View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Explore Bristol Research

Wyatt, M. C., Foxall-Smith, M., Roberton, A., Beswick, A., Kieser, D. C., & Whitehouse, M. R. (2019). The use of silver coating in hip megaprostheses: a systematic review. *Hip International*, *29*(1), 7-20. https://doi.org/10.1177/1120700018811070

Peer reviewed version

Link to published version (if available):
10.1177/1120700018811070

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Sage at https://journals.sagepub.com/doi/10.1177/1120700018811070 . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/pure/about/ebr-terms

Full title: The use of silver coating in hip megaprostheses – a systematic review

Short title: Silver in hip arthroplasty

Authors: Michael C. Wyatt[1] (MBChB, FRACS), Michael Foxall-Smith (MBBS BSc), Andrew Roberton (MBChB, MRCS), Andrew Beswick[2] (BSc), David C. Kieser[1] (PhD, FRACS), Michael R. Whitehouse[2,3] (PhD, FRCS)

Affiliations:

[1]Department of Orthopaedic Surgery and Musculoskeletal Medicine, University of Otago, Christchurch School of Medicine

[2]Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, 1st Floor Learning & Research Building, Southmead Hospital, Bristol, BS10 5NB

[3]National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol.

Corresponding author:

Mr Michael Wyatt

Email: michaelcharleswyatt@icloud.com

Abstract:

Retrospective studies of silver-coated hip implants have demonstrated promising results and safety profile however the potential benefits are so far unproven in prospective studies. Silver-coated implants may have a role in patients undergoing revision or primary surgery with a high risk of infection but as yet there are no human studies investigating silver in primary hip arthroplasty. Adequately powered robust prospective studies are needed in this area to determine if silver-coated implants would be efficacious and cost-effective. The purpose of this systematic review article is to review the current literature regarding the use of silver in hip arthroplasty. Our review showed that there is some encouraging evidence that silver coatings can reduce infection.

Introduction

Background

Silver is a chemical element discovered in approximately 3000BC with an atomic number of 47. Its chemical symbol Ag, is derived from the Latin word *argentum*. Silver has a plethora of uses: from jewellery to being woven into gloves, making them compatible with touchscreen phones. Its use in Medicine is a function of its antimicrobial properties and in this context, it was first used in the eighteenth century to treat ulcers [1].

Mechanism of action of silver

Silver has activity against bacteria, fungi and viruses [2]. It has been described as "oligodynamic" due to being toxic to bacteria at very low concentrations [3]. The mechanism of action is complex and multifaceted. Silver ions are biologically active and facilitate the bactericidal effect. Silver ions interact with 3 specific bacterial cell structures (Figure 1) [4]. At the peptidoglycan cell wall and plasma membrane they cause destruction and cell lysis [5,6]. They interact with bacterial DNA preventing DNA replication and thereby reproduction via binary fission. They also interact with bacterial proteins, denaturing ribosomes, disabling protein synthesis and causing degradation of the plasma membrane [7- 10]. An additional mechanism of toxicity to bacteria is through formation of reactive oxygen species (ROS) by silver ions. Park et al. have demonstrated ROS- mediated silver toxicity with an increased antimicrobial activity in aerobic compared to anaerobic conditions [11].

The multifaceted mechanism reduces the opportunity for the development of bacterial resistance in comparison to traditional antibiotics. Current literature suggests resistance to silver is rare and sporadic although it is known that silver-resistance genes exist in certain types of bacteria. Randall et al. have discussed and try to further elucidate the endogenous (mutational) and exogenous (horizontally acquired) mechanisms through which silver resistance has developed.{randall et al, journal of antimicrobial chemotherapy, 2015}. As observed by Percival et al. bacterial resistance to antibiotics has occurred in the last 70 years but on the contrary, no widespread resistance to silver has developed

in over 4 billion years of exposure[12].

Medical application of silver

Clement and Jarrett comment that the use of silver has been documented since the time of the King of Persia using water storage in flagons of silver when going to war[3]. Since then, silver has become widespread in different medical applications. These include silver-coated catheters [13], municipal water systems[14], hospital surfaces disinfection [15] and wound dressings particularly in the care of burns[16].

Silver has been used in both compound forms such as silver nitrate and more recently as nanosilver following advancement in manufacturing processes. Furthermore, the antimicrobial efficacy of silver has been shown to be related to its structural make up, with nanosilver proving more effective than silver chloride and silver nitrate [17]. Nanoparticles can be used in coating medical devices, with the aim of preventing biofilm formation and technology has developed to enable silver to adhere to the surface of a device [18]. This development is of potentially huge significance as it allows silver to be used to potentially reduce the risk of prosthetic joint infection (PJI) – a complication seen in 1.5-2.5% of all primary hip and knee arthroplasty[19].

Antibiotic prophylaxis therapy is common practice after surgery, but it is difficult to demonstrate a clear supremacy of a particular antibiotic over another[20]. The most common pathogens associated with post-operative infection are *staphylococcii* yet gram negative organisms such as *Pseudomonas Aeruginosa* can often be very challenging to eradicate given the biofilms produced [21]. By introducing prostheses, pathogenic microbes have a surface on which they can develop biofilms. Bacteria grow in aggregates that become encased in an extracellular matrix produced by the bacteria, where the matrix is often rich in polysaccharides, proteins and DNA[22]. They are associated with increased rates of infection on human surfaces such as teeth, skin, and the urinary tract, as well as medical devices such as catheters, heart valves, and orthopaedic implants[22,23]. The biofilm forms a haven for safe growth, making them more difficult to be destroyed by the immune system and more resistant to antibiotics[24,25].

This provides the rationale for research into orthopaedic applications of silver, such as in tumour prostheses, external fixator pins, bone cement and coating of implants[18]. PJI can have devastating effects on a patient's quality of life[26]. Reducing the incidence of PJI would lead to a reduction in the number of revision procedures, improved outcomes for patients and reduce the cost to society. In bone cement the addition of nanosilver has shown promising in vitro results and low levels of toxicity [27]. Similarly, in vitro results of silver coated trauma implants have shown promise but with mixed in vivo results [28,29]. Silver has been demonstrated to cause toxicity to human tissue, particularly renal, hepatic and neural tissues. Additionally local argyria, a blue/purple discoloration of the skin, around implants has also been reported. However clinical studies have so far not elucidated any malignant toxicity. The number of silver implants currently used are low and sporadic at present.

The purpose of this article is to review the current literature regarding the use of silver in hip arthroplasty.

Materials and Methods:

Our review team used a rigorous and systematic approach conforming to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the critical evaluation of studies relating to the use of silver in total hip replacement surgery.

Protocol

A protocol was registered online before commencing the study with PROSPERO (International prospective register of systematic reviews, CRD42017082680) as recommended by the Quality of Reporting of Meta-analyses (QUOROM) statement [30].

Search strategy

We searched all studies indexed in OVID MEDLINE, EMBASE, ACM, ADS, arXiv, CERN DS, Crossref DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAlster, Open Content, Pubget, PubMed, Web of Science for the last 10 years using the search strategy shown in Figure 2. The search strategy was not limited by language or patient age. We also evaluated the grey literature with hand searches of 6 major Orthopaedic journals over the last 5 years. The bibliographies of the relevant articles were then cross-checked to search for articles not identified in the search. The initial screening of studies was performed by two independent assessors with any disagreements meaning that the study in question was included. An electronic spreadsheet was constructed to summarise the findings of relevant studies.

Eligibility criteria

We included all studies that related to silver implants in hip surgery.

Screening

A total of 117 records were identified from the searches described above. The titles and abstracts were screened to identify articles for inclusion in this

systematic review. After screening 63 articles were assessed for eligibility against criteria and from these 11 articles were reviewed formally. A flow diagram of the progression of studies through this systematic review is provided in Figure 2.

Data extraction

Two of the authors worked independently to extract the data using standardized forms. We extracted data on participants, joint involved, survivorship of implants, prevention of infection and toxicity.

Funding

This study was supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Results

There were 63 articles reporting a mix of laboratory studies, animal studies, review articles and 11 studies using silver coated implants in patients providing level III evidence. Study characteristics are summarised in Table 1.

Endoprosthesis

Much of the source material gathered around silver-coated prostheses was centred on megaendoprosthesis. Endoprostheses are used to address large bone defects when conventional prostheses may not suffice. Examples include: major osteolysis causing implant loosening, tumours, periprosthetic fractures, or periprosthetic infection. Megaendoprostheses are commonly modular, allowing intra-operative flexibility, but in contrast to regular prostheses have a larger surface area, typically require larger surgical exposures, are used in operations of long duration due to the complexity of the indications, and have higher bloods loss [31]; all factors associated with an increased risk of PJI.

Revision surgery for tumour endoprostheses has been shown to carry a reinfection rate of up to 43%. Often the bacterial biofilm proves too difficult to remove and the prosthesis must be removed [32]. Commonly oncological patients are immunologically deficient due to chemotherapy, or may be weakened by simultaneous disease in other organs, or the malignancy itself, and are at higher risk of infection [20].

In Vitro

Silver-coated nanotubes have been shown to be effective in preventing biofilm formation and lowering bacteria numbers in the early post-operative period [33]. In vitro and in vivo evaluations show that nanotubes on titanium surfaces encourage osseointegration, cell differentiation, mineralisation, and anti-microbial properties (including reducing the initial adhesion and colonisation of *Staphylococcus epidermidis*). Nanotube surface treatment can be applied to existing macro and micro porous titanium implants. Nanotubes have been shown

to improve bone bonding nine-fold and mineralisation by three times that of non-treated titanium surfaces[34].

Thermal sprayed coatings of calcium phosphate containing silver showed significant decrease in the adherence of *Escherichia Coli*, *Staphylcoccus Aureus* and *Methicillin-Resistant Staphylococcus Aureus* [35]. In megaendoprostheses, silver coating may be accomplished by galvanic deposition of elementary silver. This first layer is additionally coated with another layer of gold (the cathode) to enable continuous release of silver ions (the anode) [21,36].

Albers et al. investigated silver ion, and nanoparticle, induced cytotoxicity in primary osteoblasts (OB) and osteoclasts (OC). They found that the treatment of OBs and OCs with silver particles lowered the cell differentiation and number of viable cells, OBs more so than OCs; OBs viability being reduced at 128 μg/ml silver nanoparticles and differentiation being reduced at 64 μg/ml, with OCs viability and differentiation being reduced at 256 μg/ml and 128 μg/ml respectively. Dose and size also played a key part with nanoparticles (average size 50 nm) being more damaging than microparticles (3 μm). The bactericidal effects of silver occurred at two to four times the levels that induced cytotoxic effects [37].

Ando et al. found that hamster lung cells grew on the silver calcium phosphate coating in a cytotoxicity test [35]. In the presence of hydroxyapatite, silver has a much higher photocatalytic activity than titanium oxide-silver mixtures alone, due to the generation of free radicals. These free radicals may lead to oxidative stress and cell death [24].

Fielding et al. found that the antibacterial properties of the silver coatings, tested against *Pseudomonas aeruginosa*, were highly effective. They then tested cell-material interactions using human foetal osteoblasts in vitro. Cells grown on silver-hydroxyapatite surfaces demonstrated dysfunctional features such as premature apoptosis, delayed differentiation and cell death, with nearly complete impediment of functional alkaline phosphate activity.

To combat these effects of silver, strontium was added as a coating mixture acting as a binary dopant. The strontium acts to stimulates bone formation, while inhibiting bone resorption. By adding strontium oxide to the silver-hydroxyapatite mixture they effectively offset the damaging effects and enhanced the performance when compared to pure hydroxyapatite coated samples [38].

In Vivo

Silver reduces infection in medical devices such as external fixation pins, heart valves, endotracheal tubes, and cardiac and urinary catheters [32]. Unlike the majority of antibiotics, silver is not limited to one mechanism but can use several: blocking the cells respiratory chain, disrupting cell transport, and binding to nucleotides and nucleosides of RNA and DNA to limit transcription and translation without significant reports of resistance [21].

Kose et al. used a silver ion-doped calcium phosphate-based ceramic nanopowder to look at resistance of bacterial colonisation in knee prostheses in rabbits. They inoculated the femoral canals of 27 rabbits with MRSA, and replaced the joints after 6 weeks with titanium implants (9 uncoated, 9 hydroxyapatite-coated (HA), and 9 silver-coated). Eight of nine uncoated prostheses showed positive cultures, five of nine HA were positive, and only one of nine silver-coated prostheses was positive [39].

Gosheger et al. demonstrated in rabbit models that silver levels were elevated in silver prostheses, but were within their pre-defined safety parameters with no histological change to the organs of the animal [40]. Alongside Hauschild, they later demonstrated silver levels in canines. Mean values of silver trace elemental concentrations in serum samples ranged from 0.20 to 1.82ppb with baseline data representing normal values ranged from 0.20 to 1.38 ppb [41]. Therapeutic bactericidal effect can be seen at low concentrations (starting at 35 ppb) whereas toxic effects for human cells are expected at much higher concentrations (300–1200 ppb) [21].

In dentistry, implants have been trialled with antimicrobial coatings such as antibiotics and chlorhexidine, but have not been viable due to short-term efficacy or cytotoxicity respectively. In addition to silver, strontium, gallium, gold/palladium, and zinc alloyed with magnesium have also been found to have antimicrobial effects whilst demonstrating biocompatibility [24,42]. Other methods of coating include chitosan coating, photoactive-based coatings, resorbable antibiotic loaded hydrogels, and silver coatings [21].

33 patients that received Porag (Porous Argentum) megaprostheses between 2010 and 2014 were followed up by Scoccianti et al.. The implants were used for a variety of reasons including oncological disease, arthroplasty, and trauma. In such prostheses the shaft is silver-coated whilst the bone-implant interface in general is not. The megaprostheses included proximal, distal and total femurs as well as knee arthrodesis prostheses. 3 of the 33 patients developed post-operative infections; 1 that had had no previous infection and 2 patients developed recurrent infections. Scoccianti displayed no local or systemic side effects [43].

Donati et al. followed up 68 patients with primary or metastatic proximal femur bone tumours. Of the 18% that required further surgery, 13% were due to infection. Patients that had been given silver-coated prostheses developed early infection (under 6 months after surgery) in 2% of cases, whereas standard tumour prostheses developed early infection in 11% of cases. Late infection (occurring after six months) occurred at similar rates in both groups. Two silver- coated prostheses removed at 27 and 82 months after surgery showed near total absence of silver. Bloods taken at various times after surgery showed serum silver levels to be significantly below the toxic threshold, and no patients exhibited any symptoms of silver toxicity. Donati reported no local or systemic side effects [44].

Over a 10-year period, Wafa et al. matched 85 patients with Algluna-treated tumour implants (silver-coated megaendoprosthesis) with 85 identical, but uncoated, tumour prostheses. The infection rate in uncoated prostheses was almost double, with Agluna infection rates at 11% and the control at 22% ($p=0.033$). 7 of the infected

10 Agluna prostheses were treated with debridement and implant retention and antibiotics, versus 6 of the 19 control implants; 70% versus 32% respectively. Chronic infection rates were found to be 4% in the silver group, and 15% in the control group. Wafa reported no local or systemic side effects and commented that the Agluna prosthetic uses less silver in its coating than traditional prostheses (less than 2% of the lowest estimate of Hardes' prosthesis) [45].

In 2010, Hardes et al. compared the infection rate between silver-coated and titanium megaprostheses. The silver group consisted of 51 patients (22 proximal femur, 29 proximal tibia) and the titanium group 74 patients (33 proximal femur, 41 proximal tibia). 6% of those that received silver implants developed periprosthetic infection, compared to 18% of those that received titanium implants. Infection rates were decreased in the silver prostheses. 5 patients ultimately underwent amputation due to infected proximal tibia prostheses, whereas none to that received a silver implant had undergone amputation. One patient of Hardes (a silver-coated prostheses patient) presented 50 months postoperatively with a blue-grey discolouration of the skin over the area operated on. The differential diagnoses were known varicosis with venous insufficiency and suspected local argyrosis [32]. In an analysis of 56 patients that received silver implants for proximal tibia replacement in sarcoma; 4 were alive with disease (7%), and 5 dead of disease (9%), and of the 42 that received titanium 2 were alive with disease (5%), and 9 were dead of disease (21%) [46].

Toxicity

Given the known problems with metal ion toxicity following metal-on-metal arthroplasty, there is concern about potential toxicity of silver. Silver nanoparticles can cause toxic effects to human tissues [47] and there is evidence of an immunosuppressive effect [48]. Silver nanoparticle-mediated cytotoxicity to mesenchymal stem cells and osteoblasts has been shown to occur at higher concentrations, with the inference that a therapeutic window is likely to exist [49]. Necula et al. looked at the cytotoxicity of different concentrations of silver nanoparticles on an implant surface against a human osteoblastic cell line and found an optimum cell growth combined with antibacterial effect at certain

concentrations [50]. However it has been demonstrated that antibacterial effects of silver occur at levels higher than those which induce cytotoxic effects, and indeed the authors commented that their study provides evidence of potential problems associated with orthopaedic implants [37]. In their review, Brennan et al. comment that further research is required to find a method of controlling release of nanoparticles from an implant so that it is compatible with the host as well as providing antibacterial activity [18]. Silver toxicity may occur at serum levels as low as 0.3mg/mL and present as argyria and leukopenia, as well as causing alterations in renal, hepatic, and neural tissues [20]. The minimum doses mentioned in the literature to cause argyria are approximately 4–6g [51].

Glehr et al. followed up 31 patients that underwent megaendoprostheses for infection or resection of malignant tumours between 2004 and 2011. Levels of silver locally in drains and seromas were measured. 7 patients (23%) developed local argyria (median 25 months). No malignant symptoms of silver poisoning (neurological/ renal/ hepatic) were found. They stated that local argyria is generally benign, although fairly irreversible. The size of the implant was not associated with argyria. Patients with and without argyria, both had similar levels of serum silver [52].

Discussion

Silver has established antimicrobial properties. By interacting with the cell wall, plasma membrane, DNA and RNA silver ions can cause cell lysis. Its widespread effects and low resistance rates make it a good candidate for use in hip arthroplasty. Silver is a versatile material and is relatively easy to apply to implants, where the risk of biofilm formation is high, it can help to reduce the risk of prosthetic joint infection.

In vitro case demonstrate promise. The antimicrobial effects of silver are reproduced in cell cultures and are effective against *Staphylococcus epidermis* (the most common bacteria to colonise prostheses), *Staphylococcis aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. However, silver demonstrates cytotoxic effects at the cellular level, inhibiting osteoblast and osteoclast performance. This osteoblastic cytotoxicity presents concerns about the longevity of implant fixation and, secondarily, revision for loosening. This effect could potentially be reduced with the addition of other elements such as strontium that act to stimulate osteoblast and osteoclast cells. Alternatively the silver coating could be localized away from the implant-bone interface such as adjacent to the hip articulation itself.

Silver is used to reduce the risk of infection in implants and devices such as catheters and stents. The majority of the data published in relation to silver-coated orthopaedic implants involves megaendoprostheses used in tumour surgery. Silver's antibacterial properties are attractive in patients that may be immunocompromised due to disease or chemotherapy. The included studies indicate that infection rates in the post-operative period were lower in those that had received silver-coated implants over controls. It is difficult to pinpoint the level at which silver may cause serious local or systemic damage. Most of the cases had no significant side effects from silver, though trace elements of silver in the blood were often raised but below the toxic threshold. Local argyria occurred in a small number of cases but did not seem to cause any systemic upset.

Conclusion

Silver has antimicrobial properties. It is easily applied to implants and has shown efficacy in smaller devices or implants. In vitro studies of silver have shown signs of cell toxicity, but it does not seem to cause systemic upset in in vivo studies. The available literature is predominated by silver coated megaendoprostheses used in malignancy or recurrent infection; in this context, it has proved effective in reducing infection rates. There is no randomised trial evidence of its use in primary hip arthroplasty. Furthermore silver coated primary implants would need to be monitored closely via the National Joint Registries.

The potential benefits of silver-coated hip implants are so far unproven in prospective studies. Retrospective studies have demonstrated promising results and safety profile. Silver coated hip implants may have a role in patients undergoing revision or primary surgery with a high risk of infection. Prospective robust studies are needed in this area to determine if silver-coated implants would be efficacious and cost-effective in this setting.

Figure Legends:

Figure 1: Illustration of the mechanisms of action of silver ions [4]

Figure 2: PRISMA flow diagram

Table 1: Characteristics of included studies

Author	Journal/year	Study type/Level of evidence	Number of patients	Implant	Indication/context	Evidence of infection prevention	Risk/safety
Ando et al. [35] Calcium phosphate coating containing silver shows high antibacterial activity and low cytotoxicity and inhibits bacterial adhesion	Materials Science and Engineering: C 2010	Laboratory study	-	Novel coating technology of calcium phosphate containing silver, using thermal spraying technique	Evaluated antibacterial efficacy and biological safety of coating.	In vitro antibacterial activity showed growth of bacteria to be completely suppressed.	Animal cells were found to grow on the coating in a cytotoxicity test.
Chen et al. [53] Silver release from silver-containing hydroxyapatite coating.	Surface and Coatings Technology 2010	Laboratory study	-	Silver-containing hydroxyapatite coatings were prepared by coprecipitation or plasma spraying	Behaviour of silver release from composite coating in buffering fluid and simulated body fluid monitored.	Rate of release of silver particles was higher for coprecipitation method compared to plasma spraying. Phase composition and surface morphology of coatings may affect their bioactive properties.	-
Hardes et al. [32] Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma.	Journal of Surgical Oncology 2010	Prospective cohort (silver group) . Retrospective cohort (titanium group)	125 (Silver = 51 Titanium = 74)	MUTARS proximal femur and proximal tibia replacement	Proximal femur/tibia sarcoma requiring replacement.	Incidence of periprosthetic infection reduced from 17.6% to 5.9% (p=0.062).	1 case of suspected local argyrosis 50 months postoperativ ely
Mondanelli et al. [54] Modular prosthesis with a	Journal of Orthopaedic	Case series	10	MegasystemC with a silver	Septic arthroplasty (4), septic meta-	Preliminary results demonstrate	No comment.

silver coating for periarticular reconstruction in septic prosthetic and post-traumatic failures.	Traumatology (In-depth oral presentations and oral communications) 2012			coating	epiphyseal post-traumatic deformity of non union (5), epithelioid hemangio-endothelioma (1)	resolution of infection in all cases.	
Trujilo et al. [55] Antibacterial effects of silver-doped hydroxyapatite thin films sputter deposited on titanium	Materials Science and Engineering: C 2012	Laboratory study	-	Plain titanium, titanium coated with hydroxyapatite, titanium coated with silver-doped hydroxyapatite	Bacterial adhesion study	Less bacteria adhere to surfaces containing hydroxyapatite and silver	-
Swieczko-Zurek B [25] The influence of biological environment on the appearance of silver-coated implants.	Advances in Material Sciences 2012	Laboratory study		Polymer vein implant covered with silver and stainless steel intramedullary nail covered with silver	In vitro study.	Strong protection against biofilm production in polymer and metallic implants.	-
Kose et al. [39] A silver ion-doped calcium phosphate-based ceramic nanopowder-coated prosthesis increased infection resistance	Clinical Orthopaedics and Related Research 2013	Animal study	27 (9 uncoated 9 hydroxapatite coated 9 silver coated)	Titanium implants		Silver ion-doped ceramic nanopowder coating of titanium implants led to an increase in resistance to bacterial colonization compared to	No cellular inflammation of foreign-body granuloma was observed around the silver-coated prostheses.

						uncoated implants	
Zimmerli W. [56] Clinical presentation and treatment of orthopaedic implant-associated infection.	Journal of Internal Medicine 2014	Review	-	-	-	Antimicrobial agents have limited efficacy against biofilm infections; novel preventative options are needed. Prevention may be achieved in the future by implant coating with novel substances.	-
Brennan et al. [18] Silver nanoparticles and their orthopaedic applications.	The Bone and Joint Journal 2015	Review	-	-	-	Silver nanoparticle technology in orthopaedic devices has great potential to reduce implant infection.	Further research warranted, particularly to elucidate potential harmful effects.
Wafa et al. [45] Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high risk patients: case-control study.	The Bone and Joint Journal 2015	Retrospective case-control	170 (Silver = 85 Titanium = 85	Agluna-treated tumour implants vs uncoated implants	50 primary reconstructions, 79 one-stage revisions and 41 two-stage revisions	Overall post op infection rate 11.8% in silver group vs 22.4% in control group (p=0.033)	No comment
Donati et al. [44] Silver coated prosthesis in oncological limb salvage surgery reduce the infection rate.	Journal of Biological Regulators and Homeostatic Agents	Retrospective case-control	158	Silver coated vs non silver coated	Primary or metastatic bone tumours treated with excision and tumour implant reconstruction	Early infection: 2.2% with silver implant vs 10.7% with standard.	No evidence of silver toxicity

	2015						
Donati et al. [57] Silver-coated hip prosthesis reduce the infection rate in oncological limb salvage surgery.	Abstracts from International Combined Meeting BHS-SldA 26-27 November 2015	Retrospective cohort	68	Silver coated vs non silver coated	Primary or metastatic proximal femur bone tumours treated with excision and tumour implant reconstruction	Early infection: 2.2% with silver implant vs 10.7% with standard. Similar rate of infection at 6 months.	No evidence of silver toxicity
Eto et al. [58] First Clinical Experience with Thermal-Sprayed Silver Oxide-containing Hydroxyapatite coating implant.	Primary Arthroplasty 2015	Prospective case series	20	AMS HA Cup and 910 PerFix Fullcoat D stem thermal sprayed with silver	Inclusion criteria: Age ≥ 65 and an indication for THA	Harris Hip Scores were improved after surgery in line with traditional implants.	1 hip dislocation at 6 weeks. 4 cases showed detectable spot welds at 1 year X-ray. No argyria or neurologic symptoms. No infections.
Furko et al. [59] Complex electrochemical studies on silver-coated metallic implants for orthopaedic application	Journal of Solid State Electrochemistry 2015	Laboratory study	-	Silver grains deposited onto different implant materials common used in orthopaedic surgery	Electrochemical behaviour of the coating and silver ion release rate were investigated		
Furko et al. [60] Comparative corrosion study on silver coated metallic implants	Material Science Forum 2015	Laboratory study	-	Nanostructured silver layer was deposited onto different implant	Electrochemical behaviour of the coatings investigated		

				materials common used in orthopaedic surgery			
Amin Yavari et al. [33] Antibacterial behaviour of additively manufactured porous titanium with nanotubular surfaces releasing silver ions.	ACS Applied Materials and Interfaces 2016	Laboratory study	-	Titanium nanotubes loaded with silver	Antimicrobial activity and cell viability of developed material were assessed.	Silver loaded nanotubes extremely effective in preventing biofilm formation.	Specimens with highest concentrations of silver adversely affected cell viability
Funao et al. [23] A novel hydroxyapatite film coated with ionic silver via inositol hexaphosphate chelation prevents implant-associated infection.	Scientific Reports 2016	Animal trial.	10 (Silver = 5 Titanium = 5)	Hydroxyapatite film coated ionic silver vs titanium implant	In vivo study: antibacterial effects of ionic-silver coating in a murine model of implant-associated osteomyelitis.	No bacteria detectable after inoculation. Serum IL-6 reduced. CRP reduced.	No comment
Donati et al. [20] Silver-coated hip megaprosthesis in oncological limb salvage surgery.	BioMed Research International 2016	Retrospective cohort	68	Silver-coated hemiarthroplasty (MUTARS) vs uncoated megaprostheses	Primary or metastatic bone tumour proximal femur	Early infection 2.6% vs 10% (not statistically significant)	No evidence of silver toxicity
Scoccianti et al. [43] Levels of silver ions in body fluids and clinical results in silver-coated megaprostheses after tumour, trauma or failed arthroplasty.	Injury 2016	Retrospective case series	33	MegasystemC with a silver coating	A silver-coated prosthesis was chosen for the following causes: septic failure of previous megaprosthesis: 8 patients. Septic complication after fracture: 7 patients. Septic failure of previous standard	There was no infection during the first two years after surgery in the 12 patients who received a silver-coated megaprosthesis and had no previous history of	No evidence of silver toxicity

					joint arthroplasty: 6 patients. Oncological resection with patient at particular risk of infection complication: 8 patients. Non-oncological resection with patient at particular risk of infection complication: 4 patients.	infection. Infection recurred in 2 out of 21 patients who had received the implant because of previous septic complications.	
Besinis et al. [24] Antibacterial activity and biofilm inhibition by surface modified titanium alloy medical implants following application of silver, titanium dioxide and hydroxyapatite nanocoatings	Nanotoxicology 2017	Laboratory study		Titanium alloy implants modified to create silver, titanium oxide and hydroxyapatite coatings	In vitro study. Antibacterial performance assessed	Silver coating inhibited bacterial growth in surrounding media and bacterial biofilm production reduced by 97.5%	-
Devlin-Mullin et al. [42] Atomic layer deposition of a silver nanolayer on advanced titanium orthopaedic implants inhibits bacterial colonization and supports vascularized de novo bone ingrowth	Advanced Healthcare Materials 2017	Laboratory study			In vitro and in vivo study.	Bacterial growth slower on silver coated titanium scaffolds. Also reduced bacterial recovery and biofilm formation.	Strong adherence and growth of human bone or endothelial cells in titanium and silver coated implants.
Nandi et al. [61] Silver nanoparticle deposited	Journal of Biomedical	Animal study	15 (rabbits)	Silver coated pins	Osteomyelitis rabbit model	Silver coated pins offered promising	No toxicity to major organs

implants to treat osteomyelitis	Materials Research Part B 2017					result in terms of eradication of infection in rabbit osteomyelitis model	
Schmidt-Braekling et al. [21] Silver –coated megaprostheses: review of the literature	European Journal of Orthopaedic Surgery and Traumatology 2017	Review	-	-	-	Evidence of potential benefit of silver coated megaprostheses so far not been confirmed in prospective and randomized studies alone. Reduced infection rate seen in retrospective studies.	Several side effects reported in earlier studies but most recent studies have confirmed lack of systemic toxicity to silver.
Schmolders et al. [62] The role of a modular universal tumour and revision system (MUTARS) in lower limb endoprosthetic revision surgery – outcome analysis of 25 patients	Zeitschrift Fur Orthopadie Und Unfallchirurgie 2017	Retrospective case series	25	MUTARS	Patients undergoing revision surgery for failed endoprosthetic replacement or failed trauma surgery, using MUTARS	Good clinical and functional results. High rates of infection.	-
Schmolders et al. [63] Lower limb reconstruction in tumour patients using modular silver-coated megaprostheses with regard to perimegaprosthetic joint infection: a case series, including 100 patients and	Archives of Orthopaedic and Trauma Surgery 2017	Case series	100		Tumour-related lower limb salvage surgery	10% suffered periprosthetic infection	No evidence of silver toxicity

review of the literature							
Volker A. [36] Antimicrobial coated implants in trauma and orthopaedics – A clinical review and risk-benefit analysis.	Injury 2017	Review	-	-	-	Low amount silver Agluna technologies have shown the "proof of concept" for antimicrobial coatings of implants with good risk benefit ratio.	High amount silver coating associated with local argyria. Further data from randomizes controlled trials desirable.
Zajonz et al. [31] Silver-coated modular Megaendoprostheses in salvage revision arthroplasty after periimplant infection with extensive bone loss – a pilot study of 34 patients	BMC Musculoskeletal Disorders 2017	Retrospective cohort	34 (14 non-silver coated group 20 silver-coated group)	MML Munchen-Lubeck modular endoprosthesis system vs MUTARS	All patients fitted with modular endoprosthesis of lower extremity after a cured bone infection	Reinfection rate after healed reinfection in silver group was 40% compared to 57% in non silver group. Not statisticially significant.	No comment.
Origin-One and Logical-One Clinical Evidence Evaluation Report						These devices are safe and effective for their intended use. Warrant further clinical research to establish their effectiveness in a total hip replacement procedure and in reducing periprosthetic infection.	

References

1. Klasen HJ. Historical review of the use of silver in the treatment of burns. I. Early uses. Burns. 2000 Mar;26(2):117–30.

2. Nair LS, Laurencin CT. Nanofibers and nanoparticles for orthopaedic surgery applications. J Bone Joint Surg Am. 2008 Feb;90 Suppl 1(Suppl 1):128–31.

3. Clement JL, Jarrett PS. Antibacterial Silver. Metal-Based Drugs. Hindawi; 1994;1(5-6):467–82.

4. Chaloupka K, Malam Y, Seifalian AM. Silver nanoparticles: A new view on mechanistic aspects on antimicrobial activity. Trends Biotechnol. 2016 Apr;12(3):789–99.

5. Yamanaka M, Hara K, Kudo J. Bactericidal actions of a silver ion solution on Escherichia coli, studied by energy-filtering transmission electron microscopy and proteomic analysis. Appl Environ Microbiol. American Society for Microbiology; 2005 Nov;71(11):7589–93.

6. Jung WK, Koo HC, Kim KW, Shin S, Kim SH, Park YH. Antibacterial activity and mechanism of action of the silver ion in Staphylococcus aureus and Escherichia coli. Appl Environ Microbiol. American Society for Microbiology; 2008 Apr;74(7):2171–8.

7. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramirez JT, et al. The bactericidal effect of silver nanoparticles. Nanotechnology. 2005 Oct;16(10):2346–53.

8. Shrivastava S, Bera T, Roy A, Singh G, Ramachandrarao P, Dash D. Characterization of enhanced antibacterial effects of novel silver nanoparticles. Nanotechnology. IOP Publishing; 2007 May 4;18(22):225103–10.

9. Yang W, Shen C, Ji Q, An H, Wang J, Liu Q, et al. Food storage material silver nanoparticles interfere with DNA replication fidelity and bind with DNA. Nanotechnology. 2009 Feb 25;20(8):085102.

10. Lok C-N, Ho C-M, Chen R, He Q-Y, Yu W-Y, Sun H, et al. Silver nanoparticles: partial oxidation and antibacterial activities. J Biol Inorg Chem. 2007 May;12(4):527–34.

11. Park H-J, Kim JY, Kim J, Lee J-H, Hahn J-S, Gu MB, et al. Silver-ion-mediated reactive oxygen species generation affecting bactericidal activity. Water Research. 2009 Mar;43(4):1027–32.

12. Percival SL, Bowler PG, Russell D. Bacterial resistance to silver in wound care. Journal of Hospital Infection. 2005 May;60(1):1–7.

13. Sampath LA, Chowdhury N, Caraos L, Modak SM. Infection resistance of surface modified catheters with either short-lived or prolonged activity. J Hosp Infect. 1995 Jul;30(3):201–10.

14. Lin YS, Stout JE, Yu VL, Vidic RD. Disinfection of water distribution systems for Legionella. Semin Respir Infect. 1998 Jun;13(2):147–59.

15. Boyce JM. Modern technologies for improving cleaning and disinfection of environmental surfaces in hospitals. Antimicrob Resist Infect Control. BioMed Central; 2016;5(1):10.

16. Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: Comparative patient care audits. Burns. Elsevier; 2005 Aug 1;31(5):562–7.

17. Choi O, Deng KK, Kim N-J, Ross L, Surampalli RY, Hu Z. The inhibitory effects of silver nanoparticles, silver ions, and silver chloride colloids on microbial growth. Water Research. 2008 Jun;42(12):3066–74.

18. Brennan SA, Ní Fhoghlú C, Devitt BM, O'Mahony FJ, Brabazon D, Walsh A. Silver nanoparticles and their orthopaedic applications. The Bone & Joint Journal. British Editorial Society of Bone and Joint Surgery; 2015 May;97-B(5):582–9.

19. Lentino JR. Prosthetic joint infections: bane of orthopedists, challenge for infectious disease specialists. Clin Infect Dis. 2003 May 1;36(9):1157–61.

20. Donati F, Di Giacomo G, D x2019 Adamio S, Ziranu A, Careri S, Rosa MA, et al. Clinical Study Silver-Coated Hip Megaprosthesis in Oncological Limb Savage Surgery. Biomed Res Int. Hindawi Publishing Corporation; 2016 Aug 23;:1–6.

21. Schmidt-Braekling T, Streitbuerger A, Gosheger G, Boettner F, Nottrott M, Ahrens H, et al. Silver-coated megaprostheses: review of the literature. Eur J Orthop Surg Traumatol. Springer Paris; 2017 Mar 6;27(4):1–7.

22. López D, Vlamakis H, Kolter R. Biofilms. Cold Spring Harb Perspect Biol. 2010 Jul;2(7):a000398–8.

23. Funao H, Nagai S, Sasaki A, Hoshikawa T, Tsuji T, Okada Y, et al. A novel hydroxyapatite film coated with ionic silver via inositol hexaphosphate chelation prevents implant-associated infection. Sci Rep. Nature Publishing Group; 2016 Mar 17;6(1):23238.

24. Besinis A, Hadi SD, Le HR, Tredwin C, Handy RD. Antibacterial activity and biofilm inhibition by surface modified titanium alloy medical implants following application of silver, titanium dioxide and hydroxyapatite nanocoatings. Nanotoxicology. Taylor & Francis; 2017 Apr;11(3):327–38.

25. Swieczko-Zurek B. The influence of biological environment on the appearance of silver-coated implants. Advances in Materials Sciences.

2012;12(2).

26. Andersson AE, Bergh I, Karlsson J, Nilsson K. Patients' experiences of acquiring a deep surgical site infection: an interview study. Am J Infect Control. 2010 Nov;38(9):711–7.

27. Alt V, Bechert T, Steinrücke P, Wagener M, Seidel P, Dingeldein E, et al. An in vitro assessment of the antibacterial properties and cytotoxicity of nanoparticulate silver bone cement. Biomaterials. 2004 Aug;25(18):4383–91.

28. Das K, Bose S, Bandyopadhyay A, Karandikar B, Gibbins BL. Surface coatings for improvement of bone cell materials and antimicrobial activities of Ti implants. J Biomed Mater Res Part B Appl Biomater. Wiley Subscription Services, Inc., A Wiley Company; 2008 Nov;87(2):455–60.

29. Sheehan E, McKenna J, Mulhall KJ, Marks P, McCormack D. Adhesion of Staphylococcus to orthopaedic metals, an in vivo study. J Orthop Res. Wiley Subscription Services, Inc., A Wiley Company; 2004 Jan;22(1):39–43.

30. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. 1999. pp. 1896–900.

31. Zajonz D, Birke U, Ghanem M, Prietzel T, Josten C, Roth A, et al. Silver-coated modular Megaendoprostheses in salvage revision arthroplasty after periimplant infection with extensive bone loss – a pilot study of 34 patients. BMC Musculoskeletal Disorders; 2017 Aug 31;:1–7.

32. Hardes J, Eiff von C, Streitbuerger A, Balke M, Budny T, Henrichs MP, et al. Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. Journal of Surgical Oncology. Wiley Subscription Services, Inc., A Wiley Company; 2010;388(5):n/a–n/a.

33. Amin Yavari S, Loozen L, Paganelli FL, Bakhshandeh S, Lietaert K, Groot JA, et al. Antibacterial Behavior of Additively Manufactured Porous Titanium with Nanotubular Surfaces Releasing Silver Ions. ACS Appl Mater Interfaces. American Chemical Society; 2016 Jun 29;8(27):17080–9.

34. Su EP, Justin DF, Pratt CR, Sarin VK, Nguyen VS, Oh S, et al. Effects of titanium nanotubes on the osseointegration, cell differentiation, mineralisation and antibacterial properties of orthopaedic implant surfaces. Bone Joint J. British Editorial Society of Bone and Joint Surgery; 2018 Jan 1;100-B(1 Supple A):9–16.

35. Ando Y, Miyamoto H, Noda I, Sakurai N, Akiyama T, Yonekura Y, et al. Calcium phosphate coating containing silver shows high antibacterial activity and low cytotoxicity and inhibits bacterial adhesion. Materials Science and Engineering: C. 2010 Jan;30(1):175–80.

36. Alt V. Antimicrobial coated implants in trauma and orthopaedicsâ€“A clinical review and risk-benefit analysis. Injury. Elsevier Ltd; 2017 Mar 1;48(3):599–607.

37. Albers CE, Hofstetter W, Siebenrock KA, Landmann R, Klenke FM. In vitro cytotoxicity of silver nanoparticles on osteoblasts and osteoclasts at antibacterial concentrations. Nanotoxicology. Taylor & Francis; 2013 Jan 9;7(1):30–6.

38. Fielding GA, Roy M, Bandyopadhyay A, Bose S. Antibacterial and biological characteristics of silver containing and strontium doped plasma sprayed hydroxyapatite coatings. Acta Biomater. 2012 Aug;8(8):3144–52.

39. Kose N, Otuzbir A, Pekşen C, Kiremitçi A, Doğan A. A silver ion-doped calcium phosphate-based ceramic nanopowder-coated prosthesis increased infection resistance. Clin Orthop Relat Res. Springer US; 2013 Aug;471(8):2532–9.

40. Gosheger G. Silver-coated megaendoprostheses in a rabbit model—an analysis of the infection rate and toxicological side effects. Biomaterials. 2004 Nov;25(24):5547–56.

41. Hauschild G, Hardes J, Gosheger G, Stoeppeler S, Ahrens H, Blaske F, et al. Evaluation of osseous integration of PVD-silver-coated hip prostheses in a canine model. Biomed Res Int. Hindawi; 2015;2015(388):292406–10.

42. Devlin-Mullin A, Todd NM, Golrokhi Z, Geng H, Konerding MA, Ternan NG, et al. Atomic Layer Deposition of a Silver Nanolayer on Advanced Titanium Orthopedic Implants Inhibits Bacterial Colonization and Supports Vascularized de Novo Bone Ingrowth. Adv Healthc Mater. 2017 Jun;6(11):1700033.

43. Scoccianti G, Frenos F, Beltrami G, Campanacci DA, Capanna R. Levels of silver ions in body fluids and clinical results in silver-coated megaprostheses after tumour, trauma or failed arthroplasty. Injury. 2016 Oct;47 Suppl 4:S11–6.

44. Donati F, Di Giacomo G, Ziranu A, Spinelli S, Perisano C, Rosa MA, et al. SILVER COATED PROSTHESIS IN ONCOLOGICAL LIMB SALVAGE SURGERY REDUCE THE INFECTION RATE. J Biol Regul Homeost Agents. 2015 Oct;29(4 Suppl):149–55.

45. Wafa H, Grimer RJ, Reddy K, Jeys L, Abudu A, Carter SR, et al. Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case-control study. The Bone & Joint Journal. British Editorial Society of Bone and Joint Surgery; 2015 Feb;97-B(2):252–7.

46. Hardes J, Henrichs MP, Hauschild G, Nottrott M, Guder W, Streitbuerger A. Silver-Coated Megaprosthesis of the Proximal Tibia in Patients With Sarcoma. J Arthroplasty. 2017 Jul;32(7):2208–13.

47. AshaRani PV, Mun GLK, Hande MP, Valiyaveettil S. Cytotoxicity and Genotoxicity of Silver Nanoparticles in Human Cells. ACS Nano. American Chemical Society; 2008 Dec 30;3(2):279–90.

48. De Jong WH, Van Der Ven LTM, Sleijffers A, Park MVDZ, Jansen EHJM, Van Loveren H, et al. Systemic and immunotoxicity of silver nanoparticles in an intravenous 28 days repeated dose toxicity study in rats. Biomaterials. 2013 Nov;34(33):8333–43.

49. Pauksch L, Hartmann S, Rohnke M, Szalay G, Alt V, Schnettler R, et al. Biocompatibility of silver nanoparticles and silver ions in primary human mesenchymal stem cells and osteoblasts. Acta Biomater. Elsevier; 2014 Jan 1;10(1):439–49.

50. Necula BS, van Leeuwen JPTM, Fratila-Apachitei LE, Zaat SAJ, Apachitei I, Duszczyk J. In vitro cytotoxicity evaluation of porous TiO2–Ag antibacterial coatings for human fetal osteoblasts. Acta Biomater. Elsevier; 2012 Nov 1;8(11):4191–7.

51. Hussmann B, Johann I, Kauther MD, Landgraeber S, Jäger M, Lendemans S. Measurement of the silver ion concentration in wound fluids after implantation of silver-coated megaprostheses: correlation with the clinical outcome. Biomed Res Int. Hindawi; 2013;2013(1):763096–11.

52. Glehr M, Leithner A, Friesenbichler J, Goessler W, Avian A, Andreou D, et al. Argyria following the use of silver-coated megaprostheses: No association between the development of local argyria and elevated silver levels. Bone Joint J. British Editorial Society of Bone and Joint Surgery; 2013 Jul 1;95-B(7):988–92.

53. Chen Y, Zheng X, Xie Y, Ji H, Ding C, Li H, et al. Silver release from silver-containing hydroxyapatite coatings. Surface and Coatings Technology. 2010 Dec;205(7):1892–6.

54. In-Depth Oral Presentations and Oral Communications. J Orthopaed Traumatol. 2012 Aug 30;13(S1):25–55.

55. Trujillo NA, Oldinski RA, Ma H, Bryers JD, Williams JD, Popat KC. Antibacterial effects of silver-doped hydroxyapatite thin films sputter deposited on titanium. Materials Science and Engineering: C. 2012 Dec;32(8):2135–44.

56. Zimmerli W. Clinical presentation and treatment of orthopaedic implant-associated infection. Journal of Internal Medicine. 2014 Jul 14;276(2):111–9.

57. Abstracts from the International Combined Meeting BHS-SIdA | Oral presentations. Hip Int. Wichtig Publishing s.r.l; 2015 Nov 24;25(Suppl. 1):2–59.

58. PhD SEM, PhD SKM, MD SS, PhD HMM, PhD MSM, PhD MMM. First Clinical

Experience With Thermal-Sprayed Silver Oxide-Containing Hydroxyapatite Coating Implant. Journal of Arthroplasty. Elsevier Ltd; 2016 Jul 1;31(7):1498–503.

59. Furko M, Lakatos-Varsányi M, Balázsi C. Complex electrochemical studies on silver-coated metallic implants for orthopaedic application. Journal of Solid State Electrochemistry. Springer Berlin Heidelberg; 2015;20(1):263–71.

60. Furko M, Lakatos-Varsányi M, Balázsi C. Comparative Corrosion Study on Silver Coated Metallic Implants. Materials Science Forum. Trans Tech Publications; 2015 Feb;812:327–32.

61. Nandi SK, Shivaram A, Bose S, Bandyopadhyay A. Silver nanoparticle deposited implants to treat osteomyelitis. J Biomed Mater Res. 2nd ed. 2017 May 15;32:1112.

62. Schmolders J, Koob S, Schepers P, Gravius S, Wirtz D, Burger C, et al. Tumorprothesen in der endoprothetischen Revisionschirurgie der unteren Extremität – Ergebnisse von 25 Patienten nach Versorgung mit einem modularen Tumor- und Revisionssystem (MUTARS®). Z Orthop Unfall. 2017 Mar 1;155(01):61–6.

63. Schmolders J, Koob S, Schepers P, Pennekamp PH, Gravius S, Wirtz DC, et al. Lower limb reconstruction in tumor patients using modular silver-coated megaprostheses with regard to perimegaprosthetic joint infection: a case series, including 100 patients and review of the literature. Arch Orthop Trauma Surg. Springer Berlin Heidelberg; 2017 Feb;137(2):149–53.

Figure 1

Click here to download Figure Figure 1

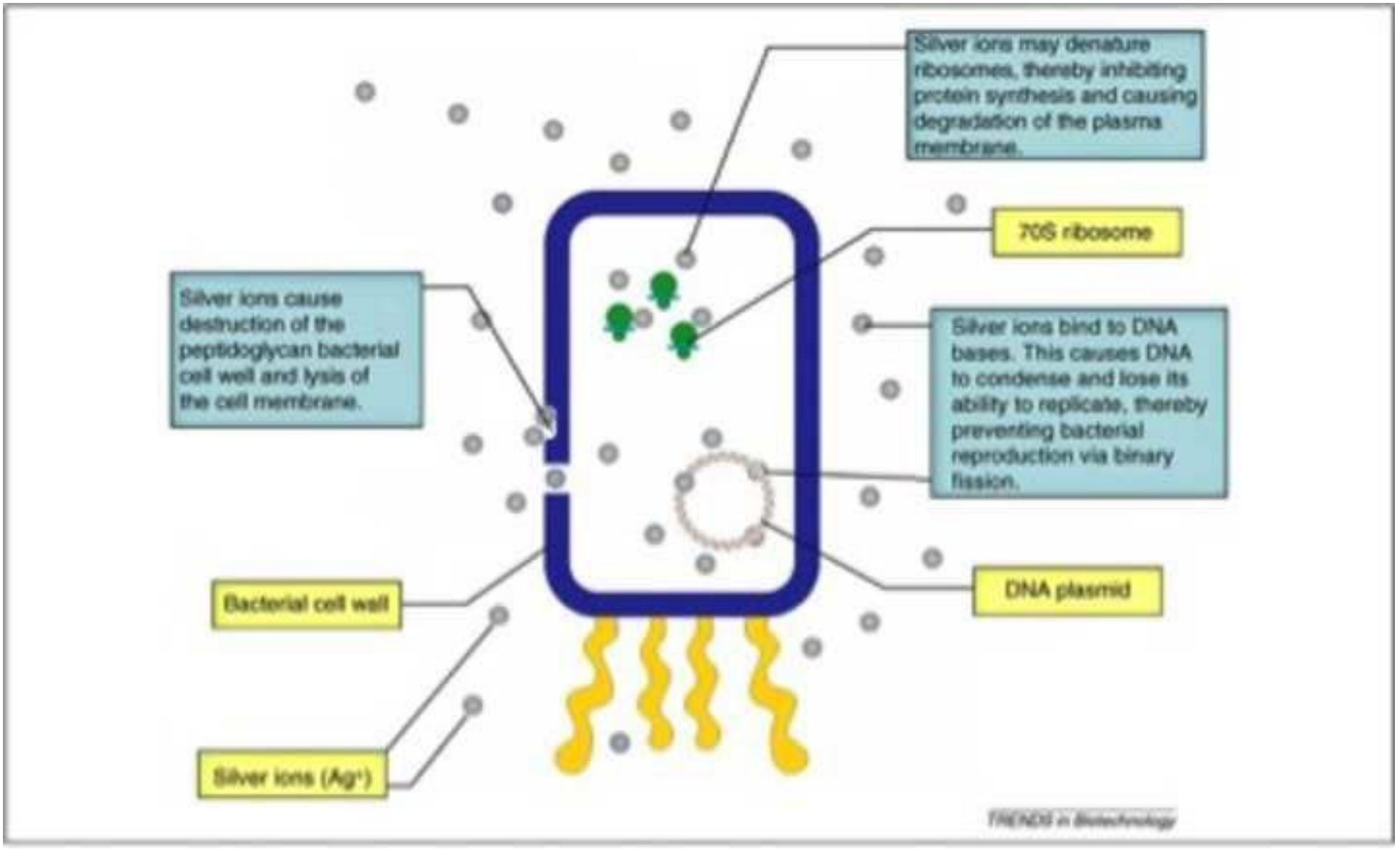
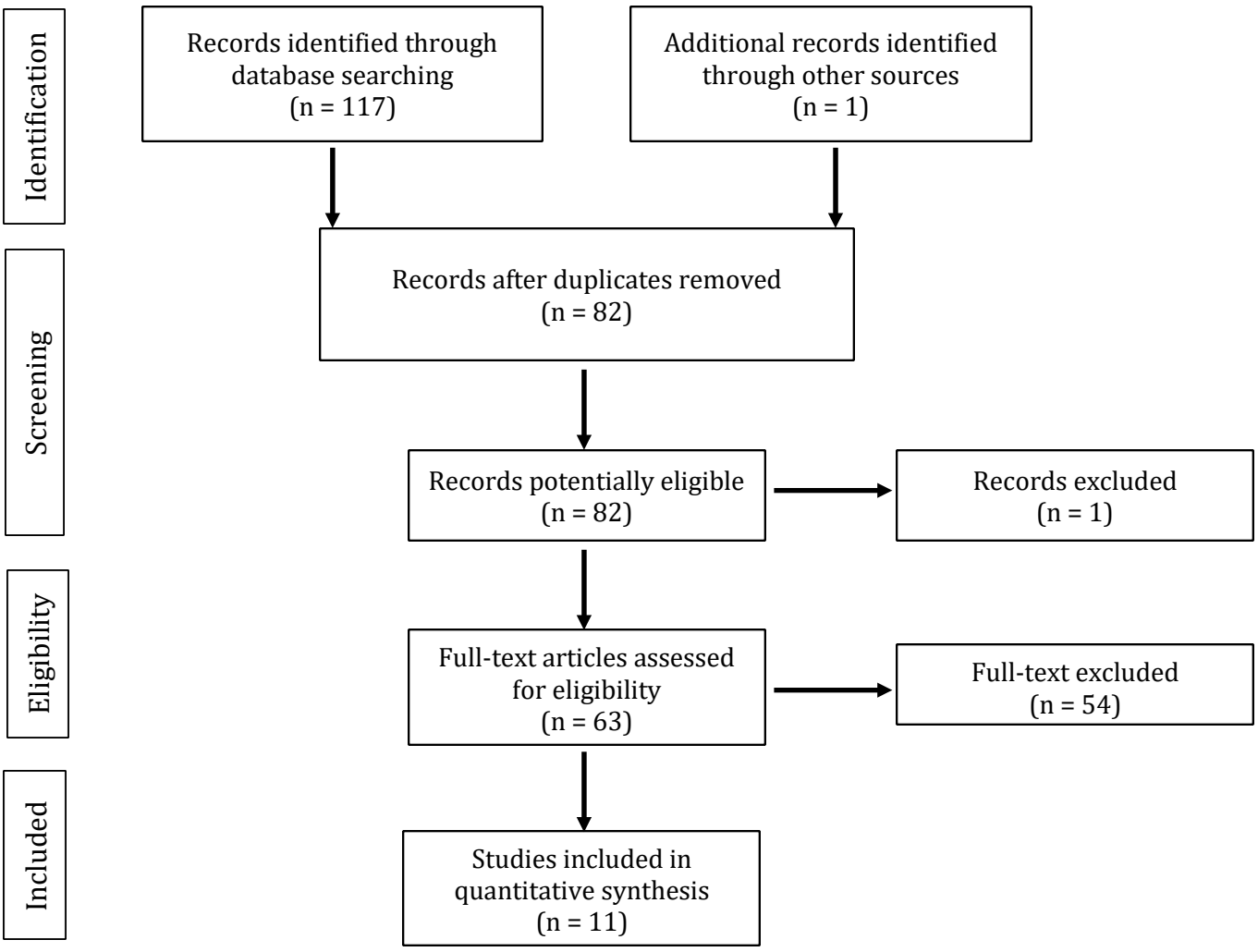


Figure 2


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 117)
Additional records identified through other sources (n = 1)
Records after duplicates removed (n = 82)
Records potentially eligible (n = 82)
Records excluded (n = 1)
Full-text articles assessed for eligibility (n = 63)
Full-text excluded (n = 54)
Studies included in quantitative synthesis (n = 11)