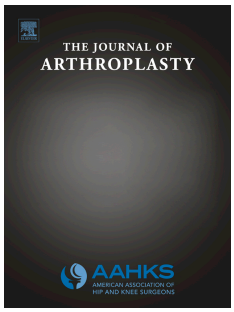
Accepted Manuscript



Economic Evaluation of Antibacterial Coatings on Healthcare Costs in First Year Following Total Joint Arthroplasty

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PII: S0883-5403(18)30095-0

DOI: 10.1016/j.arth.2018.01.057

Reference: YARTH 56378

To appear in: *The Journal of Arthroplasty*

Received Date: 10 May 2017

Revised Date: 24 December 2017

Accepted Date: 22 January 2018

Please cite this article as: Trentinaglia M, Van Der Straeten C, Morelli I, Logoluso N, Drago L, Romanò C, Economic Evaluation of Antibacterial Coatings on Healthcare Costs in First Year Following Total Joint Arthroplasty, *The Journal of Arthroplasty* (2018), doi: 10.1016/j.arth.2018.01.057.

TITLE PAGE

Title

Economic Evaluation of Antibacterial Coatings on Healthcare Costs in First Year Following Total Joint Arthroplasty

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Word count

Abstract: 247

Manuscript: 2951

Ethical approval

None

Title

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ABSTRACT

Background

Antibacterial coatings (ABCs) of implants have proven safe and effective to reduce post-surgical infection, but little is known about their possible economic impact on large-scale use. This study evaluated the point of economic balance, during the first year after surgery, and the potential overall annual healthcare cost savings of three different antibacterial technologies applied to joint arthroplasty: a dual antibiotic-loaded bone cement (COPAL G+C®), an antibacterial hydrogel coating (DAC®) and a silver coating (Agluna®).

Methods

The variables included in the algorithm were: average cost and number of primary joint replacements; average cost per patient of the ABC; incidence of periprosthetic joint infections and expected reduction using the ABCs; average cost of infection treatment and expected number of cases.

Results

The point of economic balance for COPAL G+C®, DAC®, and Agluna® in the first year after surgery was reached in patient populations with an expected post-surgical infection rate of 1.5%, 2.6%, and 19.2%, respectively. If applied on a national scale, in a moderately high-risk population of patients with a 5% expected post-surgical infection rate, COPAL G+C® and DAC® hydrogel would provide annual direct cost savings of approximately €48,800,000 and €43,200,000 (€1,220 and €1,080 per patient), respectively, while the silver coating would be associated with an economic loss of approximately €136,000,000.

Conclusion

This economic evaluation shows that ABC technologies have the potential to decrease healthcare costs primarily by decreasing the incidence of surgical site infections, provided that the technology is used in the appropriate risk class of patients.

Keywords

Cost; Economics; Antibacterial; Coating; Infection; Arthroplasty.

INTRODUCTION

Infection remains among the chief reasons for joint replacement failure [1]. Periprosthetic joint infections (PJI) are associated with increased costs for public health systems mainly because of additional surgeries, prolonged hospitalization, increased length of rehabilitation, and increased use of antibiotics [2]. Moreover, PJIs are associated with an increase in morbidity and mortality [3]. Unless novel, effective measures are taken to reduce the incidence of surgical site infections (SSIs), these complications will become an accruing burden to the health care system in the next two decades [4, 5].

Antibacterial coatings (ABC) of implants offer an attractive option to reduce post-surgical infections [6]. A strong recommendation was delivered in a recent international consensus meeting on PJIs concerning the need to develop effective antibacterial surfaces that prevent bacterial adhesion, implant colonization, and proliferation into surrounding

tissues [7]. In line with this vision, various technologies have been introduced in the clinical setting to protect joint prostheses from bacterial colonization [8, 9], including antibiotic-loaded polymethylmethacrylate (antibiotic-loaded bone cements) [10-12], antibiotic-loaded bone allografts [13], antibacterial hyaluronic-based hydrogel [14-17], and silver coatings [18-21]. Furthermore, several other promising technologies are under development and may reach the market in the near future [6, 22].

Among the various factors for an ABC technology to be successful and implemented in routine clinical practice, its economic sustainability plays a strategic role. Health technology assessment is increasingly used to inform coverage, access, and utilization of medical technologies [23] as, for example, in molecular diagnostics [24] and medical devices [25]. To the best of our knowledge, no study to date has addressed the possible economic impact of antibacterial technologies designed to protect orthopedic implants [26]. Furthermore, the cost-to-benefit ratio of any device employed to reduce post-surgical infection is strictly related to the expected complications rate, which may be 20 times higher in patients with specific co-morbidities [27]. The aim of this health economics study was to assess the cost-effectiveness of three currently available antibacterial coatings of joint prostheses and compare their direct and indirect hospital costs with those of unprotected implants, taking into consideration the expected SSI rate. To this aim, we asked the following questions: (1) What is the point of economic balance of using an antibacterial coating per 1,000 patients at our institution, during the first year after surgery? (2) What are the overall potential annual cost savings for a large, European national healthcare system when an antibacterial coating is applied to joint prosthesis for implantation in a high-risk patient population?

METHODS

The decision-analytic modelling approach to the cost-effectiveness analysis presented here is based upon the framework of Diaz-Ledezma et al. [28], who assessed the effectiveness of different diagnostic tests for PJI in relation to benefits, opportunities, economics costs, and risks, and on a recent analysis by Kapadia et al. [29]. We investigated the consequences of post-surgical PJI on the economic impact in the first year following surgery of three different antibacterial coating technologies versus unprotected implants: 1) a high-dose, dual-antibiotics (gentamicin and clindamycin) loaded bone cement (COPAL G+C®, Heraeus Medical GmbH, Wehrheim, Germany) [30]; 2) a fast-resorbable hydrogel coating composed of covalently linked hyaluronan and poly-D,L-lactide (Defensive Antibacterial Coating, DAC®, Novagenit Srl, Mezzolombardo, Italy) [17] which is applied by the surgeon at the time of surgery to the surface of all components of a cementless joint prosthesis; and 3) Agluna® (Accentus Medical Ltd, Oxfordshire, UK, a silver-enhanced, custom-made tumor endoprosthesis (Stanmore Implants Worldwide Ltd, Elstree, UK) [21].

For each technology we evaluated and compared the average direct hospital cost per patient at our institution. Furthermore, we assessed and estimated the cost of joint replacement procedures and the indirect hospital costs associated with the expected rate of post-surgical infection and relative costs. We adopted a static perspective that focused only on the short-term costs that may arise in the immediate postsurgical period (one year) after a primary operation. Hence, our methodology does not allow for long-term economic assessment, which would also account for the treatment of late infections, infection recurrences, and complications arising from infection treatment.

(A) Direct costs

The total direct costs to hospitals refer to the costs of the primary procedure, as assessed from a review of the related European literature, and to the cost of the antibacterial coating applied during surgery, as measured by the undiscounted list prices at our institution. On an aggregate level, the total direct costs per total joint arthroplasty (TJA) are given by the following equation:

$$\textbf{Total direct costs} = \textbf{Number of TJA} * (\textbf{Cost of primary TJA} + \textbf{Cost of antibacterial coating}) \quad \textbf{(1)}$$

The cost of a primary joint replacement was derived from the analysis by Stargardt [31], who assessed the average cost of primary hip replacement in nine Member States of the European Union in 2008: the total cost of treatment ranged from € 1,290 (Hungary) to € 8,739 (The Netherlands), with a mean cost of € 5,043 ± 2,071. In Italy, the average cost was € 6,795.04, with a Diagnosis-Related Group (DRG) reimbursement of € 8,963.60. Similar results were reported for primary knee replacement, with an average cost of € 6,889 for treatment in Germany [32] and £ 6,363 in the UK [33]. Considering an annual cost increase of 2% and that these studies were published between 5 and 10 years ago, for the purpose of our analysis we set the average cost at € 8,000 per primary joint replacement procedure.

We took the cost of each of the three ABC technologies applied to a hip or knee implant at our facility. For this analysis we considered the undiscounted list price of COPAL G+C®, DAC®, and Agluna® silver coating. An average of two packages of COPAL® and DAC® products per patient were entered in our calculations, assuming this as the average need per patient. The undiscounted price list cost of two packages (considered as the standard use per patient) of COPAL® or DAC® at our institution was € 480 and € 1,170, respectively; the cost of a silver-coated implant exceeded that of an uncoated one by € 4,600 on average.

(B.1) Indirect costs – Cost of the revision procedure

Costs arising from the treatment of PJIs in the first year after the primary surgery were considered as indirect costs. For our calculations, we started with the cost of a two-stage revision surgery as standard of care for PJI. The average cost was derived from our previous observations and from the literature [34-37]. We did not consider potential costs arising from the treatment of complications or failures, which may refer, instead, to long-term economic assessment which is beyond the scope of the present analysis. The average cost per patient of PJI treatment with a two-stage revision surgery was set at € 50,000, following our and other studies, with values ranging from approximately € 40,000 to € 60,000 [34-37].

(B.2) Indirect costs – Coating efficacy

Antibacterial coatings have proven able to abate the probability of a post-surgical site infection. To translate this medical ability into economic terms, and, more precisely, into a reduction in indirect costs, we computed the expected indirect cost, which is given by the cost of the surgical procedure, times the PJI rate and times the probability of reduction in PJI, i.e., the aggregate expected, total indirect cost of a TJA is given by the following equation:

Expected indirect cost *=Number of TJA * Cost* ***of septic revision * Probability of PJI * (1 – coating abatement rate).*** **(2)**

To compute the indirect costs that actually arise in TJAs with and without coating, we initially assessed the relative rate of post-surgical infection following joint replacement, with and without the use of the ABCs, based on our previous studies and the available literature [17, 21, 30].

To calculate the economic impact of the three ABC technologies, we derived the respective potential reduction of post-surgical infection from the available clinical studies. The reduction in SSI achievable using COPAL G+C was obtained from a recent study published by Sprowson and co-workers [30] ~~[30]~~. In this prospective, quasi-randomized study, 848 patients with an intracapsular hip fracture were treated with cemented hemiarthroplasty in a large teaching hospital; 448 received low-dose single-antibiotic impregnated cement (control group) and 400 received high-dose dual-antibiotic impregnated cement (COPAL G+C, intervention group). At 1-year post-surgery, the incidence of deep SSI was significantly lower in the intervention group compared to the controls (1.1% versus 3.5%; Fisher's exact test; $p = 0.04$), with an overall approximately 68% reduction in infections.

The potential reduction of SSIs using the DAC hydrogel anti-bacterial coating was obtained from the results of a prospective, randomized study performed in six European centers [17]. A total of 380 patients, scheduled for primary (n=270) or revision (n=110) total hip (N=298) or knee (N=82) joint replacement with a cementless or a hybrid implant, were randomly assigned to receive an implant with either the antibiotic-loaded DAC coating (treatment group) or without coating (control group). At a mean follow-up of 14.5 ± 5.5 months (range 6 to 24), 11 SSIs were observed in the control group and 1 in the treatment group (6% vs. 0.6%; p=0.003), with an average infection rate reduction of approximately 90%.

Only retrospective studies concerning silver coating are available. A retrospective case-control study on a silver-coated tumor prosthesis in 85 patients treated between 2006 and 2011 was recently published by Wafa et al. [21] with a minimum follow up of 12 months. These data were matched with outcome in 85 control patients who received an identical but uncoated tumor prosthesis between 2001 and 2011. Indications included 50 primary reconstructions (29.4%), 79 one-stage revisions (46.5%), and 41 two-stage revisions for infection (24.1%). Comparing the matched silver-free control group versus the silver-coated mega-endoprosthesis group, there was a significant reduction in the overall postoperative infection rate from 22.4% to 11.8% (p = 0.03) in favor of the silver-coated implant group, with an average reduction of approximately 48% in infection rate.

In a further analysis of the potential impact of the ABC technologies in selected cohorts of patients with at least one co-morbidity (type B hosts, according to McPherson's staging system [38]), we identified several conditions known to at least double the risk of SSI after hip or knee arthroplasty (Table 2). For the purpose of this study, the prevalence of patients with at least one risk factor for post-surgical infection after joint arthroplasty was conservatively set at 25%, in line with recent surveys [39, 40].

(C) Algorithm to calculate the economic impact of anti-bacterial coatings

Table 1 reports the algorithm we used to calculate the overall economic impact of ABC technologies during the first year after the primary surgery. The variables included in calculation were: average cost and number of primary joint replacements; average cost of the ABC technology per patient; incidence of PJI and expected reduction in infection rate with use of the ABC; average cost of PJI treatment and expected number of cases. Our cost assessment thus sums the total direct costs presented in equation (1) and the indirect costs of equation (2). The total, resulting costs are given by the following equation:

$$\boldsymbol{Total\ cost\ = Total\ direct\ cost + Expected\ indirect\ cost.} \quad \textbf{(3)}$$

To identify the point of economic balance for each technology, we included patient subpopulations with a progressively higher risk of infection in the analysis. This algorithm was initially applied to a benchmark setting with an infection incidence of 2% (Table 3), which is the infection rate of the general population according to recent reports investigating the SSI rate after primary knee or hip replacement in northern Italy [41] and other countries [42, 43]. Doing so, we computed the economic impact per patient implanted with a TJA with no coating versus a TJA with a hypothetical antibacterial able to half the above-mentioned infection rate.

We then identified the economic balance of each coating (Table 4), i.e., we derived the risk of infection for the general population such that a primary procedure without antibacterial coating costs as much as a procedure performed with antibacterial coating. For this purpose, we applied the abatement rate specific to each coating as previously discussed.

Finally, the potential cost savings (Table 5) of large-scale application of the ABC technologies was simulated in patients with at least one co-morbidity known to at least double the risk of post-surgical infection following TJA (odds ratio or relative risk ≥2.0).

RESULTS

(A) Direct costs

As mentioned above, total direct costs account for both the cost of the primary procedure and for the cost of the applied antibacterial coating. For each coating considered, we applied equation (1) to compute the total direct costs for each patient undergoing a primary TJA. The resulting direct costs range from a minimum of €8,000, when no coating is applied, to a maximum of €12,600, which is the total cost whenever Agluna® is used. The total costs of COPAL G+C® and DAC® fall in between: €8,480 and €9,170, respectively. Clearly, each technology carries an increase in total direct costs: by 6% with COPAL G+C®, by 15% with DAC®, and by 58% with Agluna®.

(B.1) Indirect costs – Cost of the revision procedure

As stressed earlier, the average cost of PJI treatment per patient with a two-stage revision surgery was set at € 50,000, following our and other studies showing values ranging from approximately € 40,000 to € 60,000 [34-37].

(B.2) Indirect costs – Coating efficacy

The indirect cost of performing a septic revision can be reduced with the application of an antibacterial coating. The greater the coating's ability to abate the infection rate, the greater the reduction in indirect costs. We initially computed the indirect, expected costs of a hypothetical coating able to half the incidence of infection in a population with a 2% infection rate. If applied in 1,000 procedures, this hypothetical coating would generate €500,000 expected indirect costs for the treatment of septic revisions already in the first year after surgery, 50% less than the corresponding expected costs without coating (Table 3).

For each coating considered, we computed the corresponding expected indirect costs considering the infection abatement ability of each single coating discussed in the Methods section. Hence, the expected indirect costs would be reduced by 68% with COPAL G+C®, by 90% with DAC®, and by 48% with AGLUNA®.

(C) Algorithm application

The various scenarios anticipated earlier were simulated with the algorithm reported in Table 1. Table 3 shows the point of economical balance of the hypothetical antibacterial coating mentioned earlier, which is assumed able to reduce the infection rate from 2.0% to 1.0%. As this simulation demonstrates, the point of economic balance of the antibacterial coating would be reached at an average price of € 500 of the ABC technology.

Applying the algorithm to the three technologies, we calculated the point of economic balance for each coating while taking into account its direct application costs and its ability to reduce infections. As already stressed, this assessment refers to the costs that may arise in the first year after the primary surgery. In particular, COPAL G+C®, at an average price per patient of € 480 and a SSI rate reduction of 68%, is in economical balance even if used routinely in a general population of patients, with an average risk of septic complications of 1.5% (Table 4). On the other hand, DAC®, at an average price of € 1,170per patient, if able to reduce SSI by 90%, is in economical balance when applied to a patient population with an expected rate of septic complications of 2.6% (Table 4). This would apply to the majority of patients with at least one of the risk factors listed in Table 2 but not to a general, low-risk population. Silver coating (Table 4), with an average price of € 4,600 per patient and an expected SSI rate reduction of 48%, would be in economical balance only if applied to a patient population with high risk of septic complications (19.2%), i.e., patients with particularly high-risk factors or with an association of risk factors for a minimum odds ratio ≥9.

Table 5 shows a simulation of a large-scale application of the three ABC technologies to a selected population of patients with an expected 5% incidence of infection. Assuming a medium-size country, like Italy, with approximately 160,000 joint replacements performed per year [44] and 40,000 (25%) of them performed in patients with at least one of

the risk factors listed in Table 2, we can demonstrate that the COPAL G+C® or of DAC® hydrogel would provide annual direct cost savings of approximately € 52,800,000 or € 43,200,000 (€1,320 or €1,080 per patient), respectively, while the silver coating would generate an economic loss of approximately €136,000,000.

DISCUSSION

To our knowledge, this is the first study to investigate the potential economic impact of antibacterial coatings applied to joint prosthesis. Health technology assessment is considered among the main priorities within the European Community as a tool to better allocate resources and to drive healthcare policies in a more scientific and transparent way. Economic analysis of antibacterial technologies applied to implants are lacking, however [25].

SSIs remains a feared complication for which the best treatment is prevention. In spite of various measures to reduce the risk of developing SSI following joint replacement [45-47], the economic burden of PJI is expected to increase dramatically in the near future unless new, effective solutions are found [4, 5].

Our analysis shows for the first time that local antibacterial protection of joint prostheses can be in economic balance already during the first year after surgery, and may allow significant cost savings, provided that each technology is used in properly selected populations of patients based on the respective risk for developing SSI. The economic balance also depends on the cost-per-patient of each technology and on its expected efficacy in reducing postsurgical infections.

Our findings are shared by other epidemiologic investigations that assessed the cost-effectiveness of pre- and intra-operative preventative measures and found that healthcare cost savings mainly accrue from the reduced incidence of SSI and the lower financial expenditures for managing them, particularly the costs associated with revision procedures. In their study, Cummins et al. used a Markov decision model to assess the effects on the overall healthcare costs of using an antibiotic-impregnated bone cement in primary total hip arthroplasty [48]. They found that when revision due to infection was defined as the primary outcome of all infections, the use of this protocol resulted in a cost effectiveness ratio of approximately $37,000 per quality-adjusted life year as compared to cement without antibiotics [48]. Similarly, a study by Slover et al. showed that implementing a *Staphylococcus aureus* screening and decolonizing protocol for all TJA patients would result in overall healthcare cost savings by reducing SSI incidence, effectively offsetting any costs associated with the use of this protocol [49]. The use of chlorhexidine gluconate-impregnated cloths prior to total knee arthroplasty has also recently demonstrated the potential to decrease costs to the healthcare system by reducing SSI incidence[29].

In line and beyond these previous observations, we present an algorithm that can be adapted to diverse technologies and patient populations for simulating the point of economic balance and eventually to calculate the potential economic saving or loss associated with large-scale application. While the scenarios presented here may better represent the potential economic impact in our local situation, the algorithm still allows to weight all variables according to the specificities of any given institution/country. This mitigates one of the main limitations of any economic evaluation: generalization of the data. In fact, the price of the device, the estimated cost of PJI treatment, the infection rate, etc. may all vary across hospitals and countries. For example, the cost for periprosthetic knee infection treatment has been recently evaluated at $130,000 by Kapadia et al. [29] in the United States, a value that is more than double the one we used in our analysis. Doubling the expected cost of SSI treatment would obviously have a strong impact on the point of economic balance for any infection prevention strategy. In this regard it is also worth noting that in the present analysis, we did not differentiate between the economic impact of the technologies according to the joint involved, assuming that the effect would be similar for both periprosthetic hip and knee implants. This limitation mainly results from the lack of data showing a difference in the efficacy of the antibacterial coatings in different joints. Similarly, as concerns the

estimated infection rates with and without the coating, we acknowledge that the rates derived from national databases and previous studies may represent an over- or underestimation. A further limitation of the present study is the use of the list price of the devices, while discounted prices are often available for large volume hospitals. Also, it should be noted that while the use of the direct costs of hospitalization has been suggested as the best method to estimate the costs related to infection treatment, this approach probably underestimates total resource utilization and also misjudges the overall financial and personal impact of PJI on the patients themselves [36, 50]. In this regard it should be noted that we did not include potential additional costs arising from late infections, treatment complications or failures of PJI treatment, reduction in the quality of life and working ability, and increase in the mortality rate due to periprosthetic infection. A recent study [51] reported that the adjusted relative mortality risk for patients with revision for PJI was 2.18 (95% confidence interval [CI] 1.54-3.08) compared with those who did not undergo revision for any cause ($p < 0.001$) and 1.87 (95% CI, 1.11-3.15; $p = 0.019$) compared with those with aseptic revision. Patients with difficult-to-treat bacteria, like enterococci-infected total hip arthroplasty, had a 3.10 (95% CI, 1.66-5.81) higher mortality risk than those infected with other types of bacteria ($p < 0.001$) [51]. To further investigate the economic impact of ABC technologies in the long run and on patients' quality of life and mortality, we are working on a separate study that develops a dynamic Markov model.

In conclusion, healthcare institutions may be hesitant to initially invest in new technologies to prevent infections; however, its many limitations notwithstanding, this analysis highlights the potential benefits of large-scale use of antibacterial coatings for joint prosthesis, with a substantial economic balance or advantage, depending on their direct cost, efficacy, and the relative risk of infection in the targeted population.

REFERENCES

1. Wolf, C.F., et al., *Comparison of one and two-stage revision of total hip arthroplasty complicated by infection: a Markov expected-utility decision analysis.* J Bone Joint Surg Am, 2011. **93**(7): p. 631-9.
2. Parvizi, J., et al., *Periprosthetic joint infection: the economic impact of methicillin-resistant infections.* J Arthroplasty, 2010. **25**(6 Suppl): p. 103-7.
3. Berend, K.R., et al., *Two-stage treatment of hip periprosthetic joint infection is associated with a high rate of infection control but high mortality.* Clin Orthop Relat Res, 2013. **471**(2): p. 510-8.
4. Kurtz S, O.K., Lau E, et al. , *Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030.* J Bone Joint Surg Am, 2007. **89**: p. 780-5.
5. Kurtz, S.M., et al., *Future clinical and economic impact of revision total hip and knee arthroplasty.* J Bone Joint Surg Am, 2007. **89 Suppl 3**: p. 144-51.
6. Romanò, C.L., et al., *Antibacterial coating of implants in orthopaedics and trauma: a classification proposal in an evolving panorama.* J Orthop Surg Res, 2015. **10**: p. 157.
7. Cats-Baril W, G.T., Huff K, Kendoff D, Maltenfort M, Parvizi J. , *International consensus on periprosthetic joint infection: Description of the consensus process.* Clin. Orthop. Relat. Res., 2013. **471**: p. 4065–4075.
8. Gallo, J., M. Holinka, and C.S. Moucha, *Antibacterial surface treatment for orthopaedic implants.* Int J Mol Sci, 2014. **15**(8): p. 13849-80.
9. Cancienne, J.M., et al., *Applications of Local Antibiotics in Orthopedic Trauma.* Orthop Clin North Am, 2015. **46**(4): p. 495-510.
10. Buchholz, H.W., et al., *Management of deep infection of total hip replacement.* J Bone Joint Surg Br, 1981. **63-B**(3): p. 342-53.
11. Wroblewski, B.M., *One-stage revision of infected cemented total hip arthroplasty.* Clin Orthop Relat Res, 1986(211): p. 103-7.
12. Garvin, K.L., et al., *Palacos gentamicin for the treatment of deep periprosthetic hip infections.* Clin Orthop Relat Res, 1994(298): p. 97-105.
13. Winkler, H., et al., *One stage uncemented revision of infected total hip replacement using cancellous allograft bone impregnated with antibiotics.* J Bone Joint Surg Br, 2008. **90**(12): p. 1580-4.
14. Drago, L., et al., *Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonization and biofilm formation in vitro?* Clin Orthop Relat Res, 2014. **472**(11): p. 3311-23.
15. Giavaresi, G., et al., *Efficacy of antibacterial-loaded coating in an in vivo model of acutely highly contaminated implant.* Int Orthop, 2014. **38**(7): p. 1505-12.
16. Boot, W., et al., *Hyaluronic Acid-Based Hydrogel Coating Does Not Affect Bone Apposition at the Implant Surface in a Rabbit Model.* Clin Orthop Relat Res, 2017. **475**(7): p. 1911-1919.
17. Romanò, C.L., et al., *Does an Antibiotic-Loaded Hydrogel Coating Reduce Early Post-Surgical Infection After Joint Arthroplasty?* J Bone Jt Infect, 2016. **1**: p. 34-41.
18. Chernousova, S. and M. Epple, *Silver as antibacterial agent: ion, nanoparticle, and metal.* Angew Chem Int Ed Engl, 2013. **52**(6): p. 1636-53.
19. Scoccianti, G., et al., *Levels of silver ions in body fluids and clinical results in silver-coated megaprostheses after tumour, trauma or failed arthroplasty.* Injury, 2016. **47 Suppl 4**: p. S11-S16.
20. Hardes, J., et al., *Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma.* J Surg Oncol, 2010. **101**(5): p. 389-95.
21. Wafa, H., et al., *Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case-control study.* Bone Joint J, 2015. **97-B**(2): p. 252-7.
22. Raphel, J., et al., *Multifunctional coatings to simultaneously promote osseointegration and prevent infection of orthopaedic implants.* Biomaterials, 2016. **84**: p. 301-14.
23. Organization, W.H., *EB134/2014*.
24. Garfield, S., et al., *Health Technology Assessment for Molecular Diagnostics: Practices, Challenges, and Recommendations from the Medical Devices and Diagnostics Special Interest Group.* Value Health, 2016. **19**(5): p. 577-87.

25. Schnell-Inderst, P., et al., *Health technology assessment of medical devices: What is different? An overview of three European projects.* Z Evid Fortbild Qual Gesundhwes, 2015. **109**(4-5): p. 309-18.
26. V, A., *Antimicrobial coated implants in trauma and orthopaedics-A clinical review and risk- benefit analysis* 2016, Inury.
27. Zhu, Y., et al., *Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis.* J Hosp Infect, 2015. **89**(2): p. 82-9.
28. Diaz-Ledezma, C., et al., *Diagnosis of periprosthetic joint infection in Medicare patients: multicriteria decision analysis.* Clin Orthop Relat Res, 2014. **472**(11): p. 3275-84.
29. Kapadia, B.H., et al., *Economic evaluation of chlorhexidine cloths on healthcare costs due to surgical site infections following total knee arthroplasty.* J Arthroplasty, 2013. **28**(7): p. 1061-5.
30. Sprowson, A.P., et al., *The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip: The Fractured Hip Infection trial.* Bone Joint J, 2016. **98-B**(11): p. 1534-1541.
31. Stargardt, T., *Health service costs in Europe: cost and reimbursement of primary hip replacement in nine countries.* Health Econ, 2008. **17**(1 Suppl): p. S9-20.
32. Haenle, M., et al., *Economic impact of infected total knee arthroplasty.* ScientificWorldJournal, 2012. **2012**: p. 196515.
33. Dakin, H., et al., *Rationing of total knee replacement: a cost-effectiveness analysis on a large trial data set.* BMJ Open, 2012. **2**(1): p. e000332.
34. Romanò, C.L., et al., *Septic versus aseptic hip revision: how different?* J Orthop Traumatol, 2010. **11**(3): p. 167-74.
35. Kurtz, S.M., et al., *Economic burden of periprosthetic joint infection in the United States.* J Arthroplasty, 2012. **27**(8 Suppl): p. 61-5.e1.
36. Hernández-Vaquero, D., et al., *Treatment of periprosthetic infections: an economic analysis.* ScientificWorldJournal, 2013. **2013**: p. 821650.
37. Garrido-Gómez, J., et al., *Descriptive analysis of the economic costs of periprosthetic joint infection of the knee for the public health system of Andalusia.* J Arthroplasty, 2013. **28**(7): p. 1057-60.
38. McPherson, E.J., et al., *Periprosthetic total hip infection: outcomes using a staging system.* Clin Orthop Relat Res, 2002(403): p. 8-15.
39. Bozic, K.J., et al., *Estimating risk in Medicare patients with THA: an electronic risk calculator for periprosthetic joint infection and mortality.* Clin Orthop Relat Res, 2013. **471**(2): p. 574-83.
40. Eka, A. and A.F. Chen, *Patient-related medical risk factors for periprosthetic joint infection of the hip and knee.* Ann Transl Med, 2015. **3**(16): p. 233.
41. Castella, A., et al., *Incidence of surgical-site infections in orthopaedic surgery: a northern Italian experience.* Epidemiol Infect, 2011. **139**(5): p. 777-82.
42. Gundtoft, P.H., et al., *The "true" incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties: a prospective cohort study.* Acta Orthop, 2015. **86**(3): p. 326-34.
43. Roth, V.R., et al., *Periprosthetic Infection following Primary Hip and Knee Arthroplasty: The Impact of Limiting the Postoperative Surveillance Period.* Infect Control Hosp Epidemiol, 2017. **38**(2): p. 147-153.
44. M, T., et al., *Il Registro Italiano ArtroProtesi (RIAP): stato dell'arte*. 2013, Giornale Italiano di Ortopedia e Traumatologia (GIOT). p. 96-103.
45. Mangram, A.J., et al., *Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee.* Am J Infect Control, 1999. **27**(2): p. 97-132; quiz 133-4; discussion 96.
46. Matar, W.Y., et al., *Preventing infection in total joint arthroplasty.* J Bone Joint Surg Am, 2010. **92 Suppl 2**: p. 36-46.
47. Lindsay, W., E. Bigsby, and G. Bannister, *Prevention of infection in orthopaedic joint replacement.* J Perioper Pract, 2011. **21**(6): p. 206-9.
48. Cummins, J.S., et al., *Cost-effectiveness of antibiotic-impregnated bone cement used in primary total hip arthroplasty.* J Bone Joint Surg Am, 2009. **91**(3): p. 634-41.

49. Slover, J., et al., *Cost-effectiveness of a Staphylococcus aureus screening and decolonization program for high-risk orthopedic patients.* J Arthroplasty, 2011. **26**(3): p. 360-5.
50. Whitehouse, J.D., et al., *The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost.* Infect Control Hosp Epidemiol, 2002. **23**(4): p. 183-9.
51. Gundtoft, P.H., et al., *Increased Mortality After Prosthetic Joint Infection in Primary THA.* Clin Orthop Relat Res, 2017.

REFERENCES

1. Wolf, C.F., et al., *Comparison of one and two-stage revision of total hip arthroplasty complicated by infection: a Markov expected-utility decision analysis.* J Bone Joint Surg Am, 2011. 93(7): p. 631-9.
2. Parvizi, J., et al., *Periprosthetic joint infection: the economic impact of methicillin-resistant infections.* J Arthroplasty, 2010. 25(6 Suppl): p. 103-7.
3. Berend, K.R., et al., *Two-stage treatment of hip periprosthetic joint infection is associated with a high rate of infection control but high mortality.* Clin Orthop Relat Res, 2013. 471(2): p. 510-8.
4. Kurtz S, O.K., Lau E, et al. , *Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030.* J Bone Joint Surg Am, 2007. 89: p. 780-5.
5. Kurtz, S.M., et al., *Future clinical and economic impact of revision total hip and knee arthroplasty.* J Bone Joint Surg Am, 2007. 89 Suppl 3: p. 144-51.
6. Romanò, C.L., et al., *Antibacterial coating of implants in orthopaedics and trauma: a classification proposal in an evolving panorama.* J Orthop Surg Res, 2015. 10: p. 157.
7. Cats-Baril W, G.T., Huff K, Kendoff D, Maltenfort M, Parvizi J. , *International consensus on periprosthetic joint infection: Description of the consensus process.* Clin. Orthop. Relat. Res., 2013. 471: p. 4065–4075.
8. Gallo, J., M. Holinka, and C.S. Moucha, *Antibacterial surface treatment for orthopaedic implants.* Int J Mol Sci, 2014. 15(8): p. 13849-80.
9. Cancienne, J.M., et al., *Applications of Local Antibiotics in Orthopedic Trauma.* Orthop Clin North Am, 2015. 46(4): p. 495-510.
10. Buchholz, H.W., et al., *Management of deep infection of total hip replacement.* J Bone Joint Surg Br, 1981. 63-B(3): p. 342-53.
11. Wroblewski, B.M., *One-stage revision of infected cemented total hip arthroplasty.* Clin Orthop Relat Res, 1986(211): p. 103-7.
12. Garvin, K.L., et al., *Palacos gentamicin for the treatment of deep periprosthetic hip infections.* Clin Orthop Relat Res, 1994(298): p. 97-105.
13. Winkler, H., et al., *One stage uncemented revision of infected total hip replacement using cancellous allograft bone impregnated with antibiotics.* J Bone Joint Surg Br, 2008. 90(12): p. 1580-4.
14. Drago, L., et al., *Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonization and biofilm formation in vitro?* Clin Orthop Relat Res, 2014. 472(11): p. 3311-23.
15. Giavaresi, G., et al., *Efficacy of antibacterial-loaded coating in an in vivo model of acutely highly contaminated implant.* Int Orthop, 2014. 38(7): p. 1505-12.
16. Boot, W., et al., *Hyaluronic Acid-Based Hydrogel Coating Does Not Affect Bone Apposition at the Implant Surface in a Rabbit Model.* Clin Orthop Relat Res, 2017. 475(7): p. 1911-1919.
17. Romanò, C.L., et al., *Does an Antibiotic-Loaded Hydrogel Coating Reduce Early Post-Surgical Infection After Joint Arthroplasty?* J Bone Jt Infect, 2016. 1: p. 34-41.
18. Chernousova, S. and M. Epple, *Silver as antibacterial agent: ion, nanoparticle, and metal.* Angew Chem Int Ed Engl, 2013. 52(6): p. 1636-53.
19. Scoccianti, G., et al., *Levels of silver ions in body fluids and clinical results in silver-coated megaprostheses after tumour, trauma or failed arthroplasty.* Injury, 2016. 47 Suppl 4: p. S11-S16.
20. Hardes, J., et al., *Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma.* J Surg Oncol, 2010. 101(5): p. 389-95.
21. Wafa, H., et al., *Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case-control study.* Bone Joint J, 2015. 97-B(2): p. 252-7.
22. Raphel, J., et al., *Multifunctional coatings to simultaneously promote osseointegration and prevent infection of orthopaedic implants.* Biomaterials, 2016. 84: p. 301-14.
23. Organization, W.H., *EB134/2014*.
24. Garfield, S., et al., *Health Technology Assessment for Molecular Diagnostics: Practices, Challenges, and Recommendations from the Medical Devices and Diagnostics Special Interest Group.* Value Health, 2016. 19(5): p. 577-87.
25. Schnell-Inderst, P., et al., *Health technology assessment of medical devices: What is different? An overview of three European projects.* Z Evid Fortbild Qual Gesundhwes, 2015. 109(4-5): p. 309-18.
26. V, A., *Antimicrobial coated implants in trauma and orthopaedics-A clinical review and risk- benefit analysis* 2016, Inury.

27. Zhu, Y., et al., *Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis.* J Hosp Infect, 2015. 89(2): p. 82-9.
28. Diaz-Ledezma, C., et al., *Diagnosis of periprosthetic joint infection in Medicare patients: multicriteria decision analysis.* Clin Orthop Relat Res, 2014. 472(11): p. 3275-84.
29. Kapadia, B.H., et al., *Economic evaluation of chlorhexidine cloths on healthcare costs due to surgical site infections following total knee arthroplasty.* J Arthroplasty, 2013. 28(7): p. 1061-5.
30. Sprowson, A.P., et al., *The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip: The Fractured Hip Infection trial.* Bone Joint J, 2016. 98-B(11): p. 1534-1541.
31. Stargardt, T., *Health service costs in Europe: cost and reimbursement of primary hip replacement in nine countries.* Health Econ, 2008. 17(1 Suppl): p. S9-20.
32. Haenle, M., et al., *Economic impact of infected total knee arthroplasty.* ScientificWorldJournal, 2012. 2012: p. 196515.
33. Dakin, H., et al., *Rationing of total knee replacement: a cost-effectiveness analysis on a large trial data set.* BMJ Open, 2012. 2(1): p. e000332.
34. Romanò, C.L., et al., *Septic versus aseptic hip revision: how different?* J Orthop Traumatol, 2010. 11(3): p. 167-74.
35. Kurtz, S.M., et al., *Economic burden of periprosthetic joint infection in the United States.* J Arthroplasty, 2012. 27(8 Suppl): p. 61-5.e1.
36. Hernández-Vaquero, D., et al., *Treatment of periprosthetic infections: an economic analysis.* ScientificWorldJournal, 2013. 2013: p. 821650.
37. Garrido-Gómez, J., et al., *Descriptive analysis of the economic costs of periprosthetic joint infection of the knee for the public health system of Andalusia.* J Arthroplasty, 2013. 28(7): p. 1057-60.
38. McPherson, E.J., et al., *Periprosthetic total hip infection: outcomes using a staging system.* Clin Orthop Relat Res, 2002(403): p. 8-15.
39. Bozic, K.J., et al., *Estimating risk in Medicare patients with THA: an electronic risk calculator for periprosthetic joint infection and mortality.* Clin Orthop Relat Res, 2013. 471(2): p. 574-83.
40. Eka, A. and A.F. Chen, *Patient-related medical risk factors for periprosthetic joint infection of the hip and knee.* Ann Transl Med, 2015. 3(16): p. 233.
41. Castella, A., et al., *Incidence of surgical-site infections in orthopaedic surgery: a northern Italian experience.* Epidemiol Infect, 2011. 139(5): p. 777-82.
42. Gundtoft, P.H., et al., *The "true" incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties: a prospective cohort study.* Acta Orthop, 2015. 86(3): p. 326-34.
43. Roth, V.R., et al., *Periprosthetic Infection following Primary Hip and Knee Arthroplasty: The Impact of Limiting the Postoperative Surveillance Period.* Infect Control Hosp Epidemiol, 2017. 38(2): p. 147-153.
44. Torre, M., et al., Il Registro Italiano ArtroProtesi (RIAP): stato dell'arte. 2013, Giornale Italiano di Ortopedia e Traumatologia (GIOT). p. 96-103.
45. Mangram, A.J., et al., *Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee.* Am J Infect Control, 1999. 27(2): p. 97-132; quiz 133-4; discussion 96.
46. Matar, W.Y., et al., *Preventing infection in total joint arthroplasty.* J Bone Joint Surg Am, 2010. 92 Suppl 2: p. 36-46.
47. Lindsay, W., E. Bigsby, and G. Bannister, *Prevention of infection in orthopaedic joint replacement.* J Perioper Pract, 2011. 21(6): p. 206-9.
48. Cummins, J.S., et al., *Cost-effectiveness of antibiotic-impregnated bone cement used in primary total hip arthroplasty.* J Bone Joint Surg Am, 2009. 91(3): p. 634-41.
49. Slover, J., et al., *Cost-effectiveness of a Staphylococcus aureus screening and decolonization program for high-risk orthopedic patients.* J Arthroplasty, 2011. 26(3): p. 360-5.
50. Whitehouse, J.D., et al., *The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost.* Infect Control Hosp Epidemiol, 2002. 23(4): p. 183-9.
51. Gundtoft, P.H., et al., *Increased Mortality After Prosthetic Joint Infection in Primary THA.* Clin Orthop Relat Res, 2017.

52. Wu C, Qu X, Liu F, Li H, Mao Y, Zhu Z. *Risk factors for periprosthetic joint infection after total hip arthroplasty and total knee arthroplasty in Chinese patients*. PLoS One 2014; 9: e95300 [PMID: 24748009 DOI: 10.1371/journal.pone.0095300]
53. Ong KL, Kurtz SM, Lau E, Bozic KJ, Berry DJ, Parvizi J. *Prosthetic joint infection risk after total hip arthroplasty in the Medicare population*. J Arthroplasty 2009; 24: 105-109 [PMID: 19493644 DOI: 10.1016/j.arth.2009.04.027]
54. Crowe B, Payne A, Evangelista PJ, Stachel A, Phillips MS, Slover JD, Inneh IA, Iorio R, Bosco JA. *Risk Factors for Infection Following Total Knee Arthroplasty: A Series of 3836 Cases from One Institution*. J Arthroplasty 2015; 30: 2275-2278 [PMID: 26187387 DOI: 10.1016/j.arth.2015.06.058]
55. Maoz G, Phillips M, Bosco J, Slover J, Stachel A, Inneh I, Iorio R. *The Otto Aufranc Award: Modifiable versus nonmodifiable risk factors for infection after hip arthroplasty*. Clin Orthop Relat Res 2015; 473: 453-459 [PMID: 25024028 DOI: 10.1007/s11999-014-3780-x]
56. Berbari EF, Osmon DR, Carr A, Hanssen AD, Baddour LM, Greene D, Kupp LI, Baughan LW, Harmsen WS, Mandrekar JN, Therneau TM, Steckelberg JM, Virk A, Wilson WR. *Dental procedures as risk factors for prosthetic hip or knee infection: a hospital-based prospective case-control study*. Clin Infect Dis 2010; 50: 8-16 [PMID: 19951109 DOI: 10.1086/648676]
57. Somayaji R, Barnabe C, Martin L. *Risk factors for infection following total joint arthroplasty in rheumatoid arthritis*. Open Rheumatol J 2013; 7: 119-124 [PMID: 24454587 DOI: 10.2174/1874312920131210005]
58. Jiang SL, Schairer WW, Bozic KJ. *Increased rates of periprosthetic joint infection in patients with cirrhosis undergoing total joint arthroplasty*. Clin Orthop Relat Res 2014; 472: 2483-2491 [PMID: 24711129 DOI: 10.1007/s11999-014-3593-y]
59. Kuo SJ, Huang PH, Chang CC, Kuo FC, Wu CT, Hsu HC, Lin CC. *Hepatitis B Virus Infection Is a Risk Factor for Periprosthetic Joint Infection Among Males After Total Knee Arthroplasty: A Taiwanese Nationwide Population-Based Study*. Medicine (Baltimore) 2016; 95: e3806 [PMID: 27258517 DOI: 10.1097/MD.0000000000003806]
60. Coelho-Prabhu N, Oxentenko AS, Osmon DR, Baron TH, Hanssen AD, Wilson WR, Steckelberg JM, Baddour LM, Harmsen WS, Mandrekar J, Berbari EF. *Increased risk of prosthetic joint infection associated with esophago-gastro-duodenoscopy with biopsy*. Acta Orthop 2013; 84: 82-86 [PMID: 23350577 DOI: 10.3109/17453674.2013.769079]
61. Peel TN, Dowsey MM, Daffy JR, Stanley PA, Choong PF, Buising KL. *Risk factors for prosthetic hip and knee infections according to arthroplasty site*. J Hosp Infect 2011; 79: 129-133 [PMID: 21821313 DOI: 10.1016/j.jhin.2011.06.001]
62. Malinzak RA, Ritter MA, Berend ME, Meding JB, Olberding EM, Davis KE. *Morbidly obese, diabetic, younger, and unilateral joint arthroplasty patients have elevated total joint arthroplasty infection rates*. J Arthroplasty 2009; 24: 84-88 [PMID: 19604665 DOI: 10.1016/j.arth.2009.05.016]
63. Bohl DD, Shen MR, Kayupov E, Della Valle CJ. *Hypoalbuminemia Independently Predicts Surgical Site Infection, Pneumonia, Length of Stay, and Readmission After Total Joint Arthroplasty*. J Arthroplasty 2016; 31: 15-21 [PMID: 26427941 DOI: 10.1016/j.arth.2015.08.028]
64. Sousa R, Muñoz-Mahamud E, Quayle J, Dias da Costa L, Casals C, Scott P, Leite P, Vilanova P, Garcia S, Ramos MH, Dias J, Soriano A, Guyot A. *Is asymptomatic bacteriuria a risk factor for prosthetic joint infection?* Clin Infect Dis 2014; 59: 41-47 [PMID: 24723280 DOI: 10.1093/cid/ciu235]
65. Lai K, Bohm ER, Burnell C, Hedden DR. *Presence of medical comorbidities in patients with infected primary hip or knee arthroplasties*. J Arthroplasty 2007; 22: 651-656 [PMID: 17689771 DOI: 10.1016/j.arth.2006.09.002]
66. Dale H, Fenstad AM, Hallan G, Havelin LI, Furnes O, Overgaard S, Pedersen AB, Kärrholm J, Garellick G, Pulkkinen P, Eskelinen A, Mäkelä K, Engesæter LB. *Increasing risk of prosthetic joint infection after total hip arthroplasty.* Acta Orthop 2012; 83: 449-458 [PMID: 23083433 DOI: 10.3109/17453674.2012.733918]
67. Namba RS, Inacio MC, Paxton EW. *Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees*. J Bone Joint Surg Am 2013; 95: 775-782 [PMID: 23636183 DOI: 10.2106/JBJS.L.00211].
68. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. *Patient-Related Risk Factors for Periprosthetic Joint Infection after Total Joint Arthroplasty: A Systematic Review and Meta-Analysis*. Virdi AS, ed. PLoS ONE. 2016;11(3):e0150866. doi:10.1371/journal.pone.0150866.

69. Debreuve-Theresette A, Diallo S, Siboni R, Ohl X, Dehoux E, Bajolet O. *Infections in Total Hip and Total Knee Arthroplasty: Development of a Score To Assess Endogenous Risk of Surgical Site Infections.* Surg Infect (Larchmt) 2015; 16: 794-798 [PMID: 26258446 DOI: 10.1089/sur.2014.155]

Table 1: Algorithm used to estimate the first year economic impact of anti-bacterial coating technologies. (ABC: Anti-Bacterial Coating)

	Without ABC	**With ABC**
Number of joint replacements/year	a	
Joint replacement, average cost per patient	b	
ABC, cost per patient	0 (zero)	c
Total direct cost per year (equation (1))	*d=a*b*	*e=a*(b+c)*
% of expected PJI	f	
% reduction of PJI with ABC	g	
Expected number of infections	a*(f/100)	a*(f/100)*(1-g/100)
PJI treatment, cost per case	h	
Expected indirect cost for all septic complication treatment/year (equation (2))	*i=a*h* (f/100)*	*i=a*h* (f/100)*(1-g/100)*
Total costs (equation (3))	**l=d+i**	**m=e+i**
Balance (Medical costs without ABC – with ABC)	**n= l-m**	
% Balance (Medical costs without ABC/with ABC)	**n' = (l/m)*100**	

Table 2: List of common risk factors for PJI with a Hazard Ratio (HR), Odds Ratio (OR) or Relative Risk (RR) equal or greater than 2.0, according to the literature.

	Ref.	Statistical parameter					Site
		HR	OR	RR	95%CI	*P* value	
General							
Age: 65-75 years (compared to 45-65)	[52]		3.36		1.30-8.69	0.013	Hip/knee
Charlson index +5 (compared to 0)	[53]		2.57		1.96-3.37	< 0.001	Hip
Place of residence (rural)	[52]		2.63		1.13-6.10	0.025	Hip/knee
Alcohol abuse	[52]		2.95		1.06-8.23	0.039	Hip/knee
Tobacco use	[54]		3.40		1.23-9.44	0.029	Hip/knee
Tobacco use (S aureus colonization)	[55]		12.76		2.47-66.16	0.017	Hip
Gender							
Male	[54]		3.55		1.60-7.84	0.002	Hip/knee
Endocrine disorders							
Diabetes mellitus	[52]		5.47		1.77-16.97	0.003	Hip/knee
Malignancy							
Tumour 5 yr before implant	[56]		3.10		1.30-7.20	< 0.01	Hip/knee
Cardiovascular disorders							
Coronary artery disease	[57]		5.10		1.30-19.8	0.017	Hip/knee
Gastroenterology disorders							
Liver cirrhosis	[58]	5.4				< 0.001	Hip
	[58]	3.4				< 0.001	Knee
Hepatitis B virus (amongst males)	[59]		4.32		1.85-10.09	< 0.001	Knee
OGD with biopsy	[60]		2.80		1.10-7.10	0.03	Hip/knee
Respiratory disorders							
Chronic pulmonary disease	[54]		4.34		1.28-14.70	0.041	Both
Rheumatoid arthritis							
Rheumatoid arthritis	[61]		3.30		0.80-13.90	0.09	Hip/knee
ASA grade							
ASA score ≥ 3	[61]		2.20		1.30-4.00	0.006	Hip/knee
Body mass index							
BMI (kg/m^2) < 20	[57]		6.00		1.20-30.9	0.033	Hip/knee
≥ 28 (compared to 18.5-28)	[52]		2.77		1.20 - 6.40	0.017	Hip/knee
> 40	[55]		4.13		1.30-12.88	0.01	Hip
> 50	[62]		18.3			< 0.001	Hip/knee
Serum albumin < 3.5 g/dL	[63]		2		1.50-2.80	< 0.001	Hip/knee
Immuno-compromised							
Immuno-compromised	[56]		2.2		1.60-3.00	< 0.001	Hip/knee
Prednisone dose exceeds 15 mg/d	[57]		21.0		3.50-127.2	< 0.001	Hip/knee
Systemic steroid therapy	[61]		3.30		0.80-13.90	0.09	Hip/knee
Infection							
Distant organ infection	[56]		2.2		1.50-3.25	< 0.001	Hip/knee
Nasal *S. Aureus* Infection	[54]		3.95		1.80-8.71	< 0.001	Hip/knee
Nasal MRSA Infection	[54]		8.24		3.23-21.02	< 0.001	Hip/knee
Asymptomatic bacteriuria	[64]		3.23		1.67-6.27	0.001	Hip/knee
Genitourinary infection	[65]		2.80		1.01-7.77	0.048	Hip/knee
Operative indication							
Hip fracture	[66]			2.1	1.90-2.40	< 0.001	Hip
Post-traumatic osteoarthritis	[67]	3.23			1.68-6.23	< 0.001	Knee
Previous joint surgery vs no previous joint surgery	[68]	2.98			1.49-5.93	0.001	Hip/knee
Revision arthroplasty versus primary arthroplasty	[68]	2.26			1.30-3.92	0.02	Hip/knee

Per additional surgery	[69]	2.88	1.45-5.80	0.018	Hip/knee

Legend:

BMI: Body Mass Index. CI: Confidence Interval. Ref: References. OGD: Oesophagogastroduodenoscopy. ASA: American Society of Anesthesiologists. MRSA: methicillin-resistant Staphylococcus Aureus

Table 3: Point of economic balance in the first year after surgery, for a hypothetical anti-bacterial coating, able to reduce the infection rate by 50%, when applied to a population with an average risk of surgical site infection of 2%.

	No Coating	Hypothetical coating
Number of joint replacements/per year	1,000	
Joint replacement, average cost per patient	€ 8,000	
ABC, cost per patient	€ 0	€ 500
Total direct cost per year (equation (1))	*€ 8,000,000*	*€ 8,500,000*
% of expected PJI	2%	
% of expected PJI with ABC	0%	50%
Expected number of infections	20	10
Cost of septic revision per patient	€ 50,000	
Expected indirect cost per year (equation (2))	*€ 1,000,000*	*€ 500,000*
Total costs per year (equation (3))	**€ 9,000,000**	**€ 9,000,000**
Balance	**€ 0**	
% Balance	**100%**	

Table 4: Points of economic balance of COPAL G+C®, DAC®, and AGLUNA® reached in the first year after surgery in a population with a baseline risk of SSI respectively equal to 1.5%, 2.6%, and 19.2%.

	No Coating vs COPAL G + V©		**No coating vs DAC©**		**No coating vs AGLUNA©**	
Number of joint replacements/per year	1,000		1,000		1,000	
Joint replacement, average cost per patient	€ 8,000		€ 8,000		€ 8,000	
ABC, cost per patient	€ 0	€ 480	€ 0	€ 1,170	€ 0	€ 4,600
Total direct cost per year (equation (1))	*€ 8,000,000*	*€ 8,480,000*	*€ 8,000,000*	*€ 9,170,000*	*€ 8,000,000*	*€ 12,600,000*
% of expected PJI	1.50%		2.60%		19.20%	
% of expected PJI with ABC	0	68.0%	0	90.0%	0	48.0%
Expected number of infections	15	4.8	26	2.6	192	99.84
Cost of septic revision, per patient	€ 50,000		€ 50,000		€ 50,000	
Expected indirect cost per year (equation (2))	*€ 750,000*	*€ 240,000*	*€ 1,300,000*	*€ 130,000*	*€ 9,600,000*	*€ 4,992,000*
Total costs per year (equation (3))	**€ 8,750,000**	**€ 8,720,000**	**€ 9,300,000**	**€ 9,300,000**	**€ 17,600,000**	**€ 17,592,000**
Balance	**€30,000**		**€0**		**€8,000**	
% Balance	**99.66%**		**100.00%**		**99.95%**	

Table 5: Economic impact in the first year after surgery of the three coatings under study, applied in a selected population with an average risk of surgical site infection of 5.0%.

	No Coating	COPAL G + V©	DAC©	AGLUNA©
Number of joint replacements/per year	40,000			
Joint replacement, average cost per patient	€ 8,000			
ABC, cost per patient	€ 0	€ 480	€ 1,170	€ 4,600
Total direct cost per year (equation (1))	*€ 320,000,000*	*€ 339,200,000*	*€ 366,800,000*	*€ 504,000,000*
% of expected PJI	5%			
% of expected PJI with ABC	0	68.0%	90.0%	48.0%
Expected number of infections	2000	640	200	1040
Cost of septic revision, per patient	€ 50,000			
Expected indirect cost per year (equation (2))	*€ 100,000,000*	*€ 32,000,000*	*€ 10,000,000*	*€ 52,000,000*
Total costs per year (equation (3))	**€ 420,000,000**	**€ 371,200,000**	**€ 376,800,000**	**€ 556,000,000**
Balance		**€ 48,800,000**	**€ 43,200,000**	**-€ 136,000,000**
% Balance		**113.15%**	**111.46%**	**75.54%**