

Supplementary information to the manuscript

**Efficacy of Chlorhexidine after oral surgery procedures on wound healing:
systematic review and meta-analysis**

María de Nuria Romero-Olid^{1,2}, Elena Bucataru^{1,2}, Pablo Ramos-García^{1,2,*} and Miguel Ángel González-Moles^{1,2}

1- School of Dentistry, University of Granada, 18071 Granada, Spain

2- Instituto de Investigación Biosanitaria ibs.GRANADA, 18012 Granada, Spain

***Corresponding Author:**

Pablo Ramos-García (pabloramos@ugr.es)

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1. Search strategy

Table S1. Search strategy for each database, number of results, and execution date.

	Query/Search Strategy	Results/ Items found	Search time limits
MEDLINE PubMed	("Wound Healing"[Mesh] OR "wound"[All Fields] OR "healing"[All Fields] OR "cicatrizacion"[All fields] OR "re-epithelialization"[All fields] OR "mucosal recovery"[All Fields] OR "Dry Socket"[Mesh] OR "alveolar osteitis"[All Fields] OR "dry socket"[All Fields] OR "alveolitis sicca dolorosa"[All Fields] OR "fibrinolytic alveolitis"[All Fields]) AND ("mouth"[MeSH] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("Chlorhexidine"[Mesh] OR "chlorhexidine"[All fields])	452	January, 2023
Embase	('wound healing'/exp OR 'wound' OR 'healing' OR 'cicatrizacion' OR 're-Epithelialization' OR 'mucosal recovery' OR 'alveolar osteitis' OR 'dry socket' OR 'alveolitis sicca dolorosa' OR 'fibrinolytic alveolitis') AND ('mouth'/exp OR 'mouth') AND ('chlorhexidine'/exp OR 'chlorhexidine')	646	January, 2023
Web of Science	TS=("wound healing" OR "wound" OR "healing" OR "cicatrizacion" OR "re-Epithelialization" OR "mucosal recovery" OR "alveolar osteitis" OR "dry socket" OR "alveolitis sicca dolorosa" OR "fibrinolytic alveolitis") AND TS=("mouth" OR "oral") AND TS=("chlorhexidine")	272	January, 2023
Scopus	TITLE-ABS-KEY(("wound healing" OR "wound" OR "healing" OR "cicatrizacion" OR "re-Epithelialization" OR "mucosal recovery" OR "alveolar osteitis" OR "dry socket" OR "alveolitis sicca dolorosa" OR "fibrinolytic alveolitis") AND ("mouth" OR "oral") AND "chlorhexidine")	651	January, 2023
CENTRAL	#1 MeSH descriptor: [Wound Healing] explode all trees #2 MeSH descriptor: [Mouth] explode all trees #3 MeSH descriptor: [Chlorhexidine] explode all trees #4 #1 AND #2 AND #3	9	January, 2023
Total			2030

2. Table S2. Characteristics of analyzed studies (n = 33).

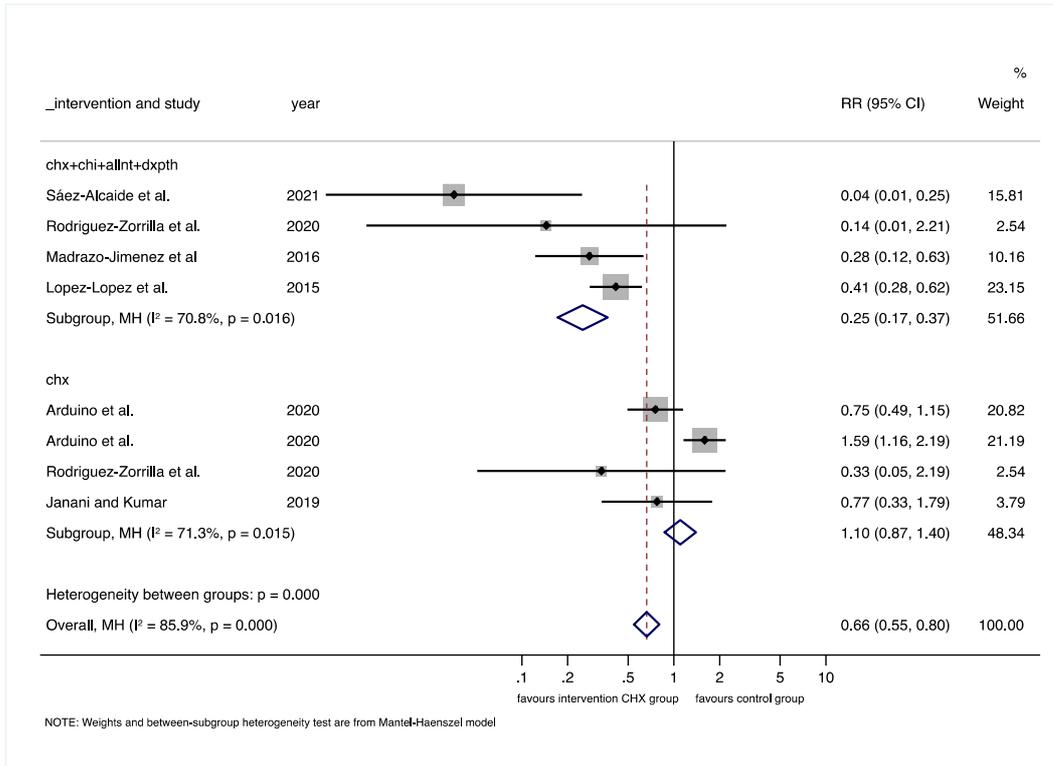
Study (year)	Country	Study design	Sample, n (I/C)	Sex m/f	Age, y mean±SD (range)	Intervention group (CHX form)	Control group	Oral Surgery	Study parameters
Amaliya <i>et al.</i> (2022)	Indonesia	Parallel-group RCT	32 (16/16)	11/21	26.09±8.51 (19-46)	0.20% CHX (gel) + 500 mg of mefenamic acid	Placebo gel + 500 mg of mefenamic acid	Unilateral extraction of 1M	-Erythema -Epithelization
Collins <i>et al.</i> (2021)	Dominican Republic	Parallel-group RCT	37 (17/20)	18/19	48.95±11.38 (30-68)	0.12% CHX (rinse)	NaCl	Periodontal Surgery	-Pain
Sáez-Alcaide <i>et al.</i> (2021)	Spain	Parallel-group RCT	72 (36/36)	13/23	22.94±2.67 (nr)	0.20% chlorhexidine, chitosan (gel)	Placebo gel	Lower 3M surgery	-Alveolar osteitis -Wound healing -Pain
Arduino <i>et al.</i> (2020)	Italy	Parallel-group RCT	354 (118/115/121)	133/221	57.40±16.3 (nr)	0.12% CHX (rinse) 0.20% CHX (rinse)	No intervention	Oral mucosal biopsy	-Wound healing -Pain
Katsaros <i>et al.</i> (2020)	USA	Parallel-group q-RCT	35 (11/13/11)	22/26 missing = 13	49.50±nr (18-65)	0.12% CHX (rinse) 5% dilution of 0.12% CHX (rinse)	Water	Periodontal surgery	-Epithelization
Rodriguez-Zorrilla <i>et al.</i> (2020)	Spain	Parallel-group RCT	35 (7/7/21)	5/16	24.50±4.10 (18-37)	0.20% CHX (gel) 0.20% CHX + chitosan (gel)	Placebo	Surgical extraction of inferior 3M (bilateral)	-Wound healing -Erythema -Epithelization -Pain
Janani and Kumar (2019)	India	Split-mouth q-RCT	25 (12/13)	14/11	nr (18-45)	0.20% CHX (rinse)	NaCl	Surgical extraction of 3M	-Wound healing -Dehiscence
Halabi <i>et al.</i> (2018)	Chile	Parallel-group RCT	744 (372/372)	363/381	43.43±14.99 (nr)	0.12% CHX (rinse)	Placebo	Simple tooth extraction	-Alveolar osteitis
Palaia <i>et al.</i> (2018)	Italy	Parallel-group RCT	29 (15/14)	19/37	56.8±15.49 54.2±17.29 (14-81)	0.20% CHX (rinse)	Placebo	Oral mucosal biopsy	-Pain
Kaur <i>et al.</i> (2017)	India	Split-mouth q-RCT	300 (150/150)	86/64	30.50±2.50 (20-45)	0.20% CHX (gel) + antibiotic	Placebo	Bilateral extraction of 3M	-Alveolar osteitis
Madrazo-Jimenez <i>et al.</i> (2016)	Spain	Split-mouth RCT	50 (25/25)	15/10	26.47±6.74 (18-45)	0.20% chlorhexidine, chitosan (gel)	No intervention	3M	-Wound healing
Freudenthal <i>et al.</i> (2015)	Sweden	Parallel-group RCT	95 (48/47)	45/50	33±10.30 (19-65)	0.20% CHX (gel)	Placebo	3M	-Alveolar osteitis
Haraji and Rakhshan (2015)	Iran	Split-mouth q-RCT	90 (45/45)	24/21	22.09±2.79 (17-31)	0.20% CHX (gel on gelatin sponge)	Dry gelatin sponge	3M	-Alveolar osteitis -Pain
Inamdar <i>et al.</i> (2015)	Saudi Arabia	Parallel-group q-RCT	20 (10/10)	17/13	28.15±6.21 (18-60)	0.20% CHX (gel)	No intervention	3M	-Alveolar osteitis
Khan <i>et al.</i> (2015)	Pakistan	Parallel-group RCT	253 (128/125)	106/147	36.65±11 (nr)	0.20% CHX (gel)	Placebo	Simple tooth extraction	-Alveolar osteitis
Lopez-Lopez <i>et al.</i> (2015)	Spain	Parallel-group RCT	94 (47/47)	22/25	34±7 (19-47)	0.20% chlorhexidine, chitosan (gel)	Bicarbonate	3M	-Wound healing
Rubio-Palau <i>et al.</i> (2015)	Spain	Parallel-group RCT	160 (80/80)	74/86	25.04±nr (nr)	0.20% CHX (gel)	Placebo	3M	-Alveolar osteitis

Ahmedi <i>et al.</i> (2014)	Republic of Kosovo	Split-mouth q-RCT	50 (25/25)	nr	nr (18-30)	1% CHX (gel)	NaCl	3M	-Alveolar osteitis
Shaban <i>et al.</i> (2014)	Iran	Split-mouth RCT	82 (41/41)	14/27	24.15±5.02 (nr)	0.20% CHX (gel)	No intervention	3M	-Alveolar osteitis
Channar <i>et al.</i> (2013)	India	Parallel-group RCT	214 (73/69/72)	129/85	30.44±5.20 (24-40)	0.20% CHX (rinse) 0.20% CHX (rinse) + antibiotics	NaCl	3M	-Alveolar osteitis
Haraji <i>et al.</i> (2013)	Iran	Split-mouth RCT	160 (80/80)	39/41	21.60±2.50 (17-31)	0.12% CHX (gel)	Dry sponge	3M	-Alveolar osteitis -Pain
Babar <i>et al.</i> (2012)	Pakistan	Parallel-group q-RCT	100 (50/50)	65/35	29±6 (18-40)	0.20% CHX (gel)	No intervention	3M	-Alveolar osteitis
Torres-Lagares <i>et al.</i> (2010)	Spain	Parallel-group RCT	38 (14/24)	33/5	32.18±13.63 (18-57)	0.12% CHX (gel)	Placebo	3M	-Alveolar osteitis
Torres-Lagares <i>et al.</i> (2006)	Spain	Parallel-group RCT	103 (53/50)	34/69	26.78±8.52 (18-64)	0.20% CHX (gel)	Placebo	3M	-Alveolar osteitis
Delilbasi <i>et al.</i> (2002)	Turkey	Parallel-group RCT	177 (62/56/59)	82/95	24±nr (nr)	0.20% CHX (rinse) 0.20% CHX (rinse) + antibiotics	NaCl	3M	-Alveolar osteitis
Hermesch <i>et al.</i> (1998)	USA	Parallel-group RCT	479 (239/240)	101/170	22.30±nr (18-52)	0.12% CHX (rinse)	Placebo	3M	-Alveolar osteitis
Ragno and Szkutnik (1991)	USA	Split-mouth RCT	160 (80/80)	nr	nr	0.12% CHX (rinse)	Placebo	3M	-Alveolar osteitis
Berwick and Lessin (1990)	USA	Parallel-group RCT	77 (39/38)	nr	21.40±nr (16-40)	0.12% CHX (rinse)	NaCl	3M	-Alveolar osteitis
Larsen (1990)	USA	Parallel-group RCT	278 (144/134)	62/78	nr	0.12% CHX (rinse)	Placebo	3M	-Alveolar osteitis
Sanz <i>et al.</i> (1989)	USA	Parallel-group RCT	38 (17/21)	nr	nr	0.12% CHX (rinse)	Placebo	Periodontal surgery	-Ephitelization
Fied <i>et al.</i> (1988)	United Kingdom	Parallel-group q-RCT	216 (108/108)	223/101	nr	0.20% CHX (rinse)	NaCl	Tooth extraction	-Alveolar osteitis
Krekmanov and Nordenram (1986)	Sweden	Parallel-group q-RCT	110 (37/37/36)	59/51	29±nr (19-59)	0.20% CHX (rinse) + antibiotic 0.20% CHX (rinse) 0.20% CHX + antibiotics (rinse)	No intervention	3M	-Alveolar osteitis
Tjernberg (1979)	Sweden	Parallel-group q-RCT	60 (30/30)	29/31	26.30±nr (19-38)	0.20% CHX (rinse)	No intervention	3M	-Alveolar osteitis
Abbreviations: n, number; I, intervention group; C, control group; m, males; f, females; y, years; CHX, chlorhexidine; NaCl, saltwater rinse; 3M, third molar; 1M, first molar; SD, standard deviation; nr, not reported; RCT, randomized controlled trial; q-RCT, quasi-randomized controlled trial									

3. Meta-analysis on wound healing

3.1 Subgroup meta-analysis by type of intervention

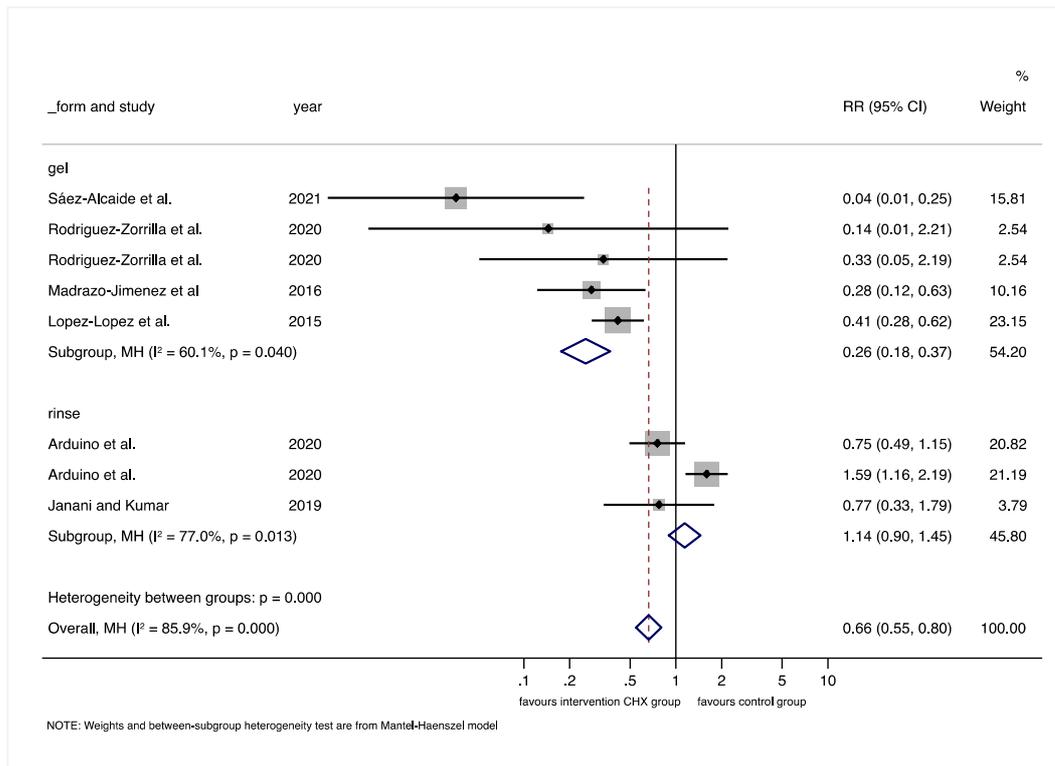
Figure S1. Forest plot graphically representing the stratified meta-analysis by type of intervention on the association between the application of CHX and wound healing.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound healing. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

3.2 Subgroup meta-analysis by type of vehicle

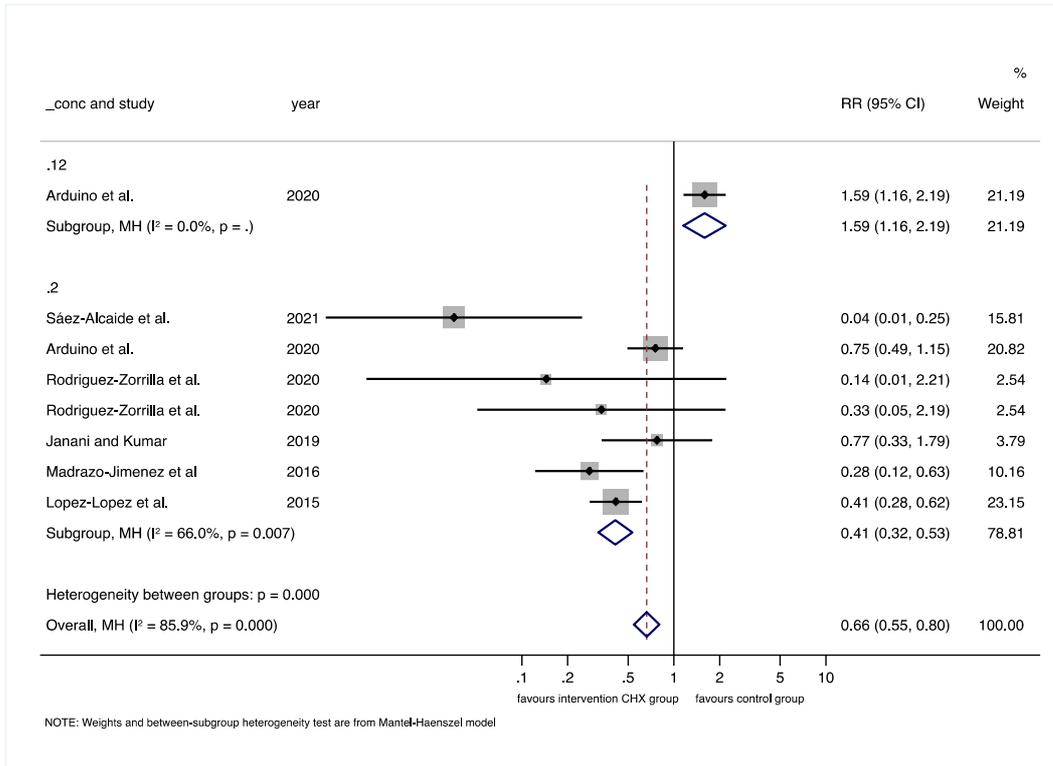
Figure S2. Forest plot graphically representing the stratified meta-analysis by type of vehicle on the association between the application of CHX and wound healing.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound healing. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

3.3 Subgroup meta-analysis by type of concentration

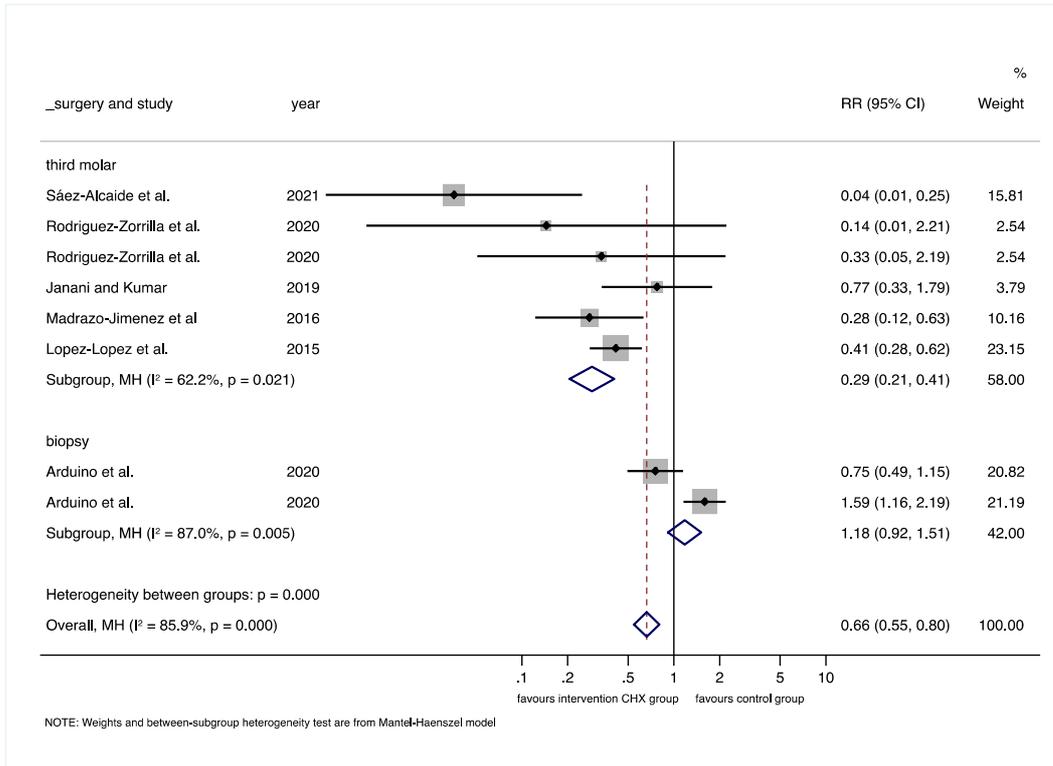
Figure S3. Forest plot graphically representing the stratified meta-analysis by type of concentration on the association between the application of CHX and wound healing.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound healing. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

3.4 Subgroup meta-analysis by type of oral surgery

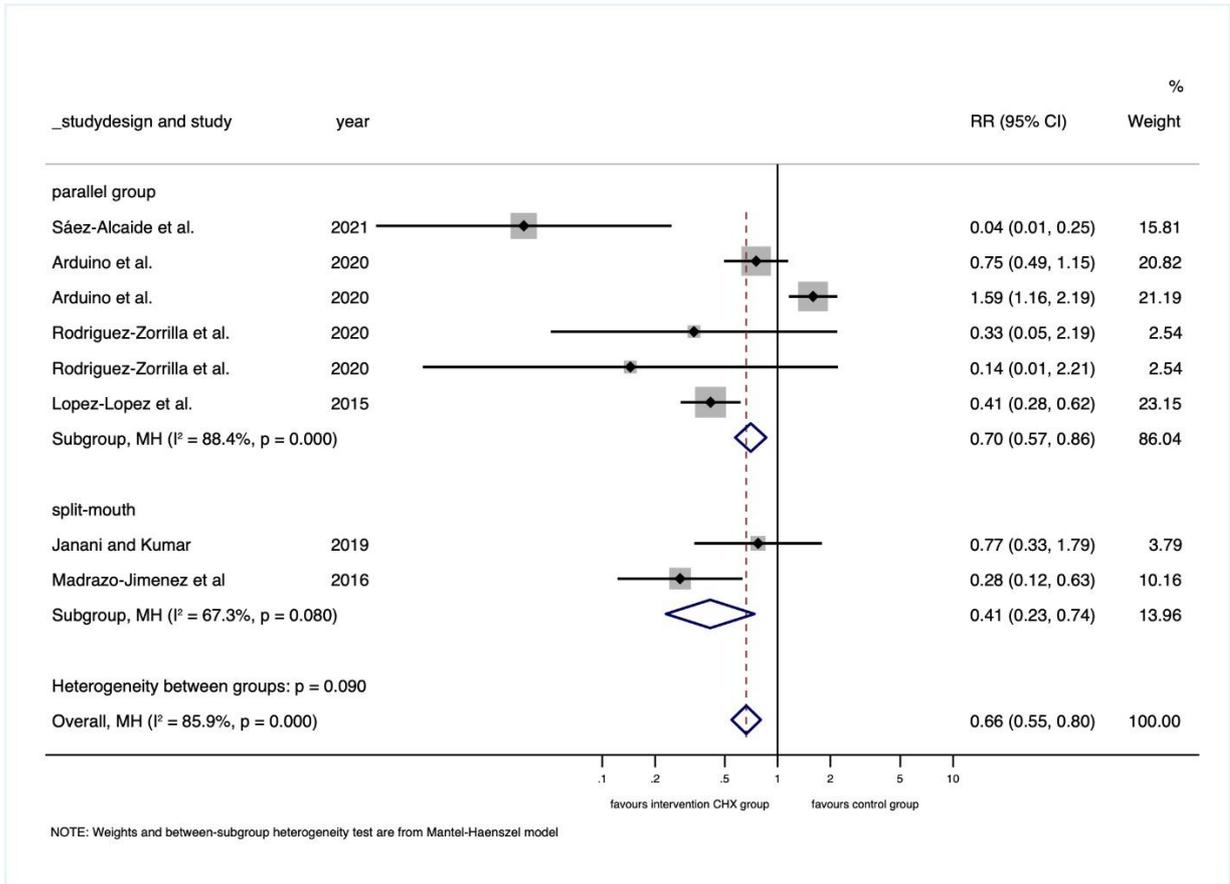
Figure S4. Forest plot graphically representing the stratified meta-analysis by type of oral surgery on the association between the application of CHX and wound healing.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound healing. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

3.5 Subgroup meta-analysis by study design

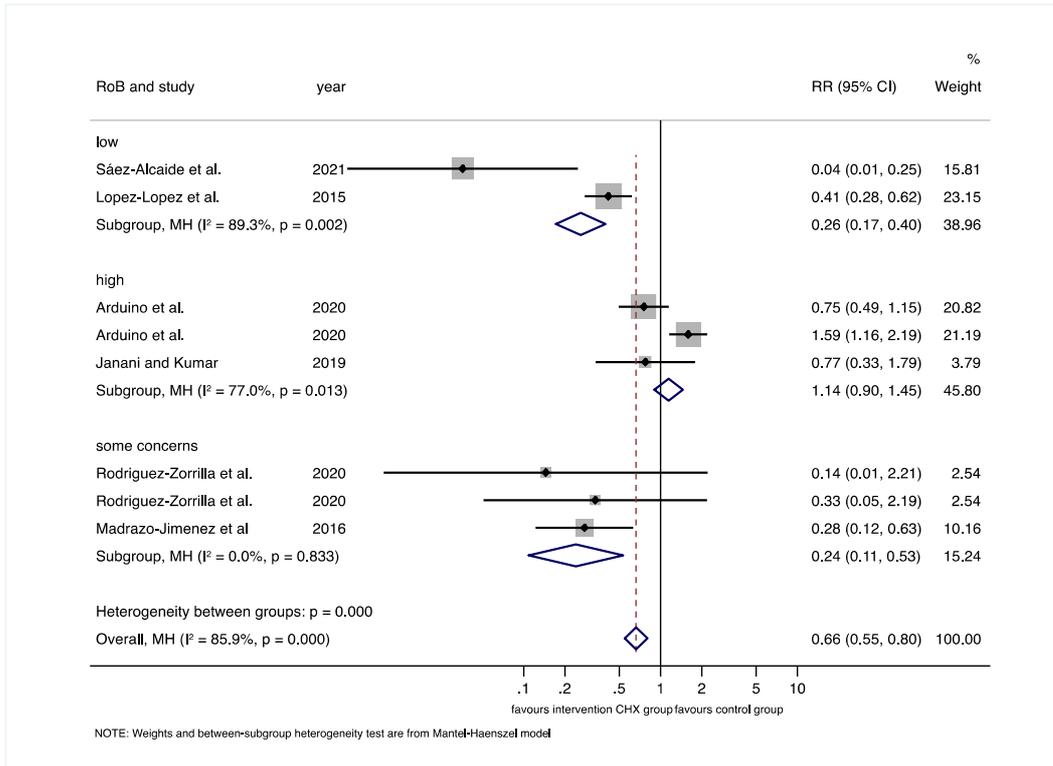
Figure S5. Forest plot graphically representing the stratified meta-analysis by study design on the association between the application of CHX and wound healing.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound healing. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

3.6 Subgroup meta-analysis by overall RoB

Figure S6. Forest plot graphically representing the stratified meta-analysis by overall RoB on the association between the application of CHX and wound healing.

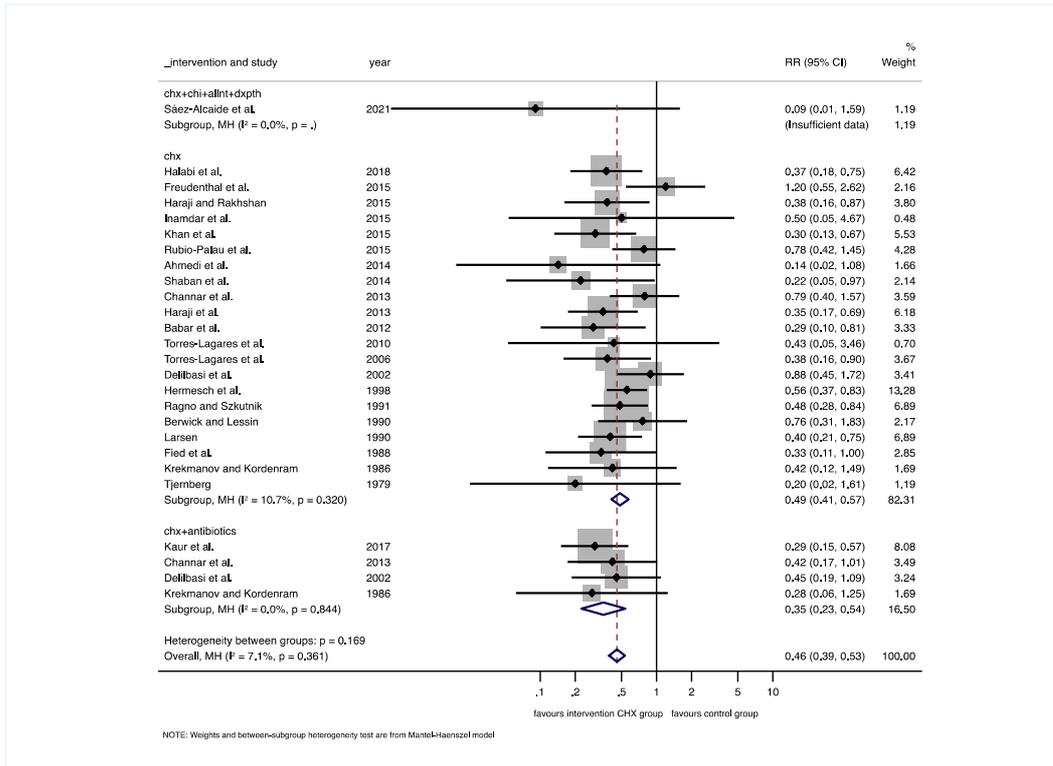


CHX, chlorhexidine; RoB, risk of bias; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound healing. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

4. Meta-analysis on alveolar osteitis

4.1 Subgroup meta-analysis by type of intervention

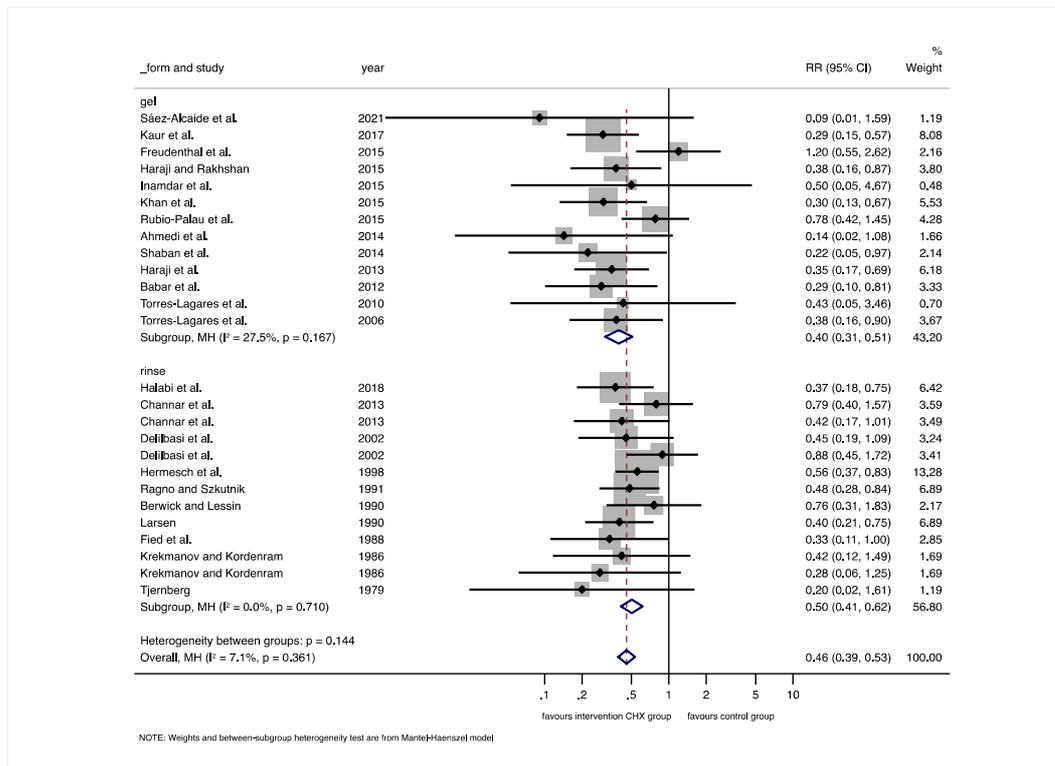
Figure S7. Forest plot graphically representing the stratified meta-analysis by type of intervention on the association between the application of CHX and alveolar osteitis.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with a lower risk of alveolar osteitis. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

4.2 Subgroup meta-analysis by type of vehicle

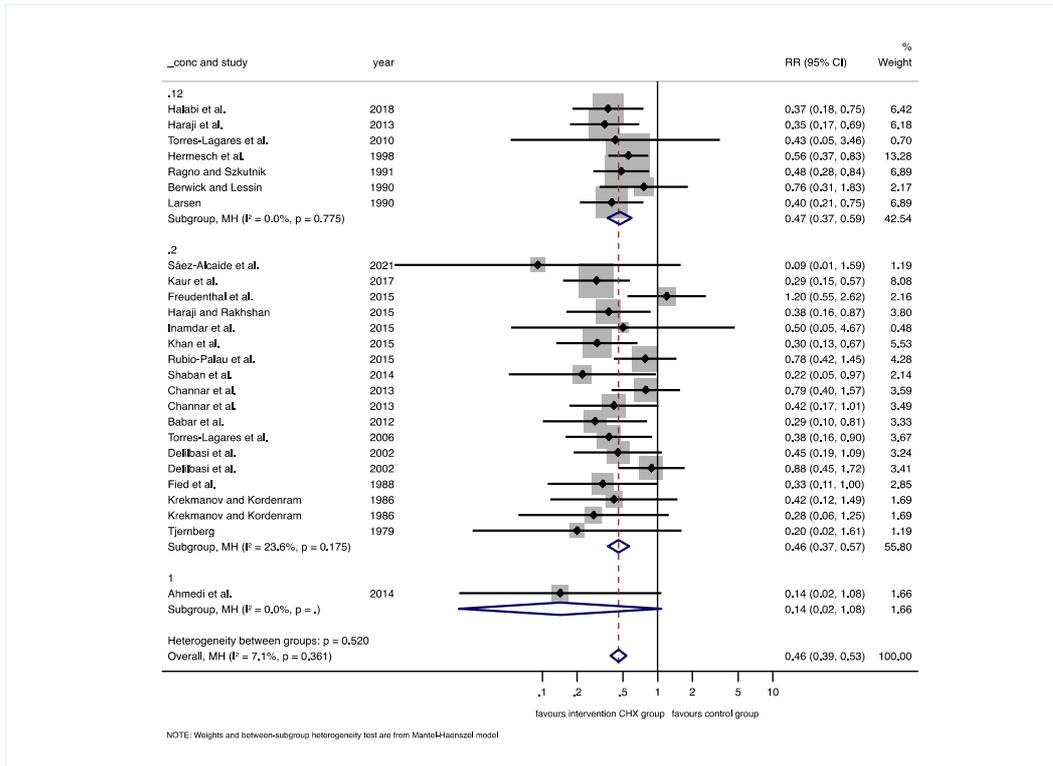
Figure S8. Forest plot graphically representing the stratified meta-analysis by type of vehicle on the association between the application of CHX and alveolar osteitis.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with a lower risk of alveolar osteitis. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

4.3 Subgroup meta-analysis by type of concentration

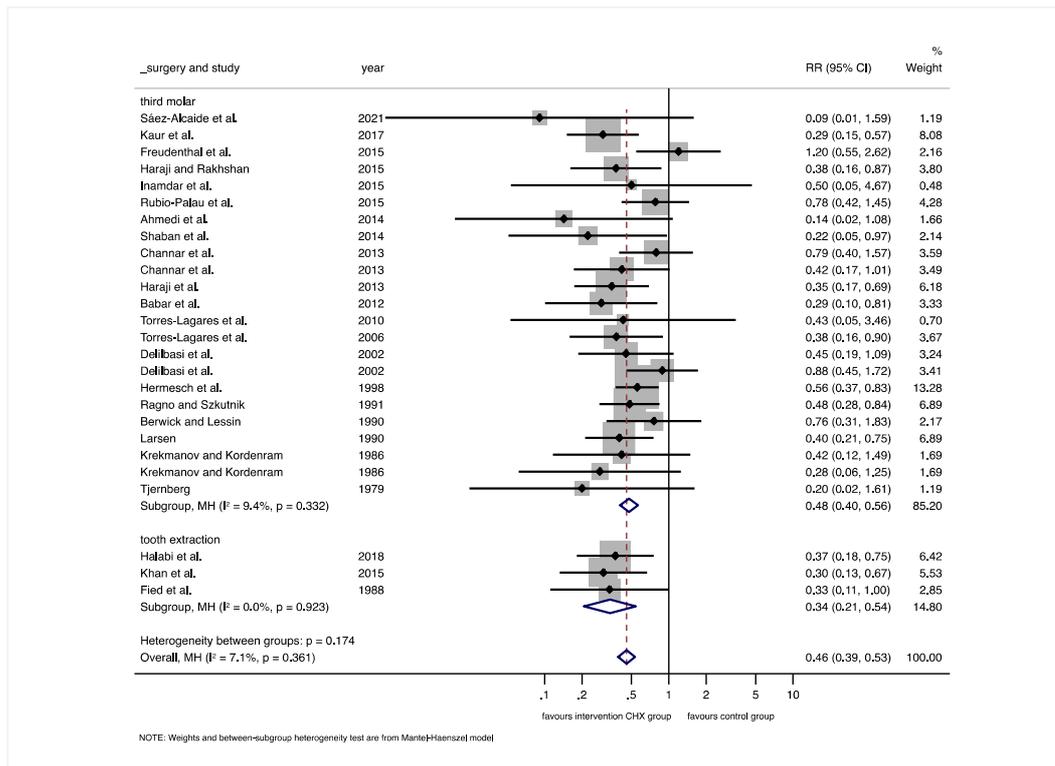
Figure S9. Forest plot graphically representing the stratified meta-analysis by type of concentration on the association between the application of CHX and alveolar osteitis.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with a lower risk of alveolar osteitis. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

4.4 Subgroup meta-analysis by type of oral surgery

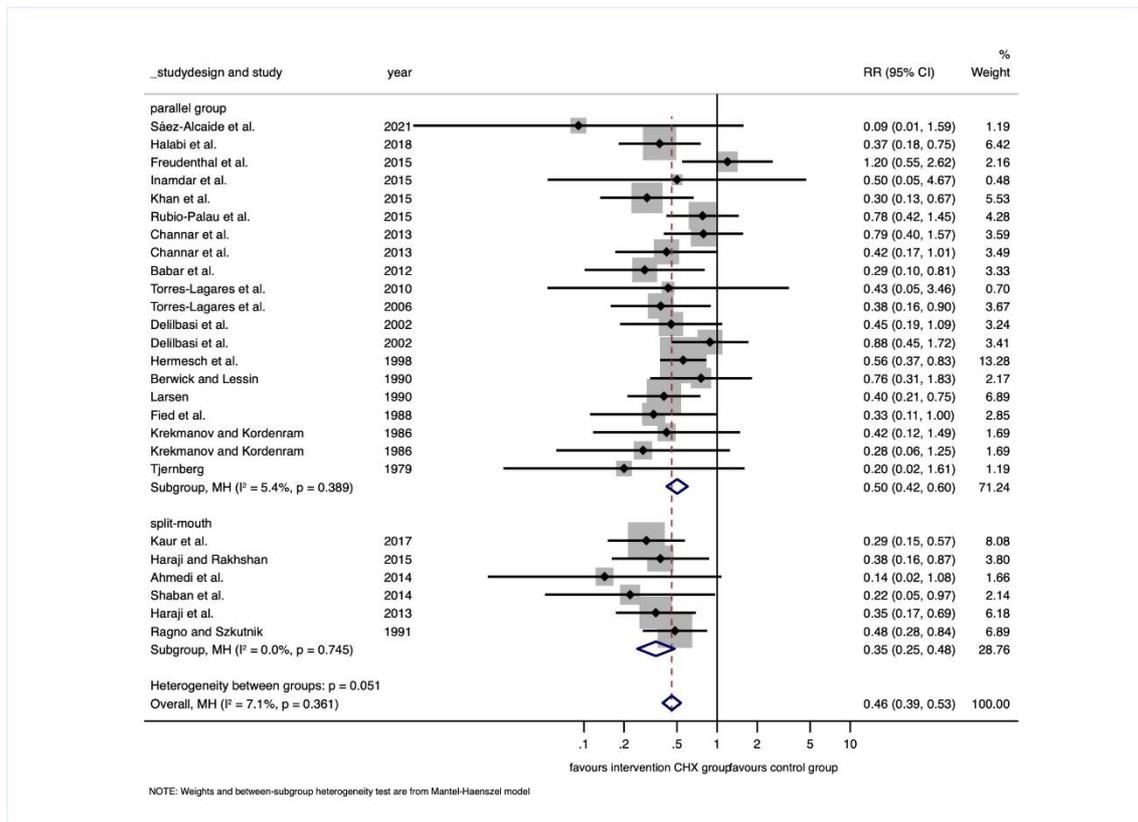
Figure S10. Forest plot graphically representing the stratified meta-analysis by type of oral surgery on the association between the application of CHX and alveolar osteitis.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with a lower risk of alveolar osteitis. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

4.5 Subgroup meta-analysis by type of study design

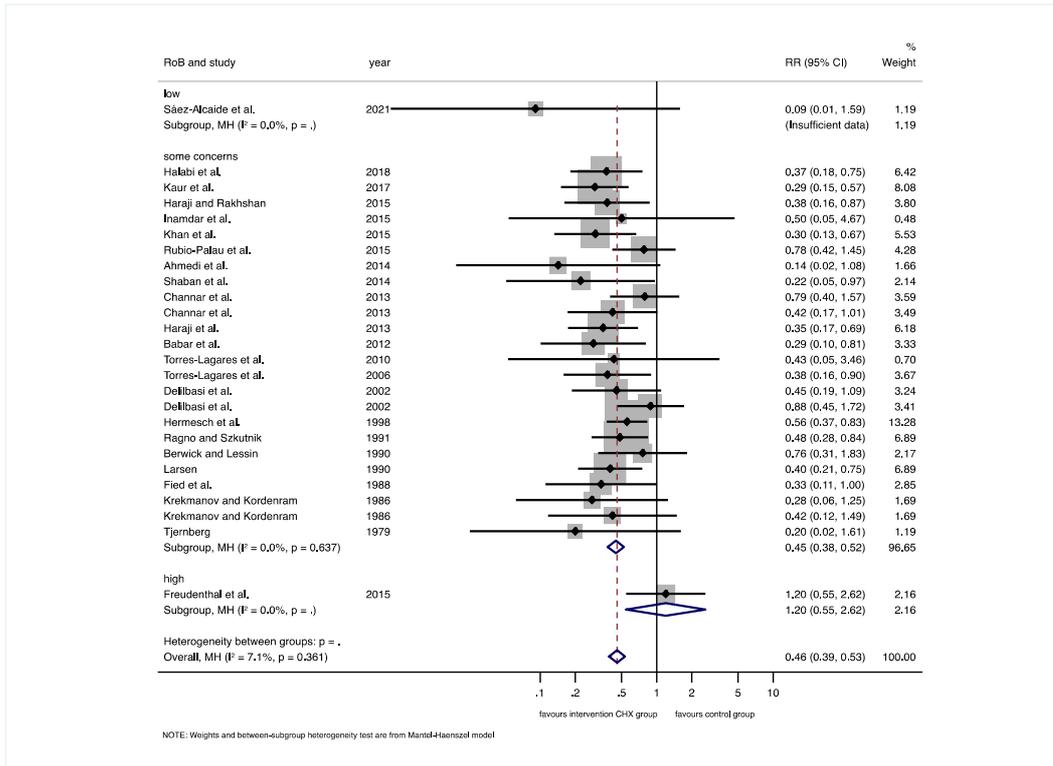
Figure S11. Forest plot graphically representing the stratified meta-analysis by type of study design on the association between the application of CHX and alveolar osteitis.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with a lower risk of alveolar osteitis. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

4.6 Subgroup meta-analysis by overall RoB

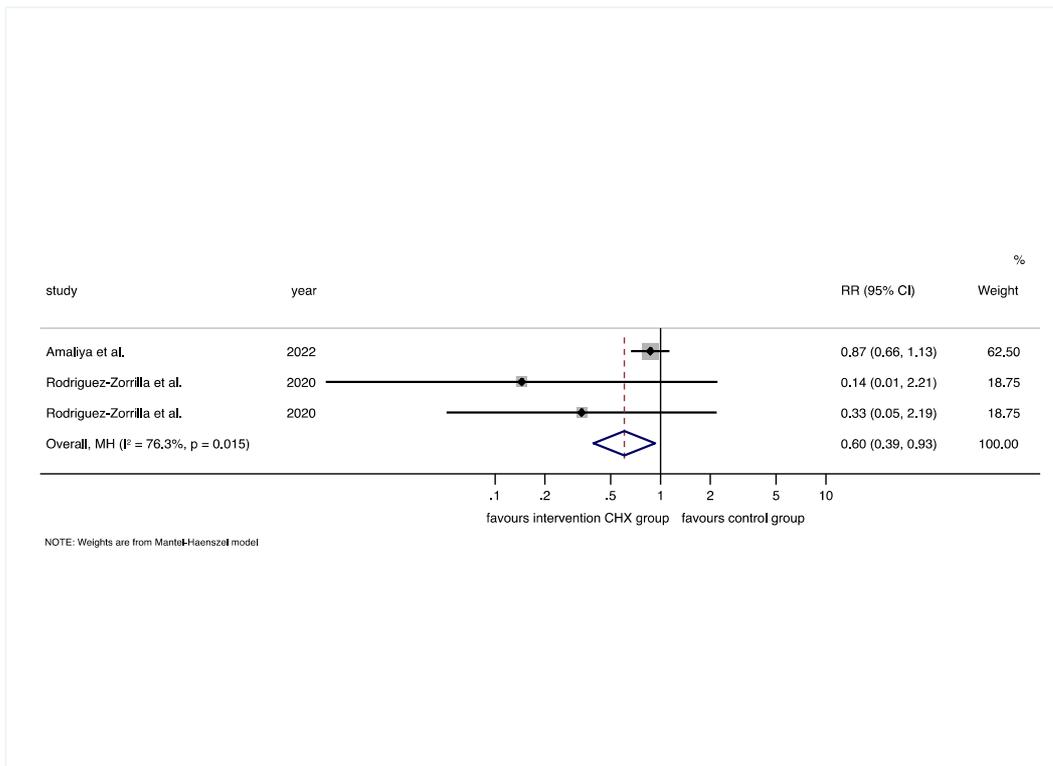
Figure S12. Forest plot graphically representing the stratified meta-analysis by overall RoB on the association between the application of CHX and alveolar osteitis.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with a lower risk of alveolar osteitis. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

5. Meta-analysis on wound erythema

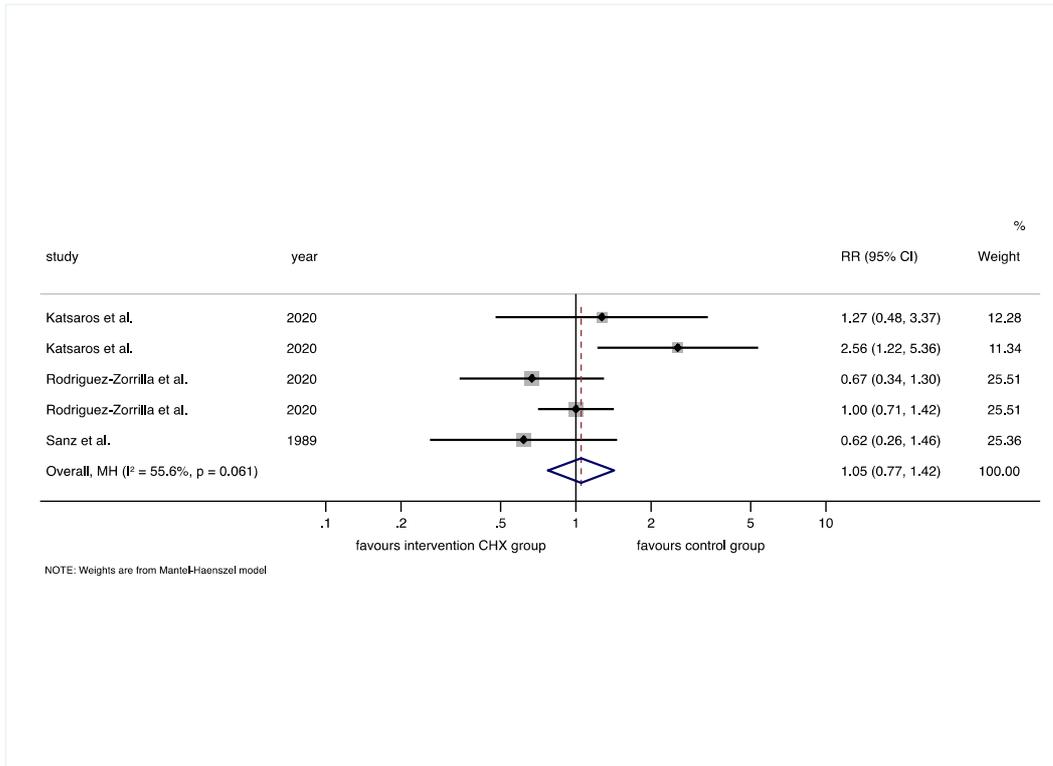
Figure S13. Forest plot graphically representing the meta-analysis on the association between the application of CHX and wound erythema.



CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound erythema. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

6. Meta-analysis on wound epithelization

Figure S14. Forest plot graphically representing the meta-analysis on the association between the application of CHX and wound epithelization.

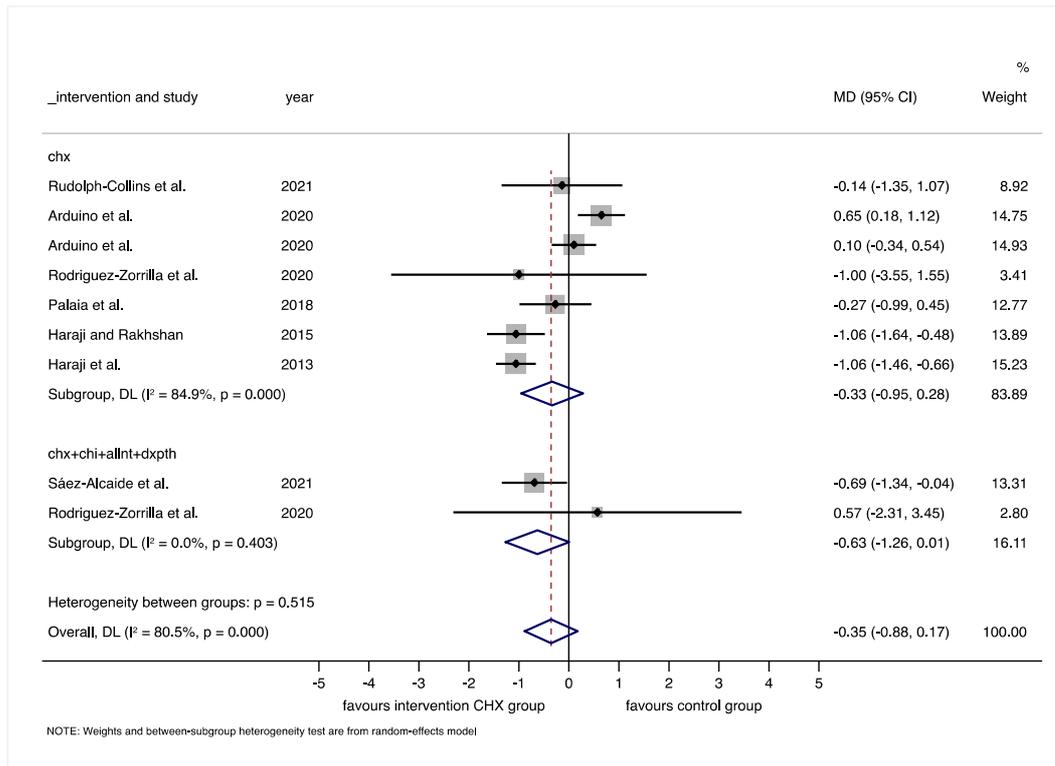


CHX, chlorhexidine; RR, relative risk; CI, confidence intervals. Fixed-effect model, Mantel-Haenszel method. A RR < 1 suggests that the application of CHX is associated with better wound epithelization. Diamonds indicate the pooled RRs with their corresponding 95% CIs.

7. Meta-analysis on pain

7.1 Subgroup meta-analysis by type of intervention

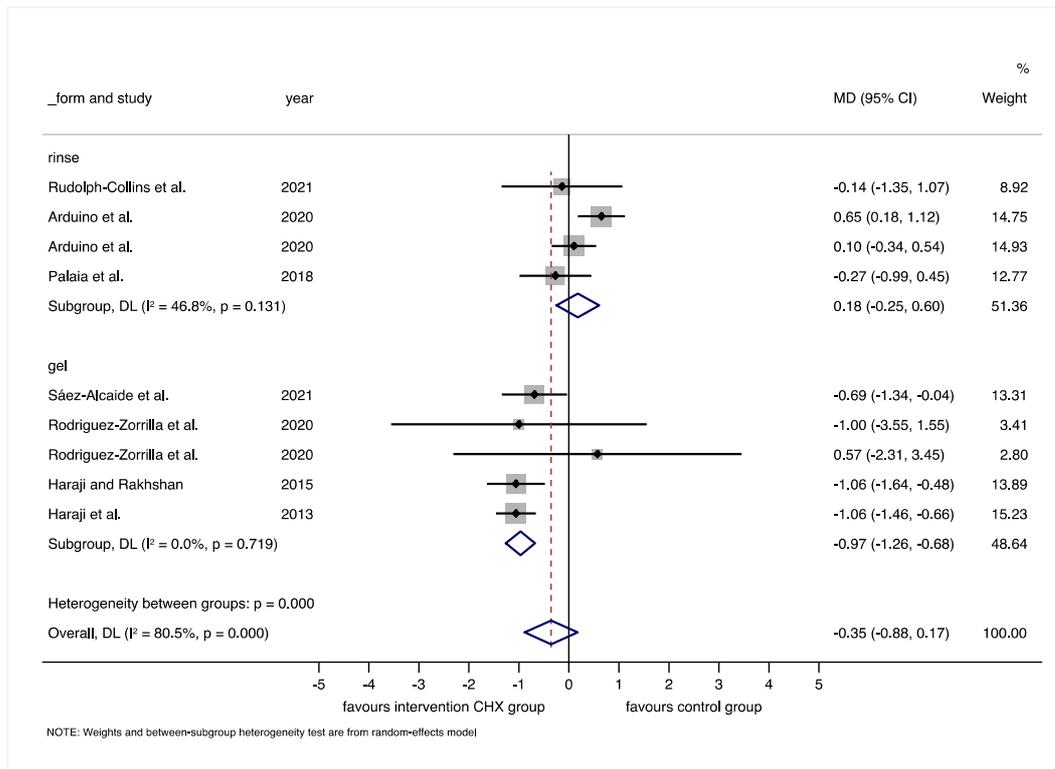
Figure S15. Forest plot graphically representing the stratified meta-analysis by type of intervention on the differences in pain between the CHX group and controls.



CHX, chlorhexidine; MD, mean difference; CI, confidence intervals. Random-effects model, inverse-variance method. A MD < 0 suggests that pain levels were lower for the CHX group. Diamonds indicate the pooled MD with their corresponding 95% CIs.

7.2 Subgroup meta-analysis by type of vehicle

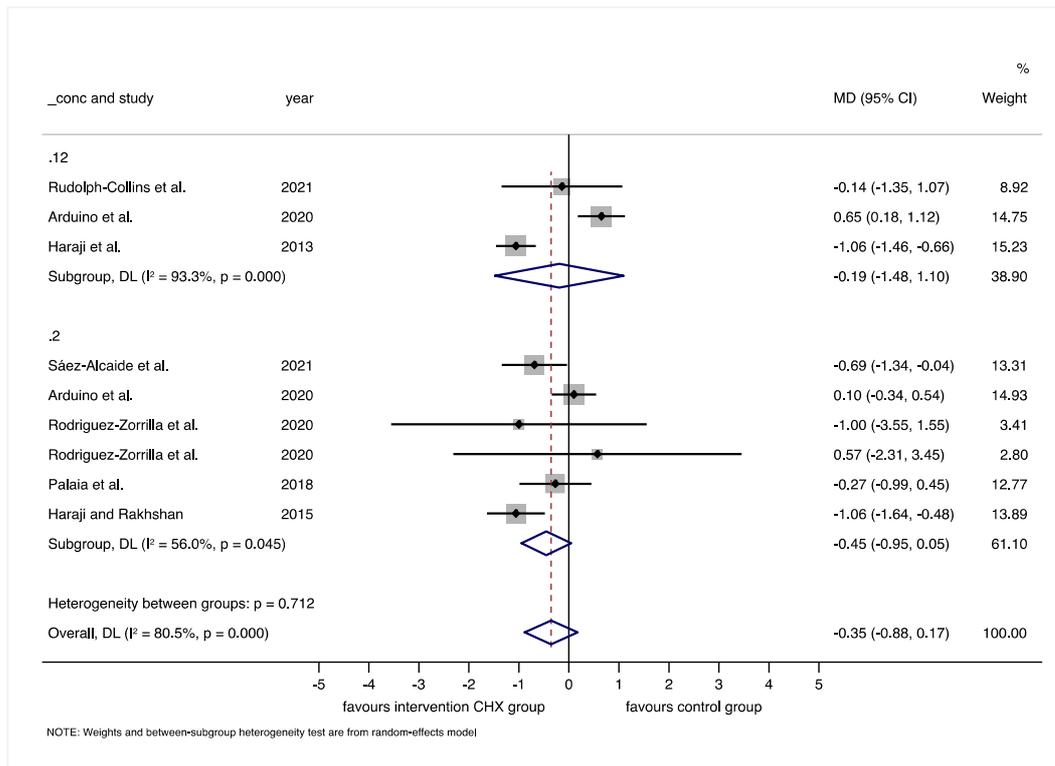
Figure S16. Forest plot graphically representing the stratified meta-analysis by type of vehicle on the differences in pain between the CHX group and controls.



CHX, chlorhexidine; MD, mean difference; CI, confidence intervals. Random-effects model, inverse-variance method. A MD < 0 suggests that pain levels were lower for the CHX is group. Diamonds indicate the pooled MD with their corresponding 95% CIs.

7.3 Subgroup meta-analysis by type of concentration

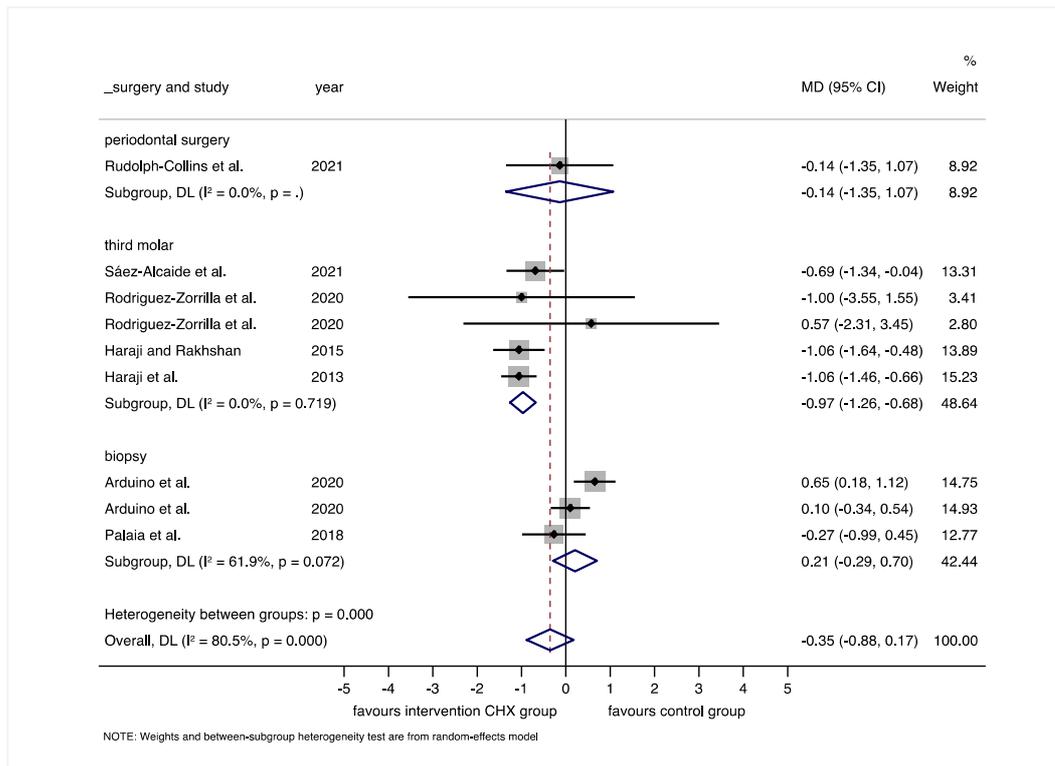
Figure S17. Forest plot graphically representing the stratified meta-analysis by type of concentration on the differences in pain between the CHX group and controls.



CHX, chlorhexidine; MD, mean difference; CI, confidence intervals. Random-effects model, inverse-variance method. A MD < 0 suggests that pain levels were lower for the CHX is group. Diamonds indicate the pooled MD with their corresponding 95% CIs.

7.4 Subgroup meta-analysis by type of oral surgery

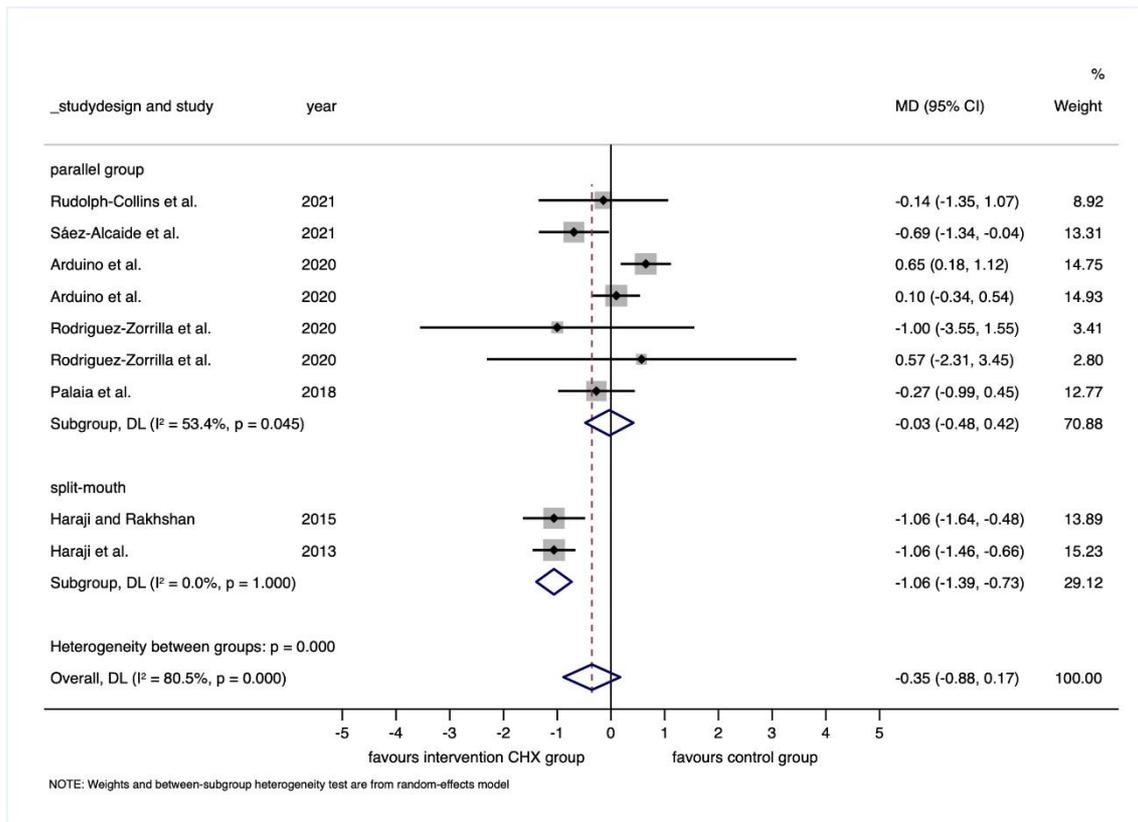
Figure S18. Forest plot graphically representing the stratified meta-analysis by type of oral surgery on the differences in pain between the CHX group and controls.



CHX, chlorhexidine; MD, mean difference; CI, confidence intervals. Random-effects model, inverse-variance method. A MD < 0 suggests that pain levels were lower for the CHX is group. Diamonds indicate the pooled MD with their corresponding 95% CIs.

7.5 Subgroup meta-analysis by type of study design

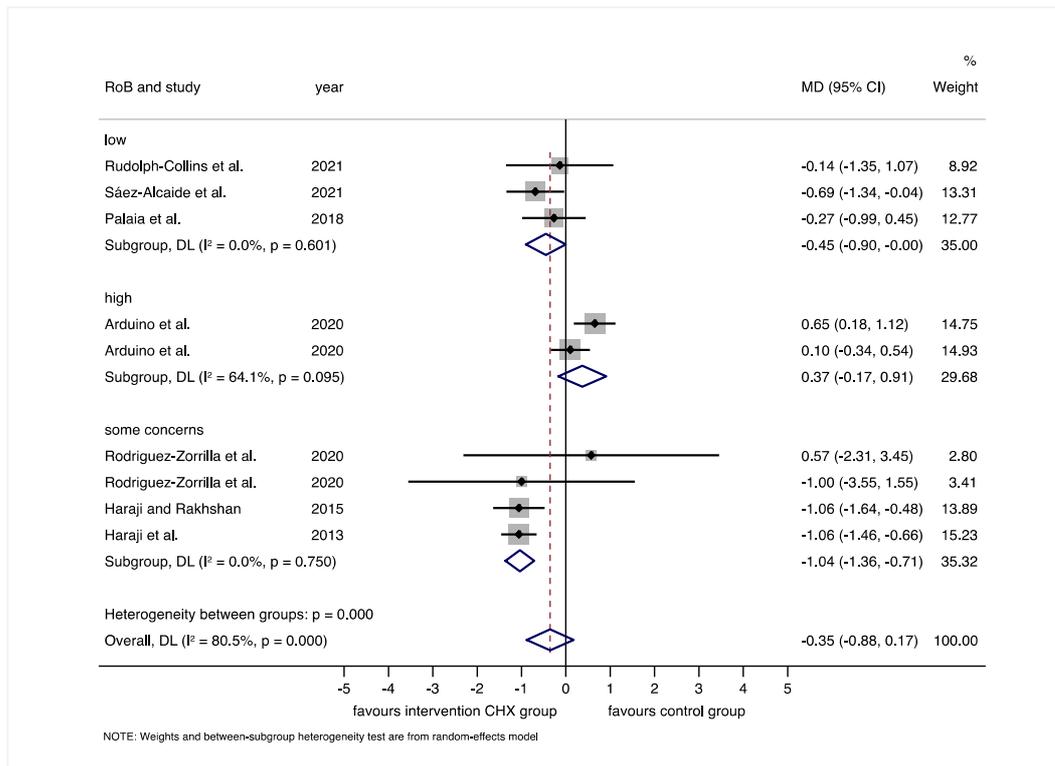
Figure S19. Forest plot graphically representing the stratified meta-analysis by type of study design on the differences in pain between the CHX group and controls.



CHX, chlorhexidine; MD, mean difference; CI, confidence intervals. Random-effects model, inverse-variance method. A MD < 0 suggests that pain levels were lower for the CHX is group. Diamonds indicate the pooled MD with their corresponding 95% CIs.

7.6 Subgroup meta-analysis by overall RoB

Figure S20. Forest plot graphically representing the stratified meta-analysis by overall RoB on the differences in pain between the CHX group and controls.

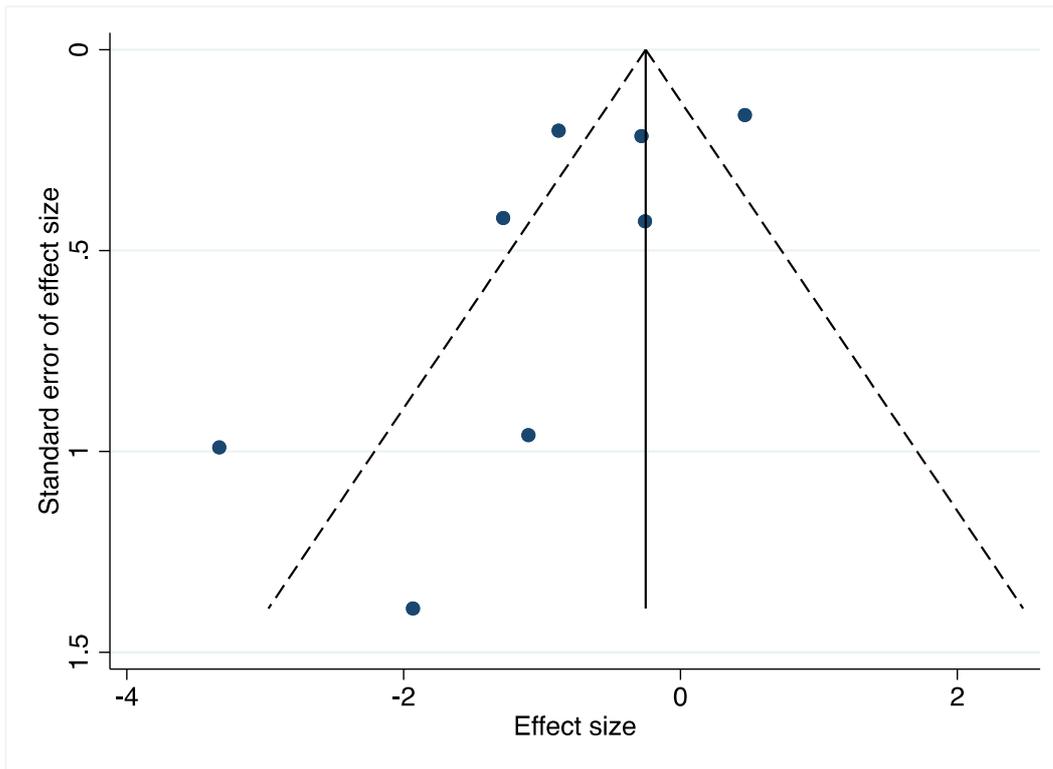


CHX, chlorhexidine; MD, mean difference; CI, confidence intervals. Random-effects model, inverse-variance method. A MD < 0 suggests that pain levels were lower for the CHX is group. Diamonds indicate the pooled MD with their corresponding 95% CIs.

8. Analysis of small-study effects

8.1 Wound healing

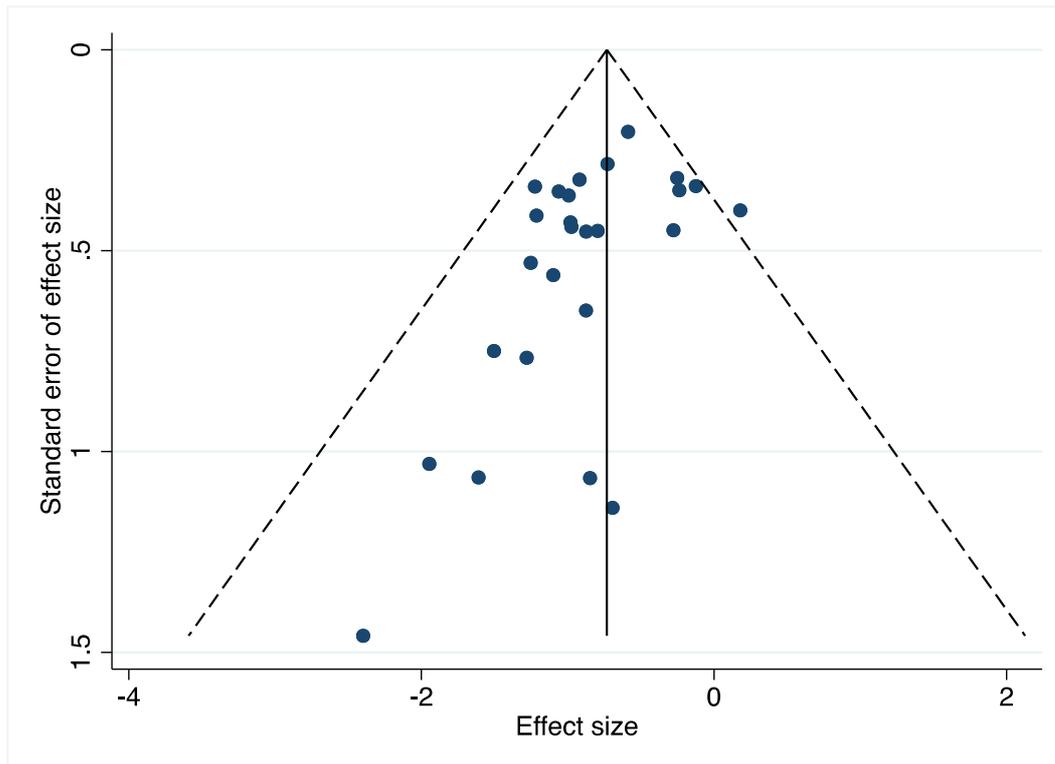
Figure S21. A funnel plot of estimated effect sizes against their standard errors, graphically representing the analysis of small-study effects on the association between the application of CHX and wound healing.



SE, standard error; ES, effect sizes. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

8.2 Alveolar osteitis

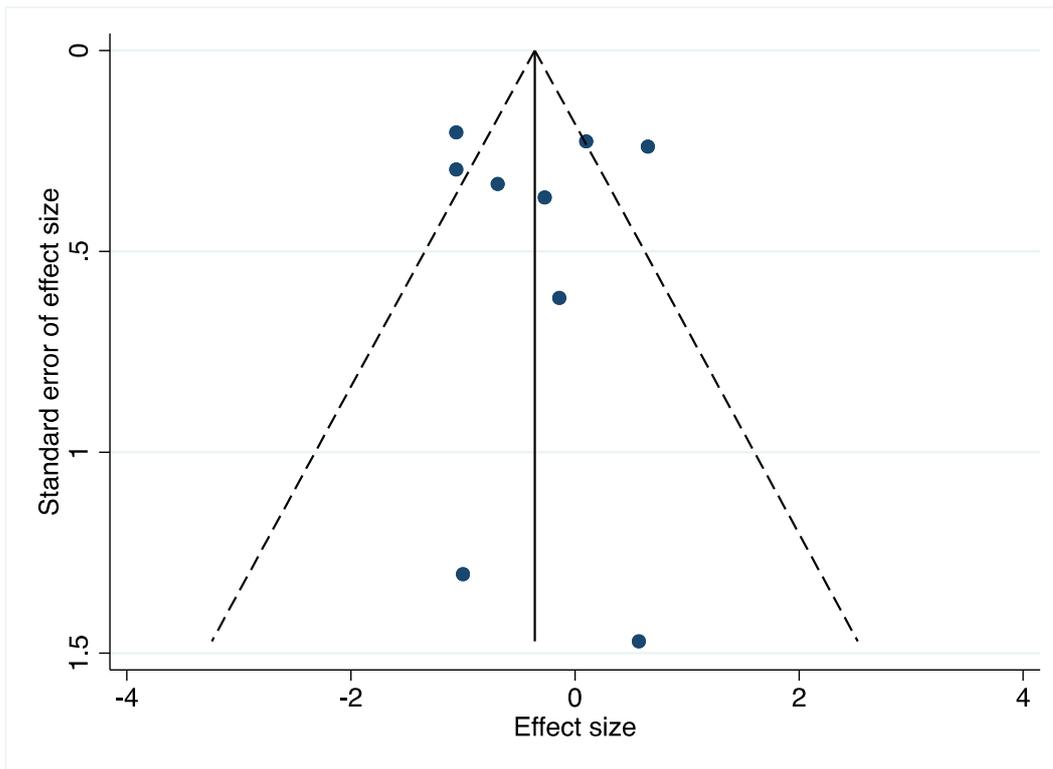
Figure S22. A funnel plot of estimated effect sizes against their standard errors, graphically representing the analysis of small-study effects on the association between the application of CHX and alveolar osteitis.



SE, standard error; ES, effect size. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

8.3 Pain

Figure S23. A funnel plot of the differences in pain between CHX group and controls, expressed as mean differences against their standard errors.



SE, standard error; ES, effect size. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

9. List of full-text articles excluded with reasons

Inappropriate control group (n=27)

- Abu-Mostafa NA, Alqahtani A, Abu-Hasna M, Alhokail A, Aladsani A. A randomized clinical trial compared the effect of intra-alveolar 0.2 % Chlorohexidine bio-adhesive gel versus 0.12% Chlorohexidine rinse in reducing alveolar osteitis following molar teeth extractions. *Med Oral Patol Oral Cir Bucal*. 2015 Jan 1;20(1):e82-7.
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- Almushalbn A, Albassal A, Harfouch M. Comparative Clinical Study Between Chlorhexidine Gel (0.2%) and Hyaluronic Gel (1%) in the Prevention of a Dry Socket After Tooth Extraction for Orthodontic Treatment. *Cureus*. 2022 Dec 11;14(12):e32391.
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- Coello-Gómez A, Navarro-Suárez S, Diosdado-Cano JM, Azcárate-Velázquez F, Bargiela-Pérez P, Serrera-Figallo MA, Torres-Lagares D, Gutiérrez-Pérez JL. Postoperative effects on lower third molars of using mouthwashes with super-oxidized solution versus 0.2% chlorhexidine gel: A randomized double-blind trial. *Med Oral Patol Oral Cir Bucal*. 2018 Nov 1;23(6):e716-e722.
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(chlorhexidine with or without alcohol and C31G), adjunct to periodontal surgery, in early wound healing. *Clin Oral Investig*. 2018 Sep;22(7):2581-2591.

- Heitz F, Heitz-Mayfield LJA, Lang NP. Effects of post-surgical cleansing protocols on early plaque control in periodontal and/or periimplant wound healing. *J Clin Periodontol*. 2004;31:1012-1018.

- Hita-Iglesias P, Torres-Lagares D, Flores-Ruiz R, Magallanes-Abad N, Basallote-Gonzalez M, Gutierrez-Perez JL. Effectiveness of chlorhexidine gel versus chlorhexidine rinse in reducing alveolar osteitis in mandibular third molar surgery. *J Oral Maxillofac Surg*. 2008 Mar;66(3):441-5.

- Horwitz J, Machtei EE, Zuabi O, Peled M. Amine fluoride/stannous fluoride and chlorhexidine mouthwashes as adjuncts to single-stage dental implants: a comparative study. *J Periodontol*. 2005 Mar;76(3):334-40.

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No outcomes of interest (n=7)

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Inappropriate study design (nonrandomized) (n=2)

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Lack of essential data (n = 2)

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Overlapping population (n = 2)

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Off topic (n = 1)

- Binahmed A, Stoykewych A, Peterson L. Single preoperative dose versus long-term prophylactic antibiotic regimens in dental implant surgery. Int J Oral Maxillofac Implants. 2005 Jan-Feb;20(1):115-7.