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Local Antibacterial Implant Protection in Orthopedics and Trauma: What's New?

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Abstract

Current prophylactic and hygienic measures notwithstanding, implant-related infection remains among leading reasons for failure in orthopaedics and trauma surgery, resulting in extremely high social and economic costs. Various antibacterial coating technologies have been proven safe and effective both in preclinical and in clinical settings and able to reduce post-surgical infections up to 90%, depending on the type of the coating and on the experimental setup. In spite of this findings, the widespread use of these technologies is still limited by several factors. After reviewing the latest evidence on currently available antibacterial coatings, an algorithm is proposed to calculate the impact of the delayed introduction of these technologies in the clinical practice. When applied to joint arthroplasties, our calculator shows that each year of delay to implement an antibacterial coating, able to reduce post-surgical infection by 80% at a final user's cost price of €600, causes an estimated 35 200 new cases of periprosthetic joint infection in Europe and additional annual hospital costs of approximately €440 million. Faster and more affordable regulatory pathways for antibacterial coating technologies and an adequate reimbursement policy for their clinical use appear a feasible solution to mitigate the impact of implant-related infections and may benefit patients, healthcare systems, and related research.

Keywords: infection, prosthesis, implant coating, periprosthetic joint infection, PJI.

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Применение имплантатов с антибактериальным покрытием в ортопедии и травматологии: современное состояние проблемы

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Реферат

Несмотря на современные достижения профилактики и гигиены, имплант-ассоциированная инфекция остается одной из основных причин несостоятельных результатов ортопедических и травматологических вмешательств, что приводит к чрезвычайно высоким социальным и экономическим издержкам. Различные технологии антибактериального покрытия имплантатов зарекомендовали себя как безопасное и эффектив-

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ное решение проблемы инфицирования в процессе как доклинических исследований, так и в клинической практике, что способствует снижению частоты послеоперационной инфекции до 90% в зависимости от типа покрытия и условий использования. Несмотря на такие выводы, широкое внедрение подобных технологий по-прежнему ограничено несколькими факторами. Изучив наиболее актуальные данные по доступным антибактериальным покрытиям, авторы предлагают алгоритм для расчета влияния несвоевременного внедрения таких технологий в клиническую практику. Применение предлагаемого калькулятора к операциям по эндопротезированию суставов демонстрирует, что каждый год отсрочки внедрения антибактериальных покрытий, который позволил бы снизить частоту послеоперационной инфекции на 80% при стоимости для конечного пользователя в размере 600 евро, приведет примерно к 35 200 новых случаев возникновения перипротезной инфекции в странах Европы и к дополнительным ежегодным госпитальным расходам в размере около 440 млн евро. Ускоренные и более доступные с точки зрения затрат процессы нормативного регулирования в отношении технологий антибактериального покрытия имплантатов, а также адекватная политика возмещения расходов по клиническому использованию таких технологий представляются возможным решением для снижения частоты имплант-ассоциированной инфекции, улучшения качества лечения пациентов, снижения нагрузки на систему здравоохранения и для стимулирования научных изысканий.

Ключевые слова: эндопротезирование, имплантаты, антибактериальное покрытие, перипротезная инфекция, расходы на лечение.

Relevance

Approximately 2 million joint arthroplasties are performed annually in Europe [1], while osteosynthesis for long bone fractures shows similar figures [2]. Undoubtedly, these numbers reflect the high success of biomaterials and related technologies in orthopedics and trauma in the last decades. However, even if the routine use of biomaterials has been pivotal in reducing the burden of disability worldwide, the long-term durability of implants is not guaranteed, and infection remains one of the main reasons for failure. In fact, considering high risk and oncological cases, periprosthetic joint infection (PJI) affects between 0.5% and 15% of patients undergoing primary or revision joint arthroplasty [3, 4]. Similarly, surgical site infection (SSI) after internal osteosynthesis for closed fracture has a reported incidence ranging from 0.5% to 10% [5, 6, 7, 8], and up to 50% after open fractures [9]. In line with this figures, SSI following spine surgery occurs in 1% to 14% of patients, depending on the preoperative diagnosis and type of surgery [10, 11].

The economic and social costs of implant-related infections are significant [12, 13, 14, 15], with high morbidity and a possible increase in mortality [6], In particular, direct hospital costs, related to the management of PJI, range from approximately €20 000 to €60 000, while the long-term economic effect of post-surgical infection after joint arthroplasty has been calculated to exceed US$ 390 000 per case [16, 17, 18,19, 20, 21, 22, 23, 24].

Rationale for local antibacterial implant protection

Whenever a biomaterial is implanted, a competition for surface colonization starts between the host's and the bacterial cells, that may eventually be present. Whenever the bacteria adhere to the implant, immediate biofilm formation takes place, making the microorganisms extremely resistant to host's defense mechanisms and to antimicrobials [25, 26, 27, 28, 29]. The colonization of the implant from the bacteria is then decided at the very time of surgery, even if the clinical consequences, the "post-surgical infection", may become evident only weeks, months or even years after surgery, depending on the relative balance between the microorganisms and the host's individual inflammatory response.

This observation grounds the basis for protecting the implant at the very time of surgery with surface finishing or coatings specifically designed to selectively prevent bacterial adhesion and biofilm formation, without interfering with the biocompatibility and the long-term duration and function of the implant [30].

Various technologies have been investigated in the last decades and can be classified according to their mechanism of action as follows [31] (Table 1):

– Passive surface finishing/modification: this approach aims at preventing or reducing bacterial adhesion to implants through surface chemistry and/or physical modifications, without the use of any pharmacologically active substance. Examples of this approach include modified titanium dioxide surface or polymer coatings.

– Active surface finishing/modification: pharmacologically active pre-incorporated bactericidal agents, such as antibiotics, antiseptics, metal ions, or other organic and inorganic substances, are actively released from the implant in order to reduce bacterial adhesion. Examples of this approach are "contact killing" active surface with silver- or iodine-coated joint implants.

– Local carriers or coatings: this strategy employs local antibacterial carriers, or coatings, that are not built into the device, but rather are applied during surgery, immediately prior to the insertion of the implant. They may have direct or synergistic antibacterial/antiadhesive activity or may deliver high local concentrations of loaded antibiotics or antibacterial agents.

Table 1

Classification of antibacterial implant protection strategies [31]

Features/examples	Development stage
Passive Surface/Finishing Modifications (PSM)	
Prevention of bacterial adhesion	
Hydrophilic surface	Preclinical
Superhydrophobic surface	Preclinical
Anti-adhesive polymers	Preclinical
Nanopatterned surface	Preclinical
Albumin	Preclinical
Hydrogels	Preclinical
Biosurfactants	Preclinical
Active Surface/Finishing Modifications (ASM)	
Inorganic	
silver ions and nanoparticles	Market
other metals (copper, zinc, titanium dioxide, etc.)	Preclinical
non-metals: iodine	Clinical
other non-metal ions (selenium, graphene, etc.)	Preclinical
Organic	
coated/linked antibiotics	Market
covalently linked antibiotics	Preclinical
antimicrobial peptides	Preclinical
cytokines	Preclinical
enzymes and biofilm-disrupting agents	Preclinical
chitosan derivatives	Preclinical
Synthetic	
non-antibiotic antimicrobial compounds	Preclinical
“smart” coatings	Preclinical
Combined	
multilayer coating	Preclinical
Local Carriers or Coatings (LCC)	
Non-biodegradable	
antibiotic-loaded poly (methyl methacrylate)	Market
Biodegradable	
antibiotic-loaded bone grafts and substitutes	Market
fast-resorbable hydrogel (acting both as passive surface modification system and as local antibiotic carrier)	Market

In spite of several products found effective at a research level, translating preclinical findings into clinical practice appears particularly challenging, time-consuming, and expensive. As a result, many promising coating technologies fail to reach the market due to regulatory, commercial or economic restrictions, with a loss of chance for the patients and for the health care systems, which is difficult to quantify [32].

Antibacterial coating of implants: current technologies

Besides antibiotic-loaded poly(methyl methacrylate) (PMMA), bone grafts, and calcium-based bone substitutes that, even if adopted in the clinical setting, were not specifically designed to act as antimicrobial coatings of implants, only four technologies are currently available in orthopedics and trauma for clinical use, or at least with reported clinical results [33]. These include silver and iodine coatings, gentamicin poly(D, L-lactide) (PLLA) coating, and a fast-resorbable hydrogel coating composed of covalently linked hyaluronan and PLLA (Defensive Antibacterial Coating (DAC®); Novagenit Srl, Mezzolombardo, Italy) (Table 2).

Silver coatings

Silver antibacterial activity is known since ancient ages. Silver dissolved cations are capable of interfering with bacterial cell membrane permeability and cellular metabolism and, when released in an aqueous medium, contribute to the formation of reactive oxygen species that potentially influence prokaryotic cells [33]. Different technologies are currently used to apply the silver coating to metallic orthopaedic implants [33, 34, 35]. Comparative and prospective studies are not available and only retrospective case series have been published, with coating application restricted to tumour prostheses [36, 37].

Wafa et al. [38] reported the results of silver-coated tumour prostheses in 85 patients compared with 85 matched control patients. Indications included 50 primary reconstructions (29.4%), 79 one-stage revisions (46.5%), and 41 two-stage revisions for infection (24.1%). At a minimum follow-up of 12 months, there was a significant reduction in the overall postoperative infection rate from 22.4% to 11.8% (p = 0.03) in favour of the silver-coated implant group, with a mean reduction of approximately 48% in infection rate.

Table 2

Comparison of clinically available antimicrobial coating technologies, specifically designed for orthopaedics and trauma implants

Technology	Regulatory phase	Trademark and manufacture company	Mechanism of action	Main applications
Silver	Market	Agluna® (Accentus Medical Ltd, Didcot, United Kingdom); Mutars® (Implantcast GmbH, Buxtehude, Germany); PorAg (Waldemar Link GmbH & Co. KG, Hamburg, Germany)	Silver ion release	Tumour mega-prosthesis
Iodine	Clinical trials	Not applicable	Iodine release	Titanium implants including spine instrumentation, hip and knee joint arthroplasties, plates and screws
Gentamicin poly(D, L-lactide) matrix	Market	UTN PROtect Tibial Nail® (DePuy Synthes, Bettlach, Switzerland); Expert Tibial Nail (ETN) PROtect® (DePuy Synthes, Johnson & Johnson, New Brunswick, New Jersey)	Gentamicin release	Tibial nail for the treatment of tibial fractures and nonunions
Hyaluronic acid and poly(D, L-lactide) hydrogel	Market	Defensive Antibacterial Coating (DAC®) (Novagenit Srl, Mezzolombardo, Italy)	Antifouling activity with ancillary antibiotic release	Orthopaedics, traumatology, dentistry, and maxillofacial implants

The routine use of silver-coated implants remains rather limited for several reasons, including possible toxicity of silver ions [39], and incomplete protection of the implant, since the intramedullary part of the prosthesis and some modular components cannot be coated. Moreover, only a few implant designs are offered with silver coating protection, while the cost of the technology remains quite high when considering applications outside oncology [40].

Iodine coating

Povidone-iodine can be used as an electrolyte, resulting in the formation of an adhesive, porous anodic oxide with the antiseptic properties of iodine [41]. Besides extensive preclinical studies [41, 42, 43], excellent clinical efficacy was reported for iodine coating of titanium alloys in a continuous, non-comparative series of 222 patients [44]. Preoperative diagnoses included tumour in 95 cases (42.8%), 34 limb deformities (15.3%), 29 cases of degenerative disease (13.1%), 27 osteomyelitis (12.2%), 24 nonunions (10.8%), and 16 fractures (7.2%). A variety of implants were used: 82 spinal instrumentations, 55 plates for osteosynthesis, 36 external fixations (pins and wires), 32 tumour prostheses, ten hip prostheses, four knee prostheses, two nails, and one cannulated screw. At a mean follow-up of 18.4 months (3 to 44), acute infection developed in three tumour cases (1.9%).

Two more recent non-comparative studies — one investigating iodine coating and megaprosthesis [45], the other investigating total hip arthroplasty (THA) [46] — confirmed the safety and efficacy of the technology at longer follow-ups. Based on these findings, clinical trials are currently ongoing to meet the regulatory requirements for market approval (Fig. 1). While no adverse event has been reported to date, the longer-term effects of local application of iodine coating and the application to materials other than titanium are yet to be assessed.

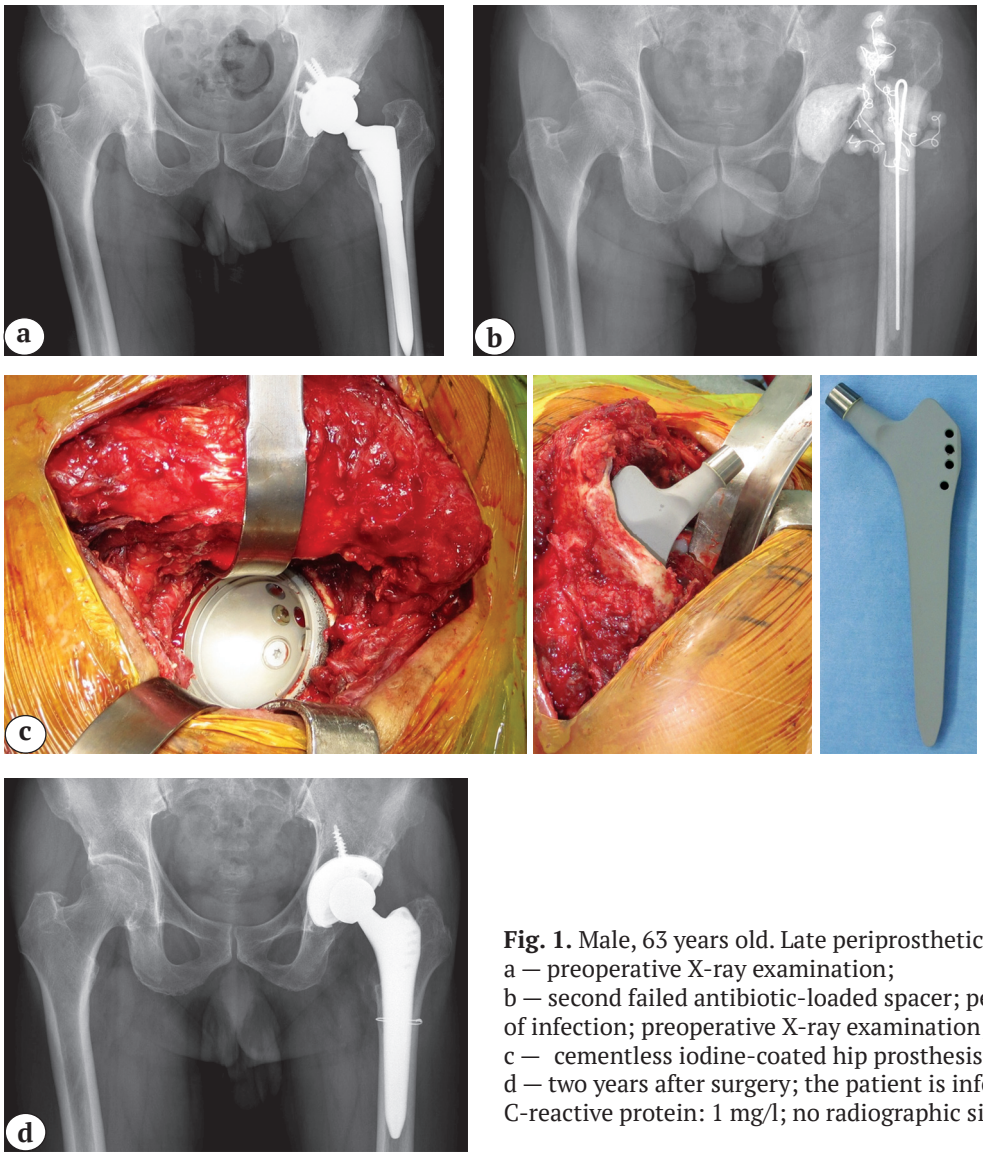

Fig. 1. Male, 63 years old. Late periprosthetic joint infection:
a — preoperative X-ray examination;
b — second failed antibiotic-loaded spacer; persistence of infection; preoperative X-ray examination;
c — cementless iodine-coated hip prosthesis; intra-operative pictures;
d — two years after surgery; the patient is infection free;
C-reactive protein: 1 mg/l; no radiographic signs of implant loosening

Gentamicin PLLA coating

A coating for tibial nails, composed of a poly-l-lactic acid (PLLA) matrix, loaded with gentamicin, was first introduced into clinical use in Europe approximately fifteen years ago. The coating provides 80% release of the antibiotic within the first 48 hours [47]. In the first published clinical report, Fuchs et al. [48] observed no deep infections at six months' follow-up in 21 patients treated with a UTN PROtect Tibial Nail (DePuy Synthes, Bettlach, Switzerland) for closed or open tibial fractures, as well as for revisions. Metsemakers et al. [49] reported a retrospective analysis, including nine patients with a Gustilo and Anderson grade II or grade III open tibial fracture, four infected nonunions, two acute tibial shaft fractures pretreated with external fixation, and one aseptic nonunion with a soft tissue defect. At 18 months' follow-up, no implant-associated deep infection was reported. Finally, in the most recent and largest study, data from four centres, analyzed the outcome of 99 patients with fresh open or closed tibial fractures or undergoing nonunion revision surgery [50]. At 18 months' follow-up, deep surgical site infection or osteomyelitis was noted in 4/55 patients (7.2%) after fresh fracture and in 2/26 patients (7.7%) after revision surgery. The heterogeneous material and the lack of a comparator makes the interpretation of these results particularly difficult.

Apart from the absence of comparative trials, a limit of this technology is the fact that it is only available for the tibia and for one specific nail design. Furthermore, screws and fixation holes are not protected by the coating, while gentamicin resistance, ranging from 2% to 50% in Europe [51], may reduce the efficacy of the coating in some cases.

D.A.C. hydrogel

The Defensive Antibacterial Coating (D.A.C.) hydrogel is the first antimicrobial coating specifically designed to protect a variety of biomaterials in orthopedics, traumatology, dentistry, and maxillofacial surgery [52, 53]. The device is based on the ability of hyaluronic-based compounds to reduce bacterial adhesion and biofilm formation, and to protect against various infectious agents [54, 55, 56]. Although designed as a stand-alone product, the DAC hydrogel is capable of entrapping several antibacterial agents at concentrations ranging from 2% to 10%, released locally for up to 72 hours, with an amount of drug released that is hundreds or thousands of times higher than the minimum inhibitory concentration (MIC), in a time- and dose-dependent manner [52]. This is why, according to the classification mentioned earlier, the DAC hydrogel features and intermediate mechanism of action and can both be classified as a Passive Surface Modification and as a Local Antibiotic Carrier.

The safety and efficacy of DAC hydrogel have been tested in several preclinical in vitro and in vivo studies [57, 58, 59]. Clinically, a first multicenter, randomized prospective trial was conducted in Europe, on a total of 380 patients, scheduled to undergo primary or revision hip or knee joint arthroplasty [60]. Overall, 373 patients were available at a mean follow-up of 14.5 months (sd 5.5). A total of 11 SSIs were observed in the control group, with only one observed in the treatment group (6% vs 0.6%; $p = 0.003$). No local or systemic side effects related to the DAC hydrogel coating were reported, and no detectable interference with implant osteointegration was noted. In another multicentre prospective study, 256 patients undergoing osteosynthesis for a closed fracture were randomly assigned to receive the antibiotic-loaded DAC coating or to a control group without coating. At a mean follow-up of 18.1 months (sd 4.5), six SSIs (4.6%) were observed in the control group compared with none in the treated group ($p<0.02$). No local or systemic side effects related to DAC hydrogel coating were observed, and no detectable interference with bone healing was reported [61]. More recently, DAC hydrogel-coated cementless was tested safe for one-stage exchange for infected prosthesis (Fig. 2) [62]. However, longer-term data are required to examine delayed or late prosthetic joint infections. In fact, while the quick resorption of the hydrogel makes long-term side effects quite unlikely, this same feature may limit or prevent the ability of this technology to protect the implant from late, haematogenous infections.

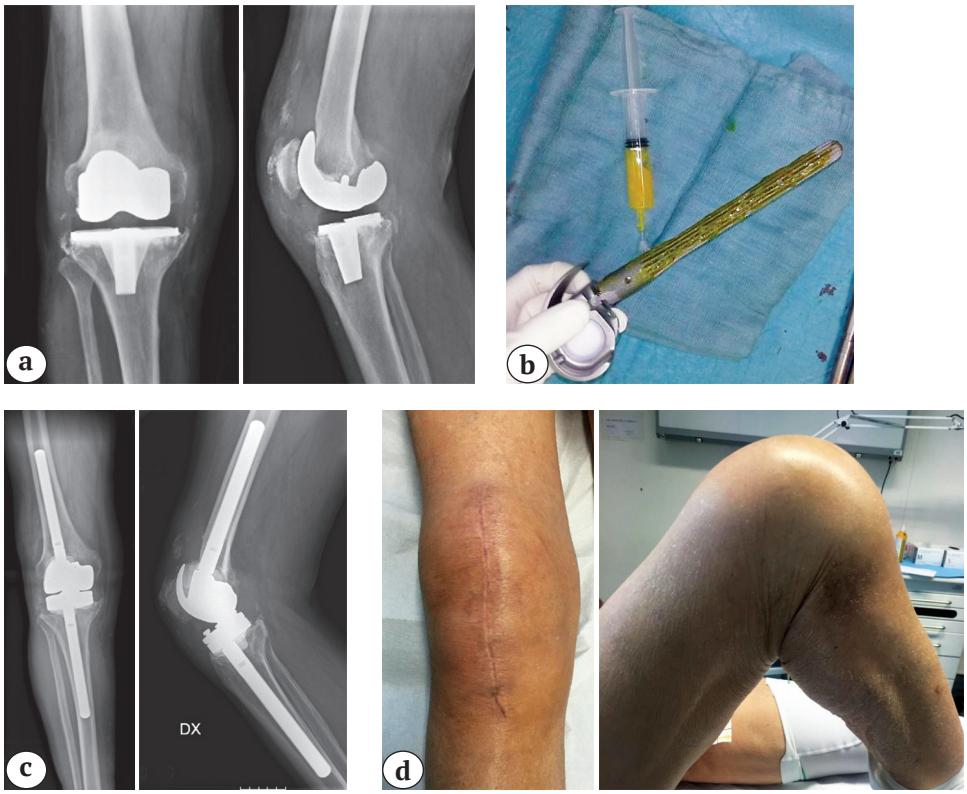

Fig. 2. Male, 82 years old. Delayed periprosthetic knee infection. Failed debridement and irrigation and prolonged suppressive antibiotic therapy. Multi-resistant *Staph. Aureus.* Joint instability due to severe medial ligaments insufficiency:
a — pre-operative X-ray examination;
b — intra-operative picture, at the time of "one-stage" knee revision surgery; based on pre-operative antibiogram, tigecycline-loaded Defensive Antibacterial Coating hydrogel is applied on the cementless stem of the revision implant;
c — radiographic control, two years after surgery; no sign of osteolysis or loosening;
d — clinical images at two years from revision surgery; no signs of infection recurrence and full function recovery; the patient has just been operated on the contralateral knee for osteoarthritis

Potential impact of large-scale application of antibacterial coatings

Implementing measures against post-surgical infection after joint arthroplasty may result in a measurable reduction of PJI, with significant cost saving and improved quality of life.

According to Graves et al. [63], considering a cohort of 77 321 patients undergoing primary total hip replacement in the United Kingdom, a combined treatment strategy able to reduce post-surgical infection (odds ratio 0.13) may prevent 1481 cases of deep infection, leading to annual cost savings of £8 325 277, when compared with a baseline strategy (plain cement, conventional ventilation, and no systemic antibiotics).

Shearer et al. [64] calculated that the net monetary benefit resulting from a 10% reduction in PJIs was $278 per index procedure and concluded that strategies aimed at reducing PJI may have a greater effect on cost and long-term effectiveness of THA than further enhancements in implant longevity.

Our group recently proposed an algorithm to calculate the cost-effectiveness of different antibacterial coating strategies applied to joint prostheses, taking both direct and indirect hospital costs into account [40]. According to this model, an antibacterial coating technology able to reduce post-surgical infection by 80%, at a cost per patient of €600, would provide a reduction in hospital costs of €200 per patient if routinely applied in a population that would otherwise have an expected post-surgical infection rate of 2%. Projecting these figures at a European level, with approximately 2.2 million joint arthroplasties performed per year, we may speculate that a year of delay in the routine use of such a coating would result in 35 200 additional PJI cases per year with additional annual costs of approximately € 440 million per year (Table 3 and 4) [65]. These calculations do not include any costs that might result from an increased mortality rate, permanent disability deriving from post-surgical infection, or medicolegal claims.

Table 3

Algorithm to calculate the economic impact of an antibacterial coating of joint arthroplasty; a positive balance indicates that, for the selected parameters, the ABC technology is associated with a net cost saving, a negative value would indicate a net economic loss [40]

	No coating	ABC
Joint replacement, average cost per patient	a	
Joint arthroplasties per year, n	b	
Total cost of joint arthroplasties per year	c = a*b	
ABC cost per patient	0	d
% of expected PJI	e	
% reduction of PJI with ABC	f	
Expected infections, n	g = b*(e/100)	h = b*(e/100)*(1-f/100)
PJI treatment, cost per case	i	
Costs per all septic complication treatment	k = g*i	l = h*i
Costs for joint arthroplasty including septic complications	m = c+k	n = c+l
Total costs for ABC		o = b*d
Total costs	p = m	q = n+o
Balance	r = p-q	
% Balance (Total costs with ABC/without)	r′ = q/p	

ABC — antibacterial coating; PJI — prosthetic joint infection.

Table 4

Simulation of the algorithm application to a cohort of 2.2 million patients, approximately equivalent to the number of total joint replacements performed each year in Europe. According to this scenario, the routine use of the coating would be associated to annual costs savings of €440 000 000 and 8000 new cases of PJI, compared to 44 000 new cases of PJI if the coating is not used

	No coating	ABC
Joint arthroplasty, average cost per patient	€8 000	
Joint arthroplasties per year, number	2 200 000	
Total cost of joint arthroplasties per year	€17 600 000 000	
ABC cost per patient	€0	€600
% of expected PJI (without the coating)	2,0	
% reduction of PJI with ABC	80	
Expected infections, number	44 000,0	8 800,0
PJI treatment, cost per case	€50 000	
Costs per all septic complication treatment	€2 200 000 000	€440 000 000
Costs for joint arthroplasty including septic complications	€19 800 000 000	€18 040 000 000
Total costs for ABC		€1 320 000 000
Total costs	€19 800 000 000	€19 360 000 000
Balance	+ €440 000 000	
% Balance (Total costs with ABC/without)	97,8	

ABC — antibacterial coating; PJI — prosthetic joint infection.

Conclusions

Implant-related infections in orthopedics and trauma have a tremendous social and economic impact projected to grow over the next decades and associated with increased rates of morbidity and mortality. Despite the recognized need for implant-related infection containment and the demonstrated efficacy of some antibacterial coatings notwithstanding, only a few technologies are currently available in orthopaedics and trauma.

Given the potential benefits that can be anticipated scientifically by a wider application of antibacterial implant coating technologies, in our opinion, any effort should be made to increase the awareness of health care providers and their patients concerning the existing technologies and their possible contribution to mitigate septic complication; furthermore, specific reimbursements for the currently available coatings should be introduced, with faster and more affordable regulatory pathways for the most promising technologies in the pipeline. At the same time, an efficient and independent post-marketing surveillance system need to be set at national or international level, in order to monitor the clinical results and promptly report on any possible side effect or long-term complication of such new technologies.

Publication ethics

All patients provided written informed consent.

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Authors' contribution

C.L. Romanò — conceived and drafted the manuscript.

S.A. Bozhkova — design and revision the manuscript.

V. Artyukh — literature review.

D. Romanò — bibliographic search, manuscript revision.

H. Tsuchiya — manuscript revision, figure and case presentation.

L. Drago — co-drafted the manuscript.

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