1% and 60% respectively), with the small number of studies not allowing for further comparisons. At 24 months, MTA showed high percentage of apical closure (88.5%), equal to that of other less commonly used medicaments, such as PRF (88.9%) and TAB (100%). The smallest percentage of apical closure calculated was when MTA was used in conjunction with laser where only 21 cases out of 44 achieved apical closure at 12 months (47.7%).

3.4.4 Stepwise Excavation: Bacteriology results

Results from the papers evaluating efficacy of the medicaments on corresponding procedures are presented in **Table 4b**. Ozone application with or without a remineralising solution through stepwise excavation had no significant effect on dentine colour and consistency. Also, DIAGNOdent® was unreliable as a diagnostic tool in monitoring caries activity, following treatment of deep dentinal lesions.

3.4.5 Other factors possibly affecting outcome

Data regarding the effect of tooth-related factors on the efficacy of each technique and medicament were not reported in almost any of the studies. The effect of final restoration was only reported in 1

study (Özgür et al., 2017), in which two teeth showed marginal discolouration of the final restoration one in each group of sterile saline used in combination with MTA at 18 months and with CH at 24 months. None of these teeth though showed clinical or radiographic evidence of failure and therefore the effect of marginal integrity of the final restoration could not be demonstrated.

3.4.6 Secondary outcomes

None of the papers evaluated outcomes that compared between conventional (restorative) treatment modalities versus biological interventions, preventive treatment alone or no treatment. Additionally, none of the included studies reported on the intended evaluations for treatment cost-effectiveness, and comparison of patient reported Oral Health Related Quality of Life

3.5 Quantitative Synthesis

Quantitative synthesis was performed by mathematically combining 6 papers [19, 21, 22, 24-26] comparing the efficacy of MTA as a pulpotomy agent against alternative medicaments. A second synthesis was performed by combining four papers in pairs of 2: (i) Comparing MTA with CH [19, 25] and, (ii) Comparing MTA with bioceramic materials, i.e. BioD and CEM [21, 22]. (**Fig. 4a, 4b and 4c**)

Random-effect meta-analysis did not indicate any statistically significant differences in success rates when MTA was compared to CH (RR 2.22 [95% CI 0.27, 17.89], p=0.42), bioceramic materials separately (RR 0.48 [95% CI 0.04, 5.63], p=0.56) or all pulpotomy medicaments (RR 0.68 [95% CI 0.21, 2.18], p=0.48). The non-significant difference indicates that all materials performed equally well. The degree of heterogeneity between studies was found to be low (I^2=0%). Statistical analysis of publication bias was not indicated, as fewer than 10 studies were included in the quantitative synthesis.

4.0 Discussion

This systematic review, is the first one to assess and summarize all available data regarding treatment of deep caries in immature permanent teeth with vital pulps. Results showed that success rates for all

vital pulp techniques, regardless of the medicament used, exceeded 75%, with clinical and radiographic success being similar in majority of cases. Completion of root development was achieved in more than 83% of the cases, regardless of VPT technique used. The most common clinical symptom reported was pain and tenderness to percussion, while the most common radiographic findings were periapical radiolucency and widening of PDL.

This is in accordance with previous reports, where weighted pooled success rate of direct pulp capping, partial and full pulpotomy treatment for vital primary teeth was in the range of 72.9%–99.4%. It was also reported that both MTA and CH provide satisfactory outcomes when used as pulpal medicaments in vital pulp therapy. This supports evidence that permanent teeth with deep caries can be managed successfully with VPT, although results regarding superiority of material remains inconclusive.

In this review, cumulative results were presented as there were no statistically significant differences recorded in the success rates between various follow-up intervals in all studies. A systematic review found that 6 months of monitoring can be considered an appropriate period when evaluating the success of a partial pulpotomy although more clinical and radiographic controls are essential to ensuring success [30]. This is in agreement with the results of this review, in which the clinical and success rates did not show statistically different results among the 3 review periods evaluated (6 months, 1 year, and 2 years). On the other hand, results of completion of root development should be interpreted with caution, as the results reported were based on the last review time frame, which is variable among the studies included for review. Since it takes a range of 2-4 years duration for complete root development in permanent posterior teeth [31], consequently the normal review time of postoperative 1-2 years follow-up examination as often reported in studies, may not be adequate. As such, it is recommended that longer reviews of up to 3 years duration may be necessary to determine success of complete root formation.

Immature permanent teeth are considered good candidates for VPT as they have open root apices, robust pulpal blood supply, and pulps unaffected by aging-associated changes. However, the challenge in the management of immature permanent teeth with deep caries is, maintaining the balance between adequate removal of infected carious dentine versus protection of pulp vitality for facilitation of

continued root development. There are various factors which may influence treatment success rates, including accuracy of pre-treatment pulpal diagnosis, practice of aseptic techniques, adequate removal of infected dentine and correspondingly reduction of microorganism quantity, size of pulp exposure, and technique or materials used in pulp protection.

Success of VPT hinges on pre-treatment pulpal condition and adequate removal of microorganism from the tooth [32]. A crucial determinant of a successful outcome, however lies in ascertaining the actual state of pulpal inflammation, which is essential to prevent erroneous pulpal diagnosis and hence improper treatment [33]. A detailed pain history, meticulous clinical examination supplemented with a high-quality periapical radiograph, and pulp sensibility testing using low temperature cold testing in combination with EPT are necessary to assess pulpal status [12]. In this review, it was found that only 3 studies evaluated pulpal status using sensibility testing prior to study commencement, out of which only 2 evaluated this during review visits. However, the benefit of sensibility testing in pulpal diagnosis in immature teeth remains indeterminate. Studies have demonstrated that sensitivity to electrical stimulation appears to be related to the stage of root development [34], in which immature permanent teeth tend to give minimal or no response to electrical testing [35] as full development of the plexus of Rashkow only occurs 5 years post eruption [36]. Additionally, unlike fully developed teeth, pulpal nerves in immature teeth do not terminate among the odontoblasts to reach the predentine or dentine region [34]. Moreover, there is always the risk of false positive response to EPT testing especially in multi-rooted teeth which may have co-existence of both partially necrotic and healthy pulp in the root canal system [37]. Physiology aside, EPT testing in anxious young patients cannot always be substantiated and are often premature or unreliable. Hence, it has been suggested that testing with cold may be a more consistent and effective method in immature permanent teeth [38]. Other suggested forms of pulp testing which are the most accurate diagnostic methods and may be considered for use in evaluating the tooth's vascular supply include the use of Laser Doppler Flowmetry (LDF) or pulse oximetry [39]. However, these methods may not be suitable for daily clinical practice due to the practicalities and cost of these applications. Caution should also be taken during radiographic analysis especially in immature teeth, as radiolucent areas at teeth apices may be misdiagnosed as non-vital pulp

with periapical pathology or other pathological processes, when they are, in fact, normal structures of the apical papilla synonymous with open apex developing teeth. It is, therefore, imperative that radiographic evaluations be carried out in combination with good clinical examination to facilitate accurate pulpal diagnosis prior to commencement of treatment.

The prognosis of VPT can also be affected by other factors. It is essential to consider the depth of caries penetration when deciding between the various choices of VPT, which may directly affect treatment prognosis. Practically, two depths of caries should be considered: deep caries which reaches the inner quarter of dentine, but with a distinct band of radiographically detectable affected dentine between caries and the pulp in which pulpal exposure is potentially avoidable, versus extremely deep caries penetrating the full thickness of the dentine in which pulp exposure is unavoidable during caries operative procedure. Within the current review, some included studies did not define the depth of caries penetration and of those which did, the definitions of carious depth varied and it was not possible to categorize them adequately for more in-depth and meaningful analysis.

Additionally, only one study [23] among those included quantified the size of pulpal exposure, in which the incidence of unfavourable outcomes was markedly higher in teeth with pulp exposure areas >5mm. However, the numbers with large exposure areas were small, making it impracticable to draw conclusions from the outcomes. Location of carious exposure could also affect survival rates of VPT. Studies have shown more favourable survival rates when exposure site was limited to occlusal surfaces as compared to proximal surfaces [40]. This can be attributed to multiple factors, including isolation difficulties leading to compromised coronal seal and challenges in completion of caries removal or application of pulp-capping material. [41]

In line with this, ability to maintain asepsis during the treatment process is paramount to achieving success in VPT. Among the studies included in this review, only 2 studies [25, 26] utilized NaOCl for haemostasis control, of which only 1 paper [25] evaluated the use of saline versus NaOCl for haemostasis control. Majority of studies only utilized physiological saline for haemostasis control and cavity cleansing. Although physiological saline has been the acceptable standard in majority of pulp

capping scenarios, its efficacy in facilitation of cavity cleansing is limited by a lack of disinfection properties. The European Society of Endodontology (ESE) recommends that pulpal haemostasis and disinfection be achieved using cotton pellets soaked ideally with sodium hypochlorite (0.5 -5%) or chlorhexidine (0.2 -2%)[12]. This is also supported by the American Association of Endodontists (AAE) [42]. The implications of this on success rates is uncertain, and higher number of patients are needed in future studies to re-evaluate the impact of exposure size, size and cavity preparation-related factors on VPT treatment outcomes.

Historically, CH was considered as the material of choice in pulp capping procedures [43]. The ESE currently recommends that a hydraulic calcium silicate material be placed during procedures aimed at avoiding pulp exposure, as well as those in which pulpal exposure is encountered prior to placement of a definitive restoration [12]. Regardless of treatment method, the most evaluated dental material among included studies was MTA. It is important to note the availability of several types of contemporary materials with similar biocompatibility and biomineralization that are presently gaining popularity as pulp capping or pulpotomy materials e.g. Biodentine, Theracal, Abscess Remedy, PRF, CEM and TAP. The existing literature regarding the use of some materials such as Abscess Remedy and TAP for VPT in immature permanent teeth is sparse, and more results of prospective clinical studies and trials are needed before they can be recommended for routine use. It should be noted that in the included studies, some of the materials which are compared against each other have different use and mechanisms of action. Broadly, they can be classified into hydraulic calcium silicate materials, intracanal disinfection medicaments and autologous biological scaffolds. There is a possibility that comparisons of this nature may not be equivalent and there should be a consideration for future studies to compare materials with similar mechanism of action such that outcomes are more comparable.

A systematic review [6] found that dentists tended to rely heavily on invasive strategies for treating deep lesions in permanent teeth, with around half of all surveyed dentists preferring non-selective removal or even immediate endodontic treatment for vital teeth where maintaining pulp vitality was still theoretically possible. They also found that younger dentists tended to be less invasive than older

dentists in most studies, suggesting that there may be a paradigm shift in education concepts as more evidence on VPT is published in the existing scientific literature. It was also found that treatment approaches differed depending on the country the dentist is from. A multi-national study found that the majority of French and German practitioners would perform complete excavation even for deep lesions, while most Norwegian dentists opted for stepwise excavation [44]. These studies are mainly in permanent teeth with mature apices. Nevertheless, there are limited studies which evaluate the clinician's decision-making processes on how dentists make the choice on which clinical procedure to undertake for deep caries management in young persons with immature permanent teeth, and is an area which warrants further research [45].

The evaluation of oral health-related quality of life (OHRQoL) has gained much attention in the last decade and has important implications for clinical practice and dental research [46]. Although it was intended for review as a secondary outcome of this study, this was not evaluated in any of the included studies. Some aspects which warrant further evaluation include the cost effectiveness of multiple treatment visits (such as in 2-visit IPC or stepwise excavation) and success rates of selective caries removal versus non-selective caries removal techniques (i.e. pulpotomy treatment). A cost effectiveness analysis on carious tissue removal and direct pulp capping in adult with mature permanent teeth found that selective carious tissue removal and, in case of pulp exposure, direct pulp capping with MTA was the most cost-effective strategy [47]. Similar health outcome (effectiveness) modelling studies of this nature simulating the management of deep caries in immature permanent teeth in a young patient are much needed, especially where lifelong retention of the permanent tooth is desired. Additionally, feasibility of some clinical protocols in a regular clinic setting and the young patient's perspective regarding treatment acceptability (e.g. drawing of intravenous blood for PRF preparation) have also yet to be evaluated in any of the current published studies on this topic. Other patient reported outcomes relevant to children and their parents, including frequency of inter appointment pain requiring unscheduled returns, ability to cooperate for treatment, perceived treatment discomfort and treatment efficiency including acceptability for multiple visits have also yet to be evaluated.

A marked lack of studies evaluating more biological VPT treatment methods was also noted. There is also certainly much room for exploration of other techniques which assist in rapid arresting of soft dentinal caries, e.g. Silver Diamine Fluoride application, independent or in combination with stepwise or selective caries removal techniques.

In this systematic review, all included manuscripts were randomized controlled clinical trials. However, the quality of evidence for the treatment modalities at 12 months was found to be variable. Majority of included studies were assessed to be at unclear or high risk of bias, with many having methodological procedures that were incompletely reported. One of the major limitations noted among the studies was difficulty in achieving blinding of both participants and operators. It should be noted that based on the nature of the procedures performed, operator blinding is difficult as consistency, colour and the preparation procedure of the carious tissue could inform the operator of the treatment group, thus increasing the risk of performance bias. To circumvent this and minimize detection bias, most studies excluded the operator during outcome assessments. As such, most studies were rated as having low risk of bias for outcome measurement.

Overall quality of evidence was also affected by the low number of studies of DPC, IPC and SE (7 of 13 studies), thus resulting in possible imprecision and methodological discrepancies which limits the strength of the comparisons. Although the initial search strategy was extensive, it was found that many studies had mixed samples consisting of VPT done in teeth with both mature and immature roots with many of these studies combining the reporting of results in their analysis. Attempts were made to contact authors for data to request individual data specifically for immature teeth within their sample, however this was met with either a lack of response or answers that no distinction in analysis between open versus closed apex teeth was conducted. Therefore, many of these papers were omitted and hence the risk of selective reporting cannot be excluded.

Data synthesis was also problematic as different studies used different units of measurement and evaluation criteria. Data analysis based on clinical or radiographic criteria was also challenging as criteria for success or failure differed among the included studies. For example, some studies evaluated only continued root development, while others evaluated apical closure in addition to root development. Data pooling in some studies was based on single roots as the unit of analysis, while others considered the tooth, making transformation into either tooth or root-based analysis in multi-rooted teeth impossible. Additionally, direct comparison of the success rates among various vital pulp treatments might be inappropriate, as there is a lack of clinical studies directly comparing one treatment against another. There were also limited number of studies evaluating other VPT techniques apart from PP. Moreover, study designs, case selection, material used, and treatment protocol varied among various studies and thus did not allow for direct comparisons to be performed.

Based on the limitations mentioned above, those planning future research should focus on designing studies with clearly defined methodologies, including randomization and blinding of both participants and personnel to the degree that this is feasible, and standardization of specific criteria and measurement units for outcome assessment of clinical and radiographic findings. For specific conclusions to be drawn, the criteria of success for each procedure in immature permanent teeth should be unified following the guidelines of AAE [42] and ESE [12]. The authors also strongly suggest the use of standardized definition of procedures [12] and outcomes [48], including homogeneous treatment protocols and follow up durations, to assist in improving the conduct and reporting quality of clinical trials in endodontics in hope that better comparability and synthesis of outcomes among studies can be possible.

Conclusion

Within the scope of this systematic review, the following conclusions can be made:

1. For PP procedures, all medicaments appeared to be equally efficient with high overall success rates.

2. Biodentine showed high success rates for use in IPC, DPC and PP.

3. No significant differences were found in the clinical and radiographic success rates between various follow-up intervals in all studies.

4. There are no clear conclusions regarding superiority of either VPT technique on completion root development and more studies are required to evaluate the success rates of IPC and DPC against PP.

5. Until more evidence emerges, in view of the current propensity towards minimally invasive therapies, selection of the least invasive therapy that preserves pulp vitality and induces further root development should be considered.

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Conflict of Interest

The authors declare no conflict of interest

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Table 1: PICO Criteria

Criteria	Definition
Population	Young human subjects with immature vital permanent teeth presenting with deep caries into dentine (ICDAS 4-6 and /or radiographic lesions ≥ 2/3^{rds} depth of dentine), with minimum follow up of 12 months.
Intervention	Treatment of deep carious lesions may be using any of the following vital pulp therapy/management techniques: 1. Conventional restorative management: Carious tissue removal restorative treatment under local anaesthesia and rubber dam isolation ▪ Indirect pulp capping and restoration placement ▪ Selective caries removal in one stage and restoration placement ▪ Stepwise excavation and restoration placement ▪ Direct pulp capping and restoration placement ▪ Pulpotomy (partial and full) and restoration placement 2. Biological management: Partial/selective caries removal with or without local anaesthesia and sealing in carious tooth tissue with various methods including but not limited to ▪ Hall technique crowns, ▪ Photochemotherapy, ▪ Remineralisation therapies (e.g. silver diamine fluoride) ▪ Ozone therapy, ▪ Laser therapy and ▪ Atraumatic restorative techniques (ART)
Comparators	• No treatment

- Any of the above conventional restorative techniques or biological interventions.
- Preventive management alone. The interventions may be any of the following, including but not limited to:
  - Diet: diet modification, diet advice
  - Plaque removal: prophylaxis; toothbrushing;
  - Use of products: e.g. tooth mousse, probiotics, xylitol containing products, topical fluorides: fluoride varnish, fluoride and antibacterial mouthrinses

Outcomes

1. Primary outcomes

(A) Clinical signs:

- Vitality (parameters for evaluation: sensibility, EPT, cold test, mobility, tenderness to percussion, tenderness to palpation)
- Pain
- Swelling, abscess, fistula
- Discolouration,
- Longevity of restorative seal
- Secondary caries
- Presence, absence of tooth, longevity of tooth, tooth extraction

(B) Radiographic presence/absence of:

- Continuing root development
- Reparative dentinogenesis
- Pulp pathology: Periapical pathology, pulp canal obliteration,
- Root resorption
- Defective restoration
- Secondary caries,

(C) Other clinical outcomes including but not restricted to e.g. dentine characteristics and bacteriological analyses

2. **Secondary outcomes:**

   - Treatment Cost-effectiveness
   - Comparison of patient reported Oral Health related quality of life

Table 2: Reasons for exclusion of studies

Reasons for exclusion (for studies with more than 1 reason, only 1 reason will be given)	Title, Year and Authors	No.
Wrong population – not evaluating deep caries or deep caries management	*Dugergil et al 2005a ; Wilson et al 2000 ; Milsom et al 2011 ; Alves et al 2017 ; Opal et al. 2017 ; Villat et al. 2016 ; Lindberg et al. 2007 ; Mandari et al. 2003	8
Wrong population –not evaluating open apex/immature teeth	Awawdeh et al., 2018 ; Jokstad and Myor 1991 ; Kang et al 2017 ; Mertz-Fairhurst et al 1992 ; Vural et al 2017 ; Corralo and Maltz 2013 ; Frencken et al 2007 ; Wang et al 2020 ; Maltz et al. 2013a ; Mallow et al. 1998 ; Oz et al. 2019 ; Marques et al. 2015 ; De C Luz et al. 2001 ; Clarkson et al., 2021 ; Dommisch et al., 2008 ; Emara et al., 2020 ; Ericson et al., 1999 ; Peskersoy et al., 2021 ; Valenti et al., 2021	19
Less than 12 months follow up	Tauiq et al 2019	1
Less than 10 immature permanent teeth in study	Mass and Zilberman 2011 ; Bjordal et al., 2000 ; Orhan et al., 2008 ; Orhan et al., 2010, Qudeimat et al., 2007	5
Unable to ascertain exact numbers of open apex teeth in sample or no details on root development or root	Bruizuela et al 2017 ; Chesters et al 2002 ; Frencken et al 1994 ; Petrou et al 2014 ; *Dugergil et al 2005b ; Peric et al 2009 ; Ericson et al 1999 ; Mickenautsch et al 2000 ; Lo et al. 2001 ; Rahimtoola and van Amerongen 2002 ; Durmus et al. 2019 ; Elchaghaby et al 2020 ; Bjorndal	24

development not evaluated or no distinction in analysis between open vs closed apex teeth.	et al 1997 ; Luengas-Quintero et al. 2013 ; Maltz et al. 2018b ; Atabek et al. 2017 ; Maltz et al. 2012c ; Leksell et al. 1996 ; Kuhn et al. 2014d ; Maltz et al. 2011e ; Kikwilu et al. 2001 ; Khokhar et al., 2018 ; Manhas et al., 2020 ; Vu et al., 2020	
Wrong outcome (does not evaluate pulpal vitality)	Baginska et al., 2014 ; Kabil et al 2017 ; Andrade et al 2012 ; Fagundes et al 2006 ; Candan et al 2013 ; Mandari et al 2001 ; Taha et al. 2018 ; Estupinan-Day et al. 2013 ; Koc Vural et al. 2017 ; Kuhn et al. 2016f ; Memarpour et al. 2011 ; Chittem et al., 2015 ; Goldman et al., 2017 ; Ari et al., 2001 ; 2003 ; Valerio et al., 2020	16
Wrong study design (i.e. not CCT or RCT with prospective design)	Aggarwal et al., 2017 ; AlHumaid et al., 2018 ; Alqahtani et al., 2020 ; Bacaksiz et al., 2013 ; Hamama et al 2013 ; Casagrande et al 2017 ; Gruythuysen et al. 2010 ; Mejare 1993 ; De Moor et al., 2010 ; Gupta et al., 2013 ; Hasani et al., 2015 ; Sawicki et al., 2020	12
Wrong publication type (i.e. study protocol, conference proceeding)	Viera et al 2019 ; Olegario et al 2016 ; Galia et al 2013 ; Berrebi et al. 2009 ; Bjorndal et al. 2005 ; 2008 ; Edwards et al., 2021 ; Dorri et al., 2015 ; Hayashi et al., 2011 ; Hoefler et al., 2016	10
Unable to locate paper	Lumbau et al et al 2003 (Italian); Parvin et al 2018; Waly 1995	3
	Total:	98

Legend: **AR** – Abscess Remedy; **BioD**- Biodentine; **CEM** - Calcium-enriched mixture cement; **CH** – Calcium hydroxide; **CR** – Composite resin; **DCE** - Direct complete excavation; **Er:CrYSGG**- Erbium, chronium-doped yttrium, scandium, gallium and garnet laser; **GIC** – Glass ionomer cement; **IPC** - Indirect pulp capping; **MTA** –

Mineral trioxide aggregate; **NR**- not reported; **PRF** - Platelet-rich fibrin; **SE**: Stepwise excavation; **SH** - Sodium hypochlorite; **SS** - Sterile saline; **PDL** – Periodontal ligament; **PP** – Pulpotomy; **RMGIC** – Resin modified glass ionomer cement; **TAB** – Triple antibiotic; **ZOE** – Zinc oxide eugenol;

Table 3: Study Characteristics

Study	Country of origin	Funding source	RCT Design	Participants randomized (Number of teeth) / Age range	Intervention(s)/ Test group(s)	Intervention/ Control	Final restoration	Follow-up (months)	Drop-out (teeth) (%)	Outcome Measures	
										Clinical	Radiographic
Chailertvanitkul et al 2014	Thailand	NR	Parallel	80 patients (84 teeth) Age: 7-10	DPC MTA (n=44)	DPC CH (n=40)	Amalgam	3, 6, 12, 24	8/84 (9.5%)	Pain, swelling, sinus tract, tenderness to percussion	Continuation of root development, root resorption, peri-radicular, interradicular pathosis
Katge et al 2017	India	MTA supplied by Angelus Industria de Produtos Odontologicos S/A	Split mouth	29 patients (58 teeth) Age: 7-9	DPC BioD (n=29)	DPC MTA (n=29)	CR	6, 12	16/58 (27.6%)	Response to vitality test, pain, swelling, abscess, sinus tract	Root resorption, dentine bridge, widened PDL, periapical radiolucency
Rahman and Goswami 2021	India	None	Parallel	55 patients (60 teeth) Age: 7-15	IPC BioD (n=20) Theracal (n=20)	IPC CH (n=20)	GIC base + CR	3 weeks, 3, 6,12,18,24 months	6/60 (10%)	Pain, swelling, sinus tract, tenderness	Root resorption, widening of PDL, peri-apical radiolucency
Safwat et al 2017 and 2018	Egypt	None	Split mouth	81 patients (162 teeth) Age: 7-9	SE Ozone (n=40) Ozone + remineralizing agent (n=41)	SE CH (n=81)	CR	6, 12	None	Bacteriology: Colour, dentine consistency, Bacterial count (SM, LB, Candida, Total CFU) DIAGNOdent® readings	Not Eval
Abuelniel et al 2019 & 2021 (same paper)	Egypt	None	Split mouth	30 patients (60 teeth) Age: 7-8	PP BioD (n=30)	PP MTA (n=30)	CR	6, 12, 18	6/60 (10%)	Pain, Swelling Excessive Mobility	Continuation of root development, apical closure peri-radicular, interradicular, radicular rarefaction
El Meligy et al 2006	Egypt	University grant	Spilt mouth	13 children (26 teeth) Age: 6-12	PP CH (n=13)	PP MTA (n= 13)	Amalgam	3, 6, 12	None	Pain, swelling, sinus tract	Widening of PDL, continuation of root development,

											root resorption, periapical radiolucency
Eppa et al 2018	India	None	Parallel	60 children (60 teeth) Age: 6-14	PP TAB (n=20) AR (n=20)	PP MTA (n=20)	Preformed Metal Crowns	1, 6, 9, 12, 18, 24	None	Pain, swelling, abscess, fistula, mobility, tenderness	Continuation of root development, apical closure periapical radiolucency
Keswani et al 2014	India	NR	Parallel	62 patients (62 teeth) Age: 6-12	PP PRF (n=31)	PP MTA (n=31)	Amalgam + Preformed Metal Crown	6, 12, 24	9/ 62 (14.5%)	Pain, swelling, abscess mobility	Continuation of root development, apical closure, root resorption, widening of PDL, peri-radicular, interradicular radiolucency
Nosrat et al 2013	Iran	University grant	Parallel	51 patients (51 teeth) Age: 6-10	PP CEM (n=26)	PP MTA (n=25)	GIC + Final restoration (material unspecified)	6, 12	2/51 (3.9%)	Pain, swelling, sinus tract, mobility, tenderness	Continuation of root development, root resorption, peri-radicular, interradicular radiolucency
Özgür et al 2017	Turkey	University grant	Parallel	63 patients (80 teeth) Age: 6-13	PP SH + MTA (n=20) SS + MTA (n=20) SH + CH (n=20)	PP SS + CH (n=20)	CR	6, 12, 18, 24	4/80 (5%)	Pain, tenderness, swelling, fistula, mobility	Peri-radicular, interradicular radiolucency, widening of PDL, loss of lamina dura, root resorption, hard-tissue formation
Tozar and Almez 2020	Turkey	University grant	Parallel	90 patients (90 teeth) 6-15	PP MTA+ Er:CrYSGG (n=45)	PP MTA (n=45)	RMGIC + CR	1, 3, 6, 12	3/90 (3.3%)	Pain, tenderness, mobility, fistula, swelling	Continuation of root development, apical closure, widening of PDL, loss of lamina dura, peri-radicular radiolucency, root resorption

Table 4a: Study outcomes: Clinical and Radiographic

Study; Country	Intervention	Treatment sprat distribution	Dropout (Tooth level)	Overall Success		Breakdown of clinical and radiographic findings										
						Clinical						Radiographic				
												Pathological			Physiological	
				Clinical N (%)	Radiographic N (%)	Pain	Swelling/ Abscess/ Inflammation	Mobility	TTP	Sinus tract/ Fistula	Periapical/ furation Radiolucency (poly ~~QADE~~)	Root resorption (internal and external)	Widening of PDL/ Loss of lamina dura	Root Development	PCO/ Calcific metamorphosis
Chaitanya nikhil et al 2014 **Thailand.**	DPC	CH: 60 MTA: 66	8/66 (9.5%) CH: 5 MTA: 3	CH: 34/35 (97.1%) MTA: 38/41 (85.1%)	CH: 34/35 (97.1%) MTA: 38/41 (85.1%)	NR	NR	NR	NR	NR	NR	None in all groups.	NR	Continuation of root development CH: 34 MTA:39 Apexification NE	None in all groups.
Bidgar et al 2017 **India**	DPC	~~QAD~~: 29 MTA: 28	16/58 (27.6%) ~~QAD~~: 8 MTA: 8	~~QAD~~: 21/21 (100%) MTA: 21/21 (100%)	~~QAD~~: 21/21 (100%) MTA: 21/21 (100%)	None in all groups	None in all groups.	NE	NE	None in all groups.	None in all groups.	None in all groups.	None in all groups.	Continuation of root development NE Apexification NE	NE
Rahman and Cawood 2021 **India**	IPC	~~QAD~~: 20 ~~QAD~~: 20 CH: 20	6/68 (10%) ~~QAD~~: 2 ~~QAD~~: 2 CH: 2	~~QAD~~: 17/18 (94.4%) ~~QAD~~: 18/18 (100%) CH: 14/18 (77.8%)	~~QAD~~: 18/18 (100%) ~~QAD~~: 18/18 (100%) CH: 16/18 (88.9%)	~~QAD~~: 1 ~~QAD~~: 0 CH: 3	None in all groups.	NE	~~QAD~~: 0 ~~QAD~~: 0 CH: 3	None in all groups.	~~QAD~~: 0 TheraCO CH: 1	None in all groups.	~~QAD~~: 0 TheraCO CH: 1	Continuation of root development NE Apexification NE	NE
Ghoneim et al 2019 & 2021 (same paper) **Egypt**	PP	~~QAD~~: 30 MTA: 30	6/60 (10%) ~~QAD~~: 3 MTA: 3	~~QAD~~: 24/27 (88.9%) MTA: 24/27 (88.9%)	~~QAD~~: 22/27 (81.5%) MTA: 23/27 (85.2%)	~~QAD~~: 3 MTA: 2	~~QAD~~: 3 MTA: 3	~~QAD~~: 3 MTA: 2	None in all groups.	None in all groups.	~~QAD~~: 5 MTA: 4	None in all groups.	None in all groups.	Continuation of root development ~~QAD~~: 7 MTA: 6 Apexification ~~QAD~~: 20 MTA: 21	NE
El-Mekky et al 2000 **Egypt**	PP	CH: 11 MTA: 13	None	CH: 9/11 (81.8%) MTA: 13/13 (100%)	CH: 9/11 (81.8%) MTA: 13/13 (100%)	CH: 2 MTA: 0	CH: 2 MTA: 0	None in all groups.	None in all groups.	None in all groups.	CH: 2 MTA: 8	None in all groups.	CH: 2 MTA: 8	Continuation of root development CH: 11 MTA: 13 Apexification NR	CH: 2 MTA: 4
Eppe et al 2018 **India**	PP	MTA: 20 AB paste: 20 AR: 20	None	MTA: 20/20 (100%) TAB: 20/20 (100%) AR: 16/20 (80%)	MTA: 20/20 (100%) TAB: 20/20 (100%) AR: 16/20 (80%)	MTA:0 TAB: 0 AR: 4	None in all groups.	None in all groups.	MTA: 0 TAB: 0 AR: 4	None in all groups.	MTA: 0 TAB: 0 AR: 4	None in all groups.	None in all groups.	Continuation of root development MTA: 20 TAB: 20 AR: 16 Apexification NR	NE
Sharma et al 2014 **India**	PP	PRF: 31 MTA: 31	9/62 (14.5%) PRF: 4 MTA: 5	PRF: 23/27 (100%) MTA: 26/26 (100%)	PRF: 27/27 (100%) MTA: 26/26 (100%)	None in all groups	None in all groups	None in all groups	None in all groups	None in all groups	None in all groups	None in all groups	None in all groups	Continuation of root development PRF: 3 MTA: 6 Apexification PRF 24 MTA 28	NE
Ozurat et al 2013 **Iran**	PP	MTA: 25 CEM: 26	2/51 (3.9%) MTA: 1 CEM: 1	MTA: 24/25 (100%) CEM: 25/25 (100%)	MTA: 17/25 (70.8%) CEM: 20/25 (80%)	None in all groups	None in all groups	None in all groups	None in all groups	None in all groups	None in all groups	None in all groups	NR	Continuation of root development MTA 19 CEM 20 Apexification MTA 19 CEM 20	NR
Ozgur et al 2017 **Turkey**	PP	SH MTA: 28 SS MTA: 28 SH CH: 28 SS CH: 28	4/84 (5%) SH + MTA: 2 SS + MTA: 1 SH + CH: 1 SS + CH: 1	SH + MTA: 18/19 (94.4%) SS + MTA: 18/19 (100%) SH + CH: 18/19 (95%)	SH + MTA: 17/18 (94.4%) SS + MTA: 18/19 (100%) SH + CH: 18/20 (95%) SS + CH: 18/19 (100%)	SH + MTA: 1 SS + MTA: 0 SH + CH: 1 SS + CH: 0	SH + MTA: 1 SS + MTA: 0 SH + CH: 0 SS + CH: 0	SH + MTA: 1 SS + MTA: 0 SH + CH: 0 SS + CH: 0	SH + MTA: 3 SS + MTA:3 SH + CH: 3 SS + CH: 3	None in all groups.	SH + MTA: 1 SS + MTA: 0 SH + CH: 1 SS + CH: 1	None in all groups.	SH + MTA: 1 SS + MTA: 0 SH + CH: 1 SS + CH: 1	Continuation of root development SH + MTA: 17 SS + MTA: 19 SH + CH: 19 SS + CH: 19 Apexification NR	SH + MTA: 2 SS + MTA: 1 SH + CH:1 SS + CH: 1
				SS + CH: 18/19 (100%)											
Ozan et al 2020 **Turkey.**	PP	MTA: 45 MTA + Laser: 45	3/90 (3.3%) MTA: 2 MTA + Laser: 1	MTA: 40/43 (93.3%) MTA + Laser: 43/44 (97.7%)	MTA: 38/43 (88.4%) MTA + Laser: 43/44 (97.7%)	MTA: 2 MTA+ Laser: 1	MTA: 2 MTA+ Laser: 1	MTA: 1 MTA+ Laser: 1	MTA: 2 MTA+ Laser: 1	MTA: 1 MTA+ Laser: 1	MTA: 5 MTA+ Laser: 1	MTA: 1 MTA+ Laser: 1	MTA: 2 MTA+ Laser: 1	Continuation of root development MTA: 16 MTA + Laser: 22 Apexification MTA: 26 MTA + Laser: 21	NR

Legend: **AR** – Abscess Remedy; ~~**BioD**~~- ~~**Biodentine**~~; **CEM** - Calcium-enriched mixture cement; **CH** – Calcium hydroxide; **DCE** - Direct complete excavation; **DPC** – Direct pulp capping; ; **GIC** – Glass ionomer cement; **IPC** - Indirect pulp capping; **MTA** – Mineral trioxide aggregate; **NE** – Not evaluated; **NR** – Not reported; **PCO**: Pulp canal obliteration; **PDL** – Periodontal ligament; **PP** – Pulpotomy; **PRF**-Platelet-rich fibrin; **SE**: Stepwise excavation; **SH** - Sodium hypochlorite; **SS** - Sterile saline; **TAB** – Triple antibiotic; ~~**TheraC**~~ -~~**Theracal**~~- **ZOE** – Zinc oxide eugenol;

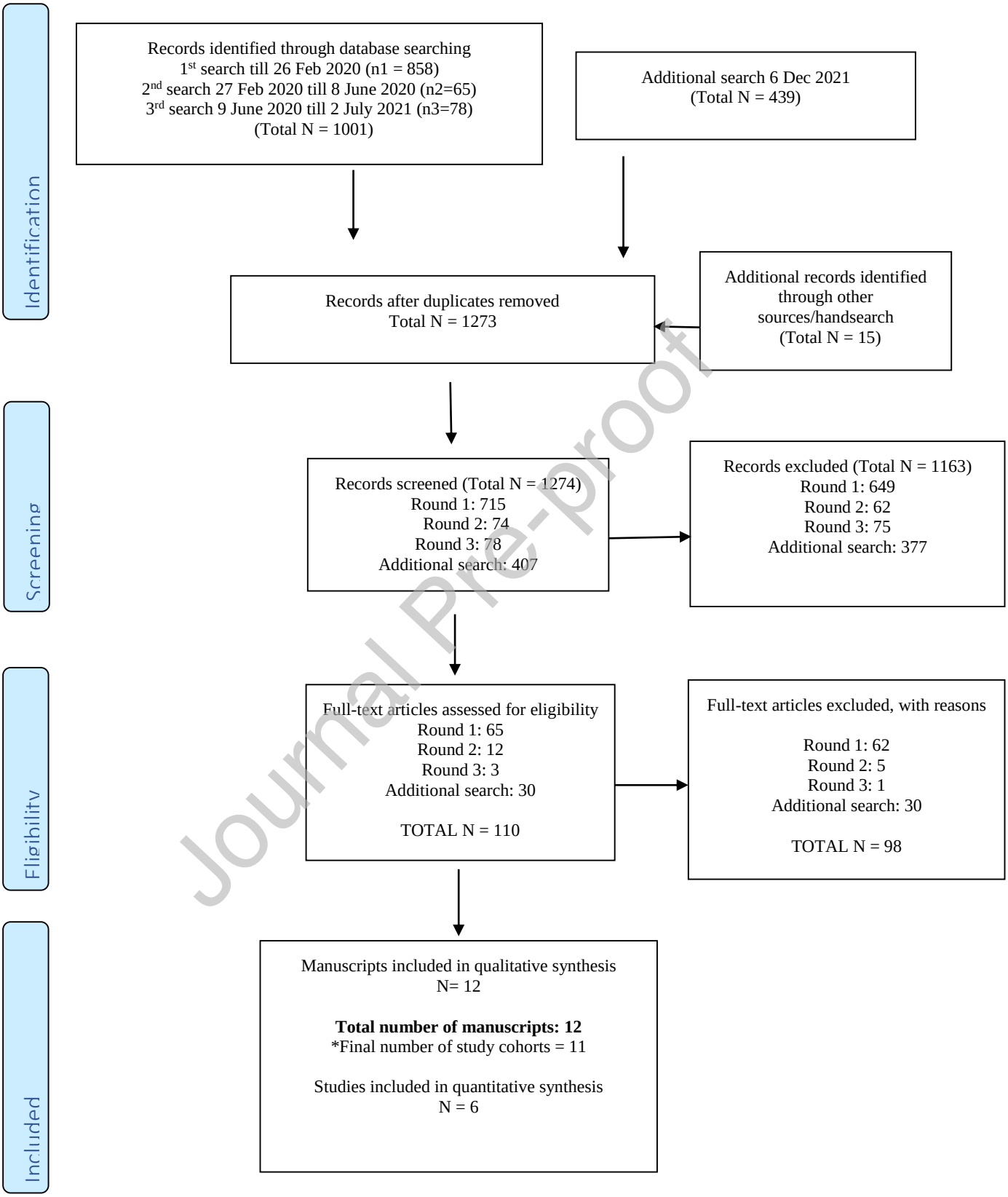
Legend: **CFU** – colony-forming units; **SM** - ~~mutans~~ streptococci; **LB** – Lactobacilli; **IPC** - Indirect pulp capping; **DCE** - Direct complete excavation; **SE**: Stepwise Excavation; **Stat Sig** – Statistically significant; **N Sig** – Not significant; **NE** – Not evaluated

Table 4b: Study outcomes: Bacteriology and DIAGNOdent® readings

Study; Country	Intervention	Treatment agent distribution	Drop out (Tooth level)	Assesments (significant difference between baseline and final evaluation)							
				Colour	Dentine consistency	Dentine humidity	DIAGNOdent®	Bacteria count			
								SM	LB	Candida	Total CFU (mean)
Safwat et al 2017 and 2018 **Egypt**	SE	▪ Test 1a (6 months) - Ozone =20 ▪ Test 1a (12 months) - Ozone =20 ▪ Test 2a (6 months) - Ozone + remin agent = 21 ▪ Test 2a (12months) - Ozone + remin agent = 20 ▪ Control 1a (6 months) – CH1 =20 ▪ Control 1b (12 months) – CH1 = 20 ▪ Control 2b (6 months) – CH1 = 21 ▪ Control 2b (12 months) – CH1 = 20	Not reported	Group 1 (Ozone only): - Baseline: N Sig difference between 1a and 1b; - Final assessment (6 months): • Stat Sig between 1a and 1b - Final assessment (12 months): • N Sig between 1a and 1b Group 2 (Ozone + remin agent): - Baseline: N Sig difference between 1a and 1b; - Final assessment (6 months): • N Sig betw	Group 1 (Ozone only): - Baseline: N Sig difference between 1a and 1b; - Final assessment (6 months): • N Sig between 1a and 1b - Final assessment (12 months): • N Sig between 1a and 1b Group 2 (Ozone + remin agent): - Baseline: N Sig difference between 1a and 1b; - Final assessment (6 months): • N Sig betw	NE	Group 1 (Ozone only): - Baseline: Stat Sig difference between 1a and 1b; - Final assessment (6 months): Stat Sig difference between 1a and 1b; - Final assessment (12 months): Stat Sig between 1a and 1b Group 2 (Ozone + remin agent): - Baseline: Stat Sig difference between 1a and 1b; - Final assessment (6 months): N Sig betwee	Group 1 (Ozone only): - 6 months: • N Sig between 1a and 1b - 12 months: • N Sig between 1a and 1b Group 2 (Ozone + remin agent: NE Comparing Group 1a and Group 2a: - Not done	Group 1 (Ozone only): - 6 months: • N Sig between 1a and 1b - 12 months: • N Sig between 1a and 1b Group 2 (Ozone + remin agent): NE Comparing Group 1a and Group 2a: - Not done	Group 1 (Ozone only): - 6 months: • N Sig between 1a and 1b - 12 months: • N Sig between 1a and 1b Group 2 (Ozone + remin agent): NE Comparing Group 1a and Group 2a: - Not done	NE

2a and 2b - Final assessment (12 months): • N Sig between 2a and 2b Comparing Group 1a and Group 2a: - 1st dentine assessment: • N Sig difference between 1a & 2a at 6 months and 12 months - 2nd dentine assessment: • N Sig difference between 1a & 2a at 6 months and 12 months	2a and 2b - Final assessment (12 months): • N Sig between 2a and 2b Comparing Group 1a and Group 2a: - 1st dentine assessment: • N Sig difference between 1a & 2a at 6 months and 12 months - 2nd dentine assessment: • N Sig difference between 1a & 2a at 6 months and 12 months	n 2a and 2b - Final assessment (12 months): N Sig between 2a and 2b Comparing Group 1a and Group 2a: - N Sig difference at baseline, immediate post ozone treatment; 6 months and 12 months

Fig 1: PRISMA Flow Diagram



NOTE: * 2 papers (Safwat et al in 2017 and 2018) reported on different outcome measures, they were analysed as 2 separate papers.

Fig 2: Quality Assessment Graph

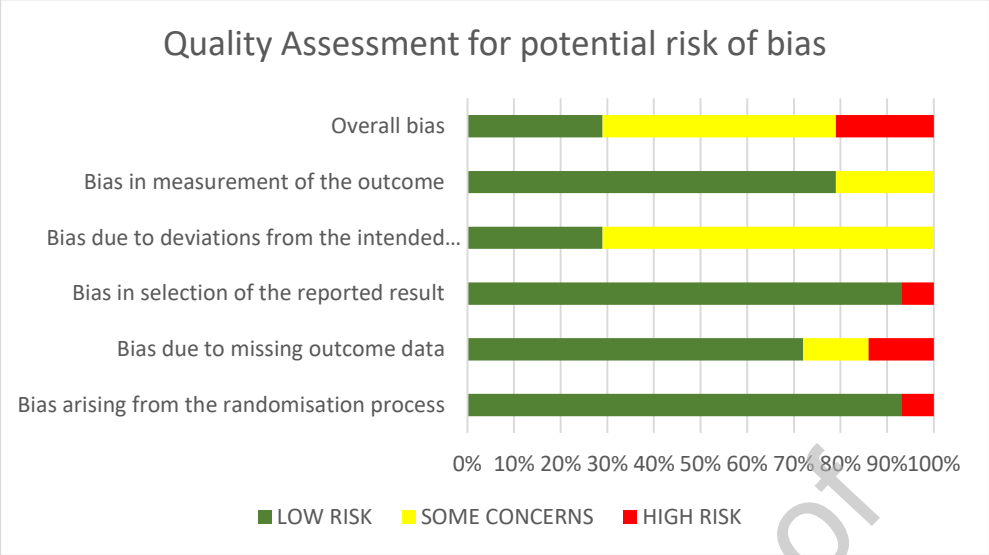


Figure 3: Quality Assessment of potential risk of bias in included studies.

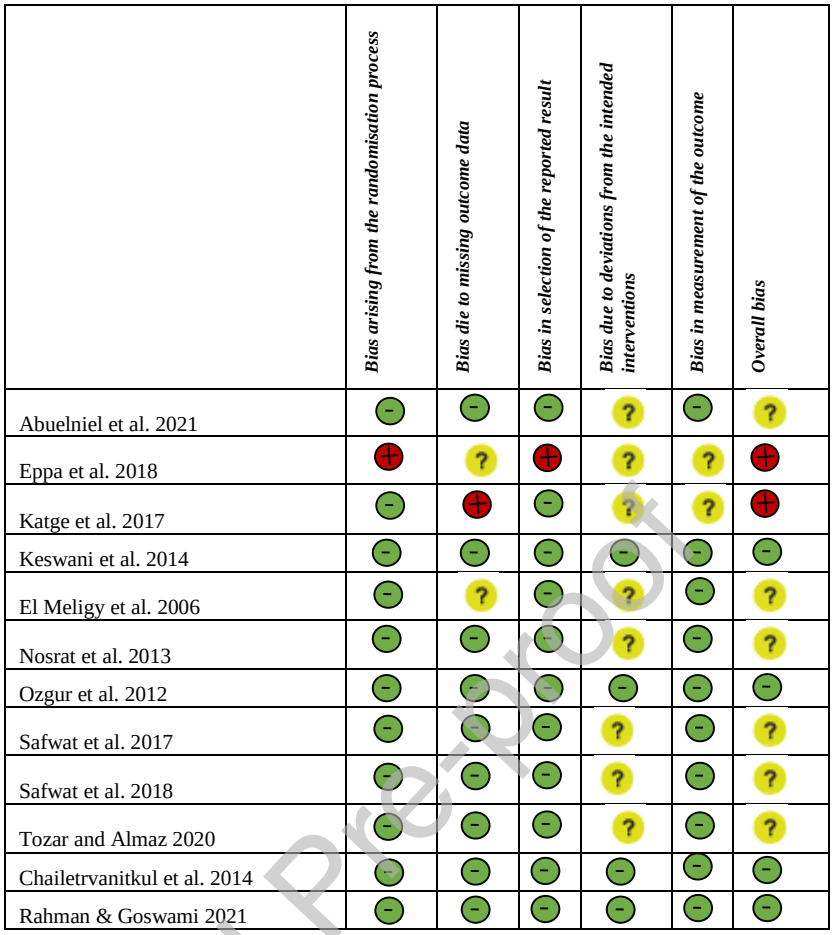


Fig 4: Meta-analysis – Success of pulpotomy agents

Fig 4a: MTA versus Calcium Hydroxide

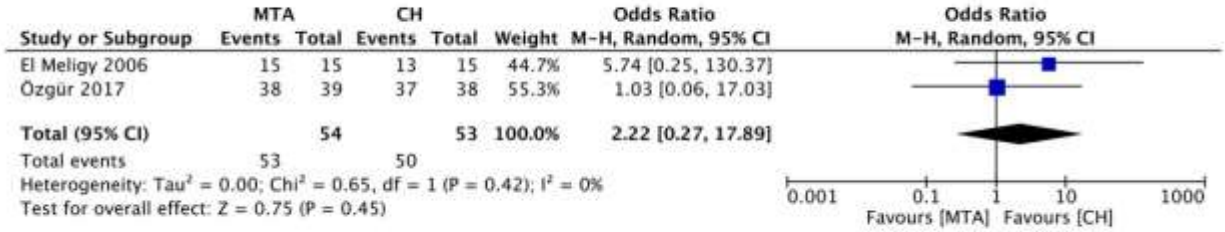


Fig 4b: MTA versus Bioceramic materials

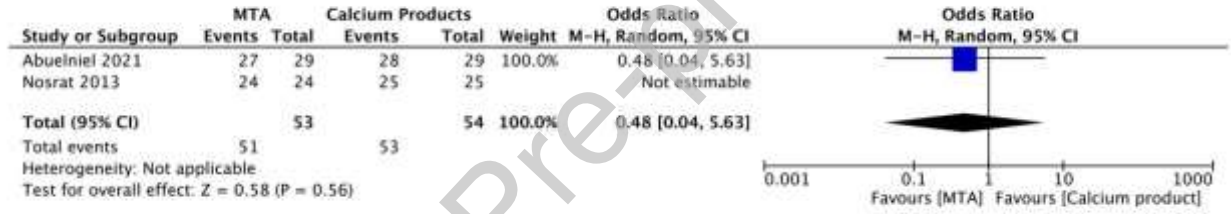


Fig 4c: MTA versus all pulpotomy materials