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DISSERTATION

Aufrechterhaltung der Vitalität der Pulpa: Kostenwirksamkeits-Analyse zur Entfernung kariösen Gewebes und zur direkten Überkappung der Pulpa

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Aufrechterhaltung der Vitalität der Pulpa: Kostenwirksamkeits-Analyse zur Entfernung kariösen Gewebes und zur direkten Überkappung der Pulpa

Abstrakt

Ziele: Bei der Behandlung tiefer kariöser Läsionen können Zahnärzte die Vitalität der Pulpa aufrechterhalten, indem sie eine Exposition und Komplikationen der Pulpa durch den Einsatz einer selektiven (SE) anstelle einer nicht selektiven (NS) Entfernung kariösen Gewebes vermeiden und / oder exponierte Pulpen durch eine direkte Überkappung mit Mineral-Trioxid-Aggregat (MTA) statt Kalziumhydroxid (CH) therapieren. Die vorliegende Dissertation untersuchte die Kostenwirksamkeit von SE vs. NS in Kombination mit einer direkten Überkappung der Pulpa durch MTA vs. CH.

Methoden: Im Kontext des deutschen Gesundheitssystems wurde die Perspektive von öffentlichen und privaten Zahlern angewendet. Wir modellierten einen bleibenden Molaren mit einer tiefen kariösen Läsion und einer vitalen, asymptomatischen Pulpa eines initial 30-jährigen Patienten. Die Läsion wurde durch SE / NS und im Falle einer Exposition durch direkte Überkappung der Pulpa unter Verwendung von MTA / CH behandelt. Der Zahn wurde über die Lebensdauer der Patienten unter Verwendung von Markov-Modellen verfolgt, wobei paarweise und Bayes'sche Netzwerk-Metaanalysen sowie weitere Datenquellen für die Ermittlung von Übergangswahrscheinlichkeiten eingesetzt wurden. Der Zielpunkt war die Zahnretentionsdauer. Die Kosten wurden anhand von Gebührenpositionen von Gesetzlicher und Privater Krankenversicherung in Kombination mit Mikrokostenschätzungen abgeleitet. Eine Monte-Carlo-Mikrosimulation wurde durchgeführt und Unsicherheiten durch probabilistische und univariate Sensitivitätsanalysen abgebildet. Eine Value-of-Information-Analyse wurde zusätzlich durchgeführt, um den monetären Wert weiterer Forschung zu quantifizieren.

Ergebnisse: SE und, bei Exposition der Pulpa der Einsatz von MTA, hatten eine hohe Wahrscheinlichkeit (> 95%), kostenwirksam zu sein. In dieser Interventionskombination würden Zähne 37 Jahre lang bei Kosten von durchschnittlich 2140 Euro erhalten. Alternative Strategien waren sowohl teurer als auch weniger wirksam. Dieses Ranking war in Sensitivitätsanalysen robust. Die Value-of-Information betrug 1,18 Euro pro behandeltem Zahn bzw. 12,86 Millionen Euro auf Bevölkerungsebene.

Schlussfolgerung: Die Behandlung tiefer kariöser Läsionen durch den Einsatz einer selektiven Entfernung von kariösem Gewebe und, bei Exposition der Pulpa, eine direkte Überkappung mittels MTA war die kostenwirksamste Strategie, weil teure Wiederbehandlungen vermieden werden können.

Klinische Bedeutung: Die Vermeidung einer Pulpaexposition war für die Kostenwirksamkeit relevanter als die Behandlung der exponierten Pulpa. Die aufgezeigten Unterschiede waren jedoch begrenzt groß; Zahnärzte sollte bei der Therapiewahl weitere Aspekte wie ihre eigene Erfahrung und die Patientenerwartungen berücksichtigen.

Maintaining pulpal vitality: Cost-effectiveness analysis on carious tissue removal and direct pulp capping

Abstract

Objectives: Dentists can maintain pulp vitality when treating deep carious lesions by avoiding pulp exposure and complications by performing selective (SE) instead of non-selective (NS) carious tissue removal, and/or direct pulp capping of exposed pulps using mineral-trioxide-aggregate (MTA) instead of calcium hydroxide (CH). The present study examined the cost-effectiveness of SE vs. NS combined with direct pulp capping using MTA vs. CH.

Methods: This study adopted a mixed public/private payer perspective in the context of German healthcare. We modeled a population of initially 30-year old patients with one deeply carious molar and a vital asymptomatic pulp. Carious tissue removal was performed by SE/NS, and in case of pulp exposure, treated via direct pulp capping with either MTA or CH. We used Markov models to follow the tooth over the patients' lifetime, informed by pairwise and Bayesian network meta-analyses and further data sources. The health outcome was time of tooth retention. Costs calculations were based on fee-items catalogues of public and private German insurance, combined with microcosting. We performed Monte-Carlo microsimulation and parameter uncertainty introduced via probabilistic and univariate sensitivity analyses. We also assessed the benefit of further research by performing a Value-of-information-analysis (VOI).

Results: SE and, in case of pulp exposure, MTA was the most cost-effective option (>95%), retaining teeth for 37.37 years at costs of 2140 Euro in mean. Other treatments were found to be more costly and less effective; this ranking was robust in sensitivity analyses. The VOI was relatively low at 1.18 Euro per treated case, and the population level VOI was considerable at 12.86 million Euro.

Conclusion: Management of deep carious lesions by selective carious tissue removal and, in case of pulp exposure, direct capping with MTA was the most cost-effective treatment, since expensive retreatments were avoided.

Clinical significance: Avoidance of pulp exposure with SE was more relevant for cost-effectiveness than how the exposed pulp was treated. In general, differences in cost-effectiveness remain limited; however, dentists may need to customize the suitable treatment plan for each individual patient according to their clinical experience and patients' needs. *"Abstract reference [1]".*

Introduction

Deep caries lesions usually induce inflammatory reactions in the pulp which require in many instances invasive treatments such as root canal treatments in adults [2]. During excavation of deep caries, the dentin barrier might be broken due to pulp exposure which results in impairment of pulp healing. The traditional technique in the treatment of teeth presenting deep caries lesions involves the non-selective (NS) removal of the carious tissue; a procedure that commonly results in pulp exposure [3-5].

Direct pulp capping is the most common treatment used if the pulp is exposed, which entails placing a medicament, traditionally calcium hydroxide (CH), directly over the exposed pulp to prevent irreversible pulp damage. However, in a retrospective study evaluating the treatment outcomes of pulp-capped teeth, 79.7% of the teeth exhibited necrosis and required root canal treatment or extraction after 10 years [6]. Furthermore, a randomized clinical trial evaluating direct pulp capping using CH performed on teeth with deep caries reported a success of only 31.8% after 1 year [7].

In case of failure of direct pulp capping, i.e. pain, necrosis or development of apical pathosis, the only possible line of treatment to avoid tooth extraction is to perform root canal treatment followed by crown placement. Although root canal treated teeth can survive for more than 10 years [8, 9], the associated endodontic procedures are complex, time consuming, and costly. In low and middle-income countries that offer limited insurance coverage for dental procedures, many patients have to pay out of their own pockets for such treatments. Taking into account the poor prognosis of CH-based direct pulp capping and the high cost of root canal treatment, a more conservative and cost-effective excavation approach for managing deep caries lesions has been sought.

Considering the pathogenesis of caries and the ecological interactions in dental biofilms, NS might not be necessary, since re-shifting the ecologic and metabolic balance within the biofilm promotes its cariogenic activity to cease and the lesion to arrest [10]. In selective (SE) carious tissue removal, this principle is actively used, with carious dentin in close proximity to the pulp being sealed beneath a definitive restoration, with an adequate seal leading to bacterial inactivation and arrest of the lesion [11, 12]. SE has been shown to avoid pulp exposure compared over NS, and recent evidence indicates that sealing a limited amount of carious dentin beneath restorations does not compromise pulp vitality or restoration survival [13-16]. SE has been shown to be more cost-effective than NS, if any pulp exposures are managed conservatively using CH, as described, with teeth being retained longer and at lower costs after SE than NS [17].

Notably, it has been argued that this inferiority of NS followed by possible direct capping of exposed pulps might be grounded in the capping material [18, 19]. For decades, CH has been the gold standard material for direct pulp capping due to its antibacterial effects and ability to induce dentin bridge formation following pulp exposure [20]. However, it presents some disadvantages such as lack of satisfactory sealing due to poor adherence to dentin, dissolution over time [21], and numerous tunnel defects in the formed dentin bridges [22]. As has been emphasized in previous studies, the presence of bacteria plays a significant role in inhibiting healing of pulp exposures and delay or failure of dentin bridging [23-25]. Unfortunately, the presence of tunnel defects in the formed dentin bridges under CH can act as pathways for microleakage which might prevent the clinical hermetic seal needed for pulpal healing [26]. Moreover, calcium hydroxide is highly soluble in oral fluids and it washes out after 6 months, leaving a void beneath the restoration which eventually results in leakage of microbes and recurring bacterial infections [22].

In contrast, mineral trioxide aggregate (MTA) has been suggested as an alternative, which is composed of calcium oxide in the form of tricalcium silicate, dicalcium silicate and tricalcium aluminate, and bismuth oxide being added as a radiopacifier agent [27]. MTA exerts antibacterial effects via CH release, while being relatively stable, thus providing better seal [28]. In addition, MTA promotes formation of higher quality dentin bridge with less severe pulpal inflammation than that induced by CH [29]. The histological examination of exposed pulps capped with MTA revealed that the pulpal tissue reaction to MTA is more favorable than CH in terms of hyperemia, inflammatory response and pulpal necrosis [30, 31]. The hard tissue-forming ability of MTA has been shown to be higher than CH, since MTA induces the formation of greater amount of reparative dentin, with a superior structural integrity [32], and at a faster rate [33]. Moreover, it has been reported that MTA can stimulate rapid cell growth [34] and release of certain cytokines in human osteoblasts in vitro, which allows for better adherence of cells to the material and may play an important role in reparative dentin formation [35].

A practice based randomized clinical trial by Hilton et al [36] showed superior success of direct pulp capping using MTA (80.3%) compared with CH (68.5%) after

2-year follow-up. Moreover, a retrospective study evaluating the clinical long-term success of direct pulp capping for both MTA and CH pointed to higher success rates in teeth capped with MTA (78%) compared to CH (60%) at 80 months follow-up [37]. Overall, there is agreement that MTA is more effective than CH for direct pulp capping [38].

However, it should be noted that material costs of MTA are significantly higher than those for CH, and its application requires more time and skilled handling. However, since the need for re-treatments or more costly interventions is decreased with MTA, this might have considerable impact on the cost-effectiveness of the treatment.

Aim and significance of study

As described, certain treatments such as NS might result in transition to more costly interventions. Besides, the cost of CH is initially far less expensive than MTA; however, additional follow-up visits are needed after its use as a capping material, which possibly increases the overall costs. Accordingly, establishing cost-effectiveness might help in effective clinical decision making and influence future decisions of payers towards incentivizing certain therapies. Although, cost-effectiveness of SE versus NS, and MTA versus CH has been previously compared in separate studies [16, 17, 19], so far, no studies have compared the combination of SE/NS and MTA/CH. Therefore, the present study aimed to assess the cost-effectiveness of SE vs. NS for treating deep caries lesions and, in case of pulp exposure, direct pulp capping using MTA vs. CH, in a nested health economic analysis.

Additionally, we aimed to evaluate the value of having better information on the effectiveness of different types of treatments by applying a value-of-information (VOI) analysis. VOI quantifies the benefit of undertaking research and determines whether future studies are potentially worthwhile and of value to assume. Therefore, the findings of this study are important for payers, dentists, patients and healthcare researchers, since they might be helpful in developing the ideal treatment plan, selection of the most appropriate materials and in guiding future research.

Methods

Reporting of this study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [39].

Population, settings and comparisons

The statutory health insurance in Germany occupies a leading position in the healthcare system. The vast majority of the German population is publicly insured, where a wide range of dental care services is fully covered. Few services have to be paid by the patient out of pocket or by his or her private insurer. In consequence, this study adopted a mixed public-private payer perspective in the context of German healthcare. A model based approach was employed to evaluate the long term outcomes of initial treatments on both costs and effectiveness.

We chose to model a population of initially 30-year old male individuals with one deeply carious molar with a vital asymptomatic pulp with no signs of necrosis, treated with different carious tissue removal strategies (SE vs. NS), and in case of pulp exposure, treated with direct pulp capping using MTA vs. CH. The molar was followed over the patients' average lifetime (TreeAge Pro 2013; TreeAge Software, Williamstown, MA, USA), however, patients' age was varied in a sensitivity analysis (simulating a patient aged 45 years). It should be noted that cost-effectiveness assessments were performed per one molar to avoid clustering and enhance the interpretation of our findings.

In the present study, a nested cost-effectiveness comparison was performed involving two sets of comparisons. The first comparison was attempted to compare the strategies of carious tissue removal, i.e. SE vs. NS, while the second comparison was between pulp capping materials used in case of pulp exposure (MTA vs. CH). Following carious tissue removal or direct pulp capping, it was assumed that all molars were directly restored with a 3-surfaced composite resin restoration.

Simulation modeling and assumptions

In this study a Markov simulation model was used. The constructed model is shown in Figure 1. It should be mentioned that the model was constructed according to routine clinical sequences and published data in the literature [40]. Model validation was performed internally by varying key parameters to check their impact on the results, evaluating different model structures and performing sensitivity analysis. In this model, the molar was followed starting from the initial treatment, i.e. removal of carious tissue, passing through the possible clinical consequences which involve restorative and endodontic complications, ending with tooth loss and possible tooth replacement using implant-supported crown (ISC).

Simulation was performed in discrete annual cycles. Owing to the large number of modeled cycles, no half-life correction was applied, since we did not expect that this might have a significant effect. The probabilities of teeth transitioning from one health state to another, i.e. risks of complications and possible re-interventions, are summarized in Table 1. Each transition was performed by traversing treatment states; thereby introducing treatment cost.

As described, the tooth was at risk for restorative and endodontic complications. Restorative complications were mended by restoration renewal, crown re-cementation or crown replacement. Replacement of restoration was assumed to be possible once; afterwards, we assumed a crown placement. Endodontic complications (excluding pulp exposures capped by MTA or CH) are assumed to be addressed by primary root-canal treatment and placement of a crown. In case of failure of the initial endodontic therapy, non-surgical root canal re-treatment was assumed. In case of further complications, surgical root canal re-treatment and tooth extraction were considered. In the base-case scenario, tooth replacement by an implant and ISC was assumed. However, taking into account that tooth replacement will not be always provided, no replacement was assumed in a sensitivity analysis. Since biologic or technical complications might develop after the placement of implant and ISC, the need for peri-implantitis therapy and crown re-cementation or renewal were also assumed.

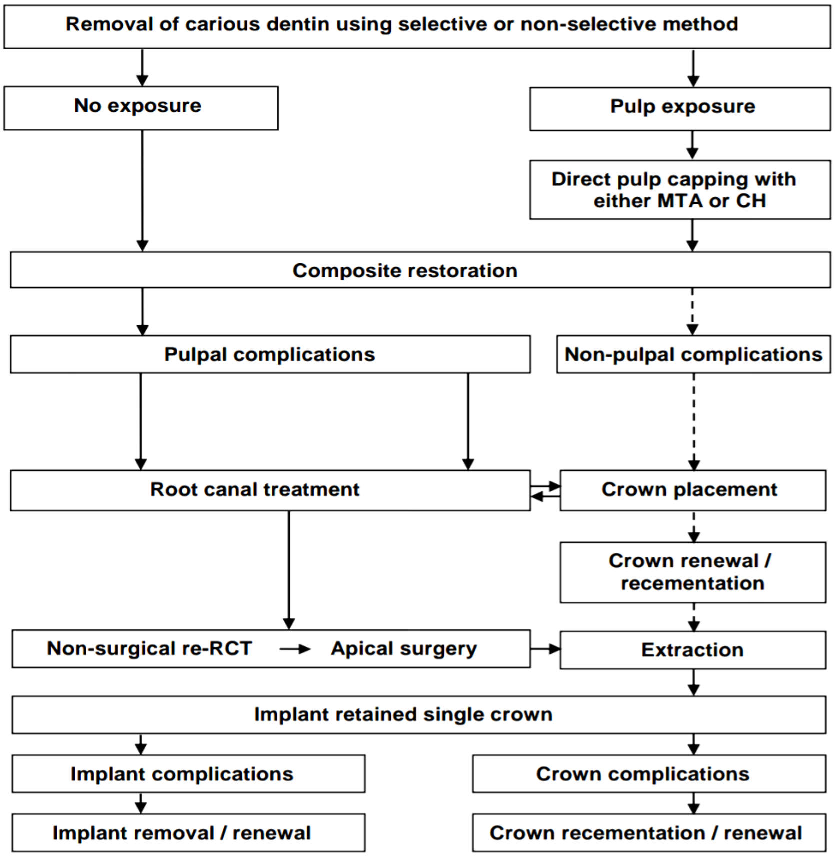

Figure 1: State transition diagram. A deeply carious molar was modeled and treated by selective or non selective carious tissue removal, and in case of pulp exposure, the exposed pulp capped by either MTA or CH. Solid arrows indicate pulpal complications while dotted arrows indicate non-pulpal complications. The sequence of interventions and the need for re-treatments are based on the transition probabilities described in Table 1. *"Figure taken from reference [1], reuse permitted by the journal".*

Table 1: Transition probabilities used within the model. *"Table taken from reference [1], reuse permitted by the journal".*

Probability of	Reference	Transition probability per cycle (year)	Min./max.	Allocation to	Allocation probability
Pulp exposure in NS	Appendix	0.35	0;0.40	Direct pulp capping	0.95
				Root-canal treatment	0.05
Relative risk of pulp exposure when using SE	Appendix	0.13	0.03;0.53	-	-
Pulpal complications after NS	Appendix	0.04	0;0.13	Root-canal treatment	1.00
Relative risk of pulpal complications after SE	Appendix	0.73	0.25;2.6	-	-
Non-pulpal complications after NS	[41]	0.013	0.01;0.016	Crown	1.00
Relative risk of non-pulpal complications after SE	Appendix	0.86	0.17;4.5	-	-
Pulpal complications after direct pulp capping using CH	Appendix	0.13	0.03;0.31	Root-canal treatment	1.00
Relative risk of pulpal complications when using MTA	Appendix	0.47	0.31;0.69	-	-
Non-pulpal complications after direct capping with CH	[41]	0.013	0.01;0.016	Crown	1.00
Relative risk when using MTA	Appendix	0.94	0.19;4.71	-	-
Root-canal treatment	[42]	0.05	0.04;0.06	Non-surgical re-RCT	0.05
				Surgical retreatment	0.45
				Extraction	0.50
Crown	[43]	0.015	0.013;0.016	Recementation	0.50
				Re-new	0.25
				Extraction	0.25
Non-surgical re-RCT	[44]	0.059	0.02;0.12	Surgical re-RCT	0.80
				Extraction	0.20
Surgical re-RCT	[45]	0.057	0.028;0.060	Extraction	1.00
Peri-implantitis	[46]	0.012	0.008;0.014	Peri-implantitis therapy	1.00
Implant crown failure or loss	[47]	0.047	0.028;0.085	Renewal	0.40
				Recement	0.60

Search strategy and study selection

We conducted two independent systematic reviews, with two separate electronic searches being carried out in Medline via PubMed to identify eligible studies published in English. The first search was performed to retrieve original studies comparing SE vs. NS carious tissue removal of deep caries lesions extending more than half the dentin thickness and requiring a restoration. It should be highlighted that we additionally included studies involving stepwise carious tissue removal (where cavity re-entry is needed in a second visit) to provide a more reliable comparison, since this was a common comparator in some studies. The second search was carried out to identify original studies comparing MTA versus CH, as direct pulp capping materials being used in case of pulp exposure during carious tissue removal.

We included randomized controlled studies performed on healthy permanent teeth, comparing at least two of the described treatments against each other. For a study to be included, it should report data on clinical and/or radiographic success or failure of treatments, in regards to pulpal and non-pulpal (restorative) complications. For randomized trials with multiple follow-up periods, data extraction was based on the longest follow-up reported. Two reviewers (FS, RE) examined the titles and abstracts in accordance with the predefined inclusion and exclusion criteria. Any disagreements were discussed by the two reviewers until consensus was reached. Then these reviewers examined the full text of all articles considered as relevant or possibly relevant. The search flow is illustrated in the appendix (Figures S1, S2). Details of the inclusion criteria and excluded studies with reasons for exclusion are given in the appendix (Tables S1-S3).

Outcomes

For the first comparison (SE vs. NS), we assessed the risk of pulp exposure during removal of carious tissue, pulpal complications (if the pulp had not been exposed during carious tissue removal) and non-pulpal (restorative) complications. Pulpal complications that might develop after treatment include post-operative pulpal symptoms demanding further intervention, i.e. clinical or radiographic pulp symptoms indicating irreversible pulp damage or pulp necrosis. Non-pulpal or restorative complications include formation of secondary caries, loss of restoration, or tooth fracture. For the second comparison (MTA vs. CH), the risk of pulpal complications was compared, such as signs of pulpitis, loss of pulp vitality, need for endodontic treatment. Also, the risk of non-pulpal (restorative) complications has been compared, i.e. loss of restoration, need for restoration replacement etc..

Effectiveness data

The first review (SE vs. NS) included 9 studies with mean follow-up 2.4 years (appendix Tables S4, S5). For the second review (MTA vs. CH), 5 studies with mean follow-up 2.6 years were included (appendix Tables S6, S7). Risk of bias assessment was performed and found unclear or high for most studies (more details are shown in appendix Tables S8, S9) mostly as operator blinding was not performed (which is not suitable here), but also as allocation concealment was usually unclear.

As risks of restorative complications are frequently thought to be higher with SE than with NS, and considering lack of long-term treatment outcomes, we performed a sensitivity analysis to investigate the effect of increasing the restorative risks on cost-effectiveness following SE vs. NS by the factor three. To provide comparative effectiveness estimates, pairwise and network meta-analyses (NMA) were performed. It should be mentioned that we did not consider clustering due to multiple teeth that being treated in the same patient, since such clustering was nearly absent. Pairwise random-effects and Bayesian random-effects modeling and Markov Chain Monte Carlo simulations using JAGS implemented in the R package *gemtc* 0.8-2 [48] were performed. Mean and median RR and their 95% confidence and credible intervals (95% CrI) were reported for pairwise and NMA, respectively. CrI are the range of estimated parameters after exclusion of extreme values [49].

The effectiveness of the treatments compared in NMA were as well assessed by using SUCRA values [50, 51]. Given that NMA is subjected to distortions in case of lacking transitivity, it was also assessed by comparing distribution of key parameters across the different pairwise comparisons of the network meta-analysis (more details on transitivity assessment are available in appendix Table S10). No statistical inconsistency was observed in NMA, and we also detected little evidence of significant violations of transitivity. Further details on the meta-analyses, including forest plots, node split results and SUCRA-values are shown in the appendix (Figures S3-S13). The probabilities of restorative and endodontic complications as well as complications of ISCs, i.e. technical and biological problems, were based on insurance claims data from the statutory German health insurance, existing cost-effectiveness studies or systematic reviews [17, 40, 52]. In case of restoration failure, we assumed that a restoration is only replaced once. In addition, we assumed that a crown should be placed following root canal treatment, which is considered a common procedure in Germany for restoring endodontically treated teeth.

Measurement of effectiveness

The health outcome (effectiveness) was tooth retention years, i.e. the mean time a tooth was retained in a patient's mouth in years, which is considered a common measure for effectiveness in dental health economics. Effectiveness was based on the used model, with teeth transitioning from one health state to another (i.e. risks of complications following initial therapy) depending on the transition probabilities previously explained, until they are extracted at the end (whether replaced or not).

Costs, currency, and discounting

The cost calculations were based on the German public and private dental fee catalogues, Bewertungsmaßstab (BEMA) and Gebührenordnung für Zahnärzte (GOZ). In Germany, the fees of the majority of provided dental services are derived from the public catalogue BEMA. However, the costs of certain treatments i.e. composite restorations in posterior teeth, implants and ISC, are estimated using fee items from the private catalogue GOZ. In this case, patients covered by public health insurance are requested to provide additional coverage or take care of the whole bill at their own expense. For private dental treatment in Germany, basic item-points are usually multiplied with a factor to determine fees. The present study used the standard multiplication factor (x2.3). Detailed calculations of costs per course of treatment are given in the Appendix (Table S12).

Given that material costs between MTA and CH are significantly different and that time required for their application differs, a micro-costing approach was useful. Data from previous study which had used a micro-costing approach [19] was used to assign costs for direct capping with MTA vs. CH.

We calculated all costs in Euro. Future costs were discounted at 3% per annum [53]. The process of discounting determines the chances forgone if spending money now instead of later or obtaining health advantages later instead of now. We did not account for opportunity costs such as patient’s lost work time, time spent in the dental chair, or individuals requiring more follow-up treatments. Discount rates were varied to investigate the influence of higher or lower discounting.

Analytical methods

Monte-Carlo microsimulations were performed for the analysis, with 1000 independent individuals (molars) being followed over their average expected lifetime. Costs and effectiveness for different strategies were assessed. Strategies were ranked according to their costs, and incremental-cost-effectiveness ratios (ICERs) were used to express cost differences per gained or lost effectiveness when comparing the least costly with the most effective treatment. Positive ICERs refer to additional costs per additional effectiveness, (such a strategy is considered to be undominated) while negative ICERs indicate higher costs per effectiveness loss (such strategy is considered to be dominated by the alternative).

To introduce parameter uncertainty, we sampled transition probabilities randomly from triangular distributions of parameters between the calculated 95% CI or ranges of parameters [54]. Samples were drawn 1000 times. Using estimates for costs (c, in Euro) and effectiveness (e, in years), the net benefit of each strategy combination was calculated using the following formula: net benefit = $\lambda \times \Delta e - \Delta c$, with λ denoting the ceiling threshold value of willingness to pay (i.e., the additional costs a decision maker is willing to sacrifice for gaining an additional unit of effectiveness) [55]. If $\lambda > \Delta c/\Delta e$, an alternative intervention is considered more cost-effective than the comparator despite possibly being more costly [54]. The net benefit approach was used to estimate the probability of a strategy being cost-effective for payers with different willingness-to-pay ceiling thresholds.

In addition, we estimated the VOI, being a helpful tool to direct future research efforts to where it can attain the highest expected return for finite funding [56]. The VOI of the uncertainty around the studied effectiveness parameters SE vs. NS, and MTA vs. CH was assessed. The willingness-to-pay threshold was assumed to be 0 Euro, as no threshold has been specified for Germany and for this study, and that from the payer's perspective, this threshold appears to be reasonable. Moreover, we also estimated the population level economic savings of payers when having optimum data, as the VOI is assessed per treated case/restoration. To carry out this, we assumed that a particular share from the 49.671 million restorations placed within the statutory insurance in 2018 in Germany, would be placed for teeth with deep caries lesions. To assume that proportion, we relied on previously published data from Sweden [57], where this percentage was assumed to be at least 22% (10.928 million restorations). To provide population level VOI, the number of restorations was multiplied by the VOI.

Results

Estimated effectiveness parameters, risks, and costs of different procedures can be found in Tables 1 and 2. The probability of pulp exposure in SE was significantly lower than that in NS. Also, SE showed lower risk of pulpal complications compared to NS. The use of MTA yielded lower risk of pulpal complications compared to CH. There were limited differences between comparators in regards to non-pulpal (restorative) complications. No difference was found in terms of initial costs between SE and NS, however, were higher for MTA than CH. Further details on costs calculations are given in the Appendix (Table S12). ICERs and cost-effective rankings are shown in Table 3. Figure 2 shows the cost-effectiveness plane.

In our base case, SE and, in case of pulp exposure, MTA was the most cost-effective option, retaining teeth for 37.37 years at costs of 2141 Euro in mean. SE+MTA was found to be more effective and less costly compared with other treatments. Even so, the differences in cost effectiveness were considered limited in general. SE+MTA had the higher probability of being cost-effective than other strategies (>95%), at a willingness-to-pay ceiling threshold of 0 Euro. With increasing willingness-to-pay, the cost differences became of less importance and the chance of being cost-effective is somewhat reduced.

The high possibility of SE+MTA being the most cost-effective strategy was also shown in the VOI, which was relatively low at 1.18 Euro per treated case at willingness-to-pay of 0 Euro. The population level VOI was still considerable at 12.86 million Euro per year, since management of deep caries lesions was assumed to be one of the most common procedures in dental practice.

The effects of parameter uncertainty and heterogeneity on cost-effectiveness were explored using a number of sensitivity analyses (Table 3). Costs were reduced by more than half when assuming that extracted teeth were not to be replaced by implants; even so effectiveness was unaffected since our health outcome was tooth retention years. The ranking of cost-effectiveness was not significantly affected by varying patients' age, with commonly reduced costs and effectiveness. Cost-effectiveness was very slightly influenced by increasing the risk of restorative complications after SE, but not NS, with no pronounced effect on ranking. Cost-effectiveness ranking was not altered by variation of the discount rates.

Table 2: Costs per course of treatment. Details can be found in the appendix. *"Table taken from reference [1], reuse permitted by the journal".*

Course of treatment	Costs (Euro)	Source
Composite[1]	148.15	[58]
Direct pulp capping CH and composite	154.45	[19]
Direct pulp capping MTA and composite	187.59	[19]
Root-canal treatment[2]	347.55	[58]
Full-metal crown	365.27	[58]
Re-cementation of a crown	64.05	[58]
Orthograde re-RCT[2]	592.00	[58]
Apical surgery	179.55	[58]
Tooth/implant removal	76.65	[58]
Implant insertion	958.68	[59]
Implant-supported crown	866.55	[59]
Peri-implantitis treatment	41.73	[60]

[1]Assuming 3 surfaces

[2]Assuming 3 root canals *per* tooth

Table3: Cost-effectiveness and sensitivity analyses. *"Table taken from reference [1], reuse permitted by the journal".*

Scenario	**Carious tissue removal**	**Direct capping material**	**Mean costs (Euro)**	**Mean effectiveness (years)**	**Mean ICER (∆€/∆years)**
Base-case scenario	SE	CH	2155.12	37.22	-94.66
	NS	CH	2245.66	36.29	-96.98
	SE	**MTA**	**2140.92**	**37.37**	**Ref.**
	NS	MTA	2176.42	37.24	-273.07
No tooth replaced after extraction	SE	CH	937.55	37.22	-0.60
	NS	CH	977.18	36.29	-36.77
	SE	**MTA**	**937.46**	**37.37**	**Ref.**
	NS	MTA	971.28	37.24	-260.15
Restorative risk in SE increased by 3-times	SE	CH	2178.63	37.21	-124.28
	NS	CH	2245.66	36.29	-79.65
	SE	**MTA**	**2161.23**	**37.35**	**Ref.**
	NS	MTA	2176.42	37.24	-138.09
Patient’s age 45 years	SE	CH	1719.24	32.21	-121.07
	NS	CH	1834.58	31.56	-167.45
	SE	**MTA**	**1702.29**	**32.35**	**Ref.**
	NS	MTA	1750.18	32.28	-684.14
1% annual discount rate	SE	CH	2157.31	37.24	-103.52
	NS	CH	2246.41	36.31	-97.11
	SE	**MTA**	**2137.64**	**37.43**	**Ref.**
	NS	MTA	2169.25	37.30	-243.15
5% annual discount rate	SE	CH	2125.97	37.16	-119.00
	NS	CH	2235.04	36.20	-114.30
	SE	**MTA**	**2109.31**	**37.30**	**Ref.**
	NS	MTA	2155.59	37.17	-356.00

The least costly strategy was indicated in **bold**. Incremental cost-effectiveness ratio (ICER) indicates the cost difference per effectiveness difference between strategies. Strategies were found either dominated (more costly and less effective) or undominated (more costly and more effective). Positive values indicate additional money being spent per year of tooth retention, while negative values indicate additional costs per decreased effectiveness. Base-case and sensitivity scenario analyses were performed. Sensitivity analyses evaluated how varying patients' age, replacement ratios for missing teeth, and different discounting rates affected the cost-effectiveness.

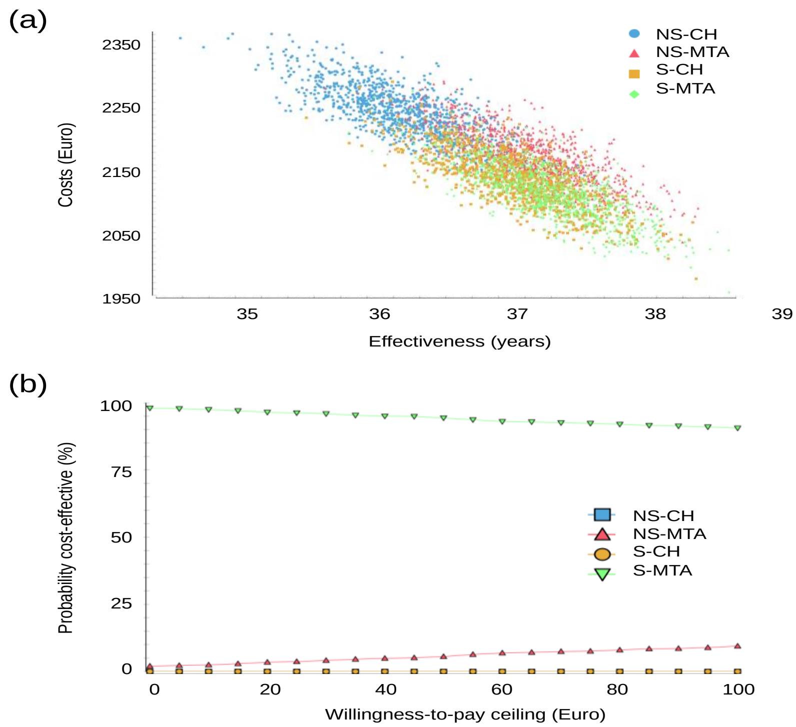

Figure 2: Cost-effectiveness of carious tissue removal strategies combined with direct pulp capping using MTA or CH. (a) Costs and effectiveness of different treatments were plotted. Horizontal and vertical axes represent effectiveness (retention time of the tooth) and costs of treatment (in Euro), respectively. Selective carious tissue removal and, in case of pulp exposure, direct pulp capping with MTA, was the most cost-effective strategy. Alternative strategies were both more costly and less effective. (b) The probability of a strategy being acceptable regarding its cost effectiveness was plotted against willingness to pay ceiling values (in Euro). SE+MTA had the highest probability of being cost-effective compared with other strategies (> 95%) at a willingness-to-pay ceiling threshold of 0 Euro. *"Figure taken from reference [1], reuse permitted by the journal".*

Discussion

Management of deep caries lesions in close proximity to the pulp exhibits an important challenge to dental practitioners. Traditionally, treatment of deep caries necessitates the total elimination of the caries lesion in an attempt to arrest caries progression and to create a caries-free environment beneath the restoration thereafter. NS carious tissue removal followed by a restoration is usually associated by immediate or long-term unfavorable complications, that require re-treatment involving invasive dental hard tissue removal, which might result in tooth de-vitalization or tooth loss [61].

Alternative approaches such as stepwise excavation and SE carious tissue removal have been suggested to protect the pulp and decrease the possible complications of NS carious tissue removal [3, 14, 62]. Caries removal in stepwise technique is carried out in two visits. In the first visit, carious dentin is incompletely removed, where caries in proximity to the pulp is sealed under a temporary restoration; in the second visit (some months later), cavity re-opening is performed to remove the remaining carious tissue followed by placement of a definitive restoration.

The main idea behind stepwise excavation is that, by the second visit, all residual bacteria will have died, remaining carious dentin (both affected and infected) will have been remineralized, and reparative dentin will have been formed, which enhances easy removal of residual carious dentin [3]. However, despite the fact that stepwise excavation enhances the maintenance of pulp vitality by reducing the risk of pulp exposure, it still bears a remaining risk of pulp exposure during the final excavation step [62, 63]. In addition, failure to provide an adequate cavity seal, i.e. loss of temporary restoration before the second visit, might result in progression of cariogenic activity and failure of the treatment [62].

SE carious tissue removal entails that soft carious tissue toward the pulpal aspect of the cavity should be left behind and sealed under a definitive restoration, with no need to re-open the cavity in a second visit [64]. Growing evidences support the use of SE technique in management of deep caries lesions, since it decreases the risk of pulpal exposure and post-operative pulpal complications in comparison with NS carious tissue removal [14, 65]. In addition, SE carious tissue removal offers significant time saving to both dentists and patients, since the whole procedure is performed in one visit.

Regarding the clinical performance of restorations, it is well established that providing an adequate marginal seal between the restoration and tooth surface plays an important role in long-term survival of restorations and prevention of microleakage. However, leaving carious dentin in place might cause dentin shrinkage and possible impairment of the coronal restoration, which could result in the development of pulpal complications [66]. Also, it remains unclear whether the soft carious dentin left behind could increase the risk of non-pulpal complications. An in vitro study investigating the fracture strength of teeth with deep caries lesions following complete and incomplete excavation [67] showed that fracture strength of incompletely excavated teeth was significantly decreased in comparison with teeth assigned to complete excavation. Contrarily, another study analyzing the fracture resistance and cuspal deflection of extracted premolars after incomplete excavation [68] reported that leaving demineralized dentin was not found to affect the fracture resistance of incompletely excavated teeth. Moreover, the results of long-term clinical studies in which restorations were followed-up over a 10-year period indicated that leaving a residual layer of carious dentin beneath the restoration did not seem to impair the integrity of restorations in shallow cavities [69] or even in deeply cavitated lesions [12].

However, despite increasing calls for more conservative treatments, NS carious tissue removal, with its higher risk of pulp exposure, might still be a valid option in management of deep caries lesions, considering the careful management of the exposed pulp and selection of the suitable capping material [70-72]. Therefore, it seems that there is lack of consensus concerning the suitability of the abovementioned techniques for treatment of deep caries lesions and on which strategy has the best prognosis in maintaining pulp vitality.

Occurrence of pulp exposure during excavation of deep caries might be inevitable in some instances, even with the use of less invasive treatment strategies. Following pulp exposure, treatment options include direct pulp capping, pulpotomy or pulpectomy [73]. Although, it is restricted to very specific cases with certain indications, direct pulp capping is undoubtedly one of the most conservative treatments in maintaining the vitality of permanent teeth in which pulp tissue has been exposed, as an alternative to root canal treatment or extraction. Clinicians usually pay extra attention to preserve pulp integrity in cariously exposed immature permanent teeth to avoid more complicated treatments with unpredictable outcomes. This is mainly due to difficulty in cleaning and obturating root canals with open apices, and high susceptibility to future vertical root fracture caused by thin divergent or parallel dentinal walls [74, 75]. Therefore, maintenance of pulp vitality at different stages of root development by direct pulp capping is of prime importance to avoid early tooth loss. Direct pulp capping is best performed in teeth diagnosed with pulp status no more severe than reversible pulpitis, normal apical tissues, pulp exposure less than 1 mm and control of pulpal hemorrhage [76]. It should be highlighted that the true state of pulp health cannot be determined by clinical signs and symptoms [21], nevertheless, success of direct pulp capping depends mainly on careful management of the exposed pulp.

Apart from accurate clinical assessment of pulp condition and proper handling of the exposed pulp tissue, type of capping material might be another influencing factor affecting the potential prognosis of pulp capped teeth [18]. The ideal material for direct pulp capping should be able to provide a bacteria-tight seal, prevent irreversible damage of pulp tissue and induce reparative dentin formation [32]. Unlike CH, MTA seems to be the ideal material for achieving these objectives, with significantly decreased risk of failure [38]. A nine-year observational study investigating the long-term treatment outcomes of direct pulp capping using MTA reported success rate exceeding 97%, based on clinical and radiographic follow-up examinations [77].

Dental care differs from other health services in terms of cost-related barriers, since out-of-pockets payments might be necessary in some cases to receive treatments beyond routine dental services. Therefore, possible reduction of treatment cost might increase the patients' compliance, which could in turn aid in improving the efficiency of dental services [78]. It is clearly evident that the recent advances in dental care have led to more accurate diagnosis and better treatments, but have also increased the healthcare cost accordingly, i.e. using dental operating microscope, use of MTA instead of CH, placement of implants instead of dental bridges, etc. Therefore, both dentists and patients today have had to make medical decisions involving dental treatments, typically with limited healthcare resources and confined objective data on cost effectiveness of best practice. To fill the gap in knowledge, our cost-effectiveness analyses aimed at comparing the combination of SE/NS and MTA/CH.

In the present study, effectiveness has been measured as the retention time of a tooth. Tooth retention is considered an important parameter, which could determine if further possible interventions, with subsequent complications and costs can be delayed or avoided [79, 80]. Our results indicated that avoidance of pulp exposure with SE was more relevant for cost-effectiveness than how effective the exposed pulp was managed by using MTA instead of CH. In addition, we found that SE is less costly than NS, and in case of pulp exposure, MTA was more cost effective than CH for direct pulp capping, retaining teeth and their vitality for longer period of time.

The most reasonable explanation for the high cost effectiveness of SE vs. NS is that SE is known to prevent pulp exposure [81], thus preventing subsequent more costly re-interventions. On the other hand, it should be mentioned that we found no pronounced differences between SE and NS in regard to non-pulpal (restorative) complications. We also conducted sensitivity analyses and found that the strategy ranking was not affected by extreme increases in risks of restorative complications following SE vs. NS. Furthermore, the risk of complications following the application of MTA for direct pulp capping was lowered to half compared to CH. This favorable outcome could considerably reduce the possibility of pulp necrosis and the need for more expensive treatments, i.e. root canal treatment, or need for implant placement in case of tooth loss. It should be highlighted that this study focused on MTA, being the most common alternative to CH. However, there are several other tricalcium silicate-based cements available in the market today with variable prices, such as Biodentine, Bioaggregate, TheraCal, etc. For example, Biodentine has presented clinical success rates comparable to that of MTA [82, 83], while being sold at a lower price. Therefore the cost effectiveness of the whole treatment might vary if a less expensive calcium silicate material is used.

Although SE+MTA was the most cost-effective strategy, differences in cost-effectiveness were limited. However, we assessed cost-effectiveness-acceptability which verified that SE+MTA had a >95% probability of being the most cost-effective treatment. Interestingly, we found that the VOI was considerable at around 13 million Euro per year, and future studies comparing SE vs. NS and MTA vs. CH might be beneficial. Research funders may find such analyses useful to categorize research proposals in terms of the expected economic benefits. It should be highlighted that our investigations were based on data derived from clinical trials with randomly allocated interventions, which are known to accurately assess cause-effect relationship between a treatment and outcome, thus improving the validity of our findings. However, our results cannot be passed on to primary teeth since they necessitate various treatment modalities, other than those discussed here, i.e. performing pulpotomy instead of direct pulp capping, placement of stainless steel crown, no need for teeth replacement or use of space maintainer in case of early tooth loss, etc. Finally, it should be pointed out that this study is built on a simulation model that reflects the complex situations seen in practice by assuming possible restorative and endodontic complications following caries removal and pulp exposure. Therefore, variation in treatment planning between dentists might cause alteration in the sequence of clinical events that this study assumes.

Conclusion

Based on German healthcare and within the limitations of this study, we found selective carious tissue removal and, in case of pulp exposure, direct pulp capping with MTA to be the most cost-effective strategy. Alternative strategies were both more costly and less effective. In general, though, differences in cost-effectiveness were limited.

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Statutory Declaration

"I, Ramy Emara, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "Maintaining pulpal vitality: Cost-effectiveness analysis on carious tissue removal and direct pulp capping / Aufrechterhaltung der Vitalität der Pulpa: Kostenwirksamkeits-Analyse zur Entfernung kariösen Gewebes und zur direkten Überkappung der Pulpa", independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

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Declaration of your own contribution to the top-journal publication for a PhD or MD/PhD degree

R. Emara, J. Krois, F. Schwendicke, Maintaining pulpal vitality: Cost-effectiveness analysis on carious tissue removal and direct pulp capping, Journal of Dentistry 96 (2020) 103330.

- Contributing to development and preparation of the manuscript until accepted for publication with support from Professor Dr Falk Schwendicke.
- Conducting literature searches and screening of articles to identify eligible studies.
- Extracting data from relevant studies in order to examine and compare the study findings.
- Contributing to the analysis of data obtained and results interpretation.
- Illustrating the detailed calculations of costs of treatments.
- Contributing to data presentation in tables and figures to describe findings more effectively.
- Calculation of incremental cost-effectiveness ratios in Table 3.
- Calculation of costs per course of treatment in Table 2.
- Own contribution in regard to tables and figures: Tables: S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, S11 and S12. Figures: 1, S1 and S2.
- Responded together with Professor Dr Falk Schwendicke to the reviewers' comments until the paper is published online.

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Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

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10	Clinical Implant Dentistry and Related Research	3,945	3.212	0.008420
11	Molecular Oral Microbiology	889	2.925	0.001800

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Maintaining pulpal vitality: Cost-effectiveness analysis on carious tissue removal and direct pulp capping

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ABSTRACT

Objectives: When managing deep carious lesions, dentists can maintain pulp vitality via (1) avoiding pulp exposure and complications by performing selective (SE) instead of non-selective (NS) carious tissue removal, and/or (2) treat exposed pulps by direct capping with mineral-trioxide-aggregate (MTA) instead of calcium hydroxide (CH). We assessed the cost-effectiveness of SE vs. NS combined with direct pulp capping using MTA vs. CH.

Methods: A mixed public-private-payer perspective within German healthcare was applied. We modeled a permanent molar with a deep carious lesion and a vital asymptomatic pulp. The lesion was treated by SE/NS and, in case of exposure, direct pulp capping using MTA/CH. The tooth was followed over the lifetime of an initially 30-year-old patient using Markov-models, informed by pairwise and Bayesian network meta-analyses and further data sources. The primary health outcome was tooth-retention time. Costs were derived from German fee item catalogues, combined with micro-costing. Monte-Carlo micro-simulation was performed, and uncertainty introduced via probabilistic and univariate sensitivity analyses. Value-of-information-analysis (VOI) was performed to quantify the value of further research.

Results: SE and, in case of pulp exposure, MTA had a high chance (> 95 %) of being cost-effective, with teeth being retained for 37.37 years at costs of 2140 Euro in mean. Alternative strategies were both more costly and less effective; this ranking was robust in sensitivity analyses. The VOI was 1.18 Euro per treated case and 12.86 million Euro on population-level.

Conclusion: Selective carious tissue removal and, in case of pulp exposure, direct capping with MTA was the most cost-effective strategy.

Clinical significance: Avoiding pulp exposure was more relevant for cost-effectiveness than how the exposed pulp was managed. Overall differences remain limited, though, and dentists may want to tailor treatment strategies according to their expertise and patients' expectations.

1. Introduction

When treating deep carious lesions in teeth with vital, asymptomatic pulps, dentists should strive to maintain pulp vitality to increase the chance of retaining the teeth while reducing long-term treatment costs. Selective (SE) carious tissue removal, where residual carious tissue is left in proximity to the pulp and the lesion afterwards sealed using an adhesive restoration, has been propagated for this purpose to reduce the risk of pulp exposure compared with the conventional non-selective (NS) removal [1]. Exposing the pulp has been found detrimental mainly as the common treatment for exposed pulps, direct pulp capping using calcium hydroxide (CH), shows low success rates long-term, with the majority of teeth eventually requiring root-canal treatment due to irreversible pulpitis or pulp necrosis [2,3]. International and national guidance documents have been produced, mainly by scientific societies or groups routed in cariology or conservative dentistry, supporting SE for maintaining pulp vitality [4,5].

In an alternative argumentation, improving the success rates of direct pulp capping, for example when using mineral trioxide aggregate (MTA), may compensate the negative effects of any exposure, mainly as MTA induces an alkali pH (similar to CH) but also tightly and stably seals the exposed area [6–10]. Following such argument, one could perform NS instead of SE and, in case of pulp exposure, provide direct pulp capping using MTA. This argument has been propagated by a recent statement from an endodontic society [11].

Deciding between SE and NS, and MTA and CH, has further

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implications beyond the generated health benefits. Payers, which may be insurers or patients, might be interested in the costs associated with initial and re-treatments. For example, applying NS may lead to more pulps requiring direct pulp capping, with higher costs early on compared with SE. Costs will even be higher when MTA instead of CH is used. On the other hand, long-term pulpal and non-pulpal (restorative) complications may be higher in SE than NS, which may compensate for early cost-savings. There have been cost-effectiveness evaluations comparing SE and NS (using data accumulated until 2014, while a range of studies have been published since), and MTA and CH (using data accumulated until 2015; again, more data is available now) [12–14]. No study compared the combination of SE/NS and MTA/CH.

Dentists, but also payers are interested in learning on the long-term consequences of initial treatment decisions associated with carious tissue removal and direct pulp capping using MTA/CH. We aimed to assess the cost-effectiveness of SE vs. NS and, in case of pulp exposure, direct capping using MTA vs. CH, in a nested health economic analysis. We further aimed to quantify the uncertainty around these cost-effectiveness estimates by applying a value-of-information (VOI) analysis.

2. Methods

A modeling study was performed, which allows to assess the described long-term consequences of initially provided treatments on both costs and effectiveness. Reporting of this study follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [15].

2.1. Setting, perspective, population, horizon

This study adopted a mixed public-private payer perspective, which is characteristic for the German healthcare context. In Germany, the medical insurance is 2-tiered, with most individuals (> 87 %) being publicly insured (statutory insurance) and only a minority being privately insured [16]. The German insurances are mainly financed by insurance contributions. For members of the statutory insurance, nearly all dental procedures are fully covered, while only few need to be partially or fully paid out-of-pocket or by private (additional) insurances.

We modeled a population of initially 30-year old male individuals with one deeply carious molar with a non-symptomatic (i.e., painless) pulp, with normal signs of vitality to sensitivity testing, treated with different carious tissue removal strategies and, in case of pulp exposure during carious tissue removal, treated with direct pulp capping using MTA vs. CH. Modelling was performed using TreeAge Pro 2013 (TreeAge Software, Williamstown, MA, USA). The molar was followed up over the patients' average lifetime, which was determined by his initial age and his sex [17]. Patients' age was varied in a sensitivity analysis. All evaluations were performed per one molar to avoid clustering effects and increase the ease of interpretations of our results.

2.2. Comparators

A nested cost-effectiveness comparison was performed, with our first level comparison being between SE vs. NS, and our second level comparison being between MTA vs. CH for direct capping of exposed pulps. All molars were assumed to receive a 3-surfaced direct restoration using composite after carious tissue removal or direct pulp capping.

2.3. Model and assumption

We used a Markov simulation model, consisting of initial and follow-up health states. Construction of the model (Fig. 1) was performed according to clinical routine, current evidence and previous studies using a similar methodology [18]. The model allowed to follow each tooth from the initial therapy over possible restorative and endodontic complications and treatments up to its extraction and replacement using an implant-supported crown (ISC), if required. The possibility of teeth transitioning to the next health state was based on transition probabilities. For each transition, costs were accrued. Simulation was performed in discrete annual cycles. No half life correction was applied, as we expected only very limited impact of this in view of the decade-long horizon of this study and the high number of modelled cycles.

Restorative complications were assumed to be treated via restoration replacement and/or, in case of crowns, re-cementation. Failing composite restorations were assumed to be replaced with a crown. Endodontic complications (excluding pulp exposure, which was treated as described by capping with MTA or CH) were assumed to be treated via root-canal treatment, followed by the placement of a crown, as would be the standard within German healthcare in most cases. In case of endodontic complications after primary root-canal treatment, non-surgical (orthograde) endodontic re-treatment, surgical endodontic re-treatment (apicectomy) and extraction were considered. For molars which had been re-treated non-surgically, surgical re-treatment and extraction were assumed to be options in case of complications. For extracted molars, the placement of an implant and an ISC was assumed in the base-case scenario. In a sensitivity analysis, no replacement was modeled, as molar replacement will not always be provided [19]. Implants and ISC were assumed to suffer from biologic (e.g. peri-implantitis) or technical complications (like crown de-cementation or crown loss), leading to the need for peri-implantitis therapy as outlined elsewhere [20], crown re-cementation or replacement, respectively. Model validation was performed internally by varying key parameters to check their impact on the results, by evaluating different model structures, and by performing sensitivity analyses.

2.4. Input variables

To estimate the transition probabilities of the comparators, i.e. SE vs. NS, and direct capping with MTA vs. CH, two separate systematic reviews of the literature were performed. Details of inclusion criteria, search strategies and excluded studies can be found in the Appendix (Supplemental Fig. S1 and S2 and supplemental Tables S1-S3). Briefly, trials allocating SE/NS and MTA/CH at random in permanent teeth were included. For the first comparison (SE vs. NS), we additionally included studies on stepwise carious tissue removal, as this was the third and common comparator, yielding a more robust comparison and making better use of the available data (some studies had compared SE vs. stepwise, others NS vs. stepwise, see below). For this comparison, we assessed the risk of pulp exposure, pulpal complications during follow-up (in case the pulp had not been exposed), and non-pulpal (restorative) complications. For the second comparison (MTA vs. CH), we compared the risk of pulpal complications during follow-up, denoted by the absence of signs of irreversible pulpitis or pulp necrosis and a healthy periapical area, and non-pulpal (restorative) complications. Note that data on restorative complications were sparse (mainly given the limited follow-up of the included studies), which is why we relied on reported risks of restorative complications in composite restorations reported elsewhere. As it is often claimed that SE is associated with higher risks of restorative complications compared with NS, but the data of our NMA did not support that, we performed a sensitivity analyses to explore how such increased restorative risk in SE impacted on cost-effectiveness.

For SE vs. NS, 9 studies including a total of 912 participants with a total of 957 teeth (mean follow-up 2.4 years) were included (appendix Fig. S1, Tables S4, S5). For MTA vs. CH, 5 studies including a total of 839 participants with a total of 842 teeth (mean follow up 2.6 years) were included (appendix Fig. S2, Tables S6, S7). Risk of bias was assessed and found unclear or high for most studies (appendix Tables S8, S9), mainly as operator blinding was not performed (which is not feasible here), but also as allocation concealment was usually unclear.

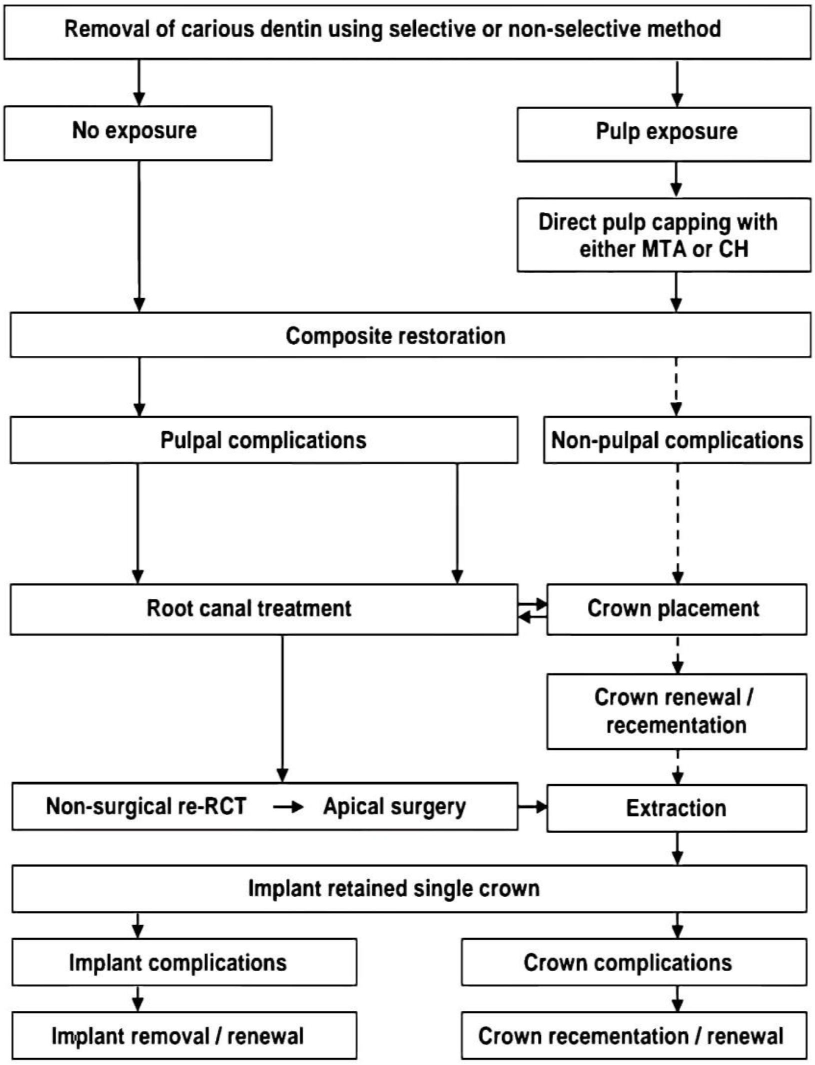

Fig. 1. State transition diagram. We modeled deeply carious teeth, treated with selective or non-selective carious tissue removal and, in case of pulp exposure, treated with direct pulp capping using either MTA or CH. Both pulpal (solid arrows) and non-pulpal (dotted arrows) were modeled. Complications occurred according to transition probabilities (Table 1) and led to treatments, transitioning teeth to another health state. Transition to the next health state accrued cost (Table 2). Pulpal failures were treated by root canal treatment. Pulpal and non-pulpal re-treatments involved non-surgical and surgical re-RCT and crowns. For extracted molars, implant placement was assumed. Implant and crown complications were also modeled.

Pairwise and network meta-analyses (NMA) were performed to yield comparative effectiveness estimates. As clustering was nearly absent, we did not adjust for multiple teeth being treated in the same individuum. Pairwise random-effects and Bayesian random-effects modeling and Markov Chain Monte Carlo simulations using JAGS implemented in the R package *gemtc* 0.8–2 [21] were performed. Mean and median RR and their 95 % confidence and credible intervals (95 % CrI) were reported for pairwise and NMA, respectively. CrI are the range of estimated parameters after exclusion of extreme values [22]. SUCRA values were used to additionally assess the effectiveness of strategies compared in NMA [23,24]. More details on the meta-analyses, including forest plots, node split results and SUCRA-values are displayed in the appendix (Fig. S3-S13). As NMA is known to be prone to distortions in case of lacking transitivity, this was also assessed (appendix Tables S10). We did not detect statistical inconsistency in NMA, and found also only limited indication of significant transitivity violations.

The probabilities for possible transitions in further states were based on insurance claims data from the statutory German health insurance or available cost-effectiveness studies or systematic reviews. Placed restorations were at risk for failure and replacement. Replacement was assumed to be possible once; afterwards, we assumed a crown to be placed. In parallel, the tooth was at risk for endodontic complications, which we also derived from insurance claim data [25]. After root-canal treatment, we assumed a crown to be placed, as would be common for a heavily restored endodontically treated molar in Germany. The risk for complications for crowns (de-cementation or failure, leading to re-cementation, renewal or extraction) had been estimated by previous studies, mainly using systematic reviews. The probabilities of endodontic complications in surgically and non-surgically endodontically retreated teeth as well as technical and biological complications of ISCs were extracted from previous cost-effectiveness analyses [18,26].

2.5. Health outcomes, costs, and discounting

The health outcome (effectiveness) was measured as the time a tooth was retained (in years), based on the applied model, with teeth translating between health stages depending on the described transition probabilities, until they eventually required extraction (with or without replacement). The cost calculations were based on the German public and private dental fee catalogues, Bewertungsmaßstab (BEMA) and Gebührenordnung für Zahnärzte (GOZ), as described in detail elsewhere [26]. German dentists use fee items to claim for reimbursement for dental treatments. As described, for most dental procedures and patients, items will be drawn from the public catalogue BEMA. For few treatments (composite restorations in posterior teeth, implants and ISC), fees are usually derived from the private catalogue, and publicly insured patients top up their public fee amount or pay completely out of their own pocket. Because factoring of the chargeable item points is common to determine the fees of private treatment in Germany, the standard multiplication factor (2.3) was used. Using fee items allowed us to estimate costs occurring to payers, which was in line with our study perspective [14].

To assign costs for direct capping with MTA vs. CH, we additionally relied on a previous study which had used a micro-costing approach [12]. Micro-costing accounts for the value of used resources like material or personnel [27]. Such approach was useful, as material costs are significantly different between MTA and CH, as is the time required for performing the procedure.

Costs were calculated in Euro, and future cost and effectiveness were discounted at 3% per annum [28]. Discounting accounts for time preference, with effectiveness gains or costs being valued higher if they are realized now than later. Discount rates were varied to explore the impact of higher or lower discounting. Given our study's perspective, opportunity costs were not accounted for.

2.6. Analytical methods

Monte-Carlo microsimulations were performed to estimate cost-effectiveness, with a 1000 independent individuals (molars) being followed over their average expected lifetime. Strategies were ranked according to their costs, and incremental-cost-effectiveness ratios (ICERs) used to express cost differences per gain or loss of effectiveness between strategies. A positive ICER indicates additional costs per additional effectiveness (such a strategy is considered to be undominated), while negative ICERs indicate higher costs at lower effectiveness (such strategy is considered to be dominated by the alternative).

Parameter uncertainty was introduced by random sampling of transition probabilities from triangular distributions (with the most likely value being the mean, and minimum and maximum being set at 2.5 % and 97.5 % CI or CrI, respectively) [29]. Samples were drawn 1000 times. Using estimates for costs in Euro (c, in Euro) and effectiveness (e, in years), the following formula was used to calculate the net benefit of each strategy combination:

$$\text{net benefit} = \lambda \times \Delta e - \Delta c,$$

with λ denoting the ceiling threshold value of willingness to pay (i.e., the additional costs a decision maker is willing to sacrifice for gaining an additional unit of effectiveness) [30]. If $\lambda > \Delta c/\Delta e$, an alternative intervention is considered more cost-effective than the comparator despite possibly being more costly [29]. This approach was used to plot the probability of being cost effective against different λ.

We then estimated the VOI. VOI analysis quantifies the costs of making the wrong decision (more money spent than required and/or lower health benefit than optimally possible) due to uncertainty [31,32]; it translates uncertainty into monetary value. If further research reduces or eliminates this uncertainty and allows better resource allocation, it is itself a cost-effective investment. We assessed the VOI of the uncertainty around the effectiveness parameters SE vs. NS, and MTA vs. CH. The VOI builds on the described concept of NMB; for these estimations, we assumed the willingness-to-pay threshold to be 0 Euro. This assumption was (1) needed, as no threshold has been defined for Germany and within the context of the study, and (2) this threshold seems justifiable from a payer's perspective. As the VOI is estimated per treated case/restoration, we further quantified the population level savings of payers when having perfect information. To do so, we assumed that from the 49.671 million restorations placed within the statutory insurance in 2018 in Germany, a certain proportion would be placed for deep carious lesions. Based on data from a study from Sweden [33], we assumed this proportion to be at least 22 %, i.e. 10.928 million restorations. Note that the Swedish study only assessed 14 – 15-years old, but similar findings were found in a Finnish population of 18-years old [34]. It remains unclear if these findings are translatable to 30-year olds or older adults, though. The number of restorations was multiplied with the VOI to yield population level VOI.

3. Results

3.1. Study parameters

The risk of pulp exposure was significantly reduced in SE vs. NS, and SE also yielded lower risk of pulpal complications (Table 1). The risk of pulpal complications was reduced in MTA vs. CH. Non-pulpal (restorative) complications did only limitedly differ between comparators. Initial costs did not differ between SE and NS, but were higher for MTA than CH (Table 2). Further transition probabilities, risks and costs can be found in Tables 1 and 2.

3.2. Cost-effectiveness and VOI

In the base-case scenario, SE and, in case of pulp exposure, MTA was the most cost-effective strategy, with teeth being retained for 37.37 years at costs of 2141 Euro in mean (Table 3, Fig. 2). Compared with other strategies, SE + MTA was more effective and less costly. Overall, though, differences in cost-effectiveness were limited. Nevertheless, SE + MTA had a far higher chance of being cost-effective than comparators (> 95 %) at a willingness-to-pay ceiling threshold of 0 Euro (Fig. 2); the probability of being cost-effective moderately decreased with increasing willingness-to-pay (and cost-differences became less important). The high chance of SE + MTA being most cost-effective was also reflected in the VOI, which was relatively low at 1.18 Euro at a willingness-to-pay of 0 Euro. Given that treatment of deep lesions was assumed to be a common event, the population level VOI was nevertheless considerable at 12.86 million Euro per year.

3.3. Sensitivity analyses

A number of sensitivity analyses were performed to explore parameter uncertainty and heterogeneity (Table 3). Assuming that extracted teeth were not replaced with implants more than halved costs, but effectiveness was stable (as our effectiveness outcome was tooth retention years, i.e. unaffected). The ranking hold. Varying patients' age did not have significant impact on the cost-effectiveness ranking, with genereally decreased costs and effectiveness. Increasing the risk of restorative complications after SE, but not NS had very limited impact on cost-effectiveness, without affecting the ranking. Variation of the discount rates did not affect the cost-effectiveness ranking.

4. Discussion

Conflicting guidance on maintaining pulpal vitality is available. Selective or stepwise carious tissue removal, aiming at reducing the risk of pulp exposure, have been favored by a number of publications [1,4]. Other publications and recommendations do not see these techniques

Table 1
Transition probabilities used within the model.

Probability of	Reference	Transition probability per cycle (year)	Min./max.	Allocation to	Allocation probability
Pulp exposure in NS	Appendix	0.35	0;0.40	Direct pulp capping	0.95
				Root-canal treatment	0.05
Relative risk of pulp exposure when using SE	Appendix	0.13	0.03;0.53	–	–
Pulpal complications after NS	Appendix	0.04	0;0.13	Root-canal treatment	1.00
Relative risk of pulpal complications after SE	Appendix	0.73	0.25;2.6	–	–
Non-pulpal complications after NS	[43]	0.013	0.01;0.016	Crown	1.00
Relative risk of non-pulpal complications after SE	Appendix	0.86	0.17;4.5	–	–
Pulpal complications after direct pulp capping using CH	Appendix	0.13	0.03;0.31	Root-canal treatment	1.00
Relative risk of pulpal complications when using MTA	Appendix	0.47	0.31;0.69	–	–
Non-pulpal complications after direct capping with CH	[43]	0.013	0.01;0.016	Crown	1.00
Relative risk when using MTA	Appendix	0.94	0.19;4.71	–	–
Root-canal treatment	[44]	0.05	0.04;0.06	Non-surgical re-RCT	0.05
				Surgical retreatment	0.45
				Extraction	0.50
Crown	[45]	0.015	0.013;0.016	Recementation	0.50
				Re-new	0.25
				Extraction	0.25
Non-surgical re-RCT	[46]	0.059	0.02;0.12	Surgical re-RCT	0.80
				Extraction	0.20
Surgical re-RCT	[47]	0.057	0.028;0.060	Extraction	1.00
Peri-implantitis	[48]	0.012	0.008;0.014	Peri-implantitis therapy	1.00
Implant crown failure or loss	[49]	0.047	0.028;0.085	Renewal	0.40
				Recement	0.60

Table 2
Costs per course of treatment. Details can be found in the appendix.

Course of treatment	Costs (Euro)	Source
Composite[1]	148.15	[50]
Direct pulp capping CH and composite	154.45	[12]
Direct pulp capping MTA and composite	187.59	[12]
Root-canal treatment[2]	347.55	[50]
Full-metal crown	365.27	[50]
Re-cementation of a crown	64.05	[50]
Orthograde re-RCT[2]	592.00	[50]
Apical surgery	179.55	[50]
Tooth/implant removal	76.65	[50]
Implant insertion	958.68	[51]
Implant-supported crown	866.55	[51]
Peri-implantitis treatment	41.73	[20]

[1] Assuming 3 surfaces.
[2] Assuming 3 root canals *per* tooth.

Table 3
Cost-effectiveness and sensitivity analyses.

Scenario	Carious tissue removal	Direct capping material	Mean costs (Euro)	Mean effectiveness (years)	Mean ICER (Δ€/Δyears)
Base-case scenario	SE	CH	2155.12	37.22	−94.66
	NS	CH	2245.66	36.29	−96.98
	SE	**MTA**	**2140.92**	**37.37**	**Ref.**
	NS	MTA	2176.42	37.24	−273.07
No tooth replaced after extraction	SE	CH	937.55	37.22	−0.60
	NS	CH	977.18	36.29	−36.77
	SE	**MTA**	**937.46**	**37.37**	**Ref.**
	NS	MTA	971.28	37.24	−260.15
Restorative risk in SE increased by 3-times	SE	CH	2178.63	37.21	−124.28
	NS	CH	2245.66	36.29	−79.65
	SE	**MTA**	**2161.23**	**37.35**	**Ref.**
	NS	MTA	2176.42	37.24	−138.09
Patient's age 35 years	SE	CH	1719.24	32.21	−121.07
	NS	CH	1834.58	31.56	−167.45
	SE	**MTA**	**1702.29**	**32.35**	**Ref.**
	NS	MTA	1750.18	32.28	−684.14
1% annual discount rate	SE	CH	2157.31	37.24	−103.52
	NS	CH	2246.41	36.31	−97.11
	SE	**MTA**	**2037.64**	**37.43**	**Ref.**
	NS	MTA	2169.25	37.30	−243.15
5% annual discount rate	SE	CH	2125.97	37.16	−119.00
	NS	CH	2235.04	36.20	−114.30
	SE	**MTA**	**2009.31**	**37.30**	**Ref.**
	NS	MTA	2155.59	37.17	−356.00

Costs (in Euro), effectiveness (in retention years), cost-effectiveness and incremental cost-effectiveness ratios (ICER) were calculated. In **bold**, the least costly strategy was shown. Negative ICERs indicate additional costs per decreased effectiveness; the strategy with negative ICER was always dominated by the comparator. Univariate scenario sensitivity analyses were performed to explore structural uncertainty (proportion of teeth being replaced via implant-supported crowns), parameter uncertainty (discount rate), and heterogeneity (simulating a patient aged 35 years).

superior, but argue that also non-selective carious tissue removal, with its higher risk of pulp exposure, may be acceptable as long as the exposed pulp is treated adequately, for example using MTA instead of CH for direct capping [11,35]. The present study compared SE vs. NS and, for exposed pulps, MTA vs. CH, for their simulated long-term cost-effectiveness. We found that preventing pulp exposure via applying SE was more relevant for cost-effectiveness than managing the exposed pulp more successfully with MTA than CH. The highest cost-effectiveness was found when SE was used and, for the very few cases of exposures, MTA applied for direct capping.

Our study comes with a range of strengths and limitations. First, the underlying database considered randomized controlled trials, i.e. rather robust evidence, and synthesized these data using network or pairwise meta-analyses, thereby allowing to partially mitigate the individual variability between trials (in methods, populations etc.). Consistency and transitivity were assessed and can be assumed to a large degree, strengthening the confidence in the data. Notably, risk of bias was unclear or high for most studies due to limited options for operator blinding, but also lacking allocation concealment. More important, and a weakness of this study, was the low number of events observed in many trials, which ran through only short to midterm periods. Longer term data was absent, while especially restorative complications can be expected only after longer periods of time. It should be highlighted that hence, our extrapolation of data from 2–3-years follow-up (in mean) from randomized trials may come with bias, as the differences in risk may be de- or increased over time, but also as general risks of failure (regardless of the groups) may not be continuous lifelong.

We gauged the impact of this uncertainty via sensitivity analyses, and found our strategy ranking to hold true even when increasing the

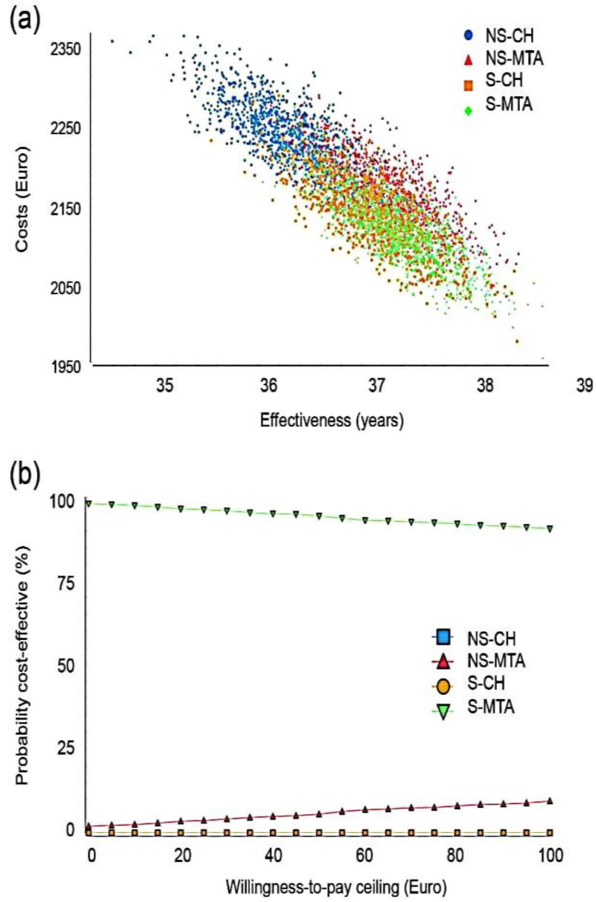

Fig. 2. Cost-effectiveness plane and net-benefit analysis. (a) The costs and effectiveness of different combinations of carious tissue removal and, in case of pulp exposure, direct pulp capping materials was assessed. For 1000 sampled individuals in each group, this cost-effectiveness was plotted. (b) We plotted the probability of treatments being acceptable in terms of their cost-effectiveness depending on the willingness-to-pay threshold of a payer.

risk of restorative complications after SE vs. NS by the factor three. Second, our study used an established methodology which had been validated by previous studies in the field, for example for the robustness of cost assumptions etc. Moreover, we reflected on the general uncertainty around parameters using extensive sensitivity analyses, including probabilistic ones, which further allowed us to estimate a VOI. Notably, the uncertainty was considerable, which calls for future studies on specific aspects around both comparisons (see below). Third, and as a limitation, data from different sources and settings were employed and used to model cost-effectiveness within German healthcare. We expect certain biases from that, and also assume our findings not to be generalizable in full to other settings. Also, costs were estimated using fee items from the German insurances, and only for MTA we borrowed from micro-costing analyses previously performed. This was done to reflect the costs of placing MTA as well as possible (given that there is no fee item for this specific treatment available), but is likely to come with some distortions (e.g. if less costly calcium silicate cements are used, overall cost-effectiveness may change). Moreover, fee items will not reflect true costs. We also did not at all account for opportunity costs, which may differ to some degree (e.g. by individuals who require more follow-up treatments also spending more time off work and at the dentist etc.). Fourth, this study only applies to permanent teeth, while treatment of primary teeth was not assessed. This was justified, as a different set of interventions is available in the primary dentition, where decision-making will consider a range of further aspects [36]. Last, this is a simulation study. Such studies are suited to explore the long-term effects of making different decisions initially, which has been argued to be highly relevant in dentistry, where the sequels of any decision can be tracked for decades. However, individual decision-making of each dentist together with his or her patient will deviate from the modeled pathways, and many of our assumptions are simplifications.

A number of aspects require discussion. First, we found the carious tissue removal strategy to be more relevant for long-term cost-effectiveness than the direct capping material. That is notable, as MTA has been found to reduce the risk of complications after direct capping by 40–50 % compared with CH. However, by reducing the general need for pulp capping, SE seems to mitigate these advantages efficiently; avoiding any kind of endodontic complications was found most relevant for cost-effectiveness. Moreover, and based on the very few data available, we could not track any relevant differences in restorative complications after SE compared vs. NS. In vitro studies have shown that leaving larger amounts of carious tissue beneath restorations may indeed compromise restoration survival, likely via reduced support against masticatory forces and reduced bond strength to carious tissue [37,38]. Clinical data also point into this direction for studies where carious dentin has not at all been removed, but sealed [39,40]. Notably, the included studies did remove carious tissue in the periphery of the cavity and only left small areas of pulpo-proximal carious dentin, as recommended. Moreover, we conducted sensitivity analyses and found even drastic increases in restorative risks to not change the strategy ranking.

It generally needs highlighting that the underlying risks are also determining the relevance of pulpal vs. restorative complications; the choice of data informing transition probabilities hence influences the study outcomes to some considerable degree. This is why we largely relied on systematically compiled and meta-analyzed data (which was coherent for all analyses), and primary-source data from the German public health insurance. The differences in the underlying data sources also partially explain the difference in overall lifetime costs in our study compared with that from previous studies with a similar scope in the same healthcare setting.

Generally, cost-effectiveness differences were limited between strategies. While, as described, SE + MTA had advantages over alternative strategies, the overall absolute difference in retention years or costs was relatively small. This, on the other hand, resulted in high ICER values, which are not particularly informative in such cases, which is why we additionally assessed cost-effectiveness-acceptability. Acceptability reflected the uncertainty around our findings, but confirmed that SE combined with MTA had a > 95 % probability of being the most cost-effective strategy. This acceptability was further only limitedly independent from a payer's willingness-to-pay.

Uncertainty was also reflected in the VOI. As described, the provided population-level estimate should be considered with caution, as it is prone to a range of distortions. Nevertheless, at around 13 million Euro per year, such VOI indicates that further studies into both comparisons (SE vs. NS, CH vs. MTA) seem worthwhile, mainly as the described uncertainty in data is multiplied with the high number of provided procedures.

A number of methodologic choices need further discussion. First, our outcome was tooth retention, which has been widely used by previous studies, and is certainly relevant to patients (when considering the disability stemming from severe tooth loss, for example) [41]. However, it is a late outcome and hence rather distant from the initial decisions. This partially explains the limited differences between comparisons; a wide range of further factors nivellate the initial differences over time. Second, further choices could have been modeled. For example, partial or full pulpotomy has recently been investigated as an option to manage exposed pulps in the permanent dentition [42]. While this treatment is likely beyond the scope of many general practitioners at present, future studies may want to consider this comparator in case the underlying database is further expanded. Third, we modelled MTA as being a full alternative to CH. However, it needs to be considered that MTA is currently reserved to more specialized dentists in many cases, which might impact on both cost-effectiveness and acceptance of this strategy. Further studies assessing the usability and costs of direct capping with MTA in general practice may be required.

In conclusion, and within the limitations of this study, selective carious tissue removal and, in case of pulp exposure, direct capping with MTA was the most cost-effective strategy. Generally, though, differences in cost-effectiveness were limited. Avoiding pulp exposure was more relevant for cost-effectiveness than how the exposed pulp was managed.

Authorship

RE, FS authors conceptualized and planned the study, collected the data, prepared the model, analyzed and interpreted the data, and wrote the manuscript. JK analyzed and interpreted the data and revised the manuscript. All authors agree to be accountable for the manuscript.

Declaration of Competing Interest

The authors do not have any conflict of interest. The authors are solely responsible for the contents of this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdent.2020.103330.

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Appendix

Two systematic reviews were conducted, with two independent electronic searches being carried out in Medline via PubMed to identify eligible manuscripts. The first search was conducted to retrieve original studies comparing selective (SE) versus non-selective (NS) carious tissue removal in deep (radiographic extension into >1/2 dentin thickness) lesions. The second search was performed to identify original studies comparing mineral trioxide aggregate (MTA) against calcium hydroxide (CH) for direct pulp capping after pulp exposure during carious tissue removal.

Two reviewers (FS, RE) screened the identified titles and abstracts of records against the inclusion criteria. Possibly eligible full-texts were assessed and, if found eligible, included. Cross referencing from retrieved full-texts was performed to identify further articles. Only articles in the English language and those available in full-text were included. Neither authors nor journals were blinded to the reviewers.

We included trials which randomly allocated interventions and were performed on vital permanent teeth, comparing minimum two of the described procedures against each other. Only studies evaluating clinically and/or radiographically determined success or reporting information on pulpal and non-pulpal (restorative) failures were included. Our outcomes were occurrence of pulp exposure (for the first review), and pulpal complications (e.g. signs of irreversible pulp inflammation, loss of vitality, need for root canal treatment) and non-pulpal (restorative) complications (e.g. secondary caries, fracture, restoration loss, tooth fracture) for both reviews. Details of the inclusion criteria can be found in Table S1.

The search flow is summarized in Figure S1 and S2. The excluded studies and reasons for exclusion are displayed in Tables S2 and S3.

Duplicative data extraction was performed independently by two calibrated reviewers (RE, FS). Any disagreements were resolved through discussion. Data extraction was performed only from the most recent publication of a study (longest follow-up).

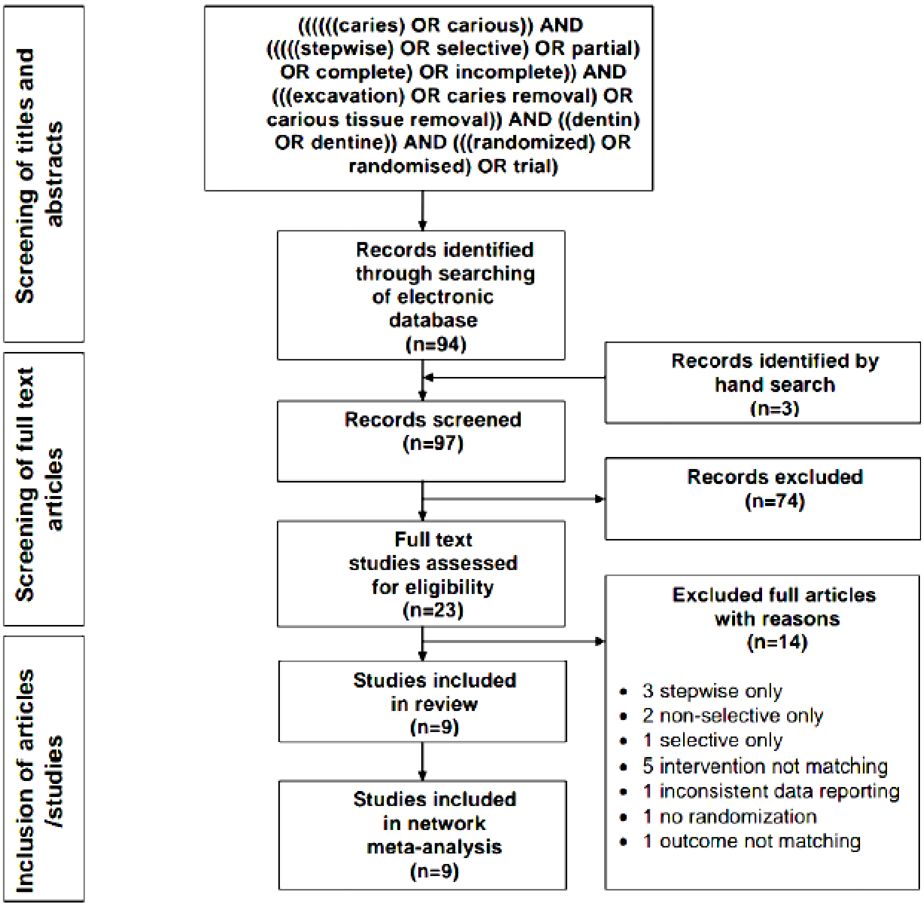

Figure S1. Flow chart of systematic searching process for selective and non-selective carious tissue removal.

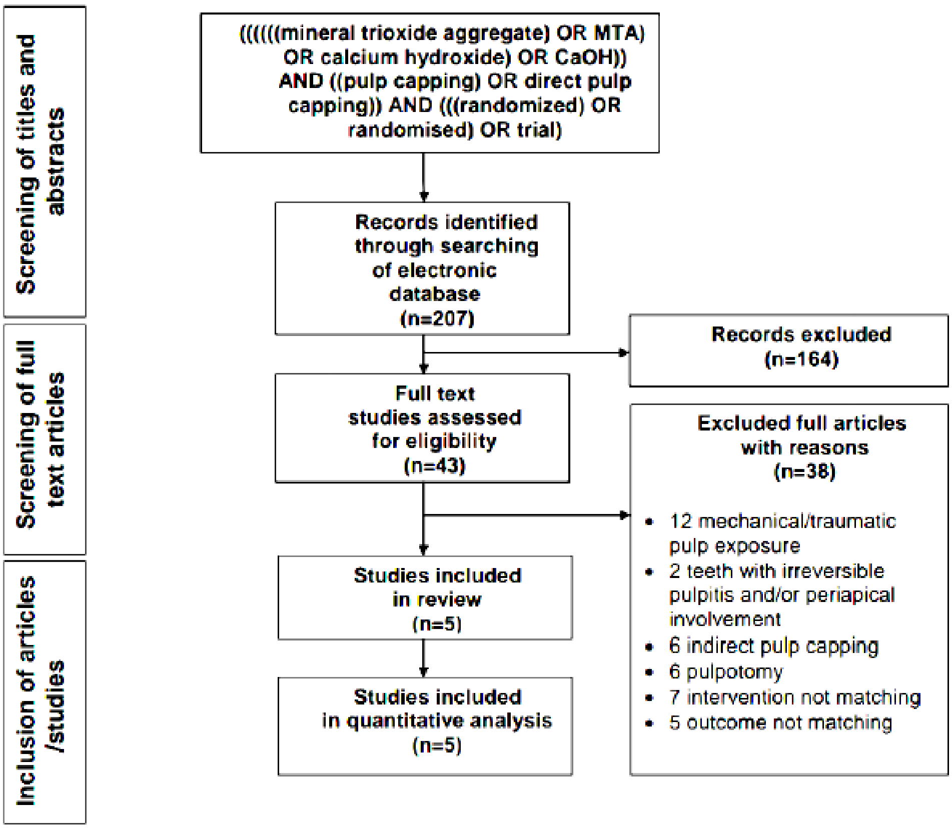

Figure S2. Flow chart of systematic searching process for direct pulp capping

Table S1: Inclusion criteria used to identify eligible articles

	Selective vs. non-selective carious tissue removal	**Direct pulp capping**
Studies	Randomized controlled trials (RCTs) published 1996 or later	
Participants	Humans with deep dentin caries extending more than half dentin thickness of permanent teeth requiring a restoration	Pulp exposure during carious tissue removal in permanent teeth with ability to control the bleeding in exposed pulp within several minutes
Intervention	Selective and/or stepwise carious tissue removal	Direct pulp capping using MTA
Control	Non-selective or stepwise carious tissue removal	Calcium hydroxide
Outcomes	One or more of the following clinical outcomes: Pulpal exposure during carious tissue removal, post-operative pulpal symptoms requiring treatment, other complications demanding treatment	Clinical and radiographic success denoted by absence of signs of irreversible pulpitis or pulp necrosis and healthy periapical area

Table S2: Excluded studies for selective and non-selective carious tissue removal with reasons

Study	Title	Reason for exclusion
(Safwat et al. 2017)	Clinical evaluation of ozone on dentinal lesions in young permanent molars using the stepwise excavation.	**Stepwise only**
(Pereira et al. 2017)	No additional benefit of using a calcium hydroxide liner during stepwise caries removal: A randomized clinical trial.	
(Kabil et al. 2017)	Effect of the addition of chlorhexidine and miswak extract on the clinical performance and antibacterial properties of conventional glass ionomer: an in vivo study.	
(Asgary et al. 2018)	Treatment outcomes of 4 vital pulp therapies in mature molars.	**Non-selective only**
(Koc Vural et al. 2017)	Randomized clinical trial to evaluate MTA indirect pulp capping in deep caries lesions after 24-months.	
(Petrou et al. 2014)	A randomized clinical trial on the use of medical Portland cement, MTA and calcium hydroxide in indirect pulp treatment.	**Selective only**
(Ali et al. 2018)	Self limiting versus conventional caries removal: A Randomized Clinical Trial.	**Intervention not matching**
(Ericson et al. 1999)	Clinical evaluation of efficacy and safety of new method for chemo mechanical removal of caries. A multi-centre study.	
(Orhan et al. 2008)	A clinical and microbiological comparative study of deep carious lesion treatment in deciduous and young permanent molars	
(Schwass et al. 2013)	Evaluating the efficiency of caries removal using an Er:YAG laser driven by fluorescence feedback control.	
(Sirin Karaarslan et al. 2012)	Evaluation of micro-tensile bond strength of caries-affected human dentine after three different caries removal techniques.	
(Khokhar and Tewari 2018)	Outcomes of partial and complete caries excavation in permanent teeth: A 18 month clinical study.	**Inconsistent data reporting**
(Oz et al. 2019)	Long-term survival of different deep dentin caries treatments: A 5-year clinical study.	**No randomization**
(Bitello-Firmino et al. 2018)	Microbial load after selective and complete caries removal in permanent molars: a randomized clinical trial.	**Outcome not matching**

Table S3: Excluded studies for direct pulp capping with reasons

Study	Title	Reason for exclusion
(Nowicka et al. 2015)	Tomographic evaluation of reparative dentin formation after direct pulp capping with Ca(OH)2, MTA, Biodentine, and dentin bonding system in human teeth.	**Mechanical/ traumatic pulp exposure**
(Sawicki et al. 2008)	Histological evaluation of mineral trioxide aggregate and calcium hydroxide in direct pulp capping of human immature permanent teeth.	
(Swarup et al. 2014)	Pulpal response to nano hydroxyapatite, mineral trioxide aggregate and calcium hydroxide when used as a direct pulp capping agent: an in vivo study.	
(Iwamoto et al. 2006)	Clinical and histological evaluation of white ProRoot MTA in direct pulp capping.	
(Accorinte et al. 2008)	Response of human dental pulp capped with MTA and calcium hydroxide powder.	
(Accorinte Mde et al. 2008)	Evaluation of mineral trioxide aggregate and calcium hydroxide cement as pulp-capping agents in human teeth.	
(Aeinehchi et al. 2003)	Mineral trioxide aggregate (MTA) and calcium hydroxide as pulp agents in human teeth: a preliminary study.	
(Parolia et al. 2010)	A comparative histological analysis of human pulp following direct pulp capping with Propolis, mineral trioxide aggregate and Dycal.	
(Shahravan et al. 2011)	A histological study of pulp reaction to various water/powder ratios of white mineral trioxide aggregate as pulp-capping material in human teeth: a double-blinded, randomized controlled trial.	
(Nair et al. 2008)	Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: a randomized controlled trial.	
(Min et al. 2008)	Effect of mineral trioxide aggregate on dentin bridge formation and expression of dentin sialoprotein and heme oxygenase-1 in human dental pulp.	
(Eskandarizadeh et al. 2011)	A comparative study on dental pulp response to calcium hydroxide, white and grey mineral trioxide aggregate as pulp capping agents.	
(Asgary et al. 2018)	Treatment outcomes of 4 vital Pulp therapies in mature molars.	**Teeth with irreversible pulpitis and/or periapical involvement**
(Parinyaprom et al. 2018)	Outcomes of direct pulp capping by using either mineral trioxide aggregate or Biodentine in permanent teeth with carious pulp exposure in 6- to 18-year-old patients: A randomized controlled trial.	
(Safwat et al. 2017)	Clinical Evaluation of ozone on dentinal lesions in young permanent molars using the stepwise excavation.	**Indirect pulp capping**
(Koc Vural et al. 2017)	Randomized clinical trial to evaluate MTA indirect pulp capping in deep caries lesions after 24-months.	
(Leye Benoist et al. 2012)	Evaluation of mineral trioxide aggregate (MTA) versus calcium hydroxide cement (Dycal) in the formation of a dentine bridge: a randomised controlled trial.	
(Mathur et al. 2016)	Evaluation of indirect pulp capping using three different materials: A randomized control trial using cone-beam computed tomography.	
(Hashem et al. 2015)	Clinical and radiographic assessment of the efficacy of calcium silicate indirect pulp capping: a randomized controlled clinical trial.	
(Petrou et al. 2014)	A randomized clinical trial on the use of medical Portland cement, MTA and calcium hydroxide in indirect pulp treatment.	
(Ghoddusi et al. 2012)	Clinical and radiographic evaluation of vital pulp therapy in open apex teeth with MTA and ZOE.	**Pulpotomy**

(Özgür et al. 2017)	Partial pulpotomy in immature permanent molars after carious exposures using different hemorrhage control and capping materials.	
(Qudeimat et al. 2007)	Calcium hydroxide vs mineral trioxide aggregates for partial pulpotomy of permanent molars with deep caries.	
(Bakhtiar et al. 2017)	Human pulp responses to partial pulpotomy treatment with theraCal as compared with biodentine and proRoot MTA: a clinical trial.	
(Kang et al. 2017)	A randomized controlled trial of various MTA materials for partial pulpotomy in permanent teeth,	
(Nosrat et al. 2013)	Pulpotomy in caries-exposed immature permanent molars using calcium-enriched mixture cement or mineral trioxide aggregate: a randomized clinical trial.	
(Jang et al. 2015)	A randomized controlled study of the use of proRoot mineral trioxide aggregate and endocem as direct pulp capping materials: 3-month versus 1-year outcomes.	**Intervention not matching**
(Bjørndal et al. 2017)	Randomized clinical trials on deep carious lesions: 5-year follow-up.	
(Katge and Patil 2017)	Comparative analysis of 2 calcium silicate-based Cements (Biodentine and Mineral Trioxide Aggregate) as direct pulp-capping agent in young permanent molars: a split mouth study.	
(Cengiz and Yilmaz 2016)	Efficacy of Erbium, Chromium-doped:Yttrium, Scandium, Gallium, and Garnet laser Irradiation combined with resin-based tricalcium silicate and calcium hydroxide on direct pulp capping: a randomized clinical trial.	
(Awawdeh et al. 2018)	Outcomes of vital pulp therapy using mineral trioxide aggregate or biodentine: A prospective randomized clinical trial.	
(AlShwaimi et al. 2016)	Pulpal responses to direct capping with Betamethasone/Gentamicin cream and mineral trioxide aggregate: Histologic and micro-computed tomography assessments.	
(Song et al. 2015)	A randomized controlled study of the use of proroot mineral trioxide aggregate and Endocem as direct pulp capping materials.	
(Nowicka et al. 2016)	Clinical and histological evaluation of direct pulp capping on human pulp tissue using a dentin adhesive system.	**Outcome not matching**
(Silva et al. 2013)	Subclinical failures of direct pulp capping of human teeth by using a dentin bonding system.	
(Baldissera et al. 2013)	Tenascin and fibronectin expression after pulp capping with different hemostatic agents: a preliminary study.	
(Eid et al. 2012)	Characterization of the mineral trioxide aggregate-resin modified glass ionomer cement interface in different setting conditions.	
(Koubi et al. 2013)	Clinical evaluation of the performance and safety of a new dentine substitute, Biodentine, in the restoration of posterior teeth - a prospective study.	

Table S4: Included studies for selective and non-selective carious tissue removal

Study	Settings	Study design	No. of patients; No. of teeth	Age	Intervention = selective and/or stepwise carious tissue removal (No. of teeth)	Control = non-selective or stepwise carious tissue removal (No. of teeth)	Follow-up period; Drop-out	Pulpal exposure (PE), Pulpal failures (PF), Non pulpal failures (NPF)
(Leksell et al. 1996)	University and clinics; Sweden	Multi-centered parallel-group RCT	116; 134 permanent teeth	6-16 yrs	Stepwise (64), the bulk of carious dentin removed and remaining innermost layer of carious dentin left; re-entry after 8-24 wks	Non-selective (70), removal of all carious dentin during the first visit	24 wks, 80 teeth > 1year; 4.3% yearly	PE; SW: 18%, NS: 40% PF; Non-exposed teeth remained asymptomatic **NPF**; SW: 0%, NS: 0%
(Orhan et al. 2010)	University; Turkey	Parallel-group RCT	123; 60 permanent molars (primary molars excluded)	4-15 yrs	Selective (19), elimination of the superficial part of the necrotic dentin, a layer of soft carious dentin was left on the cavity floor; Stepwise (17), re-entry after 3 mos	Non-selective (24), carious tissue removal was completed during the first visit	12 mos; 0% yearly	PE; SE: 5%, SW: 6%, NS: 25% PF; SE: 0%, SW: 0%, NS: 0%
(Rando-Meirelles et al. 2013)	University; Brazil	RCT Preliminary study	11; 18 permanent molars	12-17 yrs	Selective (9), carious dentin was partially removed with an excavator, elimination of the peripheral carious dentin and leaving the carious dentin on the pulp wall	Non-selective (9), carious tissue removal was completed during the first visit	24 mos, 5.2% yearly	PE; SE: 0%, NS: 0% PF; SE: 0%, NS: 0% **NPF**; SE: 0%, NS: 0%
(Maltz et al. 2012; Maltz et al. 2013; Maltz et al. 2018)	University; Brazil	Multi-centered parallel-group RCT	233; 299 permanent molars	6-53 yrs	Selective (152), partial removal of carious dentin on the pulpal wall (only disorganized dentin was removed)	Stepwise (147), first step: indirect pulp capping with calcium hydroxide cement and temporary filling. Re-entry after median 90 days and remaining decayed dentin was removed, then tooth was restored	5 yrs; 8% yearly	PE; SE: 0%, SW: 1% and 2% in 1st/2nd step PF; SE: 16%, SW: 32% **NPF**; SE: 0%, SW: 1%
(Bjørndal et al. 2017; Bjørndal et al. 2010)	Universities; Sweden and Denmark	Multi-centered parallel-group RCT	314; 314 permanent teeth	>18 yrs	Stepwise (156), (removal to soft dentin combined with removal of the peripheral demineralized dentin leaving soft, wet, and discolored dentin centrally on the pulpal wall); re-entry after 8-12 wks	Non-selective (158), carious tissue removal was completed during the first visit	5 yrs; 4.7% yearly	PE; SW: 17%, NS: 29% PF; SW: 19%, NS: 18%
(Labib et al. 2019)	University; Egypt	Uni-centered RCT	115; 132 permanent teeth	18-47 yrs	Selective (66), peripheral carious tissue removal to hard dentin was performed. Pulpo-proximally, soft dentin was left	Stepwise (66), removal of carious tissue on pulpal floor/axial wall, soft dentin was left; re-entry after 3-4 mos	1 yr ;19.7% yearly	PE; SE: 0%, SW: 8% PF; SE: 13%, SW: 11%

In case of studies done as follow-up to an initial study, data extraction was performed only from the most recent publication. Abbreviations: mos, months; NS, non-selective carious tissue removal; RCT, randomized controlled trial; SE, selective carious tissue removal; SW, stepwise carious tissue removal; wks, weeks; yrs, years.

Table S5: Occurrence of complications during or after selective (SE), non-selective (NS), or stepwise (SW) carious tissue removal

Probability of	Follow up (mos)	SE events / Total (%)	AFR	SW events / Total (%)		AFR	NS events / Total (%)	AFR
				First step	Second step			
Pulp Exposure								
(Leksell et al. 1996)		-	-	0/57 (0)[1]	10/57 (18)	-	28/70 (40)	-
(Orhan et al. 2010)		1/19 (5)	-	0/17 (0)[1]	1/17 (6)	-	6/24 (25)	-
(Rando-Meirelles et al. 2013)		0/9 (0)	-	-	-	-	0/9 (0)	-
(Maltz et al. 2012; Maltz et al. 2013; Maltz et al. 2018)		0/153 (0)	-	1/146 (1)	3/146 (2)	-	-	-
(Bjørndal et al. 2017; Bjørndal et al. 2010)		-	-	3/143 (2)	22/143 (15)	-	43/149 (29)	-
(Labib et al. 2019)		0/66 (0)	-	0/66 (0)	5/66 (8)	-	-	-
Pulpal failure								
(Leksell et al. 1996)	6	-	-	0/40 (0)		0%	0/40 (0)	0%
(Orhan et al. 2010)	12	0/18 (0)	0%	0/16 (0)		0%	0/18 (0)	0%
(Rando-Meirelles et al. 2013)	24	0/8 (0)	0%	-		-	0/8 (0)	0%
(Maltz et al. 2012; Maltz et al. 2013; Maltz et al. 2018)	60	19/115 (16)	4%	36/114 (31)		7%	-	-
(Bjørndal et al. 2017; Bjørndal et al. 2010)	60	-	-	22/93 (24)		5%	22/78 (28)	6%
(Labib et al. 2019)	12	7/54 (13)	13%	5/47 (11)		11%	-	-
Non-pulpal failure								
(Maltz et al. 2012; Maltz et al. 2013; Maltz et al. 2018)	60	0/115 (0)	0%	1/114 (1)		0%	-	-

[1] If not exactly reported when the exposure occurred (first or second step), exposure in the second step only was assumed.

Table S6: Included studies for direct pulp capping

Study	Settings	Study Design	No. of patients; No. of teeth	Age	Intervention / samples distribution	Follow-up period; Drop-out	Results
(Hilton et al. 2013)	Practices, USA	Practice – based RCT	376; 376 permanent teeth	>7yrs	Hemostasis using cotton pellet moistened with 5.25% sodium hypochlorite placed over the exposure site. MTA (195) or calcium hydroxide (181) was then applied. Resin modified glass ionomer (Vitrebond, 3M/ESPE) was then placed followed by final restoration	6 mos, 12 mos, 18 mos, 24 mos; 2.4 % yearly	Calcium hydroxide: 45 failures; (extraction: 7, root canal therapy: 38). MTA: 25 failures; (extraction: 6, root canal therapy: 19), additional 3 MTA failures detected in secondary analysis. Pulp cap failures at 24 mos: Calcium hydroxide (31.5%), MTA (19.7%)
(Kundzina et al. 2017)	University and clinics; Norway	Multi-centered parallel-group RCT	70; 70 permanent molars	18–55 yrs	Hemostasis using cotton pellets soaked in buffered 0.5% NaOCl. Calcium hydroxide (37) or MTA (33) placed directly over the pulpal exposure. Both groups were temporarily restored by glass ionomer cement (Fuji IX, GC Corp). Composite resin restoration after 1 week (unknown manufacturer)	1 wk, 6 mos, 12 mos, 24 mos, 36 mos; 2.4% yearly	Cumulative survival rate at 36 mos: MTA (85%) > Calcium hydroxide (52%). Postoperative pain at 1 wk: MTA (10/33) = Calcium hydroxide (8/37). Apical periodontitis at 6 mos: 1 sample in each group
(Brizuela et al. 2017)	University; Chile	Parallel-group RCT	169; 169 permanent molars	7-16 yrs	Hemostasis by applying pressure over the exposed pulp with cotton pellets soaked with sterile saline. Calcium hydroxide (53) or MTA (56) applied over the exposed pulp followed by glass ionomer liner (Vitrebond, 3M ESPE) and composite resin (Filtek Z350, 3M ESPE)	1 wk, 3 mos, 6 mos, 12 mos; 59.2% yearly	1 wk: 100% clinical success in both groups. 3 mos: 1 failure in calcium hydroxide. 6 mos: 1 failure in calcium hydroxide, 3 failures in MTA. 12 mos: 1 failure in calcium hydroxide. Accumulated failures: 13. 64% for both MTA and calcium hydroxide
(Caliskan and Guneri 2017) [1]	University; Turkey	Retrospective assessment of randomly allocated interventions	169; 172 permanent teeth	14-55 yrs	Hemostasis using a sterile saline-soaked cotton pellet, applied with gentle pressure for 1–10 min. Calcium hydroxide mixed with distilled water (75) or MTA (97) applied on the exposure. A sterile wet cotton pellet placed over the MTA. In both groups, the cavity was provisionally restored with zinc oxide-eugenol (ZOE) cement (Kemdent). After 2–7 days, permanent restorations with resin modified glass ionomer (Vitrebond, 3M/ESPE) and composite resin (Filtek Z250, 3 M ESPE) or amalgam (Degussa)	24–72-mos (6 mos intervals for 2 yrs, 10-12 mos intervals until end of study); 2% yearly	Overall success rates: MTA (85.9%), calcium hydroxide (77.6%). Cumulative pulp survival rate at 24 mos, 48 mos, 72 mos: MTA (93%, 89%, 71%, respectively), calcium hydroxide (90%, 78%, 59%, respectively). Failures: 12 failures in MTA (11 pulpal failure and 1 vertical root fracture),15 failures in calcium hydroxide (14 pulpal failure and 1 vertical root fracture)
(Suhag et al. 2019)	University; India	RCT	64; 64 permanent teeth	15-40 yrs	Hemostasis using cotton pellet moistened with 2.5% NaOCl placed over the exposure site for 10 minutes. Exposure covered by calcium hydroxide mixed with saline (32), followed by a layer of resin-modified glass ionomer (Fusion iseal, Prevest) and composite restoration (Ivoclar Vivadent), or MTA (32), covered by wet cotton pellet and tooth provisionally restored (IRM). After 24 hrs, a layer of resin-modified glass ionomer followed by direct composite restoration is placed over the MTA.	1 wk, 3 mos, 6 mos,12 mos; 12.5% yearly	Success rates: MTA (93%), calcium hydroxide (68%). Failures: 2 failures in MTA, 9 failures in calcium hydroxide (all failures in both groups are pulpal failures). Postoperative pain up to 7 days: lower pain scores with MTA (6.3 ± 9.5) compared with calcium hydroxide (18.5 ± 20.8) after 18 hrs

[1] This study was added despite the fact that it is a retrospective study, since it used random sampling and reported long–term outcomes (6 yrs.). Abbreviations: mos, months; MTA, mineral trioxide aggregate; NaOCl, sodium hypochlorite; RCT, randomized controlled trial; wk, week; yrs, years.

Table S7: Occurrence of complications after direct pulp capping

Probability of	Follow up (mos)	Calcium Hydroxide/Total (%)	AFR	MTA/Total (%)	AFR
Pulpal failure					
(Hilton et al. 2013)	24	45/175(26)	13%	28/183(15)	8%
(Kundzina et al. 2017)	36	16/34 (47)	16%	5/31 (16)	5%
(Brizuela et al. 2017)	12	3/22 (14)	14%	3/22 (14)	14%
(Caliskan and Guneri 2017)	72	14/67 (21)	4%	11/85 (13)	2%
(Suhag et al. 2019)	12	9/29 (31)	31%	2/27 (8)	8%
Non-pulpal failure					
(Caliskan and Guneri 2017)	72	1/67 (2)	0%	1/85 (1)	0%

Abbreviations: AFR, annual failure rate; mos, months; MTA, mineral trioxide aggregate.

Table S8. Risk of bias of included studies in review 1 (Higgins and Green 2011). Note that an updated Risk of Bias Tool is available, but has not been used here.

	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants and Personnel (performance bias)	Blinding of Outcome Assessment (detection bias)	Incomplete Outcome Data Addressed (attrition bias)	Selective Reporting (reporting bias)
(Leksell et al. 1996)	?	?	-	-	-	?
(Orhan et al. 2010)	?	?	-	+	+	?
(Rando-Meirelles et al. 2013)	+	+	-	-	-	?
(Maltz et al. 2012)	+	+	+	-	+	+
(Bjørndal et al. 2017)	+	+	-	+	+	+
(Labib et al. 2019)	?	?	+	+	+	?

Table S9. Risk of bias of included studies in review 2 (Higgins and Green 2011)

	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants and Personnel (performance bias)	Blinding of Outcome Assessment (detection bias)	Incomplete Outcome Data Addressed (attrition bias)	Selective Reporting (reporting bias)
(Hilton et al. 2013)	+	-	-	-	+	+
(Kundzina et al. 2017)	+	+	+	?	+	?
(Brizuela et al. 2017)	+	+	-	-	+	?
(Caliskan and Guneri 2017)	?	?	-	-	+	+
(Suhag et al. 2019)	+	+	+	-	+	+

Table S10. Assessment of transitivity by comparing distribution of key parameters across the different pairwise comparisons of the network meta-analysis.

	Gender	Age group	Tooth type	Lesion depth	Surfaces involved	Filling material	Risk of bias
NS-SW							
(Leksell et al. 1996)	Gender distribution not reported	6-16 yrs	Molars (94%) and premolars (6%)	A depth that pulp exposure could be expected during carious tissue removal	Occlusal and/or proximal surface	Glass-ionomer (44%), Composite resin (9%), Amalgam (47%)	High
(Orhan et al. 2010)	Male: 52%, Female: 48%	4-15 yrs	Molars only	≥ 3/4 of the entire dentin thickness	Occlusal and/or proximal surface	Composite resin	High
(Bjørndal et al. 2010)	Male: 42%, Female: 58%	18-49 yrs	Incisors (4%), Premolars (41%) and Molars (55%)	≥ 3/4 of the entire dentin thickness	Occlusal surface (4%), proximal surface (96%)	Composite resin	High
SE-NS							
(Orhan et al. 2010)	Male: 52%, Female: 48%	4-15 yrs	Molars only	≥ 3/4 of the entire dentin thickness	Occlusal and/or proximal surface	Composite resin	High
(Rando-Meirelles et al. 2013)	Male: 55%, Female: 45%	12-17 yrs	Molars only	≥ middle third of the dentin thickness	Occlusal surface only	Composite resin	High
SE-SW							
(Orhan et al. 2010)	Male: 52%, Female: 48%	4-15 yrs	Molars only	≥ 3/4 of the entire dentin thickness	Occlusal and/or proximal surface	Composite resin	High
(Maltz et al. 2013)	Male: 37%, Female: 63%	6-53 yrs	Molars only	≥ 1/2 of the dentin thickness	One surface (89%), multi-surface (11%)	Amalgam (40%), Composite resin (60%)	High
(Labib et al. 2019)	Male: 31%, Female: 69%	18-50 yrs	Molars (56%) and premolars (44%)	>2/3 of the dentin thickness	One surface (36%), multi-surface (64%)	Composite resin	Unclear

Abbreviations: NS, non-selective carious tissue removal; SE, selective carious tissue removal; SW, stepwise carious tissue removal; yrs, years.

Pairwise and network meta-analyses

Network meta-analysis was performed using Bayesian random-effects modelling and Markov Chain Monte Carlo simulations using JAGS implemented in the R package gemtc 0.8-2 (van Valkenhoef et al. 2012). Networks of interventions were constructed by plotting different treatments (as nodes) and comparisons (as edges) (Salanti et al. 2008a; Salanti et al. 2008b). Binomial likelihood was used to model the data (Ades et al. 2006; Dias et al. 2013). To fit the model, we used non-informative priors, for the basic parameters from a normal distribution N(0,1000), and a uniform prior U(0,4) for the random-effects standard deviation. The first 10,000 iterations were discarded as "burn-in" and then further 90,000 iterations were undertaken for 4 chains with a thinning interval of 2. The convergence was assessed based on the Brooks-Gelman-Rubin criteria (Brooks and Gelman 1998) and inspection of trace plots. Median RR and their 95% credible intervals (95% CrI) were reported. Credible intervals are the range of estimated parameters after exclusion of extreme values (Tu et al. 2012). Statistical heterogeneity was estimated by calculating total I-squared (Jackson et al. 2014). In order to evaluate the level of (in)consistency, we applied node-splitting, which evaluates one comparison at a time by separating the direct evidence on that comparison from the network of indirect evidence (van Valkenhoef et al. 2016).

Findings from pairwise and network meta-analyses

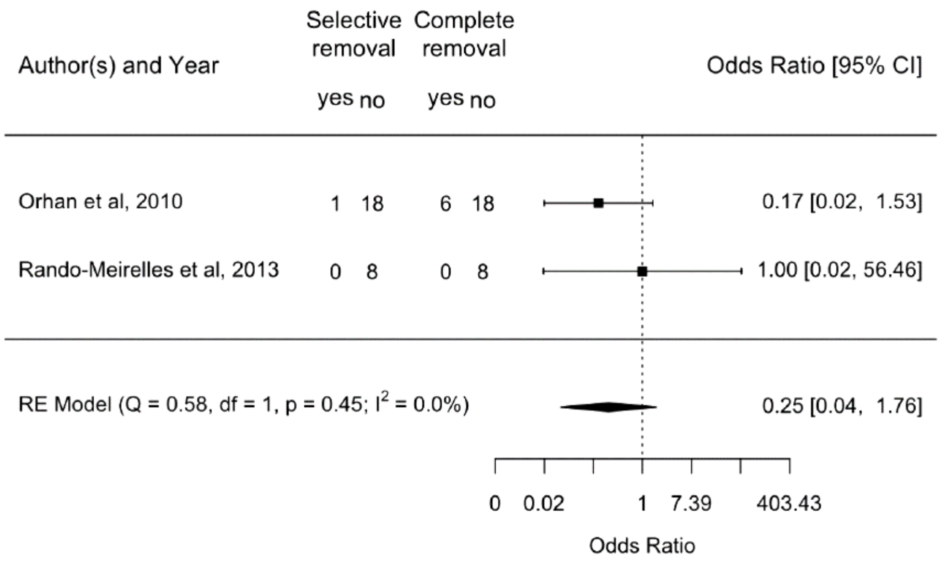

Figure S3: Pairwise comparison of different methods of carious tissue removal for the risk of pulp exposure.

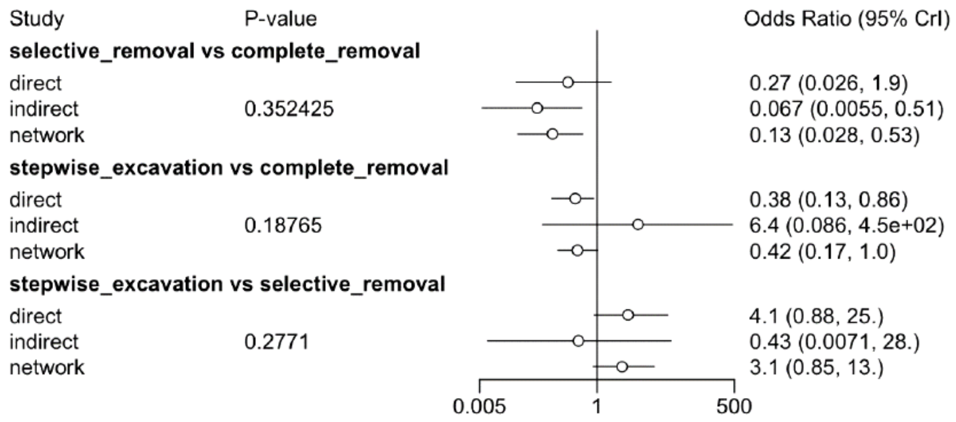

Figure S4: Node-split within NMA on the risk of pulp exposure. No significant inconsistency was detected.

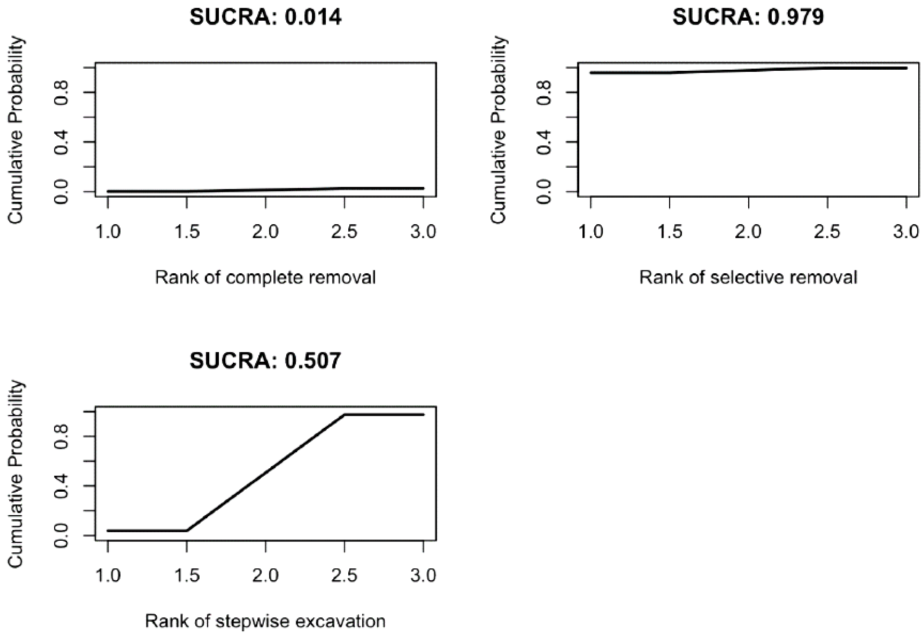

Figure S5: Surface Under the Cumulative Ranking (SUCRA) plots for the comparison of interventions for the risk of pulp exposure. Treatments are plotted based on their probability of ranking 1st, 2nd, 3rd. The SUCRA value ranges between 0 (i.e. 0% ranked last) and 1 (i.e. 100% ranked first). A higher SUCRA value indicates a higher chance of being the superior treatment.

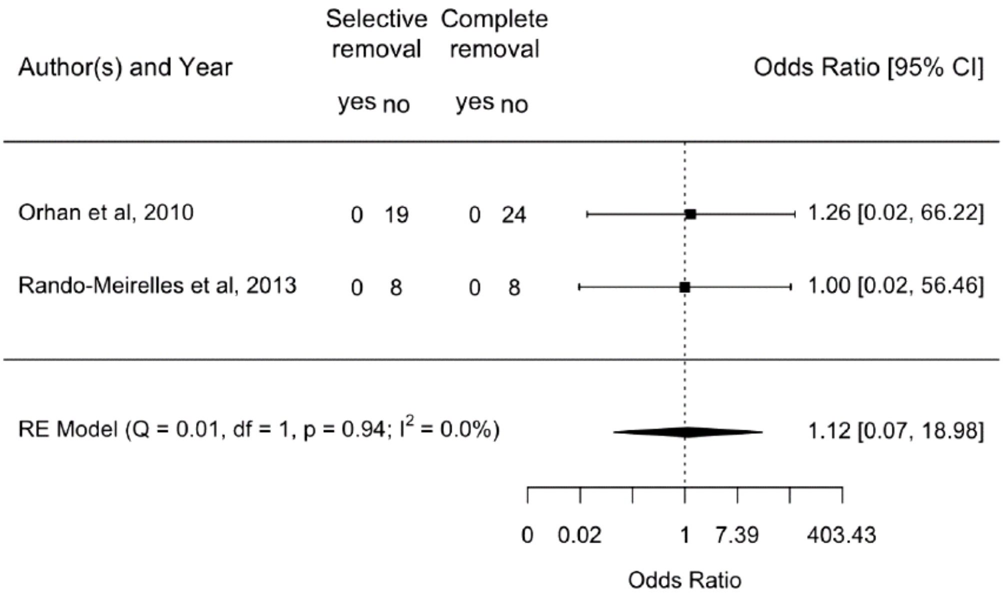

Figure S6: Pairwise comparison of different methods of carious tissue removal for the risk of pulpal complications.

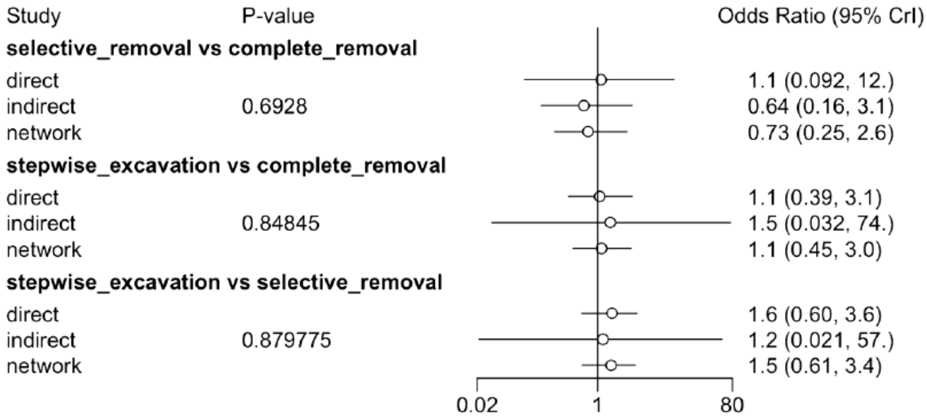

Figure S7: Node-split within NMA on the risk of pulpal complications. No significant inconsistency was detected.

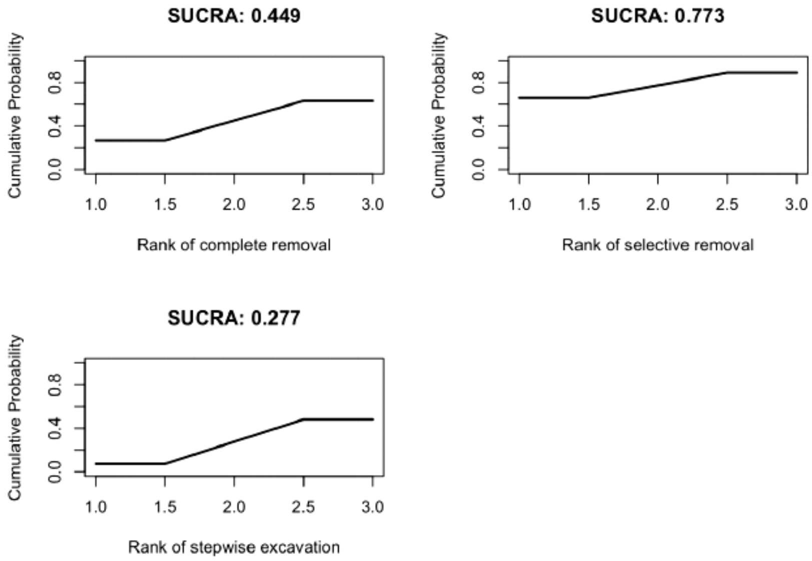

Figure S8: Surface Under the Cumulative Ranking (SUCRA) plots for the comparison of interventions for the risk of pulpal complications. Treatments are plotted based on their probability of ranking 1st, 2nd, 3rd. The SUCRA value ranges between 0 (i.e. 0% ranked last) and 1 (i.e. 100% ranked first). A higher SUCRA value indicates a higher chance of being the superior treatment.

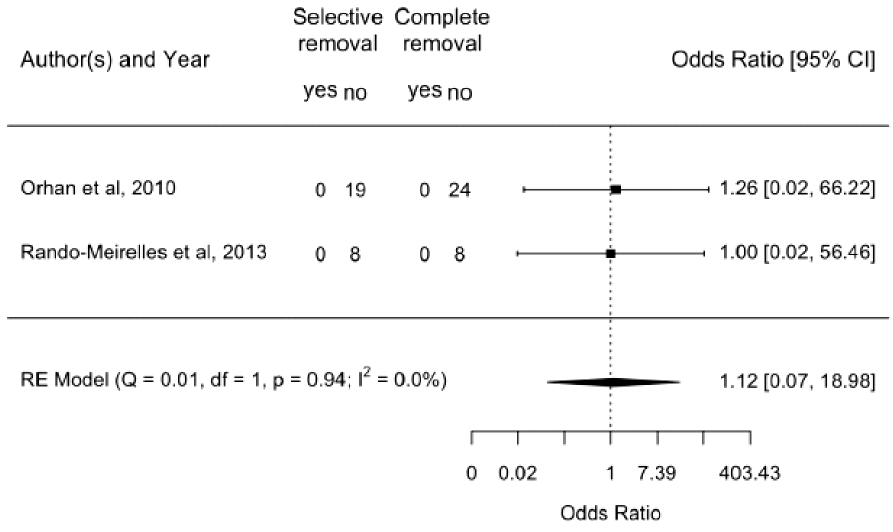

Figure S9: Pairwise comparison of different methods of carious tissue removal for the risk of non-pulpal (restorative) complications.

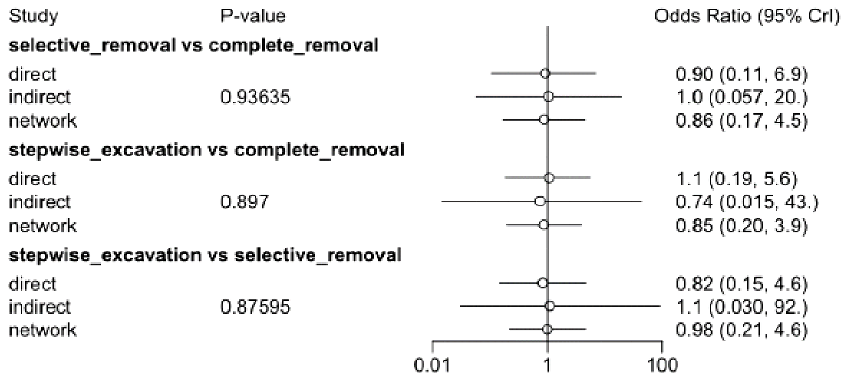

Figure S10: Node-split within NMA on the risk of non-pulpal (restorative) complications. No significant inconsistency was detected.

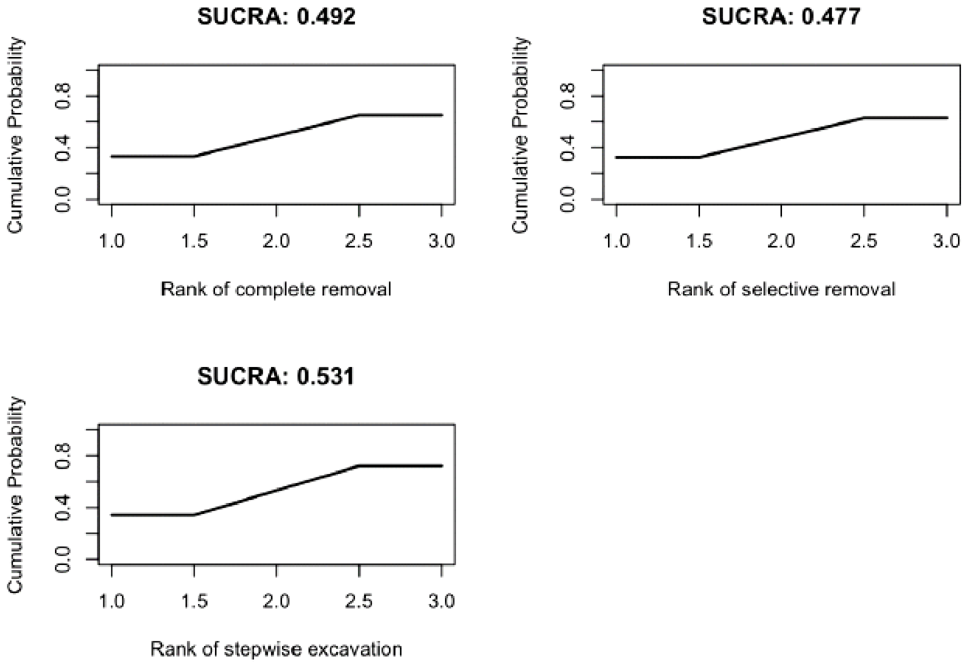

Figure S11: Surface Under the Cumulative Ranking (SUCRA) plots for the comparison of interventions for the risk of restorative complications. Treatments are plotted based on their probability of ranking 1st, 2nd, 3rd. The SUCRA value ranges between 0 (i.e. 0% ranked last) and 1 (i.e. 100% ranked first). A higher SUCRA value indicates a higher chance of being the superior treatment.

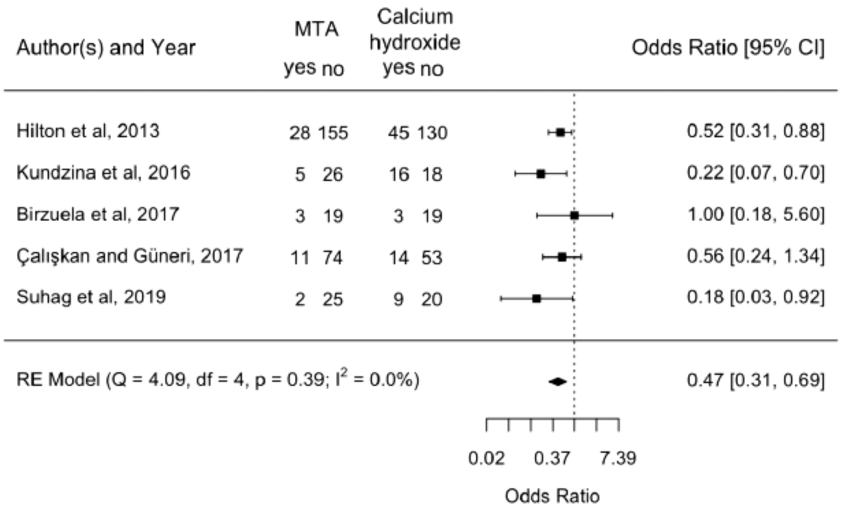

Figure S12: Pairwise comparison of different materials for direct pulp capping for the risk of pulpal complications.

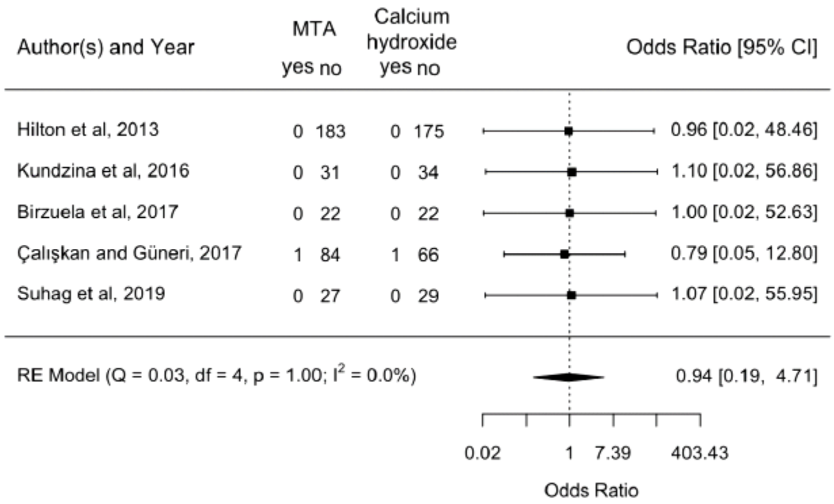

Figure S13: Pairwise comparison of different materials for direct pulp capping for the risk of non-pulpal (restorative) complications.

Table S11: Summary of costs per course of treatment

Course of treatment	Costs (€)
Composite restoration	**148.15**
Repair of existing restoration	**99.75**
Direct capping and composite restoration	**154.45**
First step of two-step excavation	**65.1**
Root canal treatment	**347.55**
Full-metal crown	**365.27**
Post-core crown	**505.23**
Re-cementation of a crown	**64.05**
Non-surgical root canal re-treatment	**592**
Surgical root canal re-treatment	**179.55**
Tooth/implant removal	**76.65**
Implant insertion	**958.68**
Implant-supported porcelain-bonded crown	**866.55**

Table S12: Detailed calculation of costs per course of treatment

(1) Selective or non-selective carious tissue removal, direct capping, and direct restoration

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	1	12.6
Anesthesia	40/41a	8/12	1	10.5
Special measurements during restorative therapy	12	10	1	10.5
Adhesive restoration, three surfaces	GOZ 2100	642	1	83.05
Liner	25	6	1	6.3
Direct capping	26	6	1	6.3
Total				**154.45**

(2) Selective or non-selective carious tissue removal, no capping, and direct restoration or re-filling

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	1	12.6
Anesthesia	40/41a	8/12	1	10.5
Special measurements during restorative therapy	12	10	1	10.5
Adhesive restoration, three surfaces	GOZ 2100	642	1	83.05
Liner	25	6	1	6.3
Total				**148.15**

(3) Repair of existing restorations

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	1	12.6
Anesthesia	40/41a	8/12	1	10.5
Filling, three surfaces	13c	49	1	51.45
Total				**99.75**

(4) Stepwise carious tissue removal, no direct capping, and temporary restoration (1st step)

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	1	12.6
Anesthesia	40/41a	8/12	1	10.5
Special measurements during restorative therapy	12	10	1	10.5
Liner	25	6	1	6.3
Total				**65.1**

(5) Root-canal treatment

Treatment	Position BEMA/GOÄ/ GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	3	37.8
Anesthesia	40/41a	8/12	1	10.5
Rubber dam	12	10	3	31.5
Direct core build-up	13B	39	1	40.95
Vital pulp extirpation	28	18 per canal	3	56.7
Root canal treatment	32	29 per canal	3	91.35
Root canal filling	35	17 per canal	3	53.55
Total				**347.55**

(6) Full metal crown

Treatment	Position BEMA/GOÄ/ GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	1	12.6
Anesthesia	40/41a	8/12	1	10.5
Special measurements during restorative therapy	12	10	1	10.5
Temporary crown	19	19	1	16.75
Full metal crown	20a	148	1	130.53
Dental materials				22.07
Laboratory				
Situation model	0010	5.74	2	11.48
Used resin	0023	12.14	1	12.14
Single-tooth dye	0051	9.19	1	9.19
Occludator	0120	8.42	1	8.42
Full-metal crown	1021	72.27	1	72.27
Non-precious metal alloy	9700	11.68	1	11.68
Delivery	9330	3.98	3	11.94
Total				**365.27**

(7) Post-core crown

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	1	12.6
Post–core metal	18b	80	1	84
Temporary post	21	28	1	24.69
Temporary crown	19	19	1	16.75
Recementation of temporary crown	24c	7	1	7.35
Full metal crown	20a	148	1	130.53
Dental materials				22.07
Laboratory				
Situation model	0010	5.74	2	11.48
Used resin	0023	12.14	1	12.14
Single-tooth dye	0051	9.19	1	9.19
Occludator	0120	8.42	1	8.42
Metal post casting	1050	44.92	1	44.92
Full-metal crown	1021	72.27	1	72.27
Non-precious metal alloy	9700	11.68	1	11.68
Delivery	9330	3.98	3	11.94
Total				**505.23**

(8) Recementation

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	1	12.6
Recementation of a crown	24a	25	1	26.25
Total				**64.05**

(9) Non-surgical root canal retreatment

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ 5000	50	3	19.40
Anesthesia	GOÄ 0090/0100	60/70	1	8.41
Rubber dam	GOZ 2040	65	3	25.23
Root canal treatment	GOZ 2410	392 per canal	3	152.13
Irrigation	GOZ 2420	70	3	27.15
Microscopy	GOZ 0110	400	3	155.20
Root canal filling	GOZ 2440	258 per canal	3	100.11
Medication	GOZ 2430	204 per visit	3	79.17
Total				**592**

(10) Surgical root canal retreatment

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Anesthesia	40/41a	8/12	1	10.5
Radiographic assessment	GOÄ925 a	12	2	25.2
Apicectomy	54b	96	1	100.8
Retrograde filling	35	17 per canal	1	17.85
Total				**179.55**

(11) Tooth/implant removal

Treatment	Position BEMA/GOÄ/GOZ/L	Points	Number of Treatments	Euros
Clinical investigation	01	18	1	18.9
Sensitivity testing	8	6	1	6.3
Radiographic assessment	GOÄ925 a	12	2	25.2
Anesthesia	40/41a	8/12	1	10.5
Extraction of multirooted tooth	44	15	1	15.75
Total				**76.65**

(12) Implant insertion

Treatment	Position BEMA/GOÄ/GOZ/L	Number of Treatments	Euros
Initial charting and consultation	GOÄ1	1	10.72
Intra-oral investigation	GOÄ6	1	13.41
Detailed consultation	GOÄ3	1	20.11
Cost estimation	GOZ 0030	1	25.87
Panoramic radiograph	GOÄ 5004	2	107.24
Diagnostic models	GOZ 0050	1	15.52
Radiographic diagnosis and guide	GOZ 9000	1	114.35
Use of radiographic guide	GOZ9003	1	12.94
Implant insertion	GOZ 9010	1	199.86
Implant		1	131.86
Suture material		1	7.68
Post-operative care	GOZ 3300	2	16.82
Prescription and medication	GOÄ 70	1	5.36
Topical anesthesia	GOZ 0080	2	7.76
Anesthesia	GOÄ 0090/0100	2	16.82
Implant re-exposure	GOZ 9040	1	80.98
Gingiva-former		1	25.70
Laboratory			
Situation model	0002	3	28.08
Replica	0241	1	15.20
Occludator	0402	1	10.16
Diagnostic wax-up	0832	1	10.30
Positioning splint	1224	1	60.20
Radiographic guide	1311	1	3.92
Delivery	0701	3	17.82
Total			**958.68**

(13) Implant-supported porcelain-bonded crown

Treatment	Position BEMA/GOÄ/GOZ/L	Number of Treatments	Euros
Crown preparation	GOZ 2200	1	171.01
Temporary crown	GOZ 2270	1	34.93
Manipulation of abutments	GOZ 9050	2	80.98
Individual impression	GOZ 5170	1	32.34
Dental materials			22.07
Laboratory			
Situation model	0010	3	17.22
Individual tray	0211	1	19.51
Used resin	0023	1	12.14
Single-tooth dye	0051	1	9.19
Occludator	0120	1	8.42
Gingival mask	0223	1	10.99
Working with a supra-structure	2971	1	25.77
Working on abutment	2973	1	47.47
Crown core	2122	1	70.26
Porcelain coverage	2612	1	99.83
Non-precious metal alloy	9700	1	11.68
Delivery	9330	6	25.98
Impression post	9237	1	56.54
Laboratory implant	9238	1	25.40
Abutment and screw	9239	1	84.82
Total			**866.55**

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"My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection."

List of publications

1. Emara R, Krois J, Schwendicke F. Maintaining pulpal vitality: Cost-effectiveness analysis on carious tissue removal and direct pulp capping. Journal of dentistry. 2020 May;96:103330.

2. Youssef AR, Emara R, Taher MM, Al-Allaf FA, Almalki M, Almasri MA, Siddiqui SS. Effects of mineral trioxide aggregate, calcium hydroxide, biodentine and Emdogain on osteogenesis, Odontogenesis, angiogenesis and cell viability of dental pulp stem cells. BMC oral health. 2019 Jul 2;19(1):133.

3. Ekert T, Krois J, Meinhold L, Elhennawy K, Emara R, Golla T, Schwendicke F. Deep Learning for the Radiographic Detection of Apical Lesions. Journal of endodontics. 2019 Jul;45(7):917.

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