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REVIEW ARTICLE

Pulp Response to Materials Used in the Management of Deep Carious Lesions Without Pulp Exposure: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Background: Placing a pulp-capping material over the remaining dentine is integral to managing deep carious lesions in permanent teeth without pulp exposure. However, current guidelines do not favour any specific pulp-capping material, and there is no direct clinical evidence that pulp-capping materials maintain pulp vitality better than placing the restoration directly on dentine.

Objectives: To compare the effectiveness of various biomaterials, including pulp-capping materials and restorative materials applied directly over the remaining dentine, against one another in preserving pulp health in permanent teeth with deep carious lesions without pulp exposure.

Methods: On June 9, 2024, MEDLINE, Embase, Scopus, and Web of Science were searched, supplemented by a screening of clinical trial registries, grey literature, and reference lists. Randomised controlled trials (RCTs) evaluating the effectiveness of indirect pulp capping in permanent teeth affected by deep carious lesions without pulp exposure were included. Risk of bias was assessed using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2). Network meta-analyses and meta-regression were performed using a Bayesian approach and a random-effects model for the primary outcome (loss of pulp vitality), followed by an assessment of confidence in the evidence using the CINeMA framework.

Results: Sixteen RCTs (19 reports; 1039 participants; 1093 teeth; seven biomaterials) were included. Most comparisons involving the dentine bonding agent (DBA; control) were supported by low-confidence evidence and lacked statistical significance; however, they always resulted in RRs favouring the pulp-capping materials. Notably, moderate-confidence evidence indicated that during the second follow-up year Biodentine (RR = 0.00; 95% CI: 0.00–0.53) and glass ionomer cement (GIC) (RR = 0.30; 95% CI: 0.00–0.99) outperformed the DBA. Moderate-confidence evidence also demonstrated that during the first follow-up year mineral trioxide aggregate (MTA) (RR = 0.30; 95% CI: 0.09–0.84) outperformed calcium hydroxide cement. Meta-regression found that neither study-level demographic covariates nor clinical-technique covariates were significantly associated with pulp-vitality outcome.

Conclusions: While most findings in this review were of low confidence, the evidence nevertheless supports the use of pulp-capping materials in permanent teeth with deep carious lesions. Among these materials, Biodentine, MTA, and GIC have the strongest supporting evidence for preserving pulp vitality.

Trial Registration: PROSPERO number: CRD42024507641

1 | Introduction

The management of deep carious lesions in permanent teeth has shifted over the past few decades from a non-selective caries removal technique to more conservative, partial caries removal approaches, placing greater emphasis on sealing carious dentine with an adhesive restoration (Schwendicke et al. 2016; Duncan et al. 2019). However, the recommendation to place an indirect pulp-capping material over the remaining dentine, which may actively interact with the dentine-pulp complex to promote a favourable biological response and protect the pulp, remains an integral part of the contemporary approach (Duncan et al. 2019; American Association of Endodontists 2021). This is mainly because the thickness of the remaining dentine after caries excavation, an important prognostic factor for maintaining pulp health, cannot be accurately assessed clinically (About et al. 2001b; Murray et al. 2003). The placement of pulp-capping materials, therefore, provides additional pulpal protection by maintaining the viability of odontoblasts, supporting remineralisation of affected dentine, providing an antimicrobial effect, promoting tertiary dentine formation, and isolating the pulp from noxious stimuli (About et al. 2001a; Schwendicke et al. 2015; Mickenautsch et al. 2010).

One of the first pulp-capping materials used in the management of deep carious lesions was calcium hydroxide ($Ca(OH)_2$) cement, and it was considered the gold standard for a long time (Kunert and Lukomska-Szymanska 2020). While the use of $Ca(OH)_2$ cement for managing deep carious lesions without pulp exposure has been reported to have a reasonable success rate in preserving vital pulp functions (Al-Sabri et al. 2019), several limitations remain, such as poor bonding to dentine and gradual dissolution over time (Song et al. 2017; Tam et al. 1989). Other pulp-capping materials that have the potential to overcome many of the limitations of $Ca(OH)_2$ cement have also been reported for use in the management of deep carious lesions without pulp exposure, including mineral trioxide aggregate (MTA), calcium silicate cements such as Biodentine (Septodont, France), glass ionomer cement (GIC), and other resin-based liners (Hashem et al. 2019; Mahapatra et al. 2022).

Current guidelines for managing deep carious lesions without pulpal exposure do not indicate a preference for one pulp-capping material over another (American Association of Endodontists 2021; Duncan et al. 2019). This is because, while several randomised controlled trials have investigated the effectiveness of various pulp-capping materials in maintaining pulp vitality in teeth with deep carious lesions, most did not demonstrate a significant difference among these materials (Mahapatra et al. 2022; Hashem et al. 2019). In fact, even studies comparing pulp-capping materials with restorative materials applied directly over the remaining dentine have also failed to detect such differences (Gözetici-Çil et al. 2023; Semprum-Clavier et al. 2024). The lack of statistical significance in individual studies, which might be due to their insufficient statistical power, could be overcome by pooling data through a systematic review and network meta-analysis, which could also help identify the most effective pulp-capping materials. Therefore, this systematic review aimed to compare the effectiveness of various biomaterials, including pulp-capping materials and restorative materials applied directly over the remaining dentine, against each other (Interventions/Comparators) in preserving pulp health (Outcome) in permanent teeth with deep carious lesions without pulp exposure (Population), as reported in randomised controlled trials (Study design).

2 | Methods

2.1 | Protocol Registration and Reporting

The protocol of this systematic review was registered before the study commenced in the International Prospective Register of Systematic Reviews (PROSPERO) database under the registration number CRD42024507641. The review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021; Hutton et al. 2015).

2.2 | Eligibility Criteria

The inclusion and exclusion criteria for selecting eligible studies in this review were based on the PICOS format:

Population: Permanent teeth with vital pulps and deep caries extending into the dentine with a zone of hard or firm dentine between the caries and the pulp (as defined by Duncan et al. (2019)), excluding studies that involved primary teeth or teeth with irreversible pulpitis in their sample.

Intervention: Caries excavation and restoration using a restorative material applied directly over the remaining dentine or with a pulp-capping material covering the remaining dentine. Studies involving cases of caries excavation leading to pulp exposure or mainly assessing the effectiveness of adjunctive therapies (e.g., antibacterial therapeutic agents) were excluded.

Comparator: All restorative materials and pulp-capping materials used for managing deep carious lesions were included. Studies without at least two arms evaluating different types of directly placed restorative materials or pulp-capping materials were excluded.

Outcomes: The primary outcome in this review was the maintenance or loss of pulp vitality due to pulp necrosis or root canal treatments performed in response to irreversible pulpitis. Dentine deposition and postoperative pain or discomfort were the secondary outcomes. No exclusions were made based on the types of outcome-assessment measures used, provided they were validated measures.

Study Design: Randomised controlled clinical trials conducted on human subjects with a minimum follow-up period of 3 months were included. No publication date restrictions were applied. Studies published in a language other than English or with the full text not available were excluded.

2.3 | Literature Search Strategy

Four bibliographic databases were searched from their inception to March 14, 2024, and later were updated on June 9, 2024: MEDLINE via Ovid, Embase via Ovid, Scopus, and Web of Science. In addition, several sources of ongoing studies were searched on March 14, 2024, including the International Clinical Trials Registry Platform (ICTRP) and the U.S. clinical studies registry (www.ClinicalTrials.gov). On the same date, the ProQuest Dissertations and Theses database was searched for grey literature. The search strategies for these databases and sources were developed using relevant thesaurus terms and keywords (Table S1). The reference lists of all included studies were also manually searched for additional eligible studies for inclusion.

2.4 | Study Selection Process

Two independent reviewers (JA and SA) initially screened the titles and abstracts of identified studies using Rayyan (Ouzzani et al. 2016), a web-based platform, applying the pre-established inclusion and exclusion criteria. In cases where the eligibility of a study was uncertain at this stage, it was provisionally included, pending a definitive decision post full-text review.

Full texts of all potentially eligible studies identified during the screening phase underwent the same inclusion/exclusion assessment to determine the studies' relevance for inclusion in the review. Any disagreements between the two independent reviewers (FB and SA) were resolved through discussion, involving a third reviewer (JA) when necessary.

2.5 | Data Extraction and Management

Data extraction was conducted in duplicate by two independent reviewers (JA and SA) using an adapted version of the Cochrane data collection form for randomised controlled clinical trials. Any disagreements were resolved through discussion between the two reviewers, and with a third reviewer (FB) when necessary. The following data were extracted from the included studies:

1. Publication information
2. Study aim
3. Study design and methodological characteristics
4. Participant demographics and baseline characteristics
5. Details of the interventions
6. Outcomes and results related to the interventions
7. Key conclusions

If additional clarification was required during the data extraction process, the corresponding authors were contacted via email.

2.6 | Risk of Bias Assessment

The risk of bias was assessed independently and in duplicate by two reviewers (JA and SA) for all included studies at the primary outcome level (loss of pulp vitality) using the Cochrane Revised Tool for Risk of Bias in Randomised Trials (RoB 2) (Sterne et al. 2019). The decision to assess risk of bias at the outcome level and to limit full assessments to the primary outcome is in accordance with the Cochrane Handbook, which recommends selecting specific results for assessment because risk of bias is outcome-specific and notes that focusing on main outcomes may be the most appropriate approach (Higgins et al. 2019). Disagreements were resolved through discussion between the two reviewers, and a third reviewer (FB) was consulted when necessary. The outcomes of the risk of bias assessment informed sensitivity analyses and the assessment of the evidence quality.

2.7 | Data Synthesis and Analysis

Review Manager (RevMan) Version 8.13.0 (The Cochrane Collaboration 2024) was used to conduct standard pairwise meta-analyses for any two biomaterials that were directly compared in more than one study. Heterogeneity among the included studies was assessed prior to conducting standard pairwise meta-analyses to ensure the validity of data pooling and to choose the most appropriate statistical approach. Clinical and methodological heterogeneity was assessed by examining variability in participant characteristics, the nature of interventions, outcome measurement methods, study designs, and risk of bias. In addition, statistical heterogeneity was evaluated using the Chi-squared test, the I^2 statistic, and Tau^2 (τ^2; estimated with restricted maximum likelihood, REML) to quantify both the presence and the degree of variability in effect estimates.

Dichotomous data (loss of pulp vitality) from the longest follow-up period available for each follow-up year were pooled using the generic inverse-variance method with a random-effects model. This approach accounts for clinical and methodological heterogeneity, primarily arising from variations in participant ages, root maturity levels, caries depth, rubber dam application, extent of caries excavation toward the pulp, the type of final restoration placed, and methods used to assess pulp health. Risk ratios (RRs) were calculated as effect measures along with their 95% confidence intervals (95% CI).

Many included studies randomised or treated multiple teeth per participant, creating data clustering within participants.

Therefore, a unit-of-analysis error would occur if these teeth were analysed as independent observations. To address this, each participant was considered a cluster in each study, and trial arms were adjusted to their effective sample sizes using the design effect (DE) formula: $DE = 1 + (M - 1) \times ICC$. In this formula, M is the average cluster size, calculated as (total number of treated teeth) ÷ (total number of participants). Because the included studies did not report an intracluster correlation coefficient (ICC), an ICC value of 0.20 was used, based on reports of clustering of caries lesions within patients (Masood et al. 2015; Meinhold et al. 2020). After the DE was calculated for each study, both the number of participants and the number of events (loss of pulp vitality) in each study arm were divided by the DE to obtain the effective sample size and effective number of events, respectively.

A Bayesian network meta-analysis (NMA) was conducted using the MetaInsight tool (version 6.4.0) to compare the biomaterials within a single, connected network using data on loss of pulp vitality from the longest available follow-up period for each year (Owen et al. 2019). The transitivity assumption was upheld because the populations, interventions, and outcomes in the included studies were deemed sufficiently similar to allow valid indirect comparisons. RRs were calculated based on the number of adjusted events of loss of pulp vitality, which served as the primary measure of effect. A random-effects model was used to account for variability across studies. MetaInsight's default Bayesian statistical model, with non-informative priors and Markov Chain Monte Carlo simulation was used.

The Gelman–Rubin shrink factor plots were used to verify the convergence of the Bayesian network meta-analysis models and to ensure the reliable estimation of the posterior distribution (Dias et al. 2013). Figure S1 presents these plots, which visualise the evolution of between-chain and within-chain variance over iterations and show that the values approach below 1.1, a threshold considered indicative of convergence. Model fit was assessed using the deviance report generated via MetaInsight, which compared expected and residual deviance to evaluate how well the model explained the observed data.

Network geometry was visualised through plots in which nodes (interventions) were scaled by total sample size and edges (pairwise comparisons) were weighted by the number of trials. Inconsistency was evaluated using node-splitting analyses (Dias et al. 2013). Inconsistency between direct and indirect comparisons was assessed based on the overlap of 95% CIs and a p-value threshold of 0.1, with minimal or no overlap indicating significant inconsistency.

Effect estimates (RRs with 95% CIs) were presented in league tables displaying pairwise biomaterial comparisons. The ranking of biomaterials was evaluated using Surface Under the Cumulative Ranking Curve (SUCRA) values, Litmus Rank-O-Gram, and treatment rank probabilities, with higher rankings indicating greater effectiveness (Nevill et al. 2023).

To ensure the robustness of the results with respect to the methodological risk of bias, sensitivity analyses were conducted for each network meta-analysis by excluding studies at high risk of bias. Further sensitivity analyses were performed to assess the robustness of the results with respect to potential sources of clinical heterogeneity. For instance, a sensitivity analysis was conducted by excluding studies without documented rubber dam use. In addition, because data on all calcium hydroxide–containing materials were pooled together as they share the same active ingredient and clinical purpose, an additional sensitivity analysis was conducted by restricting to studies that utilised Dycal (Dentsply Sirona, York, PA, USA), the most widely tested product (11 of 13 studies) to assess the impact of potentially varying degrees of antibacterial activity due to differences in calcium hydroxide concentrations on the results.

Meta-regression was conducted to explore how various study-level characteristics influenced the binary outcome of pulp vitality, expressed as odds ratios, using MetaInsight v6.4.0 with its default Bayesian settings. Four separate random-effects regressions were run for mean patient age (per one-year increment; 11 studies), male proportion (per one-percent increment; 11 studies), rubber dam use (yes vs. no; 15 studies), and caries-excavation depth (ordinally coded 1 = hard, 2 = firm, 3 = soft; 14 studies). All models assumed consistency across comparisons within the network. The meta-regression was conducted only for the first follow-up year, as only six studies reported data for the second follow-up, below the recommended threshold of 10 studies (Deeks et al. 2019).

Meta-analyses were not performed for secondary outcomes because almost all included studies evaluated a unique pair of biomaterials. In the only instance where more than one study shared the same pair of biomaterials, differing measurement scales prevented data pooling (Leye Benoist et al. 2012; Sultana et al. 2016).

2.8 | Quality of Evidence Assessment

The quality of the evidence was assessed using the Confidence in Network Meta-Analysis (CINeMA) framework (Papakonstantinou et al. 2020; Nikolakopoulou et al. 2020). CINeMA evaluates several key domains, including within-study bias (assessed using RoB 2), reporting bias (assessed using the Risk of Bias due to Missing Evidence in Network Meta-Analysis [ROB-MEN] tool) (Chiocchia et al. 2021), indirectness, imprecision, heterogeneity, and incoherence. Each domain was systematically reviewed, and an overall confidence rating for each effect estimate was assigned, ranging from high to very low.

3 | Results

3.1 | Search Result

A total of 2965 records were identified through the literature search. After removing duplicates, 1472 records underwent title and abstract screening. This process led to a full-text review of 44 records, along with five additional records identified through manual search, of which 30 were excluded. A detailed list of the excluded records, along with the reasons for exclusion, is provided in Table S2. Ultimately, 16 studies, documented across 19 reports, were included in this systematic review. The identification, screening, and selection processes are summarised in the PRISMA flow diagram (Figure 1).

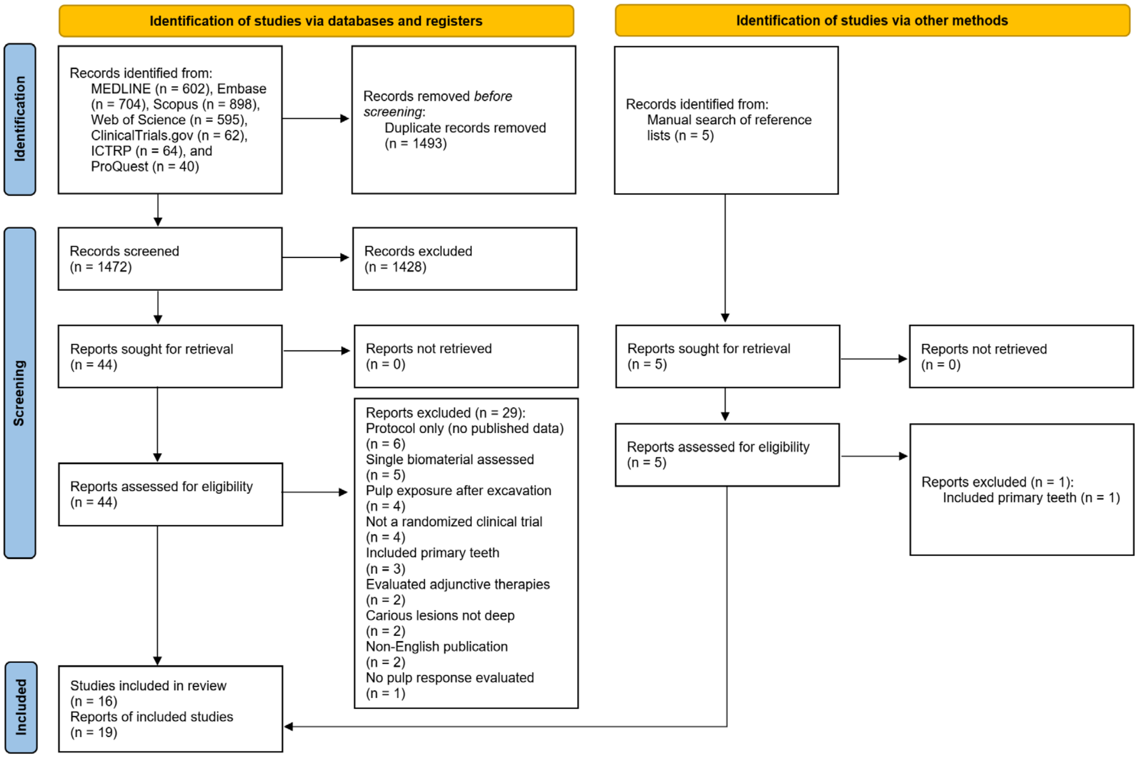

FIGURE 1 | PRISMA flow diagram summarising the retrieval, screening and selection processes.

3.2 | Characteristics of the Included Studies

Table 1 presents the main characteristics of the included studies along with their primary outcome findings. Most of the included randomised controlled trials followed a parallel design, with one adopting a split-mouth design (Soliman et al. 2019) and another employing a cluster design (Banomyong and Messer 2013). Of the 16 studies, seven (43.75%) were conducted in India and two (12.50%) in Turkey. The remaining seven studies (43.75%) were each conducted in a different country, reflecting broad regional representation. All studies were conducted in academic settings. Operator details were reported in 10 studies. In nine of these, the operators were dentists, six of whom reported that the operators had been calibrated. Only one study reported that the operator was a specialist (Table 1).

In 11 studies, participants could receive interventions on more than one tooth (Banomyong and Messer 2013; Gözetici-Çil et al. 2023; Hashem et al. 2015; Kaul et al. 2021; Koc Vural et al. 2017a; Mahapatra et al. 2022; Opal et al. 2017; Rahman and Goswami 2021; Semprum-Clavier et al. 2024; Soliman et al. 2019; Sultana et al. 2016). Most studies used rubber dam isolation during the restorative procedures, except for two in which it was not used (Banomyong and Messer 2013; Koc Vural et al. 2017a), and one in which its use was unclear (Gözetici-Çil et al. 2023). The extent of caries excavation near the pulp ranged from soft dentine to hard dentine. Seven biomaterials were evaluated in 1093 randomised teeth from 1039 patients aged 6–76 years: Biodentine, $Ca(OH)_2$ cement, dentine bonding agent (DBA), GIC, MTA, resin-modified glass ionomer cement (RMGIC), and TheraCal LC (Bisco Inc., Schaumburg, IL, USA). Two types of final restorations were placed: resin-based composite or GIC. The follow-up periods ranged from 3 to 48 months. Pulp vitality (the primary outcome) was evaluated using one or more of the following diagnostic methods: pain history; presence of a sinus tract; presence of swelling; tenderness to palpation or percussion; abnormal tooth mobility; periapical radiography; electric pulp testing; and cold testing. Among the studies included, only two statistically significant findings were reported. Leye Benoist et al. (2012) found MTA superior to $Ca(OH)_2$ cement in maintaining pulp vitality over 3 months, while Rahman and Goswami (2021) reported that Biodentine and TheraCal LC outperformed $Ca(OH)_2$ cement over 24 months.

Table 2 summarises the findings on secondary outcomes, including dentine deposition (measured by periapical or bite-wing radiography) and postoperative pain or discomfort (measured on a visual analog scale). Although both outcomes were initially defined as efficacy measures, data on postoperative pain or discomfort could be considered a safety endpoint, helping to estimate the adverse effects of various biomaterials. Only Sultana et al. (2016) reported statistically significant results at the secondary outcomes level, demonstrating that MTA outperformed $Ca(OH)_2$ cement in increasing reactionary dentine thickness and reducing postoperative pain at 3, 6, and 12 months of follow-up.

No potential conflicts of interest were identified in any of the included studies except for Semprum-Clavier et al. (2024), which was the only industry-funded trial. It was funded by Bisco Inc., Schaumburg, IL, USA, and evaluated three materials, two of which (TheraCal LC and DBA) are manufactured by that company. Nevertheless, the authors declared that they have no proprietary, financial, or other personal interests in any product, service, or company involved in the study. Moreover, the performance of TheraCal LC reported in this study was inferior to that

TABLE 1 | Characteristics of the included studies.

Study no.	Report(s) (country), operator	Sample size (males%), age range	Materials evaluated and randomised teeth count	Caries excavation depth, aseptic technique, final restoration material	Diagnostic methods	Success rate of pulp vitality (teeth dropout count)
1	Banomyong and Messer (2013) (Thailand) One dentist	53 (41.51%) 18–30	**RMGIC** (Fuji Lining LC Paste Pak; GC Corporation, Tokyo, Japan) = 31 **DBA** (Single Bond 2; 3 M ESPE, St. Paul, MN, USA) or (Clearfil SE Bond; Kuraray Medical Inc., Okayama, Japan) = 31	Firm dentine Cotton rolls, saliva ejector, high-power suction Resin-based composite restoration	Pain history, Sinus tract, Swelling, Tenderness to palpation or percussion, Mobility, Periapical radiograph, Electric pulp test, Cold test	**12 months**: RMGIC = 100.00% (13), DBA = 100.00% (6) **24 months:** RMGIC = 100.00% (13), DBA = 100.00% (6)
2	Eranhikkal et al. (2019) (India) Operator's details were not reported	30 (Sex data not reported) 6–14	**$Ca(OH)_2$** (Dycal; Dentsply Sirona, York, PA, USA) = 10 **Biodentine** (Septodont, Saint-Maur-des-Fossés, France) = 10 **Er, Cr: YSGG laser** (Waterlase iPlus, Biolase Inc., Irvine, CA, USA) = 10[a]	Excavation depth is not reported Rubber dam Resin-based composite restoration	Pain history, Sinus tract, Swelling, Tenderness to palpation or percussion, Mobility, Periapical radiograph	**3 months:** $Ca(OH)_2$ = 100.00% (0), Biodentine = 100.00% (0), Er, Cr: YSGG laser = 100.00% (0) **6 months:** $Ca(OH)_2$ = 100.00% (0), Biodentine = 100.00% (0), Er, Cr: YSGG laser = 90.00% (0) **9 months:** $Ca(OH)_2$ = 90.00% (0), Biodentine = 80.00% (0), Er, Cr: YSGG laser = 80.00% (0)
3	Gözetici-Çil et al. (2023) (Turkey) One calibrated dentist	134 (42.54%) 13–44	**Biodentine** (Septodont, Saint-Maur-des-Fossés, France) = 45 **DBA** (3 M Single Bond Universal Adhesive; 3 M ESPE St. Paul, MN, USA) = 45 **Pulp exposure (PE)** = 29[a] **Selective removal to firm dentine (SRFD)** = 46[a]	Soft dentine Isolation technique not reported Resin-based composite restoration	Sinus tract, Swelling, Tenderness to palpation or percussion, Periapical radiograph, Cold test	**3 months**: Biodentine = 100.00% (4), DBA = 97.50% (5), PE = 89.29% (1), SRFD = 94.44% (10) **6 months**: Biodentine = 100.00% (5), DBA = 97.37% (7), PE = 88.46% (3), SRFD = 88.57% (11) **12 months**: Biodentine = 100.00% (6), DBA = 97.30% (8), PE = 88.00% (4), SRFD = 85.29% (12) **24 months**: Biodentine = 100.00% (10), DBA = 93.55% (14), PE = 84.00% (4), SRFD = 82.35% (12)

(Continues)

TABLE 1 | (Continued)

Study no.	Report(s) (country), operator	Sample size (males%), age range	Materials evaluated and randomised teeth count	Caries excavation depth, aseptic technique, final restoration material	Diagnostic methods	Success rate of pulp vitality (teeth dropout count)
4	Hashem et al. (2015) Hashem et al. (2019) (United Kingdom) One calibrated dentist	53 (60.38%) 18–76	**GIC** (GC Fuji IX Glass Ionomer Restorative; GC Corporation, Tokyo, Japan) = 36 **Biodentine** (Septodont, Saint-Maur-des-Fossés, France) = 36	Firm dentine Rubber dam Resin-based composite restoration	Pain history, Sinus tract, Swelling, Tenderness to palpation or percussion, Mobility, Periapical radiograph, Electric pulp test, Cold test	**6 months**: GIC = 84.38% (4), Biodentine = 86.67% (6) **12 months**: GIC = 81.82% (3), Biodentine = 79.31% (7) **24 months**: GIC = 66.67% (9), Biodentine = 77.78% (9)
5	Kaul et al. (2021) (India) One dentist	54 (Sex data not reported) 12–18	**$Ca(OH)_2$** (Dycal; Dentsply Sirona, York, PA, USA) = 24 **Biodentine** (Septodont, Saint-Maur-des-Fossés, France) = 24 **2% chlorhexidine gluconate followed by RMGIC** (GC Fuji II LC; GC Corporation, Tokyo, Japan) = 24[a]	Firm dentine Rubber dam Resin-based composite restoration	Pain history, Periapical radiograph, Cold test	**4 months**: $Ca(OH)_2$ = 100.00% (0), Biodentine = 100% (0), RMGIC = 95.83% (0) **8 months**: $Ca(OH)_2$ = 95.83% (0), Biodentine = 100.00% (0), RMGIC = 91.67% (0) **16 months:** $Ca(OH)_2$ = 91.67% (0), Biodentine = 95.83% (0), RMGIC = 87.50% (0)
6	Koc Vural et al. (2017a) Koc Vural et al. (2017b) Koc Vural et al. (2022) (Turkey) One calibrated dentist	73 (35.62%) 18–30	**$Ca(OH)_2$** (Dycal; Dentsply Sirona/Tulsa Dental, York, PA, USA) = 49 **MTA** (product name not reported) = 51	Hard dentine Saliva ejector, cotton rolls Resin-based composite restoration	Pain history, Tenderness to palpation or percussion, Periapical radiograph, Electric pulp test, Cold test	**6 months:** $Ca(OH)_2$ = 95.92% (0), MTA = 100% (0) **12 months:** $Ca(OH)_2$ = 91.84% (0), MTA = 98.04% (0) **24 months:** $Ca(OH)_2$ = 91.67% (1), MTA = 96.08% (0) **36 months:** $Ca(OH)_2$ = 83.72% (6), MTA = 89.58% (3) **48 months:** $Ca(OH)_2$ = 80.49% (8), MTA = 84.44% (6)
7	Leye Benoist et al. (2012) (Senegal) One specialist	60 (56.67%) 16–34	**$Ca(OH)_2$** (Dycal; Dentsply Sirona, York, PA, USA) = 30 **MTA** (ProRoot; Dentsply/Tulsa Dental, Tulsa, OK, USA) = 30	Hard dentine Rubber dam GIC restoration	Pain history, Periapical radiograph, Electric pulp test, Cold test	**3 months:** $Ca(OH)_2$ = 84.62% (4), MTA = 96.55% (1)[b] **6 months:** $Ca(OH)_2$ = 84.62% (4), MTA = 93.10% (1)

(Continues)

TABLE 1 | (Continued)

Study no.	Report(s) (country), operator	Sample size (males%), age range	Materials evaluated and randomised teeth count	Caries excavation depth, aseptic technique, final restoration material	Diagnostic methods	Success rate of pulp vitality (teeth dropout count)
8	Mahapatra et al. (2022) (India) Operator's details were not reported	21(Sex data not reported) Age data not reported	**$Ca(OH)_2$** (Prevest Cal LC; Prevest DenPro, Brussels, Belgium) = 14 **TheraCal LC** (Bisco Inc., Schaumburg, IL, USA) = 14	Firm dentine Rubber dam Resin-based composite restoration	Pain history, Tenderness to palpation or percussion, Periapical radiograph, Electric pulp test, Cold test	**3 months**: $Ca(OH)_2$ = 100.00% (0), TheraCal LC = 100.00% (0) **6 months**: $Ca(OH)_2$ = 92.86% (0), TheraCal LC = 100.00% (0)
9	Opal et al. (2017) (India) One calibrated dentist	30 (53.33%) 6–14	**$Ca(OH)_2$ (**Dycal; Dentsply Sirona, York, PA, USA) = 11 **RMGIC** (GC Fuji II LC; GC America Inc., Alsip, IL, USA) = 10 **Gutta-percha (GP)** (control, Dentsply, Mailleffer, Tulsa, OK, USA) = 11[a]	Soft dentine Rubber dam GIC restoration	Pain history, Sinus tract, Swelling, Tenderness to palpation or percussion, Periapical radiograph	**3 months**: $Ca(OH)_2$ = 100% (2), RMGI = 88.89% (1), GP = 77.78% (2)
10	Pereira et al. (2017) (Brazil) Operator's details were not reported	98 (42.86%) Age data not reported	**$Ca(OH)_2$ (**Dycal; Dentsply Sirona, York, PA, USA) = 49 **RMGIC** (Riva Light Cure, SDI Limited, Bayswater, Victoria, Australia) = 49	Soft dentine Rubber dam GIC restoration	Cold test	**3 months**: $Ca(OH)_2$ = 82.50% (9), RMGIC = 82.05% (10)
11	Rahman and Goswami (2021) (India) One calibrated dentist	55 (Sex data not reported) 7–15	**$Ca(OH)_2$ (**Dycal; Dentsply Sirona, York, PA, USA) = 20 **Biodentine** (Septodont, Saint-Maur-des-Fossés, France) = 20 **TheraCal LC** (Bisco Inc., Schaumburg, IL, USA) = 20	Firm dentine Rubber dam Resin-based composite restoration	Pain history, sinus tract, swelling, tenderness to palpation or percussion, Mobility, Periapical radiograph	**3 months**: $Ca(OH)_2$ = 100.00% (1), Biodentine = 100.00% (1), Theracal LC = 100.00% (1) **6 months**: $Ca(OH)_2$ = 94.74% (1), Biodentine = 100.00% (1), Theracal LC = 100.00% (1) **12 months**: $Ca(OH)_2$ = 89.47% (1), Biodentine = 94.74% (1), Theracal LC = 100.00% (1) **18 months**: $Ca(OH)_2$ = 83.33% (2), Biodentine = 94.74% (1), Theracal LC = 100.00% (2) **24 months**: $Ca(OH)_2$ = 77.78% (2), Biodentine = 94.44% (2), Theracal LC = 100.00% (2)[b]

(Continues)

TABLE 1 | (Continued)

Study no.	Report(s) (country), operator	Sample size (males%), age range	Materials evaluated and randomised teeth count	Caries excavation depth, aseptic technique, final restoration material	Diagnostic methods	Success rate of pulp vitality (teeth dropout count)
12	Selvendran et al. (2022) (India) Operator's details were not reported	36 (55.56%) 19–40	**$Ca(OH)_2$** (Dycal; Dentsply Sirona, York, PA, USA) = 12 **MTA** (Angelus; Londrina, Paraná, Brazil) = 12 **Biodentine** (Septodont, Saint-Maur-des-Fossés, France) = 12	Firm dentine Rubber dam GIC restoration	Pain history, Electric pulp test, Cold test	**3 months:** $Ca(OH)_2$ = 75.00% (0), MTA = 91.67% (0), Biodentine = 100.00% (0) **6 months:** $Ca(OH)_2$ = 58.33% (0), MTA = 83.33% (0), Biodentine = 91.67% (0)
13	Semprum-Clavier et al. (2024) (USA) Three calibrated dentists	71 (Sex data not reported) 19–61	**$Ca(OH)_2$** (Dycal; Dentsply Sirona, York, PA, USA) = 30 **TheraCal LC** (Bisco Inc., Schaumburg, IL, USA) = 30 **DBA** (All-Bond Universal; Bisco Inc., Schaumburg, IL, USA) = 30	Firm dentine Rubber dam Resin-based composite restoration	Pain history, Tenderness to palpation or percussion, Periapical radiograph, Cold test	**3 months:** $Ca(OH)_2$ = 100.00% (4), TheraCal LC = 96.30% (3), DBA = 100.00% (1) **6 months:** $Ca(OH)_2$ = 100.00% (1), TheraCal LC = 96.55% (1), DBA = 100.00% (2) **12 months:** $Ca(OH)_2$ = 100.00% (3), TheraCal LC = 96.15% (4), DBA = 100.00% (3)
14	Singh et al. (2019) (India) One dentist	198 (58.59%) 14–54	**$Ca(OH)_2$** (Dycal; Dentsply Sirona, York, PA, USA) = 66 **RMGIC** (GC Fuji II Lining LC; GC Corporation, Tokyo, Japan) = 66 **DBA** (Te-Econom Bond; Ivoclar Vivadent, Schaan, Liechtenstein) = 66	Firm dentine Rubber dam Resin-based composite restoration	Pain history, sinus tract, swelling, mobility, periapical radiograph, electric pulp test, cold test	**3 months:** not reported **6 months:** not reported **12 months:** $Ca(OH)_2$ = 96.83% (3), RMGIC = 96.49% (9), DBA = 94.64% (10)
15	Soliman et al. (2019) (Egypt) Operator's details were not reported	30 (Sex data not reported) 6–10	**$Ca(OH)_2$** (Dycal; Dentsply Sirona, York, PA, USA) = 30 **Biodentine** (Septodont, Saint-Maur-des-Fossés, France) = 30	Excavation depth is not reported Rubber dam GIC restoration	Tenderness to palpation or percussion, Periapical radiograph	**3 months:** $Ca(OH)_2$ = 86.67% (0), Biodentin = 100.00% (0) **6 months:** $Ca(OH)_2$ = 86.21% (1), Biodentin = 100.00% (1) **9 months:** $Ca(OH)_2$ = 85.19% (3), Biodentin = 100.00% (3)

(Continues)

TABLE 1 | (Continued)

Study no.	Report(s) (country), operator	Sample size (males%), age range	Materials evaluated and randomised teeth count	Caries excavation depth, aseptic technique, final restoration material	Diagnostic methods	Success rate of pulp vitality (teeth dropout count)
16	Sultana et al. (2016) (Bangladesh) Operator's details were not reported	43 (Sex data not reported) 16–30	**$Ca(OH)_2$** (Deepti Dental Product; India) = 25 **MTA** (ProRoot; Dentsply Sirona/Tulsa Dental, Tulsa, OK, USA) = 25	Firm dentine Rubber dam Resin-based composite restoration	Cold test	**3 months**: $Ca(OH)_2$ = 100.00% (0), MTA = 100.00% (0) **6 months**: $Ca(OH)_2$ = 76.00% (0), MTA = 100.00% (0) **12 months**: $Ca(OH)_2$ = 76.00% (0), MTA = 96.00% (0)

Abbreviations: $Ca(OH)_2$, calcium hydroxide cement; DBA, dentine bonding agent; GIC, glass ionomer cement; MTA, mineral trioxide aggregate; RMGIC, resin-modified glass ionomer cement.
[a]Indicates that the trial arm did not meet the inclusion criteria for the systematic review.
[b]Indicates statistical significance at $p < 0.05$.

in non-industry-funded studies (Mahapatra et al. 2022; Rahman and Goswami 2021).

3.3 | Risk of Bias Assessment

Using the RoB 2 tool, four of the 19 included reports (21.05%) were judged at high risk of bias, while the remaining 15 (78.95%) were judged to have some concerns. Among the latter, concerns predominantly arose in the measurement of the outcome domain (i.e., assessors aware of the intervention received by study participants) in 11 studies (73.33%), and in the selection of the reported result domain (i.e., absence of a pre-registered protocol to mitigate selective reporting) in 13 studies (86.67%). In the four high-risk studies, major flaws were also identified in the randomisation process in three studies (75.00%) and in the handling of missing outcome data in two studies (50.00%). For instance, Leye Benoist et al. (2012) employed a quasi-randomisation approach that risks selection bias. Moreover, all studies with randomisation-related high risk exhibited compromised allocation sequence concealment. Two studies were judged to have a high risk in the outcome measurement domain because missing outcome data may have depended on their true values. Figure 2 summarises the risk of bias findings.

3.4 | Results of Data Synthesis and Analysis

For the first follow-up year, the network meta-analysis included 16 studies evaluating seven biomaterials across 982 randomly assigned teeth. Of the 21 possible biomaterial pairs, 11 direct comparisons were available. The most frequent comparison was between $Ca(OH)_2$ cement and Biodentine ($n = 5$). Furthermore, both $Ca(OH)_2$ cement and Biodentine were the most interconnected interventions, each being directly compared with five other biomaterials. $Ca(OH)_2$ cement accounted for the largest number of randomised teeth within the network ($n = 345$). In contrast, GIC was the least connected intervention, having only been directly compared with Biodentine, and also included the fewest randomised teeth at 33. The network was fully connected, with no disconnected nodes (Figure 3).

The network meta-analysis compared all possible pairs of biomaterials for the first follow-up year. The league table (Figure 4) summarises the RRs, 95% CI, and their respective CINeMA overall confidence ratings (green for high confidence, blue for moderate confidence, yellow for low confidence, and red for very low confidence). Only MTA (RR = 0.30; 95% CI: 0.09–0.84), and Biodentine (RR = 0.30; 95% CI: 0.07–0.95) were statistically significantly superior to $Ca(OH)_2$ cement. No other comparisons in the network meta-analysis reached statistical significance. Although most results were classified as low confidence, the comparison between MTA and $Ca(OH)_2$ cement was rated as moderate confidence, whereas three comparisons involving TheraCal LC were rated as very low confidence. Figure S2 provides a detailed breakdown of the CINeMA ratings across individual confidence domains.

Table 3 and Figure 5 demonstrate the probability of each biomaterial achieving every possible rank in the network meta-analysis. Two clear clusters of biomaterials can be identified based on the

TABLE 2 | Secondary outcomes main findings.

Report	Dentine deposition outcome	Postoperative pain outcome
Gözetici-Çil et al. (2023)	N/A	No statistically significant difference was observed between the DBA and Biodentine groups in the first week after restoration placement. Exact numbers were not reported.
Leye Benoist et al. (2012)	**Mean ± Standard deviation (SD):** **3 months:** MTA = 0.121 ± 0.059, $Ca(OH)_2$ = 0.136 ± 0.060 **6 months:** MTA = 0.235 ± 0.110, $Ca(OH)_2$ = 0.221 ± 0.059	N/A
Mahapatra et al. (2022)	**Presence of calcified barrier at the restored site:** **3 months:** $Ca(OH)_2$ = 85.71%, TheraCal LC = 92.85% **6 months:** $Ca(OH)_2$ = 92.85%, TheraCal LC = 100%	N/A
Pereira et al. (2017)	**Mean ± Standard deviation (SD):** **3 months:** $Ca(OH)_2$ = −0.02 ± 0.43, RMGIC = 0.03 ± 0.22	N/A
Semprum-Clavier et al. (2024)	N/A	**Mean and range (of 100):** **12 months:** TheraCal LC = 0, 0 $Ca(OH)_2$ = 0.07, 0–2, DBA = 1.6, 0–41
Sultana et al. (2016)	**Percentage of teeth with increased reactionary dentine thickness at the restored site:** **3 months**: MTA = 92%, $Ca(OH)_2$ = 68%* **6 months**: MTA = 96%, $Ca(OH)_2$ = 76%* **12 months**: MTA = 96%, $Ca(OH)_2$ = 76%*	**Percentage of teeth causing pain:** **3 months**: MTA = 8%, $Ca(OH)_2$ = 32%* **6 months**: MTA = 4%, $Ca(OH)_2$ = 24%* **12 months**: MTA = 4%, $Ca(OH)_2$ = 24%*

Abbreviations: $Ca(OH)_2$, calcium hydroxide cement; DBA, dentine bonding agent; MTA, mineral trioxide aggregate; RMGIC, resin-modified glass ionomer cement.
*Indicates statistical significance at $p < 0.05$.

SUCRA values. GIC (72.55), MTA (71.29), Biodentine (70.90), and TheraCal LC (70.64) formed a higher-ranking group. In contrast, $Ca(OH)_2$ cement (24.89), RMGIC (21.73), and DBA (18.00) clustered into a lower-ranking group.

From the node-splitting analysis for the first follow-up year (Figure S3), the only inconsistencies between the direct and indirect estimates are observed in comparisons involving TheraCal LC. Although the overall model has a good fit according to the deviance report (Figure S4), a few outliers may partially explain the identified inconsistency. Most notably, the data from Semprum-Clavier et al. (2024), which investigated TheraCal LC against multiple biomaterials, have a high deviance contribution, indicating that their observed data deviate significantly from the model's predictions.

A sensitivity analysis was performed by excluding studies deemed to have a high risk of bias. This improved the overall fit of the model for data from the first follow-up year and reduced the magnitude of inconsistency (Figures S5 and S6). The recalculated RRs and ranking of biomaterials did not differ meaningfully from those of the original analysis (Figures S7 and S8 and Table S3), indicating that the results were generally robust to the exclusion of lower-quality evidence. An exception was for TheraCal LC, whose SUCRA value changed from 70.64 to 29.84, resulting in its clustering with the lower-ranking group, and with all RRs favouring other biomaterials versus TheraCal LC. In addition, while the pooled RR for Biodentine vs. $Ca(OH)_2$ cement remains in favour of Biodentine, the difference is no longer statistically significant.

Sensitivity analysis performed after excluding studies without documented rubber dam use resulted in RRs and material rankings that closely matched the original analysis (Table S4, Figures S9 and S10). Similarly, studies that used non-Dycal $Ca(OH)_2$ materials had minimal impact (Table S5 and Figures S11 and S12), except for the pooled RRs for Biodentine vs. $Ca(OH)_2$ cement and MTA vs. $Ca(OH)_2$ cement, which, although still favouring these hydraulic calcium silicate cements, lost statistical significance. In addition, TheraCal LC shifted out of the high-ranking cluster to occupy an intermediate position between the high- and low-ranking groups.

The available data for the second follow-up year were limited in contrast to the first year. The network meta-analysis included only six studies evaluating seven biomaterials across 364

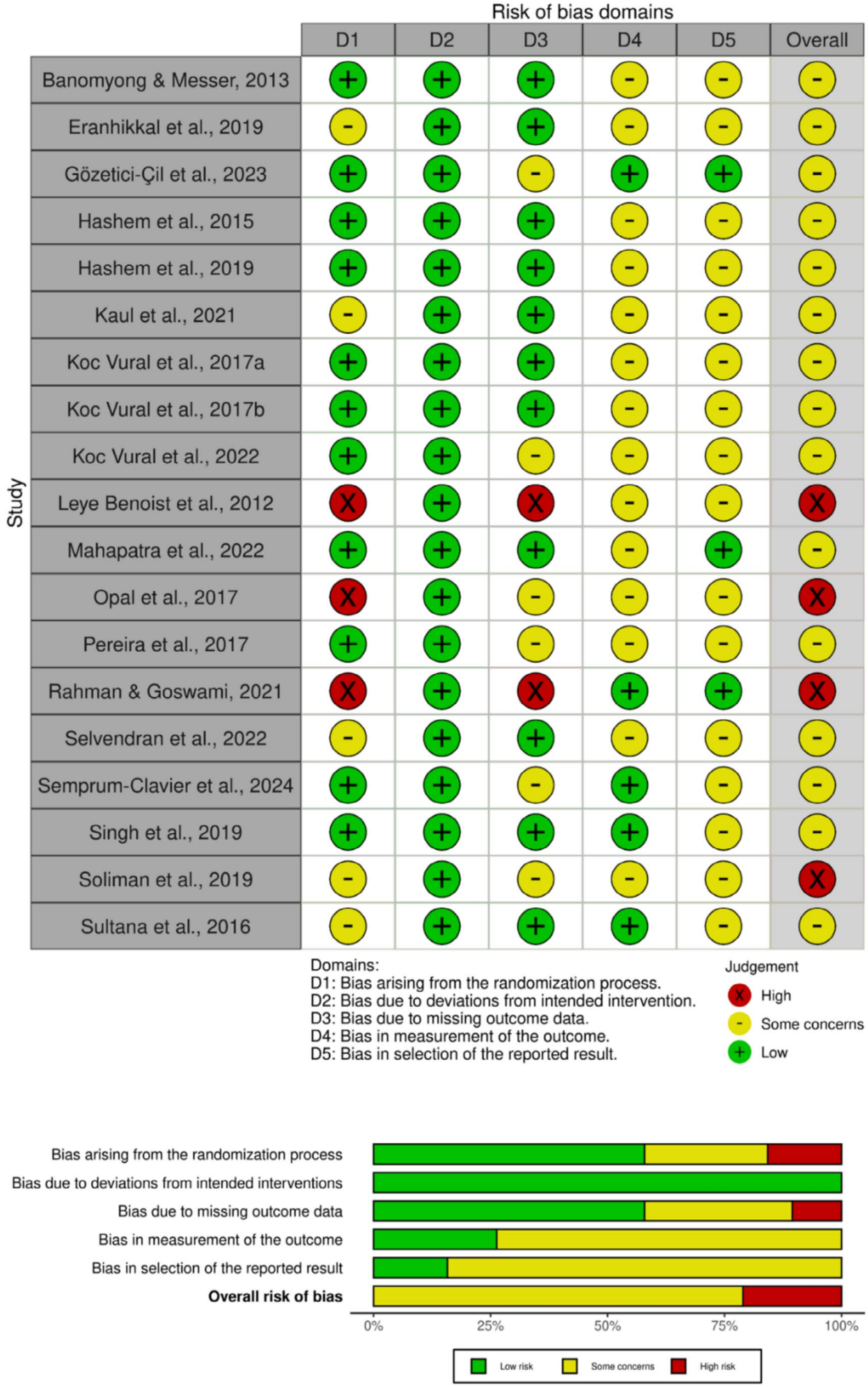

FIGURE 2 | Risk of bias findings using the RoB 2 tool.

randomly assigned teeth (Figure S13). This resulted in reduced statistical power, possibly explaining the wide CIs around many effect estimates (Figure S14). Nonetheless, the overall model has a good fit according to the deviance report (Figure S15). Biodentine (RR = 0.00; 95% CI: 0.00–0.53) and GIC (RR = 0.00; 95% CI: 0.00–0.99) showed statistically significant superiority over DBA. In addition, TheraCal LC demonstrated a statistically significantly better performance than Biodentine, $Ca(OH)_2$ cement, DBA, MTA, and GIC (Figure S14). TheraCal LC was also ranked as having the highest probability of being the best biomaterial in the second follow-up year (Table S6 and Figure S16). Figure S17 provides a detailed breakdown of the CINeMA ratings across individual confidence domains and shows that most results were classified as low confidence.

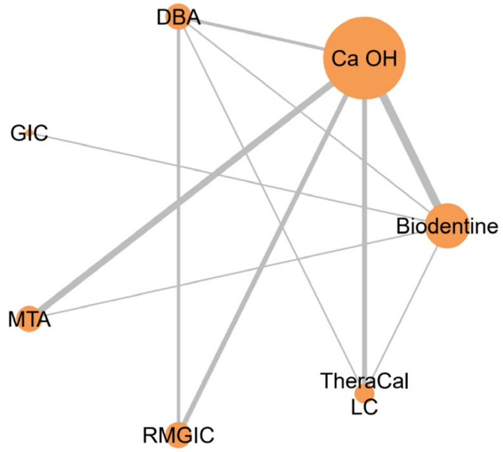

FIGURE 3 | Network plot of all studies for the first follow-up year. $Ca(OH)_2$, calcium hydroxide cement; DBA, dentine bonding agent; GIC, glass ionomer cement; MTA, mineral trioxide aggregate; RMGIC, resin-modified glass ionomer cement.

Results about TheraCal LC at the two-year follow-up were based solely on data from Rahman and Goswami (2021), which have been deemed to be at high risk of bias. Once this study was excluded in sensitivity analysis, no conclusion could be drawn about the performance of TheraCal LC. Nonetheless, it was found that both Biodentine (RR = 0.00; 95% CI: 0.00–0.52) and GIC (RR = 0.00; 95% CI: 0.00–0.96) were still superior to DBA after performing the sensitivity analysis (Figure S18). Biomaterial rankings after sensitivity analysis approximately match those for the first follow-up year, with a clear separation in the low-ranking cluster group, where DBA is most likely the

TheraCal LC						
0.93 (0.02, 26.25)	GIC					
0.84 (0.03, 12.72)	0.88 (0.14, 5.25)	Biodentine				
0.85 (0.03, 11.72)	0.86 (0.07, 9.20)	0.99 (0.19, 4.85)	MTA			
0.25 (0.01, 2.46)	0.26 (0.02, 2.03)	**0.30 (0.07, 0.95)**	**0.30 (0.09, 0.84)**	$Ca(OH)_2$		
0.21 (0.01, 2.78)	0.23 (0.01, 2.25)	0.26 (0.03, 1.26)	0.26 (0.04, 1.19)	0.88 (0.20, 2.78)	RMGIC	
0.18 (0.00, 3.02)	0.19 (0.01, 2.58)	0.21 (0.02, 1.58)	0.21 (0.03, 1.76)	0.71 (0.13, 4.52)	0.83 (0.14, 6.28)	DBA

FIGURE 4 | League table of biomaterial comparisons for the first follow-up year. The table presents pairwise comparisons from the network meta-analysis, where results should be read from the column-defining biomaterial compared to the row-defining treatment. Each cell contains the Risk Ratio (RR) and its corresponding 95% Confidence Interval (95% CI). A bolded RR and 95% CI indicate a statistically significant result ($p < 0.05$). The cell colour represents the overall confidence in the evidence as rated by the CINeMA framework: Blue indicates moderate confidence, yellow indicates low confidence, and red indicates very low confidence. $Ca(OH)_2$, calcium hydroxide cement; DBA, dentine bonding agent; GIC, glass ionomer cement; MTA, mineral trioxide aggregate; RMGIC, resin-modified glass ionomer cement.

TABLE 3 | Ranking probabilities of biomaterials for the first follow-up year.

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	SUCRA
TheraCal LC	0.39	0.14	0.12	0.17	0.07	0.06	0.05	70.64
GIC	0.29	0.25	0.19	0.15	0.05	0.04	0.03	72.55
Biodentine	0.11	0.31	0.35	0.19	0.03	0.01	0.00	70.90
MTA	0.19	0.26	0.26	0.24	0.04	0.01	0.00	71.29
$Ca(OH)_2$	0.00	0.00	0.01	0.10	0.40	0.34	0.15	24.89
RMGIC	0.00	0.01	0.03	0.09	0.24	0.34	0.28	21.73
DBA	0.01	0.02	0.04	0.08	0.16	0.21	0.48	18.00

Note: $Ca(OH)_2$, calcium hydroxide cement; DBA, dentine bonding agent; GIC, glass ionomer cement; MTA, mineral trioxide aggregate; RMGIC, resin-modified glass ionomer cement.

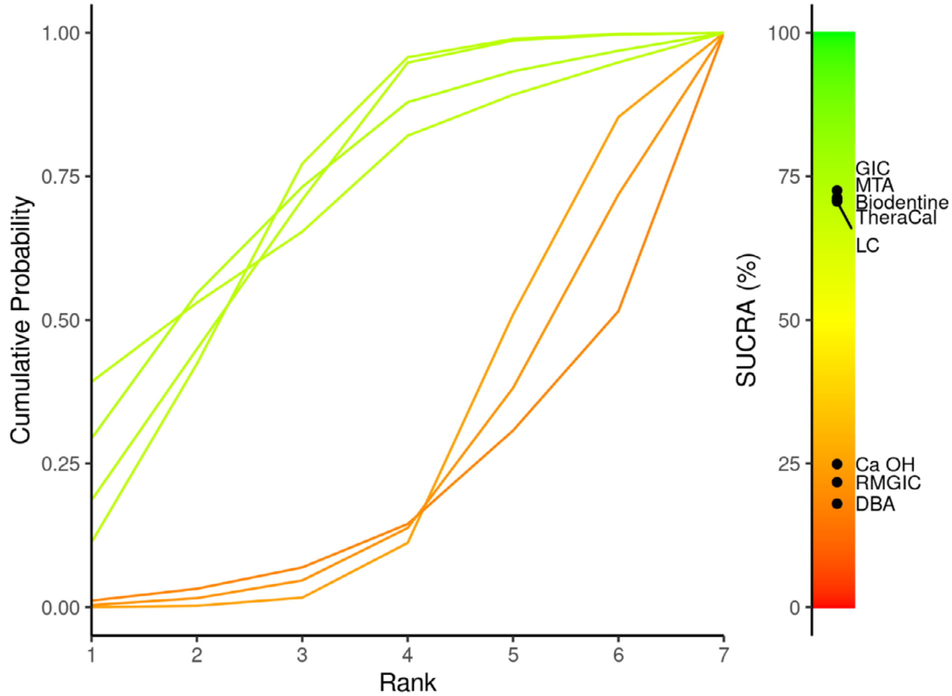

FIGURE 5 | Rank-O-Gram for the first follow-up year. Ca(OH)$_2$, calcium hydroxide cement; DBA, dentine bonding agent; GIC, glass ionomer cement; MTA, mineral trioxide aggregate; RMGIC, resin-modified glass ionomer cement.

lowest-ranked biomaterial in the second year (Table S7 and Figure S19).

Findings from the standard pairwise meta-analyses for the first follow-up year are presented in Figure S20, and those for the second follow-up year are presented in Figure S21.

Table 4 summarises the outcomes of meta-regression for pulp-vitality success at the 1-year follow-up period across four study-level covariates. Although the regression coefficients for all covariates were positive, their 95% confidence intervals all crossed zero, preventing any definitive conclusions about how these covariates modify treatment effects. This lack of statistical significance may reflect the limited data available, since exploration of these covariates was not a primary aim of the review.

4 | Discussion

This systematic review aimed to compare the effectiveness of various biomaterials, including pulp-capping and restorative materials applied directly over residual dentine, in preserving pulp health in permanent teeth with deep carious lesions without pulp exposure. Although direct clinical comparisons of these materials exist, they have not demonstrated clear effectiveness, and current guidelines do not endorse any specific pulp-capping materials (Duncan et al. 2019; Semprum-Clavier et al. 2024). A comprehensive search of four electronic databases was conducted, and supplemented by clinical trial registries, grey literature, and manual searches to identify eligible studies. Using a Bayesian network meta-analysis, direct and indirect evidence was integrated to compare these materials' efficacy and to rank them by their relative performance in preserving pulp vitality.

Findings from this systematic review highlight the importance of using indirect pulp-capping materials in permanent teeth during the management of deep carious lesions to maintain vital pulp health. Specifically, moderate-confidence evidence shows that the DBA group (the only control) performed statistically significantly worse than two pulp-capping materials, Biodentine and GIC, over the 2-year follow-up. In addition, although not statistically significant, all other pairwise comparisons with the remaining pulp-capping materials resulted in RRs favouring those materials. The DBA group's suboptimal performance may be further supported by its consistently low SUCRA values and high probability of ranking last across both follow-up years, most notably in the second year (64% probability of ranking last). Nevertheless, these ranking results should be interpreted with caution because they are based on pairwise comparisons that were mostly not statistically significant and on low-confidence evidence.

While performance differences may exist among various DBA generations, only fifth-generation and universal adhesives were tested in the included studies. Banomyong and Messer (2013) evaluated both but did not report their performance separately, further limiting the ability to draw conclusions regarding differences in performance between DBA generations in this systematic review.

The comparatively inferior performance of DBAs may be attributed to potential toxic effects of the bonding procedure on pulp tissue in deep carious lesions, particularly when not protected by an indirect pulp-capping material. The deep dentine layer near the pulp has a high tubule density and a large tubule diameter, resulting in increased permeability (Lenzi et al. 2013; Gevkaliuk et al. 2023). Consequently, the acidic pH of self-etch and etch-and-rinse adhesives, solvents, and unpolymerised resin

TABLE 4 | Univariable random-effects meta-regression for pulp-vitality success at the 1-year follow-up.

Covariate (unit of change)	Regression coefficient	95% CI
Mean patient age (per 1 years)	0.41	−5.51 to 7.78
Male proportion (per 1% increase)	0.12	−1.53 to 1.83
Rubber dam use (yes or no)	0.22	−2.30 to 3.05
Caries-excavation depth (Hard, firm to soft)	0.03	−1.84 to 1.92

monomers can irritate the pulp and place it under additional stress, potentially leading to loss of pulp vitality (Cui et al. 2009; Kwon et al. 2015). Furthermore, in the deep dentine layer near the pulp, the integrity of the adhesive layer has been shown to be compromised, increasing the risk of microleakage, bacterial infiltration, and subsequent pulp damage (Schwendicke et al. 2014). Moreover, DBAs lack the sustained antimicrobial, remineralising, and regenerative properties that are commonly found in many pulp-capping materials, which may play a crucial role in maintaining pulp vitality (Vaidyanathan et al. 2009; Ashtijoo et al. 2022).

The conclusion about the importance of indirect pulp capping when managing deep carious lesions aligns with existing guidelines and position statements, which have long recommended the use of pulp-capping materials in cases without pulpal exposure to provide additional pulpal protection (Duncan et al. 2019; Hilton 2009; Bjørndal et al. 2019). However, this recommendation has traditionally been based on laboratory research and indirect clinical evidence focusing on surrogate outcomes (Eidelman et al. 1965; Leung et al. 1980). This systematic review is the first to provide direct clinical evidence supporting this recommendation.

Another novel finding from this systematic review is the variation in the performance of different pulp-capping materials in preserving pulp health. Hydraulic calcium silicate cements (Biodentine and MTA) performed statistically significantly better than $Ca(OH)_2$ during the first follow-up year. These findings, along with the favourable comparisons for Biodentine vs. the DBA group and GIC vs. the DBA group presented above, may explain the consistent clustering of Biodentine, MTA, and GIC within a higher-ranking group, with a probability of being among the most effective pulp-capping materials.

MTA was first formulated as a root-end filling material by Torabinejad and his colleagues in the early 1990s (Torabinejad et al. 1993). The proposal to use it in the management of deep carious lesions was made later (Ford et al. 1996). In its basic form, MTA consists of a mixture of purified Portland cement and bismuth oxide (Parirokh and Torabinejad 2010). MTA possesses many properties that are essential for an ideal pulp-capping material. MTA has superior sealing ability, which might be attributed to its expansion during setting and the formation of an interfacial layer and tag-like structures within the dentinal tubules (Shipper et al. 2004; Han and Okiji 2011). MTA also has a well-documented antimicrobial effect, especially against certain facultative bacterial strains (Hasan Zarrabi et al. 2009). In addition, MTA is highly biocompatible and does not have any mutagenic or cytotoxic effects, while also causing minimal soft tissue inflammation (Ribeiro et al. 2005). Furthermore, MTA was found to significantly promote remineralisation of affected dentine and the deposition of reactionary dentine (Han and Okiji 2016). This is demonstrated by the significantly higher number of teeth with deep carious lesions that developed reactionary dentine at the restored site with MTA compared to $Ca(OH)_2$ cement (Sultana et al. 2016).

Few limitations of MTA, however, may restrict its use in indirect pulp capping procedures. For instance, MTA exhibits poor handling characteristics, as evidenced by its prolonged setting time of 2–3 h (Torabinejad et al. 1995). To avoid disruption of the MTA setting, a two-step procedure has been proposed, involving the placement of a wet cotton pellet and a temporary restoration over the MTA, which is later removed once the MTA is fully set. Alternatively, a quick-setting liner can be placed over partially set MTA to address this limitation (Camilleri and Pitt Ford 2006). In addition, the original grey MTA has been associated with tooth discoloration and darkening. Although white MTA was developed to mitigate this limitation by excluding tetracalcium aluminoferrite, it too has been reported to cause some discoloration, possibly due to oxidation of bismuth oxide, which is included as a radiopacifier (Marciano et al. 2014). This limits the use of MTA in teeth located in the aesthetic zone.

Biodentine was introduced to the market in 2009 as a dentine substitute, addressing several MTA's drawbacks. It has a faster setting time of approximately 12 min, allowing for the immediate and direct placement of a definitive restoration over the material (Rajasekharan et al. 2018). In addition, Biodentine has been reported to demonstrate a stronger antimicrobial effect than MTA (Bhavana et al. 2015). Furthermore, unlike MTA, Biodentine does not cause tooth discoloration or darkening, making it suitable for use in the aesthetic zone (Slaboseviciute et al. 2021).

GIC is the other pulp-capping material that belongs to the higher-ranking group in this systematic review. Although GIC outperformed most other pulp-capping materials in pairwise comparisons across both follow-up years, findings regarding GIC should be interpreted with caution since its effect estimates are not statistically significant and the supporting evidence is of low confidence. In addition, GIC was the least connected intervention in the network meta-analyses and included the fewest randomised teeth.

The promising results of GIC in this systematic review may primarily be attributed to its fluoride release potential. Released fluoride ions can enhance the remineralisation of affected dentine and exhibit antimicrobial effects, both of which are critical for the successful management of deep carious lesions (Maciel Pires et al. 2022). However, when compared with other pulp-capping materials, such as hydraulic calcium silicate cements and $Ca(OH)_2$ cement, GIC demonstrates lower performance in certain properties that are important for treatment success. For instance, GIC lacks a strong bactericidal effect and primarily exhibits a bacteriostatic property (Bhavana et al. 2015). In addition, although GIC is reasonably biocompatible, it becomes slightly acidic upon setting, which may cause some pulpal irritation (Ribeiro et al. 2020). Furthermore, GIC has limited regenerative potential and minimally promotes reactionary dentine deposition (Ghorpade et al. 2024). Moreover, some pulp-capping materials have demonstrated better sealing capability than GIC, possibly due to GIC's moisture sensitivity and higher porosity (Navya and Shivamurthy 2007).

Although $Ca(OH)_2$ cement was long considered the gold standard for pulp-capping materials and remains one of the most widely used (De Miranda et al. 2024), results for $Ca(OH)_2$ cement in this systematic review did not demonstrate any statistically significant performance advantage over other biomaterials. These results persisted in sensitivity analysis restricted to studies using only Dycal, a rigid-setting calcium-hydroxide liner. Calcium ion release from $Ca(OH)_2$ cement has been associated with maintaining a larger number of viable odontoblasts and with a greater deposition of reactionary dentine (About et al. 2001a). Meanwhile, hydroxyl ion release increases the pH value in the surrounding environment, which is the main cause of $Ca(OH)_2$ cement's antimicrobial property (Poggio et al. 2014). However, $Ca(OH)_2$ cement shows reduced antibacterial activity over time (Coogan and Creaven 1993). Another limitation of $Ca(OH)_2$ cement is its inferior mechanical properties such as a low elastic modulus and compressive strength (Tam et al. 1989). In addition, it has high solubility and water sorption. Furthermore, its sealing ability is significantly lower than that of many other pulp-capping materials (Francisconi et al. 2009). Thus, $Ca(OH)_2$ cement liners are at a higher risk of microleakage, which could lead to bacterial penetration and further pulp irritation.

TheraCal LC, a light-cured resin-modified calcium silicate-based material, was the only pulp-capping material that showed a significant inconsistency between direct and indirect evidence, along with significant variation in its effectiveness before and after sensitivity analyses. This variability limits the ability to draw a definitive conclusion about its performance. One possible explanation is that the study by Semprum-Clavier et al. (2024) may have underestimated its effectiveness against $Ca(OH)_2$ cement and DBA. This potential underestimation is supported by the poor fit between their observed data and the model's predictions, as indicated by the deviance report. Semprum-Clavier et al. (2024) had some risk of bias, which might have led to an underestimation of TheraCal LC's effectiveness. In addition, the insufficient power may have introduced random errors, further contributing to this underestimation. On the contrary, Rahman and Goswami (2021), which was deemed to be at high risk of bias, may have overestimated the effectiveness of TheraCal LC relative to Biodentine and $Ca(OH)_2$ cement, thereby contributing to the discrepancies between the direct and indirect evidence and the observed variation in the sensitivity analyses. Along with the variability in the estimation of TheraCal LC's effectiveness, many pairwise comparisons involving TheraCal LC were supported only by evidence with very low confidence, further limiting the possibility of drawing any conclusions about its performance.

TheraCal LC was introduced to address several limitations of previous pulp-capping materials by combining the bioactivity of calcium silicate with the improved handling and mechanical properties provided by a resin matrix (Arandi and Rabi 2018). One of the main advantages of TheraCal LC is that it allows for the immediate placement of final resin-based composite restorations, while still maintaining superior bond strength with the restoration (Meraji and Camilleri 2017; Deepa et al. 2016). In addition, it demonstrated lower solubility and superior sealing ability compared to other pulp-capping materials (Gandolfi et al. 2012; Makkar et al. 2015). Another advantage of TheraCal LC is its ability to release calcium ions over time, potentially aiding in the induction of tertiary dentine formation (Gandolfi et al. 2012). This is demonstrated by greater dentine deposition following indirect pulp-capping compared to $Ca(OH)_2$ cement and RMGIC after 1 year of follow-up (Altaf et al. 2024). However, although the initial calcium ion concentration released from TheraCal LC falls within the range required for stimulatory activity, it decreases over time and is significantly lower than that observed with conventional hydraulic calcium silicate cements such as MTA and Biodentine (Camilleri 2014). This reduced ion release is also reflected in its lower remineralisation potential compared to these conventional cements (Li et al. 2017; Yamamoto et al. 2017). Another limitation of TheraCal LC is its reduced antimicrobial effectiveness compared to other pulp-capping materials. It has been shown to exhibit less antimicrobial activity than $Ca(OH)_2$ cement against various bacterial strains (Poggio et al. 2014). In addition, TheraCal LC produces a lower pH alkalisation relative to both MTA and $Ca(OH)_2$ cement, further diminishing its antimicrobial effectiveness (Yamamoto et al. 2017; Gandolfi et al. 2015). Another histologic limitation of TheraCal LC was revealed in a randomised controlled clinical trial of partial pulpotomy, which demonstrated that TheraCal LC induced more severe histologic inflammation and greater disruption of pulp-tissue architecture than MTA or Biodentine (Bakhtiar et al. 2017). This may be due to leakage of unpolymerised monomers into the pulp tissue.

In the included studies, the extent of caries excavation near the pulp ranged from soft to hard dentine, reflecting the utilisation of different caries excavation techniques among research teams. This variation is also apparent in guidelines and position statements on the management of deep carious lesions, published by various dental associations and societies. For instance, the European Society of Endodontology and the American Dental Association favour a selective caries-removal approach (Duncan et al. 2019; Dhar et al. 2023), whereas the American Association of Endodontists recommends non-selective removal (American Association of Endodontists 2021). This conflicting guidance may stem from a lack of robust clinical evidence demonstrating the superiority of one approach over another in maintaining pulp vitality (Ramezanzade et al. 2025). Therefore, none of the excavation approaches were considered exclusion criteria in this review, although excavation depth was considered a potential effect modifier. Meta-regression revealed that excavation depth did not significantly modify the treatment effects in this systematic review.

Due to the loss of institutional access to Embase and Scopus in June 2024, the literature search could not be updated beyond that point. This may have had a negative effect on the impact and relevance of the review. However, to mitigate this limitation, a supplementary search of PubMed and Web of Science was carried out on 10

March 2025, identifying five new eligible studies (Altaf et al. 2024; Ghorpade et al. 2024; Oburo et al. 2024; Mangat et al. 2025; Yavuz et al. 2025). Because this supplementary search fell outside the original protocol, its findings were not included in the analysis. Six pulp-capping materials were evaluated in these studies: Biodentine, $Ca(OH)_2$ cement, GIC, light-cured MTA, RMGIC, and TheraCal PT (Bisco Inc., Schaumburg, USA). $Ca(OH)_2$ cement remained the most tested material, as it was included in all five studies except for Mangat et al. (2025). None of the five studies detected a significant difference between various pulp-capping materials in maintaining the pulp vitality of teeth with deep carious lesions. However, the trend observed in these studies aligns with the findings of this systematic review, particularly in those with a relatively larger sample size. For example, Ghorpade et al. (2024) reported that the GIC group experienced fewer instances of pulp vitality loss compared to $Ca(OH)_2$ cement. Meanwhile, Yavuz et al. (2025) found that Biodentine had the fewest cases of pulp vitality loss compared to $Ca(OH)_2$ cement and TheraCal PT.

A few studies included in this systematic review deviated from accepted clinical standards. For instance, Banomyong and Messer (2013) and Koc Vural et al. (2017a) did not use rubber dam isolation. The rationale for including these studies was to reflect real-world variability, where rubber dam use remains low among clinicians (Vodoriz et al. 2022). However, there is a risk that the effect estimates in this systematic review's meta-analyses might not reflect outcomes under accepted clinical standards, which could potentially limit the usefulness of the synthesised evidence for informed clinical decision-making. Therefore, sensitivity analyses and meta-regression were conducted in relation to rubber-dam use. These analyses demonstrated that rubber-dam use exerted a negligible influence on effect estimates, relative material rankings, and pulp-vitality outcomes in this systematic review.

Another limitation of this systematic review is that most findings were supported by low-confidence evidence, primarily due to biases in the included studies and the imprecision of many pooled effect estimates. This imprecision may be partially attributed to the limited statistical power of many included studies, possibly stemming from the absence of, or inadequate, sample size calculations. Many of the included studies arbitrarily selected their sample sizes without formal calculations (Kaul et al. 2021; Soliman et al. 2019). Others based their calculations on data from studies evaluating less relevant interventions, such as indirect pulp capping in primary teeth or direct pulp capping in permanent teeth (Eranhikkal et al. 2019; Mahapatra et al. 2022). Few studies calculated the sample size for outcomes other than the preservation of pulp vitality, such as reactionary dentine thickness and postoperative pain (Banomyong and Messer 2013; Opal et al. 2017).

One more limitation of this systematic review is the relatively short follow-up period in the included studies, with only one study reporting data beyond two years (Koc Vural et al. 2022). Extended follow-up periods may be necessary to clearly detect differences in the effectiveness of various pulp-capping materials. This can be supported by the observation that the inferior performance of DBA was more evident in the second follow-up year, despite fewer randomised teeth in the network. Future research should aim to address these limitations in order to establish more robust evidence regarding the role of various pulp-capping materials in preserving pulp vitality.

5 | Conclusions

Findings from this systematic review highlight the importance of using pulp-capping materials in permanent teeth with deep carious lesions without pulp exposure. Of the six evaluated pulp-capping materials, Biodentine, MTA, and GIC showed the most promising potential for preserving pulp vitality. This is supported mostly by moderate-confidence evidence indicating statistically significant superiority of Biodentine and GIC over the DBA group, and of MTA and Biodentine over $Ca(OH)_2$ cement. However, as other evidence in this systematic review is of low and very low confidence, further high-quality research is needed to validate these conclusions and ensure that clinical decision-making is grounded in robust evidence.

Author Contributions

Fahad BaHammam: conceptualisation, data curation, formal analysis, funding acquisition, investigation, project administration, visualisation, writing – original draft preparation – review and editing. **Sultan Aldakhil:** data curation, investigation, writing – review and editing. **Jamal Akhil:** data curation, investigation, writing – review and editing. **John Whitworth:** conceptualisation, supervision, writing – review and editing.

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Disclosure

The review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Ethics Statement

This study was exempted from the ethics approval process because it is a systematic review.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Thesaurus terms and keywords used in the database search strategy. **Table S2:** List of excluded reports with the reason for exclusion. **Table S3:** Ranking probabilities of biomaterials for the first follow-up year after sensitivity analysis, excluding high-risk bias studies. **Table S4:** First-year ranking probabilities after sensitivity analysis, excluding studies without documented rubber-dam use. **Table S5:** First-year ranking probabilities after sensitivity analysis, excluding studies used non-Dycal $Ca(OH)_2$ materials. **Table S6:** Ranking probabilities of biomaterials for the second follow-up year. **Table S7:** Ranking probabilities of biomaterials for the second follow-up year after sensitivity analysis, excluding high-risk bias studies. **Figure S1:** The Gelman–Rubin shrink factor plots. $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding Agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S2:** Detailed breakdown of CINeMA ratings across individual confidence domains. $Ca(OH)_2$ = Calcium Hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S3:** Node-splitting analysis for the first follow-up year. $Ca(OH)_2$ = Calcium Hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S4:** Deviance report for the first follow up year. **Figure S5:** Node-splitting analysis for the first follow-up year after sensitivity analysis (excluding studies at a high risk of bias). $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA =

mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S6:** Deviance report for the first follow up year after sensitivity analysis (excluding studies at a high risk of bias). **Figure S7:** League table of biomaterial comparisons for the first follow-up year after sensitivity analysis (excluding studies at a high risk of bias). The table presents pairwise comparisons from the network meta-analysis, where results should be read from the column-defining biomaterial compared to the row-defining treatment. Each cell contains the Risk Ratio (RR) and its corresponding 95% Confidence Interval (95% CI). A bolded RR and 95% CI indicate a statistically significant result ($p < 0.05$). $Ca(OH)_2$ = calcium hydroxide; DBA = dentine bonding agent; GIC = glass ionomer cement; MTA = mineral trioxide aggregate; RMGIC = resin-modified glass ionomer cement. **Figure S8:** Rank-O-Gram for the first follow-up year after sensitivity analysis (excluding studies at a high risk of bias). $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S9:** League table of biomaterial comparisons for the first follow-up year after sensitivity analysis (excluding studies without documented rubber-dam use). The table presents pairwise comparisons from the network meta-analysis, where results should be read from the column-defining biomaterial compared to the row-defining treatment. Each cell contains the Risk Ratio (RR) and its corresponding 95% Confidence Interval (95% CI). A bolded RR and 95% CI indicate a statistically significant result ($p < 0.05$). $Ca(OH)_2$ = calcium hydroxide; DBA = dentine bonding agent; GIC = glass ionomer cement; MTA = mineral trioxide aggregate; RMGIC = resin-modified glass ionomer cement. **Figure S10:** Rank-O-gram for the first follow-up year after sensitivity analysis (excluding studies without documented rubber-dam use). $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S11:** League table of biomaterial comparisons for the first follow-up year after sensitivity analysis (excluding studies used non-Dycal $Ca(OH)_2$ materials). The table presents pairwise comparisons from the network meta-analysis, where results should be read from the column-defining biomaterial compared to the row-defining treatment. Each cell contains the Risk Ratio (RR) and its corresponding 95% Confidence Interval (95% CI). A bolded RR and 95% CI indicate a statistically significant result ($p < 0.05$). $Ca(OH)_2$ = calcium hydroxide; DBA = dentine bonding agent; GIC = glass ionomer cement; MTA = mineral trioxide aggregate; RMGIC = resin-modified glass ionomer cement. **Figure S12:** Rank-O-gram for the first follow-up year after sensitivity analysis (excluding studies used non-Dycal $Ca(OH)_2$ materials). $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S13:** Network plot of all studies for the second follow-up year. $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S14:** League table of biomaterial comparisons for the second follow-up year. The table presents pairwise comparisons from the network meta-analysis, where results should be read from the column-defining biomaterial compared to the row-defining treatment. Each cell contains the Risk Ratio (RR) and its corresponding 95% Confidence Interval (95% CI). A bolded RR and 95% CI indicate a statistically significant result ($p < 0.05$). The cell colour represents the overall confidence in the evidence as rated by the CINeMA framework: blue indicates moderate confidence, yellow indicates low confidence, and red indicates very low confidence. $Ca(OH)_2$ = calcium hydroxide cement; DBA = dentine bonding agent; GIC = glass ionomer cement; MTA = mineral trioxide aggregate; RMGIC = resin-modified glass ionomer cement. **Figure S15:** Deviance report for the second follow up year. **Figure S16:** Rank-O-Gram for the second follow-up year. $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S17:** Detailed breakdown of CINeMA ratings across year 2 individual confidence domains. $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S18:** League table of pairwise comparisons of biomaterials for year 2 after sensitivity analysis (excluding studies at a high risk of bias). The table presents pairwise comparisons from the network meta-analysis, where results should be read from the column-defining biomaterial compared to the row-defining treatment. Each cell contains the Risk Ratio (RR) and its corresponding 95% Confidence Interval (95% CI). A bolded RR and 95% CI indicate a statistically significant result ($p < 0.05$). $Ca(OH)_2$ = calcium hydroxide cement; DBA = dentine bonding agent; GIC = glass ionomer cement; MTA = mineral trioxide aggregate; RMGIC = resin-modified glass ionomer cement. **Figure S19:** Rank-O-gram for the second follow-up year after sensitivity analysis (excluding studies at a high risk of bias). $Ca(OH)_2$ = calcium hydroxide cement, DBA = dentine bonding agent, GIC = glass ionomer cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S20:** Meta-analyses for the first follow-up year. $Ca(OH)_2$ = calcium hydroxide cement, MTA = mineral trioxide aggregate, RMGIC = resin-modified glass ionomer cement. **Figure S21:** Meta-analysis for the second follow-up year. $Ca(OH)_2$ = calcium hydroxide cement.