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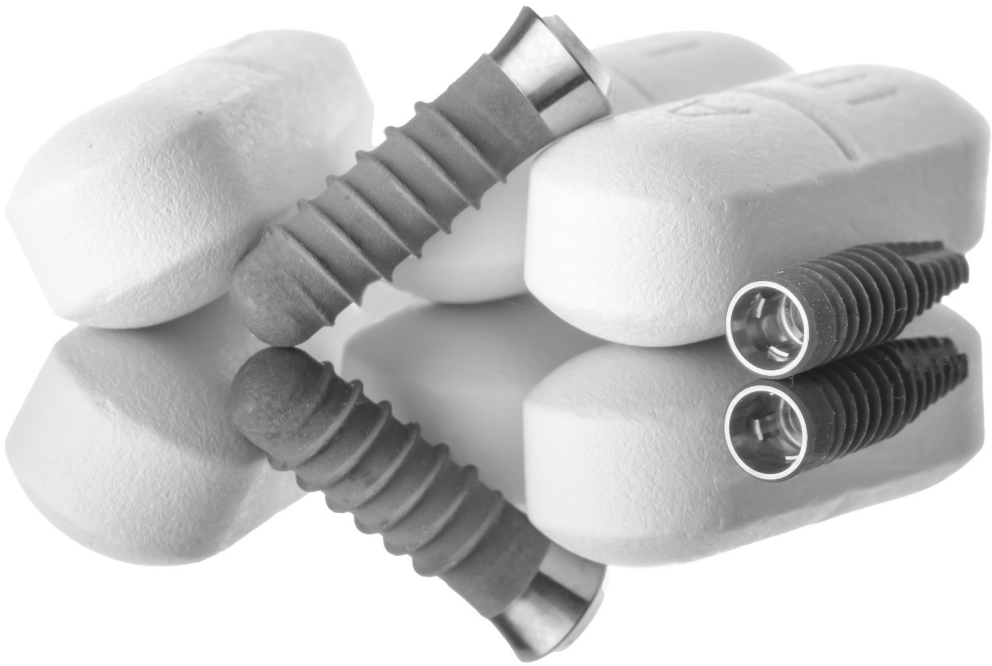

Palwasha Momand

Antibiotic prophylaxis in dental implant surgery

Antibiotic prophylaxis is widely used in dental implant surgery to reduce the risk of infections, yet its role remains a topic of debate, especially amid the rising concern of antibiotic resistance. This thesis explores the effectiveness of antibiotic prophylaxis in dental implant surgery by examining clinical outcomes, administration patterns, and stewardship practices. It aims to contribute to a more informed and responsible approach to antibiotic use in implant dentistry.

Palwasha Momand is a dentist who graduated from Faculty of Odontology, Malmö University in 2011. This thesis was written at the Department of Oral Diagnostics at the Faculty of Odontology, Malmö University.

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Antibiotic prophylaxis in dental implant surgery

Thesis for Doctoral Degree (Ph.D)
By Palwasha Momand

The thesis will be defended in public at the Faculty of Odontology, Malmö University
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Antibiotic prophylaxis in dental implant surgery

Malmö University, 2025
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LIST OF ARTICLES

This thesis is based on the following studies, referred to in the text by their Roman numerals:

I. Momand P, Becktor JP, Naimi-Akbar A, Tobin G, Götrick B. **Effect of antibiotic prophylaxis in dental implant surgery: A multicenter placebo-controlled double-blinded randomized clinical trial.** *Clin Implant Dent Relat Res.* 2022;24(1):116-124

II. Momand P, Naimi-Akbar A, Hultin M, Lund B, Götrick B. **Is routine antibiotic prophylaxis warranted in dental implant surgery to prevent early implant failure? - a systematic review.** *BMC Oral Health.* 2024;24(1):842.

III. Momand P, Naimi-Akbar A, Hämén von Essen N, Götrick B. **Use of antibiotic prophylaxis in conjunction with dental implant surgery in Sweden – a cross-sectional study**
Submitted

IV. Momand P, Götrick B, Hanson K. **Antibiotic prophylaxis in dental implant surgery – a qualitative study on the attitudes and routines of Swedish dentists**
Submitted

Contribution of the author

The author of this thesis has performed most of the work regarding the planning, data collection, analysis of data, and writing of the articles.

ABSTRACT

Antibiotic prophylaxis in dental implant surgery is intended to prevent postoperative infections and early implant failure, but its necessity, particularly in healthy patients undergoing straightforward procedures, remains controversial. While some dentists administer prophylaxis for all cases, others argue against routine use due to its minimal clinical benefit and the potential harm it causes by contributing to the rise of antibiotic resistance. This thesis evaluates the use of antibiotic prophylaxis in implant surgery, focusing on implant survival, infection prevention, administration patterns, and dentists' decision-making processes. It includes a randomised clinical trial comparing a single preoperative dose of amoxicillin to placebo, a systematic review and meta-analysis assessing the effectiveness of antibiotic prophylaxis in preventing implant failure, a cross-sectional study on administration patterns among Swedish dentists, and a qualitative study exploring dentists' perspectives. The findings show that routine antibiotic prophylaxis does not significantly reduce implant failure or postoperative infections in healthy patients, and that administration practices suggest that more antibiotics are prescribed than are needed, particularly in complex cases involving bone augmentation. Dentists recognise the risk of antibiotic resistance but often prioritise immediate infection prevention that may not be needed, contributing to the potential overuse of antibiotics. These findings underscore the urgent need for clearer, evidence-based guidelines to minimise unnecessary administration and strengthen antibiotic stewardship in dental implant surgery.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Antibiotika används ibland inom tandvården för att förebygga postoperativ infektion i samband med ingrepp, till exempel vid insättning av tandimplantat. Syftet med antibiotikaprofylax vid implantatkirurgi är att minska risken för en infektion som kan leda till att implantatet inte växer fast ordentligt i käkbenet. Nyttan av denna antibiotikaprofylax, särskilt hos friska patienter, är omdebatterad. Dessutom ökar problemet med antibiotikaresistenta bakterier, vilket medför att det är viktigt att alltid använda antibiotika ansvarsfullt. Dessvärre saknas en enhetlig praxis när det gäller antibiotika i samband med implantatkirurgi, och befintliga rekommendationer varierar.

I denna avhandling studeras i fyra olika delarbeten antibiotikaprofylax i samband med implantatkirurgi. Delarbete I är en randomiserad klinisk studie som jämför preoperativ antibiotikaprofylax med placebo. Delarbete II är en systematisk översikt och metaanalys som utvärderar befintlig forskning avseende antibiotikaprofylax vid implantatkirurgi. Delarbete III är en tvärsnittsstudie som via patientjournaler granskar hur antibiotika används i samband med implantatkirurgi. Delarbete IV är en kvalitativ studie som med hjälp intervjuer undersöker hur tandläkare resonerar kring antibiotikaanvändning i samband med implantatkirurgi.

Resultaten visar att det saknas vetenskapligt stöd för antibiotikaprofylax i samband med implantatoperationer och att tandläkare i Sverige är ganska restriktiva med antibiotikaprofylax. Det finns dock en variation och en del tandläkare använder fortfarande antibiotika för säkerhets skull trots en generell medvetenhet om att all användning av antibiotika medför en risk för spridning av antibiotikaresistenta bakterier.

Avhandlingens slutsats är att rutinmässig antibiotikaprofylax vid implantatkirurgi inte är nödvändigt och därför bör undvikas. Det behövs mer forskning för att fastställa den optimala antibiotikaanvändningen vid komplexa implantatkirurgiska ingrepp som involverar benuppbyggnad, där infektionsrisken kan vara högre. Avsaknaden av tydliga riktlinjer bidrar till osäkerhet och en överanvändning av antibiotika, vilket ökar risken för spridning av antibiotikaresistens. För att säkerställa en ansvarsfull användning av antibiotika inom tandvården behövs mer enhetliga och evidensbaserade riktlinjer samt implementeringsinsatser för att minska onödig användning.

ABBREVATIONS AND VOCABULARY

DNA	Deoxyribonucleic acid
PBP	Penicillin-binding protein
AMR	Antimicrobial resistance
WHO	World Health Organisation
STRAMA	Swedish strategic program against antibiotic resistance (Strategigruppen för rationell antibiotikaanvändning och minskad antibiotikaresistens)
DDD	Defined daily dose
ESBL	Extended-spectrum beta-lactamases
MRSA	Methicillin-resistant Staphylococcus aureus
VRE	Vancomycin-resistant Enterococcus
GBR	Guided bone regeneration
BMP	Bone morphogenetic proteins
PRF	Platelet-rich fibrin
RCT	Randomised clinical/controlled trial
CONSORT	Consolidated standards of reporting trials
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PICO	Population, Intervention, Comparison, Outcome
GRADE	Grading of recommendations, assessment, development, and evaluations
STROBE	Strengthening the reporting of observational studies in epidemiology
PDS	Public dental service
RR	Risk ratio
OR	Odds ratio

CI	Confidence interval
COREQ	Consolidated criteria for reporting qualitative research
HBM	Health belief model
NNT	Number needed to treat
CHX	Chlorhexidine
Antibiotic prophylaxis	Preventive use of antibiotics to reduce infection risk before surgery or medical procedure
Implant failure	When implant fails to integrate properly with the bone
Postoperative infection	Infection that occurs at the surgical site after a surgery, often caused by bacteria entering the wound
Bone augmentation	Procedures that increase bone volume in deficient areas to support dental implant

INTRODUCTION

Antibiotics

Antibiotics have revolutionised modern medicine, serving as one of the most significant advancements in the treatment of bacterial infections.[1] The discovery of penicillin by Alexander Fleming in 1928 marked the beginning of the antibiotic era. By the 1940s, penicillin was being mass-produced, leading to unprecedented improvements in healthcare.[2,3] Antibiotics enabled the safe execution of complex medical procedures such as organ transplants, cancer chemotherapy, and major surgeries by effectively managing and preventing bacterial infections.[3]

Mechanistically, antibiotics function by targeting essential processes in bacterial cells, such as cell wall synthesis, protein production, or DNA replication.[4,5] Penicillin and its derivatives, like amoxicillin, are examples or beta-lactam antibiotics that disrupt bacterial cell walls. They achieve this by inhibiting penicillin-binding proteins (PBPs), which are necessary for synthesis of peptidoglycan – a key structural component of bacterial cell walls.[6,7] Without peptidoglycan, bacteria lose integrity and succumb to osmotic pressures. This specificity allows antibiotics to target bacteria without harming human cells, making them vital tools in combating infections.[8,9] Penicillin is particularly effective against Gram-positive bacteria, while certain derivatives also have an expanded efficacy against Gram-negative species.[10]

Penicillin and its derivatives are among the most commonly used antibiotics worldwide.[11] For patients allergic to penicillin, alternative antibiotics such as clindamycin are used. Clindamycin inhibits bacterial protein synthesis by targeting the 50S ribosomal subunit, halting the production of essential proteins.

Antibiotic resistance

Despite their success, antibiotics face a critical challenge: resistance. Antibiotic resistance occurs when bacteria evolve mechanisms to neutralise or evade the effects of these drugs, undermining their efficacy. This phenomenon has become one of the most pressing global health issues of the 21st century.[12]

The global crisis of antibiotic resistance

The World Health Organization (WHO) identifies antimicrobial resistance (AMR) as one of the most critical threats to global health.[13] Annually, AMR directly causes an estimated 1.27 million deaths (Figure 1), with another 4.95 million fatalities linked to drug-resistant infections. These figures emphasise the alarming global burden and mortality rates associated with resistance, which are expected to worsen without immediate and coordinated action.[12,14] Antibiotic resistance is a major global health challenge, driven by the ability of bacteria to evolve and adapt in response to the widespread use of antimicrobial agents.[14] While antimicrobial resistance refers to resistance in various microbes, including fungi and other microorganisms, the term 'antibiotic resistance' is used throughout this thesis specifically to describe bacteria adapting to withstand antibiotics.

The scale of the problem extends across continents, with multidrug-resistant pathogens increasingly common in hospitals, communities, and agricultural settings.[15] Bacteria such as Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus are developing resistance to frontline antibiotics, limiting treatment options. What were once simple infections are becoming life-threatening, and routine medical procedures such as surgeries, organ transplants, and cancer treatments are now at risk due to a diminished ability to prevent and treat postoperative infections.[16]

The pace of this crisis is staggering. Misuse and overuse of antibiotics in human health, veterinarian medicine, and agriculture accelerate resistance, and low- and middle-income countries face disproportionate burdens due to limited access to healthcare, substandard medications, and insufficient regulatory frameworks (Figure 2).[17] Moreover, global interconnectedness allows resistant bacteria to cross borders with alarming speed, heightening the need for international cooperation.[12,18]

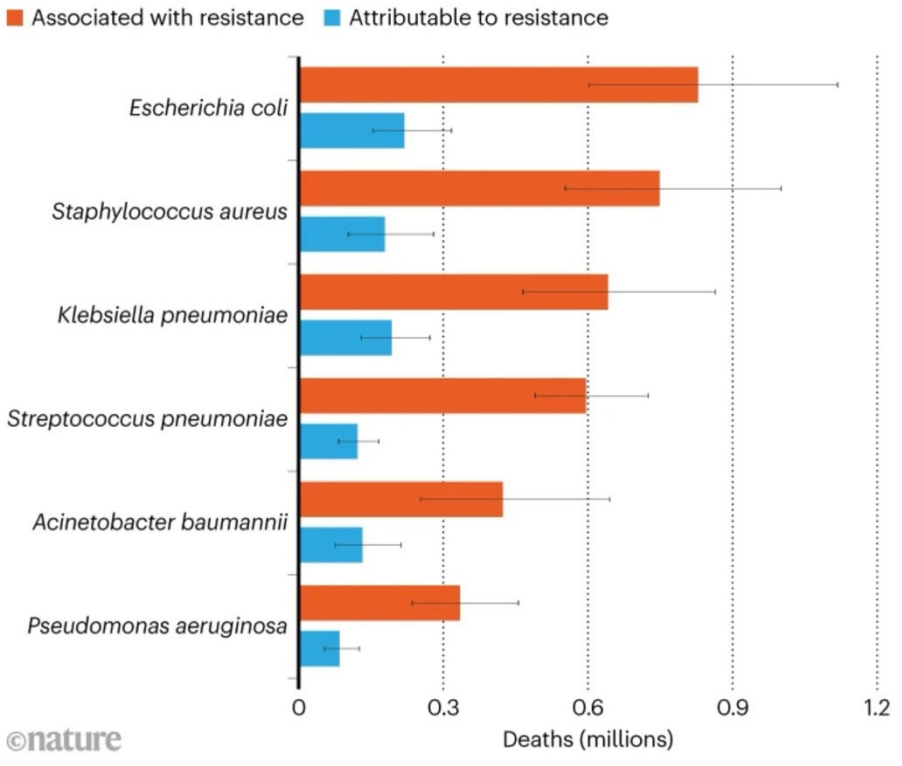

Figure 1. These 6 pathogens were responsible for almost 80% of the 1.27 million deaths attributed directly to antimicrobial resistance in 2019. Source: Murray, C. L. J. *et al. Lancet* https://doi.org/10.1016/S0140-6736(21)02724-0 (2022).

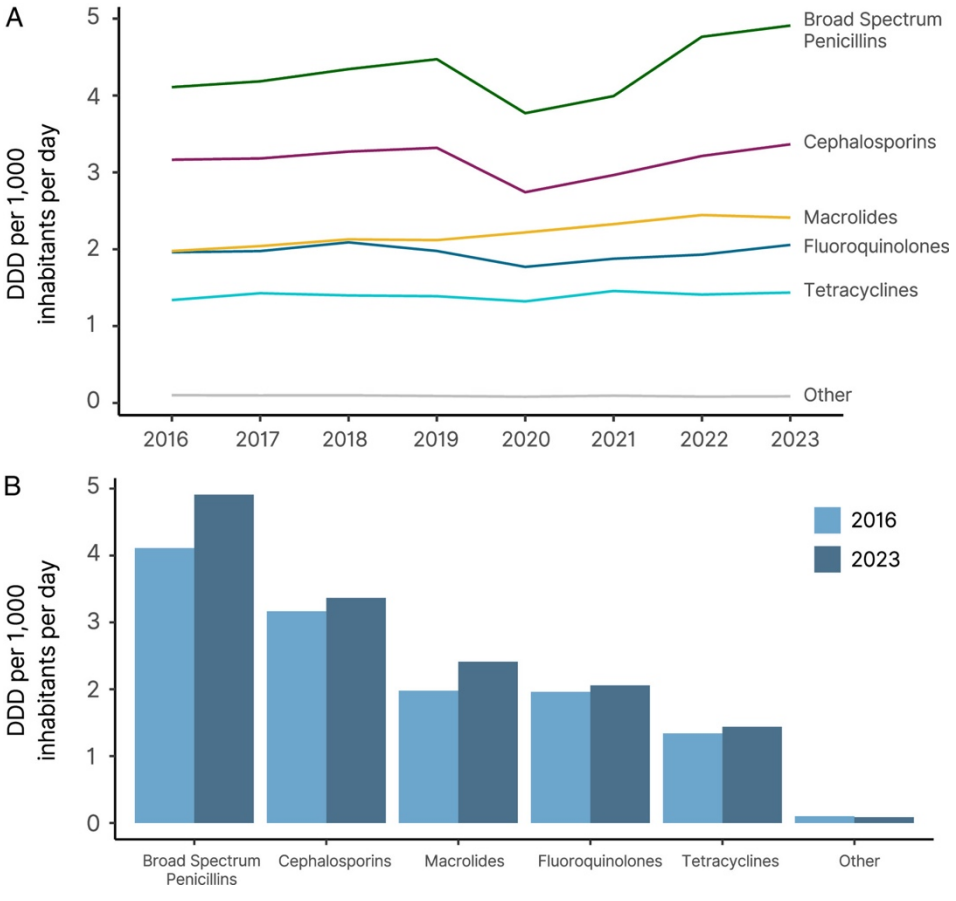

Figure 2. Global antibiotic consumption by antibiotic class. (A) Yearly changes in DDDs per 1000 inhabitants per day for the top five antibiotic classes by consumption amount. All other classes were combined into others. (B) Antibiotic consumption differences between 2016 and 2023 for the top five antibiotic classes by consumption amount, with all other classes combined into others. Data Source: Based on IQVIA MIDAS® sales data for period 2016–2023. Copyright IQVIA. All rights reserved.

The situation in Sweden

Sweden is widely regarded as a global leader in antibiotic stewardship and has implemented some of the most effective policies to combat antibiotic resistance.[19] The Swedish Strategic Program Against Antibiotic Resistance (STRAMA), established in the mid-1990s, has been instrumental in reducing antibiotic consumption through a combination of public health initiatives, education, and strict regulations.[20] As a result, Sweden consistently reports one of the lowest

rates of antibiotic use in Europe with a consumption rate of approximately 10.9 defined daily doses (DDD) per 1,000 inhabitants as of 2023.[21]

Despite having strong strategies to combat antibiotic resistance, Sweden continues to face challenges in addressing this global issue. The country has observed a concerning rise in infections caused by multidrug-resistant bacteria. In 2023, Sweden reported over 10,000 cases of infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, which are resistant to many commonly used antibiotics such as penicillin and cephalosporins (Figure 3).[21] Furthermore, the emergence of ESBL Carba-producing Enterobacterales, which exhibit resistance to nearly all beta-lactam antibiotics, including carbapenems, poses an even greater threat to treatment options.[22] Additionally, methicillin-resistant Staphylococcus aureus (MRSA) remains a significant public health concern, with increasing cases reported in both healthcare and community settings (Figure 4).[21,23]

The severity of the issue in Sweden mirrors global trends, albeit at a more controlled level due to stringent policies and a strong healthcare infrastructure. Nonetheless, the continued emergence of resistant bacteria highlights the necessity of sustaining and expanding current initiatives.

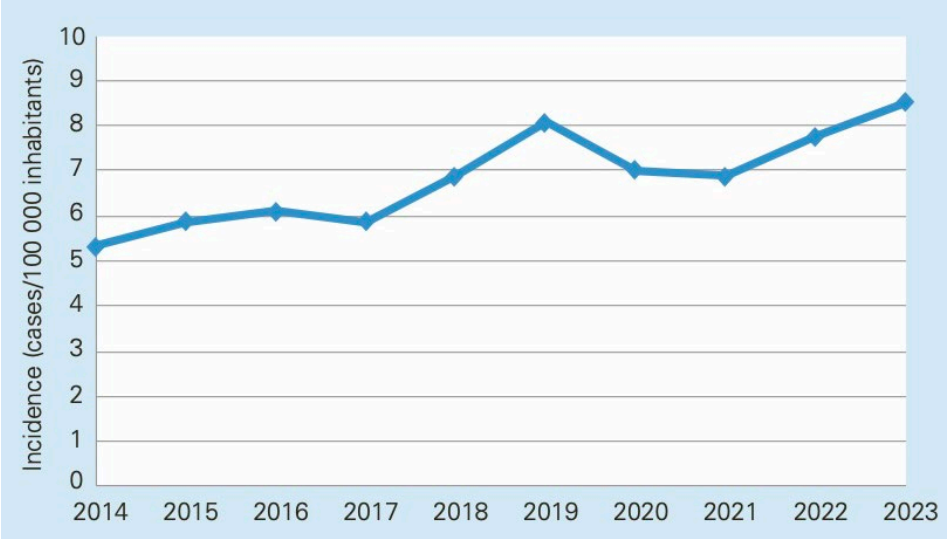

Figure 3. The incidence (case/100 000 inhabitants) of invasive cases with ESBL-producing Enterobacterales, reported during year 2014 to 2023. Reference: Swedres-Svarm 2023. Sale of antibiotics and occurrence of antibiotic resistance in Sweden. Solna/Uppsala. ISSN2001-7901.

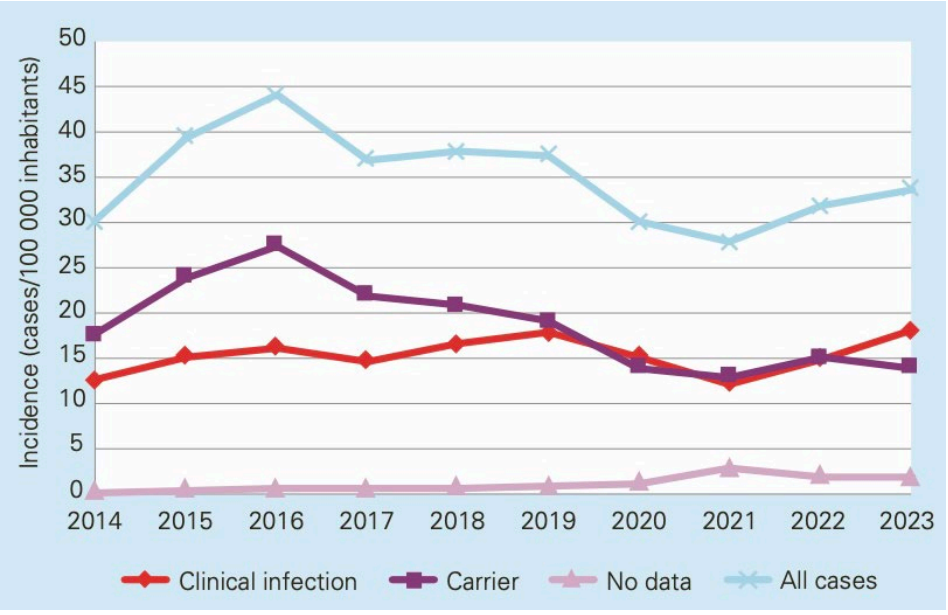

Figure 4. The incidence (cases/100 000 inhabitants) of cases with MRSA in relation to the type of infection, year 2014 to 2023. Reference: Swedres-Svarm 2023. Sale of antibiotics and occurrence of antibiotic resistance in Sweden. Solna/Uppsala. ISSN2001-7901.

Mechanism of resistance

Bacteria employ a variety of sophisticated mechanisms to resist the effects of antibiotics, enabling their survival and proliferation even in the presence of these drugs. These resistance strategies are often encoded by genes that can be transferred between bacteria, further accelerating the spread of resistance.[24] Below, the key mechanisms by which bacteria evade the action of antibiotics are explained:

- **Enzymatic degradation**
  One of the most common resistance mechanisms involves the production of enzymes that degrade or modify antibiotics before they can exert effects. A well-known example is the production of beta-lactamases, enzymes that break down the beta-lactam ring structure of antibiotics such as penicillins and cephalosporins, rendering them ineffective. Of particular concern are extended-spectrum beta-lactamases (ESBLs), which can hydrolyse a broad range of beta-lactam antibiotics, including third-generation cephalosporins. The rapid spread of ESBL-producing bacteria is highly problematic, as there are severely limited treatment options for the infections they cause.[25,26]

- **Target modification**
  Bacteria can develop resistance by altering the molecular targets of antibiotics, reducing their binding affinity and efficacy. Penicillin-binding proteins (PBPs) are targets of beta-lactam antibiotics, but structural changes in these proteins can prevent the drug from binding effectively. This mechanism is notably observed in methicillin-resistant Staphylococcus aureus (MRSA), where the acquisition of an altered PBP (PBP2a) confers resistance to nearly all beta-lactam antibiotics. Such target modifications allow bacteria to evade the action of antibiotics while maintaining their essential cellular functions.[27]
- **Efflux pumps**
  Efflux pumps are specialised proteins embedded in bacterial cell membranes that actively expel antibiotics from the cell, preventing the drugs from reaching therapeutic concentrations. These pumps can transport a wide range of structurally diverse antibiotics, contributing to multidrug resistance. Efflux systems are particularly prevalent in Gram-negative bacteria, where they work in conjunction with other resistance mechanisms to enhance bacterial survival. The overexpression of efflux pumps is a major challenge in treating infections caused by pathogens such as Pseudomonas aeruginosa and Escherichia coli.[28,29]
- **Reduced permeability**
  Gram-negative bacteria possess an outer membrane that acts as an additional barrier to antibiotic entry. By modifying this membrane's structure of composition, bacteria can reduce its permeability and limit the uptake of antibiotics. One common strategy involves changes in the expression or function of porin channels, which facilitate the diffusion of antibiotics across the outer membrane and can significantly decrease drug influx. When there is a decreased drug influx, fewer antibiotic molecules can enter bacterial cell, which reduces their ability to reach their intracellular targets. This weakens the antibiotic's effect, allowing bacterial to survive and proliferate despite drug exposure. This mechanism is particularly effective against hydrophilic antibiotics, such as beta-lactams and quinolones, and is often combined with other resistance strategies to enhance bacterial survival.[30-32]

The ability of bacteria to resist antibiotics through enzymatic degradation, target modification, efflux pumps, and reduced permeability underscores the complexity of the antibiotic resistance crisis.[16] These mechanisms are not mutually exclusive; bacteria often employ multiple strategies simultaneously,

making infections increasingly difficult to treat.[24] It is important to recognise that the more antibiotics are used, the more resistance is generated, creating a vicious cycle that exacerbates the problem.[33] Therefore, it is of paramount importance to develop and implement comprehensive approaches and strategies to reduce antibiotic use across all sectors – human medicine, agriculture and veterinarian practices.[34]

Types of bacteria prone to resistance

Certain bacterial groups are more likely to develop resistance due to their genetic plasticity and ability to acquire resistance genes from other bacteria. These bacteria often possess intrinsic resistance mechanisms.[35] Examples include:

- **Gram-negative bacteria:** These bacteria, such as Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa, are particularly adept at developing resistance. Their double membrane structure reduces antibiotic permeability, and they often possess efflux pumps and enzymes like carbapenemases and ESBLs. These bacteria are commonly associated with infections such as urinary tract infections and pneumonia.[36,37]
- **Staphylococcus aureus**: This Gram-positive bacterium is a leading cause of skin and soft tissue infections, as well as more severe conditions like sepsis. Staphylococcus aureus is notorious for its ability to develop resistance to beta-lactam antibiotics leading to the emergence of methicillin-resistant Staphylococcus aureus (MRSA). MRSA is a major challenge in clinical settings.[27]
- **Enterococcus species:** Enterococci, particularly Enterococcus faecium and Enterococcus faecalis, are known for their ability to develop resistance to vancomycin, a last-resort antibiotic for severe infections. Vancomycin-resistant Enterococci (VRE) are a significant concern in healthcare settings, as they are often resistant to multiple antibiotics. These bacteria commonly cause urinary tract infections, endocarditis, and surgical site infections.[38,39]
- **Streptococcus pneumoniae:** Penicillin-resistant Streptococcus pneumoniae (PRSP) is a significant concern in clinical settings. This Gram-positive bacterium has developed resistance to beta-lactam antibiotics, including penicillin, primarily through alterations in penicillin-binding proteins (PBPs). These modifications reduce the binding affinity of beta-lactam antibiotics, diminishing their effectiveness. PRSP is responsible for various infections, such as pneumonia, meningitis, and otitis media, and its resistance complicates treatment strategies.[40]

Antibiotics most affected by resistance

Certain antibiotic classes are more likely to be associated with resistance due to their frequent use, broad-spectrum activity, and the ability of bacteria to develop specific resistance mechanisms against them.[41] Below are the key classes most affected by resistance:

- **Beta-lactam antibiotics**: Penicillin, cephalosporins, and carbapenems are among the most widely used antibiotics and are heavily affected by resistance mechanisms like beta-lactamase production and altered PBPs.[42]
- **Fluoroquinolones**: Drugs like ciprofloxacin and levofloxacin are broad-spectrum antibiotics that target essential bacterial enzymes used in DNA replication. The drugs face resistance due to mutations in bacterial DNA enzymes and efflux pump activity.[43]
- **Tetracyclines:** Resistance occurs via efflux pumps and ribosomal protection proteins.[44]

Consequences and future directions

Unchecked antibiotic resistance poses dire consequences, with the most serious one being that once-common infections may become increasingly difficult – or even impossible – to treat with antibiotics, leading to higher morbidity and mortality rates. This growing resistance threatens the efficacy of surgeries, cancer treatments, and routine medical procedures. As resistance grows, antibiotics becomes less reliable, increasing the risk of life-threatening infections.[45]

Global efforts to combat antibiotic resistance include the development of new antibiotics, investment in rapid diagnostics, and adherence to the WHO's Global Action Plan on Antimicrobial Resistance (AMR).[34,46] The WHO's plan emphasised a One Health approach, integrating efforts across human health, animal health, and the environment. The pipeline for new antibiotics remains limited, underscoring the need to refine the use of antibiotics across all sectors and reduce unnecessary consumption.[34]

Antibiotics in dentistry

Antibiotics are used in dentistry, both for therapeutic and prophylactic purposes. They are prescribed to manage existing bacterial infections, such as dental abscesses, periodontitis, and pericoronitis, and to prevent infections in specific cases, such during dental care for patients with compromised immune systems or in conjunction with complicated oral surgery procedures. The use of antibiotics

helps mitigate the risk of complications that can arise from untreated infections, preventing them from spreading to deeper tissues and vital organs.[47-49]

In Sweden penicillins, such as phenoxymethylpenicillin (penicillin V) and amoxicillin, are the most commonly used antibiotics in dentistry due to their efficacy and favourable safety profile (Figure 5). For patients with penicillin allergies, clindamycin serves as a widely used alternative, ensuring effective treatment. Metronidazole is another frequently used antibiotic, particularly effective against anaerobic bacteria involved in periodontal and endodontic infections. In some cases, combination therapies may be employed to extend bacterial coverage.[50-53]

Globally, the use of antibiotics in dentistry varies significantly, reflecting differences in prescribing practices, healthcare systems, and antibiotic stewardship efforts.[54] In many countries, dentistry contributes a substantial proportion of outpatient antibiotic prescriptions. For instance, in the United States, dentistry accounts for approximately 10% of all outpatient antibiotic prescriptions.[55,56] In European countries, dentists are responsible for about 7-9 % of total outpatient antibiotic use.[57,58]

In Sweden dentists accounted for approximately 6.1% of all systemic antibiotics sold during 2023, a reduction from previous years.[21] Notably, since 2007, the volume of antibiotics prescribed by Swedish dentists has halved due to robust public health initiatives and adherence to national guidelines.[21,59]

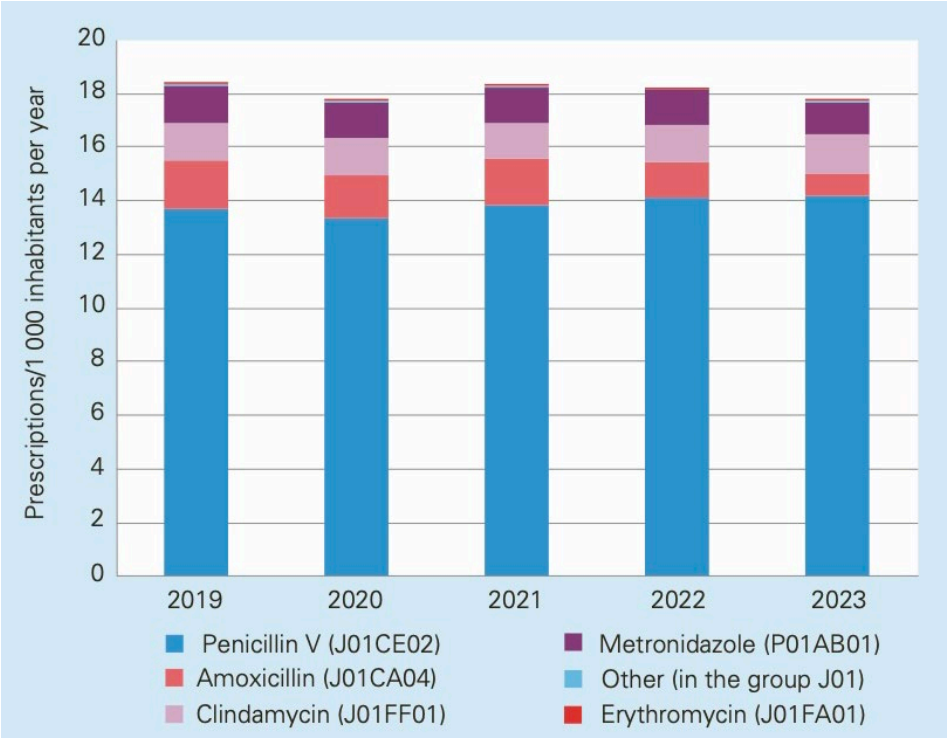

Figure 5. Sales of antibiotics prescribed by dentists in outpatient care between 2019 to 2023. Reference: Swedres-Svarm 2023. Sale of antibiotics and occurrence of antibiotic resistance in Sweden. Solna/Uppsala. ISSN2001-7901.

Despite the success of stewardship efforts, challenges persist. Overprescription in certain situations, such as prophylactic use for straightforward implant surgeries and overall healthy patients, remains a concern. Additionally, the global rise in antibiotic resistance underscores the necessity for continued vigilance and adherence to guidelines.[60]

To further strengthen efforts against antibiotic resistance in dentistry, it is crucial to integrate enhanced surveillance mechanisms, ensuring detailed data collection on antibiotic use in dental care. This enables trends to be analysed and compliant with treatment guidelines, to be monitored effectively. Equally important is the implementation of robust preventative measures, such as maintaining stringent hygiene protocols in dental clinics and educating patients on the importance of oral health to reduce the need for antibiotics in the first place.[61] Responsible prescribing remains at the heart of combating antibiotic resistance in dentistry.

Dentists must adhere to guidelines, avoiding unnecessary use of broad-spectrum antibiotics and updating diagnostics and treatment recommendation regularly.[54]

Moreover, interdisciplinary collaboration between dental professionals, researchers, and policymakers is essential for address existing knowledge gaps and explore innovative solutions. This includes advancing diagnostic tools, investigating the environmental impact of antibiotic use, and postering international cooperation to share best practices.[17]

Swedish national guidelines for antibiotic treatment and antibiotic prophylaxis in dentistry

Sweden has implemented stringent national guidelines for the use of antibiotics in both therapeutic and prophylactic contexts, which are overseen by the Swedish Medical Products Agency and the Public Health Agency of Sweden. These guidelines are part of a broader strategy under STRAMA (Swedish Strategic Program Against Antibiotic Resistance) to reduce unnecessary antibiotic use and combat resistance.[62,63]

For treatment, the guidelines emphasise the use of narrow-spectrum antibiotics whenever possible. Penicillin V is the first-line choice for most dental infections, such as periapical abscesses and acute periodontitis. Amoxicillin is recommended in cases requiring broader coverage, such as infections involving facial swelling or systemic symptoms. The duration of antibiotic treatment is short, 5 to 7 days, and adapted to the severity of the infection.[62]

In terms of prophylaxis, the Swedish guidelines recommend antibiotics to certain so-called risk patients and in specific risk interventions where the potential benefits outweigh the risks of contributing to resistance. Risk patients include patients with immunosuppression, patients with high-dose radiation to the head and neck area and cancer patients currently receiving, or who have previously received, intravenous bisphosphonate or denosumab treatment. Risk interventions include orthognatic surgery, fracture surgery, or bone grafting procedures (block grafts). Amoxicillin is the preferred agent for prophylaxis, typically administrated as a single dose one hour prior to the procedure. Clindamycin is used for penicillin-allergic patients.[63]

When it comes to implant surgery in healthy patients, however, the recommendations are remarkably vague. The Swedish guidelines acknowledge the limited evidence for the benefit of antibiotic prophylaxis in implant surgery.

Data suggest only a marginal reduction in implant loss with preoperative antibiotics, and there is no clear evidence supporting continued administration after the procedure. As a result, the decision to use antibiotics in such cases often hinges on clinical judgment. The guidelines suggest considering prophylaxis for patients with a combination of several risk factors, recommending 2 g of amoxicillin one hour prior to surgery when deemed necessary. The Swedish guidelines do not provide further details of antibiotic prophylaxis in patients undergoing bone augmentation; however, for bone grafting (block grafts) procedures a preoperative dose of amoxicillin is recommended.[63]

Antibiotic prophylaxis in dental implant surgery

Dental implants, first developed in their modern form during the 1960s by professor Per-Ingvar Brånemark, revolutionised restorative dentistry. These titanium fixtures are designed to replace missing teeth and rely on the process of osseointegration—a direct structural and functional connection between the implant surface and surrounding bone.[64,65] Dental implants have now become a cornerstone of restorative dentistry, with millions of implants placed annually worldwide. Long-term studies have reported success rates exceeding 90%, making them one of the most predictable and effective treatment options for partially or fully edentulous patients.[66,67]

Despite these high success rates, implant failures do occur. Failures can be categorised as early (occurring prior to prosthetic restoration) or late (occurring after the prosthetic phase). Early failures are often attributed to a lack of primary stability, surgical trauma, or bacterial contamination during surgery,[68] while late failures may stem from peri-implantitis, occlusal overload, or poor maintenance.[69,70] Among the factors influencing early implant failures, bacterial contamination during implant insertion is a critical concern. Research has demonstrated that bacterial infiltration can disrupt the osseointegration process, leading to fibrous encapsulation instead of bone integration. This process often results in implant loss, highlighting the importance of infection control during surgical procedures.[71,72]

Furthermore, the general health conditions of the patient play a crucial role in the healing process. Systemic conditions such as diabetes, osteoporosis, or immune system disorders can impair wound healing and increase the risk of postoperative infections, ultimately jeopardising osseointegration and implant stability.[69,73]

Patients with poorly controlled diabetes, for instance, often exhibit delayed healing due to impaired vascularisation and increased susceptibility to infection.[74]

Additionally, lifestyle factors like tobacco use have a substantial impact on the outcomes of dental implant surgeries. Smoking is well-documented to adversely affect wound healing by reducing blood flow and oxygen supply to the tissues, which are critical for proper osseointegration. The toxic components in tobacco also impair the immune response, making it harder for the body to fight off bacterial contamination during and after surgery. Studies have consistently shown that smokers have significantly higher rates of implant failure (early and late) compared to non-smokers, highlighting the need for patient-specific risk assessments and counselling prior to implant placement.[75,76] These interrelated factors emphasise the importance of a comprehensive approach to patient evaluation and management to optimise implant success and reduce complications.[77]

During the early years of dental implant surgery, the threats of bacterial contamination prompted the adoption of comprehensive antibiotic regimens. These often included both preoperative doses and prolonged postoperative courses aimed at preventing infection and ensuring osseointegration.[78] However, the effectiveness of these regimens was questioned as early as 30 years ago[79] when researchers began to scrutinise the necessity of extended antibiotic use, particularly in straightforward cases involving healthy patients.[80] Meta-analyses and systematic reviews revealed that the benefits of prolonged antibiotic prophylaxis were often marginal, leading to a shift towards more restrained approaches.[81,82]

Today, antibiotic prescribing practices in dental implant surgery vary widely. In Sweden, national guidelines suggest a single 2 g of amoxicillin administrated one hour prior to surgery, or 600 mg of clindamycin for penicillin-allergic patients, to all patients with a combination of several risk factors. However, these recommendations also acknowledge that there is a lack of robust evidence to clearly map the effect of antibiotic prophylaxis in dental implant surgeries. The guidelines, first introduced in 2012, reflect an evidence-based approach aimed at reducing unnecessary antibiotic use.[63] Available data, at the time when the guidelines were formed, suggested a slight reduction in the number of implant losses when preoperative antibiotic is administrated.[63]

Guidelines in other countries vary from those in Sweden. For example, in Spain and Italy the national guidelines advocate for routine antibiotic prophylaxis for

all patients undergoing implant placement, regardless of the complexity of the case.[83,84] This underscores the ongoing lack of consensus within the global dental community. The varying guidelines tend to lead to a variability in the administration patterns of clinicians. Some clinicians administrate antibiotic prophylaxis routinely, citing concerns about patient-specific factors such as smoking or systemic conditions.[85] Others question the necessity of antibiotics in such cases, given the growing evidence that good surgical techniques and infection control measures are often sufficient.[86]

Importantly, research in the last few years have shown that even a single dose of antibiotics can cause significant ecological disturbances in the oral microflora. For instance, a 2016 study by Khalil et al. demonstrated that a single 2 g dose of amoxicillin significantly increased the proportion of antibiotic-resistant bacterial strains in the oral cavity, with effects lasting for weeks.[87] This is a deeply concerning finding, especially in the context of the escalating global issue of antibiotic resistance. This underscores the need for judicious antibiotic use, even in cases where prophylaxis is deemed necessary.[88]

While dental implants remain a highly successful and transformative treatment, the question of antibiotic prophylaxis continues to spark debate. Swedish guidelines advocating for single-dose regimens represent an evidence-based approach aimed at minimising unnecessary antibiotic exposure. However, the lack of universal standards highlights the complexity of balancing infection prevention with the broader public health goal of combating antibiotic resistance.

Moving forward, continued research and global collaboration will play a pivotal role in refining clinical guidelines and promoting the responsible use of antibiotics in dental implant surgery.[54,88]

Bone augmentation in dental implant surgery

Bone augmentation is a critical component of modern dental implant surgery, addressing the challenges posed by insufficient bone volume in patients requiring implants. Dental implants rely on the process of osteointegration, where the titanium implant integrates with the surrounding bone to achieve stability.[89] However, the success of this process depends on the presence of adequate bone volume and quality. For patients with insufficient bone, augmentation procedures are often necessary to create a suitable foundation for implant placement.[90]

Types of bone augmentation techniques

Bone augmentation encompasses a variety of surgical techniques designed to enhance bone volume and quality, of which some are described below:

- **Guided bone regeneration (GBR)**
  This widely used technique involves the use of barrier membranes to protect the bone defect from soft tissue invasion, allowing bone regeneration to occur. GBR is often combined with bone grafting materials to enhance the regenerative process. Clinical studies have demonstrated high success rates for GBR in increasing bone volume and facilitating implant placement.[91]
- **Sinus augmentation**
  A sinus augmentation is performed to increase bone height in the posterior maxilla by elevating the sinus membrane and placing graft materials beneath it. This procedure is particularly valuable for patients with significant bone resorption in the upper jaw. Recent studies indicate that sinus augmentations, when performed with appropriate graft materials and techniques, result in predictable outcomes and high implant survival rates.[92]
- **Ridge expansion**
  For patients with narrow alveolar ridges, ridge expansion or splitting is employed to widen the ridge and create sufficient space for implant placement. It is common to add grafting material in conjunction with ridge expansion to maintain the expanded ridge, enhance bone volume and aid in stabilisation.[93]
- **Block grafting**
  In cases of severe bone deficiency, autologous bone blocks harvested from the patient's intraoral or extraoral donor sites are used to reconstruct the defect. While block grafting is more invasive than other techniques, it provides excellent bone volume and quality for implant placement.[94]
- **Bone morphogenetic proteins (BMPs)**
  BMPs are growth factors that stimulate bone formation and have been incorporated into bone grafting procedures to enhance regenerative outcomes. Studies show that BMPs can significantly improve the success of bone augmentation procedures, particularly in challenging cases.[95,96]

Factors influencing the success of bone augmentation

Several factors influence the outcome of bone augmentation procedures. Patient-related factors such as systemic conditions, including diabetes, osteoporosis, and smoking, can adversely affect bone healing and regeneration. Patients with these conditions require careful evaluation and management to optimise outcomes.[97]
The choice of grafting material is another critical factor. The selection of appropriate graft materials, such as autografts, allografts, xenografts, or synthetic materials, plays a crucial role in the success of bone augmentation. Autografts, considered the gold standard, provide osteogenic, osteoinductive, and osteoconductive properties but involve donor site morbidity.[98] Allografts and xenografts are commonly used alternative with excellent clinical outcomes.
Surgical technique also greatly influences success. Precision during the procedure and adherence to aseptic protocols are essential for minimising complications and ensuring successful bone regeneration.[99]

Postoperative care significantly impacts outcome as well. Effective infection control and patient compliance with postoperative instructions are crucial. Antibiotic prophylaxis is often recommended for these surgeries to reduce the risk of infection, particularly in complex cases involving large bone defects or multiple grafting materials.[100]

The role of antibiotic prophylaxis in bone augmentation

The use of antibiotic prophylaxis in conjunction with bone augmentation procedures aims to mitigate the risk of postoperative infections, which can compromise graft success and implant outcomes.[101] However, the necessity of antibiotics in healthy patients undergoing minor bone augmentations is a topic of debate.[102,103] While some clinicians advocate routine use for all bone augmentation cases to provide an added layer of protection against infections, other emphasised strict surgical asepsis and patient-assessments to minimise antibiotic exposure.[102,104,105]

Recent advances in regenerative materials and techniques have significantly improved the predictability of bone augmentation procedures. For instance, bioactive materials, such as bioactive glass and platelet-rich fibrin (PRF), are gaining popularity for their ability to enhance bone regeneration and reduce healing times.[106,107] Furthermore, computer-aided design and manufacturing (CAD/CAM) technology has enabled the creation of patient specific grafts and surgical guides, improving precision and outcomes.[108]

Meta-analysis and long-term studies continue to evaluate the efficacy of various bone augmentation techniques. Current evidence suggests that while all methods have their merits, the choice of technique should be tailored to the patient's specific needs and anatomical considerations.[109,110] Additionally, the role of antibiotic prophylaxis in bone augmentation surgeries ought to be examined, with an emphasis on balancing infection prevention with the need to minimise antibiotic resistance. As research evolves, evidence-based practices will further refine the field of bone augmentation, enhancing both patient care and surgical success.

RATIONALE FOR THE THESIS

The use of antibiotic prophylaxis in dental implant surgery is a subject of ongoing debate, positioned at the intersection of infection prevention and antibiotic stewardship. While antibiotics have traditionally been used to reduce the risk of postoperative infection, their actual benefit in preventing implant failure remains uncertain. Existing evidence suggests that the protective effect of prophylactic antibiotic is minimal, raising questions about the routine use, particularly in otherwise healthy patients, and in straightforward surgeries. At the same time, the overuse of antibiotics contributes to the growing global challenge of antibiotic resistance, making it crucial to establish clear, evidence-based guidelines that optimise their use.

This thesis explores the clinical efficacy of antibiotic prophylaxis in dental implant surgery and the factors influencing its use in practice. By integrating clinical outcomes, systematic evidence, real-world administration patterns, and dentists' perspectives, it provides a comprehensive assessment of the necessity, efficacy, implementation and perceptions of antibiotics in implant surgery. The results have direct implication for refining Swedish guidelines, promoting uniform administration practice, and ultimately balancing the goals of infection prevention and antibiotic stewardship in dental care.

AIMS OF THE THESIS

The overreaching aim of this thesis is to advance understanding and improve practices related to the use of antibiotic prophylaxis in dental implant surgery, with a particular focus on balancing infection prevention and antibiotic stewardship.

Specific aims based on the articles:

- To evaluate the efficacy of preoperative antibiotic prophylaxis in preventing early implant failure and postoperative infections in healthy or relatively healthy patients undergoing dental implant surgery.
- To assess and synthesise existing evidence on the impact of antibiotic prophylaxis in dental implant surgery and determine whether its routine use is justified in preventing early implant failure.
- To investigate the real-world administration patterns of antibiotic prophylaxis in dental implant surgery among Swedish dentists, identifying factors that influence clinical decision-making and adherence to national guidelines.
- To explore the attitudes, perceptions, and decision-making processes of Swedish dentists regarding antibiotic prophylaxis in dental implant surgery.

These aims together provide a comprehensive approach to evaluating both the clinical necessity and practical application of antibiotic prophylaxis in dental implant surgery.

METHODS

Study I – Randomised clinical trial

This study employed a randomised clinical trial (RCT) design, which is regarded as the golden standard for evaluating the efficacy of medical interventions due to its ability to minimise bias and establish causality.[111] Conducted across seven dental clinics in southern Sweden, the trial aimed to evaluate the efficacy of a single preoperative dose of 2 g amoxicillin in reducing early implant failure and postoperative infections. Inclusion criteria encompassed adults aged 18 or older, without significant systemic diseases and undergoing dental implant surgery. Exclusion criteria included ongoing infections, severe diabetes, immunosuppressive therapy, or penicillin allergy.

Randomisation and blinding

The study population included 474 patients who were randomly assigned to either the antibiotic group (2 g amoxicillin) or the placebo group. The randomisation process was conducted by sequentially assigning each enrolled patient a medicine container labelled with a unique code number, generated through a computer-based randomisation sequence with a block size of six. This ensured an even distribution of patients between the test and control groups. Each patient's assigned code number was recorded in their study file.

The study implemented a double-blind design, ensuring that neither the participants, the clinicians, or the researchers were aware of the group assignments. The antibiotic and placebo tablets were identical in size, colour, shape, and packaging, and they were pre-packaged in coded containers. To maintain blinding, the list linking code numbers to treatment allocation remained sealed until the completion of the clinical trial and full data collection.

Sample size calculation

The sample size calculation was based in prior studies reporting early implant failure rates of 2% in antibiotic-treated patients and 5% in those receiving placebo. To detect a statistically significant difference with 80% power and a 5% significance level, a sample size of 500 patients per group (1000 total participants) was initially estimated. However, due to limitations in patient recruitment and the expiration of trial drugs, the final sample size was 731 patients, of whom 257 were excluded; hence, 474 participants were included (Figure 6).

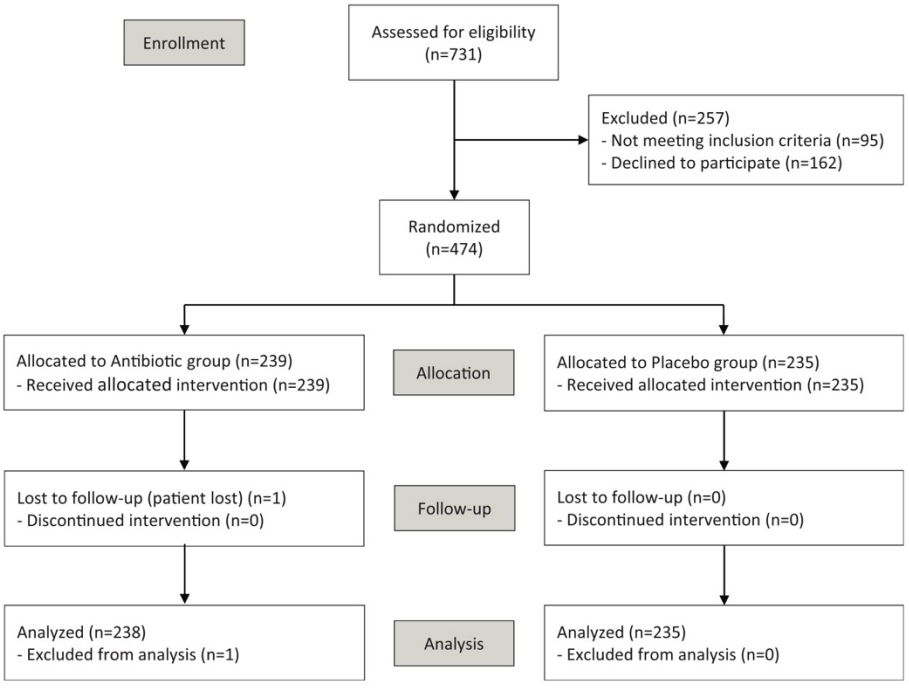

Figure 6. Flowchart diagram of the study protocol according to CONSORT guidelines.

Study outcomes and follow-up

The primary outcome was implant failure, defined as implants lost during follow-up or unstable implants discovered during hand tightening of the implant abutment at the second follow-up. Secondary outcomes included the rate of postoperative infections and adverse reactions to antibiotics. Patients underwent

postoperative follow-ups at 7-14 days and 3-6 months post-surgery to assess outcomes.

Statistical analyses

The statistical analyses were conducted using Pearson's chi-square test to analyse proportional differences between the antibiotic and placebo groups for categorical outcomes such as implant failure and postoperative infections. Logistic regression was employed to explore associations between implant failure and potential confounding variables, including smoking status, age, bone augmentation, and the number of implants placed. Relative risks were calculated with 95% confidence intervals, and p-values less than 0.05 were considered statistically significant.

Adherence to CONSORT (Consolidated Standards for Reporting Trials) guidelines[112] ensured transparency and methodological rigour throughout the trial.

Study II – Systematic review and meta-analysis

This study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[113] to ensure a systematic and transparent methodology. The review focused on randomised clinical trials that compared antibiotic prophylaxis to placebo or no antibiotics in patients undergoing dental implant surgery. The predefined components of the study – PICO – were as follows: The population included healthy patients undergoing surgery; the intervention was antibiotic prophylaxis; the comparator was placebo or not antibiotics; and the outcomes were early implant failure and postoperative infections. The focused question of the study was: "What is the effect of antibiotic prophylaxis compared to placebo/no antibiotics in overall healthy patients undergoing dental implant surgery regarding implant failure?"

Search strategy

A comprehensive search strategy was developed in collaboration with information specialists to ensure a broad and exhaustive literature review. The electronic databases PubMed (Medline), Web of Science, and the Cochrane Library were searched for relevant studies published up to October 2023. The search strategy included a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to "antibiotic prophylaxis", "dental

implants", "implant failure", and "randomised controlled trials". Boolean operators (AND, OR) were applied to optimise sensitivity and specificity. The search was further refined by manually screening the reference lists of included studies and relevant systematic reviews to identify additional eligible trials. To ensure completeness, databases providing information on ongoing clinical trials, such as ClinicalTrials.gov, were also consulted.

The inclusion criteria specified randomised controlled trials with at least 20 participants per group and a minimum follow-up of two months. Studies involving mini-implants or immediate placement in infected sites were excluded. Two independent reviewers screened titles and abstracts for eligibility, with full-text reviews conducted for studies meeting the inclusion criteria. Any disagreements were resolved through discussion or consultation with a third reviewer.

Handling of heterogeneity

Due to expected variations in study design, surgical techniques, and patient populations, heterogeneity was assessed using statistical and methodological approaches. A random-effects meta-analysis model was applied to account for inherent variability among studies. Statistical heterogeneity was quantified using the I^2 statistics, with values interpreted as follows: low (0-25%), moderate (26-50%), substantial (51-75%), and high (>75%). The Q statistics were also computed to assess the presence of significant heterogeneity.

Subgroup analyses were performed to explore potential sources of heterogeneity, including:

- Studies using only amoxicillin versus those using other antibiotics.
- Studies involving immediate implant placement versus conventional implant surgeries; and
- Studies with varying follow-up times.

A sensitivity analysis was conducted by excluding studies with high risk of bias and reassessing the pooled estimates to determine the robustness of the findings. Additionally, publication bias was evaluated using funnel plots and Egger's test to detect asymmetry, which could indicate selective reporting.

GRADE criteria and certainty of evidence

The certainty of evidence was evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework.[114] The GRADE approach considers the following factors:

- **Risk of bias:** Assessed using the RoB-2 tool,[115] with each study classified as having low, moderate, or high risk or bias.
- **Inconsistency:** Determined by assessing heterogeneity (I^2) and variability in effect sizes.
- **Indirectness:** Evaluated by considering how well the included studies represent the target population and intervention.
- **Imprecision:** Based on confidence intervals and the number of events across studies.
- **Publication bias:** Examined using funnel plot asymmetry and statistical tests.

Each outcome was assigned a certainty level of high, moderate, low, or very low based on the overall assessment of these domains. High-certainty evidence indicates that further research is unlikely to change confidence in the estimate of effect, whereas low-certainty evidence suggests that additional studies may have a significant impact on the findings.

Study III - Cross-sectional study

This study analysed real-world patterns of antibiotic prophylaxis use in dental implant surgery in Sweden. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines[116] to ensure transparency and methodological rigour.

Study population and data collection

Patient records were obtained from two major dental care providers in Sweden: The Public Dental Service (PDS) Stockholm and Smile Dentistry, a private dental service organisation. A total of 450 patient records were retrieved, including 250 records from PDS Stockholm and 200 from Smile Dentistry. These institutions were selected to provide a representative sample of both public and private dental healthcare settings. The records were identified using registry codes for implant surgery, and consecutive cases were extracted retrospectively from January 2023 backward until required sample size was reached.

The collected data encompassed demographics (age, sex), health factors (chronic diseases, medication use, tobacco consumption), procedural details (implant placement type, bone augmentation, sinus lift), antibiotic prophylaxis administration (type, dosage, duration), and postoperative recommendations (chlorhexidine use).

Statistical analyses

Descriptive statistical methods were employed to summarise the frequency of antibiotic prophylaxis use, categorised by surgical complexity (straightforward implant placement vs. additional interventions such as bone augmentation or sinus lift). The chi-square test was used to evaluate differences in antibiotic prescribing patterns across patient and procedural subgroups.

Logistic regression analysis was conducted to identify factors associated with antibiotic prophylaxis administration. The outcome variable was whether antibiotics were prescribed (Yes/No), while independent variables included:

- Surgical complexity (straightforward vs. bone augmentation/sinus lift); and
- Patient-specific factors (age, smoking status, chronic diseases).

To assess the strength of associations, results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). The logistic regression model accounted for multiple covariates simultaneously, reducing confounding effects. The likelihood ratio rest was employed to compare nested models and evaluate whether including specific variables significantly improved model fit. This approach ensured that only meaningful predictors were retained in the final model. Multicollinearity was moreover assessed using variance inflation factors (VIFs) to ensure that independent variables did not exhibit high correlation, which could distort statistical interpretations.

Further sensitivity analyses were conducted to test the robustness of findings. This included running models with different stratifications, such as excluding cases with missing health data and reanalysing results with alternative categorisations of surgical complexity.

Study IV – Qualitative study

This study explored the perceptions and decision-making processes of Swedish dentists regarding antibiotic prophylaxis in conjunction with dental implant surgery in the context of antibiotic resistance. The COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines[117] were followed to maintain methodological rigour.

Interview process and question structuring

A qualitative inductive research design was employed to ensure that the study captured nuanced perspectives and experiences of clinicians. Semi-structured interviews were conducted with 17 Swedish dentists, following a purposive and snowball sampling approach to ensure diverse representation in terms of clinical experience, practice setting and geographical location. The interviews were conducted by a single researcher, who was a dentist. Each interview lasted between 13 to 46 minutes, with a median duration of 33 minutes, and was conducted in person or via video conference (Zoom or Teams), depending on the participant's preference. Prior to the interview, participants were informed about the purpose of the study and provided consent for participation, audio recording and transcription.

An interview guide was developed collaboratively by the research team, ensuring that it covered key areas relevant to the study's objectives. The guide contained open-ended questions designed to explore participants' attitudes, experiences, and clinical reasoning regarding antibiotic prophylaxis. The questions were structured to encourage deep reflection and discussion.

Throughout the interviews, probing questions were used to encourage elaboration, ensuring that responses were not superficial but rather provided insight into participants thought processes. To assess data saturation, interviews continued until no new information was obtained, ensuring comprehensive exploration of the topic.

Data analysis and theme development

All interviews were audio-recorded, transcribed verbatim, and reviewed for accuracy. Transcripts were then uploaded into NVivo, a qualitative data analysis software, to facilitate systematic coding and theme development.

A content analysis approach, following Graneheim and Lundman's method,[118] was applied. Initially, meaning units (sentences or paragraphs expressing relevant

ideas) were identified. These meaning units were then condensed while retaining their essential meaning and assigned codes based on their primary conceptual focus. Codes were systematically reviewed and refined to ensure clarity and relevance.

Following initial coding, the research team engaged in an iterative categorisation process, where similar codes were grouped into categories that capture broader conceptual patterns. Categories were continuously compared and adjusted to reflect commonalities and variations across the dataset. The development of categories was guided by constant comparison, ensuring that emerging interpretations remained grounded in the data.

Themes were identified through a thematic abstraction process, where categories were further synthesised into overarching themes that encapsulate the underlying patterns in participants narratives. This step involved multiple rounds of discussion within the research team to ensure that the themes accurately represented the data and were not unduly influenced by researcher bias.

To enhance trustworthiness, the first author conducted the initial analysis, supported by collaborative input from the second and third author. Coding was conducted iteratively within the research team to ensure consistency and validity, and discrepancies in coding were resolved through discussion and consensus-building. Additionally, regular meetings within the research team were held to refine the analytical framework and validate the emerging themes against the raw data.

Ethical considerations

Ethical approval for three of the studies was obtained from the Swedish Ethical Review Authority, and all research was conducted in accordance with the Declaration of Helsinki[119] and relevant ethical regulations for medical and dental research.

In study I ethical approval was granted by the Regional Ethics Board in Lund, Sweden (Dnr: 2013/257). The study was also registered at ClinicalTrials.gov (NCT03412305). Informed consent was obtained from all participants before enrolment, ensuring that they were fully aware of the study's purpose, potential risks, and benefits. Confidentiality was safeguarded by coding patient data and storing the code list securely in a separate place.

Study II did not involve any direct research participant nor the handling of sensitive personal data; hence, ethical approval was not required. However, ethical considerations were upheld by ensuring transparent reporting and adherence to PRISMA guidelines.[113] The included studies were assessed for ethical compliance, particularly regarding informed consent and institutional approvals.

In study III ethical approval was obtained from the Swedish Ethical Review Board Authority (Dnr: 2023-07228-01). Since all data were anonymised, no sensitive data were handled, and therefore no consent was required.

In study IV no formal ethical assessment was required according to the Swedish Ethical review Authority (Dnr: 2024-00801-01). However, all research was conducted in accordance with ethical guidelines warranting that participants were provided with comprehensive written and verbal information about the study's purpose, procedures, and their rights. Informed consent was obtained from all participants, who were assured of confidentiality and anonymity. Participants were also informed that they could withdraw from the study at any time without providing a reason. Data confidentiality was ensured through secure storage of transcripts, and interview recordings were anonymised during transcription.

Theoretical frameworks

This thesis draws upon the frameworks of Antibiotic Stewardship[120] and the Health Belief Model (HBM)[121] to guide its approach to investigating antibiotic prophylaxis in dental implant surgery. These frameworks provide complementary perspectives: while Antibiotic Stewardship offers a systemic and policy-driven lens for optimising antibiotic use, HBM explains the individual decision-making processes influencing administration behaviours. Their integration allows for a comprehensive understanding of both institutional and behavioural factors shaping antibiotic use in dental implant surgery. While antibiotic stewardship is not a theoretical framework, which the HBM is, it functions as a guiding principle or analytical framework for research related to antibiotic use, antibiotic resistance, and policy implementation.

Antibiotic Stewardship provides a structured approach for evaluating how antibiotics are prescribed and utilised in clinical settings, emphasising the importance of balancing effective infection prevention with the need to minimise antibiotic resistance. It advocates for evidence-based prescribing, encouraging dental practitioners to follow best practice that protect both individual patients

and public health.[122,123] This framework has been successfully applied in various medical fields, offering valuable insights for dentistry. In orthopaedics, antibiotic prophylaxis is a critical component of infection control in joint replacement surgeries. Stewardship programmes have led to standardised single-dose regimens, reducing overprescription while maintaining infection prevention.[124,125] Similar principles can be applied to dental implant surgery, where prophylactic antibiotic use varies widely and is often inconsistent with establish guidelines.[86] In dentistry, Antibiotic Stewardship initiatives focus on developing and enforcing clinical protocols, educating dentists on antibiotic resistance, and implementing monitoring systems to track prescribing patterns.[126]

While Antibiotic Stewardship provides a framework for institutional policies and systemic regulation,[127] the HBM complements this by offering insights into the psychological and behavioural aspects of clinical decision-making.[128] It examines how clinicians' perceptions of risk, benefits, and barriers influence their antibiotic prescribing patterns. Key components such as perceived severity of infections, perceived susceptibility of resistance issues, and cues to action (e.g., guidelines or patient specific factors) help to explain the variability in clinical practices.[128]

This thesis integrates these frameworks to address gaps in knowledge surrounding antibiotic prophylaxis by examining not only clinical outcomes but also the decision-making process of clinicians. This dual approach provides a comprehensive understanding of the challenges and opportunities in optimising antibiotic use in dental implant surgery.

RESULTS

Study I – Randomised clinical trial

Primary outcome: implant failure

Implant failures were evaluated at follow-ups conducted 7-14 days post-surgery and again at 3-6 months. Among the 474 participants, six patients experienced failures in the antibiotic group (2.5%) as did seven patients in the placebo group (3.0%). The between-group difference in implant failure was nonsignificant at the patient level (RR 0.85; CI: 0.29-2.48, p = 0.75). A subgroup analysis indicated no significant variations when stratifying by implant location, patient age, or surgical complexity. Importantly, the overall implant success rate was 97.3% at the patient level, showcasing the effectiveness of modern implant protocols irrespective of antibiotic use.

Secondary outcome: postoperative infections

Postoperative infections were evaluated at the same follow-up times as implant failures, at 7-14 days and 3-6 months postoperatively. Infections were reported in two cases (0.8%) in the antibiotic group and five cases (2.1%) in the placebo group during the first follow-up. The between-group difference was not significant (RR: 0.29; 95% CI: 0.08-2.01, p = 0.25). During the second follow-up, infections were reported in five cases in the antibiotic group and in seven cases in the placebo group. While this suggests a potential trend toward reduced infection risk with antibiotics, the between-group difference in postoperative infections at the patient level was not significant (RR:0.70; 95% CI: 0.23-2.18, p = 0.54), Table 1. The infections were managed effectively with additional treatment, and none resulted in implant failure.

Table 1. Primary and secondary outcomes during postoperative implant surgery follow-ups in the two study groups comparing preoperative antibiotic prophylaxis with placebo.

Outcome	Antibiotic group (n= 238)	Placebo group (n= 235)	P-value
Implant failure	6 (2.5%)	7 (3.0%)	0.75
Postoperative infection First follow-up	2 (0.8%)	5 (2.1%)	0.25
Postoperative infection Second follow-up	5 (2.1%)	7 (3.0%)	0.54

Adverse events

Adverse events were systematically recorded, including any allergic reactions, gastrointestinal disturbances, or other side effects associated with antibiotic use. No adverse events were reported in either group, underscoring the safety of a single-dose prophylactic regimen with amoxicillin.

Further analyses

To ensure robustness, additional multivariate logistic analysis of the exposure variables was obtained with the following results:

- **Smoking Status:** Among smokers (n = 86), implant failure rates were slightly higher in both groups compared to nonsmokers (3.4% vs. 2.1%), but this difference was not significant (OR 1.4, 95% CI: 0.4–5.6).
- **Patient age:** Age was analysed in three categories: <50 years, 50-64 years, and ≥ 65. Compared to patients under 50 years, those aged 50-64 had an OR of 4.3 (96% CI: 0.5-37.0) for implant failure, while those aged 65 and above had an OR of 4.4 (95% CI: 0.5-38.5).
- **Bone augmentation:** Simple procedures showed a 98% success rate overall, while complex procedures involving bone augmentation demonstrated a slightly lower success rate of 95.5% (OR 1.7, 95% CI: 0.5–5.5), irrespective of antibiotic administration.
- **Number of implants:** Patients receiving multiple implants (2 or more) showed a slightly higher failure rate, though the differences were not statistically significant. Compared to patients receiving a single implant, the OR for failure was 2.2 (95% CI: 0.6-7.3) for patients receiving 2-3 implants, and 2.9 (95% CI: 0.5-16.0) for those receiving four or more implants.

No variable in the analysis was significantly associated with implant failure. The logistic regression model confirmed that the difference in implant failure between the antibiotic and placebo groups was not significant (OR: 1.2; 95% CI: 0.4-3.6, $p > 0.05$). The absolute risk reduction for implant failure was 0.46%, with a

number needed to treat (NNT) of 219, indicating that only 1 in every 219 patients would benefit from antibiotic prophylaxis.

Study II – Systematic review and meta-analysis

Study selection

A comprehensive search of PubMed (Medline), Web of Science, and the Cochrane Library yielded 1,086 unique records, which were screened against strict inclusion criteria. From these, 17 full-text articles were read in full-text and included for further assessment. Five of these articles were excluded because they were either not randomised or the lacked a control group given no antibiotics or a placebo. Hence, twelve studies were eligible for risk of bias assessment and seven were ultimately included in the meta-analyses. Table 2 presents the risk of bias in the twelve studies included in the qualitative analysis.

Table 2. Methodological assessment of the remaining RCTs after full text assessment (n=12) with the Risk of Bias in RCTs of interventions tool (RoB-2).

RCTs	Overall risk of bias	Risk of bias arising from randomization process	Risk of bias due to deviations from intended interventions	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported results	Conflicts of interest
Abu-Ta'a (2007)	🔴	🟢	🟢	🟢	🔴	🟢	🟢
Anitua (2009)	🟡	🟢	🟢	🟢	🟢	🟢	🟡
Caiazzo (2021)	🔴	🟡	🔴	🟢	🟡	🟡	🟡
Esposito (2008)	🟡	🟢	🟢	🟢	🟢	🟢	🟡
Esposito (2010)	🟡	🟢	🟢	🟢	🟢	🟢	🟡
Kashani (2019)	🔴	🔴	🔴	🟢	🟡	🔴	🟢
Momand (2021)	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Moslemi (2015)	🔴	🟢	🟢	🟢	🟢	🔴	🟢
Nolan (2013)	🔴	🟢	🟢	🔴	🟢	🔴	🟢
Payer (2020)	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Santamaría Arrieta (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Tan (2013)	🟢	🟢	🟢	🟢	🟢	🟢	🟢

Risk of bias: 🟢 = low, 🟡 = moderate, 🔴 = serious

Characteristics of included studies

The seven included studies involved 1,859 patients and 3,014 implants. Six studies were conducted in Europe, and one in Asia, with publication dates ranging from 2005 to 2023. The majority utilised amoxicillin as the prophylactic agent,

with one study including clindamycin for penicillin-allergic patients. All studies employed double-blinded methodologies and were assessed as low or moderate risk of bias using the RoB-2 tool.[115]

Primary outcome: implant failure

The pooled analysis revealed a risk ratio (RR) of 0.66 (95% CI: 0.30–1.47), indicating no significant reduction in implant failure rates with antibiotic prophylaxis (Figure 7). The absolute risk reduction was 0.07% (95% CI: –0.035 to 0.020). The number needed to treat (NNT) was calculated at 143 (CI: 29-∞), meaning that antibiotics would need to be administered to 143 patients to prevent one implant failure.

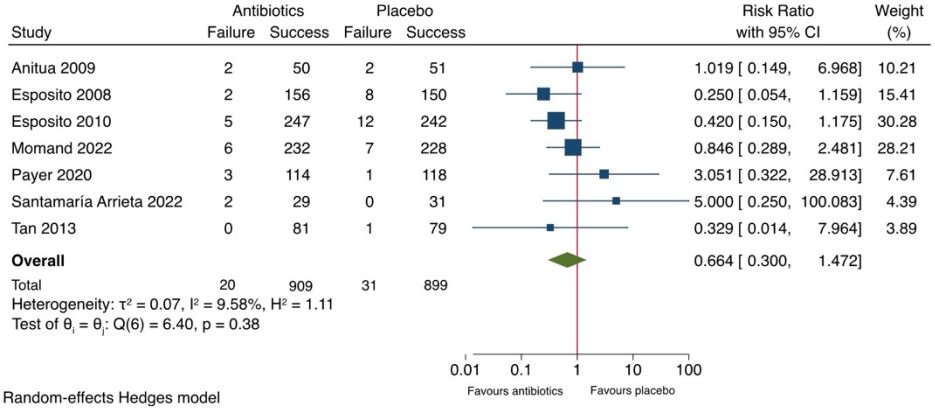

Figure 7. Forrest plot (risk ratio) of comparison between treatment with antibiotic prophylaxis and placebo in all RCTs using the outcome: patients with implant failure.

Secondary outcomes and subgroup analyses

Beyond the primary outcome of early implant failure, additional analyses examined postoperative infection rates and adverse events associated with antibiotic prophylaxis in dental implant surgery. While postoperative infections were reported in several of the included trials, the meta-analysis did not reveal a significant reduction in infection rates among patients receiving antibiotic prophylaxis compared to those given a placebo. The overall infection rate was low across all studies, regardless of antibiotic use. The incidence of antibiotic-related adverse events, such as gastrointestinal disturbances and allergic

reactions, was consistently low in the included trials. However, some studies noted that antibiotic use led to mild side effects in a subset of patients.

Additional analyses focused on postoperative infection rates and adverse events. Subgroup analyses included:

- **Antibiotic Type:** Trials exclusively using amoxicillin showed results consistent with the overall findings, with no significant difference observed.
- **Surgical Complexity:** Excluding studies involving immediate implant placement did not alter the conclusions, reinforcing the robustness of the findings.
- **Study Quality:** Trials with lower risk of bias demonstrated similar outcomes to the overall analysis.

Certainty of evidence

The GRADE assessment rated the certainty of evidence as moderate due to heterogeneity among studies and limited effect sizes, Table 3.

Table 3. Effects and certainty of evidence regarding antibiotic prophylaxis for prevention of early implant failure in healthy patients.

Outcome measure	Risk Ratio (95% CI)	Risk Difference (95 % CI)	Certainty of evidence (GRADE)	Comments
Patients with implant failure	RR: 0.66 (95% CI: 0.30-1.47)	RD: -0.007 (95% CI: -0.035-0.020)	Moderate certainty of evidence for a very small effect of antibiotic prophylaxis	Transferability: -1

Details on excluded studies

Five studies were excluded due to methodological issues such as lack of randomisation or absence of a placebo group. By excluding these studies, the meta-analysis ensured that only high-quality, placebo-controlled, and RCTs with a low or moderate risk of bias were included.

Study III – Cross-sectional study

Patient characteristics

The study analysed 450 patient records, including 250 from the Public Dental Service Stockholm and 200 from Smile Dentistry, a private dental provider. The study population consisted of 48.0% male (n = 216) and 52.0% female (n = 234) patients, with a mean age of 59.9 years (SD = 13.4), ranging from 20 to 94 years.

Tobacco use was reported by 12.6% of patients, with 5.7% smoking cigarettes and 6.9% using snuff. Data on tobacco use was missing for 45 patients (10.0%). Systemic conditions in the study population included diabetes (6.4%), cancer (2.9%), and osteoporosis (1.3%).

Procedural details

Regarding surgical procedures, 72.2% (n = 325) were straightforward implant placements, while 8.9% (n = 40) involved a closed sinus lift without bone augmentation. Immediate implant placement without bone augmentation was performed in 1.6% (n = 7) of the surgeries, and bone augmentation was carried out in 15.6% (n = 70). Among the bone augmentation cases, 7.8% (n = 35) involved bone augmentation alone, 4.9% (n = 22) combined it with a closed sinus lift, and 2.9% (n = 13) combined it with immediate implant placement. The total number of implants placed was 616. Most surgeries were one-stage procedures (78.4%, n = 353), while 21.6% (n = 97) were two-stage surgeries.

Antibiotic use patterns

Antibiotic prophylaxis was administered to 45.6% (n = 205) of patients, whereas 54.4% (n = 245) did not receive antibiotics. In straightforward implant placements, 29.5% (n = 96) of patients received antibiotics. The use of antibiotic prophylaxis was significantly higher in bone augmentation procedures, with 88.6% (n = 62) receiving antibiotics. Within the bone augmentation subgroup, 90.0% (n = 18) of autologous bone cases received antibiotics, while 81.0% (n= 17) of synthetic bone cases did not. In cases where both autologous and synthetic bone were used, 75.0% (n = 3) received antibiotics. The highest antibiotic administration rates were observed in cases involving membranes, with 100% of autologous bone + membrane (n = 3) and autologous + synthetic bone + membrane (n = 5) cases receiving antibiotics. For synthetic bone + membrane procedures, 94.1% (n = 16) of patients received antibiotics.

Duration and type of antibiotics

The duration of antibiotic prophylaxis varied based on surgical complexity. Among patients who did not undergo bone augmentation, 62.4% received no antibiotics, 30.5% received a single preoperative dose, 5.8% received antibiotics for 3–10 days postoperatively, and 1.3% received both a preoperative dose and a postoperative regimen. For bone augmentation procedures, antibiotic use was more extensive. Among autologous bone cases, 40.0% received a single

preoperative dose, 15.0% received antibiotics postoperatively for 3–10 days, and 35.0% received both a preoperative dose and a postoperative course. In synthetic bone procedures, 66.7% received a single preoperative dose, 9.5% had postoperative antibiotics for 3–10 days, and 4.8% had both. In cases where both autologous and synthetic bone were used, 25.0% received a preoperative dose, while 50.0% had both preoperative and postoperative antibiotics. Among synthetic bone + membrane cases, 17.6% had a preoperative dose, 47.1% received postoperative antibiotics for 3–10 days, and 29.4% had both. In autologous + synthetic bone + membrane procedures, 40.0% had a preoperative dose, while 60.0% received both preoperative and postoperative antibiotics. Amoxicillin was the predominant antibiotic prescribed (86.0%), followed by clindamycin (9.0%) for patients with penicillin allergies. Single-dose regimens were frequently used in straightforward cases, while extended courses lasting up to 10 days were common in complex surgeries.

Predictors of antibiotic use

Logistic regression analysis identified surgical complexity as the strongest predictor of antibiotic prophylaxis administration. Compared to straightforward implant placements, the odds of receiving antibiotics were significantly higher for closed sinus lift without bone augmentation (OR = 17.5, 95% CI: 6.7–45.9, $p < 0.001$), bone augmentation (OR = 14.7, 95% CI: 5.3–40.3, $p < 0.001$), closed sinus lift with bone augmentation (OR = 68.6, 95% CI: 8.8–537.1, $p < 0.001$), and immediate implant placement with bone augmentation (OR = 10.8, 95% CI: 1.7–101.0, $p = 0.016$). Patient-specific factors, such as age, tobacco use, and chronic diseases, showed limited influence on antibiotic prescription. Patients aged 75+ had a slightly higher likelihood of receiving antibiotics (OR = 1.8, 95% CI: 0.7–4.6, $p = 0.234$), though this was not statistically significant. Tobacco users who used snuff had a lower likelihood of receiving antibiotics (OR = 0.3, 95% CI: 0.1–1.1, $p = 0.067$). Among patients with chronic conditions, diabetes (OR = 1.8, 95% CI: 0.6–4.7, $p = 0.266$) and cancer (OR = 1.9, 95% CI: 0.6–6.4, $p = 0.307$) were not significantly associated with increased antibiotic use. However, osteoporosis was strongly associated with antibiotic administration (OR = ∞, $p = 0.006$), meaning all osteoporosis patients in the study received antibiotics.

Study IV – Qualitative study

The study explored the attitudes and practices of dentists regarding antibiotic prophylaxis in dental implant surgery amidst concerns about antibiotic resistance. Through in-depth qualitative interviews, three major themes emerged, each with distinct underlying categories. These themes and categories encapsulate the complex factors influencing dentists' decision-making and perspectives on the use of antibiotics.

Theme 1: Perceptions of antibiotic resistance

This theme highlights dentists' awareness of the global issue of antibiotic resistance and its implications for clinical practice. Three categories were identified under this theme:

Describing increased antibiotic resistance

Dentists recognised the growing prevalence of antibiotic-resistant bacteria and expressed concerns about its long-term societal impact. Many acknowledged that every antibiotic prescription contributes to resistance, emphasising the need to use antibiotics sparingly and responsibly.

Experiencing the risk of antibiotic resistance as abstract

Although aware of antibiotic resistance, many dentists perceived it as an abstract and distant issue compared to the immediate clinical challenges they face. This perception often led to a prioritisation of individual patient outcomes over broader public health concerns.

Experiencing the risk of postoperative infection as concrete

In contrast to the abstract nature of antibiotic resistance, the risk of postoperative infection was seen as an immediate and tangible concern. Dentists often prioritised the prevention of infections in their clinical decision-making, even if it involved antibiotic use.

Theme 2: Attitudes on antibiotic prophylaxis

This theme explores the varied attitudes dentists hold regarding the necessity of antibiotic prophylaxis. The following categories were identified:

The surgical procedure and patient needs determine antibiotic prophylaxis

Dentists tailored their antibiotic use based on the complexity of the procedure and individual patient factors. For instance, procedures involving bone augmentation or sinus lifts were more likely to warrant prophylaxis compared to straightforward implant placements.

Clinical experience and aseptic procedures reduce the need for antibiotic prophylaxis

More experienced dentists relied on aseptic techniques and minimally invasive approaches to reduce infection risks, often eliminating the need for antibiotics. These practitioners emphasised that careful surgical techniques could be as effective as prophylactic antibiotics in preventing infections.

Routine use of antibiotic prophylaxis

Some dentists continued to advocate for routine antibiotic prophylaxis as a precautionary measure, particularly in risk patients or complex surgical cases. This approach reflected a belief that antibiotics added an extra layer of protection against potential complications.

Theme 3: Need for clear guidelines

The third theme underscores the importance of clear, evidence-based guidelines to support dentists in making consistent decisions about antibiotic use. Three categories emerged:

Awareness of and responsiveness to new research

Dentists expressed a willingness to adapt their practices based on emerging evidence but emphasised the need for authoritative recommendations to ensure consistency.

Lack of evidence-based knowledge

The absence of robust evidence on the effectiveness of antibiotics led to uncertainty and variability in prescribing practices.

Variability in existing guidelines

Participants noted inconsistencies across national and international guidelines, which created confusion and left room for personal interpretation. This variability further compounded the challenge of standardising practices.

DISCUSSION

Findings and contextualisation

The findings of this thesis, derived from the four studies, provide a comprehensive perspective on the role of antibiotic prophylaxis in dental implant surgery. The randomised clinical trial (study I) demonstrates no statistically significant differences in implant failure rates or postoperative infections between patients receiving antibiotics and those receiving a placebo. This finding aligns with the conclusions of the systematic review and meta-analysis (study II), which reinforced that the clinical benefit of routine antibiotic prophylaxis in healthy patients undergoing implant surgery is minimal. The systematic review further revealed a high number of needed to treat (NNT=143), underscoring that antibiotic use in this context may not be justified.

The cross-sectional study (study III) explored real-world antibiotic prescribing patterns among Swedish dentists. The findings revealed considerable variability, with antibiotics frequently administrated for complex cases involving bone augmentation, whereas straightforward implant surgeries were often managed without prophylaxis. These variations reflect both surgical complexity and inconsistencies amongst clinicians, as vast variations were observed amongst dose and durations of antibiotics regimens. The qualitative study (study IV) provided further insight into the decision-making processes behind antibiotic use, revealing a tension between dentists' awareness of antibiotic resistance and their immediate clinical concerns about postoperative infections. Many participants expressed frustration over the lack of clear, evidence-based guidelines, which led to subjective interpretation and variability in practice. This highlights a significant challenge in bridging the gap between research findings (studies I and II) and their practical implementations in clinical settings (studies III and IV).

The discrepancy highlights the necessity for more explicit guidelines and enhanced educational initiatives to ensure that evidence-based practices are effectively translated into routine clinical decision-making.

The findings of this thesis support and contribute to the ongoing efforts in antibiotic stewardship, reinforcing its importance in responsible antibiotic use and management. As highlighted in the thesis introduction, antibiotic resistance is an urgent global crisis, exacerbated by the overuse and misuse of antibiotics.[14] The debated impact of antibiotic prophylaxis in implant surgery suggests that routine prescription should be re-evaluated, particularly in light of the growing prevalence of resistant bacterial strains. Sweden's relatively low antibiotic consumption reflects a successful model of stewardship, yet even here, concerns persist regarding antibiotic resistant infections.[21] The convergence of these findings necessitates a shift in clinical practice, ensuring that antibiotics are reserved for cases where their benefits outweigh the risks.

Integrating key factors in successful dental implant surgery

A nuanced understanding of successful dental implant surgery necessitates the consideration of several factors beyond antibiotic use. These include aseptic techniques, the complexity of the surgery, clinician's experience, and patient-specific factors such as smoking, oral hygiene and chronic diseases.[73,129,130] These elements not only influence surgical outcomes but may also help contextualise the finding of the studies in this thesis.

Aseptic techniques in implant surgery

Aseptic techniques are a cornerstone in preventing infections and ensuring the long-term success dental implants. Given the high microbial load in the oral cavity, strict adherence to aseptic protocols is crucial to prevent bacterial contamination, which can compromise osseointegration and ultimately lead to implant failure.[130] The duration of the surgical procedure also plays a critical role in infection risk. Prolonged surgeries increase the exposure time to potential contaminants, thereby elevating the risk of postoperative infections.[131] Efficient surgical practices that minimise operative time, ensuring minimal tissue trauma and maintaining strict sterile conditions, are essential components of aseptic practice.

Findings from the RCT (study I) suggest that the benefit of antibiotic prophylaxis in dental implant surgery is minimal and may not be necessary in most cases. The study found no significant difference in implant failure or postoperative infection between patients who received antibiotic prophylaxis and those who received a placebo. These findings could suggest that strict aseptic techniques can compensate for the lack of antibiotic prophylaxis, ensuring favourable clinical outcomes without unnecessary antibiotic use. This perspective supports the idea that surgeon expertise and adherence to aseptic protocols can significantly reduce infection risks, minimising the need for prophylactic antibiotic. A study by Rogers et al. (2010) found that surgical procedures performed with meticulous aseptic techniques, including sterile draping, appropriate hand hygiene, and proper instrument sterilisation, resulted in a low surgical site infection, even in the absence of prophylactic antibiotic.[132] These findings reinforce the importance of strict asepsis in surgical procedures, demonstrating that well-trained clinicians who follow evidence-based infection control measures can achieve similar success rates regardless of antibiotic administration.

The qualitative study (study IV) revealed a strong awareness of antibiotic resistance and the need for alternative infection control strategies. Several dentists emphasised that they rely in high surgical standards, meticulous tissue handling, and controlled operative environments to ensure successful implant outcomes.

The systematic review and meta-analysis (study II) found that antibiotic prophylaxis provided a minimal absolute risk reduction for early implant failure, suggesting that infection prevention could focus on aseptic surgical protocols rather than routine antibiotic use.

Complexity of the surgery

The complexity of dental implant surgeries is another determining factor for infection risks and antibiotic necessity. Advanced procedures, such as full-arch restorations or extensive bone augmentations, inherently carry higher risks due to prolonged surgical times, larger wound areas, and the use of grafting materials. In such cases, the body's natural defences may benefit from adjunctive antibiotic prophylaxis to mitigate infection risks.[133]

The findings from the cross-sectional study reflect this reality, with extended antibiotic regimens more frequently prescribed for complex surgeries. Recent literature presents conflicting perspectives on the necessity and effectiveness of

antibiotic prophylaxis in bone augmentation procedures related to dental implant surgery. The study by Klinge et al. (2020) systematically reviewed the evidence regarding prophylactic antibiotic use in staged bone augmentation, concluding that the available scientific data remains insufficient to determine whether a single dose of antibiotics or prolonged regimens significantly reduce infection risk.[103] Similarly, Salgado-Pelvaro et al. (2022) highlighted the lack of conclusive evidence supporting the routine use of antibiotics in these procedures but suggested that a single preoperative dose of 2-3 g amoxicillin may help reduce early implant failure and the bacterial contamination of grafted bone particles.[104] Both studies emphasise the importance of balancing antibiotic use with the growing concern of antibiotic resistance. While some randomised clinical trials indicate a potential benefit in reducing postoperative infections, the lack of large-scale, high-quality studies limits definitive conclusions. The findings suggest that antibiotic prophylaxis should be tailored to individual patient risk factors rather than universally applied. More research, particularly well-controlled clinical trials, is needed to establish clear guidelines on antibiotic use in bone augmentation procedures for dental implants.

The experience of the clinician

Surgical experience is a critical factor influencing clinical outcomes across various medical disciplines. In dental implant surgery, the proficiency of the operator has been linked to implant survival rates, complication rates, and overall patient outcomes. A systematic review and meta-analysis by Sendyk et al. (2017) systematically analysed the correlation between surgical experience and dental implant survival rates.[134] Their meta-analysis confirmed that experienced surgeons achieved significantly higher implant survival rates compared to less experienced practitioners. Factors contributing to these improved outcomes include superior surgical technique, better case selection, and the ability to manage intraoperative complications effectively.

Similarly, Mascarenhas et al. (2023) conducted a randomised controlled trial evaluating antibiotic prophylaxis in implants placed by unexperienced operators.[135] Their findings indicated that the loss of implant was significantly higher in patients treated by less experienced practitioners, particularly in the absence of prophylactic antibiotics. The study highlighted that inexperience increases the risk of bacterial contamination and inadequate implant placement, leading to early implant failure.

The impact of experience on surgical outcomes extends beyond dental implant surgery. In orthopaedic surgery, research has shown that surgeons with higher caseloads and years of experience have lower rates of postoperative complications and better functional outcomes for joint replacements.[136]

In cardiovascular surgery, research has demonstrated that increased surgeon experience is associated with improved patient outcomes. A study examining reoperative cardiac surgeries found that both increasing surgeon experience and cumulative institutional experience contributed to decreased hospital mortality rates.[137]

In study IV this topic was further explored where some clinicians expressed the view that advance surgical skill experiences and adherence to strict aseptic techniques reduced the need for prophylactic antibiotics. This perspective underscores how experience not only enhances procedural success but also influences clinical decision-making regarding adjunctive therapies.

However, it is important to note that the relationship between surgeon experience and patient outcomes can vary depending on the specific procedure and patient population. A study on total hip arthroplasty reported that patients can expect similar health improvements, pain reduction, and satisfaction one year after surgery, regardless of the surgeon's years in practice after specialty certification.[138] These findings suggest that while experience often contributes to better surgical outcomes, other factors such as surgical volume, continuous professional development, and adherence to best practice also play crucial roles in ensuring patient safety and procedural success.

Patient-specific factors: smoking, oral hygiene and chronic diseases

Patient-specific factors, such as smoking, oral hygiene, and some chronic diseases, significantly influence implant success rates.[68,76,139]

Smoking is a well-documented risk factor for implant failure and impaired osseointegration. The physiological effects of smoking – including reduced blood flow and impaired immune response – compromise the healing process and increase susceptibility to infections.[75,140,141] It is essential to inform patients about these risks, and ideally, support smoking cessation programmes preoperatively. Effective communication about the benefits of quitting smoking could significantly enhance long-term implant success rates.[77]

Similarly, preoperative oral hygiene plays a foundational role in reducing surgical complications.[142,143] Several of the RCTs included in study II of this thesis had implemented strict oral hygiene protocols before surgery, emphasising professional cleanings and patient education on plaque control. These measures have been shown to improve outcomes by reducing bacterial loads and mitigating peri-implant inflammation.[144,145] The qualitative study in this thesis revealed that many dentists emphasise the importance of oral hygiene during the interviews, identifying it as a critical factor in surgical success. Integrating such protocols more systematically could further enhance patient outcomes while reducing the reliance on antibiotic prophylaxis. In study I, a substantial proportion of the patients used chlorhexidine (CHX), following clinical protocols, both preoperatively and postoperatively. Similarly, findings from study IV indicated that several dentists recommended the use of CHX in conjunction with implant surgery, viewing it as a valuable adjunct for reducing bacterial load and preventing postoperative infections. CHX is widely recognised for its antimicrobial properties, which help lower bacterial colonisation around surgical sites, thereby reducing the risk of implant-related infections. Preoperative CHX rinses have been associated with decreased postoperative infections, while postoperative use aids in biofilm control and promotes optimal healing.[143,146]

In addition to smoking and poor oral hygiene, certain chronic diseases can lead to impaired osseointegration. Diabetes, particularly uncontrolled cases, is associated with delayed wound healing, microvascular complications, and an increased risk of peri-implantitis, which may impair implant stability.[139] Moreover, cancer patients who have undergone radiotherapy in the head and neck region may experience reduced bone vascularisation, compromising osseointegration and increasing the risk of implant failure.[147] Osteoporosis, a condition characterised by reduced bone density, may also affect implant stability by altering bone remodelling processes.[148,149] Given these risks, careful preoperative assessment and patient-specific treatment planning are crucial for optimising implant success rates in individuals with chronic conditions.

Antibiotic resistance in society: a multifaceted challenge

Antibiotic resistance is a global crisis that transcends medical disciplines, requiring concerted efforts across society. The misuse and overuse of antibiotics in medicine, agriculture, and veterinary practice contribute to the acceleration of antibiotic resistance.[150] Public health initiatives aimed at reducing unnecessary antibiotic prescriptions, coupled with educational campaigns to raise awareness, are essential. For example, stricter regulatory frameworks can help curb inappropriate antibiotic use in agriculture, while advancements in rapid diagnostic tools can guide more precise and judicious prescribing in clinical settings.[45,151]

Education plays a pivotal role in combating antibiotic resistance. By fostering a deeper understanding of resistance mechanisms and the societal implications of antibiotic misuse, healthcare professionals can make more informed decisions.[150] Evidence-based prescribing practices across all fields, including dentistry, play a role in reducing unnecessary antibiotic use and supporting global efforts to combat resistance.[88] Collaborative research and interdisciplinary approaches are also necessary to address knowledge gaps and drive innovation in antibiotic stewardship.[152,153]

Study IV in this thesis, the qualitative study on Swedish dentists' attitudes towards antibiotic prophylaxis, illustrate a key dilemma in healthcare: the balance between immediate patient safety and long-term public health consequences. The results from study IV highlighted that Swedish dentists, despite being aware of antibiotic resistance, often perceived it as a distant or abstract threat, whereas the risk of immediate post-surgical infections is more tangible. This reflects a larger societal challenge where individuals may undervalue the long-term impact of antibiotic overuse. Public education and behavioural interventions aimed at changing societal attitudes toward antibiotics are crucial for reducing unnecessary prescriptions and mitigating resistance. Future policies must focus not only on regulating antibiotic use in healthcare but also on fostering a cultural shift in how antibiotics are perceived and utilised across all sectors of society.[154]

At a global level, efforts to curb antibiotic resistance must integrate multiple strategies, including improved diagnostic tools, better infection control measures, and continued research into alternative antimicrobial therapies.[150] The findings from the included studies of this thesis support the broader call for more stringent prescribing practices in dental implant surgery, where prophylactic antibiotics

have traditionally been used despite insufficient scientific support. Addressing antibiotic resistance requires a paradigm shift that prioritises long-term sustainability over immediate clinical convenience, ensuring that antibiotics remain effective for the future.

Antibiotic use in dental implant surgery: global perspectives and challenges

The administration of antibiotics in dental implant surgery varies significantly across different countries, reflecting disparities in healthcare systems, clinical guidelines, and cultural practices. In Sweden, where national recommendations emphasise antibiotic stewardship, a restrained approach is observed, with prophylaxis primarily reserved for complex cases.[63] The Swedish recommendations align with the recommendations concluded at the 4th EAO Consensus Conference in 2015, namely no antibiotic prophylaxis in straightforward surgeries; however, clinicians should consider it for complex surgical cases.[155] The risk with early implant failure and postoperative infection must be carefully balanced against the potential harm of unnecessary antibiotic administration to multiple patients. Opinions on this matter are divided. While some systematic reviews support antibiotic prophylaxis to reduce early implant loss in healthy patients,[156-158] others argue that routine antibiotic use may not be justified.[145,159-162] These conflicting conclusions and differing perspectives have made it challenging to establish clear, universally accepted guidelines for antibiotic use in implant surgery.

In study III of this thesis, it was found that over 70% of implant surgeries were straightforward, and in these cases, antibiotics were omitted in 70.5% of instances. However, despite Swedish dentists largely aligning with national recommendations, the study also found that 29.5% of straightforward cases still receive antibiotic prophylaxis. This highlights that while Sweden demonstrates a relatively judicious approach compared to other countries, there is still room for improvement in reducing unnecessary antibiotic use.

The persistence of antibiotic prophylaxis in low-risk cases could, in part, be attributed to the vagueness of Swedish guidelines, which leaves room for individual interpretations. In study IV of this thesis, it was revealed that Swedish dentists experience noteworthy uncertainty in decision-making due to the lack of clear guidelines. Many clinicians expressed frustration over the ambiguous nature of current recommendations, which do not provide specific directives for

different surgical scenarios. This uncertainty fosters clinical variation, where some dentists opt for a precautionary approach by prescribing antibiotics even when it may not be necessary, while others strictly adhere to minimal-use principles. Study IV also highlighted that many clinicians actively call for clearer, more structured guidelines to standardise antibiotic prophylaxis practices.

Despite this, the Swedish approach to antibiotic prophylaxis stands in stark contrast to practices in several other countries, where routine antibiotic use remains common, even for low-risk procedures. For example, in Spain and Italy, survey studies indicate that over 80% of dentists routinely prescribe prophylactic antibiotics for all implant procedures, regardless of complexity.[85,163] This is in part due to national guidelines that favour routine prophylaxis, a stance supported by organisations such as the Spanish Society of Implants and the Italian Academy of Osseointegration, which recommend antibiotics even for straightforward cases.[83,84] These differences illustrate the fragmented nature of global dental protocols, making it challenging to establish universal guidelines.

Similarly, in North America, particularly in the United States and Canada, prescribing patterns remain relatively liberal, with a significant portion of clinicians prescribing antibiotics as a precautionary measure even in healthy patients undergoing uncomplicated procedures.[56] This may be due to concerns over litigation, patient expectations, and historical prescribing habits, which still influence decision-making in some dental practices.[164,165]

Conversely, in countries such as the United Kingdom and the Netherlands, antibiotic stewardship programmes have led to stricter guidelines, reducing prophylactic antibiotic use in straightforward implant cases.[166,167]

The discrepancies between Sweden and other countries highlight the challenge of achieving a global consensus on antibiotic prophylaxis in implant dentistry. The Swedish model, which prioritises restrictive antibiotic use and emphasises aseptic surgical techniques over routine prophylaxis, could serve as an example for other nations looking to reduce unnecessary prescriptions. However, its implementation requires clearer, evidence-based guidelines to address the inconsistencies observed within Swedish clinical practice itself.[168]

As growing evidence questions the need for routine antibiotic prophylaxis in dental implant surgery, the emphasis should move toward alternative infection strategies. Even a single dose of antibiotics can disrupt microbial balance, potentially fostering resistance and altering the host's immune response.[87] Given

these risks, the emphasis on aseptic surgical protocols, patient-specific risk assessments, and judicious antibiotic use becomes even more critical.

Ultimately, the lack of uniformity in clinical guidelines worldwide complicates efforts to develop a global standard for antibiotic use in dental implant surgery. The evidence suggests that for straightforward surgeries, prophylactic antibiotics may not be necessary. However, for complex cases involving bone augmentation or other risk factors, their use remains a subject of ongoing investigation. Moving forward, there is a pressing need for updated, evidence-based guidelines that balance infection prevention with the imperative to curb antibiotic overuse.

Antibiotic prophylaxis in bone augmentation

Bone augmentation is a critical adjunct in dental implant surgery, addressing insufficient bone volume to ensure successful implant placement and osseointegration. The importance of infection prevention in bone augmentation cannot be overstated, as postoperative infections can compromise graft integration, jeopardising both bone stability and implant success.[100]

The Swedish guidelines do not recommend antibiotic prophylaxis for implant surgery but suggest that a single dose of amoxicillin may be considered for patients with a combination of multiple risk factors.[63] The guidelines lack more refined details regarding complex procedures such as bone augmentation and sinus lifts. This gap leaves room for dentists to reply on their own clinical judgement and personal experience when deciding on prophylactic measures, leading to variability in practice. Study III revealed that 90% of bone augmentation cases involved antibiotic use, particularly protocols utilising synthetic materials and membranes. This indicates a clear tendency among Sweden dentists to administer prophylactic antibiotics in complex procedures. Findings from study IV further support this observation, as clinicians revealed being more prone to prescribe antibiotics in complex cases, perceiving these procedures as carrying a higher risk of postoperative infection. Many interviewees justified their antibiotic use in bone augmentation procedures by citing concerns over graft integration and potential complications. However, the lack of clear surgical protocols left room for variations in prescribing habits and uncertainty about the best practices.

These findings align with international research highlighting the variability in antibiotic stewardship. A study by Becker et al. (2024) assessing antibiotic prescription patterns in implant dentistry found that despite widespread

awareness of antimicrobial resistance, many clinicians continued to prescribe antibiotics at high rates, particularly in complex cases.[86] This suggests that while antibiotics are frequently administered in bone augmentation procedures, adherence to stewardship principles remain inconsistent. Given the emphasis on reducing unnecessary antibiotic use, the need for evidence-based, standardised protocols for antibiotic prophylaxis in complex surgeries remains crucial. Striking the right balance between infection prevention and responsible antibiotic stewardship is essential, ensuring that prescribing practices align with both clinical necessity and antibiotic resistance mitigation efforts – a challenge that continues to be widely discussed in the field.

Advancements in biomaterial, such as bioactive glass and platelet-rich fibrin, have also reduced infection risks by enhancing wound healing and tissue regeneration. These innovations highlight the potential for alternative strategies to antibiotics, emphasising the need for further research into non-antibiotic-based infection prevention measures.[169,170] The findings underscore the importance of tailoring use to the complexity of the procedure and patient specific risk factors, aligning with broader goals of antibiotic stewardship.

Methodological considerations

This thesis employed a multi-methodological approach, integrating both quantitative and qualitative research to provide a comprehensive understanding of antibiotic prophylaxis in dental implant surgery. The strength of combing multiple methodologies lies in the ability to capture both clinical outcomes and real-world practice variations, ensuring that findings are not only statistically rigorous but also contextually meaningful.

The qualitative methods in this thesis, such as the RCT, systematic review, and cross-sectional analyses, offer objective, measurable data on clinical efficacy, risk factors, and adherence patterns. These approaches help establish casual relationships and generate generalisable conclusions about the effectiveness of antibiotic prophylaxis and how it is used. However, numbers alone cannot fully explain the decision-making processes behind clinical practices. This is where qualitative research plays a crucial role.

The qualitative study provided deeper insight into how and why clinicians make administration decisions, revealing that guideline ambiguity, personal experience, and risk perception influence antibiotic use. This complements

qualitative findings by illuminating the behavioural and systemic factors affecting antibiotic stewardship.

Combining quantitative and qualitative methods in a mixed-methods approach leverages the strength of both, offering a more comprehensive understanding of research questions. Quantitative data can reveal patterns and the extent of phenomena, while qualitative data can explain the 'why' and 'how' behind these patterns. This integration allows researchers to validate findings across methodologies and provides a more nuanced perspective than either approach alone.[171]

In the context of this thesis, employing both quantitative and qualitative methodologies enabled a thorough examination of antibiotic prophylaxis in dental implant surgery. Quantitative methods provided measurable evidence of clinical outcomes, while qualitative approaches offered insights into the decision-making processes of clinicians. This combination of methods is particularly valuable in addressing complex, multifaced issues like antibiotic resistance, where clinical outcomes must be considered alongside human behaviour, professional judgement, and systemic influences.

Results in the context of theoretical frameworks

The findings of this thesis are deeply rooted in the frameworks of Antibiotic Stewardship and the Health Belief Model, both of which offer essential lenses for analysing the judicious use of antibiotics in dental implant surgery.

Health Belief Model (HBM)

The HBM is a psychological framework that examines how individual perceptions of health risks and benefits influence decisions-making.[121,128] In this thesis, the HBM sheds light on the behavioural drivers of antibiotic prescribing among dentists. For instance, the qualitative study revealed that while dentists recognise antibiotic resistance as a significant societal threat, the immediate risk of postoperative infections often outweighs abstract concerns about resistance. This tension reflects key components of the HBM, such as the perceived severity (risk of infections vs. antibiotic resistance) and perceived barriers (lack of clear guidelines).

One notable example of the HBM's application beyond dentistry is its extensive application to understand individuals' decisions regarding vaccinations. Research by Limbu and Gautam (2023) have shown that individuals' decisions to vaccinate are influenced by their perceived susceptibility to diseases and the perceived benefits of vaccination.[172] This parallels decision-making in dental implant surgery, where a dentist's choice to administrate antibiotics is shaped by their assessment of patient-specific risks, the perceived severity of potential infections, and the expected benefits of antibiotic prophylaxis. Just as individuals weigh personal health risks when considering vaccination, dentists evaluate multiple factors – such as surgical complexity, patient health conditions, and infection risks – before deciding whether antibiotic prophylaxis is necessary. In study IV many of the dentist explain this decision-making process frequently. By applying the HBM, valuable insight is gained into how dentists perceive and respond to these risks, highlighting its relevance in shaping evidence-based clinical behaviours and optimising antibiotic use in dental settings.

Antibiotic Stewardship

Antibiotic stewardship is a global strategy aimed at optimising the use of antibiotics to combat resistance.[46] Its principles prioritise evidence-based prescribing, minimising unnecessary antibiotic use while ensuring effective infection prevention. In the context of this thesis, the stewardship framework provides a critical perspective on the balance between patient safety and the broader societal responsibility of reducing resistance.[173] For example, the findings of study I and II that routine prophylaxis in healthy patients offers minimal clinical benefit align with the stewardship goals by discouraging excessive antibiotic use. Additionally, the variability in prescribing practices observed in study III underscores the need for clear, standardised guidelines to enhance adherence to stewardship principles.

Integration of frameworks in this thesis

By integrating Antibiotic Stewardship and the HBM, this thesis provides a comprehensive understanding of the clinical and behavioural factors influencing antibiotic use in dental implant surgery. The stewardship framework emphasises the importance of aligning practices with evidence-based guidelines, while the HBM offers insights into the cognitive and contextual elements that drive decision-making. For example, the observed variability in prescribing practices

can be understood as a product of both systemic gaps in guidelines (stewardship) and individual risk-benefit assessments (HBM).

The integration of these frameworks also underscores the importance of targeted interventions to support clinicians in navigating these complexities. Educational initiatives that address both clinical evidence and the behavioural aspects of administrating can empower dentists to make informed, stewardship-aligned decisions. Moreover, interdisciplinary collaborations and continued research are essential for refining guidelines and addressing the contextual challenges highlighted by the HBM.

This thesis advances the discourse on antibiotic prophylaxis in dental implant surgery by providing a nuanced, evidence-based perspective that bridges clinical outcomes and public health priorities. The findings advocate for a shift toward more selective and targeted use of antibiotics, emphasising the importance of clear guidelines, education, and global collaboration. By integrating diverse methodologies and theoretical insights, this work lays the foundation for optimising antibiotic use in dentistry, safeguarding the efficacy of these critical drugs for future generations, and addressing the urgent challenge of antibiotic resistance.

CONCLUSION

This thesis provides compelling evidence that routine antibiotic prophylaxis in patients undergoing straightforward dental implant surgery is unnecessary and unjustified. While antibiotic use in Sweden is relatively restrained, there is still room for improvement. Dentists are aware that antibiotic resistance is a growing problem, yet it often feels abstract rather than an immediate concern.

The lack of clear recommendations creates uncertainty, leading to significant variations in clinical practice. To address this, new and well-defined guidelines must be established, accompanied by robust implementation strategies. Educational initiatives – both in dental training and continuous professional development – are crucial to fostering a deeper understanding of antibiotic stewardship and the global resistance crisis.

The findings of this thesis challenge long-standing clinical habits and provide clear directive: routine antibiotic prophylaxis in patients undergoing straightforward dental implant surgery is not warranted and should no longer be standard practice.

FUTURE RESEARCH

The findings of this thesis highlight several critical gaps that warrant further investigation to optimise antibiotic prophylaxis in dental implant surgery while addressing the global challenge of antibiotic resistance. Future research should focus on refining evidence-based guidelines, developing alternative infection control strategies, and exploring the broader implication of antibiotic use in implant dentistry.

Firstly, there is a specific need to investigate the effect of antibiotic prophylaxis in dental implant surgery involving bone augmentation. While this thesis demonstrated that prophylaxis may not be necessary for straightforward cases, complex procedures such as guided bone regeneration, sinus lifts, and extensive grafting presents different infection risks. Identifying the optimal antibiotic regimen for these procedures is highly sought after, as current clinical practices vary widely. Research should aim to determine whether antibiotics provide a measurable benefit in these cases and, if so, establish precise dosage and duration recommendations that minimise unnecessary exposure.

Secondly, research into alternative infection prevention methods should be prioritised. This includes investigating the role of advanced aseptic techniques, chlorhexidine rinses, photodynamic therapy, and novel antimicrobial coatings on implants. As biomaterial technology advances, studies should evaluate whether bioactive surfaces and local antimicrobial agents can replace systemic antibiotics for infection control.

Thirdly, implementation science research is needed to bridge the gap between clinical evidence and real-world practice. Future studies should explore how to effectively translate research findings into clinical guidelines that are clear, practical, and widely adopted. This includes assessing the impact of targeted

educational programmes' antibiotic stewardship initiatives on administration behaviours among dental professionals.

Additionally, qualitative and behavioural research should further investigate the psychological and decision-making factors influencing dentists' administration habits. Understanding how clinicians perceive risk, guidelines, and patient expectations can inform strategies to reduce unnecessary antibiotic use while maintaining high standards of patient care.

Finally, global comparative studies are essential to evaluate antibiotic prophylaxis trends across different healthcare systems and regulatory environments. By analysing international antibiotic administration patterns, researchers can identify best practices and work toward a unified, evidence-based global consensus on antibiotic use in dental implant surgery.

By addressing these research priorities, the dental community can move toward a more sustainable and responsible approach to antibiotic use, ensuring that infection prevention strategies are both clinically effective and aligned with global efforts to combat antibiotic resistance.

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Because you can't – I will
So, I lift my pen, reaching upward – for you
And I rise high, all the way up – for you
In another life, in another world
Where the lines between us blur,
I am you, and you are me
For we are the same – you and I
Daughters of the mighty mountains

Art by Sarah Amili. Poem by Palwasha Momand.

REFERENCES

1. Gould K. Antibiotics: from prehistory to the present day. *J Antimicrob Chemother.* 2016;71(3):572-575.
2. Mohr KI. History of Antibiotics Research. *Curr Top Microbiol Immunol.* 2016;398:237-272.
3. Hutchings MI, Truman AW, Wilkinson B. Antibiotics: past, present and future. *Curr Opin Microbiol.* 2019;51:72-80.
4. Wilson ME. *Antibiotics: what everybody needs to know.* Madison Avenue, New York, United States of America: Oxford University Press 2019.
5. Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. *Nat Rev Microbiol.* 2010;8(6):423-435.
6. Sauvage E, Kerff F, Terrak M, Ayala JA, Charlier P. The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis. *FEMS Microbiol Rev.* 2008;32(2):234-258.
7. Silver LL. Challenges of antibacterial discovery. *Clin Microbiol Rev.* 2011;24(1):71-109.
8. Spížek J, Řezanka T. Lincosamides: Chemical structure, biosynthesis, mechanism of action, resistance, and applications. *Biochem Pharmacol.* 2017;133:20-28.
9. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. *Otolaryngol Head Neck Surg.* 2007;136(3):340-347.
10. Fisher JF, Meroueh SO, Mobashery S. Bacterial resistance to beta-lactam antibiotics: compelling opportunism, compelling opportunity. *Chem Rev.* 2005;105(2):395-424.
11. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A.* 2018;115(15):E3463-e3470.
12. WHO. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *Lancet Public Health.* 2022;7(11):e897-e913.
13. WHO. Antimicrobial resistance. 2020; WHO Fact Sheets. Available at.
14. Collaborators AR. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022;399(10325):629-655.
15. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. *Microbiol Spectr.* 2016;4(2).
16. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P t.* 2015;40(4):277-283.
17. WHO. *Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022.* Geneva, Switzerland2022.

18. Robinson TP, Bu DP, Carrique-Mas J, et al. Antibiotic resistance is the quintessential One Health issue. *Trans R Soc Trop Med Hyg.* 2016;110(7):377-380.
19. STRAMA. Swedish Strategy to Combat Antibiotic Resistance 2020-2023. In. https://strama.se/wp-content/uploads/2023/06/amr_strategi_eng_web.pdf.
20. Mölstad S, Löfmark S, Carlin K, et al. Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. *Bull World Health Organ.* 2017;95(11):764-773.
21. Swedres-Svarm. *Sales of antibiotics and occurence of antibiotic resistance in Sweden.* Solna/Uppsala2023.
22. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clin Infect Dis.* 2022;75(2):187-212.
23. Folkhälsomyndigheten. Consumption of antibiotics and occurence of resistance in Sweden. Public Health Agency of Sweden and National Veterinary Institute. 2018; https://www.folkhalsomyndigheten.se/contentassets/d118ac95c12d4c11b3e61d34ee6d2332/swedres-svarm-2016-16124.pdf.
24. Darby EM, Trampari E, Siasat P, et al. Molecular mechanisms of antibiotic resistance revisited. *Nat Rev Microbiol.* 2023;21(5):280-295.
25. Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. *Clin Microbiol Rev.* 2010;23(1):160-201.
26. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis.* 2008;8(3):159-166.
27. Chambers HF, Deleo FR. Waves of resistance: Staphylococcus aureus in the antibiotic era. *Nat Rev Microbiol.* 2009;7(9):629-641.
28. Chitsaz M, Brown MH. The role played by drug efflux pumps in bacterial multidrug resistance. *Essays Biochem.* 2017;61(1):127-139.
29. Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. *Clin Microbiol Rev.* 2015;28(2):337-418.
30. Henderson JC, Zimmerman SM, Crofts AA, et al. The Power of Asymmetry: Architecture and Assembly of the Gram-Negative Outer Membrane Lipid Bilayer. *Annu Rev Microbiol.* 2016;70:255-278.
31. Pagès JM, James CE, Winterhalter M. The porin and the permeating antibiotic: a selective diffusion barrier in Gram-negative bacteria. *Nat Rev Microbiol.* 2008;6(12):893-903.
32. Delcour AH. Outer membrane permeability and antibiotic resistance. *Biochim Biophys Acta.* 2009;1794(5):808-816.
33. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis.* 2013;13(12):1057-1098.
34. McEwen SA, Collignon PJ. Antimicrobial Resistance: a One Health Perspective. *Microbiol Spectr.* 2018;6(2).
35. Abushaheen MA, Muzaheed, Fatani AJ, et al. Antimicrobial resistance, mechanisms and its clinical significance. *Dis Mon.* 2020;66(6):100971.

36. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis.* 2018;18(3):318-327.
37. Avery LM, Nicolau DP. Investigational drugs for the treatment of infections caused by multidrug-resistant Gram-negative bacteria. *Expert Opin Investig Drugs.* 2018;27(4):325-338.
38. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. *Nat Rev Microbiol.* 2012;10(4):266-278.
39. Gao W, Howden BP, Stinear TP. Evolution of virulence in Enterococcus faecium, a hospital-adapted opportunistic pathogen. *Curr Opin Microbiol.* 2018;41:76-82.
40. Cherazard R, Epstein M, Doan TL, Salim T, Bharti S, Smith MA. Antimicrobial Resistant Streptococcus pneumoniae: Prevalence, Mechanisms, and Clinical Implications. *Am J Ther.* 2017;24(3):e361-e369.
41. Huemer M, Mairpady Shambat S, Brugger SD, Zinkernagel AS. Antibiotic resistance and persistence-Implications for human health and treatment perspectives. *EMBO Rep.* 2020;21(12):e51034.
42. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother.* 2010;54(3):969-976.
43. Redgrave LS, Sutton SB, Webber MA, Piddock LJ. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. *Trends Microbiol.* 2014;22(8):438-445.
44. Grossman TH. Tetracycline Antibiotics and Resistance. *Cold Spring Harb Perspect Med.* 2016;6(4):a025387.
45. Hernando-Amado S, Coque TM, Baquero F, Martínez JL. Antibiotic Resistance: Moving From Individual Health Norms to Social Norms in One Health and Global Health. *Front Microbiol.* 2020;11:1914.
46. WHO. Global action plan on antimicrobial resistance. 2015.
47. Palmer NO. Antibiotic prescribing in general dental practice. *Prim Dent J.* 2014;3(1):52-57.
48. Cahill TJ, Harrison JL, Jewell P, et al. Antibiotic prophylaxis for infective endocarditis: a systematic review and meta-analysis. *Heart.* 2017;103(12):937-944.
49. Mahmoodi B, Weusmann J, Azaripour A, Braun B, Walter C, Willershausen B. Odontogenic Infections: A 1-year Retrospective Study. *J Contemp Dent Pract.* 2015;16(4):253-258.
50. Suda KJ, Calip GS, Zhou J, et al. Assessment of the Appropriateness of Antibiotic Prescriptions for Infection Prophylaxis Before Dental Procedures, 2011 to 2015. *JAMA Netw Open.* 2019;2(5):e193909.
51. Rega AJ, Aziz SR, Ziccardi VB. Microbiology and antibiotic sensitivities of head and neck space infections of odontogenic origin. *J Oral Maxillofac Surg.* 2006;64(9):1377-1380.
52. Heim N, Faron A, Wiedemeyer V, Reich R, Martini M. Microbiology and antibiotic sensitivity of head and neck space infections of odontogenic origin. Differences in inpatient and outpatient management. *J Craniomaxillofac Surg.* 2017;45(10):1731-1735.
53. Stein K, Farmer J, Singhal S, Marra F, Sutherland S, Quiñonez C. The use and misuse of antibiotics in dentistry: A scoping review. *J Am Dent Assoc.* 2018;149(10):869-884.e865.

54. Siddique S, Chhabra KG, Reche A, Madhu PP, Kunghadkar A, Kalmegh S. Antibiotic stewardship program in dentistry: Challenges and opportunities. *J Family Med Prim Care.* 2021;10(11):3951-3955.
55. Durkin MJ, Hsueh K, Sallah YH, et al. An evaluation of dental antibiotic prescribing practices in the United States. *J Am Dent Assoc.* 2017;148(12):878-886.e871.
56. Thompson W, Teoh L, Hubbard CC, et al. Patterns of dental antibiotic prescribing in 2017: Australia, England, United States, and British Columbia (Canada). *Infect Control Hosp Epidemiol.* 2022;43(2):191-198.
57. Halling F, Neff A, Heymann P, Ziebart T. Trends in antibiotic prescribing by dental practitioners in Germany. *J Craniomaxillofac Surg.* 2017;45(11):1854-1859.
58. Cope AL, Francis NA, Wood F, Chestnutt IG. Antibiotic prescribing in UK general dental practice: a cross-sectional study. *Community Dent Oral Epidemiol.* 2016;44(2):145-153.
59. Dahlén G. Prescription of antibiotics in dentistry - a report from the Swedish STRAMA work. *Journal of Oral Microbiology.* 2017;9:1325230.
60. Lund B, Cederlund A, Hultin M, Lundgren F. Effect of governmental strategies on antibiotic prescription in dentistry. *Acta Odontol Scand.* 2020;78(7):529-534.
61. Fabbro E, Arnau Sánchez J, Del Pilar López Acuña M, et al. Where we are in the fight against Antimicrobial Resistance and Healthcare-Associated Infections. The opinion of the stakeholders of the European Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI). *Ann Ist Super Sanita.* 2022;58(3):204-212.
62. Skogh Andrén A AB, Aust-Kettis A, Blomgren J, Claesson K, Dahlin P, Dahllöf G, Dahlén G, Edlund C, Götrick B, Hadrati M, Hermansson A, Hultin M, Roos-Jansåker A, Jonasson P, Klinge B, Knutsson K, Lund B, Lundholm P, Magnusson M, Missailidis C, Norman C, Norrsell N, Skoog G, Snygg-Martin U, Sunzel B, Ullbro C, Wahlin Y, Wexell C, Wolf E, Zimmerman M. Rekommendationer för antibiotikabehandling i tandvården. In. Vol 25. Info Läkemedelsverket2014:19-30.
63. Allander A, Aronsson, B., Baecklund, E., Blomgren, J., Cherif, H., Claesson, K., Dahlén, G., Dalén, T., Edlund, C., Ergander, U., Götrick, B., Hadrati, M., Hogevik, H., Klinge, B., Knutsson, K., Lund, B., Sunzel, B., Törnebladh, U., Wahlin, Y-B., Warfvinge, J., Wikström, G., Zethelius, B., Zimmerman, M., Örtqvist, P. Indikation för antibiotikaprofylax i tandvården. In. Vol 5. 2012-10-17 ed: *Info Läkemedelsverket*; 2012:22-35.
64. Brånemark PI, Hansson BO, Adell R, et al. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scand J Plast Reconstr Surg Suppl.* 1977;16:1-132.
65. Brånemark PI. Osseointegration and its experimental background. *J Prosthet Dent.* 1983;50(3):399-410.
66. Moraschini V, Poubel LA, Ferreira VF, Barboza Edos S. Evaluation of survival and success rates of dental implants reported in longitudinal studies with a follow-up period of at least 10 years: a systematic review. *Int J Oral Maxillofac Surg.* 2015;44(3):377-388.
67. Howe MS, Keys W, Richards D. Long-term (10-year) dental implant survival: A systematic review and sensitivity meta-analysis. *J Dent.* 2019;84:9-21.
68. Chrcanovic BR, Kisch J, Albrektsson T, Wennerberg A. Factors Influencing Early Dental Implant Failures. *J Dent Res.* 2016;95(9):995-1002.

69. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. *Eur J Oral Sci.* 1998;106(1):527-551.
70. Albrektsson T, Donos N. Implant survival and complications. The Third EAO consensus conference 2012. *Clin Oral Implants Res.* 2012;23 Suppl 6:63-65.
71. Nagano-Takebe F, Miyakawa H, Nakazawa F, Endo K. Inhibition of initial bacterial adhesion on titanium surfaces by lactoferrin coating. *Biointerphases.* 2014;9(2):029006.
72. Kolenbrander PE, Palmer RJ, Jr., Periasamy S, Jakubovics NS. Oral multispecies biofilm development and the key role of cell-cell distance. *Nat Rev Microbiol.* 2010;8(7):471-480.
73. Thomas DC, Bellani D, Piermatti J, Kodaganallur Pitchumani P. Systemic Factors Affecting Prognosis of Dental Implants. *Dent Clin North Am.* 2024;68(4):555-570.
74. Jiang X, Zhu Y, Liu Z, Tian Z, Zhu S. Association between diabetes and dental implant complications: a systematic review and meta-analysis. *Acta Odontol Scand.* 2021;79(1):9-18.
75. Chrcanovic BR, Albrektsson T, Wennerberg A. Smoking and dental implants: A systematic review and meta-analysis. *J Dent.* 2015;43(5):487-498.
76. Naseri R, Yaghini J, Feizi A. Levels of smoking and dental implants failure: A systematic review and meta-analysis. *J Clin Periodontol.* 2020;47(4):518-528.
77. More AB, Rodrigues A, Sadhu BJ. Effects of smoking on oral health: Awareness among dental patients and their attitude towards its cessation. *Indian J Dent Res.* 2021;32(1):23-26.
78. Adell R, Lekholm U, Rockler B, Brånemark PI. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *Int J Oral Surg.* 1981;10(6):387-416.
79. Gynther GW, Köndell PA, Moberg LE, Heimdahl A. Dental implant installation without antibiotic prophylaxis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;85(5):509-511.
80. Esposito M, Grusovin MG, Worthington HV. Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications. *Cochrane Database Syst Rev.* 2013;2013(7):Cd004152.
81. Ata-Ali J, Ata-Ali F, Ata-Ali F. Do antibiotics decrease implant failure and postoperative infections? A systematic review and meta-analysis. *Int J Oral Maxillofac Surg.* 2014;43(1):68-74.
82. Rodríguez Sánchez F, Arteagoitia I, Teughels W, Rodríguez Andrés C, Quirynen M. Antibiotic dosage prescribed in oral implant surgery: A meta-analysis of cross-sectional surveys. *PLoS One.* 2020;15(8):e0236981.
83. Salgado-Peralvo AO, Garcia-Sanchez A, Kewalramani N, et al. Consensus Report on Preventive Antibiotic Therapy in Dental Implant Procedures: Summary of Recommendations from the Spanish Society of Implants. *Antibiotics (Basel).* 2022;11(5).
84. Caiazzo A, Canullo L, Pesce P. Consensus Report by the Italian Academy of Osseointegration on the Use of Antibiotics and Antiseptic Agents in Implant Surgery. *Int J Oral Maxillofac Implants.* 2021;36(1):103-105.
85. Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Caiazzo A. Antibiotic prophylaxis habits in oral implant surgery among dentists in Italy: a cross-sectional survey. *BMC Oral Health.* 2019;19(1):265.

86. Becker K, Gurzawska-Comis K, Klinge B, Lund B, Brunello G. Patterns of antibiotic prescription in implant dentistry and antibiotic resistance awareness among European dentists: A questionnaire-based study. *Clin Oral Implants Res.* 2024;35(7):771-780.
87. Khalil D, Hultin M, Rashid MU, Lund B. Oral microflora and selection of resistance after a single dose of amoxicillin. *Clin Microbiol Infect.* 2016;22(11):949.e941-949.e944.
88. Contaldo M, D'Ambrosio F, Ferraro GA, et al. Antibiotics in Dentistry: A Narrative Review of the Evidence beyond the Myth. *Int J Environ Res Public Health.* 2023;20(11).
89. Esposito M, Grusovin MG, Felice P, Karatzopoulos G, Worthington HV, Coulthard P. Interventions for replacing missing teeth: horizontal and vertical bone augmentation techniques for dental implant treatment. *Cochrane Database Syst Rev.* 2009;2009(4):Cd003607.
90. Heinemann F, Hasan I, Bourauel C, Biffar R, Mundt T. Bone stability around dental implants: Treatment related factors. *Ann Anat.* 2015;199:3-8.
91. Retzepi M, Donos N. Guided Bone Regeneration: biological principle and therapeutic applications. *Clin Oral Implants Res.* 2010;21(6):567-576.
92. Antonoglou GN, Stavropoulos A, Samara MD, et al. Clinical Performance of Dental Implants Following Sinus Floor Augmentation: A Systematic Review and Meta-Analysis of Clinical Trials with at Least 3 Years of Follow-up. *Int J Oral Maxillofac Implants.* 2018;33(3):e45-e65.
93. Al Haydar B, Kang P, Momen-Heravi F. Efficacy of Horizontal Alveolar Ridge Expansion Through the Alveolar Ridge Split Procedure: A Systematic Review and Meta-Analysis. *Int J Oral Maxillofac Implants.* 2023;38(6):1083-1096.
94. Fuglsig J, Thorn JJ, Ingerslev J, Wenzel A, Spin-Neto R. Long term follow-up of titanium implants installed in block-grafted areas: A systematic review. *Clin Implant Dent Relat Res.* 2018;20(6):1036-1046.
95. Yoo D, Tovar N, Jimbo R, et al. Increased osseointegration effect of bone morphogenetic protein 2 on dental implants: an in vivo study. *J Biomed Mater Res A.* 2014;102(6):1921-1927.
96. Alhussaini AHA. Effect of Platelet-Rich Fibrin and Bone Morphogenetic Protein on Dental Implant Stability. *J Craniofac Surg.* 2019;30(5):1492-1496.
97. Guglielmotti MB, Olmedo DG, Cabrini RL. Research on implants and osseointegration. *Periodontol 2000.* 2019;79(1):178-189.
98. Ferraz MP. Bone Grafts in Dental Medicine: An Overview of Autografts, Allografts and Synthetic Materials. *Materials (Basel).* 2023;16(11).
99. Zhao R, Yang R, Cooper PR, Khurshid Z, Shavandi A, Ratnayake J. Bone Grafts and Substitutes in Dentistry: A Review of Current Trends and Developments. *Molecules.* 2021;26(10).
100. Mauceri R, Campisi G, Matranga D, Mauceri N, Pizzo G, Melilli D. The Role of Antibiotic Prophylaxis in Reducing Bacterial Contamination of Autologous Bone Graft Collected from Implant Site. *Biomed Res Int.* 2017;2017:2175019.
101. Khouly I, Braun RS, Silvestre T, Musa W, Miron RJ, Demyati A. Efficacy of antibiotic prophylaxis in intraoral bone grafting procedures: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg.* 2020;49(2):250-263.

102. Bazsefidpay N, Holmqvist F, Khalil D, et al. Antibiotic prescription in bone augmentation and dental implant procedures: a multi-center study. *BMC Oral Health.* 2023;23(1):818.
103. Klinge A, Khalil D, Klinge B, et al. Prophylactic antibiotics for staged bone augmentation in implant dentistry. *Acta Odontol Scand.* 2020;78(1):64-73.
104. Salgado-Peralvo AO, Mateos-Moreno MV, Velasco-Ortega E, Pena-Cardelles JF, Kewalramani N. Preventive antibiotic therapy in bone augmentation procedures in oral implantology: A systematic review. *Journal of Stomatology Oral and Maxillofacial Surgery.* 2022;123(1):74-80.
105. Yari A, Fasih P, Alborzi S, Nikzad H, Romoozi E. Risk factors associated with early implant failure: A retrospective review. *J Stomatol Oral Maxillofac Surg.* 2024;125(4):101749.
106. Motta C, Cavagnetto D, Amoroso F, Baldi I, Mussano F. Bioactive glass for periodontal regeneration: a systematic review. *BMC Oral Health.* 2023;23(1):264.
107. Jia K, You J, Zhu Y, et al. Platelet-rich fibrin as an autologous biomaterial for bone regeneration: mechanisms, applications, optimization. *Front Bioeng Biotechnol.* 2024;12:1286035.
108. Yen HH, Stathopoulou PG. CAD/CAM and 3D-Printing Applications for Alveolar Ridge Augmentation. *Curr Oral Health Rep.* 2018;5(2):127-132.
109. Alotaibi FF, Rocchietta I, Buti J, D'Aiuto F. Comparative evidence of different surgical techniques for the management of vertical alveolar ridge defects in terms of complications and efficacy: A systematic review and network meta-analysis. *J Clin Periodontol.* 2023;50(11):1487-1519.
110. Naenni N, Lim HC, Papageorgiou SN, Hämmerle CHF. Efficacy of lateral bone augmentation prior to implant placement: A systematic review and meta-analysis. *J Clin Periodontol.* 2019;46 Suppl 21:287-306.
111. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *Bjog.* 2018;125(13):1716.
112. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Bmj.* 2010;340:c332.
113. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj.* 2021;372:n71.
114. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. *J Clin Epidemiol.* 2021;137:163-175.
115. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj.* 2019;366:l4898.
116. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;61(4):344-349.
117. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* 2007;19(6):349-357.

118. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today.* 2004;24(2):105-112.
119. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama.* 2013;310(20):2191-2194.
120. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis.* 2016;62(10):e51-77.
121. Rosenstock IM. The Health Belief Model and Preventive Health Behavior. *Health Education Monographs.* 1974;2(4):354-386.
122. Razzaque MS. Implementation of antimicrobial stewardship to reduce antimicrobial drug resistance. *Expert Rev Anti Infect Ther.* 2021;19(5):559-562.
123. Septimus EJ. Antimicrobial Resistance: An Antimicrobial/Diagnostic Stewardship and Infection Prevention Approach. *Med Clin North Am.* 2018;102(5):819-829.
124. Tan TL, Shohat N, Rondon AJ, et al. Perioperative Antibiotic Prophylaxis in Total Joint Arthroplasty: A Single Dose Is as Effective as Multiple Doses. *J Bone Joint Surg Am.* 2019;101(5):429-437.
125. Christensen DD, Moschetti WE, Brown MG, Lucas AP, Jevsevar DS, Fillingham YA. Perioperative Antibiotic Prophylaxis: Single and 24-Hour Antibiotic Dosages are Equally Effective at Preventing Periprosthetic Joint Infection in Total Joint Arthroplasty. *J Arthroplasty.* 2021;36(7s):S308-s313.
126. Goff DA, Mangino JE, Trolli E, Scheetz R, Goff D. Private Practice Dentists Improve Antibiotic Use After Dental Antibiotic Stewardship Education From Infectious Diseases Experts. *Open Forum Infect Dis.* 2022;9(8):ofac361.
127. Palmer NO, Woodward J. An Antimicrobial Stewardship Toolkit to Promote Appropriate Antibiotic Prescribing in Dental Practice. *Prim Dent J.* 2017;6(1):16-19.
128. Champion VL, Skinner CS. The health belief model. In: *Health behavior and health education: Theory, research, and practice., 4th ed.* San Francisco, CA: Jossey-Bass; 2008:45-65.
129. Sakka S, Baroudi K, Nassani MZ. Factors associated with early and late failure of dental implants. *J Investig Clin Dent.* 2012;3(4):258-261.
130. Veitz-Keenan A, Ferraiolo DM, Keenan JR. Impact of asepsis technique on implant success. A review. *Eur J Oral Implantol.* 2018;11 Suppl 1:S113-s121.
131. Cheng H, Chen BP, Soleas IM, Ferko NC, Cameron CG, Hinoul P. Prolonged Operative Duration Increases Risk of Surgical Site Infections: A Systematic Review. *Surg Infect (Larchmt).* 2017;18(6):722-735.
132. Rogers HD, Desciak EB, Marcus RP, Wang S, MacKay-Wiggan J, Eliezri YD. Prospective study of wound infections in Mohs micrographic surgery using clean surgical technique in the absence of prophylactic antibiotics. *J Am Acad Dermatol.* 2010;63(5):842-851.
133. Milic T, Raidoo P, Gebauer D. Antibiotic prophylaxis in oral and maxillofacial surgery: a systematic review. *British Journal of Oral & Maxillofacial Surgery.* 2021;59(6):633-642.
134. Sendyk DI, Chrcanovic BR, Albrektsson T, Wennerberg A, Zindel Deboni MC. Does Surgical Experience Influence Implant Survival Rate? A Systematic Review and Meta-Analysis. *Int J Prosthodont.* 2017;30(30):341-347.

135. Mascarenhas LS, Pedreira KL, Cosme FD, et al. Effect of Antibiotic Prophylaxis on Early Loss of Implants Installed by Unexperienced Operators. *J Oral Implantol.* 2023.
136. Lau RL, Perruccio AV, Gandhi R, Mahomed NN. The role of surgeon volume on patient outcome in total knee arthroplasty: a systematic review of the literature. *BMC Musculoskeletal Disorders.* 2012;13(1):250.
137. Blackstone EH, Pettersson GB, Pande A, et al. Increasing surgeon experience and cumulative institutional experience drive decreasing hospital mortality after reoperative cardiac surgery. *J Thorac Cardiovasc Surg.* 2024;168(3):907-918.e906.
138. Jolbäck P, Rolfson O, Mohaddes M, et al. Does surgeon experience affect patient-reported outcomes 1 year after primary total hip arthroplasty? *Acta Orthop.* 2018;89(3):265-271.
139. Javed F, Romanos GE. Impact of diabetes mellitus and glycemic control on the osseointegration of dental implants: a systematic literature review. *J Periodontol.* 2009;80(11):1719-1730.
140. Madi M, Smith S, Alshehri S, Zakaria O, Almas K. Influence of Smoking on Periodontal and Implant Therapy: A Narrative Review. *Int J Environ Res Public Health.* 2023;20(7).
141. Mustapha AD, Salame Z, Chrcanovic BR. Smoking and Dental Implants: A Systematic Review and Meta-Analysis. *Medicina (Kaunas).* 2021;58(1).
142. Yaghmoor W, Ruiz-Torruella M, Ogata Y, et al. Effect of preoperative chlorhexidine, essential oil, and cetylpyridinium chloride mouthwashes on bacterial contamination during dental implant surgery: A randomized controlled clinical trial. *Saudi Dent J.* 2024;36(3):492-497.
143. Young MP, Korachi M, Carter DH, Worthington HV, McCord JF, Drucker DB. The effects of an immediately pre-surgical chlorhexidine oral rinse on the bacterial contaminants of bone debris collected during dental implant surgery. *Clin Oral Implants Res.* 2002;13(1):20-29.
144. Salvi GE, Zitzmann NU. The effects of anti-infective preventive measures on the occurrence of biologic implant complications and implant loss: a systematic review. *Int J Oral Maxillofac Implants.* 2014;29 Suppl:292-307.
145. Torof E, Morrissey H, Ball PA. Antibiotic Use in Dental Implant Procedures: A Systematic Review and Meta-Analysis. *Medicina (Kaunas).* 2023;59(4).
146. Solderer A, Kaufmann M, Hofer D, Wiedemeier D, Attin T, Schmidlin PR. Efficacy of chlorhexidine rinses after periodontal or implant surgery: a systematic review. *Clin Oral Investig.* 2019;23(1):21-32.
147. Chrcanovic BR, Albrektsson T, Wennerberg A. Dental implants in irradiated versus nonirradiated patients: A meta-analysis. *Head Neck.* 2016;38(3):448-481.
148. Holahan CM, Koka S, Kennel KA, et al. Effect of osteoporotic status on the survival of titanium dental implants. *Int J Oral Maxillofac Implants.* 2008;23(5):905-910.
149. Lemos CAA, de Oliveira AS, Faé DS, et al. Do dental implants placed in patients with osteoporosis have higher risks of failure and marginal bone loss compared to those in healthy patients? A systematic review with meta-analysis. *Clin Oral Investig.* 2023;27(6):2483-2493.
150. Viltsaniuk O, Syvak V, Vovk Y, Bondar L, Taraniuk K. Antibiotic resistance: current challenges and ways of their solution. In. *Perioperative Medicine.* Vol 7: Interdisciplinary Academy of Pain Medicine; 2024.

151. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. *Molecules.* 2018;23(4).
152. Borek AJ, Wanat M, Atkins L, et al. Optimising antimicrobial stewardship interventions in English primary care: a behavioural analysis of qualitative and intervention studies. *BMJ Open.* 2020;10(12):e039284.
153. Shallcross L, Lorencatto F, Fuller C, et al. An interdisciplinary mixed-methods approach to developing antimicrobial stewardship interventions: Protocol for the Preserving Antibiotics through Safe Stewardship (PASS) Research Programme. *Wellcome Open Res.* 2020;5:8.
154. Garbovan L, Caputo A, Pränting M, Garmendia EP. Impactful approaches for community-wide engagement on antibiotic resistance: An initiative to promote systematic and meaningful engagement of communities and civil society groups as key stakeholdersin the global response to antibiotic resistance. In:2024.
155. Klinge B, Flemming T, Cosyn J, et al. The patient undergoing implant therapy. Summary and consensus statements. The 4th EAO Consensus Conference 2015. *Clin Oral Implants Res.* 2015;26 Suppl 11:64-67.
156. Roca-Millan E, Estrugo-Devesa A, Merlos A, Jané-Salas E, Vinuesa T, López-López J. Systemic Antibiotic Prophylaxis to Reduce Early Implant Failure: A Systematic Review and Meta-Analysis. *Antibiotics (Basel).* 2021;10(6).
157. Canullo L, Troiano G, Sbricoli L, et al. The Use of Antibiotics in Implant Therapy: A Systematic Review and Meta-Analysis with Trial Sequential Analysis on Early Implant Failure. *Int J Oral Maxillofac Implants.* 2020;35(3):485-494.
158. Romandini M, De Tullio I, Congedi F, et al. Antibiotic prophylaxis at dental implant placement: Which is the best protocol? A systematic review and network meta-analysis. *J Clin Periodontol.* 2019;46(3):382-395.
159. Park J, Tennant M, Walsh LJ, Kruger E. Is there a consensus on antibiotic usage for dental implant placement in healthy patients? *Aust Dent J.* 2018;63(1):25-33.
160. Braun RS, Chambrone L, Khouly I. Prophylactic antibiotic regimens in dental implant failure: A systematic review and meta-analysis. *J Am Dent Assoc.* 2019;150(6):e61-e91.
161. Momand P, Naimi-Akbar A, Hultin M, Lund B, Götrick B. Is routine antibiotic prophylaxis warranted in dental implant surgery to prevent early implant failure? - a systematic review. *BMC Oral Health.* 2024;24(1):842.
162. Singh Gill A, Morrissey H, Rahman A. A Systematic Review and Meta-Analysis Evaluating Antibiotic Prophylaxis in Dental Implants and Extraction Procedures. *Medicina (Kaunas).* 2018;54(6).
163. Arteagoitia I, Rodríguez-Andrés C, Rodríguez-Sánchez F. Antibiotic prophylaxis habits in dental implant surgery among dentists in Spain. A cross-sectional survey. *Med Oral Patol Oral Cir Bucal.* 2018;23(5):e608-e618.
164. Hughes AM, Evans CT, Fitzpatrick MA, et al. A qualitative approach to examining antimicrobial prescribing in the outpatient dental setting. *Antimicrobial Stewardship & Healthcare Epidemiology.* 2022;2(1):e102.
165. Martine C, Sutherland S, Born K, Thompson W, Teoh L, Singhal S. Dental antimicrobial stewardship: a qualitative study of perspectives among Canadian dentistry sector leaders and experts in antimicrobial stewardship. *JAC-Antimicrobial Resistance.* 2024;6(3).

166. FGDP(UK) and FDS publish antimicrobial prescribing guidelines for all dentists. In. *BDJ In Pract.* Vol 34:6-62021.
167. Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Bruers J. Antibiotic prophylaxis prescribing habits in oral implant surgery in the Netherlands: a cross-sectional survey. *BMC Oral Health.* 2019;19(1):281.
168. Hultin M, Lund B, Lundgren F, Cederlund A. Dental implant procedures contribution to the total antibiotic use in Swedish dentistry. A register-based study. *Acta Odontol Scand.* 2022:1-8.
169. Negut I, Ristoscu C. Bioactive Glasses for Soft and Hard Tissue Healing Applications—A Short Review. *Applied Sciences.* 2023;13(10):6151.
170. Saravanan D, Rethinam S, Muthu K, Thangapandian A. The Combined Effect of Bioactive Glass and Platelet-Rich Fibrin in Treating Human Periodontal Intrabony Defects - A Clinicoradiographic Study. *Contemp Clin Dent.* 2019;10(1):110-116.
171. Verhoef MJ, Casebeer AL. Broadening horizons: Integrating quantitative and qualitative research. *Can J Infect Dis.* 1997;8(2):65-66.
172. Limbu YB, Gautam RK. How Well the Constructs of Health Belief Model Predict Vaccination Intention: A Systematic Review on COVID-19 Primary Series and Booster Vaccines. *Vaccines.* 2023;11(4):816.
173. Gross AE, Hanna D, Rowan SA, Bleasdale SC, Suda KJ. Successful Implementation of an Antibiotic Stewardship Program in an Academic Dental Practice. *Open Forum Infect Dis.* 2019;6(3):ofz067.