# IMPACT OF PHAGE THERAPY
# JOINT INFECTIONS

Report

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June 2022

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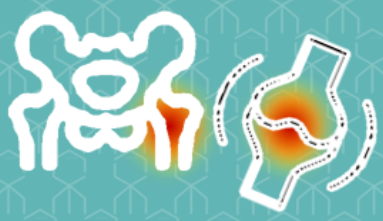
FOR MEDICAL RESEARCH

IMPACT OF PHAGE THERAPY

# JOINT INFECTIONS



104,167
HIP & KNEE PROSTHETIC JOINT SURGERIES (2022)

2,573
COHORT TREATED WITH PHAGE

1,462
RESOLVED INFECTIONS*

## AVOIDED OUTCOMES OVER A 6 YEAR PERIOD

397 RESOLVED FUNCTIONAL DISABILITY

1,899 AVOIDED REVISION SURGERIES

309 AVOIDED PREMATURE DEATHS

203 AVOIDED LONG-TERM ANTIBIOTICS

AVERAGE SAVING PER PATIENT OVER 2 YEARS $47.7K

Saving per patients over 2 years:

HIP JOINTS $49,376

KNEE JOINTS $45,131

## SAVINGS OVER A 6 YEAR PERIOD

INDIRECT SAVINGS $51.5M

TOTAL SAVINGS $122.8M

DIRECT SAVINGS $71.3M

| 43% | 33% | 18% | 6% |
|---|---|---|---|
| GOVERNMENT | PATIENT & FAMILY | PRIVATE INSURANCE | EMPLOYER |

*Based on the incremental reduction in CFU/biofilm formation for bacteriophage and antibiotics compared antibiotics alone reported in a key in vivo study (Yilmaz 2013).

**All prices are displayed in Australian Dollars (AUD)**

# EXECUTIVE SUMMARY

Prosthetic joint infections (PJI) are a catastrophic complication after a joint replacement which place a substantial economic burden on the health-care system. PJIs lead to substantial reduced quality of life, functional deficits, and increased mortality (1). The lack of success treating PJIs with conventional antibiotics alone is primarily related to the presence of bacterial biofilm on medical implants (2). Consequently, the eradication of an infection involves complex treatment strategies including multiple surgical revisions and long-term antimicrobial treatment (3). This places a significant financial burden on the government, patients and their families, private health insurers, and employers.

Numerous preclinical and cohort studies have demonstrated that bacteriophage (as an adjunct to antibiotics) is more effective at eradicating biofilms and resolving infections when compared to standard of care (antibiotics alone) (4-9). Consequently, bacteriophage therapy has the potential to effectively treat thousands of patients, avoiding the downstream high monetary cost, morbidity, and mortality associated with unresolved PJIs (2).

This analysis estimates the financial impacts (direct and indirect) of using bacteriophage therapy in patients with PJIs. The model utilises a theory of change analysis to calculate the downstream avoided costs associated with persistent PJI. Costs were calculated over a 6-year time horizon and varied depending on the infected joint (knee or hip), infection type (acute, early, chronic, or not classifiable) and the state where the patient received treatment.

## The key findings were as follows:

- If all patients across Australia with prosthetic knee and hip infections (2,573 patients) were treated with bacteriophage therapy, the **total savings over 6 years were estimated to be $122.8 million in 2022 corresponding to an average saving of $47,736 per patient over 2 years**[1].
- If all patients across NSW with prosthetic knee and hip infections (818 patients) were treated with bacteriophage therapy, the **total savings over 6 years were estimated to be $38.8 million in 2022 corresponding to an average saving of $47,424 per patient over 2 years**[1].
- The **total direct savings (healthcare relating savings) were $71.3 million** most of which was attributed to the government (63%) and private health insurers (33%). Savings were also partially attributed to patients and their families (4%).
- The **total indirect savings (non-health care related savings) were $51.5 million** most of which was attributed to patients and their families (67%), followed by the government (19%) and employers (14%).
- The highest saving per patients were reported for hip joints ($49,376) and patients with chronic infections ($45,131). Greater saving per patients were incurred in the first 4 years ($50,846 for year 0-2, $46,153 for year 2-4 and $25,207 for year 4-6).

[1] This estimate does not account for the upfront cost of bacteriophage therapy

A small reduction in the number of unresolved joint infections would generate millions of dollars in savings. The base case analysis assumes that infection is avoided with bacteriophage in 57% more patients than standard of care. If infection is only avoided in 22% more patients, there would still be significant saving of $46.5 million ($18,085 per patient over 2 years).

A summary of the direct and indirect savings associated with using bacteriophage therapy in patients with PJIs is presented in Table 1 and Table 2, respectively.

Table 1 Summary of direct savings

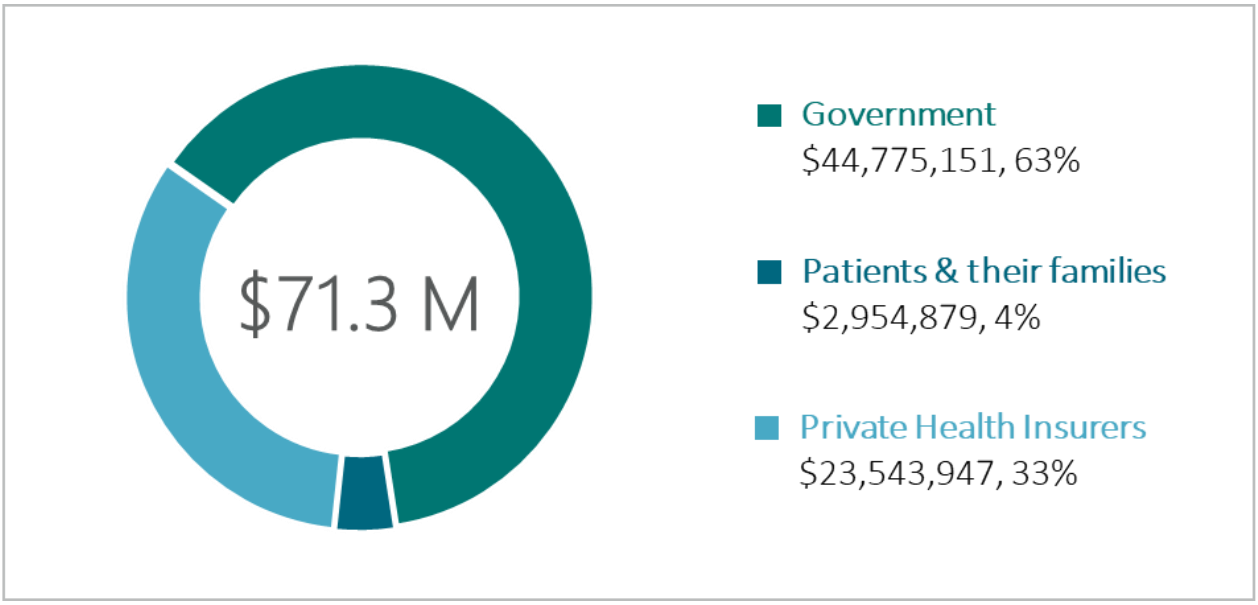
| Direct savings | Year 0-2 | Year 2-4 | Year 4-6 |
|---|---|---|---|
| **Government** | | | |
| Government hospital costs for surgical revisions (public) | $21,662,820 | $8,127,146 | $1,230,648 |
| Government hospital costs for surgical revisions (private) | $4,404,838 | $1,605,873 | $243,168 |
| Government costs of long-term suppressive antibiotics | $120,998 | $99,311 | $61,857 |
| Government costs of antibiotics (adjunct to surgery) | $4,750,220 | $1,731,789 | $262,235 |
| Government costs of consultations | $131,204 | $52,482 | $14,424 |
| Government cost of community rehab (public) | $194,495 | $70,907 | $10,737 |
| **Patients & their families** | | | |
| Out-of-pocket hospital costs (private patients) | $944,869 | $344,471 | $52,161 |
| Out-of-pocket costs long term suppressive antibiotics | $52,008 | $42,687 | $26,588 |
| Out-of-pocket costs of antibiotics (adjunct to surgical treatment) | $1,050,937 | $383,140 | $58,017 |
| **Private health insurance** | | | |
| PHI hospital costs for surgical revisions (private) | $16,135,432 | $5,882,498 | $890,754 |
| PHI cost of community rehab (private) | $447,439 | $163,123 | $24,701 |

Table 2 Summary of indirect savings

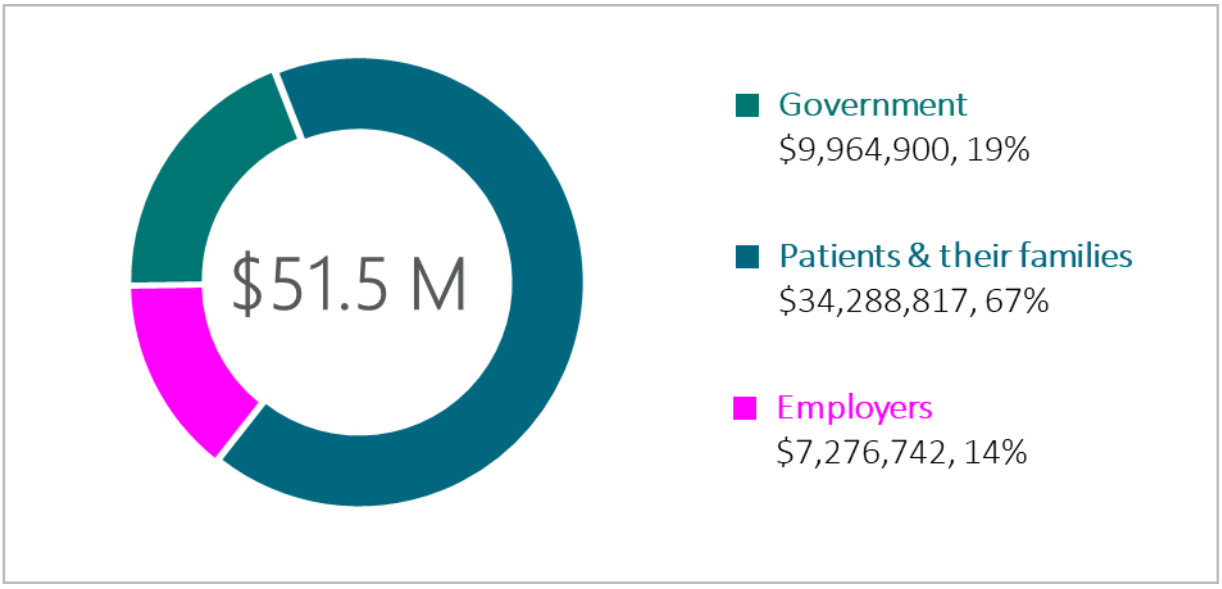
| Indirect savings | Year 0-2 | Year 2-4 | Year 4-6 |
|---|---|---|---|
| **Government** | | | |
| Cost of disability support | $1,918,344 | $420,486 | $71,312 |
| Cost of end-of-life care | $4,955,083 | $2,331,365 | $268,309 |
| **Patients & their families** | | | |
| Lost income due to unpaid leave (full time employees) | $1,818,437 | $662,948 | $100,386 |
| Lost income due to unpaid leave (part time employees) | $1,425,855 | $519,824 | $78,714 |
| Lost income due to early retirement (full time employees) | $9,582,464 | $3,493,481 | $528,998 |
| Lost income due to early retirement (part time employees) | $4,555,539 | $1,660,814 | $251,488 |
| Cost of care services | $7,648,940 | $1,676,588 | $284,340 |
| **Employers** | | | |
| Cost of paid leave (full time employees) | $367,303 | $133,908 | $20,277 |
| Cost of paid leave (part time employees) | $174,617 | $63,660 | $9,640 |
| Loss of employees due to early retirement | $289,080 | $105,390 | $15,959 |
| Loss of employees due to premature death | $3,998,897 | $1,881,480 | $216,533 |

# Savings associated with bacteriophage therapy in patients with PJIs

## Direct savings




## Indirect savings



# INTRODUCTION

PJIs are a devastating complication after a joint replacement (2). *Staphylococcus aureus* is the predominant bacteria associated with PJIs and its biofilm formation limits the penetration of antibiotics (10). Consequently, current surgical and antibiotic management strategies for PJIs are not only costly and traumatic for the patient, but also associated with considerable morbidity and mortality with high failure rates.

Bacteriophage therapy offers a potential alternate strategy for the treatment of PJIs, as bacteriophages are a unique therapeutic platform which can degrade biofilms and kill bacterial cells. Numerous preclinical and cohort studies have demonstrated that bacteriophage (as an adjunct to antibiotics) is more effective at eradicating biofilms and resolving infections when compared to standard of care (antibiotics alone) (4-9).

This analysis leverages current research publications and publicly available data to estimate the financial impacts (direct and indirect) of using bacteriophage therapy in patients with a PJI.

## Structure of the model

This impact assessment model utilises a theory of change analysis to calculate the downstream avoided costs associated with persistent PJI. These avoided costs are applied to the incremental number of patients who receive effective treatment with bacteriophage therapy and would have not been effectively treated with the current standard of care (antibiotics alone). Costs were calculated over a 6-year time horizon and varied depending on the infected joint (knee or hip), infection type (acute, early, chronic, or not classifiable) and state where the patient received treatment. The key results reported in this paper are from the base case analysis: knee and hip infections, all infection types, Australia-wide and an effectiveness proxy of 57% (average of all effectiveness proxies).

# EPIDEMIOLOGY

## Number of people with prosthetic joint infections

The number of primary knee and hip replacements in Australia were estimated to be 62,006 and 42,161, respectively, using data from The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) projected to 2022. Based on the percentage of knee and hip replacements which are revisions and the rate of revisions due to infection, the total number of primary knee infections (PKI) and primary hip infections (PHI) were estimated to be 1,114 and 590, respectively (Table 3)

**Table 3 Number of primary knee and hip infections**

| Knee replacements | | Hip replacements | |
|---|---|---|---|
| Number of primary knee replacements (2019) | 51,037 | Number of primary knee replacements (2019) | 34,576 |
| Average growth rate primary knee replacements (2016-2019) | 3.3% | Average growth rate primary hip replacements (2016-2019) | 3.4% |
| Number of primary knee replacements (2022, projected) | 62,006 | Number of primary knee replacements (2022, projected) | 42,161 |
| Percentage of knee replacements which are revisions | 7.3% | Percentage of hip replacements which are revisions | 8.0% |
| Revisions of knee replacements due to infection | 24.6% | Revisions of hip replacements due to infection | 17.5% |
| Total PKI 2022 | 1,114 | Total PHI 2022 | 590 |

Source: Australian Orthopaedic Association National Joint Replacement Registry
Abbreviations: PHI=primary hip infections, PKI=primary knee infection


The Prosthetic joint Infection in Australia and New Zealand Observational (PIANO) study, a prospective multicentre observational study conducted at 27 hospitals in Australia and New Zealand, was used to estimate the number of infections which are classified as either acute, early, chronic, or not classifiable (Table 4) (11). Early infections were defined as those diagnosed within 30 days from the original implant. Acute infections were defined as those diagnosed >30 days from the original implant with ≤7 days of symptoms and no evidence of a sinus. Chronic infections were defined as those diagnosed > 30 days from the original implant with a sinus and/or >30 days of symptoms.

**Table 4 Types of infection**

| | Early | Acute | Chronic | Not classifiable |
|---|---|---|---|---|
| Proportion | 24.5% | 40.9% | 21.7% | 12.9% |
| PKI | 273 | 455 | 242 | 143 |
| PHI | 145 | 241 | 128 | 76 |
| Total | 418 | 696 | 370 | 219 |

Source: Davis 2022
Abbreviations: PHI=primary hip infections, PKI=primary knee infection

## Incremental number of patients treated effectively with bacteriophage

Preclinical and case studies have demonstrated that bacteriophage as an adjunct to antibiotics is more effective at eradicating biofilms and resolving infection when compared to standard of care (antibiotics alone) (4-9). Biofilm formation protect bacteria from systemic antibiotics, thus leading to resistant infections which require multiple surgical revisions and long-term antimicrobial treatment. Therefore, in this model proxies for infection resolution are based on the incremental reduction in colony forming units (CFU) and biofilm formation for bacteriophage and antibiotics compared to standard of care (antibiotics alone) based on a key *in vivo* study by Yilmaz 2013 (9).

This analysis assumes that the percentage reduction in CFU and biofilm thickness is directly correlated to avoided infection. To adjust for uncertainty relating to these inputs, incremental effectiveness ranges of between 22% and 100% were includes in the model.

**Table 5 Effectiveness proxies**

| Organism | Antibiotics | Antibiotic + bacteriophage | % Reduction |
|---|---|---|---|
| **CFU** | | | |
| Methicillin-resistant *Staphylococcus aureus* | 17,165 | 5,000 | 71% |
| *Pseudomonas aeruginosa* | 2,619 | 1,705 | 35% |
| **Biofilm thickness (nm)** | | | |
| Methicillin-resistant *Staphylococcus aureus* | 294,317 | 0 | 100% |
| *Pseudomonas aeruginosa* | 17,826 | 13,990 | 22% |
| | | Average | 57% |

Source: Yilmaz 2013
Abbreviations: CFU=colony forming units, PHI=primary hip infections, PKI=primary knee infection

The average of all effectiveness proxies was used in the base case analysis (57%) which corresponds to 632 and 335 patients avoiding persistent PJI.

Table 6 Incremental number of patients treated effectively with bacteriophage

| Joint type | Acute | Early | Chronic | Not classifiable |
|---|---|---|---|---|
| PKI | 259 | 155 | 138 | 81 |
| PHI | 137 | 82 | 73 | 43 |
| Total | 395 | 238 | 210 | 124 |

Abbreviations: PHI=primary hip infections, PKI=primary knee infection

## Management of patients with prosthetic joint infections

The theory of change used in this model simplifies the management of patients with PJI to estimate the avoided direct and indirect costs associated with unresolved infections (Figure 1). The cohort which enters model are the incremental number of patients who receive effective treatment with bacteriophage therapy and avoid downstream costs of persistent infections.

The treatment algorithm for patients with joint infections were based the PIANO study and engagement with Australian clinicians. The PIANO study captured the main surgical management strategies for patients with PJI at 90 days following infection. The remaining patients were all assumed to be treated with long-term suppressive antibiotics (Table 7). It was assumed that within 24-month period patients could have up to four DAIR (debridement, antibiotics, and implant retention) procedures[2], one operation for one-stage revision and resections, and two operations for two-stage revisions. Patients who were alive following the 24-month period either transitioned to the "successful treatment" health state where they existed the model or had "unsuccessful treatment" and received further treatment within the following 24-month period.

Following unsuccessful treatment, the next treatment option was determined using a hierarchical approach based on feedback from Australian clinicians. Treatment options were ranked in the following order: (1) long term suppressive antibiotics, (2) resection, (3) one/two stage revision and (4) DAIR. Patients were assumed to transition to a higher ranked approach following treatment failure such that:

- Patients who had unsuccessful treatment with DAIR transitioned to either one stage or two stage revision.
- Patients who had unsuccessful treatment with one stage or two stage revision transitioned to resection.
- Patients who had unsuccessful treatment with resection transitioned to long term suppressive antibiotics.
- Patient who had unsuccessful treatment with long term suppressive antibiotics remained on long term suppressive antibiotics treatment.

[2] For patients in the PIANO study for whom DAIR was the initial management strategy, 25.2% of patients had two episodes, 6.2% had three episodes, and 1.7% had four episodes of operative debridement.

### Outcomes of management

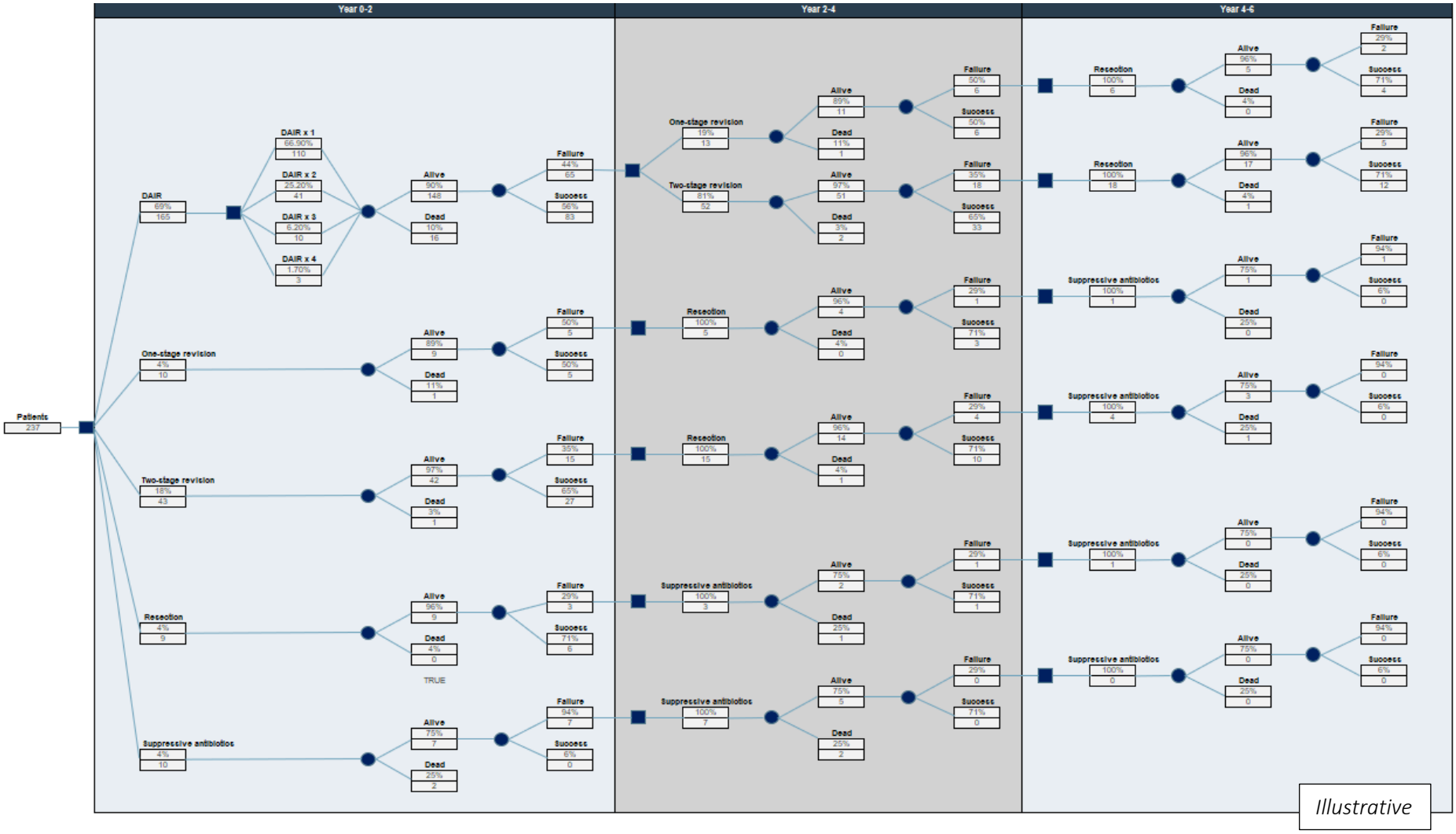
The PIANO study measured outcomes at 24 months according to the main treatment strategy at day 90. Treatment success was defined as (1) patient is alive; (2) documented absence of clinical or microbiological evidence of infection; (3) no ongoing use of antibiotics for the index joint and (4) the key prosthesis still being in place. All patients who were not successfully treated within the first 24 months were assumed to have a persistent infection which required further management (treatment failure).

**Table 7 Outcomes of management**

| Management strategy | Alive | Treatment success |
|---|---|---|
| DAIR | 90% | 56% |
| One-stage revision | 89% | 50% |
| Two-stage revision | 97% | 65% |
| Resection | 96% | 71% |
| Suppressive antibiotics | 75% | 6% |

Source: David 2022
Abbreviations: DAIR=Debridement, antibiotics, and implant retention

Figure 1 Decision Tree




Note: The above figure is one of many decision trees included in this analysis. This decision tree represents the management of patients with hip and knee infections diagnosed < 30 days from the original implant across Australia. The starting cohort are the incremental number of patients who receive effective treatment with bacteriophage therapy (57%, base case assumption).

## Population characteristics

### Employment characteristics

Given that the average age of patients with a prosthetic joint infection is 69 (based on the PIANO study), metrics for older Australians (those aged 65 years and over) were used to reflect the employment characteristics for the population included in this model (11). Employment characteristics of the population were derived from the 2015 ABS Survey of Disability, Ageing and Carers which investigates the labour force activity of Australians aged 65 years and over (Table 8) (12). Approximately 497,500 older Australians were participating in the labour force in 2015, accounting for 14% of the Australian population over 65. Of these individuals, 59.8% worked part-time and 39.4% worked full-time. The factors influencing return to work after hip and knee arthroplasty were based on a study conducted in patients undergoing lower limb arthroplasty in a private metropolitan hospital in Western Australia (13). In this study 91% of patients returned to work following arthroplasty (9% retired).

**Table 8 Employment characteristics**

| Employment parameter | Proportion |
|---|---|
| Proportion who returned to work following arthroplasty | 91% |
| Proportion who retired following arthroplasty | 9% |
| Proportion participating in the labour force (>65 years) | 14% |
| Full time employment (>65 years) | 39% |
| Part time employment (>65 years) | 61% |
| % of cohort taking paid leave (full time employee) | 5% |
| % of cohort taking paid leave (part time employee) | 8% |
| Proportion who returned to work following arthroplasty | 91% |

Source: McGonagle 2018, SDAC 2015

### Disability characteristics

Given that the average age of patients with a prosthetic joint infection is 69 (based on the PIANO study), metrics for older Australians (those aged 65 years and over) were used to reflect the proportion of the population with baseline disability (11). Pre-existing functional disability was estimated using the 2015 ABS Survey of Disability, Ageing and Carers (12). Approximately 654,600 older Australians were living with profound or severe disability in 2015, accounting for 18.5% of the Australian population over 65.

### Underlying mortality

Of the 275 patients initially enrolled in the PIANO study, 59% were male and the average age was 69 (SD 11.3) years. Based on the Australian Bureau of Statistics life tables, the weighted age-specific mortality rates of the population were estimated at 1.14%.

### Treatment location

Based the number of hospitalisations for elective surgery in Australia (14), 67% of patients were treated privately and 33% were treated publicly. Distribution of the cohort by state reflected the distribution of the general population reported by the ABS in September 2021. It is estimated that approximately 20% of patients in the public sector and 40% of patients in the private sector were referred to outpatient rehabilitation following joint replacement surgery in 2014 (15).

## Avoided outcomes from using bacteriophage therapy in patients with prosthetic joint infections

The methodology described above was used to estimate the avoided outcome from using bacteriophage therapy in patients with a PJI over a 6-year time horizon. A summary of the outputs for patients across Australia with knee and hip infections is shown in Table 9.

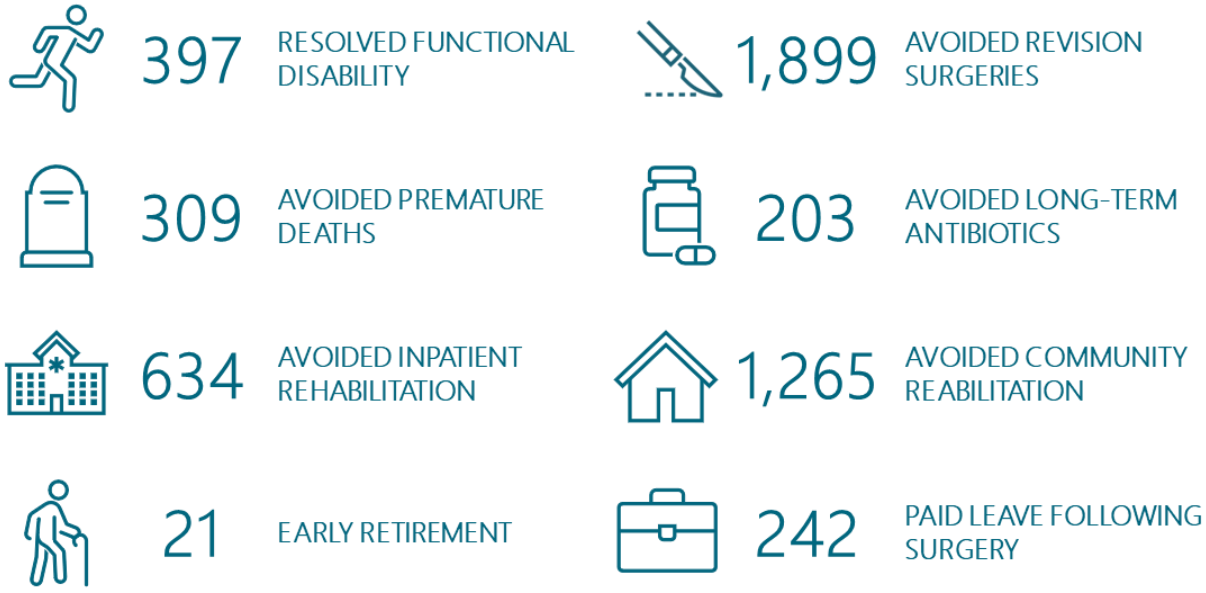



Table 9 Avoided outcomes

| Avoided outcomes | Year 0-2 | Year 2-4 | Year 4-6 |
|---|---|---|---|
| Number of surgical treatments of infection (private) | 896 | 327 | 49 |
| Number of surgical treatments of infection (public) | 441 | 161 | 24 |
| Number of suppressive antibiotics treatments | 87 | 71 | 44 |
| Number of short-course antibiotic treatments (adjunct to surgery) | 1,338 | 488 | 74 |
| Number of inpatient rehabilitation programs undertaken (private) | 358 | 131 | 20 |
| Number of inpatient rehabilitation programs undertaken (public) | 88 | 32 | 5 |
| Number of community rehabilitation programs undertaken (private) | 538 | 196 | 30 |
| Number of community rehabilitation programs undertaken (public) | 353 | 129 | 19 |
| Paid leave following surgery (full time employees) | 67 | 24 | 4 |
| Paid leave following surgery (part time employees) | 103 | 38 | 6 |
| Premature death | 203 | 95 | 11 |
| Early retirement | 15 | 5 | 1 |
| Patients with functional limitations* | 316 | 69 | 12 |

* All patients with unresolved deep PJI are assumed to have functional limitations which require support payments and care services, adjusting for patients with pre-existing functional limitations

# DIRECT SAVINGS

The direct savings of treating patients with bacteriophage were defined as healthcare costs incurred up to 6-years post implant.

Across Australia, the total direct savings were estimated to be $71.3 million, most of which was attributed to the government (63%) and private health insurers (33%). Savings were also partially attributed to patients and their families (4%).

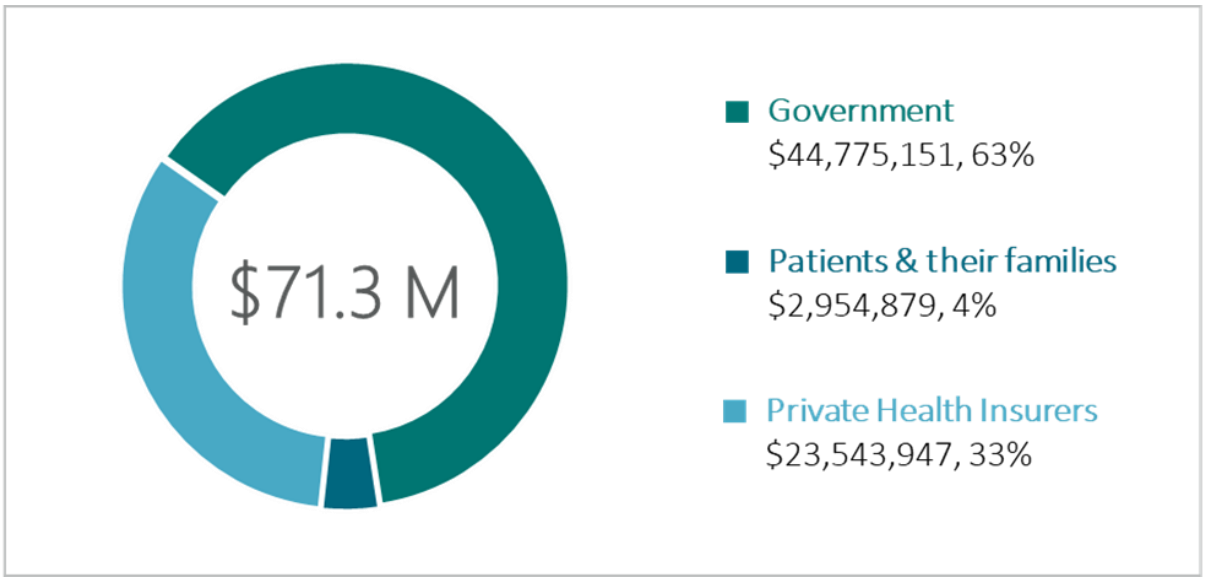



Table 10 Direct savings

| Direct savings | Year 0-2 | Year 2-4 | Year 4-6 |
|---|---|---|---|
| **Government** | | | |
| Government hospital costs for surgical revisions (public) | $21,662,820 | $8,127,146 | $1,230,648 |
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| **Patients & their families** | | | |
| Out-of-pocket hospital costs (private) | $944,869 | $344,471 | $52,161 |
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| **Private health insurance** | | | |
| PHI hospital costs for surgical revisions (private) | $16,135,432 | $5,882,498 | $890,754 |
| PHI cost of community rehab (private) | $447,439 | $163,123 | $24,701 |

Abbreviations: PHI=private health insurance

## Savings to the government

### Surgical revisions (public patients) with inpatient rehabilitation

The government cost of surgical knee revisions for patients treated in public hospitals was calculated using AR-DRG (Australian Refined Diagnosis Related Groups) 132A (Revision of Knee Replacement, Major Complexity) and for surgical hip revisions was calculating using AR-DRG 131A (Revision of Hip Replacement, Major Complexity). DAIR, one-stage revision, two stage revision and resection were all classified as surgical revision procedures. It was assumed that all patients who undertook a revision procedure for infection would be classified as 'major complexity'. Costs were calculated based on NHCDC (National Hospital Cost Data Collection) Round 23 and adjusted to 2022 prices using the national efficient price.

### Surgical revisions (private patients) with inpatient rehabilitation

The government cost of surgical knee revisions for patients treated in public hospitals was calculated using the annual report compiled from the Hospital Casemix Protocol (HCP) data submitted by Private Health Insurers to the Department of Health. The average Medicare benefit paid per separation was calculated for AR-DRG 132A (Revision of Knee Replacement, Major Complexity) and AR-DRG 131A (Revision of Hip Replacement, Major Complexity).

### Long term suppressive antibiotics

Long term suppressive antibiotics is a treatment strategy in which patients with PJIs are indefinitely on antibiotics with the objective of reducing symptoms and/or preventing progression of the infection. This approach is often selected when removal or surgical revision of the infected prostheses is infeasible or has been previously unsuccessful. The cost of long-term suppressive antibiotics was calculated using antibiotic regimes for *Staphylococcus aureus* infection (the most common pathogen associated with orthopaedic procedures) (10, 11). Proportion of patients with oxacillin-susceptible and oxacillin-resistant populations were based on 2016-17 AIHW data (16). Recommended antibiotic regimens were based on clinical practice guidelines by the Infectious Diseases Society of America; cefalexin for oxacillin-susceptible *Staphylococcus aureus* and doxycycline for oxacillin-resistant *Staphylococcus aureus*. Three drugs listed in the guidelines were not listed on the PBS (Pharmaceutical Benefits Scheme) and therefore were not included in the analysis (Cefadroxil, Cotrimoxazole, Minocycline). A weighted co-payment was calculated for both antibiotics and was subtracted from the Dispensed Price for Maximum Quantity (DPMQ) to calculate the total price paid by the government per 2 years.

### Antibiotics adjunct to surgery

Four to six weeks of pathogen-specific antimicrobial therapy is recommended following the revision/removal of infection in prosthetic joints (16). The cost of antibiotics used adjunct to surgery were calculated using antibiotic regimes for *Staphylococcus aureus* infection (the most common pathogen associated with orthopaedic procedures) (10, 11). Proportion of patients with oxacillin-susceptible and oxacillin-resistant populations were based on 2016-17 AIHW data. Recommended antibiotic regimens were based on clinical practice guidelines by the Infectious Diseases Society of America; cefazolin or ceftriaxone for oxacillin-susceptible *Staphylococcus aureus* and vancomycin for oxacillin-resistant *Staphylococcus aureus*. One drug listed in the guidelines was not listed on the PBS and therefore were not included in the analysis (Nafcillin sodium). Vancomycin dosage calculation were based on the average weight of the average joint replacement patient (average age 69). A weighted co-payment was calculated for all antibiotics and was subtracted from the DPMQ to calculate the total price paid by the government per 2 years.

### Consultations

The cost of consultations was estimated using Medicare Benefits Schedule (MBS) item 104 (Professional attendance at consulting rooms or hospital by a specialist) at a benefit rate of 75%. According to international clinical guidelines, routine follow-up of patients after a total hip/knee arthroplasty should be performed six to twelve weeks, one year and at least five years after total hip arthroplasty, or sooner if the surgeon deems it necessary (17, 18). Consequently, it was estimated that there would be an average of one consultation per 2 years over 6 years. It was assumed that the number of follow up consultation would double if an infection was not resolved.

### Community rehabilitation (public patients)

Based on a randomised controlled trial of home-based or inpatient rehabilitation following total joint replacement, the mean number of postoperative home-based rehabilitation visits was eight. It was assumed that the cost of inpatient rehabilitation is captured within the DRG cost of surgical admission (19).

## Savings to patients are their families

### Surgical revisions (private patients)

Public patients will have no out-of-pocket expenses for surgery in a public hospital. In contrast, patients in the private system, face out-of-pocket costs depending on their excess, which hospital they are admitted to and how the doctor charges. The average gap payment across of private hospital separations for surgical knee and hip revisions were extracted from the HCP.

### Out-of-pocket costs of antibiotics

Weighted co-payment was calculated for all antibiotics to calculate the total price paid by patients for antibiotics given as an adjunct to surgery or long-term suppressive antibiotics. Costs for long-term suppressive antibiotics were calculated per 2-year period.

## Savings to private health insurance

### Surgical revisions (private patients) with inpatient rehabilitation

Private health insurance cost of surgical knee revisions for patients treated in private hospitals was calculated using the HCP. It was assumed that the cost of inpatient rehabilitation is captured within the DRG cost of surgical admission.

### Community rehabilitation (private patients)

Based on a propensity score-matched cohort of privately insured patients who underwent total knee replacement in Australian hospitals in 2013-2015, outpatient rehabilitation was estimated to cost $749 ($832 when inflating 2015 to 2022 prices using an average annual inflation rate of 1.7 per cent) (20).

# INDIRECT SAVINGS

The indirect savings accrued by treating patients with bacteriophage were defined as non-healthcare costs incurred up to 6-years post implant.

Across Australia, the total indirect savings were estimated to be $51.5 million most of which was attributed to patients and their families (67%), followed by the government (19%) and employers (14%).

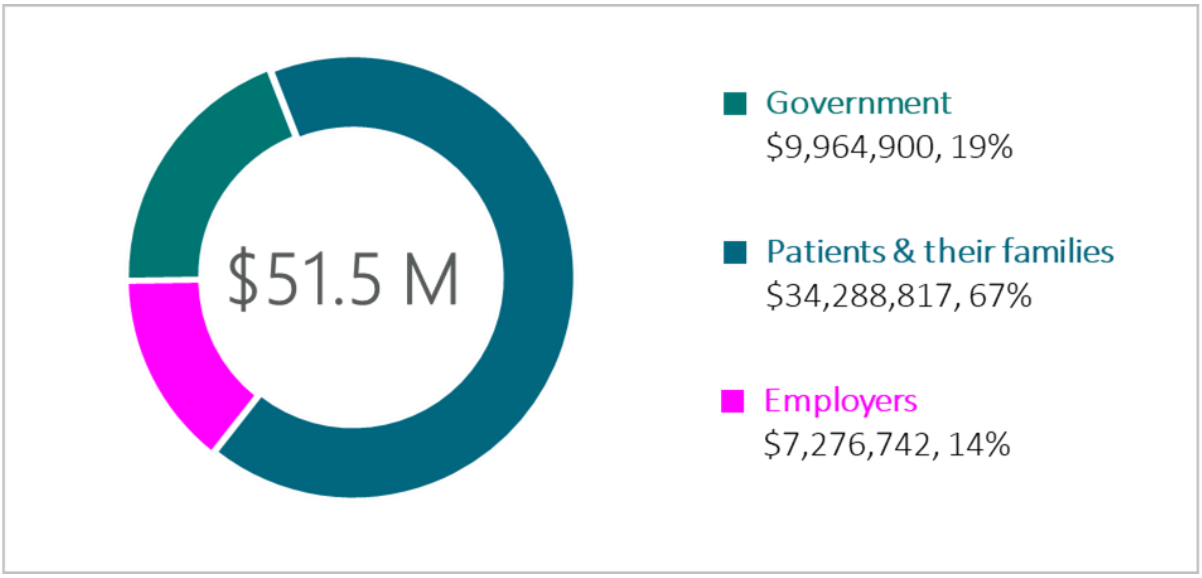


Table 11 Indirect savings

| Indirect savings | Year 0-2 | Year 2-4 | Year 4-6 |
|---|---|---|---|
| **Government** | | | |
| **Cost of disability support** | $1,918,344 | $420,486 | $71,312 |
| Cost of end-of-life care | $4,955,083 | $2,331,365 | $268,309 |
| **Patients & their families** | | | |
| Lost income due to unpaid leave (full time employees) | $1,818,437 | $662,948 | $100,386 |
| Lost income due to unpaid leave (part time employees) | $1,425,855 | $519,824 | $78,714 |
| Lost income due to early retirement (full time employees) | $9,582,464 | $3,493,481 | $528,998 |
| Lost income due to early retirement (part time employees) | $4,555,539 | $1,660,814 | $251,488 |
| Cost of care services | $7,648,940 | $1,676,588 | $284,340 |
| **Employers** | | | |
| Cost of paid leave (full time employees) | $367,303 | $133,908 | $20,277 |
| Cost of paid leave (part time employees) | $174,617 | $63,660 | $9,640 |
| Loss of employees due to early retirement | $289,080 | $105,390 | $15,959 |
| Loss of employees due to premature death | $3,998,897 | $1,881,480 | $216,533 |

## Savings to the government

### Commonwealth home support program

The CHSP helps older Australians (aged 65 years or older) access entry-level support services to live independently and safely at home. It was assumed that all patients with unresolved deep PJI have functional limitations which require CHSP support payments, adjusting for patients with pre-existing functional limitations (11). The average annual CHSP grant was quoted at $2,949 in 2018-19 ($3,039 when inflated from 2018/19 to 2022 prices based on an average annual inflation rate of 1.5 per cent). Costs were calculated per 2 period.

### End-of-life care

End of life care was calculated using the average health care costs at the end of life from a retrospective cohort study conduction in elderly Australians who died between 2005 and 2009, estimated to be $19,696 ($24,448 when inflated from 2009 to 2022 prices based on an average annual inflation rate of 2 per cent) (21).

## Savings to patients are their families

### Unpaid leave

The timing of return to work was estimated in a study conducted patients undergoing lower limb arthroplasty in a private metropolitan hospital in Western Australia. The average number of weeks was 6.4 for patents undertaking a total hip replacement and 7.7 weeks for patients undertaking a total knee replacement. Assuming that all patients with surgical revision for infection are classified as "major" complexity, the length of stay for patients with knee and hip infections was 47.7% and 101.4% longer than the average patient (weighted average of major and minor complexity procedures), respectively. This analysis assumed that the increase in length of stay directly correlates to an increase in overall recovery time, calculated to be 12.9 week for hip replacement and 11.4 for knee replacements. The average cost of unpaid leave was calculated based on the average wages in Australia ($1,368 per week), subtracting the number of weeks of paid sick leave for full time (2 weeks) and part time (0.6 weeks) employees. Costs were applied to all employed patients taking time off work and was calculated per 2 period.

### Lost income

The proportion of employees who retired following arthroplasty (9%) were assigned a cost of lost income per year. This was based on the average yearly earning in Australia ($71,379 for full time employees and $22,063 for part time employees). Costs were applied to all employed patients taking time off work and was calculated per 2 period.

## In home care services

Few studies in Australia have investigated the direct costs of care. One of the first to investigate this issue was the Taskforce on Care Costs (TOCC) who conducted a telephone survey of 512 employed carers and found that those who paid for care services spent on average $8,400 a year in 2005 on support for older people ($12,118 when inflated to 2022 prices based on an average annual inflation rate of 2.3 per cent). Costs were calculated per 2 period.

## Savings to employers

### Paid leave

The average cost of paid leave was calculated based on the average wages in Australia ($1,368 per week) multiplied by the number of annual weeks of paid sick leave for full time (2 weeks) and part time (0.6 weeks) employees. Costs were applied to all employed patients taking time off work and was calculated per 2 period.

### Loss of employees due to early retirement or premature death

A survey of over 1,500 HR professionals across Australia and New Zealand found it costs organisations $18,982 on average to hire a new employee ($19,693 when inflated to 2022 prices based on an average annual inflation rate of 1.9 per cent) (22). Costs were applied to all employed patients who either prematurely died (adjusting for underlying mortality) or retired and were calculated per 2 period.

# AVERAGE SAVING PER PATIENT

In this analysis costs were calculated over a 6-year time horizon and vary depending on the infected joint (knee or hip), infection type (acute, early, chronic, or not classifiable) and state where the patient received treatment.

The base case analysis reported knee and hip infections, all infection types, Australia-wide and an effectiveness proxy of 57% (average of all effectiveness proxies). The average saving per patient over 2 years for the base case analysis was $47,736[3].

The effectiveness of bacteriophage was the biggest driver of cost in the model, however, even an effectiveness proxy of 22% still incurred a significant saving of $18,085 per patient. Effectiveness of 100% resulted in a saving of $84,001 per patient[3].All other metrics had minor variations. The highest saving per patients were reported for hip joints ($49,376) and for chronic infections ($45,131). Greater saving per patients were incurred in the first 4 years ($50,846 for year 0-2, $46,153 for year 2-4 and $25,207 for year 4-6).

Table 12 Savings per patient over 2 years

| Analysis | Average savings |
|---|---|
| **Joint type** | |
| Knee/hip (base case) | $47,736 |
| Knee | $46,867 |
| Hip | $49,376 |
| **Infection type** | |
| Any (base case) | $47,736 |
| Early | $44,838 |
| Acute | $44,236 |
| Chronic | $45,131 |
| Not classifiable | $40,666 |
| **Time period** | |
| Year 0-6 (base case) | $47,736 |
| Year 0-2 | $50,846 |
| Year 2-4 | $46,153 |
| Year 4-6 | $25,207 |
| **Effectiveness of bacteriophage** | |
| 57% (base case) | $47,736 |
| 22% | $18,085 |
| 35% | $29,323 |
| 71% | $59,536 |
| 100% | $84,001 |





[3] This estimate does not account for the upfront cost of bacteriophage therapy

# CONCLUSION

Prosthetic joint infections (PJI) are a serious complication after a joint replacement which is associated with high morbidity and need for complex interdisciplinary treatment strategies (1). The lack of success treating PJIs with conventional antibiotics alone is primarily related to the presence of bacterial biofilm on medical implants (2). Bacteriophages are a unique therapeutic platform which can degrade biofilms. Numerous preclinical studies have demonstrated that bacteriophage (as an adjunct to antibiotics) is more effective at eradicating biofilms and resolving infections when compared to standard of care (antibiotics alone) (4-9).

This report estimates the financial impacts (direct and indirect) of using bacteriophage therapy in patients with PJIs. The model utilises a theory of change analysis to calculate the downstream avoided costs associated with persistent PJI. Costs were calculated over a 6-year time horizon and varied depending on the infected joint (knee or hip), infection type (acute, early, chronic, or not classifiable) and the state where the patient received treatment. The key results reported in this paper are from the base case analysis: knee and hip infections, all infection types, Australia-wide and an effectiveness proxy of 57% (average of all effectiveness proxies).

## The key findings were as follows:

- If all patients across Australia with prosthetic knee and hip infections (2,573 patients) were treated with bacteriophage therapy, the total savings over 6 years were estimated to be $122.8 million in 2022 corresponding to an average saving of $47,736 per patient over 2 years[1].
- If all patients across NSW with prosthetic knee and hip infections (818 patients) were treated with bacteriophage therapy, the total savings over 6 years were estimated to be $38.8 million in 2022 corresponding to an average saving of $47,424 per patient over 2 years[1].
- The total direct savings (healthcare relating savings) were $71.3 million most of which was attributed to the government (63%) and private health insurers (33%). Savings were also partially attributed to patients and their families (4%).
- The total indirect savings (non-health care related savings) were $51.5 million most of which was attributed to patients and their families (67%), followed by the government (19%) and employers (14%).
- The highest saving per patients were reported for hip joints ($49,376) and patients with chronic infections ($45,131). Greater saving per patients were incurred in the first 4 years ($50,846 for year 0-2, $46,153 for year 2-4 and $25,207 for year 4-6).

[4] This estimate does not account for the upfront cost of bacteriophage therapy

# KEY LIMITATIONS

Limitations were primarily due to gaps in data, highlighting the need for further research into the impact of PJIs in Australia. None the less, this impact assessment demonstrates that bacteriophage therapy has the potential to effectively treat thousands of patients with PJI, avoiding the high associated downstream costs, morbidity, and mortality.

## The key limitations were as follows:

- This analysis assumes that the percentage reduction in CFU and biofilm thickness is directly correlated to avoided infection based on results from one key pre-clinical study (9). To adjust for uncertainty relating to these inputs, incremental effectiveness ranges of between 22% and 100% were included in the model. Further research is required in this area to overcome gaps in data identified in this analysis.
- The PIANO study was used for many of the clinical inputs relating to patient management and the respective outcomes. Although the most common joints of patients enrolled in the PIANO study were knees (55%) and hips (39%), other joints were also included which may slightly influence the results of this analysis.
- Many of the estimates in the model are based on the average age of a patient enrolled in the PIANO study (69 years), however costs many vary when considering patients who are younger or older
- Estimates relied on national averages wages which may not be an accurate reflection of those who suffer PJIs.
- All patients with an unresolved deep PJI were assumed to have functional limitations which require support and care services; however, it is uncertain if all patients would require these additional payments.
- The analysis assumed that the increase in length of stay directly correlates to an increase in overall recovery time, however, the difference in recovery time outside of hospital is unknown.

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