IJEBM International Journal of Evidence-Based Medicine

International Journal of Evidence-Based Medicine
(eISSN 3083-1776)

Australasia Publishing Group

Review Article

Systematic Review of Antimicrobial Biomaterials for Medical Implants: Clinical Strategies for Reducing Device-Associated Infections

Adepeju Kafayat Olowookere[1], Bolawa Fredrick Babatunde[2], Ebenezer Oluwadamilare Oyekanmi[3], Adeyemo Rashidat Abolore[4]

[1]*Department of Nanoscience, University of North Carolina at Greensboro, Greensboro, NC, USA*
[2]*Department of Plant Science and Biotechnology, Adekunle Ajasin University, Akungba Akoko, Ondo State, Nigeria*
[3]*Department of Medical Laboratory Science, Ladoke Akinola University of Technology, Ogbomosho, Oyo State, Nigeria*
[4]*Department of Medical Laboratory science, Fountain University, Osogbo, Osun State, Nigeria*

Received: May 29, 2026
Accepted: Jun 21, 2026

Corresponding author's email:
pejuolowookere@gmail.com

Citation: Olowookere AK, Babatunde BF, Oyekanmi EO, Abolore AR. Systematic Review of Antimicrobial Biomaterials for Medical Implants: Clinical Strategies for Reducing Device-Associated Infections. International Journal of Evidence-Based Medicine. 2026;1(2):jebm006.
https://doi.org/10.63946/jebm/18874

ABSTRACT

Background: Device-associated infections remain major complications of medical implants, contributing to prolonged hospitalisation, revision surgery, morbidity, and increased healthcare burden. Biofilm formation provides the biological rationale for antimicrobial implant strategies, although clinical studies often assess downstream infection outcomes rather than direct biofilm measures.

Objectives: This systematic review evaluated the clinical effectiveness, safety, and certainty of evidence for antimicrobial biomaterials and implant surface modification strategies in reducing device-associated infections, reinfection, microbial colonisation, and related complications among human implant recipients.

Methodology: A systematic search of PubMed, ScienceDirect, and Dimensions was conducted for original human studies published between 2015 and 2025. Eligible studies included randomised trials and observational cohorts evaluating antimicrobial biomaterials against conventional, uncoated, or standard-care comparators. Data extraction covered implant type, antimicrobial coating, comparator, infection-related outcomes, adverse events, and follow-up duration. Quality appraisal was performed using RoB 2 and ROBINS-I, while certainty of evidence was assessed narratively. A structured narrative synthesis was conducted because of heterogeneity in implant types, interventions, indications, comparators, and outcome definitions.

Findings: Twenty studies were included. DAC hydrogel coatings showed the most consistent association with reduced surgical site infection, periprosthetic joint infection, reinfection, and complications in selected orthopaedic settings. Silver- and iodine-coated implants showed promise in high-risk oncological reconstruction, while gentamicin-coated nails and calcium sulphate-based strategies appeared useful in trauma fixation and second-stage reimplantation. However, most studies were retrospective or non-randomised, several had serious risk of bias, and none directly quantified biofilm formation.

Conclusion: Antimicrobial biomaterials may reduce infection risk in selected implant settings, especially orthopaedic applications, but broader conclusions require cautious interpretation and stronger prospective evidence.

Keywords: Antimicrobial Biomaterials; Medical Implants; Device-Associated Infection; Surgical Site Infection; Periprosthetic Joint Infection; Clinical Outcomes

Introduction

Medical implants have become indispensable to modern healthcare because they restore function, replace damaged tissues, support healing, and improve survival across orthopaedics, dentistry, cardiovascular medicine, neurosurgery, reconstructive surgery, ophthalmology, and urology. Devices such as joint prostheses, dental implants, vascular grafts, pacemakers, catheters, heart valves, stents, and fixation screws now occupy a central position in clinical practice. However, the same material surfaces that provide structural and therapeutic benefit can also create stable attachment sites for microorganisms after implantation. This dual role of implants, as both therapeutic tools and potential microbial niches, makes infection prevention a major scientific and clinical priority [1-3].

Device-associated infection remains one of the most difficult complications of implant-based medicine because it is often persistent, recurrent, expensive, and clinically disruptive. Once infection is established, patients may require prolonged antimicrobial therapy, surgical debridement, device removal, revision surgery, or long-term rehabilitation. The burden is not limited to microbial contamination itself; it extends to implant failure, delayed recovery, tissue destruction, antimicrobial resistance, increased hospitalisation, and higher mortality in vulnerable patients. Recent reviews across different implant categories show that biofilm-associated infections can compromise dental implants, orthopaedic prostheses, cochlear implants, urinary catheters, central venous catheters, tracheal stents, breast implants, and cardiac devices [2, 4-6].

The central biological problem behind many of these infections is biofilm formation. Biofilms develop when planktonic microorganisms attach to a surface, shift into a sessile state, produce extracellular polymeric substances, form microcolonies, communicate through quorum-sensing systems, and mature into structured microbial communities [6, 7]. This matrix-rich architecture protects embedded cells from antibiotics, disinfectants, shear forces, and host immune attack. As a result, bacteria in biofilms do not behave like free-floating organisms; they often display altered metabolism, stress tolerance, phenotypic heterogeneity, and increased resistance. This explains why infections caused by Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, Enterococcus spp., and other pathogens can persist even when conventional antimicrobial susceptibility tests suggest treatability [6, 7].

Conventional infection-control measures, although necessary, are not sufficient to solve the implant-biofilm problem. Aseptic surgical practice, perioperative prophylaxis, systemic antibiotics, and device revision remain essential, but they often act after microbial exposure has already occurred [3, 8]. Systemic antibiotic use may also be limited by poor penetration into biofilms, drug toxicity, resistance development, and the survival of metabolically inactive cells. In this context, antimicrobial biomaterials are not merely alternative treatments; they represent a prevention-oriented design philosophy. Their goal is to make the implant surface itself less hospitable to microbial attachment, growth, communication, and persistence while preserving tissue compatibility [9, 10].

The first theoretical basis for this review is the surface-mediated theory of bacterial adhesion. Existing literature shows that microbial attachment is shaped by interactions between the organism, the biomaterial, and the host environment [11, 12]. Surface roughness, charge, hydrophobicity, wettability, surface energy, topography, and chemical composition influence whether bacteria attach reversibly, become irreversibly anchored, and progress toward biofilm formation. After implantation, host proteins may also adsorb onto the material surface, forming a conditioning film that can either support or limit microbial colonisation [13]. Therefore, the theoretical logic is clear: if the earliest stages of adhesion are interrupted, biofilm development becomes more difficult to initiate. This has driven interest in surface engineering, nanotopography, antifouling polymers, hydrogels, and chemistry-based modifications [12, 13].

The second theoretical basis is antimicrobial biomaterial design, which organises current strategies into passive, active, and hybrid approaches. Passive or anti-adhesive systems aim to repel bacteria by modifying surface chemistry, hydration, topography, or protein adsorption. Active systems kill microorganisms through contact-mediated mechanisms or localised release of antimicrobial agents such as antibiotics, antimicrobial peptides, metal ions, nanoparticles, nitric oxide donors, enzymes, or photothermal agents. Hybrid systems combine repulsion and killing to reduce both initial colonisation and later biofilm maturation [14, 15]. Recent work on polymer coatings, chitosan systems, carbon dots, nitric oxide-releasing surfaces, antibacterial hydrogels, and nanomaterial-based coatings suggests that future implants may require multifunctional designs rather than a single antimicrobial mechanism [16-18].

Despite these advances, the evidence base remains fragmented. Studies differ in implant type, coating method, microbial strain, biofilm model, exposure time, antimicrobial endpoint,

cytocompatibility testing, and clinical relevance. Many promising materials are evaluated in simplified in vitro systems that do not adequately reproduce the biofilm-implant-host interface, tissue fluids, immune interactions, polymicrobial communities, mechanical forces, or long-term implantation conditions [19]. This makes translation from laboratory efficacy to clinical performance slow and uncertain.

Although biofilm formation provides the biological rationale for device-associated implant infections, human clinical studies often assess its consequences through downstream outcomes rather than through direct biofilm measurement. Outcomes such as surgical site infection, periprosthetic joint infection, reinfection, microbial colonisation, implant retention, infection-free survival, and infection-related complications are clinically meaningful, but they do not directly quantify biofilm biomass, biofilm architecture, surface-level microbial attachment, or biofilm maturation. Therefore, this review interprets such outcomes as clinical indicators of biofilm-associated implant infection rather than direct microbiological measures of biofilm formation or suppression. This distinction is important because it prevents overstatement of the evidence and keeps the scope of the review focused on clinical effectiveness and safety.

Recent reviews also note that although antimicrobial coatings appear promising, many technologies still require stronger in vivo validation, standardised testing, regulatory clarity, and evidence of long-term safety [5, 12]. Accordingly, this review emphasises clinical outcomes of antimicrobial biomaterials as indicators of real-world infection control while recognising that clinical infection endpoints cannot fully substitute for direct microbiological assessment of biofilm behaviour.

Therefore, this systematic review aimed to evaluate the clinical effectiveness and safety of antimicrobial biomaterials and implant surface modification strategies in reducing device-associated infections, reinfection, microbial colonisation, and biofilm-related clinical complications among human recipients of medical implants. The review focused on clinically evaluated antimicrobial implant technologies, including silver-coated implants, iodine-coated implants, antibiotic-loaded hydrogel coatings, gentamicin-coated intramedullary nails, and antibiotic-loaded calcium sulphate systems. Its scope covered implant category, antimicrobial mechanism, comparator material, target microorganisms, infection-related outcomes, implant retention, infection-free survival, adverse events, wound healing, osseointegration, aseptic loosening, and bone union, while also acknowledging heterogeneity across study designs and follow-up durations.

Methodology

Research Question

This systematic review was guided by the PICO (population, intervention, comparator, and outcomes of interest) framework [20], which is suitable for evaluating intervention-based clinical questions in human implant recipients. The population comprised adult recipients of medical implants, including orthopaedic prostheses, megaprostheses, intramedullary nails, and other clinically relevant devices. The intervention consisted of antimicrobial biomaterials or implant surface modification strategies, including silver-coated implants, iodine-coated implants, antibiotic-loaded hydrogel coatings, gentamicin-coated intramedullary nails, and calcium sulphate-based coatings. Comparators included conventional, uncoated, non-antimicrobial implants or standard care. Outcomes focused on clinically relevant infection measures, including surgical site infection, periprosthetic joint infection, reinfection, microbial colonisation, implant retention, infection-free survival, and biofilm-related complications. Based on this framework, the research question was: Among human recipients of medical implants, how effective are antimicrobial biomaterials and implant surface modification strategies, compared with conventional or non-antimicrobial implant materials, in reducing device-associated infections, reinfection, microbial colonisation, and other biofilm-related clinical complications? This question allowed the review to remain broad enough to capture different implant categories while remaining specific enough to focus on clinically relevant antimicrobial biomaterial strategies.

Study Design

This study was conducted as a systematic review of original human research articles published from 2015 to 2025. The systematic review design was selected because it provides a transparent, reproducible, and structured approach for identifying, selecting, appraising, and synthesising evidence from multiple studies on a clearly defined research question [21]. The review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, which provides current guidance for presenting the rationale, methods, study selection, appraisal, and synthesis of systematic reviews [21]. Although this review was conducted according to PRISMA 2020 principles, the review protocol was not prospectively registered in PROSPERO or another systematic review registry. This

is acknowledged as a methodological limitation because prospective registration could have further strengthened transparency and reduced the risk of post hoc methodological decisions.

Information Sources and Search Strategy

The literature search was carried out on February 6, 2026 in PubMed, Dimensions, and ScienceDirect. These databases provide broad coverage of biomedical, clinical, materials science, and interdisciplinary implant-related research.

The search strategy combined controlled vocabulary and keywords. In PubMed, Medical Subject Headings (MeSH) terms were combined with title and abstract keywords. Boolean operators ("AND" and "OR") were used to combine key concepts.

The search was limited to studies published from January 2015 to December 2025. Only English-language articles involving human populations were considered. Searches were refined using appropriate database filters (such as publication year, research articles, Full text articles, open access) were employed to refine and narrow down the search results to relevant articles. Duplicates were removed after export into a reference manager (Zotero). The search strategy adopted in this study is as shown in Table 1. The final search results from each database were documented, including the database name, search string used, and number of records retrieved.

Table 1: Search Strategy

Database	Search string used	Search yield	Filters Applied	Final yield
PubMed	(("Biocompatible Materials"[MeSH] OR "Prostheses and Implants"[MeSH] OR biomaterial*[tiab] OR implant*[tiab] OR "medical device*"[tiab]) AND ("Anti-Bacterial Agents"[MeSH] OR "Anti-Infective Agents"[MeSH] OR antimicrobial*[tiab] OR antibacterial*[tiab] OR anti-biofilm[tiab] OR antibiofilm[tiab]) AND ("Biofilms"[MeSH] OR "Device-Related Infections"[MeSH] OR biofilm*[tiab] OR "implant-associated infection*"[tiab] OR "device-associated infection*"[tiab]) AND (coating*[tiab] OR surface*[tiab] OR modification*[tiab] OR "controlled release"[tiab] OR nanomaterial*[tiab] OR hydrogel*[tiab]))	3752	2015 to 2025, Free full text, English, Humans	486
ScienceDirect	("antimicrobial biomaterial" OR "antibacterial coating" OR "anti-biofilm coating") AND ("medical implant" OR "medical device") AND (biofilm OR "device-associated infection" OR "implant-associated infection")	1083	2015 to 2025, Research articles, Open access	110
Dimensions	("antimicrobial biomaterial" OR "antibacterial biomaterial" OR "antimicrobial coating") AND ("medical implant" OR "implantable device" OR "prosthesis") AND (biofilm OR "microbial colonization" OR infection)	92	2015 to 2025, Research articles, All open access	37

Eligibility Criteria

Inclusion criteria required original research studies published between 2015 and 2025, involving human populations, reporting at least three infection-related outcomes (Surgical Site Infection (SSI), Periprosthetic Joint Infection (PJI), reinfection, implant retention, or infection-free survival), and evaluating antimicrobial biomaterials against comparators. Both primary and revision implant procedures were considered. Exclusion criteria included review articles, non-human studies, in vitro-only studies, and studies not published in English and without relevant clinical infection outcomes.

Study Selection

The study selection process was conducted in sequential stages. First, all records retrieved from PubMed, Dimensions, and ScienceDirect were exported into a reference manager, where duplicate records were identified and removed. Titles and abstracts were then screened against the eligibility criteria. At this stage, studies were excluded if they clearly did not involve antimicrobial biomaterials, medical implants, human populations, or relevant infection and biofilm outcomes.

Full-text articles were retrieved for all records that appeared eligible or uncertain after title and abstract screening. Each full text was then assessed in detail against the inclusion and exclusion criteria. Particular attention was given to whether the study involved an implantable device, whether the antimicrobial strategy was material-based, whether the population or sample context was human-relevant, and whether the reported outcomes could answer the research question. Reasons for exclusion at the full-text

stage were documented, including absence of relevant outcome data and non-implant focus. The study selection process was handled by two independent reviewers and discrepancies were resolved through discussion. The full selection process was presented in a PRISMA flow diagram (Figure 1), consistent with PRISMA 2020 reporting guidelines [21]. Ultimately 20 articles that met the inclusion criteria of this study were included.

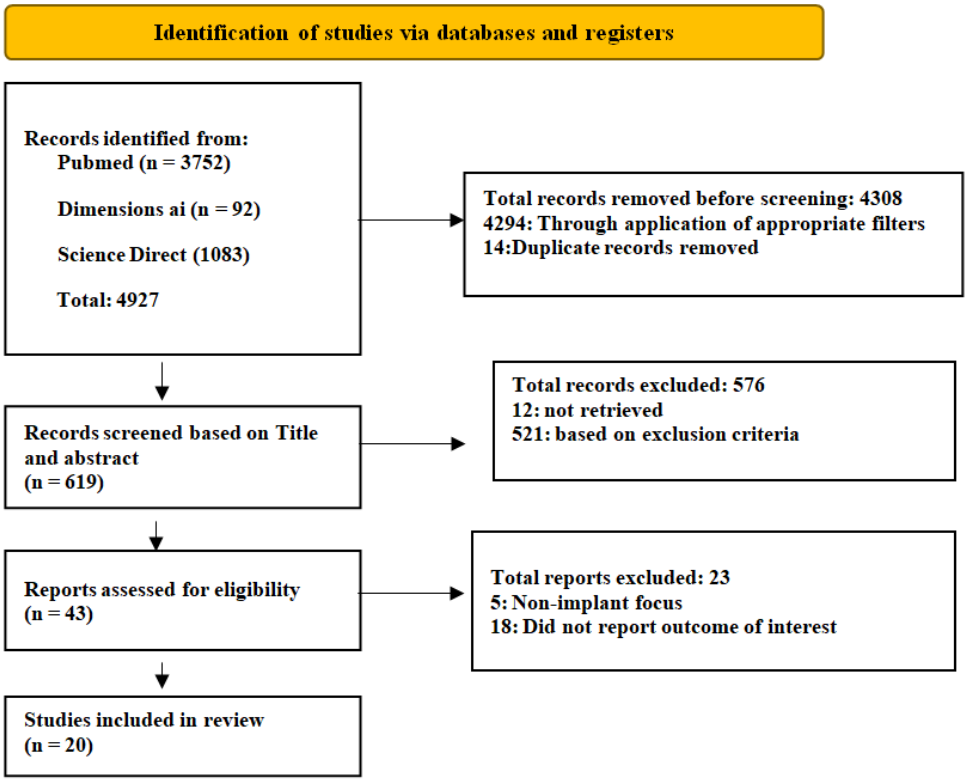

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

Data Extraction and Quality Assessment

Data were extracted using a structured extraction form developed before full-text review. The extraction form captured Study ID (Authors and year of publication), country, study design, study setting, implant type, clinical indication, sample size, population characteristics, antimicrobial biomaterial or coating type, comparator, target microorganisms, follow-up duration, outcome measures, adverse events, and main findings. Extraction also captured whether the antimicrobial strategy was anti-adhesive, contact-killing, release-based, nanomaterial-based, polymeric, hydrogel-based, antibiotic-loaded, metal-ion-based, peptide-based, or multifunctional. This structure was used to ensure that the synthesis reflected both clinical outcomes and material-design principles.

Quality assessment was conducted using tools appropriate to the design of each included study. Randomized controlled trials were assessed using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2), which evaluates bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting [22]. Non-randomized studies of interventions were assessed using ROBINS-I, which evaluates bias due to confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of reported results [23].

Each study was judged independently across the relevant domains of the appropriate tool. Randomized trials were classified as having low risk of bias, some concerns, or high risk of bias. Non-randomized studies were classified as having low, moderate, serious, critical, or no information on risk of bias. The quality assessment was handled by 2 independent reviewers and where disagreements occurred during assessment, the judgement was resolved through discussion. The final quality assessment was not used to exclude studies automatically; rather, it informed the interpretation of the strength, reliability, and applicability of the findings.

Data Synthesis

A structured narrative synthesis was conducted due to heterogeneity in implant types, antimicrobial materials, clinical settings, comparator

groups, follow-up durations, and outcome definitions. The synthesis was guided by principles for synthesis without meta-analysis in systematic reviews [24]. Studies were grouped into thematic intervention categories, including metallic antimicrobial surfaces, iodine-coated implants, antibiotic-loaded hydrogel coatings, gentamicin-coated intramedullary nails, and calcium sulphate-based coatings or carriers. Emphasis was placed on clinically relevant infection outcomes, with greater interpretive weight given to studies with prospective design, clear comparators, longer follow-up, lower risk of bias, and more directly applicable clinical populations.

Although some intervention categories, particularly DAC hydrogel coatings and silver-coated megaprostheses, appeared repeatedly across the included studies, quantitative pooling was not considered methodologically appropriate. The studies differed substantially in clinical indication, including primary arthroplasty, revision arthroplasty, tumour megaprosthesis reconstruction, infected revision cases, trauma fixation, and second-stage reimplantation. They also differed in comparator type, follow-up duration, infection definitions, surgical protocols, antibiotic-loading strategies, coating technologies, and baseline patient risk. Several studies used historical or non-randomised controls, while others involved matched cohorts or randomised designs. Pooling these data could therefore produce a misleading summary estimate and obscure clinically important differences between prevention, revision, and infection-treatment contexts. For this reason, a structured narrative synthesis was used.

Certainty of Evidence

Certainty of evidence was assessed narratively using key certainty considerations, including study design, risk of bias, consistency of findings, directness of evidence, precision of estimates, and applicability to implant category and clinical indication. A formal quantitative GRADE summary was not performed because of substantial heterogeneity in study design, implant type, antimicrobial technology, comparator, indication, follow-up duration, and outcome definition. Instead, certainty was considered across intervention categories to support cautious interpretation of the findings.

Result

Overview of Included Studies

A total of 20 studies published between 2015 and 2025 were included in this systematic review. The studies were conducted across the United Kingdom, Japan, Italy, Germany, India, the United States, and multicentre European settings, reflecting a predominantly orthopaedic evidence base. Most studies were observational, including retrospective matched case-control studies, comparative cohort studies, retrospective comparative studies, and matched cohort studies. Two studies used randomised prospective designs. The included studies evaluated antimicrobial biomaterials in tumour endoprostheses, megaprostheses, hip and knee arthroplasty implants, cementless revision femoral stems, internal fixation devices, and intramedullary tibial nails.

The antimicrobial strategies investigated included silver-coated implants, iodine-coated implants, antibiotic-loaded DAC hydrogel coatings, gentamicin-coated intramedullary nails, antibiotic-loaded calcium sulphate beads, and point-of-care calcium sulphate coatings. Comparators were mainly uncoated, titanium, conventional, or standard-care implants. Outcome measures focused on clinically relevant infection-related endpoints, including surgical site infection, periprosthetic joint infection, reinfection, implant survival, infection-free survival, implant retention, amputation, bone union, osseointegration, adverse events, and wound complications. None of the included studies directly quantified biofilm biomass, biofilm architecture, or surface-level biofilm maturation. Therefore, the infection-related outcomes reported in this review should be interpreted as downstream clinical indicators of biofilm-associated implant infection rather than direct microbiological measures of biofilm formation or suppression.

Overall, most studies reported favourable infection-related outcomes with antimicrobial coatings or local antimicrobial biomaterial strategies, although the consistency and strength of evidence varied by coating type, implant category, clinical indication, study design, and risk of bias. Table 2 summarises the characteristics of the included studies.

Table 2: Characteristics of Included studies

Study ID	Country (Study setting)	Study design	Implant type (Clinical indication)	Sample size (Population characteristics)	Antimicrobial biomaterial/coating type	Comparator	Target microorganisms	Follow-up duration	Outcome measures	Adverse events	Main findings
Wafa et al. (2015) [25]	United Kingdom (Royal Orthopaedic Hospital oncology service)	Retrospective matched case-control study	Custom tumour endoprostheses (High-risk tumour endoprosthetic reconstruction, including primary reconstruction and revision procedures)	170 (85 silver-coated Agluna implants matched with 85 uncoated controls; adults ≥18 years; mean age) 42.2 years; 106 males and 64 females	Agluna silver-treated/silver-enhanced tumour endoprosthesis	Identical uncoated tumour prosthesis	Culture isolates included coagulase-negative staphylococci, S. aureus, streptococci, Enterococcus faecalis, Pseudomonas aeruginosa, Enterobacter cloacae, E. coli, Proteus mirabilis, and others	Minimum 12 months	Postoperative infection, chronic infection, infection control after revision, implant retention	Silver exposure stated below no-observed-adverse-effect level; no specific toxicity signal reported	Infection was lower with silver-coated implants: 11.8% versus 22.4%; chronic infection was also lower in the silver group
Shirai et al. (2016) [26]	Japan (Orthopaedic oncology centres in Japan)	Comparative clinical cohort study	Frozen autograft reconstruction with metallic implants (Malignant bone tumours requiring reconstruction after tumour)	100 (62 patients with non-coated implants and 38 patients with iodine-coated implants; mean age 31.9 years in non-coated group and 29.8 years in iodine group)	Iodine-coated implants combined with frozen autograft	Frozen autograft with non-coated implants	Not pathogen-specific; study focused on deep postoperative infection	Mean 79.1 months in non-coated assessed survivors; mean 32.1 months in iodine group	Frozen bone survival, deep infection, fracture, local recurrence, bone absorption, MSTS function	No iodine-specific toxicity was highlighted in the extracted text	Deep infection was 16.1% in non-coated group and 2.6% in iodine-coated group; complication rate was lower in iodine group
Donati et al. (2016) [27]	Italy (Catholic University of the Sacred Heart, Rome)	Retrospective comparative cohort study	Hip megaprosthesis / hip hemiarthroplasty (Primary or metastatic proximal femur tumours treated with limb salvage surgery)	68 (38 silver-coated hip megaprostheses and 30 uncoated titanium megaprostheses; oncological) patients undergoing wide resection and reconstruction	Silver-coated hip megaprosthesis	Uncoated titanium megaprosthesis	Broad antibacterial silver activity; no specific target pathogen table extracted	Average 46.5 months	Early/late infection, complications, silver toxicity, coating degradation	No local or systemic silver toxicity; SEM showed coating degradation in explanted prostheses	Silver-coated hip prostheses showed lower early infection than uncoated implants, but coating wear suggested possible reduction of long-term antimicrobial activity

Study ID	Country (Study setting)	Study design	Implant type (Clinical indication)	Sample size (Population characteristics)	Antimicrobial biomaterial/coating type	Comparator	Target microorganisms	Follow-up duration	Outcome measures	Adverse events	Main findings
Romanò et al. (2016) [28]	Multicentre Europe (Six European orthopaedic centres)	Multicentre randomized prospective clinical study	Cementless or hybrid hip/knee prostheses (Primary or revision total hip or knee replacement)	373 analysed (189 treated with antibiotic-loaded DAC coating and 184 controls; primary arthroplasty and revision) arthroplasty patients)	Fast-resorbable antibiotic-loaded DAC hydrogel coating	Same implant without DAC coating	Not pathogen-specific; coating loaded with local antibiotics selected by centre	Mean 14.5 ± 5.5 months	Early SSI, wound healing, clinical scores, radiographic osteointegration, adverse effects	No local/systemic side effects; no interference with osteointegration	Early SSI was 0.6% with DAC versus 6% in controls; coating appeared safe in hip/knee arthroplasty
Malizos et al. (2017) [29]	Multicentre Europe (Five European orthopaedic centres)	Multicentre randomized controlled prospective trial	Internal fixation implants for osteosynthesis (Closed fractures requiring internal osteosynthesis)	253 analysed (126 treated with antibiotic-loaded DAC coating and 127 controls; adult fracture patients)	Fast-resorbable antibiotic-loaded DAC hydrogel coating for osteosynthesis implants	Internal fixation without coating	Not pathogen-specific; antibiotic options included gentamicin, vancomycin, daptomycin, meropenem, rifampicin, and ciprofloxacin	Mean 18.1 ± 4.5 months	SSI, wound healing, SF-12, laboratory tests, radiographic bone healing, delayed union, adverse effects	No DAC-related local or systemic adverse events; no detectable interference with bone healing	SSI occurred in 0 treated patients versus 6 controls; delayed union was not increased
Hardes et al. (2017) [30]	Germany (Münster University Hospital)	Comparative cohort study	Proximal tibial megaprosthesis (Sarcoma or giant-cell tumour of proximal tibia)	98 (56 silver-coated MUTARS prostheses and 42 titanium prostheses; median age 19 years in silver group and 16 years in titanium group)	Silver-coated MUTARS proximal tibial megaprosthesis	Titanium proximal tibial megaprosthesis	Broad silver antibacterial activity; infection organisms not fully detailed in extracted abstract	Median 38 months silver group; 128 months titanium group	Infection rate, 5-year prosthesis survival, amputation, infection treatment intensity	No major coating-specific toxicity signal reported in extracted data	Infection was 8.9% in silver group versus 16.7% in titanium group; fewer amputations occurred in infected silver-coated cases
Zajonz et al. (2017) [31]	Germany (University Hospital Leipzig)	Retrospective pilot comparative study	Modular megaendoprosthesis of lower limb (Salvage revision arthroplasty after cured bone/peri-implant infection with extensive bone loss)	34 (20 silver-coated MUTARS implants and 14 non-silver coated implants; hip or knee megaendoprosthesis patients after previous infection)	Silver-coated modular MUTARS megaendoprosthesis	Non-silver coated modular megaendoprosthesis	Reinfection after previous infection; exact organisms not central in abstract	Median 72 months, range 6–267 months	Reinfection rate, time to reinfection, mobility using New Mobility Score	No specific silver toxicity reported in abstract	Reinfection was 40% in silver group versus 57% in non-silver group; difference was not statistically significant

Study ID	Country (Study setting)	Study design	Implant type (Clinical indication)	Sample size (Population characteristics)	Antimicrobial biomaterial/coating type	Comparator	Target microorganisms	Follow-up duration	Outcome measures	Adverse events	Main findings
Capuano et al. (2018) [32]	Italy (Two orthopaedic centres)	Two-centre case-control study	Hip or knee revision prostheses (Periprosthetic joint infection treated by revision arthroplasty)	44 (22 one-stage revision patients with DAC-coated implants matched with 22 two-stage revision controls without coating)	Antibiotic-loaded DAC hydrogel coating in one-stage revision	Two-stage revision without DAC coating	Isolates included MSSA, MRSA, MSSE, MRSE, multiple staphylococci, streptococci, P. acnes, E. faecalis, E. coli, P. aeruginosa, Klebsiella pneumoniae, A. baumannii	Mean 29.3 ± 5.0 months DAC group; 29.2 ± 4.9 months control	Infection recurrence, hospital stay, systemic antibiotic duration, HHS/KSS/SF-12, radiographic signs	No adverse events associated with DAC	Infection recurrence was similar: 9.1% one-stage DAC versus 13.6% two-stage control; DAC group had shorter hospital stay and antibiotic duration
Parry et al. (2019) [33]	United Kingdom(Royal Orthopaedic Hospital oncology service)	Retrospective single-centre cohort study	Endoprosthetic replacement for extremity bone tumours (Primary extremity bone tumour reconstruction)	394 (89 silver-coated Agluna EPRs and 305 non-silver EPRs; mean age 29.9 years in silver group and 33.8 years in non-silver group)	Silver-coated Agluna endoprosthetic replacement	Conventional non-silver EPR	Periprosthetic infection organisms not extracted in table form; study focused on infection requiring revision	Mean 55.2 months silver group; 54.9 months non-silver group	PJI requiring revision, implant survival, treatment of infection, amputation	No clear silver-specific adverse signal reported in extracted abstract	Infection requiring revision was 12.4% in silver group and 7.5% in non-silver group; silver was used in higher-risk patients and achieved similar infection-free survival
Pinto et al. (2019) [34]	India (Kasturba Medical College, Mangalore)	Comparative clinical study with alternate allocation	Intramedullary interlocking tibial nail (Gustilo type I and II open tibia fractures)	28 (14 gentamicin-coated nails and 14 regular IMIL nails; open tibial shaft fracture patients)	Gentamicin-coated intramedullary interlocking nail	Regular IMIL nail	Open-fracture infection prevention; specific isolates not reported in abstract	6 months	Infection, ESR, CRP, haemoglobin, bone union	No specific coating-related adverse events reported in abstract	Infection occurred in 4 controls and 0 gentamicin-coated nail patients; bone healing was better in coated group at 6 months

Study ID	Country (Study setting)	Study design	Implant type (Clinical indication)	Sample size (Population characteristics)	Antimicrobial biomaterial/coating type	Comparator	Target microorganisms	Follow-up duration	Outcome measures	Adverse events	Main findings
Zagra et al. (2019) [35]	Italy (IRCCS San Raffaele / orthopaedic revision setting)	Retrospective matched case-control study	Cementless revision hip prostheses (Delayed or late periprosthetic hip infection treated with two-stage revision)	54 (27 DAC-coated cementless two-stage revisions and 27 matched uncoated two-stage revisions)	Antibiotic-loaded DAC hydrogel on cementless revision hip implants	Two-stage cementless revision without coating	Staphylococci, MRSA, streptococci, gram-negative cocci, anaerobes, and culture-negative cases	Mean 2.7 years, range 2.1–3.5 years	Infection recurrence, HHS, hospital stay, implant loosening, adverse events	No local/systemic adverse events attributable to DAC	No infection recurrence in DAC group versus 4 recurrences in controls; no loosening or coating-related adverse event
Streitbuerger et al. (2019) [36]	Germany (Orthopaedic oncology centre)	Comparative cohort study	Proximal femoral megaprosthesis (Proximal femur sarcoma reconstruction)	99 (64 silver-coated proximal femoral megaprostheses and 35 titanium megaprostheses)	Silver-coated proximal femoral megaprosthesis	Titanium proximal femoral megaprosthesis	Broad silver antibacterial effect; specific organisms not detailed in abstract	Median 34.5 months silver group; 96 months titanium group	Infection rate, infection-free survival, amputation, two-stage exchange	No specific silver toxicity signal reported in abstract	Overall infection rate was 10.9% in silver group and 20% in titanium group; silver group required fewer two-stage exchanges
De Meo et al. (2020) [37]	Italy (Umberto I University Hospital, Rome)	Retrospective matched case-control study	Cementless revision hip prostheses (Aseptic hip revision surgery / conversion arthroplasty)	34 (17 antibiotic-loaded hydrogel patients matched 1:1 with 17 controls; high-risk hip revision patients)	Antibiotic-loaded hydrogel coating on cementless revision hip implants	Cementless revision hip implants without coating	Infections in controls included MRSA, Klebsiella pneumoniae, E. faecalis, E. coli, MSSA, and culture-negative cases	Minimum 6 months	PJI, adverse effects, osseointegration, functional recovery	No side effects in ALH group; no significant interference with osseointegration or function	No PJIs occurred in ALH group versus 6 in controls
Sambri et al. (2020) [38]	Italy (Orthopaedic oncology/revision setting)	Retrospective comparative study	Distal femur or proximal tibia tumour endoprostheses (Two-stage revision for infected tumour prostheses)	68 (29 PorAg silver-coated prostheses and 39 uncoated prostheses; median age 30 years; all had MSIS-confirmed PJI)	Silver PorAg endoprosthesis	Uncoated Megasystem C prosthesis	PJI confirmed by MSIS criteria; 10 cases had no microorganism identified but had sinus communicating with prosthesis	3-year follow-up estimate	Reinfection, infection eradication, amputation after reinfection	Full-text adverse-event details unavailable	Reinfection was estimated at 10.3% in PorAg group versus 17.5% in uncoated group; amputation among reinfected patients

Study ID	Country (Study setting)	Study design	Implant type (Clinical indication)	Sample size (Population characteristics)	Antimicrobial biomaterial/coating type	Comparator	Target microorganisms	Follow-up duration	Outcome measures	Adverse events	Main findings
							(ResearchGate)				was lower in silver group
Greco et al. (2021) [39]	Italy (Emergency-urgency orthopaedic department)	Single-centre retrospective comparative study	Tibial intramedullary nail (Open diaphyseal tibial fracture)	46 (23 standard uncoated nails and 23 gentamicin-coated ETN PROtect nails; minimum 18-month follow-up)	Gentamicin-coated ETN PROtect tibial nail	Standard uncoated tibial nail	Open-fracture infection prevention; specific isolates not reported in abstract	Minimum 18 months	Infection, bone union, reoperation, time to nailing, safety	No adverse events recorded with antibiotic-coated nails	No deep infection occurred in antibiotic-coated nail group; superficial infections occurred in both groups
Zoccali et al. (2021) [40]	Italy (Three Italian orthopaedic-oncology centres)	Three-centre matched case-control study	Joint megaprosthesis (Bone tumour, severe trauma, or infection requiring mega-prosthetic reconstruction)	86 (43 DAC-coated megaprostheses matched with 43 uncoated mega-implants; 39 oncological and 4 non-oncological cases in DAC group)	Fast-resorbable antibiotic-loaded DAC hydrogel coating on megaprosthesis	Matched uncoated mega-implants	Not pathogen-specific; SSI/PJI prevention	Mean 2 years	Early post-surgical infection, complications, adverse events, radiographic follow-up	No infection or adverse events in DAC group	DAC group had 0 infections versus 6 infections in controls
Sacchetti et al. (2022) [41]	Italy / Switzerland (Pisa, Florence, and Lausanne orthopaedic departments)	Multicentre retrospective comparative study	Lower-limb modular megaprostheses (Non-neoplastic or post-oncological reconstruction)	142 (38 silver-coated PorAg megaprostheses and 104 conventional titanium megaprostheses; mean age 61 years)	Silver-coated PorAg lower-limb megaprosthesis	Conventional titanium megaprosthesis	Prosthesis-related infection; MSIS-based diagnosis	Mean 55 months, range 24–216 months	Infection-free survival, prosthesis failure due to infection	No clear silver-specific adverse-event signal in extracted text	Silver coating did not significantly reduce infection failure risk; HR 0.72, 95% CI 0.26–2.05

Study ID	Country (Study setting)	Study design	Implant type (Clinical indication)	Sample size (Population characteristics)	Antimicrobial biomaterial/coating type	Comparator	Target microorganisms	Follow-up duration	Outcome measures	Adverse events	Main findings
De Meo et al. (2023) [42]	Italy (Policlinico Umberto I Hospital, Rome)	Retrospective single-centre preliminary comparative study	Retained hip, knee, or shoulder prostheses (Acute periprosthetic joint infection treated with DAIR-based procedures)	16 (9 DACRI patients with antibiotic-loaded hydrogel and 7 DAPRI patients with calcium sulphate beads; mean age 67.3 years)	Antibiotic-loaded hydrogel in DACRI procedure	Antibiotic-loaded calcium sulphate beads in DAPRI procedure	S. aureus, CoNS, E. coli, P. aeruginosa, A. baumannii, Candida albicans, polymicrobial and culture-negative PJI	Mean 26.1 ± 22.2 months; DACRI follow-up longer than DAPRI	Infection control, septic revision, CRP, follow-up, safety	One DACRI failure in Candida albicans knee PJI; no major safety signal reported	Infection control achieved in 93.75%; no significant difference between DACRI and DAPRI
McPherson et al. (2024) [43]	United States (Single-surgeon revision THA practice)	Retrospective matched cohort study	Cementless revision femoral stems (Aseptic revision THA and second-stage reimplantation THA)	215 (111 antibiotic-loaded calcium sulphate-coated stems compared with 104 matched historical controls)	Point-of-care antibiotic-loaded calcium sulphate coating on cementless revision femoral stems	Matched uncoated historical revision stems	Post-infection isolates included S. epidermidis, MRSA, Enterococcus, S. hominis, VRE, S. aureus, Klebsiella pneumoniae, and others	Minimum 3 years; mean follow-up around 57 months in study group	PJI after aseptic revision, PJI after second-stage reimplantation, aseptic stem loosening	No aseptic stem loosening; no systemic toxicity signal from modest calcium sulphate volume	Coating reduced PJI in second-stage reimplantation, 4.8% versus 23.3%, but not in aseptic revision
Ding et al. (2025) [44]	Italy / Singapore affiliation (IRCCS Istituto Ortopedico Galeazzi, Milan)	Retrospective 1:1 matched cohort study	Cementless hip arthroplasty implants (High-risk primary THA, revision THA, and second-stage revision THA for PJI)	238 (119 DAC-coated cementless implants matched with 119 uncoated controls; mean age 68.3 years)	Antibiotic-impregnated DAC hydrogel coating on cementless hip implants	Matched cementless hip implants without DAC	Not pathogen-specific; focus on PJI and recurrent PJI	Mean 3.2 years DAC group; 4.2 years control	Complications requiring surgery, PJI, recurrent PJI, delayed wound healing, aseptic loosening	No local/systemic side effects related to DAC	DAC was associated with fewer overall complications and lower recurrent PJI in second-stage revision THA; aseptic loosening was lower in DAC group

[DAC = Defensive Antibacterial Coating; THA = Total Hip Arthroplasty; PJI = Periprosthetic Joint Infection; EPR = Endoprosthetic Replacement; IMIL = Intramedullary Interlocking; MUTARS = Modular Universal Tumor and Revision System; MSIS = Musculoskeletal Infection Society; DAIR = Debridement, Antibiotics, and Implant Retention; ALH = Antibiotic-Loaded Hydrogel; DACRI = Debridement, Antibiotic Coating, and Retention of the Implant; DAPRI = Debridement, Antibiotic Pearls, and Retention of the Implant; CS = Calcium Sulphate; SSI = Surgical Site Infection; CRP = C-Reactive Protein; ESR = Erythrocyte Sedimentation Rate; SEM = Scanning Electron Microscopy; MSTS = Musculoskeletal Tumor Society score; HHS = Harris Hip Score; KSS = Knee Society Score; SF-12 = 12-item Short Form Health Survey; MSSA = Methicillin-Sensitive Staphylococcus aureus; MRSA = Methicillin-Resistant Staphylococcus aureus; MSSE = Methicillin-Sensitive Staphylococcus epidermidis; MRSE = Methicillin-Resistant Staphylococcus epidermidis; CoNS = Coagulase-Negative Staphylococci; VRE = Vancomycin-Resistant Enterococci]

Quality Appraisal of Included Studies

The 20 included studies were appraised using ROBINS-I for non-randomised studies and RoB 2 for randomised trials. Overall, the evidence base was mixed. Six studies were judged as having moderate risk of bias, two randomised studies were judged as having some concerns, and the remaining studies were judged as having serious or serious/limited-information risk of bias. The main sources of bias were retrospective study design, non-randomised treatment allocation, historical controls, small sample sizes, uneven follow-up durations, predictable allocation in one study, and confounding by indication or clinical judgement.

The randomised DAC hydrogel studies provided comparatively stronger evidence because of their prospective design, although open-label intervention, centre-level antibiotic discretion, incomplete blinding, and unclear allocation-concealment details introduced some concerns [28, 29]. In contrast, most silver-coated implant, iodine-coated implant, gentamicin-coated nail, and calcium sulphate-based studies were observational and therefore more vulnerable to selection bias, temporal confounding, and baseline risk differences [25-27, 30-44]. The quality appraisal was not used to exclude studies automatically, but it informed the interpretation of evidence strength, reliability, and clinical applicability. Table 3 presents the quality appraisal of the included studies.

Table 3: Quality Appraisal

Study ID	Tool used	Overall quality / risk-of-bias judgement	Main basis for judgement
Wafa et al. (2015) [25]	ROBINS-I	Moderate risk of bias	Matched case-control design reduced some selection imbalance, but treatment allocation was non-random and partly based on perceived infection risk; historical and clinical confounding remained possible.
Shirai et al. (2016) [26]	ROBINS-I	Serious risk of bias	Comparative non-randomized design with unequal follow-up periods, different survival/loss-to-follow-up patterns, and historical group differences created meaningful confounding risk.
Donati et al. (2016) [27]	ROBINS-I	Serious risk of bias	Silver use depended on technical availability and clinical judgement; retrospective design, small cohort, and possible selection-by-risk limited causal certainty.
Romanò et al. (2016) [28]	RoB 2	Some concerns	Randomized prospective design strengthened the evidence, but open-label intervention, centre-level antibiotic discretion, and incomplete blinding raised some concerns despite objective infection outcomes.
Malizos et al. (2017) [29]	RoB 2	Some concerns	Multicentre randomized design and CONSORT-style reporting strengthened reliability; however, blinding/allocation concealment details were not fully clear, and intervention visibility may have influenced co-interventions.
Hardes et al. (2017) [30]	ROBINS-I	Serious risk of bias	Silver and titanium cohorts were treated in different time periods with unequal follow-up, producing temporal and confounding risk despite clear outcome reporting.
Zajonz et al. (2017) [31]	ROBINS-I	Serious risk of bias	Small retrospective pilot design, highly selected salvage population, and baseline complexity limited causal interpretation.
Capuano et al. (2018) [32]	ROBINS-I	Serious risk of bias	Intervention and comparator differed by both coating status and surgical strategy, one-stage versus two-stage revision, making confounding by treatment pathway substantial.
Parry et al. (2019) [33]	ROBINS-I	Serious risk of bias	A large cohort, but silver implants were used in higher-risk patients; treatment allocation was non-random and indication bias was likely.

Study ID	Tool used	Overall quality / risk-of-bias judgement	Main basis for judgement
Pinto et al. (2019) [34]	ROBINS-I	Serious risk of bias	Alternate allocation was predictable and not true randomization; small sample size and limited blinding increased selection and performance bias.
Zagra et al. (2019) [35]	ROBINS-I	Moderate risk of bias	Matched case-control design and comparable two-stage procedures improved interpretability, but coating availability rather than randomization determined treatment.
Streitbuerger et al. (2019) [36]	ROBINS-I	Serious risk of bias	Historical comparison, unequal follow-up, and non-random allocation created serious confounding risk despite a relatively large sarcoma cohort.
De Meo et al. (2020) [37]	ROBINS-I	Moderate risk of bias	Propensity matching improved comparability, but retrospective single-centre design and small sample size limited precision.
Sambri et al. (2020) [38]	ROBINS-I	Serious / limited-information risk of bias	Retrospective comparative design; full-text PDF was unavailable, so several ROBINS-I domains could not be fully assessed beyond abstract and metadata.
Greco et al. (2021)	ROBINS-I	Serious risk of bias	Retrospective single-centre design, small groups, and baseline fracture-severity differences limited comparability.
Greco et al. (2021) [39]	ROBINS-I	Moderate risk of bias	Matched multicentre case-control design improved balance, but retrospective control selection and non-random intervention assignment remained limitations.
Zoccali et al. (2021) [40]	ROBINS-I	Moderate risk of bias	Matched multicentre case-control design improved baseline comparability, but retrospective control selection and non-random intervention assignment left potential residual confounding.
Sacchetti et al. (2022) [41]	ROBINS-I	Serious risk of bias	Multicentre retrospective cohort with mixed indications and non-random silver use; confounding by indication and reconstruction type likely.
De Meo et al. (2023) [42]	ROBINS-I	Serious risk of bias	Very small pilot sample and markedly different follow-up durations between groups limited comparative inference.
McPherson et al. (2024) [43]	ROBINS-I	Serious risk of bias	Matched historical cohort and single-surgeon consistency were strengths, but historical comparison and non-random treatment assignment created temporal confounding risk.
Ding et al. (2025) [44]	ROBINS-I	Moderate risk of bias	1:1 matching and registry-based data improved reliability, but unequal follow-up and mixed indications across primary/revision/PJI procedures created residual confounding.

[RoB 2 = Revised Cochrane Risk of Bias Tool for Randomized Trials; ROBINS-I = Risk Of Bias In Non-randomized Studies of Interventions; RCT = Randomized Controlled Trial; PJI = Periprosthetic Joint Infection]

Overall Certainty of Evidence

The overall certainty of evidence varied across intervention categories. Certainty was highest for DAC hydrogel coatings because this category included two randomised prospective studies [28, 29] and several matched clinical studies. Evidence for silver-coated megaprostheses was broader but less certain because most studies were retrospective, observational, and affected by indication bias, historical comparisons, and heterogeneous patient risk. Evidence for iodine-coated implants was limited to one eligible clinical study [26]. Evidence for gentamicin-coated intramedullary nails and calcium sulphate-based strategies was promising but based on fewer studies and narrower clinical contexts [34, 39, 42, 43]. Evidence for non-orthopaedic implants was insufficient because the included human

clinical studies were overwhelmingly concentrated in orthopaedic applications.

Table 4: Overall Certainty of Evidence by Intervention Category

Intervention category	Included studies	Overall certainty	Basis for judgement
DAC hydrogel coatings	Romanò et al. (2016) [28], Malizos et al. (2017) [29], Capuano et al. (2018) [32], Zagra et al. (2019) [35], De Meo et al. (2020) [37], Zoccali et al. (2021) [40], De Meo et al. (2023) [42], Ding et al. (2025) [44]	Moderate	Most consistent clinical signal; includes randomised prospective studies, but some studies remain retrospective or have residual confounding.
Silver-coated megaprostheses	Wafa et al. (2015) [25], Donati et al. (2016) [27], Hardes et al. (2017) [30], Zajonz et al. (2017) [31], Parry et al. (2019) [33], Streitbuerger et al. (2019) [36], Sambri et al. (2020) [38], Sacchetti et al. (2022) [41]	Low to moderate	Multiple clinical studies, but mostly observational, heterogeneous, and affected by historical controls or indication bias.
Iodine-coated implants	Shirai et al. (2016) [26]	Low	Promising signal, but represented by one eligible comparative clinical study.
Gentamicin-coated intramedullary nails	Pinto et al. (2019) [34], Greco et al. (2021) [39]	Low	Encouraging trauma-specific findings, but based on small non-randomised studies.
Calcium sulphate-based coatings/carriers	De Meo et al. (2023) [42], McPherson et al. (2024) [43]	Low	Context-specific evidence in DAIR-type procedures and second-stage reimplantation; limited number of studies.
Non-orthopaedic implants	Not meaningfully represented	Very low / insufficient	Available included evidence was concentrated in orthopaedic implants, limiting generalisability beyond this context.

Narrative Synthesis

Overview of the Evidence Pattern

The narrative synthesis was organised around the clinical logic that antimicrobial biomaterials do not operate as a single uniform intervention. Rather, they represent a family of surface-based and local-delivery strategies intended to reduce the risk of microbial attachment, biofilm-associated infection, revision surgery, and other infection-related complications. Across the 20 included studies, the evidence was concentrated in orthopaedic implant settings, particularly tumour endoprostheses, megaprostheses, hip and knee arthroplasty, osteosynthesis implants, and intramedullary tibial nails.

This concentration is important because orthopaedic implants provide a useful clinical model for evaluating antimicrobial biomaterials, but it also shows that the human clinical evidence remains narrower than the broader experimental biomaterials literature. None of the included studies directly measured biofilm biomass or biofilm architecture. Instead, they used clinically meaningful infection outcomes such as periprosthetic joint infection, surgical site infection, reinfection, implant retention, infection-free survival, delayed wound healing, and need for further surgery. Therefore, this synthesis should be read as a clinical synthesis of biofilm-associated implant infection outcomes rather than as a direct microbiological synthesis of biofilm quantification.

The included studies clustered into six major intervention families: silver-coated megaprostheses, iodine-coated implants, antibiotic-loaded hydrogel coatings, gentamicin-coated intramedullary nails, antibiotic-loaded calcium sulphate coatings or carriers, and comparative local antibiotic carrier strategies. These themes differed not only by material type but also by clinical intention. Some coatings were used primarily to prevent infection in high-risk implantation, while others were used in revision settings where residual microbial contamination or previous biofilm-associated disease was already a concern. Across categories, antimicrobial biomaterials appeared most clinically relevant when used in biologically vulnerable or contamination-prone settings, such as tumour megaprostheses, second-stage reimplantation, revision arthroplasty, and open fracture fixation.

Metallic Antimicrobial Surfaces: Silver-Coated Megaprostheses

The largest thematic body of evidence concerned silver-coated megaprostheses and tumour endoprostheses. The clinical rationale was consistent across these studies: megaprostheses provide large foreign-body surfaces, are often implanted in compromised soft-tissue beds, and are frequently used in oncological or revision contexts where infection risk is already high. Wafa et al. (2015) [25] reported lower postoperative infection rates with silver-treated implants compared with identical uncoated implants in high-risk tumour endoprosthetic reconstruction. Donati et al. (2016) [27], Hardes et al. (2017) [30], and Streitbuerger et al. (2019) [36] also reported lower infection rates or favourable infection-related outcomes among patients receiving silver-coated megaprostheses.

However, the findings were not uniform across all silver-coating studies. Zajonz et al. (2017) [31] reported a numerical reduction in reinfection after salvage revision arthroplasty, but the difference was not statistically significant. Parry et al. (2019) [33] found that silver-coated implants were frequently used in higher-risk patients and produced infection-free survival that was not clearly superior to uncoated implants. Sambri et al. (2020) [38] suggested a possible reduction in reinfection after two-stage revision of infected tumour prostheses, but the available evidence remained limited. Sacchetti et al. (2022) [41] did not find a statistically significant reduction in infection-related prosthesis failure with silver-coated megaprostheses.

Taken together, silver-coated megaprostheses showed promise in selected high-risk oncological and revision settings, but the evidence should be interpreted cautiously because the studies were mainly retrospective, non-randomised, and affected by heterogeneous indications, patient risk profiles, implant types, follow-up durations, and comparator selection. The findings suggest possible clinical benefit in selected high-risk orthopaedic reconstruction rather than definitive effectiveness across all implant categories.

Iodine-Coated Implants and the Surface-Antiseptic Model

The iodine-coated implant evidence was represented by Shirai et al. (2016) [26], which compared frozen autograft reconstruction with iodine-coated implants against non-coated implants in malignant bone tumour surgery. The study reported lower deep infection in the iodine-coated group, together with lower overall complication rates and favourable functional outcomes.

Although this finding supports the potential value of antimicrobial surface engineering in biologically vulnerable oncological reconstruction, the evidence remains limited because only one eligible study evaluated this strategy. The iodine-coated implant evidence should therefore be regarded as promising but preliminary, requiring further clinical validation in larger prospective studies and broader implant settings.

Antibiotic-Loaded Hydrogel Coatings: The Strongest and Most Consistent Clinical Signal

Antibiotic-loaded DAC hydrogel coatings produced the most consistent positive clinical signal across the included studies. Romanò et al. (2016) [28] evaluated DAC coating in hip and knee arthroplasty and reported reduced early surgical site infection without detectable local or systemic adverse effects or interference with osteointegration. Malizos et al. (2017) [29] extended this evidence to internal osteosynthesis and reported no surgical site infections in the DAC group compared with infections in the control group, without detectable impairment of bone healing.

Matched and observational studies also reported favourable outcomes with DAC hydrogel coatings in revision and high-risk arthroplasty settings. Capuano et al. (2018) [32] found similar infection recurrence between one-stage revision with DAC-coated implants and two-stage revision without coating, with shorter hospital stay and systemic antibiotic duration in the DAC group. Zagra et al. (2019) [35] reported no infection recurrence in DAC-coated cementless two-stage hip revision compared with recurrences in the uncoated control group. De Meo et al. (2020) [37] reported no periprosthetic joint infections in patients receiving antibiotic-loaded hydrogel during aseptic hip revision compared with infections in controls. Zoccali et al. (2021) [40] found no infections in DAC-coated megaprostheses compared with infections

in matched uncoated controls. Ding et al. (2025) [44] reported fewer overall complications and lower recurrent PJI in selected second-stage revision THA patients receiving DAC-coated cementless implants.

Overall, DAC hydrogel coatings demonstrated the strongest and most consistent evidence among the included intervention categories. However, even in this category, conclusions should remain cautious because several supporting studies were observational or matched cohorts rather than fully blinded randomised trials. The available evidence most strongly supports DAC hydrogel coatings as a promising adjunct in selected orthopaedic settings, particularly high-risk arthroplasty, revision arthroplasty, osteosynthesis, and megaprosthesis reconstruction.

Antimicrobial Coatings in Established PJI and DAIR-Type Procedures

Some studies evaluated antimicrobial biomaterials in the context of established periprosthetic joint infection or revision surgery rather than primary infection prevention. Capuano et al. (2018) [32] compared one-stage exchange using DAC-coated implants with two-stage revision without coating and found similar infection recurrence, with shorter hospital stay and reduced antibiotic duration in the DAC group. Zagra et al. (2019) [35] and Ding et al. (2025) [44] also reported favourable infection-related outcomes when DAC coating was used in revision or second-stage reimplantation settings.

De Meo et al. (2023) [42] compared antibiotic-loaded hydrogel coating with antibiotic-loaded calcium sulphate beads in retention-based procedures for acute PJI and reported high overall infection control, although the sample size was very small and follow-up differed between groups. These findings suggest that local antimicrobial biomaterials may be useful as part of broader surgical infection-control pathways, including debridement, systemic antibiotics, implant retention or revision, and structured follow-up. However, the evidence remains limited and should not be interpreted as proof that local coatings alone can control established implant infection.

Gentamicin-Coated Intramedullary Nails and Local Antibiotic Protection in Trauma

Two studies evaluated gentamicin-coated intramedullary nails in open tibial fractures. Pinto et al. (2019) [34] reported no infections in patients treated with gentamicin-coated intramedullary interlocking nails compared with infections in controls, alongside favourable bone-healing findings at six months. Greco et al. (2021) [39] similarly reported no deep infections in the antibiotic-coated nail group and no adverse events associated with the coating.

These findings are encouraging for trauma fixation, where infection risk is driven by contamination, soft-tissue injury, and the need for urgent stabilisation. However, the evidence remains preliminary because both studies were small and non-randomised. Gentamicin-coated nails may therefore be considered a promising local prophylactic strategy in selected open-fracture settings, but stronger prospective comparative studies are needed before firm conclusions can be made.

Calcium Sulphate-Based Local Antibiotic Coatings and Carriers

Calcium sulphate-based local antibiotic delivery was evaluated in two studies. De Meo et al. (2023) [42] used antibiotic-loaded calcium sulphate beads as a comparator to antibiotic-loaded hydrogel in DAIR-type procedures, reporting high overall infection control but no clear superiority between strategies. McPherson et al. (2024) [43] evaluated point-of-care antibiotic-loaded calcium sulphate coating on cementless revision femoral stems and found reduced PJI after second-stage reimplantation, but not after aseptic revision.

This distinction suggests that calcium sulphate-based coating or carrier strategies may be most relevant where residual microbial burden is plausible, such as second-stage reimplantation after previous infection. In contrast, their added value may be smaller in aseptic revision settings where baseline infection risk is lower. The evidence remains promising but context-specific, and further comparative research is needed to define the indications, safety profile, and optimal antibiotic-loading approaches for these materials.

Discussion

Main Findings

This systematic review of 20 human clinical studies found that antimicrobial biomaterials and implant surface modification strategies were generally associated with favourable clinical infection outcomes in selected implant settings. The most consistent evidence was observed for antibiotic-loaded hydrogel coatings, particularly DAC-based systems, which were associated with lower surgical site infection, periprosthetic joint infection, reinfection, and overall complication rates in primary arthroplasty, revision arthroplasty, osteosynthesis, megaprosthesis, and

DAIR-related procedures. Silver-coated megaprostheses and iodine-coated implants also showed promise, especially in high-risk oncological reconstruction and revision surgery, although findings were more heterogeneous and largely derived from observational studies. Gentamicin-coated intramedullary nails and calcium sulphate-based local antibiotic strategies appeared beneficial in trauma fixation and second-stage reimplantation contexts, respectively, but the evidence was limited by fewer studies and narrower indications.

Overall, the findings suggest that antimicrobial biomaterials may be most useful when applied in biologically vulnerable or contamination-prone clinical settings, where early microbial attachment or residual microbial burden is more likely. However, the findings should be interpreted cautiously because most included studies were retrospective or non-randomised, several had serious risk of bias, and the evidence was concentrated mainly in orthopaedic implant applications.

Interpretation of Biofilm-Related Outcomes

Biofilm formation provides the biological rationale for antimicrobial implant surfaces, but the included clinical studies did not directly quantify biofilm formation. None of the studies directly measured biofilm biomass, biofilm architecture, surface-level microbial attachment, biofilm density, or molecular markers of biofilm maturation. Instead, the studies reported downstream clinical outcomes such as surgical site infection, periprosthetic joint infection, reinfection, implant retention, infection-free survival, delayed wound healing, and need for revision surgery.

This distinction is important for interpreting the findings. Reductions in clinical infection outcomes may suggest improved control of biofilm-associated implant infection, but they should not be interpreted as direct proof of biofilm suppression. Therefore, this review should be understood as a clinical synthesis of infection-related implant outcomes rather than a direct microbiological synthesis of biofilm formation. This interpretation helps to avoid overstatement and keeps the conclusions proportionate to the available human clinical evidence.

Evidence Strength by Implant Category and Clinical Indication

The strength of evidence varied substantially across implant categories and antimicrobial strategies. DAC hydrogel coatings had the strongest clinical support among the included intervention categories. This was because the evidence included two randomised prospective studies and several matched or comparative clinical studies across arthroplasty, osteosynthesis, revision arthroplasty, megaprosthesis, and DAIR-related settings. Although not all DAC studies were randomised, the direction of findings was relatively consistent, and most studies reported no major coating-related safety concerns or impairment of osseointegration and bone healing.

Silver-coated megaprostheses represented the largest body of evidence but with lower certainty. Several studies reported lower infection or reinfection rates in oncological and high-risk reconstructive settings [25, 30, 36], but others reported non-significant or mixed findings, particularly in salvage, mixed, or highly complex revision populations [31, 33, 41]. This suggests that silver-coated implants may be useful in selected high-risk orthopaedic reconstructions, but their benefit is not uniform and may depend on patient risk, soft-tissue condition, previous infection, anatomical site, coating technology, and follow-up duration.

The evidence for iodine-coated implants was promising but limited because only one eligible study evaluated this strategy [26]. Gentamicin-coated intramedullary nails also showed encouraging trauma-specific findings, but the evidence came from small non-randomised studies [34, 39]. Calcium sulphate-based local antibiotic delivery appeared most relevant in revision or reimplantation contexts where residual microbial burden was plausible, but the included evidence remained limited and context-specific [42, 43]. Evidence for non-orthopaedic implants, including cardiovascular, dental, urological, neurosurgical, and ophthalmic devices, was insufficient within the included clinical studies. Therefore, the conclusions of this review apply most strongly to selected orthopaedic applications and should not be generalised uncritically to all implant categories.

Risk of Bias, Certainty of Evidence, and Interpretation

The quality appraisal has important implications for interpreting findings in this review. Most included studies were observational, retrospective, or non-randomised, and several were judged to have serious risk of bias. Important sources of bias included confounding by indication, non-random treatment allocation, historical controls, small sample sizes, uneven follow-up durations, baseline risk differences, and differences in surgical strategy. These issues were particularly relevant in studies where antimicrobial coatings were preferentially used in higher-risk patients or introduced during later treatment periods.

As a result, many findings should be interpreted as associations rather than definitive evidence of causal effectiveness. The strongest confidence can be placed in the DAC hydrogel evidence

because this category included randomised prospective studies [28, 29]. However, even these studies had some concerns related to blinding, antibiotic discretion, or intervention visibility. For silver, iodine, gentamicin, and calcium sulphate-based strategies, the evidence remains clinically promising but less certain because it is more dependent on observational studies.

The overall certainty of evidence was therefore considered moderate for DAC hydrogel coatings, low to moderate for silver-coated megaprostheses, low for iodine-coated implants, gentamicin-coated nails, and calcium sulphate-based strategies, and very low or insufficient for non-orthopaedic implants. This certainty assessment supports cautious conclusions and reinforces the need for better-designed prospective comparative studies.

Comparison with Existing Literature

The findings of this review align with broader systematic reviews and meta-analyses that have reported potential clinical benefits of antimicrobial implant coatings. Fiore et al. (2021) [45] synthesised evidence on silver-coated megaprostheses and reported reduced infection rates in primary and revision surgeries, while also cautioning about toxicity, patient selection, and the need for careful interpretation. This is consistent with the present review, where silver-coated implants showed promise but produced heterogeneous outcomes across different oncological, revision, and mixed reconstruction settings.

Bulut and colleagues also reported a statistically significant reduction in infection rates among patients treated with silver-coated implants compared with titanium-coated implants [46]. However, the present review adds nuance by showing that the benefit of silver coating may be less clear in mixed non-oncological, post-oncological, salvage, and previously infected populations, where baseline risk and host factors may reduce the apparent effect of the coating alone.

The stronger and more consistent signal observed for antibiotic-loaded hydrogel coatings also aligns with broader biomaterials literature. Wang and colleagues described antibacterial hydrogel coatings as flexible platforms capable of combining bacterial repulsion, contact-killing, and local drug delivery [16]. This mechanistic flexibility helps explain why DAC-type hydrogel coatings appeared clinically useful across several orthopaedic contexts in the present review. Unlike durable metallic coatings, hydrogel systems may be particularly suited to the early postoperative period, when bacterial adhesion competes with host-cell integration at the implant surface.

The current findings are also consistent with Kaspiris et al. (2024) [47], who emphasised that antimicrobial coating success depends on achieving infection control without compromising tissue compatibility. This point is important because the included hydrogel and gentamicin-coated nail studies generally reported no major impairment of wound healing, osseointegration, or bone union [28, 37, 40]. In clinical terms, antimicrobial coatings must not only suppress microbial activity; they must also preserve the biological conditions required for implant integration and tissue repair.

The safety findings also correspond with Li et al. (2023) [48], who noted that clinical safety data on antibacterial coatings remain limited, with argyria and metal-related concerns being particularly relevant for silver coatings. In the present review, no major consistent toxicity signal was identified, but long-term safety monitoring remains important, especially for metallic coatings where ion release, coating degradation, local discolouration, systemic accumulation, allergy, and durability may affect clinical performance over time.

Evidence from other implant fields also supports the interpretation that antimicrobial surface strategies are promising but translationally uneven. Teixeira-Santos et al. [10] showed that chitosan-based antimicrobial coatings demonstrate strong antimicrobial potential, but clinical translation is limited by variation in coating preparation, testing conditions, and outcome measurement. Similarly, Teulé-Trull et al. (2025) [49] identified peptides, synthetic antimicrobial molecules, and metallic nanoparticles as important categories in dental implant coatings, while emphasising that long-term colonisation control and biocompatibility remain unresolved issues. These findings mirror the present review, where the clinical literature was rich in orthopaedic studies but limited for other implant categories.

Finally, broader reviews by Kadirvelu and colleagues and by Akay and Yaghmur reinforce the idea that future antimicrobial implants will likely require multifunctional strategies rather than single-mechanism coatings [2, 9]. Their emphasis on biofilm biology, local drug delivery, surface engineering, and non-antibiotic alternatives is consistent with the present review. However, the present review extends that discussion by focusing specifically on human clinical outcomes, showing that the most relevant clinical questions are not only whether a material can inhibit microbes in laboratory models, but whether it can reduce infection, preserve implant function, prevent revision surgery, and remain safe in real patients.

Relevance of the Study Findings and Implementation for Interventional Purposes

The findings have practical relevance for surgical infection prevention because they support a risk-stratified approach to antimicrobial biomaterial use. In low-risk primary implantation, the additional value of antimicrobial coating may be small and may not justify routine universal use. However, in tumour megaprostheses, open fractures, revision arthroplasty, previously infected implants, DAIR-related procedures, and second-stage reimplantation, local antimicrobial biomaterials may provide useful protection during clinically vulnerable periods.

For interventional purposes, antimicrobial biomaterials should be viewed as adjuncts rather than replacements for established infection-prevention strategies. Their use should be integrated with patient optimisation, aseptic surgical technique, appropriate systemic prophylaxis, careful debridement, appropriate implant selection, wound management, and structured follow-up. Antibiotic-loaded hydrogel coatings may be most relevant where early bacterial adhesion is a major concern. Silver or iodine coatings may be useful where prolonged surface antimicrobial activity is desired. Gentamicin-coated nails may be relevant in contaminated trauma fixation, while calcium sulphate-based carriers may be most useful in revision or reimplantation settings where residual microbial burden is plausible.

This interpretation supports selective implementation in high-risk clinical contexts rather than broad application across all implant procedures. It also highlights the need for local antimicrobial strategies to be aligned with the patient's risk profile, the indication for surgery, the microbial context, the implant type, and the intended mechanism of antimicrobial action.

Generalisability

The generalisability of the findings is limited by the concentration of evidence in orthopaedic implants. Most included studies involved megaprostheses, tumour endoprostheses, hip and knee arthroplasty, osteosynthesis devices, intramedullary nails, and revision femoral stems. These settings are clinically important because they carry substantial infection risk and serious consequences when infection occurs. However, they do not fully represent the range of implantable devices used in cardiovascular medicine, dentistry, neurosurgery, urology, ophthalmology, reconstructive surgery, and other fields.

Therefore, the conclusions should not be extrapolated uncritically beyond orthopaedic applications. Antimicrobial performance may differ across implant categories because of differences in material composition, anatomical location, microbial exposure, tissue environment, host immune response, mechanical stress, fluid flow, device permanence, and follow-up requirements. More clinical evidence is needed before firm conclusions can be made for non-orthopaedic implants.

Strengths and Limitations

A major strength of this review is its focus on human clinical studies rather than relying mainly on in vitro or animal evidence. This makes the findings more directly relevant to clinical decision-making. The review also used a broad clinical-outcome framework that reflected real-world implant infection consequences, including surgical site infection, periprosthetic joint infection, reinfection, infection-free survival, implant retention, adverse events, wound healing, osseointegration, aseptic loosening, and bone union. In addition, the use of ROBINS-I and RoB 2 provided a structured approach to evaluating the reliability of non-randomised and randomised evidence.

Several limitations must also be acknowledged. First, the review protocol was not prospectively registered in PROSPERO or another systematic review registry. This may reduce methodological transparency and increase the possibility that post hoc decisions influenced aspects of the review process. Second, the search was limited to English-language and open-access or full-text articles, which may have introduced language and publication-selection bias. Relevant studies published in other languages, behind paywalls, or outside open-access platforms may therefore have been missed.

Third, most included studies were retrospective or non-randomised, and several had serious risk of bias. This limits causal certainty and means that many findings should be interpreted as associations rather than definitive evidence of effectiveness. Fourth, no included study directly quantified biofilm formation, so infection outcomes were interpreted as downstream clinical indicators of biofilm-associated infection rather than direct proof of biofilm suppression. Fifth, outcome definitions varied across studies, including differences in surgical site infection, periprosthetic joint infection, reinfection, implant retention, and infection-free survival. This limited comparability across studies.

Sixth, heterogeneity in implant types, coating technologies, clinical indications, comparator groups, antibiotic-loading strategies, follow-up durations, and baseline patient risk prevented quantitative pooling. Although some intervention categories, such as DAC hydrogel coatings and silver-coated megaprostheses, appeared repeatedly, pooling these studies could have

produced a misleading summary estimate because the studies addressed different clinical contexts, including prevention, revision, established infection, trauma fixation, and second-stage reimplantation. Finally, the evidence was heavily concentrated in orthopaedic implants, limiting generalisability to dental, cardiovascular, neurosurgical, urological, ophthalmic, and other implant categories.

Conclusion

Antimicrobial biomaterials, including silver- and iodine-coated implants, antibiotic-loaded DAC hydrogels, gentamicin-coated intramedullary nails, and calcium sulphate-based local antibiotic strategies, were generally associated with reduced clinically relevant infection outcomes in selected implant settings. The strongest and most consistent clinical evidence was observed for DAC hydrogel coatings, particularly in orthopaedic applications such as arthroplasty, revision surgery, osteosynthesis, megaprosthesis reconstruction, and DAIR-related procedures. Silver- and iodine-coated implants also showed promise in high-risk oncological reconstruction, while gentamicin- and calcium sulphate-based strategies appeared useful in trauma fixation and second-stage reimplantation contexts.

However, these findings should be interpreted cautiously. Most included studies were retrospective or non-randomised, several had serious risk of bias, and the evidence was concentrated mainly in orthopaedic implant populations. In addition, none of the included studies directly quantified biofilm formation; therefore, outcomes such as surgical site infection, periprosthetic joint infection, reinfection, implant retention, and infection-free survival should be understood as downstream clinical indicators of biofilm-associated infection rather than direct microbiological proof of biofilm suppression.

Overall, antimicrobial biomaterials represent promising adjuncts to established infection-prevention strategies, rather than replacements for patient optimisation, aseptic technique, systemic prophylaxis, appropriate debridement, wound care, and structured follow-up. Their use may be most appropriate in high-risk or biologically vulnerable implant settings. Future research should prioritise well-designed prospective comparative studies, standardised outcome reporting, long-term safety surveillance, direct biofilm-related assessment where feasible, and broader evaluation across non-orthopaedic implant categories before wider generalisations can be made.

Acknowledgements

Competing Interests: All the authors declare that they have no conflict of interest.
Ethics approval and consent to participate: Not applicable.
Consent for publication: Not applicable.
Availability of data and material: All the resources consulted in the review are provided in the reference section.
Funding: No funding of any kind was received.
Authors' Contributions: This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.
Disclosure of AI Use: During the preparation of the manuscript, artificial intelligence (ChatGPT) was used solely for language editing and improving readability of the text. The authors reviewed and edited the AI-generated content as needed, and take full responsibility for the content of the publication.

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