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SYSTEMATIC REVIEW

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The efficacy of implant surface decontamination using chemicals during surgical treatment of peri-implantitis: A systematic review and meta-analysis

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Abstract

Aim: To answer the following PICOS question: "In adult patients with peri-implantitis, what is the efficacy of surgical therapy with chemical surface decontamination of implant surfaces in comparison with surgical therapy alone or surgery with placebo decontamination, on probing pocket depth (PD) reduction and bleeding on probing (BoP)/suppuration on probing (SoP), in randomized controlled clinical trials (RCTs) and non-RCTs with at least 6 months of follow-up?"

Materials and Methods: Six databases were searched from their inception up to 20 May 2022. Data on clinical outcome variables were pooled and analysed using mean differences (MDs), risk ratios (RRs), or risk differences (RDs) as appropriate, 95% confidence intervals (CIs), and prediction intervals (PIs) in the case of significant heterogeneity. Primary outcomes were determined as changes in PD and BoP/SoP. Secondary outcomes were radiographic marginal bone loss (MBL), implant loss, and disease resolution. PROSPERO registration number: CRD42022325603.

Results: Six RCTs—two with moderate, three with high, and one with low risk of bias (RoB)—were included. These studies test the adjunctive effect of photodynamic therapy (PDT), chlorhexidine (CHX), and administration of local antibiotics (LAbs) during surgery on the clinical outcome. In a single 12-month study, the adjunctive use of local antibiotics showed a clinically relevant reduction of PD [MD $=$ 1.44; 95%CI (0.40 to $-$2.48)] and MBL [MD $=$ 1.21; 95%CI (0.44–1.98); one trial, 32 participants]. PDT showed a small but significant reduction in BoP [MD $=$ 7.41%; 95%CI (0.81–14.00); $p = 0.028$; two trials; 42 participants]. Treatment with CHX resulted in no significant changes in PD, BoP, or MBL compared to placebo (saline solution). None of the interventions affected disease resolution and implant loss. Certainty of the evidence was very low for all outcome measures assessed.

Conclusions: Within the limitations of this systematic review and the meta-analysis, adjunctive use of chemicals such as PDT, CHX, and LAbs for surface decontamination during surgery of peri-implantitis cannot be recommended as superior to standard debridement procedures (mechanical debridement with or without saline).

KEYWORDS
dental implants, systematic review, therapy

Clinical Relevance

Scientific rationale for the study: Numerous surgical techniques to treat peri-implantitis have been suggested, most include various approaches of decontamination of implant surfaces. This work systematically reviews the efficacy of chemical decontamination of implant surfaces during surgery.

Principal findings: Twelve months post-treatment, PDT significantly reduced BoP, while LAbs significantly reduced PD and MBL. However, the analysis was based on a small number of studies with very low certainty of the evidence.

Practical implications: There is no decisive evidence (limited and heterogenous results) showing that the adjunctive use of chemical implant surface decontamination improves the outcome of surgical therapy of peri-implantitis.

1 | INTRODUCTION

Peri-implantitis is a chronic inflammatory disease involving the breakdown of soft and hard tissues supporting a dental implant, which may ultimately result in implant and restoration loss (Berglundh et al., 2018). Among the various factors that have been implicated in the aetiology of peri-implantitis, bacterial dysbiosis and the concomitant growth of various Gram-negative anaerobic microflora is considered a major risk factor (Sanz-Martin et al., 2017; Zhuang et al., 2016). The prevalence of peri-implantitis ranges from 10% to 22% at the implant level (Salvi et al., 2019) and between 22% and 56% at the patient level (Derks & Tomasi, 2015; Lindhe & Meyle, 2008). Thus, it is a global health concern affecting millions of people worldwide. Moreover, since dental implants are generally performed in the mature/elderly population, disease burden will further expand owing to the expected increase in life expectancy.

Since the aetiology of peri-implantitis is associated with the peri-implant biofilm, most of the suggested therapeutic strategies are aimed at reducing the biofilm load and shifting its composition. Numerous mechanical treatment protocols have been suggested for the treatment of peri-implantitis, including non-surgical techniques, surgical procedures, and combined approaches. However, non-surgical anti-infective treatments have limited efficacy in most cases of peri-implantitis (Lindhe & Meyle, 2008; Renvert et al., 2008; Schwarz et al., 2015), which is possibly due to the difficulty of completely removing the plaque from the implant surfaces by mechanical debridement alone. Therefore, surgical debridement approaches have been suggested, and the adjunctive use of various chemotherapeutic agents was advocated to allow better decontamination of implant surfaces to increase the overall effectiveness of the surgical mechanical treatment. The most common anti-microbial treatments include the local application of substances such as chlorhexidine (CHX), citric acid, hydrogen peroxide, 35% phosphoric acid gel, tetracycline, minocycline, or saline (Mellado-Valero et al., 2013). Although some studies show that surgical debridement can improve clinical parameters, such as reduced PD and bleeding on probing (BoP), and are capable of slowing or attenuating the progression of peri-implantitis (Heitz-Mayfield & Mombelli, 2014; Renvert et al., 2012), there is still no single "gold standard" treatment protocol for treating peri-implantitis. Furthermore, evidence regarding the efficacy of chemical decontamination of implant surfaces is limited (Patil et al., 2022).

The aim of the present systematic review was to answer the following PICOS question: "In adult patients with peri-implantitis (P), what is the efficacy of surgical therapy with adjunctive chemical implant surface decontamination (I), as compared to mechanical debridement with or without saline (standard therapy) (C), with regard to reduction of PD and BoP/suppuration on probing (SoP) (O), as reported in prospective controlled clinical trials with a follow-up of at least 6 months"?(S) (Table 1).

RCTs and non-RCTs were chosen because these types of studies offer the highest level of testing the efficacy of the selected interventions.

2 | MATERIALS AND METHODS

2.1 | Protocol development and systematic review reporting

The reporting of this systematic review adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and was conducted following the Cochrane's Handbook (Cumpston et al., 2019).

The protocols were presented to the Workshop Committee for the XVIII European Workshop on Periodontology. Protocol approval and registration in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42022325603) were completed prior to the study commencement.

2.2 | Eligibility criteria

2.2.1 | Inclusion criteria

Prospective controlled clinical trials with a minimum of eight randomized/allocated patients per group were included. All patients were

TABLE 1 Components of the PICOS question.

P: Population	Individuals aged above 18 years otherwise healthy with peri-implantitis as defined by the 2017 World Workshop (Berglundh et al., 2018) or with other well-defined criteria, based on clear clinical and radiographic parameters.
I: Intervention	Surgical therapy of peri-implantitis, using scalers (hand and ultrasonic) to remove hard deposits with or without saline application, with chemical surface decontamination of the implant surfaces with topical antibiotics, any antibacterial agent [chlorhexidine (CHX), cetylpyridinium chloride (CPC) etc.], acid, ethylenediaminetetraacetic acid (EDTA) and photodynamic therapy (PDT), alone or combined with other mechanical/physical approach.
C: Comparator	Surgical therapy of peri-implantitis using scalers with or without saline application or another placebo solution not aiming at chemical decontamination of the implant surface.
O: Outcomes	*Primary outcomes* • Probing depth reduction measured as mean difference of PD (mm) • Bleeding on probing/suppuration on probing • *Secondary outcomes* • Radiographic marginal bone level (MBL) changes • Composite outcomes (primary outcomes + MBL) • Dental implant/implant-supported prosthesis loss or survival • Adverse effects: gingival recession (mm) and antibiotics resistance (in studies that used local antibiotics) • Patient-reported outcome measures (PROMs): patient discomfort/pain, oral-health-related quality of life (OHIP-CP), and economic factors • Disease resolution
S: Study design and duration	Parallel, cross-over or split-mouth RCTs or CCTs with a minimum of eight randomized/allocated patients per group, with a follow-up of at least 6 months.

>18 years old and were diagnosed with peri-implantitis, as defined by the 2017 World Workshop (Berglundh et al., 2018) or by other well-defined criteria, based on clear clinical and radiographic parameters. Reports included PD and BoP/SoP measurements at 6 months or more of follow-up.

2.2.2 | Exclusion criteria

Studies carried out specifically on patients with diabetes or other known systemic conditions, studies with no supporting periodontal therapy performed at 3–6-month intervals during the first year post therapy and throughout the follow-up period, and pre-clinical in vivo studies were excluded.

2.2.3 | Information sources and search

Two investigators (CM, AL) independently searched MEDLINE (via Pubmed), Embase, Cochrane Library (CENTRAL), Web of Science, Scopus, and clinicaltrials.gov from the inception of each database up to 20 May 2022, to identify published, unpublished, and ongoing studies. The full electronic search strategy for all electronic databases is presented (exactly as run without search filters) in Table S1. To identify newly published studies, an email alert service was used on MEDLINE. Reference lists of all relevant primary studies and systematic reviews were also screened to identify additional data sources. Because of time limitations, only publications in English language were included. Reference lists of retrieved papers and previously published systematic reviews were also manually searched. Grey literature was not excluded from our search. Attempt to contact primary authors was made if additional information was needed.

2.3 | Study selection

Citations identified from the electronic searches were imported into Covidence Software. After reviewer calibration, eligibility assessment was based on a two-step approach: (1) screening of titles and abstracts, and (2) full-text analysis. Discrepancies arising from independent peer review were resolved by discussion and consultation among all authors. During the full-text screening, a list of excluded reports and the reasons for elimination from the study were recorded. Inter-observer agreement for the screening of complete articles was assessed using the kappa (κ) score.

2.4 | Data collection process

Based on the Cochrane recommendations, a standardized, pre-piloted data extraction form was designed for data collection. Data were extracted from eligible studies and recorded by two reviewers (Asaf Wilensky, Lior Shapira). Two additional examiners (Alvaro Limones, Conchita Martin) independently cross-checked the accuracy and validity of all data obtained from the studies. Studies lacking enough data for meta-analyses were kept in the systematic review but excluded from the meta-analyses. Corresponding authors of studies or published protocols were contacted for further information in cases where the data were incomplete or missing. In the event that the same study was reported in multiple publications, the data were collated in order for each study, rather than each report, to be constituted as the unit of interest for the review, giving it a unique identifier based on its primary publication.

2.5 | Risk of bias (RoB) in individual studies

RoB and quality assessment were conducted by two reviewers (Alvaro Limones, Conchita Martin) using the Cochrane RoB 2.0 tool

(Sterne, Savovic, et al., 2019). Assessments were made based on journal articles and trial protocols, when available on international registry platforms, using PD and BoP as primary outcomes. Funding for the study and perceived independence of the authors were also evaluated.

2.6 | Data analysis

When the differences between (Δ) baseline and end were not reported, they were calculated using the formula: $\Delta Var = Var2 - Var1$, where Var1 is the mean value before treatment and Var2 the mean value after treatment. In addition, the variance ΔVar was estimated using the formula $SVar^2 = SVar1^2 + SVar2^2 - (2*r*SVar1*SVar2)$, where $SVar^2$ is the variance of the difference, $SVar1^2$ is the variance of the mean baseline value, and $SVar2^2$ is the variance of the mean end value. SVar1 and SVar2 are the standard deviations (SDs) of the baseline and end values, respectively. A correlation *r* value of 0.5 was used as previously described (Paraskevas et al., 2008). If treatment effects (mean or SD) were not reported in the publications, the authors were requested to provide this information. Dichotomous outcomes were pooled and analysed using risk difference (RD) or risk ratio (RR), along with their corresponding 95% confidence intervals (CIs). Subgroup analyses were performed based on the chemical procedure type: (1) photodynamic therapy (PDT); (2) antiseptics; and (3) local antibiotics (LAbs). Forest plots were created to illustrate the effects of the global estimation in the meta-analysis and the various sub-analyses.

The extent and impact of heterogeneity between studies was assessed by inspecting the forest plots and by calculating the *Q*-test according to Dersimonian and Laird (DerSimonian & Laird, 1986). As a complement to the *Q*-test, the I^2 index was calculated in order to measure the percentage of variation in the global estimate that was attributable to heterogeneity ($I^2 = 25\%$: low; $I^2 = 50\%$: moderate; $I^2 = 75\%$: high). Study-specific estimates were pooled using both the fixed effects model (Mantel–Haenszel-Peto test) and the random effects model (Dersimonian–Laird test). In the event significant heterogeneity was found, the random effects model results were presented.

In cases of heterogeneity, in addition to the summary estimate (MD) and 95%CI, prediction intervals were reported to allow more informative inferences and illustrate the range of true effects that can be expected in future settings, by presenting heterogeneity in the same metric as the original effect size measure (IntHout et al., 2016).

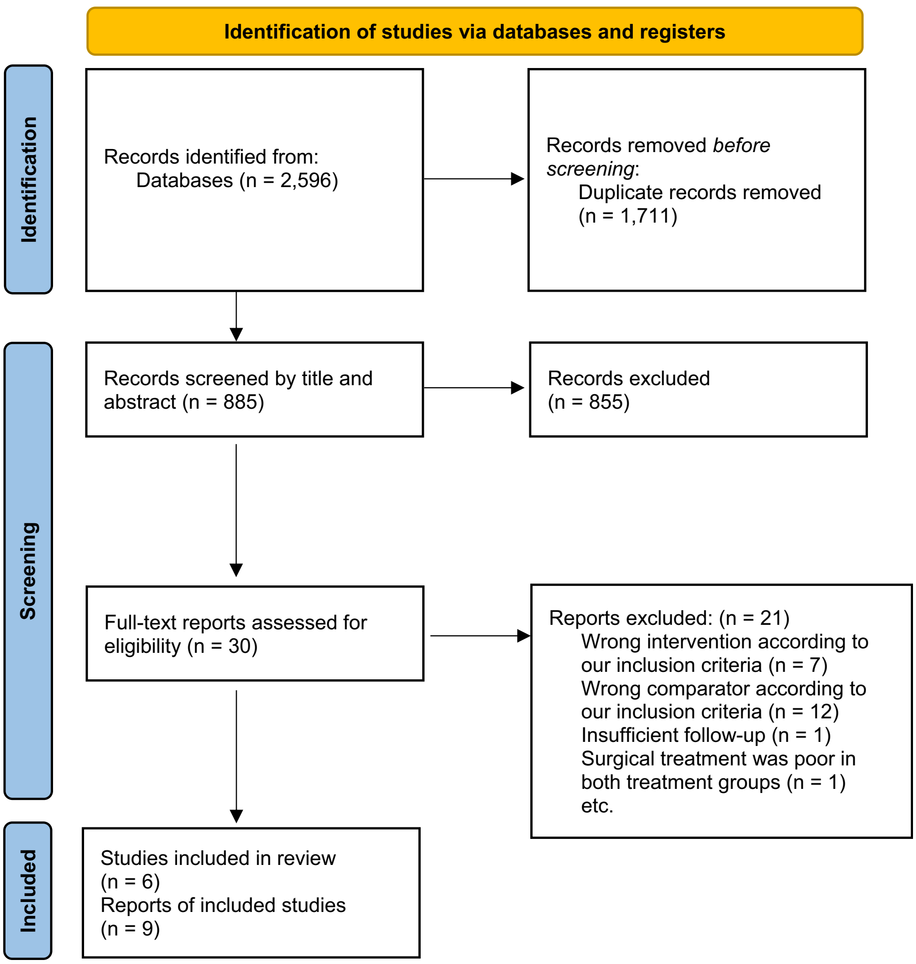


FIGURE 1 Flow diagram: selection of studies evaluating adjunctive chemical surface decontamination during surgical therapy of peri-implantitis. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Main characteristics of included studies.

First author and year	Setting	Fundin/support	Study design	Follow-up (months)	Time points (6 months or more)	Author's conclusion
Albaker et al., 2018	Private	University	RCT, Parallel	12	6 and 12	A single application of PDT as an adjunct to OFD does not provide additional benefit in improving clinical and radiographic peri-implant parameters in peri-implantitis.
Carcuac et al., 2016 (without systemic antibiotics)	Public clinics/ University setting	Swedish Research Council, University, Swedish Dental Society	RCT Parallel	12	6 and 12	The local use of chlorhexidine had no overall effect on treatment outcomes.
Carcuac et al., 2016 (with systemic antibiotics)	Public clinics/ University setting	Swedish Research Council, University, Swedish Dental Society	RCT Parallel	12	6 and 12	The local use of chlorhexidine had no overall effect on treatment outcomes. The effect of adjunctive systemic antibiotics depended on implant surface characteristics.
Cha et al., 2019	University	Industry	RCT Parallel	6	6	Repeated local delivery of minocycline would improve the success rate of the surgical treatment of peri-implantitis, in terms of increasing the peri-implant bone gain and improving clinical outcomes in the short healing period.
de Waal et al., 2013	University	Industry	RCT Parallel	12	6 and 12	Surface decontamination with 0.12% CHX + 0.05% CPC in resective surgical treatment of peri-implantitis does not translate to better clinical or radiographical outcomes of the intervention.
Emanuel et al., 2020	University	Industry	RCT Parallel	12	6 and 12	β-Tricalcium phosphate granules with doxycycline hyclate might create favourable conditions that enable implant surface decontamination and soft and hard tissue healing over a prolonged period.
Esposito et al., 2013	University and private	NR	RCT Parallel	12	4 and 12	The use of adjunctive PDT with mechanical cleaning of implants affected by peri-implantitis did not improve any clinical outcomes when compared to mechanical cleaning alone up to 1 year after treatment.

Abbreviations: CHX, chlorhexidine; CPC, cetylpyridinium chloride; NR, not reported; OFD, open flap debridement; PDT, photodynamic therapy; RCT, randomized controlled clinical trial.

STATA14 (StataCorp LP, Lakeway Drive, College Station, Texas, USA) intercooled software was used to perform all analyses. Statistical significance was set at $p \le .05$.

2.7 | RoB across studies: strength of the evidence

The overall quality of evidence was rated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach (Guyatt et al., 2011) following the summary of findings table format by Carrasco-Labra et al. (Carrasco-Labra et al., 2016). To reach an outcome-level grading of evidence, the authors considered RoB, inconsistency, imprecision, reporting bias, publication bias, large effects, plausible confounding, and dose–response gradient as per the GRADE methodology.

2.8 | Method for addressing the reporting of biases

Publication bias was addressed in several ways: (1) In the case of a sufficient number of included studies (i.e., at least 10 studies; with fewer studies, the power of the tests is too low to distinguish chance from real asymmetry), funnel plots were used, although an asymmetrical funnel plot was not equated with publication bias. (2) Egger's test was used to assess publication bias. (3) Results of tests for funnel plot asymmetry were interpreted by visual inspection of the funnel plot. The contribution made to the totality of the evidence by studies with statistically non-significant results compared to those from studies with statistically significant results was considered.

2.9 | Sensitivity analysis

Post hoc sensitivity analyses were performed by excluding studies, one by one, from the global estimation for primary outcome (PD and BoP changes). Additionally, an overall visual distribution of the specific estimators of each publication was carried out, and studies following an alternative pattern were identified.

3 | RESULTS

3.1 | Study selection

Figure 1 shows the inclusion and exclusion study flow-chart. The electronic search yielded 2596 references, of which 1711 titles were removed after deduplication. Titles and abstracts were screened in the remaining 885 references. After screening, 855 references were discarded (agreement = 95.65%; κ = 0.83), resulting in 30 references. Following the review of the full-text articles, 21 articles were excluded (Table S2) for the following reasons: 7 articles did not meet our inclusion criteria regarding intervention; 12 studies were excluded because the control group deviated from our PICOS question; and 1 study contained an insufficient follow-up period. The results of one study were vastly divergent from results previously reported in other studies on surgical treatment of peri-implantitis, especially for the control groups. Moreover, the effects on BoP reduction seemed inconsistent with changes in PD (Bombeccari et al., 2013). Six RCTs published in nine articles were included in our analysis (agreement = 90%; κ = 0.75).

3.2 | Study characteristics

The methodologies used by the six included studies are shown in Table 2. One study, by Carcuac et al., 2016, included four groups: intervention and control with administration of systemic antibiotics, and intervention and control without administration of systemic antibiotics; hence, this study was added to our analysis as two separate studies, according to the administration of pre-surgical antibiotics (Carcuac et al., 2016). All studies included in the meta-analysis were designed as parallel-arm RCTs. Three studies were conducted in a university setting (Cha et al., 2019; de Waal et al., 2013; Emanuel et al., 2020), one study was carried out at a private clinic (Albaker

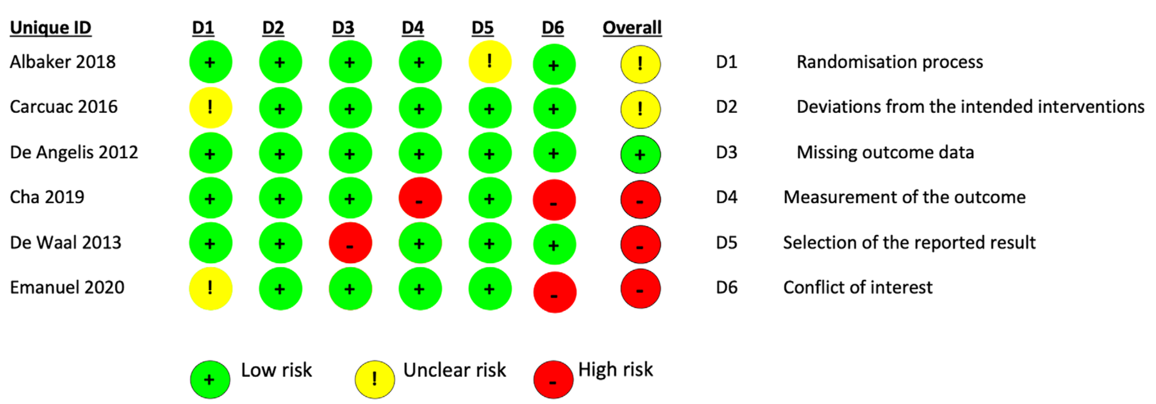


FIGURE 2 Risk-of-bias assessment of the individual studies. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Characteristics of the studies and population.

Study	Definition of peri-implantitis	Hygienic phase prior to treatment	Pre-/post-treatment systemic antibiotics	Intervention	Sample size-intention to treat (*n*)	Total no. of implants intention to treat	Overall age (years) Mean	SD	Range	Gender (females) (%)	Smokers *n*	Diabetes
Albaker et al., 2018	PD≥5 + BoP/Sup + MBL≥2 mm in 1 year or MBL≥3 mm	Yes	Yes	Debridement + PTD	24	24	NR	NR	NR	NR	12	6 pre-diabetic
Carcuac et al., 2016 (without systemic antibiotics)	PD ≥6 mm + BoP/Sup; MBL >3 mm	Yes	No	Debridement + 0.2% CHX	48	86	65.75	NR	27–88	58.3%	15	3
Carcuac et al., 2016 (with systemic antibiotics)	PD ≥6 mm + BoP/Sup; MBL >3 mm	Yes	Yes	Debridement + 0.2% CHX	52	93	66.3	NR	21–90	71%	18	2
Cha et al., 2019	PD >5, MBL >2 mm + BoP	Yes	Yes	Debridement + minocycline ointment	50	50	61.6	NR	40–84	50%	0	0
de Waal et al., 2013	PD ≥5 mm + BoP/Sup + bone loss ≥2 mm	Yes	No	Debridement + CHX/CPC	30	79	59.4	14	NR	66%	11	NR
Emanuel et al., 2020	PD 6–10 mm + BoP/Sup + bone loss >2 mm	Yes	Yes	Debridement + βTCP sustained-release doxycycline	27	28	64.81	7.61	NR	16%	0	NR
Esposito et al., 2013 de Angelis 2012	MBL ≥5 mm + inflammation (Sup/swelling/ redness)	NR	No	PDT	19	19	53	12.19	25–71	42%	4	NR

Abbreviations: BoP, bleeding on probing; βTCP, β-tricalcium phosphate; CHX, chlorhexidine; CPC, cetylpyridinium chloride; MBL, marginal bone level; NR: not reported; PD, pocket depth; PDT, photodynamic therapy; Sup, suppuration.

et al., 2018), one study was performed in a public clinic within a university setting (Carcuac et al., 2016), and one study was at a university and private clinics (Esposito et al., 2013). Three of the studies were funded or supported by the industry (Cha et al., 2019; de Waal et al., 2013; Emanuel et al., 2020) and two studies by non-industrial public funding (Albaker et al., 2018; Carcuac et al., 2016), whereas in one study the source of funding was not reported (Esposito et al., 2013). Overall, the follow-up periods relevant to the inclusion criteria of this meta-analysis varied between 6 and 12 months. In the study by Esposito et al. (Esposito et al., 2013), the first follow-up was at 4 months (de Angelis et al., 2012).

3.3 | RoB in individual studies

Figure 2 presents the RoB assessed using the Cochrane RoB 2.0 tool (Sterne, Savović, et al., 2019). One study was qualified as having a "low" RoB (de Angelis et al., 2012), two studies were qualified as having "some concerns" (Albaker et al., 2018; Carcuac et al., 2016) due to the randomization process and selection of the reported results, and three studies were qualified as having a "high" RoB due to missing outcome data (multiple implant loss in the control group; de Wall et al., 2013), the manner in which the outcome was measured (questionable blindness; Cha et al., 2019), and possible conflict of interest (Cha et al., 2019; Emanuel et al., 2020). The number of studies that contained a low RoB for specific criteria varied according to the assessed item: randomization process ($n = 4$), deviations from the intended interventions ($n = 6$), missing outcome data ($n = 5$), measurement of the outcome ($n = 5$), and selection of the reported result ($n = 5$). Detailed information about each specific domain and complete evaluation is presented in Table S3. The contribution made to the entire evidence by studies with different RoB assessments was further considered during the sensitivity analysis. No significant impact from studies rated as high or low RoB was found.

TABLE 4 Results of the meta-analyses for the primary and secondary outcomes showing the changes from baseline to 6 months at implant and at patient level. Subgroup analysis according to the interventions in the test group.

	Baseline to 6 months								
					95%CI				
Implant level		**Subgroup by test group**	***n***	**MD**	**Lower**	**Upper**	***p*-value**	**I^2 (%)**	***p*-value**
PPD changes (mm)	Overall		376	0.265	−0.29	0.821	.349	62.6	.014
		PDT	42	−0.179	−0.988	0.629	.664	0	.401
		CHX	256	0.319	−0.655	1.294	.521	83	.002
		L_Antib	78	0.592	0	1.421	.161	9.8	.292
BOP changes (%)	Overall		198	7.30	1.599	13	.012	0	.836
		PDT	42	6.622	0.047	13.197	.048	0	.916
		CHX	78	6.8	−7.607	21.207	.355	-	
		L_Antib	78	13.714	−5.121	32.548	.154	0	.331
MBL changes (mm)	Overall		180	0.481	−0.031	0.992	.065	47.2	.128
		PDT	24	−0.100	−1.221	1.021	.861	-	
		CHX	78	0.100	−0.894	1.094	.844	-	
		L_Antib	78	0.779	−0.096	1.655	.081	75.4	.044
	Baseline to 6 months								
					95%CI				
Patient level		**Subgroup by test group**	***n***	**MD**	**Lower**	**Upper**	***p*-value**	**I^2 (%)**	***p*-value**
PPD changes (mm)	Overall		115	0.146	−0.508	0.800	.663	17.3	.305
		PDT	42	−0.179	−0.988	0.629	.664	0	.410
		L_Antib	73	0.526	−0.558	1.609	.342	39.0	.200
BOP changes (%)	Overall		115	7.626	1.374	13.877	.017	0	.685
		PDT	42	6.622	0.047	13.197	.048	0	.916
		L_Antib	73	17.086	−3.100	37.272	.097	0	.46
MBL changes (mm)	Overall		97	0.698	−0.236	1.632	.143	78.5	.009
		PDT	24	−0.100	−1.221	1.021	.861	-	
		L_Antib	73	1.019	−0.297	2.336	.129	87.6	.004

Abbreviations: BOP, bleeding on probing; CI, confidence interval; CHXc Chlorhexidine; I^2, heterogeneity; L_Antib, local antibiotics; MBL, radiographic bone loss; MD, mean difference; mm, millimetre; PPD, probing pocket depth; PDT, photodynamic therapy.

3.4 | Study and participants characteristics

Information related to the general characteristics of the studies and participants included in this systematic review and meta-analysis is shown in Table 3. Overall, this review includes data from 250 patients in the age range 21–90, mainly non-smoking women, and most were not diabetic. In most studies, the inclusion criteria for peri-implantitis was based on the definition of the 2017 World Workshop (Berglundh et al., 2018). In all but one study (Esposito et al., 2013), the participants were enrolled in a hygiene regimen phase prior to surgery, while pre- or post-systemic antibiotic treatment was given in 50% of the studies. The interventions included PTD, CHX application, minocycline ointment, cetylpyridinium chloride (CPC) together with CHX, sustained-release doxycycline from a β-tricalcium phosphate (β-TCP) carrier, or combinations of the above treatments.

3.5 | Study outcomes

All included studies were designed as parallel-arm RCTs with a follow-up of 6 and 12 months following surgery. The primary outcomes of this systematic review and meta-analysis (PD, BoP/SoP) are presented as values at the 6- and 12-month follow-up. The results of the meta-analysis were divided according to the type of intervention administered in each study and is presented in the forest plots at the implant or patient level when possible.

3.5.1 | Probing depth (PD)

The results of the meta-analysis regarding PD at the implant and patient level at 6- and 12-month follow-ups are presented in Tables 4 and 5 and in forest plots in Figure 3. At 6 months, treatment with

TABLE 5 Results of the meta-analyses for the primary and secondary outcomes showing the changes from baseline to 12 months at implant and at patient level.

	Baseline to 12 months								
					95%CI				
Implant level		Subgroup by test group	*n*	MD	Lower	Upper	*p*-value	I^2 (%)	*p*-value
PPD changes (mm)	Overall		331	0.249	−0.352	0.850	.417	59.3	.031
		PDT	42	−0.073	−0.881	0.735	.860	0	.698
		CHX	257	0.089	−0.678	0.856	.819	65.5	.055
		LAbs	32	1.440	0.401	2.479	.007	-	
BOP changes (%)	Overall		152	5.686	−1.309	12.681	.111	10.4	.341
		PDT	42	7.406	0.808	14.004	.028	0	.39
		CHX	78	−2.600	−15.527	10.327	0.693	-	
		LAbs	32	21.100	−13.335	55.535	0.230	-	
MBL changes (mm)	Overall		331	0.155	−0.383	0.694	.572	62.3	.021
		PDT	42	0.052	−0.932	1.035	.918	0	.861
		CHX	257	−0.137	−0.558	0.284	0.523	31.3	0.233
		LAbs	32	1.210	0.437	1.983	0.002	-	

	Baseline to 12 months								
					95%CI				
Patient level		Subgroup by test group	*n*	MD	Lower	Upper	*p*-value	I^2 (%)	*p*-value
PPD changes (mm)	Overall		69	0.417	−0.649	1.483	.443	53.2	.118
		PDT	42	−0.073	−0.883	0.737	.860	0.0	.698
		LAbs	27	1.410	0.230	2.590	.019	-	
BOP changes (%)	Overall		69	7.976	1.476	14.475	.016	0	.426
		PDT	42	7.406	0.808	14.004	.028	0	.39
		LAbs	27	26.600	−11.122	64.322	.167	-	
MBL changes (mm)	Overall		69	0.708	−0.443	1.860	.228	61.5	.075
		PDT	42	0.052	−0.932	1.035	.918	0	.861
		LAbs	27	1.570	0.705	2.435	<.001	-	

Note: Subgroup analysis according to the interventions in the test group.
Abbreviations: BOP, bleeding on probing; CHX, chlorhexidine; CI, confidence interval; I^2, heterogeneity; LAbs, local antibiotics; MBL, radiographic bone loss; MD, mean difference; mm, millimetre; PDT, photodynamic therapy; PPD, probing pocket depth.

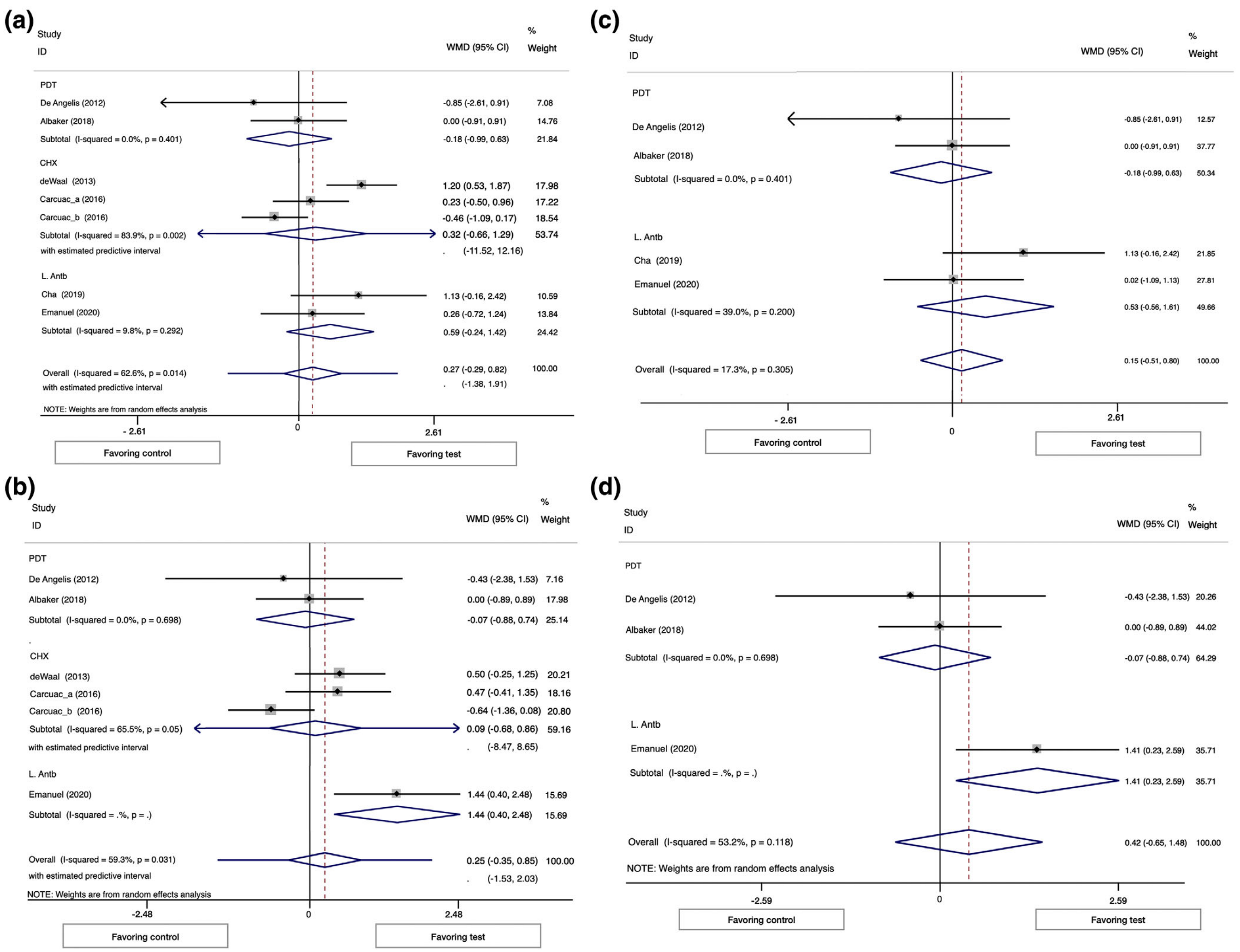


FIGURE 3 Forest plots showing comparisons of probing depth (PD) changes (in mm) between groups. Subgroup analysis according to the type of adjunctive chemical surface decontamination used: photodynamic therapy (PDT), chlorhexidine (CHX), and local antibiotic (L. Antb). (a) Implant-level 6-month follow-up results. (b) Implant-level 12-month follow-up results. (c) Patient-level 6-month follow-up results. (d) Patient-level 12-month follow-up results. Data presented are also available in Tables 4 and 5. 95%CI, 95% confidence interval; MD, mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

PDT resulted in no significant changes in PD reduction as compared to the control group at both the implant [$n = 2$; MD = −0.179; 95%CI (−0.988 to 0.629); $p = .664$; no heterogeneity: $I^2 = 0\%$] and patient levels [$n = 2$; MD = −0.179; 95%CI (−0.988 to 0.629); $p = .664$; no heterogeneity: $I^2 = 0\%$]. The use of CHX also showed no significant improvement in PD at the implant level, with or without the use of systemic antibiotics [$n = 3$; MD = 0.319; 95%CI (−0.655 to 1.294); $p = .521$; high heterogeneity: $I^2 = 83\%$]. The same pattern was observed for LAbs treatment: no significant improvement was observed in PD at the implant [$n = 2$; MD = 0.592; 95%CI (0–1.421); $p = .161$; very low heterogeneity: $I^2 = 9.8\%$] or patient level [$n = 2$; MD = 0.526; 95%CI (−0.558 to 1.609); $p = .342$; low heterogeneity: $I^2 = 39\%$]. The overall analysis for all treatments at the 6-month follow-up showed no additive effect of chemical treatment on PD reduction either at the implant level [$n = 7$; MD = 0.265; 95%CI (−0.29 to 0.821); $p = .349$; moderate heterogeneity: $I^2 = 62.6\%$] or the patient level [$n = 4$; MD = 0.146; 95%CI (−0.508 to 0.800); $p = .663$; low heterogeneity: $I^2 = 38.6\%$]. The 12-month analysis revealed significant improvement in PD following administration of LAbs only ($p = 0.007$, one study) (Table 5 and Figure 3). The overall analysis for all treatments at 12 months post surgery showed no significant change in PD at the implant level [$n = 6$; MD = 0.249; 95%CI (−0.352 to 0.85); $p = .417$; moderate heterogeneity: $I^2 = 59.3\%$] or the patient level [$n = 3$; MD = 0.417; 95%CI (−0.649 to 1.483); $p = .443$; moderate heterogeneity: $I^2 = 53.2\%$].

3.5.2 | Bleeding on probing (BoP)

Figure 4 and Tables 4 and 5 present the effect of each chemical treatment on BoP at 6 and 12 months post treatment at the implant and patient levels. Six months post treatment with PDT, BoP was

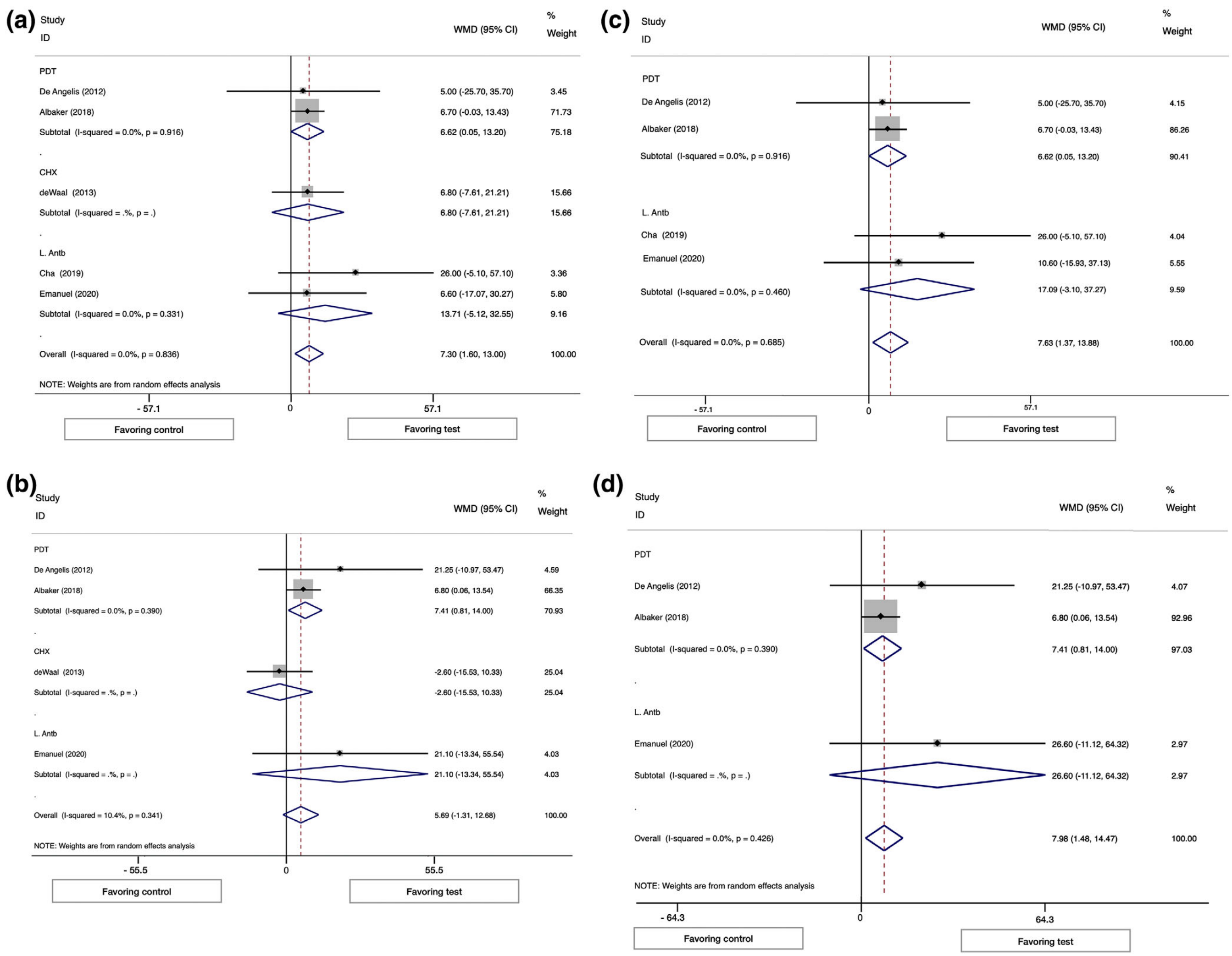


FIGURE 4 Forest plots showing comparisons of bleeding on probing (BoP) changes (in %) between groups. Subgroup analysis according to the type of adjunctive chemical surface decontamination used: photodynamic therapy (PDT), chlorhexidine (CHX), and local antibiotic (L. Antb). (a) Implant-level 6-month follow-up results. (b) Implant-level 12-month follow-up results. (c) Patient-level 6-month follow-up results. (d) Patient-level 12-month follow-up results. Data presented are also available in Tables 4 and 5. 95%CI, 95% confidence interval; MD, mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

significantly reduced at the implant level [$n = 2$; MD $= 6.622$; 95%CI (0.047–13.197); $p = .048$; no heterogeneity: $I^2 = 0\%$] and the patient level [$n = 2$; MD $= 6.622$; 95%CI (0.047–13.197); $p = .048$; no heterogeneity: $I^2 = 0\%$]. While treatments with CHX and LAbs did not result in significant changes in BoP, the overall analysis showed that chemical treatment with surgical debridement significantly reduced BoP 6 months post treatment at the implant level [$n = 5$; MD $= 7.3$; 95%CI (1.599–13); $p = .012$; no heterogeneity: $I^2 = 0\%$] and the patient level [$n = 4$; MD $= 7.626$; 95%CI (1.374–13.877); $p = .017$; no heterogeneity: $I^2 = 0\%$]. At 12 months post treatment, only PDT was found to be effective in reducing BoP at both the implant and patient levels [$n = 2$; MD $= 7.406$; 95%CI (0.808–14.004); $p = .028$; no heterogeneity: $I^2 = 0\%$]. The overall analysis at 12 months following surgery showed that chemical treatment significantly improved BoP levels at the patient level [$n = 3$; MD $= 7.976$; 95%CI (1.476–14.475); $p = .016$; no heterogeneity: $I^2 = 0\%$] but not at the implant level.

3.5.3 | Marginal bone level (MBL)

The results of the meta-analysis regarding MBL are shown in Tables 4 and 5 and Figure 5. At 6 months post surgery, none of the individual treatments or the overall analysis resulted in significant improvement in MBL at either the implant [$n = 4$; MD $= 0.481$; 95%CI (−0.031 to 0.992); $p = .065$; moderate heterogeneity: $I^2 = 47.2\%$] or patient levels [$n = 3$; MD $= 0.698$; 95% CI (−0.236 to 1.632); $p = .143$; high heterogeneity: $I^2 = 78.5\%$]. At 12 months post surgery, administration of LAbs was the only effective treatment that improved MBL at both the implant and patient levels (Table 5 and Figure 5b,d). Of note, the results of the effect of LAbs on MBL were based exclusively on one study by Emanuel et al. (Emanuel et al., 2020). The overall results demonstrated no effect for chemical treatment on MBL for both the implant [$n = 6$; MD $= 0.155$; 95%CI (−0.383 to 0.694); $p = .572$; moderate heterogeneity: $I^2 = 62.3\%$] and patient levels [$n = 3$;

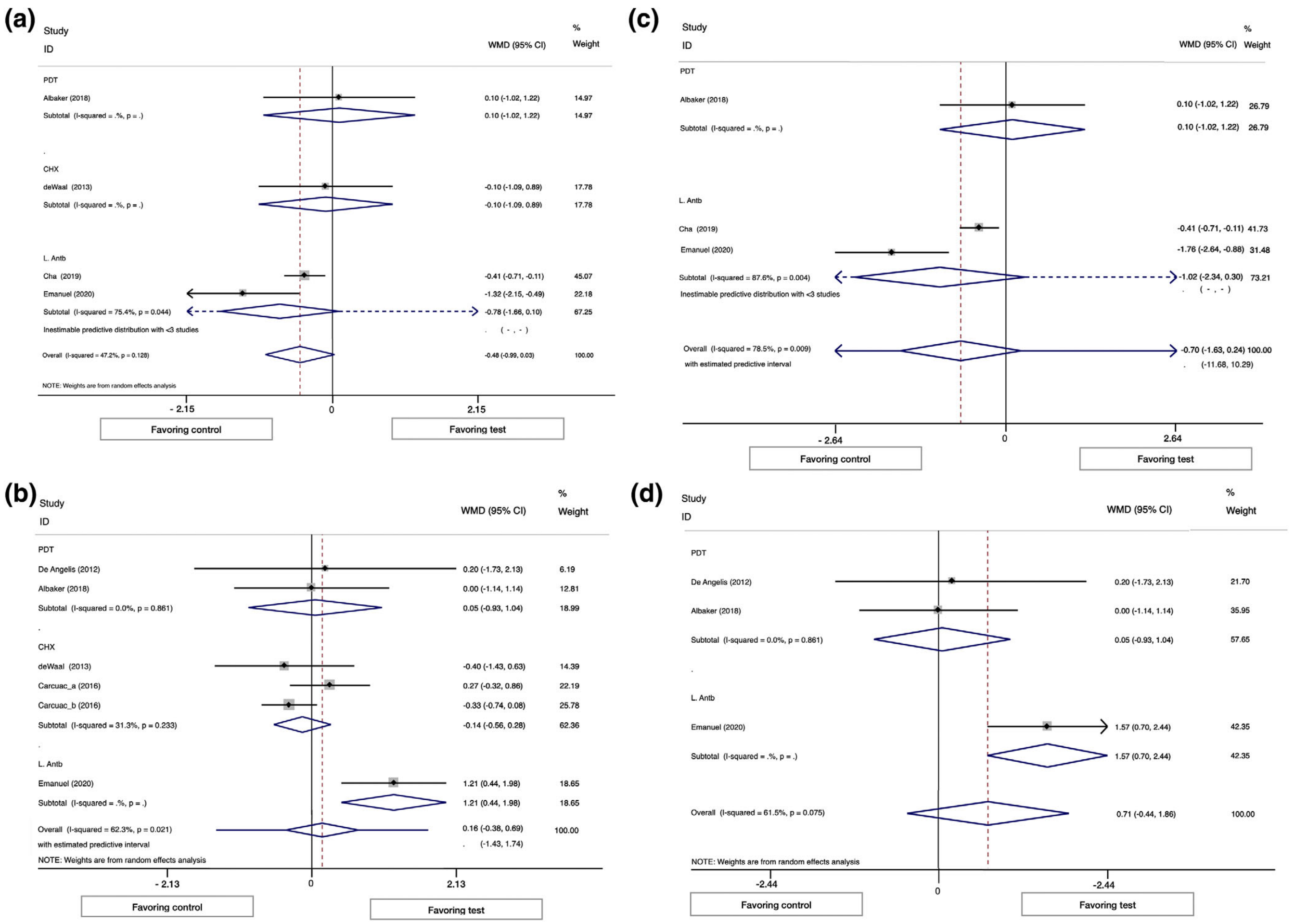


FIGURE 5 Forest plots showing comparisons of MBL (marginal bone loss) changes (in mm) between groups. Subgroup analysis according to the type of adjunctive chemical surface decontamination used: photodynamic therapy (PDT), chlorhexidine (CHX), and local antibiotic (L. Antb). (a) Implant-level 6-month follow-up results. (b) Implant-level 12-month follow-up results. (c) Patient-level 6-month follow-up results. (d) Patient-level 12-month follow-up results. Data presented are also available in Tables 4 and 5. 95%CI, 95% confidence interval; MD, mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

MD = 0.708; 95%CI (−0.443 to 1.860); $p = .228$; moderate heterogeneity: $I^2 = 61.5\%$].

3.5.4 | Implant loss

Implant loss rate (RD RI) for the different treatments at 6 and 12 months is presented in Table 6 and Figure 6. None of the individual treatments or the overall analysis resulted in reduced risk of implant loss at the implant [$n = 6$: RD = 0.–0.029; 95%CI (−0.087 to 0.029); $p = .332$; moderate heterogeneity: $I^2 = 48.2\%$] or patient level [$n = 6$: RD = 0.0.011; 95%CI (−0.035 to 0.057); $p = .641$; no heterogeneity: $I^2 = 0\%$].

3.5.5 | Disease resolution

Table 6 and Figure 7 show the results of the meta-analysis for disease resolution at 12 months following the various treatments. None of the individual treatments or the overall results was found to affect disease resolution at the implant level [$n = 4$: RR = 0.948; 95%CI (0.718–1.265); $p = .715$; moderate heterogeneity: $I^2 = 48.8\%$] or patient level [$n = 3$: RR = 0.765; 95%CI (0.466–1.257); $p = .291$; no heterogeneity: $I^2 = 0\%$]. It should be noted that the analysis at the patient level included a single study by Carcuac et al. (2016).

3.6 | RoB across studies (publication bias) and sensitivity analyses

Owing to the small number of studies (<10), publication bias could not be calculated using a statistical test. Post hoc sensitivity analysis was performed by excluding studies, one at a time, from the global estimation. Sensitivity analysis for each treatment subgroup could not be calculated because of the small number of studies in each subgroup. Considering the overall results, the global estimators for each of the reported outcomes did not change significantly after omitting each of

Journal of Clinical Periodontology —WILEY

TABLE 6 Results of the meta-analyses for failure rate (risk difference) and disease resolution (risk ratio), at implant and at patient level. Subgroup analysis according to the interventions in the test group.

Failure rate (at 6 and 12 months)		Subgroup by test group	n	RD (risk diff.)	95%CI Lower	Upper	*p*-value	I^2 (%)	*p*-value
Implant level	Overall		376	−0.029	−0.087	0.029	.332	48.2	.072
		PDT	42	0	−0.118	0.118	1	0	1
		CHX	256	−0.044	−0.160	0.072	.55	79.7	.007
		L_Antib	78	−0.040	−0.166	0.086	.531	39.6	.198
Patient level	Overall		187	0.011	−0.035	0.057	.641	0	.99
		PDT	42	0	−0.118	0.118	1.00	0	1.00
		CHX	99	0.038	−0.047	0.124	.382	0	.964
		L_Antib	46	0	−0.085	0.085	1000	-	

Disease resolution (at 12 months)		Subgroup by test group	*n*	RR (relat risk)	95% CI Lower	Upper	*p*-value	I^2 (%)	*p*-value
Implant level	Overall		274	0.948	0.718	1265	.715	48.8	.118
		PDT	18	1094	0.824	1452	.536	-	
		CHX	256	0.884	0.590	1325	.552	54,3	.112
Patient level		L_Antib	99	0.765	0.466	1257	.291	0	.401

Abbreviations: CHX, chlorhexidine; CI, confidence interval; I^2, heterogeneity; L_Antib, local antibiotics; PDT, photodynamic therapy; RD, risk difference; RR, relative risk.

the contributing studies, oscillating within the limits of the original 95%CI.

The certainty of the evidence was assessed using the GRADE approach. A summary of the key findings (SoF) from this systematic review is presented in Tables 7–9 (6 months) and Tables 10–12 (12 months) using the GRADE method for each intervention: PDT (Tables 7 and 10), CHX (Tables 8 and 11), and LAbs (Tables 9 and 12). The following outcome measures were included and assessed in the SoF table: PD, BoP, MBL, disease resolution, and implant loss at the 6- and 12-month follow-up. According to the GRADE guidelines, the certainty of the evidence was extremely low for every measure in all comparisons.

4 | DISCUSSION

The present systematic review and meta-analysis evaluated the efficacy of adjunctive chemical surface decontamination during surgical therapy of peri-implantitis. Although the present results show that the use of LAbs during surgery may have a positive effect on PD reduction at 12 months post treatment, this result is based on a single study with a very low certainty of evidence. With regard to the second primary outcome, BoP, the overall results at 6 months show that chemical treatment significantly improved this parameter at the implant and patient levels. At 12 months post surgery, the overall results showed reduced BoP at the patient level only. Of note, the reduction observed in BoP following chemical treatment at both time points was derived mainly from the PDT subgroup, which included only two studies. These studies carried heavy weight in the final analysis because of their narrow SD. In this context, the composite parameter of "disease resolution", which includes PD + BoP, may be more accurate for forecasting implant prognosis (Koldsland et al., 2018; Sanz, Chapple, & Working Group 4, 2012).

Since the integration of implants is a prerequisite to their functioning, improvement in MBL following treatment could be considered an important goal when treating peri-implantitis. The overall results of this meta-analysis suggest that chemical treatment of the implant surface has no effect on the marginal bone height. It should be noted, however, that the one study in which LAbs were used showed improved MBL (Emanuel et al., 2020), but has a very low certainty of evidence (β-tricalcium phosphate was used as a carrier in the test group only, the study was industry-funded, and the corresponding author holds a senior position in the company).

Two additional secondary outcome variables, namely implant loss and disease resolution, were also analysed. These are two end-point parameters important for verifying treatment success by practitioners. None of the chemical decontamination procedures was superior to saline with regard to these outcome variables at the 12-month follow-up. Thus, we cannot conclude that any of the chemical decontamination protocols included in this meta-analysis is an essential step during surgical treatment of peri-implantitis for determining a better outcome.

To formulate clinical guidelines, it is necessary to evaluate the effect of each treatment on the primary and secondary outcomes, and only then can we decide on the recommendations based on each specific treatment. The present meta-analysis includes too few controlled studies for evaluating the efficacy of each chemical intervention, and all results obtained are with low certainty of evidence (Tables 7–12).

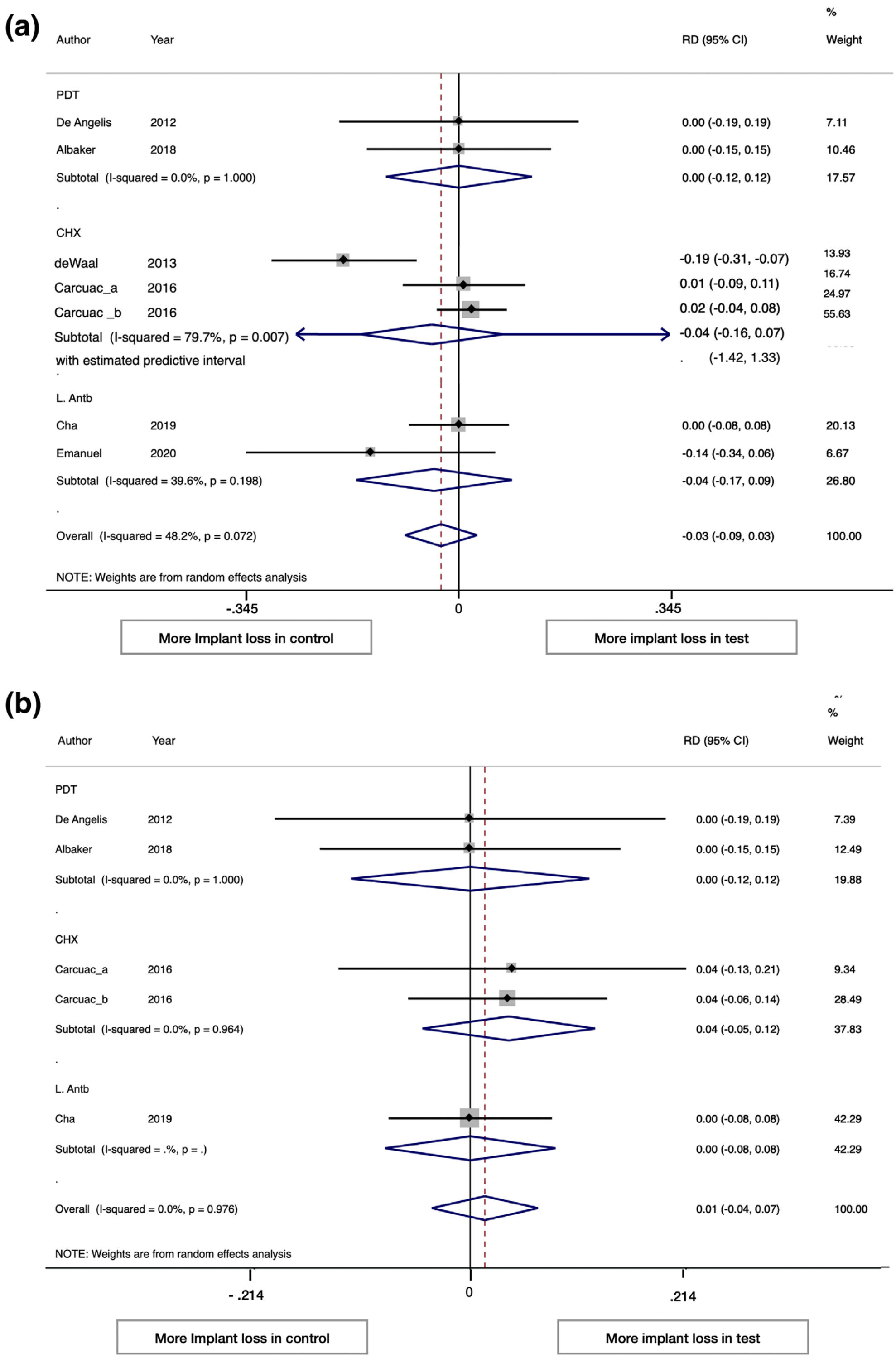
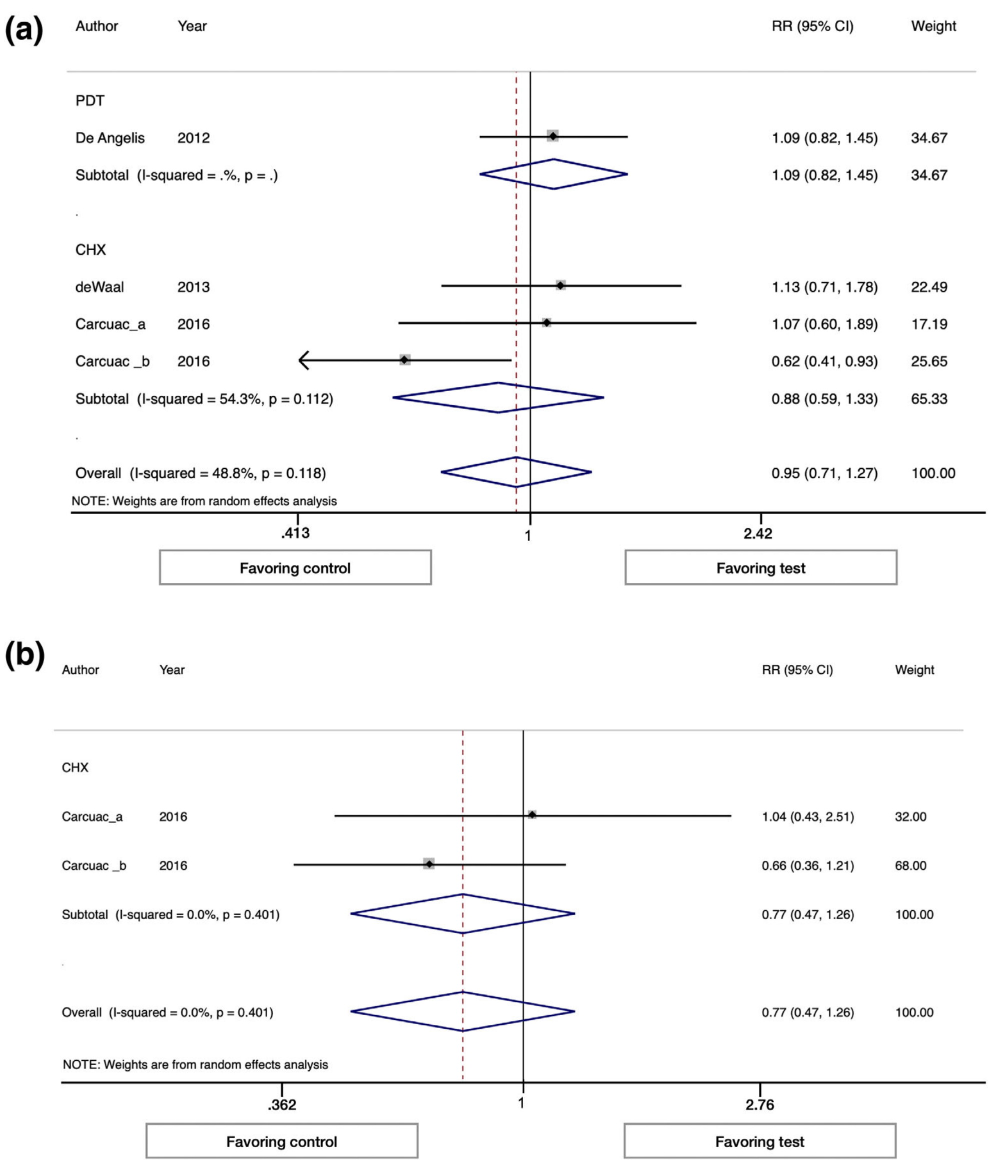


FIGURE 6 Forest plots showing comparisons of implant loss between groups. Subgroup analysis according to the type of adjunctive chemical surface decontamination used: photodynamic therapy (PDT), chlorhexidine (CHX), and local antibiotic (L. Antb). (a) Implant-level 6 and 12-month follow-up results. (b) Patient-level 6- and 12-month follow-up results. Data presented are also available in Tables 4 and 5. 95%CI, 95% confidence interval; MD, mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

Therefore, it is difficult to reach any definitive conclusions. These findings are in agreement with previous in vitro pre-clinical and other systematic reviews. Almohandes et al. examined the efficacy of various treatment modalities using a canine model of experimental peri-implantitis. They concluded that decontamination procedures, including citric acid gel or a rotating titanium brush, did not improve the outcome following surgical treatment of experimental peri-implantitis (Almohandes et al., 2022). Dostie et al. tested the efficacy of the commonly used antimicrobial agents (CHX, tetracycline, phosphoric acid, etc.) in the decontamination of multiple species of mature oral biofilm on sand-blasted, large-grit, acid-etched (SLA) titanium implants and found that rinsing the surfaces with 0.9% NaCl removed most of the biofilm. However, bacteria persisted in all specimens and none of the disinfectants tested was superior to the saline group (Dostie et al., 2017). These findings may explain the results of the aforementioned studies. In addition, other systematic reviews support our findings, showing no significant

FIGURE 7 Forest plots showing comparisons of disease resolution between groups. Subgroup analysis according to the type of adjunctive chemical surface decontamination used: photodynamic therapy (PDT), chlorhexidine (CHX). (a) Implant-level 6- and 12-month follow-up results. (b) Patient-level 6- and 12-month follow-up results. Data presented are also available in Tables 4 and 5. 95%CI, 95% confidence interval; MD, mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]



additive effect for the use of chemical decontamination of the implant surface during surgery (Faggion Jr. et al., 2013; Koo et al., 2019; Li et al., 2022; Ramanauskaite et al., 2021). Importantly, the present study and previous systematic reviews are based on a limited number of studies with various chemical agents. Therefore, we conclude that, upon analysing the currently available literature, chemical decontamination of the implant surface, in addition to surgical debridement, does not provide any additional benefit over surgical debridement.

4.1 | Limitations

The present systematic review has several limitations that should be considered: (1) Scarcity of existing evidence: In the present systematic review and meta-analysis, we included RCTs and controlled clinical trials (CCTs) with a follow-up of at least 6 months, which yielded only six studies; one study only had a follow-up of 12 months with the initial follow-up period at 4 months. (2) Owing to the small number of studies, some of the treatments were evaluated from only one or two RCTs. (3) The RCTs included only 10–27 subjects per treatment arm, and half of those studies contained less than 20 subjects per arm. This may have led to a large CI that affected the results. (4) Variability in the definition of peri-implantitis: Initially, we intended to include only studies that defined peri-implantitis according to the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions (2017), yet because of the limited amount of information using this definition, we included studies with similar definitions. (5) Heterogeneity in inclusion criteria between RCTs: Some of the studies included pre-diabetic patients, smokers, and patients with a history of periodontitis, while others included only healthy patients. (6) Surgical techniques and measurement of the outcomes varied between studies. (7) In half of the studies, systemic antibiotic treatment was administered before and after surgical treatment. This could affect the intra-subgroup comparisons. (8) Although LAbs showed

TABLE 7 Summary of findings using the grading of recommendations assessment, development and evaluation (grade) approach at 6 months: Photodynamic therapy

Patient or population: Individuals aged above 18 years, otherwise healthy, with peri-implantitis as defined by the 2017 World Workshop (Berglundh et al., 2018)
Setting: University/private clinics
Intervention: Surgical treatment + photodynamic therapy (PDT)
Control: Surgical treatment + placebo
Outcomes: Change in peri-implant outcomes

Outcomes[a]	Unit of interest	Illustrative comparative risks[a] (95%CI): Assumed risk[a] (surgical treatment + placebo – comparator)	Illustrative comparative risks[a] (95%CI): Corresponding risk[a] (surgical treatment + PDT – intervention)	Relative effect (95%CI)	No. (studies)	Certainty of the evidence (GRADE)	Comments
Pocket depth (PD) change (mm) assessed with periodontal probe Follow-up: 6 months	Implant level or patient level	Mean PD was 1.65 mm reduction	MD 0.18 mm lower reduction (0.99 lower to 0.63 higher)	-	42 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,d] Due to risk of bias, imprecision, and indirectness	PD was not affected by PDT in addition to the surgical treatment of peri-implantitis
Bleeding on probing (BoP) change (%) assessed with periodontal probe Follow-up: 6 months	Implant level or patient level	Mean BoP was 31.2% reduction	MD 6.62% higher reduction (0.05% higher to 13.20% higher)	-	42 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,d] Due to risk of bias, imprecision, and indirectness	BoP showed slightly higher reduction when PDT was used in addition to surgical treatment of peri-implantitis, but this reduction was not clinically relevant
Marginal bone loss (MBL) change (mm) assessed with periapical X-rays Follow-up: 6 months	Implant level or patient level	Mean MBL was 0.5 mm gain	MD 0.10 mm lower gain (1.22 mm loss to 1.02 gain)	-	24 (1 RCT)	⊕◯◯◯ VERY LOW[b,c,d] Due to risk of bias, imprecision, and indirectness	MBL was not affected by PDT in addition to the surgical treatment of peri-implantitis
Disease resolution (DR) assessed with clinical examination Follow-up: 6 months	Implant level or patient level	NR	NR	NR	NR	NR	NR
Implant loss assessed with clinical examination Follow-up: 6 and12 months	Implant level or patient level	0 implant loss per 1000 implants	0 per 1000	RD 0.00 (−0.12 to 0.12)	42 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,d,e] Due to risk of bias, imprecision, and indirectness	Implant loss was not affected by PDT in addition to the surgical treatment of peri-implantitis

Note: GRADE Working Group grades of evidence. High certainty—We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty—We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; MD, mean difference; RD, risk difference; RR, risk ratio.

[a]"Assumed risk" is obtained from the median control group risk across studies. "Corresponding risk" (and its 95% confidence interval) is based on the "Assumed risk" in the comparison group and the relative effect of the intervention (and its 95%CI).

[b]Downgraded one level for study limitations ("unclear risk of bias" due to some concerns about reporting bias – Albaker et al., 2018).

[c]Downgraded two levels for very serious imprecision due to the very small sample size.

[d]Downgraded one level for severe indirectness due to the partial consideration of the intervention, restricted to the surgical approach – De Angelis et al. 2012.

[e]Downgraded one level for study limitations ("unclear risk of bias" due to some concerns about reporting and selection bias – Bombeccari et al., 2013).

TABLE 8 Summary of findings using the grading of recommendations assessment, development and evaluation (grade) approach at 6 months: Clorhexidine

Patient or population: Individuals aged above 18 years, otherwise healthy, with peri-implantitis as defined by the 2017 World Workshop (Berglundh et al., 2018)
Setting: University/private clinics
Intervention: Surgical treatment + chlorhexidine solution (CHX)
Control: Surgical treatment + placebo
Outcomes: Change in peri-implant outcomes

Outcomes[a]	Unit of interest	Illustrative comparative risks[a] (95%CI): Assumed risk[a] (Surgical treatment + placebo – comparator)	Illustrative comparative risks[a] (95%CI): Corresponding risk[a] (Surgical treatment + chlorhexidine – intervention)	Relative effect (95%CI)	No. (studies)	Certainty of the evidence (GRADE)	Comments
Pocket depth (PD) change (mm) assessed with periodontal probe Follow-up: 6 months	Implant level	Mean PD was 2.28 mm reduction	MD 0.32 mm higher reduction (0.66 lower to 1.29 higher)	-	256 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	PD was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis
	Patient level	NR	NR	NR	NR	NR	NR
Bleeding on Probing (BoP) change (%) assessed with periodontal probe Follow-up: 6 months	Implant level	Mean BoP was 19.6% reduction	MD 6.80% higher reduction (7.61% lower to 21.21% higher)	-	78 (1 RCT)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	BoP was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis
	Patient level	NR	NR	NR	NR		
Marginal bone loss (MBL) change (mm) assessed with periapical X-rays Follow-up: 6 months	Implant level	Mean MBL was 0.7 mm loss	MD 0.10 mm lower loss (0.89 mm higher loss to 1.09 gain)	-	78 (1 RCT)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	MBL was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis.
	Patient level	NR	NR	NR	NR	NR	NR
Disease resolution (DR) assessed with clinical examination Follow-up: 6 months	Implant level or patient level	NR	NR	NR	NR	NR	NR
Implant loss assessed with clinical examination Follow-up: 6 &12 months	Implant level	85 implant loss per 1000 implants	4 less per 1000 (14 less to 6 more)	RD −0.04 (−0.16 to 0.07)	256 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	Implant loss was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis.
	Patient level	40 implant loss per 1000 participants	2 more per 1000 (2 less to 5 more)	RD 0.04 (−0.05 to 0.12)	99 (1 RCTs)		

Note: GRADE Working Group grades of evidence. High certainty—We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty—We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, onfidence interval; MD, mean difference; NR, not reported; RR, risk ratio; RD, risk difference.

[a]"Assumed risk" is obtained from the median control group risk across studies. "Corresponding risk" (and its 95% confidence interval) is based on the "Assumed risk" in the comparison group and the relative effect of the intervention (and its 95%CI).

[b]Downgraded one level for study limitations ("high risk of bias" due to attrition bias – De Waal et al. 2013; "unclear risk of bias" due to some concerns about selection bias – Carcuac et al., 2016).

[c]Downgraded two levels for very serious imprecision due to the very small sample size.

TABLE 9 Summary of findings using the grading of recommendations assessment, development and evaluation (grade) approach at 6 months: Local antibiotics

Patient or population: Individuals aged above 18 years, otherwise healthy, with peri-implantitis as defined by the 2017 World Workshop (Berglundh et al., 2018)
Setting: University/private clinics
Intervention: Surgical treatment + local antibiotics
Control: Surgical treatment + placebo
Outcomes: Change in peri-implant outcomes

Outcomes[a]	Unit of interest	Illustrative comparative risks[a] (95%CI): Assumed risk[a] (surgical treatment + placebo – comparator)	Illustrative comparative risks[a] (95%CI): Corresponding risk[a] (surgical treatment + local antibiotics – intervention)	Relative effect (95%CI)	No. (studies)	Certainty of the evidence (GRADE)	Comments
Pocket depth (PD) change (mm) assessed with periodontal probe Follow-up: 6 months	Implant level	Mean PD was 1.89 mm reduction	MD 0.59 mm higher reduction (0.24 lower to 1.42 higher)	-	78 (2 RCTs)	⊕○○○ VERY LOW[b,c] Due to risk of bias and imprecision	PD was not affected by the local application of antibiotics adjunct to the surgical treatment of peri-implantitis
	Patient level	Mean PD was 1.95 mm reduction	MD 0.53 mm higher reduction (0.56 lower to 1.61 higher)	-	73 (2 RCTs)		
Bleeding on Probing (BoP) change (%) assessed with periodontal probe Follow-up: 6 months	Implant level	Mean BoP was 22.5% reduction	MD 13.71% higher reduction (5.12% lower to 32.55% higher)	-	78 (2 RCTs)	⊕○○○ VERY LOW[b,c] Due to risk of bias and imprecision	BoP was not affected by the local application of antibiotics adjunct to the surgical treatment of peri-implantitis
	Patient level	Mean BoP was 22.95% reduction	MD 17.09% higher reduction (3.10% lower to 37.27% higher)	-	73 (2 RCTs)		
Marginal bone loss (MBL) change (mm) assessed with periapical X-rays Follow-up: 6 months	Implant level	Mean MBL was 0.035 mm gain	MD 0.78 mm higher gain (0.10 mm loss to 1.66 higher gain)	-	78 (2 RCTs)	⊕○○○ VERY LOW[b,c] Due to risk of bias and imprecision	MBL was not affected by the local application of antibiotics adjunct to the surgical treatment of peri-implantitis
	Patient level	Mean MBL was 0.005 mm loss	MD 1.02 mm higher gain (0.30 mm loss to 2.34 higher gain)	-	73 (2 RCTs)		
Disease resolution (DR) assessed with clinical examination Follow-up: 6 months	Implant level or patient level	NR	NR	NR	NR	NR	NR
Implant loss assessed with clinical examination Follow-up: 6 &12 months	Implant level	56 implant loss per 1000 implants	3 less per 1000 (10 less to 5 more)	RD - 0.04 (−0.17 to 0.09)	78 (2 RCTs)	⊕○○○ VERY LOW[b,c] Due to risk of bias and imprecision	Implant loss was not affected by the local application of antibiotics adjunct to the surgical treatment of peri-implantitis
	Patient level	0 implant loss per 1000 participants	0 more per 1000	RD 0.00 (−0.08 to 0.08)	46 (1 RCTs)		

Note: GRADE Working Group grades of evidence. High certainty—We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty—We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Abbreviations: CI, confidence interval; MD, mean difference; NR, not reported; RD, risk difference.
[a]"Assumed risk" is obtained from the median control group risk across studies."Corresponding risk" (and its 95% confidence interval) is based on the "Assumed risk" in the comparison group and the relative effect of the intervention (and its 95%CI).
[b]Downgraded one level for study limitations ("high risk of bias" due to detection bias – Cha et al., 2019; "unclear risk of bias" due to some concerns about selection bias – Emanuel et al., 2020).
[c]Downgraded two levels for very serious imprecision due to the very small sample size.

TABLE 10 Summary of findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach at 12 months: Photodynamic therapy

Patient or population: Individuals aged above 18 years otherwise healthy with peri-implantitis as defined by the 2017 World Workshop (Berglundh et al., 2018)
Setting: University/Private clinics
Intervention: Surgical treatment + Photodynamic therapy (PDT)
Control: Surgical treatment + Placebo
Outcomes: Change in peri-implant outcomes

Outcomes[a]	Unit of interest	Illustrative comparative risks (95% CI): Assumed risk[a] (Surgical treatment + Placebo – Comparator]	Illustrative comparative risks (95% CI): Corresponding risk[a] (Surgical treatment +PDT– Intervention)	Relative effect (95% CI)	No. (studies)	Certainty of the evidence (GRADE)	Comments
Pocket depth (PD) change (mm) assessed with periodontal probe Follow-up: 12 months	Implant level or Patient level	Mean PD was 1.65 mm reduction	MD 0.07 mm lower reduction (0.88 lower to 0.74 higher)	-	42 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,d] Due to risk of bias, imprecision, and indirectness	PD was not affected by PDT in addition to the surgical treatment of peri-implantitis.
Bleeding on Probing (BoP) change (%) assessed with periodontal probe Follow-up: 12 months	Implant level or Patient level	Mean BoP was 23.35 % reduction	MD 7.41% higher reduction (0.81% higher to 14% higher)	-	42 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,d] Due to risk of bias, imprecision, and indirectness	BoP is reduced when PDT is used in addition to surgical treatment of peri-implantitis, but this reduction was not clinically relevant.
Marginal bone loss (MBL) change (mm) assessed with periapical X-rays Follow-up: 12 months	Implant level or Patient level	Mean MBL was 0.75 mm gain	MD 0.05 mm higher gain (0.93mm loss to 1.04 gain)	-	42 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,d] Due to risk of bias, imprecision, and indirectness	MBL was not affected by PDT in addition to the surgical treatment of peri-implantitis.
Disease resolution (DR) assessed with clinical examination Follow-up: 12 months	Implant level or Patient level	900 resolved per 1000 implants or participants	9 more per 1000 (162 less to 405 more)	RR 1.09 (0.82 to 1.45)	18 (1 RCT)	⊕◯◯◯ VERY LOW[b,c,d] Due to imprecision and indirectness	DR was not affected by PDT in addition to the surgical treatment of peri-implantitis.
Implant loss assessed with clinical examination Follow-up: 6 &12 months	Implant level or Patient level	0 implant loss per 1000 implants	0 per 1000	RD 0.00 (−0.12 to 0.12)	42 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,d,e] Due to risk of bias, imprecision, and indirectness	Implant loss was not affected by PDT in addition to the surgical treatment of peri-implantitis.

Note: GRADE Working Group grades of evidence. High certainty—We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty—We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, Confidence interval; MD, Mean difference; RD, Risk difference; RR, Risk ratio.

[a]The 'Assumed risk' is obtained from the median control group risk across studies. The 'Corresponding risk' (and its 95% confidence interval) is based on the 'Assumed risk' in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Downgraded one level for study limitations ('unclear risk of bias' due to some concerns about reporting bias – Albaker et al., 2018).

[c]Downgraded two levels for very serious imprecision due to the very small sample size.

[d]Downgraded one level for severe indirectness due to the partial consideration of the intervention, restricted to the surgical approach – De Angelis et al. 2012.

[e]Downgraded one level for study limitations ('unclear risk of bias' due to some concerns about reporting and selection bias – Bombeccari et al., 2013).

TABLE 11 Summary of findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach at 12 months: Clorhexidine.

Patient or population: Individuals aged above 18 years otherwise healthy with peri-implantitis as defined by the 2017 World Workshop (Berglundh et al., 2018)
Setting: University/Private clinics
Intervention: Surgical treatment + Chlorhexidine solution (CHX)
Control: Surgical treatment + Placebo
Outcomes: Change in peri-implant outcomes

Outcomes[a]	Unit of interest	Illustrative comparative risks (95% CI): Assumed risk[a] (Surgical treatment + Placebo – Comparator)	Illustrative comparative risks (95% CI): Corresponding risk[a] (Surgical treatment + Chlorhexidine – Intervention)	Relative effect (95% CI)	No. (studies)	Certainty of the evidence (GRADE)	Comments
Pocket depth (PD) change (mm) assessed with periodontal probe Follow-up: 12 months	Implant level	Mean PD was 2.31 mm reduction	MD 0.09 mm higher reduction (0.68 lower to 0.86 higher)	-	257 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision.	PD was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis.
	Patient level	NR	NR	NR	NR	NR	NR
Bleeding on Probing (BoP) change (%) assessed with periodontal probe Follow-up: 12 months	Implant level	Mean BoP was 22.5 % reduction	MD 2.60 % lower reduction (15.53% lower to 10.33% higher)	-	78 (1 RCT)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	BoP was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis.
	Patient level	NR	NR	NR	NR	NR	NR
Marginal bone loss (MBL) change (mm) assessed with periapical X-rays Follow-up: 12 months	Implant level	Mean MBL was 0.75 mm loss	MD 0.14 mm higher loss (0.56 mm higher loss to 0.28 lower loss)	-	257 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	MBL was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis.
	Patient level	NR	NR	NR	NR	NR	NR
Disease resolution (DR) assessed with clinical examination Follow-up: 12 months	Implant level	500 resolved per 1000 implants	60 less per 1000 (205 less to 165 more)	RR 0.88 (0.59 to 1.33)	256 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	DR was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis.
	Patient level	429 resolved per 1000 participants	99 less per 1000 (227 less to 111 more)	RR 0.77 (0.47 to 1.26)	99 (1 RCT)		
Implant loss assessed with clinical examination Follow-up: 6 &12 months	Implant level	85 implant loss per 1000 implants	4 less per 1000 (14 less to 6 more)	RD −0.04 (−0.16 to 0.07)	256 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	Implant loss was not affected by local application of chlorhexidine adjunct to the surgical treatment of peri-implantitis.
	Patient level	40 implant loss per 1000 participants	2 more per 1000 (2 less to 5 more)	RD 0.04 (−0.05 to 0.12)	99 (1 RCTs)		

Note: GRADE Working Group grades of evidence. High certainty—We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty—We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, Confidence interval; MD, Mean difference; NR, Not reported; RD, Risk difference; RR, Risk ratio.

[a]The 'Assumed risk' is obtained from the median control group risk across studies. The 'Corresponding risk' (and its 95% confidence interval) is based on the 'Assumed risk' in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Downgraded one level for study limitations ('high risk of bias' due to attrition bias – De Waal et al. 2013; 'unclear risk of bias' due to some concerns about selection bias – Carcuac et al., 2016)

[c]Downgraded two levels for very serious imprecision due to the very small sample size.

TABLE 12 Summary of findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach at 12 months: Local antibiotics.

Patient or population: Individuals aged above 18 years otherwise healthy with peri-implantitis as defined by the 2017 World Workshop (Berglundh et al., 2018)
Setting: University/Private clinics
Intervention: Surgical treatment + Local antibiotics
Control: Surgical treatment + Placebo
Outcomes: Change in peri-implant outcomes

Outcomes[a]	Unit of interest	Illustrative comparative risks (95% CI): Assumed risk[a] (Surgical treatment + Placebo – Comparator)	Illustrative comparative risks (95% CI): Corresponding risk[a] (Surgical treatment + Local antibiotics – Intervention)	Relative effect (95% CI)	No. (studies)	Certainty of the evidence (GRADE)	Comments
Pocket depth (PD) change (mm) assessed with periodontal probe Follow-up: 12 months	Implant level	Mean PD was 0.96 mm reduction	MD 1.44 mm higher reduction (0.40 higher to 2.48 higher)	-	32 (1 RCT)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision.	PD is reduced when local antibiotics are employed as an adjunct to surgical treatment of peri-implantitis. This reduction was clinically relevant.
	Patient level	Mean PD was 1.04 mm reduction	MD 1.41 mm higher reduction (0.23 higher to 2.59 higher)	-	27(1 RCT)		
Bleeding on Probing (BoP) change (%) assessed with periodontal probe Follow-up: 12 months	Implant level	Mean BoP was 15.2 % reduction	MD 21.10% higher reduction (13.34 % lower to 55.54 % higher)	-	32 (1 RCT)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	BoP was not affected by the local application of antibiotics adjunct to the surgical treatment of peri-implantitis.
	Patient level	Mean BoP was 18.6 % reduction	MD 26.60 % higher reduction (11.12 % lower to 64.32 % higher)	-	27 (1 RCT)		
Marginal bone loss (MBL) change (mm) assessed with periapical X-rays Follow-up: 12 months	Implant level	Mean MBL was 0.33 mm loss	MD 1.21 mm higher gain (0.44 mm higher to 1.98 higher)	-	32 (1 RCT)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	MBL is slightly restored when topical antibiotics are used in the surgical treatment of peri-implantitis. This gain was clinically relevant.
	Patient level	Mean MBL was 0.37 mm loss	MD 1.57 mm higher gain (0.70 mm gain to 2.44 gain)	-	27 (1 RCT)		
Disease resolution (DR) assessed with clinical examination Follow-up: 12 months	Implant level or Patient level	NR	NR	NR	NR	NR	NR
Implant loss assessed with clinical examination Follow-up: 6 &12 months	Implant level	56 implant loss per 1000 implants	3 less per 1000 (10 less to 5 more)	RD - 0.04 (−0.17 to 0.09)	78 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c] Due to risk of bias and imprecision	Implant loss was not affected by the local application of antibiotics adjunct to the surgical treatment of peri-implantitis.
	Patient level	0 implant loss per 1000 participants	0 more per 1000	RD 0.00 (−0.08 to 0.08)	46(1 RCTs)		

Note: GRADE Working Group grades of evidence. High certainty—We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty—We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, Confidence interval; MD, Mean difference; NR, Not reported; RD: Risk difference.

[a]The 'Assumed risk' is obtained from the median control group risk across studies. The 'Corresponding risk' (and its 95% confidence interval) is based on the 'Assumed risk' in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Downgraded one level for study limitations ('high risk of bias' due to detection bias – Cha et al., 2019; 'unclear risk of bias' due to some concerns about selection bias – Emanuel et al., 2020)

[c]Downgraded two levels for very serious imprecision due to the very small sample size.

significant advantages in two studies, these studies were very different and have a high RoB because of industry support and strong conflicts of interest of some authors.

4.2 | Implications for research

In light of the above limitations, further parallel-arm RCTs with low RoB, a common definition of peri-implantitis, strict inclusion criteria, and similar treatment protocols need to be carried out.

5 | CONCLUSIONS

Because of the small number of studies included, the high RoB, and very low certainty of evidence, the adjunctive use of chemicals such as PDT, CHX, and LAbs for surface decontamination during surgery of peri-implantitis cannot be advised as superior to standard debridement procedures (mechanical debridement with/without saline).

AUTHOR CONTRIBUTIONS

Asaf Wilensky: designed the methodology, performed the search, analyzed the data, and drafted the manuscript; Lior Shapira: performed the search, analysed the data, and drafted the manuscript. Alvaro Limones, Conchita Martin: analyzed the data, drafted the manuscript, and critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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