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REVIEW ARTICLE

# The effect of an antibacterial mixture and non-instrumentation endodontic treatment in primary teeth: A systematic review and meta-analyses

**Nabras Alrayes [a], Yara Almaimouni [b], Abrar Tounsi [c,*], Khalid Tarabzouni [d], Faisal Alonaizan [e], Maria Salem Ibrahim [f]**

[a] *College of Dentistry, Imam Abdulrahman Bin Faisal University, Dammam 31441, Saudi Arabia*
[b] *Department of Restorative Dental Sciences, College of Dentistry, Imam Abdulrahman Bin Faisal University, Dammam 34212, Saudi Arabia*
[c] *Department of Periodontics and Community Dentistry, College of Dentistry, King Saud University, Riyadh, Saudi Arabia*
[d] *Dhahran Armed Forces Hospital, Dhahran 31932, Saudi Arabia*
[e] *Department of Restorative Dental Sciences, College of Dentistry, Imam Abdulrahman Bin Faisal University, Dammam 34212, Saudi Arabia*
[f] *Department of Preventive Dental Sciences, College of Dentistry, Imam Abdulrahman Bin Faisal University, Dammam 34212, Saudi Arabia*

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Pulpectomy;
Non-instrumentation

**Abstract** Studies assessing the clinical and radiographic success of LSTR in terms of the presence of pain, mobility, swelling, fistula/sinus tract, interradicular radiolucency, and root resorption have not been performed. We therefore performed a systematic review with the aim of evaluating the effectiveness of lesion sterilization and tissue repair (LSTR), using three antibacterial mixtures (3Mix), in treating primary teeth. Well-defined search strategies developed for four electronic databases, Web of Science, OVID, PubMed, and Scopus, were used in this study. Two independent reviewers selected relevant articles from 3,232 studies by screening titles and abstracts. Based on the inclusion criteria, 25 articles were selected. Eight analyses of clinical and radiographic results

*Abbreviations*: 3Mix, LSTR, lesion sterilization and tissue repair; RCT, root canal treatment; MTA, mineral trioxide aggregate

* Corresponding author.
E-mail addresses: ykalmaimouni@iau.edu.sa (Y. Almaimouni), atounsi@ksu.edu.sa (A. Tounsi), fAlonaizan@iau.edu.sa (F. Alonaizan), msibrahim@iau.edu.sa (M. Salem Ibrahim).

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were conducted based on 6, 12, 18, and 24-month follow-up intervals. Data extraction and quality appraisal were performed by three independent reviewers. The composition of antibiotic mixtures used for LSTR varied substantially, with inconsistent radiographic and clinical success rates across the included studies. A quantitative grouping of the studies showed no significant differences between 3Mix and the control medicaments regarding radiographical and clinical success ($p$-value > 0.05). The available evidence on different LSTR using 3Mix is scarce, and the study findings were inconsistent. Therefore, additional clinical trials on 3Mix with different compositions are needed.



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## 1. Introduction

The progression, persistence, and initiation of inflammatory root resorption are strongly influenced by microorganisms that eventually cause premature exfoliation of primary teeth (Grewal et al., 2018). Early tooth loss has several disadvantages, such as aesthetic and phonetic problems and loss of arch length leading to a mesial drift of the successor teeth and consequent malocclusion (B.Fuks et al., 2019; Nakornchai et al., 2010). Preserving the primary tooth is the best for oral health, arch integrity, and space preservation for its successor (American Academy of Pediatric Dentistry, 2020). Following the American Academy of Pediatric Dentistry's guidelines, vital pulp therapy is preferred in reversible pulpitis to allow normal exfoliation and long-term success (American Academy of Pediatric Dentistry, 2020). In contrast, carious teeth with pulpal and periapical tissue involvement may necessitate non-vital pulp therapy (American Academy of Pediatric Dentistry, 2020). Traditional root canal treatment (RCT) techniques have shifted to novel contemporary approaches, with different success and failure rates in teeth with different pulpal and apical conditions (Hargreaves et al., 2017).

To improve the prognosis of root canal-treated teeth, it is important to reduce the number of bacteria in the root dentin and periapical tissues without damaging the remaining healthy tissues. (Hoshino et al., 1996; Swimberghe et al., 2019). Medicaments for root canals, particularly antibiotics, have been gradually introduced as an adjunct to clinical approaches and are effective for sterilizing infected root dentin, thus achieving successful outcomes (Porciuncula de Almeida et al., 2021).

Antibiotic therapy has become an integral part of medicine acting as one of the main front-line defenders against microorganisms (Brötz-Oesterhelt, 2004). The Cariology Research Unit of Niigata University (Niigata, Japan) has developed a therapy concept based on lesion sterilization and tissue repair (LSTR). The concept suggests that proper disinfection of infected lesions can enable tissue repair in the treatment of deep carious lesions with or without pulp involvement (Trairatvorakul and Sastararuji, 2014). LSTR uses a mixture of three antibacterial medicaments—metronidazole, ciprofloxacin, and minocycline (Burrus et al., 2014; Porciuncula de Almeida et al., 2021; Takushige et al., 2004). The mixture has been successful in lesion disinfection in dentinal or pulpal lesions as well as in the periapical area (Burrus et al., 2014; Porciuncula de Almeida et al., 2021; Takushige et al., 2004).

The non-instrumentation technique is useful in preserving root dentin and preventing excessive irritation of periapical tissues (Nakornchai et al., 2010). It also decreases chair time and usually requires a single-visit treatment (Shankar et al., 2021). The laboratory and clinical effectiveness of LSTR have been reported in various studies that evaluated the antibacterial efficacy when using an antibiotic mixture in the root canal system (Burrus et al., 2014; Porciuncula de Almeida et al., 2021; Takushige et al., 2004). However, few systematic reviews have assessed the overall clinical and radiographic success rates of LSTR therapy for primary teeth compared to conventional root canal treatment (Duarte et al., 2020). To our knowledge, no systematic review has assessed the clinical and radiographic success of LSTR regarding the presence of pain, mobility, swelling, fistula/sinus tract, interradicular radiolucency, and root resorption. Therefore, this review aimed to determine the comparative effectiveness of LSTR using three antibacterial mixtures to preserve primary teeth compared to other conventionally used materials and techniques by assessing multiple clinical and radiographic outcomes.

## 2. Materials and methods

This systematic review was developed following the PRISMA guidelines for systematic reviews and *meta*-analysis (Moher et al., 2009). The review question was developed using the patient population, intervention, comparison, and outcome (PICO) format, where the population was pediatric patients having primary teeth with deep carious lesions; the intervention was LSTR with a mixture of three antibacterial medicaments; the comparison was any other conventional technique and material included in the study, and the outcomes were clinical and radiographic success and antibacterial efficiency.

### 2.1. Inclusion and exclusion criteria

The inclusion criteria were clinical trials conducted on primary teeth with documented follow-up and published in English. The intervention groups were a mixture of three antibacterial medicaments with or without carriers that may or may not have been compared to a control group. No restrictions on the type of antibiotic mixture or instrumentation technique were applied. Other study designs, such as case reports, cross-sectional, laboratory, or animal studies, were excluded.

### 2.2. Search strategies

Well-defined search strategies were developed for each database (Table 1). The electronic databases, Web of Science and OVID, were searched on July 17, 2020, with 217 and 1014 published studies found, respectively. On July 18, 2020, a search of PubMed and Scopus databases yielded 1822 and 596 studies, respectively. At this stage, all databases were searched with no time limitations or language restrictions. A second search of Web of Science and PubMed was conducted on February 20, 2022, for articles published within 2020——2022, and 86 and 177 articles were identified, respectively. On February 21, 2022, another search of OVID database for articles published within same time limit yielded 368 articles. The Covidence platform was used to remove duplicates and screen the articles found.

### 2.3. Study selection

Based on the inclusion and exclusion criteria, two authors (N.M.A.) and (M.S.I.) independently screened titles and abstracts of the retrieved articles for relevance. Subsequently, a full-text review was carried out, as shown in the PRISMA flow diagram (Fig. 1). Additionally, the reference lists of each article included were searched for any related articles. Calibration of reviewers was carried out before screening, and disagreements were resolved by a discussion with a senior reviewer.

**Table 1** Electronic search strategies for Web of Science, PubMed, Scopus, and OVID databases.

| | | |
|---|---|---|
| Web of Science | 1 | TS = (“Primary”OR“Deciduo*”) |
| | 2 | TS = (3Mix* OR non-instrument* OR pulpectomy) |
| | 3 | #1 AND #2 |
| PubMed | 1 | ((((Primary) OR (Deciduo*)) OR (Pediatric)) OR (children) |
| | 2 | ((3Mix*) OR (non-instrument*)) OR (pulpectomy)) |
| | 3 | #1 AND #2 |
| Scopus | | TITLE-ABS-KEY ( primary OR deciduo* ) AND<br>TITLE-ABS-KEY (3mix* OR non-instrument* OR pulpectomy ) |
| OVID | 1 | (Primary or Diciduo*).af. |
| | 2 | (3Mix* or non-instrument* or pulpectomy).af. |
| | 3 | #1 AND #2 |

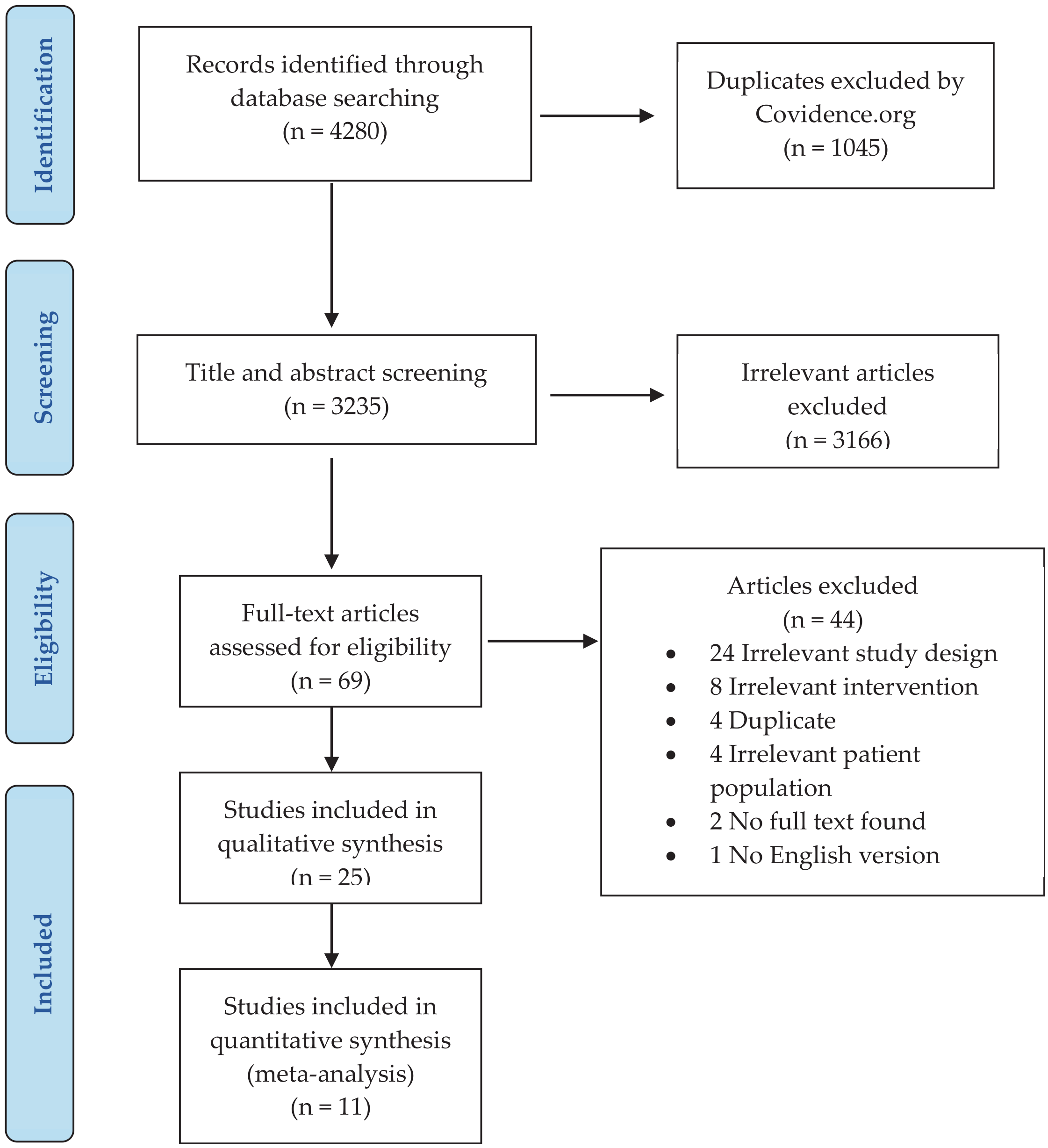


**Fig. 1** PRISMA flow diagram of study screening and selection.

### *2.4. Data extraction*

Three independent authors, (N.M.A.), (Y.K.A.), and (K.T.), extracted data from included articles in a customized data sheet using Microsoft Excel. The extracted data was then reviewed by a senior author. The data extraction sheet included open and closed-ended questions to obtain needed information such as patient demographics, sample size and description, applied materials, and assessment methods. Each clinical outcome was reported, including pain, the presence of an abscess, sinus tract and abnormal mobility. Persisting or newly formed radiographic signs, including periapical or bifurcation radiolucency, pathological root resorption (internal or external), and disruption of lamina dura were reported thoroughly. Antibacterial efficiency was determined based on bacteria type, culturing condition, intervals, and colony-forming units. Table 2 shows the characteristics of the included studies.

### *2.5. Quality assessment*

Two reviewers (N.M.A.) and (M.S.I.) independently evaluated the included studies for risk of bias using an Excel sheet adapted from the Cochrane assessment tools (Higgins et al., 2019). To measure sampling bias, a random sequence generation was used. Measurement bias was evaluated by assessing allocation concealment of the study samples, participants blinding, and blind assessment of outcomes. The tool also evaluated the presence of reporting bias when an article failed to provide definitive values, had incomplete outcome data, or performed selective reporting. If the risk of bias was unclear in an article, an "Unclear" assessment was given to that

**Table 2** Characteristics of included studies.

| Study | Group Sample Size | Participants | Intervention | Control | Follow-up Time in Months | Assessed Outcomes |
|---|---|---|---|---|---|---|
| (Ali and Raslan, 2021) | n = 22 | Health status: Healthy<br>Age: 5—11 years<br>Sex: 13 males and 4 females | 3MixMP | CH | 3, 6, 9 and 12 | Spontaneous pain, tenderness to palpation/percussion, redness, swelling, mobility, sinus tracts, sensitivity to vestibular palpation, internal or external pathological root resorption, or interradicular/periapical radiolucency |
| (Shankar et al., 2021) | n = 32 | Health status: Healthy<br>Age: 4—10 years<br>Sex: 24 males and 23 females | 3Mix-MP-R (1 mg/mL) | 3Mix-MP-R (1 g/mL) | 10 days, 1 and 3 months | Clinical and radiographic success based on Coll and Sadrian's criteria |
| (Sijini et al., 2021) | 3Mix-D: n = 28<br>Cv: n = 20 | Health status: Healthy<br>Age: 5—9 years<br>Sex: 21 males and 24 females | 3Mix-D | Cv | 6 and 12 | Pain, fistula, tenderness to percussion, mobility, bifurcation and periapical radiolucency, external and internal root resorption |
| (Thakur et al., 2021) | 3Mixin: n = 30<br>3Mix-MP: n = 29<br>RCT: n = 28 | Health status: Healthy<br>Age: 4—8 years<br>Sex: not mentioned | 3Mixin<br>3Mix-MP | RCT | 6 and 12 | Pain, mobility, swelling, failure and success rates |
| (Divya et al., 2019) | n = 15 | Health status: Healthy<br>Mean age: 6.25 years<br>Sex: not mentioned | 3Mix-MP | Cp | 3, 6 and 12 | Pain, swelling, sinus tract, mobility, deviated path of eruption of succedaneous teeth, interradicular radiolucency, and resorption |
| (Lokade et al., 2019) | C-Modified 3Mix: n = 20<br>CR-Modified 3Mix: n = 21<br>CTZ: n = 22 | Health status: not mentioned<br>Age: 4—8 years<br>Sex: not mentioned | C-Modified 3Mix<br>CR-Modified 3Mix | CTZ | 1, 6 and 12 | Pain, swelling, sinus tract, mobility, premature loss of teeth, periodontal ligament enlargement, intra radicular radiolucency, resorption, and discontinuity of lamina dura |
| (Parakh and Shetty, 2019) | n = 15 | Health status: Healthy<br>Age: 4—8 yearsSex: (male: female)<br>in the 4- to 6-year age group was 8:14, and in the 6- to 8-year age group was 20:18 | GAMN1<br>GAMR1 | GAMN2<br>GAMR2 | 3, 6 and 12 | Pain, swelling, sinus tract, mobility, discontinuity of lamina dura, resorption, and interradicular radiolucency |
| (Rai et al., 2019) | n = 35 | Health status: Healthy<br>Age: 4—9 years<br>Sex: not mentioned | 3Mix | Cv | 3 and 6 | Pain, abscess, sinus tract, interradicular/periapical radiolucency, and resorption |
| (Zacharczuk et al., 2019) | n = 23 | Health status: not mentioned<br>Mean age: 6.15 and 6.3 years<br>Sex: not mentioned | 3MixMP | Cmc | 1, 3, 6, 12 and 18 | Pain, swelling, fistula, mobility, interradicular/periapical radiolucency, and resorption |
| (Ahirwar et al., 2018) | n = 20 | Health status: not mentioned<br>Age: 4—9 years<br>Sex: not mentioned | 3MixMP | Cos | 6 and 12 | Colony-forming units |
| (Grewal et al., 2018) | n = 25 | Health status: not mentioned<br>Age: 7—10 years<br>Sex: 17 males and 13 females | 3Mix-A | RCT | 6 and 12 | Pain, swelling, sinus tract, and root length |

(*continued on next page*)

**Table 2** (*continued*)

| Study | Group Sample Size | Participants | Intervention | Control | Follow-up Time in Months | Assessed Outcomes |
|---|---|---|---|---|---|---|
| (Jamali et al., 2018) | n = 50 | Health status: not mentioned<br>Age: 3—6 years<br>Sex: 56 males and 59 females | 3Mixtatin | - Cf<br>- MTA | 6, 12 and 24 | Pain, sinus tract, mobility, PDL widening, periapical radiolucency, and resorption |
| (Doneria et al., 2017a) | Modified 3Mix:<br>n = 24<br>Cz: n = 20<br>Cv: n = 20 | Health status: not mentioned<br>Age: 4—8 years<br>Sex: not mentioned | Modified 3Mix | - Czoz<br>- Cv | 6 and 12 | Pain, swelling, mobility, interradicular radiolucency, and resorption |
| (Doneria et al., 2017b) | Modified 3Mix:<br>n = 24<br>Cz: n = 20<br>Cv: n = 20 | Health status: Healthy<br>Age: 4—8 years<br>Sex: not mentioned | Modified 3Mix | - Czoz<br>- Cv | 6, 12 and 18 | Pain, swelling, mobility, interradicular radiolucency, and resorption |
| (Raslan et al., 2017) | n = 21 | Health status: Healthy<br>Age: not mentioned<br>Sex: not mentioned | – 3MixMP<br>– 3Mix-MP-R | – | 6 and 12 | Pain, abscess, mobility, interradicular / periapical radiolucency |
| (Reddy et al., 2017) | n = 30 | Health status: not mentioned<br>Age: 4—10 years<br>Sex: not mentioned | 3Mix-MP | - Cf | 3, 6 and 12 | Pain, swelling, sinus tract, mobility, interradicular radiolucency |
| (Aminabadi et al., 2016b) | 3Mixtatin:<br>n = 37<br>3Mix-B:<br>n = 32<br>MTA:<br>n = 32<br>Sim:<br>n = 28 | Health status: Healthy<br>Age: 3—6 years<br>Sex: 29 males and 38 females | – 3Mixtatin<br>– 3Mix-B | - MTA<br>- Sim | 12 | Pain, sinus tract, resorption, furcal/ periapical radiolucency, and hard tissue barrier |
| (Aminabadi et al., 2016a) | 3Mixtatin:<br>n = 33<br>MTA:<br>n = 38 | Health status: Healthy<br>Age: 3—6 years<br>Sex: 23 males and 33 females | 3Mixtatin | MTA | 12 and 24 | Pain, sinus tract, mobility, and radiolucency |
| (Nanda et al., 2014) | n = 20 | Health status: Healthy<br>Age: 4—10 years<br>Sex: not mentioned | – 3MixMP<br>– 3Mix | – | 6 and 12 | Pain, abscess, sinus tract, mobility, and bone loss |
| (Trairatvorakul and Detsomboonrat, 2012) | n = 58 | Health status: Healthy<br>Mean age: 6.18 ± 0.96 years<br>Sex: not mentioned | 3Mix-MP | – | 6, 12, 18—21 and 24—27 | Pain, swelling, sinus tract, mobility, continuity of lamina dura, resorption, and interradicular radiolucency |
| (Jaya et al., 2012) | n = 15 | Health status: Healthy<br>Age: 6—9 years<br>Sex: not mentioned | – 3MixMP<br>– 3Mix-C | – | 6, 12 and 24 | Pain, abscess, mobility, and interradicular radiolucency |
| (Agarwal et al., 2011) | n = 20 | Health status: Healthy<br>Age: 4—9 years<br>Sex: 18 males and 16 females | 3Mix-MP | - ZOE<br>- Pulpotec | 1, 3, 6 and 12 | Failure and success rates |
| (Nakornchai et al., 2010) | n = 25 | Health status: Healthy<br>Age: 3—8 years<br>Sex: not mentioned | 3MixMP | Cv | 6 and 12 | Pain, abscess, fistula, mobility, interradicular radiolucency, and resorption |
| (Prabhakar et al., 2008) | n = 30 | Health status: Healthy<br>Age: 4—10 years<br>Sex: not mentioned | – 3MixMP-C<br>– 3MixMP-CR | – | 6 and 12 | Pain, abscess, fistula, mobility, and bone loss |
| (Takushige et al., 2004) | n = 56 | Health status: Not mentioned<br>Age: 4—18 years<br>Sex: not mentioned | 3Mix-MP<br>3Mix-sealer | – | 680–2390 days | Pain, swelling, fistula, mobility, resorption, and bone loss |

**CH:** Calcium hydroxide | **Czoz:** Zinc oxide ozonated oil | **Cv:** Vitapex | **Cp:** Propolis liquid mixed Endoflas powder mixture | **CTZ**: zinc oxide, tetracycline, chloramphenicol and eugenol | **C-Modified 3Mix**: Ornidazole, ciprofloxacin and cefaclor applied in coronal pulp | **CR-Modified 3Mix**: Ornidazole, ciprofloxacin and cefaclor applied in coronal and radicular pulp | **GAMN1:** Teeth without periapical involvement underwent pulpectomy by non-instrumentation technique | **GAMR1:** Teeth with periapical involvement underwent pulpectomy by non-instrumentation technique | **GAMN2:** Teeth without periapical involvement underwent pulpectomy by instrumentation technique | **GAMR2:** Teeth with periapical involvement underwent pulpectomy by instrumentation technique | **Cmc:** MaistoCapurro paste | **Cos:** Ocimum sanctum | **RCT:** Conventional root canal treatment | **Cf:** Formocresol | **Sim:** Simvastatin | **MTA:** Mineral trioxide aggregate | **ZOE:** Conventional zinc oxide eugenol pulpectomy | **Pulpotec:** pulpotomy and pulpotec (Pulpotec kit contains powder and liquid, carbide surgical bur, endo bur, diamond pear shaped bur and paste filler) procedure | **3MixMP-C:** Metronidazole, ciprofloxacin, and minocycline with carriers (macrogol and propylene glycol) used after removal of the coronal pulp | **3MixMP-CR:** Metronidazole, ciprofloxacin, and minocycline with carriers (macrogol and propylene glycol) used after removal of the coronal and radicular pulp | **Modified 3Mix**: Ornidazole, ciprofloxacin, and cefaclor | **3Mix-MP**: Metronidazole, ciprofloxacin, and minocycline with carriers (macrogol and propylene glycol) | **GAM**: Gentamycin, amoxicillin and metronidazole | **3Mix**: Ciprofloxacin, ornidazole, and minocycline | **3Mix-MP-R**: Metronidazole, clindamycin, and ciprofloxacin (propylene glycol [P] and polyethylene glycol) | **3Mix-A**: Metronidazole, ciprofloxacin, and cefaclor with carriers (macrogol and propylene glycol) | **3Mix-B**: Ciprofloxacin, metronidazole, and cefixime | **3Mix-C**: Ciprofloxacin, tinidazole and minocycline with carriers (propylene glycol) | **3Mix-D:** Metronidazole, minocycline, and ciprofloxacin | **3Mixin**: Simvastatin powder added to ciprofloxacin, ornidazole and cefixime | **3Mixtatin**: Simvastatin powder added to ciprofloxacin, metronidazole, and cefixime.

Notes: All studies included inclusion and exclusion criteria except Takushige et al. (2004). All studies used a non-instrumentation technique in the intervention groups except Sridevi et al. (2017); (Reddy et al., 2017); and Aminabadi et al. (2016), while Ahirwar et al. (2018) did not specify.

parameter. The results reported were compared to the outcomes listed in the methods section to detect selective reporting. Studies with more than four "Yes" were regarded as high-risk studies. When studies scored ≤ two "Yes" or three "Yes," the bias risk was considered low or moderate, respectively.

### *2.6. Data synthesis*

The authors intended to conduct a quantitative *meta*-analysis only if there were no significant clinical and methodological heterogeneities. A qualitative synthesis was conducted to include descriptions of study outcomes, differences and similarities in the methodologies used, intervention characteristics, and findings from the included studies.

## 3. Results

### *3.1. Study selection*

A total of 4,280 possibly relevant studies were identified and retrieved after searching the electronic databases. Duplicates were eliminated, resulting in 3,232 studies for title and abstract screening. After applying the predetermined inclusion criteria, 3,166 articles were excluded, and 69 full texts were further evaluated for eligibility. Manual searching led to the addition of two studies. Twenty-five studies met the inclusion criteria. Fig. 1 illustrates the screening and selection process.

### *3.2. Risk of bias appraisal*

Of the 25 included studies, the risk of bias in 16 studies was low, seven had a medium risk, and two had a high risk (Fig. 2). Neither allocation concealment nor blinding of participants or evaluators was reported in most of the included studies, resulting in a high risk of bias for all three parameters. (Fig. 2). All studies stated acceptable reasons for missing data, with no major missing outcome data (Fig. 2).

### *3.3. Characteristics of the studies*

Compositions of antibiotic mixtures used for LSTR varied substantially across the included studies, as presented in Table 2. A study utilized a mixture of ciprofloxacin, ornidazole, and minocycline as an intervention was compared to Vitapex (Rai et al., 2019). Another study compared a mixture of metronidazole, ciprofloxacin, and cefaclor to conventional RCT (Grewal et al., 2018). 3Mixtatin (ciprofloxacin, metronidazole, and cefixime) was compared to formocresol (Jamali et al., 2018), mineral trioxide aggregate (MTA) (Aminabadi et al., 2016a, 2016b; Jamali et al., 2018), 3Mix (ciprofloxacin, metronidazole, and cefixime) (Aminabadi et al., 2016b) and simvastatin (Aminabadi et al., 2016b). The modified 3Mix (ornidazole, ciprofloxacin, and cefaclor) was compared to zinc oxide ozonated oil and Vitapex (Doneria et al., 2017b, 2017a). The effect of the modified 3Mix was further compared when applied to the coronal pulp only vs. radicular and coronal application and compared to a mix of zinc oxide, tetracycline, chloramphenicol, and eugenol (Lokade et al., 2019).

The effectiveness of 3Mix-MP (metronidazole, ciprofloxacin and minocycline) was estimated by comparing it to Propolis liquid-mixed Endoflas powder mixture (Divya et al., 2019), *Ocimum sanctum* (Ahirwar et al., 2018), calcium hydroxide (Ali and Raslan, 2021), conventional RCT (Thakur et al., 2021) and formocresol (Reddy et al., 2017). For the effectiveness of 3Mix-MP with macrogol and propylene glycol carriers, it was compared to Vitapex (Nakornchai et al., 2010; Sijini et al., 2021), Maisto•Capurro paste (Zacharczuk et al., 2019), 3Mixin (simvastatin powder added to ciprofloxacin, ornidazole, and cefixime) (Thakur et al., 2021) and 3Mix-MP-R (metronidazole, clindamycin, and ciprofloxacin with propylene glycol [P] and polyethylene glycol) (Raslan et al., 2017). Some studies further compared 3Mix-MP to 3Mix (a mixture of ciprofloxacin, ornidazole, and minocycline) (Nanda et al., 2014) and 3Mix-C (ciprofloxacin, tinidazole, and minocycline) (Jaya et al., 2012) with propylene glycol carriers. The effect of 3Mix-MP after removing the coronal pulp was compared to complete pulp extirpation (Prabhakar et al., 2008). The 3Mix-MP was also compared to conventional zinc oxide eugenol pulpectomy and pulpotec pulpotomy (Agarwal et al., 2011). The success of 3Mix-MP was also assessed on teeth with radicular pathologies of different severity (Trairatvorakul and Detsomboonrat, 2012). One study assessed the success of two differently prepared 3Mix (3Mix-MP and 3Mix-sealer). In the study, the 3Mix-sealer was used in the initial stage and then changed to 3Mix-MP (Takushige et al., 2004). The effect of different concentrations of metron-

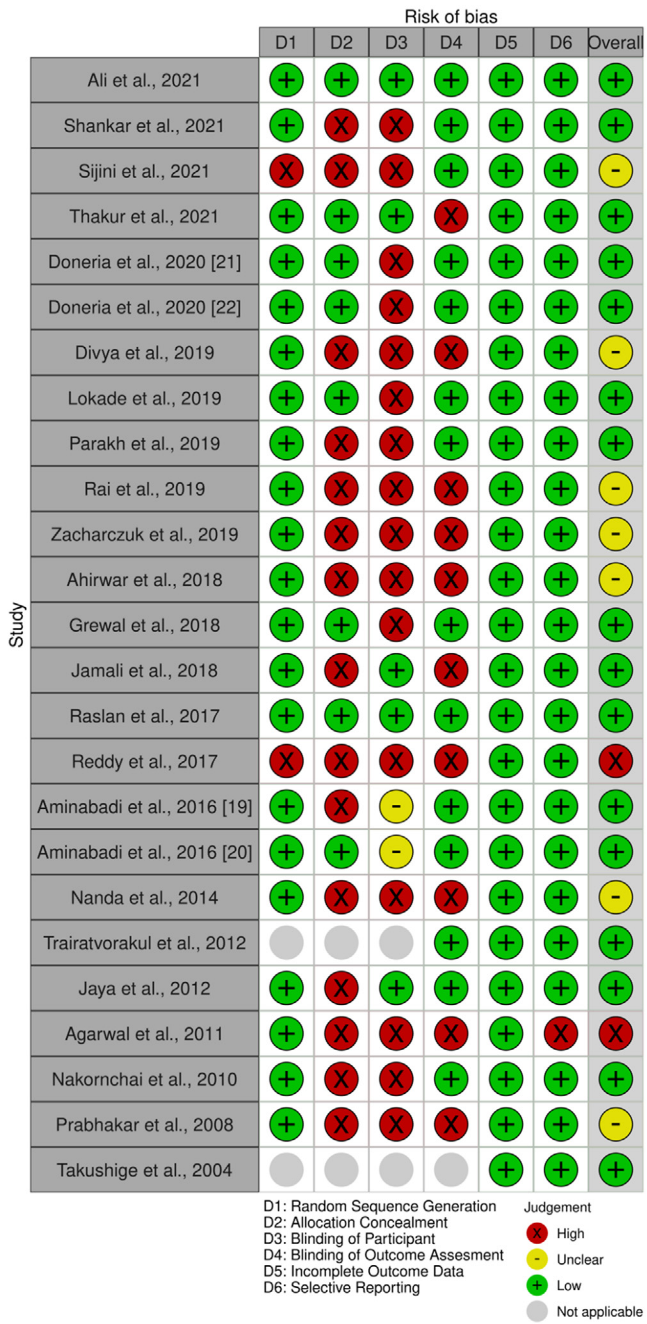


**Fig. 2** Risk of bias assessment.

idazole, clindamycin, and ciprofloxacin (1 mg/mL vs. 1 g/mL) was evaluated in one of the included studies (Shankar et al., 2021). Finally, the effect of gentamycin, amoxicillin, and metronidazole (GAM) mixture with and without instrumentation was evaluated in one of the included studies (Parakh and Shetty, 2019). The sample and participants' characteristics are summarized in Table 2.

### *3.4. Primary outcomes:*

#### *3.4.1. Radiographic success*

There were variations in assessing the radiographic success of antibiotic mixtures for treatment of primary teeth across included studies, as illustrated in Table S1 (Supporting information). Changes in radiographic radiolucency were assessed in 23 of the included clinical trials among which four reported overall radiographic success/failure (Ali and Raslan, 2021; Nakornchai et al., 2010; Shankar et al., 2021; Thakur et al., 2021; Trairatvorakul and Detsomboonrat, 2012; Zacharczuk et al., 2019), eleven focused on inter-radicular area (Aminabadi et al., 2016b; Divya et al., 2019; Doneria et al., 2017b, 2017a; Jaya et al., 2012; Nakornchai et al., 2010; Parakh and Shetty, 2019; Rai et al., 2019; Raslan et al., 2017; Trairatvorakul and Detsomboonrat, 2012; Zacharczuk et al., 2019) and six involved periapical radiolucency assessment (Aminabadi et al., 2016a; Jamali et al., 2018; Nakornchai et al., 2010; Rai et al., 2019; Raslan et al., 2017; Trairatvorakul and Detsomboonrat, 2012; Zacharczuk et al., 2019). Some of the selected studies assessed root resorption either internally (Divya et al., 2019; Doneria et al., 2017b, 2017a; Parakh and Shetty, 2019; Trairatvorakul and Detsomboonrat, 2012), externally (Rai et al., 2019), or any root resorption (Aminabadi et al., 2016b; Jamali et al., 2018; Nakornchai et al., 2010; Takushige et al., 2004; Zacharczuk et al., 2019). Bone loss was also checked radiographically in four of the included studies (Nanda et al., 2014; Prabhakar et al., 2008; Reddy et al., 2017; Takushige et al., 2004), and five studies evaluated radiographic bone regeneration (Nanda et al., 2014; Prabhakar et al., 2008; Reddy et al., 2017; Trairatvorakul and Detsomboonrat, 2012; Zacharczuk et al., 2019). Two trials used the continuity of lamina dura as an indicator of treatment success (Parakh and Shetty, 2019; Trairatvorakul and Detsomboonrat, 2012). Additionally, reduction in root length (Grewal et al., 2018), periodontal ligament widening (Jamali et al., 2018), hard tissue barrier (Aminabadi et al., 2016b), stasis of radiolucency (Aminabadi et al., 2016a), and deviation in the eruption of succedaneous teeth (Divya et al., 2019) were considered in the radiographic assessment of LSTR.

### *3.5. Secondary outcomes: Clinical success:*

Clinical successes achieved with 3Mix are described in Tables S2.1-S2.4 (Supporting information).

### *3.6. Other findings:*

One study assessed the absence of calcific metamorphosis up to 12 months of follow-up (Nakornchai et al., 2010). Aerobic and anaerobic antimicrobial efficacies of triple antibiotic paste were assessed in a single trial (Ahirwar et al., 2018). Table S3 (Supporting information).

### *3.7. Summary of findings*

The success of antibiotic mixtures was inconsistent across the included studies. Table S1 (Supporting information) summarizes the primary outcome findings. For radiographic assessment, several studies indicated that antibacterial mixtures significantly outperformed when compared to conventional treatments such as conventional RCT (Grewal et al., 2018; Thakur et al., 2021), formocresol (Reddy et al., 2017) and MTA (Aminabadi et al., 2016a). Other studies reflected no significant difference between antibacterial mixtures and control groups (Ali and Raslan, 2021; Aminabadi et al., 2016b; Jamali et al., 2018; Jaya et al., 2012; Lokade et al., 2019; Nakornchai et al., 2010; Nanda et al., 2014; Raslan et al., 2017; Shankar et al., 2021; Thakur et al., 2021; Zacharczuk et al., 2019). 3Mix-MP with a carrier was as effective as Vitapex (Nakornchai et al., 2010) and Maisto•Capurro paste (Zacharczuk et al., 2019). 3Mix-MP of various components was found comparably successful in reducing radiographic radiolucency (Jaya et al., 2012; Raslan et al., 2017) and increasing bone regeneration (Nanda et al., 2014). GAM mixture was indifferently successful in reducing radiographic symptoms when used with and without an instrumentation technique (Parakh and Shetty, 2019). Different concentrations of antibacterial mixtures with propylene glycol [P] and polyethylene glycol had similar radiographic success (Shankar et al., 2021). Furthermore, the effectiveness of the antibacterial mixture after removing coronal and radicular pulp was significantly higher than removing coronal pulp only (Prabhakar et al., 2008).

Antibacterial mixtures were inferior to Propolis liquid-mixed Endoflas powder in controlling radiographic symptoms (Divya et al., 2019). One trial demonstrated that the radiographic success rates of the antibacterial mixture at 3 and 6 months follow-up were lower than that of Vitapex (74.29% and 77.14% vs. 97.14% and 97.14%, respectively) (Rai et al., 2019). Two studies indicated that modified 3Mix paste had significantly lower radiographic success compared to zinc oxide-ozonated oil and Vitapex (Doneria et al., 2017a, 2017b).

Regarding the clinical outcomes assessment presented in Table S2 (Supporting information), most of the studies revealed that 3Mix had comparable reduction in postoperative spontaneous and percussion pain, swelling, sinus tract, and mobility compared to other treatments (Ali and Raslan, 2021; Aminabadi et al., 2016b; Grewal et al., 2018; Jamali et al., 2018; Jaya et al., 2012; Lokade et al., 2019; Nanda et al., 2014; Parakh and Shetty, 2019; Rai et al., 2019; Raslan et al., 2017; Shankar et al., 2021; Zacharczuk et al., 2019). Additionally, 3Mix effectively reduced postoperative pain and swelling regardless of tooth type and pathological severity (Trairatvorakul and Detsomboonrat, 2012). 3Mixtatin was superior in reducing provoked and spontaneous pain, mobility, and sinus tract compared to MTA (Aminabadi et al., 2016a) and in minimizing pain to percussion with sinus tract compared to simvastatin (Aminabadi et al., 2016b). The clinical success of antibacterial mixtures was insignificantly different despite their poor radiographic outcomes (Doneria et al., 2017b, 2017a; Reddy et al., 2017). However, compared to the Propolis liquid-mixed Endoflas powder, 3Mix showed lower performance in reducing postoperative pain, swelling, and mobility at 12 months postoperatively (Divya et al., 2019). Parakh and Shetty revealed that non-instrumentation techniques are more clinically effective in teeth without periapical involvement, while instrumentation techniques are more clinically effective in teeth with periapical involvement (Parakh and Shetty, 2019).

### *3.8. Meta-analyses*

Analyses of the clinical and radiographic results achieved after 6, 12, 18, and 24 months of follow-up intervals were conducted. Eight *meta*-analyses were performed; ten studies (Divya et al., 2019; Doneria et al., 2017b; Jamali et al., 2018; Lokade et al., 2019; Nakornchai et al., 2010; Rai et al., 2019; Reddy et al., 2017; Sijini et al., 2021; Thakur et al., 2021; Zacharczuk et al., 2019), eleven studies (Aminabadi et al., 2016b, 2016a; Divya et al., 2019; Doneria et al., 2017b; Jamali et al., 2018; Lokade et al., 2019; Nakornchai et al., 2010; Reddy et al., 2017; Sijini et al., 2021; Thakur et al., 2021; Zacharczuk et al., 2019) two studies (Doneria et al., 2017b; Zacharczuk et al., 2019) and two studies (Aminabadi et al., 2016a; Jamali et al., 2018) were included in the 6-, 12-, and 18-month follow-up clinical and radiographic assessments, respectively. Studies lacking control groups (Jaya et al., 2012; Nanda et al., 2014; Prabhakar et al., 2008; Raslan et al., 2017; Takushige et al., 2004; Trairatvorakul and Detsomboonrat, 2012) or having no non-antibiotic mixture as control groups (Parakh and Shetty, 2019) were excluded from the *meta*-analyses. A study was repeated with an additional 18 months of follow-up, thus excluding the former study (Doneria et al., 2017b, 2017a). Additionally, an unclear number of success/failure cases (Grewal et al., 2018) or ambiguity in differentiating between the number of clinical and radiographical failure cases (Agarwal et al., 2011) led to the exclusion of these studies from the *meta*-analyses.

Four *meta*-analyses were performed for radiographic success (Fig. 3) and four for clinical success (Fig. 4). The analyses of the 6-, 12- and 18-month radiographic and clinical performances presented low to moderate statistical heterogeneity values ($I2 < 75\%$), while the 24-month radiographical risk success showed a high statistical heterogeneity value ($I2 > 75\%$). Radiographically and clinically, the antibacterial mixture and control medicaments did not differ significantly. This was based on the radiographic success at 6 (risk ratio [RR] = 0.99, 95% confidence interval [CI], 0.92–1.06, p-value = 0.77; I2 = 42%), 12 (RR = 1.01, 95% CI, 0.94–1.09, p-value = 0.74; I2 = 73%) and 18 (RR = 0.83, 95% CI, 0.68–1.01, p-value = 0.06; I2 = 0%) months, and the clinical success at 6 (RR = 1.01, 95% CI, 0.97–1.05, *p*-value = 0.78; $I_2 = 27\%$), (RR = 1.06, 95% CI, 0.97–1.17, *p*-value = 0.21; $I_2 = 73\%$) and 18 (RR = 0.93, 95% CI, 0.82–1.06, *p*-value = 0.27; $I_2 = 0\%$) months.

## 4. Discussion

This systematic review aimed to evaluate the effectiveness of LSTR using a three-antibacterial mixture in the treatment of non-vital primary teeth. The technique is usually without instrumentation, including a mixture of antibiotics (3-Mixture) placed in the pulp chamber to disinfect inflamed pulp tissue (Coll et al., 2020). This technique saves time and helps avoid primary teeth root canal complexity, especially with uncooperative patients (Sain et al., 2018). The results showed varied success rates and levels of evidence. Most of the included studies directly compared the 3-Mixture with other medicaments and/or obturation materials used in primary teeth. Only six studies had no control groups, yet four of them included a comparison of multiple intervention groups. Clinical studies was an inclusion criterion, following the gold standard for a comprehensive evaluation of treatments, which requires a systematic review of randomized clinical trials (Barton, 2000). Consequently, the most common reason for exclusion was an irrelevant study design.

Of the twenty-three trials that assessed the radiographic success of the 3-Mixture, three trials reported that teeth treated with 3-Mixture had superior outcomes in controlling radiographic symptoms compared to conventional RCT, formocresol, or MTA (Aminabadi et al., 2016a; Grewal et al., 2018; Reddy et al., 2017). However, one clinical trial found no statistical difference in radiographic outcomes between teeth treated with 3-Mixture, formocresol, or MTA (Jamali et al., 2018). This could be due to the differences in the inclusion criteria and techniques utilized in the previous studies.

3-Mixture had inferior success rates to Vitapex at 3- and 6-month follow-ups in treating radiographic symptoms (Doneria et al., 2017a, 2017b; Rai et al., 2019). However, another study found no statistical difference between them (Nakornchai et al., 2010). This might be related to the differences in the inclusion criteria, technique used, and pre-and postoperative radiographic evaluations. However, the results were comparable, and 3-Mixture could be a plausible non-instrumentation technique for treating cases with poor prognoses and uncooperative children (Rai et al., 2019).

When comparing teeth treated with 3-Mixture to Propolis liquid-mixed Endoflas powder, evidence suggested that 3-Mixure was inferior in controlling radiographic symptoms than the latter (Divya et al., 2019). This can be attributed to flavonoids present in Propolis, which have a phagocytic effect on microorganisms as well as the potent repairability of the damaged tissues (Koo et al., 2000; Santos et al., 2019). Further, flavonoids affect the immune system by enhancing phagocytic activities, stimulating cellular immunity, and supporting the healing process by inhibiting arachidonic acid metabolism, thus inhibiting the formation of cyclooxygenase and lipoxygenase enzymes (de Almeida Santo Ramos et al., 2010). Furthermore, zinc and iron, important components in

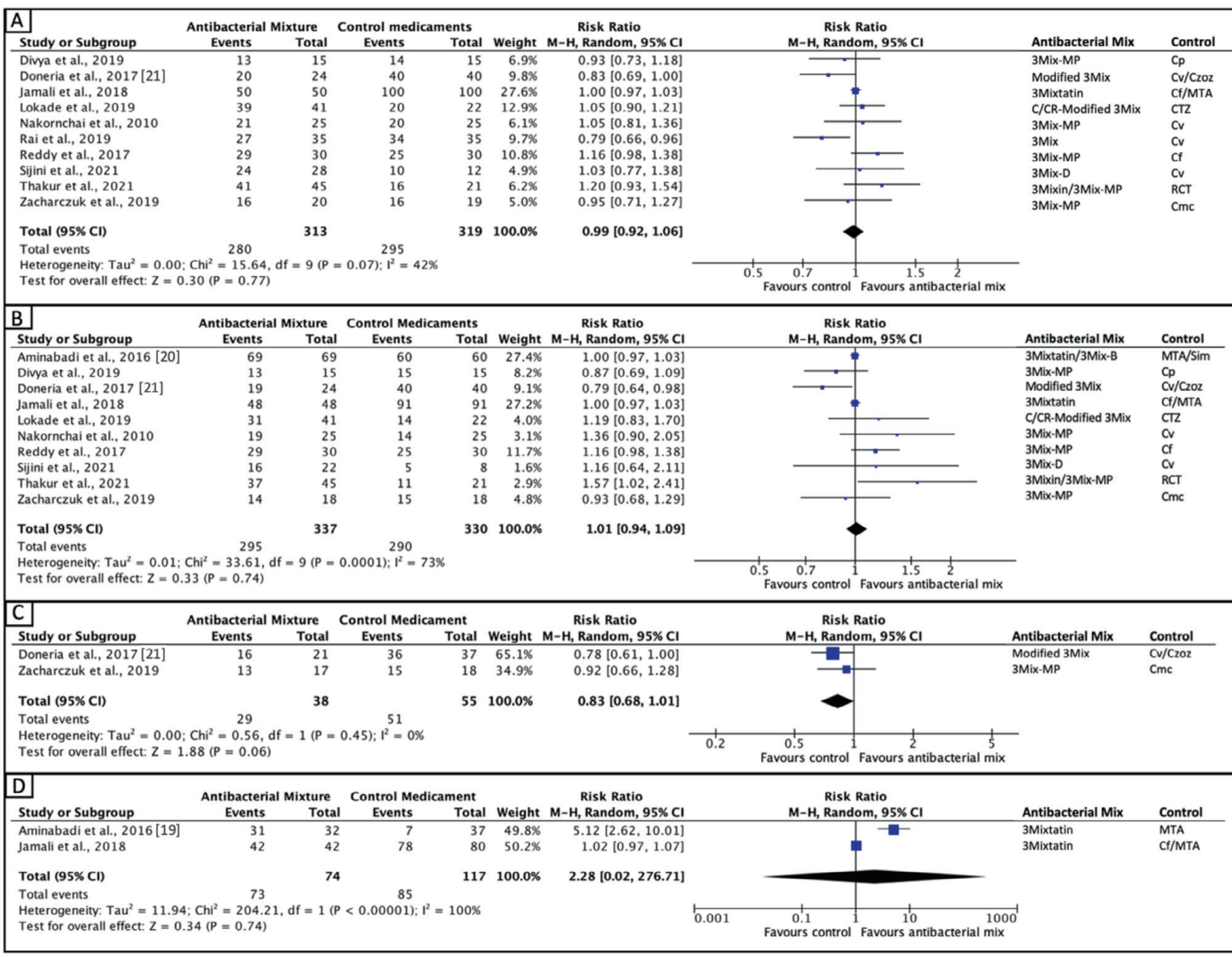


**Fig. 3** Forest plots of the performance of treatments for radiographic success at 6 (A), 12 (B), 18 (C), and 24 (D) months. Abbreviations: 3Mixtatin, simvastatin powder added to ciprofloxacin, metronidazole, and cefixime; MTA, mineral trioxide aggregate; Sim, simvastatin; 3Mix-MP, metronidazole, ciprofloxacin, and minocycline with carriers (macrogol and propylene glycol); Cp, Propolis liquid-mixed Endoflas powder mixture; Modified 3Mix, ciprofloxacin, ornidazole, and cefaclor; Cv, Vitapex; Czoz, zinc oxide ozonated oil; Cf, formocresol; C/CR-Modified 3Mix, metronidazole, ciprofloxacin, and minocycline with carriers (macrogol and propylene glycol used after removal of coronal/ coronal and radicular pulp; CTZ, zinc oxide, tetracycline, chloramphenicol, and eugenol; 3Mix-D, metronidazole, ciprofloxacin, and minocycline; 3Mixin, simvastatin powder added to ciprofloxacin, ornidazole and cefixime; Cmc, Maisto-Capurro paste; 3Mix-B, metronidazole, ciprofloxacin, and cefixime.

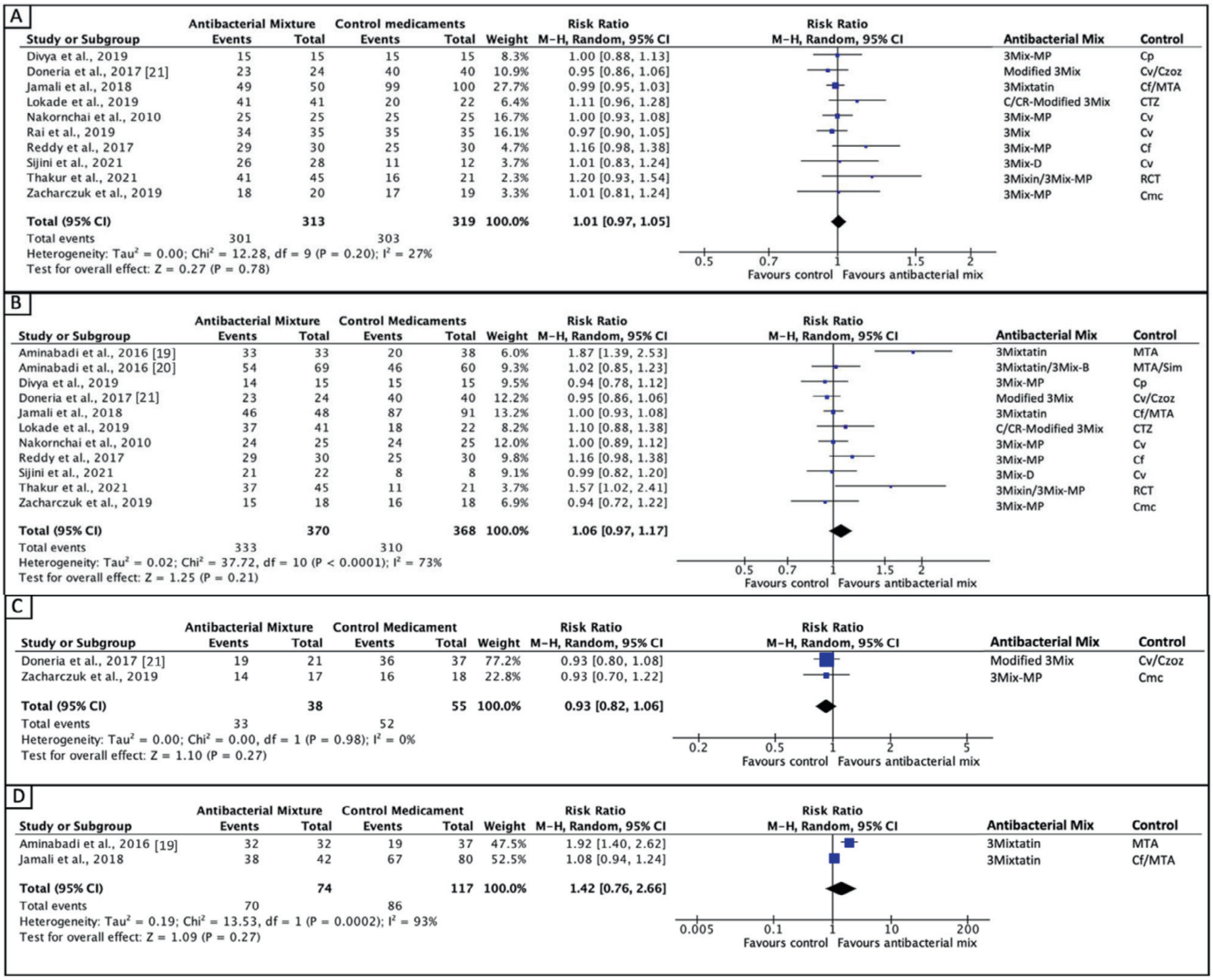


**Fig. 4** Forest plots of treatment performance for clinical success at 6 (A), 12 (B), 18 (C), and 24 (D) months. Abbreviations: 3Mixtatin, simvastatin powder added to ciprofloxacin, metronidazole, and cefixime; MTA, mineral trioxide aggregate; Sim, simvastatin; 3Mix-MP, metronidazole, ciprofloxacin, and minocycline with carriers (macrogol and propylene glycol); Cp, Propolis liquid-mixed Endoflas powder mixture; Modified 3Mix, ciprofloxacin, ornidazole, and cefaclor; Cv, Vitapex; Czoz, zinc oxide ozonated oil; Cf, formocresol; C/CR-Modified 3Mix, metronidazole, ciprofloxacin, and minocycline with carriers (macrogol and propylene glycol used after removal of coronal/ coronal and radicular pulp; 3Mix, ciprofloxacin, ornidazole, and minocycline; CTZ, zinc oxide, tetracycline, chloramphenicol, and eugenol; 3Mix-D, metronidazole, ciprofloxacin, and minocycline; 3Mixin, simvastatin powder added to ciprofloxacin, ornidazole, and cefixime; Cmc, Maisto-Capurro paste; 3Mix-B, metronidazole, ciprofloxacin, and cefixime.

Propolis, promote collagen synthesis (Trairatvorakul and Detsomboonrat, 2012).

The evidence suggests that teeth treated with different components of 3-Mixture have comparable radiographic success in terms of reducing radiographic radiolucency and increasing bone regeneration (Jaya et al., 2012; Nanda et al., 2014; Raslan et al., 2017). The bacteria of the root canal system of primary teeth form mixed communities and a complex network of several microorganisms (Nair et al., 2005; Siqueira et al., 2002). The synergistic effect and different spectra of antimicrobial activity of each component in the mixture target most bacteria in the root canal system regardless of the components of 3-Mixure.

Furthermore, one study reported no statistical difference between teeth treated with GAM when comparing instrumentation and non-instrumentation techniques in reducing radiographic symptoms (Parakh and Shetty, 2019). GAM has a good antimicrobial effect against *Enterococcus faecalis,* a common microorganism detected in endodontic infections (Stuart et al., 2006). Metronidazole and amoxicillin have proven antibacterial effects against mixed bacterial infections when used together (Eykyn, 1983). Gentamycin also has a proven rapid bactericidal effect against gram-negative pathogens (Moulds and Jeyasingham, 2010). GAM paste is easily distributed into the root canal system and induces a sterile zone through the action of the antibacterial medicaments, promoting tissue repair irrespective of the technique used (Parakh and Shetty, 2019).

When comparing clinical signs and symptoms of pain or sensitivity to percussion and palpation, an insignificant difference was found among intervention and control groups at different intervals (Doneria et al., 2017b, 2017a; Grewal et al., 2018; Jamali et al., 2018; Jaya et al., 2012; Nakornchai et al., 2010; Nanda et al., 2014; Prabhakar et al., 2008; Rai et al., 2019; Raslan et al., 2017; Reddy et al., 2017; Trairatvorakul and Detsomboonrat, 2012; Zacharczuk et al., 2019). However, a statistically significant difference was observed when comparing pre- and postoperative clinical outcomes of 3Mix-MP and Propolis liquid-mixed Endoflas powder mixture (Divya et al., 2019). Another study demonstrated significant clinical success of GAM-LSTR among all the groups when comparing the presence of pre- and postoperative spontaneous pain and tenderness to percussion (Parakh and Shetty, 2019). This indicates that using GAM with both instrumentation and non-instrumentation techniques can be an alternative to conventional pulpectomy (Parakh and Shetty, 2019).

The use of 3-Mixture was comparably effective in reducing postoperative swelling compared to other treatments (Doneria et al., 2017b, 2017a; Grewal et al., 2018; Jamali et al., 2018; Nakornchai et al., 2010; Nanda et al., 2014; Parakh and Shetty, 2019; Rai et al., 2019; Raslan et al., 2017; Reddy et al., 2017; Zacharczuk et al., 2019). The evidence suggests that teeth treated with LSTR and 3Mix antibiotics, compared to other materials and techniques, had a statistically similar effect on the healing of sinus tracts. Multiple bacteria in the root canals were found to have a positive association with the formation of sinus tracts (Qi et al., 2016). The 3Mix can help eliminate the main causative factor of treatment failure in primary teeth, which is bacterial contamination and inflammation (Aminabadi et al., 2016a). This makes it an efficient treatment option for non-vital primary teeth, similar to other treatments. A study demonstrated significant improvement in sinus tract healing when using 3Mixtatin compared to MTA (Aminabadi et al., 2016a). On the contrary, the 3Mix group in another study had significantly more sinus tracts after 12 months compared to 3Mixtatin, MTA, and simvastatin groups (Aminabadi et al., 2016b). 3Mixtatin combines the anti-inflammatory and bioinductive effects of simvastatin with the antibacterial effect of 3-Mixture (Dombrecht et al., 2007). Furthermore, statins were found to stimulate angiogenesis leading to improved healing of the sinus tract (Dombrecht et al., 2007).

Sixteen studies assessed tooth mobility based on the absence of non-physiological mobility. One study found a significant difference in the resolution of non-physiological mobility when using 3Mixtatin compared to MTA with a *p*-value of 0.005 (Aminabadi et al., 2016a). This can be related to the bio-inductive effects of simvastatin in 3Mixtatin, which promotes the transformation of mesenchymal stem cells to osteoblasts and improves its proliferation while inhibiting osteocyte apoptosis (Oxlund et al., 2001; Silveira et al., 2008; Yoshinari et al., 2006).

It was noted that in most of the included studies, allocation concealment was not done, and patients were not blinded, or it was unclear. This might impose an effect on subjective outcome measures. A limitation of the present study is that grey literature was not included in the search.

## 5. Conclusions

There is limited evidence on LSTR using different antibacterial mixtures, particularly of comparisons between different compositions of the 3-antibacterial mixture. Further subgroup *meta*-analyses are recommended if more studies are available in the future.

## CRediT authorship contribution statement

**Nabras Alrayes:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Yara Almaimouni:** Formal analysis, Writing – original draft, Writing – review & editing, Project administration. **Abrar Tounsi:** Writing – original draft, Writing – review & editing. **Khalid Tarabzouni:** Formal analysis, Writing – original draft. **Faisal Alonaizan:** Writing – original draft. **Maria Salem Ibrahim:** Conceptualization, Methodology, Software, Validation, Resources, Data curation, Writing – original draft, Visualization, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Institutional review board statement

Not applicable.

## Informed consent statement

Not applicable.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sdentj.2023.06.001.

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