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**Original Article**

# Microbial colonization and biofilm formation on polytetrafluoroethylene membranes used in guided tissue regeneration, guided bone regeneration, and alveolar ridge preservation: A systematic review of clinical, intraoral exposure-model, and in vitro evidence

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***Abstract***

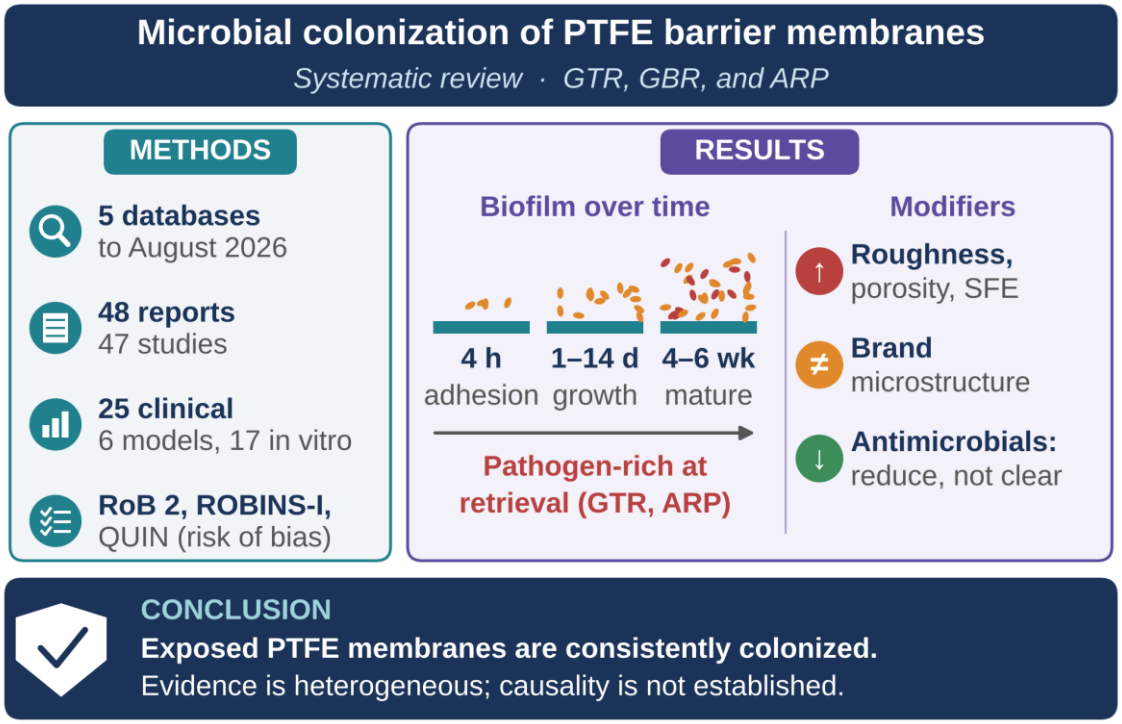
***Background.*** Non-resorbable polytetrafluoroethylene (PTFE) membranes, expanded (e-PTFE) or dense (d-PTFE), are used in guided tissue regeneration (GTR), guided bone regeneration (GBR), and alveolar ridge preservation (ARP); however, oral exposure brings them into contact with the oral microbiome. This systematic review aimed to synthesize the evidence on microbial colonization and biofilm formation on the membrane surface.

***Methods.*** Following PRISMA 2020 and SWiM (PROSPERO CRD420261445702), five databases were searched up to 15 August 2026. Therapeutic clinical, non-therapeutic intraoral exposure model, and in vitro studies were synthesized narratively; risk of bias was appraised with RoB 2, ROBINS-I, and QUIN, and single-arm studies were appraised with a structured methodological appraisal.

***Results.*** Forty-eight reports (47 studies) were included: 25 therapeutic clinical (21 periodontal GTR, one also including GBR, and 4 ARP with d-PTFE), 6 exposure models, and 17 in vitro. Bacterial adhesion was detectable within 4 hours in exposure models, and pathogen-rich polymicrobial biofilms were consistently present on membranes examined at retrieval (typically 4–6 weeks). In correlational GTR studies, heavier or pathogen-rich contamination was associated with lower attachment gain or bone fill. Antimicrobial adjuncts reduced but did not eliminate colonization. Surface roughness, micro-porosity, and surface free energy were associated with adhesion in vitro, and brand-level differences suggest that product-specific microstructure may influence colonization beyond the e-PTFE/d-PTFE distinction.

***Conclusion.*** Exposed PTFE membranes are consistently colonized; however, the evidence is heterogeneous, predominantly descriptive, and insufficient to establish causality, and standardized comparative studies are needed to clarify its clinical relevance.

**Graphical Abstract**




**Key words:** Alveolar ridge augmentation, artificial membranes, bacterial adhesion, biofilms, bone regeneration, periodontal guided tissue regeneration, polytetrafluoroethylene.

## Introduction

Although alveolar bone loss affects millions of individuals,[1,2] barrier membranes designed to protect the regenerative site[3,4] may be colonized by the microorganisms they are intended to exclude.[5,6]

Loss of alveolar bone, whether secondary to periodontal disease or to tooth loss, is a common condition that compromises masticatory function and dentofacial esthetics: severe periodontitis affects approximately one in ten adults worldwide and ranks among the most prevalent chronic diseases,[1] severe tooth loss remains a major global oral-health burden,[2] and tooth extraction is followed by substantial horizontal and vertical resorption of the alveolar ridge.[7] Guided tissue regeneration (GTR) of periodontal intrabony and furcation defects, guided bone regeneration (GBR), and alveolar ridge preservation (ARP) are established therapeutic approaches supported by clinical practice guidelines and consensus reports[8–10] to counteract this atrophy and to create favorable conditions for future implant-supported rehabilitation, relying on the principle of selectively excluding soft tissue cells from the healing bone defect while maintaining space, clot stability, and vascular supply.[11–15]

These techniques rely on a barrier membrane. Non-resorbable polytetrafluoroethylene (PTFE) membranes were first used in their expanded form (e-PTFE), which was designed to remain submerged beneath a primarily closed flap; in this historical GTR literature, exposure was an unplanned complication (premature wound dehiscence) that was frequently accompanied by bacterial contamination and compromised

regeneration.[12,15,16] The dense variant (d-PTFE), with sub-micrometer porosity, was subsequently developed to tolerate exposure and is widely favored for its low porosity, resistance to bacterial penetration, and the possibility of open, non-submerged healing without primary flap closure, followed by simple flapless removal; in contemporary ARP protocols, it is frequently left intentionally exposed.[11–13,16–19] However, the same feature that makes d-PTFE clinically convenient—intentional exposure to the oral cavity—places it in direct and prolonged contact with a highly diverse oral microbiome of over 700 bacterial species living in dynamic equilibrium, but which could colonize it if that equilibrium is lost, increasing the potential risk of infection of the tissues, thus compromising treatment.[20–25] Surface properties such as hydrophobicity, pore size, and roughness have been proposed as determinants of bacterial adhesion and biofilm maturation on these membranes, and in vitro and clinical studies have documented colonization by periodontopathogenic and cariogenic species, as well as by *Candida albicans*, on exposed d-PTFE surfaces.[17–19,23–28]

Despite this growing body of evidence, findings remain fragmented and, at times, contradictory: some studies report that d-PTFE's dense, node-free structure confers superior resistance to bacterial and connective tissue penetration compared with expanded PTFE, while others describe substantial biofilm formation and dysbiotic communities on exposed d-PTFE surfaces that may compromise regenerative outcomes.[17,18,20-24,28] This heterogeneity in study design, membrane type, clinical indication, type of exposure (unplanned or intentional), and microbiological methodology, together with the clinical relevance of graft site infection for the success of GTR, GBR, and ARP, justifies a systematic appraisal of the topic. To date, no systematic review has been identified that specifically synthesizes the clinical and in vitro evidence regarding microbial colonization and biofilm formation on PTFE membranes (e-PTFE and d-PTFE) used in these procedures. Therefore, this systematic review aims to synthesize the available clinical, intraoral exposure model, and in vitro evidence on microbial colonization and biofilm formation on PTFE (expanded and dense) membranes used in GTR, GBR, and ARP, distinguishing throughout between clinical indications and between unplanned and intentional exposure, and to critically appraise the risk of bias and methodological limitations of the available evidence.

## Methods

### *Protocol and Registration*

This systematic review was conducted and reported in accordance with the PRISMA 2020 statement.[29] The protocol was registered in PROSPERO (registration number: CRD420261445702; registered on 22 August 2026). The registration record was first submitted on 22 August 2026 and published on the same day (version 1.0). As declared in the "Stage of the review at this submission" field of the record, at the time of submission only pilot work had been started, and formal searching, screening against the eligibility criteria, data extraction, risk-of-bias assessment, and data synthesis had not begun. The date of 15 August 2026 that appears in the registered record and in the Search strategy below is the upper limit of the publication date window applied to the database searches, not the date on which the searches were run: the final searches of all databases were executed on 25 August 2026, after registration, and the retrieved records were imported into Rayyan for deduplication and screening on the same day; the record was subsequently updated (version 1.1, 6 October 2026) to report the search date and the completed review stage, without changes to the registered methods. The following safeguards protected against post hoc decisions: the population, exposure, main

outcome, eligible study designs, the three synthesis lines, the risk-of-bias tools, and the rules for quantitative synthesis were fixed in the published record before any search result was screened; title/abstract and full-text screening were conducted independently and in duplicate with the Rayyan blind mode enabled, so that each reviewer's decisions were concealed from the other until unblinding; and no eligibility criterion was modified after screening had begun. The registered eligibility criteria already encompassed periodontal GTR, GBR, and ARP, as well as short-term non-therapeutic intraoral exposure models in human volunteers, and prespecified the three synthesis lines described below. All deviations from the registered protocol, together with their rationale and expected impact, are listed in Supplementary File 1 (PRISMA 2020 item 24c; completed PRISMA 2020 checklist in Supplementary File 2): (i) authors were contacted to request unavailable full texts and data; (ii) single-arm clinical studies and non-randomized exposure models, for which ROBINS-I is not applicable in the absence of a comparator, underwent a structured methodological appraisal instead of ROBINS-I risk-of-bias categorization; (iii) outcome data were categorized post hoc into outcome domains; and (iv) the review title was revised to reflect all clinical indications and evidence lines covered by the registered eligibility criteria (registered title: "Microbial colonization and biofilm formation on polytetrafluoroethylene membranes used in alveolar ridge preservation and guided bone regeneration: a systematic review of clinical and in vitro evidence"); the eligibility criteria, search strategy, and synthesis methods were not modified.

***Eligibility criteria***

Eligibility was defined using a PECOS framework without a mandatory comparator, given that a substantial portion of the primary literature is descriptive. Population: (a) patients undergoing periodontal GTR, GBR, or ARP with a PTFE membrane; (b) human volunteers in whom PTFE membrane material was exposed intraorally in short-term non-therapeutic exposure models, as prespecified in the registered protocol; or (c) for in vitro/ex vivo studies, PTFE specimens exposed to artificial saliva, bacterial culture media, or representative oral biofilm models. Exposure: dense (d-PTFE) or expanded (e-PTFE) PTFE membranes of any commercial brand. Comparator: optional (membrane-type, brand-to-brand, antimicrobial adjunct, or none in single-arm studies). Outcome: qualitative or quantitative microbial colonization or biofilm formation on the membrane surface itself. Studies designed primarily to assess bacterial penetration or permeability were eligible when they also reported data on microorganisms on the exposed membrane surface; penetration data were then extracted as a separate outcome domain. Study design: randomized and non-randomized clinical trials, observational clinical studies, non-therapeutic intraoral exposure models, and in vitro/ex vivo laboratory studies. We excluded reviews, letters, expert opinions, conference abstracts without extractable data, protocols without results, and studies whose outcome was not microbial colonization or biofilm formation on the membrane itself. An English-language restriction was applied as a secondary eligibility criterion at the full-text stage.

***Outcome Definitions and Outcome Domains***

The following operational definitions were applied consistently throughout the review. Bacterial adhesion denotes the attachment of microbial cells to the membrane surface, typically assessed in vitro after short incubation periods or in early (≤24 h) intraoral models. Contamination denotes the presence of microorganisms on or within a retrieved membrane, irrespective of their organization or viability, as reported in clinical retrieval studies. Colonization denotes the establishment of a viable or morphologically

documented microbial population on the membrane surface over time. Biofilm formation denotes an organized, matrix-embedded, multilayered microbial community on the membrane, documented ultrastructurally (scanning or transmission electron microscopy, confocal microscopy) or by biomass quantification. Penetration (permeability) denotes the passage of microorganisms through the membrane thickness and was not considered, by itself, evidence of surface colonization. For synthesis and tabulation, the outcome data of each report were categorized into five domains: surface colonization/adhesion (SC; presence or quantity of microorganisms on the membrane); biofilm biomass/architecture (BB; thickness, biomass, maturity, or extracellular matrix); microbial composition (MC; species, morphotypes, pathogens, or sequencing-based diversity); penetration/permeability (PP); and clinical outcomes analyzed in relation to membrane colonization (CO; e.g., attachment gain, bone fill, or infection).

***Search Strategy***

We searched PubMed/MEDLINE, Scopus, Web of Science, Embase, and Cochrane CENTRAL from inception, restricting the search to records published up to 15 August 2026 (publication-date limit prespecified in the registered protocol); the searches were executed on 25 August 2026, after protocol registration (see Protocol and registration). The search combined PTFE material terms (including brand names), ARP/GBR/GTR terms, and microbial colonization/biofilm terms using MeSH/Emtree headings and free-text terms (full strategies in Supplementary File 3). ClinicalTrials.gov and the WHO ICTRP were searched for unpublished/ongoing trials, and reference lists of included studies were hand-searched.

***Study Selection and Data Extraction***

Duplicate removal and title/abstract screening were performed using Rayyan software (records imported on 25 August 2026). Two reviewers (NHS, JAL) independently screened titles, abstracts, and full texts against the eligibility criteria, with the Rayyan blind mode enabled; disagreements were resolved by discussion or by a third reviewer (ME). Of 71 reports sought for retrieval, 17 could not be obtained (Supplementary File 4); of the 54 full-text reports assessed, 48 reports were included[5,6,21–28,30–67] and 6 excluded (reasons in Supplementary File 5; Figure 1). Data were extracted independently in duplicate using a piloted standardized form (author, year, country, design, clinical indication, membrane material/brand, population or in vitro model, comparator, outcome-assessment method, outcome domain, and key findings). All quantitative data were extracted directly from tables and numeric text in the primary publications. Full texts were sought through institutional library access, publisher websites, and open-access repositories. The corresponding authors (or, for trial-registry records, the responsible parties) of 18 reports were contacted by email: the 17 reports whose full texts could not be retrieved and the one included report available only as an abstract (Yoshinari et al.[48], 2001). No responses were received (0% response rate), and analysis proceeded using published data only. For Yoshinari et al.[48] (2001), data were extracted from the abstract alone, as noted in Table 1 and Supplementary File 6. For the 17 unretrieved reports, the published abstract or registry record was consulted only to describe their potential relevance (Supplementary File 4); no information from these sources was used in the synthesis.

***Data synthesis***

Given the marked heterogeneity across studies, included reports were classified a priori, as specified in the registered protocol, into three synthesis lines: (1) therapeutic clinical

studies, in which a PTFE membrane was placed as part of a GTR, GBR, or ARP procedure (n=25 reports; 24 independent studies); (2) non-therapeutic intraoral exposure models, in which PTFE material was exposed intraorally in human volunteers outside a regenerative procedure (n=6); and (3) in vitro studies (n=17). Within the therapeutic line, evidence was further stratified by clinical indication—periodontal GTR (n=21 reports, one of which also included GBR around dental implants) and ARP (n=4 reports; 3 studies)—and by type of exposure (unplanned exposure of e-PTFE intended for submerged healing versus intentional exposure of d-PTFE). Throughout the review, a report denotes a publication; a study denotes an independent investigation (cohort, trial, or laboratory experiment) that may be described in more than one report; and a trial denotes a randomized study. The companion reports by Franović et al.[22] and Mohar Vitezić et al.,[21] which describe the same randomized cohort (ClinicalTrials.gov NCT06694844), were linked and counted as a single study in all study-level counts, in the risk-of-bias assessment, and in any quantitative comparison; they were retained as separate reports only to describe their distinct outcomes. The randomized in situ split-mouth study by Turri et al.,[23] in which membrane discs were bonded to tooth surfaces without a regenerative procedure, was allocated to the non-therapeutic exposure-model line; because of its randomized design, its risk of bias was assessed with RoB 2. Findings were synthesized narratively and tabularly (Tables 1 and 2), consistent with Synthesis Without Meta-analysis (SWiM) guidance.[68]

***Risk-of-bias Assessment***

Risk of bias was assessed independently by two reviewers (NHS, JAL; disagreements resolved by a third reviewer, ME), using the independent study as the unit of assessment and a tool matched to each design: Cochrane RoB 2 for randomized studies (including the randomized in situ study),[69] ROBINS-I for non-randomized clinical studies with an explicit comparator group,[70] and QUIN for in vitro studies.[71] For RoB 2 Domain 4 (measurement of the outcome), signaling questions 4.3 to 4.5 were answered at the level of the colonization outcome: when the outcome was an instrument-based laboratory measure unlikely to be influenced by knowledge of the allocated intervention (culture/colony counts, DNA-probe, qPCR or sequencing reads, or automated image analysis), the domain was judged at low risk even when assessor blinding was not reported; when the outcome relied on observer-dependent scoring (e.g., counting of bacteria-positive fields in scanning electron or light microscopy, or morphotype classification by darkfield microscopy) without reported blinding, the domain was judged as raising some concerns (Supplementary File 7). For RoB 2 Domain 5 (selection of the reported result), trials without an accessible, prospectively registered protocol or prespecified analysis plan were judged as raising some concerns, because the fidelity of outcome reporting could not be verified; for trials conducted before prospective trial registration became standard practice, this judgment reflects the absence of an a priori protocol against which reporting could be audited—an intrinsic limitation of the historical literature—rather than empirical evidence of selective outcome reporting. Because ROBINS-I requires a comparator to assess confounding, it was not applied to single-arm clinical studies or to non-randomized exposure models without a comparison group; these studies underwent a structured methodological appraisal across six domains (comparator availability, participant selection, exposure definition, adjustment for exposure duration, outcome measurement, and reporting completeness), each rated as showing moderate or substantial limitations, with the overall rating reflecting the most serious domain-level limitation. These appraisals are

descriptive indicators of methodological quality and are reported separately from, and are not equivalent to, formal risk-of-bias judgments.

### *Statistical analysis*

All statistical analyses and risk-of-bias visualizations were performed in R (version 4.5.1)[72] via RStudio, using metafor (version 5.0-1),[73] meta (version 8.5-0),[74] robvis,[75] ggplot2, dplyr, and tidyr. For continuous CFU-based colonization outcomes, the effect measure was the log response ratio, computed with metafor::escalc (measure = "ROM"). Only four in vitro comparisons (from two independent source studies) reported means, standard deviations, and per-arm sample sizes; three shared a common control arm within a single source study,[66] precluding statistical independence. Where multiple intervention arms from the same study were combined into a single material-category comparison (Suzzin et al.:[30] two d-PTFE arms combined and two non-PTFE arms combined), arm-level means and standard deviations were combined into a single pairwise comparison using the standard formulas for combining groups described in the Cochrane Handbook for Systematic Reviews of Interventions. Given this non-independence and the small number of independent sources ($k<3$), a pooled random-effects estimate was not computed; effects are presented individually in an exploratory forest plot without a pooled summary, consistent with SWiM guidance.[68] In the therapeutic clinical line, only one publication reported continuous quantitative data, precluding pooled synthesis for that line.[40] Formal publication-bias testing (e.g., funnel plot, Egger's test) and a formal GRADE certainty-of-evidence assessment were not performed, given the small number of independent comparative studies with continuous data ($k<10$) and the predominantly narrative, exploratory nature of the synthesis.

## Results

### *Study Selection*

The study selection process is summarized in the PRISMA 2020 flow diagram (Figure 1). After removing duplicates and screening titles and abstracts (using Rayyan, the most recent version), we sought 71 reports for full-text retrieval; 17 could not be retrieved, leaving 54 full-text reports assessed for eligibility. The 17 unretrieved reports (Supplementary File 4) comprised four trial-registry records of two trials whose results are already included through their journal publications (NCT04329351, reported by García-Braz et al;[28] NCT06694844, reported by Franović et al.[22] and Mohar Vitezić et al.[21]), three conference abstracts, and ten journal articles published between 1992 and 2021. Information from the abstracts or registry records of these unretrieved reports was used only to characterize them in Supplementary File 4 and was excluded from the synthesis. Of the 54 assessed reports, 48 met the eligibility criteria and were included in this review (Table 1), and 6 were excluded, with reasons listed in Supplementary File 5. All six exclusions were because the reported outcome did not correspond to microbial colonization or biofilm formation on the membrane itself (e.g., subgingival plaque microbiology unrelated to the membrane, cytotoxicity assays, or antimicrobial zone-of-inhibition assays), rather than study design or population. Because two of the 48 included reports (Franović et al.[22] and Mohar Vitezić et al.[21]) derive from the same underlying randomized trial, the 48 included reports correspond to 47 independent studies; both reports were retained for qualitative characterization, as detailed in the Methods section (Data synthesis). Searches of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) identified no additional eligible trials beyond those already captured by the database searches.

### *Study Characteristics*

The 48 included reports (47 independent studies; Table 1) were published between 1990 and 2026 and originated from at least 15 countries. Twenty-five reports (24 independent studies) formed the therapeutic clinical line. Of these, 21 reports evaluated e-PTFE in periodontal GTR (intrabony, furcation, or other periodontal defects), one of which (Nowzari & Slots[6], 1994) also included e-PTFE membranes used for GBR around dental implants; in all of these studies, membranes were intended to remain submerged and exposure, when present, was unplanned (premature wound dehiscence). The remaining four reports (three studies) evaluated d-PTFE in ARP, in which the membrane was intentionally left exposed to the oral cavity for approximately four weeks. No other included clinical study evaluated PTFE membranes in GBR. Six reports formed the non-therapeutic intraoral exposure model line: one randomized in situ split-mouth study (Turri et al.[23]) and five non-randomized device or strip models, with exposure periods ranging from 4 hours to 4 weeks. Seventeen reports assessed bacterial adhesion, colonization, biofilm formation, or penetration on PTFE material in vitro. Outcome assessment methods varied widely and included scanning or transmission electron microscopy, confocal laser scanning microscopy, culture and colony counting, DNA-probe and quantitative PCR assays, and, in recent studies, next-generation 16S rRNA sequencing. The outcome domains addressed by each report are shown in Table 2. Surface colonization/adhesion data were reported directly in 46 reports; the remaining two (Cheng et al.,[61] 2009; Nocca et al.,[65] 2022) were in vitro permeability studies in which membrane surface data were limited to indirect or qualitative observations and which therefore contributed mainly to the penetration/permeability domain. Penetration/permeability was assessed in 9 reports, biofilm biomass or architecture in 14, microbial composition in 27, and clinical outcomes in relation to membrane colonization in 13.

### *Risk of Bias in Included Studies*

Risk of bias was independently evaluated by two reviewers (NHS, JAL) using domain-based assessment tools tailored to each study design, with the independent study as the unit of assessment. Disagreements were resolved through consensus or by consultation with a third reviewer (ME). Study-level judgments are displayed in Figure 2, and domain-level summaries of the risk-of-bias and methodological appraisal assessments are provided in Supplementary File 8.

Eleven randomized studies (12 reports) were assessed with RoB 2 (Figure 2A): ten therapeutic trials, in which the companion reports by Franović et al.[22] and Mohar Vitezić et al.[21] were assessed jointly as one trial, and the randomized in situ study by Turri et al.[23] Three studies were judged at low overall risk of bias (Franović et al.[22]/Mohar Vitezić et al.,[21] Turri et al.,[23] and García-Braz et al.[28]) and eight raised some concerns. Concerns arose mainly in the randomization process (Domain 1; 8/11 studies), reflecting unreported sequence generation or allocation concealment in trials published between 1993 and 2001, and in the selection of the reported result (Domain 5; 8/11), reflecting the absence of an accessible prespecified analysis plan or trial registration against which outcome reporting could be checked; because all eight trials were published between 1993 and 2001, before prospective trial registration became standard, these judgments indicate that outcome-reporting fidelity could not be verified, not that selective reporting was demonstrated; one trial (Frandsen et al.[39]) also raised concerns regarding deviations from intended interventions. Following re-examination of the Domain 4 signaling questions at the outcome level, measurement of the outcome was judged at low risk for eight studies because their colonization outcomes were

instrument-based laboratory measures (culture/colony counts, DNA-probe, qPCR, 16S rRNA sequencing, or automated confocal image analysis) that are unlikely to be influenced by knowledge of the allocated intervention even without reported assessor blinding; three studies (Mombelli et al.,[41] 1996; Zucchelli et al.,[46] 1999; Yoshinari et al.,[48] 2001) raised some concerns in this domain because their outcomes relied on observer-dependent scoring of microscopy fields or darkfield morphotypes without reported blinding (Supplementary File 7). Missing outcome data (Domain 3) were at low risk in all studies.

Four non-randomized clinical studies with an explicit comparator (membrane-type or exposed-versus-non-exposed comparisons) were assessed with ROBINS-I (Figure 2B): three were judged at moderate overall risk of bias (Guillemin et al.,[36] Ling et al.,[50] and Toygar et al.[51]) and one at serious risk (Apinhasmit et al.[49]), driven by confounding. The ten single-arm clinical studies (Figure 2C) and the five non-randomized exposure-model studies (Figure 2D) were not assigned ROBINS-I risk-of-bias categories. The structured methodological appraisal identified substantial limitations in nine of the ten single-arm studies—chiefly the absence of a comparator, convenience selection of retrieved membranes, and incomplete accounting for exposure duration—and moderate limitations in the remaining study (Mazzucchi et al.[27]); all five exposure-model studies showed moderate limitations, reflecting standardized, short-term exposure protocols but small volunteer samples.

Among the 17 in vitro studies assessed with QUIN (Figure 2E), 11 were judged at low risk of bias, 5 at medium risk (most commonly reflecting incomplete reporting of blinding of outcome assessors or of sample-size justification), and 1 (Wang et al.[57], 1994) at high risk of bias.

### *Synthesis of Findings*

Across the 25 reports in the therapeutic clinical line, bacterial colonization of PTFE membranes was a consistent finding once membranes were exposed to the oral environment, although the clinical context differed markedly between indications. In the 21 periodontal GTR reports, all of which used e-PTFE intended for submerged healing, exposure occurred as an unplanned complication (early wound dehiscence), and membranes examined at retrieval, typically four to six weeks after placement, were frequently colonized by periodontal pathogens; in several correlational studies, heavier or pathogen-rich contamination, particularly of the tooth-facing surface, was associated with lower attachment gain or bone fill. The implant sites reported by Nowzari & Slots,[6] the only GBR data available, showed the same pattern. In the four ARP reports (three studies), d-PTFE membranes were intentionally exposed for approximately four weeks and, when examined at retrieval, were colonized on both surfaces by structured multispecies biofilms, with brand-dependent differences in bacterial load and community composition, whereas uneventful healing without clinical infection was reported in the studies that described the clinical course. Systemic or local antimicrobial adjuncts (e.g., amoxicillin–clavulanate, metronidazole, minocycline, tetracycline coating, or chlorhexidine) reduced bacterial counts in some but not all trials, without eliminating colonization. In most therapeutic studies, membrane microbiology was assessed once, on the retrieved membrane at a predetermined removal time; the few studies with additional time points (Nowzari et al.,[42] 1996, who sampled the membrane at placement and again at retrieval, and Demolon et al.[34] 1993, who sampled the treated sites weekly with paper points but the membrane itself only at retrieval) provide only coarse temporal information. These findings therefore describe the biofilm state at membrane retrieval rather than the course of colonization within individual patients.

The six non-therapeutic exposure model reports, which exposed PTFE material intraorally in volunteers outside a regenerative procedure and retrieved specimens at serial, predefined intervals (thus providing the only time–course data obtained in humans), showed that bacterial adhesion to PTFE begins within hours: bacteria-positive surfaces and measurable biofilm biomass were detected as early as 4 hours, adhesion increased over 1 to 14 days, and bacteria penetrated the full thickness of e-PTFE within three to four weeks. These models provided complementary short-term evidence, without the confounding introduced by a surgical wound or regenerative defect, that early plaque/biofilm formation on PTFE surfaces follows a pattern and time–course broadly similar to that on natural tooth surfaces.

Among the 17 in vitro studies, surface roughness, micro-porosity, and surface free energy were the material properties most consistently associated with the degree of early bacterial adhesion; several studies found that dense and expanded PTFE performed similarly to one another in the absence of a surface modification, while antimicrobial coatings, impregnated agents, or nanostructured surface treatments significantly reduced bacterial load relative to unmodified PTFE.

### *Quantitative comparisons*

Four in vitro comparisons met criteria for quantitative synthesis: three brand-to-brand comparisons from a single source study sharing the same PTFE control arm (Weitkamp et al.[66]), and one combined d-PTFE-versus-non-PTFE comparison from an independent source study (Suzzin et al.[30]). Individual ratios of means ranged from 0.05 to 1.22, with the three comparisons by Weitkamp et al.,[66] all favoring lower colonization on PTFE and the comparison by Suzzin et al.[30] favoring the opposite direction (Figure 3). Because three of the four comparisons share a common control arm and are therefore not statistically independent, and because data were available from only two independent source studies, these comparisons are presented individually rather than as a pooled random-effects estimate; a formal meta-analysis was not considered statistically defensible for this dataset (see Methods, Statistical analysis).

## Discussion

Across 48 reports (47 independent studies) spanning more than three decades and three complementary lines of evidence, microbial colonization of polytetrafluoroethylene barrier membranes was consistently reported once these materials were exposed to the oral environment, across membrane types (expanded or dense) and clinical indications, although its magnitude and ecological composition varied between products and surfaces, as detailed below. The present synthesis indicates that colonization is a consistent feature of exposed PTFE membranes rather than an occasional technical complication; the available correlational data suggest that the amount and composition of the adherent biofilm, rather than its mere presence, may be associated with differing clinical outcomes, although the heterogeneous and predominantly descriptive evidence does not permit causal inference.

In the periodontal GTR literature, in which e-PTFE membranes were designed to remain submerged, and exposure represented an unplanned complication, contamination of PTFE membranes was documented from the earliest scanning electron microscopy studies of retrieved e-PTFE barriers, which described plaque-like biofilms forming on membrane surfaces exposed through early wound dehiscence, with minimal contamination only in specimens that remained submucosally covered throughout healing.[5,33] Several subsequent cohorts linked the extent of this contamination to clinical outcome: bacterial load on retrieved membranes was inversely related to attachment

gain,[6] and regression modeling identified membrane bacterial contamination, particularly by *Porphyromonas gingivalis*, as a significant predictor of reduced attachment gain.[42] This association was corroborated by histological correlational work reporting a negative relationship between contamination and attachment gain,[44] and by studies distinguishing the tooth-facing from the gingiva-facing membrane surface, where contamination of the internal, tooth-facing layer appeared to carry the greater clinical consequence.[40] These findings should be interpreted as associations derived from correlational or non-randomized designs; a causal role for membrane colonization in impaired regeneration cannot be established from this evidence. Moreover, because these colonization rates derive from unplanned exposure of an open-microstructure e-PTFE membrane intended for submerged healing, they should not be directly extrapolated to contemporary protocols in which d-PTFE is intentionally exposed.

Attempts to pharmacologically modulate this colonization produced a consistent pattern: antimicrobial adjuncts reduced bacterial counts without eliminating colonization. Systemic amoxicillin–clavulanate significantly lowered the total organism count recovered from membranes compared with untreated controls,[40] and topical metronidazole gel reduced anaerobic counts at one week[39] and the proportion of bacteria-positive SEM fields relative to systemic antibiotics;[46] in both cases, however, membranes in the treated arms remained substantially colonized by the time of removal, and reduced contamination did not consistently translate into superior clinical outcomes. Tetracycline-coated e-PTFE similarly achieved greater attachment gain than uncoated e-PTFE, yet periodontal pathogens were detectable on both coated and uncoated gingiva-facing surfaces at removal (six weeks).[45] Taken together, this body of work suggests that local or systemic antimicrobial strategies attenuate, rather than prevent, the ecological pressure exerted by membrane exposure.

More recent d-PTFE literature extends this picture from periodontal regeneration to alveolar ridge preservation, where exposure is intentional rather than accidental, and reframes the question from whether colonization occurs to which community forms and how membrane design may shape it. Intentionally exposed d-PTFE membranes used for ridge preservation harbored a more homogeneous, anaerobic microbial community than unassisted socket healing, but the material's low nominal porosity failed to prevent colonization of its inner, socket-facing surface.[28] A separate cohort using granular nanocrystalline hydroxyapatite under an exposed d-PTFE barrier reported comparably low, non-differential bacterial counts on both membrane faces, with a structured biofilm present at 28 days but without associated clinical infection, suggesting that low-level colonization is compatible with uneventful healing under chlorhexidine coverage.[27] Brand-to-brand comparisons of two commercially available d-PTFE membranes used for socket preservation add a further layer to this picture: one brand supported a denser extracellular matrix, a higher overall bacterial load by qPCR, and a significantly higher per-sample alpha diversity (Shannon index, which integrates richness and evenness; $P=0.019$) than the other,[22] and companion microbiome profiling of the same cohort showed that the more colonized brand was also enriched in periodontal and peri-implant pathobionts, whereas the less colonized brand favored health-associated genera.[21] The companion report also described fewer distinct species on the more colonized brand (242 vs. 275 species); this figure is a cumulative, group-level species richness (the total number of distinct taxa detected across all 16 and 20 membranes, respectively), which depends on the number of samples analyzed and was not compared statistically, and it therefore does not contradict the higher per-sample Shannon diversity reported in the primary report.[21,22] Beta diversity did not differ significantly between brands in either report ($P=0.512$ and $P=0.5$).[21,22] Because both reports derive from a single randomized

trial, these findings suggest, but do not establish, that microstructural or surface differences between commercial d-PTFE products, and not only the dense-PTFE category as a whole, may be associated with the ecological character of the colonizing community, a distinction that the earlier e-PTFE-focused clinical literature could not address.

The non-therapeutic exposure models, in which PTFE specimens were applied intraorally outside a surgical defect, offer a complementary, deconfounded view of early colonization kinetics and, because specimens were retrieved at serial intervals, provide the only human data in this review describing a time course. A randomized split-mouth comparison of dense and expanded PTFE bonded directly to tooth surfaces found greater biofilm biomass and thickness on the dense membrane at four hours, a difference that was no longer significant by 24 hours, while *Staphylococcus* species increased on both membrane types over time to a significantly greater extent than on natural tooth surfaces.[23] This is consistent with earlier permeability-chamber work showing that bacterial penetration through e-PTFE membrane thickness was essentially complete by three to four weeks of intraoral exposure,[52] and that topical chlorhexidine reduced the amount and structural complexity of plaque on the external membrane surface without retarding penetration through the membrane itself.[53] Comparative adhesion studies using e-PTFE, polyglactin 910, and polylactic acid strips bonded to teeth similarly found early bacterial accumulation on all three materials, with e-PTFE generally more colonized than the resorbable polylactic acid comparator; because this difference was not explained by surface roughness alone, factors other than roughness, such as microstructure, may contribute to early adhesion.[55] A comparable pattern of time-dependent bacterial adhesion across nonresorbable and resorbable barrier materials was also reported using a slot-immunoblot adherence model.[54] Read together, these exposure models indicate that PTFE membranes are colonized with a time–course broadly comparable to, and in the case of *Staphylococci* exceeding, that of natural dentition, and that chemical antisepsis delays without preventing this process—mirroring the pattern seen in the therapeutic clinical line.

In the in vitro evidence base, material surface properties were consistently associated with the degree of early bacterial adhesion. Surface roughness, micro-porosity, and surface free energy were the properties most consistently associated with the degree of colonization across the 17 in vitro studies. Direct comparisons of expanded and dense PTFE reported that dense PTFE developed a thicker, more mature biofilm with greater viable counts at 48 hours than expanded variants, despite all PTFE types remaining impermeable to *Streptococcus oralis* over the same period.[63] Brand-level comparisons within the d-PTFE category found that two coded commercial membranes differed significantly in roughness and hydrophobicity, with these differences correlating with differential adhesion of a four-species panel,[32] and a separate direct-contact assay likewise found brand-specific differences in bacterial growth between two commercially available d-PTFE products.[31] *Candida albicans* adhesion assays extended this pattern to a non-bacterial organism, showing significantly greater adhesion to all tested PTFE membranes than to a PVDF control, with textured brands supporting higher counts than non-textured ones;[26] a subsequent multi-brand comparison across three species found that adhesion correlated strongly with surface roughness, particularly for *P. gingivalis*, and that the least rough, highest-surface-free-energy brand consistently supported the least adhesion of the six products tested.[25] Not all comparisons align with a straightforward roughness–adhesion relationship, however: one in vitro panel found that a dense-PTFE membrane and one collagen product supported significantly lower adhesion than two other collagen membranes, yet all tested materials, including the

dense PTFE, were permeable to a multispecies inoculum within two hours—a finding that diverges from the impermeability reported for dense PTFE elsewhere in this evidence base and may reflect differences in inoculum composition, exposure duration, or the specific d-PTFE product tested rather than a general property of the material class.[24] The four extractable quantitative in vitro comparisons available for this review pointed in different directions: three comparisons sharing a common PTFE control arm favored lower colonization on PTFE relative to collagen membranes,[66] while an independent comparison of two d-PTFE brands against non-PTFE alternatives favored the opposite direction, with one d-PTFE product showing the highest contamination among the four materials tested despite comparable surface chemistry to the better-performing d-PTFE brand.[30] Because these comparisons are not statistically independent and originate from only two source studies, they are presented individually rather than pooled, and they should be read as illustrative of brand- and protocol-dependent variability rather than as evidence of a consistent material-level effect.

Together with the clinical retrievals, these data point to a dual behavior of d-PTFE. In the permeability models that tested it, d-PTFE generally resisted through-and-through bacterial passage over the periods examined (up to 48 hours for *Streptococcus oralis* and 72 hours for *P. gingivalis*),[63,65] whereas e-PTFE was fully penetrated within 3–4 weeks of intraoral exposure;[52] yet the exposed outer surface of d-PTFE consistently supported dense, structured biofilms, both in vitro and on membranes retrieved after ridge preservation.[22,27,30,63] This barrier function is not absolute, since one multispecies model recorded passage across all membranes, including d-PTFE, within two hours,[24] and the socket-facing surface of intentionally exposed d-PTFE was also colonized in vivo.[28] The clinical premise of d-PTFE is therefore better described as resistance to trans-membrane penetration than as protection from colonization: an exposed d-PTFE membrane remains a plaque-retentive niche for biofilm maturation, which is why strict plaque control and planned retrieval are integral to open healing protocols (see the chairside considerations below).

The translational value of the in vitro evidence is further limited by model design. Fourteen of the 17 in vitro studies exposed membrane specimens to one or a few laboratory strains, typically each in monoculture, under static (batch) conditions—single-species adhesion, permeability, or direct-contact assays—whereas only three used multispecies consortia or human oral biofilm inocula.[24,30,64] Static monoculture assays measure the affinity of a given strain for a given surface under controlled conditions, but they do not reproduce the salivary pellicle that conditions every intraorally exposed surface, the cooperative co-aggregation and metabolic interactions through which early colonizers recruit later, often pathogenic, colonizers, or the shear forces and nutrient flow of the oral environment; none of the included studies reported the use of flow-cell or other dynamic bioreactor models. Results from static single-species assays should therefore be interpreted as indicators of relative surface affinity rather than predictions of biofilm formation on exposed membranes in vivo, and dynamic, multispecies, pellicle-conditioned models would more closely approximate clinical conditions.

Considered across all three lines of evidence, this synthesis is consistent with an ecological framework in which exposure creates a rigid, non-shedding, protein-adsorbing surface with locally altered oxygen tension at the tissue–membrane interface, conditions that may favor the transition from an early, aerobic, *Streptococcus*-dominated community toward a more homogeneous, anaerobic one with longer exposure. This sequence is inferred by juxtaposing the serially sampled exposure models and in vitro time–course experiments with membranes retrieved at a single time

point in clinical studies; it has not been documented by repeated sampling of the same membrane in patients. This interpretation remains a plausible mechanism rather than a demonstrated causal pathway, since none of the included designs permit direct causal inference between membrane colonization and bone or soft tissue outcomes. The recurring observation that, within the same material class, brand and microstructure were associated with differences in colonization intensity and community composition in the most recent clinical and in vitro literature suggests that future comparative research—and future material selection in ridge preservation and guided bone regeneration—may need to move beyond material class toward product-specific characterization of surface topography and its microbiological consequences.[21,22,25,32]

From a practical standpoint, several chairside considerations can be proposed. These considerations are translational clinical inferences grounded in general principles of periodontal and implant surgery and in the broader regenerative literature; they are not evidence-based deductions from comparative outcomes tested in the included PTFE studies. Comparative clinical trials testing different chlorhexidine regimens, suture materials, or removal times specifically over exposed PTFE barriers are lacking in the primary literature. First, for intentionally exposed d-PTFE in socket preservation, colonization of both membrane surfaces should be expected. The ARP protocols in the included studies combined perioperative antibiotic prophylaxis and/or chlorhexidine rinsing, a membrane stabilized subperiosteally several millimeters beyond the socket margins, and removal at approximately four weeks,[21,22,27,28] in line with the original descriptions of open-healing d-PTFE techniques.[76–78] Because bacterial adhesion to PTFE begins within hours in exposure models and membranes retrieved after four to six weeks in clinical studies consistently harbored Gram-negative anaerobes and periodontal pathogens (e.g., *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Fusobacterium nucleatum*),[23,34,37,42,45,55] removal after approximately 3–4 weeks, meticulous patient-performed chemical plaque control (e.g., 0.12–0.2% chlorhexidine rinse or gel), and regular professional review with gentle cleaning of the exposed surface appear reasonable as empirical precautions, recognizing that chlorhexidine reduces but does not prevent colonization or penetration.[53,56] The 3–4-week retrieval interval derives from the original open-healing d-PTFE protocols and from wound-healing considerations—allowing a dense, immature connective tissue matrix to form beneath the membrane while limiting the duration of biofilm exposure[76–78]—and the use of chlorhexidine rests on general principles of chemical plaque control after periodontal and implant surgery; neither is supported by randomized trials comparing different retrieval time points or antiseptic regimens over exposed PTFE barriers, which remain unavailable. Second, sutures may act as an additional bacterial reservoir: multifilament materials such as silk favor bacterial wicking, plaque retention, and more intense tissue inflammation than monofilament or PTFE sutures,[79,80] so monofilament (e.g., PTFE or polypropylene) sutures, placed without tension and away from the exposed membrane margin where possible, appear preferable. Third, exposure by itself does not mandate removal of a d-PTFE membrane intended for open healing, but clinical indicators of infection at the exposed site—purulent exudate, spontaneous pain, swelling or abscess formation, progressive enlargement of the dehiscence with membrane mobility, or loss or exposure of graft particles beneath the membrane—should prompt early removal, debridement, and antimicrobial management, as proposed in classifications of GBR healing complications.[17,81] For e-PTFE and other membranes intended for submerged healing, premature exposure has been associated with poorer regenerative outcomes,[82,83] and early removal is generally advisable when exposure is accompanied by inflammation or suppuration. Because no included study directly compared

maintenance protocols, chlorhexidine concentrations, suture materials, or removal thresholds, these recommendations remain empirical and should be tested in prospective trials.

This systematic review has several limitations worth noting. The marked heterogeneity in membrane brand, microbiological outcome assessment method (scanning electron microscopy, culture, quantitative PCR, and next-generation 16S rRNA sequencing), and study design across the three synthesis lines, together with the predominance of single-arm descriptive studies with substantial methodological limitations, precluded a formal meta-analysis and limited the comparability of findings; the only four extractable quantitative in vitro comparisons originated from just two independent source studies sharing a common control arm, which further constrained statistical power and made a pooled random-effects estimate statistically indefensible. Most of the included clinical and in vitro evidence was correlational or non-randomized, so the associations observed between membrane colonization and impaired regenerative outcomes cannot be interpreted as causal. The clinical evidence is dominated by historical periodontal GTR studies with unplanned e-PTFE exposure; only three studies evaluated d-PTFE in ARP, and GBR was represented only by the implant sites of a single case series, which limits the transferability of the findings to contemporary GBR and ridge augmentation. Seventeen of the 71 reports sought (24%) could not be retrieved in full text despite attempts to contact their authors (Supplementary File 4). However, four of these were trial-registry records of two trials whose results are included through their journal publications, and three were conference abstracts; for the ten unretrieved journal articles, the brief published abstracts that were available did not report overt findings contrary to those of the present synthesis. Nevertheless, an abstract does not permit assessment of internal validity, selective outcome reporting, or the quantitative characterization of membrane biofilms, so these reports carry a risk of reporting bias that cannot be ruled out by abstract inspection alone; information from these abstracts was used only to describe their potential relevance (Supplementary File 4) and was excluded from the synthesis. Their omission may also have reduced precision and, in particular, further limited the scarce evidence on GBR around implants, so a non-retrieval bias cannot be excluded. Furthermore, the therapeutic clinical studies examined membranes at a single retrieval time, so they describe the biofilm present at removal and cannot establish when, or in what sequence, colonization developed in patients. The “some concerns” judgments for RoB 2 Domain 5 in the eight trials published between 1993 and 2001 reflect the absence of a prospectively registered protocol against which outcome reporting could be audited, an intrinsic limitation of this historical literature, rather than confirmed selective outcome reporting. Moreover, most in vitro data come from static, single-species assays that do not reproduce salivary pellicle formation, multispecies co-aggregation, or oral flow conditions, limiting their transferability to exposed membranes in patients. In addition, the single-arm clinical studies and exposure models were appraised with a structured, non-validated methodological framework because ROBINS-I is not applicable in the absence of a comparator; these appraisals are descriptive and not directly comparable with formal risk-of-bias judgments. A formal GRADE certainty-of-evidence rating and publication bias testing were not undertaken given the small number of independent comparative studies with continuous outcome data, and the absence of any response from contacted study authors (0% response rate) prevented retrieval of unreported or incomplete data. Finally, restricting eligibility to English-language full texts at the screening stage may have excluded relevant evidence published in other languages, introducing a potential language bias into the synthesized evidence base.

## Conclusion

Across 48 reports (47 independent studies) spanning more than three decades of clinical, intraoral exposure-model, and in vitro research, microbial colonization of PTFE barrier membranes—whether expanded or dense—was consistently reported once these materials were exposed to the oral environment, with bacterial adhesion detectable within hours in intraoral exposure models and pathogen-enriched biofilms consistently present on membranes retrieved after four to six weeks in clinical studies. Local and systemic antimicrobial adjuncts frequently reduced, but did not eliminate, bacterial colonization. Correlational clinical data, mostly from historical periodontal GTR studies with unplanned e-PTFE exposure, linked heavier or pathogen-rich contamination to less favorable regenerative outcomes, and the most recent brand-level comparisons suggest that product-specific microstructure and surface properties may contribute to colonization intensity and microbial community composition beyond the broad e-PTFE/d-PTFE classification. However, the current evidence base is heterogeneous, predominantly descriptive or observational, and at moderate to serious risk of bias; it is insufficient to establish causality or to support product-specific recommendations, and evidence for contemporary GBR and for intentionally exposed d-PTFE in ARP is particularly limited. Standardized comparative clinical and in vitro studies with product-specific characterization of surface topography, uniform microbiological outcome measures, and clinical endpoints are needed to clarify the clinical relevance of membrane colonization for the success of GTR, GBR, and ARP.

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## Competing Interests

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

## Data Availability

All data generated or analyzed during this study are included in this article and its Supplementary files.

## Ethical Approval

Not applicable. This systematic review was based exclusively on previously published, publicly available data; no new data involving human participants, human tissue, or animals were collected by the authors.


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## Supplementary Files

**Supplementary File 1: Deviations from the registered protocol (PROSPERO CRD420261445702) and their rationale (PRISMA 2020 item 24c).**

**Supplementary File 2: PRISMA 2020 checklist.**

**Supplementary File 3: Full database-specific search strategies (PRISMA-S).**

**Supplementary File 4: Reports sought but not retrieved in full text, with retrieval attempts and potential relevance.**

**Supplementary File 5: Reports excluded at full-text screening, with reasons.**

**Supplementary File 6: Unabridged data-extraction table of the 48 included reports.**

**Supplementary File 7: RoB 2 Domain 4 signaling-question rationale for the 11 randomized studies.**

**Supplementary File 8: Figures S1–S3, domain-level risk-of-bias and methodological-appraisal summaries.**

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**Table 1. Characteristics of the included reports (n=48 reports; 47 independent studies), grouped by synthesis line and clinical indication**

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Therapeutic clinical line (n=25 reports; 24 studies) — periodontal GTR with e-PTFE intended for submerged healing; exposure unplanned (n=21 reports)** | | | | | | |
| **Selvig et al.[5] (1990)** | USA/Norway | Clinical, single-arm descriptive | e-PTFE, single arm | 14 retrieved membranes | SEM, cell population + contamination | Foundational SEM study; contamination varied with early oral exposure. |
| **Selvig et al.[33] (1992)** | USA/Norway | Clinical, single-arm correlational | e-PTFE, single arm | 12 pts, 16 membranes | SEM vs clinical attachment | Contamination via early exposure associated with poorer attachment gain; covered membranes had minimal contamination. |
| **Demolon et al.[34] (1993)** | USA | RCT, antibiotic vs no-antibiotic | e-PTFE | Class II furcation defects; weekly paper-point site samples x4wk, membrane at removal (4wk) | DNA probe, subgingival + membrane | Membranes colonized by pathogens at removal (4wk); antibiotic reduced but did not eliminate colonization. |
| **Grevstad & Leknes[35] (1993)** | Norway | Clinical, single-arm descriptive | e-PTFE, single arm | 8 retrieved membranes | TEM ultrastructure | Organized multilayered biofilm resembling mature subgingival plaque; ultrastructural confirmation on PTFE. |
| **Guillemin et al.[36] (1993)** | USA | Clinical, non-randomized comparative | ePTFE+DFDBA vs. DFDBA alone | Periodontal osseous defects | SEM of retrieved membranes | Colonization associated with early exposure; membrane+graft carries added infection risk vs graft alone. |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Mombelli et al.[37] (1993)** | Switzerland | Clinical, single-arm descriptive | e-PTFE, single arm | 10 pts, 1 lesion each, 6wk | Culture + darkfield | All colonized (mean $19.7\times10^6$ CFU/mL); Gram-negative anaerobic rods 32% of microbiota. |
| **Tempro & Nalbandian[38] (1993)** | USA | Clinical, single-arm descriptive | e-PTFE, single arm | 6 retrieved membranes | SEM + culture | Variable colonization correlating with clinical exposure; species typical of subgingival plaque. |
| **Frandsen et al.[39] (1994)** | Denmark | RCT, split-mouth | e-PTFE | 12 pts; metronidazole gel vs no gel | Culture, subgingival + membrane | Metronidazole reduced anaerobic counts at 1wk (P=0.02); membranes heavily colonized in both groups at removal (6 wk). |
| **Nowzari & Slots[6] (1994)** | USA | Clinical, case series (teeth + implants; GTR and GBR) | e-PTFE, single arm | 11 periodontal + 16 implant sites | Culture + DNA probes | Inverse relationship between microbial counts and outcome; 80–90% low-bacteria sites had good healing. |
| **Nowzari et al.[40] (1995)** | USA | RCT | e-PTFE (PIP2) | 18 pts; Augmentin vs no antibiotic | Culture, DNA probe, gingiva- vs. tooth-facing | Augmentin group: fewer organisms (52.2 vs. $488.6\times10^6$, P=0.004); tooth-facing contamination determined outcome. |
| **Mombelli et al.[41] (1996)** | Switzerland | RCT, 2×2 factorial | e-PTFE | 10 pts, bilateral defects; ±membrane, ±ornidazole | Culture + darkfield, subgingival & membrane | Membrane sites frequently pathogen-positive at removal; ornidazole improved attachment independent of membrane. |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Nowzari et al.[42] (1996)** | USA | Clinical, single-arm correlational | e-PTFE, single arm | 42 pts, mandibular defects | DNA probe + culture | Significant colonization at removal (6 wk); contamination (esp. *P. gingivalis*) predicted less attachment gain ($R^2$ =0.86). |
| **MacDonald et al.[43] (1998)** | USA | RCT | ePTFE vs bioabsorbable (Guidor) | 10 pts, paired contralateral defects | Culture, DNA probe, PCR (HCMV/EBV-1) | No difference in pathogens/virus between materials; low-pathogen/no-virus sites gained more attachment (P=0.005). |
| **Yoshinari et al.[44] (1998)** | Japan | Clinical, single-arm correlational | e-PTFE, single arm | 40 membranes/66 pts, 4–6 wk | Light microscopy + immunohistochemistry | Negative correlation between contamination and attachment gain (P<0.05). |
| **Zarkesh et al.[45] (1999)** | USA | RCT | ePTFE vs. tetracycline-coated ePTFE | 22 pts; coated vs. uncoated | Culture + DNA probe, external/internal | T-ePTFE greater attachment gain (3.3 vs. 1.9 mm, P=0.02); pathogens present on both at removal (6wk) regardless of coating. |
| **Zucchelli et al.[46] (1999)** | Italy | RCT | Ti-reinforced ePTFE | 56 pts; topical metronidazole vs. systemic antibiotics | SEM, bacteria-positive fields | Fewer bacteria-positive fields with topical metronidazole (P<0.001); no clinical benefit despite less contamination. |
| **Lin et al.[47] (2000)** | Taiwan | Clinical, pus vs non-pus comparative | e-PTFE + DFDBA | 28 sites (14 pus vs. 14 non-pus) | SEM bacterial adhesion score (BAS) | Coronal 2/3 heavily colonized regardless of infection status; higher BAS in pus group (P<0.05). |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Yoshinari et al.[48] (2001)** | Japan | RCT | ePTFE ± local minocycline | 40 pts (20 control, 20 minocycline) | Light microscopy, 9 fields | Local minocycline application evaluated for effect on attachment and histologic bacterial contamination; extracted from the published abstract only, as full text could not be accessed. |
| **Apinhasmit et al.[49] (2002)** | Thailand | Clinical, non-randomized comparative | e-PTFE vs silicone sheet | 18 pts (9 vs. 9) | SEM, by membrane portion | e-PTFE more bacterial deposit fields than silicone (P<0.001). |
| **Ling et al.[50] (2003)** | Taiwan | Clinical, exposed vs. non-exposed | e-PTFE | 30 pts/30 defects; exposed vs. non-exposed | PCR (*P. gingivalis*, *A. actinomycetemcomitans*) on membranes | *A. actinomycetemcomitans* higher on exposed membranes (P=0.029), less attachment gain (P=0.041); *P. gingivalis* not different. |
| **Toygar et al.[51] (2009)** | Turkey | Clinical, split-mouth | e-PTFE vs. titanium mesh | Bilateral Class II furcation defects | SEM, by membrane region | e-PTFE more contaminated than titanium mesh, especially coronal/exposed regions. |
| **Therapeutic clinical line — ARP with d-PTFE; exposure intentional (n=4 reports; 3 studies)** | | | | | | |
| **Mazzucchi et al.[27] (2020)** | Italy | Clinical, case series | d-PTFE (Cytoplast TXT-200) | 6 pts, socket preservation; single-arm | BioTimer assay + FE-SEM | Both sides colonized (~6.5 log CFU); central sector more colonized (P=0.005); structured biofilms, no infection. |
| **García-Braz et al.[28] (2024)** | Brazil | RCT, secondary microbiome analysis (NCT04329351) | d-PTFE (Cytoplast Ti-250), exposed | 44 sockets (22 dPTFE vs 22 unassisted) | 16S NGS, inner vs. outer | dPTFE sites: more gram-negative/anaerobic pathogen taxa; inner surface also colonized despite low porosity. |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Franović et al.[22] (2025)** | Croatia | RCT, socket preservation (NCT06694844) | d-PTFE: Permamem vs. Cytoplast | 39 pts/48 sites; brand-to-brand | SEM, qPCR, 16S NGS | Cytoplast: denser biofilm, higher qPCR bacterial load, and higher per-sample alpha diversity (Shannon index; P=0.019) than Permamem; beta diversity similar (P=0.512). |
| **Mohar Vitezić et al.[21] (2025)** | Croatia | RCT, companion microbiome analysis (same trial as Franović 2025; NCT06694844) | d-PTFE: Permamem vs. Cytoplast | 36 membranes (20 Permamem, 16 Cytoplast), same cohort as Franović 2025 | 16S NGS microbiome | Cytoplast: fewer species detected cumulatively across all samples (242 vs. 275; group-level richness, not tested statistically), more pathobionts; Permamem favored health-associated genera; beta diversity similar (P=0.5). |
| **Non-therapeutic intraoral exposure models (n=6)** | | | | | | |
| **Simion et al.[52] (1994)** | Italy | In vivo permeability model (non-therap.) | e-PTFE | 5 volunteers, 2-chamber device, weekly × 4 wk | SEM + light microscopy | Complete bacterial penetration by 3-4wk; porosity delays but does not prevent penetration. |
| **Simion et al.[53] (1995)** | Italy | In vivo permeability model (non-therap.) | e-PTFE (GTAM) | 3 volunteers; chlorhexidine gel vs control, 2/4wk | SEM + light microscopy | Chlorhexidine reduced external surface plaque but did not prevent bacterial penetration through membrane. |
| **Chen et al.[54] (1997)** | USA | In vivo adherence model (non-therap.) | ePTFE vs. collagen vs PLA | 10 volunteers, supragingival, 1-14 days | Slot immunoblot (SIB), 0-3 scale | All materials colonized over time; ePTFE adherence increased significantly; no overall difference among materials. |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Zucchelli et al.[55] (1998)** | Italy | In vivo adherence model (non-therap.) | ePTFE vs. polyglactin 910 vs PLA | 8 volunteers, 4 h/24 h | SEM bacteria-positive fields + profilometry | ePTFE and polyglactin 910 had more bacteria-positive fields than PLA at 4 h (P=0.008) and ePTFE more than both others at 24 h (P=0.002); differences not explained by surface roughness. |
| **Zucchelli et al.[56] (2000)** | Italy | In vivo adherence model, split-mouth (non-therap.) | ePTFE vs. polyglactin 910 vs PLA | 8 volunteers; chlorhexidine vs. saline | SEM bacteria-positive fields | Chlorhexidine reduced fields at 4 h (P<0.0001), not at 24 h; ePTFE consistently more colonized than PLA. |
| **Turri et al.[23] (2021)** | Sweden | Randomized split-mouth in situ exposure model (non-therap.) | e-PTFE vs. d-PTFE (Cytoplast) | 12 volunteers, 4 h/24 h; vs. tooth plaque | CFU, CLSM/Comstat2, SEM | d-PTFE greater biomass/thickness at 4 h (P<0.05); no CFU difference; both > tooth plaque for *Staphylococcus* spp. |
| **In vitro studies (n = 17)** | | | | | | |
| **Wang et al.[57] (1994)** | USA | In vitro comparative adherence/degradation | ePTFE vs. polyglactin 910 vs collagen | 15 species (qual.), then 6 species (quant.) | Two-part adherence + degradation assay | ePTFE distinct adherence vs resorbable materials, which also degraded; species-dependent affinity. |
| **Ricci et al.[58] (1996)** | Italy | In vitro | 6 barrier membranes (ePTFE, Resolut, Guidor, etc.) | *P. gingivalis* permeability, 6/24/48h | CFU counts + SEM | ePTFE poor barrier (crossed 6-24 h); Guidor/Resolut best barrier (~48 h); *P. gingivalis* formed continuous layer on ePTFE. |
| **Sela et al.[59] (1999)** | Israel | In vitro comparative adherence | Collagen vs. 3 PTFE/Teflon variants | 3 radiolabeled pathogen species | Radiolabeled adherence assay | Adherence varied by material and species; some pathogens preferred PTFE over collagen. |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Hung et al.[60] (2002)** | Taiwan | In vitro | ePTFE vs glycolide fiber vs. collagen | Permeability device + PDL cell attachment | CFU penetration + SEM | ePTFE best barrier; contamination reduced PDL cell attachment, most on ePTFE. |
| **Cheng et al.[61] (2009)** | Taiwan | In vitro | ePTFE vs glycolide fiber vs. collagen, ± antibiotic | Permeability device; *S. mutans*, *A. actinomycetem comitans*, 12 days | CFU penetration counts | Unloaded ePTFE had best barrier effect; tetracycline loading reduced penetration ($P<0.001$). |
| **Cheng et al.[62] (2015)** | Taiwan | In vitro | ePTFE vs. glycolide vs collagen, ± antibiotic | Adhesion assay; *S. mutans*, *A. actinomycetem comitans* | CFU adhesion + SEM | Antibiotic loading reduced adhesion on ePTFE vs unloaded; distinct pattern vs bioabsorbable membranes. |
| **Trobos et al.[63] (2018)** | Sweden | In vitro | e-PTFE (3 variants) vs. d-PTFE vs. titanium | *S. oralis* biofilm, static, 2/24/48h | SEM, CLSM/Comstat2, CFU, permeability | All PTFE impermeable to *S. oralis*; d-PTFE thicker/more mature biofilm than e-PTFE at 48 h ($P<0.05$). |
| **Bueno et al.[64] (2020)** | Spain | In vitro | d-PTFE (Cytoplast) vs. novel NMs vs. HA | 6-species biofilm, 12-72h | SEM/EDX, qPCR (CFU) | d-PTFE biofilm biomass similar to controls; only doxycycline-doped NMs reduced bacterial load ($p < 0.001$). |
| **Begić et al.[32] (2022)** | Croatia | In vitro | d-PTFE: PTFE-W vs. PTFE-B | 4-species MATS adhesion assay | MATS + surface characterization | Roughness/hydrophobicity differed between brands and correlated with adhesion; PTFE-B had higher adhesion. |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Nocca et al.[65] (2022)** | Italy | In vitro | d-PTFE vs. cross-linked vs. native collagen | *P. gingivalis* permeability, transwell, 24/72 h | CFU permeability + cytotoxicity | d-PTFE impermeable to *P. gingivalis* at 72 h, no cytotoxicity; both collagens crossed within 24 h. |
| **Zelikman et al.[31] (2022)** | Israel | In vitro | d-PTFE: Permamem vs. Cytoplast vs. NeoGen collagen | Direct contact test (DCT) | Bacterial growth/turbidity | Brand-specific differences between the 2 d-PTFE brands; collagen grew differently than both. |
| **Kuerten-Gil et al.[24] (2023)** | Brazil | In vitro | d-PTFE (Lumina) vs. 3 collagens vs. foil | Multispecies transwell, 2 h/7 d | CFU + SEM | d-PTFE and Lumina Coat lower adhesion than other collagens ($p < 0.05$); all permeable by 2 h. |
| **Al-Asfour et al.[26] (2024)** | Kuwait | In vitro | 6 PTFE brands vs. PVDF control | *C. albicans* adhesion, 2-day | SEM + qPCR | All PTFE > PVDF ($P \leq 0.001$); textured brands higher counts than non-textured ($P=0.001$). |
| **Weitkamp et al.[66] (2024)** | Germany | In vitro | PTFE (PermaPro) vs. 3 collagens | *E. faecalis*, 6-day; ± cold plasma (CAP) | CFU, Live/Dead, SEM | Collagen more colonized than PTFE at baseline ($P=0.037$); CAP fully decontaminated PTFE. |
| **Al-Asfour et al.[25] (2025)** | Kuwait | In vitro | 6 PTFE brands (textured/non-textured) | *S. mutans*, *P. gingivalis*, *C. albicans* adhesion | SEM, qPCR, roughness/SFE | Adhesion correlated with roughness ($r^2 = 0.98$ for *P. gingivalis*); OsseoGuard-TXT had least adhesion overall. |
| **Tsang et al.[67] (2025)** | China (Hong Kong) | In vitro | d-PTFE (Cytoplast) vs. collagen | *P. gingivalis* & *A. naeslundii* culture, ± LPRF, 2–4 d | SEM + CFU | Both adhered; LPRF reduced adhesion on both, most on Cytoplast. |

| Study (author, year) | Country | Design | Membrane | Population / Comparator | Outcome Method | Key Findings |
|---|---|---|---|---|---|---|
| **Suzzin et al.[30] (2026)** | Brazil | In vitro | 2 d-PTFE vs. polypropylene vs. titanium | Human oral biofilm, 7-day | CFU + SEM/EDS | All contaminated; Lumina PTFE most contaminated (P=0.005 vs. Bone Heal); pattern varies by surface. |

**Note:** Reports are grouped by synthesis line and, within the therapeutic clinical line, by clinical indication and type of exposure (unplanned exposure of e-PTFE intended for submerged healing in GTR/GBR; intentional exposure of d-PTFE in ARP). Franović et al.[22] and Mohar Vitezić et al.[21] are companion reports of one randomized trial (NCT06694844) and are counted as one study. Alpha diversity denotes per-sample diversity indices (e.g., Shannon index, which integrates richness and evenness); cumulative species richness denotes the total number of distinct taxa detected across all samples of a group. ARP, alveolar ridge preservation; CFU, colony-forming units; CLSM, confocal laser scanning microscopy; DFDBA, demineralized freeze-dried bone allograft; e-PTFE, expanded polytetrafluoroethylene; d-PTFE, dense polytetrafluoroethylene; GBR, guided bone regeneration; GTR, guided tissue regeneration; NGS, next-generation sequencing; PCR, polymerase chain reaction; PLA, polylactic acid; PTFE, polytetrafluoroethylene; RCT, randomized controlled trial; SEM, scanning electron microscopy; TEM, transmission electron microscopy; wk, week(s).

**Table 2. Outcome domains reported by each included report (n = 48)**

| Report (author, year) | Line / indication | SC | BB | MC | PP | CO |
|---|---|---|---|---|---|---|
| **Therapeutic clinical line — periodontal GTR (e-PTFE; unplanned exposure)** | | | | | | |
| Selvig et al.[5] (1990) | GTR | ● | ● | ● | | |
| Selvig et al.[33] (1992) | GTR | ● | ● | ● | | ● |
| Demolon et al.[34] (1993) | GTR | ● | | ● | | |
| Grevstad & Leknes[35] (1993) | GTR | ● | ● | ● | | |
| Guillemin et al.[36] (1993) | GTR | ● | | | | ● |
| Mombelli et al.[37] (1993) | GTR | ● | | ● | | |
| Tempro & Nalbandian[38] (1993) | GTR | ● | | ● | | |
| Frandsen et al.[39] (1994) | GTR | ● | | ● | | |
| Nowzari & Slots[6] (1994) | GTR + GBR (implants) | ● | | ● | | ● |
| Nowzari et al.[40] (1995) | GTR | ● | | ● | | ● |
| Mombelli et al.[41] (1996) | GTR | ● | | ● | | |
| Nowzari et al.[42] (1996) | GTR | ● | | ● | | ● |
| MacDonald et al.[43] (1998) | GTR | ● | | ● | | ● |
| Yoshinari et al.[44] (1998) | GTR | ● | | | | ● |
| Zarkesh et al.[45] (1999) | GTR | ● | | ● | | ● |
| Zucchelli et al.[46] (1999) | GTR | ● | | | | ● |
| Lin et al.[47] (2000) | GTR | ● | | ● | | ● |
| Yoshinari et al.[48] (2001) | GTR | ● | | | | ● |
| Apinhasmit et al.[49] (2002) | GTR | ● | | | | |
| Ling et al.[50] (2003) | GTR | ● | | ● | | ● |
| Toygar et al.[51] (2009) | GTR | ● | | | | |

| Report (author, year) | Line / indication | SC | BB | MC | PP | CO |
|---|---|---|---|---|---|---|
| **Therapeutic clinical line — ARP (d-PTFE; intentional exposure)** | | | | | | |
| Mazzucchi et al.[27] (2020) | ARP | ● | ● | ● | | ● |
| García-Braz et al.[28] (2024) | ARP | ● | | ● | ● | |
| Franović et al.[22] (2025) | ARP | ● | ● | ● | | |
| Mohar Vitezić et al.[21] (2025) | ARP | ● | | ● | | |
| **Non-therapeutic intraoral exposure models** | | | | | | |
| Simion et al.[52] (1994) | Exposure model | ● | | | ● | |
| Simion et al.[53] (1995) | Exposure model | ● | ● | ● | ● | |
| Chen et al.[54] (1997) | Exposure model | ● | | ● | | |
| Zucchelli et al.[55] (1998) | Exposure model | ● | | ● | | |
| Zucchelli et al.[56] (2000) | Exposure model | ● | | ● | | |
| Turri et al.[23] (2021) | Exposure model (randomized) | ● | ● | ● | | |
| **In vitro studies** | | | | | | |
| Wang et al.[57] (1994) | In vitro | ● | | ● | | |
| Ricci et al.[58] (1996) | In vitro | ● | ● | | ● | |
| Sela et al.[59] (1999) | In vitro | ● | | ● | | |
| Hung et al.[60] (2002) | In vitro | ● | | | ● | |
| Cheng et al.[61] (2009) | In vitro | ○ | | | ● | |
| Cheng et al.[62] (2015) | In vitro | ● | | | | |
| Trobos et al.[63] (2018) | In vitro | ● | ● | | ● | |
| Bueno et al.[64] (2020) | In vitro | ● | ● | ● | | |
| Begić et al.[32] (2022) | In vitro | ● | | | | |

| Report (author, year) | Line / indication | SC | BB | MC | PP | CO |
|---|---|---|---|---|---|---|
| Nocca et al.[65] (2022) | In vitro | ○ | | | ● | |
| Zelikman et al.[31] (2022) | In vitro | ● | | | | |
| Kuerten-Gil et al.[24] (2023) | In vitro | ● | ● | | ● | |
| Al-Asfour et al.[26] (2024) | In vitro | ● | ● | | | |
| Weitkamp et al.[66] (2024) | In vitro | ● | ● | | | |
| Al-Asfour et al.[25] (2025) | In vitro | ● | | | | |
| Tsang et al.[67] (2025) | In vitro | ● | | | | |
| Suzzin et al.[30] (2026) | In vitro | ● | ● | | | |
| **Reports with domain (n)** | | **46 (+2 indirect)** | **14** | **27** | **9** | **13** |

**Note:** ●Outcome domain reported directly; ○ reported only indirectly or qualitatively (membrane-surface data in permeability models). SC, surface colonization/adhesion; BB, biofilm biomass/architecture; MC, microbial composition (species, morphotypes, pathogens, or sequencing-based diversity); PP, penetration/permeability through the membrane; CO, clinical outcome analyzed in relation to membrane colonization. ARP, alveolar ridge preservation; GBR, guided bone regeneration; GTR, guided tissue regeneration. Operational definitions are given in Methods (Outcome definitions and outcome domains).

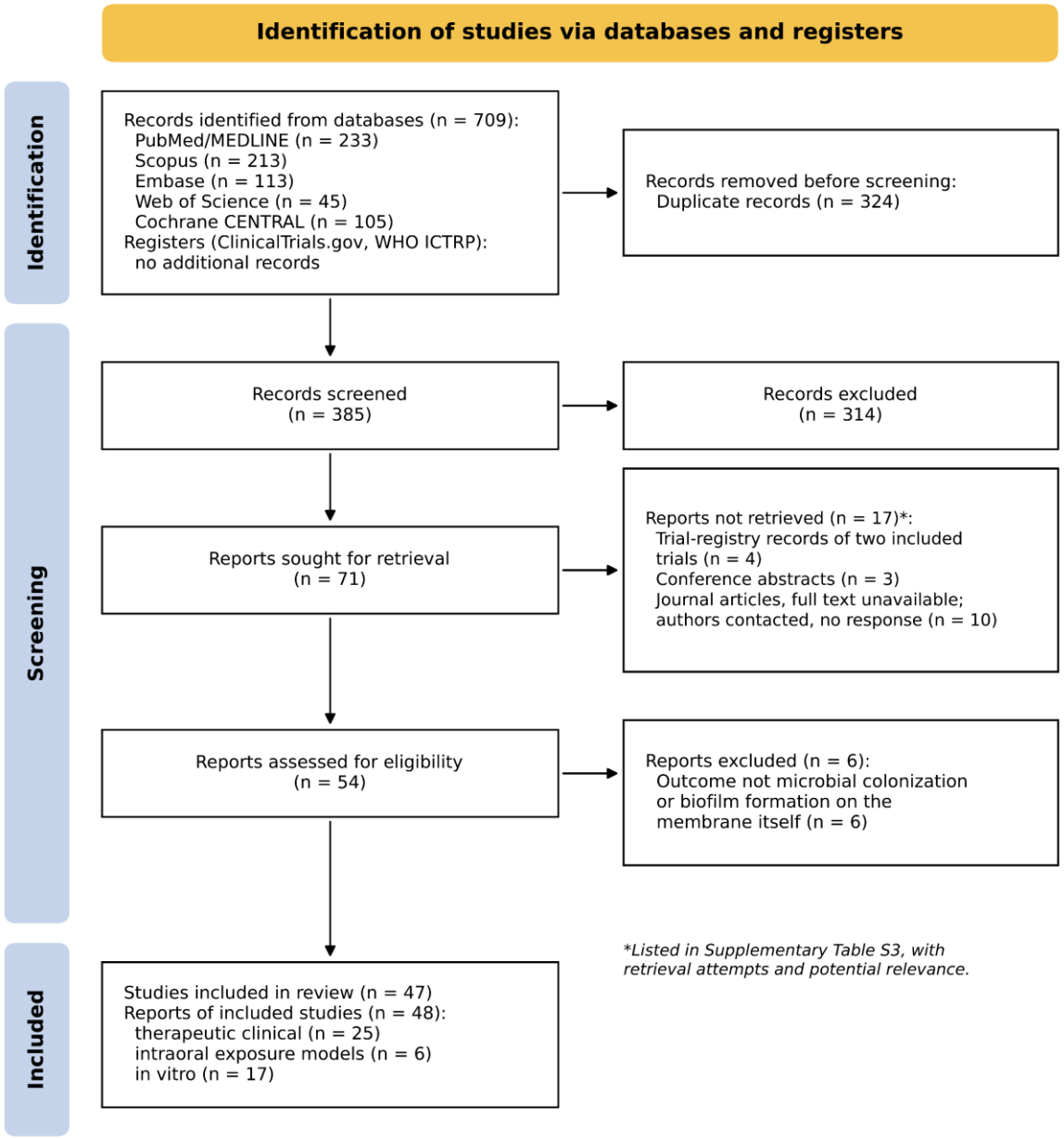



**Figure 1. PRISMA 2020 flow diagram of study identification, screening, and inclusion. The 17 reports not retrieved are listed in Supplementary File 4; the 48 included reports correspond to 47 independent studies.**

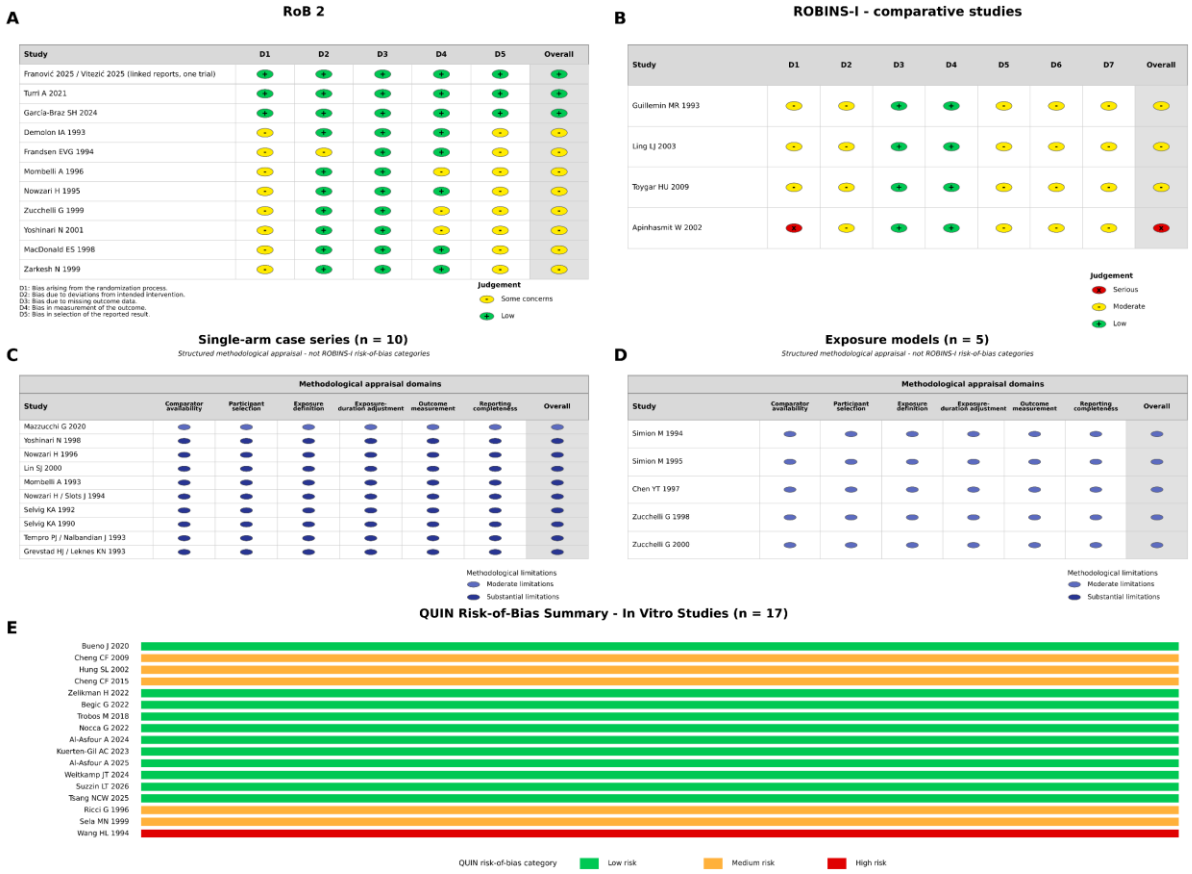
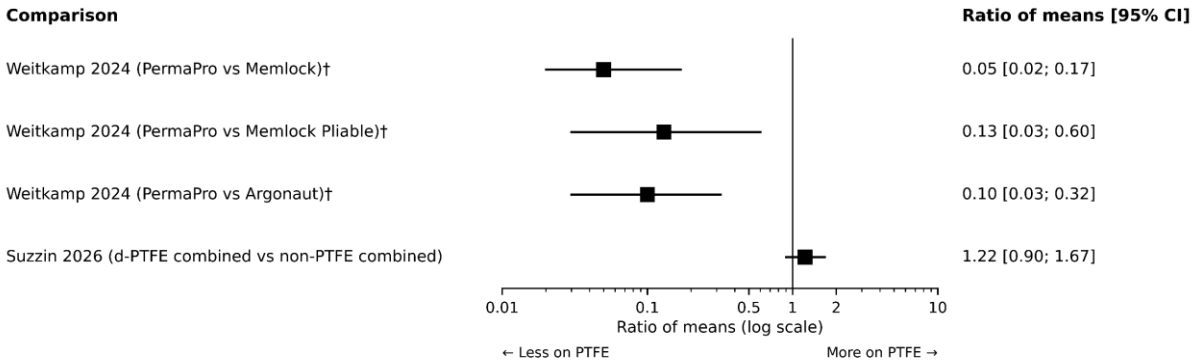



**Figure 2. Risk-of-bias and methodological appraisal of the included studies, using the independent study as the unit of assessment. (A) RoB 2 domain-level judgments for the 11 randomized studies (12 reports; the companion reports by Franović et al.[22] and Mohar Vitezić et al.[21] are assessed jointly as one trial), including the randomized in situ study by Turri et al.[23] (B) ROBINS-I domain-level judgments for the four non-randomized clinical studies with an explicit comparator. (C) Structured methodological appraisal of the ten single-arm clinical studies and (D) of the five non-randomized intraoral exposure-model studies; panels C and D do not represent ROBINS-I risk-of-bias categories. (E) QUIN risk-of-bias category of the 17 in vitro studies. RoB 2 domains: D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result. ROBINS-I domains: D1, confounding; D2, selection of participants; D3, classification of interventions; D4, deviations from intended interventions; D5, missing data; D6, measurement of outcomes; D7, selection of the reported result. The Domain 4 rationale for RoB 2 is provided in Supplementary File 7, and domain-level summaries in Supplementary File 8. Studies shown: (A) Franović et al.[22]/Mohar Vitezić et al.,[21] Turri et al.,[23] García-Braz et al.,[28] Demolon et al.,[34] Frandsen et al.,[39] Mombelli et al.[41] (1996), Nowzari et al.[40] (1995), Zucchelli et al.[46] (1999), Yoshinari et al.[48] (2001), MacDonald et al.,[43] and Zarkesh et al.;[45] (B) Guillemin et al.,[36] Ling et al.,[50] Toygar et al.,[51] and Apinhasmit et al.;[49] (C) Mazzucchi et al.,[27] Yoshinari et al.[44] (1998), Nowzari et al.[42] (1996), Lin et al.,[47] Mombelli et al.[37] (1993), Nowzari & Slots,[6] Selvig et al.[33] (1992), Selvig et al.[5] (1990), Tempro & Nalbandian,[38] and Grevstad & Leknes;[35] (D) Simion et al.[52] (1994), Simion et al.[53] (1995), Chen et al.,[54] Zucchelli et al.[55] (1998), and Zucchelli et al.[56] (2000); (E) Bueno et al.,[64] Cheng et al.[61] (2009), Hung et al.,[60] Cheng et al.[62] (2015), Zelikman et al.,[31] Begić et al.,[32] Trobos et al.,[63] Nocca et al.,[65] Al-Asfour et al.[26] (2024), Kuerten-Gil et al.,[24] Al-Asfour et al.[25] (2025), Weitkamp et al.,[66] Suzzin et al.,[30] Tsang et al.,[67] Ricci et al.,[58] Sela et al.,[59] and Wang et al.[57]**




*† Comparisons share the same PermaPro (PTFE) control arm and are not statistically independent; no pooled estimate is presented.*

**Figure 3. Individual in vitro CFU comparisons with extractable numeric data, expressed as ratios of means (log response ratio) with 95% confidence intervals; no pooled estimate is presented. Values below 1 indicate lower colonization on PTFE/d-PTFE than on the comparator. The three comparisons from Weitkamp et al.[66] share the same PTFE (PermaPro) control arm and are therefore not statistically independent, and the fourth comparison is from Suzzin et al.;[30] because data were available from only two independent source studies, a random-effects pooled estimate was not computed (see Methods, Statistical analysis, and Results, Quantitative comparisons).**